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Synthesis of 2-amino-5-mercapto-1,3,4-thiadiazole derivatives

Abstract: 2-Amino-5-mercapto-1,3,4-thiadiazole (AMT) was used to synthesize 24 new compounds. The structures were confirmed by ^{1}H NMR and ^{13}C NMR.

Keywords: 2-amino-5-mercapto-1,3,4-thiadiazole; chloroacetyl chloride; heterocyclic.

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Introduction

Recent drug studies are highly focused on heterocyclic ring systems. Thiadiazoles are one of the privileged structural fragments. Fused systems containing the thiadiazole ring give rise to compounds with varied bioactivities, such as anticancer [1], antimicrobial [2, 3], and antiviral [4] properties. Currently, compounds **A** [5] and **B** [6, 7] (Figure 1) are in clinical trials, and several other 1,3,4-thiadiazole derivatives including **C** [8, 9], **D** [10], and the parent compound 2-amino-5-mercapto-1,3,4-thiadiazole (AMT) [11–15] display a variety of biological activities. Several synthetic strategies to AMT have been reported [16]. The easy accessibility of AMT prompted us to prepare a new series of 2-amino-5-mercapto-1,3,4-thiadiazole derivatives.

Results and discussion

First, the Michael addition reaction of AMT with α,β-unsaturated compounds was studied. With acrylonitrile as the substrate, the products **1a** and **2a** were obtained in the respective yields of 47% and 49% under optimal conditions. This reaction was studied using EtOH, acetone, DMSO, water, and MeOH. The results indicated that MeOH is the optimal solvent. The reaction hardly proceeded in the remaining solvents. The highest yields of **1a** and **2a** were obtained in the presence of triethylamine, lower yields were obtained in the presence of EtONa, and no products were detected in the attempted reactions in the presence of NaOH or $NaHCO_3$. Products **1b,c** and **2b,c** were prepared in a similar manner by subjecting AMT to the Michael addition with methyl acrylate and butyl acrylate (Scheme 1).

Then, our attention focused on the acylation reaction of **1a–c** and **2a–c** with chloroacetyl chloride, which yielded the respective derivatives **3a–c** and **4a–c**. These products were cyclized to two different rings by the reaction with potassium isothiocyanate. The imidazole derivatives **5a–c** and **7a–c** are formed in the reaction with KSCN conducted in acetonitrile, and the thiazole derivatives **6a–c** and **8a–c** are obtained in DMF at 80°C. A unified mechanism that accounts for these two different outcomes is proposed in Scheme 2.

