1,3,4-Thiadiazoles of pharmacological interest: Recent trends in their synthesis via tandem 1,3-dipolar cycloaddition: Review

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ABSTRACT

This review article presents a survey of the utility of a new synthetic strategy for 1,3,4-thiadiazole derivatives based on reactions of nitrilimines with various functionalized sulfur dipolarophiles which proceed via tandem in situ 1,3-dipolar cycloaddition and β-elimination of simple molecule from the initially formed cycloadduct. The biological activities of some of the compounds prepared by such a strategy are pointed out. Only the literature reports within the period from 2000 to mid 2012 are covered.

Introduction and scope of the review

A survey of the literature revealed that differently substituted 1,3,4-thiadiazoles and anelated 1,3,4-thiadiazoles have wide range of pharmacological activities such as antibacterial, anti-fungal, antituberculous, antihepatitis B viral, antileishmanial, anti-inflammatory, analgesic, CNS depressant, anticancer, antioxidant, antidiabetic, molluscidical, antihypertensive, diuretic, analgesic, antimicrobial, antitubercular, and anticonvulsant activities [1–11]. These important biological activities encouraged several research groups to find out different methods for synthesis of new thiadiazoles using different synthones, such as thiosemicarbazides, thiocarbazides, dithiocarbazates, thiourea, carbonothioic dihydrazide [4,7–11].

We would like to report in this review the recent developments of a new synthetic strategy for the synthesis of 1,3,4-thiadiazoles. This strategy is based on an in situ 1,3-dipolar cycloaddition of nitrilimines A to functionalized sulfur dipolarophiles B, followed by β-elimination of simple molecule from the initially formed cycloadducts C (Scheme 1). This strategy proved useful and convenient for synthesis of various functionalized 1,3,4-thiadiazole derivatives D (Scheme 1). Such a target...
has not been covered hitherto in the foregoing review articles surveying the chemistry of both 1,3,4-thiadiazoles [1–11] and nitrilimines as well as their precursors [12–24].

Regarding the 1,3-dipolar cycloaddition, it is a process in which two reactants, namely a 1,3-dipole and a dipolarophile combine together to form a five-membered ring via the formation of two new sigma bonds without loss of any small fragment (Fig. 1). The 1,3-dipole is basically a system of three atoms amongst which are distributed four $p$ electrons, whereas the dipolarophile is usually an unsaturated system having two $p$ electrons. It is usually a system with either a double or a triple bond. The 1,3-dipolar cycloaddition reactions are usually referred to either as $(4p+2p)$cycloadditions or $(3+2)$cycloadditions on the basis of the number of electrons or the number of atoms in the two reactants, respectively.

Several types of 1,3-dipoles are found in the literature. One class of such 1,3-dipolar species is the so-called nitrilimines of the general formula $\text{E}$. Such nitrilimines are 1,3-dipoles readily generated in situ from stable precursors. They are usually generated in the presence of an appropriate dipolarophile. If they are generated in the absence of suitable dipolarophile, they undergo head-to-tail dimerization to afford the corresponding cycloadduct, namely the corresponding 1,3,4,6-tetrasubstituted-1,2,4,5-tetrazine $\text{F}$ as given below.

Several convenient methods have been reported for the generation of nitrilimines [25–39]. These include (i) thermolysis of either 2,5-disubstituted tetrazoles $\text{I}$, 1,3,4-oxadiazol-5-ones $\text{II}$ or 1,2,3,4-oxathiadiazol-2-oxides $\text{III}$ (ii) base treatment of either hydrazonoyl halides $\text{I}$ under such conditions, afforded the corresponding 1,3,4-thiadiazole derivatives $\text{IV}$ in 64–92% yield (Scheme 2).

Regarding the dipolarophile, it can be almost any molecule having a double or triple bond of the following types (Chart 2). In this review, only cycloaddition reactions of nitrilimines to compounds having the $\text{C=S}$ double bond as dipolarophilic site are surveyed.

