Novel Method for the Synthesis of *s*-Triazolo[3,4-*b*][1,3,4]thiadiazines

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Abstract: The reaction of 4-amino-3-mercapto-5-phenyl-*s*-triazole with aromatic or aliphatic ketones containing active α-hydrogens as a methyl or methylene group using an acidified acetic acid method afforded the corresponding *s*-triazolo[3,4-*b*][1,3,4]thiadiazines. In a similar way, applying the same reaction with cyclic ketones afforded the corresponding tricyclic compounds. Interaction of 4-amino-3-mercapto-5-phenyl-*s*-triazole with chloroacetonitrile under the same reaction conditions directly gave the cyclized 6-amino-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivative. On treatment of 4-amino-3-mercapto-5-phenyl-*s*-triazole with acetonitrile or ethyl cyanoacetate under the same reaction conditions, an *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivative was obtained; the reaction carried out with malononitrile or cyanoacetamide gave an alternative *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivative. The mechanism of the reactions was investigated and the structures of all new compounds were elucidated using IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data, and elemental analyses.

Key words: α-hydrogens, ketones, nitriles, one-pot reaction, triazolothiadiazines

The importance of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines lies in their possession of antibacterial and antifungal activity.[1–5] These compounds have shown analgesic,[6] insecticidal,[7] antiviral,[8,9] antiparasitic,[10] diuretic,[11] anti-inflammatory,[12] antitubercular,[9] anticancer[9,13,14] and antioxidant[15] activity. It has been reported that these compounds have marked antidepressant,[16] anthelmintic[17] and plant-growth-promoting effects.[18] The synthesis of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines by reacting either 4-amino-3-mercapto-*s*-triazoles[10,19–23] or 2-hydrazino-1,3,4-thiadiazines[24–26] as starting materials with α-halo carbonyl compounds has been reported. The disadvantages of these methods include the many steps, the long reaction times, the use of highly toxic and irritating halo carbonyl compounds, and the poor to moderate overall yields. Recently, we have reported the synthesis of triazolo[1,3,5]thiadiazines via a double Mannich reaction.[27,28] In the present work we report a facile synthesis of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines, using our method that we previously applied for the synthesis of thiazoloimidazoles **1** and thiazolotriazoles **2** (Figure 1),[29–32] in short reaction time and good reaction yields.

As we have previously described, an acidified acetic acid method was generally applicable for the synthesis of various fused heterocyclic systems which had been found difficult to obtain.[29] The advantages of this method are short reaction time, one-pot reaction, direct use of ketones without the formation of highly toxic and irritating phenacyl bromides, ease of handling, very inexpensive materials and the ease of removal of the reaction waste by neutralization of the liquor with ammonium hydroxide. We believe that this reaction can be considered a clean reaction and environmentally safe. In this work, we have tried to generalize this reaction to be much more effective and applicable for the synthesis of many substituted fused heterocycles which could not be obtained by other reported methods.

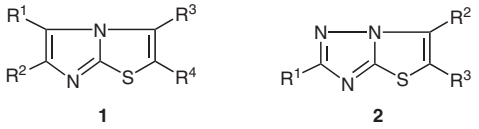

Figure 1

Interaction of 4-amino-3-mercapto-5-phenyl-*s*-triazole (**3**) with aromatic or aliphatic ketones **4a–k** containing an active methyl or methylene group in boiling acetic acid in the presence of sulfuric acid as a catalyst for 3 hours directly afforded an unexpected cyclized product which was identified as the 3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines **5a–k** (Table 1). The reaction pathway is assumed to involve S-alkylation to give a nonisolable intermediate, followed by intramolecular cyclization to give **5a–k**, or to occur via the formation of imine followed by attack of enamine on the disulfide intermediate.

The structures of compounds **5a–k** were assigned on the basis of elemental analyses, and IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. The IR spectra of compounds **5a–k** lacked NH_2 and NH absorption bands, except for **5f** with bands at 3400 and 3200 (NH_2) cm^{-1}; all compounds showed bands at 3074–3000 (C–H aromatic), 2997–2921 (C–H aliphatic) and 1695–1560 (C=N) cm^{-1}, as well as the aromatic skeleton bands at 1473–1418 cm^{-1}. Additionally, compounds **5g** and **5j** showed hydroxy and carbonyl absorption bands at 3450 and 1707 cm^{-1}, respectively. The ^{1}H NMR spectra of compounds **5a–i** were characterized by the appearance of a singlet signal at δ = 4.5–3.5 which is attributed to the methylene group, while a signal which appeared at δ = 4.2–3.8 for compounds **5j** and **5k** is attributed to C–H, in addition to the other protons at the expected chemical shifts. The ^{13}C NMR spectra of compounds **5g** and **5i** showed one signal at δ = 23.0 and 25.7, respectively, attributed to the meth-

