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Preliminary Communication

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Synthesis of thiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine derivatives

Abstract: Synthesis of a series of 8-phenylthiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(4*H*)-one and 5-piperazino-8-phenylthiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*] pyrmidine compounds with promising biological activity is described.

Keywords: cyclization; phenylhydrazide; piperazine; thiazolotriazolopyrimidine.

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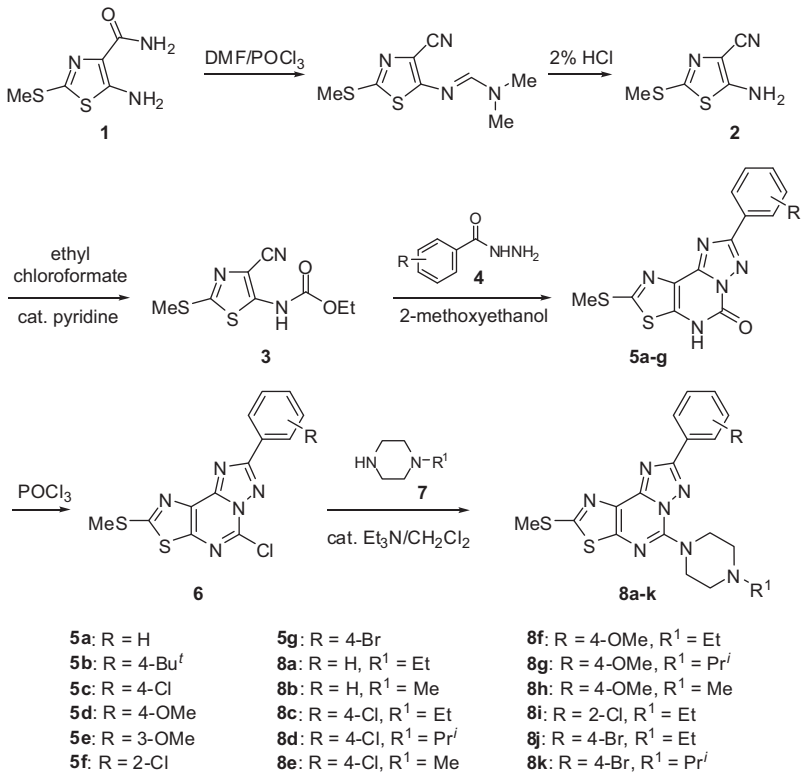
Much attention has been recently paid to the synthesis of thienotriazolopyrimidines and thienotriazolopyrimidinones because of their biological activities such as inhibitors of Shiga toxin trafficking and A_1/A_2 or A_{2A}/A_3 adenosine receptor antagonists, respectively [1–3]. We have previously designed and synthesized thienotriazolopyrimidine derivatives with promising biological activity [4–8]. By contrast, thiazolopyrimidine derivatives have been reported to possess pharmacological activities including A_{2A} adenosine receptor antagonism, CDC25B phosphatase inhibition, and antitumor and anticancer properties [9–12]. Keeping in mind the potential biological activities of thienotriazolopyrimidine and thiazolopyrimidines, it was perceived that the synthesis of new thiazolotriazolopyrimidines might result in the formation of some valuable molecules with a synergistic biological effect. Thiazolotriazolopyrimidinethiones are known to exhibit anti-Parkinsonian and A_{2A} adenosine receptor antagonist activities [13, 14]. Therefore, here we describe a synthesis of 8-phenylthiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(4*H*)-one and 5-piperazinyl-8-phenylthiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrmidine derivatives in the hope of obtaining compounds of diverse biological activities.

