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Synthesis of new sulfur-linked di- and triheterocyclic compounds containing thienotriazolopyrimidine and triazolothiadiazole moieties

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Abstract

The synthesis of new sulfur-linked di- and triheterocyclic compounds containing thienotriazolopyrimdine and triazolothiadiazole systems with promising biological activity is described.

Keywords: cyclization; heterocyclic compound; sodium acetate; thienotriazolopyrimidine; triazolothiadiazole.

Introduction

Much attention has been recently paid to the synthesis of thieno-1,2,4-triazolopyrimidines and sulfur-containing 1,2,4-triazoles (3-thio-1,2,4-triazoles) because of their biological activities and potential therapeutic use (Almajan et al., 2005; Contour-Galcéra et al., 2005; Nagamatsu et al., 2007; Prasad et al., 2008; Siwek et al., 2008; Guetzoyan et al., 2010). We previously designed and synthesized thienotriazolopyrimidine derivatives with promising biological activity (Jo et al., 2008; Song and Son, 2010, 2011). 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazole derivatives obtained by fusing 1,2,4-triazole and the 1,3,4-thiadiazole ring together have been reported to possess antibacterial, antifungal, anti-inflammatory and analgesic effects as well as anticancer activity (Omar and Aboulwafa, 1986; Zhang and Sun, 1998; Bhat et al., 2004). We therefore designed the molecular combinations of a 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole moiety and the thieno[1,2,4]triazolo[4,3-*c*]-pyrimidine system linked by a sulfur atom to produce novel di- and triheterocyclic derivatives using the concept of molecular hybridization (Viegas-Junior et al., 2007). In continuation of our recent synthetic work (Whang and Song, 2011), here we describe the synthesis of derivatives **5** and **7**, the molecules of which are composed of the two and three heterocyclic systems mentioned above (Schemes 1 and 2).

[a]Participated as an undergraduate student.

Results and discussion

The required starting material thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione **(1)** was prepared as reported in Song and Son (2010). Phenyl(thieno[2,3-*e*][1,2,4]triazolo-[4,3-*c*]pyrimidin-3-ylthio)acetic acid **(3)** and its derivatives were obtained in good yield by treatment of **1** with substituted α-bromophenylacetic acids **2** in refluxing ethanol in the presence of sodium acetate, as shown Scheme 1. The disappearance of characteristic peaks at 1200 (weak) and 3190 cm^{-1} for the C=S and NH groups in the infrared spectrum and the lack of the signal for the proton of the NH(C=S) group near δ 14.0 in the ^{1}H nuclear magnetic resonance (NMR) spectrum indicated that the thione **1** was converted into the corresponding thioether **3a–e**. The new sulfur-linked diheterocyclic compounds **5** were synthesized by condensation of compound **3** with 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol (**4**) (Sandström, 1961) using phosphorus oxychloride as the cyclizing agent, as seen in Scheme 1 (Khalil, 2007). The structures of all new compounds were confirmed by elemental analyses and spectral [Mass (MS), ^{1}H-NMR, infrared] data.

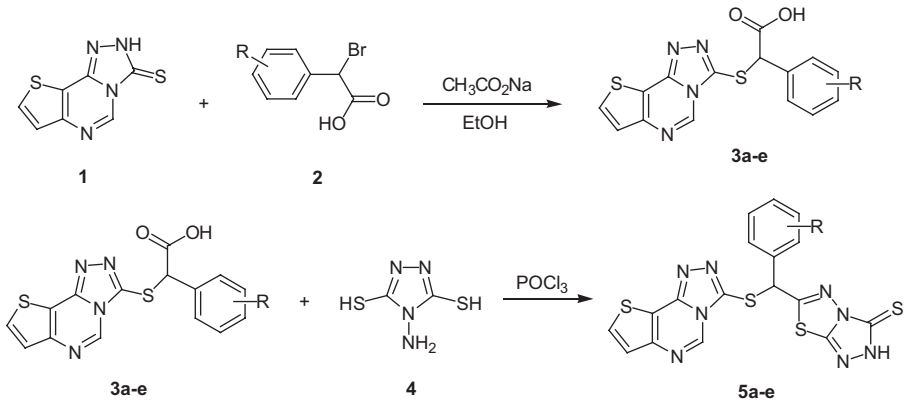
The triheterocyclic compounds **7a–e** are a new class of heterocycles. These compounds were prepared in moderate yield, as shown Scheme 2, by treatment of **5** with one of the chlorothienotriazolopyrimidines **6** (Whang and Song, 2011) in refluxing ethanol containing sodium acetate. The structure of product **7** was established on the basis of its spectral data and elemental analysis.

