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SYNTHESIS OF 2,3-DISUBSTITUTED DERIVATIVES OF PYRANO-, THIO-PYRANO-, AND BENZOANNELATED PYRIDO[2,3-*b*]THIENO-[3,2-*d*]PYRIMIDINES

E. G. Paronikian, Sh. F. Akopian, and A. S. Noravian

A new methods have been developed for the synthesis of condensed pyrido[2,3-b]thieno[3,2-d]pyrimidines based on cyclic derivatives of 4-cyanopyridine-3-thiones. The presence of two different reactive functional groups NH_2 and CONH gives the possibility of carrying out different conversions of thieno[2,3-b]pyridines.

Keywords: N-alkyl-4-oxothieno[3,2-*d*]pyrimidine-2-thiones, pyrano(thiopyrano)(4',3':4,5]pyrido[2,3-*b*]-thieno[3,2-*d*]pyrimidines, pyridothieno[3,2-*d*]pyrimidines, pyrimido[5',4':2,3]thieno[2,3-*c*]isoquinolines, 4-cyanopyridin-3-thiones.

Pyridothieno[3,2-*d*]pyrimidines are one of the interesting classes of heterocycles. Many of them are of interest as biologically active compounds [1-3]. In the present paper we describe methods for the synthesis of new tetracyclic heterocyclic systems – pyrano(thiopyrano)[4',3':4,5]-pyrido[2,3-*b*]thieno[3,2-*d*]pyrimidines and pyrimido[5',4':2,3]thieno[2,3-*c*]isoquinolines.

4-Cyanopyridine-3-thiones **1a-e**, condensed with cyclohexane or tetrahydropyrane (thiopyrane) ring [4], were used as starting materials to obtain the 2,3-substituted derivatives. Reaction of compounds **1** with chloroacetamides in basic media gave the corresponding 1-amino-2-carbamoylpyrano[4,3-*d*]thieno[2,3-*b*]pyridines and -thieno[2,3-*b*]isoquinolines **3a-h.** In some cases we isolated intermediate compounds – condensed 3-aminoacylthio(N-alkylaminoacyl)-4-cyanopyridines **2a-d** (Table 1). The structures of products **3** were confirmed by IR and ^{1}H NMR spectra (Table 2). For examples, in the IR spectra of compounds there are absorption bands of the nitrile groups in the 2220 cm^{-1} region. After closure of the thiophene ring and formation of products **3** this band disappears and some absorption bands appear in the 3160-3420 cm^{-1} region, characteristic of NH_2 and NH groups.

The presence of NH_2 and CONH groups permitted further reactions of compounds **3**. For example, condensation with tri-methyl esters of orthoacids gave the corresponding thieno[3,2-*d*]pyrimidin-4-(3H)ones **4a-i**, and treatment with hydrogen sulfide gave N-alkyl-4-oxothieno[3,2-*d*]pyrimidine-2-thiones **5a-d**. The corresponding S-substituted derivatives **6a-f** were obtained by alkylation of compounds **5** with alkyl halides.

