A Convenient Synthesis for Some New Pyrido[3',2':4,5]thieno-[3,2-*d*]pyrimidine Derivatives with Potential Biological Activity

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Ready, convenient synthesis for 8-cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-1,2,3,4-tetrahydropyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidines **5**, 8-cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **6**, 4-chloro-8-cyano-7-ethoxy-9-phenyl-2-substitutedpyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidines **7** and 8-cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenyl-4-substitutedpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **8-18** from 2-chloro-3,5-dicyano-6-ethoxy-4-phenylpyridine **1** *via* 3,5-dicyano-6-ethoxy-2-mercapto-4-phenylpyridine **2** and aminocarboxamide **4** are reported. In addition, the reaction of hydrazino derivative **12** with reagents such as formic acid and triethyl orthoformate yielded the fused tetraheterocyclic 8-cyano-9-ethoxy-5-(2'-nitrophenyl)-7-phenylpyrido[3',2':4,5]thieno[2,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidine system **19**.

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Pyridothienopyrimidines have been the subject of chemical and biological studies on account of their interesting pharmacological properties. Synthesis of substituted derivatives of this triheterocyclic ring system, which feature a variety of pharmacological activities have been reported in a number of papers. Such derivatives have analgesic [1], antipyretic [2a-b], antianaphylactic [3a-b] and antiinflammatory [4-7] effects. Also, some of these compounds are clinically effective antialergic [8] or potential antineoplastic [9] agents and a few of them have a significant hypocholesterolenic [10-11] activity. These assests prompted us to prepare new pyridothienopyrimidines with potential biological activity in our search for novel heterocyclic compounds of pharmacological interest.

Thus, we developed a straightforward, convenient synthetic method for some novel pyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidines **5**, **6** and their substituted derivatives. The pyridothienopyrimidine trihetherocyclic ring can be synthesized from an appropriate pyridothieno derivative system upon treatment with a one-carbon reagent such as ethyl carbonate. Other one-carbon reagents that can be used for this purpose include formic acid, esters and ortho esters, amides, urea, cyanates, isothiocyanaytes, chlorocarbonates, carbon disulphide and thiophosgene [12]. However, a literature survey revealed no reports on the reaction between 3-aminothieno[2,3-*b*]pyridine-2-carboxamides and aliphatic or aromatic aldehydes. The reaction sequence involved is outlined in Scheme 2.

The required compound **4** was prepared by the procedure summarized in Scheme 1. The conveniently available 2-chloro-3-cyanopyridine **1** [13] was employed as the starting material. Reaction of this compound with sodium sulfide in ethanol provided 3,5-dicyano-6-ethoxy-2-mercapto-4-phenylpyridine **2**. Treatment of **2** with 2-chloroacetamide and subsequent base-promoted intramolecular ring formation yielded 3-aminothieno[2,3-*b*]pyridine-2-carboxamide **4** in 70%. Alternatively, the reaction of **1** with thiourea in refluxing ethanol gave exclusively bis(3,4-dicyano-6-ethoxy-5-phenyl-2-pyridyl) sulfide **3**. Treatment of

Scheme 1

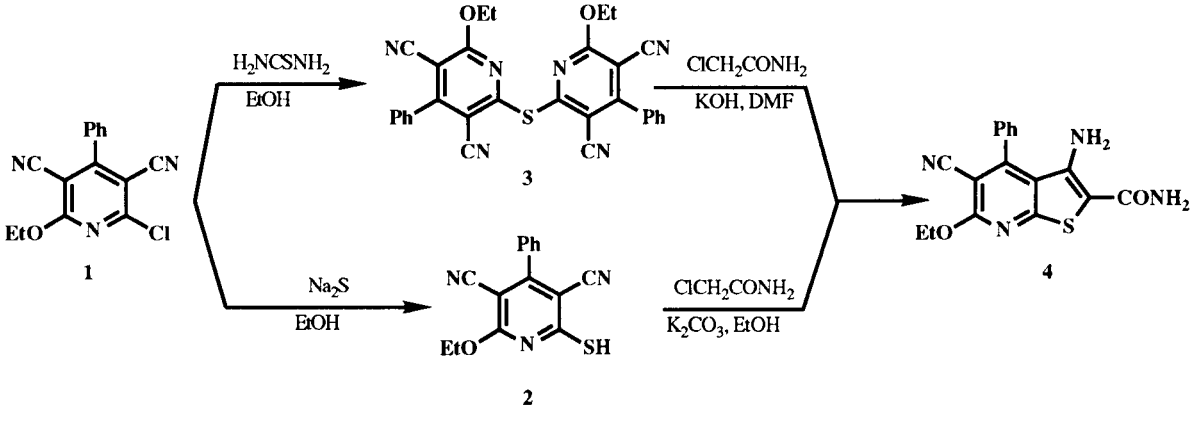
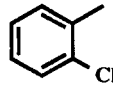
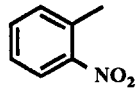
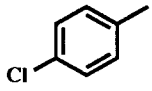
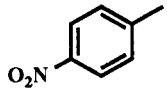
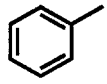
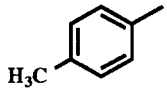
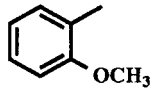
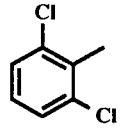
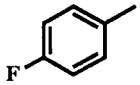
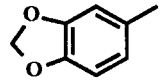
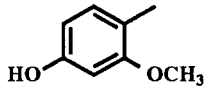
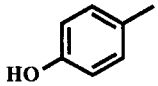
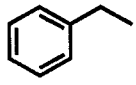
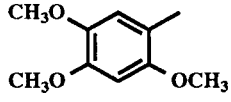


