SYNTHESIS OF 1,2,4-TRIAZOLO[5,1-*b*]1,3,5-THIADIAZEPIN-5-YLAMINE DERIVATIVES

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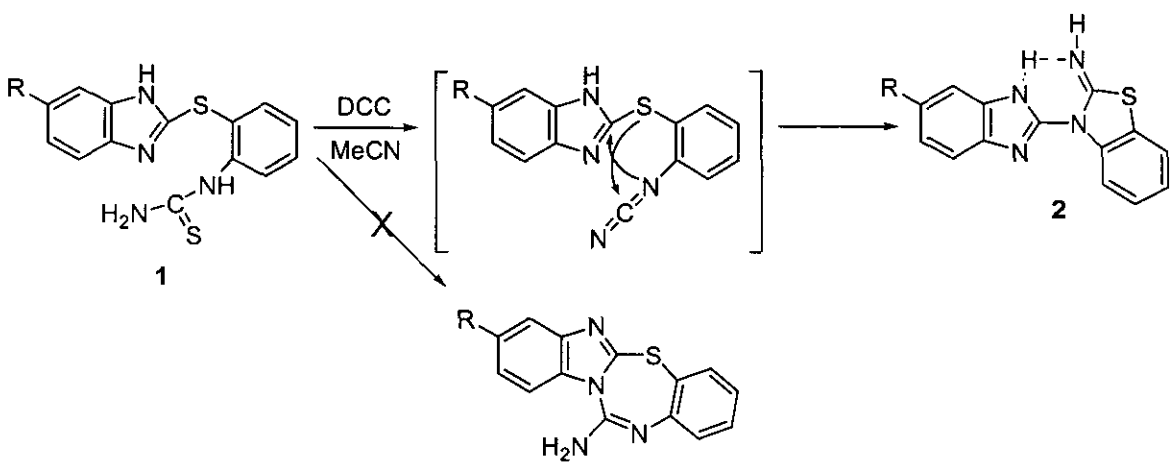
Abstract - 1,2,4-Triazolo[5,1-*b*]1,3,5-thiadiazepin-5-ylamine derivatives were synthesized by the reaction of *N*-[2-(1,2,4-triazol-5-ylthio)phenyl]thioureas with DCC *via* cyclodesufurization.

INTRODUCTION

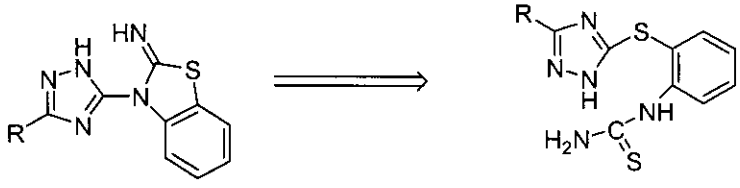
During our studies towards the synthesis of new biologically active heterocyclic compounds, it has been recently founded that the reaction of *N*-[2-(1*H*-benzimidazol-2-ylthio)phenyl]thioureas (**1**) with DCC afforded the 2-imino-3-benzimidazolylbenzothiazolines (**2**) *via* the Smiles-type rearrangement as shown in Scheme 1.[1]



1 **2** **3**

Scheme 1

Moreover, these compounds showed anti-cancer activity *in vitro*. We expected that if the observed anti-cancer activity is arisen from direct interaction of **2** with DNA *via* intercalation, the planar structure of **2** may play an important role. Thus, to investigate their structure-activity relationship for the anti-tumor activity, we decided to synthesis of triazole analogues (**4**) using analogous synthetic methods for **2** starting from thiourea derivatives (**5**) of triazole as shown in Scheme 2. However, the reaction of thioureas (**5**) with DCC did not afford the expected benzothiazolines (**4**). Instead, the cyclized product, triazolo-1,3,5-benzothiadiazepines (**10**), could only be isolated as a product. We report here the synthesis and crystal structure of 1,3,5-thiadiazepines (**10**).



