SYNTHESIS OF PYRIMIDO[5'',4'':5',6']PYRIDO[2',3':4,5]-THIENO[2,3-*c*]PYRIDAZINE AND PYRIDAZINO[4',3':4,5]-THIENO[3,2-*b*][1,8]NAPHTHYRIDINE, NEW TETRAHETEROCYCLIC RING SYSTEMS

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Abstract- Preparation of a number of pyrimido[5'',4'':5',6']pyrido-[2',3':4,5]thieno[2,3-*c*]pyridazine derivatives (**4a-h**) has been effected by reaction of appropriately heterocyclic aminonitrile precursor (**1**) and *N,N*-dimethyldichloromethyleniminium chloride. In addition, pyridazino[4',3':4,5]-thieno[3,2-*b*][1,8]naphthyridines (**9a-i**), were prepared *via* the Friedländer synthesis of the *N*-heteroaromatic carbaldehyde (**8**) with acyclic, cyclic, heterocyclic or α,β-unsaturated ketones and other active methylene compounds.

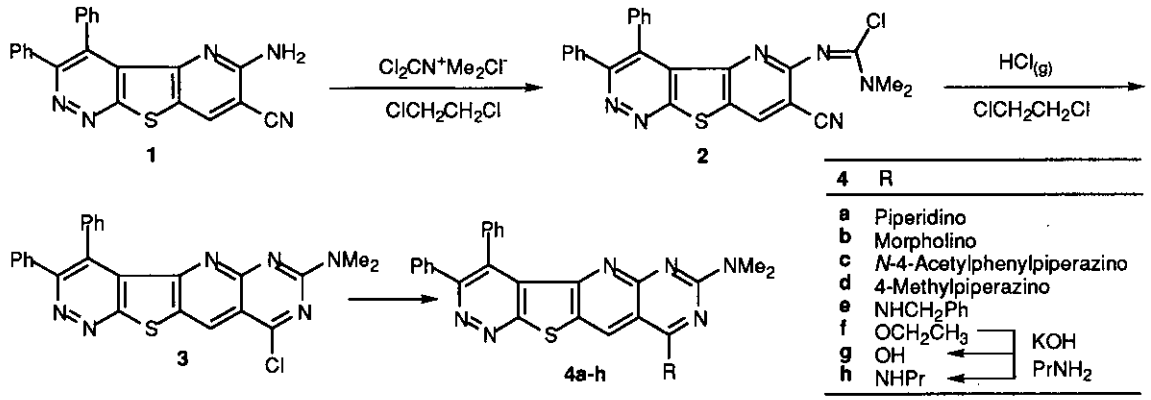
The importance of pyrimidine and its annelated substrates is well recognised.[1] Heterocyclic annelated pyridazines continue to attract considerable attention which mainly arises from the large variety of interesting pharmacological activities observed with pyridazine derivatives.[2] Numerous papers dealing with the preparation of heterocyclic annelated pyridazines were reported due to the activity claimed, but very few attention has been devoted to molecules of this type which contain a thienopyridazine moiety. Heterocyclic β-enamino nitriles are versatile synthons for various cyclization reactions.[3] In continuation of our interest in the synthesis of fused compounds of the thieno[2,3-*c*]pyridazine type,[4] we report the *preparation of substituted pyrimido*[5'',4'':5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine and pyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine derivatives employing the heterocyclic amino nitrile (**1**)[4b] as a conveniently accessible precursor.

Dialkyldichloromethyleniminium chlorides (phosgeniminium chlorides) are known to be useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a dialkylamino group.[5] Recently, some new methods for the preparation of polyheterocyclic compounds containing the pyrimidine ring utilizing phosgeniminium chloride and β-enamino nitriles have been developed in our laboratory.[6]

Results of the cyclization of **1** with phosgeniminium chloride are summarized in Scheme 1. On treatment with (dichloromethylene)dimethylammonium chloride in refluxing 1,2-dichloroethane, the enamino nitrile (**1**) gave the imide halide intermediate (**2**) which underwent smooth cyclization to produce the cyclized product (**3**) by reaction with dry hydrogen chloride. The structure of compounds (**2** and **3**) was determined from microanalyses and spectra data. The MS spectra showed the expected molecular ion peak

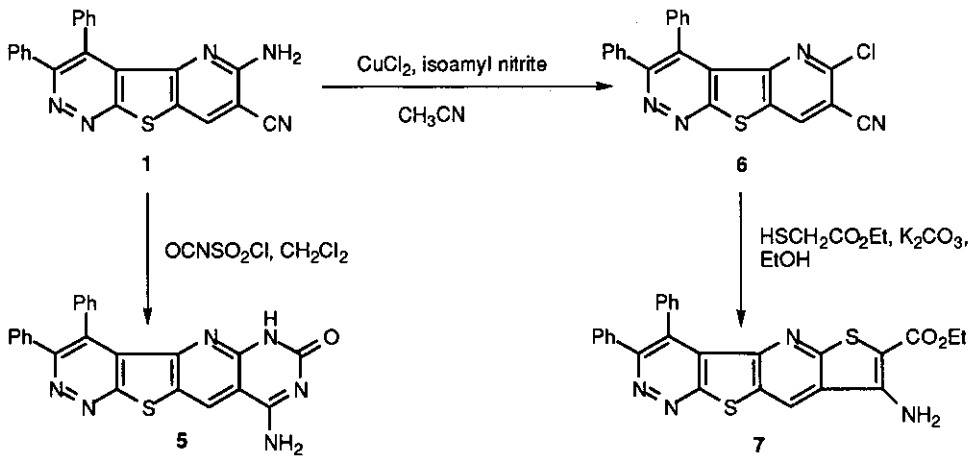
and the IR spectrum of **2** exhibited a strong absorption band at $\nu = 1640\ cm^{-1}$ due to the imino group and presented the characteristic signal at $\nu = 2210\ cm^{-1}$ (CN), while the decoupled ^{13}C NMR spectrum showed one signal at $\delta = 116.4$ due to the carbon atom in the one cyano group. After cyclization, the spectrum of compound (**3**) did not include those type of signals. Nucleophilic displacement reaction of the chloride in the key intermediate pyrimidopyridothienopyridazine (**3**) resulted in the formation of the corresponding substituted tetraheterocyclic derivatives (**4a-h**). The structures of these compounds were determined from microanalyses and spectral data.

