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SYNTHESIS OF NEW SULFUR-LINKED THIENOTRIAZOLOPYRIMIDINE DERIVATIVES CONTAINING TRIAZOLOTHIADIAZOLE MOIETY

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Abstract
A series of new sulfur-linked heterocyclic compounds **11** were synthesized by the successive reactions of thieno[1,2,4]triazolo[4,3-*c*]pyrimidine-3-thione with α-bromophenylacetic acid derivatives and 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol.

Keywords: thienotriazolopyrimidine, triazolothiadiazole, cyclization, phosphorus oxychloride

Introduction

Thienotriazolopyrimidine derivatives have attracted much attention and are of great interest as potential therapeutic agents. For instance, thienotriazolopyrimidine **1** as shown in Figure 1 and its analog have been recently explored for inhibitor of Shiga toxin trafficking and adenosine A_1/A_{2A} or A_{2A}/A_3 receptor antagonists, respectively.[1,2] We have previously designed and synthesized thienotriazolopyrimidine derivatives **2** with promising biological activity using iodobenzene diacetate.[3]

Moreover, sulfur-containing 1,2,4-triazoles (3-thio-1,2,4-triazoles) were also reported to possess an impressive array of biological activities such as antibacterial, antifungal, analgesic, somatostatin sst_2/sst_5 agonist and carbonic anhydrase inhibitior.[4-7] Particularly, sulfur-linked dihetrocyclic compounds containing triazolopyrimidine or triazole such as **3** and **4** were investigated for antifungal agent and plant growth regulator, respectively.[8,9] We also have recently reported the synthesis of diheterocyclic compound **5** and its analogs.[10]

In the other hand, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives obtained by fusing 1,2,4-triazole and 1,3,4-thiadiazole ring together, have been reported to possess antibacterial, antifungal, anti-inflammatory, analgesic effects and anticancer activity.[11-13] For example, compound **6** and other 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives were reported to have anti-inflammatory and antimicrobial activities, respectively. [14-16]

Therefore, we devised the introduction of a 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole moiety to the thieno[1,2,4]triazolo[4,3-*c*]pyrimidine ring by sulfur to produce novel diheterocyclic systems using the concept of molecular hybridization.[17]

As a continuation of our synthetic works on heterocyclic compounds related to thienopyrimidines and thienopyridine with biological interest,[18] we wish to report herein the synthesis of new sulfur-linked thienotriazolopyrimidines **11a-e** containing a 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole, which are structurally related to **5** and **6** in the hope of obtaining compounds of diverse biological activities.

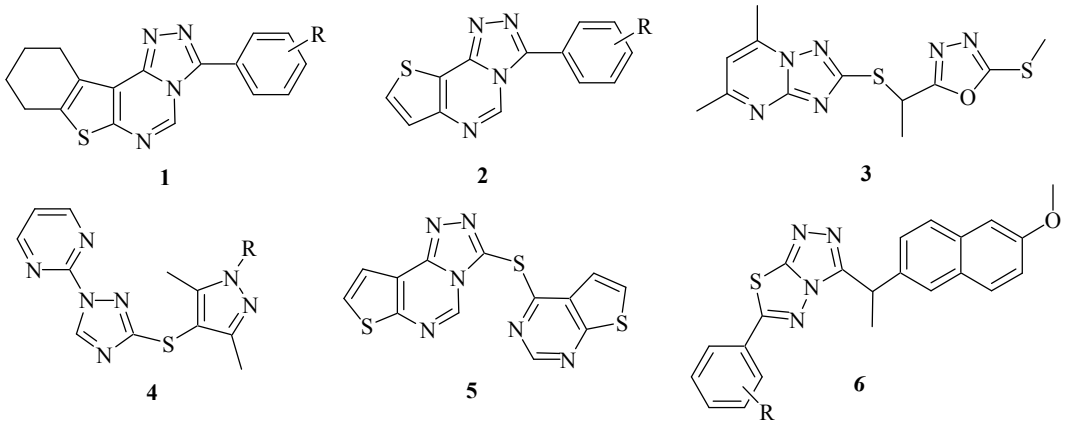
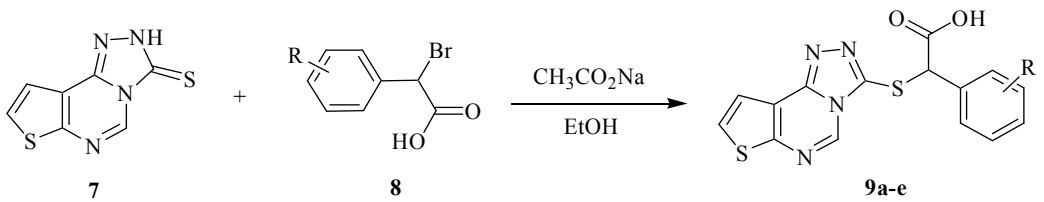


