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Two decades of the synthesis of mono- and bis-aminomercapto[1,2,4]triazoles

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4-Amino-5-mercapto[1,2,4]triazole and its 3-substituted derivatives have proven to be of biological interest and provide access to a new class of biologically active heterocyclic compounds for biomedical applications. This study will be helpful for scientific researchers interested in the chemistry of bifunctional versatile compounds as it provides a collection of all the methods for the preparation of 3-substituted-4-amino-5-mercapto[1,2,4]triazoles with aliphatic, aromatic, and heterocyclic moieties during the period from 2000 to mid-2020.

1. Introduction

[1,2,4]Triazoles and their fused heterocyclic derivatives have occupied a unique position as novel biologically active agents with remarkably diverse pharmacological properties such as antimicrobial, antifungal, anticancer, anticonvulsant, antiviral, anti-inflammatory, anti-HIV, and anti-mycobacterial activities.^{1–8} A large number of ring systems containing [1,2,4]triazoles have been incorporated into a wide variety of therapeutically interesting drug candidates such as fluconazole, ravuconazole, itraconazole, voriconazole, posaconazole, vorozole, letrozole, ribavirin, triazolam, alprazolam, etizolam, furacylin, hexaconazole, triadimefon, myclobutanil, rizatriptan, propiconazole, and flutrimazole (Chart 1).⁹ Moreover, the synthesis of bis-heterocyclic compounds containing triazole rings has attracted attention due to the diverse applications of these compounds in numerous pharmacological and biological fields.^{10–13}

Bis-[4-amino-5-mercapto[1,2,4]triazoles] (1) and 3-substituted-4-amino-5-mercapto[1,2,4] triazoles (2–4) (Chart 2) contain both amino and mercapto groups as ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings. The introduction of these groups in different nuclei enhances their biological activities. Accordingly, the objective of the present review is to highlight the synthetic methods used to obtain 3-substituted-4-amino-5-mercapto[1,2,4]triazoles and bis-[4-amino-5-mercapto[1,2,4]triazoles] from 2000 until mid-2020.

2. Synthetic routes using thiocarbohydrazide as the precursor

2.1. Reactions with carboxylic acids

3-Substituted-4-amino-5-mercapto[1,2,4]triazoles 2–4 were prepared from the treatment of thiocarbohydrazide (5) with carboxylic acids (Scheme 1) (Table 1).

A series of dicarboxylic acids such as tartaric, malic,^{41–43} succinic,⁴⁴ glutaric,⁴⁵ and others⁴⁶ were treated with thiocarbohydrazide (5) to afford the respective series of bis-(4-amino-5-mercapto[1,2,4]triazoles) 8, 9 (Scheme 2).

Similarly, a condensation reaction between 5-(3-formyl-4-methoxybenzyl)-2-methoxybenzoic acid (10) and thiocarbohydrazide (5) at the melt temperature afforded bis[4-methoxy-3-[4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl]phenyl]methane (11) (Scheme 3).⁴⁷

2.2. Reactions with esters

In addition, Demirbas *et al.*⁴⁸ reported the treatment of ethyl(3-alkyl-4-amino-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl) acetates (12) with thiocarbohydrazide (5), which furnished 5-alkyl-4-amino-2-[(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (13) (Scheme 4).

Moreover, refluxing thiocarbohydrazide (5) with diethyl terephthalate 14 using magnetic iron oxide (Fe₃O₄) nanoparticles as an eco-friendly catalyst yielded the respective 3,3'-(1,4-phenylene)bis(4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione) (15) (Scheme 5).⁴⁹

2.3. Reactions with lactones

4-Amino-3-(3-hydroxypropyl)-5-mercapto[1,2,4]triazole (17) was prepared *via* the treatment of thiocarbohydrazide (5) with lactone 16, as reported by Zhang *et al.*⁵⁰ [Scheme 6].

The synthetic routes for the preparation of 4-amino-3-(D-galactopentitol-1-yl)-5-mercapto[1,2,4]triazole (21),⁵¹ 4-

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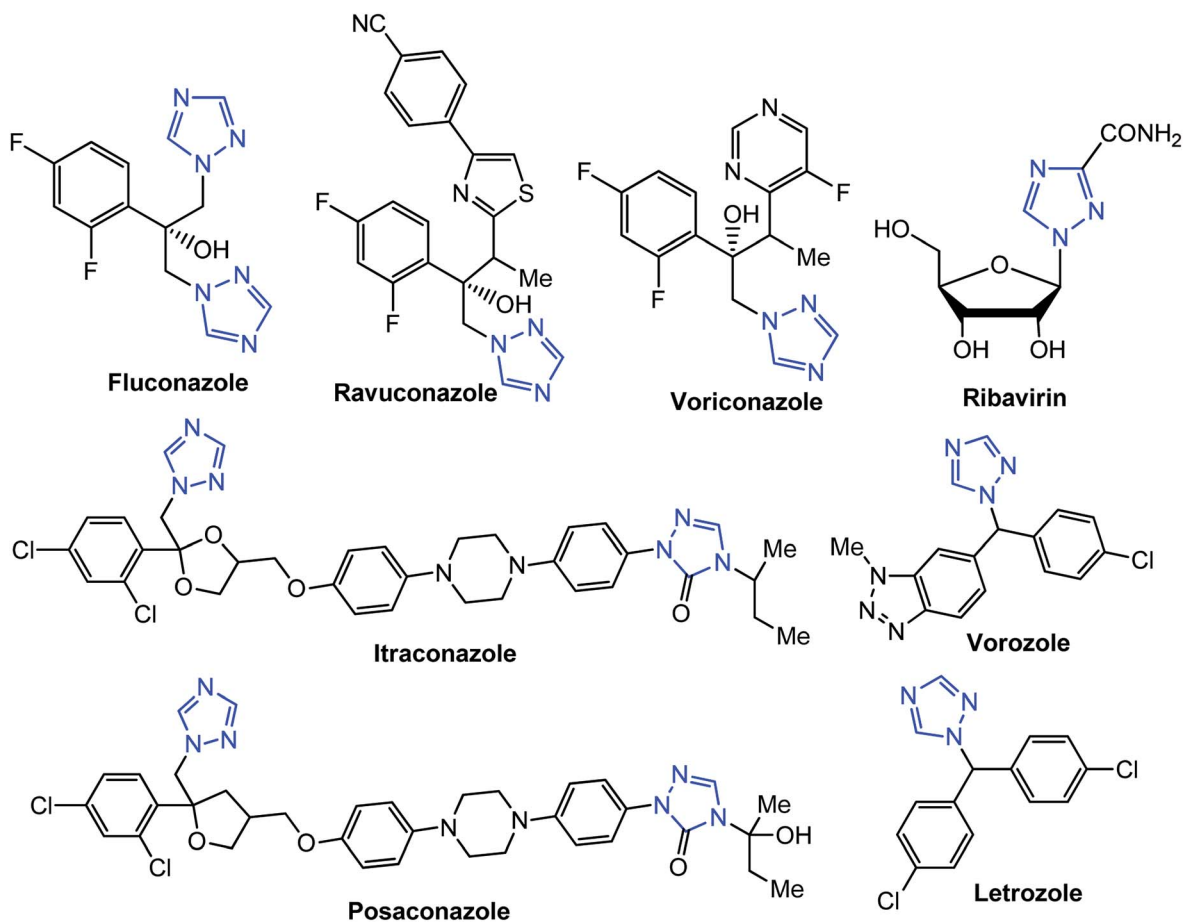


Chart 1 Examples of [1,2,4]triazole bearing drugs.