Scheme 1



Amino nitrile (**1**) condensed with chlorosulfonyl isocyanate to give 9-amino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazin-7-(6*H*)-one (**5**). Treatment of **1** with isoamyl nitrite and copper (II) chloride in acetonitrile at 65°C yielded the chloro derivative (**6**) which, by reaction with ethyl 2-mercaptoacetate in refluxing ethanol in the presence of excess anhydrous potassium carbonate, underwent Thorpe-Ziegler cyclization to yield ethyl 7-amino-3,4-diphenylthieno[3",2":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-8-carboxylate (**7**) (Scheme 2).

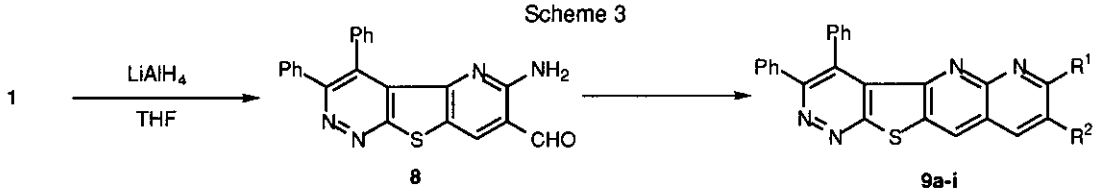
Scheme 2



Annelation reactions involving suitable aromatic hydrocarbon compounds carrying the amino aldehyde moiety provide synthetic entry into heterocyclic systems[7] and numerous *N*-heteroaromatic carbaldehydes are extensively used as versatile building blocks for the preparation of condensed heterocyclic

compounds.[8] The 6-amino-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-7-carbaldehyde (**8**) could be obtained in moderate yield by $LiAlH_4$ reduction of the cyano precursor (**1**). Base-catalyzed condensation of **8** with aromatic and aliphatic ketones gave the substituted pyridazinothienonaphthyridine derivatives (**9a-e**) (Scheme 3). The condensation of amino aldehyde (**8**) with unsymetrical aliphatic ketones gives two different products depending on which α-carbon is used for bond formation. Cyclization of **8** with ethyl methyl ketone under a catalytic alkaline condition was found to occur preferentially at the α-methylene carbon, even though the isomeric product (**9e**) was isolated in a low yield from the reaction mixture. The reaction of the amino aldehyde (**8**) with an appropriated *α,β*-unsaturated ketone such as *trans*-4-phenyl-3-buten-2-one gave pyridazino[4',3':4,5]thieno[3,2-*b*][1,8]-naphthyridine (**9f**). Similarly, treatment of **8** with 2,4-pentanedione gave the expected compound (**9g**) and cyclization reaction with phenylacetonitrile or malononitrile takes place *via* intramolecular addition of the amino group to the cyano function on the intermediate produced by initial intermolecular condensation to give **9h** and **9i**, respectively.

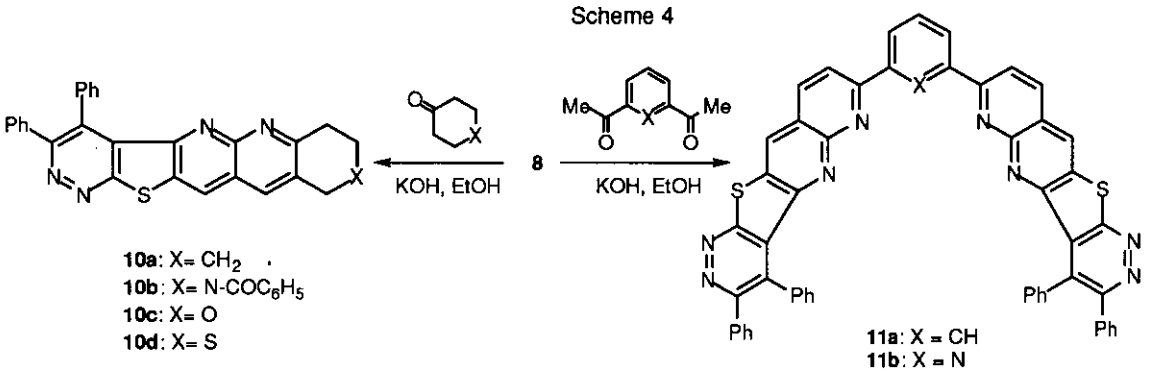
Scheme 3



9	R^1	R^2	9	R^1	R^2
a	Ph	H	f	CHCHPh	H
b	2-Py	H	g	Me	COMe
c	Me	H	h	NH_2	Ph
d	Me	Me	i	NH_2	CN
e	Et	H			

Pentacyclic derivatives (**10**) were obtained by Friedländer condensation of the heterocyclic amino aldehyde (**8**) with cyclic ketones and heterocyclic 6-membered ring ketones (Scheme 4). The structural variety of cyclic ketones provides a direct access to a number of polyheterocyclic systems for which in many cases alternate annelation methods are not readily available.

Scheme 4



Dinaphthyridine terminal polycyclic compounds (**11a,b**) are easily obtained by base-catalyzed reaction of the heterocyclic aminoaldehyde (**8**) with 1,3-diacetylbenzene and 2,6-diacetylpyridine, respectively. In the

design of artificial receptors, the most important task is to place the hydrogen bonding groups in a rigid or semirigid cavity.[9] Recently, a new simple dinaphthyridine receptor for urea was reported.[10] This one-pot procedure may be useful in view of the potential interest of dinaphthyridines (**11**) on molecular recognition.

