One-Pot Four-Component Synthesis of Thieno[2,3-*d*]pyrimidin-4-amines *via* Sequential *Gewald*/Cyclocondensation Reactions

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A one-pot four-component synthesis of thieno[2,3-*d*]pyrimidin-4-amines *via* sequential *Gewald*/cyclocondensation reactions is described. 2-Aminothiophene-3-carbonitriles obtained from the *Gewald* reaction between cyclic ketones, malononitrile, and sulfur underwent a condensation–cyclization reaction with benzonitriles under solvent-free conditions to afford the title compounds in excellent yields.

Introduction. – Multicomponent reactions (MCRs) have become important tools in synthetic chemistry due to efficient access to complex molecules from readily available starting materials, construction of interesting biologically active organic compounds, and rapid generation of drug-like molecule libraries [1].

Thiophene ring is an important heterocycle found in biologically active molecules and is the backbone of numerous important organic compounds, such as pharmaceuticals, dyes, and agrochemicals [2–4]. *Gewald* reaction is one of the known MCRs for the preparation of substituted 2-aminothiophenes [5].

Thieno[2,3-*d*]pyrimidines, bicyclic 5–6 systems with three heteroatoms (1:2), are an important structural motif found in many biologically active compounds [6–8]. They are interesting structural elements in developing pharmaceuticals and agrochemicals [9]. In recent years, the synthesis of thienopyrimidines has received increasing attention because of their great application as anticancer [10], antiviral [11], anti-inflammatory [12], antifungal [13], antidiabetic [14], antimicrobial [15], antibacterial [16], and ulcerogenic compounds [17]. *N*-[4-Fluoro-3-(morpholin-4-yl)phenyl]thieno[2,3-*d*]pyrimidin-4-amine (**1**; *Fig.*) has shown good anti-inflammatory activity [18], 5,6,7,8-tetrahydro-4-(morpholin-4-yl)[1]benzothieno[2,3-*d*]pyrimidine (**2**; *Fig.*) is active against *Candida albicans* [19], and 4-benzylidenehydrazono-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidine (**3**; *Fig.*) has shown excellent antifungal activity [20]. 6,7-Dihydro-4-(4-methylpiperazin-1-yl)-2-(methylsulfanyl)-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine (**4**; *Fig.*) has been shown to be a 5-HT_3 receptor antagonist [21], and thienopyrimidine bisphosphonate **5** (*Fig.*) has displayed human farnesyl pyrophosphate synthase inhibitory activity [22]. Thieno[2,3-*d*]pyrimidine **6** (*Fig.*) has exhibited submicromolar LIMK1 inhibitory activity [23].

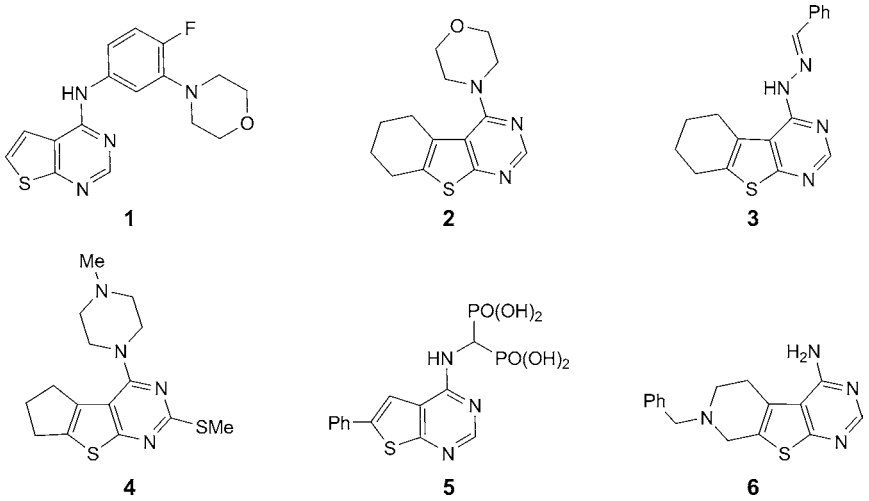


Figure. *Examples of Biologically Active Thieno[2,3-*d*]pyrimidin-4-amines*

So far, most of the common synthetic approaches for the preparation of thieno[2,3-*d*]pyrimidines involve: *i*) syntheses from pyrimidines and closure of the thiophene ring; reaction of pyrimidines containing an S-atom at C(6) and a CN or C=O group at C(5) with C_1-donating reagents, or reaction of pyrimidines bearing a leaving group at C(6) and a CN or C=O group at C(5) with a S–C donating reagent; *ii*) syntheses from thiophenes and closure of the pyrimidine ring; cyclocondensation of thiophenes having a 2-NH_2 function, and a CN or C=O group at C(3) with different reagents such as acids, amides, orthoesters, urea, guanidine, isothiocyanates, isocyanates, and nitriles; and *iii*) syntheses by transformation of other rings such as thieno[2,3-*d*][1,3]thiazines, isothiazolo[5,4-*d*]pyrimidines, and 1,2,4-triazines [6][7].