**Reactions**

**Reaction with alkyl dithiocarboxylates**

Several reports on the reactions of alkyl dithiocarboxylates with nitrilimines have been published. In all cases, such reactions were carried out by stirring a mixture of the appropriate ester and hydrazonoyl halide in ethanol at room temperature in the presence of triethylamine [40–45]. For example, Abdelhamid et al. [40,41] reported that reaction of methyl 2-cyano-2-(benzoazol-2-yl)dithioacetates $\text{IX}$ with each of nitrilimines, derived from the corresponding hydrazonoyl halides $\text{I}$ under such conditions, afforded the corresponding 1,3,4-thiadiazole derivatives $\text{X}$ in 64–92% yield (Scheme 2).
Likewise, the reactions of methyl 2-cyano-2-(benzothiazol-2-yl)dithiocarboxylates 9 with hydrazonoyl chlorides II [42] and VII(IX) [43] yielded the corresponding 1,3,4-thiadiazole derivatives 11 in 92% and 12 in 52–59% yields, respectively (Scheme 3).

In another report [44], it was indicated that 1,3,4-thiadiazole derivatives 12 were formed in 55–68% yield when N-hetaryl-hydrazonoyl halides V(VI) were treated with methyl 2-cyano-2-(benzothiazol-2-yl)dithiocarboxylates 9 (Scheme 4).

Reaction of bis-nitrilimines, derived from the bis-hydrazonoyl chlorides IV with methyl 2-cyano-2-(hetaryl)dithiocarboxylates 9, gave the corresponding bis-2,2'-1,3,4-thiadiazole) derivatives 13 in 83–90% yield (Scheme 5) [45].

Also, the 1,3,4-thiadiazole derivatives 15 were furnished in 70–75% yield by reaction of methyl pyrazole-4-dithiocarboxylates 14 with hydrazonoyl halides I, V, and VI (Scheme 6) [41,44].

**Reaction with thioamides**

Many reactions of thioamides with nitrilimines were carried out by refluxing a mixture of the appropriate hydrazonoyl halide and thioamide in ethanol in the presence of triethylamine [49,50,54–57]. For example, when N-phenyl 2-benzoyl-3-oxothiobutanamide 16 was reacted with hydrazonoyl bromide XII under such reaction conditions, it afforded the corresponding 3-benzoyl-4-aryl-5-[acetyl,benzoyl)methylene]-1,3,4-thiadiazoles 17a–c (Scheme 7) [49].

Also, treatment of the thioanilide 18 with each of the hydrazonoyl chlorides I and II under the same reaction conditions afforded the corresponding 1,3,4-thiadiazole derivatives 19a–c (Scheme 8) [50].

In a similar manner, the thioacetanilide 20 reacted with the hydrazonoyl halides I, VII, and IX gave also the corresponding 1,3,4-thiadiazole derivatives 21 in 62–68% yields (Scheme 9) [54].

Treatment of the thioanilides 22 with the hydrazonoyl chlorides furnished also the corresponding thiadiazole derivatives 23 (Scheme 10) [55].

Likewise, the hydrazonoyl chlorides I, VII, IX, and XI were reported to react with the thioanilide 24 under the same reaction conditions and yielded the corresponding 1,3,4-thiadiazole derivatives 25 in 82–90% yields (Scheme 11) [56].
The reaction of the hydrazonoyl chlorides I, II, VII, IX, or XI with the thioanilide 26 in refluxing ethanol in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazole derivatives 27 in 73–80% yield (Scheme 12) [57].

In some other reports, several 1,3,4-thiadiazole derivatives were also obtained by reaction of hydrazonoyl halides with the appropriate thioamides in ethanol containing triethylamine at room temperature. For example, the 1,3,4-thiadiazole derivatives 10 have been prepared in 64–92% yield by reaction of 2-hetaryl-cyanothioacetanilides 28 with the hydrazonoyl halides I and VIII under such reaction conditions [42] or in refluxing chloroform in the presence of triethylamine [40] (Scheme 13).

