A CONVENIENT METHOD FOR THE SYNTHESIS OF THIOPYRANO[2,3-*d*:6,5-*d'*]DIPYRIMIDINE DERIVATIVES

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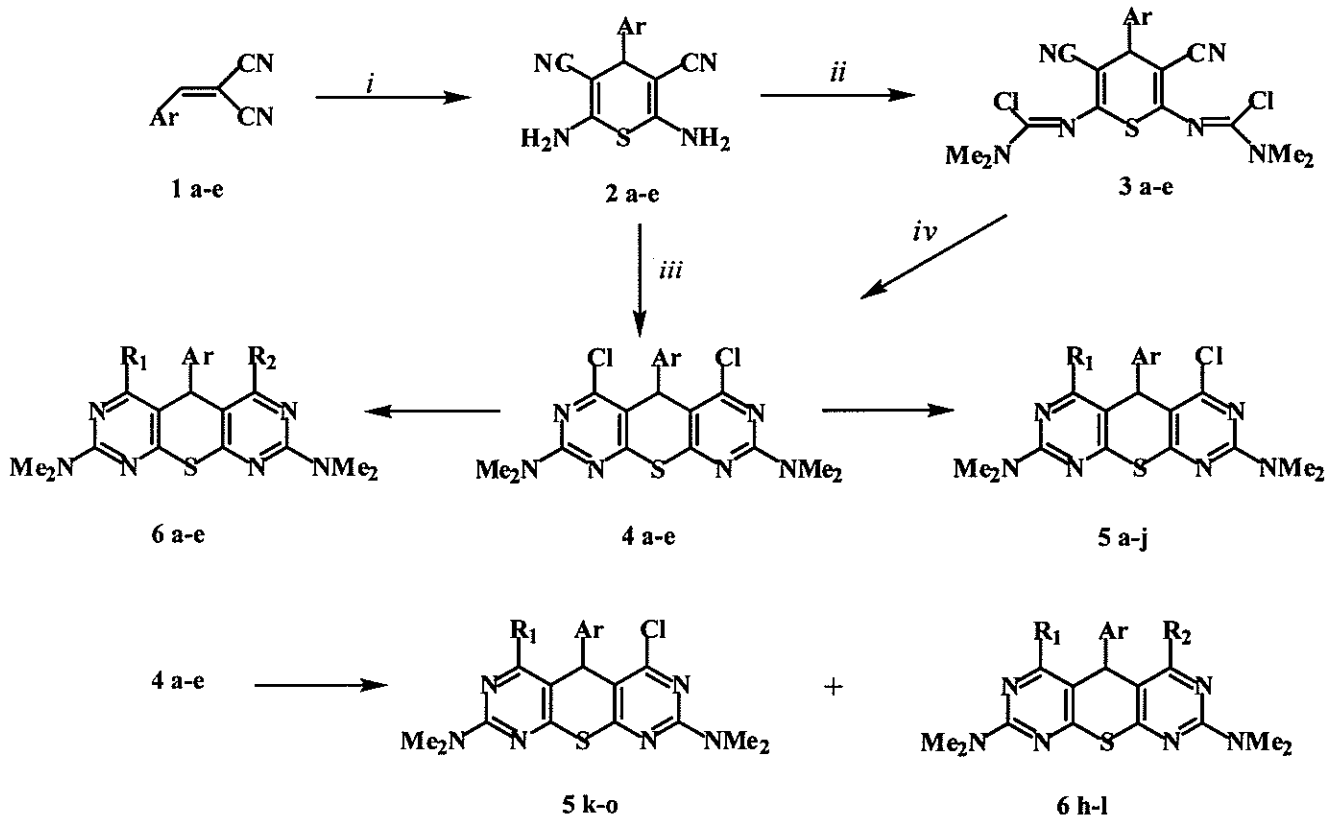
Abstract- A convenient and efficient one-pot synthesis of thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidine derivatives has been developed. The first solid-state structure elucidation of triheterocyclic system is also reported.

Heterocyclic β-enamino nitriles are useful synthetic intermediates for the preparation of heterocyclic systems having potential biological activity.[1] The chemical reactivity of cyclic β–enamino nitriles has been well explored.[2] However, it has been hardly reported, comparatively, the chemistry of six-membered cyclic enamino nitriles.

Nitrogen-containing heterocycles bearing amino substituents are of broad pharmaceutical interest and this justifies continuing efforts in the development of structure-activity relationship of new compounds in this series and of new synthetic strategies.[3] There is a continuous widespread interest in the synthesis of pyranopyrimidines because of the diverse physiological activities associated with this system.[4] Whereas a high number of methods for the preparation of these compounds have been developed,[5] surprisingly the synthesis of thiopyranopyrimidines was less documented: to our knowledge, only one preparation of the tricyclic thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidine system has been described briefly.[6]

Phosgeniminium salts are valuable synthons for heterocyclic synthesis and have proved to be very useful one carbon atom reagents, condensing with many types of nucleophiles and having, due to the presence in their molecule of three mobile chlorine atoms, greater synthetic potential than corresponding Vilmeier-Haack, Arnold and Mannich reagents.[7] Dichloromethyleniminium salts condense readily with CH-acidic compounds such as ketones, carboxylic acids and chlorides, nitriles and amides to give new electrophilic synthons such as chloromethyleniminium chlorides, α–chloroenamines, 1,3-dichlorotrimethinecyanines, etc, able to react further with nucleophiles and to produce, through either inter- or intramolecular processes, various types of functionalized 5-, 6- and 7-membered ring systems.[8]

In connection with our ongoing interest in exploring new synthetic routes for the formation of heterocyclic compounds deriving from β–enamino nitriles[9] we now report an easy and convenient method to reach thiopyranodipyrimidine derivatives (**4**) by treatment of six-membered cyclic enamino nitriles (**2a-e**) with phosgeniminium chloride under mild conditions.



Reagents and reactions conditions: *i)* $NCCH_2CSNH_2$, EtOH, rt. *ii)* $Cl_2CN^+Me_2Cl^-$, THF, rt, 2 h. *iii)* 1. $Cl_2CN^+Me_2Cl^-$, THF, rt, 2 h. 2. $HCl_{(g)}$, rt. *iv)* $HCl_{(g)}$, rt.

1-4	Ar	5	Ar	R_1	6	Ar	R_1	R_2
a	C_6H_5	a	C_6H_5	piperidino	a	C_6H_5	OEt	OEt
b	4-ClC_6H_4	b	C_6H_5	4-piperonylpiperazino	b	4-ClC_6H_4	OEt	OEt
c	4-$NO_2C_6H_4$	c	4-ClC_6H_4	piperidino	c	4-$NO_2C_6H_4$	OEt	OEt
d	3,4-$CH_2O_2C_6H_3$	d	4-ClC_6H_4	4-piperonylpiperazino	d	3,4-$CH_2O_2C_6H_3$	OEt	OEt
e	4-MeC_6H_4	e	4-$NO_2C_6H_4$	piperidino	e	4-MeC_6H_4	OEt	OEt
		f	4-$NO_2C_6H_4$	4-piperonylpiperazino	f	C_6H_5	4-piperonylpiperazino	OEt
		g	3,4-$CH_2O_2C_6H_3$	piperidino	g	4-ClC_6H_4	4-piperonylpiperazino	OEt
		h	3,4-$CH_2O_2C_6H_3$	4-piperonylpiperazino	h	C_6H_5	propylamino	propylamino
		i	4-MeC_6H_4	piperidino	i	4-ClC_6H_4	propylamino	propylamino
		j	4-MeC_6H_4	4-piperonylpiperazino	j	4-$NO_2C_6H_4$	propylamino	propylamino
		k	C_6H_5	propylamino	k	3,4-$CH_2O_2C_6H_3$	propylamino	propylamino
		l	4-ClC_6H_4	propylamino	l	4-MeC_6H_4	propylamino	propylamino
		m	4-$NO_2C_6H_4$	propylamino				
		n	3,4-$CH_2O_2C_6H_3$	propylamino				
		o	4-MeC_6H_4	propylamino				

Scheme 1

The 2,6-diamino-4-aryl-3,5-dicyano-4*H*-thiopyrans (**2a-e**) used in this study were prepared *via* reaction the arylidenemalononitriles (**1a-e**) with 2-cyanothioacetamide by a previously reported method.[10] On treatment

with dichloromethylene-dimethylammonium chloride in THF at room temperature the enamino nitrile derivatives (**2**) afforded a mixture of the amide halide intermediates (**3**) and the thiopyranodipyrimidines (**4**), which were isolated by concentration of the reaction mixture and purified by flash chromatography. Intermediates (**3**) underwent cyclization to the corresponding fused heterocyclic compounds (**4**) *via* reaction with dry hydrogen chloride.

One-pot synthesis using **2** and phosgeniminium salt in THF at room temperature and subsequent treatment with hydrogen chloride provided the substituted thiopyranodipyrimidines (**4a-e**). The structure of compounds (**3**) and (**4**) was consistent with their elemental analyses and spectral data. The MS showed the expected molecular ion peak and the IR spectra of **3** exhibited an absorption band at ν = 1620-1640 cm^{-1} due to the imino group and presented a characteristic signal at ν = 2200-2240 cm^{-1}, while the decoupled ^{13}C NMR spectra showed one signal at δ = 116.6-117.0 ppm due to the carbon atom in the cyano groups. Nevertheless, spectra of compounds (**4a-e**) did not include those types of signals. The most salient features of the ^{1}H NMR and ^{13}C NMR spectra are summarized under Experimental. The constitution of these products was confirmed by a X-Ray crystal structure elucidation of **4a** (Figure 1; see Table 1).

