Microwave-Assisted Synthesis of 4-Amino-2-arylthieno[2,3-*d*]pyrimidines and Their Subsequent Functionalization

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Received 11 March 2010; revised 23 March 2010

Abstract: New 4-amino-2-arylthieno[2,3-*d*]pyrimidines were synthesized by reacting 2-amino-3-cyanothiophenes and aryl nitriles under microwave irradiation. Functionalization of 4-amino group was made by acetic anhydride and several isocyanates.

Key words: 2-amino-3-cyanothiophenes, 4-amino-2-arylthieno[2,3-*d*]pyrimidines, microwave irradiation

2-Amino-3-cyanothiophenes can be considered as useful starting materials. Especially, we used this scaffold to access thienopyridines,[1] thienopyridinones,[2] thienopyrimidin-4-ones,[3] and 4-arylthienopyrimidines.[4] We report here the preparation of 4-amino-2-arylthieno[2,3-*d*]pyrimidines by reacting the 2-amino-3-cyanothiophenes with aromatic nitriles under microwave irradiation.

Indeed, the 4-aminothieno[2,3-*d*]pyrimidine core is present in many compounds having biological activities: 4-amino-6-imidazolylthieno[2,3-*d*]pyrimidines were reported as kinase inhibitors with activity against Tie-2 in vitro and in vivo.[5] 2-Alkylthio-4-aminothieno[2,3-*d*]pyrimidines were proved to be modulators of P-glycoprotein substrate specificity.[6] 4-Amino-5-(4-substituted phenyl)thieno[2,3-*d*]pyrimidines were described as inhibitors of all the vascular endothelial growth factor and platelet-derived growth factor receptor tyrosine kinases.[7,8]

The synthesis of heterocondensed 4-aminopyrimidines starting from *ortho*-aminocyanoheterocycles often requires harsch conditions[9] or prolonged heating.[10] However since a few years, microwave-assisted organic synthesis has allowed milder conditions and reduced reaction times. The pioneering work of Seijas et al.[11] using a domestic microwave oven has demonstrated the power of this methodology. Anthranilonitrile was efficiently coupled with several aromatic nitriles in the presence of catalytic amount of *t*-BuOK under microwave irradiation; good yields were obtained after only few minutes of irradiation. Those conditions were successfully applied to 3-amino-4-cyanopyrazoles by La Motta and Lavecchia.[12] Recently, the synthesis of pyrazolo[3,4-*d*]pyrimidines starting from 5-amino-4-cyanopyrazoles was reported under almost the same conditions.[13]

SYNTHESIS 2010, No. 14, pp 2413–2418
Advanced online publication: 05.05.2010
DOI: 10.1055/s-0029-1218770; Art ID: Z06010SS
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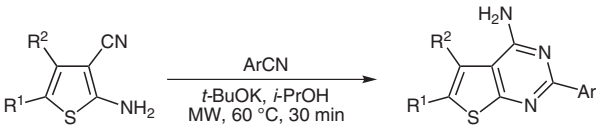
So far, only three 4-amino-2-arylthieno[2,3-*d*]pyrimidines were previously described. Two of them were synthesized in the presence of HCl gas in dioxane[14] whereas the last one was formed in the presence of MeONa in isopropanol on heating for 24 hours.[15] Those compounds were evaluated as antifungal and antibacterial agents.[16] Our aim was to use a faster and more efficient protocol. So, we first tried the conditions described for the synthesis of pyrazolo[3,4-*d*]pyrimidines (microwave 145 °C, 10 min, *t*-BuOK cat.), but unfortunately these reactions failed. We have then modified these conditions and finally succeeded in coupling 2-amino-3-cyanothiophenes with aromatic nitriles under microwave activation (Scheme 1). Five different thiophenes were studied and condensed with five different aromatic nitriles leading to 25 new compounds (Table 1).



Scheme 1

We next wanted to further functionalize the 4-amino group and especially to introduce an amide or urea linker by reaction with anhydride and isocyanate, respectively. This was a challenging reaction as this amino group seems to be poorly reactive. Indeed, Dai et al.[7] have worked on 4-amino-5-[4-anilino]thieno[2,3-*d*]pyrimidines with isocyanates and have shown that compounds with two potential reactive amine sites were acylated only at the aniline moiety. Moreover, Barnes et al.[8] have described that overacylation to form the bis-acyl product (one acyl on each of the two amino groups) was always a minority process whatever the conditions used. However, protection of the 4-amino group has been realized by using an excess of pivaloyl anhydride[17] or with a Boc by reaction with NaH and Boc_2O.[7]