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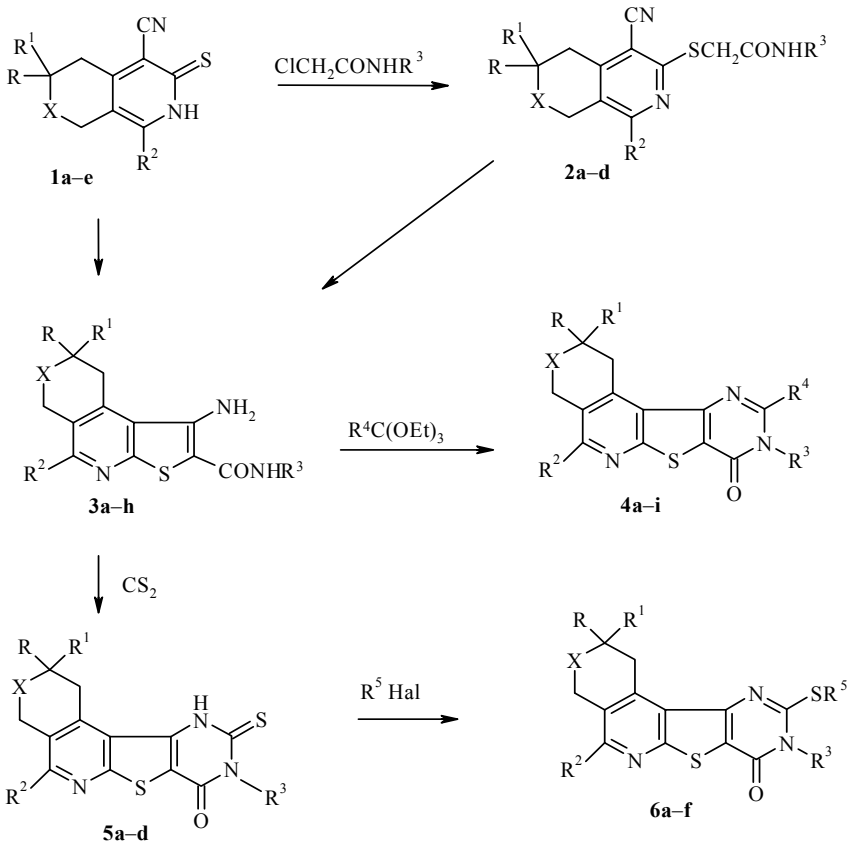

1 a X = O, R = R^1 = Me; **b** X = O, R = R^1 = Me; **c** X = CH_2, R = R^1 = H; **d** X = O, R = H, R^1 = *i*-Pr; **e** X = S, R = R^1 = Me; **a**, **c**–**e** R^2 = morpholino, **b** R^2 = pyrrolidino; **2**, **3 a** X = O, R = R^1 = Me, R^3 = H; **b** X = O, R = R^1 = Me, R^3 = Ph; **c** X = CH_2, R = R^1 = Me, R^3 = Ph; **d** X = CH_2, R = R^1 = R^3 = H; **3 e** X = CH_2, R = R^1 = H, R^3 = *o*-$MeOC_6H_4$; **f** X = O, R = H, R^1 = *i*-Pr, R^3 = 2,4-$(MeO)_2C_6H_3$; **g** X = S, R = R^1 = Me, R^3 = H; **h** X = S, R = R^1 = Me, R^3 = *o*-ClC_6H_4; **2 a**,**d**, **3 a**,**d**–**h** R^2 = morpholino, **2**, **3 b**, **c** R^2 = pyrrolidino; **4 a**–**d** X = O, R = R^1 = Me; **a** R^3 = R^4 = H; **b** R^3 = H, R^4 = Me; **c** R^3 = Ph, R^4 = H; **d** R^3 = Ph, R^4 = H; **e** X = O, R = H, R^1 = *i*-Pr, R^3 = 2,4-$(MeO)_2C_6H_3$, R^4 = H; **f** X = S, R = R^1 = Me, R^3 = R^4 = H; **g** X = S, R = R^1 = Me, R^3 = *o*-ClC_6H_4, R^4 = H; **h** X = CH_2, R = R^1 = R^3 = R^4 = H; **i** X = CH_2, R = R^1 = R^3 = H, R^4 = Me; **a**–**c**, **e**–**i** R^2 = morpholino, **b** R^2 = pyrrolidino; **5 a** X = O, R = R^1 = Me, R^3 = H; **b** X = O, R = R^1 = Me, R^3 = Ph; **c** X = O, R = H, R^1 = *i*-Pr, R^3 = H; **d** X = CH_2, R = R^1 = R^3 = H; **a**–**d** R^2 = morpholino; **6 a**–**d** X = O, **a** R = R^1 = R^5 = Me, R^3 = H; **b** R = R^1 = Me, R^3 = Ph, R^5 = Et; **c** R = R^1 = Me, R^3 = H, R^5 = Et; **d** R = H, R^1 = *i*-Pr, R^3 = H, R^5 = Et; **e, f** X = CH_2, R = R^1 = R^3 = H, **f** R^5 = Me; **f** R^5 = Et; **a**–**f** R^2 = morpholino

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-20 spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Mercury 300 (300 MHz) instrument. Mass spectra were recorded on an MX-1320 instrument with direct insertion into the ion source. Purity of compounds was monitored by TLC on Silufol UV-254 plates.

