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단신 (Notes)

A Synthesis of Novel Sulfur-Linked Fused Thienotriazolopyrimidine Derivatives

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INTRODUCTION

Interleukin-6 (IL-6) binds to its receptor (IL-6R, a ligand-binding 80 kDa glycoprotein chain) and induces the homodimerization of a signal transducing glycoprotein 130 (gp130), leading to the activation of the Janus kinase (Jak)/signal transducer and signal activator of transcription-3 (STAT3).[1] STAT3 is also frequently over-expressed or persistently activated in most tumors and cancer, and activated STAT3 was found to suppress tumor-immune surveillance.[2] Therefore, the blockade of STAT3 activation pathway stimulated by IL-6 could be an attractive therapeutic target for discovery of new drugs and is currently under intense investigation.[3]

In the other hand, thienotriazolopyrimidines have recently attracted much interest because of their pharmacological and therapeutic properties including anticancer, anti-inflammatory, urea transport protein (UT-B) inhibitor, Shiga toxin trafficking inhibitor **1**, and xanthine oxidase inhibitor **2**, as shown in *Figure* 1[4]. Furthermore, sulfur-linked triazoles (3-thio-1,2,4-triazoles) have been reported to possess a wide range of biological activities such as antifungal agent, diacylglycerol acyltransferase 1 (DGAT1) inhibitor **3**, carbonic anhydrase inhibition, somatostatin sst2/sst5 agonists, and dopamine D_3 receptor antagonist **4**.[5] We have synthesized over the years thienopyrimidine and thienotriazolopyrimidine derivatives of promising biological activity.[6] From a programme to discover novel inhibitors using thienopyrimidine derivatives, some of sulfur-linked thienotriazolopyrimidine compounds were recently found to possess potent IL-6/STAT3 inhibition.[7] This result encouraged us to prepare new sulfur-linked tetracyclic thienotriazolopyrimidines in attempt to improve the IL-6/STAT3 inhibitory activity.

EXPERIMENTAL

Chemistry

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatography of Merck Kieselgel $60F_{254}$ and purified by column chromatography Merck silica gel (70–230 mesh). The ^{1}H NMR spectra were recorded on Unity Inova 400NB FT NMR spectrometer (400 MHz) with Me_4Si as internal standard and chemical shifts are given in ppm (δ). 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 7 and 8

Thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione **(5)** or thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione **(6)**[6(f)] (5 mmol) and methyl iodide (10 mmol) were stirred in ethanol (20 mL) containing sodium acetate (20 mmol) for 8 h at room temperature. The reaction mix-

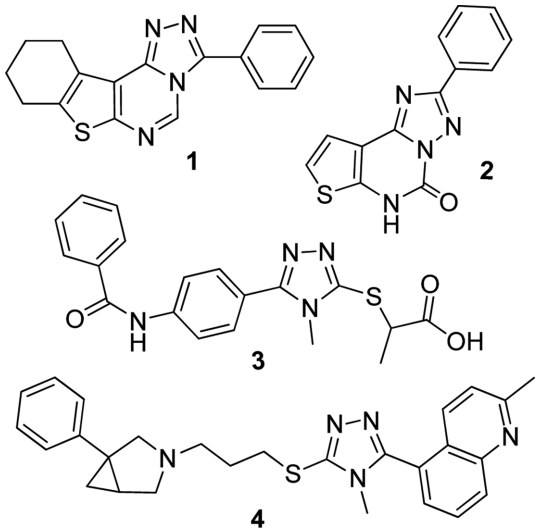


***Figure* 1.** Thienotriazolopyrimidines **1**, **2** and sulfur-linked triazoles **3**, **4**.

ture was diluted with water, and the solid was filtered, dried and recrystallized from ethanol to give **7** and **8**, respectively.

3-(Methylthio)thieno[3,2-*e*][1,2,4]triazolo[4,3-c] pyrimidine (7)

Yield 82%; mp 222–223 °C; ^{1}H NMR (DMSO-d_6): δ 9.60 (s, 1H), 8.05 (d, 1H, *J*= 5.6 Hz), 7.78 (d, 1H, *J*= 5.6 Hz), 2.71 (s, 3H); MS (ESI): (m/z) 222.4 (M^+). *Anal*. Calcd. For $C_8H_6N_4S_2$: C, 43.23; H, 2.72; N, 25.20. Found: C, 43.40; H, 2.63; N, 25.08.

