Research Article **Open Access**

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Synthesis and spectral characteristics of *N*-(1-([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)carboxamides

https://doi.org/10.1515/hc-2019-0020
Received February 07, 2019; accepted June 04, 2019.

Abstract: Based on readily available *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides, *N*-(2,2,2-trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl)thioureido)ethyl) carboxamides, dehydrosulfurization–under the influence of excess HgO–led to the formation of *N*-(1-([1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)carboxamides. The reaction was carried out in boiling glacial acetic acid for 1-1.5 hours. The cyclization products were obtained in 42-62% yields and easily isolated from the reaction mixture. The structure of all synthesized compounds was confirmed by complex spectral studies.

Keywords: dehydrosulfurization; [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole; thioureas; *N*-amidoalkylated

Introduction

Heterocyclic systems containing a 1,3,4-thiadiazole or 1,2,4-triazole ring are of great importance for medical chemistry and the pharmaceutical industry [1-3]; they are widely used in agriculture [1,4] and in the production of polymers, semiconductors [1,5,6] and dyes [1,7-10].

Of particular interest are the [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazole derivatives, which are condensed heterocyclic systems containing both a 1,3,4-thiadiazole ring and a 1,2,4-triazole ring. A large number of studies are devoted to the antimicrobial activity of these compounds, including antibacterial [11-22], antifungal [16-21] and antitubercular [23,24] one. Among the derivatives of [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole, there are substances having an inhibitory effect on certain enzymes, for example, acetylcholinesterase [25] and protein tyrosine phosphatase 1B [26]. These compounds are very promising as antioxidants and cytotoxic agents [12,27-29]. The presence of activity against HIV-1 and HIV-2 [20,21], herpes viruses [30], JC and BK viruses [31] in these compounds is of particular note. In addition, the use of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives as ligands makes it possible to create a number of complexes of Terbium, Copper and Cadmium having luminescent activity [32,33].

In this article, we report the synthesis of a number of new [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing an alkylamide fragment, which in our view can enhance their biological activity.

Results and Discussion

Based on readily available *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides **1** [34], we obtained a series of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides**2**(Scheme1). As a result of the addition of 4-amino-4*H*-1,2,4-triazole-3-thiol **3** [35] to isothiocyanates **2** [36], *N*-amidoalkylated thioureas **4** were synthesized (Scheme 1). The addition reaction was carried out in acetonitrile, which greatly facilitated the isolation of products **4a-f** and allowed yields of 61-72% with sufficient purity for use in further conversions without further purification. Compounds **4** are promising polyfunctional reagents, and we successfully used them as starting reagents for the preparation of new [1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole derivatives.

Dehydrosulfurization of thiourea **4** was carried out by refluxing glacial acetic acid with 20% excess HgO (yellow) for 1-1.5 hours. During the reaction, the mixture acquired

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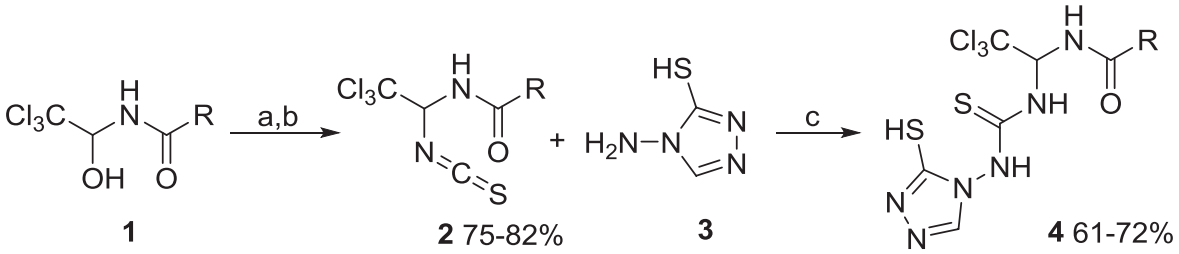
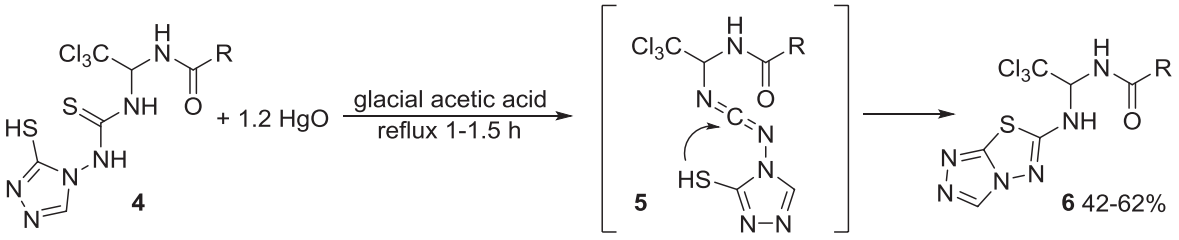