EXPERIMENTAL

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 783 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at rt. MS spectra 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.

7-Cyano-6-chlorodimethylaminomethyleneamino-3,4-diphenylpyrido[2',3':4,5]-thieno[2,3-*c*]pyridazine (2):

A solution of **1** (1.30 g, 3.43 mmol) and phosgeniminium salt (0.67 g, 4.11 mmol) in 1,2-dichloroethane (40 mL) was refluxed for 20 h. The solid formed was filtered off and recrystallized from $CHCl_3$ to yield **2** (1.51 g, 94%); mp 249-251°C. IR (KBr): 3050, 2210 (CN), 1640, 1570, 1505, 1440, 1350. ^1H NMR δ ($CDCl_3$): 3.20 (s, 6H, NMe_2), 7.25-7.40 (m, 10H, C_6H_5), 8.39 (s, 1H, H-8). ^{13}C NMR δ ($CDCl_3$): 40.2 (NMe_2), 104.5 (C-7), 116.4 (CN), 127.2 (C-4a), 127.7, 127.9, 128.0, 128.2, 128.3, 130.4, 130.5, 133.0, 136.1 (C_6H_5+C-8a), 136.2 (C-8), 136.5 (C-4), 142.3 (C-4b), 150.4 (C-Cl), 157.3 (C-3), 158.0 (C-6), 164.6 (C-9a). MS (EI, *m/z*, %): 470 (M^++2, 39), 468 (M^+, 97), 433 (100), 431 (60), 417 (58), 378 (35). *Anal.* Calcd for $C_{25}H_{17}N_6ClS$: C, 64.03; H, 3.65; N, 17.92. Found C, 63.97; H, 3.52; N, 18.03.

9-Chloro-7-dimethylamino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]-thieno[2,3-*c*]pyridazine (3):

Dry HCl was bubbled through a solution of **2** (2.57 g, 5.47 mmol) in 1,2-dichloroethane (100 mL) for 1 h. The solution was stirred at rt for 5 d. The solvent was removed under reduced pressure and water (100 mL) was added. The solution was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3X100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel using CH_2Cl_2/AcOEt (100/1, v/v) as eluent to give **3** (2.3 g, 89%); mp 260°C (decomp, EtOH). IR (KBr): 3050, 2900, 1600, 1500, 1450, 1400, 1350. ^1H NMR δ ($CDCl_3$): 3.27 (br s, 6H, NMe_2), 7.28-7.46 (m, 10H, C_6H_5), 8.81 (s, 1H, H-10). MS (EI, *m/z*, %): 470 (M^++2, 22), 468 (M^+, 51), 467 (40), 360 (11), 258 (15), 239 (39). *Anal.* Calcd for $C_{25}H_{17}N_6ClS$: C, 64.03; H, 3.65; N, 17.92. Found C, 64.12; H, 3.49; N, 18.01.

General Procedure for the Synthesis of 7-Dimethylamino-3,4-diphenylpyrimido-[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (4a-e).

A solution of **3** (0.15 g, 0.32 mmol) and the appropriate amine (0.38 mmol) in ethanol/THF (16 mL, 1/7) was refluxed until all starting material had disappeared as checked by TLC (0.5-2 h). The solid formed was filtered off and purified by flash chromatography or recrystallization.

7-Dimethylamino-3,4-diphenyl-9-piperidinopyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (**4a**). Purified by flash chromatography on silica gel using CH_2Cl_2/AcOEt (2/1, v/v) as eluent. Yield 66%; mp 274-276°C (EtOH). IR (KBr): 2900, 1550, 1500, 1450, 1390, 1370, 1320, 1240. ^1H NMR δ ($CDCl_3$): 1.78 (br s, 6H, CH_2), 3.20 (s, 6H, NMe_2), 3.66 (s, 4H, NCH_2), 7.26-7.45 (m, 10H, C_6H_5), 8.42 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 24.7 (CH_2), 25.8 (CH_2), 36.9 (NMe_2), 51.1 (NCH_2), 106.7, 125.1 (C-4a), 127.8, 128.1, 128.6, 129.0, 130.4, 130.5, 133.1, 135.7, 136.2, 136.9, 160.6, 165.2. MS (EI, *m/z*, %): 517 (M^+, 100), 503 (15), 502 (38), 474 (12). *Anal.* Calcd for $C_{30}H_{27}N_7S$: C, 69.61; H, 5.26; N, 18.94. Found C, 69.72; H, 5.18; N, 18.89.

7-Dimethylamino-9-morpholino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]-pyridazine (**4b**). Purified by flash chromatography on silica gel using CH_2Cl_2/AcOEt (1/1) as eluent. Yield 60%; mp >300°C (EtOH). IR (KBr): 2940, 1550, 1500, 1450, 1400, 1350, 1320. ^1H NMR δ ($CDCl_3$): 3.22 (s, 6H, NMe_2), 3.71 (t, 4H, J = 4.5 Hz, CH_2), 3.89 (t, 4H, J = 4.5 Hz, CH_2), 7.24-7.47 (m, 10H, C_6H_5), 8.45 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 36.8 (NMe_2), 50.4 (NCH_2), 66.4 (OCH_2), 106.1, 125.3, 127.1, 127.7, 127.8, 128.0, 128.5, 130.3, 130.5, 132.9, 136.3, 136.8, 154.0, 157.4, 159.9, 160.3, 165.1. MS (EI, *m/z*, %): 519 (M^+, 100), 505 (11), 418 (12), 417 (21). *Anal.* Calcd for $C_{29}H_{25}N_7OS$: C, 67.03; H, 4.85; N, 18.87. Found C, 66.90; H, 4.93; N, 18.94.