Similar treatment of each of the hydrazonoyl chlorides VII and IX with the N-methylthioacetamide derivative 29 in ethanol containing triethylamine at room temperature afforded the corresponding 1,3,4-thiadiazole derivatives 30 in 57–60% yield (Scheme 14) [59].

**Scheme 7**

**Scheme 8**

**Scheme 9**

**Scheme 10**

**Scheme 11**

**Scheme 12**

**Scheme 13**

**Scheme 14**
when carried out in refluxing ethanol in the presence of sodium ethoxide, it afforded the corresponding 3-phenyl-5-substituted-2-N-(arylimino)-1,3,4-thiadiazoles (Scheme 16) [51]. Abunada [46], Hassaneen et al. [47], and Abdallah et al. [48] demonstrated that treatment of the thioanilides 32A(B) each with hydrazonoyl halides I, II, VII, IX, and XII in refluxing chloroform in the presence of triethylamine yielded the thiadiazole derivatives 33 (Scheme 17).

Several thioamides reacted with hydrazonoyl halides in dimethyl formamide in the presence of potassium hydroxide at room temperature to give the corresponding 1,3,4-thiadiazole derivatives [53,58,60–62]. For example, the interaction of 2-hetaryl-2-cyanothioacetanilide 36 with various nitrilimines derived from the respective hydrazonoyl halides II, VII, IX, XI, and XII under such reaction conditions gave mainly the 1,3,4-thiadiazole derivatives 37 in 53–60% yield (Scheme 19) [53].

Likewise, reaction of the thioanilide 38 with the hydrazonoyl chlorides I, VII, and XI in refluxing chloroform in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazole derivatives 35 in 74–80% yield (Scheme 18) [52].

Several thioamides reacted with hydrazonoyl halides in dimethyl formamide in the presence of potassium hydroxide at room temperature to give the corresponding 1,3,4-thiadiazole derivatives [53,58,60–62]. For example, the interaction of 2-hetaryl-2-cyanothioacetanilide 36 with various nitrilimines derived from the respective hydrazonoyl halides II, VII, IX, XI, and XII under such reaction conditions gave mainly the 1,3,4-thiadiazole derivatives 37 in 53–60% yield (Scheme 19) [53].

Likewise, reaction of the thioanilide 38 with the hydrazonoyl chlorides I, VII, and XI was reported to furnish the corresponding thiadiazole derivatives 35 in 74–80% yield (Scheme 18) [52].

In another report [60], it was indicated that similar reaction of the thioanilides 40 with the bis-hydrazonoyl chlorides IV furnished the corresponding bis-(1,3,4-thiadiazole) derivatives 41 in 66–70% yield (Scheme 21). In contrast to this finding, it was indicated that reaction of the same bis-hydrazonoyl
chloride with cyanothioacetamide 42 in boiling ethanol in the presence of triethylamine yielded the thiazole derivative 43 (Scheme 22) [60].

Recently, it was found that reaction of each of the hydrazonoyl halides I, VII, and IX with the bis-thioanilide 44 in DMF containing KOH furnished the bis-1,3,4-thiadiazole derivatives 45 in 49–66% yield (Scheme 23) [61].

Hassaneen et al. reported that treatment of (2-phenylimino-3-phenyl-4-oxothiazolidin-5-yl)thiocarboxanilide 46 with each of hydrazonoyl halides I, VII, VIII, IX, XI, and XII in DMF containing KOH afforded the corresponding thiadiazoline derivatives 47 (Scheme 24) [62]. Similar reaction of 1,3-diphenyl-2-thioxo-5-oxo-4-thiocarboxanilide 48 with the aforementioned hydrazonoyl halides under the same reaction conditions yielded also the corresponding 1,3,4-thiadiazole derivatives 49 (Scheme 25) [62].