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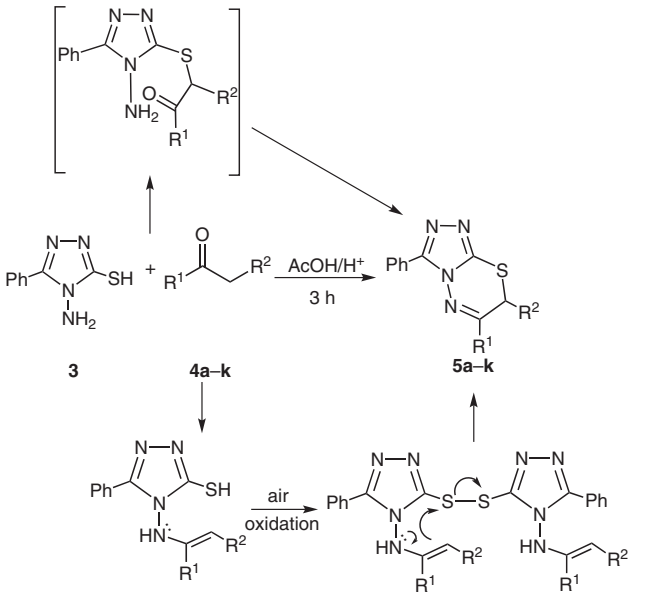
Table 1



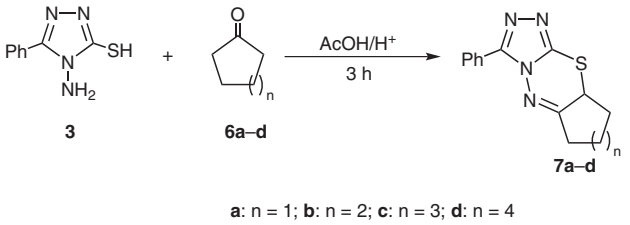
	R^1	R^2
a	Ph	H
b	4-ClC_6H_4	H
c	4-BrC_6H_4	H
d	4-Tol	H
e	4-$MeOC_6H_4$	H
f	4-$H_2NC_6H_4$	H
g	4-HOC_6H_4	H
h	1-Naph	H
i	Me	H[a]
j	Me	Ac
k	Me	Me

[a] For **4i**, $R^2 = CO_2Et$.

ylene group, in addition to the other carbons at the expected chemical shifts. The mass spectra of compounds **5c**, **5g**, **5h**, **5i**, **5j** and **5k** showed the expected molecular ion peaks at *m*/*z* = 370, 308, 342, 230, 272 and 244, respectively, each peak with 100% intensity. Further, the melting points of the previously reported compounds[10] were in agreement with those obtained from the compounds using our synthetic method.

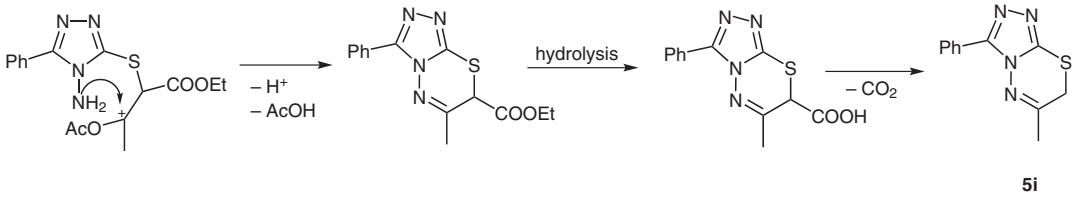
It is noteworthy that the interaction of *s*-triazole **3** with ethyl acetoacetate gave a product whose IR spectrum lacked carbonyl group absorption bands, while its ^{1}H NMR spectrum showed aromatic protons at δ = 7.45–8.1 (m, 5 H) and two singlet signals at δ = 3.5 (s, 2 H, CH_2) and 2.25 (s, 3 H, CH_3), but lacked the signals that are characteristic for an ethyl group. The ^{13}C NMR spectrum exhibited signals at δ = 156.4 (C_6=N), 152.1 (C_3), 141.4 (C_9), 130.2 (CH-aromatic), 128.5 (2 CH-aromatic), 128.3 (CH-aromatic), 128.2 (CH-aromatic), 126.0 (C-aromatic), 25.7 (C_7) and 23.9 (CH_3). The mass spectrum showed the molecular ion peak at *m*/*z* = 230 (100%). Based on the IR, ^{1}H NMR and ^{13}C NMR spectra, TLC, melting point and mixed melting point with the product obtained from the reaction of *s*-triazole **3** with acetone in boiling acidified acetic acid, the reaction product **5i** was identified as 6-methyl-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine.
This is explained as postulated in Scheme 1, via hydrolysis of the ester group followed by decarboxylation.

Furthermore, when alicyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone (**6a–d**) were allowed to react with *s*-triazole **3** under the same reaction conditions, the corresponding fused tricyclic compounds **7a–d** were obtained in high yield (Scheme 2).