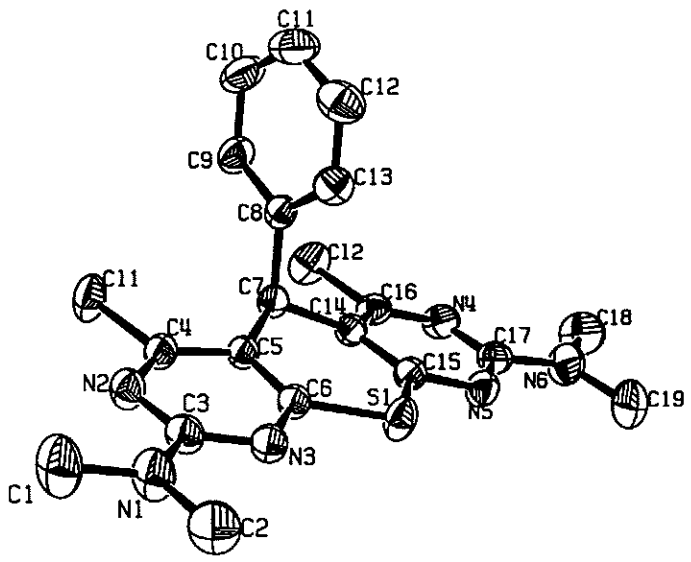


Figure 1. ORTEP diagram of compound (**4a**) showing the numbering scheme used in the crystallographic study.

The results also revealed a nearly coplanar disposition for the three heterocyclic rings of the thiopyranodipyrimidine system (Figure 2).

Table 1. Selected Bonds (Å) and Angles (deg) for Compound **(4a)**.

	Length (Å)		Angle (deg)
C(5)-C(7)	1.519 (2)	C(5)-C(6)-S(1)	124.18 (12)
C(7)-C(14)	1.515 (2)	C(14)-C(15)-S(1)	124.05 (13)
S(1)-C(6)	1.754 (2)	C(15)-C(14)-C(7)	125.38 (14)
S(1)-C(15)	1.753 (2)	C(6)-C(5)-C(7)	125.20 (14)
C(5)-C(6)	1.396 (2)	C(14)-C(7)-C(5)	113.46 (13)
C(14)-C(15)	1.396 (2)	N(5)-C(15)-S(1)	110.83 (13)

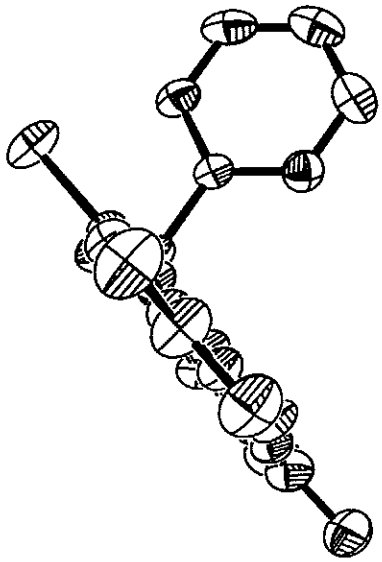
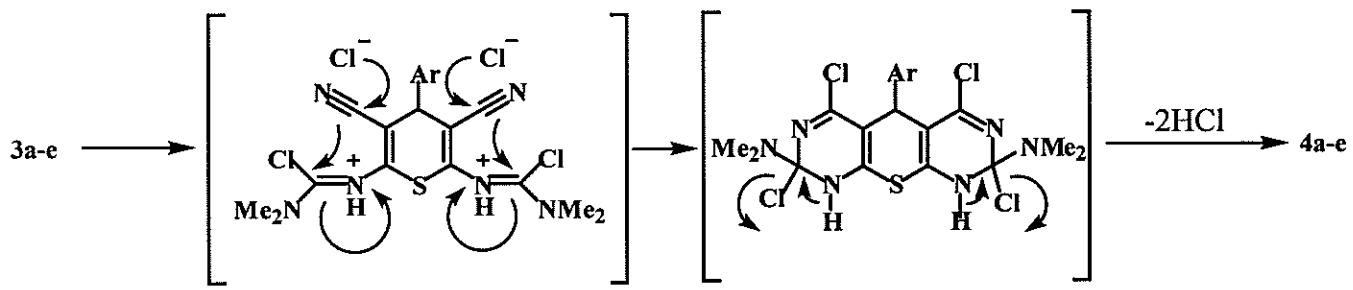


Figure 2

Since the intermediate adducts **(3)** were isolated, the reaction can be assumed to proceed as outlined in Scheme 2.[11]



Scheme 2

Nucleophilic displacement reaction of the chloride bearing group in the tricyclic compounds (**4a-e**) resulted in the formation on the corresponding substituted products (**5**) and (**6**) in good yields. Compounds (**5**) and (**6**) were characterized from microanalytical and spectral data.

In conclusion, we have discovered a new facile and general synthesis for substituted thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidine derivatives from *o*-aminocyanothiopyrans and dichloromethylene-dimethylammonium chloride. This synthetic approach would appear to have application in view of the pharmacological interest in this class of compounds.

EXPERIMENTAL

All reagents used were comercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. IR spectra were recorded on potassium bromide disks on a Perkin-Elmer 783 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC200F instrument at room temperature. MS were obtained on a VG-QUATTRO spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for flash chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

2,6-Diamino-4-aryl-3,5-dicyano-4*H*-thiopyrans (2a-e):

Compounds (**2a**) and (**2b**) were prepared and isolated similarly to the reported procedure.[12] Thiopyran derivatives (**2c-e**) were obtained by a similar preparation from the appropriate arylidenemalononitrile and 2-cyanothioacetamide.

2,6-Diamino-3,5-dicyano-4-(4-nitrophenyl)-4H-thiopyran (2c) (60%); mp 202-204 °C (EtOH). IR (KBr): 3480 (NH), 3350 (NH), 2200 (CN), 1640, 1590. ^{1}H NMR δ (DMSO-*d6*): 4.51 (s, 1H, H-4), 7.09 (s, 4H, NH_2), 7.50, 8.23 (AA'XX' system, 4H, J = 8.7 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ (DMSO-*d6*): 42.8 (C-4), 70.7 (C-3, C-5), 118.6 (CN), 124.2, 128.1, 146.8, 151.0 ($C_6H_4NO_2$), 152.1 (C-2, C-6) ppm. MS (EI, *m/z*, %): 299 (M^+, 15), 126 (58), 66 (100). *Anal.* Calcd for $C_{13}H_9N_5O_2S$: C, 52.17; H, 3.03; N, 23.40. Found C, 52.05; H, 3.15; N, 23.48.

2,6-Diamino-3,5-dicyano-4-(3,4-methylenedioxyphenyl)-4H-thiopyran (2d) (75%); mp 161-163 °C (EtOH). IR (KBr): 3460 (NH), 3320 (NH), 2200 (CN), 1640, 1360. ^{1}H NMR δ (DMSO-*d6*): 4.19 (s, 1H, H-4); 5.98 (s, 2H, OCH_2O), 6.70-7.00 (m, 7H, J = 8.7 Hz, $C_6\underline{H}_3CH_2O_2$, NH_2) ppm. ^{13}C NMR δ (DMSO-*d6*): 43.0 (C-4), 72.3 (C-3, C-5), 101.1 (OCH_2O), 106.9, 108.3 (C-2', C-5'), 119.0 (CN), 120.0 (C-6'), 137.6 (C-1'), 146.5, 147.7 (C-3', C-4'), 150.9 (C-2, C-6) ppm. MS (EI, *m/z*, %): 298 (M^+, 12), 197 (100), 66 (51). *Anal.* Calcd for $C_{14}H_{10}N_4O_2S$: C, 56.37; H, 3.38; N, 18.78. Found C, 56.50; H, 3.18; N, 18.63.

2,6-Diamino-3,5-dicyano-4-(p-tolyl)-4H-thiopyran (2e) (50%); mp 140-142 °C (EtOH). IR (KBr): 3440 (NH), 3320 (NH), 2200 (CN), 1650, 1620. ^{1}H NMR δ (DMSO-*d6*): 2.26 (s, 3H, CH_3), 4.21 (s, 1H, H-4), 6.90 (s, 4H, 2 NH_2), 7.08-7.17 (m, 4H, $C_6\underline{H}_4CH_3$) ppm. ^{13}C NMR δ (DMSO-*d6*): 20.7 (CH_3), 43.1 (C-4), 72.3 (C-3, C-5), 119.0 (CN), 126.6, 129.3, 136.4, 140.5 ($\underline{C}_6H_4CH_3$), 151.1 (C-2, C-6) ppm. MS (EI,

m/z, %): 268 (M^+, 36), 177 (100). *Anal.* Calcd for $C_{14}H_{12}N_4S$: C, 62.66; H, 4.50; N, 20.88. Found C, 62.82; H, 4.22; N, 21.03.

