SUBSTITUTED 3-AMINOTHIENO[2,3-*b*]PYRIDINE-2-CARBOXAMIDE AS A SYNTHON FOR POLYHETEROCYCLIC COMPOUNDS. PREPARATION OF NEW PYRIDOTHIENO-1,2,3-TRIAZINES AND RELATED DERIVATIVES

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Abstract- Pyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazines **(2)** and **(3)** were synthesized from 3-aminothieno[2,3-*b*]pyridine **(1)** by diazotization and subsequent treatment with electrophilic reagents. Reaction of triazinone **(2)** with phosphorus oxychloride lead to a mixture of the triheterocyclic compound **(4)** and the 4-chlorosubstituted triazine **(5)**. Aminolysis of **4** with either hydrazine or primary and secondary amines yielded the derivatives **(7a-h)**. Nitrosation of **7a** afforded the 4-substituted triazinone **(8)**. Finally, substituted 1,3,4-oxadiazole **(9)** was prepared from acylhydrazine **(7a)** and triethyl orthoformate.

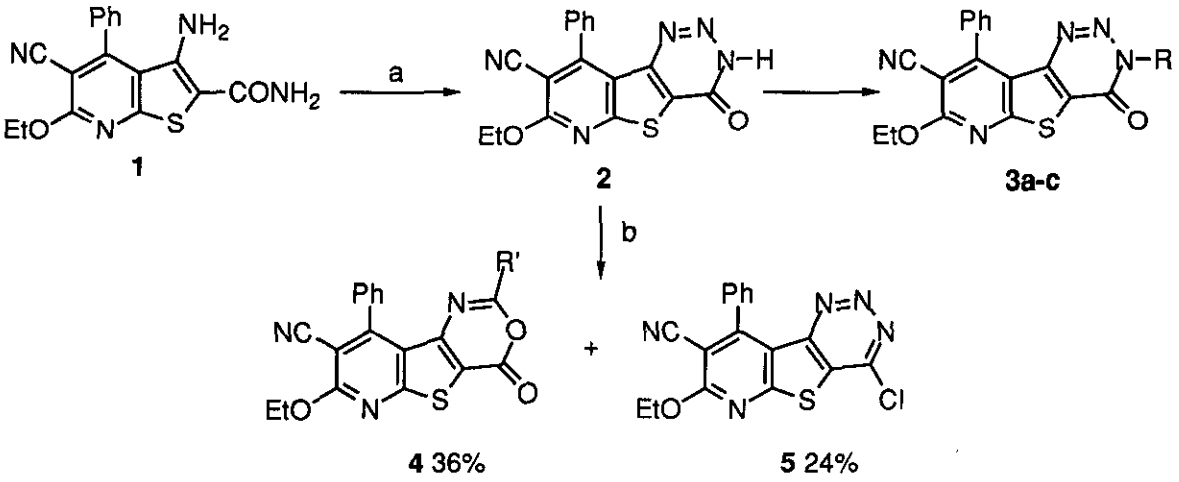
Few papers[1] dealing with monocyclic 1,2,3-triazines have so far been published; also, the number of known compounds of this type is still fairly small.[2] Much more information is available on 1,2,3-benzotriazines, the earliest member of which was prepared in the last century.[3] The increased interest[4] in the chemistry of these compounds is a result of the wide range of biological activity associated with many derivatives of 1,2,3-benzotriazin-4(3*H*)-one. In addition to 1,2,3-benzotriazines, other 1,2,3-triazine systems condensed with carbocycles or heterocycles are known.[5] Because some triazinones exhibit antiallergic activity,[6] and as part of our research programme[7] aimed at the preparation of novel thiophene-fused heterocycles of therapeutical significance, we report on the utility of 3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide[8] as a synthon for the preparation of pyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazines with potential biological activity.

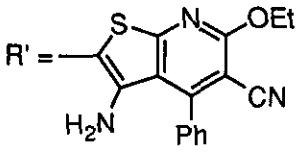
Diazonium ion condensation with an adjacent nucleophilic function to form a five- or six-membered ring has proved useful for synthesizing various nitrogen heterocycles including a number of 1,2,3-triazines[9] that are formed *via* intramolecular attack of an electrophilic nitrogen function. Thus,

1,2,3-triazin-4-ones, 4-chloro-1,2,3-triazines or 1,2,3-triazine 3-oxides are obtained by condensation of the diazonium ion with an adjacent carboxamide,[10] cyanide[11] or ketoxime,[12] respectively.

As part of a study of tricyclic hetero systems arrays possessing a pyridothiophene nucleus, these reactions were used to prepare new pyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazines. The triazinones were synthesized as shown in Scheme 1.

