Synthesis of Thienotriazolopyrimidine Derivatives Containing Triazolothiadiazole Moiety

Jina Whang and Yang-Heon Song*

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

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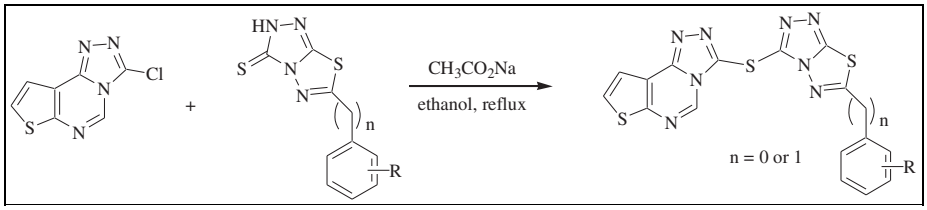

A series of diheterocyclic compounds **15** and **16** was synthesized by the introduction of 6-aryl or 6-benzyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole moiety to thieno[1,2,4]triazolo[4,3-*c*]pyrimidine ring through a sulfur linkage.

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INTRODUCTION

Thienopyrimidines and their condensed derivatives have attracted the constantly increasing attention of researchers because of wide-ranging biological activities. For instance, thienotriazolopyrimidine **1** as shown in Figure 1 and its analog have been explored for adenosine A_1/A_{2A} or A_{2A}/A_3 receptor antagonists [1,2]. We have previously designed and synthesized thienotriazolopyrimidine derivatives **2** with promising biological activity [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 inhibitor [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 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing sugar moiety 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 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 sulfur-linked dihetrocyclic compounds **15a–h** and **16a–h**, which are structurally related to **5** and **6** in the hope of obtaining compounds of diverse biological activities.

RESULTS AND DISCUSSION

As reported in a previous communication [10], key intermediates, fused triazolopyrimidine-3-thiones **11** and **12** can be, respectively, prepared in a few step sequence using 2-aminothiophene-3-carbonitrile **(7)** and ethyl 3-aminothiophene-2-carboxylate **(8)** as starting materials (Scheme 1). The compounds 3-chlorothieno[3,2-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine **(13)** and 3-chlorothieno[2,3-*e*] [1,2,4]triazolo[4,3-*c*]pyrimidine **(14)** were obtained, respectively, in moderate yield by treatment of thieno [3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione (**11**) or thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione (**12**) with thionyl chloride containing two drops of DMF [19]. They were used for the next reaction without further purification. The structure of these compounds was evident from their elemental analysis, ^{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 that the thiones **11** and **12** were converted into the corresponding chlorinated cyclization products. The mass spectral data of **13** and **14** showed a molecular ion peak at *m/z* 210 and also showed ions at *m/z* 175 (21%) that could be attributed to the loss of chlorine atom from the molecular ion. The 6-aryl and 6-benzyl-2*H*-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole-3-ones (**19a–e** and **20a–c**) were prepared from the reaction of 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol (**18**) with the appropriate benzoic acid or phenylacetic

acid using phosphorus oxychloride as the cyclizing agent (Scheme 2) [15].

The synthesis of sulfur-linked dihetrocyclic compounds **15a–h** and **16a–h** was achieved in moderate yield by treatment of **13** and **14** with **19** and **20** in refluxing ethanol containing sodium acetate, respectively. The structures of **15a–h** and **16a–h** were established by elemental analysis, mass spectra, ^{1}H NMR, and IR spectra. IR spectra of these compound revealed characteristic absorption bands at 1625–1470 cm^{-1} for aromatic C=C, C=N stretching vibrations. The ^{1}H NMR signals of 3-(6-(4-fluorophenyl) [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 (**15e**), for example, showed two doublets at 8.06 and 7.78 for thiophene protons, two doublet signals at δ 7.99 and 7.43 for aromatic protons, and singlet at δ 9.63 for pyrimidine proton, respectively. The more deshielded α proton (H-8) of thiophene of thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimi-dine ring in (3-(6-(4-fluorophenyl)[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 (**16e**) appeared as a doublet at d 8.32, whereas the β proton (H-7) was found to appear at δ 7.69 in little higher field as a doublet when compared with **15e**. The mass spectral data of these two compounds showed same molecular ion peak at *m/z* = 426 with very similar fragmentation pattern and showed *m/z* = 252 (99%) and 208 (22%) as the most intense ion, corresponding to the fragment obtained from the cleavage of sulfide bond of the molecular ion. Fragments of *m/z* = 84 and 66 (15%) for triazole and thiadiazole ion were also identified.