**Reaction with alkyl dithiocarbamates**

A number of papers have been published on reactions of alkyl dithiocarbamates with nitrilimines. In all of these papers, the reactions were carried out by stirring a mixture of the appropriate hydrazonoyl halide and the dithiocarbamate in ethanol in the presence of triethylamine at room temperature [44, 63–69]. For example, 1,3,4-thiadiazole derivatives 51 were readily obtained in 68–85% yield by reaction of diaryl nitrilimines derived from the respective hydrazonoyl halides I, VII, IX, XI, and XII under such conditions with methyl N-aryldithiocarbamates 50 (Scheme 26) [63, 64].
In like manner, the related 1,3,4-thiadiazole derivatives of type 52 were obtained in 55–87% yield by reaction of N-aryl-C-heteroyl hydrazonoyl halides II with methyl N-phenyldithiocarbamate 50A (Scheme 27) [42,66–68].

Also, reaction of hydrazonoyl chlorides V(VI) with methyl N-phenyldithiocarbamate 50A in ethanolic triethylamine at room temperature furnished the corresponding 5-phenylimino-1,3,4-thiadiazole derivatives 53 in 55–65% yield (Scheme 28) [44].

Abdelhamid and Abdel-Wahab [64] and Abdelhamid et al. [69] investigated the reaction of methyl N-hetaryldithiocarbamate 54 with nitrilimines derived from the hydrazonoyl chlorides I, II, VII, IX, XI, and XII in ethanolic triethylamine at room temperature and characterized the products as 5-hetarylimino-1,3,4-thiadiazole derivatives 55. The latter products were obtained in 50–82% yield (Scheme 29) [66].

**Reaction with thiourea and its derivatives**

Direct synthesis of 5-phenylimino-1,3,4-thiadiazole derivatives 58 in 65–82% yield from C,N-diarylnitrilimines, derived by base-catalyzed dehydrohalogenation of the respective hydrazonoyl halides I in refluxing ethanol in the presence of triethylamine, and mono-substituted-thiourea and its N,N0-disubstituted derivatives 57A,B were recently reported (Scheme 31) [40,63,64].

Also, it was reported that N-phenyl benzene-carbohydrazonoyl bromide reacted with bis-thiourea 59 in refluxing pyridine and yielded the azine derivative 60 (Scheme 32) [86]. The latter was also produced by heating 2-hydrazono-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole 61 in DMF containing triethylamine as catalyst (Scheme 32) [86].

**Reactions with alkyl dithiocarbazates**

**Unsubstituted dithiocarbazates**

The thia diazole derivatives 61a–d were readily produced from methyl dithiocarbamate 62 through its reaction with each of the
hydrazonoyl bromides I in ethanol in the presence of triethylamine at room temperature [41]. However, the thiadiazole derivatives 61e–g were produced by refluxing a mixture of each halide VIII and alkyl dithiocarbazate 62 in ethanol [70] (Scheme 33). The yields of the compounds prepared were not pointed out, however.

Likewise, reaction of N-hetaryl hydrazonoyl chlorides V and VI each with alkyl dithiocarbazates 62 in ethanol in the presence of triethylamine at room temperature furnished the corresponding thiadiazole derivatives 63 in 65% yield (Scheme 34) [40].

**Alkyl N-acyldithiocarbazates**

Several publications concerning reaction of alkyl N-acyldithiocarbazates with nitrilimines have been reported. Most of the reactions were studied by stirring a mixture of the appropriate hydrazonoyl halide and the alkyl N-acyldithiocarbazate in ethanol at room temperature [42,63–65,71,72]. Only in one report [66], the reaction between the hydrazonoyl halide and alkyl N-acyldithiocarbazate was carried out in refluxing chloroform containing triethylamine. Thus, reaction of alkyl N-benzoyldithiocarbazate 66 with nitrilimines generated from various hydrazonoyl halides I [63,64,71], II [65], and X [42,66,72] afforded the corresponding thiadiazole derivatives 67 in 71–85% yields (Scheme 36).
Furthermore, N-[5-acetyl-3-(aryl)-1,3,4-thiadiazol-2(3H)-ylidene]-5-(1H-indol-3-yl)-1-phenyl-1H-pyrazole-3-carboxy- 
hydrazides 69 was prepared in 43–50% by direct heating the 
potassium salt of dithiocarbazate 68A with hydrazonoyl 
chlorides IX in ethanol (Scheme 37) [73].