4-Aryl-3,5-dicyano-2,6-bis(chlorodimethylaminomethylenamino)thiopyran (3a-e). General Procedure.

A solution of **2** (3.5 mmol) and phosgene iminium salt (10 mmol) in THF (20 mL) was stirred at rt for 2 h. The solvent was removed under reduced pressure and the resulting solid was purified by flash chromatography using the appropiate solvent as eluent to obtain **3**.

3,5-Dicyano-2,6-bis(chlorodimethylaminomethylenamino)-4-phenyl-4H-thiopyran (3a) (60%). Purified using dichloromethane as eluent; mp 190-192 °C (EtOH). IR (KBr): 2220 (CN), 1620, 1440. ^{1}H NMR δ ($CDCl_3$): 3.17 (s, 12H, NMe_2), 4.54 (s, 1H, H-4), 7.29-7.44 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ ($CDCl_3$): 40.4 (NMe_2), 46.7 (C-4), 92.1 (C-3, C-5), 117.0 (CN), 127.6, 128.1, 128.9, 140.3 (C_6H_5), 142.7 (C=N); 153.8 (C-2, C-6) ppm. MS (EI, *m/z*, %): 434 (M^++2, 19), 432 (M^+, 27), 76 (100). *Anal.* Calcd for $C_{19}H_{18}N_6Cl_2S$: C, 52.66 H, 4.18; N, 19.39. Found C, 52.46; H, 4.44; N, 19.52.

3,5-Dicyano-2,6-bis(chlorodimethylaminomethylenamino)-4-(4-chlorophenyl)-4H-thiopyran (3b) (46%). Purified using dichloromethane/hexanes (10:1) as eluent; mp 150-152 °C (EtOH). IR (KBr): 2220 (CN), 1620, 1480, 1440. ^{1}H NMR δ ($CDCl_3$): 3.16 (s, 12H, NMe_2), 4.54 (s, 1H, H-4), 7.32-7.43 (m, 4H, C_6H_4Cl) ppm. ^{13}C NMR δ ($CDCl_3$): 40.4 (NMe_2), 46.1 (C-4), 91.5 (C-3, C-5), 116.8 (CN), 129.0, 129.1, 133.9, 138.9 (C_6H_4Cl), 142.7 (C=N), 154.1 (C-2, C-6) ppm. MS (EI, *m/z*, %): 470 (M^++4, 6), 468 (M^++2, 8), 466 (M^+, 17), 149 (52), 76 (100). Anal. Calcd for $C_{19}H_{17}N_6Cl_3S$: C, 48.78 H, 3.66; N, 17.96. Found C, 48.92; H, 3.46; N, 18.18.

3,5-Dicyano-2,6-bis(chlorodimethylaminomethylenamino)-4-(4-nitrophenyl)-4H-thiopyran (3c) (46%). Purified using dichloromethane/hexanes (4:1) as eluent; mp 148-150 °C (EtOH). IR (KBr): 2240 (CN), 1640, 1540, 1360. ^{1}H NMR δ ($CDCl_3$): 3.17 (s, 12H, NMe_2), 4.69 (s, 1H, H-4), 7.63, 8.24 (AA'XX' system , 4H, J = 8.8 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 40.4 (NMe_2), 46.3 (C-4), 90.4 (C-3, C-5), 116.6 (CN), 124.2, 128.5, 147.1, 147.6 ($C_6H_4NO_2$), 142.7 (C=N), 155.1 (C-2, C-6) ppm. MS (EI, *m/z*, %): 481 (M^++4, 8), 479 (M^++2, 40), 477 (M^+, 54), 76 (100). *Anal.* Calcd for $C_{19}H_{17}N_7O_2Cl_2S$: C, 47.69; H, 3.55; N, 20.50. Found C, 47.57; H, 3.72; N, 20.23.

3,5-Dicyano-2,6-bis(chlorodimethylaminomethylenamino)-4-(3,4-methylenedioxyphenyl)-4H-thiopyran (3d) (72%). Purified using dichloromethane as eluent; mp 228-230 °C (EtOH). IR (KBr): 2220 (CN), 1630, 1500, 1450. ^{1}H NMR δ ($CDCl_3$): 3.17 (s, 12H, NMe_2), 4.45 (s, 1H, H-4), 5.96 (s, 2H, OCH_2O), 6.74-6.96 (m, 3H, $C_6\underline{H}_3O_2CH_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 40.4 (NMe_2), 46.5 (C-4), 92.2 (C-3, C-5), 108.1, 108.4 (C-2', C-5'), 101.1 (OCH_2O), 117.0 (CN), 134.6 (C-1'), 142.7 (C=N), 147.5, 148.2 (C-3', C-4'), 153.4 (C-2, C-6) ppm. MS (EI, *m/z*, %): 480 (M^++4, 6), 478 (M^++2, 22), 476 (M^+, 31), 76 (100). *Anal.* Calcd for $C_{20}H_{18}N_6O_2Cl_2S$: C, 50.32; H, 3.80; N, 17.60. Found C, 50.46; H, 3.62; N, 17.74.

3,5-Dicyano-2,6-bis(chlorodimethylaminomethylenamino)-4-(p-tolyl)-4H-thiopyran (3e) (40%). Purified using dichloromethane as eluent; mp 165-167 °C (EtOH). IR (KBr): 2220 (CN), 1620, 1440. ^{1}H NMR δ ($CDCl_3$): 2.34 (s, 3H, CH_3), 3.17 (s, 12H, NMe_2), 4.53 (s, 1H, H-4), 7.16-7.36 (m, 4H, $C_6\underline{H}_4CH_3$) ppm. ^{13}C NMR δ ($CDCl_3$): 21.1 (CH_3), 40.3 (NMe_2), 46.3 (C-4), 92.2 (C-3, C-5), 117.0 (CN), 127.5, 129.6, 137.5, 137.7 ($\underline{C}_6H_4CH_3$), 142.6 (C=N), 153.4 (C-2, C-6) ppm. MS (EI, *m/z*, %): 450 (M^++4, 5), 448

(M^++2, 24), 446 (M^+, 36), 149 (84), 76 (100). *Anal.* Calcd for $C_{20}H_{20}N_6Cl_2S$: C, 53.69; H, 4.47; N, 18.79. Found C, 53.92; H, 4.32; N, 18.92.

5-Aryl-4,6-dichloro-2,8-bis(dimethylamino)-5*H*-thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidine (4a-e).

General Procedure.

Method A:

A solution of **2** (3.5 mmol) and phosgene iminium salt (10 mmol) in THF (20 mL) was stirred at rt for 2 h. A stream of dry hydrogen chloride was passed through the mixture for 1 h and the reaction mixture was allowed to stand overnight at rt. The solvent was then removed under reduced pressure and the resulting solid was purified by flash chromatography using CH_2Cl_2/hexanes (1:1) as eluent to obtain **4**.

4,6-Dichloro-2,8-bis(dimethylamino)-5-phenyl-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(4a)*** (94%); mp 278-280 °C (EtOH). IR (KBr): 1580, 1500, 1400. ^{1}H NMR δ ($CDCl_3$): 3.15 (s, 12H, NMe_2), 5.75 (s, 1H, H-5), 7.18-7.24 (m, 3H, C_6H_5), 7.40-7.45 (m, 2H, C_6H_5) ppm. ^{13}C NMR δ ($CDCl_3$): 37.0 (NMe_2), 42.5 (C-5), 113.3 (C-4a, C-5a), 127.2, 127.6, 128.4, 141.8 (C_6H_5), 159.0, 159.5, 165.1 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 434 (M^++2, 4), 432 (M^+, 17), 355 (100). *Anal.* Calcd for $C_{19}H_{18}N_6Cl_2S$: C, 52.66; H, 4.18; N, 19.39. Found C, 52.80; H, 4.02; N, 19.63.

4,6-Dichloro-2,8-bis(dimethylamino)-5-(4-chlorophenyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(4b)*** (95%); mp 300-302 °C (EtOH). IR (KBr): 1580, 1500, 1400. ^{1}H NMR δ ($CDCl_3$): 3.16 (s, 12H, NMe_2), 5.70 (s, 1H, H-5), 7.17-7.38 (m, 4H, C_6H_4Cl) ppm. ^{13}C NMR δ ($CDCl_3$): 37.0 (NMe_2), 42.0 (C-5), 112.9 (C-4a, C-5a), 128.6, 129.0, 133.0, 140.3 (C_6H_4Cl), 159.0, 159.5, 165.0 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 470 (M^++2, 4), 468 (M^+, 16), 355 (100). *Anal.* Calcd for $C_{19}H_{17}N_6Cl_3S$: C, 48.78; H, 3.66; N, 17.95. Found C, 48.86; H, 3.48; N, 18.18.

4,6-Dichloro-2,8-bis(dimethylamino)-5-(4-nitrophenyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(4c)*** (65%); mp 260-262 °C (EtOH). IR (KBr): 1580, 1510, 1410. ^{1}H NMR δ ($CDCl_3$): 3.16 (s, 12H, 2 NMe_2), 5.81 (s, 1H, H-5), 7.60, 8.09 (AA'XX' system, 4H, J = 8.8 Hz, C_6H_4Cl) ppm. ^{13}C NMR δ ($CDCl_3$): 37.0 (NMe_2), 42.4 (C-5), 111.8 (C-4a, C-5a), 123.7, 128.6, 146.8, 149.0 ($\underline{C}_6H_5NO_2$), 159.0, 159.5, 165.1 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 479 (M^++2, 4), 477 (M^+, 17), 355 (100). *Anal.* Calcd for $C_{19}H_{17}N_7O_2Cl_2S$: C, 47.69; H, 3.55; N, 20.50. Found C, 47.81; H, 3.40; N, 20.68.