The ^{1}H NMR spectra of **15f** and **16f** having benzyl groups instead of phenyl groups showed patterns similar to those of **15a** and **16a** except singlet signals at δ 4.35

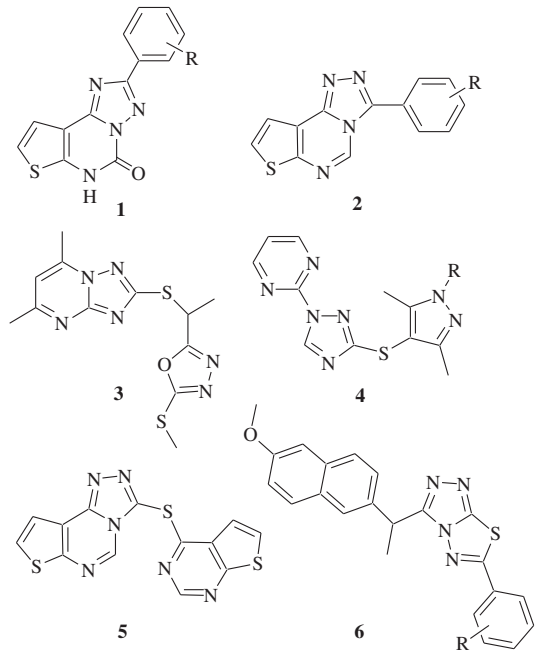
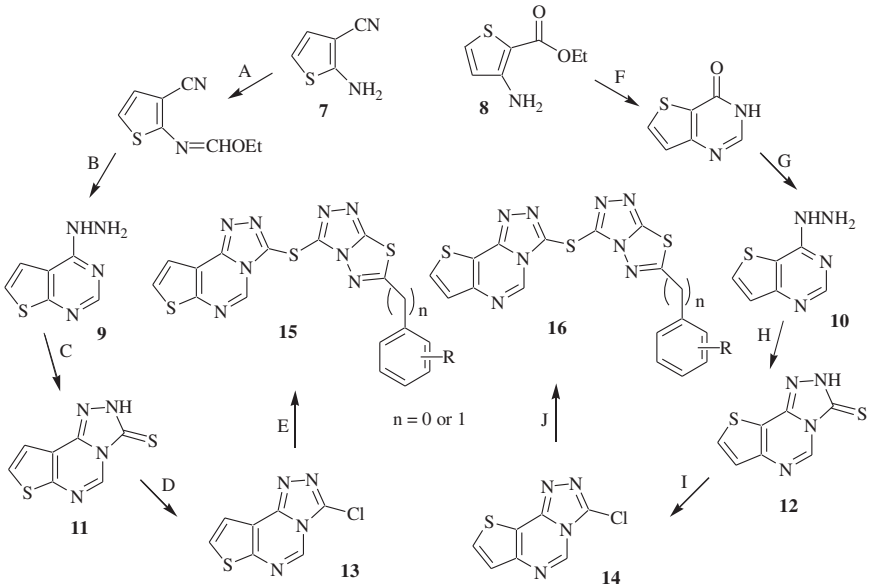


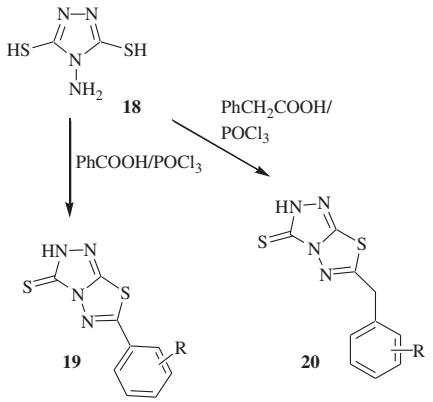
Figure 1. Compounds **1–6**.

Scheme 1. Reagent and conditions. (A): $HC(OEt)_3$, reflux; (B): NH_2NH_2-H_2O, reflux; (C): CS_2/KOH, ethanol, reflux; (D): $SOCl_2$, DMF(two drops), reflux; (E): 19 or 20, CH_3CO_2Na, ethanol, reflux; (F): $HCONH_2$, reflux; (G): (i) $POCl_3$, reflux; (ii) NH_2NH_2-H_2O, reflux; H: CS_2/KOH, ethanol, reflux; I: $SOCl_2$, DMF(two drops), reflux; and (J): 19 or 20, CH_3CO_2Na, ethanol, reflux.



