

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

Maryan Lelyukh <sup>1,\*</sup> , Olha Kasianchuk <sup>2</sup> , Roksoliana Bukliv <sup>3,4</sup> , Andriy Mylyanych <sup>4,5</sup> , Andrii Vergun <sup>6</sup> , Ihor Chaban <sup>1</sup> , Rostyslav Sogujko <sup>7</sup> , Stefan Harkov <sup>8</sup> , Taras Chaban <sup>9</sup> 

- <sup>1</sup> Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska St. 69, Lviv, 79010, Ukraine; lelyukh.m@gmail.com (M.L.); chabanigor@ukr.net (I.C.);
  - <sup>2</sup> Student of the Pharmaceutical Faculty, Danylo Halytsky Lviv National Medical University, Pekarska St. 69, Lviv, 79010, Ukraine; olyafoxy2fox@gmail.com;
  - <sup>3</sup> Department of Chemistry and Technology of Inorganic Substances, Lviv Polytechnic National University, Stepana Bandery St. 14, 79000, Lviv, Ukraine; roksoliana.l.bukliv@lpnu.ua;
  - <sup>4</sup> Institute of Chemistry and Chemical Technologies, 9 St. Yura sqr., Lviv, 79013, Ukraine
  - <sup>5</sup> Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Lviv Polytechnic National University, Stepana Bandery St. 14, 79000, Lviv, Ukraine; Amylyanych@gmail.com;
  - <sup>6</sup> Department of Family Medicine, Danylo Halytsky Lviv National Medical University, General Chuprynyk St. 62, Lviv, 79057, Ukraine; plagi@mail@meta.ua;
  - <sup>7</sup> Department of Operative Surgery with Topographic Anatomy, Danylo Halytsky Lviv National Medical University, Pekarska St. 52, Lviv, 79010, Ukraine; r.sogujko@gmail.com;
  - <sup>8</sup> Department of Pharmacy, Medical College of Burgas University “Prof. Dr. Asen Zlatarov”, St. Stambolov 69 Blv., Burgas, 8000, Bulgaria; stefan.harkov@mail.bg;
  - <sup>9</sup> Department of General, Bioinorganic, Physical and Colloidal Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska 69, Lviv, 79010, Ukraine; chabantaras@ukr.net;
- \* Correspondence: lelyukh.m@gmail.com;

Received: 18.03.2025; Accepted: 17.07.2025; Published: 30.09.2025

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

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

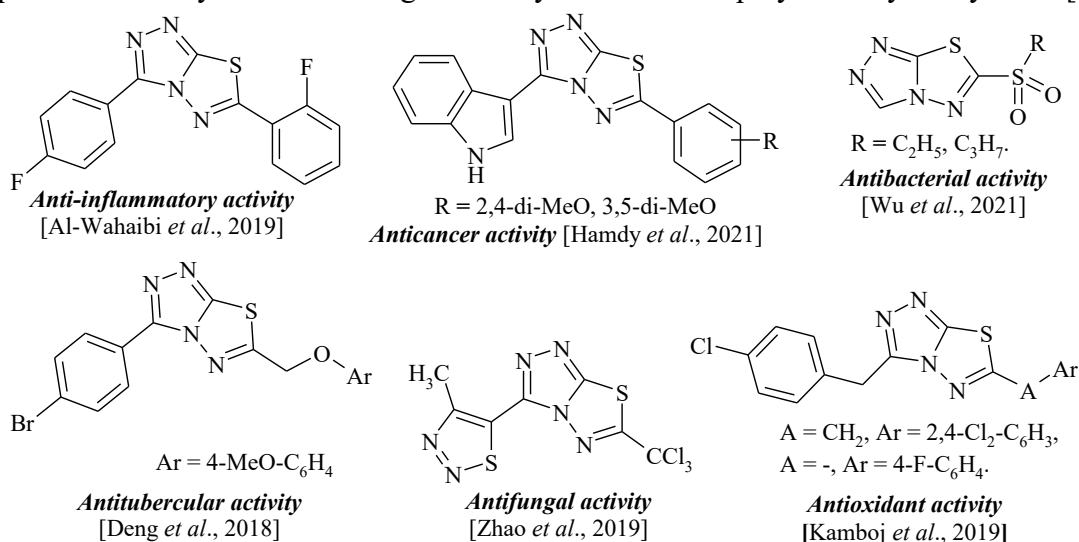
© 2025 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The authors retain copyright of their work, and no permission is required from the authors or the publisher to reuse or distribute this article, as long as proper attribution is given to the original source.

## 1. Introduction

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

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

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



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

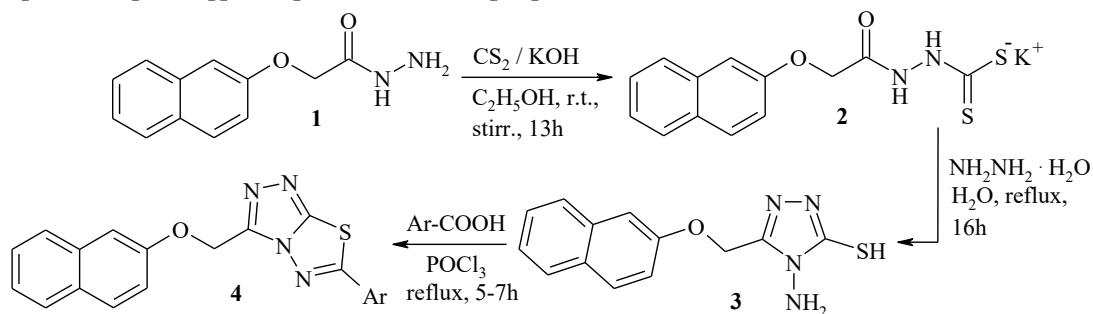
It is worth emphasizing that condensed heterocyclic systems are no less interesting and undeniably important compounds in organic chemistry. They are well-known for their excellent biological effects and are often of greater efficiency in terms of their biological activity than their individual monocyclic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

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

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

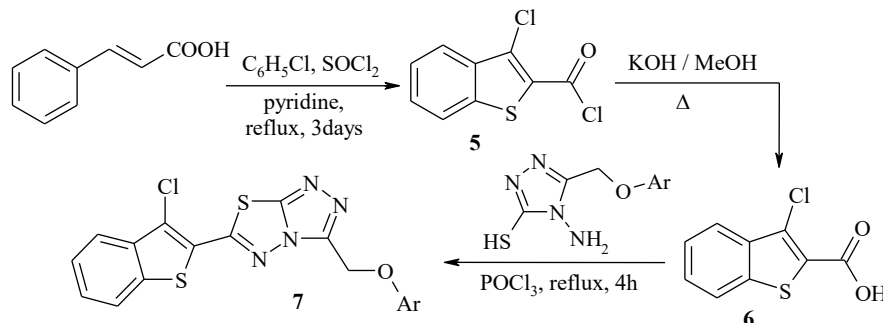
## 2. Synthetic Approaches for Obtaining and Chemical Modification of Heterocyclic Compounds Based on Condensed [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole System

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



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

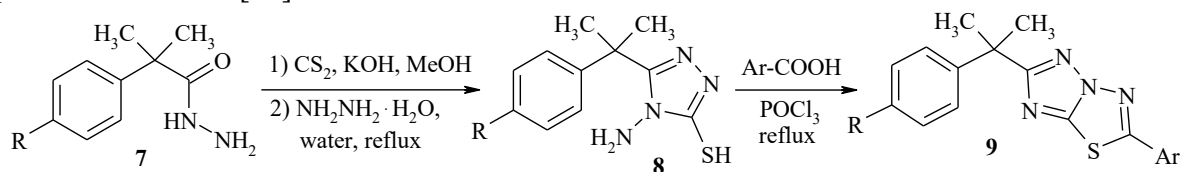
Following the hydrolysis of 3-chlorobenzo[*b*]thiophene-2-carboxyl chloride **5**, previously obtained from cinnamic acid and thionyl chloride in chlorobenzene medium, with methanolic potassium hydroxide, the corresponding benzo[*b*]thiophene-2-carboxylic acid **6** was formed (Scheme 2). Further interaction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



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

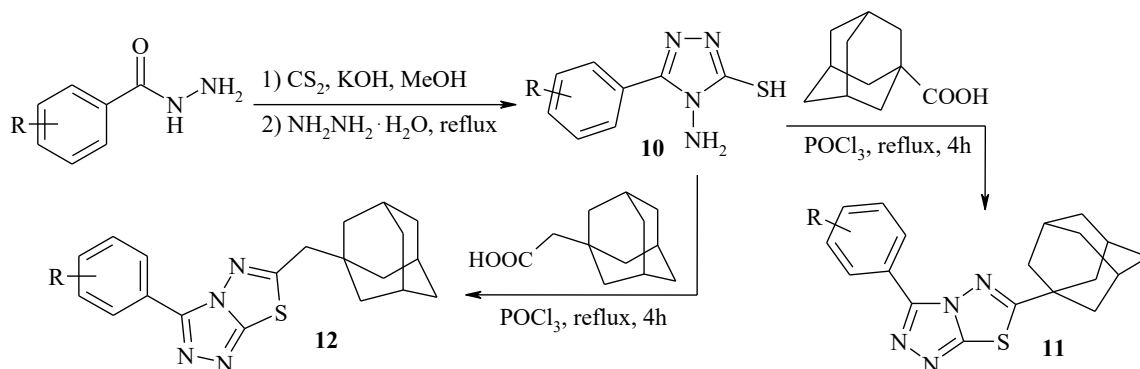
3,6-Disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing *gem*-dimethyl benzyl moiety **9** (Scheme 3) were prepared by condensation of 5-aryl/aralkyl substituted 4-

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



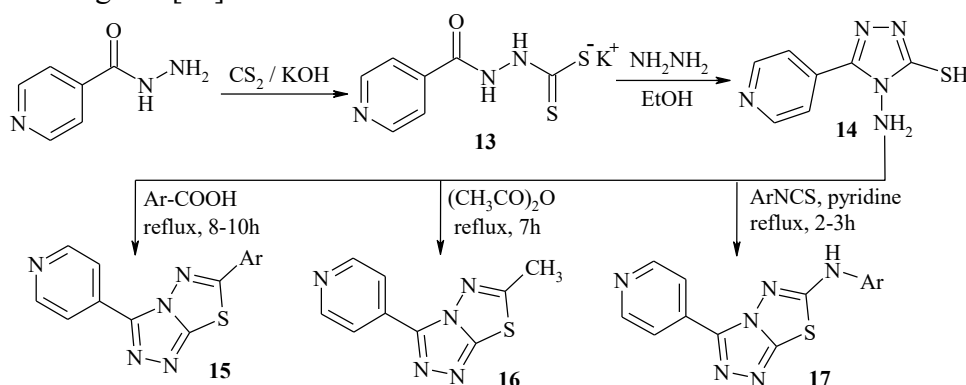
**Scheme 3.** Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing *gem*-dimethyl benzyl moiety by condensation of 5-aryl/aralkyl-4-amino-4*H*-1,2,4-triazole-3-thiols with fluoro substituted aromatic acids.