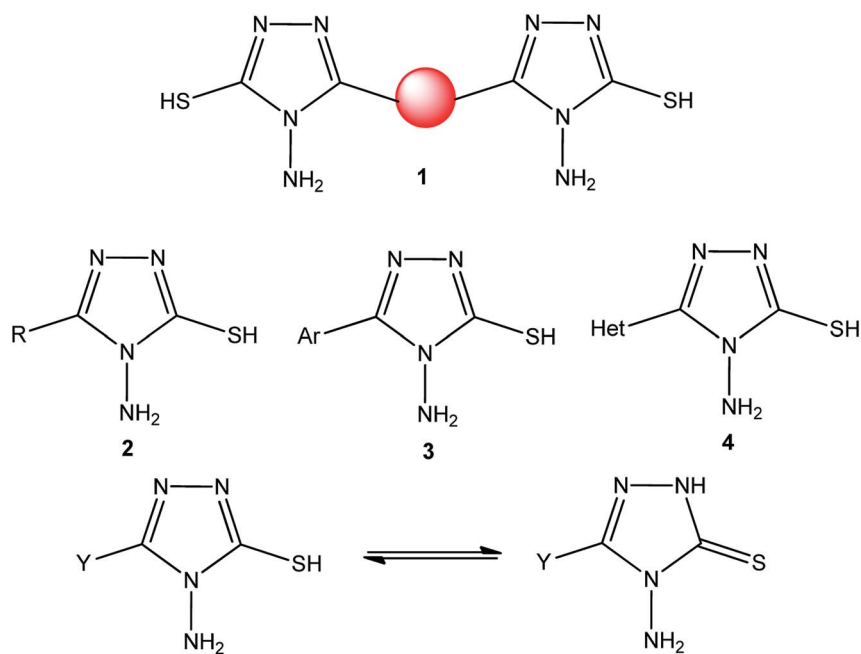
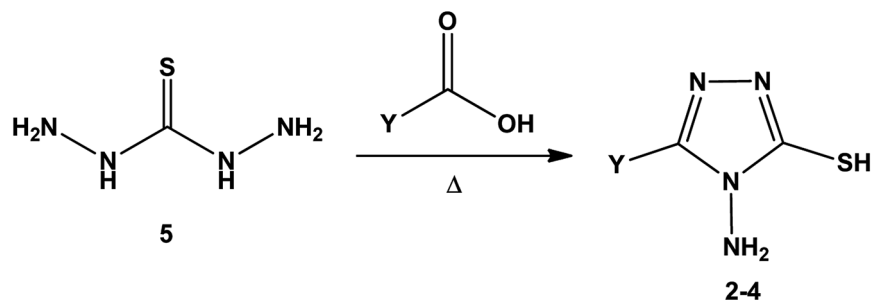


Chart 2 Structures of bis-[4-amino-5-mercapto[1,2,4]triazoles] (1) and 3-substituted-4-amino-5-mercapto[1,2,4]triazoles (2–4).



Scheme 1 Synthesis of triazoles 2–4.

Table 1 Derivatives of 3-substituted-4-amino-5-mercapto[1,2,4]triazoles

Y	Ref.
H, -CH ₃ , -C ₂ H ₅	14
-CH ₃	15 and 16
-CH ₃ , -CF ₃	17
H, -C ₂ H ₅ , ,	18
	19
-CH ₃ , -CF ₃ , -C ₂ H ₅ , , , ,	20
Substituted phenyl	21–23
Ar-CH ₂ -CH ₂ - & cyclohexyl-CH ₂ -CH ₂ -	24
Ar-O-CH ₂ - & Ar-NH-CH ₂ - & Ar-S-CH ₂ - & Ar-SO ₂ NH-CH ₂ - & Ar-CONH-CH ₂ - & Ar-CH(CH ₃)- & triazole-CH ₂ -	25
	26
	26
	26 and 27

Table 1 (Contd.)

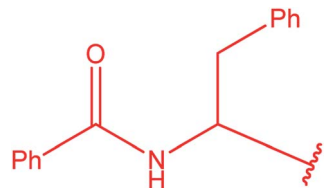
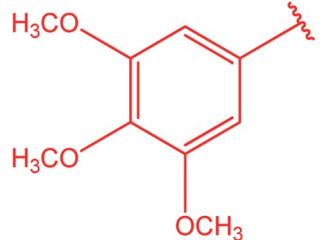
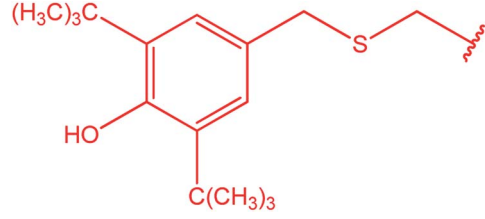
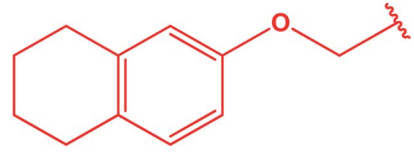
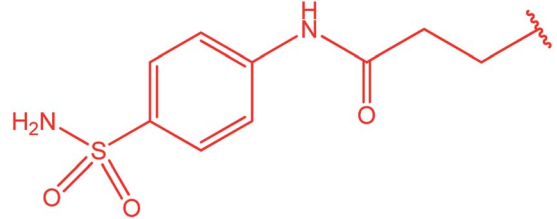
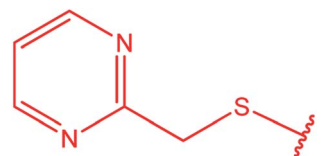
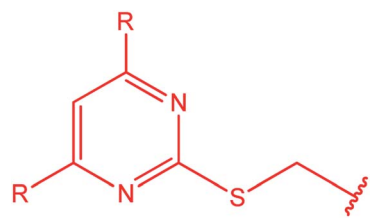
Y	Ref.
 <p>Chemical structure of N-benzyl-N-phenylacetamide derivative. The structure shows a benzamide core with a benzyl group attached to the nitrogen atom and a wavy line representing a substituent on the alpha carbon.</p>	28
 <p>Chemical structure of 3,4,5-trimethoxybenzyl derivative. The structure shows a benzene ring with three methoxy groups (H₃CO) at the 3, 4, and 5 positions and a wavy line representing a substituent on the benzyl group.</p>	29
 <p>Chemical structure of 2-hydroxy-3,6-dimethylbenzyl derivative. The structure shows a benzene ring with a hydroxyl group (HO) at the 2 position, two tert-butyl groups (C(CH₃)₃) at the 3 and 6 positions, and a wavy line representing a substituent on the benzyl group.</p>	30
 <p>Chemical structure of 1,2,3,4-tetrahydronaphthalen-1-ylmethyl derivative. The structure shows a tetrahydronaphthalene ring system with a wavy line representing a substituent on the methyl group attached to the 1-position.</p>	31
 <p>Chemical structure of N-(4-sulfamoylphenyl)butylamine derivative. The structure shows a benzene ring with a sulfamoyl group (H₂N-SO₂-) at the 4 position and a wavy line representing a substituent on the butyl group attached to the nitrogen atom.</p>	32
 <p>Chemical structure of 2-(methylsulfanyl)pyrimidine derivative. The structure shows a pyrimidine ring with a wavy line representing a substituent on the methylsulfanyl group (-S-CH₃) attached to the 2-position.</p>	33
 <p>Chemical structure of 2-(methylsulfanyl)pyrimidine derivative with R groups. The structure shows a pyrimidine ring with two R groups at the 4 and 6 positions and a wavy line representing a substituent on the methylsulfanyl group (-S-CH₃) attached to the 2-position.</p>	34

Table 1 (Contd.)