R: a, H (n=0); b, 4-Cl (n=0); c, 4-NH_2 (n=0); d, 4-NO_2 (n=0); e, 4-F (n=0); f, H (n=1); g, 4-Cl (n=1); h, 4-Br (n=1)

Scheme 2



for benzyl protons, respectively. The mass spectra of these compounds revealed $m/z = 422$ corresponding the molecular formula, $C_{17}H_{10}N_8S_3$. The ions at 248 (61%) and 175 (55%) were fragments because of the cleavage of sulfide bond of the molecular ion. Just as the results of previous study have shown [10], it is noteworthy that the chemical shifts of thiophene and pyrimidine protons for thienotriazolopyrimidine ring of **15a–h** and **16a–h** were changed a bit in higher field or more downfield because of sulfur-linked 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring.

The compounds **15a–h** and **16a–h** were examined for the antibacterial activity *in vitro* against *Escherichia coli* and *Staphylococcus aureus*. They exhibited no to very low activities. However, some of them were identified as strong inhibitors of interleukin-6 (IL-6) action, which inhibit IL-6 induced STAT3-dependent luciferase activities. They are under evaluation for systematic biological activities, and the results will be published elsewhere.

CONCLUSION

In conclusion, we have reported the synthesis of sulfur-linked diheterocyclic compounds **15a–h** and **16a–h**.

EXPERIMENTAL

Melting points were determined in capillary tubes on Büchi (Flawil, Switzerland) apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatography of Merck Kieselgel 60 F_{254} and purified by column chromatography Merck (Darmstadt, Germany) silica gel (70–230 mesh). The ^{1}H NMR spectra were recorded on Bruker (Rheinstetten, Germany) 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 (Hercules, CA) FTS-3000 FTIR 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 13 and **14**. The thieno[1,2,4]triazolo[4,3-*c*]pyrimidine-3(2*H*)-thione **11** or **12** (17 mmol) and thionyl chloride (20 mL) were mixed under nitrogen. Two drops of DMF were added, and the mixture was heated to 70°C for 5 h. The dark brown solution was cooled to room temperature and diluted with dichloromethane (70 mL). After evaporation of the solvent and excess thionyl chloride, the solid product was purified by recrystallization from ethanol.

***3-Chlorothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine* (13)**. The compound was obtained from **11** in 59% yield, mp 191°C (decompose); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 8.98 (s, 1H, H-5, pyrimidine), 8.32 (s, 1H, $J = 5.8$ Hz, H-8), 7.73 (1 H, $J = 5.8$ Hz, H-9), MS: (*m/z*) 210 (M^+), 175, 157, 78, 63. *Anal*. Calcd for $C_7H_3ClN_4S$: C, 39.91; H, 1.44, N, 26.60. Found: C, 40.13; H, 1.51; N, 26.44.

***3-Chlorothieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine* (14)**. The compound was obtained from **11** in 66% yield, mp 189°C (decompose); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 8.84 (s, 1H, H-5, pyrimidine), 8.02 (d, 1H, $J = 5.8$ Hz, H-8), 7.70 (d, 1H, $J = 5.8$ Hz, H-7), MS: (*m/z*) 210 (M^+), 175, 78, 63. *Anal*. Calcd for $C_7H_3ClN_4S$: C, 39.91; H, 1.44, N, 26.60. Found: C, 39.75; H, 1.60; N, 26.49.

General procedure for the preparation of 19a–e and 20a–c. A mixture of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**18**) (6.7 mmol) and the appropriate carboxylic acid (6.7 mmol) in phosphorus oxychloride (10 mL) was heated at reflux for 6 h. The excess phosphorus oxychloride was removed under reduced pressure, and the residue was diluted with ice–water mixture. The precipitated solid was collected by filtration and purified by recrystallization from DMF.

6-Phenyl-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (19a). Mp 235–237°C (Lit. [15] 238–240°C).

6-(4-Chlorophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4]thia- diazole-3-thione (19b). Mp 277–279°C (Lit. [15] 260–262°C).

6-(4-Aminophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole-3-thione (19c). Mp >300°C (Lit. [15] >324°C).