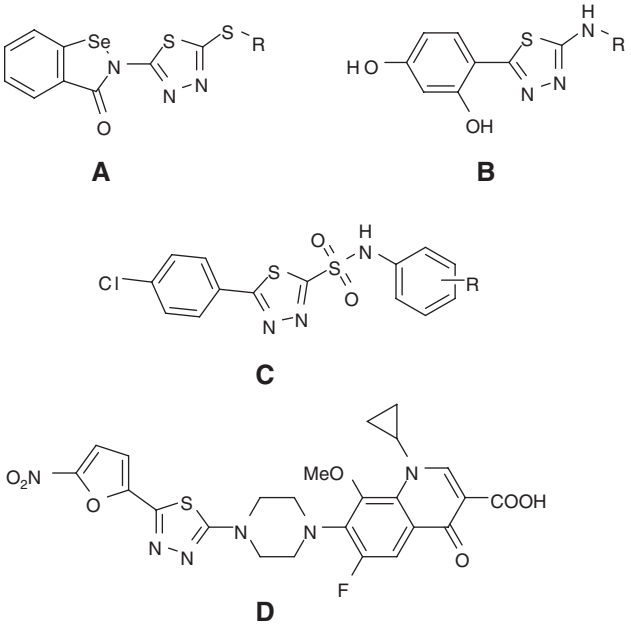
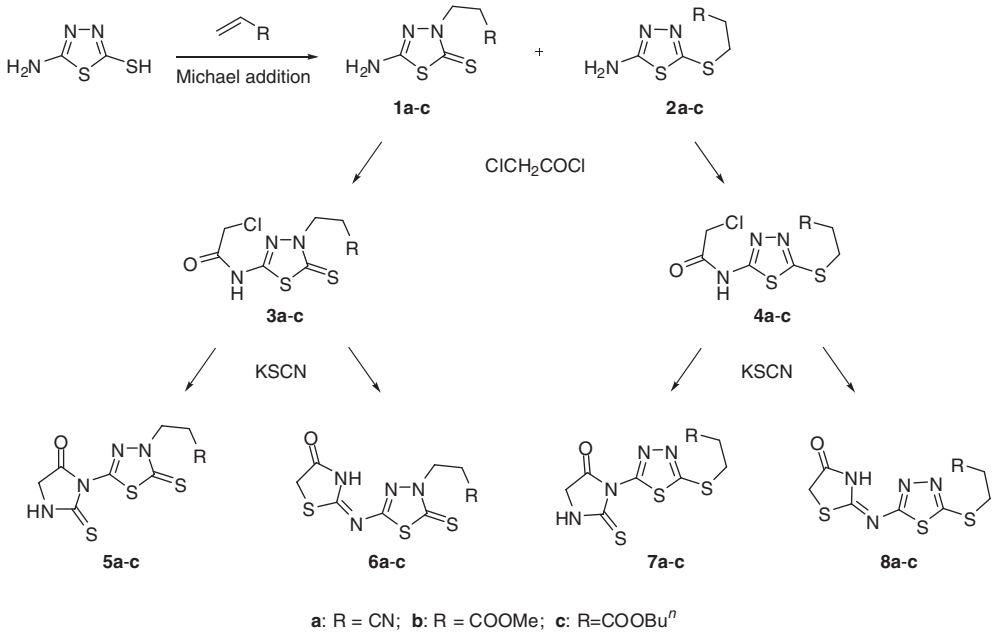
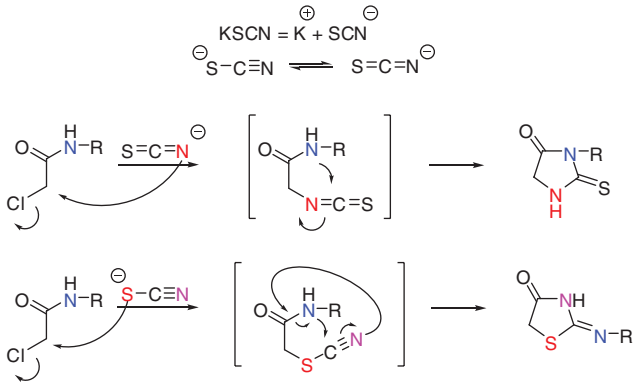


Figure 1 Selected biologically active 1,3,4-thiadiazole derivatives.



Scheme 1



Scheme 2

Experimental

General

Melting points were determined on a Perkin-Elmer differential scanning calorimeter and are uncorrected. The IR spectra were run on a Nicolete spectrometer using KBr pellets. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Varian Mercury plus-400 instrument.

General procedure for synthesis of compounds 1a–c and 2a–c

Triethylamine (0.6 mL, 0.86 mmol) was slowly added to a solution of AMT (0.66 g, 5 mmol), acrylonitrile, methyl acrylate or butyl acrylate (2 mmol) in CH_3OH (50 mL) under nitrogen, and the mixture was heated under reflux for 4–8 h. After cooling, the mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with dichloromethane/methanol (95:5) to give starting AMT followed by the products **1a–c** and **2a–c**.

3-(5-Amino-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl)propanenitrile (1a) Yield 47%; mp 103–105°C; IR (cm^{-1}): 3415, 3284, 2173, 1619, 1553, 1182, 1066; ^{1}H NMR ($CDCl_3$): δ 3.04 (t, *J* = 7 Hz, 2H), 4.41 (t, *J* = 7 Hz, 2H), 6.68 (s, 2H). Anal. Calcd for $C_5H_6N_4S_2$: C, 32.24; H, 3.25; N, 30.08; S, 34.43. Found: C, 32.22; H, 3.26; N, 30.07; S, 34.45.

Methyl 3-(5-amino-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl)propanoate (1b) Yield 29%; mp 119–121°C; IR (cm^{-1}): 3416, 3285, 2924, 1718, 1620, 1556, 1213, 1068; ^{1}H NMR ($CDCl_3$): δ 2.82 (t, *J* = 7 Hz, 2H), 3.64 (s, 3H), 4.36 (t, *J* = 7 Hz, 2H), 6.60 (s, 2H). Anal. Calcd for $C_6H_9N_3O_2S_2$: C, 32.86; H, 4.14; N, 19.16; O, 14.59; S, 29.25. Found: C, 32.88; H, 4.13; N, 19.18; O, 14.57; S, 29.23.