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



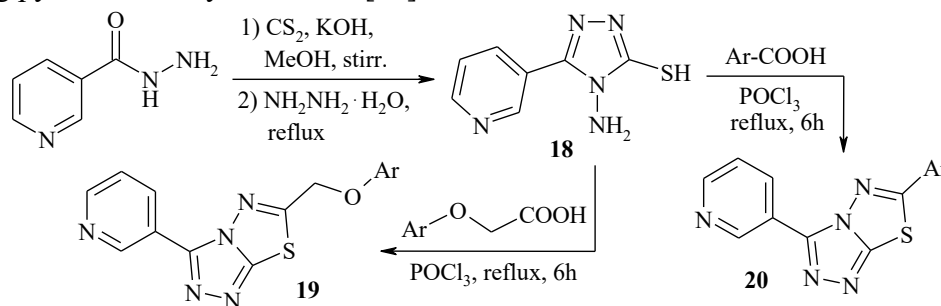
**Scheme 4.** Synthesis of 6-adamantyl(methyl) substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols with adamantyl-1-carboxylic(acetic) acids.

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



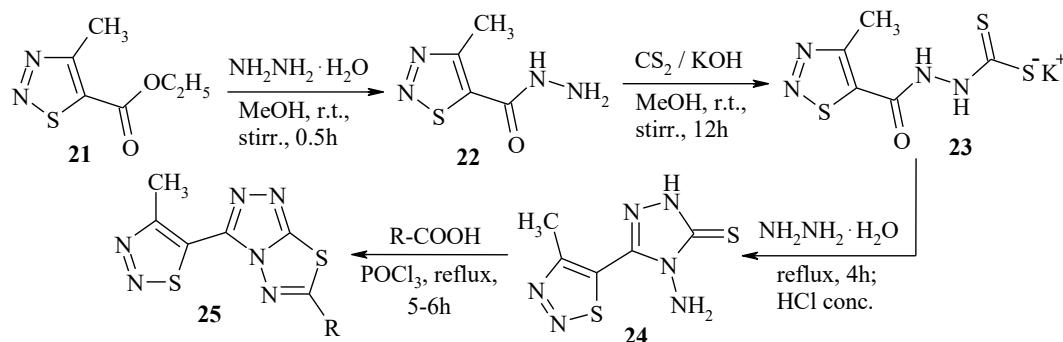
**Scheme 5.** Synthesis of 6-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles from condensation of 4-amino-5-(pyridin-4-yl)-1,2,4-triazol-3-thiol with aromatic carboxylic acids, acetic anhydride, or aryl isothiocyanates.

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



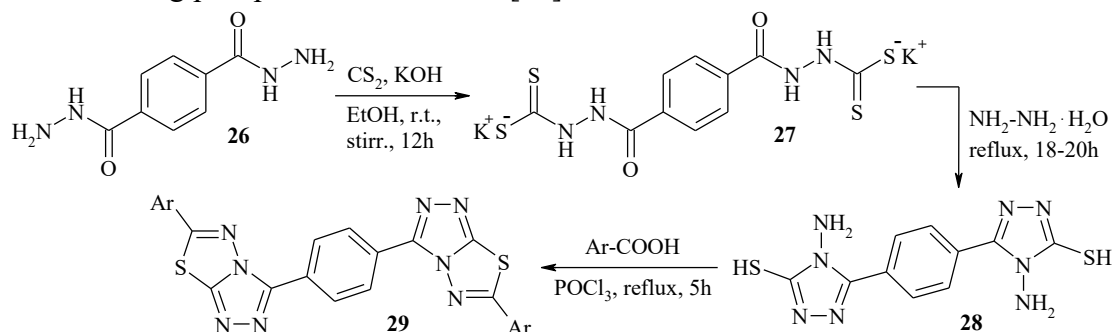
**Scheme 6.** Synthesis of 6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine fragment by condensation of 4-amino-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-thiol with aromatic or phenyloxyacetic acids.

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



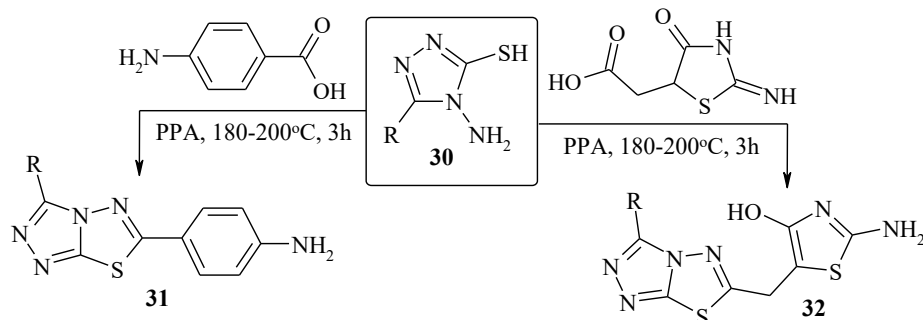
**Scheme 7.** Synthesis of 4-methyl-1,2,3-thiadiazole-containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 3-(4-methyl-1,2,3-thiadiazolyl)-4-amino-1,2,4-triazole-5-thione with carboxylic acids.

Following the multistep reaction sequence starting from terephthalic dihydrazide **26** through an intermediate stage of bis-dithiocarbamate potassium salt **27** formation, the corresponding 1,4-phenylene-bis-(4-amino-4*H*-1,2,4-triazole-3-thiol) **28** was obtained (Scheme 8). The synthesis of target 1,4-bis-(6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole) phenylenes **29** was achieved through the one-pot condensation of compound **28** with aromatic acids in refluxing phosphorus oxychloride [74].



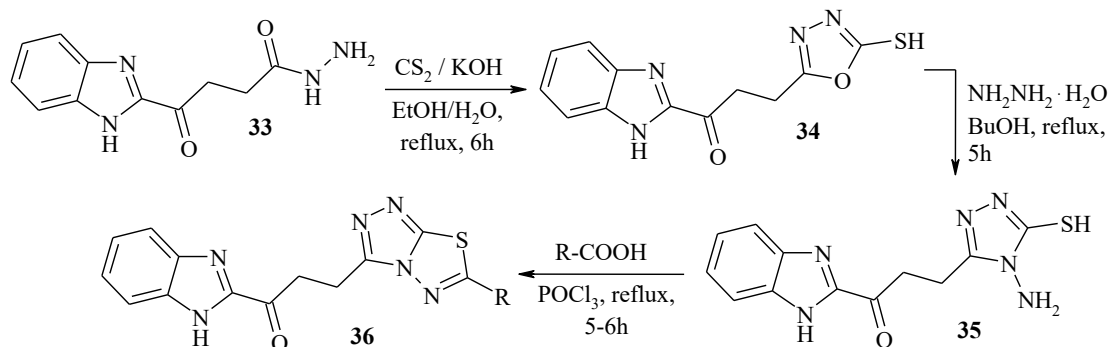
**Scheme 8.** Synthesis of 1,4-bis-(6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole)phenylenes by condensation of 1,4-phenylene-bis(4-amino-4*H*-1,2,4-triazole-3-thiol) with aromatic acids.

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



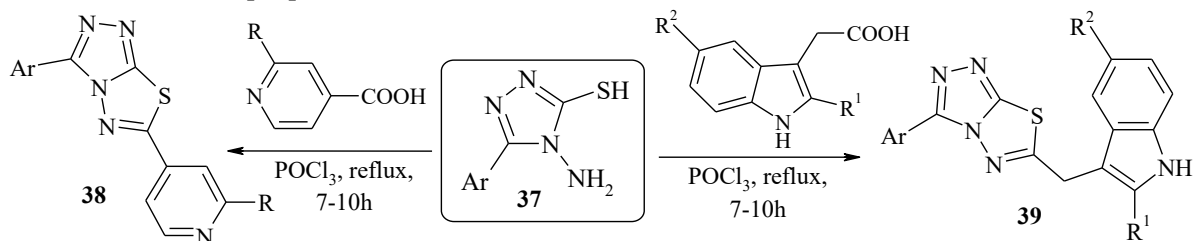
**Scheme 9.** Synthesis of 3,6-disubstituted triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 5-substituted 4-amino-1,2,4-triazole-3-thiol with 4-aminobenzoic acid or (2-iminothiazol-4-one-5-yl)acetic acid.