We first started to study the reaction with acetic anhydride to form an amide moiety. Acetylation of **2** and **8** with acetic anhydride for six hours at reflux gave very good results (compounds **26** and **27**, respectively, in 79 and 52% yield) (Scheme 2). Surprisingly the reaction led to the diacetylated compounds. Monoacetylation on similar compounds has been described using acetic anhydride whereas di-

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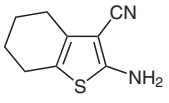
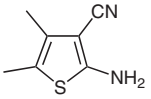
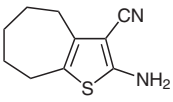
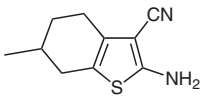
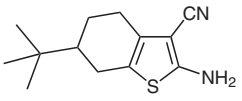
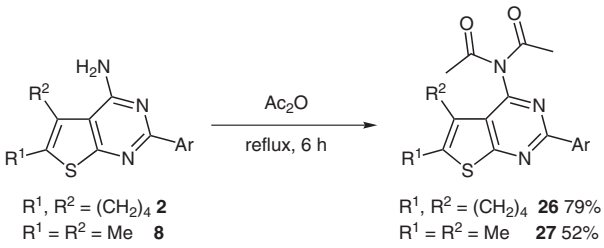
Table 1 4-Amino-2-arylthieno[2,3-*d*]pyrimidines Prepared

Thiophene	Ar	Product	Yield (%)
	Ph	**1**	75
	4-MeC_6H_4	**2**	73
	4-$MeOC_6H_4$	**3**	70
	4-ClC_6H_4	**4**	20
	2-ClC_6H_4	**5**	63
	Ph	**6**	49
	4-MeC_6H_4	**7**	62
	4-$MeOC_6H_4$	**8**	49
	4-ClC_6H_4	**9**	28
	2-ClC_6H_4	**10**	62
	Ph	**11**	20
	4-MeC_6H_4	**12**	20
	4-$MeOC_6H_4$	**13**	22
	4-ClC_6H_4	**14**	25
	2-ClC_6H_4	**15**	12
	Ph	**16**	47
	4-MeC_6H_4	**17**	45
	4-$MeOC_6H_4$	**18**	34
	4-ClC_6H_4	**19**	70
	2-ClC_6H_4	**20**	62
	Ph	**21**	45
	4-MeC_6H_4	**22**	24
	4-$MeOC_6H_4$	**23**	18
	4-ClC_6H_4	**24**	28
	2-ClC_6H_4	**25**	87

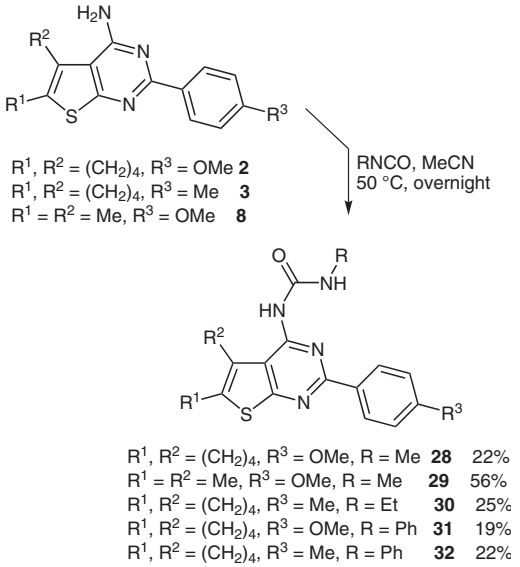


Scheme 2

acetylation was reported using a mixture of acetic anhydride and pyridine.[18]

In contrast, reactions with isocyanates were more difficult and gave only moderate yields of urea derivatives. Using 10 equivalents of methyl isocyanate, compounds **28** and **29** were isolated in 22 and 56% yield, respectively. Coupling of **3** with ethyl isocyanate led to **30** in 25% yield (Scheme 3). Results obtained with phenyl isocyanate seemed at the beginning to be more complex: the ^{1}H NMR spectrum recorded in DMSO-d_6 indicated the presence of two isomers in a 2:1 ratio. Recording the ^{1}H NMR spectrum in pyridine-d_5 greatly simplified it, certainly due to the absence of hydrogen bonding with solvent. Compounds **31** and **32** were obtained in moderate yields.

In conclusion, we have achieved the synthesis and functionalization of new 4-amino-2-arylthieno[2,3-*d*]pyrimidines. Evaluation of the biological potential will follow.



Scheme 3

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra (δ in parts per million) were recorded on an AC Bruker 250 MHz spectrometer in DMSO-d_6. MS spectra were recorded on an Electrospray Ionization Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (ESI-FTICR/MS, QFT-9, 4T, Varian-Ion Spec, CA, USA) with Omega 9, Varian, Software for acquisition and analysis of Fourier transform mass spectra and Exact Mass Calculator, Ion Spec, for calculate mass and *m*/*z* values and isotope distribution from an elemental formula. A CEM Discover microwave oven was used in open-vessel mode for the microwave-assisted synthesis; the temperature was monitored by an infrared sensor located in the microwave cavity floor.