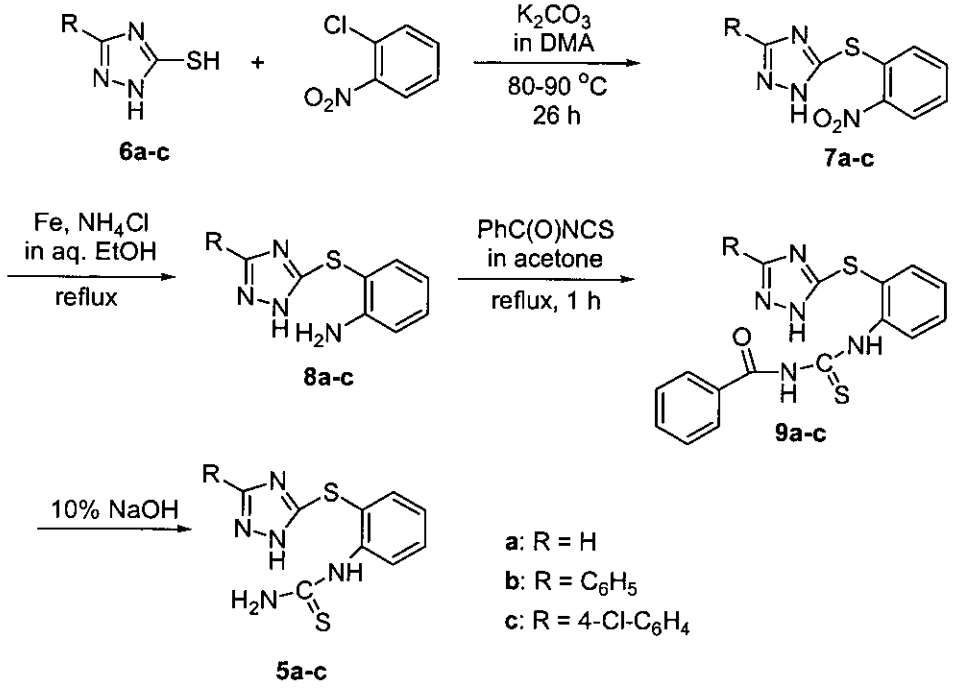
4 **5**

Scheme 2

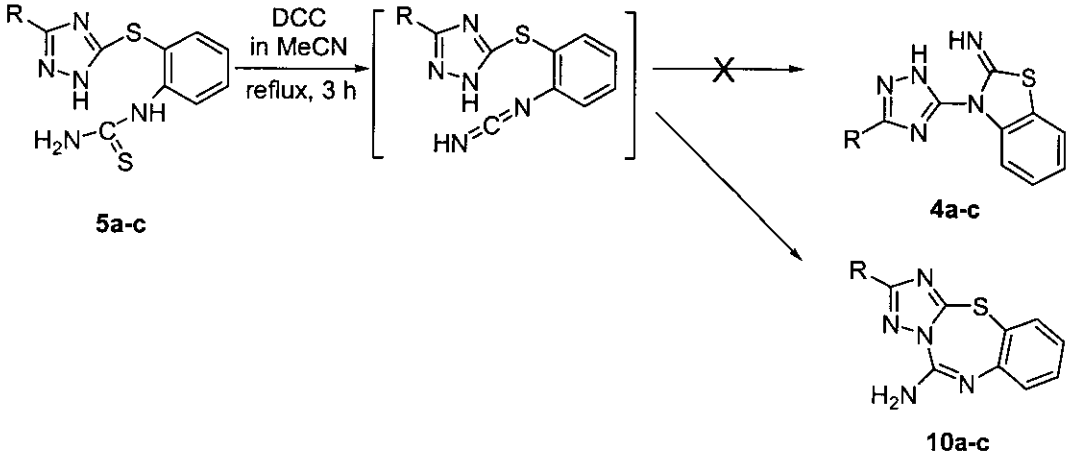
CHEMISTRY

The synthesis of thioureas (**5**) was easily performed as shown in Scheme 3. 3-Mercapto-1,2,4-triazole (**6**) reacted with 1-chloro-2-nitrobenzene in the presence of potassium carbonate in dimethylacetamide to give the nitro compounds (**7**). The nitro compounds (**7**) were easily reduced to the corresponding amines (**8**) using iron dust and ammonium chloride in aqueous ethanol in good yields. The reaction of amines (**8**) with 1.1 equimolar amounts of benzoyl isocyanate in acetone gave *N*-benzoylthioureas (**9**) which were hydrolyzed with 10% NaOH aqueous solution to give the desired thioureas (**5**).

