Synthesis of Derivatives of Pyrido[4,3-*d*]pyrimidin-4(3*H*)-one *via* an Iminophosphorane

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A series of new, 2-substituted 3-aryl-8,9,10,11-tetrahydro-5-methyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones, compounds **5a**–**q**, were designed and synthesized *via* the aza-*Wittig* reaction as the key step. The iminophosphorane **1** reacted with phenyl isocyanate (or 4-chlorophenyl isocyanate) to the carbodiimide **4**, which was cyclized to **5** upon addition of different amines, EtOH, or phenols in the presence of a catalytic amount of EtONa or K_2CO_3 (*Schemes 1* and *2*). The structures of compounds **5** were confirmed by IR, ^{1}H- and ^{13}C-NMR, EI-MS, elemental analyses, and, in the case of **5l**, by single-crystal X-ray diffraction (*Figure*).

Introduction. – The derivatives of pyridopyrimidines have attracted the interest of pharmaceutical companies recently. This is due, in part, to the wide range of biological activities associated with this heterocyclic scaffold. For example, some related 4-(phenylamino)pyrido[*d*]pyrimidines have been reported as selective inhibitors of tyrosine phosphorylation by the epidermal growth-factor receptor (EGFR), and have become an important class of potential anticancer drugs [1][2]. The methods described so far for the preparation of some representative derivatives of this ring system involve two general routes: *a*) formation of the pyridine ring by cyclization of suitable substituents of a pyrimidine [3][4]; *b*) formation of the pyrimidine ring by cyclization of a suitable pyridine derivative [5]. Unfortunately, these methods often require forcing conditions, long reaction times, and complex synthetic pathways.

The aza-*Wittig* reactions of iminophosphoranes have received increasing attention in view of their utility in the synthesis of N-heterocyclic compounds [6]. Recently, we have become interested in the synthesis of pyrazolopyrimidinones, thienopyrimidinones, and pyridopyrimidinones from various iminophosphoranes, with the aim of evaluating their biological activities [7]. Here, we wish to report a facile synthesis of fused pyridopyrimidine derivatives from the easily accessible iminophosphorane **1**.

Results and Discussion. – The 5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine **2**, easily obtained from 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**3**) and ethyl acetoacetate (=ethyl 3-oxobutanoate) in the presence of $SnCl_4$, was converted to the iminophosphorane **1** *via* reaction with Ph_3P in hexachloroethane and Et_3N (*Scheme 1*).

The iminophosphorane **1** reacted with phenyl isocyanate (or 4-chlorophenyl isocyanate) to the carbodiimide **4**. In refluxing toluene, **4** did not react with alkylamines to

Scheme 1

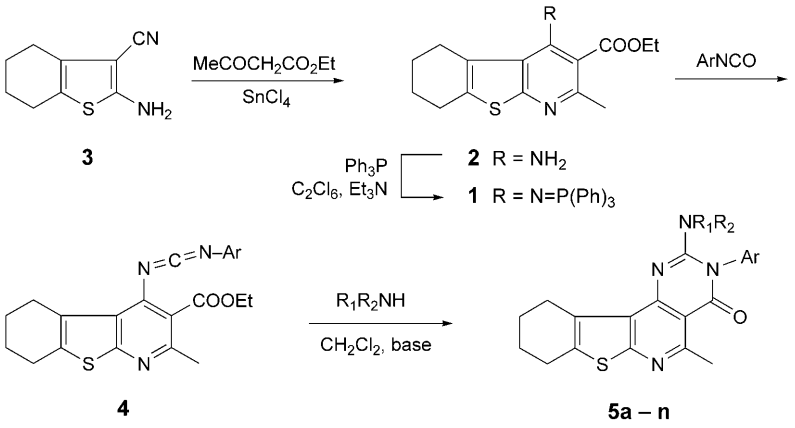


Table. *Substituents, Physico-Chemical Data, and Synthetic Details for Compounds* **5**