Butyl 3-(5-amino-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl)propanoate (1c) Yield 17%; red brown foam; IR (cm^{-1}): 3315, 3191, 2959, 1724, 1559, 1256, 1184, 1068; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 8 Hz, 3H), 1.41 (m, *J* = 8 Hz, 2H), 1.61 (m, *J* = 8 Hz, 2H), 2.83 (t, *J* = 8 Hz, 2H), 4.07 (t, *J* = 8 Hz, 2H), 4.37 (t, *J* = 8 Hz, 2H), 6.55 (s, 2H). Anal. Calcd for $C_9H_{15}N_3O_2S_2$: C, 41.36; H, 5.78; N, 16.08; O, 12.24; S, 24.54. Found: C, 41.37; H, 5.76; N, 16.06; O, 12.23; S, 24.56.

3-[(5-Amino-1,3,4-thiadiazol-2-yl)thio]propanenitrile (2a) Yield 49%; mp 136–137°C; IR (cm^{-1}): 3297, 3102, 2170, 1631, 1579, 1504, 1068; ^{1}H NMR ($CDCl_3$): δ 2.93 (t, *J* = 7 Hz, 2H), 3.33 (t, *J* = 7 Hz, 2H), 7.38 (s, 2H). Anal. Calcd for $C_5H_6N_4S_2$: C, 32.24; H, 3.25; N, 30.08; S, 34.43. Found: C, 32.25; H, 3.27; N, 30.09; S, 34.44.

Methyl 2-[(5-amino-1,3,4-thiadiazol-2-yl)thio]propanoate (2b) Yield 58%; mp 102–104°C, IR (cm^{-1}): 3311, 3101, 2926, 1728, 1633, 1503, 1246, 1066; ^{1}H NMR ($CDCl_3$): δ 2.81 (t, *J* = 7 Hz, 2H), 3.34 (t, *J* = 7 Hz, 2H), 3.65 (s, 3H), 6.64 (s, 2H). Anal. Calcd for $C_6H_9N_3O_2S_2$: C, 32.86; H,

4.14; N, 19.16; O, 14.59; S, 29.25. Found: C, 32.85; H, 4.16; N, 19.17; O, 14.60; S, 29.26.

Butyl 2-[(5-amino-1,3,4-thiadiazol-2-yl)thio]propanoate (2c) Yield 42%; mp 93–95°C, IR (cm^{-1}): 3298, 3102, 2958, 1723, 1502, 1247, 1066; ^1H NMR ($CDCl_3$): δ 0.92 (t, *J* = 7 Hz, 3H), 1.38 (m, *J* = 7 Hz, 2H), 1.58 (m, *J* = 7 Hz, 2H), 2.80 (t, *J* = 7 Hz, 2H), 3.34 (t, *J* = 7 Hz, 2H), 4.08 (t, *J* = 7 Hz, 2H), 6.60 (s, 2H). Anal. Calcd for $C_9H_{15}N_3O_2S_2$: C, 41.36; H, 5.78; N, 16.08; O, 12.24; S, 24.54. Found: C, 41.35; H, 5.79; N, 16.07; O, 12.27; S, 24.51.

General procedure for synthesis of compounds 3a–c and 4a–c

Chloroacetyl chloride (2 mmol) was added dropwise to a stirred cold solution (0°C) of **1a–c** or **2a–c** (1 mmol) in DMF (3 mL) and the mixture was stirred at room temperature for an additional 8 h. After concentration under reduced pressure, the residue was crystallized from ethanol.

2-Chloro-*N*-(4-(2-cyanoethyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide (3a) Yield 61%; mp 164–167°C; IR (cm^{-1}): 3439, 2926, 2221, 1712, 1569, 1556, 1079. Anal. Calcd for $C_7H_7ClN_4OS_2$: C, 32.00; H, 2.69; Cl, 13.49; N, 21.32; O, 6.09; S, 24.41. Found: C, 32.02; H, 2.70; Cl, 13.50; N, 21.33; O, 6.08; S, 24.42.

Methyl 3-(5-(2-chloroacetamido)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl)propanoate(3b) Yield: 88%; mp 112–116°C, IR (cm^{-1}): 3441, 2917, 1710, 1691, 1582, 1212, 1183, 1075. Anal. Calcd for $C_8H_{10}ClN_3O_3S_2$: C, 32.49; H, 3.41; Cl, 11.99; N, 14.21; O, 16.23; S, 21.68. Found: C, 32.50; H, 3.43; Cl, 11.97; N, 14.20; O, 16.25; S, 21.69.