3-(Methylthio)thieno[2,3-*e*][1,2,4]triazolo[4,3-c] pyrimidine (8)

Yield 88%; mp 155–157 °C; ^{1}H NMR (DMSO-d_6): δ 9.61 (s, 1H), 8.31 (d, 1H, *J*= 5.6 Hz), 7.72 (d, 1H, *J*= 5.6 Hz), 2.70 (s, 3H); MS (ESI): (m/z) 222.6 (M^+). *Anal*. Calcd. For $C_8H_6N_4S_2$: C, 43.23; H, 2.72; N, 25.20. Found: C, 43.11.; H, 2.69; N, 25.31.

General Procedure for the Preparation of 9 and 10

A mixture of **7** or **8** (5 mmol) and hydrazine hydrate (40 mmol) in ethanol (30 mL) was refluxed for 3 h. After cooling and evaporation, the solid formed was filtered, dried and recrystallized from ethanol to give **9** and **10**, respectively.

3-Hydrazinylthieno[3,2-*e*][1,2,4]triazolo[4,3-c] pyrimidine (9)

Yield 78%; mp 260–262 °C; ^{1}H NMR (DMSO-d_6): δ 8.48 (s, 1H), 8.03 (d, 1H, *J*= 5.6 Hz), 7.33 (d, 1H, *J*= 5.6 Hz); MS (ESI): (m/z) 206.5 (M^+). *Anal*. Calcd. For $C_7H_6N_6S$: C, 40.77; H, 2.93; N, 40.75. Found: C, 40.88; H, 2.89; N, 40.56.

3-Hydrazinylthieno[3,2-*e*][1,2,4]triazolo[4,3-c] pyrimidine (10)

Yield 75%; mp 264–266 °C; ^{1}H NMR (DMSO-d_6): δ 8.39 (s, 1H), 7.75 (d, 1H, *J*= 5.6 Hz), 7.55 (d, 1H, *J*= 5.6 Hz); MS (ESI): (m/z) 206.1 (M^+). *Anal*. Calcd. For $C_7H_6N_6S$: C, 40.77; H, 2.93; N, 40.75. Found: C, 40.68; H, 2.83; N, 40.68.

General Procedure for the Preparation of 11 and 12

A mixture of **9** or **10** (3 mmol) and carbon disulfide (30 mmol) in ethanolic potassium hydroxide (10%, 20 mL) was refluxed for 6 h. After cooling and evaporation of solvent, the residue was dissolved in water and acidified by adding 10% HCl. The solid formed was filtered, dried and recrystallized from ethanol to give **11** and **12**, respectively.

[1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[3,2-*e*] pyrimidine-9(8*H*)-thione (11)

Yield 80%; mp 256–258 °C; ^{1}H NMR (DMSO-d_6): δ 13.5 (s, 1H), 9.45 (s, 1H), 8.10 (d, 1H, *J*= 5.6 Hz), 7.56 (d, 1H, *J*= 5.6 Hz); MS (ESI): (m/z) 248.1 (M^+). *Anal*. Calcd. For $C_8H_4N_6S_2$: C, 38.70; H, 1.62; N, 33.85. Found: C, 38.88; H, 1.69; N, 33.69.

[1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[2,3-*e*]pyrimidine-9(8*H*)-thione (12)

Yield 80%; mp 279–281 °C; ^{1}H NMR (DMSO-d_6): δ 14.0 (s, 1H), 8.90 (s, 1H), 8.30 (d, 1H, *J*= 5.6 Hz), 7.51 (d, 1H, *J*= 5.6 Hz); MS (ESI): (m/z) 248.5 (M^+). *Anal*. Calcd. For $C_8H_4N_6S_2$: C, 38.70; H, 1.62; N, 33.85. Found: C, 38.80; H, 1.55; N, 33.70.

General Procedure for the Preparation of 13a–f and 14a–f

Sodium acetate (2 mmol) was added to a solution of **11** or **12** (1.2 mmol) in ethanol (20 mL) with stirring at room temperature. After 5 min, an α-bromocarboxylic acid (1.2 mmol) was slowly added in small portions and the resulting solution was heated at reflux for 6 h. After cooling, the solid was filtered, washed with water and recrystallized from ethanol or ethyl acetate to give products, respectively.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidin-9-ylthio)-2-phenylacetic acid (13a)

Yield 71%; mp 223–224 °C; ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 1H), 8.01 (d, 1H, *J*= 5.6 Hz), 7.73 (d, 1H, *J*= 5.6 Hz), 7.38 (m, 2H), 7.25–7.18 (m, 3H), 5.55 (s, 1H); MS (ESI): (m/z) 382.2 (M^+). *Anal*. Calcd. For $C_{16}H_{10}N_6O_2S_2$: C, 50.25; H, 2.64; N, 21.98. Found: C, 50.38; H, 2.59; N, 22.10.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidin-9-ylthio)-2-(2-chlorophenyl)acetic acid (13b)