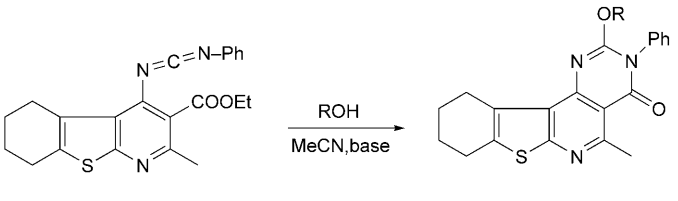
No.	R_1R_2N or RO	Ar	Formula	M.p. [°]	Reaction time [h]	Yield [%][a])
5a	PrNH	C_6H_5	$C_{23}H_{24}N_4OS$	243–244	11	65
5b	i-PrNH	C_6H_5	$C_{23}H_{24}N_4OS$	209–211	11	58
5c	BuNH	C_6H_5	$C_{24}H_{26}N_4OS$	233–234	11	72
5d	Et(Me)CHNH	C_6H_5	$C_{24}H_{26}N_4OS$	242–244	11	80
5e	*t*-BuNH	C_6H_5	$C_{24}H_{26}N_4OS$	213–214	11	66
5f	Furfurylamino[b])	C_6H_5	$C_{25}H_{22}N_4O_2S$	250–251	11	72
5g	$Me_2CH(CH_2)_2NH$	C_6H_5	$C_{25}H_{28}N_4OS$	202–204	11	54
5h	Et_2N	C_6H_5	$C_{24}H_{26}N_4OS$	>300	13	57
5i	Piperidin-1-yl	C_6H_5	$C_{25}H_{26}N_4OS$	263–264	13	69
5j	Bu_2N	C_6H_5	$C_{28}H_{34}N_4OS$	142–143	13	67
5k	Pr_2N	C_6H_5	$C_{26}H_{30}N_4OS$	194–195	13	59
5l	PrNH	4-Cl-C_6H_5	$C_{23}H_{23}ClN_4OS$	228–230	12	82
5m	i-PrNH	4-Cl-C_6H_5	$C_{23}H_{23}ClN_4OS$	238–240	14	89
5n	BuNH	4-Cl-C_6H_5	$C_{24}H_{25}ClN_4OS$	273–275	11	71
5o	EtO	C_6H_5	$C_{22}H_{21}N_3O_2S$	186–189	14	39
5p	C_6H_5O	C_6H_5	$C_{26}H_{21}N_3O_2S$	217–218	14	91
5q	4-Cl-C_6H_5O	C_6H_5	$C_{26}H_{20}ClN_3O_2S$	240–241	14	95

[a]) Yields of isolated products based on **1**. [b]) (Furan-2-ylmethyl)amino.

the target compounds. However, in CH_2Cl_2 and in the presence of a catalytic amount of EtONa, compounds **4** were converted smoothly to the 2-(alkylamino)-8,9,10,11-tetrahydrobenzo[4′,5′]thieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **5a**–**n** in satisfactory yields at room temperature (*Table*). Irrespective of whether primary or secondary amines were used, the cyclization proceeded very smoothly.

The reaction of the carbodiimide **4** with phenols (or with EtOH) in MeCN did not lead to the desired 2-(aryloxy)- or 2-ethoxy-substituted congeners **5**. However, when carried out in the presence of catalytic amounts of K_2CO_3, the reaction took place to give **5o**–**q** in good yields (*Scheme 2*).

Scheme 2



4 **5o – q**

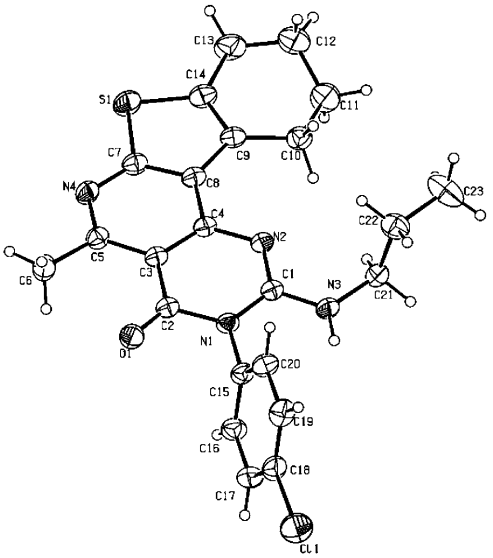


Figure. *ORTEP Plot* [11] *of the molecular structure of* **5l** (50% probability ellipsoids, arbitrary atom numbering)

