Synthesis and Characterization of Substituted Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines and Related Molecules

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Received 14 December 2010; revised 24 January 2011

Abstract: An efficient access for the synthesis of substituted pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines and pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazines, heteroaromatic nitrogen ligands, is reported. The title compounds were obtained by functionalization of the corresponding chloro precursors, synthesized by reaction between 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile and *N*,*N*-dimethyldichloromethyleniminium chloride (Viehe's salt) or sodium nitrite/hydrochloric acid, respectively. Moreover, this procedure provided a convenient synthetic route to bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines), functionalized molecules that are not readily available by other synthetic methods.

Key words: heterocycles, ligands, ring closure, antitumor agents, fused-ring systems

Heteroaromatic rings are important constituents of drugs and bioactive molecules. Within drug discovery there is currently considerable interest in fragment-based approaches for the identification of novel ligands.[1] Compounds containing a pyrimidine ring play a very important part in the biochemistry of the living cell and have attracted attention in the past few years owing to their wide range of biological activity, particularly in cancer and virus research.[2] Their fused bicyclic analogues have also been reported to exhibit a variety of biological activity and constitute the backbone of several marketed drugs. Among these fused bicyclic compounds, thienopyrimidines, which are well-known bioisosteres of quinazolines, are of great importance because of their role as phamacophores of considerable historical importance[3] and their remarkable effects on the central nervous system as well as a wide variety of other biological activity.[4] Our previous work on the search for novel heterocyclic compounds of pharmacological interest have shown that certain tri- and tetracyclic ring systems, containing the pyridothienopyrimidine and pyridothienotriazine skeletons exert acute anti-inflammatory, analgesic, and anti-angiogenic effects. Thus, they represent a new approach for the potential treatment of different inflammatory pathologies, such as rheumatoid arthritis.[5] This was the first time that pyridothieno-1,2,3-triazine derivatives have been identified as effective inhibitors of nitric oxide and eicosanoid biosynthesis.[6] Besides, we showed that other analogues based on the pyridothienopyrimidine and pyridazinothienotriazine moieties were new antiprotozoals active against *Philasteridis dicentrarchi*, the causative agent of scuticociliatosis in farmed turbot and Black Sea bass-bream.[7] The pyrazine ring is found in the fungal metabolite aspergillic acid as well as in marine metabolites which exhibit mild cytotoxicity against certain human cancer cells,[8] and it is also present in other biologically natural products.[9] Besides, substituted pyrazine motifs are often found in compounds with applications as anticancer agents, including currently marketed drugs[10] and those recently reported.[11] The introduction of a pyrazine moiety to the thienopyrimidine system is expected to influence the biological activity significantly.

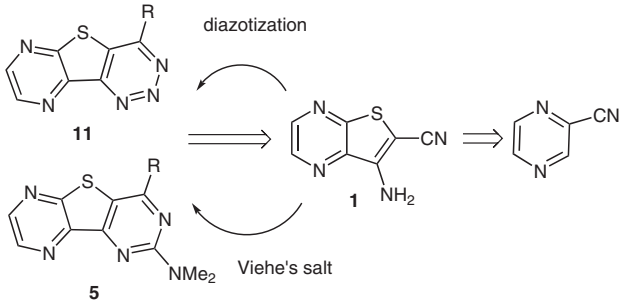
On the other hand, heteroaromatic ligands have attracted strong interest because they have found applications in several important research and technological fields.[12] Over the years, the development of aromatic azaheterocycles as ligands has provided a valuable resource for researchers who work in the field of metal–ligand coordination.[13] One of the most extensively studied N-heterocyclic chelating agents is the bidentate ligand 1,10-phenanthroline. The latter, and related N-heterocycles, are widely employed as metal-binding components in all aspects of coordination chemistry, and in many of its modern applications to areas such as supramolecular chemistry and bioinorganic chemistry.[14] The vast majority of heteroaromatic nitrogen ligands are mainly pyridine-based structures, which appears to be a serious limitation to the strong potential coordinating properties of other heteroaromatic structures. In this context, an increasingly important area of ligand design involves the synthesis and study of new bridging ligands and their use as chelating ligands.[15]

Recently, we reported the synthesis of pyrazinothienopyrimidine scaffolds by domino reactions: aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization.[16] In this work, we describe an efficient access for the synthesis of **5** and **11** which, as isosteres of pharmaceutically relevant pyridothienopyrimidines and pyridothienotriazines, could play an important role in the pathophysiology of inflammation and arthritis.