4-Amino-2-arylthieno[2,3-*d*]pyrimidines 1–25; General Procedure

A mixture of 2-amino-3-cyanothiophene (1 equiv), aromatic nitrile (2 equiv), and *t*-BuOK (2–3 equiv) in *i*-PrOH (2.5 mL/mol) was submitted to microwave irradiation for 30 min at 65 °C. After cooling, the reaction mixture was poured onto H_2O (100 mL). The precipitate was collected by filtration and washed with Et_2O (50 mL) (Table 1).

2-Phenyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-amine (1)

Yield: 75%; brown solid; mp 200 °C (Lit.[14b] mp 195–197 °C).

IR (KBr): 3428, 3308, 1608 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.81 (m, 4 H, 2 × CH_2), 2.75 (m, 2 H, CH_2), 2.92 (m, 2 H, CH_2), 6.84 (br s, 2 H, NH_2), 7.43–7.48 (m, 3 H), 8,33–8.37 (m, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.9, 22.2, 24.9, 25.4, 113.7, 126.9, 127.5, 128.2, 129.8, 131.2, 137.7, 157.9, 158.1, 166.5.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{16}H_{16}N_3S$: 282.1059; found: 282.1059.

2-*p*-Tolyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-amine (2)

Yield: 73%; brown solid; mp 209 °C.

IR (KBr): 3486, 3296, 3163, 1634 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.83 (m, 4 H, 2 × CH_2), 2.37 (s, 3 H, CH_3), 2.77 (m, 2 H, CH_2), 2.94 (m, 2 H, CH_2), 6.83 (br s, 2 H, NH_2), 7.27 (d, *J* = 8.0 Hz, 2 H), 8.25 (d, *J* = 8.0 Hz, 2 H).

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^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.9, 21.9, 22.2, 24.9, 25.4, 113.5, 126.9, 127.5, 128.8, 130.8, 135.0, 139.4, 157.9, 158.0, 166.5.

HRMS (ESI): *m*/*z* calcd for [M + Na] $C_{17}H_{17}N_3S$ + Na: 318.1035; found: 318.1057.

2-(4-Methoxyphenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-amine (3)
Yield: 70%; brown solid; mp 200 °C.

IR (KBr): 3384, 1621 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.80 (m, 4 H, 2 × CH_2), 2.73 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 6.77 (br s, 2 H, NH_2), 7.01 (d, *J* = 8.6 Hz, 2 H), 8.27 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.9, 22.2, 24.9, 25.4, 55.2, 113.2, 113.5, 126.9, 129.0, 130.2, 130.4, 157.9, 158.0, 160.7, 166.6.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{18}N_3OS$: 312.1165; found: 312.1183.

2-(4-Chlorophenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-amine (4)
Yield: 20%; brown solid; mp 208 °C.

IR (KBr): 3511, 3465, 3269, 1621 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.80 (m, 4 H, 2 × CH_2), 2.75 (m, 2 H, CH_2), 2.91 (m, 2 H, CH_2), 6.88 (br s, 2 H, NH_2), 7.51 (d, *J* = 8.6 Hz, 2 H), 8.32 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.9, 22.2, 24.9, 25.3, 113.8, 127.0, 128,3, 129.2, 131.6, 134.6, 136.5, 156.9, 158.1, 166.4.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{16}H_{15}ClN_3S$: 316.0670; found: 316.0695.

2-(2-Chlorophenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-amine (5)
Yield: 63%; brown solid; mp 200 °C (Lit.[15] mp 210–211 °C).

IR (KBr): 3506, 3272, 1631 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.81 (m, 4 H, 2 × CH_2), 2.75 (m, 2 H, CH_2), 2.93 (m, 2 H, CH_2), 6.92 (br s, 2 H, NH_2), 7.39–7.43 (m, 2 H), 7.49–7.52 (m, 1 H), 7.57–7.60 (m, 1 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 22.0, 22.2, 24.9, 25.3, 113.5, 126.7, 126.9, 129.7, 129.8, 131.0, 131.3, 131.5, 138.6, 158.0, 159.2, 165.7.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{16}H_{15}ClN_3S$: 316.0670; found: 316.0695.

5,6-Dimethyl-2-phenylthieno[2,3-*d*]pyrimidin-4-amine (6)
Yield: 49%; brown solid; mp 186 °C.