Fused 4-aminopyrimidines have been synthesized starting from *ortho*-aminonitriles. Anthranilonitrile was coupled with aromatic nitriles in the presence of ^{t}BuOK under microwave irradiation to prepare 4-amino-2-aryl-quinazolines [23]. Condensation of 3-aminopyrazole-4-carbonitriles under the same conditions afforded pyrazolo[3,4-*d*]pyrimidines [24]. 4-Amino-2-aryl-thieno[2,3-*d*]pyrimidines were synthesized by condensation of 2-aminothiophene-3-carbonitriles and aromatic nitriles in the presence of HCl in dioxane [25], MeONa in i-PrOH [26], or ^{t}BuOK in i-PrOH under microwave irradiation [27]. To the best of our knowledge, the synthesis of thieno[2,3-*d*]pyrimidines through one-pot sequential *Gewlad*/cyclocondensation reactions has not been reported in the literature.

Results and Discussion. – As part of our current studies on the development of efficient methods for the preparation of biologically active heterocyclic compounds [28], herein, we describe an efficient one-pot and four-component synthesis of thieno[2,3-*d*]pyrimidin-4-amines. Thus, a mixture of a ketone **6**, malononitrile, and elemental sulfur in the presence of morpholine at 75° underwent the *Gewald* reaction to afford the corresponding 2-aminothiophenes **7**. After complete conversion to the

corresponding 2-aminothiophene, as indicated by TLC monitoring, an arylnitrile **8** and 20% NaOH were added to the reaction mixture which was further stirred at 120° for 1 h to afford thieno[2,3-*d*]pyrimidin-4-amines **9a**–**9q** in 87–96% yields (*Scheme*). TLC and ^{1}H-NMR spectroscopic analysis of the reaction mixtures clearly indicated the formation of the corresponding thieno[2,3-*d*]pyrimidin-4-amines **9** in excellent yields. No product other than **9** could be detected by NMR spectroscopy. The results are summarized in the *Table* (see also *Exper. Part*).

The structures of the isolated products were confirmed by IR, ^{1}H- and ^{13}C-NMR, and MS spectra, and elemental analyses. The IR spectrum (KBr) of **9a** showed stretching bands for N–H and C=N functionalities at 3423, 3295, 3160, and 1605 cm^{-1}. The MS spectrum of **9a** displayed the molecular-ion (M^+) peak at *m*/*z* 281, consistent with the product structure. The ^{1}H-NMR spectrum of **9a** exhibited characteristic

Scheme. *Four-Component Synthesis of Thieno[2,3-*d*]pyrimidin-4-amines* **9**

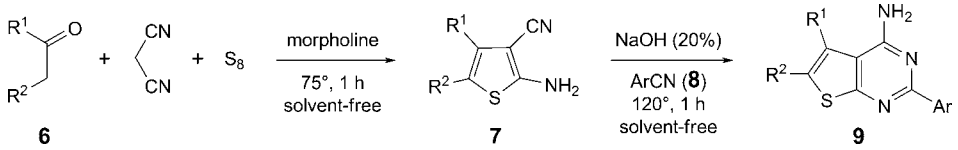
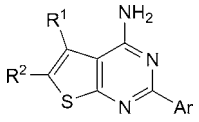