Scheme 1





Reagents: a: $NaNO_2$, AcOH, 5°C, 2 h or *i*-amyl nitrite, EtOH, room temperature, 24 h

b: $POCl_3$, MeCN, reflux 6 h

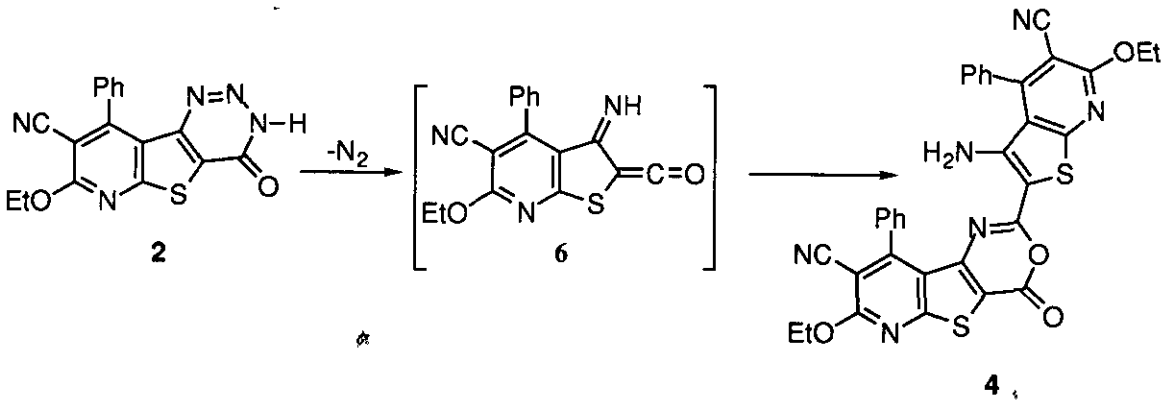
3	R
a	Me
b	CH_2COPh
c	CH_2CN

Nitrosation of 3-aminothieno[2,3-*b*]pyridine-2-carboxamide **(1)**[8] with sodium nitrite in acetic acid at 5°C or isoamyl nitrite in ethanol at room temperature gave the triazin-4(3*H*)-one **(2)**, which was obtained in analytically pure form directly from the reaction mixture in 77% and 48% yields, respectively. Methylation of the thieno[3,2-*d*]-*N*-triazin-4(*3H*)-one with methyl iodide reportedly yields the 3-methylated product.[13] By using the same procedure, the triazinone **(2)** was converted into 3-substituted pyridothienotriazin-4(3*H*)-ones **(3a-c)** on treatment with electrophilic reagents such as methyl iodide, 2-bromoacetophenone and chloroacetonitrile, respectively.

Preparation of the 4-chlorotriazine derivative by using standard reagents such as phosphorus oxychloride, thionyl chloride or phosphorus trichloride led to decomposition of **2**, seemingly because of the instability of the triazine ring under these conditions. Thus, refluxing triazinone **(2)** with phosphorus oxychloride in acetonitrile afforded a mixture of the 4-chloro derivative **(5)** and the

2-(3-aminothienopyridyl)pyridothienoxazine derivative **(4)** (Scheme 1). The formation of compound **(4)** can be ascribed to that of the ketene intermediate **(6)**[14] (Scheme 2).

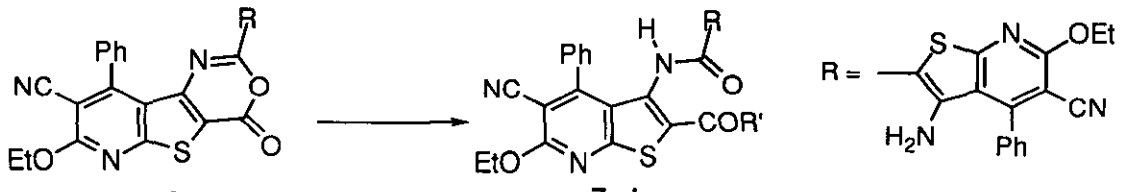
Scheme 2



2 **6** **4**

The structure of compounds **(4)** and **(5)** was established from analytical and spectral data. The mass spectra showed the expected molecular ion peaks. The most salient features of the ir, ^1H nmr and ^{13}C nmr spectra are given under Experimental.

Scheme 3

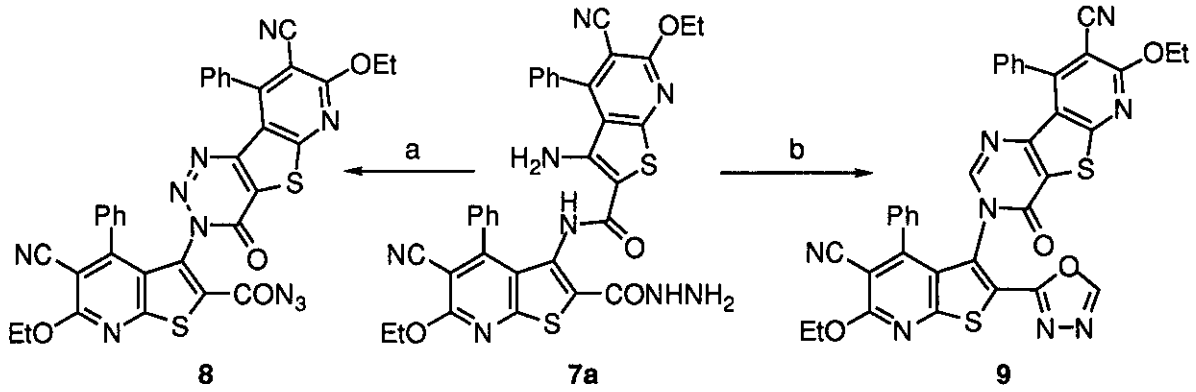


4 **7a-i**

7	R'	7	R'
a	$NHNH_2$	**f**	piperidino
b	$NMeNH_2$	**g**	morpholino
c	NHMe	**h**	4-methylpiperazino
d	NHPr	**i**	OEt
e	$NHCH_2Ph$		