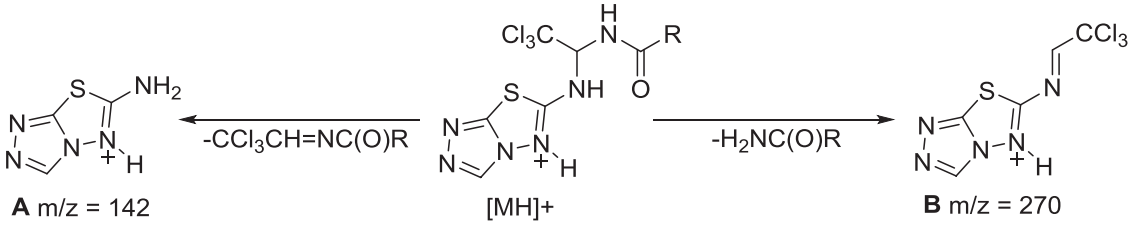
R = CH_3 (**a**); $CH{=}CH_2$ (**b**); C_6H_5 (**c**); 4-Me-C_6H_4 (**d**); 2,4-diCl-C_6H_3 (**e**); C_4H_3O (**f**).

Scheme 1 Synthesis of *N*-(2,2,2-trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl)thioureido)ethyl)carboxamides **4**. *Reagents and conditions*: a: $SOCl_2$, CCl_4, reflux, 1-1.2 h; b: KSCN, acetonitrile, stirring for 1.5-2 h; c: acetonitrile, reflux 5-7 min., r.t., 48 h.



R = CH_3 (**a**); $CH{=}CH_2$ (**b**); C_6H_5 (**c**); 4-Me-C_6H_4 (**d**); 2,4-diCl-C_6H_3 (**e**); C_4H_3O (**f**).

Scheme 2 Synthesis of *N*-(1-([1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)carboxamides **6**.



Scheme 3 Fragmentation of *N*-(1-([1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)carboxamides **6**.

a black color due to the formation of HgS. It was assumed that this reaction passed through the formation of a carbodiimide **5** intermediate (Scheme 2) [37]. *N*-Amidoalkylated derivatives of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-amine **6** were prepared in suitable yields and isolated, without special difficulty, from the reaction mixture.

We attempted to use dicyclohexylcarbodiimide as a dehydrosulfurization agent. The reaction was carried out in anhydrous 1,4-dioxane, but the dicyclohexylthiourea formed thereby greatly complicating the isolation and purification of the target products.

The structure of the compounds obtained was confirmed by complex spectral studies. In the ^{1}H NMR spectra of isothiocyanates **2**, the N–H and C–H signals of the protons appeared as doublets in the ranges 10.4-9.2 ppm and 6.7-6.5 ppm, respectively. The isothiocyanate group in the IR spectra of compounds **2** appeared as an intense absorption band at 2060-2035 cm^{-1}, and the carbon signal of this group in the ^{13}C NMR spectra appeared at 140 ppm.

In the ^{1}H NMR spectra of compounds **6**, there were no signals of isolated S–H and N–H protons, characteristic for the starting thioureas **4**, which appeared as singlets in the range 13.9-13.8 ppm and 11.5-11.0 ppm, respectively. In the ^{13}C NMR spectra of compounds **4**, a carbon signal C=S was observed at 185 ppm, which was absent in the spectra of compounds **6**. At the same time, in the ^{13}C NMR spectra of compounds **6**, there were carbon signals of three imino groups located in the range 135-166 ppm. While there were only two signals for compounds **4** in this range.

In the mass spectra of all compounds **6**, the molecular ion appeared in the protonated form $[M+H]^+$ (Scheme 3).

Protonation was also characteristic for certain fragment ions. The decomposition of compounds **6** took place in two ways: in the first case, the elimination of *N*-(2,2,2-trichloroethylidene)carboxamide with the formation of the ion **A** (m/z = 142) was observed, and in the second case, the elimination of the carboxylic acid amide was observed, forming fragmental ion **B** (m/z = 270).

The spectral data confirmed the occurance of the dehydrosulfurization process followed by heterocyclization to the mercapto group and excluded any transformation involving the amide fragment, as in [38,39].