9-[*N*-(4-Acetylphenylpiperazino)]-7-dimethylamino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]-thieno[2,3-*c*]pyridazine (**4c**). Recrystallized from DMF. Yield 76%; mp >300°C. IR (KBr): 1650 (CO), 1590, 1550, 1500, 1420, 1390. ^1H NMR δ (DMSO-d_6): 2.46 (s, 3H, $COCH_3$), 3.12 (s, 6H, NMe_2), 3.62 (br s, 4H, NCH_2), 3.88 (br s, 4H, NCH_2), 7.00, 7.84 (AA'XX' system, 4H, J = 8.6 Hz, C_6H_4), 7.29-7.34 (m, 10H, C_6H_5), 9.07 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 26.2 (CH_3), 37.0 (NMe_2), 46.9 (NCH_2), 49.4 (NCH_2), 106.2, 125.4 (C-4a), 113.4, 127.8, 128.2, 128.6, 130.4, 133.0, 136.2, 136.9, 153.6, 154.0, 157.5, 159.8, 160.1, 164.9, 165.2, 196.5 (CO). MS (FAB, *m/z*, %): 637 [$(MH)^+$, 100)], 462 (10), 316 (22), 181 (100). *Anal.* Calcd for $C_{37}H_{32}N_8OS$: C, 69.79; H, 5.06; N, 17.60. Found C, 69.84; H, 4.94; N, 17.69.

7-Dimethylamino-9-(4-methylpiperazino)-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (**4d**). Purified by flash chromatography on silica gel using CH_2Cl_2/EtOH (20/1, v/v) as eluent. Yield 76%; mp 273-275°C (EtOH). IR (KBr): 1560, 1500, 1450, 1400, 1320. ^1H NMR δ ($CDCl_3$): 2.38 (s, 3H, CH_3), 2.61 (t, 4H, J = 4.7 Hz, NCH_2), 3.19 (br s, 6H, NMe_2), 3.75 (t, 4H, J = 4.9 Hz, NCH_2), 7.24-7.45 (m, 10H, C_6H_5), 8.44 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 37.0 (NMe_2), 46.1 (CH_3), 49.8 (NCH_2), 54.6 (NCH_2), 106.3, 125.2, 127.2, 127.8, 128.0, 128.6, 130.4, 130.5, 133.1, 136.2, 136.8, 153.8, 157.5, 160.0, 160.4, 164.9, 165.2 MS (EI, *m/z*, %): 532 (M^+, 10), 462 (29), 449 (18), 448 (16), 70 (100). *Anal.* Calcd for $C_{30}H_{28}N_8S$: C, 67.65; H, 5.30; N, 21.04. Found C, 67.56; H, 5.39; N, 20.98.

9-Benzylamino-7-dimethylamino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]-pyridazine (**4e**). Recrystallized from EtOH/THF. Yield 65%; mp 185-187°C. IR (KBr): 3300 (NH), 1600, 1580, 1540, 1450, 1400, 1350. ^1H NMR δ ($CDCl_3$): 3.09 (s, 6H, NMe_2), 4.73 (d, 2H, J = 5.3 Hz, CH_2), 6.29 (t, 1H, J = 5.3 Hz, NH), 7.19-7.43 (m, 15H, C_6H_5), 8.42 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 37.1 (NMe_2), 45.2 (CH_2), 106.0, 126.0 (C-4a), 126.5, 127.4, 127.7, 127.8, 128.1, 128.5,

128.6, 130.3, 130.5, 133.2, 136.3, 136.9, 138.2, 153.7, 157.7, 158.8, 159.2, 161.3, 165.5. MS (EI, *m/z*, %): 539 (M^+, 14), 91 (100). *Anal.* Calcd for $C_{32}H_{25}N_7S$: C, 71.22; H, 4.67; N, 18.17. Found C, 71.30; H, 4.72; N, 18.10.

9-Ethoxy-7-dimethylamino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno-[2,3-*c*]pyridazine (4f):

To a solution of sodium ethoxide (0.08 g of Na, 3.80 mmol) in ethanol (15 mL) compound (**3**) (0.15 g, 0.32 mmol) was added. The solution was refluxed for 10 min. The solid formed was filtered off and recrystallized from ethanol/acetone to yield **4f** (0.11 g, 72%); mp 264-266°C. IR (KBr): 1610, 1599, 1560, 1450, 1400. ^{1}H NMR δ ($CDCl_3$): 1.53 (t, 3H, J = 7.1 Hz, CH_3), 3.29 (s, 6H, NMe_2), 4.62 (q, 2H, J = 7.1 Hz, CH_2), 7.25-7.48 (m, 10H, C_6H_5), 8.77 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 14.1 (CH_3), 37.6 (NMe_2), 64.0 (OCH_2), 106.3, 127.0 (C-4a), 127.9, 128.0, 128.1, 128.4, 128.8, 130.4, 130.5, 133.0, 136.5 (C_6H_5+ C-10), 136.8 (C-4), 154.8, 157.7 (C-3), 159.6, 165.1, 166.3. MS (EI, *m/z*, %): 478 (M^+, 100), 450 (22), 449 (68), 435 (11), 322 (14), 225 (32). *Anal.* Calcd for $C_{27}H_{22}N_6OS$: C, 67.76; H, 4.63; N, 17.56. Found C, 67.65; H, 4.74; N, 17.63.