All products of type **5** were obtained as colorless crystals after recrystallization from CH_2Cl_2/petroleum ether, and were fully characterized by IR, ^{1}H- and ^{13}C-NMR, EI-MS, and elemental analysis. Selected data are listed in the *Table*. In the case of **5l**, the structure was additionally solved by single-crystal X-ray diffraction (*Figure*). All structures were supported spectroscopically. For example, the IR spectrum of **5a** revealed absorption bands at 1677 (C=O), 3145 (C_6H_5), and 3381 cm^{-1} (NH). The corresponding ^{1}H-NMR spectrum showed the 5-Me group at δ(H) 2.96 (*s*), and the CH_2 signals of the cyclohexenyl ring appeared at δ(H) 1.91, 2.88, and 3.31. The other signals resonated at δ(H) 7.26–7.65 (*m*, 5 arom. H), 0.88 (*t*, J = 7.2 Hz, Me), 1.60 (*q*, J = 7.2 Hz, CH_2), and 3.41–3.44 (*m*, NCH_2). The mass spectrum of **5a** showed the molecular ion peak at *m*/*z* 404 as the base peak (100%). The structures of **5a** and the other analogs were further confirmed on the basis of elemental analysis.

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Experimental Part

General. All solvents and materials were reagent-grade and purified as required. Melting point (m.p.): *WRS-1B Digital* apparatus; uncorrected. IR Spectra: *PE-983* IR spectrometer, as KBr pellets, in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian Mercury-400* spectrometer, in $CDCl_3$ soln.; δ in ppm rel. to Me_4Si, *J* in Hz. EI-MS: *Finnigan Trace MS* spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Vario EL-III* instrument.

Ethyl 4-Amino-5,6,7,8-tetrahydro-2-methyl[1]benzothieno[2,3-b*]pyridine-3-carboxylate* (**2**) [8]. *2-Amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile* (**3**; 1.78 g, 10 mmol) and $SnCl_4$ (2.3 ml, 20 mmol) were added to a stirred soln. of ethyl acetoacetate (1.08 ml, 10 mmol) in anh. toluene (20 ml). The mixture was stirred at r.t. for 1 h, and then heated at reflux for 5 h. The mixture was added to sat. aq. Na_2CO_3 soln. (60 ml, pH 10), and the resulting suspension was extracted with AcOEt (3×50 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford **2** in 64% yield. Colorless crystals. M.p. 137–138°. ^1H-NMR: 1.42 (*t*, *J* = 7.2, Me); 1.87–1.94 (*m*, CH_2CH_2); 2.73 (*s*, Me); 2.79–2.83 (*m*, CH_2); 2.99–3.02 (*m*, CH_2); 4.39 (*q*, *J* = 7.2, CH_2O); 6.60 (*s*, NH_2).

Ethyl 5,6,7,8-Tetrahydro-2-methyl-4-[(triphenyl-λ^5-phosphanylidene)amino][1]benzothieno[2,3-b*]-pyridine-3-carboxylate* (**1**) [9][10]. To a soln. of **2** (1.06 g, 4 mmol) in MeCN (15 ml) was added Ph_3P (1.31 g, 5 mmol), C_2Cl_6 (1.19 g, 5 mmol) and, in this order, Et_3N (8.0 ml). The mixture was stirred for 18–24 h at 0°. Then, the soln. was concentrated, and the residue was recrystallized from EtOH to give **1** in 90.2% yield. M.p. 225–226°. ^1H-NMR: 0.99 (*t*, *J* = 7.2, Me); 1.40–1.64 (*m*, CH_2CH_2); 2.41 (*s*, Me); 2.50–2.54 (*m*, CH_2); 2.65–2.69 (*m*, CH_2); 3.38 (*q*, *J* = 7.2, CH_2O); 7.44–7.62 (*m*, 15 arom. H).