4,6-Dichloro-2,8-bis(dimethylamino)-5-(3,4-methylenedioxyphenyl)-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(4d)*** (97%); mp 274-276 °C (EtOH). IR (KBr): 1580, 1510, 1420. ^{1}H NMR δ ($CDCl_3$): 3.15 (s, 12H, NMe_2), 5.66 (s, 1H, H-5), 5.88 (s, 2H, OCH_2O), 6.64-6.93 (m, 3H, $C_6\underline{H}_3CH_2O_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 37.0 (NMe_2), 42.0 (C-5), 101.0 ($O\underline{C}H_2O$), 107.9, 108.0 (C-2', C-5'), 113.4 (C-4a, C-5a), 121.3 (C-6'), 135.8 (C-1'), 146.6, 147.5 (C-3',C-4'), 153.4 (C-2, C-6), 159.0, 159.5, 165.0 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 478 (M^++2, 10), 476 (M^+, 14), 355 (100). *Anal.* Calcd for $C_{20}H_{18}N_6O_2Cl_2S$: C, 50.32; H, 3.80; N, 17.60. Found C, 50.42; H, 3.62; N, 17.84.

4,6-Dichloro-2,8-bis(dimethylamino)-5-(p-tolyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(4e)*** (60%); mp 293-294 °C (EtOH). IR (KBr): 1590, 1510, 1420. ^{1}H NMR δ ($CDCl_3$): 2.27 (s, 3H, CH_3), 3.15 (s, 12H, NMe_2), 5.72 (s, 1H, H-5), 7.01-7.33 (m, 4H, $C_6\underline{H}_4CH_3$) ppm. ^{13}C NMR δ ($CDCl_3$): 21.0 (CH_3), 37.0 (NMe_2), 42.1 (C-5), 113.6 (C-4a, C-5a), 127.5, 129.1, 136.9, 138.9 ($\underline{C}_6H_4CH_3$), 159.1, 159.5, 165.0 (C-2,

C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 448 (M^++2, 10), 446 (M^+, 14), 355 (100). *Anal.* Calcd for $C_{20}H_{20}N_6Cl_2S$: C, 53.69; H, 4.51; N, 18.78. Found C, 53.83; H, 4.34; N, 18.92.

Method B:

A stream of dry hydrogen chloride was passed through a mixture of **3** (3 mmol) in THF (10 mL) for 1 h. The reaction mixture was allowed to stand overnight at rt. The solvent was then removed under reduced pressure and the resulting solid was recrystallized from EtOH to obtain **4a** (93%), **4b** (60%), **4c** (56%), **4d** (90%), **4e** (40%).

5-Aryl-6-chloro-2,8-bis(dimethylamino)-5*H*-thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidines (5a-j). General Procedure.

A solution of **4** (0.4 mmol) and the appropriate amine (1.6 mmol) in THF (10 mL) was refluxed until all starting material had disappeared as checked by TLC (9-48 h); but the work up for the isolation of the products was dependent on the amine used in the reaction. Thus, compounds **(5c-g)** and **(5j)** precipited from the reaction mixture and were recrystallized from ethanol, while for isolation of **5a, 5b, 5h** and **5i** it was necessary to concentrate the resulting solutions to dryness and the resulting crude products were then purified by flash chromatography.

6-Chloro-2,8-bis(dimethylamino)-5-phenyl-4-piperidino-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5a)***. (68%). Purified using hexanes/dichloromethane (1:1) as eluent; mp 209-210 °C (EtOH). IR (KBr): 1560, 1510, 1410, 1330. ^{1}H NMR δ(CDCl$_3$): 1.70-2.80 (m, 6H, CH_2), 3.15 (s, 6H, NMe_2), 3.18 (s, 6H, NMe_2), 3.22-3.53 (m, 4H, NCH_2), 5.81 (s, 1H, H-5), 7.12-7.25 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ (CDCl$_3$): 24.6, 26.0 (CH_2), 36.6 (NMe_2), 36.9 (NMe_2), 40.1 (C-5), 51.2 (NCH_2), 104.3 (C-4a), 113.7 (C-5a), 126.6, 128.1, 141.5 (C_6H_5), 158.5, 159.1, 159.4, 163.9, 160.0, 166.0 (C-2, C-4, C-6, C-8, C-9a, C-10a). MS (EI, *m/z*, %): 481 (M^+, 22), 404 (100). *Anal.* Calcd for $C_{24}H_{28}N_7ClS$: C, 59.80; H, 5.85; N, 20.34. Found C, 59.94; H, 5.68; N, 20.60.

6-Chloro-2,8-bis(dimethylamino)-5-phenyl-4-(4-piperonylpiperazino)-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(5b)*** (95%). Purified using dichloromethane/EtOH (10:1) as eluent; mp 118-120 °C (EtOH). IR (KBr): 1540, 1490, 1330. ^{1}H NMR δ(CDCl$_3$): 2.57-2.67 (m, 4H, NCH_2), 3.13 (s, 6H, NMe_2), 3.17 (s, 6H, NMe_2), 3.29-3.44 (m, 2H, CH_2), 3.48-3.50 (m, 4H, NCH_2), 5.80 (s, 1H, H-5), 5.95 (s, 2H, OCH_2O), 6.80-6.90 (m, 3H, $C_6H_3O_2CH_2$), 7.15-7.19 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ(CDCl$_3$): 36.7 (NMe_2), 37.0 (NMe_2), 40.1 (C-5), 49.9 (NCH_2), 52.8 (NCH_2), 62.6 (CH_2), 100.8 (OCH_2O), 104.5 (C-4a), 107.8, 109.3 (C-2', C-5'), 113.7 (C-5a), 122.0 (C-6'), 126.7, 128.2, 141.4 (C_6H_5), 135.8 (C-1'), 146.5, 147.6 (C-3',C-4'), 158.4, 159.2, 159.4, 164.0 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 618 (M^++ 2, 4), 616 (M^+, 8), 135 (100). *Anal.* Calcd for $C_{31}H_{33}N_8O_2ClS$: C, 60.33; H, 5.39; N, 18.15. Found C, 60.44; H, 5.28; N, 18.22.

6-Chloro-5-(4-chlorophenyl)-2,8-bis(dimethylamino)-4-piperidino-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(5c)*** (64%); mp 158-160 °C (EtOH). IR (KBr): 1560, 1400, 1320. ^{1}H NMR δ(CDCl$_3$): 1.67-1.85 (m, 6H, CH_2), 3.13 (s, 6H, NMe_2), 3.18 (s, 6H, NMe_2), 3.24-3.36 (m, 4H, NCH_2), 5.71 (s, 1H, H-5), 7.04-7.17 (m, 4H, C_6H_4Cl) ppm. ^{13}C NMR δ (CDCl$_3$): 24.6, 26.0 (CH_2), 36.7 (NMe_2), 37.9 (NMe_2), 39.8 (C-5), 51.3 (NCH_2), 104.0 (C-4a), 113.3 (C-5a), 128.1, 128.3, 132.4, 140.2 (C_6H_4Cl), 158.6, 159.3, 159.6, 163.9, 160.0 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 517 (M^++2, 4), 515 (M^+, 8),

404 (100). *Anal.* Calcd for $C_{24}H_{27}N_7Cl_2S$: C, 55.81; H, 5.27; N, 18.98. Found C, 55.92; H, 5.09; N, 19.21.

6-Chloro-5-(4-chlorophenyl)-2,8-bis(dimethylamino)-4-(4-piperonylpiperazino)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5d)*** (47%); mp 194-196 °C (EtOH). IR (KBr): 1560, 1480, 1400, 1240. ^{1}H NMR δ ($CDCl_3$): 2.55-2.66 (m, 4H, NCH_2), 3.12 (s, 6H, NMe_2), 3.17 (s, 6H, NMe_2), 3.26-3.50 (m, 2H, CH_2), 3.48-3.50 (m, 4H, NCH_2), 5.71 (s, 1H, H-5), 5.95 (s, 2H, OCH_2O), 6.80-6.90 (m, 3H, $C_6H_3O_2CH_2$), 7.08-7.17 (m, 4H, C_6H_4Cl) ppm. ^{13}C NMR δ ($CDCl_3$): 37.3 (NMe_2), 37.6 (NMe_2), 40.2 (C-5), 50.5 (NCH_2), 53.4 (NCH_2), 63.2 (CH_2), 101.4 (OCH_2O), 104.7 (C-4a), 108.4, 109.9 (C-2', C-5'), 113.8 (C-5a), 122.7 (C-6'), 128.6, 128.9, 132.3, 140.0 (C_6H_4Cl), 133.0 (C-1'), 147.0, 148.2 (C-3', C-4'); 159.0, 159.8, 160.1, 164.8, 165.9 (C-2, C-4, C-6, C-8, C-9a, C-10a). MS (EI, *m/z*, %): 650 (M^+, 14); 135 (100). *Anal.* Calcd for $C_{31}H_{32}N_8O_2Cl_2S$: C, 57.14; H, 4.95; N, 17.19. Found C, 57.42; H, 4.79; N, 17.32.