Aminolisys of compound **(4)** with hydrazine, methylhydrazine and primary amines such methylamime, *n*-butylamine and benzylamine gave the corresponding substituted derivatives **(7a-d)** (Scheme 3). Similarly, reaction of **4** with secondary amines such as piperidine, morpholine and *N*-methylpiperazine afforded compounds **(7f-h)**; likewise, treatment of intermediate **(4)** with sodium ethoxide also gave rise to ring cleavage and afforded **7i**. The data used to characterize of all the compounds prepared are given under Experimental.

Scheme 4



Reagents: a: $NaNO_2$, H_2SO_4, AcOH, 5°C, 5 h
b: *p*-TsOH, $HC(OEt)_3$, reflux, 30 min

Diazotization of **7a** with nitrous acid lead directly to the 4-substituted triazine **(8)** in a 72% yield. A similar cyclization was reported for the diazotization of anthraniloylanthranilamide to 3-(2-carbamoyl-phenyl)-1,2,3-benzotriazin-4(3*H*)-one.[15] The ir spectrum of **7a** exhibited strong absorption bands at ν 3480 and 3310 cm^{-1} for -NH_2 and -CONH- groups, whereas the ir spectrum of compound **(8)** showed none of these bands. The ^1H nmr spectrum of **7a** showed characteristic shifts for the protons in the -NH_2 and -CONH- groups; also, compound **(8)** exhibited none such signals, thus indicating the occurrence diazotization and dehydrocyclization to yield the fused triazine derivative **(8)**. On the other hand, reaction between the acylhydrazine **(7a)** and ethyl orthoformate yields oxadiazole **(9)** through the respective imidol ether because it is well known that imidol ethers, prepared from acylhydrazines and ortho esters, cyclize on heating to monosubstituted oxadiazoles.[16] The structure of compound **(9)** was established from analytical and spectral data. The most salient features of the ^1H nmr, ^{13}C nmr and mass spectra are given under Experimental.

EXPERIMENTAL SECTION

All reagents used were commercial 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 383 spectrophotometer. ^1H and ^{13}C Nmr spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained at 70 eV by using a Kratos Ms-50 or VG4 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 (mplc) were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

8-Cyano-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazine (2):

Method A: To an ice-cooled solution of **1** (1.20 g, 3.55 mmol) in acetic acid (30 ml) a solution of sodium nitrite (0.43 g, 6.23 mmol) in sulphuric acid (85%) (5 ml) was added dropwise. The mixture was stirred in an ice-cooled bath for 2 h and at room temperature for 24 h. The solution was poured into water (150 ml) and the solid material was collected and recrystallized from EtOH/acetone to obtain **2** (0.95 g, 77%); mp 225 °C (decomp.). Ir (KBr): *v* 3160 (NH); 2220 (CN); 1690 (CO); 1560; 1380; 1330 cm^{-1}. ^1H Nmr (DMSO-d_6): δ 1.45 (t, 3H, *J* = 7.1 Hz, CH_3); 4.64 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.58 (s, 5H, C_6H_5); 15.61 (br s, exchangeable with D_2O, 1H, NH). ^{13}C Nmr (DMSO-d_6): δ 14.0 (CH_3); 64.7 (CH_2); 97.3 (C-8); 114.1 (CN); 118.8 (C-9a); 125.3 (C-4a); 128.1, 129.1, 130.0, 133.1 (C_6H_5); 147.5 (C-9b); 153.2 (C-5a); 155.3 (CO); 163.2, 163.7 (C-7, C-9). Ms (DEI): *m/z* (%) 642 ($2M^+ - 2N_2$, 62); 349 (M^+, 28); 320 (48); 292 (67); 267 (35). *Anal.* Calcd for $C_{17}H_{11}N_5O_2S$: C, 58.44; H, 3.17; N, 20.05. Found C, 58.28; H, 3.29; N, 20.21.

Method B: To an ice-cooled suspension of **1** (0.30 g, 0.89 mmol) in EtOH (5 ml) were added one drop of HCl (conc) and *i*-amyl nitrite (0.24 g, 2.14 mmol). The reaction mixture was stirred at room temperature for 24 h. The solid formed was finally filtered off and recrystallized from EtOH/acetone to obtain **2** (0.15, 48%).

8-Cyano-7-ethoxy-3,4-dihydro-4-oxo-9-phenyl-3-substituted Pyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazines 3a-c; General Procedure:

To a solution of **2** (0.2 g, 0.6 mmol) in acetone (10 ml) were added KOH (15%) (1 ml, 3.2 mmol) and the appropriate electrophilic reagent (1.25 mmol). The reaction mixture was stirred at room temperature for 1.5 h (**3a** and **3b**) or at reflux temperature for 5 h (**3c**). The solvent was removed at reduced pressure, water (20 ml) was added and neutralized with HCl (2N). The solid was recrystallized or purified by mplc. The following derivatives **(3a-c)** were obtained.

