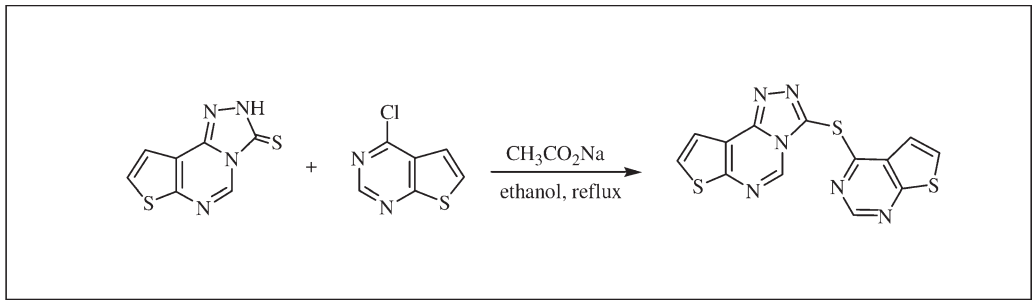
Synthesis of New Sulfur-Linked 1,2,4-Triazolothienopyrimidine and 1,2,4-Triazolopyrazolopyrimidine Derivatives Containing Fused Heterocyclic Pyrimidines

Yang-Heon Song* and Hoon Young Son

Department of Chemistry, Mokwon University, Daejeon 302-729, South Korea
*E-mail: yhsong@mokwon.ac.kr

Received August 29, 2009
DOI 10.1002/jhet.461
Published online 26 July 2010 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel *bis*-heterocyclic compounds **12–20** were synthesized by integrating fused heterocyclic pyrimidines, such as thienopyrimidine and pyrazolopyrimidine into the scaffold of thienotriazolopyrimidines, and pyrazolotriazolopyrimidines through a sulfur-linkage.

J. Heterocyclic Chem., **47**, 1183 (2010).

INTRODUCTION

The chemistry of heterocycles containing pyrimidine moiety have attracted considerable interest for many years because of their diverse biological activities, such as anti-inflammatory, anti-HIV-1, antimicrobial, and antitumor activities [1–4]. Some fused heterocyclic pyrimidines have acquired much importance because of their wide range of biological applications.

For instance, pyrazolopyrimidine **1** was as shown in Figure 1 investigated as antifungal and antibacterial agents [5], and other similar pyrazolopyrimidines were also reported to possess inhibitory activities of the insulin-like growth factor receptor (IGF-IR) and human cyclin-dependent kinase 2 [6,7]. Various triazolopyrimidine derivatives were known as dual thrombin/factor Xa inhibitors, human adenosine A_{2A} receptor ligands, and herbicides [8–10]. Also, new thienopyrimidine derivatives have been identified as potent inhibitors of VEGF receptor-2 kinase and selective and potent ligands for the 5-HT_3 receptor [11,12]. Furthermore, it has been noticed that introduction of an additional ring to the fused heterocyclic pyrimidines tends to exert profound influence in conferring new biological activities in these molecules. Recently, thienotriazolopyrimidine **2** and pyrazolotriazolopyrimidine **3** derivatives as tricyclic heterocyclic compounds (five-six-five ring systems) have been explored for adenosine A_1/A_{2A} or A_{2A}/A_3 receptor antagonists [13,14].

Starting from using the thienotriazolopyrimidine derivatives **4** and **5** which have been recently reported from our laboratories [15] and in continuation to our works for biologically active heterocyclic compounds [16] we now report the synthesis of new *bis*-heterocyclic compounds **12–20** prepared by integrating fused heterocyclic pyrimidines, such as thienopyrimidines and pyrazolopyrimidines into the scaffold of thienotriazolopyrimidines and pyrazolotriazolopyrimidines through a sulfur-linkage in the hope of obtaining compounds of diverse pharmaceutical activities.