Figure 1. Compounds 1-6.

Result and Discussion

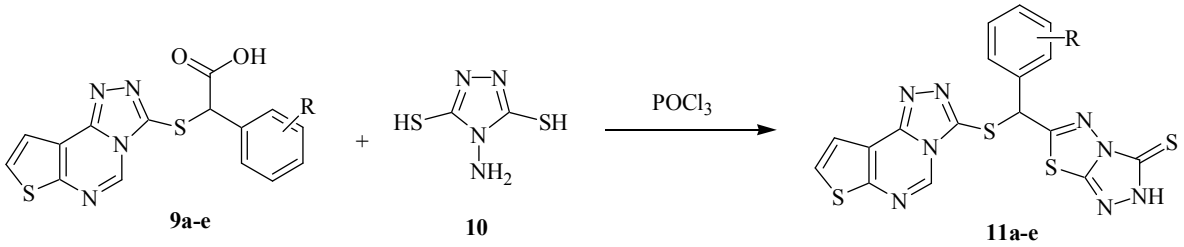
As reported in a previous communication,[10] a key intermediate thieno[3,2-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione **(7)** can be prepared in a few step sequence using 2-aminothiophene-3-carbonitrile as a starting material. The compounds of phenyl-(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)-acetic acid **(9)** and its derivatives were obtained in good yield by treatment of **7** with α-bromophenylacetic acid derivatives **8** containing sodium acetate (Scheme 1). The structure of these compounds was evident from their elemental analysis, mass spectra, ^{1}H NMR and IR spectra. The disappearance of characteristic peaks at 1200 (weak) and 3190 cm^{-1} for the C=S and NH groups in IR spectrum and the secondary amino signal near at δ 14.0 in ^{1}H NMR spectrum indicated the thione **7** was converted into the corresponding cyclic triazole products **9a-e**. For instance, the ^{1}H NMR spectrum of **9a** showed two doublets at δ 8.02-7.73 for thiophene protons, multiplet signals at δ 7.58-7.14 for aromatic protons and two singlets at δ 9.49 and 5.44 for pyrimidine and benzylic proton, respectively. The mass spectral data of **9a** showed a molecular ion peak at m/z 342 (12%), and also showed ions at m/z 324 (22%) and 298 (78%) which could be attributed to the loss of H_2O and CO_2, respectively, from the molecular ion.



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

Scheme 1

6-[Phenyl(thieno[3,2-*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 and its derivatives (**11a-e**) were prepared from the reaction of **9a-e** with 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol (**10**)[19] using phosphorus oxychloride as the cyclizing agent (Scheme 2).[15,20]



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

Scheme 2

The structure of these compounds was also characterized from their elemental analysis, mass spectra, ^{1}H NMR and IR spectra. For example, the characteristic bands at 1210 and 3190 cm^{-1} for the C=S and NH stretching vibrations in IR spectrum of **11b** were identified, like compound **7** having the same functional groups. The ^{1}H NMR spectrum of **11b** showed two doublets at δ 8.05 and 7.77 for thiophene protons, three multiplets at δ 7.59, 7.51 and 7.38-7.35 for aromatic protons and two singlets at δ 9.59 and 6.07 for pyrimidine and benzylic proton, respectively. The mass spectral data of **11b** showed a molecular ion peak at m/z 487 (1.2%), and also showed ions at m/z 332 (100%), 297 (54%), 155 (42%) and 135 (62%) which could be attributed to the loss of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole moiety and followed by next fragmentation, respectively, from the molecular ion. The ions at 208, 177 were fragments obtained from cleavage of sulfide bond of **11b**.