The required starting material 5-amino-2-(methylthio) thiazole-4-carboxamide (**1** in Scheme 1) was prepared through a series of reactions starting with ethyl aminocyanoacetate according to a previously reported procedure [15]. Compound **1** was converted into 5-amino-2-(methylthio)thiazole-4-carbonitrile (**2**) using DMF/$POCl_3$ and acidic hydrolysis [16]. The reaction of **2** with ethyl chloroformate in the presence of pyridine afforded ethyl 4-cyano-2-(methylthio)thiazol-5-ylcarbamate (**3**) in 76% yield. 8-Phenylthiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(4*H*)-one and its derivatives **5a–g** were obtained in good yield by treatment of **3** with benzohydrazide derivatives **4** in refluxing 2-methoxyethanol for 24 h, as shown in Scheme 1. Compounds **5** were treated with excess $POCl_3$ to form the chlorinated thiazolotriazolopyrimidines **6**. Other chlorinated thiazolotriazolopyrimidines except **6a** (R=H) were used in the subsequent reaction without further purification. The displacement of chlorine of **6** by piperazines **7** in the presence of triethylamine led to the final 5-piperazino-8-phenylthiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*] pyrimidines **8**. The structures of all new compounds were confirmed by elemental analyses, MS and NMR spectra data. The preliminary biological test [17] of the synthesized compounds **6** and **8** for human A_3 adenosine receptor showed that **5b** and **8b** have affinity values of 5.0 and 8.2 μM, respectively. The biological studies with compounds **5** and **8** are in progress.

Experimental

Melting points were measured 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 using Merck silica gel (70–230 mesh). ^{1}H NMR spectra were recorded on a Bruker DRX-300 FT-NMR spectrometer (300 MHz) in DMSO-d_6 with Me_4Si as internal standard. Electron impact mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Compounds were biologically evaluated *in vitro* as reported previously [17].

Ethyl 4-cyano-2-(methylthio)thiazol-5-ylcarbamate (3) To ethyl chloroformate (30 mL) was added pyridine (1 mL) and **2** (1.71 g, 10 mmol), and the resultant mixture was heated under reflux for 4 h.



Scheme 1 Synthesis of **5a–g** and **8a–k**.

The resultant solid product **3** was filtered off, washed with cold water, and crystallized from ethanol; yield 76%; mp 137–139°C; ^{1}H NMR: δ 4.18 (q, 2H, *J* = 7 Hz, O–CH_2), 2.62 (s, 3H, S–Me), 1.22 (t, 3H, *J* = 7 Hz, –CH_3); MS: m/z 243 (M^+). Anal. Calcd for $C_9H_{11}N_3OS_2$: C, 44.79; H, 4.59; N, 17.41. Found: C, 44.60; H, 4.66; N, 17.60.

General procedure for the preparation of thiazolotriazolopyrimidinones 5a–g

To a solution of **3** (1.2 mmol) in 2-methoxyethanol (20 mL), the appropriate benzohydrazide derivative **4** (1.2 mmol) was added with stirring and the resulting solution was heated at reflux for 24 h. After cooling, the resultant solid product **5** was filtered, washed with water, and crystallized from ethanol.

2-(Methylthio)-8-phenylthiazolo[4,5-*e*][1,2,4]triazolo[1,5-*c*] pyrimidin-5(4*H*)-one (5a) This compound was obtained in 68% yield; mp 258–260°C; ^{1}H NMR: δ 7.97 (d, 2H, *J* = 8.4 Hz), 7.61 (t, 1H, *J* = 8.4 Hz), 7.51 (t, 2H, *J* = 8.4 Hz), 2.74 (s, 3H, -SMe), MS: m/z 315 (M^+). Anal. Calcd for $C_{13}H_9N_5OS_2$: C, 49.51; H, 2.88; N, 22.21. Found: C, 49.79; H, 2.73; N, 22.10.

8-(4-*tert*-Butylphenyl)-2-(methylthio)thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-5(4*H*)-one (5b) This compound was obtained in 72% yield; mp 269–270°C; ^{1}H NMR: δ 7.90 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 2.68 (s, 3H), 1.28 (s, 9H, *tert*-Bu), MS: m/z 372 (M^+). Anal. Calcd for $C_{17}H_{17}N_5OS_2$: C, 54.96; H, 4.61; N, 18.85. Found: C, 54.82.79; H, 4.72; N, 18.77.

8-(4-Chlorophenyl)-2-(methylthio)thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-5(4*H*)-one (5c) This compound was obtained in 75% yield; mp 270–272°C; ^{1}H NMR: δ 7.96 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 2.68 (s, 3H), MS: m/z 349 (M^+). Anal. Calcd for $C_{13}H_8ClN_5OS_2$: C, 44.63; H, 2.31; N, 20.02. Found: C, 44.65; H, 2.38; N, 19.91.