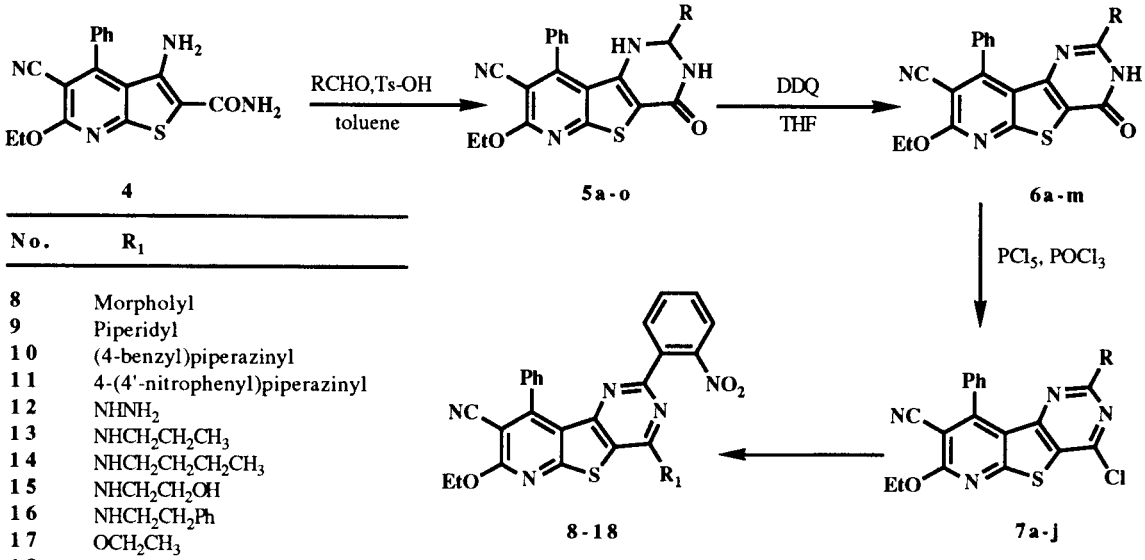
Table 1

8-Cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **5a-o**

No.	Yield (%)	R	Mp (°C)	Molecular formula	Analysis (%) Calcd./Found		
					C	H	N
5a	87		280-282 [a]	$C_{24}H_{17}ClN_4O_2S$ 460.94	62.54 62.74	3.72 3.75	12.16 12.01
5b	81		291-293 dec [b]	$C_{24}H_{17}N_5O_4S$ 471.50	61.14 61.31	3.63 3.75	14.85 14.64
5c	87		>300 [b]	$C_{24}H_{17}ClN_4O_2S$ 460.94	62.54 62.67	3.72 3.91	12.16 12.10
5d	97		>300 [b]	$C_{24}H_{17}N_5O_4S$ 471.50	61.14 60.95	3.63 3.51	14.85 14.89
5e	89		280 dec [b]	$C_{24}H_{18}N_4O_2S$ 426.50	67.59 67.52	4.25 4.28	13.14 13.17
5f	70		>300 [c]	$C_{25}H_{20}N_4O_2S$ 440.52	68.16 68.19	4.58 4.44	12.72 12.85
5g	82		245-247 [a]	$C_{25}H_{20}N_4O_3S$ 456.52	65.77 65.59	4.42 4.67	12.27 12.32
5h	97		260-262 [b]	$C_{24}H_{16}Cl_2N_4O_2S$ 495.39	58.19 58.27	3.26 3.10	11.31 11.21
5i	76		258-260 [b]	$C_{24}H_{17}FN_4O_2S$ 444.49	64.85 64.69	3.85 3.97	12.60 12.68
5j	88		290-292 [d]	$C_{25}H_{18}N_4O_4S$ 470.51	63.82 63.77	3.86 3.99	11.91 11.83
5k	88		>300 [d]	$C_{25}H_{20}N_4O_4S$ 472.52	63.55 63.70	4.27 4.35	11.86 11.63
5l	90		>300 [a]	$C_{24}H_{18}N_4O_3S$ 442.50	65.14 65.37	4.10 4.02	12.66 12.52
5m	67		283-285 [e]	$C_{25}H_{20}N_4O_2S$ 440.52	68.16 68.19	4.58 4.62	12.72 12.66
5n	52		256-258 [b]	$C_{27}H_{24}N_4O_5S$ 516.58	62.78 62.59	4.68 4.53	10.85 10.97
5o	64		296-298 dec [c]	$C_{19}H_{15}ClN_4O_2S$ 398.87	57.21 57.40	3.79 3.59	14.05 14.03

[a] Recrystallized from ethanol. [b] Recrystallized from ethanol/acetone. [c] Recrystallized from ethanol/dichloromethane. [d] Purified by column chromatography on silica gel with 1% ethanol in dichloromethane. [e] Purified by column chromatography on silica gel with dichloromethane.

Scheme 2



No.	R_1
8	Morpholyl
9	Piperidyl
10	(4-benzyl)piperazinyl
11	4-(4'-nitrophenyl)piperazinyl
12	$NHNH_2$
13	$NHCH_2CH_2CH_3$
14	$NHCH_2CH_2CH_2CH_3$
15	$NHCH_2CH_2OH$
16	$NHCH_2CH_2Ph$
17	OCH_2CH_3
18	N_3

Table 2

8-Cyano-7-ethoxy-4-oxo-9-pheny-2-substituted-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **5a-o**

No.	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%)	^{1}H-NMR (DMSO-d_6/TMS) δ, J (Hz) [a]	^{13}C-NMR (DMSO-d_6 /TMS) [a]
5a	3390 (NH), 3260 (NH) 2220 (CN), 1640 (CO)	462 (M^++2, 24), 460 (M^+, 55), 349 (100), 322 (91), 294 (36)	1.37 (t, 3H, J = 7, CH_3), 4.52 (q, 2H, J = 7, CH_2O), 5.07 [b] (d, 1H, J = 3.5, NH), 5.92 (t, 1H, J = 3.4, NHC*H*RNH), 7.30-7.45 (m, 9H arom), 8.27 [b] (d, 1H, J = 3.1, NH)	14.08 64.07 64.29
5b	3410 (NH), 3170 (NH) 2220 (CN), 1650 (CO)	471 (M^+, 80), 349 (100), 322 (69), 294 (49)	1.37 (t, 3H, J = 7, CH_3), 4.52 (q, 2H, J = 7, CH_2O), 5.13 [b] (d, 1H, J = 3.5, NH), 6.25 (t, 1H, J = 3.4, NHC*H*RNH), 7.28-7.79 (m,9H arom), 8.26 [b] (d, 1H, J = 3.3, NH)	14.06 63.21 64.05
5c	3390 (NH), 3150 (NH) 2220 (CN), 1640 (CO)	462 (M^++2, 36), 460 (M^+, 75), 349 (67), 322 (100), 294 (40)	1.37 (t, 3H, J = 7, CH_3), 4.52 (q, 2H, J = 7, CH_2O), 5.16 [b] (d, 1H, J = 4.5, NH), 5.69 (t, 1H, J = 3.8, NHC*H*RNH), 7.22-7.63 (m, 9H arom), 8.42 [b] (d, 1H, J = 3.4, NH)	14.08 64.03 65.08
5d	3400 (NH), 3180 (NH) 2220 (CN), 1660 (CO)	471 (M^+, 85), 439 (77), 349 (69), 322 (100), 294 (46)	1.38 (t, 3H, J = 7, CH_3), 4.52 (q, 2H, J = 7, CH_2O), 5.41 [b] (br s, 1H, NH), 5.84 (t, 1H, J = 4.4, NHC*H*RNH), 7.45-7.64 (m, 9H arom), 8.57 [b] (br s, 1H, J = 3.5, NH)	14.08 64.05 64.64
5e	3410 (NH), 3180 (NH) 2220 (CN), 1650 (CO)	426 (M^+, 100), 423 (95), 349 (68), 322 (70), 294 (32)	1.38 (t, 3H, J = 7, CH_3), 4.52 (q, 2H, J = 7, CH_2O), 5.04 [b] (d, 1H, J = 4.3, NH), 5.71 (t, 1H, J = 3.3, NHC*H*RNH), 7.21-7.61 (m, 10H arom), 8.39 [b] (d, 1H, J = 3.1, NH)	14.08 64.02 65.85
5f	3400 (NH), 3180 (NH) 2220 (CN), 1650 (CO)	440 (M^+, 100), 438 (63), 349 (79), 322 (81), 294 (36)	1.50 (t, 3H, J = 7, CH_3), 2.34 (s, 3H, $PhCH_3$), 4.02 (br s, 1H, NH), 4.61 (q, 2H, J = 7, CH_2O), 5.67 (br s, 1H, NHC*H*RNH), 5.67 (br s, 1H, NH), 7.15-7.49 (m, 9H arom)	14.23, 21.11 64.43, 68.90
5g	3400 (NH), 3180 (NH) 2220 (CN), 1650 (CO)	456 (M^+, 89), 454 (49), 349 (100), 322 (85), 294 (45)	1.36 (t, 3H, J = 7, CH_3), 3.55 (s, 3H, OCH_3), 4.51 (q, 2H, J = 7, CH_2O), 4.83 [b] (br s, 1H, NH), 5.78 (br s, 1H, NHC*H*RNH), 6.86-7.70 (m, 9H arom), 8.14 [b] (d, 1H, J = 3.1, NH)	14.03, 55.65 62.81, 63.98