Conclusion

By a chain of simple transformations, we synthesized a number of new [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-6-amine derivatives **6**. Initially, based on *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides **1**, *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides **2** were prepared. As a result of the addition of 4-amino-4*H*-1,2,4-triazole-3-thiol **3** to isothiocyanates **2**, *N*-amidoalkylated thioureas **4** were synthesized. Dehydrosulfurization of the latter, under the influence of excess HgO, resulted in the formation of compounds **6**. The cyclization products were obtained with acceptable yields and were isolated without special difficulty from the reaction mixture.

Experimental

Melting points were determined in open capillaries and are not corrected. IR spectra were recorded in KBr tablets using the device Spectrum BX II. The mass spectra of FAB were recorded on the device VG7070, desorption of ions from solution samples in *meta*-nitrobenzyl alcohol were conducted by beam of argon atoms with 8 keV energy. ^{1}H NMR and ^{13}C spectra were measured on spectrometer Varian VXR-400 (standard TMS). Chemical shifts (δ) are given in ppm downfield. The constants value of the spin-spin interaction (J) is given in Hz. Elemental analysis was performed on a LECO CHNS-900 instrument. The monitoring of the reaction progress and identity of the compounds obtained has been performed by TLC (Silufol UV-254, eluent – chloroform: acetone – 3:1).

The starting *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides **1a-f** were obtained according to the procedure described in [34]. The spectral characteristics for compounds **1a-e** are described in [34], and for compound **1f**, they are listed below and are described for the first time.

N-(2,2,2-trichloro-1-hydroxyethyl)furan-2-carboxamide (1f) [40]

Cream colored crystals; yield 84%; m.p. 153-155 °C; R_f = 0.36. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (d, J = 8.3 Hz, 1H, OH), 7.90-7.87 (m, 2H, $H_{arom.}$ + NH), 7.45 (br. s, 1H, $H_{arom.}$), 6.66 (br. s, 1H, $H_{arom.}$), 5.93 (dd, J = 8.3, 5.9 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2 (C=O), 137.8, 132.6, 127.3, 118.8 (arom.), 102.24 (CCl_3), 80.8 (CH); IR (KBr) (ν cm^{-1}): 3316 (OH), 3162, 3140 (NH), 2957, 2878, 2733, (CH), 1651 (C=O), 1572, 1527, 1471, 1348, 1293, 1149, 1196,1083, 1015, 940, 800, 752, 625, 599, 461; FAB-MS: *m/z* 258 $[M+H]^+$. Anal. Calcd (%) for $C_7H_6Cl_3NO_3$ (258.48): C, 32.53; H, 2.34; Cl, 41.14; N, 5.42. Found: C, 32.50; H, 2.32; Cl, 41.17; N, 5.45.

General procedure for the synthesis of isothiocyanates (2a-e)

12 mmol (0.9 mL) of thionyl chloride was added to the suspension of 10 mmol *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides (**1**) [34] in 30-35 mL of CCl_4. The mixture was refluxed for 1-1.2 hours. After completion of the reaction, the still-warm solution was filtered, and the filtrate was evaporated on a rotary evaporator. The residue after evaporation was treated with hexane (2×10 mL), filtered and dissolved in 30-35 mL of anhydrous acetonitrile. 10 mmol (0.97 g) of carefully dried KSCN was added in portions to the resulting solution. The reaction mixture was stirred for 1.5-2 hours. The precipitated KCl was filtered off, the filtrate was evaporated on a rotary evaporator without raising the heating temperature above 55-60 °C. The residue after evaporation was treated with water (3×50 mL), filtered and dried at room temperature for 48 hours. The product was recrystallized from acetonitrile. The yields are given on a crystallized product. Compounds **2a**, **2c** and **2d** were obtained previously. Compounds **2b, 2e** and **2f** were obtained for the first time.

N-(2,2,2-Trichloro-1-isothiocyanatoethyl)acetamide (2a) [41]

Light yellow solid; yield 82% (2.03 g); m.p. 93-95 °C; R_f = 0.71. Anal. Calcd (%) for $C_5H_5Cl_3N_2OS$ (247.52): C, 24.26; H, 2.04; Cl, 42.97; N, 11.32; S, 12.95. Found: C, 24.23; H, 2.06; Cl, 42.95; N, 11.36; S, 12.98.