8-(4-Methoxyphenyl)-2-(methylthio)thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-5(4*H*)-one (5d) This compound was obtained in 68% yield; mp 255–257°C; ^{1}H NMR: δ 7.93 (d, 2H, *J* = 8.4 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 3.80 (s, 3H, -OMe), 2.70 (s, 3H), MS: m/z 345 (M^+). Anal. Calcd for $C_{14}H_{11}N_5O_2S_2$: C, 48.68; H, 3.21; N, 20.28. Found: C, 48.77; H, 3.36; N, 20.11.

8-(3-Methoxyphenyl)-2-(methylthio)thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-5(4*H*)-one (5e) This compound was obtained in 59% yield; mp 217–219°C; ^{1}H NMR: δ 7.88 (m, 1H), 7.46 (m, 2H), 7.00 (m, 1H), 3.78 (s, 3H), 2.68 (s, 3H), MS: m/z 345 (M^+). Anal. Calcd for $C_{14}H_{11}N_5O_2S_2$: C, 48.68; H, 3.21; N, 20.28. Found: C, 48.59; H, 3.29; N, 20.15.

8-(2-Chlorophenyl)-2-(methylthio)thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-5(4*H*)-one (5f) This compound was obtained in 71% yield; mp 247–248°C; ^{1}H NMR: δ 8.31 (d, 1H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.43–7.40 (m, 2H), 2.65 (s, 3H), MS: m/z 349 (M^+). Anal. Calcd for $C_{13}H_8ClN_5OS_2$: C, 44.63; H, 2.31; N, 20.02. Found: C, 44.78; H, 2.40; N, 20.15.

8-(4-Bromophenyl)-2-(methylthio)thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-5(4*H*)-one (5g) The compound was obtained in 66% yield, mp 253–255°C; ^{1}H NMR: 7.87 (d, 2H, *J* = 8.4 Hz),

7.73 (d, 2H, *J* = 8.4 Hz), 2.67 (s, 3H), MS: m/z 393 (M^+). Anal. Calcd for $C_{13}H_8BrN_5OS_2$: C, 39.60; H, 2.05; N, 17.76. Found: C, 39.48; H, 2.11; N, 17.88.

5-Chloro-2-(methylthio)-8-phenylthiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (6a) A solution of **5a** (3.15 g, 10 mmol) in phosphorus oxychloride (20 mL) was heated at reflux for 10 h. The excess phosphorus oxychloride was removed under reduced pressure, and the residue was diluted with chloroform and concentrated. The crude product was purified with column chromatography (ethyl acetate:hexane, 1:2) to give **6a** (2.60 g, 78%); mp 218–220°C; ^{1}H NMR: 7.97 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 1H, *J* = 8.4 Hz), 7.52 (t, 2H, *J* = 8.4 Hz), 2.83 (s, 3H), MS: m/z 333 (M^+). Anal. Calcd for $C_{13}H_8ClN_5S_2$: C, 46.77; H, 2.42; N, 20.98. Found: C, 46.60; H, 2.49; N, 20.83.

General procedure for the preparation of 5-piperazino-8-phenylthiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines 8a–k

To a solution of the appropriate **6** (2.0 mmol) in dichloromethane (15 mL), piperazine derivatives **7** (2.2 mmol) and triethylamine (0.5 mL) were added. The mixture was stirred at room temperature for 5 h and then concentrated. The residue was washed with water and recrystallized from ethanol to afford the product.

5-(4-Ethylpiperazino)-2-(methylthio)-8-phenylthiazolo[4,5-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine (8a) This compound was obtained in 76% yield; mp 233–235°C; ^{1}H NMR: δ 7.97 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 1H, *J* = 8.4 Hz), 7.51 (t, 2H, *J* = 8.4 Hz), 4.17 (bs, 4H, N–CH_2–), 2.86 (s, 3H, S–Me), 2.74 (bs, 4H, –CH_2–N), 2.55 (q, 2H, *J* = 6.8 Hz, –CH_2–), 1.17 (t, 3H, *J* = 6.8 Hz, –CH_3), MS: m/z 412 (M^+). Anal. Calcd for $C_{19}H_{21}N_7S_2$: C, 55.45; H, 5.14; N, 23.82. Found: C, 55.59; H, 5.25; N, 23.70.