Yield 78%; mp 246–247 °C; ^{1}H NMR (DMSO-d_6): δ 9.56 (s, 1H), 8.04 (d, 1H, *J*= 5.6 Hz), 7.75 (d, 1H, *J*= 5.6 Hz), 7.56 (d, 1H), 7.49 (d, 1H), 7.44–7.38 (m, 2H), 5.72 (s, 1H); MS (ESI): (m/z) 416.9 (M^+). *Anal*. Calcd. For $C_{16}H_9ClN_6O_2S_2$: C, 46.10; H, 2.18; N, 20.16. Found: C, 46.01; H, 2.22; N, 20.30.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidin-9-ylthio)-2-(3-chlorophenyl)acetic acid (13c)

Yield 77%; mp 243–244 °C; ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 1H), 8.02 (d, 1H, *J*= 5.6 Hz), 7.72 (d, 1H, *J*= 5.6

Hz), 7.59 (s, 1H), 7.44 (m, 1H), 7.35–7.27 (m, 2H), 5.88 (s, 1H); MS (ESI): (m/z) 416.3 (M^+). *Anal*. Calcd. For $C_{16}H_9ClN_6O_2S_2$: C, 46.10; H, 2.18; N, 20.16. Found: C, 45.96; H, 2.08; N, 20.05.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidin-9-ylthio)-2-(4-chlorophenyl)acetic acid (13d)

Yield 86%; mp 240–242 °C; ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H), 8.03 (d, 1H, *J* = 5.6 Hz), 7.76 (d, 1H, *J* = 5.6 Hz), 7.50 (d, 2H), 7.31 (d, 2H), 5.91 (s, 1H); MS (ESI): (m/z) 416.3 (M^+). *Anal*. Calcd. For $C_{16}H_9ClN_6O_2S_2$: C, 46.10; H, 2.18; N, 20.16. Found: C, 46.19; H, 2.04; N, 20.24.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidin-9-ylthio)-2-(4-bromophenyl)acetic acid (13e)

Yield 66%; mp 266–267 °C; ^{1}H NMR (DMSO-d_6): δ 9.60 (s, 1H), 8.07 (d, 1H, *J* = 5.6 Hz), 7.78 (d, 1H, *J* = 5.6 Hz), 7.58 (d, 2H), 7.50 (d, 2H), 5.77 (s, 1H); MS (ESI): (m/z) 461.8 (M^+). *Anal*. Calcd. For $C_{16}H_9BrN_6O_2S_2$: C, 41.66; H, 1.97; N, 18.22. Found: C, 41.61; H, 2.07; N, 18.39.

2-([1,2,4]triazolo[4',3':1,5][1,2,4]triazolo[4,3-c]thieno-[3,2-e]pyrimidin-9-ylthio)propanoic acid (13f)

Yield 38%; mp 122–123 °C; ^{1}H NMR (DMSO-d_6): δ 9.56 (s, 1H), 8.05 (d, 1H, *J* = 5.6 Hz), 7.73 (d, 1H, *J* = 5.6 Hz), 4.33 (q, 1H), 1.42 (d, 3H); MS (ESI): (m/z) 320.8 (M^+). *Anal*. Calcd. For $C_{11}H_8N_6O_2S_2$: C, 41.24; H, 2.52; N, 26.23. Found: C, 41.10; H, 2.59; N, 26.40.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[2,3-*e*]pyrimidin-9-ylthio)-2-phenylacetic acid (14a)

Yield 73%; mp 202–203 °C; ^{1}H NMR (DMSO-d_6): δ 9.48 (s, 1H), 8.24 (d, 1H, *J* = 5.6 Hz), 7.66 (d, 1H, *J* = 5.6 Hz), 7.55 (m, 2H), 7.32–7.20 (m, 3H), 5.37 (s, 1H); MS (ESI): (m/z) 382.6 (M^+). *Anal*. Calcd. For $C_{16}H_{10}N_6O_2S_2$: C, 50.25; H, 2.64; N, 21.98. Found: C, 50.20; H, 2.56; N, 21.85.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[2,3-*e*]pyrimidin-9-ylthio)-2-(2-chlorophenyl)acetic acid (14b)