8-Cyano-7-ethoxy-3-methyl-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazine **(3a)**. Recrystallized from EtOH/CH_2Cl_2; yield: (80%); mp 220-222 °C. Ir (KBr): *v* 2220 (CN); 1680 (CO); 1560; 1450; 1340; 1030 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.55 (t, 3H, *J* = 7.1 Hz, CH_3); 4.04 (s, 3H, NCH_3); 4.66 (q, 2H, *J* = 7.1, OCH_2); 7.51-7.59 (m, 5H, C_6H_5). ^{13}C Nmr ($CDCl_3$): δ 14.2 (CH_3); 37.5 (NCH_3); 65.0 (OCH_2); 97.9 (C-8); 113.7 (CN); 118.6 (C-9a); 125.3 (C-4a); 128.3, 128.9, 130.4, 132.6 (C_6H_5); 147.7 (C-9b); 153.1 (C-5a); 155.8 (CO); 163.9, 164.9 (C-7, C-9). Ms (DEI): *m/z* (%) 363 (M^+, 100); 320 (33); 306 (50); 278 (53); 266 (34). *Anal.* Calcd for $C_{18}H_{13}N_5O_2S$: C, 59.49; H, 3.61; N, 19.27. Found C, 59.67; H, 3.70; N, 19.10.

8-Cyano-7-ethoxy-3-phenacyl-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazine **(3b)**. Purified by mplc. Elution with CH_2Cl_2/hexane (2:1); yield: (65%); mp 189-191 °C. Ir (KBr): *v* 2220 (CN); 1690 (CO); 1560; 1450; 1340 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.57 (t, 3H, *J* = 7.0 Hz, CH_3); 4.72 (q, 2H, *J* = 7.0, OCH_2); 5.89 (s, 2H, CH_2CO); 7.50-8.03 (m, 10H, $2C_6H_5$). ^{13}C Nmr ($CDCl_3$): δ 14.3 (CH_3); 55.5 (NCH_2); 65.1 (OCH_2); 98.0 (C-8); 113.9 (CN); 118.7 (C-9a); 125.6 (C-4a); 128.1, 128.3, 129.0, 129.1, 130.4, 132.6, 134.2, 134.4 ($2C_6H_5$); 147.5 (C-9b); 153.0 (C-5a); 155.9 (CO); 163.9, 165.9 (C-7, C-9); 190.2 ($COCH_2$). Ms (DEI): *m/z* (%) 467 (M^+, 2); 305 (4); 105 (100). *Anal.* Calcd for $C_{25}H_{17}N_5O_3S$: C, 64.23; H, 3.67; N, 14.98. Found C, 64.29; H, 3.43; N, 15.15.

8-Cyano-3-cyanomethyl-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazine **(3c)**. Purified by mplc. Elution with CH_2Cl_2/hexane (2:1); yield: (20%); mp 208-210 °C. Ir (KBr): *v* 2220 (CN); 1690 (CO); 1560; 1450;

1340 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.56 (t, 3H, J = 7.1 Hz, CH_3); 4.70 (q, 2H, J = 7.1, OCH_2); 5.28 (s, 2H, CH_2CN); 7.50-7.61 (m, 5H, C_6H_5). ^{13}C Nmr ($CDCl_3$): δ 14.3 (CH_3); 37.2 (CH_2CN); 65.3 (OCH_2); 98.5 (C-8); 112.7, 113.6 (CN); 118.5 (C-9a); 125.5 (C-4a); 128.5, 128.8, 130.6, 132.4 (C_6H_5); 147.2 (C-9b); 151.9 (C-5a); 156.1 (CO); 164.1, 165.0 (C-7, C-9). Ms (DEI): *m/z* (%) 388 (M^+, 62); 305 (26); 266 (19); 264 (23); 292 (25). *Anal.* Calcd for $C_{19}H_{12}N_6O_2S$: C, 58.76; H, 3.11; N, 21.64. Found C, 58.83; H, 3.01; N, 21.69.

Thermal decomposition of 8-Cyano-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]-thieno[3,2-*d*]-1,2,3-triazine (2):

A solution of **2** (1.4 g, 4.1 mmol) and $POCl_3$ (2.5 ml, 26.8 mmol) in MeCN (40 ml) was refluxed for 6 h. The solvent was removed at reduced pressure and the resulting solid was separed by mplc on a silica gel column, using CH_2Cl_2/hexane (3:1) (compound **4**), and CH_2Cl_2/hexane (3:2) (compound **5**) as eluents.