Table. *Synthesis of Thieno[2,3-*d*]pyrimidin-4-amines* **9**



Product **9**	R^1, R^2	Ar	Yield [%][a])	M.p. [°] (Lit.)
9a	–$(CH_2)_4$–	Ph	93	194–195 (195–197) [25a]
9b	–$(CH_2)_4$–	4-F–C_6H_4	87	215–217
9c	–$(CH_2)_4$–	4-Cl–C_6H_4	90	206–208 (208) [27]
9d	–$(CH_2)_4$–	4-Br–C_6H_4	91	217–218
9e	–$(CH_2)_4$–	4-MeO–C_6H_4	88	197–198 (200) [27]
9f	–$(CH_2)_4$–	3-Me–C_6H_4	96	201–203
9g	–$(CH_2)_5$–	Ph	95	171–172 (174) [27]
9h	–$(CH_2)_5$–	4-F–C_6H_4	88	189–190
9i	–$(CH_2)_5$–	4-Cl–C_6H_4	90	183–184 (182) [27]
9j	–$(CH_2)_5$–	4-Br–C_6H_4	91	177–178
9k	–$(CH_2)_5$–	4-MeO–C_6H_4	91	172–173 (164) [27]
9l	–$(CH_2)_5$–	3-Me–C_6H_4	94	193–194
9m	–$(CH_2)_2CH(Me)CH_2$–	Ph	94	225–227 (230) [27]
9n	–$(CH_2)_2CH(Me)CH_2$–	4-F–C_6H_4	87	245–246
9o	–$(CH_2)_2CH(Me)CH_2$–	4-Cl–C_6H_4	89	249–250 (255) [27]
9p	–$(CH_2)_2CH(Me)CH_2$–	4-MeO–C_6H_4	95	214–216 (217) [27]
9q	–$(CH_2)_2CH(Me)CH_2$–	3-Me–C_6H_4	92	208–209

[a]) Yield of isolated product.

*multiplet*s at δ(H) 1.77–2.98 arising from the four CH_2 entities, as well as a broad signal in the range of 6.70–7.00 for the NH_2 group, along with characteristic signals with appropriate chemical shifts and coupling constants for the five H-atoms of the Ph substituent. The ^{1}H-decoupled ^{13}C-NMR spectrum of **9a** showed 14 distinct resonances, which were in agreement with the proposed structure. Three characteristic signals in the down-field region of the spectrum were observed at δ(C) 158.4, 158.6, and 167.0 due to the three heteroatom linked C-atoms of the pyrimidine ring (see *Exper. Part*).

In summary, we have developed the efficient one-pot and four-component sequential *Gewald*/cyclocondensation reactions between cyclic ketones, malononitrile, sulfur, and benzonitriles under solvent-free conditions for the preparation of thieno[2,3-*d*]pyrimidin-4-amines, which are of potential synthetic and pharmacological interest. Solvent-free conditions, easy workup, excellent yields of the products, and use of simple starting materials are the main advantages of this method.

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Experimental Part

General. All the chemicals were obtained from *Merck* (Germany) and were used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-400 AVANCE* (at 400.1 (^{1}H) and 100.6 (^{13}C) MHz, resp.) instrument; in (D_6)DMSO soln.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS (20 eV): *Agilent Technologies (HP) 5973* mass spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer; in %.

General Procedure for the Preparation of Compounds **9** (*exemplified with* **9a**). A mixture of cyclohexanone (0.196 g, 2.0 mmol), malononitrile (0.132 g, 2.0 mmol), elemental sulfur (0.064 g, 2.0 mmol), and morpholine (0.174 g, 2.0 mmol) was heated at 75° for 1 h. After nearly complete conversion to the corresponding 2-aminothiophene, as indicated by TLC monitoring, benzonitrile (0.309 g, 3.0 mmol) and 20% NaOH (0.420 g) were added to the mixture, and stirring was continued at 120° for 1 h. After completion of the reaction, as indicated by TLC monitoring, the mixture was cooled to r.t. Then, H_2O (10 ml) was added, and the product was extracted with CH_2Cl_2 (3 × 10 ml). The org. phase was separated and dried (Na_2SO_4). The solvent was evaporated under vacuum, and the crude product was recrystallized from AcOEt to afford the pure product **9a**.

*5,6,7,8-Tetrahydro-2-phenyl[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9a**). White solid. Yield: 0.523 g (93%). M.p. 194–195°. IR (KBr): 3423, 3295, and 3160 (NH), 1605 (C=N), 1544, 1507, 1407, 1269, 992, 960, 852, 771, 701, 636. ^{1}H-NMR: 1.77–1.86 (*m*, 4 H); 2.72–2.80 (*m*, 2 H); 2.88–2.98 (*m*, 2 H); 6.70–7.00 (br., 2 H); 7.44–7.48 (*m*, 3 H); 8.35 (*dd*, *J* = 7.7, 1.6, 2 H). ^{13}C-NMR: 22.4; 22.7; 25.4; 25.9; 114.2; 127.5; 128.0; 128.7; 130.3; 131.7; 138.2; 158.4; 158.6; 167.0. EI-MS: 281 (100, M^+), 266 (23), 253 (15), 225 (6), 177 (8), 150 (15), 104 (73), 77 (42), 69 (15), 57 (12). Anal. calc. for $C_{16}H_{15}N_3S$ (281.38): C 68.30, H 5.37, N 14.93; found: C 68.31, H 5.40, N 14.85.