Our strategy for the synthesis of these compounds was based on the disconnection illustrated in Scheme 1. Retrosynthetic pathway indicates that the most direct and versatile route to ring systems **5** and **11**, which present the necessary functionality for fusion of the desired pyrimidine and triazine rings, was via the easily accessible 7-

SYNTHESIS 2011, No. 6, pp 0943–0953
Advanced online publication: 10.02.2011
DOI: 10.1055/s-0030-1258432; Art ID: T53410SS

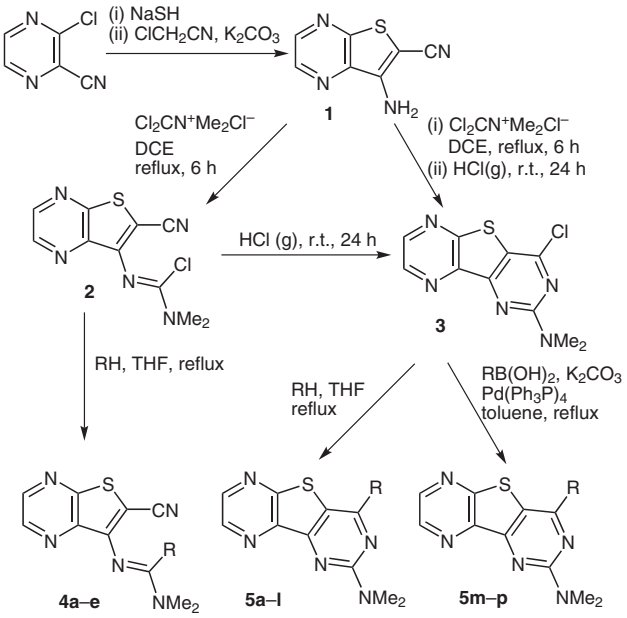
aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1**). Compound **1** was prepared by reaction between commercially available 3-chloropyrazine-2-carbonitrile and sodium hydrosulfide.[17] The resulting thiol reacted with chloroacetonitrile to give the thienopyrazine **1**.[18] In our scheme, the conversion of **1** into **5** involves the introduction of two substituents, R and NMe_2 on to the fused heterocyclic compound. To this end, we selected a dichloromethyleniminium chloride (phosgeniminium chloride), a well-known multiple electrophilic one carbon atom synthon,[19] as the reagent of choice. The dimethylamino substituent was introduced during the formation of the pyrimidine ring, and the substituent R was introduced in the last step by means of an aromatic nucleophilic substitution reaction. The above-mentioned phosgeniminium salts are very useful synthetic reagents that can function as Vilsmeier or Mannich acceptors and can lead to the insertion of a one-carbon unit bearing a dialkylamino group. This makes them especially useful in one-step heterocyclization reactions such as those considered here. In particular, cyclization reactions of aromatic *ortho*-aminonitriles with *N*,*N*-dimethyldichloromethyleniminium chloride (Viehe's salt) provided a convenient access to a number of fused pyrimidine derivatives, including natural products.[20]



Scheme 1 Retrosynthetic pathway for pyrazinothienopyrimidines **5** and pyrazinothienotriazines **11**

For the preparation of pyrazinothienotriazines **11** we were pleased to find that the intramolecular condensation of a diazonium ion with an adjacent nucleophilic function indeed furnished the desired compounds in good yields. Herein, we report the participation of 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1**) in the synthesis of triazine compounds **11** by way of diazotization followed by intramolecular condensation reaction. We considered that this methodology would be attractive due to its conciseness and practical utilization of readily synthesized or commercially available starting materials.