Scheme 2

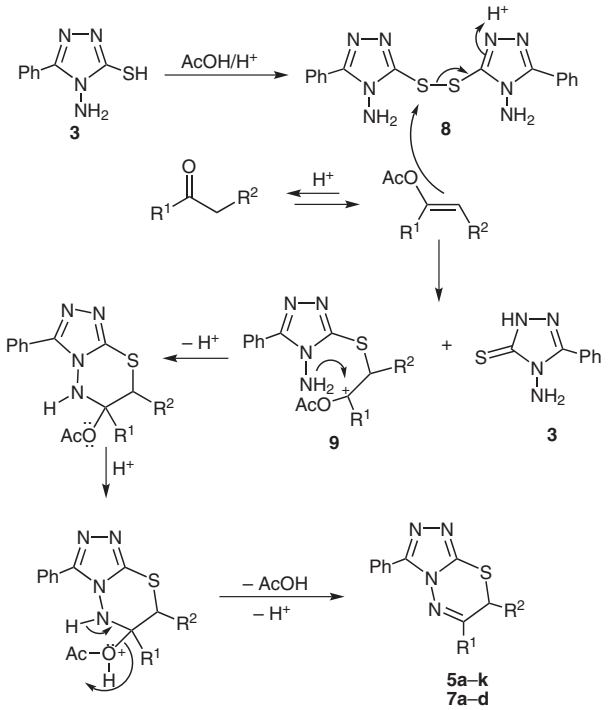
The structures of tricyclic compounds **7a–d** were confirmed on the basis of elemental analyses and spectroscopic data. The IR spectra of compounds **7a–d** showed bands at 3069–3020 (C–H aromatic), 2997–2850 (C–H aliphatic) and 1695–1612 (C=N) cm^{-1}, along with the aromatic skeleton bands at 1473–1456 cm^{-1}. The ^{1}H NMR spectra of these compounds were characterized by the appearance of a triplet signal at δ = 4.0–3.85 which is attributed to the cyclic CH and multiple signals at δ = 3.0–1.2 attributable to the cyclic CH_2 groups, in addition to the other protons at the expected chemical shifts. The ^{13}C NMR spectra of compounds **7a**, **7c** and **7d** in $CDCl_3$ showed signals at δ = 39.49–36.68 attributed to the cyclic



Scheme 1

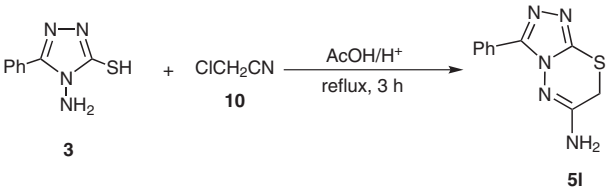
CH and at δ = 36.17–21.22 attributed to the cyclic CH_2 groups, in addition to the other carbons at the expected chemical shifts. The mass spectra of compounds **7a–d** showed the molecular ion peaks [M^+], [$M^+ + 1$] and [$M^+ + 2$].

The mechanism of these reactions is still under investigation. The S-alkylation may proceed via formation of the disulfide **8** followed by nucleophilic attack by α-aryl/alkyl-α-hydroxymethylene carboxylates (formed by esterification of the enol forms) to give the carbonium ions **9**, which undergo intramolecular cyclization to directly produce the cyclized compounds (Scheme 3).



Scheme 3

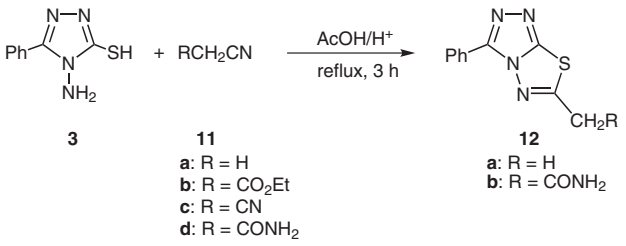
Reaction of *s*-triazole **3** with chloroacetonitrile (**10**) under the same reaction conditions resulted in the 6-amino-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivative **5l** in good yield (Scheme 4).



Scheme 4

The structure of compound **5l** was confirmed by elemental analysis and spectroscopic data. The IR spectrum of **5l** lacked a cyano group absorption band and showed, besides other bands, two characteristic bands at 3400–3200 cm^{-1} due to the NH_2 group. The ^1H NMR spectrum showed signals at δ = 7.2 (exchangeable with D_2O) attributed to the amino group and at δ = 3.9 attributed to the methylene group, while the mass spectrum showed the expected molecular ion peak at *m*/*z* = 231 (54%). In addition, the structure of **5l** was in agreement with authentic compound prepared by an unequivocal method.[22] The overall yield of compound **5l** using the reported method was 25%, but the yield obtained using our method was found to be 70%.

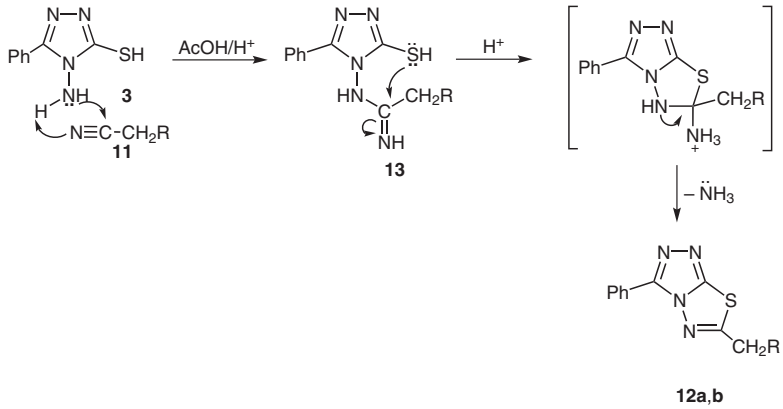
Furthermore, treatment of *s*-triazole **3** with acetonitrile (**11a**) or ethyl cyanoacetate (**11b**) under the same reaction conditions gave the *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivative **12a**, while on using malononitrile (**11c**) or cyanoacetamide (**11d**), the *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivative **12b** was isolated (Scheme 5).