N-(2,2,2-Trichloro-1-isothiocyanatoethyl)acrylamide (2b)

Light yellow solid; yield 78% (4.87 g); m.p. 125-127 °C; R_f = 0.88. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.80 (d, J = 8.8 Hz,

1H, NH), 6.56 (d, *J* = 8.8 Hz, 1H, CH), 6.45 (dd, *J* = 9.8, 17.1 Hz, 1H, CH=CH_2), 6.31 (d, *J* = 17.1 Hz, 1H, =CH_2-*trans*), 5.85 (d, *J* = 9.8 Hz, 1H, =CH_2-*cis*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.4 (C=O), 140.3 (-N=C=S), 129.4 (CH=CH_2), 129.2 (CH=CH_2), 98.9 (CCl_3), 72.5 (CH); IR (KBr) (ν cm^{-1}): 3227, 3192 (NH), 3017, 2933, 2742 (CH), 2057 (-N=C=S), 1667 (C=O), 1636, 1533, 1409, 1313, 1220, 1130, 1073, 982, 799, 758, 615, 547; FAB-MS: *m/z* 259 $[M+H]^+$. Anal. Calcd (%) for $C_6H_5Cl_3N_2OS$ (259.53): C, 27.77; H, 1.94; Cl, 40.98; N, 10.79; S, 12.35. Found: C, 27.75; H, 1.96; Cl, 41.01; N, 10.81; S, 12.34.

N-(2,2,2-Trichloro-1-isothiocyanatoethyl)benzamide (2c) [42]

Light yellow solid; yield 75% (2.32 g); m.p. 152-154 °C; R_f = 0.83. Anal. Calcd (%) for $C_{10}H_7Cl_3N_2OS$ (309.59): C, 38.80; H, 2.28; Cl, 34.35; N, 9.05; S, 10.36. Found: C, 38.78; H, 2.26; Cl, 34.38; N, 9.09; S, 10.38.

4-Methyl-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl) benzamide (2d) [42]

Light yellow solid; yield 80% (3.03 g); m.p. 119-121 °C; R_f = 0.89. Anal. Calcd (%) for $C_{11}H_9Cl_3N_2OS$ (323.62): C, 40.83; H, 2.80; Cl, 32.86; N, 8.66; S, 9.91. Found: C, 40.79; H, 2.78; Cl, 32.89; N, 8.70; S, 9.93.

2,4-Dichloro-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl) benzamide (2e)

Light yellow crystals; yield 78% (2.95 g); mp. 113-115 °C (MeCN); R_f = 0.72. ^{1}H NMR: δ 10.39 (d, *J* = 8.8 Hz, 1H, NH), 7.76 (s, 1H, $H_{arom.}$), 7.57-7.55 (m, 1H, $H_{arom.}$), 7.50-7.48 (m, 1H, $H_{arom.}$), 6.68 (d, *J* = 8.8 Hz, 1H, CH). ^{13}C NMR: δ 165.6 (C=O), 140.7 (-N=C=S), 135.4, 133.5, 131.2, 130.3, 129.2, 127.3, (arom.), 98.8 (CCl_3), 72.4 (CH). IR: ν_{max} 3226, 3188 (NH), 3024, 2927, 2852 (CH), 2033 (-N=C=S), 1667 (C=O), 1591, 1533, 1283, 1220, 1163, 1129, 1001, 813, 795, 624, 509 cm^{-1}. MS (FAB): m/z 377 $[M+H]^+$. Anal. Calcd (%) for $C_{10}H_5Cl_5N_2OS$ (378.47): C, 31.74; H, 1.33; Cl, 46.83; N, 7.40; S, 8.47. Found: C, 31.71; H, 1.35; Cl, 46.87; N, 7.44; S, 8.51.

N-(2,2,2-trichloro-1-isothiocyanatoethyl)furan-2-carboxamide (2f)

Yellow crystals; yield 75% (2.25 g); mp. 165-167 °C (EtOH); R_f = 0.63. ^{1}H NMR: δ 9.24 (d, *J* = 8.8 Hz, 1H, NH), 8.52-8.50 (m, 1H, $H_{arom.}$), 7.79 (br. s, 1H, $H_{arom.}$), 7.29-7.28 (m, 1H, $H_{arom.}$), 6.72 (br. s, 1H, CH). ^{13}C NMR: δ 166.2 (C=O), 142.8 (-N=C=S), 137.6, 129.3, 127.4, 111.4 (arom.), 95.4 (CCl_3), 79.4 (CH). IR: ν_{max} 3354, 3321 (NH), 2990, 2961 (CH), 2055 (-N=C=S), 1668 (C=O), 1572, 1533, 1495, 1355, 1288, 1209, 1135, 1014, 945, 800, 757, 662, 547 cm^{-1}. MS (FAB): m/z 299 $[M+H]^+$. Anal. Calcd (%) for $C_8H_5Cl_3N_2O_2S$ (299.55): C, 32.08; H, 1.68; Cl, 35.50; N, 9.35; S, 10.70. Found: C, 32.05; H, 1.66; Cl, 35.54; N, 9.37; S, 10.73.