2-(3-Amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)-8-cyano-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido-[3',2':4,5]thieno[3,2-*d*]-1,3-oxazine (**4**); yield: (36%); mp > 300 °C. Ir (KBr): ν 3460 (NH); 2220 (CN); 1750 (CO); 1550; 1450; 1340; 1150 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.49 (t, 6H, J = 7.1 Hz, $2CH_3$); 4.58 (q, 4H, J = 7.1 Hz, $2OCH_2$); 6.90-7.88 (m, 10H, $2C_6H_5$). ^{13}C Nmr ($CDCl_3$): δ 14.3 (CH_3); 64.7, 65.0 (CH_2); 94.1; 95.4 ; 97.9; 109.5; 113.7, 113.9 (CN); 116.1; 118.5; 128.1; 128.3; 128.8; 129.0; 129.6; 130.6; 132.7; 134.3; 147.6; 151.1; 153.4; 154.4; 155.0; 160.1; 162.9; 163.4; 164.2; 166.2. *Anal.* Calcd for $C_{34}H_{22}N_6O_4S_2$: C, 63.53; H, 3.46; N, 13.08. Found C, 63.46; H, 3.43; N, 13.22.

8-Cyano-4-chloro-7-ethoxy-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazine (**5**); yield: (24%); mp 209-211 °C. Ir (KBr): ν 2220 (CN); 1540; 1390; 1340 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.58 (t, 3H, J = 7.1 Hz, CH_3); 4.75 (q, 2H, J = 7.1 Hz, OCH_2); 7.53-7.64 (m, 5H, C_6H_5). ^{13}C Nmr ($CDCl_3$): δ 14.1 (CH_3); 65.6 (CH_2); 98.6 (C-8); 113.4 (CN); 117.0; 128.7; 128.8; 129.6; 130.9; 132.1; 151.6; 152.7; 157.2; 165.3, 165.6 (C-7, C-9). Ms (FAB): *m/z* (%) 368 [$(MH)^+$, 17]; 301 (100). *Anal.* Calcd for $C_{17}H_{10}N_5OClS$: C, 55.51; H, 2.74; N, 19.04. Found C, 55.62; H, 2.68; N, 19.13.

Reaction of 2-(3-Amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)-8-cyano-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]-1,3-oxazine (4) with hydrazine, methylhydrazine or primary amines (7a-e); General Procedure:

A solution of **4** (0.23 mmol) and hydrazine, methylhydrazine or primary amine (0.28 mmol) in DMF (1 ml) was stirred at room temperature for 1 h (30 min at 65 °C for **7e**). The solvent was removed under reduced pressure and the resulting solid was purified by mplc on a silica gel column to obtain **7a,b** or recrystallized from EtOH/acetone to give **7c-e**. The following derivatives (**7a-e**) were obtained:

3-[(3-Amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]-pyridine -2-carbohydrazide (**7a**): Mplc was performed by using CH_2Cl_2/EtOH (99:1) as eluent; yield (85%); mp 170 °C (decomp.). Ir (KBr): ν 3480; 3320; 2220 (CN); 1650; 1550 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.52 (t, 3H, J = 7.1 Hz, CH_3); 1.54 (t, 3H, J = 7.1 Hz, CH_3); 3.37 (br s, 2H, NH_2); 4.63 (q, 2H, J = 7.1 Hz, OCH_2); 4.64 (q, 2H, J = 7.1 Hz, OCH_2); 5.59 (br s, 2H, NH_2); 7.15-7.64 (m, 11H, $2C_6H_5$ + NH); 8.10 (br s, 1H, NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.2 (CH_3); 64.3 (OCH_2); 95.0; 95.4; 96.8; 114.0, 114.2 (CN); 116.4; 120.8; 122.4; 127.8; 128.4; 128.9; 129.3; 130.5; 130.9; 132.4; 132.9; 147.5; 153.4; 154.3; 160.3; 162.1; 162.5; 162.6; 162.9; 164.3. Ms (FAB): *m/z* (%) 675 [$(MH)^+$, 2]; 643 [$(MH)^+$-NH_2NH_2, 8]; 322 (100); 294 (44). *Anal.* Calcd for $C_{34}H_{26}N_8O_4S_2$: C, 60.52; H, 3.88; N, 16.61. Found C, 60.40; H, 3.69; N, 16.82.

N-Methyl 3-[(3-Amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine -2-carbohydrazide **(7b)**: Mplc was performed by using CH_2Cl_2/EtOH (99:1) as eluent; yield (90%); mp > 300 °C. Ir (KBr): *v* 3480; 3340; 2220 (CN); 1640; 1550 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.49 (t, 3H, *J* = 7.1 Hz, CH_3); 1.50 (t, 3H, *J* = 7.1 Hz, CH_3); 4.60 (q, 4H, *J* = 7.1 Hz, OCH_2); 3.30 (s, 3H, NCH_3); 4.12 (br s, 2H, NH_2); 5.41 (br s, 2H, NH_2); 7.06-7.63 (m, 10H, $2C_6H_5$); 10.32 (br s, 1H, NHCO). Ms (FAB): *m/z* (%) 689 [$(MH)^+$, 2]; 643 [$(MH)^+$-$NHCH_3NH_2$, 14]; 322 (28). *Anal.* Calcd for $C_{35}H_{28}N_8O_4S_2$: C, 61.03; H, 4.10; N, 16.27. Found C, 60.87; H, 4.01; N, 16.09.