The synthesis of pyrazinothienopyrimidines **5** is summarized in Scheme 2. The conversion of **1** into **3** involves the introduction of one additional carbon that must conserve its electrophilic character in **3**. Thus, beginning with 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1**), the pyrimidine ring was fused to the thiophene ring by treatment with Viehe's salt in refluxing 1,2-dichloroethane to give the amide halide intermediate **2**, which was isolated by concentration of the reaction mixture and purified by medium-pressure chromatography. Intermediate **2** underwent cyclization to the corresponding pyrazinothienopyrimidine **3** by reaction with dry hydrogen chloride. One-pot synthesis using enaminonitrile **1** and *N*,*N*-dimethyldichloromethyleniminium chloride in refluxing 1,2-dichloroethane for six hours and subsequent treatment with hydrogen chloride afforded directly the chloropyrazinothienopyrimidine **3**, a fruitful precursor of the expected molecules.

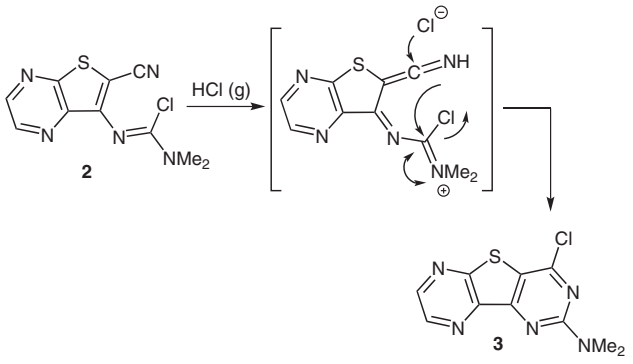


Scheme 2 Synthesis of amide halide thienopyrazines **2** and **4**, and pyrazinothienopyrimidines **3** and **5**

The structures of compounds **2** and **3** were consistent with their elemental analyses and spectral data. The mass spectra showed the expected molecular ion peak at $m/z = 266$ and the IR spectrum of **2** exhibited an absorption band at 1600 cm^{-1} due to the imino group and presented a characteristic signal at 2200 cm^{-1} (CN), while the decoupled ^{13}C NMR spectrum showed one signal at $\delta = 125.4$ due to the carbon atom in the one cyano group. In addition, IR and ^{13}C NMR spectra of compound **3** did not include those types of signals.

Phosgeniminium salts are known to undergo condensation with CH-acidic compounds such as ketones, carboxylic acids and chlorides, nitriles, and amides to give amide halides. Amide chlorides have been similarly obtained from enamines, fulvenes, barbituric acid derivatives, and pyridopyrimidines by reaction with dichloromethyleniminium salts. In addition, phosgeniminium salts do not react with the nitrile group unless it is sufficiently activated or the salts are previously transformed into chloroiminium chlorides by means of dry hydrogen chloride. Since the amide halide intermediate **2** was isolated, the reaction can be assumed to proceed as described in Scheme 3.[21]

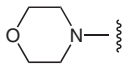
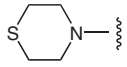
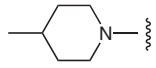
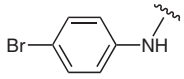
The chloride bearing group in the 7-{[chloro(dimethylamino)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbo-



Scheme 3

nitrile (**2**) reacted readily with nucleophilic agents to give the corresponding substituted products **4a–e** in good yields (Table 1). Similarly, pyrazinothienopyrimidine **3** also exhibited remarkable reactivity of its 4-chloro substituent toward nucleophilic agents such as alcohols, thiols, and amines. Thus, aliphatic and aromatic amines and hydrosulfide, alkoxide, or aryloxide anions afforded the corresponding derivatives **5a–l** (Table 2). Interestingly, the aryl derivatives **5m–p** can be prepared via a Suzuki–Miyaura cross-coupling reaction between tricyclic chloro derivative **3** and arylboronic acids using a commercially available preformed palladium catalyst (entries 13–16). Compound **5p** could be of particular interest because biaryl moieties, often found in natural products and biologically active compounds, are important fragments in medicinal chemistry.[22]

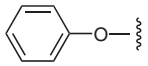
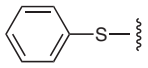
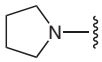
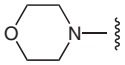
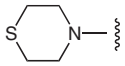
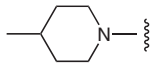
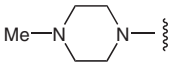
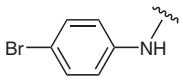
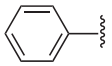
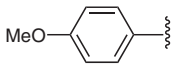
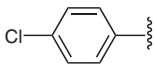
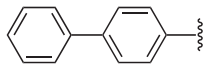
Table 1 7-{[(Dimethylamino)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitriles **4a–e**

Entry	Compd	R	Time (h)	Yield[a] (%)	Mp (°C)
1	**4a**	OEt	3	78	140–142[b]
2	**4b**		3	79	218–220[c]
3	**4c**		2	75	199–201[c]
4	**4d**		6	60	141–143[c]
5	**4e**		3	73	279–281[c]

[a] Yields refer to pure isolated products.
[b] Recrystallized (EtOH).
[c] Purified by flash chromatography (CH_2Cl_2).