General procedure for the synthesis of thioureas (4a-f)

10 mmol (1.16 g) of 4-amino-4*H*-1,2,4-triazole-3-thiol **3** [35] dissolved in 15-18 mL of acetonitrile were added to 10 mmol of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamide **2** dissolved in 10-12 mL of acetonitrile. The mixture was refluxed for 5-7 minutes, filtered and left for 48 hours at room temperature. The precipitate formed was filtered and washed with acetonitrile 2×5 mL. The product was first dried at room temperature for 24 hours, and then, at 100-110 °C - for an additional 3 hours. The resulting crude product is suitable for use in further conversions without further purification. Analytical samples were purified by recrystallization from acetonitrile. The yields are given on a crystallized product.

N-(2,2,2-Trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl) thioureido)ethyl)acetamide (4a)

Light yellow solid; yield 67% (2.44 g); m.p. 147-149 °C; R_f = 0.32. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.82 (s, 1H, SH), 11.01 (s, 1H, NH), 8.98 (br. s, 1H, NH), 8.84 (br. s, 1H, NH), 8.58 (s, 1H, -N=CH-N=), 7.20 (dd, *J* = 9.3, 8.8 Hz, 1H, CH), 1.95 (s, 1H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.0 (C=S), 168.9 (C=O), 166.3 (C=N), 141.9 (C=N), 101.0 (CCl_3), 69.9 (CH), 22.5 (CH_3). IR (KBr) (ν cm^{-1}): 3592 (SH), 3470, 3418, 3256, 3206 (NH), 3095, 3006, 2928, 2852, 2791 (CH), 1650 (C=O), 1590, 1562, 1489, 1420, 1309, 1221, 1110, 1043, 918, 869, 820, 798, 721, 662, 559; FAB-MS: *m/z* 363 $[M+H]^+$. Anal. Calcd (%) for $C_7H_9Cl_3N_6OS_2$ (363.66): C, 23.12; H, 2.49; Cl, 29.24; N, 23.11; S, 17.63. Found: C, 23.09; H, 2.47; Cl, 29.27; N, 23.15; S, 17.65.

N-(2,2,2-Trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl) thioureido)ethyl)acrylamide (4b)

Light yellow solid; yield 64% (2.40 g); m.p. 165-167 °C; R_f = 0.29. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.81 (s, 1H, SH), 11.00 (s, 1H, NH), 9.13 (br. s, 1H, NH), 8.86 (br. s, 1H, NH), 8.59 (s, 1H, -N=CH-N=), 7.30 (dd, *J* = 8.8, 8.3 Hz, 1H, CH), 6.40 (dd, *J* = 16.6, 9.8 Hz, 1H, CH=CH_2), 6.23 (d, *J* = 16.6 Hz,

1H, $=CH_2$-*trans*), 5.77 (d, *J* = 9.8 Hz, 1H, $=CH_2$-*cis*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.0 (C=S), 166.3 (C=O), 163.8 (C=N), 143.3 (C=N), 130.2 (-CH=CH_2), 128.0 (-CH=CH_2), 100.8 (CCl_3), 70.1 (CH); IR (KBr) (*v* cm^{-1}): 3282 (SH), 3243, 3160, 3126, (NH), 3092, 2993, 2953, 2931, 2876, 2834, 2792 (CH), 1671 (C=O), 1637, 1552, 1503, 1482, 1414, 1323, 1302, 1215, 1120, 994, 929, 843, 797, 722, 683, 662, 549; FAB-MS: *m/z* 375 $[M+H]^+$. Anal. Calcd (%) for $C_8H_9Cl_3N_6OS_2$ (375.67): C, 25.58; H, 2.41; Cl, 28.31; N, 22.37; S, 17.07. Found: C, 25.54; H, 2.39; Cl, 28.36; N, 22.40; S, 17.10.

N-(2,2,2-Trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl) thioureido)ethyl)benzamide (4c)

Light yellow solid; yield 61% (2.60 g); m.p. 158-160 °C; R_f = 0.45. ^1H NMR (400 MHz, DMSO-d_6): δ 13.87 (s, 1H, SH), 11.43 (s, 1H, NH), 9.39 (br. s, 1H, NH), 8.64 (m, 2H, NH+-N=CH-N=), 7.88-7.87 (m, 2H, $H_{arom.}$), 7.63-7.47 (m, 4H, $3H_{arom.}$+CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.0 (C=S), 166.5 (C=O), 165.7 (C=N), 143.2 (C=N), 133.0, 132.1, 128.5, 127.5 (arom.), 101.3 (CCl_3), 70.5 (CH); IR (KBr) (*v* cm^{-1}): 3252 (SH), 3090 (NH), 2925, 2854 (CH), 1673 (C=O), 1646, 1506, 1485, 1323, 1224, 1141, 1116, 1027, 924, 798, 710, 685, 561; FAB-MS: *m/z* 425 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_{11}Cl_3N_6OS_2$ (425.73): C, 33.86; H, 2.60; Cl, 24.98; N, 19.74; S, 15.06. Found: C, 33.84; H, 2.58; Cl, 25.01; N, 19.77; S, 15.09.