In contrast to benzimidazole analogues (**1**), the reaction of *N*-[2-(1,2,4-triazol-5-ylthio)phenyl]thioureas (**5a-c**) with DCC in acetonitrile did not give the rearranged products (**4**), but gave 1,3,5-benzothiadiazepine derivatives (**10a-c**) in good yields *via* cyclodesulfurization (Scheme 4). The structure of **10a-c** was assigned by spectroscopic and element analytical analysis, and confirmed by X-Ray single crystal structure analysis. Figure 1 shows the crystal structure of **10c** having a puckered seven-membered 1,3,5-thiadiazepine ring.



Scheme 3



Scheme 4

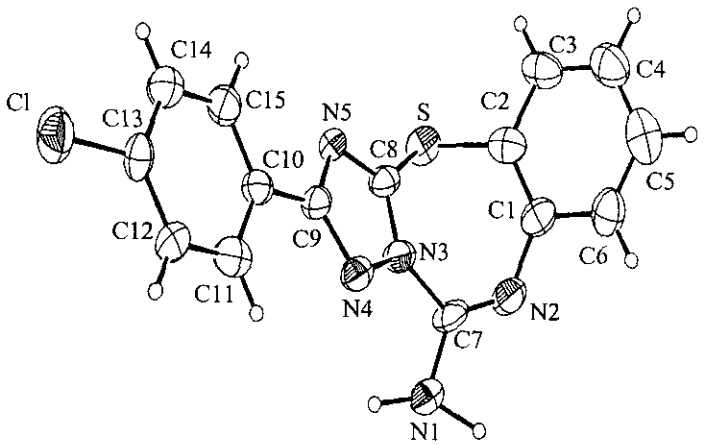


Figure 1. Crystal structure of **10c**

Table 1. Selected bond lengths (Å) and angles (°)

S–C(8)	1.733(8)	C(9)–C(10)	1.455(10)
Cl–C(13)	1.740(7)	S–C(2)	1.764(8)
N(2)–C(7)	1.262(10)	N(1)–C(7)	1.357(10)
N(3)–C(8)	1.344(9)	N(2)–C(1)	1.404(10)
N(3)–C(7)	1.438(9)	N(3)–N(4)	1.369(8)
N(5)–C(8)	1.325(9)	N(4)–C(9)	1.328(9)
C(1)–C(2)	1.392(11)	N(5)–C(9)	1.376(9)
C(8)–S–C(2)	96.9(3)	C(7)–N(2)–C(1)	125.6(6)
C(8)–N(3)–N(4)	110.5(6)	C(8)–N(3)–C(7)	127.2(6)
N(4)–N(3)–C(7)	122.2(6)	C(9)–N(4)–N(3)	102.3(6)
C(8)–N(5)–C(9)	103.6(6)	C(2)–C(1)–C(6)	118.3(8)
C(2)–C(1)–N(2)	124.9(7)	C(6)–C(1)–N(2)	16.5(7)
C(1)–C(2)–C(3)	120.7(8)	C(1)–C(2)–S	122.1(6)
C(3)–C(2)–S	117.1(6)	N(2)–C(7)–N(1)	122.8(7)
N(2)–C(7)–N(3)	125.2(7)	N(1)–C(7)–N(3)	112.0(6)
N(5)–C(8)–N(3)	109.6(6)	N(5)–C(8)–S	127.2(6)
N(3)–C(8)–S	123.1(5)	N(4)–C(9)–N(5)	114.0(6)
N(4)–C(9)–C(10)	124.3(7)	N(5)–C(9)–C(10)	121.7(6)