Based upon these results, we next examined the reactivity of pyrazinothienopyrimidine **3** using various sulfur and nitrogen bis(nucleophiles) and, fortunately, this procedure provided a convenient synthetic route to bis(pyrazinothienopyrimidines) **6**, functionalized molecules that are not readily available by other synthetic methods. In these

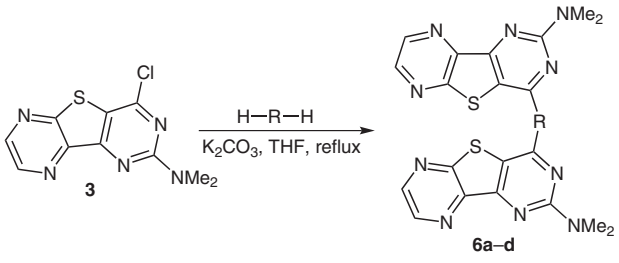
Table 2 Substituted Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines **5a–p**

Entry	Compd	R	Time (h)	Yield[a] (%)	Mp (°C)
1	**5a**	OEt	3	66	>300[b]
2	**5b**	NHBu	12	75	186–188[c]
3	**5c**	NEt_2	2	84	140–142[d]
4	**5d**	SH	24	72	>300[e]
5	**5e**		12	72	182–184[g]
6	**5f**		24	70	156–158[g]
7	**5g**		0.5	98	290–292[b]
8	**5h**		12	69	220–222[b]
9	**5i**		3	90	198–200[d]
10	**5j**		12	80	143–145[f]
11	**5k**		8	65	166–168[e]
12	**5l**		24	60	288–290[c]
13	**5m**		12	71	223–225[g]
14	**5n**		12	80	230–232[g]
15	**5o**		10	88	209–211[g]
16	**5p**		24	79	290 (dec.)[g]

[a] Yields refer to pure isolated products.
[b] Recrystallized (EtOH).
[c] Purified by flash chromatography (CH_2Cl_2–hexanes, 8:2).
[d] Purified by flash chromatography (CH_2Cl_2–EtOAc, 9:1).
[e] Washed with EtOH–THF.
[f] Purified by flash chromatography (acetone–hexanes, 1:1).
[g] Purified by flash chromatography (CH_2Cl_2).

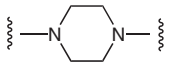
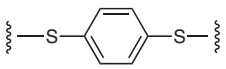
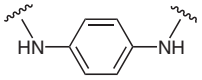
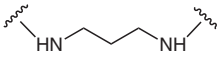
compounds, two pyrazinothienopyrimidine rings are linked via their respective C4 carbon atoms by a 1,4-phenylenedisulfanyl , piperazine-1,4-diyl, propane-1,3-diyldiamino, or 1,4-phenylenediamino chain (Scheme 4). Therefore, compound **3** was converted into the bis(pyrazinothienopyrimidine) **6a** using piperazine as the bis(nucleophile) (Table 3, entry 1). Similarly, bis(heterocycle) **6b** was obtained in acceptable yield (70%) using benzene-1,4-dithiol (entry 2). Compound **3** also reacted with diamines, and the nature of the reaction product appeared to depend on the diamine employed. When the reaction of **3**

and 1,4-phenylenediamine or propane-1,3-diamine is carried out the corresponding bis(heterocycles) **6c** and **6d** are obtained as crystalline solids in moderate yields (entry 3 and 4). However, solubility seems to be a limitation to the reaction, since the reaction with benzidine or 1,5-diaminonaphthalene afforded only pyrazinothienopyrimidines **7** and **8** (Figure 1). Finally, bis(pyrazinothienopyrimidine) **9** was obtained by reaction of chloro derivative **3** with tris(2-aminoethyl)amine in 60% yield.