Table 1. Physicochemical Characteristics of Compounds **2-6**

Compound	Empirical formula	Found, % / Calculated, %				mp,°C	Yield, %
		C	H	N	S		
1	2	3	4	5	6	7	8
2a	$C_{17}H_{22}N_4O_3S$	56.47 56.33	6.31 6.11	15.22 15.46	8.78 8.84	226-229	74
2b	$C_{23}H_{26}N_4O_3S$	63.24 62.99	5.84 5.98	12.65 12.77	7.24 7.31	246-250	77
2c	$C_{23}H_{26}N_4O_2S$	65.54 65.37	6.32 6.20	13.44 13.25	7.39 7.58	203-205	73
2d	$C_{16}H_{20}N_4O_2S$	57.78 57.81	6.24 6.06	16.74 16.85	9.48 9.65	194-196	64
3a	$C_{17}H_{22}N_4O_3S$	56.52 56.33	6.31 6.12	15.24 15.46	8.98 8.85	308-309	80
3b	$C_{23}H_{26}N_4O_3S$	63.27 62.99	5.78 5.98	12.98 12.77	7.49 7.31	259-261	79
3c	$C_{23}H_{26}N_4O_2S$	65.58 65.37	6.31 6.20	13.45 13.26	7.36 7.59	234-235	83
3d	$C_{16}H_{20}N_4O_2S$	57.68 57.81	6.21 6.06	16.98 16.85	9.41 9.65	255-256	80
3e	$C_{23}H_{26}N_4O_3S$	63.17 62.99	5.72 5.98	12.95 12.77	7.57 7.31	221-222	60
3f	$C_{26}H_{32}N_4O_5S$	60.84 60.92	6.41 6.29	10.78 10.93	6.35 6.25	218-220	67
3g	$C_{17}H_{22}N_4O_2S_2$	53.71 53.94	5.69 5.86	14.68 14.80	16.74 16.94	264-266	64
3h	$C_{23}H_{25}ClN_4O_2S_2$	56.67 56.48	5.36 5.15	11.62 11.46	13.34 13.11	226-227	80
4a	$C_{18}H_{20}N_4O_3S$	58.22 58.05	5.12 5.41	15.24 15.04	8.88 8.61	371-372	75
4b	$C_{19}H_{22}N_4O_3S$	59.27 59.05	5.58 5.74	14.62 14.49	8.43 8.29	>360	64
4c	$C_{24}H_{24}N_4O_3S$	64.14 64.26	5.11 5.39	12.64 12.49	7.32 7.15	205-208	87
4d	$C_{24}H_{24}N_4O_2S$	66.85 66.64	5.32 5.59	12.84 12.95	7.68 7.41	210-213	88
4e	$C_{27}H_{30}N_4O_5S$	62.25 62.05	5.56 5.79	10.84 10.72	6.28 6.14	257-260	98
4f	$C_{18}H_{20}N_4O_2S_2$	55.84 55.65	5.38 5.19	14.57 14.42	16.62 16.51	>360	98
4g	$C_{24}H_{23}ClN_4O_2S_2$	57.54 57.76	4.74 4.64	11.35 11.23	12.94 12.85	210-212	97
4h	$C_{17}H_{18}N_4O_2S$	59.84 59.63	5.54 5.29	16.58 16.36	9.11 9.36	>360	73
4i	$C_{18}H_{20}N_4O_2S$	60.79 60.65	5.45 5.65	15.52 15.72	8.72 8.99	>360	65
5a	$C_{18}H_{20}N_4O_3S_2$	53.64 53.45	4.85 4.98	13.67 13.85	15.64 15.85	>360	80
5b	$C_{24}H_{24}N_4O_3S_2$	59.84 59.98	5.25 5.03	11.47 11.66	13.46 13.34	269-271	85
5c	$C_{19}H_{22}N_4O_3S_2$	54.64 54.53	5.41 5.29	13.14 13.39	15.54 15.32	228-230	98
5d	$C_{17}H_{18}N_4O_2S_2$	54.67 54.52	4.94 4.84	14.78 14.96	17.33 17.12	313-316	85
6a	$C_{19}H_{22}N_4O_3S_2$	54.65 54.53	5.44 5.29	13.54 13.39	15.47 15.32	>360	88
6b	$C_{26}H_{28}N_4O_3S_2$	61.21 61.39	5.67 5.55	11.15 11.01	12.75 12.61	233-235	94
6c	$C_{20}H_{24}N_4O_3S_2$	55.44 55.53	5.34 5.59	12.84 12.95	14.65 14.82	324-326	42
6d	$C_{21}H_{26}N_4O_3S_2$	56.34 56.48	5.76 5.87	12.69 12.54	14.21 14.36	283-286	83
6e	$C_{18}H_{20}N_4O_2S_2$	55.41 55.65	5.34 5.19	14.54 14.42	16.68 16.51	>360	86
6f	$C_{19}H_{22}N_4O_2S_2$	56.85 56.69	5.31 5.51	13.72 13.92	15.78 15.93	345-350	58