Experimental

Melting points were measured by using capillary tubes on Büchi apparatus and are uncorrected. The infrared spectra were recorded on the Fourier transform (FT)-IR Brucker Tensor 27. The ^{1}H NMR spectra were recorded on the Bruker DRX-300 FT-NMR spectrometer (300 MHz) in dimethyl sulfoxide (DMSO)-d_6 with Me_4Si as the internal standard. Electron impact mass spectra were recorded on an HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General procedure for the preparation of 3a–e

Anhydrous sodium acetate (2 mmol) was added to a solution of thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione (**1**, 1.2 mmol) in ethanol (20 ml) with stirring at room temperature. After 5 min, an α-bromophenylacetic acid (**2**, 1.2 mmol) was slowly added in small portions and the resulting solution was heated at reflux for 6 h. After cooling, the resultant solid product was filtered, washed



a: R=H; **b**: R=2-Cl; **c**: R=3-Cl; **d**: R=4-Cl; **e**: R=4-Br

Scheme 1 Synthesis of **3a–e** and **5a–e**.

with water and purified by chromatography using Merck silica gel (70–230 mesh) and eluting with $CHCl_3$/MeOH (1:1).

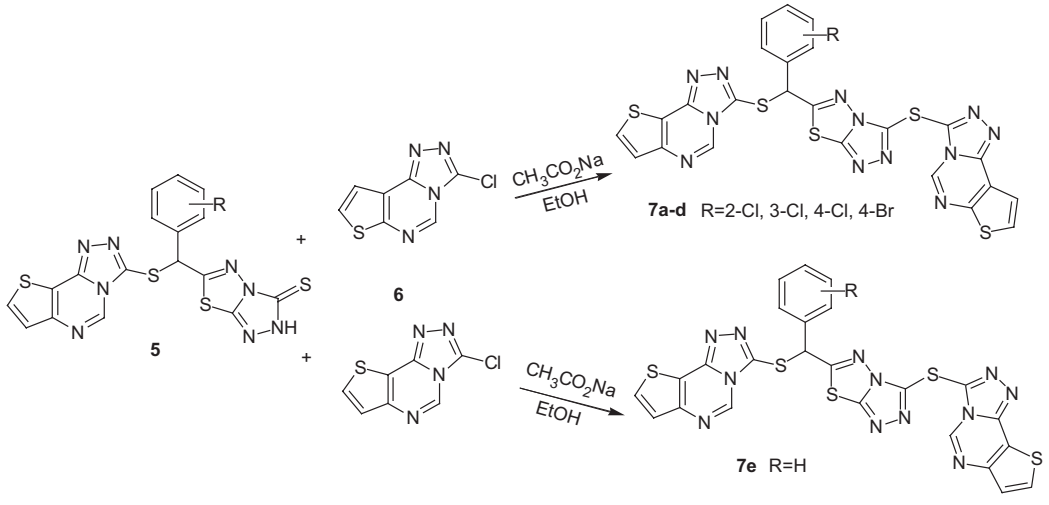
Phenyl(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)-acetic acid (3a) This compound was obtained in 62% yield; mp 200–203°C; ^{1}H NMR: δ 9.48 (s, 1H, H-5, pyrimidine), 8.24 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.65 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.56 (m, 2H, Ar), 7.35–7.16 (m, 3H, Ar), 5.36 (s, 1H, benzyl); MS: m/z 342 (M^+), 324, 298, 265, 208, 135, 121. Analysis calculated for $C_{15}H_{10}N_4O_2S_2$: C, 52.62; H, 2.94; N, 16.36. Found: C, 52.55; H, 2.76; N, 16.49.

2-Chlorophenyl(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (3b) This compound was obtained in 71% yield; mp 237–239°C; ^{1}H NMR: δ 9.44 (s, 1H, H-5, pyrimidine), 8.26 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.70 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.66 (d, 1H, Ar), 7.58 (d, 1H, Ar), 7.35–7.23 (m, 2H, Ar), 5.80 (s, 1H, benzyl); MS: m/z 376 (M^+), 331, 297, 208, 135. Analysis calculated for $C_{15}H_9ClN_4O_2S_2$: C, 47.81; H, 2.41; N, 14.87. Found: C, 47.93; H, 2.51; N, 14.80.

3-Chlorophenyl(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (3c) This compound was obtained in 59% yield; mp 232–235°C; ^{1}H NMR: δ 9.47 (s, 1H, H-5, pyrimidine), 8.24 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.65 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.58 (s, 1H, Ar), 7.43 (m, 1H, Ar), 7.30–7.21 (m, 2H, Ar), 5.30 (s, 1H, benzyl), MS: m/z 376 (M^+), 332, 299, 264, 182, 125, 66. Analysis calculated for $C_{15}H_9ClN_4O_2S_2$: C, 47.81; H, 2.41; N, 14.87. Found: C, 47.70; H, 2.51; N, 14.79.