General Procedure for the Preparation of Carbodiimides **4**. To a soln. of **1** (0.525 g, 1 mmol) in anh. CH_2Cl_2 (10 ml) was added the appropriate aryl isocyanate (1.1 mmol) under N_2 at r.t. The mixture was left standing for 30–40 min. Then, the solvent was removed *in vacuo*, and Et_2O/petroleum ether was added to precipitate $Ph_3P{=}O$. Filtration and removal of the solvent gave the crude carbodiimides **4**, which were used directly without further purification.

General Procedure for the Preparation of Compounds **5a**–**n**. To a soln. of **4** in CH_2Cl_2 (10 ml) was added the appropriate alkylamine (1.1 mmol), and the mixture was stirred for 30 min. The solvent was removed, anh. EtOH (10 ml), containing several drops of a soln of EtONa in EtOH, was added, and the mixture was stirred for 11–14 h at r.t. (*Table*). After solvent removal, the residue was recrystallized from EtOH to afford the target compounds.

8,9,10,11-Tetrahydro-5-methyl-3-phenyl-2-(propylamino)[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5a**). IR: 3381 (N–H), 3145 (Ar), 2895 (C–H), 1677 (C=O), 1558, 1510, 1401, 1146, 806. ^1H-NMR : 0.88 (*t*, *J* = 7.2, Me); 1.58–1.62 (*m*, CH_2); 1.88–1.92 (*m*, 2 CH_2); 2.88–3.31 (*m*, 2 CH_2); 2.96 (*s*, Me–C(5)); 3.41–3.43 (*m*, NCH_2); 4.36 (*s*, NH); 7.26–7.65 (*m*, 5 arom. H). MS: 406 (21), 404 (100, M^+), 363 (38), 349 (30), 335 (97), 259 (49), 230 (15), 216 (16), 189 (42), 173 (29), 80 (97). Anal. calc. for $C_{23}H_{24}N_4OS$: C 68.29, H 5.98, N 13.85; found: C 68.11, H 6.06, N 14.00.

8,9,10,11-Tetrahydro-5-methyl-2-[(1-methylethyl)amino]-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5b**). IR: 3339 (N–H), 3112 (Ar), 2964, 2929 (C–H), 1672 (C=O), 1558, 1510, 1448, 1409, 1280, 1164, 1017, 691. ^1H-NMR: 1.18 (*d*, *J* = 6.8, 2 Me); 1.90–1.94 (*m*, 2 CH_2); 2.89–3.29 (*m*, 2 CH_2); 2.97 (*s*, Me–C(5)); 4.06 (*s*, NH); 4.30–4.34 (*m*, NCH); 7.26–7.66 (*m*, 5 arom. H). ^{13}C-NMR: 162.9; 162.6; 157.8; 152.6; 149.0; 134.4; 133.6; 130.7; 130.1; 129.9; 128.7; 124.7; 124.4; 41.8; 31.2; 27.2; 25.9; 22.9; 20.1; 13.7. MS: 406 (21), 404 (100, M^+), 389 (22), 362 (81), 347 (51), 334 (20), 286 (69), 216 (29), 180 (29), 118 (40), 76 (61). Anal. calc. for $C_{23}H_{24}N_4OS$: C 68.29, H 5.98, N 13.85; found: C 68.48, H 6.12, N 13.81.

2-(Butylamino)-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5c**). IR: 3415 (N–H), 3231 (Ar), 1672 (C=O), 1557, 1517, 1450, 1155, 805. ^1H-NMR: 0.92 (*q*, *J* = 7.2, Me); 1.28–1.31 (*m*, CH_2); 1.52–1.60 (*m*, CH_2); 1.90–1.93 (*m*, 2 CH_2); 2.87–3.32 (*m*, 2 CH_2); 2.96 (*s*, Me–C(5)); 3.44–3.48 (*m*, NCH_2); 4.34 (*s*, NH); 7.25–7.65 (*m*, 5 arom. H). MS: 418 (100, M^+), 403 (21), 363 (42), 350 (52), 318 (43), 260 (12), 189 (45), 173 (30), 81 (44), 76 (55). Anal. calc. for $C_{24}H_{26}N_4OS$: C 68.87, H 6.26, N 13.39; found: C 68.99, H 5.99, N 13.09.