Butyl 3-(5-(2-chloroacetamido)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl)-propanoate (3c) Yield 87%; mp 92–94°C, IR (cm^{-1}): 3432, 2929, 1729, 1709, 1579, 1213, 1184, 1080. Anal. Calcd for $C_{11}H_{16}ClN_3O_3S_2$: C, 39.11; H, 4.77; Cl, 10.49; N, 12.44; O, 14.21; S, 18.98. Found: C, 39.13; H, 4.75; Cl, 10.50; N, 12.42; O, 14.23; S, 19.00.

2-Chloro-*N*-[5-((2-cyanoethyl)thio)-1,3,4-thiadiazol-2-yl]acetamide (4a) Yield 91%; mp 174–178°C, IR (cm^{-1}): 3439, 2925, 2230, 1707, 1582, 1065. Anal. Calcd for $C_7H_7ClN_4OS_2$: C, 32.00; H, 2.69; Cl, 13.49; N, 21.32; O, 6.09; S, 24.41. Found: C, 31.98; H, 2.67; Cl, 13.51; N, 21.30; O, 6.10; S, 24.43.

Methyl 3-[(5-(2-chloroacetamido)-1,3,4-thiadiazol-2-yl)thio]propanoate(4b) Yield 93%; mp 144–145°C, IR (cm^{-1}): 3439, 2946, 1734, 1706, 1587, 1197, 1177, 1069. Anal. Calcd for $C_8H_{10}ClN_3O_3S_2$: C, 32.49; H, 3.41; Cl, 11.99; N, 14.21; O, 16.23; S, 21.68. Found: C, 32.47; H, 3.43; Cl, 12.01; N, 14.23; O, 16.21; S, 21.67.

Butyl 3-((5-(2-chloroacetamido)-1,3,4-thiadiazol-2-yl)thio)propanoate (4c) Yield 83%; mp 105–106°C, IR (cm^{-1}): 3435, 2961, 1729, 1704, 1577, 1296, 1183, 1065. Anal. Calcd for $C_{11}H_{16}ClN_3O_3S_2$: C, 39.11; H, 4.77; Cl, 10.49; N, 12.44; O, 14.21; S, 18.98. Found: C, 39.10; H, 4.79; Cl, 10.51; N, 12.42; O, 14.20; S, 18.97.

General procedure for synthesis of compounds 5a–c and 7a–c

A solution of **3a–c** or **4a–c** (1 mmol) in acetonitrile (3 mL) was treated with tetrabutylammonium bromide (TBAB, 0.1 g) and KI (0.11 g, 0.66 mmol) and the mixture was stirred for 15 min at room temperature. After addition of KSCN (0.1 g, 1 mmol), the mixture was heated to 80°C for 1 h, then cooled and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane/methanol (95:5).

3-[5-(5-Oxo-2-thioxoimidazolidin-1-yl)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl]propanenitrile (5a) Yield 56%; mp 162°C, IR (cm^{-1}): 3432, 2273, 1749, 1625, 1571, 1175, 1083; ^1H NMR ($CDCl_3$): δ 3.16 (t, *J* = 7 Hz, 2H), 4.18 (s, 2H), 4.61 (t, *J* = 7 Hz, 2H), 11.05 (s, 1H). Anal. Calcd for $C_8H_7N_5OS_3$: C, 33.67; H, 2.47; N, 24.54; O, 5.61; S, 33.71. Found: C, 33.69; H, 2.45; N, 24.51; O, 5.63; S, 33.68.

Methyl 3-[5-(5-oxo-2-thioxoimidazolidin-1-yl)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl]propanoate (5b) Yield 50%; mp 103–104°C, IR (cm^{-1}): 3420, 2922, 1738, 1582, 1251, 1184, 1078; ^1H NMR ($CDCl_3$): δ 2.95 (t, *J* = 7 Hz, 2H), 3.67 (s, 3H), 4.16 (s, 2H), 4.52 (t, *J* = 7 Hz, 2H), 10.91 (s, 1H). Anal. Calcd for $C_9H_{10}N_4O_3S_3$: C, 33.95; H, 3.17; N, 17.60; O, 15.08; S, 30.21. Found: C, 33.94; H, 3.19; N, 17.59; O, 15.10; S, 30.23.