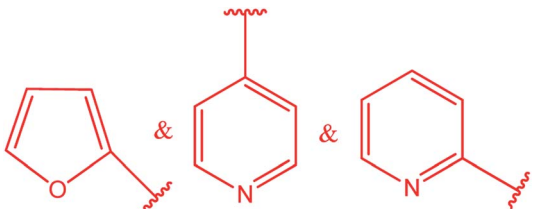
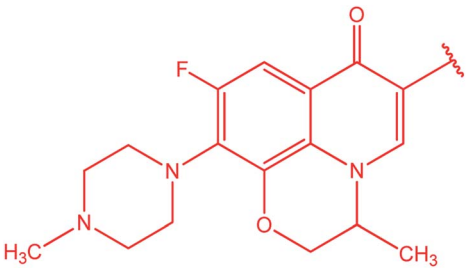
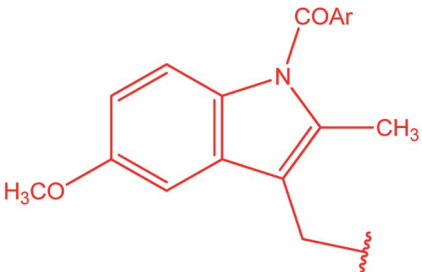
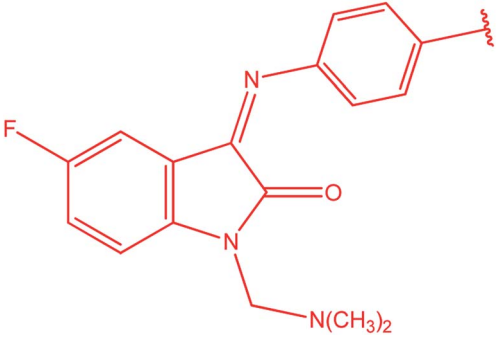
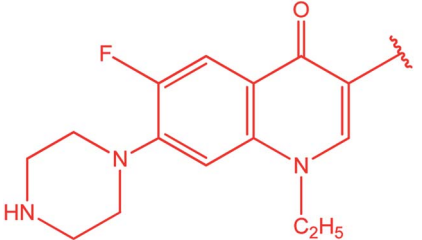
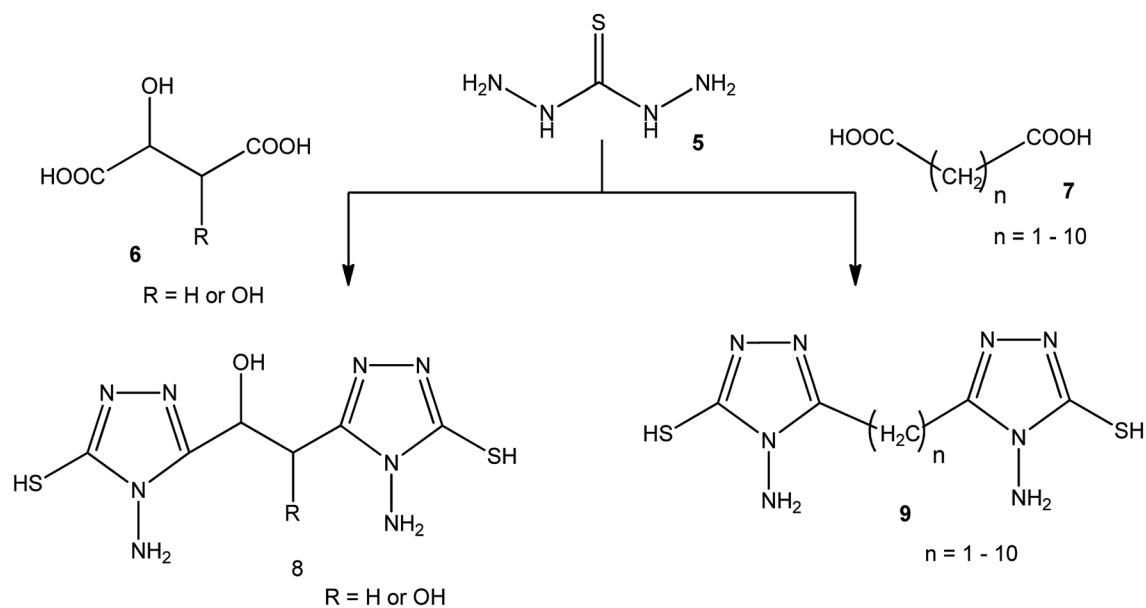