Scheme 5

The structures of compounds **12a** and **12b** were confirmed on the basis of elemental analyses, and IR, ^1H NMR, ^{13}C NMR and mass spectroscopic data. The IR spectra of compounds **12a** and **12b** lacked a CN absorption band and showed bands at 3050–3010 (C–H aromatic), 2920–2900 (C–H aliphatic) and 1600–1540 (C=N) cm^{-1}, while compound **12b** additionally showed bands at 3400–3150 cm^{-1} attributed to the NH_2 group and for the amidic carbonyl at 1680 cm^{-1}. The ^1H NMR spectrum of compound **12a** showed a singlet signal at δ = 2.9 attributed to the methyl group, while the spectrum of **12b** showed two signals at δ = 7.9 (exchangeable with D_2O) and 4.1 attributed to the amino and methylene groups, respectively, in addition to the aromatic protons for **12a** and **12b** at δ = 7.2–8.3. The ^{13}C NMR spectrum of compound **12b** showed the following signals: δ = 168.60 (C=O), 166.30 (C_6=N), 155.87 (C_3), 142.12 (C_8), 130.63 (CH-aromatic), 129.57 (2 CH-aromatic), 126.16 (2 CH-aromatic), 126.03 (C-aromatic) and 37.91 (CH_2CO). The mass spectra of compounds **12a** and **12b** showed the expected molecular ion peaks at *m*/*z* = 216 and 259, respectively. Further, the structure of compound **12a** was chemically confirmed by unequivocal synthesis by the reaction of *s*-triazole **3** with acetyl chloride or acetic acid following the previously reported methods.[33,34]

The mechanism of the formation of compounds **12a**,**b** could be explained by nucleophilic attack of the amino group in compound **3** onto the cyano group of compounds **11a–d** to yield the uncyclized imine derivatives **13** which undergo intramolecular cyclization with the loss of ammonia to give the cyclized compounds **12a**,**b** (Scheme 6).



Scheme 6

It is apparent that the ester group of compound **12** (R = CO_2Et) derived from **11b** undergoes hydrolysis which is followed by decarboxylation to give derivative **12a** (R = H), while the cyano group of compound **12** (R = CN) derived from **11c** undergoes hydrolysis to provide the amide derivative **12b** (R = $CONH_2$).

In this study, 4-amino-3-mercapto-5-phenyl-*s*-triazole (**3**) was condensed with a variety of ketones containing an active methyl or methylene group by refluxing in acetic acid in the presence of sulfuric acid. Some of the resulting *s*-triazolo[3,4-*b*][1,3,4]thiadiazines were synthesized as new compounds with anticipated biological activity and their structures were confirmed using spectroscopic data and elemental analyses. The versatile, novel one-step synthesis of these compounds derived in our laboratory has the distinct advantage of dispensing with the use of highly toxic and irritating halo carbonyl compounds which are also not easy to obtain. Furthermore, the use of this method afforded a variety of substituents in the 6- and 7-positions of the *s*-triazolo[3,4-*b*][1,3,4]thiadiazines, derivatives which could not be obtained using the classical methods.

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Shimadzu 470 spectrometer using KBr techniques. ^{1}H NMR spectra were measured on a Varian EM-390 90-MHz spectrometer (Spectral Unit, Assiut University, Egypt) or a Bruker DX 400-MHz spectrometer (Department of Physical Chemistry, Geneva) using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. ^{13}C NMR spectra were measured on a Bruker DX 400-MHz spectrometer. Mass spectra were recorded on a Jeol JMS-600H spectrometer using a direct inlet system. Elemental analyses were performed using a Perkin-Elmer 240-C elemental analyzer.

6-Substituted 3-Phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines 5a–k; General Procedure

A mixture of 4-amino-3-mercapto-5-phenyl-*s*-triazole (**3**; 0.96 g, 0.005 mol) and an aromatic or aliphatic ketone **4a–k** (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of concd H_2SO_4 was refluxed for 3 h then, after cooling, was diluted with H_2O (20 mL) and neutralized with NH_3 soln. The crude product thus obtained was collected by filtration, washed with H_2O and crystallized from the appropriate solvent to give **5a–k** as colorless crystals in 58–88% yield.

3,6-Diphenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5a)

Yield: 1.01 g (69%); colorless crystals (EtOH); mp 216–217 °C (Lit.[10] 213–214 °C).

IR: 3059 (C–H arom.), 2997 (C–H aliph.), 1600 (C=N), 1473 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, DMSO-d_6): δ = 4.1 (s, 2 H, CH_2), 7.5–8.1 (m, 10 H, H-arom.).