Scheme 4 Synthesis of bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines) **6a–d**

Table 3 Bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines) **6a–d**

Entry	Compd	R	Time (h)	Yield[a] (%)	Mp (°C)
1	**6a**		48	67	>300[b]
2	**6b**		18	70	296–298[b]
3	**6c**		48	58	>300[b]
4	**6d**		30	53	>300[c]

[a] Yields refer to pure isolated products.
[b] Washed with EtOH–THF.
[c] Purified by flash chromatography (CH_2Cl_2–EtOH, 8:2).

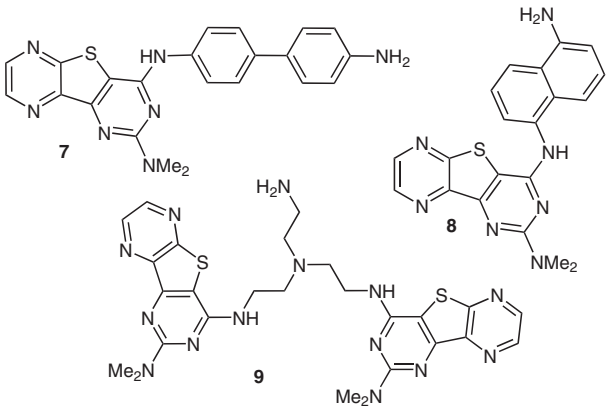
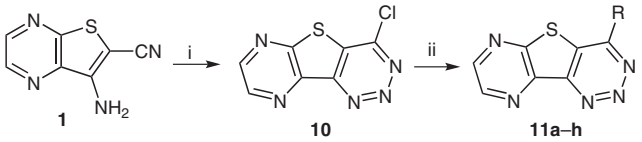


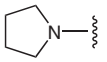
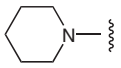
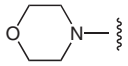
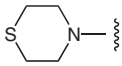
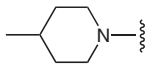
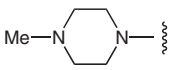
Figure 1

The preparation of pyrazinothienotriazines **10** and **11** was accomplished in good yields by intramolecular condensation of a diazonium ion with an adjacent nucleophilic function. This procedure has proven useful in the synthesis of various five- and six-membered ring nitrogen heterocycles.[23] We found, in fact, that the diazotization of the key compound 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1**) constituted a direct and very convenient route to the pyrazinothienotriazine core. The synthesis of compounds **10** and **11** is outlined in Scheme 5. Diazotization of **1** with sodium nitrite in hydrochloric acid gives a high yield (86%) of the condensed 4-chloropyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (**10**), which produced the pyrazinothieno-1,2,3-triazines **11** by halide displacement with the appropriate nucleophile (Table 4). The molecular formula of compounds **10** and **11** are supported by elemental analyses and mass spectra, which gave the expected molecular ion peaks.



Scheme 5 Synthesis of pyrazinothienotriazines **11a–h**. *Reagents and conditions*: (i) $NaNO_2$, HCl; (ii) RH, THF, reflux.

Table 4 Substituted Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazines **11a–h**

Entry	Compd	R	Time (h)	Yield[a] (%)	Mp (°C)
1	**11a**	OEt	24	79	201–203[b]
2	**11b**	NEt_2	48	81	154–155[c]
3	**11c**		12	89	285 (dec.)[b]
4	**11d**		48	70	223–224[c]
5	**11e**		24	78	274–275[d]
6	**11f**		24	59	244–246[c]
7	**11g**		2	88	204–205[c]
8	**11h**		2	73	254–256[c]

[a] Yields refer to pure isolated products.
[b] Washed with EtOH–THF.
[c] Purified by flash chromatography (CH_2Cl_2).
[d] Purified by flash chromatography (EtOAc).

These results indicate the importance and utility of 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1**) as a versatile building block in the preparation of complex polycyclic compounds. Moreover, this process represents a novel reaction sequence in the preparation of bis(pyrazinothienopyrimidines), a class of compounds that are particularly challenging to access using existing technologies.