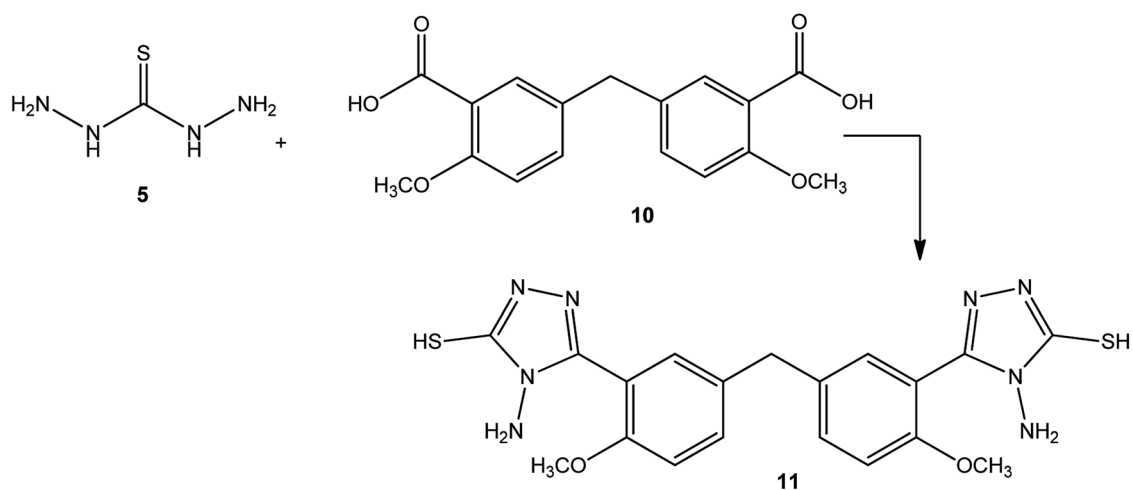
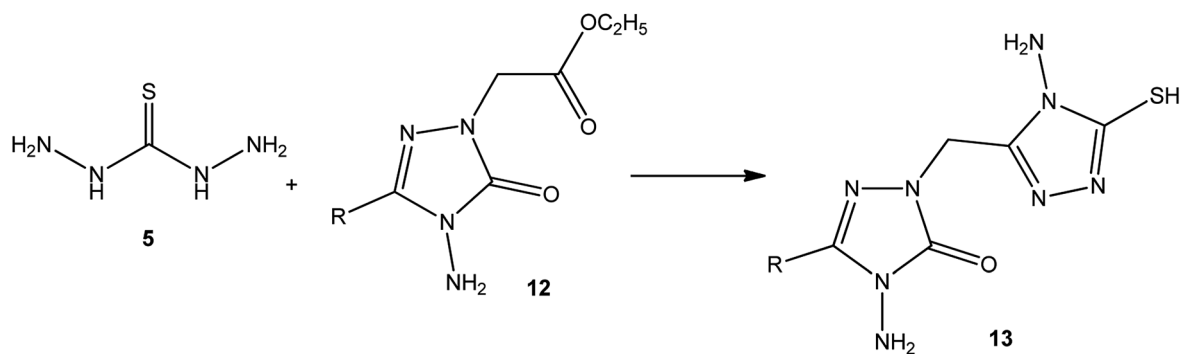
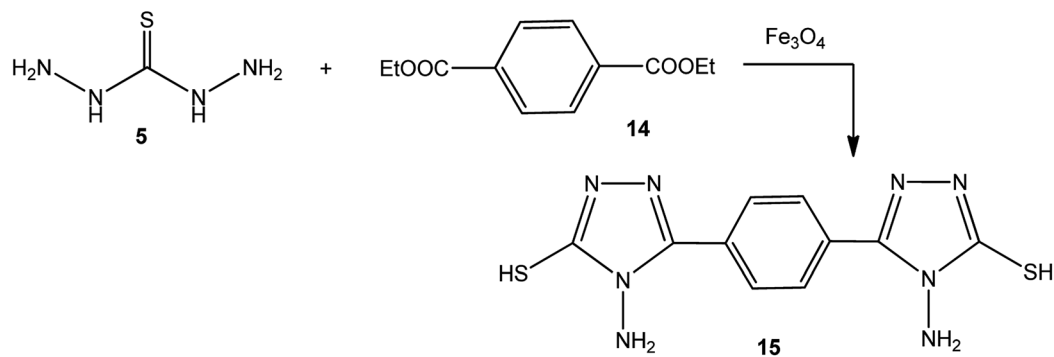
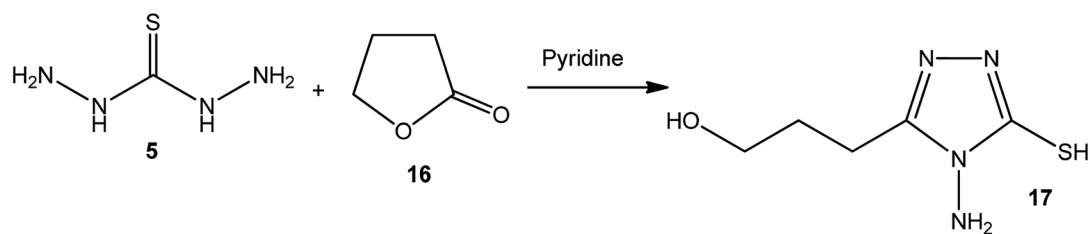
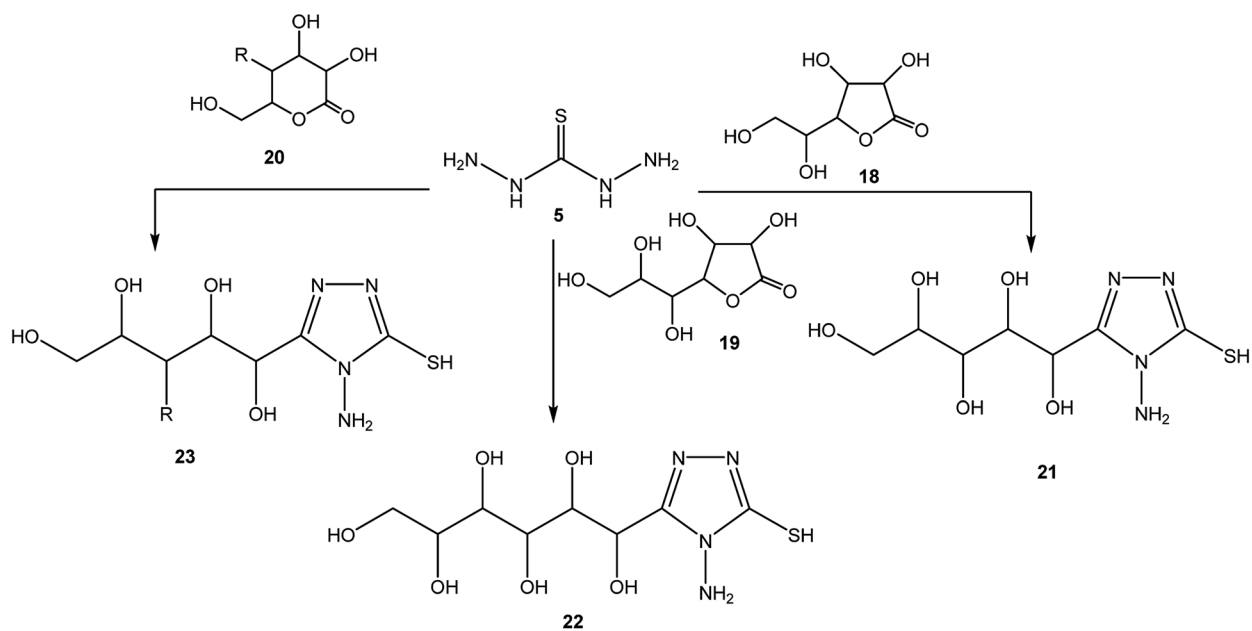
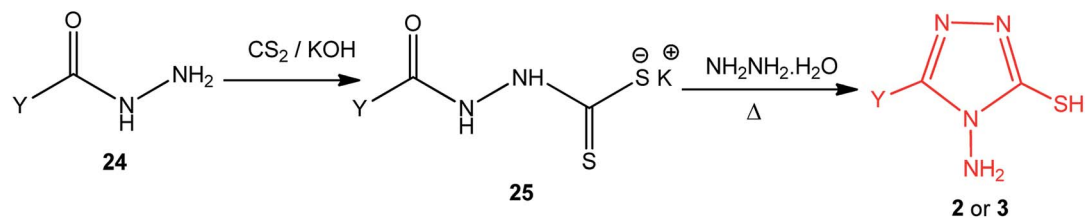
Y	Ref.
	35
	36
	37
	38
	39