Anal. Calcd for $C_{16}H_{12}N_4S$ (292.36): C, 65.73; H, 4.14; N, 19.16; S, 10.97. Found: C, 65.88; H, 4.34; N, 19.04; S, 10.80.

6-(4-Chlorophenyl)-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5b)

Yield: 0.95 g (58%); colorless crystals (EtOH); mp 240–242 °C (Lit.[10] 239–240 °C).

IR: 3034 (C–H arom.), 2990 (C–H aliph.), 1560 (C=N), 1463 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, DMSO-d_6): δ = 4.4 (s, 2 H, CH_2), 7.55–8.0 (m, 9 H, H-arom.).

Anal. Calcd for $C_{16}H_{11}ClN_4S$ (326.80): C, 58.80; H, 3.39; N, 17.14; S, 9.81. Found: C, 59.00; H, 3.45; N, 17.07; S, 9.55.

6-(4-Bromophenyl)-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5c)

Yield: 1.26 g (68%); colorless crystals (EtOH); mp 250–251 °C (Lit.[10] 244–245 °C).

IR: 3031 (C–H arom.), 2993 (C–H aliph.), 1586 (C=N), 1463 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, DMSO-d_6): δ = 4.5 (s, 2 H, CH_2), 7.5–8.0 (m, 9 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 372.1 [M^+ +2] (95), 370.1 [M^+] (100), 197.0 (11), 181.1 (27), 147 (15), 121.1 (13), 115.1 (9), 104.1 (25), 102.1 (41), 91.1 (2), 76.1 (21), 63.9 (3), 51.2 (4).

Anal. Calcd for $C_{16}H_{11}BrN_4S$ (371.25): C, 51.76; H, 2.99; N, 15.09; S, 8.64. Found: C, 51.61; H, 3.06; N, 15.08; S, 8.65.

3-Phenyl-6-(4-tolyl)-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5d)

Yield: 1.19 g (78%); colorless crystals (EtOH); mp 190–192 °C (Lit.[10] 192–194 °C).

IR: 3000 (C–H arom.), 2963 (C–H aliph.), 1616 (C=N), 1464 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, DMSO-d_6): δ = 2.3 (s, 3 H, CH_3), 4.35 (s, 2 H, CH_2), 7.6–8.0 (m, 9 H, H-arom.).

Anal. Calcd for $C_{17}H_{14}N_4S$ (306.38): C, 66.64; H, 4.61; N, 18.29; S, 10.47. Found: C, 66.82; H, 4.64; N, 18.22; S, 10.35.

6-(4-Methoxyphenyl)-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5e)
Yield: 1.18 g (73%); colorless crystals (EtOH); mp 198–200 °C (Lit.[10] 216–217 °C).

IR: 3005 (C–H arom.), 2986 (C–H aliph.), 1604 (C=N), 1456 (C=C) cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 3.9 (s, 3 H, OCH_3), 4.3 (s, 2 H, CH_2), 7.0–8.1 (m, 9 H, H-arom.).

Anal. Calcd for $C_{17}H_{14}N_4OS$ (322.38): C, 63.33; H, 4.38; N, 17.38; S, 9.95. Found: C, 63.15; H, 4.32; N, 17.12; S, 10.13.

6-(4-Aminophenyl)-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5f)
Yield: 0.92 g (60%); colorless crystals (DMF); mp 210–211 °C.

IR: 3400–3200 (NH_2), 3000 (C–H arom.), 2900 (C–H aliph.), 1695 (C=N), 1460 (C=C) cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 4.35 (s, 2 H, CH_2), 7.6–8.1 (m, 9 H, H-arom.), 10.4 (s, 2 H, NH_2).

Anal. Calcd for $C_{16}H_{13}N_5S$ (307.37): C, 62.52; H, 4.26; N, 22.78; S, 10.43. Found: C, 62.41; H, 4.41; N, 22.65; S, 10.50.

6-(4-Hydroxyphenyl)-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5g)
Yield: 1.36 g (88%); colorless crystals (DMF); mp 296–298 °C.

IR: 3450 (OH), 3016 (C–H arom.), 2990 (C–H aliph.), 1691 (C=N), 1460 (C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.2 (s, 2 H, CH_2), 6.4 (d, *J* = 5 Hz, 2 H, H-arom.), 7.5 (m, 3 H, H-arom.), 7.9 (d, *J* = 5 Hz, 2 H, H-arom.), 8.0 (d, *J* = 5 Hz, 2 H, H-arom.), 10.1 (s, 1 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.4 (C_6=N), 155.4 (COH), 151.7 (C_3), 142.8 (C_9), 130.2 (2 CH-arom.), 129.8 (CH-arom.), 128.8 (2 CH-arom.), 128.1 (2 CH-arom.), 126.6 (C-arom.), 124.1 (C-arom.), 116.2 (2 CH-arom.), 23.0 (C_7).

MS (EI, 70 eV): *m*/*z* (%) = 307.8 [M^+] (100), 276.8 (1), 255 (19), 214.7 (1), 191.6 (5), 189.1 (11), 176.7 (13), 146.9 (12), 132.9 (27), 120.9 (14), 118.9 (41), 102.9 (70), 90.9 (24), 88.9 (13), 76.9 (17), 64.8 (20), 51.7 (5).