IR (KBr): 3500, 3298, 1631 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.41 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 6.94 (br s, 2 H, NH_2), 7.46 (m, 3 H), 8.35 (m, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0, 13.8, 114.7, 124.8, 127.4, 127.9, 128.2, 129.8, 137.7, 157.8, 158.2, 165.8.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{14}H_{14}N_3S$: 256.0903; found: 256.0904.

5,6-Dimethyl-2-*p*-tolylthieno[2,3-*d*]pyrimidin-4-amine (7)
Yield: 62%; brown solid; mp 216 °C.

IR (KBr): 3511, 3282, 1607 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 6.90 (br s, 2 H, NH_2), 7.28 (d, *J* = 8.0 Hz, 2 H), 8.25 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0, 13.8, 20.9, 114.6, 124.8, 127.5, 127.7, 128.8, 135.0, 139.4, 157.9, 158.2, 165.9.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{15}H_{16}N_3S$: 270.1059; found: 270.1056.

2-(4-Methoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine (8)
Yield: 49%; brown solid; mp 217 °C.

IR (KBr): 3495, 3300, 1619 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.40 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 6.85 (br s, 2 H, NH_2), 7.02 (d, *J* = 8.9 Hz, 2 H), 8.30 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0, 13.8, 55.2, 113.6, 114.3, 124.8, 127.2, 129.0, 130.2, 157.8, 158.2, 160.7, 165.9.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{15}H_{16}N_3OS$: 286.1009; found: 286.1002.

2-(4-Chlorophenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine (9)
Yield: 30%; brown solid; mp 215 °C.

IR (KBr): 3283, 1634 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 6.96 (br s, 2 H, NH_2), 7,51 (d, *J* = 8.5 Hz, 2 H), 8.32 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0, 13.8, 114.8, 124.9, 128.3, 128.3, 129.2, 134.5, 136.6, 156.8, 158.2, 165.7.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{14}H_{13}ClN_3S$: 290.0513; found: 290.0527.

2-(2-Chlorophenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine (10)
Yield: 62%; brown solid; mp 226 °C.

IR (KBr): 3508, 3283, 1634 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.40 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 7.00 (br s, 2 H, NH_2), 7.40 (m, 2 H), 7.48 (m, 1 H), 7.59 (m, 1 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.0, 13.8, 114.5, 124.7, 126.7, 128.3, 129.6, 129.8, 131.0, 131.3, 138.6, 158.1, 159.0, 165.0.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{14}H_{13}ClN_3S$: 290.0513; found: 290.0527.

6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]-2-phenylthieno[2,3-*d*]pyrimidin-4-amine (11)
Yield: 20%; brown solid; mp 174 °C.

IR (KBr): 3438, 3333, 1609 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.68 (m, 4 H, 2 × CH_2), 1.82 (m, 2 H, CH_2), 2.84 (m, 2 H, CH_2), 3.01 (m, 2 H, CH_2), 6.96 (br s, 2 H, NH_2), 7.44 (m, 3 H), 8.32 (m, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.4, 26.8, 28.5, 28.6, 30.8, 114.8, 127.4, 128.2, 129.7, 132.2, 135.2, 137.7, 157.5, 158.2, 165.3.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{18}N_3S$: 296.1216; found: 296.1221.

2-*p*-Tolyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4-amine (12)
Yield: 20%; brown solid; mp 178 °C.

IR (KBr): 3469, 3364, 1603 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.67 (m, 4 H, 2 × CH_2), 1.82 (m, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 2.83 (m, 2 H, CH_2), 3.02 (m, 2 H, CH_2), 6.91 (br s, 2 H, NH_2), 7.25 (d, *J* = 8.0 Hz, 2 H), 8.22 (d, *J* = 8.0 Hz, 2 H).

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^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.9, 26.4, 26.8, 28.6, 28.6, 30.7, 114.7, 127.4, 128.8, 132.1, 134.9, 134.9, 139.3, 157.0, 157.6, 165.4.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{18}H_{20}N_3S$: 310.1372; found: 310.1371.

2-(4-Methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4-amine (13)
Yield: 22%; brown solid; mp 164 °C.

IR (KBr): 3464, 3357, 1605 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.68 (m, 4 H, 2 × CH_2), 1.82 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 3.01 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 6.88 (br s, 2 H, NH_2), 6.99 (d, *J* = 8.8 Hz, 2 H), 8.27 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.4, 26.9, 28.6 (2 C), 30.8, 55.2, 113.5, 114.4, 129.0, 130.2, 132.1, 134.5, 157.4, 158.1, 160.7, 165.4.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{18}N_3OS$: 326.1322; found: 326.1316.

2-(4-Chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4-amine (14)
Yield: 25%; brown solid; mp 182 °C.