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



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

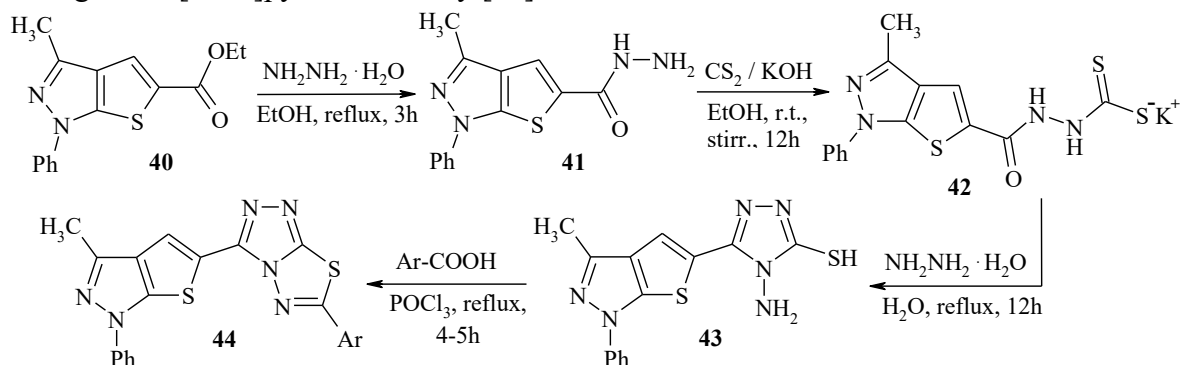
Condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols **37** with isonicotinic or indol-3-ylacetic acid derivatives in the presence of phosphorus oxychloride (Scheme 11) resulted in the expected 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine **38** or indole **39**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



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

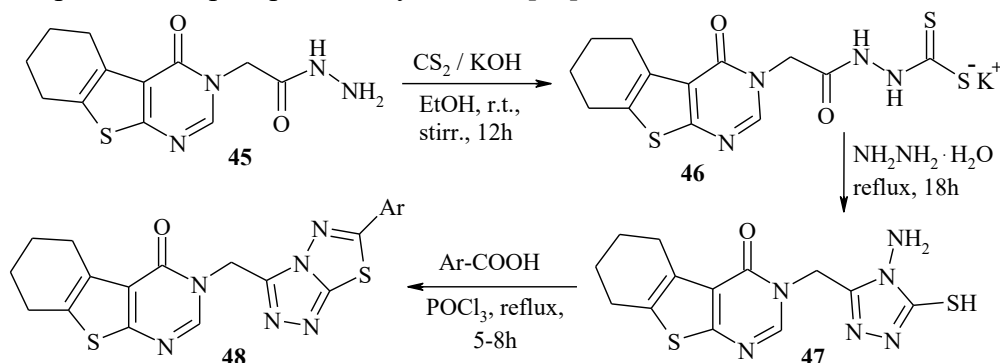
Starting from 3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid ethyl ester **40** through the multistep reaction sequence (Scheme 12), the synthesis of 4-amino-5-

(thieno[2,3-*c*]pyrazol-5-yl)-substituted-4*H*-1,2,4-triazole-3-thiol 43 was carried out. Further one-pot condensation of the obtained 4-amino-4*H*-1,2,4-triazole-3-thiol 43 with aromatic acids in POCl<sub>3</sub> medium resulted in 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 44 bearing thieno[2,3-*c*]pyrazolo moiety [79].

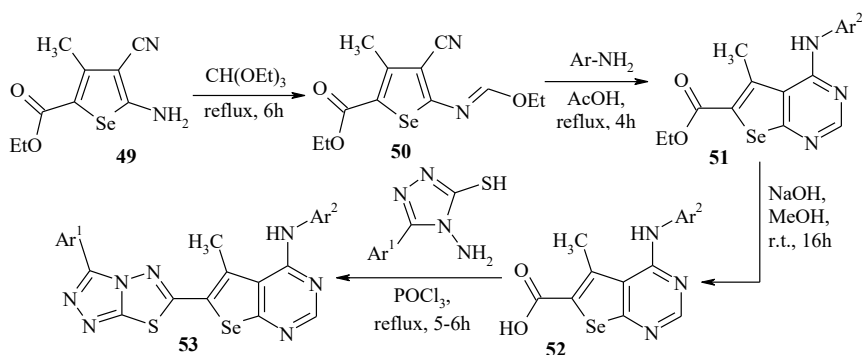


**Scheme 12.** Synthesis of thieno[2,3-*c*]pyrazole containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of corresponding 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol with aromatic acids.

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



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

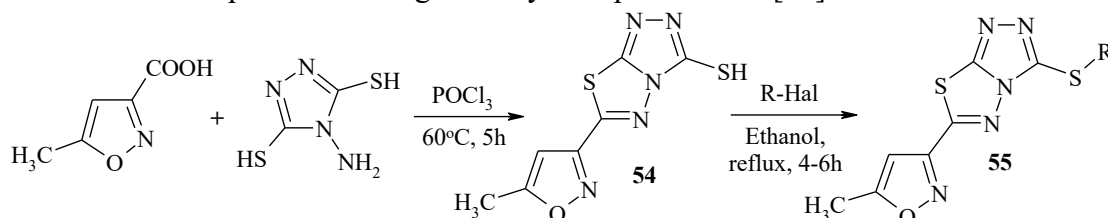


**Scheme 14.** Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl selenopheno[2,3-*d*]pyrimidines from the reaction of 4-amino-5-aryl-1,2,4-triazol-3-thiols with corresponding carboxylic acids.

Modification of ethyl 5-amino-4-cyano-3-methylselenophene-2-carboxylate 49 with triethyl orthoformate (50), then substituted anilines in acetic acid (51), followed by hydrolysis of the corresponding 5-methyl-4-arylamino-selenopheno[2,3-*d*]pyrimidine-6-carboxylic acids

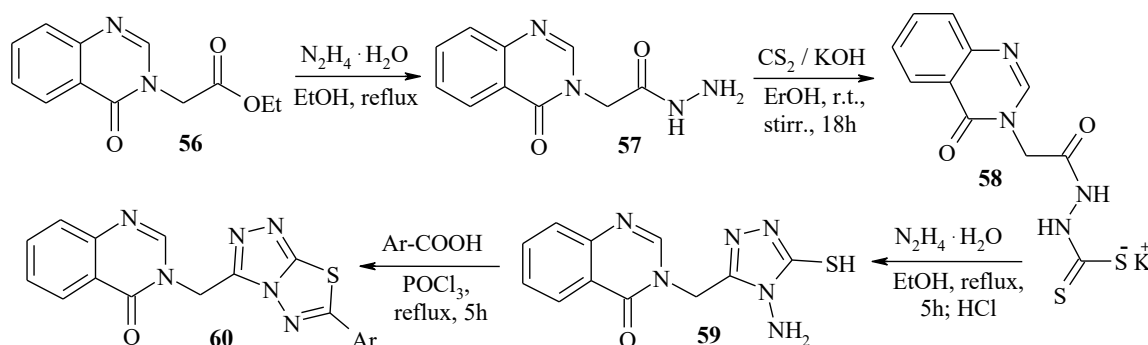
52 were obtained (Scheme 14). A series of title [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl selenopheno[2,3-*d*]pyrimidines 53 were synthesized from the reaction of carboxylic acids 52 with 4-amino-5-aryl-1,2,4-triazol-3-thiols in the presence of POCl<sub>3</sub> [81].

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

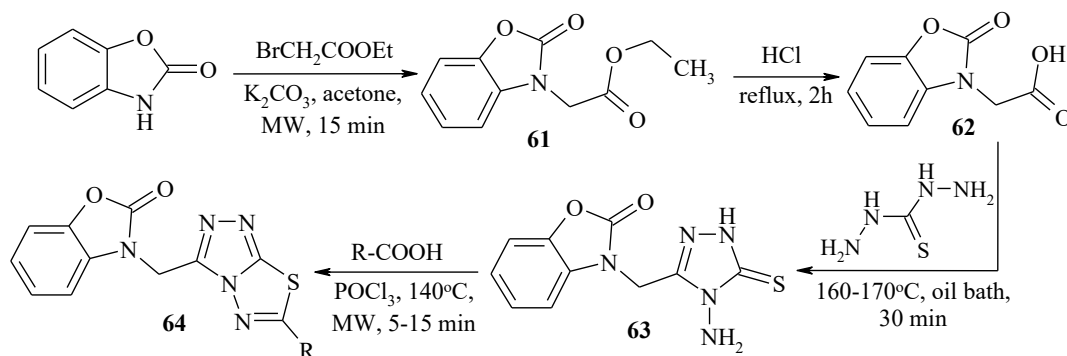


**Scheme 15.** Synthesis of isoxazole substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles *via* cyclocondensation of 5-methylisoxazole-3-carboxylic acid with 4-amino 1,2,4-triazole-3,5-dithiol followed by alkylation.

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



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

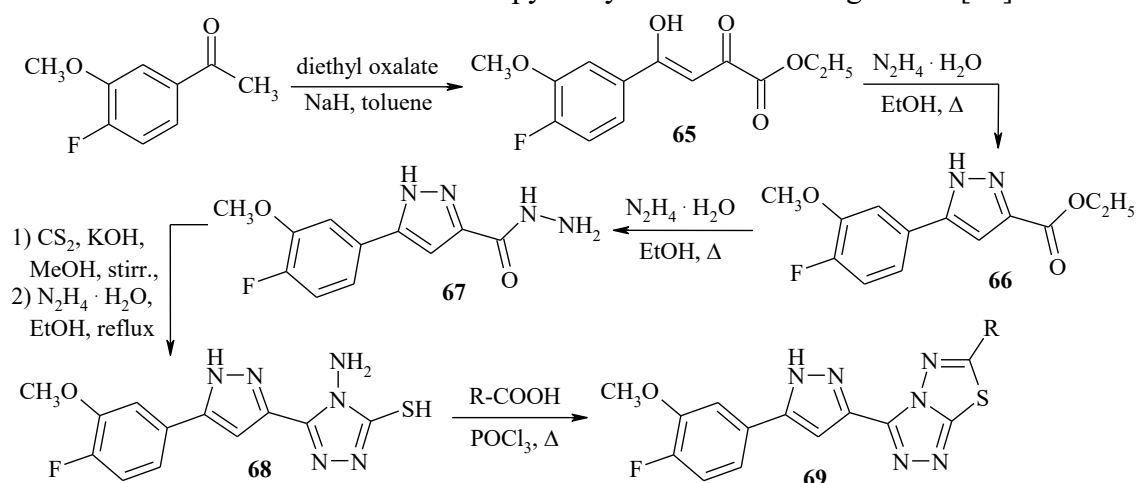


**Scheme 17.** Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles having benzoxazolone moiety by condensation of 2(3*H*)-benzoxazolone substituted 4-amino-5-thio-1,2,4-triazole with benzoic or phenylacetic acids.