7-Dimethylamino-3,4-diphenyl-9-hydroxypyrimido[5",4":5',6']pyrido[2',3':4,5]-thieno[2,3-*c*]pyridazine (4g):

A solution of **4f** (0.2 g, 0.42 mmol) and 35% KOH (1 mL) in ethanol (15 mL) was refluxed for 30 min. The solid formed was filtered off and recrystallized from DMF to give **4g** (0.13 g, 70%); mp >300°C. IR (KBr): 1670, 1610, 1580, 1510, 1360. ^{1}H NMR δ (DMSO-d_6): 3.05 (s, 6H, NMe_2), 7.23-7.36 (m, 10H, C_6H_5), 9.06 (s, 1H, H-10), 11.46 (br s, 1H, OH). MS (EI, *m/z*, %): 450 (M^+, 75), 436 (22), 435 (27), 322 (17). *Anal.* Calcd for $C_{25}H_{18}N_6OS$: C, 66.65; H, 4.03; N, 18.65. Found C, 66.74; H, 3.95; N, 18.73.

7-Dimethylamino-3,4-diphenyl-9-propylaminopyrimido[5",4":5',6']pyrido[2',3':4,5]-thieno[2,3-*c*]pyridazine (4h):

A solution of **4f** (0.15 g, 0.31 mmol) in propylamine (5 mL, 61 mmol) was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using CH_2Cl_2/EtOH (50/1, v/v) as eluent to yield **4h** (0.1 g, 65%); mp 169°C (decomp). IR (KBr): 1560, 1520, 1400, 1340. ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H, J = 7.4 Hz, CH_3), 1.66 (m, 2H, CH_2), 3.18 (s, 6H, NMe_2), 3.43 (m, 2H, NCH_2), 6.80 (br s, 1H, NH), 7.27-7.49 (m, 10H, C_6H_5), 8.61 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 11.6 (CH_3), 22.0 (CH_2), 37.1 (NMe_2), 43.3 (NCH_2), 106.1, 126.0, 127.1, 126.5, 127.9, 128.0, 128.7, 130.3, 130.6, 133.5, 135.9, 136.8, 152.8, 157.6, 158.2, 159.1, 161.0, 165.0. MS (EI, *m/z*, %): 491 (M^+, 25), 476 (8). *Anal.* Calcd for $C_{28}H_{25}N_7S$: C, 68.41; H, 5.12; N, 19.94. Found C, 68.53; H, 5.20; N, 19.87.

9-Amino-3,4-diphenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazin-7-(6*H*)-one (5):

To an ice-cooled solution of **1** (0.20 g, 0.53 mmol) in dry THF (20 mL) a solution of chlorosulfonyl isocyanate (0.084 g, 0.58 mmol) in THF (2 mL) was added. The solution was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue was triturated with water. The solid formed

was filtered off and purified by flash chromatography using CH_2Cl_2/EtOH (1/1, v/v) as eluent to give **5** (0.085 g, 38%); mp >300°C (DMF). IR (KBr): 3400, 3050 (NH), 1650 (CO), 1600, 1570, 1480, 1340,. ^{1}H NMR δ (DMSO-d_6): 7.29-7.34 (m, 10H, C_6H_5), 8.19 (br s, 2H, NH_2, exchangeable with D_2O), 9.18 (s, 1H, H-10), 11.12 (br s, 1H, NH, exchangeable with D_2O). MS (EI, *m/z*, %): 422 (M^+, 12), 379 (16), 378 (16), 207 (33). *Anal.* Calcd for $C_{23}H_{14}N_6OS$: C, 65.39; H, 3.34; N, 19.89. Found C, 65.27; H, 3.45; N, 19.77.

7-Cyano-6-chloro-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (6):

To an ice-cooled solution of $CuCl_2$ (0.16 g, 1.21 mmol) and isoamyl nitrite (0.18 mL, 1.35 mmol) in acetonitrile (13 mL) a suspension of **1** (0.40 g, 1.05 mmol) in acetonitrile (24 mL) was added dropwise. The solution was heated at 65°C for 4 h and then cooled and poured into 2N HCl (80 mL). The solution was extracted with CH_2Cl_2 (3X40 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using CH_2Cl_2/AcOEt (45/1 to 10/1, v/v) as eluent gradient to give **6** (0.20 g, 47%); mp 273-275°C (EtOH). IR (KBr): 3070, 2240 (CN), 1570, 1445, 1360, 1255. ^{1}H NMR δ ($CDCl_3$): 7.20-7.52 (m, 10H, $2C_6H_5$), 8.57 (s, 1H, H-8). ^{13}C NMR δ ($CDCl_3$): 109.7 (C-7), 114.3 (CN), 125.8 (C-4a), 128.0, 128.9, 129.2, 130.0, 130.4, 131.9, 133.3 (C_6H_5), 135.9 (C-8a), 136.3 (C-4), 137.3 (C-8), 148.7 (C-4b), 150.6 (C-6), 157.7 (C-3), 163.9 (C-9a). MS (EI, *m/z*, %): 400 (M^++2, 40), 398 (M^+, 100), 334 (18), 333 (22). *Anal.* Calcd for $C_{22}H_{11}N_4SCl$: C, 66.25; H, 2.78; N, 14.05. Found C, 66.32; H, 2.83; N, 13.97.

Ethyl 7-amino-3,4-diphenylthieno[3",2":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]-pyridazine-8-carboxylate (7):

To a solution of **6** (0.17 g, 0.43 mmol) and ethyl mercaptoacetate (0.064 g, 0.53 mmol) in EtOH (20 mL) K_2CO_3 (0.074 g, 0.53 mmol) was added. The reaction mixture was refluxed for 3 h. The solid formed was filtered off and recrystallized from EtOH/THF to give **7** (0.18 g, 86%); mp >300°C. IR (KBr):3420, 3300, 3200 (NH), 1675, 1625. ^{1}H NMR δ (DMSO-d_6): 1.24 (t, 3H, J = 7.1 Hz, CH_3), 4.21 (q, 2H, J = 7.1 Hz, CH_2), 7.31-7.42 (m, 12H, $2C_6H_5$+NH_2), 9.21 (s, 1H, H-9). MS (EI, *m/z*, %): 482 (M^+, 18), 239 (12). *Anal.* Calcd for $C_{26}H_{18}N_4O_2S_2$: C, 64.71; H, 3.76; N, 11.61. Found C, 64.82; H, 3.69; N, 11.70.