The 1,3,5-benzothiadiazepine derivatives (**10a-c**) were evaluated for antitumor activity against a panel of cancer cell lines including K-562 (leukemia), A 549 (non-small cell lung cancer), HCT-15 (colon cancer), SF-268 (CNS cancer), SK-MEL-2 (melanoma), SK-OV3 (ovarian cancer), MCF7 (breast cancer). However, in contrast to iminobenzothiazoline derivatives (**2**), none of 1,3,5-benzothiadiazepine

compounds (**10**) were effective against these tumor cell lines. It is here noteworthy that imidazole derivatives of 1,3,5-benzothiadiazepine showed potential antipsychotic activity.[2,3]

In summary, 1,2,4-triazolo[5,1-*b*]1,3,5-thiadiazepin-5-ylamine derivatives (**10a-c**) were synthesized by the reaction of *N*-[2-(1,2,4-triazol-5-ylthio)phenyl]thioureas (**9a-c**) with DCC *via* cyclodesulfurization, whereas the analogous reaction of *N*-[2-(benzimidazol-2-ylthio)phenyl]thioureas (**1**) with DCC gave 2-imino-3-benzimidazoylbenzothiazolines (**2**) exhibiting considerable antitumor activity. None of 1,3,5-thiadiazepine compounds (**10a-c**) showed antitumor activity.

EXPERIMENTAL

Chromatographic purification of products was performed on Merck silica gel 60 (230 ~ 400 mesh). Thin layer chromatography was carried out using glass sheets precoated with Merck silica gel 60F254. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and main absorption frequencies were given in cm^{-1}. Chemical analyses were carried out at the Advanced Analytical Research Center in KIST using a Perkin-Elmer 240C elemental analyzer. Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4 diffractometer using Mo radiation.

1-(1*H*-1,2,4-Triazol-5-ylthio)-2-nitrobenzene (7a)

To a stirred suspension containing 5.0 g (49.4 mmol) of 3-mercapto-1,2,4-triazole (**6a**) and 13.65 g (98.8 mmol) of K_2CO_3 in 50 mL of *N*,*N*-dimethylacetamide, 8.40 g (53.3 mmol) of 2-chloro-2-nitrobenzene was added dropwise for 30 min. The stirred suspension was heated at 80-90 °C for 26 h. After cooling to rt, 100 mL of ice water was added and stirring was continued for 2 h. The yellow solids were collected by filtration, washed with water until the washings were neutral to litmus. The crude product was purified by column chromatography (EtOAc:hexane = 2:1, R_f = 0.31) to give 3.95 g (36%) of **7a**.

mp 143-144 °C (CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 14.70 (br s, 1H), 8.91 (s, 1H), 8.36 (d, J = 8.2 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.2, 1H). IR (KBr) 1518, 1334, 1308, 736 cm^{-1}; Anal. Calcd for $C_8H_6N_4O_2S$, C 43.2; H 2.72; N; 25.2. Found C 43.0; H 2.55; N 24.8.

1-(3-Phenyl-1*H*-1,2,4-triazol-5-ylthio)-2-nitrobenzene (7b)

The compound (**7b**) as a yellow solid was prepared from 3-phenyl-1,2,4-triazole-5-thiol (**6b**) as for **7a** (EtOAc:hexane = 1:2, R_f = 0.25; 76% yield); mp 154-156 °C (CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 15.17 (br s, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.15-8.10 (m, 2H), 7.78-7.54 (m, 5H), 7.25 (d, J = 8.1 Hz, 1H). IR (KBr) 3130, 3066, 1518, 1334, 1306, 730, 692 cm^{-1}; Anal. Calcd for $C_{14}H_{10}N_4O_2S$, C 56.4; H 3.38; N; 18.8.

Found C 56.3; H 3.42; N 19.1.