IR (KBr): 3323, 1620 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.68 (m, 4 H, 2 × CH_2), 1.82 (m, 2 H, CH_2), 2.84 (m, 2 H, CH_2), 3.01 (m, 2 H, CH_2), 7.01 (br s, 2 H, NH_2), 7.51 (d, *J* = 8.6 Hz, 2 H), 8.32 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.4, 26.8, 28.5, 28.6, 30.7, 114.9, 128.3, 129.1, 132.2, 134.5, 135.6, 136.5, 156.4, 158.2, 165.2.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{17}ClN_3S$: 330.0826; found: 330.0826.

2-(2-Chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4-amine (15)
Yield: 25%; brown solid; mp 182 °C.

IR (KBr): 3425, 3323, 1620 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.68 (m, 4 H, 2 × CH_2), 1.83 (m, 2 H, CH_2), 2.86 (m, 2 H, CH_2), 3.04 (m, 2 H, CH_2), 7.04 (br s, 2 H, NH_2), 7.39–7.42 (m, 2 H), 7.48–7.52 (m, 1 H), 7.56–7.60 (m, 1 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.4, 26.8, 28.5, 28.6, 30.8, 114.6, 126.7, 129.6, 129.8, 131.0, 131.3, 132.1, 135.6, 138.5, 158.0, 158.7, 164.5.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{17}ClN_3S$: 330.0826; found: 330.0826.

7-Methyl-2-phenyl-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (16)
Yield: 47%; yellow solid; mp 230 °C.

IR (KBr): 3492, 3284, 1596 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.01–1.06 (d, *J* = 6.3 Hz, CH_3, 3 H), 1.31–1.52 (m, 1 H), 1.87–1.92 (m, 2 H), 2.37–2.41 (m, 1 H), 2.78–2.99 (m, 3 H), 6.84 (br s, 2 H, NH_2), 7.41–7.47 (m, 3 H), 8.31–8.35 (m, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.0, 25.1, 28.4, 30.0, 32.8, 113.5, 126.6, 127.5, 128.2, 129.8, 130.7, 137.7, 158.0, 158.1, 166.6.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{18}N_3S$: 296.1216; found: 296.1211.

7-Methyl-2-(4-methylphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (17)
Yield: 45%; yellow solid; mp 221 °C.

IR (KBr): 3494, 3295, 1635 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.03–1.06 (d, *J* = 6.3 Hz, CH_3, 3 H), 1.31–1.52 (m, 1 H), 1.88–1.91 (m, 2 H), 2.34 (s, 3 H, CH_3), 2.37–2.41 (m, 1 H), 2.78–2.98 (m, 3 H), 6.80 (br s, 2 H, NH_2), 7.25 (d, *J* = 8.1 Hz, 2 H), 8.22 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.9, 21.0, 25.1, 28.4, 30.0, 32.8, 113.4, 126.6, 127.5, 128.8, 130.4, 135.0, 139.3, 158.0, 158.0, 166.7.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{18}H_{20}N_3S$: 310.1372; found: 310.1373.

2-(4-Methoxyphenyl)-7-methyl-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (18)
Yield: 34%; yellow solid; mp 217 °C.

IR (KBr): 3520, 3378, 1621 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.01–1.05 (d, *J* = 6.3 Hz, CH_3, 3 H), 1.31–1.52 (m, 1 H), 1.87–1.91 (m, 2 H), 2.28–2.45 (m, 1 H), 2.77–2.97 (m, 3 H), 3.81 (s, 3 H, CH_3), 6.77 (br s, 2 H, NH_2), 6.99 (d, *J* = 7.0 Hz, 2 H), 8.27 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.1, 25.1, 28.4, 30.0, 32.8, 55.2, 113.0, 113.5, 126.5, 129.0, 130.0, 130.2, 157.9, 157.9, 160.7, 166.7.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{18}H_{20}N_3SO$: 326.1322; found: 326.1320.

2-(4-Chlorophenyl)-7-methyl-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (19)
Yield: 70%; brown solid; mp 255 °C.

IR (KBr): 3467, 3284, 1604 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.01–1.04 (d, *J* = 6.3 Hz, CH_3, 3 H), 1.31–1.52 (m, 1 H), 1.86–1.89 (m, 2 H), 2.31–2.47 (m, 1 H), 2.79–2.97 (m, 3 H), 6.89 (br s, 2 H, NH_2), 7.49 (d, *J* = 8.5 Hz, 2 H), 8.31 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.0, 25.0, 28.4, 30.0, 32.8, 113.6, 126.6, 128.3, 129.2, 131.0, 134.5, 136.6, 156.9, 158.1, 166.5.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{17}ClN_3S$: 330.0826; found: 330.0839.