Following the interaction of 2-(2-oxo-3*H*-benzoxazol-3-yl)acetic acid 62, obtained by hydrolysis of the corresponding ethyl ester 61, with thiocarbonylhydrazide, the synthesis of 3-[(4-

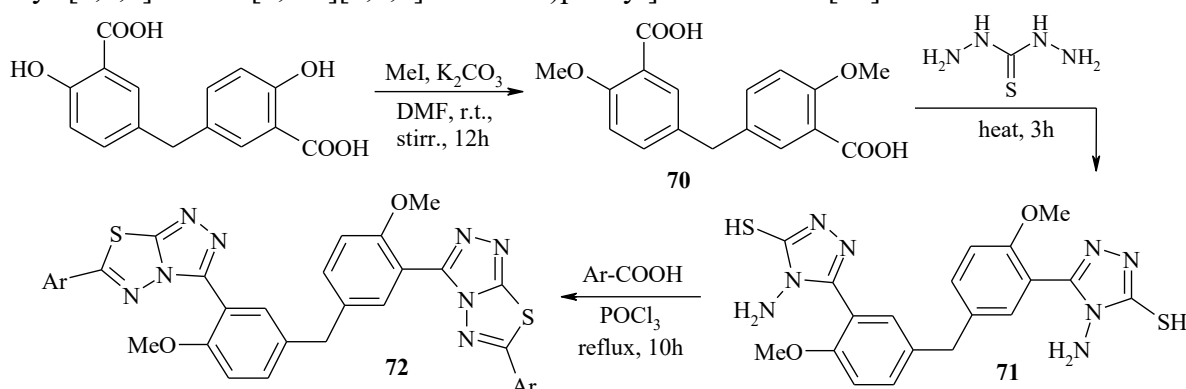
amino-5-thioxo-1,2,4-triazol-3-yl)methyl]-2(3*H*)-benzoxazolone **63** was performed (Scheme 17). A series of 2(3*H*)-benzoxazolone substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **64** were synthesized by condensation of compound **63** with substituted benzoic or phenylacetic acids in phosphorus oxochloride medium under microwave irradiation [84].

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



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

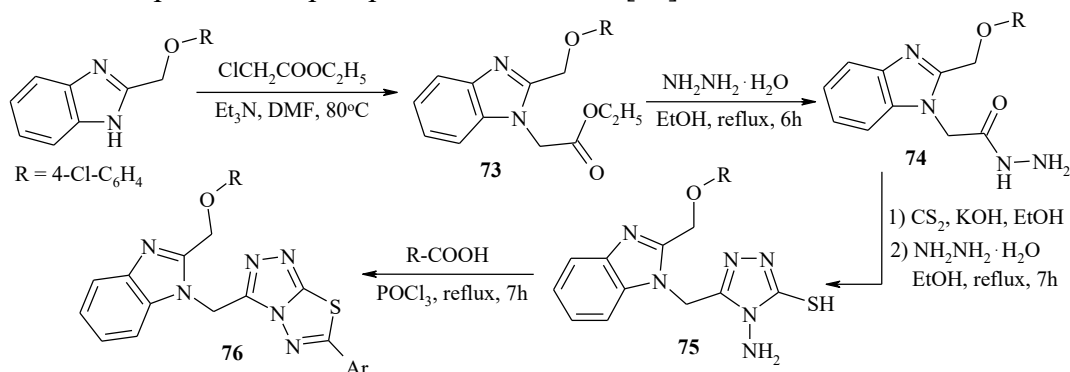
By a two-step procedure, 5-(3-carboxy-4-methoxybenzyl)-2-methoxybenzoic acid **70** was synthesized and converted, upon reaction with thiocarbohydrazide, into bis[4-methoxy-3-[4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl]phenyl]methane **71**, as shown in Scheme 19. Further, the interaction of **71** with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



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

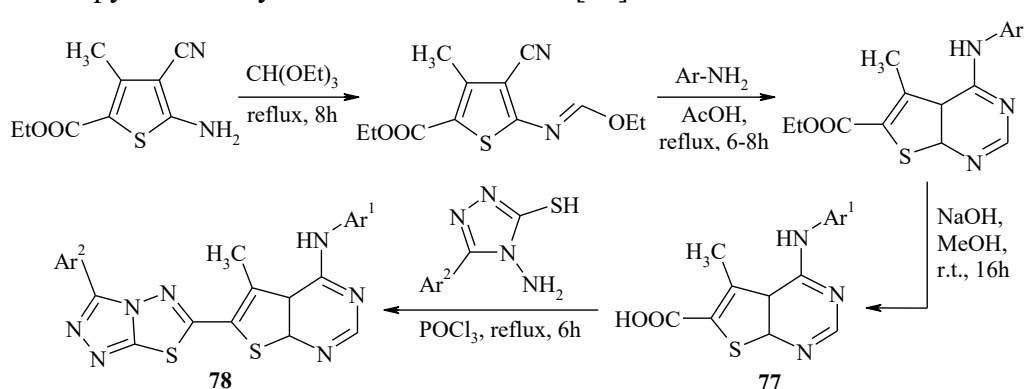
Using 2-[2-(4-chlorophenoxymethyl)-1*H*-benzimidazole-1-yl]-acetic acid ethyl ester **73** as starting material by sequential interactions with hydrazine hydrate (**74**) followed by cyclization with carbon disulfide in ethanolic potassium hydroxide, the synthesis of 4-amino-

1,2,4-triazole-3-thiol **75** was carried out (Scheme 20). A series of 6-(benzimidazole-1-methylene) substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **76** were synthesized by condensation of 4-amino-3-mercapto-1,2,4-triazoles **75** with various (un)substituted aromatic acids in the presence of phosphorus oxochloride [87].

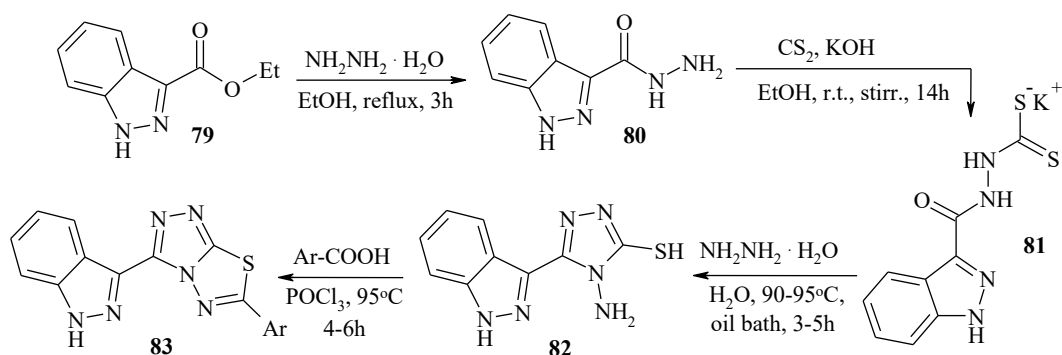


**Scheme 20.** Synthesis of benzimidazole-1-methylene substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-3-mercapto-4*H*-1,2,4-triazoles with (un)substituted aromatic acids.

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



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

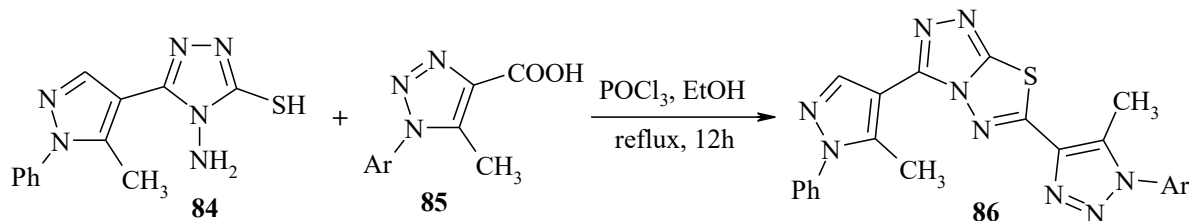


**Scheme 22.** Synthesis of 1*H*-indazole substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-1,2,4-triazole-3-thiol with substituted arylcarboxylic acids.

Starting from 1*H*-indazole-3-carboxylic acid ethyl ester **79** through an intermediate stage of the corresponding hydrazide **80** and potassium dithiocarbamate **81** formation, the synthesis of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-1,2,4-triazole-3-thiol **82** was achieved (Scheme

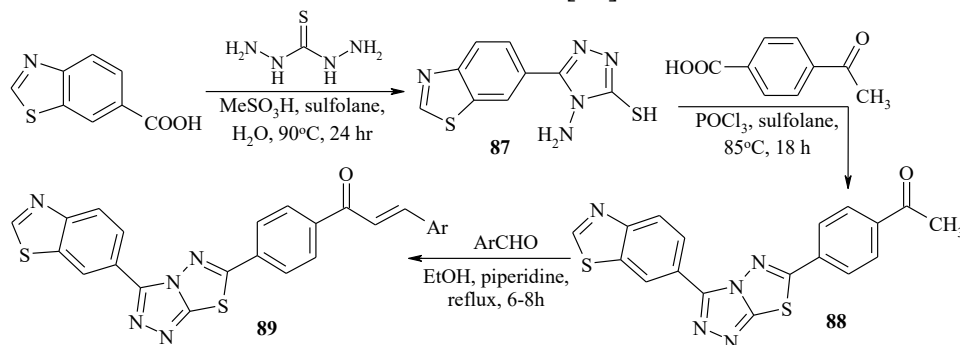
22). Further, intermolecular condensation of compound 82 with substituted arylcarboxylic acids in refluxing POCl<sub>3</sub> provided a series of target 3-(1*H*-indazol-3-yl) substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 83 [89].

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



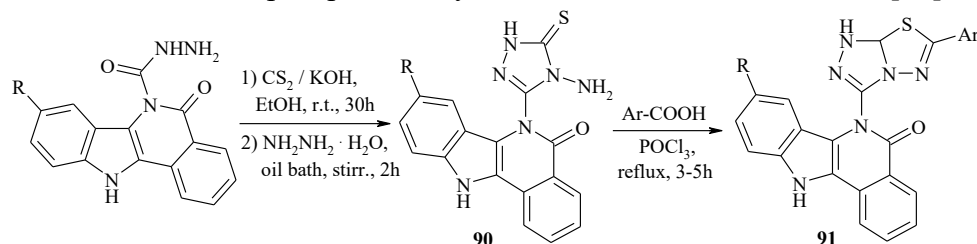
**Scheme 23.** Synthesis of pyrazole and 1,2,3-triazole having [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiol with 1-aryl-1,2,3-triazole-4-carboxylic acids.