Table 2. ^{1}H NMR Spectra of Compounds **2-6**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2a	1.30 (6H, s, $2CH_3$); 2.69 (2H, s, CH_2); 3.33 (4H, m, $N(CH_2)_2$); 3.71 (4H, m, $O(CH_2)_2$); 3.76 (2H, s, SCH_2); 4.47 (2H, s, OCH_2); 6.90 (1H, br) and 7.16 (1H, br, NH_2)
2b	1.30 (6H, s, $2CH_3$); 2.70 (2H, s, CH_2); 3.24 (4H, m, $N(CH_2)_2$); 3.59 (4H, m, $O(CH_2)_2$); 4.01 (2H, s, SCH_2); 4.46 (2H, s, OCH_2); 6.98 (1H, tt, ^3J = 7.4, ^4J = 1.2, H_{Ph}-4); 7.24 (2H, m, H_{Ph}-3,5); 7.57 (2H, m, H_{Ph}-2,6); 9.90 (1H, s, NH)
2c	1.28 (6H, s, $2CH_3$); 1.85 (4H, m, $(CH_2)_2$); 2.62 (2H, s, CH_2); 3.62 (4H, m, $N(CH_2)_2$); 3.98 (2H, s, SCH_2); 4.70 (2H, s, OCH_2); 6.97 (1H, tt, ^1J = 7.4, ^2J = 1.2, H_{Ph}-4); 7.22 (2H, m, H_{Ph}-3,5); 7.56 (2H, m, H_{Ph}-2,6); 9.80 (1H, s, NH)
2d	1.70 (2H, m, CH_2); 1.85 (2H, m, CH_2); 2.51 (2H, t, *J* = 5.7, CH_2); 2.82 (2H, t, *J* = 6.5, CH_2); 3.31 (4H, m, $N(CH_2)_2$); 3.72 (4H, m, $O(CH_2)_2$); 3.76 (2H, s, SCH_2); 6.87 (1H, br) and 7.10 (1H, br, NH_2)
3a	1.29 (6H, s, $2CH_3$); 3.08 (4H, m, $N(CH_2)_2$); 3.20 (2H, s, CH_2); 3.73 (4H, m, $O(CH_2)_2$); 4.64 (2H, s, CH_2); 6.81 (2H, s, NH_2); 7.07 (2H, s, NH_2)
3b	1.33 (6H, s, $2CH_3$); 3.15 (4H, m) and 3.77 (4H, m, C_4H_8NO); 3.22 (2H, s, CH_2); 4.65 (2H, s, OCH_2); 6.81 (2H, s, NH_2); 7.00 (1H, tt, ^3J = 7.3, ^4J = 1.2, H_{Ph}-4); 7.25 (2H, m, H_{Ph}-3,5); 7.69 (2H, m, H_{Ph}-2,6); 8.85 (1H, s, NH)
3c	1.34 (6H, s, $2CH_3$); 1.96 (4H, m, $(CH_2)_2$); 3.16 (2H, s, CH_2); 3.56 (4H, m, $N(CH_2)_2$); 4.70 (2H, s, OCH_2); 6.77 (2H, br, NH_2); 6.97 (1H, tt, ^3J = 7.3, ^4J = 1.2, H_{Ph}-4); 7.23 (2H, m, H_{Ph}-3,5); 7.67 (2H, m, H_{Ph}-2,6); 8.62 (1H, s, NH)