6-(4-Nitrophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4]thia- diazole-3-thione (19d). Mp 286–288°C (Lit. [15] 244–246°C).

6-(4-Fluorophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole-3-thione (19e). Yield 80%, mp 265–267°C; IR(KBr) 3195, 1600 cm^{-1}, ^{1}H NMR (dimethyl sulfoxide-d_6): δ 8.49 (s, 1H, NH), 7.98 (d, 2H, ArH), 7.43 (d, 2H, ArH), MS: (*m/z*) 252 (M^+), 139, 121, 102, 95. *Anal*. Calcd for $C_9H_5FN_4S_2$: C, 42.85; H, 2.00, N, 22.21. Found: C, 42.60; H, 2.21; N, 22.02.

6-Benzyl-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (20a). Yield 86%, mp 86–88°C; IR(KBr) 3190, 1605 cm^{-1}, ^{1}H NMR (dimethyl sulfoxide-d_6): δ 11.9 (s, 1H, NH), 7.33–7.24 (m, 5H, ArH), 4.33 (s, 2H, benzyl), MS: (*m/z*) 248 (M^+), 121, 102. *Anal*. Calcd for $C_{10}H_8N_4S_2$: C, 48.37; H, 3.25, N, 22.56. Found: C, 48.55; H, 3.40; N, 22.38.

6-(4-Chlorobenzyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole-3-thione (20b). Yield 88%, mp 106–108°C; IR(KBr) 3195, 1602 cm^{-1}, ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.33 (d, 2H, ArH), 7.22 (d, 2H, ArH), 4.33 (s, 2H, benzyl), MS: (*m/z*) 282 (M^+), 121, 102. *Anal*. Calcd for $C_{10}H_7ClN_4S_2$: C, 42.47; H, 2.50, N, 19.81. Found: C, 42.62; H, 2.32; N, 19.99.

6-(4-Bromobenzyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole-3-thione (20c). Yield 76%, mp 99–101°C; IR(KBr) 3195, 1600 cm^{-1}, ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.48 (d, 2H, ArH), 7.22 (d, 2H, ArH), 4.34 (s, 2H, benzyl), MS: (*m/z*) 328 (M^+). *Anal*. Calcd for $C_{10}H_7BrN_4S_2$: C, 36.70; H, 2.16, N,17.12. Found: C, 36.81; H, 2.02; N, 17.40.

General procedure for the preparation of sulfur-linked bis-heterocyclic compounds (15a–h and **16a–h**). A suspension of anhydrous sodium acetate (2 mmol), **13** or **14** (1.2 mmol), and the appropriate [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione **19** or **20** (1.2 mmol) in ethanol (20 mL) was refluxed for 6–8 h. After cooling, the solid products formed were filtered, washed with water, and recrystallized from ethanol.

3-(6-Phenyl-[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 (15a). The compound was obtained in 65% yield, mp 259–261°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.65 (s, 1H, H-5, pyrimidine), 8.06 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.88 (t, 2H, J = 7.5 Hz, ArH), 7.78 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.65 (d, 1H, J = 7.5 Hz, ArH), 7.52 (t, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 408 (M^+), 252, 208, 139, 84, 66. *Anal*. Calcd for $C_{16}H_8N_8S_3$: C, 47.04; H, 1.97, N, 27.43. Found: C, 46.90; H, 2.05; N, 27.29.

3-(6-(4-Chlorophenyl)-[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 (15b). The compound was obtained in 60% yield, mp 128–130°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.68 (s, 1H, H-5, pyrimidine), 8.05 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.88 (d, 2H, J = 7.5 Hz, ArH), 7.79 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.60 (d, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 442 (M^+), 252, 234, 84, 66. *Anal*. Calcd for $C_{16}H_7ClN_8S_3$: C, 43.39; H, 1.59, N, 25.30. Found: C, 43.47; H, 1.49; N, 25.48.

3-(6-(4-Aminophenyl)-[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 (15c). The compound was obtained in 71% yield, mp 285–287°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.65 (s, 1H, H-5, pyrimidine), 8.05 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.94 (d, 2H, J = 7.5 Hz, ArH), 7.78 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.74 (d, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 423 (M^+), 216, 208, 84, 66. *Anal*. Calcd for $C_{16}H_9N_9S_3$: C, 45.38; H, 2.14, N, 29.77. Found: C, 45.45; H, 2.01; N, 29.60.