Table 2 (Continued)

No.	IR (KBr) ν (cm^{-1})	MS (70eV) m/z (%)	^{1}H-NMR (DMSO-d_6/TMS) δ, j (Hz) [a]	^{13}C-NMR (DMSO-d_6 /TMS) [a]
5h	3400 (NH), 3180 (NH) 2220 (CN), 1650 (CO)	496 (M^++2, 24), 494 (M^+, 45), 349 (100), 322 (89), 294 (32)	1.40 (t, 3H, J = 7, CH_3), 4.55 (q, 2H, J = 7, CH_2O), 4.61 (br s, 1H, NH), 6.44 (br s, 1H, NHC*H*RNH), 7.21-7.61 (m, 8H arom +1H[b], NH), 8.13 [b] (br s, 1H, NH)	14.08 64.05 65.54
5i	3390 (NH), 3160 (NH) 2220 (CN), 1650 (CO)	444 (M^+, 90), 349 (76), 322 (100), 294 (64)	1.38 (t, 3H, J = 7, CH_3), 4.53 (q, 2H, J = 7, CH_2O), 5.07 [b] (d, 1H, J = 4.0, NH), 5.70 (t, 1H, J = 3.6, NHC*H*RNH), 7.12-7.61 (m, 9H arom), 8.38 [b] (br s, 1H, NH)	14.05 64.00 65.32
5j	3400 (NH), 3180 (NH) 2220 (CN), 1660 (CO)	470 (M^+, 100), 349 (97), 322 (93), 294 (73)	1.37 (t, 3H, J = 7, CH_3), 4.53 (q, 2H, J = 7, CH_2O), 4.92 [b] (br s, 1H, NH), 5.62 (t, 1H, J = 3.5, NHC*H*RNH), 5.98 (s, 2H, OCH_2O), 6.81-7.61 (m, 10H arom), 8.28 [b] (br s, 1H, NH)	14.10 65.26 68.23
5k	3400 (NH) 3300 (br,OH) 2220 (CN), 1640 (CO)	472 (M^+,100), 349 (86), 322 (94), 294 (47)	1.38 (t, 3H, J = 7, CH_3), 3.74 (s, 3H, OCH_3), 4.52 (q, 2H, J = 7, CH_2O), 4.73 [b] (d, 1H, J = 3.3, NH), 5.59 (br s, 1H, NHC*H*RNH), 6.66-7.59 (m,8H arom), 8.21 [b] (br s, 1H, NH), 9.06 [b] (s, 1H, OH)	14.10 55.58 64.03 66.46
5l	3400 (NH) 3200 (br, OH) 2220 (CN), 1640 (CO)	442 (M^+, 100), 349 (71), 322 (82), 294 (63)	1.38 (t, 3H, J = 7, CH_3), 4.52 (q, 2H, J = 7, CH_2O), 4.75 [b] (br s, 1H, NH), 5.59 (br s, 1H, NHC*H*RNH), 6.66-7.59 (m,9H arom), 8.20 [b] (br s, 1H, NH), 9.48 [b] (s,1H, OH)	14.06 64.00 65.55
5m	3390 (NH), 3180 (NH) 2220 (CN), 1660 (CO)	349 (100), 322 (12), 294 (3)	1.38 (t, 3H, J = 7, CH_3), 2.83 (m, 2H, CH_2Ph), 4.17 [b] (d, 1H, J = 2.7, NH), 4.52 (q, 2H, J = 7, CH_2O), 4.87 (m, 1H, NHC*H*RNH), 6.89-7.63 (m,10H arom), 8.05 [b] (br s, 1H, NH)	14.06 63.95 66.54
5n	3390 (NH), 3180 (NH) 2220 (CN), 1660 (CO)	516 (M^+, 56), 349 (65), 322 (40), 294 (52)	1.47 (t, 3H, J = 7, CH_3), 3.61 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.45 [b] (br s, 1H, NH), 4.57 (q, 2H, J = 7, CH_2O), 5.99 (br s, 1H, NHC*H*RNH), 6.41 (s, 1H arom), 6.46 [b] (br s, 1H, NH), 6.87 (s, 1H arom), 7.36-7.58 (m,5H arom)	14.22, 55.92 56.16, 56.68 63.75, 64.38
5o	3460 (NH), 3280 (NH) 2220 (CN), 1670 (CO)	398 (M^+, 8), 349 (100), 322 (16), 294 (7)	1.40 (t, 3H, J = 7, CH_3), 3.41-3.70 (m, 2H, CH_2Cl), 4.54 (q, 2H, J = 7, CH_2O), 4.76-4.80 (m, 1H, NHC*H*RNH), 4.87 [b] (d, 1H, J = 3.8, NH), 7.50-7.65 (m, 5H arom), 8.10 [b] (d, 1H, J = 3.1, NH)	14.05, 44.96 64.03, 65.23

[a] **5f** in deuteriochloroform. [b] Exchangeable with deuterium oxide.

compound **3** with 2-chloroacetamide provided the carboxamide **4**, which was readily isolated from the crude reaction product by medium-pressure chromatography as a crystalline solid in appreciable yield. On treatment with an appropriate aliphatic or aromatic aldehyde in refluxing toluene containing a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal or water, **4** underwent cyclization to 8-cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **5** (Scheme 2) in good yields. The structures of these compounds were consistent with their elemental analyses and spectral data (ir, ^{1}H nmr, ^{13}C nmr and ms) (Tables 1 and 2).

All of the isolated pyridothienopyrimidines **5** yielded a characteristic absorption band between δ = 4.76 and δ = 6.84 for the H-2 proton in the ^{1}H nmr spectra, and two signals between δ = 4.02-5.41 and δ = 6.46-8.57, exchangeable with deuterium oxide, which can be attributed to *N*-bonded protons at positions 1 and 3 respectively, on this trihetherocyclic ring system. After ring rearrangement to **6-7**, their signals disappeared from the spectra. On the other hand, the ^{13}C nmr spectra of compounds **5** showed one signal which appears at δ = 63.21-68.90 corresponding to the carbon at position 2 on the newly synthesized pyrimidine ring. The EI-mass spectra showed the expected molecular ion peak and other characteristic peaks at m/z = 349 $(M-R^{\cdot})^+$, 322 $(M-R^{\cdot}-HCN)^+$ and 294 $(M-R^{\cdot}-HCN-CO)^+$. Furthermore, the absence of the characteristic bands of the amide group in the ir spectra indicated the condensation products to be **5**. Salient features of the ^{1}H nmr, ^{13}C nmr, ir and ms spectra are given in Table 2.