3d	1.71 (2H, m, CH_2); 1.88 (2H, m, CH_2); 2.65 (2H, m, CH_2); 3.12 (2H, t, *J* = 6.5, CH_2); 3.30 (4H, m, $N(CH_2)_2$); 3.74 (4H, m, $O(CH_2)_2$); 6.51 (2H, s, NH_2); 6.63 (2H, s, NH_2)
3e	1.74 (2H, m, CH_2); 1.91 (2H, m, CH_2); 2.68 (2H, t, *J* = 5.9, CH_2); 3.16 (4H, m, $N(CH_2)_2$); 3.33 (2H, t, *J* = 6.4, CH_2); 3.76 (4H, m, $O(CH_2)_2$); 3.97 (3H, s, OCH_3); 6.8 (2H, s, NH_2); 6.86-7.00 (3H, m, H_{Ar}-3,4,5); 7.83 (1H, s, NH); 8.31 (2H, d. d, ^3J = 7.8, ^4J = 1.3, H_{Ar}-6)
3f	1.05 (6H, d, ^3J = 6.7, CH_3); 1.06 (3H, d, ^3J = 6.7, CH_3); 1.84 (1H, oct, ^3J = 6.7, CH); 3.01-3.42 (7H, m, CH_2, $N(CH_2)_2$ and OCH); 3.67-3.84 (4H, m, $O(CH_2)_2$); 3.79 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 4.59 (1H, d, ^2J = 14.6) and 4.76 (1H, d, ^2J = 14.6, OCH_2); 6.44 (1H, dd, ^3J = 8.9, ^4J = 2.7, H_{Ar}-5); 6.53 (1H, d, ^4J = 2.7, H_{Ar}-3); 6.73 (2H, br, NH_2); 7.70 (1H, s, NH); 8.08 (1H, d, ^3J = 8.9, H_{Ar}-6)
3g	1.35 (6H, s, $2CH_3$); 3.21 (4H, m, $N(CH_2)_2$); 3.55 (2H, s, CH_2); 3.79 (4H, m, $O(CH_2)_2$); 3.81 (2H, s, CH_2); 7.43 (2H, s, NH_2); 7.21-7.41 (4H, m, C_6H_5); 8.26 (1H, s, NH)
3h	1.42 (6H, s, $2CH_3$); 3.18 (4H, m) and 3.80 (4H, m, C_4H_8NO); 3.35 (2H, s, CH_2); 3.79 (2H, s, SCH_2); 6.97 (2H, s, NH_2); 7.06 (1H, td, ^3J = 7.7, ^4J = 1.3) and 7.28 (1H, td, ^3J = 7.8, ^4J = 1.3, H_{Ar}-4,5); 7.40 (1H, dd, ^3J = 7.8, ^4J = 1.3, H_{Ar}-3); 8.05 (1H, s, NH); 8.28 (1H, dd, ^3J = 8.0, ^4J = 1.3, H_{Ar}-6)
4a	1.35 (6H, s, $2CH_3$); 3.21 (4H, m) and 3.79 (4H, m, C_4H_8NO); 3.43 (2H, s, CH_2); 4.68 (2H, s, OCH_2); 8.06 (1H, s, N=CHN); 12.61 (1H, br, NH)