4-Methyl-*N*-(2,2,2-trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl)thioureido)ethyl)benzamide (4d)

Light yellow solid; yield 72% (3.17 g); m.p. 198-200 °C; R_f = 0.34. ^1H NMR (400 MHz, DMSO-d_6): δ 13.87 (s, 1H, SH), 11.48 (s, 1H, NH), 9.29 (br. s, 1H, NH), 8.63 (m, 2H, NH+-N=CH-N=), 7.80-7.78 (m, 2H, $H_{arom.}$), 7.48 (dd, *J* = 8.8, 8.8 Hz, 1H, CH), 7.35-7.33 (m, 2H, $H_{arom.}$), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.0 (C=S), 166.5 (C=O), 165.5 (C=N), 143.1 (C=N), 142.3, 130.1, 129.0, 127.5 (arom.), 101.4 (CCl_3), 70.5 (CH), 21.1 (CH_3). IR (KBr) (*v* cm^{-1}): 3288 (SH), 3169, 3114, 3071 (NH), 3004, 2944, 2853, 2775, 2616 (CH), 1644 (C=O), 1610, 1546, 1495, 1479, 1419, 1309, 1149, 1032, 925, 797, 754, 661, 565; FAB-MS: *m/z* 439 $[M+H]^+$. Anal. Calcd (%) for $C_{13}H_{13}Cl_3N_6OS_2$ (439.76): C, 35.51; H, 2.98; Cl, 24.18; N, 19.11; S, 14.58. Found: C, 35.48; H, 2.95; Cl, 24.21; N, 19.15; S, 14.61.

2,4-Dichloro-*N*-(2,2,2-trichloro-1-(3-(3-mercapto-4*H*-1,2,4-triazol-4-yl)thioureido)ethyl)benzamide (4e)

Light yellow solid; yield 71% (3.51 g); m.p. 162-164 °C; R_f = 0.37. ^1H NMR (400 MHz, DMSO-d_6): δ 13.86 (s, 1H, SH), 11.09 (s, 1H, NH), 9.73 (br. s, 1H, NH), 8.90 (br. s, 1H, NH), 8.63 (s, 1H, -N=CH-N=), 7.74 (s, 1H, $H_{arom.}$), 7.56-7.54 (m, 1H, $H_{arom.}$), 7.47-7.45 (m, 1H, $H_{arom.}$), 7.34 (dd, *J* = 8.8, 9.3 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.2 (C=S), 166.4 (C=O), 164.8 (C=N), 143.2 (C=N), 135.2, 134.1, 131.4, 130.3, 129.3, 127.3 (arom.), 100.5 (CCl_3), 70.4 (CH). IR (KBr) (*v* cm^{-1}): 3545 (SH), 3345, 3213, 3150 (NH), 3080, 3010, 2947, 2866, 2642 (CH), 1679 (C=O), 1539, 1497, 1319, 1218, 1124, 936, 805, 761, 735, 552; FAB-MS: *m/z* 493 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_9Cl_5N_6OS_2$ (494.62): C, 29.14; H, 1.83; Cl, 35.84; N, 16.99; S, 12.96. Found: C, 29.11; H, 1.80; Cl, 35.87; N, 17.04; S, 12.98.

N-(2,2,2-trichloro-1-(3-(3-mercapto-4H-1,2,4-triazol-4-yl) thioureido)ethyl)furan-2-carboxamide (4f)

Yellow solid; yield 67% (2.79 g); m.p. 178-180 °C; R_f = 0.35. ^1H NMR (400 MHz, DMSO-d_6): δ 13.86 (s, 1H, SH), 11.44 (s, 1H, NH), 9.39 (br. s, 1H, NH), 8.64-8.44 (m, 3H, -N=CH-N= + NH + $H_{arom.}$), 8.03 (brs, 1H, $H_{arom.}$), 7.39-7.37 (m, 1H, $H_{arom.}$), 7.03 (dd, *J* = 8.8, 6.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 184.6 (C=S), 164.6 (C=O), 152.4 (C=N), 146.1 (C=N), 136.7, 131.9, 129.5, 112.18 (arom.), 101.6 (CCl_3), 70.2 (CH). IR (KBr) (*v* cm^{-1}): 3458 (SH), 3315, 3270, 3086 (NH), 3000, 2979, 2811 (CH), 1665 (C=O), 1531, 1475, 1333, 1136, 1013, 934, 702, 628, 483; FAB-MS: *m/z* 415 $[M+H]^+$. Anal. Calcd (%) for $C_{10}H_9Cl_3N_6O_2S_2$ (415.69): C, 28.89; H, 2.18; Cl, 25.58; N, 20.22; S, 15.42. Found: C, 28.86; H, 2.16; Cl, 25.61; N, 20.24; S, 15.45.