4-Chlorophenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (3d) This compound was obtained in 55% yield; mp 103–105°C; ^{1}H NMR: δ 9.56 (s, 1H, H-5, pyrimidine), 8.30 (d, *J*=5.8 Hz, 1H, H-8, tahiophene), 7.71 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.58 (d, 2H, Ar), 7.40 (d, 2H, Ar), 5.60 (s, 1H, benzyl); MS: m/z 376 (M^+), 332, 299, 208, 155, 135, 125, 89, 77. Analysis calculated for $C_{15}H_9ClN_4O_2S_2$: C, 47.81; H, 2.41; N, 14.87. Found: C, 47.64; H, 2.34; N, 14.94.

4-Bromophenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (3e) This compound was obtained in 53%



Scheme 2 Synthesis of **7a–e**.

yield; mp 248–250°C; ^{1}H NMR: δ 9.46 (s, 1H, H-5, pyrimidine), 8.23 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.72 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.48 (d, 2H, Ar), 7.38 (d, 2H, Ar), 5.26 (s, 1H, benzyl); MS: m/z 421 (M^+), 332, 297, 264, 177, 155, 135, 125, 83. Analysis calculated for $C_{15}H_9BrN_4O_2S_2$: C, 42.76; H, 2.15; N, 13.30. Found: C, 42.62; H, 2.10; N, 13.41.

General procedure for the preparation of 5a–e

A mixture of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**4**, 6.7 mmol) and the appropriate carboxylic acid **3a–e** (6.7 mmol) in phosphorus oxychloride (10 ml) was heated at reflux for 10 h. The excess phosphorus oxychloride was removed under reduced pressure, and the residue was treated with ice-water mixture. The precipitated solid was filtered, washed several times with water, dried at room temperature, and crystallized from dimethylformamide (DMF).

6-[Phenyl(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)-methyl]-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (5a) This compound was obtained in 48% yield; mp 160–162°C; ^{1}H NMR: δ 9.50 (s, 1H, H-5, pyrimidine), 8.29 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.71 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.55 (d, 2H, Ar), 7.38–7.21 (m, 3H, Ar), 5.82 (s, 1H, benzyl); MS: m/z 454 (M^+), 297, 177, 135, 77. Analysis calculated for $C_{17}H_{10}N_8S_4$: C, 44.92; H, 2.22; N, 24.65. Found: C, 44.76; H, 2.15; N, 24.56.

6-[(2-Chlorophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)methyl]-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (5b) This compound was obtained in 49% yield; mp 110–112°C; ^{1}H NMR: δ 9.54 (s, 1H, H-5, pyrimidine), 8.27 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.65 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.57 (m, 1H, Ar), 7.48 (m, 1H, Ar), 7.36–7.30 (m, 2H, Ar), 6.00 (s, 1H, benzyl); MS: m/z 488 (M^+), 341, 332, 297, 264 177, 155, 135. Analysis calculated for $C_{17}H_9ClN_8S_4$: C, 41.75; H, 1.86; N, 22.91. Found: C, 41.90; H, 1.94; N, 22.84.

6-[(3-Chlorophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)methyl]-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (5c) This compound was obtained in 55% yield; mp 180–182°C; ^{1}H NMR: δ 9.53 (s, 1H, H-5, pyrimidine), 8.25 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.64 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.54 (s, 1H, Ar), 7.44 (m, 1H, Ar), 7.27–7.20 (m, 2H, Ar), 5.88 (s, 1H, benzyl); MS: m/z 488 (M^+), 332, 297, 208, 155, 135, 77. Analysis calculated for $C_{17}H_9ClN_8S_4$: C, 41.75; H, 1.86; N, 22.91. Found: C, 41.60; H, 1.91; N, 22.99.

6-[(4-Chlorophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)methyl]-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (5d) This compound was obtained in 66% yield; mp 185–187°C; ^{1}H NMR: δ 9.59 (s, 1H, H-5, pyrimidine), 8.32 (d, *J*=5.9 Hz, 1H, H-8, thiophene), 7.72 (d, *J*=5.9 Hz, 1H, H-7, thiophene), 7.58 (d, 2H, Ar), 7.41 (d, 2H, Ar), 5.78 (s, 1H, benzyl); MS: m/z 488 (M^+), 332, 297, 177, 155, 135. Analysis calculated for $C_{17}H_9ClN_8S_4$: C, 41.75; H, 1.86; N, 22.91. Found: C, 41.90; H, 1.94; N, 22.99.

6-[(4-Bromophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)methyl]-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (5e) This compound was obtained in 48% yield; mp 185–187°C; ^{1}H NMR: δ 9.48 (s, 1H, H-5, pyrimidine), 8.24 (d, *J*=5.8 Hz, 1H, H-8, thiophene), 7.72 (d, *J*=5.8 Hz, 1H, H-7, thiophene), 7.50 (d, 2H, Ar), 7.40 (d, 2H, Ar), 5.70 (s, 1H, benzyl); MS: m/z 533 (M^+), 375, 177, 135. Analysis calculated for $C_{17}H_9BrN_8S_4$: C, 38.27; H, 1.70; N, 21.00. Found: C, 38.39; H, 1.77; N, 21.16.