4b	1.34 (6H, s, $2CH_3$); 2.48 (3H, m, CH_3); 3.20 (4H, m, $N(CH_2)_2$); 3.43 (2H, s, CH_2); 3.78 (4H, m, $O(CH_2)_2$); 4.67 (2H, s, OCH_2); 12.56 (1H, br, NH)
4c	1.37 (6H, s, $2CH_3$); 3.26 (4H, m) and 3.81 (4H, m, C_4H_8NO); 3.44 (2H, s, CH_2); 4.69 (2H, s, OCH_2); 7.49-7.62 (5H, m, C_6H_5); 8.29 (1H, s, N=CHN)
4d	1.36 (6H, s, $2CH_3$); 1.99 (4H, m, $(CH_2)_2$); 3.99 (2H, s, CH_2); 3.66 (4H, m, $N(CH_2)_2$); 4.81 (2H, s, OCH_2); 7.47-7.61 (5H, m, C_6H_5); 8.23 (1H, s, N=CH)
4e	1.07 (6H, d, *J* =6.8, CH_3); 1.86 (1H, oct, *J* = 6.8, CH); 3.11-3.21 (3H, m) and 3.32 (2H, ddd, ^2J = 12.9, ^3J = 6.5, ^3J = 3.0, $N(CH_2)_2$ and CH_2); 3.46 (1H, ddd, ^3J = 11.0, ^3J = 6.8, ^3J = 3.6, OCH); 3.67-3.88 (5H, m, $O(CH_2)_2$ and CH_2); 3.84 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 4.68 (1H, d, ^2J = 14.6) and 4.80 (1H, d, ^2J = 14.6, OCH_2); 6.64 (1H, dd, ^3J = 8.7, ^4J = 2.6, H_{Ar}-5); 6.71 (1H, d, ^4J = 2.6, H_{Ar}-3); 7.26 (1H, d, ^3J = 8.7, H_{Ar}-6); 8.05 (1H, s, N=CH)
4f	1.38 (6H, s, $2CH_3$); 3.24 (4H, m) and 3.81 (4H, m, C_4H_8NO); 3.75 (2H, s, CH_2); 3.80 (2H, s, SCH_2); 8.09 (1H, s, N=CHN); 12.65 (1H, br, NH)
4g	1.41 (3H, s, CH_3); 1.45 (3H, s, CH_3); 3.29 (4H, m) and 3.84 (4H, m, C_4H_8NO); 3.72 (2H, d, ^2J = 15.8, CH_2); 3.84 (1H, d, ^2J = 15.8) and 3.84 (1H, d, ^2J = 15.8, CH_2); 3.84 (2H, s, SCH_2); 7.52-7.70 (4H, m, C_6H_4); 8.18 (1H, s, N=CHN)
4h	1.77 (2H, m) and 1.92 (2H, m, $(CH_2)_2$); 2.72 (2H, t, *J* = 5.8, CH_2); 3.23 (4H, m, $N(CH_2)_2$); 3.53 (2H, t, *J* = 6.5, CH_2); 3.78 (4H, m, $O(CH_2)_2$); 8.03 (1H, s, N=CH); 12.56 (1H, br, NH)