*2-(4-Fluorophenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9b**). White solid. Yield: 0.521 g (87%). M.p. 215–217°. IR (KBr): 3479, 3310, and 3191 (NH), 1615 (C=N), 1537, 1497, 1403, 1286, 1004, 838, 785, 729. ^{1}H-NMR: 1.74–1.86 (*m*, 4 H); 2.70–2.80 (*m*, 2 H); 2.86–2.93 (*m*, 2 H); 6.70–7.00 (br., 2 H); 7.28 (*dd*, ^3J(F,H) = 8.8, ^3J(H,H) = 8.8, 2 H); 8.38 (*dd*, ^3J(H,H) = 8.8, ^4J(F,H) = 5.6, 2 H). ^{13}C-NMR: 22.4; 22.7; 25.4; 25.9; 114.1; 115.6 (*d*, ^2J(F,C) = 21.5); 127.4; 130.2 (*d*, ^3J(F,C) = 8.5); 131.7; 134.7 (*d*, ^4J(F,C) = 2.5); 157.6; 158.6; 164.0 (*d*, ^1J(F,C) = 245.2); 167.0. EI-MS: 299 (100, M^+), 284 (35), 271 (30), 177 (4), 160 (8), 150 (23), 122 (42), 95 (15), 75 (4), 69 (4), 57 (3). Anal. calc. for $C_{16}H_{14}FN_3S$ (299.37): C 64.19, H 4.71, N 14.04; found: C 64.08, H 4.64, N 13.85.

*2-(4-Chlorophenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9c**). White solid. Yield: 0.568 g (90%). M.p. 206–208°. IR (KBr): 3509, 3267, and 3108 (NH), 1615 (C=N), 1552, 1504,

1408, 1359, 1285, 1173, 1086, 1014, 837, 786, 730, 683. ^{1}H-NMR: 1.76–1.88 (*m*, 4 H); 2.72–2.82 (*m*, 2 H); 2.88–2.98 (*m*, 2 H); 6.75–7.05 (br., 2 H); 7.53 (*d*, *J* = 8.4, 2 H); 8.34 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR: 22.8; 23.1; 25.8; 26.3; 114.7; 127.9; 129.2; 130.0; 132.4; 135.2; 136.5; 157.8; 159.0; 167.3. EI-MS: 317 (19, M^+(^{37}Cl)), 315 (52, M^+(^{35}Cl)), 300 (13), 177 (14), 159 (15), 150 (32), 138 (100), 122 (34), 111 (64), 102 (88), 91 (40), 83 (32), 75 (68), 69 (68), 57 (78), 55 (80). Anal. calc. for $C_{16}H_{14}ClN_3S$ (315.83): C 60.85, H 4.47, N 13.30; found: C 60.80, H 4.50, N 13.17.

*2-(4-Bromophenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9d**). White solid. Yield: 0.655 g (91%). M.p. 217–218°. IR (KBr): 3510, 3315, and 3131 (NH), 1614 (C=N), 1550, 1504, 1408, 1359, 1284, 1174, 1008, 861, 836, 785, 728, 681. ^{1}H-NMR: 1.75–1.90 (*m*, 4 H); 2.70–2.82 (*m*, 2 H); 2.87–3.00 (*m*, 2 H); 6.75–7.10 (br., 2 H); 7.66 (*d*, *J* = 8.4, 2 H); 8.27 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR: 22.4; 22.7; 25.4; 25.8; 114.3; 124.0; 127.5; 130.0; 131.7; 132.0; 137.5; 157.5; 158.6; 166.9. EI-MS: 361 (92, M^+(^{81}Br)), 359 (92, M^+(^{79}Br)), 346 (14), 344 (15), 333 (13), 331 (12), 281 (73), 266 (19), 253 (15), 184 (38), 182 (38), 160 (23), 147 (38), 104 (61), 97 (38), 83 (50), 76 (38), 69 (77), 57 (100). Anal. calc. for $C_{16}H_{14}BrN_3S$ (360.28): C 53.34, H 3.92, N 11.66; found: C 53.33, H 3.94, N 11.59.

*5,6,7,8-Tetrahydro-2-(4-methoxyphenyl)[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9e**). White solid. Yield: 0.548 g (88%). M.p. 197–198°. IR (KBr): 3434, 3287, and 3182 (NH), 1610 (C=N), 1548, 1506, 1408, 1248, 1175, 1132, 1031, 840, 788, 739, 694, 642. ^{1}H-NMR: 1.76–1.86 (*m*, 4 H); 2.70–2.80 (*m*, 2 H); 2.87–2.97 (*m*, 2 H); 3.82 (*s*, 3 H); 6.65–6.90 (br., 2 H); 7.01 (*d*, *J* = 8.8, 2 H); 8.29 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR: 22.5; 22.7; 25.4; 25.9; 55.7; 113.7; 114.0; 127.4; 129.6; 130.7; 131.0; 158.4; 158.5; 161.2; 167.1. EI-MS: 311 (23, M^+), 295 (58), 280 (27), 267 (8), 149 (15), 118 (15), 84 (100), 77 (8), 69 (12), 57 (12), 51 (46). Anal. calc. for $C_{17}H_{17}N_3OS$ (311.41): C 65.57, H 5.50, N 13.49; found: C 65.45, H 5.58, N 13.37.