Likewise, reaction of the hydrazonoyl halides IX and XII each with potassium salt of the dithiocarbamate 68B in refluxing ethanol yielded the corresponding 1,3,4-thidiazole derivat 
es 70 in 72–76% yields (Scheme 38) [74].

Alkyl N-cinnamylidene dithiocarbazates

The azine derivatives 72 were reported to be obtained in 65–90% in yields from the interaction of alkyl 
stryrylmethylidenedithiocarbazate 71 with various nitrilimines 
derived from hydrazonoyl chlorides IX in ethanol (Scheme 39). The formation of the latter products 72 was 
considered to result from initial cycloaddition of nitrilimines to 
the C=S to form the cycladducts which in turn underwent 
elimination of methanethiol [63,67,71,75].

Alkyl N-arylmethylene dithiocarbazates

Several publications covering reactions of nitrilimines with alk 
l N-alkylidene dithiocarbazates have been reported. In all 
cases examined, the reactions were carried out by stirring a 
mixture of the appropriate hydrazonoyl halide and alkyl
N-alkylidene dithiocarbazate in ethanol containing triethylamine at room temperature. For example, reactions of the dithiocarbazates with nitrilimines derived from various hydrazonoyl halides \( \text{II}, \text{VII}, \text{IX}, \text{XI}, \text{XII} \) [40–42, 53, 63–68, 71, 72, 75, 76, 78, 79] under such conditions furnished the corresponding azine derivatives \( \text{74} \) (Scheme 40).

Also, the thiazole derivatives \( \text{75} \) have also been prepared by reaction of N-aryl 2-hetaryl-2-oxoethanehydrazonoyl chlorides \( \text{II} \) with alkyl N-arylidenedithiocarbazate \( \text{73} \) in ethanolic triethylamine at room temperature (Scheme 41) [71, 80].

Similarly, reaction of N-hetarylhydrazonoyl chlorides \( \text{V}, \text{VI}, \text{IX}, \text{X} \) each with alkyl N-arylidenedithiocarbazate \( \text{73} \) under the same reaction conditions was reported to furnish the corresponding thiazole derivatives \( \text{76} \) in 60–80% yields (Scheme 42) [44].

**Scheme 40**

Alkyl N-(1-aryl)ethylidene dithiocarbazates

Numerous azine derivatives \( \text{78} \) were prepared in 56–90% yield by reactions of alkyl 1-substituted-ethylidene-dithiocarbazate

77 with various nitrilimines, generated from hydrazonoyl bromides \( \text{I}, \text{V}, \text{VII}, \text{XII} \) [40, 41, 63, 67, 68, 71, 72, 77, 78, 81, 83] in ethanol in the presence of triethylamine at room temperature (Scheme 43).

Likewise, 2,3-dihydro-1,3,4-thiadiazolyl steroids \( \text{80} \) were analogously prepared in 60–68% yields by reaction of alkyl dithiocarbazate \( \text{79} \) with various hydrazonoyl halides \( \text{II}, \text{VII}, \text{IX}, \text{XI}, \text{XII} \) under the same reaction conditions (Scheme 44) [82].

Reactions of alkyl 1-substituted-ethylidene-dithiocarbazates with each of N-hetaryl hydrazonoyl chlorides \( \text{V}, \text{VI} \) and gave the respective 1,3,4-thiadiazoles \( \text{83} \) (Scheme 45) [44].