6-Amino-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-7-carbaldehyde (8):

To an ice-cooled solution of **1** (0.20 g, 0.53 mmol) in dry THF (20 mL) $LiAlH_4$ (0.041 g, 1.1 mmol) was added in portions. Stirring at 5°C was continued for 18 h. A solution of THF/H_2O (1/1, 10 mL) was added carefully and the solution was acidified (pH=3) with 25% H_2SO_4. The reaction mixture was decanted and the solution was evaporated under reduced pressure to 10 mL. The solid formed was filtered off and purified by flash chromatography using hexanes/AcOEt (3/2) as eluent to give **8** (0.07 g, 35%); mp 264-266°C (EtOH). IR (KBr): 3450, 3300, 3190 (NH), 1670 (CO), 1620, 1600, 1580, 1540. ^{1}H NMR δ ($CDCl_3$): 6.29 (br s, 2H, NH_2), 7.21-7.43 (m, 10H, C_6H_5), 8.34 (s, 1H, H-8), 9.98 (s, 1H, CHO). MS (EI, *m/z*, %): 382 (M^+, 100), 353 (12), 307 (10). *Anal.* Calcd for $C_{22}H_{14}N_4OS$: C, 69.09; H, 3.69; N, 14.65. Found C, 69.17; H, 3.59; N, 14.72.

General Procedure for the Synthesis of Derivatives (9a-f).

A solution of **8** (0.10 g, 0.26 mmol), the appropriate ketone (0.37 mmol) and a few drops of 10% KOH (ethanolic) in EtOH (10 mL) was refluxed until starting material had disappeared as checked by TLC and

then worked up in one of the following ways: (A) After cooling, the solid formed was filtered off and recrystallized from a suitable solvent. (B) The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

3,4,7-Triphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (**9a**). Recrystallized from EtOH/CH_2Cl_2. Yield 55%; mp 286-287°C. IR (KBr): 3050, 1600, 1580, 1540, 1490, 1470, 1440, 1400, 1380. ^{1}H NMR δ ($CDCl_3$): 7.24-7.61 (m, 13H), 8.07 (d, 1H, J = 8.6 Hz, H-8), 8.17-8.24 (m, 2H), 8.33 (d, 1H, J = 8.6 Hz, H-9), 8.70 (s, 1H, H-10). MS (EI, *m/z*, %): 466 (M^+, 100), 444 (16), 437 (12). *Anal.* Calcd for $C_{30}H_{18}N_4S$: C, 77.23; H, 3.89; N, 12.01. Found C, 77.11; H, 4.02; N, 11.89.

3,4-Diphenyl-7-(2-pyridiyl)pyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (**9b**). Recrystallized from EtOH/CH_2Cl_2. Yield 71%; mp >300°C. IR (KBr): 3050, 1600, 1570, 1540, 1460, 1380. ^{1}H NMR δ ($CDCl_3$): 7.29-7.58 (m, 11), 7.90 (dt, 1H, J = 7.8 Hz, J = 1.8 Hz), 8.39 (d, 1H, J = 8.7 Hz, H-8), 8.62 (d, 1H, J = 8.1 Hz, H-9). MS (EI, *m/z*, %): 467 (M^+, 100), 434 (9), 359 (8), 254 (12). *Anal.* Calcd for $C_{29}H_{17}N_5S$: C, 74.50; H, 3.66; N, 14.98. Found C, 74.67; H, 3.72; N, 14.88.

7-Methyl-3,4-diphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (**9c**). Recrystallized from EtOH/acetone. Yield 76%; mp 251-253°C. IR (KBr): 3060, 2970, 1610, 1550, 1540, 1490, 1480, 1440, 1375. ^{1}H NMR δ ($CDCl_3$): 2.77 (s, 3H, CH_3), 7.23-7.54 (m, 11H), 8.16 (d, 1H, J = 8.5 Hz), 8.68 (s, 1H). MS (EI, *m/z*, %): 404 (M^+, 100), 375 (10). *Anal.* Calcd for $C_{25}H_{16}N_4S$: C, 74.24; H, 3.99; N, 13.85. Found C, 74.16; H, 4.05; N, 13.96.

7,8-Dimethyl-3,4-diphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (**9d**). Purified by flash chromatography using CH_2Cl_2/AcOEt/hexane (1/2/2) as eluent. Yield 54%; mp 270-272°C (EtOH/acetone). IR (KBr): 1620, 1540, 1420. ^{1}H NMR δ ($CDCl_3$): 2.50 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.24-7.53 (m, 10H, $2C_6H_5$), 7.94 (s, 1H, H-9), 8.60 (s, 1H, H-10). MS (EI, *m/z*, %): 418 (M^+, 100), 389 (7). *Anal.* Calcd for $C_{26}H_{18}N_4S$: C, 74.62; H, 4.33; N, 13.39. Found C, 74.75; H, 4.21; N, 13.26.

7-Ethyl-3,4-diphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (**9e**). Purified by flash chromatography using CH_2Cl_2/AcOEt/hexanes (1/2/2) as eluent. Yield 9%; mp 176-178°C (EtOH/acetone). IR (KBr): 1610, 1550, 1480, 1450, 1380. ^{1}H NMR δ ($CDCl_3$): 1.39 (t, 3H, J = 7.4 Hz, CH_3), 3.04 (q, 2H, J = 7.4 Hz, CH_2), 7.28-7.53 (m, 11H), 8.18 (d, 1H, J = 8.4 Hz), 8.69 (s, 1H). MS (EI, *m/z*, %): 418 (M^+, 100), 403 (20). *Anal.* Calcd for $C_{26}H_{18}N_4S$: C, 74.62; H; 4.33, N, 13.39. Found C, 74.57; H, 4.22; N, 13.45.