*5,6,7,8-Tetrahydro-2-(3-methylphenyl)[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9f**). White solid. Yield: 0.567 g (96%). M.p. 201–203°. IR (KBr): 3458, 3273, and 3161 (NH), 1611 (C=N), 1550, 1507, 1440, 1398, 1355, 1267, 813, 777, 710, 676, 632. ^{1}H-NMR: 1.75–1.87 (*m*, 4 H); 2.39 (*s*, 3 H); 2.70–2.80 (*m*, 2 H); 2.88–2.98 (*m*, 2 H); 6.70–7.00 (br., 2 H); 7.26 (*d*, *J* = 7.4, 1 H); 7.34 (*t*, *J* = 7.6, 1 H); 8.14 (*d*, *J* = 7.6, 1 H); 8.19 (*s*, 1 H). ^{13}C-NMR: 21.6; 22.5; 22.7; 25.4; 25.9; 114.1; 125.2; 127.4; 128.5; 128.6; 130.9; 131.6; 137.8; 138.2; 158.5; 158.6; 167.0. EI-MS: 295 (36, M^+), 280 (8), 266 (8), 177 (8), 161 (9), 149 (20), 118 (100), 91 (92), 77 (32), 65 (64), 57 (56), 51 (36). Anal. calc. for $C_{17}H_{17}N_3S$ (295.41): C 69.12, H 5.80, N 14.22; found: C 69.31, H 5.77, N 14.24.

*6,7,8,9-Tetrahydro-2-phenyl-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine* (**9g**). White solid. Yield: 0.561 g (95%). M.p. 171–172°. IR (KBr): 3493, 3308, and 3165 (NH), 1635 (C=N), 1547, 1504, 1404, 1283, 996, 808, 769, 708, 669. ^{1}H-NMR: 1.62–1.74 (*m*, 4 H); 1.80–1.89 (*m*, 2 H); 2.83–2.90 (*m*, 2 H); 3.01–3.09 (*m*, 2 H); 6.85–7.10 (br., 2 H); 7.44–7.48 (*m*, 3 H); 8.34 (*dd*, *J* = 7.6, 2.0, 2 H). ^{13}C-NMR: 26.9; 27.4; 29.1; 29.2; 31.3; 115.3; 127.9; 128.7; 130.2; 132.7; 135.7; 138.2; 158.0; 158.7; 165.8. EI-MS: 295 (19, M^+), 280 (8), 266 (38), 225 (5), 161 (8), 149 (10), 137 (10), 121 (15), 104 (100), 91 (15), 77 (88), 69 (23), 57 (19), 51 (38). Anal. calc. for $C_{17}H_{17}N_3S$ (295.41): C 69.12, H 5.80, N 14.22; found: C 69.11, H 5.82, N 14.19.

*2-(4-Fluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine* (**9h**). White solid. Yield: 0.551 g (88%). M.p. 189–190°. IR (KBr): 3476, 3289, and 3170 (NH), 1598 (C=N), 1544, 1500, 1403, 1223, 1150, 845, 787, 739, 683, 628. ^{1}H-NMR: 1.63–1.75 (*m*, 4 H); 1.80–1.90 (*m*, 2 H); 2.83–2.91 (*m*, 2 H); 3.00–3.08 (*m*, 2 H); 6.96–7.03 (br., 2 H); 7.29 (*dd*, ^3J(F,H) = 8.8, ^3J(H,H) = 8.8, 2 H); 8.37 (*dd*, ^3J(H,H) = 8.8, ^4J(F,H) = 5.6, 2 H). ^{13}C-NMR: 27.0; 27.4; 29.0; 29.1; 31.3; 115.2; 115.6 (*d*, ^2J(F,C) = 21.4); 130.1 (*d*, ^3J(F,C) = 8.6); 132.7; 134.7; 135.7; 157.1; 158.7; 163.8 (*d*, ^1J(F,C) = 245.1); 165.8. EI-MS: 313 (19, M^+), 284 (35), 163 (8), 149 (15), 137 (15), 130 (12), 122 (100), 95 (81), 75 (38), 69 (38), 63 (19), 55 (50). Anal. calc. for $C_{17}H_{16}FN_3S$ (313.40): C 65.15, H 5.15, N 13.41; found: C 65.19, H 5.16, N 13.37.