6-Chloro-2,8-bis(dimethylamino)-5-(4-nitrophenyl)-4-piperidino-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(5e)*** (55%); mp 174-176 °C (EtOH). IR (KBr): 1540, 1400, 1370, 1240. ^{1}H NMR δ ($CDCl_3$): 1.25-1.84 (m, 6H, CH_2), 3.13 (s, 6H, NMe_2), 3.19 (s, 6H, NMe_2), 3.23-3.38 (m, 4H, 2 NCH_2), 5.81 (s, 1H, H-5), 7.30, 8.04 (AA'XX' system, 4H, J = 9.0 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 24.6 (CH_2), 26.0 (CH_2), 36.7 (NMe_2), 37.1 (NMe_2), 40.4 (C-5), 51.4 (CH_2), 103.0 (C-4a), 112.4 (C-5a); 123.6, 127.5, 146.7, 149.2 ($C_6H_4NO_2$), 158.7, 159.4, 159.7, 164.0, 166.0, 168.1 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 528 (M^++2, 10), 526 (M^+, 23), 404 (100). *Anal.* Calcd for $C_{24}H_{27}N_8O_2ClS$: C, 54.69; H, 5.16; N, 21.26. Found C, 54.80; H, 5.02 ; N, 21.38.

6-Chloro-2,8-bis(dimethylamino)-5-(4-nitrophenyl)-4-(4-piperonylpiperazino)-5H-thiopyrano[2,3-d:6,5d']dipyrimidine ***(5f)*** (22%); mp 170-172 °C (EtOH). IR (KBr): 1560, 1400, 1340, 1240. ^{1}H NMR δ ($CDCl_3$): 2.57-2.68 (m, 4H, 2 NCH_2), 3.12-3.50 (m, 18H, NMe_2, NCH_2, CH_2), 5.81 (s, 1H, H-5), 5.96 (s, 2H, OCH_2O), 6.80-6.90 (m, 3H, $C_6\underline{H}_3O_2CH_2$), 7.29, 8.05 (AA'XX' system, 4H, J = 8.7 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 36.8 (NMe_2), 37.1 (NMe_2), 40.3 (C-5), 50.1 (NCH_2), 52.8 (NCH_2), 62.7 (CH_2), 100.9 (OCH_2O), 103.4 (C-4a), 107.9, 109.4 (C-2', C-5'), 112.2 (C-5a), 122.0 (C-6'), 123.6, 127.6, 146.7 ($C_6H_4NO_2$), 147.7 (C-3', C-4'), 149.1, 159.6, 165.5 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 661 (M^+, 4); 135 (100). *Anal.* Calcd for $C_{31}H_{32}N_9O_4ClS$: C, 56.23; H, 4.87; N, 19.04. Found C, 56.02; H, 4.64; N, 18.86.

6-Chloro-2,8-bis(dimethylamino)-5-(3,4-methylenedioxyphenyl)-4-piperidino-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5g)*** (73%); mp 211-213 °C (EtOH). IR (KBr): 1560, 1480, 1340, 1240. ^{1}H NMR δ ($CDCl_3$): 1.70-1.82 (m, 6H, CH_2), 3.13 (s, 6H, NMe_2), 3.17 (s, 6H, NMe_2), 3.27-3.30 (m, 4H, NCH_2), 5.67 (s, 1H, H-5), 5.87 (s, 2H, OCH_2O), 6.52-6.69 (m, 3H, $C_6\underline{H}_3O_2CH_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 24.7 (CH_2), 26.0 (CH_2), 36.7 (NMe_2), 37.0 (NMe_2), 40.0 (C-5), 51.4 (CH_2), 100.8 (OCH_2O), 104.5 (C-4a), 107.5, 107.8 (C-2', C-5'), 113.8 (C-5a), 119.6 (C-6'), 135.6 (C-1'), 146.2, 147.5 (C-3', C-4'), 158.5, 159.2, 159.6, 163.9, 165.9, 168.1 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 525 (M^+, 26), 404 (100). *Anal.* Calcd for $C_{25}H_{28}N_7O_2ClS$: C, 57.08; H, 5.36; N, 18.64. Found C, 57.32; H, 5.28; N, 18.72.

6-Chloro-2,8-bis(dimethylamino)-4-(4-piperonylpiperazino)-5-(3,4-methylenedioxyphenyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5h)*** (72%). Purified using dichloromethane/AcOEt (10:1) as eluent;

mp 106-108 °C (EtOH). IR (KBr): 1570, 1420, 1340, 1250. ^{1}H NMR δ(CDCl$_3$): 2.60-2.67 (m, 4H, NCH$_2$), 3.13 (s, 6H, NMe$_2$), 3.16 (s, 6H, NMe$_2$), 3.30-3.49 (m, 6H, NCH$_2$, CH$_2$), 3.47-3.49 (m, 4H, NCH$_2$), 5.71 (s, 1H, H-5), 5.86 (s, 2H, OCH$_2$O), 5.93 (s, 2H, OCH$_2$O), 6.60-6.90 (m, 6H, C$_6$H$_3$O$_2$CH$_2$) ppm. ^{13}C NMR δ (CDCl$_3$): 36.6 (NMe$_2$), 36.9 (NMe$_2$), 39.7 (C-5), 49.8 (NCH$_2$), 53.2 (NCH$_2$), 62.5 (CH$_2$), 100.7 (OCH$_2$O), 104.5 (C-4a), 107.3, 107.7, 109.2 (C-2', C-2", C-5', C-5"), 113.5 (C-5a), 119.5, 122.0 (C-6', C-6"), 131.8, 135.3 (C-1', C-1"), 146.2, 146.4, 147.4, 147.5 (C-3', C-3", C-4', C-4"), 158.3, 159.0, 159.3, 164.1, 165.2, 167.7 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 660 (M$^+$, 5), 135 (100). Anal. Calcd for $C_{32}H_{33}N_8O_4ClS$: C, 58.13; H, 5.03; N, 16.95. Found C, 58.32; H, 4.87; N, 17.18.

6-Chloro-2,8-bis(dimethylamino)-4-piperidino-5-(p-tolyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5i)*** (55%). Purified using dichloromethane as eluent; mp 120-122 °C (EtOH/acetone). IR (KBr): 1560, 1520, 1410, 1330. ^{1}H NMR δ(CDCl$_3$): 1.67-1.82 (m, 6H, CH$_2$), 2.26 (s, 3H, CH$_3$), 3.13 (s, 6H, NMe$_2$), 3.17 (s, 6H, NMe$_2$), 3.26-3.31 (m, 4H, 2NCH$_2$), 5.74 (s, 1H, H-5), 7.00-7.06 (m, 4H, C$_6$H$_4$CH$_3$) ppm. ^{13}C NMR δ(CDCl$_3$): 20.9 (CH$_3$), 24.7, 26.0 (CH$_2$), 36.7, 37.0 (NMe$_2$), 39.9 (C-5), 51.3 (NCH$_2$), 104.6 (C-4a), 114.0 (C-5a), 126.6, 128.9, 136.2, 138.6 (C$_6$H$_4$CH$_3$), 158.5, 159.2, 159.5, 163.9, 165.9, 168.1 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 497 (M$^+$+2, 12), 495 (M$^+$, 30), 404 (100). *Anal.* Calcd for $C_{25}H_{30}N_7ClS$: C, 60.53; H, 6.09; N, 19.76. Found C, 60.64; H, 5.96; N, 19.90.

6-Chloro-2,8-bis(dimethylamino)-4-(4-piperonylpiperazino)-5-(p-tolyl)-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(5j)*** (50%); mp 214-216 °C (EtOH/acetone). IR (KBr): 1540, 1410, 1320, 1250. ^{1}H NMR δ (CDCl$_3$): 2.26 (s, 3H, CH$_3$), 2.55-2.65 (m, 4H, NCH$_2$), 3.13 (s, 6H, NMe$_2$), 3.17 (s, 6H, NMe$_2$), 3.28-3.50 (m, 6H, NCH$_2$, CH$_2$), 5.74 (s, 1H, H-5), 5.95 (s, 2H, OCH$_2$O), 6.77-7.06 (m, 7H, C$_6$H$_4$CH$_3$, C$_6$H$_3$CH$_2$O$_2$) ppm. ^{13}C NMR δ (CDCl$_3$): 21.0 (CH$_3$), 36.7 (NMe$_2$), 37.0 (NMe$_2$), 39.8 (C-5), 49.9 (NCH$_2$), 52.9 (NCH$_2$), 62.7 (CH$_2$), 100.8 (OCH$_2$O), 104.7 (C-4a), 107.8, 109.3 (C-2', C-5'), 113.9 (C-5a), 122.1 (C-6'), 126.6, 128.9, 136.3, 138.4 (C$_6$H$_4$CH$_3$), 132.0 (C-1'), 146.6, 147.6 (C-3', C-4'), 158.4, 159.2, 159.5, 164.3, 165.4, 167.9 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 632 (M$^+$+ 2, 10); 630 (M$^+$, 8), 135 (100). *Anal.* Calcd for $C_{32}H_{35}N_8O_2ClS$: C, 60.89; H, 5.59; N, 17.75. Found C, 60.62; H, 5.48; N, 17.96.