N-Methyl 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide **(7c)**; yield: (73%); mp 257-259 °C. Ir (KBr): *v* 3440; 3320; 3290; 2220 (CN); 1630; 1600 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.49 (t, 3H, *J* = 7.1 Hz, CH_3); 1.50 (t, 3H, *J* = 7.1 Hz, CH_3); 2.91 (d, 3H, *J* = 4.9 Hz, $NHCH_3$); 4.60 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.62 (q, 2H, *J* = 7.1 Hz, OCH_2); 5.49 (br s, 2H, NH_2); 6.29 (q, 1H, *J* = 4.8 Hz, $NHCH_3$); 7.05-7.63 (m, 10H, $2C_6H_5$); 8.70; (br s, 1H, NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.3 (CH_3); 26.7; 64.4 (OCH_2); 95.5; 96.9; 114.2, 114.5 (CN); 116.7; 121.0; 122.0; 127.7; 127.9; 128.8; 129.0; 129.4; 130.6; 132.0; 132.6; 133.2; 147.5; 153.5; 154.7; 160.0; 162.0; 162.4; 162.8; 163.1; 164.5. Ms (FAB): *m/z* (%) 643 [$(MH)^+$-NH_2CH_3, 29]; 322 (100). *Anal.* Calcd for $C_{35}H_{27}N_7O_4S_2$: C, 62.39; H, 4.04; N, 14.55. Found C, 62.17; H, 3.88; N, 14.67.

N-Butyl 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno-[2,3-*b*]pyridine-2-carboxamide **(7d)**; yield: (71%); mp 246-248°C. Ir (KBr): *v* 3480; 3320; 3180; 2220 (CN); 1640; 1620 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 0.80 (t, 3H, *J* = 7.2 Hz, CH_3); 1.18-1.50 (m, 4H, $CH_2CH_2CH_3$); 1.48 (t, 3H, *J* = 7.1 Hz, CH_3); 1.52 (t, 3H, *J* = 7.1 Hz, CH_3); 3.28 (q, 2H, *J* = 6.8 Hz, CH_2NH); 4.60 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.63 (q, 2H, *J* = 7.1 Hz, OCH_2); 5.50 (br s, 2H, NH_2); 6.55 (t, 1H, *J* = 6.7 Hz, CH_2NH); 7.08-7.63 (m, 10H, $2C_6H_5$); 8.32 (s, 1H, NHCO). ^{13}C Nmr ($CDCl_3$): δ 13.6, 14.3 (CH_3); 20.0; 31.2; 39.8; 64.3, 64.4 (OCH_2); 95.4; 95.5; 96.9; 114.1, 114.4 (CN); 116.6; 121.2; 125.1; 127.9; 128.5; 129.0; 129.5; 130.3; 130.6; 132.6; 133.2; 147.5; 153.5; 154.4; 160.1; 162.0; 162.1; 162.2; 162.8; 164.7. Ms (FAB): *m/z* (%) 716 [$(MH)^+$, 9]; 643 [$(MH)^+$-$CH_3(CH_2)_3NH_2$, 15]; 322 (100); 294 (44). *Anal.* Calcd for $C_{38}H_{33}N_7O_4S_2$: C, 63.76; H, 4.65; N, 13.70. Found C, 63.73; H, 4.80; N, 13.73.

N-Benzyl 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide **(7e)**; yield: (77%); mp 277-279 °C. Ir (KBr): *v* 3500; 3340; 3180; 2220 (CN); 1640; 1620 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.48 (t, 3H, *J* = 7.1 Hz, CH_3); 1.52 (t, 3H, *J* = 7.1 Hz, CH_3); 4.50 (d, 2H, *J* = 5.5 Hz, $NHCH_2$); 4.58 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.62 (q, 2H, *J* = 7.1 Hz, OCH_2); 5.47 (br s, 2H, NH_2); 6.78 (t, 1H, *J* = 5.5 Hz, $NHCH_2$); 7.10-7.63 (m, 15H, $3C_6H_5$); 8.22 (s, 1H, NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.3, 14.4 (CH_3); 44.0 (CH_2NH); 64.4, 64.5 (OCH_2); 95.3; 95.5; 97.0; 114.1, 114.4 (CN); 116.6; 121.1; 124.3; 127.5; 127.6; 128.0; 128.5; 128.6; 129.2; 129.4; 130.6; 130.7; 132.6; 133.2; 137.0; 147.6; 153.4; 154.4; 160.2; 162.0; 162.1; 162.3; 162.8; 164.6. Ms (DEI): *m/z* (%) 458 (18); 295 (24); 267 (33); 91 (100). *Anal.* Calcd for $C_{41}H_{31}N_7O_4S_2$: C, 65.67; H, 4.17; N, 13.08. Found C, 65.47; H, 4.14; N, 13.22.