In conclusion, we have reported the synthesis of new sulfur-linked heterocyclic compounds **11a-e** with potential biological activities.

Experimental section

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatograpohy of Merck Kieselgel $60F_{254}$ and purified by column chromatograpohy Merck silica gel (70-230 mesh). The ^{1}H NMR spectra were recorded on Bruker DRX-300 FT NMR spectrometer (300 MHz) with Me_4Si as internal standard and chemical shifts are given in ppm (δ). IR spectra were recorded using an EXCALIBUR FTS-3000 FT IR spectrophotometer. Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General procedure for the preparation of 9a-e. To a solution of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione **(7)** (1.2 mmol) in ethanol (20 mL) anhydrous sodium acetate (2 mmol) was added with stirring at room temperature. After 5 min, α-bromophenylacetic acid derivatives **8** (1.2 mmol) was added slowly in small portions and the resulting solution was heated at reflux for 6 hours. After cooling, the solid products formed were filtered, washed with

water and purified with silica gel column chromatography eluting with 50:50 v/v $CHCl_3$/MeOH mixture .

Phenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (9a).
The compound was obtained in 65% yield, mp 206-208°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.45 (s, 1H, H-5, pyrimidine), 8.02 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.73 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.58 (m, 2H, Ar), 7.37-7.14 (m, 3H, Ar), 5.44 (s, 1H, benzyl), ms: (m/z) 342 (M^+), 324, 298, 265, 208, 135, 121. *Anal*. Calcd. for $C_{15}H_{10}N_4O_2S_2$: C, 52.62; H, 2.94; N, 16.36. Found: C, 52.49; H, 2.82; N, 16.42.

2-Chlorophenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (9b).
The compound was obtained in 80% yield, mp 222-223°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.54 (s, 1H, H-5, pyrimidine), 8.04 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.75 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.65 (d, 1H, Ar), 7.48 (d, 1H, Ar), 7.35-7.27 (m, 2H, Ar), 6.01 (s, 1H, benzyl), ms: (m/z) 376 (M^+), 331, 297, 264, 208, 135, 77. *Anal*. Calcd. for $C_{15}H_{19}ClN_4O_2S_2$: C, 47.81; H, 2.41; N, 14.87. Found: C, 47.89; H, 2.48; N, 14.77.

3-Chlorophenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (9c).
The compound was obtained in 72% yield, mp 233-235°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.49 (s, 1H, H-5, pyrimidine), 8.02 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.73 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.62 (s, 1H, Ar), 7.52 (m, 1H, Ar), 7.28-7.21 (m, 2H, Ar), 5.40 (s, 1H, benzyl), ms: (m/z) 376 (M^+), 332, 299, 264, 208, 177, 155, 135, 77. *Anal*. Calcd. for $C_{15}H_{19}ClN_4O_2S_2$: C, 47.81; H, 2.41; N, 14.87. Found: C, 47.74; H, 2.35; N, 14.80.

4-Chlorophenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (9d).
The compound was obtained in 70% yield, mp 214-216°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.56 (s, 1H, H-5, pyrimidine), 8.04 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.75 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.60 (d, 2H, Ar), 7.41 (d, 2H, Ar), 5.72 (s, 1H, benzyl), ms: (m/z) 376 (M^+), 358, 332, 299, 155, 135, 77. *Anal*. Calcd. for $C_{15}H_{19}ClN_4O_2S_2$: C, 47.81; H, 2.41; N, 14.87. Found: C, 47.75; H, 2.44; N, 14.95.