Table 1 (Contd.)

Y	Ref.
	40
	9

Scheme 2 Synthesis of bis-triazoles **8** and **9**.Scheme 3 Synthesis of bis-triazole **11**.

Scheme 4 Synthesis of triazoles **13**.Scheme 5 Synthesis of bis-triazole **15**.Scheme 6 Synthesis of triazole **17**.Scheme 7 Synthesis of triazoles **21**–**23**.



Scheme 8 Synthesis of triazoles 2 and 3.

Table 2 Derivatives of 3-substituted-4-amino-5-mercapto[1,2,4]triazoles

Y	Ref.
-CH ₃ , -C ₂ H ₅ , -C ₃ H ₇	54
CH ₃ -(CH ₂) ₁₃ -CH ₂ -	55
CH ₃ -(CH ₂) ₁₅ -CH(SO ₃ Na)-	56
C ₆ H ₅ -	57–60
3-ClC ₆ H ₄ -	8
4-CH ₃ OC ₆ H ₄ -	61
2-HOC ₆ H ₄ -	62
2-CH ₃ C ₆ H ₄ - & 2-CH ₃ -4-ClC ₆ H ₃ -	63
C ₆ H ₅ - & 2-HOC ₆ H ₄ -	64
2-C ₂ H ₅ OC ₆ H ₄ -	65
3-Br-4-CH ₃ OC ₆ H ₃ -	66
2-HOC ₆ H ₄ - & 4-HOC ₆ H ₄ - & 4-C ₂ H ₅ OC ₆ H ₄ - & 2-HO-5-ClC ₆ H ₃ - & 4-HOC ₆ H ₄ -CH ₂ - & 4-C ₂ H ₅ OC ₆ H ₄ -CH ₂ -	67
2-FC ₆ H ₄ -CH ₂ - & 2-BrC ₆ H ₄ -CH ₂ - & 4-HOC ₆ H ₄ -CH ₂ - & 2-CH ₃ OC ₆ H ₄ -CH ₂ - & 4-NO ₂ C ₆ H ₄ -CH ₂ -	68
C ₆ H ₅ - & 2-ClC ₆ H ₄ - & 2-NO ₂ C ₆ H ₄ - & 2-HOC ₆ H ₄ - & 2-furyl	69
C ₆ H ₅ - & 4-ClC ₆ H ₄ - & 4-BrC ₆ H ₄ - & 4-CH ₃ OC ₆ H ₄ - & 2-naphthyl-CH ₂ -	70
2-HOC ₆ H ₄ - & 4-HOC ₆ H ₄ - & 2-NH ₂ C ₆ H ₄ - & 4-NH ₂ C ₆ H ₄ - & 3,4,5-(HO) ₃ C ₆ H ₂ -	71
C ₆ H ₅ -CH ₂ -CH ₂ -	72
2-(CH ₃) ₂ NC ₆ H ₄ - & 4-CH ₃ NHC ₆ H ₄ - & 1-naphthyl-CH ₂ -	73
	74
	75
	76
	77
	77

Table 2 (Contd.)

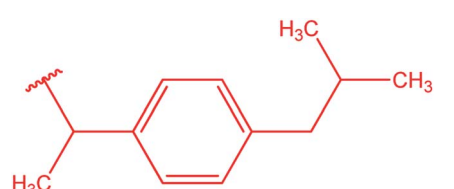

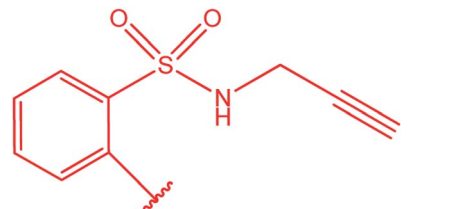
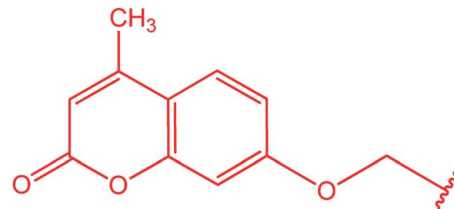
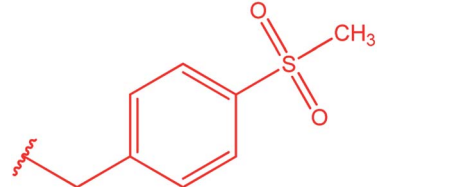
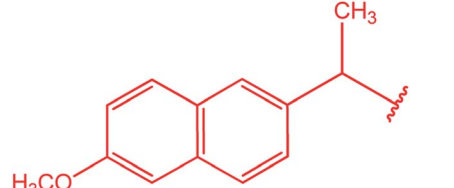
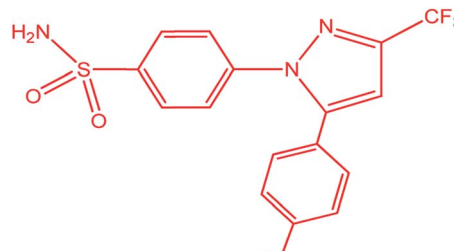
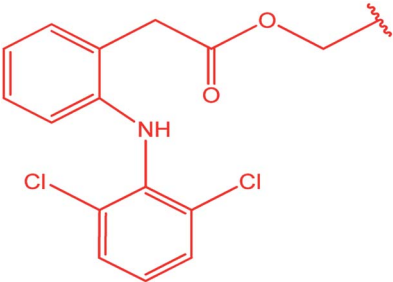
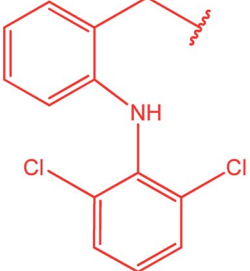
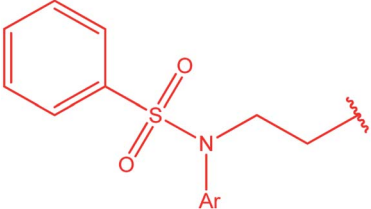
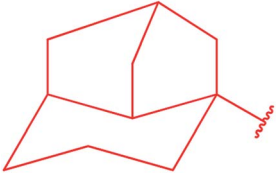
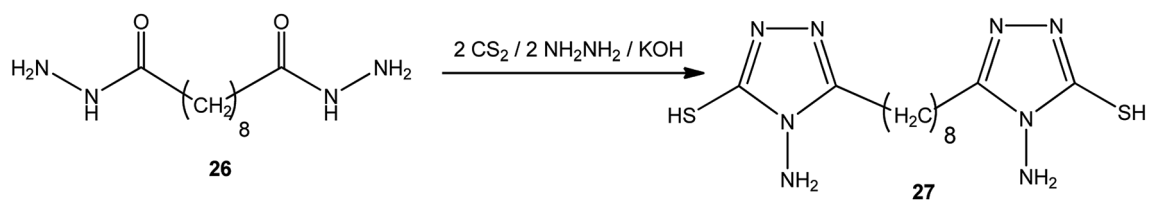
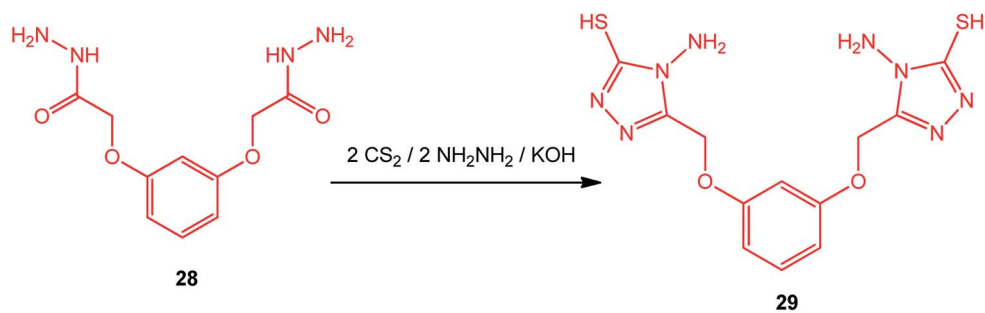
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	79
	80
	81
	82
	83
	84

Table 2 (Contd.)