Reaction of oxazine (4) with secondary amines (7f-h); General Procedure:

A solution of **4** (0.23 mmol) and appropriate secondary amine (0.28 mmol) in DMF (1 ml) was heated at 100 °C for 1 h. The solvent was removed under reduced pressure and the residue was purified by mplc. Elution with CH_2Cl_2 afforded **7f-h**. The following derivatives **(7f-h)** were obtained:

N-Piperidino 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide (**7f**); yield: (88%); mp > 300°C. Ir (KBr): *v* 3460; 3310; 2220 (CN); 1640; 1620 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.43-1.55 (m, 12H, $(CH_2)_3$ + $2CH_3$); 3.52 (br s, 4H, CH_2NCH_2); 4.59 (q, 2H, J = 7.1 Hz, OCH_2); 4.62 (q, 2H, J = 7.1 Hz, OCH_2); 5.53 (br s, 2H, NH_2); 7.14-7.73 (m, 11H, $2C_6H_5$ + NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.2 (CH_3); 24.2; 25.7; 45.8; 64.1, 64.2 (OCH_2); 95.4; 95.5; 96.7; 114.0, 114.3 (CN); 116.8; 120.5; 126.0; 126.8; 128.0; 128.1; 128.6; 129.0; 129.3; 130.5; 132.8; 133.2; 147.2; 153.2; 153.4; 160.6; 161.6; 161.8; 162.1; 162.7; 163.5. Ms (FAB): *m/z* (%) 728 [$(MH)^+$, 17]; 643 [$(MH)^+$-piperidine, 58]; 322 (83); 294 (47). *Anal.* Calcd for $C_{39}H_{33}N_7O_4S_2$: C, 64.35; H, 4.58; N, 13.47. Found C, 64.23; H, 4.55; N, 13.63.

N-Morpholino 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide (**7g**); yield: (88%); mp 195 °C (decomp.). Ir (KBr): *v* 3460; 3320; 2220 (CN); 1630; 1550 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.49 (t, 3H, J = 7.1 Hz, CH_3); 1.52 (t, 3H, J = 7.1 Hz, CH_3); 3.61 (br s, 8H, $H_{morpholine}$); 4.58 (q, 2H, J = 7.1 Hz, OCH_2); 4.62 (q, 2H, J = 7.1 Hz, OCH_2); 5.62 (br s, 2H, NH_2); 7.24-7.63 (m, 11H, $2C_6H_5$ + NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.3 (CH_3); 45.4; 64.2, 64.3 (OCH_2); 66.5; 94.7; 95.5; 96.8; 114.0, 114.2 (CN); 116.7; 120.1; 126.8; 127.9; 128.3; 128.6; 129.2; 129.4; 129.6; 130.5; 132.5; 132.9; 147.6; 152.9; 153.5; 160.6; 161.6; 162.4; 162.7; 163.0. Ms (FAB): *m/z* (%) 643 [$(MH)^+$- morpholine, 100]; 322 (62); 294 (69). *Anal.* Calcd for $C_{38}H_{31}N_7O_5S_2$: C, 62.54; H, 4.28; N, 13.43. Found C, 62.50; H, 4.07; N, 13.29.

N-(4-Methylpiperazino) 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide (**7h**); yield: (86%); mp 197 °C (decomp.). Ir (KBr): *v* 3480; 3320; 2220 (CN); 1640; 1630; 1550 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.38 (t, 3H, J = 7.1 Hz, CH_3); 1.42 (t, 3H, J = 7.1 Hz, CH_3); 2.15 (s, 3H, NCH_3); 2.31 (br s, 4H, CH_2NCH_2); 3.53 (br s, 4H, CH_2NCH_2); 4.51 (q, 2H, J = 7.1 Hz, OCH_2); 4.54 (q, 2H, J = 7.1 Hz, OCH_2); 5.46 (br s, 2H, NH_2); 7.11-7.52 (m, 11H, $2C_6H_5$ + NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.2 (CH_3); 45.1; 45.5; 54.5; 64.2, 64.3 (OCH_2); 95.1; 95.6; 96.8; 113.9, 114.1 (CN); 116.8; 120.3; 124.7; 127.0; 128.0; 128.5; 129.4; 130.5; 132.8; 133.1; 147.4; 153.1; 153.5; 160.7; 161.7; 162.5; 162.8; 163.3. Ms (FAB): 743 [$(MH)^+$, 16]; 643 [$(MH)^+$-methylpiperazine, 100]. *Anal.* Calcd for $C_{39}H_{34}N_8O_4S_2$: C, 63.06; H, 4.61; N, 15.08. Found C, 63.22; H, 4.49; N, 15.00.

Ethyl 3-[(3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-yl)carbamoyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-2-carboxylate (7i):