8,9,10,11-Tetrahydro-5-methyl-2-[(1-methylpropyl)amino]-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido-[4,3-d*]pyrimidin-4(3*H*)-one* (**5d**). IR: 3350 (N–H), 3114 (Ar), 2928, 2861 (C–H), 1672 (C=O), 1581, 1557, 1511, 1448, 1352, 1269, 1155, 1067, 819. ^1H-NMR: 0.87 (*d*, *J* = 6.8, 2 Me); 1.90–1.93 (*m*, 2 CH_2);

2.89–3.30 (*m*, 2 CH_2); 2.97 (*s*, Me–C(5)); 1.94–1.98 (*m*, CH), 3.58–3.62 (*m*, NCH_2); 4.43 (*s*, NH); 7.26–7.65 (*m*, 5 arom. H). MS: 418 (100, M^+), 403 (21), 376 (20), 363 (36), 361 (42), 348 (13), 346 (13). Anal. calc. for $C_{24}H_{26}N_4OS$: C 68.87, H 6.26, N 13.39; found: C 68.86, H 6.11, N 13.34.

2-[(1,1-Dimethylethyl)amino]-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5e**). IR: 3425 (N–H), 3102 (Ar), 2959, 2930 (C–H), 1687 (C=O), 1580, 1558, 1511, 1449, 1294, 1213, 955, 806. ^{1}H-NMR: 1.42 (*s*, *t*-Bu); 1.92–1.95 (*m*, 2 CH_2); 2.88–3.29 (*m*, 2 CH_2); 2.99 (*s*, Me–C(5)); 4.24 (*s*, NH); 7.26–7.65 (*m*, 5 arom. H). MS: 420 (23), 418 (96, M^+), 365 (20), 361 (100), 347 (82), 344 (23), 332 (38), 214 (21), 186 (20), 118 (23), 76 (58). Anal. calc. for $C_{24}H_{26}N_4OS$: C 68.87, H 6.26, N 13.39; found: C 69.03, H 6.09, N 13.21.

2-[(Furan-2-ylmethyl)amino]-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido-[4,3-d*]pyrimidin-4(3*H*)-one* (**5f**). IR: 3137 (Ar), 2958, 2935 (C–H), 1686 (C=O), 1558, 1509, 1449, 1399, 1302, 1166, 1072, 742. ^{1}H-NMR: 1.90–1.94 (*m*, 2 CH_2); 2.89–3.31 (*m*, 2 CH_2); 2.98 (*s*, Me–C(5)); 4.70 (*s*, NH); 6.20 (*s*, C=CH); 6.30 (*s*, C=CH); 6.32 (*s*, C=CH); 7.26–7.63 (*m*, 5 arom. H). MS: 442 (100, M^+), 414 (34), 385 (30), 361 (33), 344 (12), 96 (10), 95 (18), 92 (10), 80 (90), 76 (24). Anal. calc. for $C_{25}H_{22}N_4O_2S$: C 67.85, H 5.01, N 12.66; found: C 67.71, H 4.87, N 12.58.

2-[(2,2-Dimethylpropyl)amino]-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5g**). IR: 3126 (Ar), 2959, 2930 (C–H), 1687 (C=O), 1580, 1558, 1511, 1448, 1284, 1142, 852, 705. ^{1}H- NMR: 0.73 (*t*, *J* = 7.6, Me); 1.37 (*s*, 2 Me); 1.78 (*q*, *J* = 7.6, CH_2); 1.91–1.94 (*m*, 2 CH_2); 2.89–3.28 (*m*, 2 CH_2); 2.98 (*s*, Me–C(5)); 4.17 (*s*, NH); 7.27–7.66 (*m*, 5 arom. H). MS: 434 (28), 432 (68, M^+), 362 (100), 361 (38), 347 (30), 334 (23). Anal. calc. for $C_{25}H_{28}N_4OS$: C 69.41, H 6.52, N 12.95; found: C 69.61, H 6.47, N 13.06.