5-(4-Methylpiperazino)-2-(methylthio)-8-phenylthiazolo[4,5-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine (8b) This compound was obtained in 70% yield, mp 242–243°C; ^{1}H NMR: δ 7.97 (d, 2H, *J* = 8.4 Hz), 7.61 (d, 1H, *J* = 8.4 Hz), 7.52 (t, 2H, *J* = 8.4 Hz), 4.15 (bs, 4H, N–CH_2–), 2.86 (s, 3H, S-Me), 2.69 (bs, 4H, –CH_2–N), 2.41 (s, 3H, N-Me), MS: m/z 397 (M^+). Anal. Calcd for $C_{18}H_{19}N_7S_2$: C, 54.39; H, 4.82; N, 24.66. Found: C, 54.22; H, 4.88; N, 24.50.

8-(4-Chlorophenyl)-5-(4-ethylpiperazin-1-yl)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8c) The compound was obtained in 77% yield, mp 192–193°C; ^{1}H NMR: δ 8.31 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 4.14 (bs, 4H, N–CH_2–), 2.85 (s, 3H, S–Me), 2.72 (bs, 4H, –CH_2–N), 2.54 (q, 2H, *J* = 6.8 Hz, –CH_2–), 1.17 (t, 3H, *J* = 6.8 Hz, –CH_3), MS: m/z 446 (M^+). Anal. Calcd for $C_{19}H_{20}ClN_7S_2$: C, 51.17; H, 4.52; N, 21.98. Found: C, 51.29; H, 4.46; N, 21.85.

8-(4-Chlorophenyl)-5-(4-isopropylpiperazino)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8d) This compound was obtained in 62% yield; mp 176–178°C; ^{1}H NMR: δ 8.32 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 4.14 (bs, 4H, N–CH_2–), 2.86 (s, 3H, S-Me), 2.80 (bs, 4H, –CH_2–N), 2.50 (m, 1H, –CH–), 1.13 (d, 6H, *J* = 6.8 Hz, –Me_2), MS: m/z 460 (M^+). Anal. Calcd for $C_{20}H_{22}ClN_7S_2$: C, 52.22; H, 4.82; N, 21.31. Found: C, 52.10; H, 4.90; N, 21.44.

8-(4-Chlorophenyl)-5-(4-methylpiperazino)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8e) This compound was obtained in 66% yield; mp 201–203°C; ^{1}H NMR: δ 8.33 (d, 2H, *J* = 8.4 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 4.13 (bs, 4H, N–CH_2–), 2.86 (s, 3H, S-Me), 2.67 (bs, 4H, –CH_2–N), 2.40 (s, 3H, -N-Me), MS: m/z 432 (M^+). Anal. Calcd for $C_{18}H_{18}ClN_7S_2$: C, 50.05; H, 4.20; N, 22.70. Found: C, 50.18; H, 4.11; N, 22.59.

5-(4-Ethylpiperazino)-8-(4-methoxyphenyl)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8f) This compound was obtained in 56% yield; mp 195–197°C; ^{1}H NMR: δ 8.08 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 4.15 (bs, 4H, N–CH_2–), 3.89 (s, 3H, O-Me), 2.86 (s, 3H, S-Me), 2.71 (bs, 4H, –CH_2–N), 2.54 (q, 2H, *J* = 6.8 Hz, –CH_2–), 1.17 (t, 3H, *J* = 6.8 Hz, –CH_3), MS: m/z 442 (M^+). Anal. Calcd for $C_{20}H_{23}N_7OS_2$: C, 54.40; H, 5.25; N, 22.20. Found: C, 54.28; H, 5.20; N, 22.10.

5-(4-Isopropylpiperazino)-8-(4-methoxyphenyl)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8g) The compound was obtained in 60% yield; mp 198–199°C; ^{1}H NMR: δ 8.08 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 4.13 (bs, 4H, N–CH_2–), 3.89 (s, 3H, O–Me), 2.85 (s, 3H, S–Me), 2.72 (bs, 4H, –CH_2–N), 2.52 (m, 1H, –CH–), 1.13 (d, 6H, *J* = 6.8 Hz, –Me_2), MS: m/z 456 (M^+). Anal. Calcd for $C_{21}H_{25}N_7OS_2$: C, 55.36; H, 5.53; N, 21.52. Found: C, 55.49; H, 5.44; N, 21.66.