Refluxing compounds **5** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in tetrahydrofuran for a few hours yielded compounds **6**, the EI-mass spectra of which showed the expected molecular ion peak and other characteristic peaks at m/z = $(M-OCN^{\cdot})^+$ and 292 $(M-OCN^{\cdot}-RHC^{\cdot})^+$. The pyridothienopyrimidone **6** reacted with phosphorus oxychloride to yield the expected 4-chloropyridothienopyrimidine derivative **7** which, in turn, showed the

Table 3

8-Cyano-7-ethoxy-4-oxo-9-pheny-2-substituted-3,4dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **6a-m**

No.	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	IR (KBr) ν (cm^{-1})	MS (70eV) m/z(%)	^{1}H-NMR (DMSO-d_6/TMS) δ, J (Hz)
6a	70	266-268	$C_{24}H_{15}ClN_4SO_2$ 458.93	62.81 62.99	3.29 3.10	12.21 12.35	2220 (CN) 1640 (CO)	460 (M^++2, 40), 458 (M^+, 85), 416 (30), 292 (27)	1.43 (t, 3H, J = 7, CH_3), 4.60 (q, 2H, J = 7, CH_2O), 7.38-7.57 (m, 9H arom), 13.17[a] (br s, 1H, NH).
6b	70	>300	$C_{24}H_{15}N_5SO_4$ 469.48	61.40 61.56	3.22 3.14	14.92 14.99	2220 (CN) 1640 (CO)	469 (M^+, 61), 292 (69), 264 (42)	1.43 (t, 3H, J = 7, CH_3), 4.60 (q, 2H, J = 7, CH_2O), 7.34-8.14 (m, 9H arom), 13.21[a] (br s, 1H, NH).
6c	93	>300	$C_{24}H_{15}ClN_4SO_2$ 458.93	62.81 62.89	3.29 3.40	12.21 12.30	2220 (CN) 1660 (CO)	460 (M^++2, 40), 458 (M^+, 100), 416 (32), 292 (24)	[b]
6d	98	>300	$C_{24}H_{15}N_5SO_4$ 469.48	61.40 61.47	3.22 3.12	14.92 14.83	2220 (CN) 1650 (CO)	469 (M^+, 69), 427 (20), 292 (33), 264 (30), 236 (48)	1.44 (t, 3H, J = 7, CH_3), 4.60 (q, 2H, J = 7, CH_2O), 7.45-8.23 (m, 9H arom), 13.34[a] (br s, 1H, NH).
6e	90	>300	$C_{24}H_{16}N_4SO_2$ 424.48	67.91 67.95	3.80 4.05	13.20 13.03	2220 (CN) 1640 (CO)	424 (M^+, 100), 382 (28), 292 (25)	1.43 (t, 3H, J = 7, CH_3), 4.59 (q, 2H, J = 7, CH_2O), 7.32-7.68 (m, 10H arom), 13.05[a] (br s, 1H, NH).
6f	95	>300	$C_{25}H_{18}N_4SO_2$ 438.50	68.48 68.31	4.14 4.19	12.78 12.86	2220 (CN) 1660 (CO)	438 (M^+, 100), 396 (27), 292 (21)	1.44 (t, 3H, J = 7, CH_3), 2.33 (s, 3H, CH_3), 4.61 (q, 2H, J = 7, CH_2O), 7.15-7.59 (m, 9H arom), 13.17[a] (br s, 1H, NH).
6g	91	283-285	$C_{25}H_{18}N_4SO_3$ 454.50	66.07 66.27	3.99 4.09	12.33 12.12	3290 (NH) 2220 (CN) 1660 (CO)	454 (M^+, 100), 412 (11), 292 (11)	1.45 (t, 3H, J = 7, CH_3), 3.88 (s, 3H, OCH_3), 4.61 (q, 2H, J = 7, CH_2O), 6.88-7.54 (m, 9H arom), 12.08[a] (br s, 1H, NH).
6h	82	>300	$C_{24}H_{14}Cl_2N_4SO_2$ 493.37	58.43 58.63	2.86 2.80	11.36 11.19	2220 (CN) 1660 (CO)	496 (M^++4, 20), 494 (M^++2, 78), 492 (M^+, 100), 450 (36), 292 (18)	1.44 (t, 3H, J = 7, CH_3), 4.60 (q, 2H, J = 7, CH_2O), 7.34-7.58 (m, 8H arom), 13.43[a] (br s, 1H, NH).
6i	93	>300	$C_{24}H_{15}FN_4SO_2$ 442.47	65.15 65.20	3.42 3.51	12.66 12.61	2220 (CN) 1650 (CO)	442 (M^+, 100), 400 (25), 292 (13)	1.44 (t, 3H, J = 7, CH_3), 4.61 (q, 2H, J = 7, CH_2O), 7.18-7.44 (m, 9H arom), 13.06[a] (br s, 1H, NH).
6j	89	>300	$C_{25}H_{16}N_4SO_4$ 468.49	64.10 64.34	3.44 3.57	11.96 11.83	2220 (CN) 1650 (CO)	468 (M^+, 50), 426 (14), 292 (31), 264 (22), 236 (33)	1.44 (t, 3H, J = 7, CH_3), 4.60 (q, 2H, J = 7, CH_2O), 6.01 (s, 2H, OCH_2O), 6.88-7.64 (m, 8H arom), 12.82[a] (s, 1H, NH).
6k	95	>300	$C_{25}H_{18}N_4SO_2$ 470.50	63.82 63.98	3.86 3.69	11.91 11.85	3500-3200 (br, OH), 2220 (CN), 1640 (CO)	470 (M^+, 39), 292 (37), 264 (30)	1.43 (t, 3H, J = 7, CH_3), 3.73 (s, 3H, OCH_3), 4.60 (q, 2H, J = 7, CH_2O), 6.68-7.59 (m, 8H arom), 9.78[a] (s, 1H, OH), 12.78[a] (br s, 1H, NH).
6l	97	>300	$C_{24}H_{16}N_4SO_3$ 440.48	65.44 65.40	3.66 3.51	12.72 12.89	3500-3200 (br, OH), 2220 (CN) 1645 (CO)	440 (M^+, 16), 398 (5), 292 (21)	1.44 (t, 3H, J = 7, CH_3), 4.61 (q, 2H, J = 7, CH_2O), 6.68-7.62 (m, 9H arom), 10.16[a] (s, 1H, OH), 12.73[a] (br s, 1H, NH).
6m	67	>300	$C_{25}H_{18}N_4SO_2$ 438.50	68.48 68.59	4.14 4.02	12.78 12.95	2220 (CN) 1660 (CO)	438 (M^+, 100), 396 (20), 292 (28)	1.42 (t, 3H, J = 7, CH_3), 3.58 (s, 2H, CH_2Ph), 4.60 (q, 2H, J = 7, CH_2O), 7.00-7.61 (m, 10H arom), 13.03[a] (br s, 1H, NH).