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



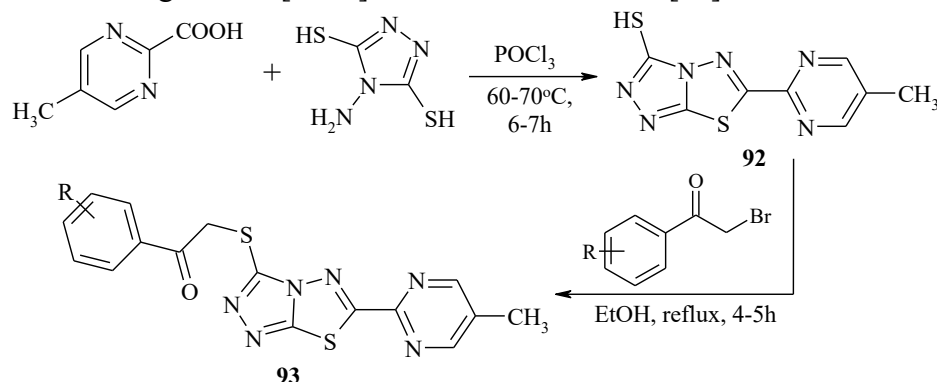
**Scheme 24.** Synthesis of benzothiazole containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole tethered chalcones by condensation of 4-amino-5-(1,3-benzothiazol-6-yl)-4*H*-1,2,4-triazol-3-thiol with 4-acetylbenzoic acid.

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



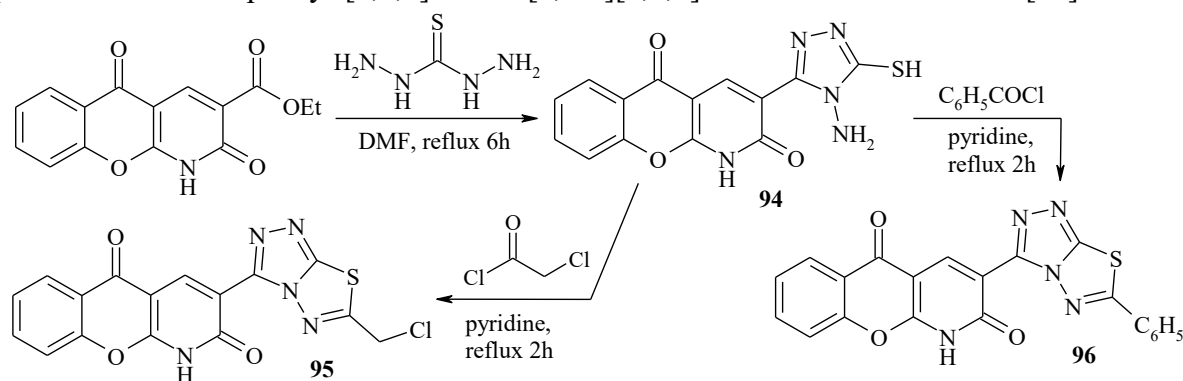
**Scheme 25.** Synthesis of indolo[3,2-*c*]isoquinolines incorporated with [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole moieties by condensation of corresponding 4-amino-1*H*-1,2,4-triazole-5-thiols with substituted aromatic acids.

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



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

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



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

### 3. Conclusions

Triazolo[3,4-*b*]thiadiazoles represent an important class of fused nitrogen and sulfur-containing heterocyclic compounds, which have attracted great interest in medicinal chemistry owing to their wide range of biological activities, such as antitumor, antibacterial, antifungal, antitubercular, anticonvulsant, anti-inflammatory, neuroprotective, and antioxidant action. The presence of triazolo[3,4-*b*]thiadiazole system as a part of various therapeutically important molecules can be a determinant for its physicochemical and pharmacokinetic properties. The simplicity and effectiveness of the synthetic procedures in the generation of these compounds, together with the structural diversity of triazolo[3,4-*b*][1,3,4]thiadiazole derivatives, make them a convenient and efficient tool for obtaining various biologically active substances.

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

### Author Contributions

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

### Institutional Review Board Statement

Not applicable

### Informed Consent Statement

Not applicable

### Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

### Funding

This research received no external funding.

### Acknowledgments

None.

### Conflicts of Interest

The authors declare no conflict of interest.

### References

1. Helmy, M.T.; Teleb, M.A.A.; Hanna, D.H.; El-Maadawy, M.W., Hassaneen, H.M.; Kamel, M.G. Convenient synthesis, characterization, evaluation and molecular docking of some new fused pyrazolo[3,4-*d*]pyrimidine derivatives and 3-methyl-8 phenylpyrazolo[3',4':4,5]pyrimido[6,1-*c*][1,2,4]triazines against HeLa cancer cells. *Tetrahedron* **2025**, *177*, 134557, <https://doi.org/10.1016/j.tet.2025.134557>.
2. Tymoshuk, O.; Oleksiv, L.; Rydchuk, P.; Chaban, T.; Tymoshuk, S.; Matiychuk, V. Spectrophotometric study of the interaction of platinum (IV) with new derivatives of azolidones. *Chem. Chem. Technol.* **2020**, *14*, 139-145, <https://doi.org/10.23939/chcht14.02.139>.

- Chaban, T.I.; Matiichuk, Y.E.; Horishny, V.Y.; Chaban, I.G.; Matiychuk, V.S. Synthesis and anticancer activity of 2-aryl-3-methylbenzofuro[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*, 10*H*)-dione and 2-aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones. *Russ. J. Org. Chem.* **2020**, *56*, 813-818, <http://dx.doi.org/10.1134/S1070428020050139>.
- Horishny, V.Y.; Chaban, T.I.; Matiychuk, V.S. Synthesis and primary antitumor screening of 5-ylidene derivatives of 3-(morpholin-4-yl)-2-sulfanylidene-1, 3-thiazolidin-4-one. *Russ. J. Org. Chem.* **2020**, *56*, 454-457, <https://doi.org/10.1134/s1070428020030148>.
- El-Wakil, M.H.; Ghazala, R.A.; El-Dershaby, H.A.; Drozdowska, D.; Wróbel-Tałała, A.; Parzych, C.; Ratkiewicz, A.; Kolesińska, B.; El-Razik H.A.A.; Soliman, F.S.G. Rational design, synthesis, and molecular modelling insights of dual DNA binders/DHFR inhibitors bearing arylidene-hydrazinyl-1,3-thiazole scaffold with apoptotic and anti-migratory potential in breast MCF-7 cancer cells. *J. Enzyme Inhib. Med. Chem.* **2025**, *40*, 2468353, <https://doi.org/10.1080/14756366.2025.2468353>.
- Chaban, T.; Matiychuk, V.; Chulovska, Z.; Myrko, I.; Drapak, I.; Sogujko, R.; Chaban, I.; Ogurtsov, V.; Nektegaev, I. Synthesis and evaluation of anti-inflammatory activity of some thiazolo[4,5-*b*]pyridines. *Biointerface Res. Appl. Chem.* **2022**, *12*, 7226. <https://doi.org/10.33263/BRIAC126.72267238>.
- Liao, Y.-M.; Cheng, L.; Luo, R.-S.; Guo, Q.; Shao, W.-B.; Feng, Y.-M.; Zhou, X.; Liu, L.-W.; Yang, S. Discovery of new 1,2,4-triazole/1,3,4-oxadiazole-decorated quinolinones as agrochemical alternatives for controlling viral infection by inhibiting the viral replication and self-assembly process. *J. Agric. Food Chem.* **2024**, *72*, 27750-27761, <https://doi.org/10.1021/acs.jafc.4c05234>.
- Majrashi, T.A.; Sabt, A.; El Salam, H.A.A.; Al-Ansary, G.H.; Hamissa, M.F.; Eldehna, W.M. An updated review of fatty acid residue-tethered heterocyclic compounds: Synthetic strategies and biological significance. *RSC Adv.* **2023**, *13*, 13655-13682, <https://doi.org/10.1039/D3RA01368E>.
- Matiichuk, Y.E.; Ostapiuk, Y.V.; Chaban, T.I.; Ogurtsov, V.V.; Matiychuk, V.S. Synthesis and anticancer properties of *N*-(5-*R*-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides. *Biopolym. Cell* **2020**, *36*, 75-84, <https://doi.org/10.7124/bc.000A22>.
- Drapak, I.; Chaban, T.; Foliush, V.; Matiychuk, V. Synthesis antimicrobial and antitumor activities of 2-[5-(2-*R*-benzyl) thiazol-2-ylimino] thiazolidin-4-ones. *Biointerface Res. Appl. Chem.* **2020**, *10*, 5507-5511, <https://doi.org/10.33263/BRIAC103.507511>.
- Chulovska, Z.; Chaban, T.; Drapak, I.; Matiychuk, V.; Chaban, I.; Nektegaev, I. Synthesis of some C<sup>5</sup> substituted 4-phenylimino-thiazolidin-2-ones as possible anti-inflammatory agents. *Biointerface Res. Appl. Chem.* **2021**, *11*, 8009-8017, <https://doi.org/10.33263/BRIAC111.80098017>.
- Subtelna, I.; Kryshchshyn-Dylevych, A.; Jia, R.; Lelyukh, M.; Ringler, A.; Kubicek, S.; Zagrijtschuk, O.; Kralovics, R.; Lesyk, R. 5-Arylidene-2-(4-hydroxyphenyl)aminothiazol-4(5*H*)-ones with selective inhibitory activity against some leukemia cell lines. *Arch. Pharm.* **2021**, *354*, 2000342, <https://doi.org/10.1002/ardp.202000342>.
- Pone, K.B.; Dalhatou, S.; Paumo, H.K.; Katata-Seru, L.M.; Ferreira, E.I. Triazole-containing heterocycles: Privileged scaffolds in anti-*Trypanosoma Cruzi* drug development. *Curr. Drug Targets* **2022**, *23*, 33-59, <https://doi.org/10.2174/1389450122666210412125643>.
- Rydehuk, P.; Tymoshuk, O.; Oleksiv, L.; Chaban, T.; Matiychuk, V. Voltammetric determination of Pt (IV) using 5-hydroxyimino-4-imino-1,3-thiazolidine-2-one. *Methods Objects Chem. Anal.* **2019**, *14*, 130-139, <http://dx.doi.org/10.17721/moca.2019.130-139>.
- Mortada, S.; Karrouchi, K.; Hamza, El H.; Oulmidi, A.; Bhat, M.A.; Mamad, H.; Aalilou Y.; Radi, S.; Ansar, M. Masrar, A.; Faouzi, M.E.A. Synthesis, structural characterizations, in vitro biological evaluation and computational investigations of pyrazole derivatives as potential antidiabetic and antioxidant agents. *Sci. Rep.* **2024**, *14*, 1312, <https://doi.org/10.1038/s41598-024-51290-6>.
- Chulovska, Z.; Chaban, T.; Savchenko, A.; Komarytsya, O.; Dasho, M.; Lelyukh, M.; Chaban, I.; Ogurtsov, V. Antioxidant properties of some 4-arylimino-thiazolidin-2-ones. *Curr. Chem. Lett.* **2025**, *14*, 365-372, <https://doi.org/10.5267/j.ccl.2024.11.001>.
- Patel, K.R.; Brahmhatt, J.G.; Pandya, P.A.; Daraji, D.G.; Patel, H.D.; Rawal, R.; Baran, S.K. Design, synthesis and biological evaluation of novel 5-(4-chlorophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiols as an anticancer agent. *J. Mol. Struct.* **2021**, *1231*, 130000, <https://doi.org/10.1016/j.molstruc.2021.130000>.
- Tian, G.; Song, Q.; Liu, Z.; Guo, J.; Cao, S.; Long, S. Recent advances in 1,2,3- and 1,2,4-triazole hybrids as antimicrobials and their SAR: A critical review. *Eur. J. Med. Chem.* **2023**, *259*, 115603, <https://doi.org/10.1016/j.ejmech.2023.115603>.