8-(4-Methoxyphenyl)-5-(4-methylpiperazino)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8h) The compound was obtained in 60% yield; mp 175–177°C; ^{1}H NMR: δ 8.33 (d, 2H, *J* = 8.4 Hz), 7.07 (d, 2H, *J* = 8.4 Hz), 4.15 (bs, 4H, N–CH_2–), 3.90 (s, 3H, O–Me), 2.86 (s, 3H, S–Me), 2.70 (bs, 4H, –CH_2–N), 2.42 (s, 3H, N–Me), MS: m/z 428 (M^+). Anal. Calcd for $C_{19}H_{21}N_7OS_2$: C, 53.38; H, 4.95; N, 22.93. Found: C, 53.20; H, 5.01; N, 22.79.

8-(2-Chlorophenyl)-5-(4-ethylpiperazino)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8i) This compound was obtained in 79% yield; mp 187–189°C; ^{1}H NMR: δ 8.31 (d, 1H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.42–7.40 (m, 2H), 4.20 (bs, 4H, –N–CH_2–), 2.84 (s, 3H, S-Me), 2.70 (bs, 4H, –CH_2–N), 2.52 (q, 2H, *J* = 6.8 Hz, –CH_2–), 1.15 (t, 3H, *J* = 6.8 Hz, –CH_3), MS: m/z 446 (M^+). Anal. Calcd for $C_{19}H_{20}ClN_7S_2$: C, 51.17; H, 4.52; N, 21.98. Found: C, 50.07; H, 4.60; N, 21.90.

8-(4-Bromophenyl)-5-(4-ethylpiperazino)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8j) The compound was obtained in 66% yield; mp 189–190°C; ^{1}H NMR: δ 8.25 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 4.15 (bs, 4H, N–CH_2–), 2.86 (s, 3H, S–Me), 2.73 (bs, 4H, –CH_2–N), 2.54 (q, 2H, *J* = 6.8 Hz, –CH_2–), 1.17 (t, 3H, *J* = 6.8 Hz, –CH_3), MS: m/z 490 (M^+). Anal. Calcd for $C_{19}H_{20}BrN_7S_2$: C, 46.53; H, 4.11; N, 19.99. Found: C, 46.71; H, 4.05; N, 20.11.

8-(4-Bromophenyl)-5-(4-isopropylpiperazino)-2-(methylthio) thiazolo[4,5-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8k) The compound was obtained in 72% yield; mp 191–193°C; ^{1}H NMR: δ 8.25 (d, 2H, *J* = 8.4 Hz), 7.62 (d, 2H, *J* = 8.4 Hz), 4.16 (bs, 4H, N–CH_2–), 2.86 (s, 3H, S–Me), 2.82 (bs, 4H, –CH_2–N), 2.50 (m, 1H, –CH–), 1.15 (d, 6H, *J* = 6.8 Hz, –Me_2), MS: m/z 504 (M^+). Anal. Calcd for $C_{20}H_{22}BrN_7S_2$: C, 47.62; H, 4.40; N, 19.44. Found: C, 47.59; H, 4.26; N, 19.29.

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References

[1] Guetzoyan, L. J.; Spooner, R. A.; Lord, J. M.; Roberts, L. M.; Clarkson, G. J. Simple oxidation of pyrimidinylhydrazones to triazolopyrimidines and their inhibition of Shiga toxin trafficking. *Eur. J. Med. Chem.* **2010**, *45*, 275–283.

[2] Prasad, M. R.; Rao, A. R.; Rao, P. S.; Rajan, K. S.; Meena, S.; Madhavi, K. Synthesis and adenosine receptor binding studies of some novel triazolothienopyrimidines. *Eur. J. Med. Chem.* **2008**, *43*, 614–620.

[3] Nagamatsu, T.; Ahmed, S.; Hossion, A. M. L.; Ohno, S. Synthesis of thieno[3,2-e][1,2,4] triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones via their [1,2,4]triazolo[4,3-*c*]pyrimidine compounds as new ring systems by Dimroth-type rearrangement. *Heterocycles* **2007**, *73*, 777–793.