Pyrazinothienopyrimidines and pyrazinothienotriazines have been tested in vitro for their potential antitumoral activity against four standard tumoral cell lines: LLC-PK1 (kidney carcinoma), NCI-H460 (human lung carcinoma), Hela 229 (human cervix carcinoma), and A2780 (human ovary carcinoma). The results show that the compounds are, in general, inactive. Only **4** and **5h** exhibited moderate in vitro antitumoral activity toward A2780, but **4** [IC_{50} (μM) = 13] and **5h** [IC_{50} (μM) = 8.6] were both less active than the reference cisplatin [IC_{50} (μM) = 0.47].[24]

All reagents were commercial grade chemicals from freshly opened containers. Merck 60 F_{254} foils were used for TLC and Merck 60 (230–400 mesh) silica gel for flash chromatography. NMR spectra were obtained in a Bruker Avance 300 (300 MHz and 75 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$ or DMSO-d_6 as solvent relative to TMS at δ = 0.00 ppm for ^1H and to $CDCl_3$ at δ = 77.1 ppm for ^{13}C. IR spectra were recorded as KBr disks on a Bruker VECTOR 22 spectrophotometer. Mass spectrometry experiments were carried out in a Thermo MAT 95 XP spectrometer. Melting points were measured using Stuart Scientific SMP3 apparatus and are uncorrected. Microanalyses were performed by the elemental analyses general service of the University of A Coruña on a Carlo Erba EA-1108 instrument. Antitumoral activity was measured in the Plataforma de Screening de Fármacos USEF, University of Santiago de Compostela (Spain).

7-Aminothieno[2,3-*b*]pyrazine-6-carbonitrile (1)

To a soln of 3-chloropyrazine-2-carbonitrile[17] (3.82 g, 15.64 mmol) in EtOH (100 mL) was added NaSH (20 mmol), and the mixture was stirred at r.t. for 3 h (TLC monitoring). EtOH was evaporated under reduced pressure, and the residue was dissolved in H_2O and 2 M HCl was carefully added to neutralize the suspension. After evaporation of the solvent, the residue was dissolved in acetone (40 mL) and $ClCH_2CN$ (1 mL, 15.64 mmol), K_2CO_3 (2.16 g, 15.64 mmol), and a catalytic amount of KI were added. The resulting mixture was stirred at r.t. for 1 h, and then the resulting residue was separated by filtration and washed with acetone (3 × 15 mL). The filtrate was evaporated under reduced pressure, the resulting residue was dissolved in THF (200 mL), piperidine (1.55 mL, 15.64 mL) was added, and the mixture was stirred at reflux temperature for 5 h. After cooling, the soln was concentrated to dryness, and the residual material was purified by column chromatography (THF–hexanes, 1:1) to give **1** (2.31 g, 84%); mp 205–206 °C (Lit.[18] 204–206 °C).

IR (KBr): 3328, 3231, 3204, 2197, 1643, 1566, 1529, 1351 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.80 (s, 2 H, NH_2), 8.62 (d, *J* = 2.5 Hz, 1 H), 8.66 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.3, 139.5, 141.6, 144.4, 147.1, 155.5.

MS (FAB): *m*/*z* (%) = 177 [(M + H)$^+$, 30].

Anal. Calcd for $C_7H_4N_4S$: C, 47.72; H, 2.29; N, 31.80; S, 18.20. Found: C, 47.49; H, 2.20; N, 32.08; S, 18.23.

7-{[Chloro(dimethylamino)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitrile (2)

To a suspension of **1** (2.30 g, 13.20 mmol) in 1,2-dichloroethane (100 mL) was added Viehe's salt (3.00 g, 18.50 mmol), and the mixture was refluxed for 6 h. After cooling, the solvent was removed under reduced pressure and the resulting material was recrystallized (EtOH) to give **2** (2.90 g, 80%) as yellow crystals; mp 209–211 °C.

IR (KBr): 2927, 2200, 1600, 1496, 1409, 1347, 1165, 1034 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.35 (s, 6 H), 8.72 (d, *J* = 2.3 Hz, 1 H), 8.83 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7, 104.7, 117.6, 125.4, 142.4, 145.2.

MS (EI): *m*/*z* = 268 (19), 266 [M$^+$, 61].