To a solution of NaOEt (0.02 g of Na, 0.93 mmol) in EtOH (10 ml) was added **4** (0.2 g, 0.31 mmol). The solution was refluxed for 15 min. The solvent was removed under reduced pressure. Water (30 ml) was added and the solution was neutralized with HCl (2N). The solid formed was filtered off and recrystallized from EtOH to obtain **7i** (0.17 g, 84%); mp 185 °C (decomp.). Ir (KBr): *v* 3480; 3340; 2220 (CN); 1690; 1650 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.38 (t, 3H, J = 7.1 Hz, CH_3); 1.50 (t, 3H, J = 7.1 Hz, CH_3); 1.52 (t, 3H, J = 7.1 Hz, CH_3); 4.37 (q, 2H, J = 7.1 Hz, OCH_2); 4.59 (q, 2H, J = 7.1 Hz, CH_2O); 4.62 (q, 2H, J = 7.1 Hz, CH_2O); 5.46 (br s, 2H, NH_2); 7.11-7.62 (m, 10H, $2C_6H_5$); 8.78 (s, 1H, NHCO). ^{13}C Nmr ($CDCl_3$): δ 14.1, 14.2 (CH_3); 61.9, 64.3 (OCH_2); 95.2; 95.3; 96.6; 114.0, 114.5 (CN); 115.2; 116.6; 120.0; 127.2; 127.8; 128.9; 129.1; 129.3; 130.4; 132.4; 133.3; 136.6; 147.5; 153.4; 155.3; 161.7; 161.8; 162.6; 163.1; 163.4. Ms (DEI): *m/z* (%) 688 (M^+, 2); 393 (53); 295 (72); 267 (100). *Anal.* Calcd for $C_{36}H_{28}N_6O_5S_2$: C, 62.77; H, 4.10; N, 12.20. Found C, 62.59; H, 4.27; N, 12.07.

8-Cyano-3-(2-azidocarbonyl-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridine-3-yl)-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]-1,2,3-triazine (8):

To an ice-cooled solution of **7a** (0.27 g, 0.40 mmol) in AcOH (5 ml) a solution of sodium nitrite (0.035 g, 0.50 mmol) in H_2SO_4 (85%) (0.5 ml) was added dropwise . The mixture was stirred in an ice-cooled bath for 1 h and at room temperature for 4 h. The mixture was then poured into water (50 ml), filtered off and purified by mplc using CH_2Cl_2/hexane (3:1) as eluent to obtain **8** (0.20 g, 72%); mp 210 °C (decomp.). Ir (KBr): *v* 2220 (CN); 2120 (N_3); 1640 (CO); 1550; 1400; 1330 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.53 (t, 3H, J = 7.1 Hz, CH_3); 1.57 (t, 3H, J = 7.1 Hz, CH_3); 4.67 (q, 2H, J = 7.1 Hz, CH_2O); 4.72 (q, 2H, J = 7.1 Hz, CH_2O); 6.96-7.58 (m, 10H, $2C_6H_5$). ^{13}C Nmr ($CDCl_3$): δ 14.2, 14.3 (CH_3); 65.1, 65.2 (OCH_2); 98.2; 98.6; 113.3, 113.7 (CN); 118.2; 121.8; 125.3; 127.4; 127.7; 127.8; 128.1; 128.6; 128.9; 130.5; 131.8; 132.3; 133.5; 146.2; 152.0; 154.1; 155.8; 161.7; 162.9; 163.8; 164.6; 164.9. Ms (FAB): *m/z* (%) 697 [$(MH)^+$, 10]; 643 (54); 615 (39); 307 (25); 279 (100). *Anal.* Calcd for $C_{34}H_{20}N_{10}O_4S_2$: C, 58.61; H, 2.89; N, 20.10. Found C, 58.80; H, 2.77; N, 20.02.

8-Cyano-3-(5-cyano-6-ethoxy-2-(1,3,4-oxadiazoline-2-yl)-4-phenylthieno[2,3-*b*]pyridine-3-yl)-7-ethoxy-4-oxo-9-phenyl-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (9):

A solution of **7a** (0.10 g, 0.15 mmol) and a catalytic amount of *p*-toluensulfonic acid in $CH(OEt)_3$ (3 ml) was refluxed for 30 min. The solvent was removed at reduced pressure and the residue was purified by mplc. Elution with CH_2Cl_2 afforded **9** (0.08 g, 78%); mp 258-260°C. Ir (KBr): 2220 (CN); 1670 (CO); 1560; 1340 cm^{-1}. ^1H Nmr ($CDCl_3$): δ 1.54 (t, 3H, J = 7.1 Hz, CH_3); 1.56 (t, 3H, J = 7.1 Hz, CH_3); 4.68 (q, 2H, J = 7.1 Hz, CH_2O); 4.70 (q, 2H, J = 7.1 Hz, CH_2O); 6.92-7.52 (m, 11H, $2C_6H_5$ + CH=N); 8.29 (s, 1H, OCHN). ^{13}C Nmr ($CDCl_3$): δ 14.2, 14.3 (CH_3); 64.7, 65.0 (OCH_2); 97.2; 98.5; 113.3, 114.2 (CN); 119.4; 120.6; 121.4; 127.2; 127.9; 128.1; 128.2; 128.5; 128.9; 129.3; 129.8; 131.7; 132.4; 146.2; 150.6; 152.7; 153.5; 155.7; 156.0; 161.5; 162.7; 163.5; 165.3. Ms (FAB): *m/z* (%) 695 [$(MH)^+$, 100]; 301 (19). *Anal.* Calcd for $C_{36}H_{22}N_8O_4S_2$: C, 62.24; H, 3.19; N, 16.13. Found C, 61.99; H, 3.20; N, 16.16.

ACKNOWLEDGMENTS

Financial support (Project 10303B91) and a grant awarded to C.P. by the Xunta de Galicia are gratefully acknowledged.

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Received, 11th July, 1994