RESULTS AND DISCUSSION

For the synthesis of key intermediates **9**, **10**, and **11**, 2-aminothiophene-3-carbonitrile and 3-aminothiophene-2-carboxamide as starting materials were obtained, respectively, according to the modified Gewald method [17]. 5-Amino-1-phenyl-1*H*-pyrazole-4-carbonitrile was also prepared by the reaction of phenylhydrazine with ethoxymethylenemalonitrile in refluxing ethanol [18]. Compounds **6** and **8** were obtained from the reaction of starting materials with triethyl orthoformate and subsequent cyclization with hydrazine. Condensation of 3-aminothiophene-2-carboxamide with aqueous formic acid and subsequent treatment with $POCl_3$ and hydrazine gave **7**, as shown Scheme 1 [15]. Electrophilic attack of CS_2 in the presence of ethanolic KOH on the hydrazines **6**, **7**, and **8** gave via further intramolecular cyclization and elimination of H_2S fused 1,2,4-triazolopyrimidine-3-thiones **9–11**, respectively, which exhibit a

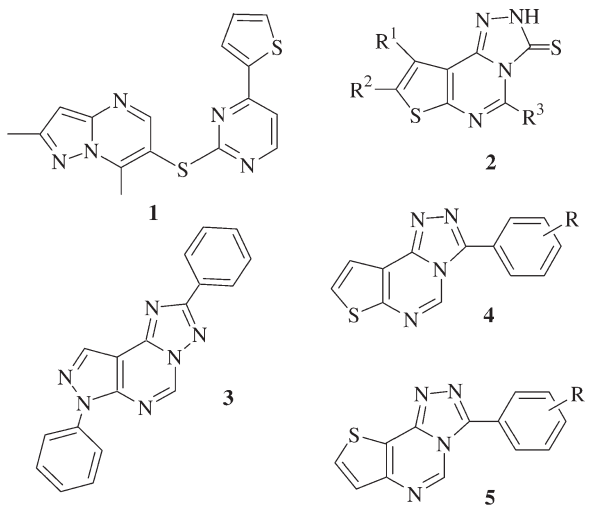


Figure 1. Compounds **1–5**.

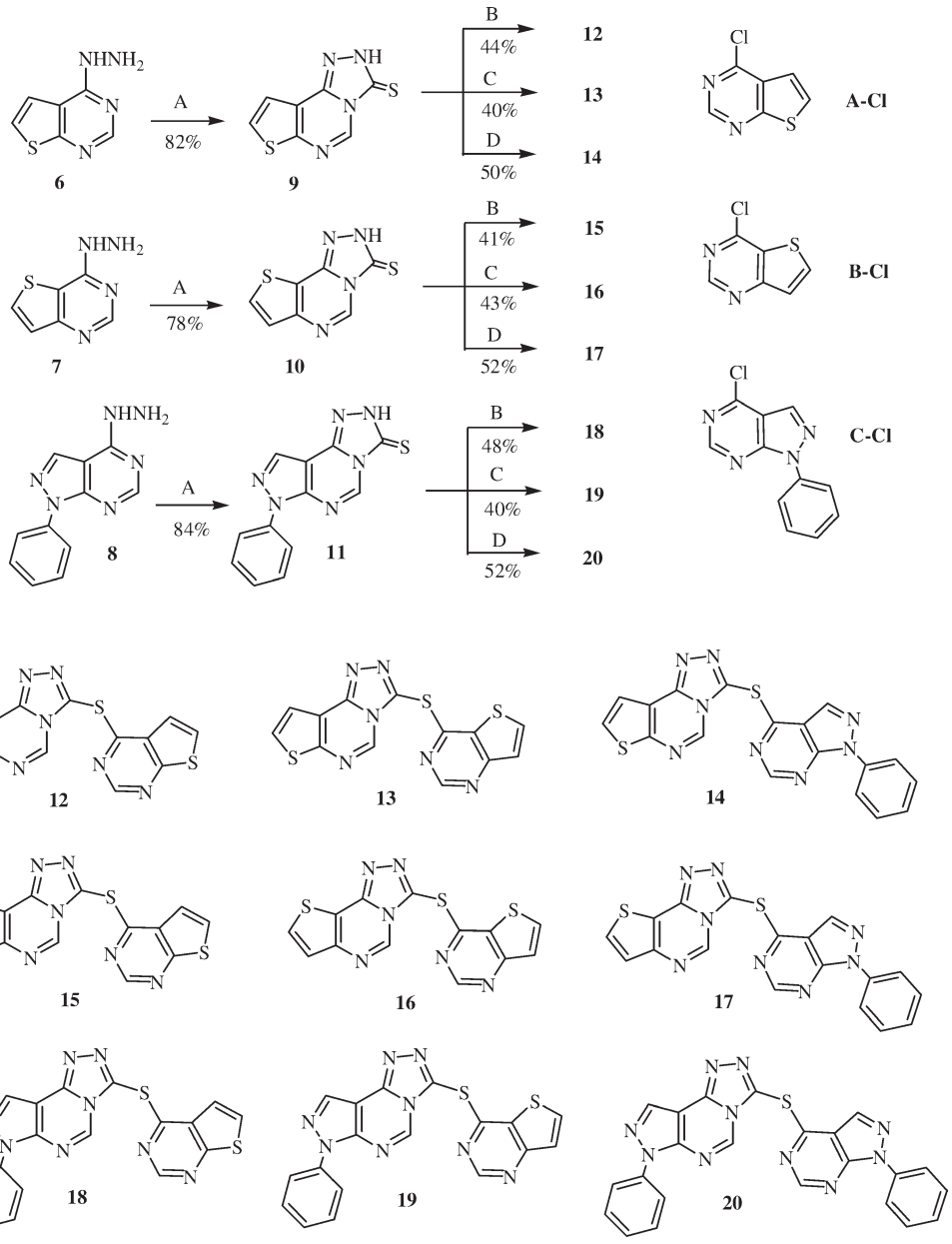
thione-thiol equilibrium. The structure of these compounds was confirmed by elemental analysis, ^{1}H-NMR and IR spectra. The IR spectra showed characteristic peaks at 1200 (weak) and 3190 cm^{-1} for the C=S and NH groups, respectively. The disappearance of the primary amino protons and the appearance of the secondary amino signal near at δ 14.0 in ^{1}H-NMR spectrum indicated the thione tautomer of cyclization products. The mass spectral data of **9** and **10**, for instance, showed a molecular ion peak at m/z 208, and also showed ion at m/z 135 which could be attributed to the loss of N—NH—C=S from the molecular ion.