[a] Exchangeable with deuterium oxide. [b] Insoluble in most common nmr solvents.

remarkable reactivity of its chloro substituent towards nucleophilic agents (Scheme 2).

The structures of these new compounds were confirmed by elemental and spectroscopic analyses. Tables 3 and 4 list the yields and physical and analytical data for all of the compounds synthesized. Their main spectroscopic features are also summarized in Tables 3 and 4.

The hydrazino compound **12**, obtained by reaction of **7b** with hydrazine hydrate, also proved to be a versatile synthon (Scheme 3). In fact, on heating derivative **12** with triethyl orthoformate or formic acid, it cyclized to the desired annelated triazole ring **19**. Compound **19** showed a signal at δ = 9.3 in the ^{1}H nmr spectrum that was assigned to the H-3 proton; also, its mass spectrum showed an intense peak at m/z = 493 corresponding to the molecular ion. In an attempt to synthesize the fused tetrazole compound, treatment of the hydrazine derivative **12** with nitrous acid yielded the azido compound **18** instead, which was obtained by reaction between **7b** and sodium azide. Finally, compound **12** was readily converted to the derivative **20** and the hydrazone **21** with ethyl chloroformate and refluxing acetone, respectively. Attempted cyclization of **21** with phosphoryl chloride failed to give compound **23**.

Table 4

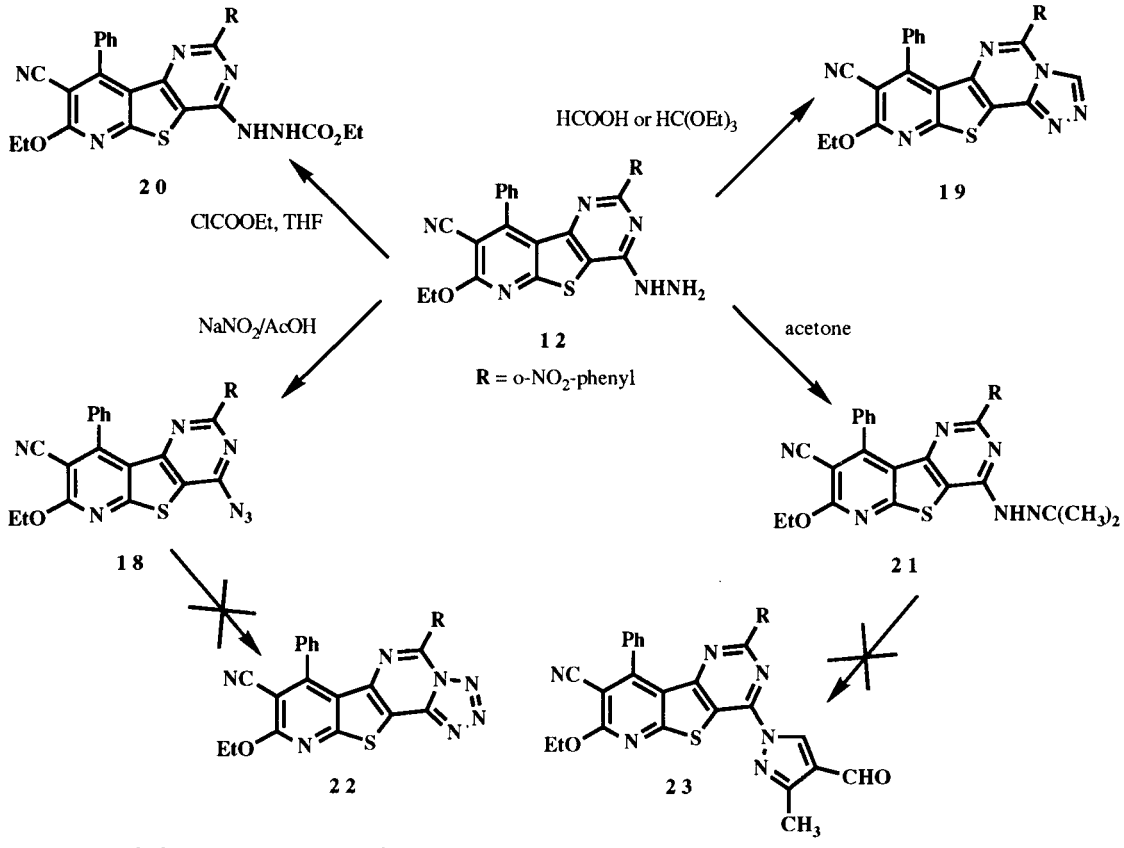
No.	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%)	^{1}H-NMR (Deuteriochloroform/TMS) δ, J (Hz) [a]
7a	83	267-269 [d]	$C_{24}H_{14}Cl_2N_4SO$ 477.37	60.39 60.60	2.96 2.85	11.74 11.61	2220 (CN), 1550, 1340, 1310, 1150, 1040, 700	480 (M$^+$+4, 14), 478 (M$^+$+2, 63), 476 (M$^+$, 80), 434 (33), 397 (18), 221 (42)	1.46 (t, 3H, J = 7, CH_3), 4.67 (q, 2H, J = 7, CH_2O), 7.49-7.59 (m, 9H arom)
7b	90	241-243 [d]	$C_{24}H_{14}ClN_5SO_3$ 487.92	59.08 59.09	2.89 2.75	14.35 14.50	2220 (CN), 1540, 1340, 1310, 1020, 720	489 (M$^+$+2, 5), 487 (M$^+$, 13),470 (100), 440 (59), 411 (36), 221 (8)	1.46 (t, 3H, J = 7, CH_3), 4.63 (q, 2H, J = 7, CH_2O), 7.52-7.93 (m, 9H arom)
7c	87	>300 [e]	$C_{24}H_{14}Cl_2N_4SO$ 477.37	60.39 60.53	2.96 2.78	11.74 11.50	2220 (CN), 1560, 1490, 1390, 1340, 1090, 700	480 (M$^+$+4, 18), 478 (M$^+$+2, 73), 476 (M$^+$, 100), 434 (38), 431 (22), 221 (32)	1.56 (t, 3H, J = 7, CH_3), 4.73 (q, 2H, J = 7, CH_2O), 7.29-7.91 (m, 9H arom)
7d	80	>300 [e]	$C_{24}H_{14}ClN_5SO_3$ 487.92	59.08 59.17	2.89 2.72	14.35 14.15	2220 (CN), 1560, 1520, 1340, 1020, 830, 700	489 (M$^+$+2, 44), 487 (M$^+$, 100), 445 (36), 412 (22), 221 (20)	1.58 (t, 3H, J = 7, CH_3), 4.74 (q, 2H, J = 7, CH_2O), 7.53-8.21 (m, 9H arom)