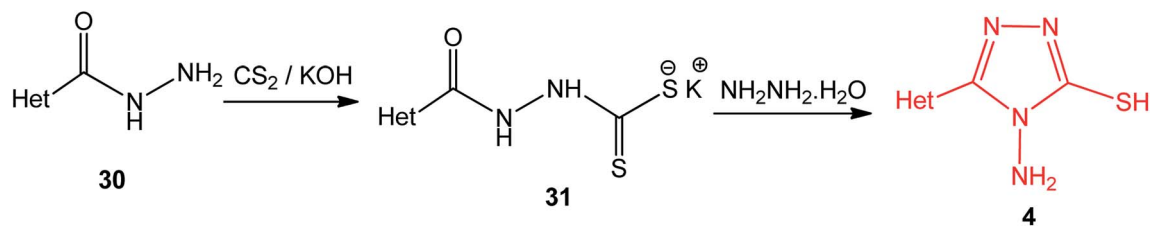
Y	Ref.
	85
	85 and 86
	87
	88



Scheme 9 Synthesis of bis-triazole 27.



Scheme 10 Synthesis of bis-triazole 29.



Scheme 11 Synthesis of triazoles 4.

Table 3 Derivatives of 3-substituted-4-amino-5-mercapto[1,2,4] triazoles

Het	Ref.
	91
	92
	93
	94
	95
	96
	97

Table 3 (Contd.)

Het	Ref.
	98
	99
	20
	100–106
	107
	108

Table 3 (Contd.)

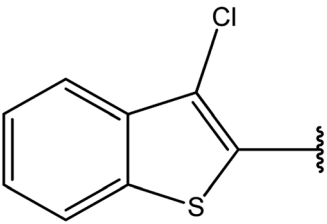
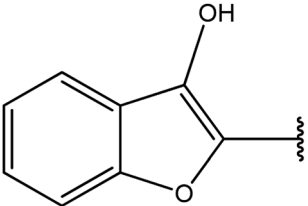
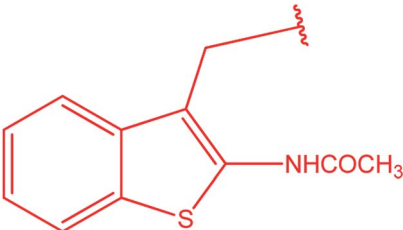
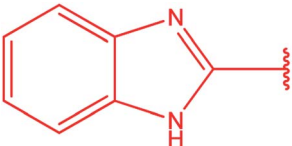
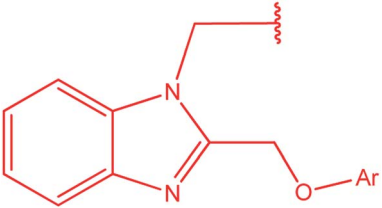
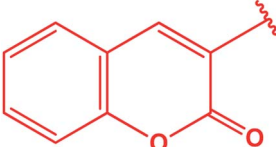
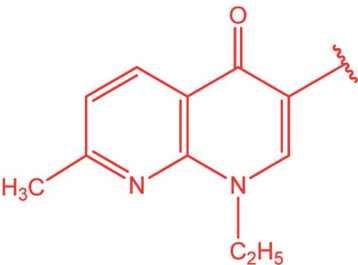
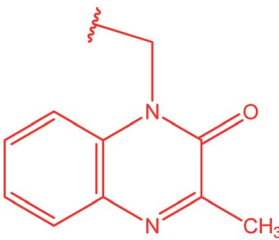
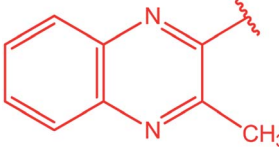
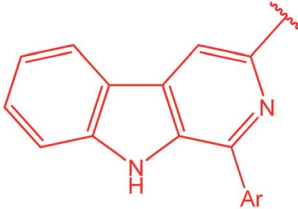
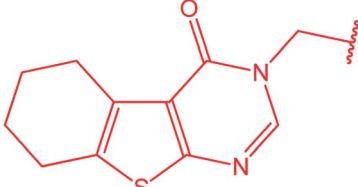
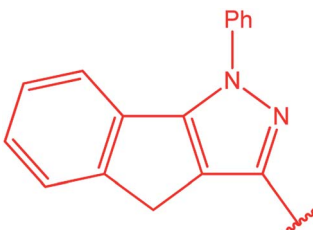
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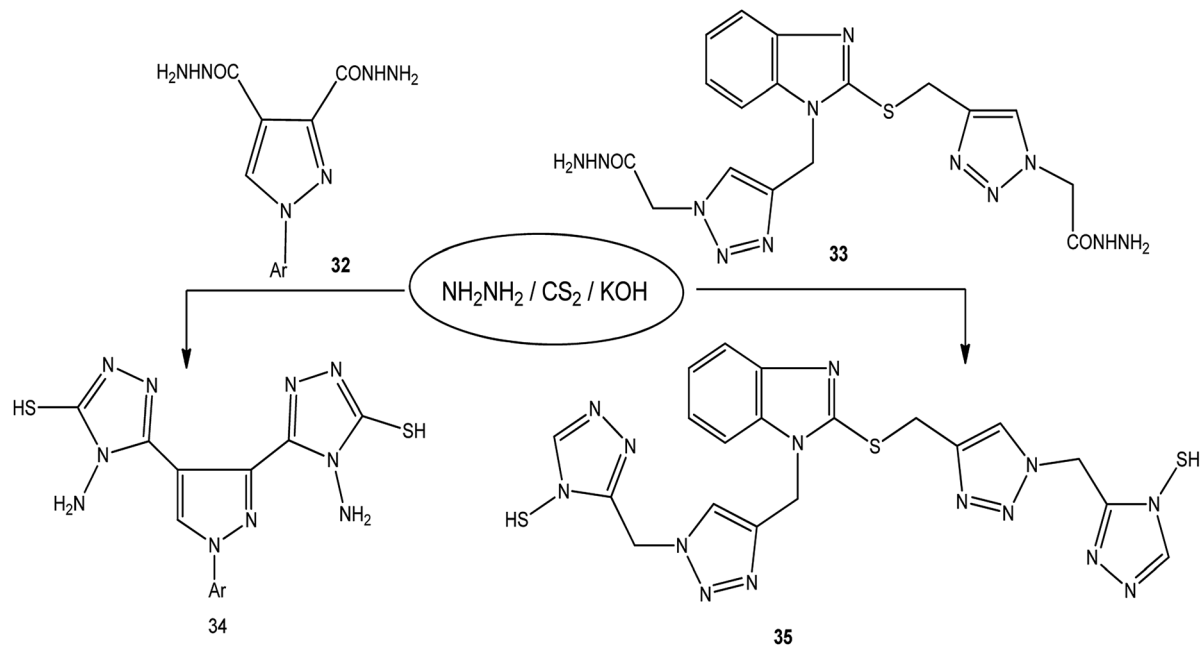
Table 3 (Contd.)