5-Aryl-2,8-bis(dimethylamino)-4,6-diethoxy-5*H*-thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidines 4-substituted; (6a-e). General Procedure.

To a solution of sodium ethoxide (40 mg of Na, 1.6 mmol) in ethanol (10 mL), **4** (0.4 mmol) was added. The resulting solution was heated at reflux until all starting material had disappeared as checked by TLC. Compounds (**6a-d**) precipited from the reaction mixture and were recrystallized from ethanol, while for isolation of compound (**6e**) it was necessary to concentrate the solution to dryness and the resulting solid was then purified by flash chromatography.

2,8-Bis(dimethylamino)-4,6-diethoxy-5-phenyl-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6a)*** (77%); mp 234-236 °C (EtOH/CH$_2$Cl$_2$). IR (KBr): 1580, 1400, 1330. ^{1}H NMR δ (CDCl$_3$): 1.33 (t, 6H, J = 7.1 Hz, CH$_3$), 3.11 (s, 12H, NMe$_2$), 4.31 (q, 4H, J = 7.1 Hz, OCH$_2$), 5.37 (s, 1H, H-5), 7.16-7.45 (m, 5H, C$_6$H$_5$) ppm. ^{13}C NMR δ(CDCl$_3$): 11.3 (CH$_3$), 36.6 (C-5), 36.7 (NMe$_2$), 61.8 (CH$_2$), 103.2 (C-4a, C-5a), 126.0, 127.7, 128.0, 145.4 (C$_6$H$_5$), 159.7, 162.2, 165.5 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %):

452 (M^+, 19), 375 (100). *Anal.* Calcd for $C_{23}H_{28}N_6O_2S$: C, 61.04; H, 6.24; N, 18.57. Found C, 61.23; H, 6.03; N, 18.74.

5-(4-Chlorophenyl)-2,8-bis(dimethylamino)-4,6-diethoxy-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6b)*** (67%); mp 210-211 °C (EtOH). IR (KBr): 1580, 1500, 1400, 1340. ^{1}H NMR δ(CDCl$_3$): 1.33 (t, 6H, J = 7.1 Hz, CH_3), 3.11 (s, 12H, NMe_2), 4.31 (q, 4H, J = 7.1 Hz, OCH_2), 5.32 (s, 1H, H-5), 7.11, 7.32 (AA'XX' system, 4H, J = 8.5 Hz, C_6H_4Cl) ppm. ^{13}C NMR δ (CDCl$_3$): 14.4 (CH_3), 36.2 (C-5), 36.7 (NMe_2), 61.8 (CH_2), 102.6 (C-4a, C-5a), 127.8, 129.4, 131.6, 144.0 (C_6H_4Cl), 159.7, 162.2, 164.5 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 488 (M^++2, 6), 486 (M^+, 18), 375 (100). *Anal.* Calcd for $C_{23}H_{27}N_6O_2SCl$: C, 56.72; H, 5.59; N, 17.25. Found C, 56.84; H, 5.24; N, 17.44.

2,8-Bis(dimethylamino)-4,6-diethoxy-5-(4-nitrophenyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6c)*** (35%); mp 212-214 °C (EtOH). IR (KBr): 1560, 1400, 1380, 1250. ^{1}H NMR δ(CDCl$_3$): 1.32 (t, 6H, J = 7.1 Hz, CH_3), 3.11 (s, 12H, NMe_2), 4.31 (q, 4H, J = 7.1 Hz, OCH_2), 5.40 (s, 1H, H-5), 7.54, 8.03 (AA'XX' system, 4H, J = 8.7 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ(CDCl$_3$): 14.4 (CH_3), 36.7 (C-5), 37.0 (NMe_2), 62.0 (CH_2), 101.6 (C-4a, C-5a), 123.1, 128.8, 146.2, 152.9 ($C_6H_4NO_2$), 159.8, 162.3, 165.5 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 497 (M^+, 18), 375 (100). *Anal.* Calcd for $C_{23}H_{27}N_7O_4S$ for: C, 55.52; H, 5.47; N, 19.70. Found C, 55.69; H, 5.32; N, 19.98.

2,8-Bis(dimethylamino)-4,6-diethoxy-5-(3,4-methylenedioxyphenyl)-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(6d)*** (77%); mp 198-200 °C (EtOH). IR (KBr): 1560, 1400, 1360, 1240. ^{1}H NMR δ(CDCl$_3$): 1.32 (t, 6H, J = 7.1 Hz, CH_3), 3.11 (s, 12H, NMe_2), 4.34 (q, 4H, J = 7.1 Hz, CH_2), 5.32 (s, 1H, H-5), 5.84 (s, 2H, OCH_2O), 6.84-6.93 (m, 3H, $C_6\underline{H}_3CH_2O_2$) ppm. ^{13}C NMR δ(CDCl$_3$): 14.4 (CH_3), 36.1 (C-5), 36.6 (NMe_2), 61.8 (CH_2), 100.0 (OCH_2O), 103.0 (C-4a, C-5a), 107.3, 108.5 (C-2', C-5'), 120.5 (C-6'), 139.4 (C-1'), 145.6, 146.9 (C-3', C-4'), 159.6, 162.1, 165.4 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 496 (M^+, 12), 375 (100). *Anal.* Calcd for $C_{24}H_{28}N_6O_4S$: C, 58.05; H, 5.68; N, 16.92. Found C, 58.18; H, 5.44; N, 17.06.

2,8-Bis(dimethylamino)-4,6-diethoxy-5-(p-tolyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6e)*** (60%). Purified using hexanes/dichloromethane (2:1) as eluent; mp 198-200 °C (EtOH). IR (KBr): 1600, 1560, 1410, 1350, 1250. ^{1}H NMR δ(CDCl$_3$): 1.35 (t, 6H, J = 7.1 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.10 (s, 12H, NMe_2), 4.32 (q, 4H, J = 7.0 Hz, OCH_2), 5.35 (s, 1H, H-5), 6.97, 7.28 (AA'XX' system, 4H, J = 7.8 Hz, $C_6\underline{H}_4CH_3$) ppm. ^{13}C NMR δ(CDCl$_3$): 14.4 (CH_3), 21.0 (CH_3), 36.1 (C-5), 36.7 (NMe_2), 61.7 (CH_2), 103.4 (C-4a, C-5a), 127.7, 128.4, 135.4, 142.4 ($\underline{C}_6H_4CH_3$), 159.6, 162.2, 165.5 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 466 (M^+, 10), 375 (100). *Anal.* Calcd for $C_{24}H_{30}N_6O_2S$: C, 61.78; H, 6.48; N, 18.01. Found C, 61.89; H, 6.32; N, 18.17.

5-Aryl-6-ethoxy-2,8-bis(dimethylamino)-4-(4-piperonylpiperazino)-5*H*-thiopyrano[2,3-*d*:6,5-*d*']-dipyrimidines (6f, g).

To a solution of sodium ethoxide (8 mg of Na, 3.2 mmol) in ethanol (10 mL), **5b** or **5d** (0.4 mmol) was added. The resulting solution was heated at reflux until all starting material had disappeared (4 h).

The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography to obtain **6f, g**.

*2,8-Bis(dimethylamino)-6-ethoxy-5-phenyl-4-(4-piperonylpiperazino)-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine (**6f**)* (95%). Purified using dichloromethane/AcOEt (4:1) as eluent; mp 275-277 °C (EtOH/CH_2Cl_2). IR (KBr): 1610, 1570, 1520, 1420, 1260. ^{1}H NMR δ ($CDCl_3$): 1.39 (t, 3H, J = 7.08 Hz), 2.50-2.68 (m, 4H, NCH_2), 3.12 (s, 6H, NMe_2), 3.13 (s, 6H, NMe_2), 3.17-3.40 (m, 6H, CH_2, NCH_2), 4.37-4.47 (m, 2H, OCH_2), 5.65 (s, 1H, H-5), 5.95 (s, 2H, OCH_2O), 6.77-6.89 (m, 3H, $C_6\underline{H}_3CH_2O_2$), 7.12-7.18 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ ($CDCl_3$): 14.5 (CH_3), 36.3 (C-5), 36.7 (NMe_2), 36.8 (NMe_2), 49.8 (NCH_2), 52.8 (NCH_2), 61.8 (CH_2), 62.7 (CH_2), 100.8 (OCH_2O), 102.9 (C-5a), 105.3 (C-4a), 107.8, 109.4 (C-2', C-5'), 122.2 (C-6'), 126.2, 126.9, 128.0, 143.0 (C_6H_5), 131.8 (C-1'), 146.6, 147.6 (C-3', C-4'), 159.4, 159.8, 164.7, 165.1, 165.3 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 626 (M^+, 13), 491 (48), 135 (100). *Anal.* Calcd for $C_{33}H_{38}N_8O_3S$: C, 63.24; H, 6.11; N, 17.88. Found C, 63.42; H, 5.94; N, 18.09.