7e	78	>300 [f]	$C_{24}H_{15}ClN_4SO$ 442.92	65.08 65.14	3.41 3.57	12.65 12.48	2220 (CN), 1550, 1490, 1390, 1340, 1020, 740, 690	444 (M$^+$+2, 39), 442 (M$^+$, 100), 415 (19), 400 (32), 221 (26)	1.56 (t, 3H, J = 7, CH_3), 4.71 (q, 2H, J = 7, CH_2O), 7.30-7.90 (m, 10H arom)
7f	92	>300	$C_{25}H_{17}ClN_4SO$ 456.95	65.71 65.62	3.75 3.98	12.26 12.10	2220 (CN), 1550, 1480, 1390, 1330, 1020, 710	458 (M$^+$+2, 16), 456 (M$^+$, 47), 414 (16), 321 (9), 221 (20)	[b]
7g	91	228-230 [d]	$C_{25}H_{17}ClN_4SO_2$ 472.95	63.49 63.40	3.62 3.52	12.85 12.92	2220 (CN), 1550, 1500, 1330, 1310, 1020, 720	474 (M$^+$+2, 44), 472 (M$^+$, 100), 443 (31), 437 (51), 367 (19), 221 (17)	1.28 (t, 3H, J = 7, CH_3), 3.51 (s, 3H, OCH_3), 4.43 (q, 2H, J = 7, CH_2O), 7.03-7.34 (m, 9H arom)
7h	90	263-265 [d]	$C_{24}H_{13}Cl_3N_4SO$ 511.81	56.32 56.51	2.56 2.63	10.95 10.82	2220 (CN), 1540, 1490, 1360, 1340, 1020, 700	516 (M$^+$+6, 3), 514 (M$^+$+4, 16), 512 (M$^+$+2, 46), 510 (M$^+$, 41), 470 (19), 221 (22)	1.56 (t, 3H, J = 7, CH_3), 4.72 (q, 2H, J = 7, CH_2O), 7.25-7.54 (m, 8H arom)
7i	80	>300 [f]	$C_{24}H_{14}ClFN_4SO$ 460.91	62.54 62.41	3.06 3.01	12.16 12.10	2220 (CN), 1560, 1480, 1340, 1150, 1020, 850, 720	462 (M$^+$+2, 43), 460 (M$^+$, 100), 433 (19), 418 (39), 221 (33)	1.56 (t, 3H, J = 7, CH_3), 4.72 (q, 2H, J = 7, CH_2O), 6.97-7.97 (m, 9H arom)
7j	73	>300 [g]	$C_{25}H_{15}ClN_4SO_3$ 486.93	61.67 61.72	3.11 3.19	11.51 11.43	2220 (CN), 1560, 1490, 1400, 1340, 1020, 820, 720	488 (M$^+$+2, 46), 486 (M$^+$, 100), 459 (11), 444 (19), 221 (8)	1.56 (t, 3H, J = 7, CH_3), 4.72 (q, 2H, J = 7, CH_2O), 6.01 (s, 2H, OCH_2O), 6.74-7.68 (m, 8H arom)
8	85	298-300	$C_{28}H_{22}N_6O_4S$ 538.58	62.44 62.60	4.12 4.01	15.60 15.75	2220 (CN), 1540, 1340, 1150, 1120, 1020, 700	538 (M$^+$, 76), 521 (100), 491 (27), 474 (48), 462 (74), 221 (28)	1.54 (t, 3H, J = 7, CH_3), 3.82-3.87 (m, 8H, NCH_2), 4.66 (q, 2H, J = 7, CH_2O), 7.40-7.59 (m, 9H arom)
9	85	250-252	$C_{29}H_{24}N_6O_3S$ 536.61	64.91 65.16	4.51 4.63	15.66 15.50	2220 (CN), 1540, 1380, 1330, 1150, 1020, 760, 720	536 (M$^+$, 47), 519 (100), 501 (22), 377 (23), 291 (8), 221 (10)	1.53 (t, 3H, J = 7, CH_3), 1.73 (br s, 6H, $(CH_2)_3$), 3.84 (br s, 4H, CH_2NRCH_2), 4.67 (q, 2H, J = 7, CH_2O), 7.44-7.54 (m, 9H arom)
10	71	209-211	$C_{35}H_{29}N_7O_3S$ 627.72	66.97 66.79	4.66 4.51	15.62 15.80	2220 (CN), 1540, 1360, 1330, 1150, 1020, 770, 700	609 (18), 518 (4), 481 (9), 146 (11), 91 (100)	1.54 (t, 3H, J = 7, CH_3), 2.61 (s, 4H,), 3.58 (s, 2H, CH_2Ph), 3.90 (s, 4H), 4.66 (q, 2H, J = 7, CH_2O), 7.34-7.58 (m, 14H arom)