The steroidal dithiocarbazates \( \text{82, A} \), \( \text{B} \) were also reported to undergo similar reaction with hydrazonoyl halides \( \text{II}, \text{VII}, \text{IX}, \text{XI}, \text{XII} \) and gave the respective 1,3,4-thiadiazoles \( \text{83A, B} \) (Scheme 46) [82].

**Scheme 41**

**Scheme 42**

**Scheme 43**

**Scheme 44**

**Scheme 45**

**Scheme 46**
Reactions of nitrilimines with alkyl cycloalkylidene dithiocarbazates have been studied by several authors. In most of these cases, the reactions were carried out by stirring the appropriate nitrilimine precursor, namely the hydrazonoyl halide, and the dithiocarbazate ester in ethanol in the presence of triethylamine at room temperature. Thus, reactions of methyl cycloalkylidene dithiocarbazates with the hydrazonoyl halides \( \text{VII(IX)} \) \([44]\) and \( \text{I} \) \([63,71]\) under such conditions have been reported to yield the corresponding azine derivatives \( \text{85} \) in 50–78% yield (Scheme 47).

Also, the 1,3,4-thiadiazole derivatives \( \text{87} \) have been obtained in 64–88% yields by reactions of nitrilimines derived from the C-heteroyl-hydrazonoyl halides \( \text{II} \) with alkyl carbodithioates \( \text{86} \) under the same reaction conditions (Scheme 48) \([43,66–68,80,83]\).

**Scheme 47**

**Scheme 48**
Rateb [84] reported that methyl dithiocarbazate reacted with nitrilimines, derived from the hydrazonoyl halides I, II, VII, and IX-XII in dimethyl formamide in the presence of potassium hydroxide at room temperature, and furnished the corresponding azine derivatives 89 in 55–67% yield (Scheme 49).

Similarly, other research groups [40,41,44,65,68] described the preparation of the thiadiazole derivatives 91 by reactions of alkyl dithiocarbazates 90 with various hydrazonoyl halides I, II, VII, and IX in ethanol in the presence of triethylamine (Scheme 50).

Alkyl N-hetarylidene diothiocarbazates

Several reports covering reactions of alkyl N-hetarylidene dithiocarbazates with nitrilimines have been published [40,41,44,65,67–69]. In these reports, it was indicated that the reaction of alkyl dithiocarbazates 92 with various hydrazonoyl halides I, II, VII, and IX in ethanolic triethylamine afforded the corresponding thiadiazole derivatives 93 in 65–85% yield (Scheme 51).

Reactions with carbonothioic dihydrazide

Different results were reported concerning reactions of carbonothioic dihydrazide 94 with hydrazonoyl halides. For example, Sayed [86] reported that treatment of 94 with hydrazonoyl chloride IX in boiling DMF gave the corresponding thiadiazine derivatives 95 in 64% yield (Scheme 52). In contrast, the same reaction of 94 with N-aryl arenecarbohydrazonoyl halides I and VIII in refluxing ethanol was reported earlier by the same author to afford the thiadiazole derivatives 96 [70]. No rationalization was given for such difference.

Similarly, reactions of carbonothioic dihydrazide 94 with the bis-hydrazonoyl chlorides IV in DMF in the presence of triethylamine furnished the corresponding 2,2'-bis(1,3,4-thiadiazole) derivatives 97 in about 60% yield (Scheme 53). Compound 97 reacted with benzaldehyde to give the bis-hydrazone 98. The latter was also obtained by reaction of the bis-hydrazonoyl chloride IV with 2-(phenylmethylene)carbonothioic dihydrazide 99 in ethanolic triethylamine [70].