3,4-Diphenyl-7-styrylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (**9f**). Recrystallized from EtOH. Yield 31%; mp 150-152°C. IR (KBr): 1600, 1590, 1480, 1450, 1380, 1310, 1210, 1190. ^{1}H NMR δ ($CDCl_3$): 7.28-7.82 (m, 18H), 8.23 (d, 1H, J = 8.6 Hz), 8.66 (s, 1H). MS (EI, *m/z*, %): 492 (M^+, 100), 491 (69). *Anal.* Calcd for $C_{32}H_{20}N_4S$: C, 78.03; H, 4.09; N, 11.37. Found C, 78.12; H, 4.03; N, 11.43.

7-Acetyl-6-methyl-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (9g):

A solution of **8** (0.1 g, 0.26 mmol), 2,4-pentanedione (0.05 g, 0.50 mmol) and a catalytic amount of piperidine in THF (10 mL) was refluxed for 48 h. The solid formed was filtered off and recrystallized from EtOH/CH_2Cl_2 to give **9h** (0.060 g, 50%); mp 271-273°C. IR (KBr): 1690 (CO), 1610, 1550, 1530, 1495, 1450, 1440, 1420, 1380, 1360, 1320. ^{1}H NMR δ ($CDCl_3$): 2.73 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 7.23-

7.56 (m, 10H, $2C_6H_5$), 8.55 (s, 1H, H-9), 8.76 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 26.1 (CH_3), 29.5 (CH_3), 119.5, 127.1, 127.9, 128.1, 128.3, 128.9, 130.3, 131.4, 137.6 (CH), 132.4, 132.7, 136.5, 136.9, 153.1, 154.6, 158.3, 162.2, 164.9, 199.1 (CO). MS (EI, *m/z*, %): 446 (M^+, 100), 373 (13), 201 (16). *Anal.* Calcd for $C_{27}H_{18}N_4OS$: C, 72.63; H, 4.06; N, 12.55. Found C, 72.75; H, 3.98; N, 12.37.

7-Amino-3,4,8-triphenylpyridazino[4',3':4,5]thieno[3,2-b][1,8]naphthyridine (9h):

Following the same procedure as described for the preparation of **9a-f** (work up B), but using phenylacetonitrile instead of appropriate ketone, compound (**9h**) was purified by flash chromatography using CH_2Cl_2/AcOEt (15/1, v/v) as eluent. Yield 67%; mp >300°C (EtOH/acetone). IR (KBr): 3480, 3380 (NH), 1640, 1430. ^1H NMR δ ($CDCl_3$): 5.31 (br s, 2H, NH_2), 7.17-7.37 (m, 15H, $3C_6H_5$), 7.52 (s, 5H, C_6H_5), 7.81 (s, 1H, H-9), 8.46 (s, 1H, H-10). MS (EI, *m/z*, %): 481 (M^+, 36), 404 (10). *Anal.* Calcd for $C_{30}H_{19}N_5S$: C, 74.82; H, 3.98; N, 14.54. Found C, 74.95; H, 4.04; N, 14.63.

7-Amino-8-cyano-3,4-diphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyridine (9i):

A solution of **8** (0.10 g, 0.30 mmol), malononitrile (0.025 g, 0.37 mmol) and a catalytic amount of piperidine in THF (10 mL) was stirred at rt for 1 d. The solvent was removed under reduced pressure and the residue was triturated with a hot mixture of EtOH/acetone (1/1). The solid was filtered off to give **9i** (0.04 g, 36%); mp >300°C (DMF). IR (KBr): 3440, 3320 (NH), 2220 (CN), 1650, 1480, 1430, 1190. ^1H NMR δ ($CDCl_3$): 5.83 (br s, 2H, NH_2), 7.30-7.50 (m, 10H, $2C_6H_5$), 8.40 (s, 1H, H-9), 8.53 (s, 1H, H-10). MS (EI, *m/z*, %): 430 (M^+, 14). *Anal.* Calcd for $C_{25}H_{14}N_6S$: C, 69.75; H, 3.28; N, 19.52. Found C, 69.82; H, 3.34; N, 19.46.

General Procedure for the Synthesis of Derivatives (10a-d).

A solution of **8** (0.10 g, 0.30 mmol), the appropriate ketone (0.37 mmol) and a few drops of 10% KOH (ethanolic) in ethanol (10 mL) was stirred at rt (**10c,d** were refluxed) until starting material had disappeared as checked by TLC and then worked up in one of the following ways: (A) After cooling, the solid formed was filtered off and recrystallized from a suitable solvent. (B) The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

3,4-Diphenyl-7,8,9,10-tetrahydropyridazino[4',3':4,5]thieno[2,3-*g*]benzo[*b*][1,8]naphthyridine (**10a**). Recrystallized from EtOH/CH_2Cl_2. Yield 75%; mp 280°C (decomp). IR (KBr): 2970, 1550, 1530, 1490, 1460, 1445, 1420, 1380. ^1H NMR δ ($CDCl_3$): 1.91 (br s, 4H, CH_2), 3.03 (t, 2H, J = 5.7 Hz, CH_2), 3.14 (t, 2H, J = 5.7 Hz, CH_2), 7.28-7.52 (m, 10H, $2C_6H_5$), 7.90 (s, 1H, H-11), 8.58 (s, 1H, H-12). MS (EI, *m/z*, %): 444 (M^+, 100), 222 (16). *Anal.* Calcd for $C_{28}H_{20}N_4S$: C, 75.65; H, 4.53; N, 12.60. Found C, 75.54; H, 4.42; N, 12.71.