19. Gupta, O.; Pradhan, T.; Chawla, G. An updated review on diverse range of biological activities of 1,2,4-triazole derivatives: Insight into structure activity relationship. *J. Mol. Struct.* **2023**, *1274*, 134487, <https://doi.org/10.1016/j.molstruc.2022.134487>.
20. Pachuta-Stec, A. Antioxidant activity of 1,2,4-triazole and its derivatives: A mini-review. *Mini-Rev. Med. Chem.* **2022**, *22*, 1081-1094, <https://doi.org/10.2174/1389557521666210401091802>.
21. Lelyukh, M.I.; Komarenska, Z.M.; Chaban, T.I.; Chaban, I.H. An overview of the synthetic routes toward [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (microreview). *Chem. Heterocycl. Compd.* **2024**, *60*, 342-344, <https://doi.org/10.1007/s10593-024-03343-x>.
22. Glomb, T.; Minta, J.; Nowosadko, M.; Radzikowska, J.; Świątek, P. Search for new compounds with anti-inflammatory activity among 1,2,4-triazole derivatives. *Molecules* **2024**, *29*, 6036, <https://doi.org/10.3390/molecules29246036>.
23. Medetalibeyoğlu, H.; Atalay, A.; Sağlamtaş, R.; Manap, S.; Ortaakarsu, A.B.; Ekinçi, E.; Yüksek, H.; Tüzün, B. Synthesis, design, and cholinesterase inhibitory activity of novel 1,2,4-triazole Schiff bases: A combined experimental and computational approach. *Int. J. Biol. Macromol.* **2025**, *306*, 141350, <https://doi.org/10.1016/j.ijbiomac.2025.141350>.
24. Çapan, İ.; Hawash, M.; Qaoud, M.T.; Jaradat, N. Next-generation carbazole-linked 1,2,4-triazole-thione derivatives: Strategic design, synthesis, molecular docking, and evaluation of antidiabetic potential. *ACS Omega* **2025**, *10*, 848-861, <https://doi.org/10.1021/acsomega.4c07896>.
25. Abdelli, A.; Azzouni, S.; Plais, R.; Gaucher, A.; Efrat, M.L.; Prim, D. Recent advances in the chemistry of 1,2,4-triazoles: Synthesis, reactivity and biological activities. *Tetrahedron Lett.* **2021**, *86*, 153518, <https://doi.org/10.1016/j.tetlet.2021.153518>.
26. Mohamed, A.E.; Elgammal, W.E.; Dawaba, A.M.; Ibrahim, A.G.; Fouda, A.; Hassan, S.S. A novel 1,3,4-thiadiazole modified chitosan: Synthesis, characterization, antimicrobial activity, and release study from film dressings. *Appl. Biol. Chem.* **2022**, *65*, 54, <https://doi.org/10.1186/s13765-022-00725-7>.
27. Lelyukh, M.; Matiichuk, Yu.; Flud, V.; Chaban, I.; Ogurtsov, V. Synthesis and antioxidant properties of novel 2-(2,4-dioxothiazolidin-5-ylidene)-acetamides containing 1,3,4-thia/oxadiazole moieties. *Biointerface Res. Appl. Chem.* **2022**, *12*, 6710-6722, <https://doi.org/10.33263/BRIAC125.67106722>.
28. Kumar, D.; Kumar, H.; Kumar, V.; Deep, A.; Sharma, A.; Marwaha, M.G.; Marwaha, R.K. Mechanism-based approaches of 1,3,4 thiadiazole scaffolds as potent enzyme inhibitors for cytotoxicity and antiviral activity. *Med. Drug Discov.* **2023**, *17*, 100150, <https://doi.org/10.1016/j.medidd.2022.100150>.
29. Lelyukh, M.; Halevyeh, H.; Zhukrovskaya, M.; Semiion-Luchyshyn, O.; Kalytovska, M. Synthesis of 5-aryl/heterylidene substituted 2-imino-4-thiazolidinones possessing 1,3,4-thiadiazole moiety and their antitrypanosomal activity. *Curr. Chem. Lett.* **2023**, *12*, 413-420, <https://doi.org/10.5267/j.ccl.2022.11.005>.
30. Kim, J.; Kadayat, T.M.; Lee, J.-E.; Kwon, S.; Jung, K.; Hwang, J.S.; Kwon, O.-b.; Kim, Y.J.; Choi, Y.-K.; Park, K.-G.; Hwang, H.; Cho, S.J.; Lee, T.; Jeon, Y.H.; Chin, J. Discovery of the therapeutic potential of PPAR $\delta$  agonist bearing 1,3,4-thiadiazole in inflammatory disorders. *Eur. J. Med. Chem.* **2024**, *279*, 116856, <https://doi.org/10.1016/j.ejmech.2024.116856>.
31. Zhou, Y.; Gong, C.; Sun, Z.; Zeng, W.; Meng, K.; An, Y.; Hu, Y.; Xue, W. Novel flavonol derivatives containing 1,3,4-thiadiazole as potential antifungal agents: Design, synthesis, and biological evaluation. *ACS Omega* **2024**, *9*, 17297-17306, <https://doi.org/10.1021/acsomega.3c10294>.
32. Oubella, A.; Bimoussa, A.; Rehman, Md T.; AlAjmi, M.F.; Auhmani, A.; Taha, M.L.; Morjani, H.; Itto, M.Y.A. Molecular hybrids based on 1,2,3-triazole and 1,3,4-thiadiazole cores: Synthesis, characterization, anticancer activity and *in silico* study. *J. Mol. Struct.* **2024**, *1311*, 138339, <https://doi.org/10.1016/j.molstruc.2024.138339>.
33. Patel, V.M.; Patel, N.B.; Chan-Bacab, M.J.; Rivera, G.; Humal, T.R. Gamit, A.S. Synthesis and computational studies of 1,3,4-thiadiazole and benzothiazole clubbed benzimidazole analogous as anti-tubercular and anti-protozoal agent. *J. Mol. Struct.* **2025**, *1319*, 139326, <https://doi.org/10.1016/j.molstruc.2024.139326>.
34. Kalagara, S.; Baddam, S.R.; Ganta, S.; Vudari, B.; Enaganti, S.; Damarancha, A.; Eppakayala, L. Synthesis and biological evaluation of aryl derivatives of indole-1,3,4-thiadiazole as anticancer agents. *Synth. Commun.* **2025**, *55*, 138-145, <https://doi.org/10.1080/00397911.2024.2431034>.
35. Lelyukh, M.; Adamchuk, S.; Harkov, S.; Chaban, I.; Demchuk, I.; Shelepeten, L.; Chaban, T. Synthetic approaches, chemical modification and biological activity of non-condensed 1,3,4-thiadiazole derivatives. *Pharmacia* **2018**, *65*, 72-88.