2-(2-Chlorophenyl)-7-methyl-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (20)
Yield: 34%; yellow solid; mp 217 °C.

IR (KBr): 3502, 3307, 1629 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.01–1.07 (d, *J* = 6.3 Hz, CH_3, 3 H), 1.31–1.52 (m, 1 H), 1.87–1.91 (m, 2 H), 2.22–2.56 (m, 1 H), 2.71–3.12 (m, 3 H), 6.93 (br s, 2 H, NH_2), 7.38–7.42 (m, 2 H), 7.48–7.52 (m, 1 H), 7.56–7.60 (m, 1 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.0, 25.0, 28.4, 30.0, 32.8, 113.3, 126.5, 126.7 129.6, 129.8, 131.0, 130.1, 131.3, 138.6, 158.0, 159.1, 165.8.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{17}H_{17}ClN_3S$: 330.0826; found: 330.0822.

7-*tert*-Butyl-2-phenyl-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (21)
Yield: 45%; yellow solid; mp 246 °C.

IR (KBr): 3458, 3278, 1614 cm^{-1}.

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^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.93 [s, 9 H, C(CH$_3$)$_3$], 1.34 (m, 1 H), 1.49 (m, 1 H), 2.02 (m, 1 H), 2.58 (m, 1 H), 2.76–2.82 (m, 2 H), 3.07–3.13 (m, 1 H), 6.84 (br s, 2 H, NH$_2$), 7.43–7.45 (m, 3 H), 8.31–8.35 (m, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.6, 26.3, 26.5, 27.0, 32.2, 44.0, 113.4, 126.9, 127.5, 128.2, 129.8, 131.8, 137.7, 157.9, 158.0, 166.7.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{20}H_{24}N_3S$: 338.1685; found: 338.1685.

7-*tert*-Butyl-2-(4-methylphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (22)
Yield: 24%; yellow solid; mp 233 °C.

IR (KBr): 3498, 3306, 1635 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.93 [s, 9 H, C(CH$_3$)$_3$], 1.34 (m, 1 H), 1.52 (m, 1 H), 2.01 (m, 1 H), 2.34 (s, 3 H, CH$_3$), 2.49 (m, 1 H), 2.76–2.82 (m, 2 H), 3.05–3.13 (m, 1 H), 6.80 (br s, 2 H, NH$_2$), 7.25 (d, *J* = 7.9 Hz, 2 H), 8.22 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.9, 23.6, 26.3, 26.5, 27.0, 32.2, 44.0, 113.2, 126.8, 127.4, 128.8, 131.5, 135.0, 139.3, 158.0 (2 C), 166.8.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{21}H_{26}N_3S$: 352.1842; found: 352.1842.

7-*tert*-Butyl-2-(4-methoxyphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (23)
Yield: 18%; yellow solid; mp 215 °C.

IR (KBr): 3477, 3282, 1605 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.93 [s, 9 H, C(CH$_3$)$_3$], 1.35 (m, 1 H), 1.52 (m, 1 H), 2.03 (m, 1 H), 2.49 (m, 1 H), 2.75–2.80 (m, 2 H), 3.05–3.12 (m, 1 H), 3.80 (s, 3 H, CH$_3$), 6.75 (br s, 2 H, NH$_2$), 6.99 (d, *J* = 8.6 Hz, 2 H), 8.27 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.6, 26.3, 26.5, 27.0, 32.2, 44.0, 55.2, 112.9, 113.5, 126.8, 129.0, 130.2, 131.0, 157.9, 158.0, 160.7, 166.8.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{21}H_{26}N_3OS$: 368.1791; found: 368.1786.

7-*tert*-Butyl-2-(4-chlorophenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (24)
Yield: 30%; colorless solid; mp 228 °C.

IR (KBr): 3436, 3289, 1602 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.93 [s, 9 H, C(CH$_3$)$_3$], 1.30 (m, 1 H), 1.47 (m, 1 H), 1.98 (m, 1 H), 2.49 (m, 1 H), 2.73–2.78 (m, 2 H), 3.02 (m, 1 H), 6.86 (br s, 2 H, NH$_2$), 7.47 (d, *J* = 8.1 Hz, 2 H), 8.29 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.6, 26.3, 26.5, 27.0, 32.1, 43.9, 113.5, 126.9, 128.3, 129.1, 132.1, 134.5, 136.6, 156.9, 158.0, 166.6.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{20}H_{23}ClN_3S$: 372.1296; found: 372.1295.

7-*tert*-Butyl-2-(2-chlorophenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-amine (25)
Yield: 87%; yellow solid; mp 224 °C.