Anal. Calcd for $C_{16}H_{12}N_4OS$ (308.36): C, 62.32; H, 3.92; N, 18.17; S, 10.40. Found: C, 62.50; H, 4.07; N, 18.13; S, 10.45.

6-(1-Naphthyl)-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5h)
Yield: 1.37 g (80%); colorless crystals (EtOH); mp 210–211 °C.

IR: 3050 (C–H arom.), 2993 (C–H aliph.), 1656 (C=N), 1457 (C=C) cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 4.30 (s, 2 H, CH_2), 7.4–8.3 (m, 12 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 342.5 [M^+] (100), 309.6 (9), 280.7 (4), 209.7 (5), 198.8 (3), 177.7 (3), 166.8 (28), 151.8 (51), 146.8 (11), 126.8 (28), 114.8 (7), 102.9 (68), 87.9 (3), 76.9 (16), 63.7 (6), 57.7 (71), 51.7 (1).

Anal. Calcd for $C_{20}H_{14}N_4S$ (342.42): C, 70.15; H, 4.12; N, 16.36; S, 9.36. Found: C, 70.20; H, 4.27; N, 16.30; S, 9.24.

6-Methyl-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5i)
Yield: 1.10 g (87.5%); colorless crystals (benzene–*n*-hexane); mp 190–192 °C.

IR: 3010 (C–H arom.), 2978 (C–H aliph.), 1616 (C=N), 1464 (C=C) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 3.5 (s, 2 H, CH_2), 7.45 (m, 3 H, H-arom.), 8.1 (d, *J* = 4 Hz, 2 H, H-arom.).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (C_6=N), 152.1 (C_3), 141.4 (C_9), 130.2 (CH-arom.), 128.5 (2 CH-arom.), 128.3 (2 CH-arom.), 128.2 (CH-arom.), 126.0 (C-arom.), 25.7 (C_7), 23.9 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 230.2 [M^+] (100), 215 (18), 189.1 (3), 147.1 (4), 129.2 (57), 115.1 (17), 103.1 (82), 8.2 (7), 76.5 (33), 63.2 (9), 58.2 (99), 51.3 (15).

Anal. Calcd for $C_{11}H_{10}N_4S$ (230.29): C, 57.37; H, 4.38; N, 24.33; S, 13.92. Found: C, 57.23; H, 4.44; N, 24.12; S, 14.15.

7-Acetyl-6-methyl-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5j)
Yield: 1.15 g (84.5%); colorless crystals (benzene–*n*-hexane); mp 141–142 °C.

IR: 3074 (C–H arom.), 2921 (C–H aliph.), 1707 (C=O), 1629 (C=N), 1471 (C=C) cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.2 (s, 3 H, CH_3), 2.23 (s, 3 H, $COCH_3$), 4.2 (s, 1 H, CH), 7.3–8.0 (m, 5 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 272.1 [M^+] (100), 259.1 (2), 230.1 (13), 217.1 (5), 185.1 (28), 178.1 (17), 165.9 (2), 146.1 (5), 119.1 (4), 102.9 (6), 92.9 (50), 75.1 (25), 66.1 (1), 57.1 (20), 50.9 (7).

Anal. Calcd for $C_{13}H_{12}N_4OS$ (272.33): C, 57.34; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.03; H, 4.59; N, 20.44; S, 11.83.

6,7-Dimethyl-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5k)
Yield: 0.67 g (55%); colorless crystals (benzene–*n*-hexane); mp 120–121 °C.

IR: 3050 (C–H arom.), 2965 (C–H aliph.), 1654 (C=N), 1418 (C=C) cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6 Hz, 3 H, $CHCH_3$), 2.2 (s, 3 H, CH_3), 3.8 (q, *J* = 6 Hz, 1 H, $CHCH_3$), 7.45–8.1 (m, 5 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 244.1 [M^+] (100), 215.1 (2), 202.1 (17), 177.1 (6), 147.1 (12), 130.1 (2), 126.1 (2), 115.1 (13), 103.1 (97), 88.9 (5), 76.1 (23), 54.8 (37), 51.8 (7).

Anal. Calcd for $C_{12}H_{12}N_4S$ (244.32): C, 58.99; H, 4.95; N, 22.93; S, 13.12. Found: C, 58.80; H, 5.15; N, 22.87; S, 13.10.

3-Phenylcycloalkano[*e*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines 7a–d; General Procedure
A mixture of 4-amino-3-mercapto-5-phenyl-*s*-triazole (**3**; 0.96 g, 0.005 mol) and a cyclic ketone **6a**–**d** (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of concd H_2SO_4 was refluxed for 3 h then, after cooling, was diluted with H_2O (20 mL) and neutralized with NH_3 soln. The crude product thus obtained was collected by filtration, washed with H_2O and crystallized (benzene–*n*-hexane) to give **7a**–**d** as colorless crystals in 66–84% yield.

3-Phenyl-6,7,8,8a-tetrahydrocyclopenta[*e*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7a)
Yield: 1.03 g (80%); colorless crystals (benzene–*n*-hexane); mp 180–182 °C.