Table 2 (continued)

1	2
4i	1.77 (2H, m, CH_2); 1.91 (2H, m, CH_2); 2.45 (3H, s, CH_3); 2.71 (2H, t, *J* = 5.7, CH_2); 3.21 (4H, m, $N(CH_2)_2$); 3.53 (2H, t, *J* = 6.5, CH_2); 3.78 (4H, m, $O(CH_2)_2$); 12.50 (1H, s, NH)
5a	1.35 (6H, s, $2CH_3$); 3.24 (4H, m) and 3.77 (4H, m, C_4H_8NO); 3.37 (2H, s, CH_2); 4.64 (2H, s, OCH_2); 11.24 (1H, br, NH); 12.59 (1H, s, NH)
5b	1.38 (6H, s, $2CH_3$); 3.28 (4H, m) and 3.78 (4H, m, C_4H_8NO); 3.42 (2H, s, CH_2); 4.66 (2H, s, OCH_2); 7.23 (2H, m, H_{Ph}-2,6); 7.43 (1H, m, H_{Ph}-4); 7.50 (2H, m, H_{Ph}-3,5); 11.65 (1H, br, NH)
5c	1.07 (3H, d, ^3J = 6.7, CH_3); 1.09 (3H, d, ^3J = 6.7, CH_3); 1.86 (1H, oct, ^3J = 6.7, CH); 3.14 (1H, dd, ^2J = 17.3, ^3J = 10.5) and 3.63 (1H, dd, ^2J = 17.3, ^3J = 3.9, CH_2); 3.71 (2H, ddd, ^2J = 11.4, ^3J = 6.5, ^3J = 2.9) and 3.81 (2H, ddd, ^2J = 11.4, ^3J = 6.5, ^3J = 2.9, $N(CH_2)_2$); 3.44 (1H, ddd, ^3J = 10.5, ^3J = 6.6, ^3J = 3.9, OCH); 3.70 (2H, ddd, ^2J = 11.4, ^3J = 6.5, ^3J = 2.9) and 3.81 (2H, ddd, ^2J = 11.4, ^3J = 6.3, ^3J = 2.9, $O(CH_2)_2$); 4.63 (1H, d, ^2J = 14.5) and 4.72 (1H, d, ^2J = 14.5, OCH_2); 11.20 (1H, br, NH); 12.59 (1H, s, NH)
5d	1.75 (2H, m, CH_2); 1.95 (2H, m, CH_2); 2.68 (2H, t, *J* = 5.9, CH_2); 3.26 (4H, m, $N(CH_2)_2$); 3.45 (2H, t, *J* = 6.7, CH_2); 3.76 (4H, m, $O(CH_2)_2$); 10.70 (1H, br, NH); 12.59 (1H, s, NH)
6a	1.33 (6H, s, $2CH_3$); 2.61 (3H, s, SCH_3); 3.21 (4H, m) and 3.78 (4H, m, C_4H_8NO); 3.45 (2H, s, CH_2); 4.67 (2H, s, OCH_2); 12.85 (1H, br, NH)
6b	1.35 (6H, s, $2CH_3$); 1.41 (3H, t, ^3J = 7.3, $CH_2\underline{CH_3}$); 3.15 (2H, q, ^3J = 7.3, SCH_2); 3.26 (4H, m) and 3.80 (4H, m, C_4H_8NO); 3.48 (2H, s, CH_2); 4.70 (2H, s, OCH_2); 7.30-7.36 (2H, m) and 7.55-7.61 (3H, m, C_6H_5)
6c	1.33 (6H, s, $2CH_3$); 1.47 (3H, t, ^3J = 7.2, CH_3); 3.21 (2H, q, ^3J = 7.2, SCH_2); 3.22 (4H, m) and 3.78 (4H, m, C_4H_8NO); 3.44 (2H, s, CH_2); 4.67 (2H, s, OCH_2); 12.80 (1H, br, NH)
6d	1.04 (3H, d, ^3J = 6.7, CH_3); 1.06 (3H, d, ^3J = 6.7, CH_3); 1.43 (3H, t, ^3J = 7.3, CH_3); 1.83 (1H, oct, ^3J = 6.7, CH); 3.22 (2H, m, SCH_2); 3.07-3.33 (5H, m, $N(CH_2)_2$ and CH_2); 3.43 (1H, ddd, ^3J = 10.9, ^3J = 6.7, ^3J = 3.6, OCH); 3.63-3.86 (5H, m, $O(CH_2)_2$ and CH_2); 4.65 (1H, d, ^2J = 14.7) and 4.77 (1H, d, ^2J = 14.7, OCH_2); 12.79 (1H, br, NH)
6e	1.75 (2H, m) and 1.91 (2H, m, $(CH_2)_2$); 2.62 (3H, s, SCH_3); 2.71 (2H, t, *J* = 5.8, CH_2); 3.22 (4H, m, $N(CH_2)_2$); 3.54 (2H, t, *J* = 6.5, CH_2); 3.77 (4H, m, $O(CH_2)_2$); 12.84 (1H, br, NH)
6f	1.45 (3H, t, *J* = 7.3, CH_3); 1.77 (2H, m, CH_2); 1.92 (2H, m, CH_2); 2.71 (2H, t, *J* = 5.8, CH_2); 3.21 (2H, q, *J* = 7.3, SCH_2); 3.22 (4H, m, $N(CH_2)_2$); 3.54 (2H, t, *J* = 6.5, CH_2); 3.78 (4H, m, $O(CH_2)_2$); 12.74 (1H, br, NH)