Reactions with heterocyclic thiones

In a recent review by Shawali and Farghaly [22] on reactions of hydrazonoyl halides with many heterocyclic thiones having no \( \alpha \)-hydrogen, it has been indicated that such reactions afford only the corresponding spiro(heterocycle[\( n,2 \)]-3H-1,3,4-thiadiazole). More recently, several research groups have reported
that reactions of N-arylhydrazonoyl halides I and X with 5-substituted-1,3,4-oxadiazol-5(4H)thione 100 in boiling ethanol [65,72,74] or chloroform [64] in the presence of triethylamine furnished in all cases examined, products that were identified as the corresponding thiadiazole derivatives 101 in 72–76% yield. The latter products were assumed to be formed via the ring opening of the initially formed spirocycloadducts (Scheme 54). The latter products 101 were also obtained by reaction of the same hydrazonoyl halides each with alkyl N-benzoyldithiocarbazate (Scheme 54) [65,72,74].

In contrast, it was reported that reactions of heterocyclic thione 102 with hydrazonoyl chlorides I, VII and X in chloroform in the presence of triethylamine were reported to afford the corresponding fused [1,2,4]triazoles 103 in 89–91% yields [85]. To account for the formation of the latter, it was suggested that the initially formed spiro-1,3,4-thiadiazole cycloaducts underwent tandem *in situ* rearrangement and elimination of hydrogen sulfide to give the respective fused [1,2,4]triazoles 103 as end products (Scheme 55) [85].

**Biological activity**

Many of the thiadiazole derivatives that have been prepared by the foregoing reactions, proved to possess wide range of pharmaceutical activities like antimicrobial, antivirus, anticancer, and molluscicidal effectiveness. In the following, a brief coverage of such activities is outlined.

**Antimicrobial activities**

Abdelhamid et al. [41] reported that certain 2,3-dihydro-1,3,4-thiadiazole derivatives 10a,b; 15a,b; 74a,b; 78a,b; 91 and 93 (Chart 3) possess high inhibitory activity against some strains of Gram positive bacteria, namely *Staphylococcus albus*, *Staphylococcus faecalis* and *Bacillus subtilis* and Gram negative bacteria *Escherichia coli*. Also compounds 74A [76] and 74B and 74C [78], 74D, 74E and 74F [79] and 74G, 74H, 74I (Charts 4–7) [79] exhibited a high inhibition toward *Candida albicans* and *Asperillus flavus* fungi. Also, 2-N-arylminono-1,3,4-thiadiazole derivatives 31a and 31b (Chart 8) were reported to exhibit moderate activity against *Candida albicans* [51].

**Antiviral activities**

The thidiazoline derivatives 69a,b (Chart 9) were reported to show no antiviral activity [73].

**Anticancer and cytotoxic activity**

Twelve of the azine derivatives 91 (Chart 10) were evaluated for their anticancer activity. The results showed that some of these compounds possess cytotoxicity against Ehrlich ascites carcinoma [65].

**Anticonvulsant and anti-inflammatory activities**

Some of the compounds 21 (Chart 11) [54] were screened for anticonvulsant activity. The results showed that 21a and 21d were found active in ScMet, whereas compound 21e was active.
in MES. Also, compounds 21 were found to exhibit antinociceptive effect and the order of their activity is in the order \(21f > 21c > 21a > 21b > 21d\). In addition, compounds 21 were screened for their anti-inflammatory activity. The results showed that 21a exhibited the most potent anti-inflammatory activity and from structure–activity relationship (SAR) the order is \(21a > 21b > 21c\).

**Molluscicidal activity**

The toxicity of compounds 17a–c to *Biomphalaria alexandrina* snails was screened, and the results showed that compound 17b showed the highest activity (Chart 12) [49].

**Conclusion**

From the foregoing survey, it seems that tandem 1,3-dipolar cycloaddition of nitrilimines to functionalized sulfur dipolarophilic compounds followed by \(\beta\)-elimination of simple molecule such as alkanethiol from the initially formed cycloadducts provides a useful and convenient strategy for synthesis of numerous 1,3,4-thiadiazole derivatives. The subject of such reactions is still ongoing and undoubtedly will provide new fused functionalized 1,3,4-thiadiazoles of both industrial and biological interests.

**Conflict of interest**

The author has declared no conflict of interest.

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