2-(Diethylamino)-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5h**). IR: 3121 (Ar), 2976, 2924 (C–H), 1686 (C=O), 1559, 1542, 1509, 1400, 1091, 1051, 880, 690. ^{1}H-NMR: 0.88 (*t*, *J* = 6.8, 2 Me); 1.90–1.94 (*m*, 2 CH_2); 2.89–3.30 (*m*, 2 CH_2); 2.97 (*s*, Me–C(5)); 3.28 (*q*, *J* = 6.8, 2 CH_2); 7.27–7.53 (*m*, 5 arom. H). MS: 420 (21), 418 (100, M^+), 390 (92), 346 (25), 314 (19), 313 (35), 287 (7). Anal. calc. for $C_{24}H_{26}N_4OS$: C 68.87, H 6.26, N 13.39; found: C 69.04, H 6.43, N 13.35.

8,9,10,11-Tetrahydro-5-methyl-3-phenyl-2-piperidin-1-yl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5i**). IR: 3193 (Ar), 2928, 2852 (C–H), 1719 (C=O), 1586, 1542, 1495, 1419, 1243, 1187, 1053, 692. ^{1}H-NMR: 1.30–1.34 (*m*, 2 CH_2); 1.58–1.62 (*m*, CH_2); 1.81–1.85 (*m*, 2 CH_2); 2.80–3.30 (*m*, 2 CH_2); 2.98 (*s*, Me–C(5)); 4.26–4.29 (*m*, 2 CH_2N); 6.96–7.27 (*m*, 5 arom. H). MS: 431 (24, $[M+1]^+$), 430 (24, M^+), 404 (100), 393 (11), 384 (25), 346 (25), 270 (28), 91 (19), 82 (16). Anal. calc. for $C_{25}H_{26}N_4OS$: C 69.74, H 6.09, N 13.01; found: C 69.58, H 6.21, N 13.36.

2-(Dibutylamino)-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5j**). IR: 3059 (Ar), 2956, 2931, 2850 (C–H), 1691 (C=O), 1590, 1551, 1470, 1419, 1231, 1052, 804. ^{1}H-NMR: 0.85 (*t*, *J* = 7.2, 2 Me); 1.14–1.15 (*m*, 2 CH_2); 1.26–1.29 (*m*, 2 CH_2); 1.90–1.94 (*m*, 2 CH_2); 2.89–3.30 (*m*, 2 CH_2); 3.00 (*s*, Me–C(5)); 3.11–3.12 (*m*, 2 NCH_2); 7.27–7.54 (*m*, 5 arom. H). MS: 476 (25), 475 (56, $[M+1]^+$), 474 (100, M^+), 418 (78), 375 (33), 346 (25). Anal. calc. for $C_{28}H_{34}N_4OS$: C 70.85, H 7.22, N 11.80; found: C 70.66, H 7.05, N 11.61.

2-(Dipropylamino)-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-d*]pyrimidin-4(3*H*)-one* (**5k**). IR: 3195 (Ar), 2960, 2930 (C–H), 1717 (C=O), 1586, 1563, 1496, 1419, 1239, 1190, 1052, 695. ^{1}H-NMR: 0.75 (*d*, *J* = 7.2, 2 Me); 1.30–1.34 (*m*, 2 CH_2); 1.91–1.95 (*m*, 2 CH_2); 2.89–3.31 (*m*, CH_2); 2.99 (*s*, Me–C(5)); 3.09–3.13 (*m*, 2 NCH_2); 7.26–7.54 (*m*, 5 arom. H). MS: 447 (21, $[M+1]^+$), 446 (57, M^+), 420 (100), 417 (15), 404 (16), 403 (66), 400 (15), 375 (38), 362 (11), 225 (67), 118 (34). Anal. calc. for $C_{26}H_{30}N_4OS$: C 69.92, H 6.77, N 12.54; found: C 69.75, H 6.63, N 12.71.