Table 4 (Continued)

No.	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%)	^{1}H-NMR (Deuteriochloroform/TMS) δ, J (Hz) [a]
11	65	282-283 dec	$C_{34}H_{26}N_8O_5S$ 658.69	62.00 62.20	3.98 3.79	17.01 17.22	2220 (CN), 1600, 1540, 1340, 1310, 1150, 1020, 720	618 (1), 232 (41), 131 (91), 45 (100)	1.55 (t, 3H, J = 7, CH_3), 3.64 (t, 4H, J = 5.2, NCH_2), 4.11 (t, 4H, J = 5.2, NCH_2) 4.68 (q, 2H, J = 7, CH_2O), 6.84-8.19 (m, 13H arom)
12	95	261-263	$C_{24}H_{17}N_7O_3S$ 483.50	59.62 59.76	3.54 3.31	20.28 20.38	3400, 3360, 2220 (CN), 1650, 1340, 1160, 1020,	354 (3), 347 (17), 264 (54), 236 (14), 88 (100)	1.59 (t, 3H, J = 7, CH_3), 1.98 (br s, 2H, NH_2), 4.72 (q, 2H, J = 7, CH_2O), 6.66 (br s, 1H, NH), 7.30-7.59 (m, 9H arom)
13	76	268-270	$C_{27}H_{22}N_6O_3S$ 510.57	63.52 63.53	4.34 4.50	16.46 16.43	3320 (NH), 2220 (CN), 1550, 1530, 1360, 1340, 1150, 1020, 770	510 (M^+, 4), 493 (9), 468 (10), 392 (10), 291 (30), 134 (31), 104 (95), 43 (100)	1.44 (t, 3H, J = 7, CH_3), 1.48-1.61 (m, 5H, CH_2CH_3), 3.56 (q, 2H, J = 6.3, $NHCH_2$), 4.68 (q, 2H, J = 7, CH_2O), 7.27-7.58 (m, 9H arom), 8.16 [c] (t, J = 5.5, 1H, NH)
14	74	236-238	$C_{28}H_{24}N_6O_3S$ 524.60	64.11 64.89	4.61 4.99	16.02 16.20	3340 (NH), 2220 (CN), 1550, 1360, 1330, 1150, 1020, 770	524 (M^+, 9), 507 (16), 468 (25), 392 (12), 291 (23), 134 (24), 104 (89), 41 (100)	1.44 (t, 3H, J = 7, CH_3), 1.48-1.51 (m, 7H, $CH_2CH_2CH_3$), 3.26 (q, 2H, J = 6.3, $NHCH_2$), 4.61 (q, 2H, J = 7, CH_2O), 4.81 (s br, 1H, NH), 7.44-7.72 (m, 9H arom)
15	63	267-269	$C_{26}H_{20}N_6O_4S$ 512.54	60.93 60.59	3.93 4.12	16.40 16.47	3360 (NH), 2220 (CN), 1600, 1540, 1380, 1340, 1260, 1030, 770	495 (3), 468 (7), 392 (3), 291 (4), 134 (19), 104 (39)	1.44 (t, 3H, J = 7, CH_3), 3.22-3.55 (m, 4H, CH_2CH_2), 4.62 (q, 2H, J = 7, CH_2O), 4.74 [c] (t, 1H, J = 5.1), 7.45-7.73 (m, 9H arom), 8.24 [c] (t, 1H, J = 5.1)
16	60	128-130	$C_{32}H_{24}N_6O_3S$ 572.64	67.12 66.91	4.22 4.36	14.68 14.81	3340 (NH), 2220 (CN),1550, 1360, 1340, 1280, 1150, 1020, 720	468 (5), 291 (4), 134 (6), 104 (42), 91 (100)	1.54 (t, 3H, J = 7, CH_3), 2.97 (t, 2H, J = 6.7, CH_2Ph), 3.83 (q, 2H, J = 6.6, $HNCH_2$), 4.67 (q, 2H, J = 7, CH_2O), 4.83 (s br, 1H, NH), 7.25-7.58 (m, 14H arom)
17	74	221-223	$C_{26}H_{19}N_5O_4S$ 497.53	62.77 62.74	3.85 4.07	14.08 14.22	2220 (CN), 1560, 1540, 1520, 1330, 1150, 720	497 (M^+, 11), 480 (66), 468 (9), 292 (21), 236 (26), 104 (100)	1.46 (t, 3H, J = 7, CH_3), 1.54 (t, 3H, J = 7, CH_3), 4.53 (q, 2H, zz J = 7, CH_2O), 4.69 (q, 2H, J = 7, CH_2O), 7.38-7.60 (m, 9H arom)
18	68	200-202 dec	$C_{24}H_{14}N_8O_3S$ 494.49	58.30 58.45	2.85 2.93	22.66 22.49	2220 (CN), 2160-2130 (N_3), 1550, 1340, 1280, 1040	494 (M^+, 19), 366 (22), 318 (62), 304 (51), 290 (30), 262 (25), 221 (9)	1.56 (t, 3H, J = 7, CH_3), 4.70 (q, 2H, J = 7, CH_2O), 7.44-7.69 (m, 9H arom)
19	80	>300	$C_{25}H_{15}N_7O_3S$ 493.50	60.85 60.98	3.06 2.91	19.87 19.80	2220 (CN), 1610, 1530, 1340, 1330, 1290, 1020, 720	493 (M^+, 87), 437 (16), 409 (15), 380 (42), 290 (24), 253 (35), 221 (30)	1.46 (t, 3H, J = 7, CH_3), 4.64 (q, 2H, J = 7, CH_2O), 7.36-8.36 (m, 9H arom), 9.33 (s, 1H, N=C*H*-N)
20	60	166-168 dec	$C_{27}H_{21}N_7O_5S$ 555.57	58.37 58.60	3.81 3.69	17.65 17.45	3350-3250 (NH), 2220 (CN), 1730 (CO), 1550, 1340, 1020, 700	509 (7), 453 (15), 291 (37), 134 (61), 104 (100)	1.25 (t, 3H, CH_3), 1.44 (t, 3H, J = 7, CH_3), 4.15 (q, 2H, CH_2O), 4.63 (q, 2H, J = 7, CH_2O), 7.46-7.60 (m, 9Harom), 7.83 (br s 1H, NH), 9.82 (br s, 1H, NH)
21	80	277-279 [f]	$C_{27}H_{21}N_7O_3S$ 523.57	61.94 61.15	4.04 4.17	18.73 18.54	3330 (NH), 2220 (CN), 1550, 1360, 1340, 1150, 1030, 760, 700	523 (M^+, 3), 508 (9), 290 (9), 134 (16), 104 (37), 44 (100)	1.40 (t, 3H, J = 7, CH_3), 2.00 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 4.51 (q, 2H, J = 7, CH_2O), 7.47-7.89 (m, 9Harom), 10.85 [c] (s, 1H, NH)

[a] **7a**, **7b**, **13** and **15** in DMSO-d_6. [b] Insoluble in most common nmr solvents. [c] Exchangeable with deuterium oxide. [d] Recrystallized from ethanol/acetone. [e] Purified by column chromatography on silica gel with 30% hexane in dichloromethane. [f] Recrystallized from ethanol/dichloromethane. [g] Purified by column chromatography on silica gel with 30% dichloromethane in hexane.

Scheme 3



The structures of these new compounds were also confirmed by elemental and spectroscopic analyses (Table 4).

The products isolated herein were subjected to biological screening tests. Research on this topic is currently in progress.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. The ir spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. The ^{1}H and ^{13}C nmr spectra were obtained on a Brucker WM 250 instrument at room temperature. Chemical shifts were determined on the δ scale, by using tetramethylsilane as the internal standard. Electron impact mass spectra were obtained at 70 eV by using a Kratos MS-50 spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for medium-pressure chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of Santiago de Compostela.

3,4-Dicyano-6-ethoxy-2-mercapto-5-phenylpyridine (**2**).

A mixture of **1** (1 g, 3.5 mmoles) and anhydrous sodium sulfide (0.9 g, 0.011 mole) in ethanol (25 ml) was refluxed for 3 hours. The solvent was removed *in vacuo* and water (75 ml) was added. Acidification (*p*H 4) of the solution with 1*N* hydrochloric acid deposited the solid, which was recrystallized from hexane/dichloromethane to yield **2** (0.79 g, 80%), mp 161-163°; ir: ν 2490 (SH), 2220 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.48 (t, 3H, CH_3), 4.57 (q, 2H, CH_2O), 4.89 (br s, 1H, SH), 6.32 (br s, 1H, NH), 7.49-7.58 (m, 5H, arom); ^{13}C nmr (deuteriochloroform): δ 14.08 (CH_3), 65.32 (CH_2O), 113.17 (CN), 115.22 (CN); ms: m/z 281 (M$^+$, 53), 253 (100), 225 (34), 197 (25), 165 (50).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.18; H, 3.77; N, 14.76.

Bis(3,4-dicyano-6-ethoxy-5-phenyl-2-pyridyl) Sulfide (**3**).

A solution of **1** (0.3 g, 1 mmole) and thiourea (0.15 g, 2 mmoles) in ethanol (20 ml) was refluxed for 10 hours. After cooling, the precipitate was filtered and recrystallized from ethanol/acetone to obtain **3** (0.23 g, 82%), mp 200-202°; ir: ν 2220 (CN), 2210 (CN), 1580 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.27 (t, 3H, CH_3), 4.37 (q, 2H, CH_2O), 7.85 (s, 5H, arom); ^{13}C nmr (deuteriochloroform): δ 14.72 (CH_3), 66.24 (CH_2O), 113.33 (CN), 114.50 (CN); ms: m/z 528 (M$^+$, 10), 499 (22), 471 (25), 165 (100).

Anal. Calcd. for $C_{30}H_{20}N_6O_2S$: C, 68.17; H, 3.81; N, 15.90. Found: C, 68.27; H, 3.68; N, 16.13.

3-Amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*d*]pyridine-2-carboxamide (**4**).