*2-(4-Chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine* (**9i**). White solid. Yield: 0.593 g (90%). M.p. 183–184°. IR (KBr): 3510, 3402, and 3193 (NH), 1613 (C=N), 1539, 1497, 1401, 1360, 1289, 1090, 1010, 845, 786, 733, 652. ^{1}H-NMR: 1.67–1.68 (*m*, 4 H); 1.83–1.84 (*m*, 2 H); 2.84–2.87 (*m*, 2 H); 3.03–3.05 (*m*, 2 H); 6.98–7.08 (br., 2 H); 7.52 (*d*, *J* = 8.4, 2 H); 8.34 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR: 26.9; 27.3; 29.0; 29.1; 31.3; 115.4; 128.8; 129.6; 132.8; 135.0; 136.1; 137.0; 156.9; 158.7; 165.7. EI-MS: 331 (32, M^+(^{37}Cl)), 329 (100, M^+(^{35}Cl)), 314 (23), 300 (69), 288 (8), 275 (9),

140 (12), 138 (38), 111 (15), 102 (23), 91 (9), 75 (12), 55 (8). Anal. calc. for $C_{17}H_{16}ClN_3S$ (329.85): C 61.90, H 4.89, N 12.74; found: C 61.84, H 4.72, N 12.66.

*2-(4-Bromophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine* (**9j**). White solid. Yield: 0.681 g (91%). M.p. 177–178°. IR (KBr): 3526 and 3412 (NH), 1597 (C=N), 1547, 1506, 1405, 1359, 1212, 1149, 847, 787, 636. ^{1}H-NMR: 1.62–1.74 (*m*, 4 H); 1.79–1.89 (*m*, 2 H); 2.81–2.90 (*m*, 2 H); 2.99–3.08 (*m*, 2 H); 6.85–7.15 (br., 2 H); 7.66 (*d*, *J* = 8.8, 2 H); 8.27 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR: 27.0; 27.3; 29.0; 29.2; 31.3; 115.4; 123.9; 129.9; 131.7; 132.8; 136.1; 137.4; 157.0; 158.7; 165.7. EI-MS: 375 (80, M^+(^{81}Br)), 373 (78, M^+(^{79}Br)), 360 (15), 358 (15), 346(42), 344 (39), 299 (100), 284 (23), 266 (54), 184 (19), 182 (19), 167 (22), 149 (84), 122 (38), 104 (31), 81 (30), 69 (62), 57 (42). Anal. calc. for $C_{17}H_{16}BrN_3S$ (374.30): C 54.55, H 4.31, N 11.23; found: C 54.40, H 4.20, N 11.08.

*6,7,8,9-Tetrahydro-2-(4-methoxyphenyl)-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine* (**9k**). White solid. Yield: 0.592 g (91%). M.p. 172–173°. IR (KBr): 3448 and 3341 (NH), 1607 (C=N), 1499, 1437, 1402, 1241, 1176, 1031, 839, 787, 744, 687, 631. ^{1}H-NMR: 1.62–1.75 (*m*, 4 H); 1.79–1.89 (*m*, 2 H); 2.80–2.89 (*m*, 2 H); 2.99–3.06 (*m*, 2 H); 3.82 (*s*, 3 H); 6.86–6.94 (br., 2 H); 7.01 (*d*, *J* = 8.8, 2 H); 8.28 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR: 26.9; 27.4; 29.0; 29.1; 31.3; 55.7; 114.0; 114.9; 129.5; 130.7; 132.6; 135.0; 157.0; 158.6; 161.2; 165.9. EI-MS: 325 (100, M^+), 310 (23), 296 (62), 271 (12), 163 (12), 149 (12), 142 (10), 134 (24), 119 (10), 103 (10), 91 (7), 77 (7), 57 (5). Anal. calc. for $C_{18}H_{19}N_3OS$ (325.43): C 66.43, H 5.88, N 12.91; found: C 66.45, H 6.04, N 12.77.