IR (KBr): 3507, 3300, 1635 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.93 [s, 9 H, C(CH$_3$)$_3$], 1.36 (m, 1 H), 1.53 (m, 1 H), 2.01–2.06 (m, 1 H), 2.58 (m, 1 H), 2.77–2.84 (m, 2 H), 3.07 (m, 1 H), 6.93 (br s, 2 H, NH$_2$), 7.38–7.44 (m, 2 H), 7.49–7.52 (m, 1 H), 7.57–7.60 (m, 1 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.6, 26.3, 26.5, 27.0, 32.2, 44.0, 113.2, 126.7, 129.6, 129.8, 131.0, 131.3, 132.1, 138.6, 157.9, 159.1, 165.9.

HRMS (ESI): *m*/*z* calcd for [M + H] $C_{20}H_{23}ClN_3S$: 372.1296; found: 372.1291.

Compounds 26 and 27; General Procedure
A mixture of 2-aminothienopyrimidine **2**, **8** (0.5 mmol) and Ac_2O (5 mL) was stirred and refluxed for 6 h. After cooling, the reaction mixture was hydrolyzed with H_2O (50 mL), the precipitate was collected by filtration, and dried.

***N*,*N*-[2-(4-Methylphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-yl]diacetamide (26)**
Yield: 79%; colorless solid; mp 210 °C.

IR (KBr): 1723, 1704 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.83 (m, 4 H, 2 × CH$_2$), 2.29 (s, 6 H, 2 × CH$_3$), 2.38 (s, 3 H, CH$_3$), 2.58 (m, 2 H, CH$_2$), 2.90 (m, 2 H, CH$_2$), 7.34 (d, *J* = 8.1 Hz, 2 H), 8.29 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.0, 21.5, 21.9, 23.9, 25.3, 26.2, 125.6, 125.8, 127.8, 129.5, 133.3, 139.8, 140.9, 152.2, 158.7, 170.5, 171.8.

HRMS (APCI): *m*/*z* calcd for [M + H] $C_{21}H_{22}N_3SO_2$: 380.1428; found: 380.1439; *m*/*z* calcd for [M – COCH$_3$ + H] $C_{19}H_{20}N_3SO$: 338.1322; found: 338.1332; *m*/*z* calcd for [M – 2 COCH$_3$ + H] $C_{17}H_{18}N_3S$: 296.1216; found: 296.1227.

***N*,*N*-[2-(4-Methoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-yl]diacetamide (27)**
Yield: 52%; colorless solid; mp 205 °C.

IR (KBr): 1727, 1705 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.17 (s, 3 H, CH$_3$), 2.29 (s, 6 H, 2 × CH$_3$), 2.52 (s, 3 H, CH$_3$), 3.83 (s, 3 H, CH$_3$), 7.07 (d, *J* = 8 Hz, 2 H), 8.33 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.1, 13.6, 26.2, 55.3, 114.2, 123.5, 126.1, 128.4, 129.5, 136.3, 152.4, 158.4, 161.6, 170.0, 171.9.

HRMS (APCI): *m*/*z* calcd for [M + H] $C_{19}H_{20}N_3SO_3$: 370.1238; found: 370.1227; *m*/*z* calcd for [M – COCH$_3$ + H] $C_{17}H_{18}N_3SO_2$: 328.1114; found: 328.1124; *m*/*z* calcd for [M – 2 COCH$_3$ + H] $C_{15}H_{16}N_3SO$: 286.1009; found: 286.1015.

Compounds 28 and 29; General Procedure
2-Aminothienopyrimidine **2**, **8** (1 equiv) was dissolved in MeCN (5 mL/mmol) at 20–50 °C and methyl isocyanate (10 equiv) was added dropwise. The mixture was stirred overnight at 50 °C. The precipitate was isolated, filtered, and dried.

***N*-[2-(4-Methoxyphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-yl]-*N*′-methylurea (28)**
Yield: 22%; colorless solid; mp 202 °C.

IR (KBr): 3374, 3265, 1686 cm^{-1}.

^{1}H NMR (250 MHz, pyridine-d_5): δ = 1.59 (m, 4 H, 2 × CH$_2$), 2.60 (m, 2 H, CH$_2$), 2.76 (m, 2 H, CH$_2$), 3.13 (d, *J* = 4.7 Hz, 3 H, NCH$_3$), 3.72 (s, 3 H, OCH$_3$), 7.14 (d, *J* = 8.8 Hz, 2 H), 7.76 (br s, 1 H, NH), 8.51 (d, *J* = 8.8 Hz, 2 H), 9.65 (d, *J* = 4.7 Hz, 1 H, NH).

^{13}C NMR (62.9 MHz, pyridine-d_5): δ = 22.8, 22.9, 26.1, 26.3, 27.2, 55.9, 115.1, 115.7, 126.2, 130.4, 130.8, 136.0, 153.5, 155.4, 157.8, 162.7, 169.2.