Yield 82%; mp 217–218 °C; ^{1}H NMR (DMSO-d_6): δ 9.48 (s, 1H), 8.28 (d, 1H, *J* = 5.6 Hz), 7.71 (d, 1H, *J* = 5.6 Hz), 7.67 (d, 1H), 7.58 (d, 1H), 7.35–7.25 (m, 2H), 5.81 (s, 1H); MS (ESI): (m/z) 416.9 (M^+). *Anal*. Calcd. For $C_{16}H_9ClN_6O_2S_2$: C, 46.10; H, 2.18; N, 20.16. Found: C, 46.22; H, 2.21; N, 20.01.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[2,3-*e*]pyrimidin-9-ylthio)-2-(3-chlorophenyl)acetic acid (14c)

Yield 75%; mp 237–239 °C; ^{1}H NMR (DMSO-d_6): δ 9.48 (s, 1H), 8.24 (d, 1H, *J* = 5.6 Hz), 7.66 (d, 1H, *J* = 5.6 Hz), 7.58 (s, 1H), 7.44 (m, 1H), 7.30-7.21 (m, 2H), 5.32 (s, 1H); MS (ESI): (m/z) 416.8 (M^+). *Anal*. Calcd. For $C_{16}H_9ClN_6O_2S_2$: C, 46.10; H, 2.18; N, 20.16. Found: C, 46.22; H, 2.10; N, 20.30.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[2,3-*e*]pyrimidin-9-ylthio)-2-(4-chlorophenyl)acetic acid (14d)

Yield 80%; mp 208–210 °C; ^{1}H NMR (DMSO-d_6): δ 9.44 (s, 1H), 8.30 (d, 1H, *J* = 5.6 Hz), 7.78 (d, 1H, *J* = 5.6 Hz), 7.58 (d, 2H), 7.38 (d, 2H), 5.62 (s, 1H); MS (ESI): (m/z) 416.5 (M^+). *Anal*. Calcd. For $C_{16}H_9ClN_6O_2S_2$: C, 46.10; H, 2.18; N, 20.16. Found: C, 46.23; H, 2.10; N, 20.04.

2-([1,2,4]Triazolo[4',3':1,5][1,2,4]triazolo[4,3-*c*]thieno-[2,32-*e*]pyrimidin-9-ylthio)-2-(4-bromophenyl)acetic acid (14e)

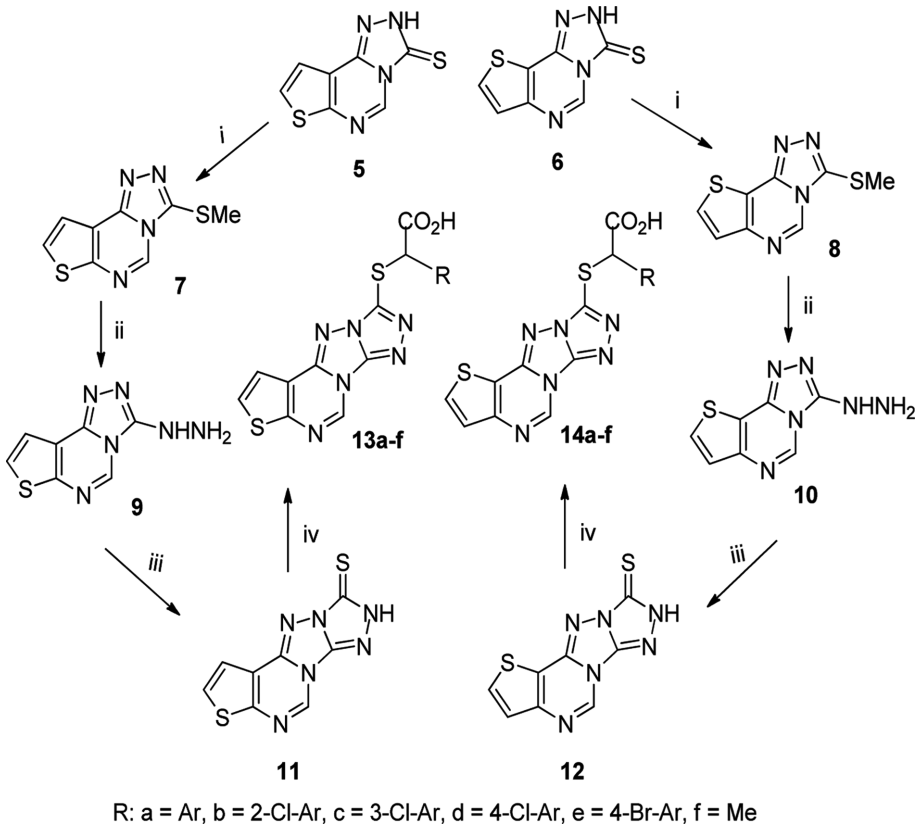
Yield 72%; mp 243–245 °C; ^{1}H NMR (DMSO-d_6): δ 9.48 (s, 1H), 8.23 (d, 1H, *J* = 5.6 Hz), 7.74 (d, 1H, *J* = 5.6 Hz), 7.48 (d, 2H), 7.38 (d, 2H), 5.28 (s, 1H); MS (ESI): (m/z) 461.8 (M^+). *Anal*. Calcd. For $C_{16}H_9BrN_6O_2S_2$: C, 41.66; H, 1.97; N, 18.22. Found: C, 41.50; H, 2.09; N, 18.10.