*2,8-Bis(dimethylamino)-5-(4-chlorophenyl)-6-ethoxy-4-(4-piperonylpiperazino)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine (**6g**)* (95%). Purified using dichloromethane/AcOEt (6:1) as eluent; mp 180-182 °C (EtOH/CH_2Cl_2). IR (KBr): 1590, 1560, 1500, 1400, 1340. ^{1}H NMR δ ($CDCl_3$): 1.39 (t, 3H, J = 7.1 Hz), 2.49-2.69 (m, 4H, NCH_2), 3.09 (s, 6H, NMe_2), 3.10 (s, 6H, NMe_2), 3.22 (m, 4H, NCH_2), 3.49 (s, 2H, CH_2), 4.35-4.47 (m, 2H, CH_2), 5.59 (s, 1H, H-5), 5.96 (s, 2H, OCH_2O), 6.77-6.90 (m, 3H, $C_6\underline{H}_3CH_2O_2$), 7.12-7.16 (m, 4H, C_6H_4Cl). ^{13}C NMR δ ($CDCl_3$): 14.6 (CH_3), 36.0 (C-5), 36.7 (NMe_2), 36.8 (NMe_2), 49.9 (NCH_2), 52.8 (NCH_2), 61.9 (CH_2), 62.8 (CH_2), 100.9 (OCH_2O), 102.4 (C-4a), 104.9 (C-5a), 107.9, 109.5 (C-2', C-5'), 122.2 (C-6'), 128.1, 128.3, 141.8 (C_6H_4Cl), 131.8 (C-1'), 146.6, 147.6 (C-3',C-4'), 159.4, 159.8, 164.5, 165.0, 165.2, 165.3 (C-2, C-4, C-6, C-8, C-9a, C-10a). MS (EI, *m/z*, %): 660 (M^+, 14), 135 (100). *Anal.* Calcd for $C_{33}H_{37}N_8O_3ClS$: C, 59.94; H, 5.64; N, 16.94. Found C, 60.12; H, 5.58; N, 17.08.

5-Aryl-6-chloro-2,8-bis(dimethylamino)-4-propylamino-5*H*-thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidines (5k-o) and 5-aryl-2,8-bis(dimethylamino)-4,6-bis(propylamino)-5*H*-thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidines (6h-l).

A solution of **4** (0.4 mmol) and propylamine (1 mL, 12 mmol) in THF (10 mL) was refluxed until all starting material had disappeared as checked by TLC. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography to obtain **5k-o** and **6 h-l**.

*6-Chloro-2,8-bis(dimethylamino)-5-phenyl-4-propylamino-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine (**5k**)* (48%). Purified using dichloromethane as eluent; mp 206-208 °C (EtOH/CH_2Cl_2). IR (KBr): 3480 (NH), 1560, 1490, 1320. ^{1}H NMR δ ($CDCl_3$): 0.82 (t, 3H, J = 7.4 Hz, CH_3), 1.47-1.61 (m, 2H, CH_2), 3.12 (s, 12H, NMe_2), 3.33-3.46 (m, 2H, CH_2), 4.66 (t, 1H, J = 5.3 Hz, NH), 5.08 (s, 1H, H-5), 7.17-7.49 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ ($CDCl_3$): 11.3 (CH_3), 22.5 (CH_2), 36.6 (NMe_2), 36.9 (NMe_2), 41.0 (C-5); 42.9 (CH_2), 99.8 (C-4a), 113.4 (C-5a), 127.2, 127.4, 128.6, 142.5 (C_6H_5), 158.8, 159.0, 159.9, 166.2 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 457 (M^++ 2, 5), 455 (M^+, 21), 378 (100). *Anal.* Calcd for $C_{22}H_{26}N_7ClS$: C, 57.95; H, 5.75; N, 21.50. Found C, 58.16; H, 5.62; N, 21.64.

*2,8-Bis(dimethylamino)-5-phenyl-4,6-bis(propylamino)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine (**6h**)* (41%). Purified using dichloromethane/AcOEt (1:1) as eluent; mp 228-230 °C (EtOH/CH_2Cl_2). IR (KBr): 3440 (NH), 3380 (NH), 1590, 1500, 1420, 1340. ^{1}H NMR δ ($CDCl_3$): 0.80 (t, 6H, J = 7.4 Hz, CH_3), 1.40-2.05 (m, 4H, CH_2), 3.08 (s, 12H, NMe_2), 3.20-3.47 (m, 4H, CH_2), 4.52 (s, 1H, H-5), 4.73 (t, 2H, J = 5.3

Hz, NH); 7.11-7.42 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ($CDCl_3$): 14.3 (CH_3), 22.5 (CH_2), 36.5 (NMe_2), 39.5 (C-5), 42.8(CH_2), 100.0 (C-4a, C-5a), 127.1, 128.7, 143.3 (C_6H_5), 158.9, 159.5, 159.6 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 478 (M^+, 8), 401 (100). *Anal.* Calcd for $C_{25}H_{34}N_8S$: C, 62.73; H, 7.16; N, 23.41. Found C, 62.86; H, 7.02; N, 23.54.

6-Chloro-5-(4-chlorophenyl)-2,8-bis(dimethylamino)-4-propylamino-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(5l)*** (48%). Purified using hexanes/dichloromethane (1:1) as eluent; mp 220-222 °C ($EtOH/CH_2Cl_2$). IR (KBr): 3480 (NH), 1560, 1480, 1320. ^1H NMR δ($CDCl_3$): 0.85 (t, 3H, J = 7.4 Hz, CH_3), 1.49-1.66 (m, 2H, CH_2), 3.15 (s, 12H, NMe_2), 3.12-3.46 (m, 2H, CH_2), 4.57 (s, 1H, NH), 5.06 (s, 1H, H-5), 7.20, 7.39 (AA'XX' system, 4H, J = 8.4 Hz, C_6H_4Cl) ppm. ^{13}C NMR δ ($CDCl_3$): 11.4 (CH_3), 22.6 (CH_2), 36.6 (NMe_2), 36.9 (NMe_2), 40.1 (C-5), 42.9 (CH_2), 99.2 (C-4a), 112.9 (C-5a), 128.7, 133.0, 140.9 (C_6H_4Cl), 158.8, 159.0, 159.2, 159.9, 166.2 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 489 (M^+, 14), 378 (100). *Anal.* Calcd for $C_{22}H_{25}N_7Cl_2S$: C, 53.88; H, 5.14; N, 20.00. Found C, 54.09; H, 5.02; N, 20.18.

5-(4-Chlorophenyl)-2,8-bis(dimethylamino)-4,6-bis(propylamino)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6i)*** (50%). Purified using dichloromethane as eluent; mp 228-230 °C ($EtOH/CH_2Cl_2$). IR (KBr): 3440 (NMe_2), 3340 (NH), 1560, 1480, 1320. ^1H NMR δ ($CDCl_3$): 0.83 (t, 6H, J = 7.4 Hz, CH_3), 1.43-1.60 (m, 4H, CH_2), 3.08 (s, 12H, NMe_2), 3.20-3.47 (m, 4H, CH_2), 4.60 (s, 1H, H-5), 4.80 (t, 2H, J = 5.3 Hz, NH), 7.20, 7.39 (AA'XX' system, 4H, J = 8.5 Hz, C_6H_4Cl) ppm. ^{13}C NMR δ($CDCl_3$): 11.4 (CH_3), 22.6 (CH_2), 36.5 (NMe_2), 38.1 (C-5), 43.0 (CH_2), 99.7 (C-4a, C-5a), 128.3, 128.7, 132.7, 141.7 (C_6H_5), 158.8, 159.6, 160.0 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 514 (M^++2, 3), 512 (M^+, 17), 401 (100). *Anal.* Calc. for $C_{25}H_{33}N_8ClS$: C, 58.52; H, 6.48; N, 21.84 . Found C, 58.64; H, 6.23; N, 21.98.

6-Chloro-2,8-bis(dimethylamino)-5-(4-nitrophenyl)-4-propylamino-5H-thiopyrano[2,3-d:6,5d']-dipyrimidine ***(5m)*** (40%). Purified using hexanes/dichloromethane (1:2) as eluent; mp 195-197 °C ($EtOH/CH_2Cl_2$). IR (KBr): 3450 (NH), 1580, 1520, 1420, 1350. ^1H NMR δ($CDCl_3$): 0.85 (t, 3H, J = 7.4 Hz, CH_3), 1.57 (q, 2H, J = 7.1 Hz, CH_2), 3.12 (s, 12H, NMe_2), 3.32-3.45 (m, 2H, CH_2), 4.69 (s, 1H, NH), 5.22 (s, 1H, H-5), 7.61, 8.09 (AA'XX' system, 4H, J = 8.7 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 11.3 (CH_3), 22.5 (CH_2), 36.6 (NMe_2), 36.9 (NMe_2), 40.4 (C-5), 42.9 (CH_2), 98.2 (C-4a), 111.9 (C-5a), 123.8, 128.2, 146.8, 149.5 ($C_6H_4NO_2$), 158.7, 158.9, 159.0, 159.5, 159.7, 166.3 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 500 (M^+, 19), 378 (100). *Anal.* Calcd for $C_{22}H_{25}N_8O_2ClS$: C, 52.74; H, 5.03; N, 22.37. Found C, 52.90; H, 4.88; N, 22.56.