HRMS (ESI): *m*/*z* calcd for [M + Na] $C_{19}H_{20}N_4O_2S$ + Na: 391.1199; found: 391.0826.

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N-[2-(4-Methoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-yl]-N′-methylurea (29)
Yield: 56%; colorless solid; mp 204 °C.

IR (KBr): 3293, 1683 cm^{-1}.

^1H NMR (250 MHz, pyridine-d_5): δ = 2.22 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 3.11 (s, 3 H, CH_3), 3.72 (s, 3 H, CH_3), 7.14 (d, *J* = 8.9 Hz, 2 H), 8.07 (br s, 1 H, NH), 8.48 (d, *J* = 8.6 Hz, 2 H), 9.63 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 13.7, 14.1, 27.2, 55.9, 115.1, 116.6, 124.1, 130.3, 130.7, 132.8, 153.6, 155.4, 167.7, 162.7, 168.5.

HRMS (ESI): *m/z* calcd for [M + Na] $C_{17}H_{18}N_4O_2S$ + Na: 365.1043; found: 365.1057.

N-[2-(4-Methylphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-yl]-N′-ethylurea (30); Typical Procedure
Aminothienopyrimidine **2** (1 mmol) was dissolved in $CHCl_3$ (10 mL) and ethyl isocyanate (0.5 mL) was added dropwise under stirring. The mixture was stirred at r.t. for 48 h. The mixture was hydrolyzed with H_2O (50 mL), and extracted with $CHCl_3$ (2 × 50 mL) (or EtOAc). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was triturated with Et_2O, the precipitate formed was collected, dried, and recrystallized from MeOH; yield: 81 mg (22%); colorless solid; mp 195 °C.

IR (KBr): 3382, 3245, 1686 cm^{-1}.

^1H NMR (250 MHz, pyridine-d_5): δ = 1.32 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.60 (m, 4 H, 2 × CH_2), 2.29 (s, 3 H, CH_3), 2.61 (m, 2 H, CH_2), 2.77 (m, 2 H, CH_2), 3.57–3.65 (m, 2 H, CH_2), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.72 (br s, 1 H, NH), 8.42 (d, *J* = 8.0 Hz, 2 H), 9.75 (m, 1 H, NH).

^{13}C NMR (62.9 MHz, pyridine-d_5): δ = 15.7, 21.7, 22.8, 22.9, 26.1, 26.3, 35.9, 116.0, 126.2, 128.7, 130.3, 135.7, 136.4, 141.6, 153.6, 154.5, 157.9, 169.1.

HRMS: *m/z* calcd for [M + H] $C_{20}H_{23}N_4OS$: 367.1587; found: 367.1585.

N-Phenyl-N′-[2-(4-methoxyphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-yl]urea (31)
Yield: 19%; colorless solid; mp 226 °C.

IR (KBr): 3442, 1714 cm^{-1}.

^1H NMR (250 MHz, pyridine-d_5): δ = 1.63 (m, 4 H, 2 × CH_2), 2.63 (m, 2 H, CH_2), 2.84 (m, 2 H, CH_2), 3.73 (s, 3 H, CH_3), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.42–7.48 (m, 3 H), 7.98 (br s, 1 H, NH), 8.06 (d, *J* = 8 Hz, 2 H), 8.57 (d, *J* = 8.8 Hz, 2 H), 12.17 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.9, 22.0, 24.9, 25.4, 55.2, 113.2, 113.5, 113.8, 115.5, 118.1, 126.9, 128.7, 129.0, 130.2, 130.4, 148.5, 157.9, 158.0, 160.7, 166.6

N-Phenyl-N′-[2-(4-methylphenyl)-5,6,7,8-tetrahydro[*b*]benzothieno[2,3-*d*]pyrimidin-4-yl]urea (32)
Yield: 22%; colorless solid; mp 228 °C.

IR (KBr): 3440, 1713 cm^{-1}.

^1H NMR (250 MHz, pyridine-d_5): δ = 1.63 (m, 4 H, 2 × CH_2), 2.29 (s, 3 H, CH_3), 2.61 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2), 7.38 (d, *J* = 7.5 Hz, 2 H), 7.44–7.50 (m, 3 H), 7.97 (br s, 1 H, NH), 8.06 (d, *J* = 6.8 Hz, 2 H), 8.49 (d, *J* = 6.8 Hz, 2 H), 12.17 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, pyridine-d_5): δ = 22.9, 24.0, 24.1, 27.3, 27.4, 116.4, 120.8, 124.3, 126.2, 128.9, 130.1, 130.4, 137.0, 139.7, 141.8, 152.2, 153.1, 157.9, 167.4, 169.5

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