2-([1,2,4]triazolo[4',3':1,5][1,2,4]triazolo[4,3-c]thieno-[3,2-e]pyrimidin-9-ylthio)propanoic acid (14f)

Yield 40%; mp 102–104 °C; ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 1H), 8.28 (d, 1H, *J* = 5.6 Hz), 7.70 (d, 1H, *J* = 5.6 Hz), 4.28 (q, 1H), 1.20 (d, 3H); MS (ESI): (m/z) 320.8 (M^+). *Anal*. Calcd. For $C_{11}H_8N_6O_2S_2$: C, 41.24; H, 2.52; N, 26.23. Found: C, 41.12; H, 2.41; N, 26.34.

RESULTS AND DISCUSSION

The required starting materials **5** and **6** were prepared according to the reported procedure.[6(f)] Treatment of **5** or **6** with methyl iodide in the presence of sodium acetate, and the subsequent reaction of the resultant compounds with hydrazine led to the replacement of thiomethyl group to afford 3-hydrazinothienotriazolopyrimidines **9** and **10** (*Scheme* 1). This substitution reaction gave better yield compared to the reaction of chlorothienotriazolopyrimidine (prepared using $SOCl_2$/DMF) with hydrazine.[6(a)] Electrophilic attack of carbon disulfide in the presence of ethanolic KOH on the hydrazines **9** and **10** gave **11** and **12**, respectively, via



***Scheme* 1.** Synthesis of **13** and **14**. Reagents and conditions: (i) CH_3I, CH_3CO_2Na, EtOH, rt; (ii) NH_2NH_2, EtOH, reflux; (iii) CS_2, KOH, EtOH, reflux; iv) α-bromocarboxylic acid, CH_3CO_2Na, EtOH, reflux.

further cyclization and elimination of hydrogen sulfide. The new sulfur-linked tetracyclic compounds, **13** and **14**, were prepared in good yield by treatment of **11** or **12** with α-bromophenylacetic acids or α-bromopropanoic acid in refluxing ethanol containing sodium acetate (*Table* 1). It should be, however, noted that α-bromopropanoic acid is much less reactive to **11** and **12** when compared to α-bromophenylacetic acids (entry 6, 12, *Table* 1). The structural assignment of **13** and **14** was based upon spectroscopic and microanalytical data. For example, **13a** did not show the NH signal near at δ 13–14 in ^{1}H NMR spectrum and characteristic peak at 3210 cm^{-1} in IR spectrum that have found in the precursor **11**, but instead showed ^{1}H signals at δ 7.18–7.38 for aromatic protons and a singlet at δ 5.55 for benzylic proton indicating the formation of desired tetracyclic triazole product containing thiophenylacetic acid. The mass spectrum of **13a** showed a molecular ion peak at m/z = 382 (M^+) for $C_{16}H_{10}N_6O_2S_2$, and also showed ions at m/z = 364, 338 and 248 which could be attributed to the loss of H_2O and CO_2, respectively, and cleavage of sulfur bond from the molecular ion.

***Table* 1.** Preparation of compounds **13a–f** and **14a–f**

Entry	R	Product	Mp (°C)	Yield (%)[a]
1	Ar	**13a**	223–224	71
2	2-ClAr	**13b**	246–247	78
3	3-ClAr	**13c**	243–244	77
4	4-ClAr	**13d**	240–242	86
5	4-BrAr	**13e**	266–267	66
6	Me	**13f**	122–123	38
7	Ar	**14a**	202–203	73
8	2-ClAr	**14b**	217–218	82
9	3-ClAr	**14c**	237–239	75
10	4-ClAr	**14d**	208–210	80
11	4-BrAr	**14e**	243–245	72
12	Me	**14f**	102–104	40

[a]Isolated yields.

CONCLUSION

In conclusion, we report the synthesis of new sulfur-linked tetracyclic thienotriazolopyrimidine compounds **13** and **14**, respectively, from **5** and **6** through cyclization

of hydrazine derivatives **9** or **10** with carbon disulfide, and the subsequent reaction with α-bromophenylacetic acids or α-bromopropanoic acid. Further biological work on IL-6/STAT3 inhibitory activity is under way.

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