3-(6-(4-Nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-3-ylthio)thieno[3,2-e][1,2,4]triazolo[4,3c] pyrimidine (15d). The compound was obtained in 69% yield, mp 253–255°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.35 (d, 2H, J = 7.5 Hz, ArH), 8.17 (d, 2H, J = 7.5 Hz, ArH), 8.06 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.78 (d, J = 5.8 Hz, 1H, H-9, thiophene), MS: (*m/z*) 453 (M^+), 278, 208, 139, 84, 66. *Anal.* Calcd for $C_{16}H_7N_9O_2S_3$: C, 42.38; H, 1.56, N, 27.80. Found: C, 42.30; H, 1.69; N, 27.60.

3-(6-(4-Fluorophenyl)-[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 (15e). The compound was obtained in 55% yield, mp 231–234°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.63 (s, 1H, H-5, pyrimidine), 8.06 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.99 (d, 2H, J = 7.5 Hz, ArH), 7.78 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.43 (d, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 426 (M^+), 252, 208, 179, 139, 84, 66. *Anal.* Calcd for $C_{16}H_7FN_8S_3$: C, 45.06; H, 1.65, N, 26.27. Found: C, 45.17; H, 1.71; N, 26.10.

3-(6-Benzyl-[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 (15f). The compound was obtained in 61% yield, mp 99–101°C;^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.05 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.78 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.30–7.26 (m, 5H, ArH), 4.35 (s, 2H, benzyl), MS: (*m/z*) 422 (M^+), 248, 208, 175, 149, 135, 117, 102, 91. *Anal*. Calcd for $C_{17}H_{10}N_8S_3$: C, 48.33; H, 2.39, N, 26.52. Found: C, 48.44; H, 2.26; N, 26.66.

3-(6-(4-Chlorobenzyl)-[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 (15g). The compound was obtained in 72% yield, mp 216–218°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.06 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.79 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.33 (d, 2H, J = 7.5 Hz, ArH), 7.25 (d, 2H, J = 7.5 Hz, ArH), 4.33 (s, 2H, benzyl), MS: (*m/z*) 456 (M^+), 414, 324, 208, 193, 135, 116, 84, 66. *Anal*. Calcd for $C_{17}H_9ClN_8S_3$: C, 44.68; H, 1.99; N, 24.52. Found: C, 44.77; H, 1.90; N, 24.41.

3-(6-(4-Bromobenzyl)-[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 (15h). The compound was obtained in 65% yield, mp 152–154°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.66 (s, 1H, H-5, pyrimidine), 8.05 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.78 (d, J = 5.8 Hz, 1H, H-9, thiophene), 7.49 (d, 2H, J = 7.5 Hz, ArH), 7.21 (d, 2H, J = 7.5 Hz, ArH), 4.35 (s, 2H, benzyl), MS: (*m/z*) 500 (M^+), 167, 149, 116, 84, 66. *Anal*. Calcd for $C_{17}H_9BrN_8S_3$: C, 40.72; H, 1.81; N, 22.35. Found: C, 44.82; H, 1.73; N, 24.40.

3-(6-Phenyl)-[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 (16a). The compound was obtained in 54% yield, mp 250–252°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.30 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.86 (t, 2H, J = 7.5 Hz, ArH), 7.69 (d, J = 5.8 Hz, 1H, H-7, thiophene), 7.63 (d, 1H, J = 7.5 Hz, ArH), 7.53 (t, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 408 (M^+), 252, 208, 139, 84, 66. *Anal*. Calcd for $C_{16}H_8N_8S_3$: C, 47.04; H, 1.97, N, 27.43. Found: C, 47.13; H, 1.90; N, 27.49.

3-(6-(4-Chlorophenyl)-[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 (16b). The compound was obtained in 68% yield, mp 222–224°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.31 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.88 (d, 2H, J = 7.5 Hz, ArH), 7.70 (d, J = 5.8 Hz, 1H, H-7, thiophene), 7.60 (d, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 442 (M^+), 234, 84, 66. *Anal*. Calcd for $C_{16}H_7ClN_8S_3$: C, 43.39; H, 1.59, N, 25.30. Found: C, 43.45; H, 1.50; N, 25.40.