1-[3-(4-Chlorophenyl)-1*H*-1,2,4-triazol-5-ylthio]-2-nitrobenzene (7c)

The compound (**7c**) as a yellow solid was prepared from 3-(4'-chlorophenyl)-1,2,4-triazole-5-thiol (**6c**) as for **7a** (EtOAc:hexane = 1:1, R_f = 0.48; 94% yield); mp 175-176 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 15.10 (br s, 1H, triazole NH), 8.37 (d, J = 8.1 Hz, 1H), 8.14-8.10 (d, J = 8.0 Hz, 2H), 7.74-7.57 (m, 4H), 7.24 (d, J = 8.0 Hz, 1H). IR (KBr) 3072, 1510, 1334, 1308 (NO_2), 736 cm^{-1}; Anal. Calcd for $C_{14}H_9N_4O_2ClS$, C 50.5; H 2.72; N; 16.8. Found C 50.6; H 2.55; N 16.6.

2-(1*H*-1,2,4-Triazol-5-ylthio)phenylamine (8a)

To a stirred solution of 3.0 g (13.5 mmol) of 1-(1*H*-1,2,4-triazol-5-ylthio)-2-nitrobenzene (**7a**) and 4.84 g (90.5 mmol) of NH_4Cl in 12 mL of H_2O and 70 mL of ethanol was added 3.77 g (67.5 mmol) of iron powder and the mixture was heated to reflux with vigorous stirring. The mixture was further refluxed for 3 h, cooled and neutralized with 28% NH_4OH. The solids were filtered off and washed with methanol. The combined filtrate and washings were evaporated *in vacuo*. The residue was purified by recrystallization from EtOAc-hexane to give 2.34 g (90%) of **8a** as a white solid.

mp 174-175 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 14.20 (br s, 1H), 8.33 (br s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 5.36 (br s, 2H). IR (KBr) 3432, 3312, 3100, 1610, 1478, 1442, 1260 cm^{-1}; Anal. Calcd for $C_8H_8N_4S$, C 50.0; H 4.19; N; 29.1. Found C 49.7; H 3.89; N 28.7.

2-(3-Phenyl-1*H*-1,2,4-triazol-5-ylthio)phenylamine (8b)

The compound (**8b**) as a white solid was prepared from 1-(3-phenyl-1*H*-1,2,4-triazol-5-ylthio)-2-nitrobenzene (**7b**) as for **8a** (93% yield); mp 175-176 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 14.10 (br s, 1H), 8.04-7.99 (m, 2H), 7.59-7.44 (m, 4H), 7.22 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 5.54 (br s, 2H). IR (KBr) 3472, 3352, 3056, 1612, 1478, 1442, 1324, 754, 726 cm^{-1}; Anal. Calcd for $C_{14}H_{12}N_4S$, C 62.7; H 4.51; N; 20.9. Found C 62.9; H 4.53; N 21.2.

2-[3-(4-Chlorophenyl)-1*H*-1,2,4-triazol-5-ylthio]phenylamine (8c)

The compound (**8c**) as a white solid was prepared from 1-[3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-ylthio]-2-nitrobenzene (**7c**) as for **8a** (73% yield); mp 158-160 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 14.50 (br s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.72-7.44 (m, 3H), 7.23 (t, J = 7.7 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 5.54 (br s, 2H). IR (KBr) 3432, 3368, 3194, 3016, 1608, 1482, 1442, 1320, 1272, 838 cm^{-1}; Anal. Calcd for $C_{14}H_{11}N_4ClS$, C 55.5; H 3.66; N; 18.5. Found C 55.0; H 3.74; N 18.1.

***N*-Benzoyl-*N'*-{2-[(1*H*-1,2,4-triazol-5-yl)sulfanyl]phenyl}thiourea (9a)**

To a stirred solution of 0.5 g (2.6 mmol) of 2-(1*H*-1,2,4-triazol-5-ylthio)phenylamine (**8a**) in 10 mL of acetone, 0.47 g (2.8 mmol) of benzoyl isothiocyanate was added dropwise and the mixture was heated to reflux for 1 h. The precipitates were collected by filtration and the crude product was recrystallized from

EtOAc-hexane to give 0.78 g (84%) of **9a** as a white solid.

mp 189-191 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 13.80 (br s, 1H), 12.61 (br s, 1H), 8.60 (br s, 1H), 8.06-7.41 (m, 10H). IR (KBr) 3380, 1680, 1532, 1260 cm^{-1}; Anal. Calcd for $C_{16}H_{13}N_5OS_2$, C 54.1; H 3.68; N; 19.7. Found C 54.0; H 3.75; N 19.3.