3-(4-Chlorophenyl)-8,9,10,11-tetrahydro-5-methyl-2-(propylamino)[1]benzothieno[3′,2′:5,6]pyrido-[4,3-d*]pyrimidin-4(3*H*)-one* (**5l**). IR: 3140 (Ar), 2939, 2862 (C–H), 1694 (C=O), 1586, 1511, 1489, 1448, 1296, 1156, 1088, 752. ^{1}H-NMR: 0.91 (*t*, *J* = 7.2, Me); 1.62 (*q*, *J* = 7.2, CH_2); 1.88–1.93 (*m*, 2 CH_2); 2.85–3.38 (*m*, 2 CH_2); 2.94 (*s*, Me–C(5)); 3.44–3.45 (*m*, NCH_2); 4.41 (*s*, NH); 7.27–7.60 (*m*, 4 arom. H). ^{13}C-NMR: 162.9; 162.0; 157.4; 152.7; 148.1; 134.4; 134.1; 131.8; 130.7; 129.7; 128.9; 124.7; 124.6; 41.8; 27.2; 26.9; 22.9; 22.7; 21.1; 19.0; 13.7. MS: 440 (35), 439 (32, $[M+1]^+$), 438 (100, M^+), 398 (14), 396 (17), 395 (24), 111 (12), 110 (15), 43 (22). Anal. calc. for $C_{23}H_{23}ClN_4OS$: C 62.93, H 5.28, N 12.76; found: C 63.20, H 5.23, N 12.55. X-Ray analysis: see the *Figure.*

*3-(4-Chlorophenyl)-8,9,10,11-tetrahydro-5-methyl-2-[(1-methylethyl)amino][1]benzothieno[3′,2′:5,6]-pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**5m**). IR: 3140 (Ar), 2929 (C–H), 1672 (C=O), 1559, 1510, 1491, 1401, 1251, 1164, 810. ^{1}H-NMR: 1.20 (*d*, *J* = 6.8, 2 Me); 1.90–1.94 (*m*, 2 CH_2); 2.87–3.28 (*m*, 2 CH_2); 2.94 (*s*, Me–C(5)); 4.05–4.06 (*m*, NCH); 4.31 (*s*, NH); 7.27–7.61 (*m*, 4 arom. H). MS: 440 (24), 439 (27, $[M+1]^+$), 438 (100, M^+), 398 (8), 396 (9), 395 (15), 380 (6), 43 (16). Anal. calc. for $C_{23}H_{23}ClN_4OS$: C 62.93, H 5.28, N 12.76; found: C 62.91, H 5.32, N 12.88.

*2-(Butylamino)-3-(4-chlorophenyl)-8,9,10,11-tetrahydro-5-methyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**5n**). IR: 3181 (Ar), 2932 (C–H), 1682 (C=O), 1581, 1550, 1510, 1489, 1401, 1299, 1154, 1015, 804. ^{1}H-NMR: 0.92 (*t*, *J* = 7.6, Me); 1.32 (*q*, *J* = 7.6, CH_2); 1.55–1.57 (*m*, CH_2); 1.90–1.95 (*m*, 2 CH_2); 2.88–3.31 (*m*, 2 CH_2); 2.96 (*s*, Me–C(5)); 3.46 (*m*, NCH_2); 4.34 (*s*, NH); 7.26–7.61 (*m*, 4 arom. H). MS: 454 (25), 452 (100, M^+), 410 (13), 397 (11), 395 (22), 110 (13), 56 (18). Anal. calc. for $C_{24}H_{25}ClN_4OS$: C 63.63, H 5.56, N 12.37; found: C 63.79, H 5.39, N 12.30.