The compounds **12–20** were prepared as shown Scheme 2 in moderate yield by treatment of fused 1,2,4-triazolopyrimidine-3-thiones **9–11** with chlorothienopyrimidines (**A-Cl** and **B-Cl**) or chlorophenylpyrazolopyrimidine (**C-Cl**) in refluxing ethanol containing sodium acetate. The structures of **12–20** were established on the basis of their spectral data and elemental analysis. The IR spectra of these compounds exhibited absorption bands in the region of 1630–1490 cm^{-1} for aromatic C=C, C=N stretching vibrations, and disappearance of NH and C=S stretching signals of cyclic thiourea. The ^{1}H-NMR spectra of 3-(thieno[2,3-*d*]pyrimidin-4-ylthio)-thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine **(12)**, for example, showed four doublet signals because of protons of two thiophenes, and two singlet signals attributed to protons of two pyrimidine rings. Thus, one pair of doublet signals at δ 8.11 and 7.85 corresponded to thiophene protons (H-8 and H-9) of thieno[3,2-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine ring, and the other one at δ 8.03 and 7.50 attributed to thiophene protons (H-5′ and H-6′) of thieno[2,3-*d*]pyrimidine ring. Two singlets at δ 9.77 and 8.81 were observed for pyrimidine proton (H-5) of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine ring, and pyrimidine proton (H-2′) of thieno[2,3-*d*]pyrimidine ring, respectively. The mass spectrum of **12** revealed m/z = 342 corresponding the molecular formula, $C_{13}H_6N_6S_3$. The ions at 208, 135 were fragments obtained from cleavage of sulfide bond of **12**. The more deshielded α proton (H-6′) of thiophene of thieno [3,2-*d*]pyrimidine ring in 3-(thieno[3,2-*d*]pyrimidin-4-ylthio)thieno[3,2-*e*][1,2,4]tri-azolo[4,3-*c*]pyrimidine **(13)** appeared as a doublet at δ 8.43, whereas the β proton (H-7′) was found to appear at δ 7.68 in little higher field as a doublet when compared with **12**. The mass fragmentation pattern of **13** was in agreement with the pattern of **12**, giving a molecular ion peak at 341. The ^{1}H-NMR of 3-(1-phenyl-1*H*-pyrazolo [3,4-*d*]pyrimidin-4-ylthio)thieno[3,2-*e*][1,2,4]triazolo [4,3-*c*]pyrimidine **(14)** displayed two singlets at δ 8.75 and 8.65, respectively for pyrimidine (H-6′) and pyrazole protons (H-3′) of phenylpyrazolopyrimidine ring. Multiplets responsible for phenyl ring appeared at δ 8.15, 7.54, and 7.71 as a doublet and two triplets, and the proton resonance of the thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine ring was observed as two doublets at δ 8.19 and 8.00 for thiophene (H-8 and H-9) and as a singlet at δ 9.34 for pyrimidine (H-5), respectively. The mass spectrum of **14** revealed m/z = 402 corresponding the molecular formula, $C_{18}H_{10}N_8S_2$. The ions at 228, 208, and 195 were fragments due to cleavage of sulfide bond of **14**.