***N*-Benzoyl-*N'*-{2-[(3-phenyl-1*H*-1,2,4-triazol-5-yl)sulfanyl]phenyl}thiourea (9b)**

The compound (**9b**) as a white solid was prepared from 2-(3-phenyl-1*H*-1,2,4-triazol-5-ylthio)phenylamine (**8b**) as for **8a** (83% yield); mp 152-154 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 14.69 (br s, 1H), 12.67 (br s, 1H), 11.80 (br s, 1H), 8.07-7.40 (m, 14H). IR (KBr) 3382, 3088, 1680, 1532, 1488, 1150 cm^{-1}; Anal. Calcd for $C_{22}H_{17}N_5OS_2$, C 61.2; H 3.97; N; 16.2. Found C 61.2; H 3.94; N 16.4.

***N*-Benzoyl-*N'*-(2-{[3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl]sulfanyl}phenyl)thiourea (9c)**

The compound (**9c**) as a white solid was prepared from 2-[3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-ylthio]phenylamine (**8c**) as for **8a** (83% yield); mp 174-176 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 13.70 (br s, 1H), 12.85 (br s, 1H), 10.51 (br s, 1H), 8.19-7.47 (m, 14H). IR (KBr) 3290, 3008, 1684, 1578, 1542, 1260, 1156 cm^{-1}; Anal. Calcd for $C_{22}H_{16}N_5OClS_2$, C 56.7; H 3.46; N; 15.0. Found C 56.5; H 3.40; N 14.7.

***N*-{[2-(1*H*-1,2,4-Triazol-5-yl)sulfanyl]phenyl}thiourea (5a)**

0.60 g (1.69 mmol) of **9a** was saponified with 10 mL of boiling solution of 10% NaOH for 0.5 h. After cooling, the solution was acidified with conc. HCl to precipitate both benzoic acid and thiourea (**5a**), and then made alkaline with 28% NH_4OH to dissolve benzoic acid. Thiourea (**5a**) was filtered and recrystallized from EtOH (0.40 g, 94% yield).

mp 152-154 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 14.10 (br s, 1H, triazole NH), 9.39 (s, 1H), 8.22 (s, 1H), 7.61-7.57 (d, J = 7.7 Hz, 1H), 7.42-7.13 (m, 5H). IR (KBr) 3416, 3008, 1616, 1472, 1148 cm^{-1}; Anal. Calcd for $C_9H_9N_5S_2$, C 43.0; H 3.61; N; 27.8. Found C 42.8; H 3.64; N 27.5.

***N*-({2-[3-Phenyl-(1*H*-1,2,4-triazol-5-yl)]sulfanyl}phenyl)thiourea (5b)**

The compound (**5b**) as a white solid was prepared from *N*-benzoyl-*N'*-{2-[(3-phenyl-1*H*-1,2,4-triazol-5-yl)sulfanyl]phenyl}thiourea (**9b**) as for **5a** (83% yield); mp 139-141 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 14.66 (br s, 1H, triazole NH), 9.55 (br s, 1H), 7.97-7.93 (m, 2H), 7.61-7.26 (m, 7H). IR (KBr) 3422, 1618, 1510, 1260 cm^{-1}; Anal. Calcd for $C_{15}H_{13}N_5S_2$, C 55.0; H 4.00; N; 21.3. Found C 54.5; H 4.22; N 20.9.