IR: 3031 (C–H arom.), 2997–2902 (C–H aliph.), 1695 (C=N), 1459 (C=C) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.9–2.3 (m, 4 H, 2 CH_2), 2.8–3.0 (m, 2 H, CH_2), 3.9 (t, *J* = 5 Hz, 1 H, CH), 7.55–8.1 (m, 5 H, H-arom.).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.41 (C_6=N), 151.95 (C_3=N), 142.20 (C_9=N), 130.18 (CH-arom.), 128.52 (CH-arom.), 128.10 (CH-arom.), 127.61 (2 CH-arom.), 126.06 (C-arom.), 37.57 (CH-cyclic), 31.62 (CH_2-cyclic), 30.69 (CH_2-cyclic), 23.68 (CH_2-cyclic).

MS (EI, 70 eV): *m*/*z* (%) = 258.3 [M$^+$ + 2] (24), 257.2 [M$^+$ + 1] (30), 256.2 [M$^+$] (100), 216.9 (1), 190.9 (7), 185.1 (38), 177.9 (26), 167.9 (2), 149.0 (15), 130.9 (13), 103.9 (18), 76.9 (10), 74.9 (32), 60.9 (12), 56.9 (36), 50.9 (27).

Anal. Calcd for $C_{13}H_{12}N_4S$ (256.33): C, 60.19; H, 4.72; N, 21.86; S, 12.51. Found: C, 60.13; H, 4.84; N, 21.71; S, 12.67.

3-Phenyl-7,8,9,9a-tetrahydro-6*H*-cyclohexa[*e*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7b)

Yield: 0.93 g (68.5%); colorless crystals (benzene–*n*-hexane); mp 172–173 °C.

IR: 3021 (C–H arom.), 2919–2874 (C–H aliph.), 1660 (C=N), 1473 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.2–2.5 (m, 6 H, 3 CH_2), 2.8–3.0 (m, 2 H, CH_2), 4.0 (t, *J* = 5 Hz, 1 H, CH), 7.5–8.1 (m, 5 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 272.3 [M$^+$ + 2] (27), 271.3 [M$^+$ + 1] (23), 270.3 [M$^+$] (100), 202.2 (13), 174.1 (3), 103.2 (21), 81.2 (9), 79.2 (4), 76.2 (4), 67.3 (2), 55.3 (3), 53.2 (5), 45.3 (2).

Anal. Calcd for $C_{14}H_{14}N_4S$ (270.35): C, 62.20; H, 5.22; N, 20.72; S, 11.86. Found: C, 61.99; H, 5.36; N, 20.84; S, 11.80.

3-Phenyl-6,7,8,9,10,10a-hexahydrocyclohepta[*e*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7c)

Yield: 0.93 g (66%); colorless crystals (benzene–*n*-hexane); mp 161–163 °C.

IR: 3020 (C–H arom.), 2950–2900 (C–H aliph.), 1665 (C=N), 1461 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.2–2.1 (m, 8 H, 4 CH_2), 2.8–2.9 (m, 2 H, CH_2), 3.85 (t, *J* = 5 Hz, 1 H, CH), 7.5–8.1 (m, 5 H, H-arom.).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.52 (C_6=N), 151.45 (C_3=N), 142.00 (C_9=N), 130.15 (CH-arom.), 128.51 (2 CH-arom.), 128.11 (2 CH-arom.), 126.18 (C-arom.), 39.49 (CH-cyclic), 36.14 (CH_2-cyclic), 30.90 (CH_2-cyclic), 28.70 (CH_2-cyclic), 28.06 (CH_2-cyclic), 26.38 (CH_2-cyclic).

MS (EI, 70 eV): *m*/*z* (%) = 286.3 [M$^+$ + 2] (24), 285.3 [M$^+$ + 1] (71), 284.3 [M$^+$] (55), 248.6 (4), 229.6 (14), 177.8 (20), 165.8 (16), 130.9 (12), 103.8 (23), 76.9 (33), 68.9 (50), 56.9 (75), 52.9 (25), 50.9 (100).

Anal. Calcd for $C_{15}H_{16}N_4S$ (284.38): C, 63.35; H, 5.67; N, 19.70; S, 11.28. Found: C, 63.21; H, 5.69; N, 19.86; S, 11.32.

3-Phenyl-7,8,9,10,11,11a-hexahydro-6*H*-cycloocta[*e*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7d)

Yield: 1.25 g (84%); colorless crystals (benzene–*n*-hexane); mp 166 °C.

IR: 3069 (C–H arom.), 2928–2850 (C–H aliph.), 1612 (C=N), 1456 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.2–1.9 (m, 10 H, 5 CH_2), 2.8–2.9 (m, 2 H, CH_2), 3.85 (t, *J* = 5 Hz, 1 H, CH), 7.5–8.1 (m, 5 H, H-arom.).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.63 (C_6=N), 151.73 (C_3=N), 142.01 (C_9=N), 130.13 (CH-arom.), 128.58 (2 CH-arom.), 127.94 (CH-arom.), 127.61 (CH-arom.), 126.24 (C-arom.), 36.68 (CH-cyclic), 36.17 (CH_2-cyclic), 34.99 (CH_2-cyclic), 28.04 (CH_2-cyclic), 24.89 (CH_2-cyclic), 23.74 (CH_2-cyclic), 21.22 (CH_2-cyclic).