General procedure for the preparation of 7a–e

A suspension of anhydrous sodium acetate (15 mmol), a chlorothienopyrimidine **6** (10 mmol) and the appropriate diheterocyclic compound **5** (10 mmol) in ethanol (30 ml) was heated under reflux for 6–8 h. After cooling, the resultant solid product was filtered, washed with water and crystallized from ethanol.

3-{6-[(2-Chlorophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidin-3-ylthio)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylthio}thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (7a) This compound was obtained in 38% yield; mp 121–123°C; ^{1}H NMR: δ 9.69 (s, 1H), 9.48 (s, 1H), 8.27 (d, *J*=5.8 Hz, 1H), 8.09 (d, *J*=5.8 Hz, 1H), 7.83 (d, *J*=5.8 Hz, 1H), 7.65 (d, *J*=5.8 Hz, 1H), 7.62 (d, 1H), 7.54 (1, 2H), 7.40 (m, 2H), 6.09 (s, 1H); MS: m/z 662 (M^+), 330, 175, 135. Analysis calculated for $C_{24}H_{11}ClN_{12}S_5$: C, 43.46; H, 1.67; N, 25.34. Found: C, 43.22; H, 1.79; N, 25.15.

3-{6-[(3-Chlorophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylthio}thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (7b) This compound was obtained in 33% yield; mp 115–117°C; ^{1}H NMR: δ 9.67 (s, 1H), 9.49 (s, 1H), 8.24 (d, *J*=5.8 Hz, 1H), 8.08 (d, *J*=5.8 Hz, 1H), 7.83 (d, *J*=5.8 Hz, 1H), 7.65 (d, *J*=5.8 Hz, 1H), 7.52 (s, 1H), 7.47 (m, 2H), 7.30 (m, 2H), 5.71 (s, 1H); MS: m/z 662 (M^+), 330, 175, 135, 66. Analysis calculated for $C_{24}H_{11}ClN_{12}S_5$: C, 43.46; H, 1.67; N, 25.34. Found: C, 43.34; H, 1.59; N, 25.20.

3-{6-[(4-Chlorophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylthio}thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (7c) This compound was obtained in 44% yield; mp 158–160°C; ^{1}H NMR: δ 9.71 (s, 1H), 9.56 (s, 1H), 8.30 (d, *J*=5.8 Hz, 1H), 8.12 (d, *J*=5.8 Hz, 1H), 7.85 (d, *J*=5.8 Hz, 1H), 7.71 (d, *J*=5.8 Hz, 1H), 7.56 (d, 2H), 7.38 (d, 2H), 5.82 (s, 1H); MS: m/z 662 (M^+), 330, 175, 135. Analysis calculated for $C_{24}H_{11}ClN_{12}S_5$: C, 43.46; H, 1.67; N, 25.34. Found: C, 43.55; H, 1.55; N, 25.26.

3-{6-[(4-Bromophenyl)(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidin-3-ylthio)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylthio}thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (7d) This compound was obtained in 30% yield; mp 138–140°C; ^{1}H NMR: δ 9.64 (s, 1H), 9.46 (s, 1H), 8.23 (d, *J*=5.8 Hz, 1H), 8.09 (d, *J*=5.8 Hz, 1H), 7.83 (d, *J*=5.8 Hz, 1H), 7.72 (d, *J*=5.8 Hz, 1H), 7.47 (d, 2H), 7.31 (d, 2H), 5.46 (s, 1H); MS: m/z 706 (M^+), 375, 175, 135. Analysis calculated for $C_{24}H_{11}BrN_{12}S_5$: C, 40.73; H, 1.57; N, 23.75. Found: C, 40.59; H, 1.42; N, 23.66.

3-{6-[Phenyl(thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)-methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylthio}thieno-[2,3-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine (7e) This compound was obtained in 36% yield; mp 102–105°C; ^{1}H NMR (DMSO-d_6): δ 9.61 (s, 1H), 9.49 (s, 1H), 8.30 (d, *J*=5.8 Hz, 1H), 8.24 (d, *J*=5.8 Hz, 1H), 7.69 (d, *J*=5.8 Hz, 1H), 7.65 (d, *J*=5.8 Hz, 1H), 7.34–7.17 (m, 5H), 5.45 (s, 1H); MS: m/z 628 (M^+), 297, 175, 135. Analysis calculated for $C_{24}H_{12}N_{12}S_5$: C, 45.85; H, 1.92; N, 26.73. Found: C, 45.66; H, 2.01; N, 26.56.

Acknowledgements

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