***N*-(2-{[3-(4-Chlorophenyl)-1*H*-1,2,4-triazol-5-yl]sulfanyl}phenyl)thiourea (5c)**

The compound (**5c**) as a white solid was prepared from *N*-benzoyl-*N'*-(2-{[3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl]sulfanyl}phenyl)thiourea (**9c**) as for **5a** (83% yield); mp 147-149 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6) δ 14.10 (br s, 1H), 9.56 (s, 1H), 8.08 (d, J = 8.2 Hz, 2H), 7.70-7.32 (m, 8H). IR (KBr) 3290, 3164, 1608, 1490, 1256 cm^{-1}; Anal. Calcd for $C_{15}H_{12}N_5ClS_2$, C 49.8; H 3.34; N; 19.3. Found C 49.5;

H 3.83; N 19.0.

Benzo[*f*]1,2,4-triazolo[5,1-*b*]1,3,5-thiadiazepin-5-ylamine (10a)

A solution of 0.40 g (1.59 mmol) of *N*-{[2-(1*H*-1,2,4-triazol-5-yl)sulfanyl]phenyl}thiourea (**5a**) and 0.36 g (1.75 mmol) of DCC in 10 mL of acetonitrile was heated under reflux for 3 h. After completion of the reaction, the precipitated dicyclohexylthiourea was filtered off and the filtrate was evaporated *in vacuo*. The product was purified on a silica gel column (EtOAc:hexane = 4:1, R_f = 0.58) and recrystallized from dioxane solution to give 0.22 g (63%) of **10a** as a white solid.

mp 178-180 °C (dioxane); ^{1}H NMR (DMSO-d_6) δ 8.40 (s, 1H), 7.65-7.42 (m, 4H), 7.23-7.15 (m, 2H). IR (KBr) 3368, 3054, 1688, 1612, 1366, 1154 cm^{-1}; Anal. Calcd for $C_9H_7N_5S$, C 49.8; H 3.24; N; 32.2. Found C 50.1; H 3.64; N; 32.2.

2-Phenylbenzo[*f*]1,2,4-triazolo[5,1-*b*]1,3,5-thiadiazepin-5-ylamine (10b)

The compound (**10b**) as a white solid was prepared from *N*-({2-[3-phenyl-(1*H*-1,2,4-triazol-5-yl)]sulfanyl}phenyl)thiourea (**5b**) as for **10a** (EtOAc:hexane = 1:1, R_f = 0.59; 65% yield); mp 178-179 °C (dioxane); ^{1}H NMR ($CDCl_3$) δ 8.08 (br s, 2H), 7.43-7.11 (m, 7H), 5.62 (br s, 2H). IR (KBr) 3480, 3084, 1702, 1578, 1442, 724 cm^{-1}; Anal. Calcd for $C_{15}H_{11}N_5S$, C 61.4; H 3.78; N; 23.8. Found C 61.5; H 3.81; N 23.6.

2-(4-Chlorophenyl)benzo[*f*]1,2,4-triazolo[5,1-*b*]1,3,5-thiadiazepin-5-ylamine (10c)

The compound (**10c**) as a white solid was prepared from *N*-(2-{[3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl]sulfanyl}phenyl)thiourea (**5c**) as for **10a** (EtOAc:hexane = 1:2, R_f = 0.45, 64% yield); mp 192-193 °C (dioxane); ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.45-7.12 (m, 6H), 5.64 (br s, 2H). IR (KBr) 3476, 3108, 1704, 1470, 1398, 750 cm^{-1}; Anal. Calcd for $C_{15}H_{10}N_5ClS$, C 55.0; H 3.07; N; 21.3. Found C 54.6; H 3.12; N 21.4.

Crystal data: $C_{16}H_{12}N_5O_{0.5}ClS$ ($C_{15}H_{10}N_5ClS$ • 1/4 dioxane), monoclinic, $P2_1/n$ (no. 14), a=12.834(2), b=4.1345(5), c=30.477 Å, b=97.92°, V=1601.8(4) Å^3, Z=4, D_c=1.451 g/cm^3, F(000)=720, (MoK_a)=0.71073 Å. 1600 Independent reflections with I/σ(I)>2.0 are used on the analysis. R=0.0681. Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4 diffractometer using Mo radiation and ϖ-2 scans in the range of θ: 1.65<θ <24.95. Structure was solved by direct methods and refined by least squares using the SHEL-X.

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