2-(5-Cyano-3,3-dimethy-8-morpholino-2,4-dihydro-1H-pyrano[3,4-c]pyridin-6-sulfanyl)acetamide (2a). Chloroacetamide (0.3 g, 3.3 mmol) was added to a solution of compound **1a** (1g, 3.3 mmol) in 20 ml of an aqueous solution of Na_2CO_3 (0.35 g, 3.3 mmol). The reaction mixture was stirred for 1h at room temperature. The crystalline precipitate was filtered off, washed with water, and dried. The product was recrystallized from ethanol.

Compounds 2b-d were prepared analogously.

1-Amino-8,8-dimethyl-5-morpholino-8,9-dihydro-6H-pyrano[4,3-*d*]thieno[2,3-*b*]pyridine-2-carboxamide (3a). Compound **2a** (3.62 g, 10 mmol) was added to a solution of sodium ethoxide, prepared from sodium (0.23 g, 10 mmol) in absolute ethanol (50 ml). The reaction mixture was heated for 2 h at 60°C. Water was added after cooling. The precipitated crystals were filtered off, washed with ethanol, dried, and recrystallized from 1:1 ethanol–chloroform.

Compounds 3b-d were prepared analogously.

1-Amino-5-morpholino-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolino-2-(3-methoxyphenyl)carboxamide (3e). Compound **1c** (2.75 g, 10 mmol) was added to a solution of sodium ethoxide, prepared from sodium (0.46 g, 20 mmol) in absolute ethanol (55 ml). The mixture was stirred to complete solution and N-(2-methoxyphenyl)-2-chloroacetamide (2.0 g, 10 mmol) was added. The reaction mixture was heated for 2 h at 60°. After cooling, water was added, the mixture was filtered, the residue was washed with ethanol, dried, and recrystallized from 1:1 ethanol–chloroform**.**

Compounds 3f-h were prepared analogously.

2,2-Dimethyl-5-morpholino-1,4,8,9-tetrahydro-2H-pyrano[4",3":4',5']pyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidin-8-one (4a). A mixture of compound **3a** (3.62 g, 10 mmol), acetic anhydride (25 ml), and ethyl orthoformate (15 ml) was boiled under reflux for 3 h. The excess of solvent was boiled off and the residue was dissolved in ethanol (10 ml). The precipitated crystals were filtered off, washed with ethanol, dried, and recrystallized from DMSO. IR spectrum, ν_{max}, cm^{-1}: 3170 (NH), 1650 (C=O). Mass spectrum: *m/z* (I_{rel}, %): 372 $[M]^+$ (100), 357 (13), 341 (30), 329 (22), 302 (78).

Compound 4b. Mass spectrum: *m/z* (I_{rel}, %): 386 $[M]^+$ (100), 385 (32), 355 (20), 343 (10), 329 (19), 315 (16).

Compounds 4b-i were prepared analogously.

Compound 4a was also prepared by another method [1].

2,2-Dimethyl-5-morpholino-10-thioxo-1,4,8,9,10,11-hexahydro-2H-pyrano[4",3":4',5']pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidin-8-one (5a). A mixture of compound **3a** (2 g, 5.5 mmol), carbon disulfide (15 ml), and pyridine (60 ml) was heated under reflux for 15 h. The solvent was distilled off and the residue was dissolved in 2 N aqueous potassium hydroxide solution. The mixture was filtered and the filtrate was acidified with 10% hydrochloric acid. The precipitated crystals were filtered off, washed with water, dried, and recrystallized from DMF. IR spectrum, ν, cm^{-1}: 3440 (NH), 1680 (C=O).

Compounds 5b-d were prepared analogously.

2,2-Dimethyl-10-methylsulfanyl-5-morpholino-10-thioxo-1,4,8,9,10,11-hexahydro-2H-pyrano-[4",3":4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-8-one (6a). DMF (50 ml) and compound **5a** (4.04 g, 10 mmol) were added to a solution of KOH (0.56 g, 10 mmol) in water (5 ml). A solution of methyl iodide (1.42 g, 10 mmol) in ethanol (30 ml) was added by degrees to the mixture, cooled to 10°C. The mixture was stirred at room temperature for 5 h. Water (50 ml) and ethanol (50 ml) were then added to the reaction mixture. The precipitated crystals were filtered off, dried, and recrystallized from 2:1 ethanol–DMF. IR spectrum, ν, cm^{-1}: 1670 (C=O).

Compounds 6b-f were prepared analogously.

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