Butyl 3-[5-(5-oxo-2-thioxoimidazolidin-1-yl)-2-thioxo-1,3,4-thiadiazol-3(2H)-yl]propanoate(5c) Yield 43%; mp 132–134°C, IR (cm^{-1}): 3429, 2957, 1748, 1633, 1589, 1266, 1179, 1084; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7 Hz, 3H), 1.40 (m, *J* = 7 Hz, 2H), 1.60 (m, *J* = 7 Hz, 2H), 2.95 (t, *J* =7 Hz, 2H), 4.07 (t, *J* = 7 Hz, 2H), 4.10 (s, 2H), 4.52 (t, *J* = 7 Hz, 2H), 11.00 (s, 1H). Anal. Calcd for $C_{12}H_{16}N_4O_3S_3$: C, 39.98; H, 4.47; N, 15.54; O, 13.32; S, 26.69. Found: C, 39.95; H, 4.49; N, 15.55; O, 13.30; S, 26.70.

3-[(5-(5-Oxo-2-thioxoimidazolidin-1-yl)-1,3,4-thiadiazol-2-yl) thio]propanenitrile (7a) Yield 67%; mp 196–198°C; IR (cm^{-1}): 3451, 2230, 1734, 1569, 1166, 1053; ^1H NMR ($CDCl_3$): δ 3.10 (t, *J* = 7 Hz, 2H), 3.63 (t, *J* = 7 Hz, 2H), 4.11 (s, 2H), 10.90 (s, 1H). Anal. Calcd for $C_8H_7N_5OS_3$: C, 33.67; H, 2.47; N, 24.54; O, 5.61; S, 33.71. Found: C, 33.68; H, 2.49; N, 24.53; O, 5.60; S, 33.70.

Methyl 3-[(5-(5-oxo-2-thioxoimidazolidin-1-yl)-1,3,4-thiadiazol-2-yl)thio]propanoate (7b) Yield 75%; mp 165–167°C, IR (cm^{-1}): 3448, 2923, 1734, 1595, 1174, 1073; ^1H NMR ($CDCl_3$): δ 2.89 (t, *J* = 7 Hz, 2H), 3.53 (t, *J* = 7 Hz, 2H), 3.67 (s, 3H), 4.10 (s, 2H), 10.90 (s, 1H). Anal. Calcd for $C_9H_{10}N_4O_3S_3$: C, 33.95; H, 3.17; N, 17.60; O, 15.08; S, 30.21. Found: C, 33.96; H, 3.18; N, 17.61; O, 15.07; S, 30.22.

Butyl 3-[(5-(5-oxo-2-thioxoimidazolidin-1-yl)-1,3,4-thiadiazol-2-yl)thio]propanoate (7c) Yield 42%; mp 110–113°C, IR (cm^{-1}): 3432, 2961, 1734, 1598, 1259, 1175, 1090; ^1H NMR ($CDCl_3$): δ 0.92 (t, *J* = 7 Hz, 3H), 1.40 (m, *J* = 7 Hz, 2H), 1.61 (m, *J* = 7 Hz, 2H), 2.89 (t, *J* = 7 Hz, 2H), 3.53 (t, *J* = 7 Hz, 2H), 4.10 (t, *J* = 7 Hz, 2H), 4.10 (s, 2H), 10.89 (s, 1H). Anal. Calcd for $C_{12}H_{16}N_4O_3S_3$: C, 39.98; H, 4.47; N, 15.54; O, 13.32; S, 26.69. Found: C, 39.97; H, 4.46; N, 15.57; O, 13.33; S, 26.67.

General procedure for synthesis of compounds 6a–c and 8a–c

A solution of **3a–c** or **4a–c** (1 mmol) in DMF (2 mL) was treated with KI (0.11 g, 0.66 mmol) and KSCN (0.1 g, 1 mmol) and the mixture was heated to 100°C for 1 h. After cooling and concentration under reduced pressure, the residue was crystallized from 80% aqueous ethanol.

3-[5-((4-Oxothiazolidin-2-ylidene)amino)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl]propanenitrile (6a) Yield 71%; mp 206–208°C, IR (cm^{-1}): 3437, 2924, 2253, 1747, 1623, 1173, 1082; ^1H NMR (DMSO-d_6): δ 3.110 (t, *J* = 6 Hz, 2H), 4.17 (s, 2H), 4.49 (t, *J* = 6 Hz, 2H), 12.48 (s, 1H). Anal. Calcd for $C_8H_7N_5OS_3$: C, 33.67; H, 2.47; N, 24.54; O, 5.61; S, 33.71. Found: C, 33.66; H, 2.45; N, 24.55; O, 5.59; S, 33.72.