The ^{1}H-NMR spectra of **15–16** and **17** showed patterns similar to those of corresponding **12–13** and **14**. It is noteworthy that the chemical shifts of thiophene and pyrimidine protons for thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine ring were changed at δ 9.78–7.69 in higher field or in more downfield because of sulfur-linked fused heterocycles, such as thienopyrimidines or pyrazolo-

Scheme 1. Reagent and conditions: A: $HC(OEt)_3$, reflux; B: NH_2NH_2-H_2O, reflux; C: HCOOH, reflux; D: (i) $POCl_3$, reflux, (ii) NH_2NH_2-H_2O, reflux; E: $HC(OEt)_3$, reflux; F: NH_2NH_2-H_2O, reflux.

Scheme 2. Reagents and conditions: A: CS_2/KOH, ethanol, reflux; B: **A-Cl**, CH_3CO_2Na, ethanol, reflux; C: **B-Cl**, CH_3CO_2Na, ethanol, reflux; D:**C-Cl**, CH_3CO_2Na, ethanol, reflux.



pyrimidine. The mass spectra of **15–16** and **17** revealed the very similar fragmentations compared with corresponding **12–13** and **14** having the same molecular formulas, respectively.

The compounds **18–19** were also characterized by ^{1}H-NMR spectra, which exhibited three singlets at δ 9.79–8.56 and two doublets at δ 8.45–7.45 for fused heterocycles and multiplet signals at δ 8.15–7.47 for phenyl ring, like patterns of **14** and **17**. The ^{1}H-NMR spectrum of **20** containing two phenylpyrazolopyrimidine moieties showed four singlets for pyrimidine and pyrazole protons of two rings. The signals attributed to pyrimidine (H-5) and pyrazole protons (H-9) of phenylpyrazolo triazolopyrimidine ring were observed at δ 8.84 and 8.32, whereas the similar signals attributed to pyrimidine (H-6′) and pyrazole protons (H-3′) of phenylpyrazolopyrimidine ring were observed δ 8.68 and 8.58, respectively. Data from the elemental analysis and molecular ion recorded in the mass spectrum further confirmed the assign structure.

The compounds **12–20** were examined preliminarily for the antibacterial activity *in vitro* against *Escherichia coli* and were found to be slightly less active than that of compound **1**. They are under evaluation for other

biological activities and the results will be published elsewhere.

In conclusion, we have reported the synthesis of new sulfur-linked *bis*-heterocyclic compounds **12–20** with potential biological activities.

EXPERIMENTAL

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions were checked on thin-layer chromatograpohy of Merck Kieselgel $60F_{254}$ and purified by column chromatography 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 a JASCO FT/IR-200 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 fused 1,2,4- triazolopyrimidine-3-thione derivatives (9–11). A solution of potassium hydroxide (10 mmol) and CS_2 (2 mL) in ethanol (30 mL) was added dropwise to a solution of appropriate thienopyrimidinyl hydrazine or pyrazolopyrimidinyl hydrazine **6-8** (20 mmole) in ethanol (20 mL). The reaction mixture was then refluxed for 8 hours. After cooling and evaporation of the solvent, the residue was dissolved in water and acidified by adding 10% HCl. The solid product was purified by recrystallization from ethanol.

Thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine-3(2H)-thione(9). Yield 82%, mp 220–222°C; IR (KBr) 3190, 1200 cm^{-1}, ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 14.0 (s, 1H, NH), 9.44 (s, 1H, H-5), 8.12 (d, J = 5.8 Hz, 1H, H-8), 7.58 (d, J = 5.8 Hz, 1H, H-9), ms: m/z (%) 208 (M^+ , 95) 181 (29), 162 (42), 135 (100), 84 (23). *Anal*. Calcd. for $C_7H_4N_4S_2$: C, 40.37; H, 1.94, N, 26.90. Found: C, 40.50; H, 1.82; N, 27.01.

Thieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine-3(2H)-thione (10). Yield 78%, mp 212–213°C; IR (KBr) 3150, 1210 cm^{-1}, ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 13.8 (s, 1H, NH), 8.84 (s, 1H, pyrimidine), 7.90 (d, J = 5.8 Hz, 1H, thiophene proton), 7.49 (d, J = 5.8 Hz, 1H, thiophene proton), ms: m/z (%) 208 (M^+, 60), 176 (61), 162 (15), 135 (34), 84 (99). *Anal*. Calcd. for $C_7H_4N_4S_2$: C, 40.37; H, 1.94, N, 26.90. Found: C, 40.44; H, 1.99; N, 26.76.

7-Phenyl-2H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimi-dine-3(7H)-thione (11). Yield 84%, mp 259–261°C; IR (KBr) 3190, 1210 cm^{-1}, ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 14.2 (s, 1H, NH), 9.47 (s, 1H, pyrimidine), 8.52 (s, 1H, pyrazole), 8.07 (d, J = 7.8 Hz, 2H, phenyl), 7.64 (t, 2H, phenyl), 7.46 (t, 1H, phenyl), ms: m/z (%) 268 (M^+, 100), 222 (15), 195 (12), 84 (15). *Anal*. Calcd. for $C_{12}H_8N_6S$: C, 53.72; H, 3.01, N, 31.32. Found: C, 53.84; H, 2.88; N, 31.44.

General procedure for the preparation of sulfur-linked bis-heterocyclic compounds (12–20). A suspension of anhydrous sodium acetate (15 mmol), chlorothienopyrimidine (**A-Cl** or **B-Cl**) or chlorophenylpyrazolopyrimidine (**C-Cl**) (10 mmol) and the appropriate fused 1,2,4-triazolopyrimidine-3-thione **9-11** (10 mmol) in ethanol (30 mL) was refluxed for 6–8 h. After cooling, the solid products formed were filtered, washed with water and recrystallized from ethanol.

3-(Thieno[2,3-d]pyrimidin-4-ylthio)thieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (12). Yield 44%, mp 253–255°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.77 (s, 1H, H-5), 8.81 (s, 1H, H-2′), 8.11 and 7.85 (d and d, J = 5.8 Hz, 2H, H-8 and H-9), 8.03 and 7.50 (d and d, J = 5.8 Hz, 2H, H-5′ and H-6′), ms: m/z (%) 342 (M^+, 99), 284 (9), 208 (12), 162 (5), 135 (22). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.51; H, 1.89; N, 24.37.

3-(Thieno[3,2-d]pyrimidin-4-ylthio)thieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (13). Yield 40%, mp 213–215°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.77 (s, 1H, H-5), 8.99 (s, 1H, H-2′), 8.43 and 7.68 (d and d, J = 5.8 Hz, 2H, H-6′ and H-7′), 8.12 and 7.84 (d and d, J = 5.8 Hz, 2H, H-8 and H-9), ms: m/z (%) 342 (M^+, 100), 284 (5), 208 (42), 162 (15), 135 (31). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.48; H, 1.85; N, 24.43.

3-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)thieno [3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (14). Yield 50%, mp 244–246°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.34 (s, 1H, H-5), 8.75 (s, 1H, H-6′), 8.65 (s, 1H, H-3′), 8.19 and 8.00 (d and d, J = 5.8 Hz, 2H, H-8 and H-9), 8.15 (d, J = 7.8 Hz, 2H, phenyl), 7.54 (t, 2H, phenyl), 7.41 (t, 1H, phenyl), ms: m/z (%) 402 (M^+, 100), 374 (10), 344 (11), 228 (8), 208 (5). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.88; H, 2.59; N, 27.63.