General Procedure for the Preparation of Compounds **5o**–**q**. To a soln. of **4** (400 mg, 1 mmol) in MeCN (15 ml) was added EtOH (or a phenol; 1.1 mmol) and a cat. amount of K_2CO_3. The mixture was stirred for 14 h at 80°. Then, the soln. was concentrated, and the residue was recrystallized from MeCN to afford the target compounds.

*2-Ethoxy-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**5o**). IR: 3120 (Ar), 2982, 2934 (C–H), 1682 (C=O), 1605, 1589, 1560, 1511, 1492, 1265, 1172, 1099, 805. ^{1}H-NMR: 1.32 (*t*, *J* = 7.2, Me); 1.92–1.96 (*m*, 2 CH_2); 2.90–3.32 (*m*, 2 CH_2); 3.02 (*s*, Me–C(5)); 4.53 (*q*, *J* = 7.2, CH_2); 7.25–7.54 (*m*, 5 arom. H). MS: 392 (100, M^+), 387 (10), 362 (91), 334 (5), 76 (9). Anal. calc. for $C_{22}H_{21}N_3O_2S$: C 67.50, H 5.41, N 10.73; found: C 67.56, H 5.25, N 10.87.

*8,9,10,11-Tetrahydro-5-methyl-2-phenoxy-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**5p**). IR: 3011 (Ar), 1698 (C=O), 1613, 1560, 1398, 1257, 1205, 806. ^{1}H-NMR: 1.56–1.80 (*m*, 2 CH_2); 2.43–2.82 (*m*, 2 CH_2); 3.06 (*s*, Me–C(5)); 7.13–7.60 (*m*, 10 arom. H). ^{13}C-NMR: 162.1; 157.6; 152.8; 149.1; 146.0; 135.6; 134.8; 134.4; 133.3; 132.5; 131.6; 130.0; 129.6; 128.2; 128.0; 125.0; 124.8; 26.1; 25.8; 25.5; 22.4; 22.2. MS: 440 (35), 439 (32, $[M+1]^+$), 438 (100, M^+), 398 (14), 396 (17), 395 (24), 111 (12), 110 (15), 43 (22). Anal. calc. for $C_{26}H_{21}N_3O_2S$: C 71.05, H 4.82, N 9.56; found: C 70.96, H 5.00, N 9.62.

*2-[(4-Chlorophenyl)oxy]-8,9,10,11-tetrahydro-5-methyl-3-phenyl[1]benzothieno[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one* (**5q**). IR: 3099 (Ar), 1700 (C=O), 1613, 1559, 1400, 1258, 1205, 841. ^{1}H-NMR: 1.60–1.84 (*m*, 2 CH_2); 2.44–2.84 (*m*, 2 CH_2); 3.04 (*s*, Me–C(5)); 7.09–7.62 (*m*, 9 arom. H). MS: 475 (41, $[M+1]^+$), 474 (100, M^+), 460 (11), 444 (12), 396 (10), 380 (14), 110 (19), 76 (8). Anal. calc. for $C_{26}H_{20}ClN_3O_2S$: C 65.88, H 4.25, N 8.87; found: C 65.96, H 4.38, N 8.89.

X-Ray Single-Crystal Structure of **5l**. The compound was recrystallized from EtOH. Parameters: triclinic, space group $P\bar{1}$, $a = 11.8884(6)$, $b = 13.3784(7)$, $c = 15.7982(8)$ Å, $\alpha = 114.0540(10)$, $\beta = 98.9260(10)$, $\gamma = 101.3350(10)°$; $V = 2169.42(19)$ Å^3; $Z = 4$; $D_c = 1.344$ g/cm^3; $S = 1.026$; $\mu = 0.295$ mm^{-1}; $M_r = 438.96$; $R_{final} = 0.0530$, $wR = 0.1345$. For a structural representation, see the *Figure*. The crystallographic data of **5l** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-278140. Copies of the data can be obtained, free of charge, *via* the internet (http://www.ccdc.cam.ac.uk/data_request/cif), by e-mail (data_request@ccdc.cam.ac.uk), or by fax (+44-1223-336033).

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