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	117
	118
	119
	120

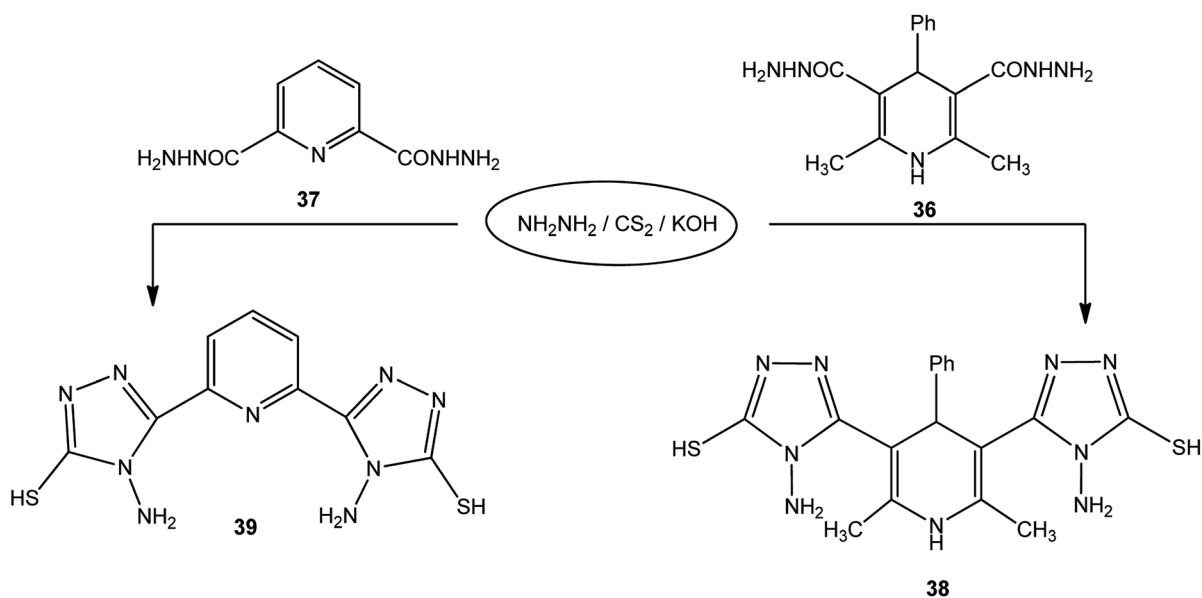
amino-3-(D-glucosyl)-1H-[1,2,4]triazole-5-thione (**22**),⁵² and 3-(D-alditol-1-yl)-4-amino-5-mercapto-[1,2,4]triazole (**23**)⁵³ were reported through reactions of thiocarbohydrazide (**5**) with D(-)galactono-1,4-lactone (**18**), D-glucosyl-γ-lactone (**19**), and D-galactono-1,5-lactones (**20**), respectively (Scheme 7).

3. Use of potassium acyldithiocarbazates with hydrazine hydrate

Potassium acyldithiocarbazates **25** is usually prepared by a reaction between the corresponding acid hydrazides **24** and carbon disulfide in an ethanolic potassium hydroxide solution.



Scheme 12 Synthesis of bis-triazoles 34 and 35.



Scheme 13 Synthesis of bis-triazoles 38 and 39.

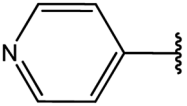
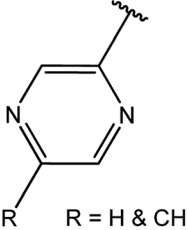
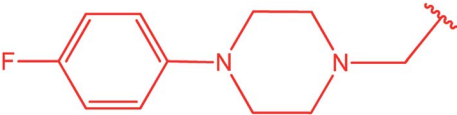
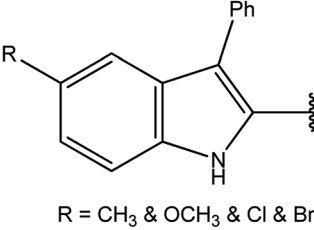
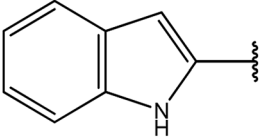
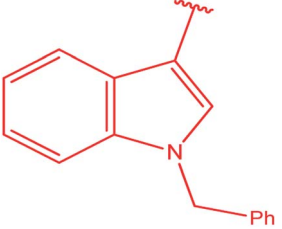
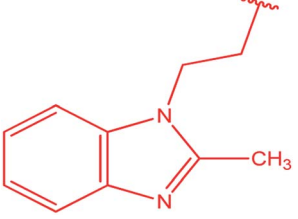
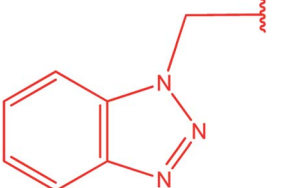
This method was extensively used in the synthesis of numerous derivatives of 4-amino-5-mercapto[1,2,4]triazoles **2** (**3**) upon treatment with hydrazine hydrate (Scheme 8) (Table 2).

1,8-Bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane (**27**) was achieved *via* the reaction of sebacic acid dihydrazide (**26**)

with carbon disulfide and hydrazine hydrate in a molar ratio of 1 : 2 : 2 in the presence of potassium hydroxide⁸⁹ (Scheme 9).

Bis-(3-mercapto-4-amino-[1,2,4]-triazole) with an aromatic moiety was prepared under similar conditions by Zhao *et al.*⁹⁰ Thus, the reaction of 2,2'-[1,3-phenylenebis(oxy)]bis-acetic hydrazide (**28**) with CS₂/NH₂NH₂ afforded 2,2'-[1,3-

Table 4 (Contd.)

Y	Ref.
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phenylenebis(oxymethylene)]bis-(4-amino-3-mercapto-[1,2,4]triazole) (29) (Scheme 10).

3-Heteroaryl-4-amino-5-mercapto[1,2,4]triazoles (4) were synthesized by the treatment of the corresponding dithiocarbamate 31 with hydrazine hydrate (Scheme 11) (Table 3).

The treatment of dicarbohydrazides 32 (ref. 121) and 33 (ref. 122) with $\text{CS}_2/\text{NH}_2\text{NH}_2$ in the presence of KOH proceeded smoothly to afford the respective bis-triazoles 34 and 35 (Scheme 12).

In addition, pyridine dicarbohydrazide derivatives 36 (ref. 123) and 37 (ref. 124 and 125) were reacted with the above reagents under similar conditions to give 38 and 39, respectively (Scheme 13).