*6,7,8,9-Tetrahydro-2-(3-methylphenyl)-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine* (**9l**). White solid. Yield: 0.582 g (94%). M.p. 193–194°. IR (KBr): 3478, 3288, and 3162 (NH), 1610 (C=N), 1543, 1500, 1436, 1392, 1358, 1278, 806, 778, 714, 678, 626. ^{1}H-NMR: 1.61–1.75 (*m*, 4 H); 1.79–1.90 (*m*, 2 H); 2.39 (*s*, 3 H); 2.80–2.91 (*m*, 2 H); 2.99–3.09 (*m*, 2 H); 6.91–7.00 (br., 2 H); 7.25 (*d*, *J* = 7.6, 1 H); 7.34 (*t*, *J* = 7.6, 1 H); 8.14 (*d*, *J* = 8.0, 1 H); 8.19 (*s*, 1 H). ^{13}C-NMR: 21.6; 26.9; 27.4; 29.1; 29.2; 31.3; 115.3; 125.2; 128.5; 128.6; 130.9; 132.7; 135.6; 137.7; 138.1; 158.1; 158.7; 165.8. EI-MS: 309 (8, M^+), 280 (16), 201 (20), 116 (96), 104 (28), 91 (92), 83 (24), 77 (64), 69 (92), 63 (40), 57 (72), 55 (100). Anal. calc. for $C_{18}H_{19}N_3S$ (309.44): C 69.87, H 6.19, N 13.58; found: C 69.90, H 6.18, N 13.54.

*5,6,7,8-Tetrahydro-7-methyl-2-phenyl[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9m**). White solid. Yield: 0.555 g (94%). M.p. 225–227°. IR (KBr): 3493, 3283, and 3151 (NH), 1608 (C=N), 1546, 1509, 1406, 1358, 1279, 848, 766, 684. ^{1}H-NMR: 1.05 (*d*, *J* = 6.4, 3 H); 1.36–1.51 (*m*, 1 H); 1.83–1.97 (*m*, 2 H); 2.36 (*dd*, ^2J = 16.8, ^3J = 9.6, 1 H); 2.82 (*dd*, ^2J = 16.8, ^3J = 4.6, 1 H); 2.88–2.95 (*m*, 1 H); 2.97–3.80 (*m*, 1 H); 6.65–7.05 (br., 2 H); 7.42–7.49 (*m*, 3 H); 8.35 (*dd*, *J* = 7.6, 2.0, 2 H). ^{13}C-NMR: 21.6; 25.6; 28.9; 30.5; 33.3; 114.0; 127.1; 128.0; 128.7; 130.3; 131.2; 138.2; 158.4; 158.6; 167.1. EI-MS: 295 (8, M^+), 256 (16), 241 (12), 160 (32), 129 (16), 97 (32), 69 (100), 57 (87). Anal. calc. for $C_{17}H_{17}N_3S$ (295.41): C 69.12, H 5.80, N 14.22; found: C 69.10, H 5.80, N 14.19.

*2-(4-Fluorophenyl)-5,6,7,8-tetrahydro-7-methyl[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9n**). White solid. Yield: 0.545 g (87%). M.p. 245–246°. IR (KBr): 3508 and 3345 (NH), 1592 (C=N), 1546, 1508, 1407, 1359, 1280, 1216, 1148, 848, 785, 738, 660. ^{1}H-NMR: 1.05 (*d*, *J* = 6.4, 3 H); 1.37–1.50 (*m*, 1 H); 1.83–1.97 (*m*, 2 H); 2.36 (*dd*, ^2J = 16.8, ^3J = 9.6, 1 H); 2.82 (*dd*, ^2J = 16.8, ^3J = 4.6, 1 H); 2.87–2.96 (*m*, 1 H); 2.97–3.80 (*m*, 1 H); 6.70–7.10 (br., 2 H); 7.28 (*dd*, ^3J(F,H) = 8.8, ^3J(H,H) = 8.8, 2 H); 8.38 (*dd*, ^3J(H,H) = 8.8, ^4J(F,H) = 5.6, 2 H). ^{13}C-NMR: 21.6; 25.6; 28.9; 30.5; 33.3; 113.9; 115.6 (*d*, ^2J(F,C) = 21.4); 127.1; 130.2 (*d*, ^3J(F,C) = 8.6); 131.2; 134.7 (*d*, ^4J(F,C) = 2.7); 157.6; 158.6; 163.8 (*d*, ^1J(F,C) = 245.1); 167.1. EI-MS: 313 (100, M^+), 298 (46), 284 (15), 271 (46), 150 (27), 122 (69), 95 (31), 83 (31), 69 (58), 57 (49), 55 (54). Anal. calc. for $C_{17}H_{16}FN_3S$ (313.40): C 65.15, H 5.15, N 13.41; found: C 65.09, H 5.24, N 13.35.