MS (EI, 70 eV): *m*/*z* (%) = 300.1 [M$^+$ + 2] (34.6), 299.1 [M$^+$ + 1] (80), 298.1 [M$^+$] (100), 265.3 (1), 230.1 (2), 216.1 (2), 202.1 (6), 177.1 (5), 146.9 (6), 138.1 (2), 103.0 (37), 91.0 (2), 76.9 (7), 67.1 (11), 54.8 (11), 51.8 (2).

Anal. Calcd for $C_{16}H_{18}N_4S$ (298.41): C, 64.40; H, 6.08; N, 18.78; S, 10.75. Found: C, 64.36; H, 6.13; N, 18.81; S, 10.83.

6-Amino-3-phenyl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (5l)

A mixture of 4-amino-3-mercapto-5-phenyl-*s*-triazole (**3**; 0.96 g, 0.005 mol) and chloroacetonitrile (**10**; 0.38 g, 0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of concd H_2SO_4 was refluxed for 3 h then, after cooling, was diluted with H_2O (20 mL) and neutralized with NH_3 soln. The crude product thus obtained was collected by filtration, washed with H_2O and crystallized (EtOH) to give **5l** as colorless needles; yield: 0.81 g (70%); mp 246–248 °C (Lit.[22] 246–247 °C).

IR: 3400–3200 (NH_2), 3005 (C–H arom.), 2910 (C–H aliph.), 1640 (C=N), 1450 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, DMSO-d_6): δ = 3.9 (s, 2 H, CH_2), 7.2 (s, 2 H, NH_2), 7.2–8.1 (m, 5 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 231.8 [M$^+$] (54), 212.6 (2), 184.9 (49), 177.9 (14), 164.8 (7), 148.8 (34), 102.8 (11), 100.8 (10), 92.9 (100), 74.9 (70), 68.9 (12), 56.9 (56), 50.9 (16).

Anal. Calcd for $C_{10}H_9N_5S$ (231.28): C, 51.93; H, 3.92; N, 30.28; S, 13.86. Found: C, 51.85; H, 3.85; N, 30.45; S, 13.93.

6-Substituted 3-Phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles 12a,b; General Procedure

A mixture of 4-amino-3-mercapto-5-phenyl-*s*-triazole (**3**; 0.96 g, 0.005 mol) and a cyano compound **11a**–**d** (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of concd H_2SO_4 was refluxed for 3 h then, after cooling, was diluted with H_2O (20 mL) and neutralized with NH_3 soln. The crude product thus obtained was collected by filtration, washed with H_2O and crystallized (EtOH) to give **12a**,**b** as colorless crystals in 50–81% yield.

6-Methyl-3-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole (12a)

Yield: 0.88 g (81%); colorless crystals (EtOH); mp 186–187 °C (Lit.[33,34] 186–187 °C).

IR: 3050 (C–H arom.), 2920 (C–H aliph.), 1540 (C=N), 1460 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.9 (s, 3 H, CH_3), 7.2–8.3 (m, 5 H, H-arom.).

MS (EI, 70 eV): *m*/*z* (%) = 16.2 [M$^+$] (100), 129.2 (17), 118.3 (4), 103.2 (54), 91.3 (1), 77.3 (10), 63.3 (1), 51.3 (6).

Anal. Calcd for $C_{10}H_8N_4S$ (216.26): C, 55.54; H, 3.73; N, 25.91; S, 14.83. Found: C, 55.35; H, 3.67; N, 26.02; S, 14.99.

6-(Aminocarbonylmethyl)-3-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole (12b)

Yield: 0.65 g (50%); colorless crystals (EtOH); mp 240–241 °C.

IR: 3400–3150 (NH_2), 3010 (C–H arom.), 2900 (C–H aliph.), 1680 (C=O), 1600 (C=N), 1480 (C=C) cm^{-1}.

^{1}H NMR (90 MHz, DMSO-d_6): δ = 4.1 (s, 2 H, CH_2), 7.9 (s, 2 H, NH_2), 7.55–8.2 (m, 5 H, H-arom.).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.60 (C=O), 166.30 (C6=N), 155.87 (C3), 142.12 (C8), 130.63 (CH-arom.), 129.57 (2 CH-arom.), 126.16 (2 CH-arom.), 126.03 (C-arom.), 37.91 (*C*H_2CO).

MS (EI, 70 eV): *m*/*z* (%) = 259.0 [M$^+$] (100), 216.9 (14), 186.1 (8), 176.9 (6), 147.0 (21), 102.9 (79), 77.1 (13), 75.9 (19), 64.9 (4), 56.8 (11), 51.8 (4).

Anal. Calcd for $C_{11}H_9N_5OS$ (259.29): C, 50.95; H, 3.50; N, 27.01; S, 12.37. Found: C, 50.85; H, 3.65; N, 26.91; S, 12.24.

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