Moreover, the reactions of dicarbohydrazide of triazole 40 (ref. 126) or indole derivatives 41 (ref. 127) with the same reagents in an alkaline solution furnished 42 or 43, respectively (Scheme 14).

4. Synthesis of 5-mercapto[1,3,4]oxadiazoles with hydrazine hydrate via ring transformation reactions

An alcoholic solution of hydrazine hydrate achieves the ring transformation of 3-substituted-5-mercapto[1,3,4]oxadiazoles (43) to 3-substituted-4-amino-5-mercapto[1,3,4]triazoles 2–4 (Scheme 15) (Table 4).

5,5'-[1,4-Phenylenebis(oxymethylene)]-bis(1,3,4-oxadiazole-2-thiol) (44) was converted into 5,5'-[[1,4-phenylenebis(oxymethylene)]-bis(4-amino-4*H*-1,2,4-triazole-3-thiol) (45) upon treatment with hydrazine hydrate in dry pyridine under thermal conditions (Scheme 16).¹⁴²

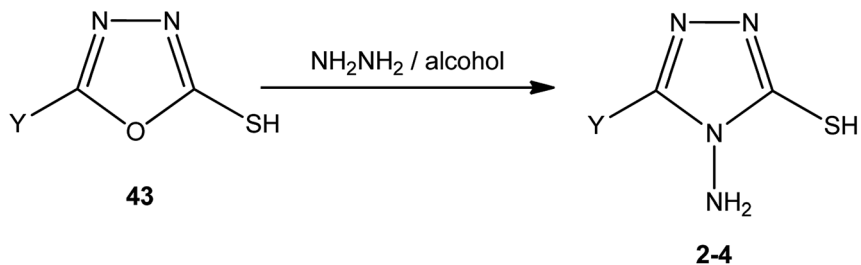
Similarly, the conversion of 5,5'-methylenebis(1,3,4-oxadiazole-2-thiol) (46) into 5,5'-methylenebis(4-amino-4*H*-1,2,4-triazole-3-thiol) (47) was achieved using an alcoholic hydrazine solution under refluxing conditions (Scheme 17).¹

In addition, the same procedure (alcoholic hydrazine solution) was applied to the conversion of 1,4-bis(2-mercapto-1,3,4-oxadiazol-5-yl)butane-1,2,3,4-tetrol (48) to 1,4-bis(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)butane-1,2,3,4-tetrol (49) (Scheme 18).¹⁴³

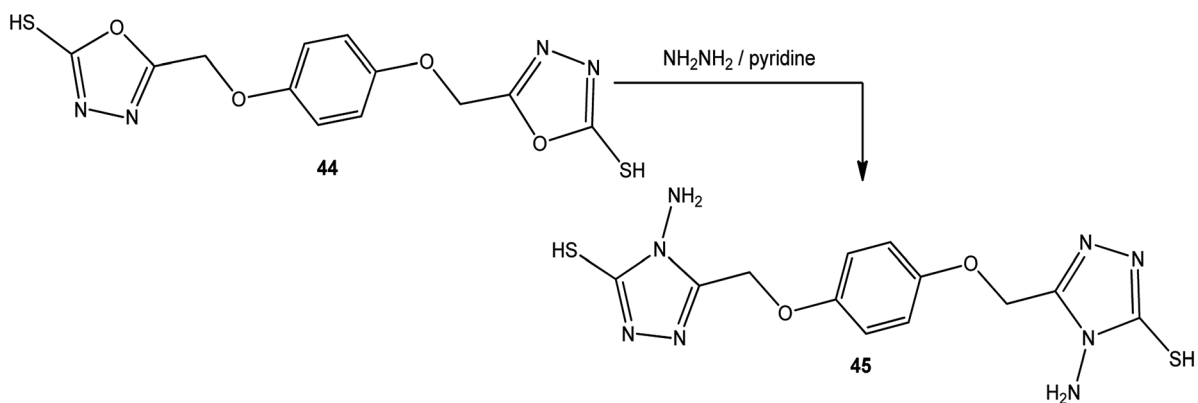
4-Amino-5-mercapto[1,2,4]triazole 1 and its 3-substituted derivatives 2–4 (Chart 2) contain both amino and mercapto groups as ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings.

5. Conclusions and future directions

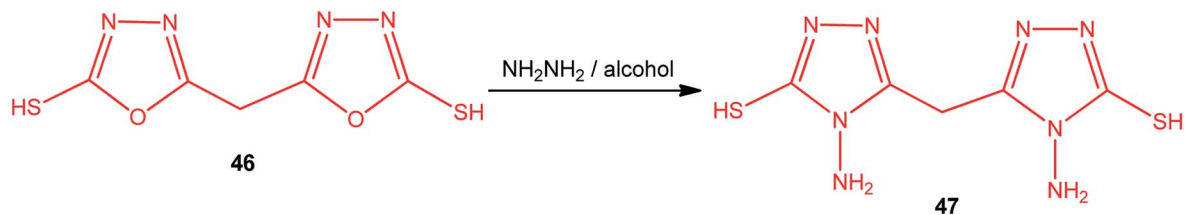
The reports in this review clearly demonstrate the elevated synthetic potential of 3-substituted-4-amino-5-mercapto[1,2,4]triazoles and bis-[4-amino-5-mercapto[1,2,4]triazoles]. Numerous scientific researchers in the fields of chemistry and pharmaceutical science are interested in the study and utilization of these compounds as building blocks in the synthesis of important bioactive compounds.



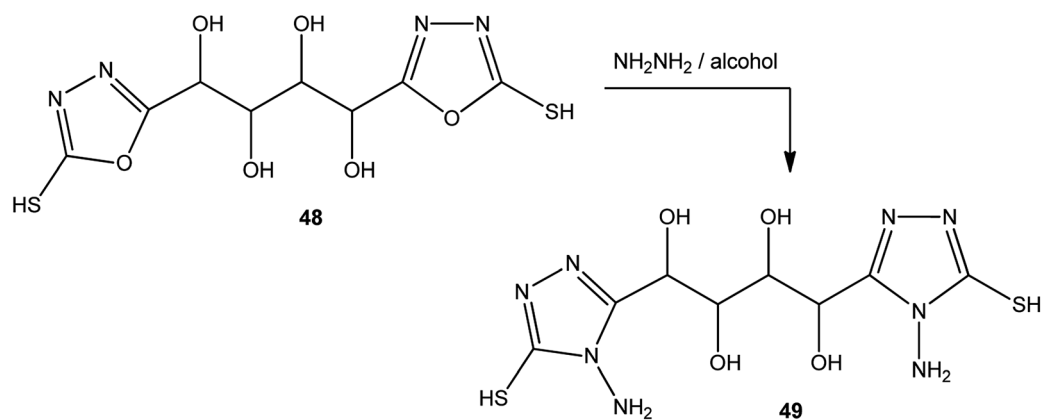
Scheme 15 Synthesis of triazoles 2–4.



Scheme 16 Synthesis of bis-triazole 45.



Scheme 17 Synthesis of bis-triazole 47.



Scheme 18 Synthesis of bis-triazole 49.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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