*2-(4-Chlorophenyl)-5,6,7,8-tetrahydro-7-methyl[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9o**). White solid. Yield: 0.587 g (89%). M.p. 249–250°. IR (KBr): 3462, 3283, and 3174 (NH), 1598 (C=N), 1547, 1505, 1407, 1283, 1088, 1011, 842, 783, 735, 681, 645. ^{1}H-NMR: 1.06 (*d*, *J* = 6.4, 3 H); 1.38–1.52 (*m*, 1 H); 1.84–1.98 (*m*, 2 H); 2.38 (*dd*, ^2J = 16.8, ^3J = 9.6, 1 H); 2.84 (*dd*, ^2J = 16.8, ^3J = 4.8, 1 H); 2.88–2.96 (*m*, 1 H); 2.98–3.04 (*m*, 1 H); 6.70–7.10 (br., 2 H); 7.53 (*d*, *J* = 8.4, 2 H); 8.34 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR: 21.6; 25.6; 28.9; 30.5; 33.4; 114.2; 127.2; 128.8; 129.7; 131.6; 135.0; 137.1; 157.4; 158.6; 167.0. EI-MS: 331 (33, M^+(^{37}Cl)), 329 (100, M^+(^{35}Cl)), 316 (17), 314 (50), 300 (14), 289 (13), 187 (38), 167 (13), 149 (33), 85 (17), 71 (25), 57 (29). Anal. calc. for $C_{17}H_{16}ClN_3S$ (329.85): C 61.90, H 4.89, N 12.74; found: C 61.89, H 4.93, N 12.68.

*5,6,7,8-Tetrahydro-2-(4-methoxyphenyl)-7-methyl[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9p**). White solid. Yield: 0.618 g (95%). M.p. 214–216°. IR (KBr): 3436, 3290, and 3172 (NH), 1606 (C=N), 1552, 1507, 1408, 1362, 1255, 1172, 1034, 841, 786, 645. ^{1}H-NMR: 1.06 (*d*, *J* = 6.4, 3 H); 1.34–1.50 (*m*, 1 H); 1.80–1.97 (*m*, 2 H); 2.33 (*dd*, ^2J(H,H) = 16.8, ^3J(H,H) = 9.6, 1 H); 2.79 (*dd*, ^2J(H,H) = 16.8, ^3J(H,H) = 4.8, 1 H); 2.84–2.94 (*m*, 1 H); 2.95–3.06 (*m*, 1 H); 6.70–6.84 (br., 2 H); 7.00 (*d*, *J* = 8.8, 2 H); 8.29 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR: 21.6; 25.6; 28.9; 30.6; 33.3; 55.7; 113.6; 114.0; 127.0; 129.6; 130.5; 130.8; 158.4; 158.5; 161.2; 167.3. EI-MS: 325 (62, M^+), 310 (27), 283 (19), 256 (12), 192 (11), 164 (15), 149 (27), 134 (35), 83 (38), 69 (100), 57 (82). Anal. calc. for $C_{18}H_{19}N_3OS$ (325.43): C 66.43, H 5.88, N 12.91; found: C 66.57, H 5.97, N 12.73.

*5,6,7,8-Tetrahydro-7-methyl-2-(3-methylphenyl)[1]benzothieno[2,3-*d*]pyrimidin-4-amine* (**9q**). White solid. Yield: 0.569 g (92%). M.p. 208–209°. IR (KBr): 3502, 3309, and 3168 (NH), 1626 (C=N), 1543, 1507, 1397, 1356, 1310, 1279, 722, 672. ^{1}H-NMR: 1.05 (*d*, *J* = 6.4, 3 H); 1.37–1.51 (*m*, 1 H); 1.82–1.97 (*m*, 2 H); 2.33 (*dd*, ^2J = 16.8, ^3J = 9.6, 1 H); 2.39 (*s*, 3 H); 2.82 (*dd*, ^2J = 16.8, ^2J = 4.6, 1 H); 2.86–2.95 (*m*, 1 H); 2.96–3.08 (*m*, 1 H); 6.75–6.90 (br., 2 H); 7.25 (*d*, *J* = 7.2, 1 H); 7.34 (*t*, *J* = 7.6, 1 H); 8.14 (*d*, *J* = 7.6, 1 H); 8.19 (*s*, 1 H). ^{13}C-NMR: 21.5; 21.6; 25.6; 28.9; 30.5; 33.3; 114.0; 125.2; 127.1; 128.5; 128.6; 130.9; 131.1; 137.7; 138.2; 158.5; 158.6; 167.1. EI-MS: 309 (69, M^+), 294 (42), 266 (31), 241 (15), 217 (15), 173 (50), 149 (19), 118 (38), 91 (35), 69 (100), 57 (82). Anal. calc. for $C_{18}H_{19}N_3S$ (309.44): C 69.87, H 6.19, N 13.58; found: C 69.90, H 6.17, N 13.40.

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