36. Anthwal, T.; Paliwal, S.; Nain, S. Diverse biological activities of 1,3,4-thiadiazole scaffold. *Chemistry* **2022**, *4*, 1654-1671, <https://doi.org/10.3390/chemistry4040107>.
37. Mittal, R.K.; Mishra, R.; Sharma, V.; Mishra, I. 1,3,4-Thiadiazole: A versatile scaffold for drug discovery. *Lett. Org. Chem.* **2024**, *21*, 400-413, <https://doi.org/10.2174/0115701786274678231124101033>.
38. Lelyukh, M.; Zhukrovska, M.; Komarenska, Z.; Flud, V.; Harkov, S. Synthetic approaches, modification ability and biological activity of 1,3,4-thiadiazole based [5+5] annelated heterosystems: Mini-review. *Curr. Chem. Lett.* **2023**, *12*, 769-780, <https://doi.org/10.5267/j.ccl.2023.4.004>.
39. Slivka, M.V.; Korol, N.I. Condensed pyridopyrimidines and pyridopyrazines containing a bridgehead nitrogen atom: Synthesis, chemical properties and biological activity. *Curr. Org. Chem.* **2021**, *25*, 1429-1440, <https://doi.org/10.2174/1385272825666210525154330>.
40. Chaban, T.; Matiychuk, V.; Ogurtsov, V.; Chaban, I.; Nektgayev, I. Development of effective anti-inflammatory drug candidates among novel thiazolopyridines. *Ukr. Biochem. J.* **2020**, *92*, 132-139, <https://doi.org/10.15407/ubj92.02.132>.
41. Abdelrehim, El-S.M.; El-Sayed, D.S. Synthesis, screening as potential antitumor of new poly heterocyclic compounds based on pyrimidine-2-thiones. *BMC Chem.* **2022**, *16*, 16, <https://doi.org/10.1186/s13065-022-00810-4>.
42. Kamel, M.G.; Sroor, F.M.; Mahmoud, K.; Shafey, H.I.; Hassaneen, H.M.; Vendiere, L. Utility of 6-aza-2-thiothymine in the synthesis of novel [1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-one derivatives: Synthesis, structure elucidation, molecular docking and in vitro anti-lung cancer activity. *RSC Adv.* **2025**, *15*, 6015-6031, <http://dx.doi.org/10.1039/D4RA08958H>.
43. Chandra; Lohith, T.N.; Gayathri, B.H.; Feizi-Dehnayebi, M.; Karthik, V.; Kumar, S.; Divya, K.; Sridhar, M.A. Mahendra, M.; Ziarani, G.M. *In-silico* studies of 3-*tert*-butyl-7-[2-phenyl ethenyl]-4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4] triazin-4-one as a potential SARS-CoV-2 inhibitor: Insights from an experimental and computational approach. *J. Mol. Struct.* **2025**, *1330*, 141356, <https://doi.org/10.1016/j.molstruc.2025.141356>.
44. Chaban, T.I.; Matiichuk, Y.E.; Shyyka, O.Y.; Chaban, I.G.; Ogurtsov, V.V.; Nektgayev, I.A.; Matiychuk, V.S. Synthesis, molecular docking and biological properties of novel thiazolo[4,5-*b*]pyridine derivatives. *Acta Chim. Slov.* **2020**, *67*, 1035-1043, <http://dx.doi.org/10.17344/acs.2019.5439>.
45. Litvinchuk, M.; Bentya, A.; Shishkina, S.; Vovk, M. Synthesis and some chemical transformations of novel 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids and their benzoannulated analogues. *Curr. Chem. Lett.* **2025**, *14*, 69-78, <https://doi.org/10.5267/j.ccl.2024.9.004>.
46. Al-Wahaibi, L.H.; Akilandeswari, G.; Anusha, R.; Al-Shaalan, N.H.; Alkmali, O.M.; El-Emam, A.A.; Percino, J.M.; Thamotharan, S. Insights into the nature of weak noncovalent interactions in 3-(4-fluorophenyl)-6-(2-fluorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole, a potential bioactive agent: X-ray, QTAIM and molecular docking analysis. *J. Mol. Struct.* **2019**, *1183*, 331-341, <https://doi.org/10.1016/j.molstruc.2019.01.106>.
47. Kamboj, V.K.; Kapoor, A.; Jain, S. Synthesis, antimicrobial, and antioxidant screening of aryl acetic acid incorporated 1,2,4-triazolo-1,3,4-thiadiazole derivatives. *J. Heterocycl. Chem.* **2019**, *56*, 1376-1382, <https://doi.org/10.1002/jhet.3513>.
48. Deng, Q.; Meng, J.; Liu, Y.; Guan, Y.; Xiao, C. IMB-SD62, a triazolothiadiazole derivative with promising action against tuberculosis. *Tuberculosis* **2018**, *112*, 37-44, <https://doi.org/10.1016/j.tube.2018.07.006>.
49. Wu, S.; Shi, J.; Chen, J.; Hu, D.; Zang, L.; Song, B. Synthesis, antibacterial activity, and mechanisms of novel 6-sulfonyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. *J. Agric. Food Chem.* **2021**, *69*, 4645-4654, <https://doi.org/10.1021/acs.jafc.1c01204>.
50. Zhao, B.; Wang, H.; Fan, Z.; Wu, Q.; Guo, X.; Zhang, N.; Yang, D.; Yu, B.; Zhou, S. Mode of action for a new potential fungicide candidate, 3-(4-methyl-1,2,3-thiadiazolyl)-6-trichloromethyl-[1,2,4]-triazolo-[3,4-*b*][1,3,4]-thiadiazole by iTRAQ. *Food Agric. Immunol.* **2019**, *30*, 533-547, <https://doi.org/10.1080/09540105.2019.1603287>.
51. Hamdy, R.; Jones, A.T.; El-Sadek, M.; Hamoda, A.M.; Shakartalla, S.B.; Al Shareef, Z.M.; Soliman, S.S.M.; Westwell, A.D. New bioactive fused triazolothiadiazoles as Bcl-2-targeted anticancer agents. *Int. J. Mol. Sci.* **2021**, *22*, 12272, <https://doi.org/10.3390/ijms222212272>.
52. Ghomi, M.K.; Noori, M.; Montazer, M.N.; Zomorodian, K.; Dastyafteh, N.; Yazdanpanah, S.; Sayahi, M.H.; Javanshir, S.; Nouri, A.; Asadi, M.; Badali, H.; Larijani, B.; Irajie, C.; Irajie, A.; Mahdavi, M.; [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole derivatives as new therapeutic candidates against urease positive

- microorganisms: Design, synthesis, pharmacological evaluations, and *in silico* studies. *Sci. Rep.* **2023**, *13*, 10136, <https://doi.org/10.1038/s41598-023-37203-z>.
53. Elwahy, A.H.M.; Ginidi, A.R.S.; Shaaban, M.R.; Mohamed, A.H.; Gaber, H.M.; Ibrahim, L.I.; Farag, A.M.; Salem, M.E. Novel bis([triazolo[3,4-*b*]thiadiazoles and bis([triazolo[3,4-*b*][thiadiazines) with antioxidant activity. *Arkivoc* **2024**, *vii*, 202412181, <https://doi.org/10.24820/ark.5550190.p012.181>.
  54. Lelyukh, M.; Havrylyuk, D.; Lesyk, R. Synthesis and Anticancer Activity of Isatin, Oxadiazole and 4-Thiazolidinone Based Conjugates. *Chem. Chem. Technol.* **2015**, *9*, 29-36, <http://dx.doi.org/10.23939/chcht09.01.029>.
  55. Lelyukh, M.; Demchuk, I.; Harkov, S.; Chaban, T.; Drapak, I.; Chaban, I.; Shelepeten, L.; Matiychuk, V. A review on synthetic routes for obtaining of 2,5-disubstituted 1,3,4-oxadiazoles *via* cyclodehydration and oxidative cyclization reactions. *Biointerface Res. Appl. Chem.* **2020**, *10*, 5960-5971, <https://doi.org/10.33263/BRIAC104.960971>.
  56. Chaban, T.; Matiychuk, V.; Mahlovanyy, A.; Chaban, I.; Ogurtsov, V.; Lelyukh, M. Antitumor properties of thiazolo[4,5-*b*]pyridin-2-one derivatives. *Biointerface Res. Appl. Chem.* **2020**, *10*, 5944-5950, <https://doi.org/10.33263/BRIAC104.944950>.
  57. Chulovska, Z.; Drapak, I.; Chaban, T.; Ogurtsov, V.; Chaban, I.; Matiychuk, V. Synthesis, anticancer and antioxidant properties of some 4-thioxo-thiazolidin-2-ones. *Eur. Chem. Bull.* **2021**, *10*, 147-154.
  58. Chaban, T.; Matiichuk, Y.; Chulovska, Z.; Tymoshuk, O.; Chaban, I.; Matiychuk, V. Synthesis and biological evaluation of new 4-oxo-thiazolidin-2-ylidene derivatives as antimicrobial agents. *Arch. Pharm.* **2021**, *354*, 2100037, <https://doi.org/10.1002/ardp.202100037>.
  59. Lelyukh, M.; Pylypchuk, I.; Kalytovska, M.; Harkov, S.; Kostyshyn, L.; Drapak, I. Synthesis and anti-cancer activity evaluation of novel 1,3,4-oxadiazole substituted 5-arylidene/isatinylidene-2-iminothiazolidin-4-ones. *Biointerface Res. Appl. Chem.* **2022**, *12*, 1161-1173, <https://doi.org/10.33263/BRIAC121.11611173>.
  60. Chaban, T.I.; Klenina, O.V.; Chaban, I.H.; Lelyukh, M.I. Recent advances in the synthesis of thiazolo[4,5-*b*]pyridines. Part 1: Focus on pyridine annulation to thiazole ring (microreview). *Chem. Heterocycl. Compd.* **2024**, *60*, 35-37, <https://doi.org/10.1007/s10593-024-03289-0>.
  61. Chaban, T.I.; Lelyukh, M.I.; Chaban, I.H.; Kasyanchuk, O.Y. Approaches to the synthesis of thiazolo[3,2-*a*]pyridines (microreview). *Chem. Heterocycl. Compd.* **2024**, *60*, 124-126, <http://dx.doi.org/10.1007/s10593-024-03305-3>.
  62. Lelyukh, M.; Paliy, A.; Zhukrovska, M.; Kalytovska, M.; Chaban, I.; Shelepeten, L.; Chaban, T. 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. *Curr. Chem. Lett.* **2024**, *13*, 737-752. <https://doi.org/10.5267/j.ccl.2024.3.007>.
  63. Chaban, T.I.; Klenina, O.V.; Chaban, I.H.; Lelyukh, M.I. Recent advances in the synthesis of thiazolo[4,5-*b*]pyridines. Part 2: Focus on thiazole annulation to pyridine ring (microreview). *Chem. Heterocycl. Compd.* **2024**, *60*, 130-132. <https://doi.org/10.1007/s10593-024-03307-1>
  64. Lelyukh, M.; Savchenko, A.; Kalytovska, M.; Zhukrovska, M.; Chaban, I.; Vergun, A.; Shelepeten, L.; Chaban, T. Pharmacological profile of condensed heterocyclic compounds based on functionally substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles: A review. *Curr. Chem. Lett.* **2025**, *14*, 567-578, <https://doi.org/10.5267/j.ccl.2025.3.001>.
  65. Amir, M.; Akhter, M.W.; Haq, S.E. Synthesis of some new condensed heterocyclic 6-substituted-1, 2, 4-triazolo [3, 4-*b*]-1, 3, 4-thiadiazole derivatives of 2-naphthoxyacetic acid as potent anti-inflammatory agents with reduced ulcerogenicity. *Indian J. Chem. Sect. B-Org. Chem. Incl. Med. Chem.* **2017**, *56B*, 1177-1184.
  66. Isloor, A.M.; Kalluraya, B.; Pai, S.K. Synthesis, characterization and biological activities of some new benzo[*b*]thiophene derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 825-830, <https://doi.org/10.1016/j.ejmech.2009.11.015>.
  67. Puthiyapurayil, P.; Poojary, B.; Kumar, S.; Hunnur, R. Synthesis and biological activities of a novel series on 3,6-disubstituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles containing gem-dimethylbenzyl moiety. *J. Heterocycl. Chem.* **2011**, *48*, 998-1005, <https://doi.org/10.1002/jhet.674>.
  68. Khan, M.-ul-H.; Akhtar, T.; Yasin, K.A.; Al-Masoudi, N.A.; Jones, P.G.; Hameed, S. Synthesis, crystal structure and antiproliferative activity of 6-adamantyl-3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles. *Z. Naturforsch.* **2010**, *65*, 178-184, <https://doi.org/10.1515/znb-2010-0214>.
  69. Khan, M.-ul-H.; Hameed, S.; Farman, M.; Al-Masoudi, N.A.; Stoeckli-Evans, H. Synthesis, anti-HIV activity and molecular modeling study of 3-aryl-6-adamantylmethyl-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. *Z. Naturforsch. B* **2015**, *70*, 609-616, <https://doi.org/10.1515/znb-2015-0032>.