Methyl 3-[5-((4-oxothiazolidin-2-ylidene)amino)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl]propanoate (6b) Yield 71%; mp 161°C, IR (cm^{-1}): 3432, 2939, 1738, 1581, 1252, 1185, 1079; ^1H NMR (DMSO-d_6): δ 2.90 (t, *J* = 7 Hz, 2H), 3.615 (s, 3H), 4.15 (s, 2H), 4.42 (t, *J* = 7 Hz, 2H), 12.43 (s, 1H). Anal. Calcd for $C_9H_{10}N_4O_3S_3$: C, 33.95; H, 3.17; N, 17.60; O, 15.08; S, 30.21. Found: C, 33.94; H, 3.16; N, 17.64; O, 15.05; S, 30.23.

Butyl 3-[5-((4-oxothiazolidin-2-ylidene)amino)-2-thioxo-1,3,4-thiadiazol-3(2*H*)-yl]propanoate (6c) Yield 61%; mp 154–155°C, IR (cm^{-1}): 3432, 2960, 1726, 1634, 1575, 1244, 1181, 1082; ^1H NMR (DMSO-d_6): δ 0.86 (t, *J* = 7 Hz, 3H), 1.28 (m, *J* = 7 Hz, 2H), 1.54 (m, *J* = 7 Hz, 2H), 2.90 (t, *J* = 7 Hz, 2H), 4.02 (t, *J* = 7 Hz, 2H), 4.15 (s, 2H), 4.42 (t, *J* = 7 Hz, 2H), 12.44 (s, 1H). Anal. Calcd for $C_{12}H_{16}N_4O_3S_3$: C, 39.98; H, 4.47; N, 15.54; O, 13.32; S, 26.69. Found: C, 39.99; H, 4.45; N, 15.53; O, 13.34; S, 26.68.

3-[(5-((4-Oxothiazolidin-2-ylidene)amino)-1,3,4-thiadiazol-2-yl)thio]propanenitrile (8a) Yield 63%; mp 208–210°C, IR (cm^{-1}): 3432, 2933, 2245, 1735, 1651, 1561, 1168; ^1H NMR (400 MHz, DMSO): δ 3.05 (t, *J* = 6 Hz, 2H), 3.55 (t, *J* = 6 Hz, 2H), 4.11 (s, 2H), 12.35 (s, 2H). Anal. Calcd for $C_8H_7N_5OS_3$: C, 33.67; H, 2.47; N, 24.54; O, 5.61; S, 33.71. Found: C, 33.69; H, 2.43; N, 24.57; O, 5.59; S, 33.70.

Methyl 3-[(5-((4-oxothiazolidin-2-ylidene)amino)-1,3,4-thiadiazol-2-yl)thio]propanoate (8b) Yield 65%; mp 176–177°C, IR (cm^{-1}): 3430, 2924, 1732, 1597, 1251, 1173, 1071; ^1H NMR (DMSO-d_6): δ 2.85 (t, *J* = 7 Hz, 2H), 3.45 (t, *J* = 7 Hz, 2H), 3.63 (s, 3H), 4.11 (s, 2H), 12.33 (s, 1H). Anal. Calcd for $C_9H_{10}N_4O_3S_3$: C, 33.95; H, 3.17; N, 17.60; O, 15.08; S, 30.21. Found: C, 33.97; H, 3.19; N, 17.62; O, 15.07; S, 30.20.

Butyl 3-[(5-((4-oxothiazolidin-2-ylidene)amino)-1,3,4-thiadiazol-2-yl)thio]propanoate (8c) Yield 72%; mp 111–112°C, IR (cm^{-1}): 3405, 2958, 1732, 1594, 1171, 1248, 1056; ^1H NMR (DMSO-d_6): δ 0.88 (t, *J* = 8 Hz, 3H), 1.33 (m, *J* =8 Hz, H), 1.55 (m, *J* = 8 Hz, 2H), 2.84 (t, *J* = 8 Hz, 2H), 3.45 (t, *J* = 8 Hz, 2H), 4.05 (t, *J* = 8 Hz, 2H), 4.11 (s, 2H), 12.33 (s, 1H). Anal. Calcd for $C_{12}H_{16}N_4O_3S_3$: C, 39.98; H, 4.47; N, 15.54; O, 13.32; S, 26.69. Found: C, 40.00; H, 4.46; N, 15.57; O, 13.30; S, 26.70.

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