General procedure for the synthesis of [1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-6-amine derivatives (6a-f)

A mixture of 10 mmol of thiourea **4**, 12 mmol (2.60 g) of HgO (yellow) and 10-12 mL of glacial acetic acid was boiled under reflux for 1-1.5 hours. The reaction mixture was cooled to room temperature and filtered twice from the resulting HgS. 15-18 mL of H_2O was added to the filtrate. The precipitate formed was filtered and treated with a 10% Na_2CO_3 solution of 2×15 mL, and then washed with 15-20 mL of water. The resulting product was dried at room temperature for 48 hours and then purified by recrystallization from ethanol. The yields are given on a crystallized product.

N-(1-([1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)acetamide (6a)

White solid; yield 58% (1.91 g); m.p. 178-180 °C; R_f = 0.31. ^1H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 1H, NH), 9.13 (br.

s, 1H, NH), 9.04 (s, 1H, -N=CH-N=), 6.57 (d, *J* = 8.8 Hz, 1H, CH), 1.98 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 169.5 (C=O), 163.6, 150.1, 135.4 (C=N), 100.2 (CCl_3), 69.0 (CH), 22.3 (CH_3). IR (KBr) (*ν* cm^{-1}): 3253, 3232, 3088 (NH), 2998, 2929, 2855, 2795 (CH), 1673 (C=O), 1584, 1514, 1491, 1371, 1238, 1113, 1040, 976, 821, 801, 620, 506; FAB-MS: *m/z* 329 $[M+H]^+$. Anal. Calcd (%) for $C_7H_7Cl_3N_6OS$ (329.58): C, 25.51; H, 2.14; Cl, 32.27; N, 25.50; S, 9.73. Found: C, 25.48; H, 2.12; Cl, 32.31; N, 25.53; S, 9.76.

N-(1-([1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)acrylamide (6b)

White solid; yield 55% (1.88 g); m.p. 184-186 °C; R_f = 0.27. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 9.35 (d, *J* = 8.8 Hz, 1H, NH), 9.27 (br. s, 1H, NH), 9.22 (s, 1H, -N=CH-N=), 6.66 (br.s, 1H, CH), 6.48 (dd, *J* = 16.8, 10.3 Hz, 1H, CH=CH_2), 6.25 (d, *J* = 16.8 Hz, 1H, =CH_2-*trans*), 5.77 (d, *J* = 10.3 Hz, 1H, =CH_2-*cis*); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 164.4 (C=O), 163.5, 150.1, 135.4 (C=N), 129.9 (CH=CH_2), 128.3 (CH=CH_2), 100.0 (CCl_3), 69.2 (CH). IR (KBr) (*ν* cm^{-1}): 3251, 3090 (NH), 2998, 2928, 2852 (CH), 1674 (C=O), 1639, 1582, 1511, 1490, 1410, 1323, 1248, 1224, 1106, 976, 958, 823, 799, 735, 679, 628, 565; FAB-MS: *m/z* 341 $[M+H]^+$. Anal. Calcd (%) for $C_8H_7Cl_3N_6OS$ (341.60): C, 28.13; H, 2.07; Cl, 31.13; N, 24.60; S, 9.39. Found: C, 28.10; H, 2.09; Cl, 31.15; N, 24.62; S, 9.42.

N-(1-([1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)benzamide (6c)

White solid; yield 42% (1.65 g); m.p. 160-162 °C; R_f = 0.29. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 9.38 (d, *J* = 8.6 Hz, 1H, NH), 9.01 (br. s, 1H, NH), 8.99 (s, 1H, -N=CH-N=), 7.92-7.90 (m, 2H, $H_{arom.}$), 7.54-7.50 (m, 1H, $H_{arom.}$), 7.46-7.42 (m, 2H, $H_{arom.}$), 6.83 (dd, *J* = 8.6, 8.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 166.2 (C=O), 163.3, 150.1, 134.8 (C=N), 133.0, 131.4, 127.8, 127.7 (arom.), 100.4 (CCl_3), 69.6 (CH). IR (KBr) (*ν* cm^{-1}): 3329, 3224, 3186, 3096 (NH), 2946, 2929, 2851 (CH), 1672 (C=O), 1584, 1491, 1327, 1236, 1118, 1077, 962, 870, 796, 694, 611, 543; FAB-MS: *m/z* 391 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_9Cl_3N_6OS$ (391.66): C, 36.80; H, 2.32; Cl, 27.15; N, 21.46; S, 8.19. Found: C, 36.78; H, 2.30; Cl, 27.18; N, 21.49; S, 8.21.