70. Gilani, S.J.; Khan, S.A.; Alam, O.; Siddiqui, N. Synthesis and in vitro antimicrobial evaluation of condensed heterocyclic 6-substituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid. *Acta Pol. Pharm.* **2011**, *68*, 205-211.
71. Kamel, M.M.; Megally Abdo, N.Y. Synthesis of novel 1,2,4-triazoles, triazolothiadiazines and triazolothiadiazoles as potential anticancer agents. *Eur. J. Med. Chem.* **2014**, *86*, 75-80, <https://doi.org/10.1016/j.ejmech.2014.08.047>.
72. Khan, I.; Ibrar, A.; Zaib, S.; Ahmad, S.; Furtmann, N.; Hameed, S.; Simpson, J.; Bajorath, J.; Iqbal, J. Active compounds from a diverse library of triazolothiadiazole and triazolothiadiazine scaffolds: Synthesis, crystal structure determination, cytotoxicity, cholinesterase inhibitory activity, and binding mode analysis. *Bioorg. Med. Chem.* **2014**, *22*, 6163-6173, <https://doi.org/10.1016/j.bmc.2014.08.026>.
73. Fan, Z.; Yang, Z.; Zhang, H.; Mi, N.; Wang, H.; Cai, F.; Zuo, X.; Zheng, Q.; Song, H. Synthesis, crystal structure, and biological activity of 4-methyl-1,2,3-thiadiazole-containing 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles. *J. Agric. Food Chem.* **2010**, *58*, 2630-2636, <https://doi.org/10.1021/jf9029628>.
74. Palekar, V.S.; Damle, A.J.; Shukla, S.R. Synthesis and antibacterial activity of some novel bis-1,2,4-triazolo[3,4-b]thiadiazole and bis-4-thiazolidinone derivatives from terephthalic dihydrazide. *Eur. J. Med. Chem.* **2009**, *44*, 5112-5116, <https://doi.org/10.1016/j.ejmech.2009.07.023>.
75. Ibrahim, D.A. Synthesis and biological evaluation of 3,6-disubstituted [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives as novel class of potential anti-tumor agents. *Eur. J. Med. Chem.* **2009**, *44*, 2776-2781, <https://doi.org/10.1016/j.ejmech.2009.01.003>.
76. Husain, A.; Rashid, M.; Mishra, R.; Parveen, S.; Shin, D.-S.; Kumar, D. Benzimidazole bearing oxadiazole and triazolo-thiadiazoles nucleus: Design and synthesis as anticancer agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5438-5444, <https://doi.org/10.1016/j.bmcl.2012.07.038>.
77. Husain, A.; Rashid, M.; Shaharyar, M.; Siddiqui, A.A.; Mishra, R. Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines: New anticancer agents. *Eur. J. Med. Chem.* **2013**, *62*, 785-798, <https://doi.org/10.1016/j.ejmech.2012.07.011>.
78. Mathew, V.; Giles, D.; Keshavayya, J.; Vaidya, V.P. Studies on synthesis and pharmacological activities of 1,2,4-triazolo[3,4-b]1,3,4-thiadiazoles and their dihydro analogues. *Arch. Pharm.* **2009**, *342*, 210-222, <https://doi.org/10.1002/ardp.200800073>.
79. Patil, S.P.; Kanawade, S.B.; Bhavsar, D.C.; Nikam, P.S.; Gangurde, S.A.; Toche, R.B. Syntheses of new unsymmetrical 2,5-disubstituted-1,3,4-oxadiazoles and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles bearing thieno[2,3-c]pyrazolo moiety. *J. Heterocycl. Chem.* **2014**, *51*, 368-373, <https://doi.org/10.1002/jhet.1584>.
80. Nagaraju, K.; Kotaiah, Y.; Sampath, C.; Harikrishna, N.; Rao, C.V. A facile synthesis of some novel fused [1,2,4]triazolo[3,4-b][1,3,4]thiadiazol derivatives. *J. Sulfur Chem.* **2013**, *34*, 264-275, <http://dx.doi.org/10.1080/17415993.2012.734306>.
81. Kotaiah, Y.; Nagaraju, K.; Harikrishna, N.; Rao, C.V.; Yamini, L.; Vijjulatha, M. Synthesis, docking and evaluation of antioxidant and antimicrobial activities of novel 1,2,4-triazolo[3,4-b][1,3,4]thiadiazol-6-yl) selenopheno[2,3-d]pyrimidines. *Eur. J. Med. Chem.* **2014**, *75*, 195-202, <https://doi.org/10.1016/j.ejmech.2014.01.006>.
82. Vaarla, K.; Vedula, R.R. Synthesis of 6-(5-methylisoxazol-3-yl)-3-alkyl sulfanyl-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazoles. *J. Heterocycl. Chem.* **2015**, *52*, 1614-1617, <https://doi.org/10.1002/jhet.2168>.
83. Lv, X.; Yang, L.; Fan, Z.; Bao, X. Synthesis and antimicrobial activities of novel quinazolin-4(3H)-one derivatives containing a 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole moiety. *J. Saudi Chem. Soc.* **2018**, *22*, 101-109, <https://doi.org/10.1016/j.jscs.2017.07.008>.
84. Gorgu, O.; Yildirim, E.; Ozkan, Y.; Cakir, B.; Erol, K.; Onkol, T. Microwave-assisted synthesis and pharmacological screening of some triazolothiadiazole derivatives. *Braz. J. Pharm. Sci.* **2020**, *56*, e18111, <http://dx.doi.org/10.1590/s2175-97902019000318111>.
85. Shingare, R.M.; Patil, Y.S.; Sangshetty, J.N.; Damale, M.G.; Rajani, D.P.; Madje, B.R. Synthesis, antimicrobial evaluation and docking study of some pyrazole bearing [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives. *ChemistrySelect* **2018**, *3*, 3899-3903, <https://doi.org/10.1002/slct.201800373>.
86. Reddy, C.S.; Rao, L.S.; Nagaraj, A. Synthesis and evaluation of novel bis[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles as potent antimicrobial agents. *Acta. Chim. Slov.* **2010**, *57*, 726-732.
87. Li, Y.J.; Liu, L.J.; Jin, K.; Xu, Y.T.; Sun, S.Q. Synthesis and bioactivity of a novel series of 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles. *Chin. Chem. Lett.* **2010**, *21*, 293-296, <https://doi.org/10.1016/j.ccl.2009.11.008>.

88. Settypalli, T.; Chunduri, V.R.; Kerru, N.; Nallapaneni, H.K.; Chintla, V.R.; Daggupati, T.; Yeguvapalli, S.; Wudayagiri, R. Design, synthesis, neuroprotective and antibacterial activities of 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole linked thieno[2,3-*d*]pyrimidine derivatives and *in silico* docking studies. *ChemistrySelect* **2019**, *4*, 1627-1634, <https://doi.org/10.1002/slct.201803917>.
89. Raut, S.; Hadi, A.; Pathan, M.A. The efficient synthesis of 3-[6-(substituted)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole. *J. Heterocycl. Chem.* **2020**, *57*, 1291-1305, <https://doi.org/10.1002/jhet.3866>.
90. Reddy, C.S.; Devi, M.V.; Sunitha, M.; Kalyani, B.; Nagaraj, A. Synthesis and antibacterial activity of di-heteryl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles. *Indian J. Chem. Sect. B-Org. Chem. Incl. Med. Chem.* **2016**, *55*, 590-597.
91. Bujji, S.; Edigi, P.K.; Subhashini, N.J.P. Synthesis and evaluation of novel 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole tethered chalcone hybrids as potential anticancer agents. *J. Heterocycl. Chem.* **2020**, *57*, 3318-3325, <https://doi.org/10.1002/jhet.4047>.
92. Verma, V.A.; Saundane, A.R.; Shamrao, R.; Meti, R.S.; Shinde, V.M. Novel indolo [3,2-*c*]isoquinoline-5-one-6-yl [1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazole analogues: Design, synthesis, anticancer activity, docking with SARS-CoV-2 Omicron protease and MESP/TD-DFT approaches. *J. Mol. Struct.* **2022**, *1264*, 133153, <https://doi.org/10.1016/j.molstruc.2022.133153>.
93. Marupati, S.; Kasula, S.; Satheesh, B.; Bireddy, S.R.; Eppakayala, L. Development of an efficient protocol for the synthesis and molecular docking studies of pyrimidine containing 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-yl)-thio)-1-phenylethanone derivatives as promising anticancer agents. *Vietnam J. Chem.* **2022**, *60*, 169-182, <https://doi.org/10.1002/vjch.202100102>.
94. Ibrahim, M.A.; Al-Harbi, S.A.; Allehyani, E.S.; Alqurashi, E.A.; Alshareef, F.M. First synthesis of the novel triazolo[3,4-*b*][1,3,4]thiadiazoles and triazolo[3,4-*b*][1,3,4]thiadiazines linked chromeno[2,3-*b*]pyridine. *Polycycl. Aromat. Compd.* **2024**, *44*, 361-374, <https://doi.org/10.1080/10406638.2023.2173621>.

## Publisher's Note & Disclaimer

The statements, opinions, and data presented in this publication are solely those of the individual author(s) and contributor(s) and do not necessarily reflect the views of the publisher and/or the editor(s). The publisher and/or the editor(s) disclaim any responsibility for the accuracy, completeness, or reliability of the content. Neither the publisher nor the editor(s) assume any legal liability for any errors, omissions, or consequences arising from the use of the information presented in this publication. Furthermore, the publisher and/or the editor(s) disclaim any liability for any injury, damage, or loss to persons or property that may result from the use of any ideas, methods, instructions, or products mentioned in the content. Readers are encouraged to independently verify any information before relying on it, and the publisher assumes no responsibility for any consequences arising from the use of materials contained in this publication.