3-(Thieno[2,3-d]pyrimidin-4-ylthio)thieno[2,3-e][1,2,4] triazolo[4,3-c]pyrimidine (15). Yield 41%, mp 234–236°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.32 (s, 1H, H-5), 8.78 (s, 1H, H-2′), 7.94 and 7.69 (d and d, J = 5.8 Hz, 2H, H-8 and H-7), 7.62 and 7.44 (d and d, J = 5.8 Hz, 2H, H-6′ and H-5′), ms: m/z (%) 342 (M^+, 95), 284 (10), 208 (12), 162 (10), 135 (15). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.49; H, 1.85; N, 24.66.

3-(Thieno[3,2-d]pyrimidin-4-ylthio)thieno[2,3-e][1,2,4] triazolo[4,3-c]pyrimidine (16). Yield 43%, mp 228–230°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.78 (s, 1H, H-5), 9.00 (s, 1H, H-2′), 8.46 and 7.69 (d and d, J = 5.8 Hz, 2H, H-6′ and H-7′), 8.37 and 7.78 (d and d, J = 5.8 Hz, 2H, H-8 and H-7), ms: m/z (%) 342 (M^+, 100), 298 (26), 284 (8), 208 (7), 168 (2), 135 (3). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.44; H, 1.90; N, 24.70.

3-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)thieno [2,3-e][1,2,4]triazolo[4,3-c]pyrimidine (17). Yield 52%, mp 183–185°C; ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 8.91 (s, 1H, H-5), 8.58 (s, 1H, H-6′), 8.28 (s, 1H, H-3′), 7.91 and 7.69 (d and d, J = 5.8 Hz, 2H, H-8 and H-7), 8.17 (d, J = 7.8 Hz, 2H, phenyl), 7.56 (t, 2H, phenyl), 7.40 (t, 1H, phenyl), ms: m/z (%) 402 (M^+, 100), 358 (32), 228 (12), 208 (25), 195 (18), 135 (45), 77 (24). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.60; H, 2.61; N, 27.90.

4-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c] pyrimidin-3-ylthio)thieno[2,3-d]pyrimidine (18). Yield 48%, mp 285–287°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.23 (s, 1H, H-5), 8.79 (s, 1H, H-2′), 8.56 (s, 1H, H-9), 7.70 and 7.45 (d and d, J = 5.8 Hz, 2H, H-6′ and H-5′), 8.15 (d, J = 7.8 Hz, 2H, phenyl), 7.60 (t, 2H, phenyl), 7.47 (t, 1H, phenyl), ms: m/z (%) 402 (M^+, 100), 374 (19), 268 (30), 222 (14), 195 (12), 135 (31), 77 (18). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.80; H, 2.64; N, 27.62.

4-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c] pyrimidin-3-ylthio)thieno[3,2-d]pyrimidine (19). Yield 40%, mp 230–232°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 9.79 (s, 1H, H-5), 9.02 (s, 1H, H-2′), 8.79 (s, 1H, H-9), 8.45 and 7.69 (d and d, J = 5.8 Hz, 2H, H-6′ and H-7′), 8.10 (d, J = 7.8 Hz, 2H, phenyl), 7.65 (t, 2H, phenyl), 7.50 (t, 1H, phenyl), ms: m/z (%) 402 (M^+, 100), 374 (18), 268 (26), 222 (28), 195 (18), 168 (12), 135 (84), 77 (43). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.88; H, 2.40; N, 27.69.

7-Phenyl-3-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)-7H-pyrazolo[4,3-e][1,2,4]triaqzolo[4,3-c]pyrimidine (20). Yield 52%, mp 297–299°C (from ethanol); ^{1}H-NMR (dimethyl sulfoxide-d_6): δ 8.84 (s, 1H, H-5), 8.68 (s, 1H, H-6′), 8.58 (s, 1H, H-3′), 8.32 (s, 1H, H-9), 8.17 (d, J = 7.8 Hz, 2H, phenyl), 8.14 (d, J = 7.8 Hz, 2H, phenyl) 7.60–7.53 (m, 4H, phenyl), 7.47–7.37 (m, 2H, phenyl), ms: m/z (%) 462 (M^+, 100), 434 (18), 404 (13), 268 (17), 228 (24), 195 (18), 168 (19), 141 (13), 77 (3). *Anal*. Calcd. for $C_{23}H_{14}N_{10}S$: C, 59.73; H, 3.05, N, 30.29 Found: C, 59.85; H, 2.91; N, 30.40.

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