N-(1-([1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)-4-methylbenzamide (6d)

White solid; yield 62% (2.52 g); m.p. 141-143 °C; R_f = 0.28. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 9.15 (br. s, 1H, NH), 8.68 (br. s, 1H, -N=CH-N=), 7.81-7.79 (m, 2H, $H_{arom.}$), 7.61 (br. s, 1H, NH), 7.36-7.34 (m, 2H, $H_{arom.}$), 6.68 (dd, *J* = 8.8, 8.8 Hz, 1H, CH), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 166.5 (C=O), 163.6, 150.2, 142.1 (C=N), 135.4, 130.1, 128.7, 127.9 (arom.), 100.3 (CCl_3), 69.7 (CH), 21.0 (CH_3). IR (KBr) (*ν* cm^{-1}): 3255, 3154 (NH), 2995, 2925, 2855 (CH), 1670 (C=O), 1575, 1486, 3123, 1239, 1142, 1097, 1039, 802, 749, 638, 547; FAB-MS: *m/z* 405 $[M+H]^+$. Anal. Calcd (%) for $C_{13}H_{11}Cl_3N_6OS$ (405.68): C, 38.49; H, 2.73; Cl, 26.22; N, 20.72; S, 7.90. Found: C, 38.47; H, 2.75; Cl, 26.25; N, 20.71; S, 7.92.

N-(1-([1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)-2,4-dichlorobenzamide (6e)

White solid; yield 61% (2.81 g); m.p. 121-123 °C; R_f = 0.23. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 9.92 (d, *J* = 8.8 Hz, 1H, NH), 9.33 (d, *J* = 8.8 Hz, 1H, NH), 9.26 (s, 1H, -N=CH-N=), 7.73 (s, 1H, $H_{arom.}$), 7.53-7.52 (m, 1H, $H_{arom.}$), 7.46-7.43 (m, 1H, $H_{arom.}$), 6.68 (dd, *J* = 8.8, 8.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 165.7 (C=O), 163.5, 150.2, 135.5 (C=N), 135.0, 134.3, 131.2, 130.3, 129.1, 127.2 (arom.), 99.7 (CCl_3), 69.5 (CH). IR (KBr) (*ν* cm^{-1}): 3285, 3241, 3078 (NH), 3008, 2944, 2855 (CH), 1660 (C=O), 1590, 1505, 1482, 1299, 1247, 1136, 1106, 822, 804, 733, 664; FAB-MS: *m/z* 459 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_7Cl_5N_6OS$ (460.54): C, 31.30; H, 1.53; Cl, 38.49; N, 18.25; S, 6.96. Found: C, 31.27; H, 1.51; Cl, 38.52; N, 18.28; S, 6.99.

N-(1-([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylamino)-2,2,2-trichloroethyl)furan-2-carboxamide (6f)

White solid; yield 44% (1.68 g); m.p. 168-170 °C; R_f = 0.30. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 9.63 (d, *J* = 8.6 Hz, 1H, NH), 9.13 (d, *J* = 5.8 Hz, 1H, NH), 9.03 (s, 1H, -N=CH-N=), 7.79 (br. s, 1H, $H_{arom.}$), 7.46-7.43 (m, 1H, $H_{arom.}$), 6.72 (br. s, 1H, $H_{arom.}$), 6.11 (dd, *J* = 8.6, 5.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 166.4 (C=O), 156.4, 148.1, 138.2 (C=N), 134.2, 132.5, 127.2, 118.8 (arom.), 103.8 (CCl_3), 73.0 (CH). IR (KBr) (*ν* cm^{-1}): 3329, 3277, 3112 (NH), 3062, 2950 (CH), 1667 (C=O), 1601, 1501, 1483, 1320, 1214, 1139, 1015, 925, 822, 795, 678, 517; FAB-MS: *m/z* 381 $[M+H]^+$. Anal. Calcd (%) for $C_{10}H_7Cl_3N_6O_2S$ (381.62): C, 31.47; H, 1.85; Cl, 27.87; N, 22.02; S, 8.40. Found: C, 31.45; H, 1.86; Cl, 27.90; N, 22.06; S, 8.43.

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