4-Bromophenyl(thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-ylthio)acetic acid (9e).
The compound was obtained in 63% yield, mp 266-267°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.58 (s, 1H, H-5, pyrimidine), 8.06 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.77 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.58 (d, 2H, Ar), 7.52 (d, 2H, Ar), 5.70 (s, 1H, benzyl), ms: (m/z) 421 (M^+), 403, 377, 344, 134, 77. *Anal*. Calcd. for $C_{15}H_{19}BrN_4O_2S_2$: C, 42.76; H, 2.15; N, 13.30. Found: C, 42.70; H, 2.08; N, 13.38.

General procedure for the preparation of 11a-e. A mixture of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**10**) (6.7 mmol) and the appropriate carboxylic acid **9a-e** (6.7 mmol) in phosphorus oxychloride (10 mL) was heated at reflux for 10 hours. The excess phosphorus oxychloride was removed under reduced pressure, and the residue was diluted with ice-water mixture. The precipitated solid was filtered, washed several times with water, dried at room temperature, and recrystallized from DMF.

6-[Phenyl(thieno[3,2-*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 (11a).
The compound was obtained in 55% yield, mp 157-159°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.62 (s, 1H, H-5, pyrimidine), 8.09 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.82 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.60 (d, 2H, Ar), 7.37-7.25 (m, 3H, Ar), 5.78 (s, 1H, benzyl), ms: (m/z) 454 (M^+), 297, 177, 135, 77. *Anal*. Calcd. for $C_{17}H_{10}N_8S_4$: C, 44.92; H, 2.22; N, 24.65. Found: C, 45.05; H, 2.11; N, 24.50.

6-[(2-Chlorohenyl)(thieno[3,2-*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 (11b).
The compound was obtained in 62% yield, mp 160-162°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.59 (s, 1H, H-5, pyrimidine), 8.05 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.77 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.59 (m, 1H, Ar), 7.51 (m, 1H, Ar), 7.38-7.35 (m, 2H, Ar), 6.07 (s, 1H, benzyl), ms: (m/z) 487 (M^+), 341, 332, 297, 264, 208, 177, 155, 135, 77. *Anal*. Calcd. for $C_{17}H_9ClN_8S_4$: C, 41.75; H, 1.86; N, 22.91. Found: C, 41.67; H, 1.90; N, 22.82.

6-[(3-Chlorohenyl)(thieno[3,2-*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 (11c).
The compound was obtained in 50% yield, mp 184-186°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.58 (s, 1H, H-5, pyrimidine), 8.05 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.75 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.64 (s, 1H, Ar), 7.53 (m, 1H, Ar), 7.29-7.23 (m, 2H, Ar), 6.00 (s, 1H, benzyl), ms: (m/z) 489 (M^+), 332, 297, 208, 155, 135, 77. *Anal*. Calcd. for $C_{17}H_9ClN_8S_4$: C, 41.75; H, 1.86; N, 22.91. Found: C, 41.69; H, 1.80; N, 22.84.

6-[(4-Chlorohenyl)(thieno[3,2-*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 (11d).
The compound was obtained in 66% yield, mp 164-166°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.59 (s, 1H, H-5, pyrimidine), 8.05 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.77 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.58 (d, 2H, Ar), 7.39 (d, 2H, Ar), 5.75 (s, 1H, benzyl), ms: (m/z) 489 (M^+), 332, 297, 177, 155, 135. *Anal*. Calcd. for $C_{17}H_9ClN_8S_4$: C, 41.75; H, 1.86; N, 22.91. Found: C, 41.80; H, 1.78; N, 22.95.

6-[(4-Bromohenyl)(thieno[3,2-*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 (11e).
The compound was obtained in 68% yield, mp 199-201°C; ^{1}H NMR (dimethyl sulfoxide-d_6): 9.61 (s, 1H, H-5, pyrimidine), 8.06 (d, *J*= 5.8 Hz, 1H, H-8, thiophene), 7.78 (d, *J*= 5.8 Hz, 1H, H-9, thiophene), 7.59 (d, 2H, Ar), 7.53 (d, 2H, Ar), 5.73 (s, 1H, benzyl), ms: (m/z) 533 (M^+), 375, 177, 135. *Anal*. Calcd. for $C_{17}H_9BrN_8S_4$: C, 38.27; H, 1.70; N, 21.00. Found: C, 38.40; H, 1.62; N, 21.12.

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