Method A.

To a solution of **3** (10 g, 0.042 mole) in dimethylformamide (90 ml) was added 2.5 *N* potassium hydroxide (63 ml) dropwise and

the solution was stirred for 1 hour. Chloroacetamide (4.04 g, 0.043 mole) was then added in several portions and the reaction mixture was stirred at room temperature for 12 hours. The precipitate obtained was filtered and chromatographed. Elution with 1% ethanol in dichloromethane yielded **4** (4.60 g, 72%), mp 237-239°; ir: ν 3480 (NH), 3350 (NH), 2220 (CN), 1650 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.40 (t, 3H, CH_3), 4.53 (q, 2H, CH_2O), 5.66 (br s, 2H, NH_2, exchangeable with deuterium oxide), 7.21 (br s, 2H, NH_2, exchangeable with deuterium oxide), 7.51-7.64 (m, 5H, arom); ^{13}C nmr (DMSO-d_6): δ 14.11 (CH_3), 63.83 (CH_2O), 114.38 (CN), 166.43 (CO); ms: m/z 338 (M^+, 100), 320 (37), 292 (16), 264 (20), 236 (7).

Anal. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.21; H, 4.33; N, 16.49.

Method B.

A mixture of **2** (0.21 g, 0.74 mmole), chloroacetamide (0.073 g, 0.78 mmole) and potassium carbonate (0.31 g, 2.24 mmoles) was refluxed in ethanol (10 ml) for 3 hours. The solvent was removed *in vacuo* and water (20 ml) was added. The solid was recrystallized from ethanol/acetone to yield **4** (0.18 g, 70%).

8-Cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **5a-o**.

General Procedure.

To a solution of 0.6 mmole of 3-aminothieno[2,3-*d*]pyridine-2-carboxamide **4** and 0.65 mmole of the appropriate aldehyde in toluene (25 ml) was added a catalytic amount of *p*-toluenesulfonic acid. The solution was refluxed for 2 hours while the water formed was continously removed by means of a Dean-Stark trap. The desired product was isolated by suction and recrystallized from a suitable solvent or purified by medium-pressure chromatography (Tables 1 and 2).

8-Cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-3,4-dihydropyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidines **6a-m**.

General Procedure.

A solution of 0.87 mmole of the appropriate pyrimidone **5** and 0.96 mmole of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in tetrahydrofuran (10 ml) was refluxed for 3 hours. After cooling, the precipitate obtained was filtered off. The crude solid was used in the next step without further purification (Table 3).

4-Chloro-8-cyano-7-ethoxy-9-phenyl-2-substituted-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **7a-j**.

General Procedure.

A stirred solution of 0.73 mmole of the corresponding pyrimidone **6** and 1.09 mmoles of phosphorus pentachloride in phosphorus oxychloride (5 ml) was refluxed for 15 hours. Then, the reaction mixture was cooled and evaporated *in vacuo*, and water (10 ml) was added. The resulting solid was filtered off and recrystallized from a suitable solvent or purified by medium-pressure chromatography (Table 4).

8-Cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenyl-4-substituted-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **8-12**.

General Procedure.

A solution of 0.40 mmole of 4-chloro-8-cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenyl[3',2':4,5]thieno[3,2-*d*]pyrimidine **7b** and 0.44 mmole of the appropriate amine in ethanol (7 ml) was refluxed for 3 hours. The solid was filtered off and recrystallized from ethanol/dichloromethane (Table 4).

8-Cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenyl-4-substituted-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **13,14**.

General Procedure.

A mixture of 0.21 mmole of 4-chloro-8-cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **7b** and the appropriate amine (1 ml) was stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the solid was then recrystallized from ethanol/acetone (Table 4).

8-Cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenyl-4-substituted-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **15,16**.

General Procedure.

A mixture of 0.21 mmole of 4-chloro-8-cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **7b** and the appropriate amine (1 ml) was stirred at room temperature for 30 minutes. The reaction mixture was poured into water (8 ml) and the solid was recrystallized from ethanol/acetone (Table 4).

8-Cyano-4,7-diethoxy-2-(2'-nitrophenyl)-9-phenylpyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidine (**17**).

To a solution of sodium ethoxide (0.07 g of sodium, 3 mmoles) in ethanol (7 ml) was added **7b** (0.2 g, 0.41 mmole). The reaction was refluxed for 6.5 hours. The solid was filtered off and recrystallized from ethanol/acetone to obtain **17** (Table 4).

4-Azido-8-cyano-7-ethoxy-2-(2'-nitrophenyl)-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**18**).

Method A.

To an ice-cooled solution of **12** (0.10 g, 0.21 mmole) in acetic acid (4 ml) a solution of sodium nitrite (0.04 g, 0.58 mmole) in concentrated sulphuric acid (0.3 ml) was added dropwise. The mixture was stirred in an ice-cooled bath for 1 hour and at room temperature for 5 hours. The mixture was then poured into water (20 ml), filtered off and recrystallized from ethanol/acetone to yield **18** (0.07 g, 68%) (Table 4).

Method B.

To a suspension of **7b** (0.10 g, 0.21 mmole) in dimethyl sulfoxide (2 ml) was added sodium azide (0.04 g, 0.61 mmole) in water (0.3 ml). The reaction mixture was stirred at room temperature for 12 hours and water (7 ml) was then added. The solid was finally filtered off and recrystallized from ethanol/acetone to yield **18** (0.08 g, 80%) (Table 4).

8-Cyano-9-ethoxy-5-(2'-nitrophenyl)-7-phenylpyrido[3',2':4,5]-thieno[2,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidine (**19**).

Method A.

A solution of **12** (0.16 g, 0.33 mmole) in formic acid (5 ml) was refluxed for 18 hours. The solvent was then removed *in vacuo* and water (10 ml) was added. The solid was purified by medium-pressure chromatography, elution with 1% ethanol in dichloromethane yielded **19** (0.13 g, 86%) (Table 4).

Method B.

A mixture of **12** (0.10 g, 0.20 mmole) and a catalytic amount of *p*-toluensulfonic acid in triethyl orthoformate (2 ml) was refluxed for 10 hours. The solvent was removed *in vacuo* and the solid was recrystallized from ethanol/dimethylsulfoxide to obtain **19** (0.06 g, 60%) (Table 4).

8-Cyano-7-ethoxy-4-ethoxycarbonylhydrazino-2-(2'-nitrophenyl)-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**20**).

To a solution of **12** (0.16 g, 0.33 mmole) in tetrahydrofuran (4 ml) was added ethyl chloroformate (0.04 g, 0.36 mmole). The reaction mixture was stirred at room temperature for 1.5 hours. The solvent was then removed *in vacuo* and the residue was chromatographed. Elution with 1% ethanol in dichloromethane yielded **20** (0.11 g, 60%) (Table 4).

8-Cyano-7-ethoxy-4-isopropylidenehydrazino-2-(2'-nitrophenyl)-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**21**).

A mixture of **12** (0.20 g, 0.41 mmole) was refluxed in acetone (10 ml) for 45 minutes. The solid was then filtered off and recrystallized from an ethanol/dichloromethane mixture to obtain **21** (0.17 g, 80%) (Table 4).

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