2,8-Bis(dimethylamino)-5-(4-nitrophenyl)-4,6-bis(propylamino)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6j)*** (56%). Purified using dichloromethane as eluent; mp 240-242 °C ($EtOH/CH_2Cl_2$). IR (KBr): 3460 (NH), 3420 (NH), 1580, 1410, 1350, 1260. ^1H NMR δ($CDCl_3$): 0.80 (t, 6H, J = 7.4 Hz, CH_3), 1.41-1.65 (m, 4H, CH_2), 3.07 (s, 12H, NMe_2), 3.10-3.40 (m, 4H, CH_2), 4.98 (s, 1H, H-5), 5.27 (s, 2H, NH), 7.61, 8.04 (AA'XX' system 4H, J = 8.7 Hz, $C_6H_4NO_2$) ppm. ^{13}C NMR δ($CDCl_3$): 11.4 (CH_3), 22.5 (CH_2), 36.6 (NMe_2), 37.6 (C-5), 43.0 (CH_2), 98.9 (C-4a, C-5a), 123.6, 127.9, 146.5, 150.5 ($C_6H_4NO_2$), 158.8, 159.6, 160.5 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 523 (M^+, 16), 401 (100); 71 (56). *Anal.* Calcd for $C_{25}H_{33}N_9O_2S$: C, 57.34; H, 6.35; N, 24.07. Found C, 57.49; H, 6.12; N, 24.20.

6-Chloro-2,8-bis(dimethylamino)-5-(3,4-methylenedioxyphenyl)-4-propylamino-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5n)*** (40%). Purified using hexanes/dichloromethane (1:1) as eluent; mp 212-214 °C (EtOH/CH_2Cl_2). IR (KBr): 3480 (NH), 1560, 1490, 1340, 1250. ^{1}H NMR δ ($CDCl_3$): 0.85 (t, 3H, J = 7.3 Hz, CH_3), 1.48-1.63 (m, 2H, CH_2), 3.12 (s, 12H, NMe_2), 3.31-3.46 (m, 2H, CH_2), 4.66 (s, 1H, NH), 5.02 (s, 1H, H-5), 6.64-6.97 (m, 3H, $C_6\underline{H}_3O_2CH_2$). ^{13}C NMR δ ($CDCl_3$): 11.3 (CH_3), 22.5 (CH_2), 36.6 (NMe_2), 36.8 (NMe_2), 40.3 (C-5), 42.8 (CH_2), 99.7 (C-4a), 101.0 (OCH_2O), 107.7, 107.9 (C-2', C-5'), 113.3 (C-5a), 120.5 (C-6'), 136.4 (C-1'), 146.7, 148.0 (C-3', C-4'), 158.7, 158.9, 159.8, 165.9 (C-2, C-4, C-6, C-8, C-9a, C-10a). MS (EI, *m/z*, %): 499 (M^+, 18), 65 (100). *Anal.* Calcd for $C_{23}H_{26}N_7O_2ClS$: C, 55.25; H, 5.24; N, 19.61. Found C, 55.42; H, 5.02; N, 19.88.

2,8-Bis(dimethylamino)-5-(3,4-methylenedioxyphenyl)-4,6-bis(propylamino)-5H-thiopyrano[2,3-d:6,5-d']-dipyrimidine ***(6k)*** (41%). Purified using dichloromethane/AcOEt (1:1) as eluent; mp 150-152 °C (EtOH/CH_2Cl_2). IR (KBr): 3460 (NH), 3380 (NH), 1580, 1490, 1400, 1250. ^{1}H NMR δ ($CDCl_3$): 0.85 (t, 6H, J = 7.4 Hz, CH_3), 1.45-1.62 (m, 4H, CH_2), 3.10 (s, 12H, NMe_2), 4.41 (s, 1H, H-5), 4.65 (t, 2H, J= 5.1 Hz, NH), 6.63-6.96 (m, 3H, $C_6\underline{H}_3O_2CH_2$) ppm. ^{13}C NMR δ ($CDCl_3$): 11.5 (CH_3), 22.6 (CH_2), 36.6 (NMe_2), 39.5 (C-5), 43.0 (CH_2), 100.0 (C-4a, C-5a), 101.1 (OCH_2O), 107.1, 108.3 (C-2', C-5'), 119.0 (C-6'), 137.6 (C-1'), 146.9, 148.8 (C-3', C-4'), 159.0, 159.6, 159.7 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, *m/z*, %): 522 (M^+, 12), 401 (100). *Anal.* Calcd for $C_{26}H_{34}N_8O_2S$: C, 59.75; H, 6.55; N, 21.44. Found C, 59.92; H, 6.32; N, 21.62.

6-Chloro-2,8-bis(dimethylamino)-4-propylamino-5-(p-tolyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(5o)*** (42%). Purified using hexanes/AcOEt (10:1) as eluent; mp 205-207 °C (EtOH/CH_2Cl_2). IR (KBr): 3460 (NH), 1560, 1490, 1340, 1250. ^{1}H NMR δ ($CDCl_3$): 0.85 (t, 3H, J = 7.5 Hz, CH_3), 1.50-1.63 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 3.12 (s, 12H, NMe_2), 3.31-3.41 (m, 2H, CH_2), 4.68 (t, 1H, J = 5.1 Hz, NH), 5.05 (s, 1H, H-5), 7.04, 7.35 (AA'XX' system, 4H, J = 7.81 Hz, $C_6\underline{H}_4CH_3$) ppm. ^{13}C NMR δ ($CDCl_3$): 11.3 (CH_3), 20.9 (CH_3), 22.5 (CH_2), 36.6 (NMe_2), 36.9 (NMe_2), 40.3 (C-5), 42.9 (CH_2), 99.9 (C-4a), 113.6 (C-5a), 127.3, 129.3, 137.0, 139.5 ($\underline{C}_6H_4CH_3$), 158.8, 158.9, 159.0, 159.8, 166.0 (C-2, C-4, C-6, C-8, C-9a, C-10a) ppm. MS (EI, m/z, %): 469 (M^+, 17), 378 (100). *Anal.* Calcd for $C_{23}H_{28}N_7ClS$: C, 58.77; H, 6.00; N, 20.86. Found C, 58.89; H, 5.89; N, 21.02.

2,8-Bis(dimethylamino)-4,6-bis(propylamino)-5-(p-tolyl)-5H-thiopyrano[2,3-d:6,5-d']dipyrimidine ***(6l)*** (46%). Purified using dichloromethane/AcOEt (1:1) as eluent; mp 220-222 °C (EtOH/CH_2Cl_2). IR (KBr): 3460 (NH), 3380 (NH), 1580, 1490, 1400, 1250. ^{1}H NMR δ ($CDCl_3$): 0.83 (t, 6H, J = 7.6 Hz, CH_3), 1.41-1.70 (m, 4H, CH_2), 2.26 (s, 3H, CH_3), 3.08 (s, 12H, NMe_2), 3.26-3.40 (m, 4H, CH_2), 4.43 (s, 1H, H-5), 4.66 (t, 2H, J = 5.12 Hz, NH), 7.05, 7.30 (AA'XX' system, 4H, J = 8.3 Hz, $C_6\underline{H}_4CH_3$). ^{13}C NMR δ ($CDCl_3$): 11.4 (CH_3), 20.9 (CH_3), 22.6 (CH_2), 36.5 (NMe_2), 39.4 (C-5), 42.9 (CH_2), 100.2 (C-4a, C-5a), 127.1, 129.5, 136.9, 140.4 ($\underline{C}_6H_4CH_3$), 158.9, 159.5 (C-2, C-4, C-6, C-8, C-9a, C-10a). MS (EI, *m/z*, %): 492 (M^+, 12), 401 (100). *Anal.* Calcd for $C_{26}H_{36}N_8S$: C, 63.38; H, 7.36; N, 22.74. Found C, 63.52; H, 7.12; N, 22.86.

X-Ray Analysis

Crystal data for **4a**: $C_{19}H_{18}N_6Cl_2S$, fw= 433.35, monoclinic, space group $P2_1/n$ with a = 9.0669 (3), b = 10.0951 (3), c = 21.9779 (7) Å, α = 90°, β = 101.82°, γ = 90°, V = 1968.99 (11) Å^3, Z = 4, D_c = 1.462

mg/m^3 and μ = 0.454 mm^{-1}. A colourless blocklike crystal (dimensions: 0.60 × 0.45 × 0.20 mm) was used for the structure determination. The chosen crystal was mounted on a glass fiber using an epoxy resin. Data was collected using a Siemens SMART CCD area detector single crystal diffractometer with graphite monochromated Mo-Ka radiation (l= 0.71073 Å) operating at rt. Preliminary unit cell constants were determined with a set of 45 narrow frames (0.3° in w) scans. A total of 1420 frames of intensity data were collected with a frame width of 0.3° per frame in w and counting time of 30s/frame at a crystal to detector distance of 4.5 cm. The collected frames were integrated using an orientation matrix determined from the narrow frame scans and refined using Siemens SAINT software on all observed reflections. A semiempirical absorption correction was carried out using an ellipsoidal model (maximum and minimum transmission coefficients, 0.856 and 0.692). The integration process yielded 10623 reflections, of which 4852 were independent. The structure was solvent using the Siemens SHELTXTL-PC software by direct methods and refined by full-matrix least-squares methods on F^2. Hydrogen atoms were included in calculated positions and refined in riding mode. The final R indices [$I>2\sigma(I)$] were $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.0399$ and $R_w = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[wF_o^4]\}^{1/2} = 0.1069$ where $w = 1/\sigma^2(F_o)$.

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