9-Benzoyl-3,4-diphenyl-7,8,9,10-tetrahydropyridazino[4',3':4,5]thieno[3,2-*b*][1,7,10]anthyridine (**10b**). Purified by flash chromatography using CH_2Cl_2/AcOEt (2/1, v/v) as eluent. Yield 49%; mp 200-202°C (EtOH/CH_2Cl_2). IR (KBr):1640 (CO), 1500, 1420, 1250. ^1H NMR δ ($CDCl_3$): 3.28 (br s, 2H, CH_2), 3.85 (br s, 2H, CH_2), 5.10 (br s, 2H, CH_2), 7.24-7.50 (m, 15H, $3C_6H_5$), 8.03 (s, 1H), 8.67 (s, 1H). ^{13}C NMR δ ($CDCl_3$): 33.8, 44.4, 45.0 (CH_2), 120.9, 126.9, 127.3, 127.9, 128.1, 128.3, 128.7, 128.8, 129.0, 130.4, 132.3, 132.9, 133.2, 135.2, 136.6, 152.3, 153.1, 158.2, 160.7, 164.9, 171.3 (CO). MS

(EI, *m/z*, %): 549 (M^+, 12), 105 (100). *Anal.* Calcd for $C_{34}H_{23}N_5OS$: C, 74.30; H, 4.22; N, 12.74. Found C, 74.38; H, 4.17; N, 12.69.

3,4-Diphenyl-7,8-dihydro-10*H*-pyridazino[4',3':4,5]thieno[2,3-*g*]pyrano[4,3-*b*][1,8]naphthyridine (**10c**). Purified by flash chromatography CH_2Cl_2/MeOH (40/1, v/v) as eluent. Yield 70%; mp 275°C (decomp, EtOH). IR (KBr): 1610, 1550, 1460, 1450, 1440, 1380, 1325. ^1H NMR δ ($CDCl_3$): 3.24 (t, 2H, J = 5.8 Hz, CH_2), 4.13 (t, 2H, J = 5.8 Hz, CH_2), 4.97 (s, 2H, CH_2), 7.24-7.54 (m, 10H, $2C_6H_5$), 7.87 (s, 1H, H-9), 8.62 (s, 1H, H-10). ^{13}C NMR δ ($CDCl_3$): 33.0 (CH_2), 65.5, 67.5 (OCH_2), 120.8, 127.3, 127.9, 128.1, 128.2, 128.7, 130.3, 130.8, 131.1, 131.9, 133.0, 136.4, 136.6, 152.2, 152.6, 158.1, 160.1, 164.8. MS (EI, *m/z*, %): 446 (M^+, 67). *Anal.* Calcd for $C_{27}H_{18}N_4OS$: C, 72.63; H, 4.06; N, 12.55. Found C, 72.58; H, 4.13; N, 12.62.

3,4-Diphenyl-7,8-dihydro-10*H*-pyridazino[4',3':4,5]thieno[2,3-*g*]thiopyrano[4,3-*b*][1,8]naphthyridine (**10d**). Recrystallized from EtOH/CH_2Cl_2. Yield 72%; mp 230°C (decomp). IR (KBr): 3000, 1610, 1550, 1500, 1470, 1460, 1440, 1420, 1380. ^1H NMR δ ($CDCl_3$): 3.08 (t, 2H, J = 6.4 Hz, CH_2), 3.42 (t, 2H, J = 6.4 Hz, CH_2), 3.96 (s, 2H, CH_2), 7.23-7.52 (m, 10H, $2C_6H_5$), 7.97 (s, 1H, H-11), 8.65 (s, 1H, H-12). MS (EI, *m/z*, %): 462 (M^+, 100), 427 (12), 416 (34), 239 (11). *Anal.* Calcd for $C_{27}H_{18}N_4S_2$: C, 70.10; H, 3.92; N, 12.11. Found C, 69.97; H, 3.89; N, 12.03.

General Procedure for the Synthesis of Derivatives (11a,b).

A solution of **8** (0.08 g, 0.21 mmol), the appropriate diketone (0.10 mmol) and a few drops of 10% KOH (ethanolic) in EtOH/THF (15 mL) was refluxed until all starting material had disappeared as checked by TLC. After cooling, the solid formed was filtered off.

1,3-Di-(3,4-diphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyrid-7-yl)benzene (**11a**). Yield 55%; mp >300°C (DMF). IR (KBr): 1600, 1530, 1440, 1360. ^1H NMR δ ($CDCl_3$): 7.31-7.71 (m, 20H), 8.09 (t, 1H), 8.15 (d, 1H, J = 8.3 Hz), 8.25 (d, 1H, J = 8.8 Hz), 8.41 (t, 4H, J= 8.8 Hz), 8.75 (d, 2H, J = 6.3 Hz), 8.90 (t, 1H). MS (FAB, *m/z*, %): 855 [$(MH)^+$, 11], 509 (100), 405 (46). *Anal.* Calcd for $C_{54}H_{30}N_8S_2$: C, 75.86; H, 3.58; N, 13.11. Found C, 75.72; H, 3.71; N, 13.28.

2,6-Di-(3,4-diphenylpyridazino[4',3':4,5]thieno[3,2-*b*][1,8]naphthyrid-7-yl)pyridine (**11b**). Yield 75%; mp >300°C (DMF). IR (KBr): 1600, 1560. ^1H NMR δ ($CDCl_3$): 7.28-7.65 (m, 20H, H), 8.09 (t, 1H, J = 7.8 Hz, H-4), 8.45 (d, 2H, J = 8.3 Hz, H-8'), 8.74 (d, 2H, J = 7.8 Hz, H-2, H-3), 8.77 (s, 2H, H-10'), 9.01 (d, 2H, J = 8.3 Hz, H-9'). MS (FAB, *m/z*, %): 856 [$(MH)^+$, 15], 548 (32), 281 (60), 185 (100). *Anal.* Calcd for $C_{53}H_{29}N_9S_2$: C, 74.37; H, 3.41; N, 14.73. Found C, 74.59; H, 3.35; N, 14.67.

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