3-(6-(4-Aminophenyl)-[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 (16c). The compound was obtained in 58% yield, mp 281–282°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.65 (s, 1H, H-5, pyrimidine), 8.30 (d, J = 5.8 Hz, 1H, H-8, thiophene), 7.95 (d, 2H, J = 7.5 Hz, ArH), 7.75 (d, 2H, J = 7.5 Hz, ArH), 7.69 (d, J = 5.8 Hz, 1H, H-7, thiophene), MS: (*m/z*) 423 (M^+), 216, 208, 84, 66. *Anal*. Calcd for $C_{16}H_9N_9S_3$: C, 45.38; H, 2.14, N, 29.77. Found: C, 45.30; H, 2.09; N, 29.84.

3-(6-(4-Nitrophenyl)-[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 (16d) The compound was obtained in 60% yield, mp 258–259°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.63 (s, 1H, H-5, pyrimidine), 8.34 (d, 2H, J = 7.5 Hz, ArH), 8.30 (d, J = 5.8 Hz, 1H, H-8, thiophene), 8.18 (d, 2H, J = 7.5 Hz, ArH), 7.70 (d, J = 5.8 Hz, 1H, H-7, thiophene), MS: (*m/z*) 453 (M^+), 278, 208, 139, 121, 84, 66. *Anal*. Calcd for $C_{16}H_7N_9O_2S_3$: C, 42.38; H, 1.56, N, 27.80. Found: C, 42.44; H, 1.50; N, 27.69.

3-(6-(4-Fluorophenyl)-[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 (16e). The compound was obtained in 66% yield, mp 243–245°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.32 (d, J = 5.8 Hz, 1H, H-8, thiophene), 8.00 (d, 2H, J = 7.5 Hz, ArH), 7.69 (d, J = 5.8 Hz, 1H, H-7, thiophene), 7.44 (d, 2H, J = 7.5 Hz, ArH), MS: (*m/z*) 426 (M^+), 252, 208, 179, 139, 84, 66. *Anal*. Calcd for $C_{16}H_7FN_8S_3$: C, 45.06; H, 1.65, N, 26.27. Found: C, 45.13; H, 1.60; N, 26.33.

3-(6-Benzyl)-[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 (16f). The compound was obtained in 60% yield, mp 154–156°C; ^{1}H NMR (dimethyl

sulfoxide-d_6): δ 9.63 (s, 1H, H-5, pyrimidine), 8.31 (d, $J = 5.8$ Hz, 1H, H-8, thiophene), 7.69 (d, $J = 5.8$ Hz, 1H, H-7, thiophene), 7.30–7.25 (m, 5H, ArH), 4.36 (s, 2H, benzyl), MS: (*m/z*) 422 (M^+), 248, 208, 175, 149, 135, 91. *Anal*. Calcd for $C_{17}H_{10}N_8S_3$: C, 48.33; H, 2.39, N, 26.52. Found: C, 48.42; H, 2.29; N, 26.60.

3-(6-(4-Chlorobenzyl)-[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 (16g). The compound was obtained in 59% yield, mp 101–103°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.64 (s, 1H, H-5, pyrimidine), 8.29 (d, $J = 5.8$ Hz, 1H, H-8, thiophene), 7.70 (d, $J = 5.8$ Hz, 1H, H-7, thiophene), 7.34 (d, 2H, $J = 7.5$ Hz, ArH), 7.24 (d, 2H, $J = 7.5$ Hz, ArH), 4.33 (s, 2H, benzyl), MS: (*m/z*) 456 (M^+), 324, 208, 193, 135, 84, 66. *Anal*. Calcd for $C_{17}H_9ClN_8S_3$: C, 44.68; H, 1.99; N, 24.52. Found: C, 44.60; H, 1.92; N, 24.60.

3-(6-(4-Bromobenzyl)-[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 (16h). The compound was obtained in 70% yield, mp 124–127°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.65 (s, 1H, H-5, pyrimidine), 8.31 (d, $J = 5.8$ Hz, 1H, H-8, thiophene), 7.71 (d, $J = 5.8$ Hz, 1H, H-7, thiophene), 7.48 (d, 2H, $J = 7.5$ Hz, ArH), 7.21 (d, 2H, $J = 7.5$ Hz, ArH), 4.34 (s, 2H, benzyl), MS: (*m/z*) 500 (M^+), 167, 149, 84, 66. *Anal*. Calcd for $C_{17}H_9BrN_8S_3$: C, 40.72; H, 1.81; N, 22.35. Found: C, 44.80; H, 1.86; N, 24.26.

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