[4] Whang, J.; Song, Y.-H. A facile one-pot synthesis of sulfur-linked thieno[1,2,4]triazolo[4,3-*c*]pyrimidine derivatives containing phenylpyrazole or thienopyrimidinylpyrazole moiety. *Heterocycles* **2012**, *85*, 155–164.

[5] Song, Y.-H.; Moon, J. Synthesis of new sulfur-linked di- and triheterocyclic compounds containing thienotriazolopyrimidine and triazolothiadiazole moieties. *Heterocycl. Commun.* **2011**, *17*, 135–138.

[6] Song, Y.-H.; Son, H. Y. Synthesis of new sulfur-linked 1,2,4-triazolothienopyrimidine and 1,2,4-triazolopyrazolopyrimidine derivatives containing fused heterocyclic pyrimidines. *J. Heterocycl. Chem*. **2010**, *47*, 1183–1187.

[7] Song, Y.-H.; Son, H. Y. Synthesis of new 1-phenylthieno[1,2,4] triazolo[4,3-*a*]pyrimidin-5(4*H*)-one derivative. *J. Heterocycl. Chem*. **2011**, *48*, 597–603.

[8] Jo, B. S.; Son, H. Y.; Song, Y.-H. A mild and efficient synthesis of new 3-phenyl-thienotriazolopyrimidine derivatives using iodobenzene diacetate. *Heterocycles* **2008**, *75*, 3091–3097.

[9] Luthra, P. M.; Mishra, C. B.; Jha, P. K.; Barodia, S. K. Synthesis of novel 7-imino-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-*d*] pyrimidine derivatives as adenosine A_{2A} receptor antagonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1214–1218.

[10] Kolb, S.; Mondesert, O.; Goddard, M. L.; Jullien, D.; Villoutreix, B. O.; Ducommun, B.; Garbay, C.; Braud, E. Development of novel thiazolopyrimidines as CDC25B phosphatase inhibitors. *Chem. Med. Chem*. **2009**, *4*, 633–648.

[11] Lin, R.; Johnson, S. G.; Connolly, P. J.; Wetter, S. K.; Binnun, E.; Hughes, T. V.; Murray, W. V.; Pandey, N. B.; Moreno-Mazza, S. J.; Adams, M.; et al. Synthesis and evaluation of 2,7-diamino-thiazolo[4,5-*d*] pyrimidine analogues as anti-tumor epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2333–2337.

[12] Selvam, T. P.; Karthick, V.; Kumar, P. V.; Ali, M. A. Synthesis and structure-activity relationship study of 2-(substituted benzylidene)-7-(4-fluorophenyl)-5-(furan-2-yl)-2*H*-thiazolo[3,2-*a*]pyrimidin-3(7*H*)-one derivatives as anticancer agents. *Drug Discov. Ther*. **2012**, *6*, 198–204.

[13] Azam, F.; Elgnidi, B. A.; Alkskas, I. A.; Ahmed, M. A. Design, synthesis and anti-Parkinsonian evaluation of 3-alkyl/aryl-8-(furan-2-yl)thiazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine-2(3*H*)-thiones against neuroleptic-induced catalepsy and oxidative stress in mice. *J. Enzyme Inhib. Med. Chem*. **2010**, *25*, 818–826.

[14] Mishra, C. B.; Barodia, S. K.; Prakash, A.; Senthil Kumar, J. B.; Luthra, P. M. Novel 8-(furan-2-yl)-3-substituted thiazolo[5,4-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine-2(3*H*)-thione derivatives as potential adenosine A(2A) receptor antagonists. *Bioorg. Med. Chem*. **2010**, *18*, 2491–2500.

[15] Cook, A. H.; Heilbron, S.; Smith, E. Studies in the azole series. Part XVII. The preparation and cyclization reaction of aminocyanoactamide. *J. Chem. Soc.* **1949**, 1440–1442.

[16] Sen, A. K.; Chattopadhyay, G. Synthesis of thiazolo[5,4-*d*] pyrimidines. *Indian J. Chem*. **1979**, *18B*, 307–311.

[17] Varani, K.; Merighi, S.; Gessi, S.; Klotz, K. N.; Leung, E.; Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Borea, P. A. [(3)H] MRE 3008F20: a novel antagonist radioligand for the pharmacological and biochemical characterization of human A(3) adenosine receptors. *Mol. Pharmacol.* **2000**, *57*, 968–975.