Anal. Calcd for $C_{10}H_8ClN_5S$: C, 45.20; H, 3.03; N, 26.36; S, 12.07. Found: C, 45.31; H, 3.20; N, 26.86; S, 11.89.

4-Chloro-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (3)

Method A: To a suspension of **1** (2.30 g, 13.20 mmol) in 1,2-dichloroethane (100 mL) was added Viehe's salt (3.00 g, 18.50 mmol), and the mixture was refluxed for 6 h. A stream of dry HCl(g) was passed through the mixture for 3 h and the mixture was allowed to stand overnight at r.t. The solvent was removed under reduced pressure and the resulting solid was recrystallized (EtOH) to afford **3** (3.17 g, 87%).

Method B: A stream of dry HCl(g) was passed trough a soln of **2** (1.45 g, 5.46 mmol) in 1,2-dichloroethane (50 mL) for 3 h. The mixture was allowed to stand overnight at r.t. The solvent was removed under reduced pressure and the resulting solid was recrystallized (EtOH) to afford **3** (1.42 g, 97%); mp 219–221 °C.

IR (KBr): 2923, 2862, 1570, 1494, 1404, 1163 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.34 (s, 6 H), 8.71 (d, *J* = 2.3 Hz, 1 H), 8.83 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 37.7, 117.6, 142.4, 143.8, 145.1, 155.6, 156.5, 159.3, 161.2.

MS (FAB): *m*/*z* (%) = 268 (13), 266 [(M + H)$^+$, 40], 246 (9), 130 (8).

Anal. Calcd for $C_{10}H_8ClN_5S$: C, 46.20; H, 3.03; Cl, 13.34; N, 26.36; S, 12.07. Found: C, 46.09; H, 3.33; N, 26.54; S, 12.20.

3-Substituted {[(Dimethylamino)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitriles 4a–e; General Procedure

To a soln of **2** (0.20 g, 0.75 mmol) in THF (10 mL) was added gradually the appropriate nucleophile (0.90 mmol). The mixture was heated at reflux temperature until **2** had disappeared (TLC monitoring). The soln was concentrated to dryness, and the residual material was purified by column chromatography or recrystallized.

7-{[(Dimethylamino)ethoxymethylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitrile (4a)

Yellow solid.

IR (KBr): 2972, 2924, 2201, 1586, 1583, 1408, 1355, 1204 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 2.90 (s, 6 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 8.61 (d, *J* = 2.3 Hz, 1 H), 8.71 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 38.0, 65.5, 88.6, 116.2, 142.4, 143.7, 154.0, 155.7, 160.1.

MS (EI): *m*/*z* = 276.

Anal. Calcd for $C_{12}H_{13}N_5OS$: C, 52.35; H, 4.76; N, 25.44; S, 11.65. Found: C, 52.56; H, 4.39; N, 25.63; S, 11.79.

7-{[(Dimethylamino)(morpholin-4-yl)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitrile (4b)

White solid.

IR (KBr): 2986, 2866, 2168, 1924, 1467, 1380, 1244, 1118, 768 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.29 (s, 6 H), 3.89 (d, *J* = 4.8 Hz, 4 H), 3.94 (d, *J* = 4.8 Hz, 4 H), 8.64 (d, *J* = 2.3 Hz, 1 H), 8.80 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.4, 46.6, 66.7, 104.7, 142.0, 144.1, 144.4, 155.6, 157.0, 158.9, 161.1.

MS (FAB): *m*/*z* (%) = 317 [(M + H)$^+$ 60], 107 (20).

Anal. Calcd for $C_{14}H_{16}N_6OS$: C, 53.15; H, 5.10; N, 26.56; S, 10.13. Found: C, 53.34; H, 5.32; N, 26.79; S, 10.45.

7-{[(Dimethylamino)(thiomorpholin-4-yl)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitrile (4c)
Yellow solid.

IR (KBr): 2990, 2854, 2169, 1561, 1522, 1264, 1225, 768 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.77–2.81 (m, 4 H), 3.28 (s, 6 H), 4.23–4.26 (m, 4 H), 8.63 (d, *J* = 2.3 Hz, 1 H), 8.79 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 37.3, 49.3, 104.7, 142.1, 144.1, 144.5, 155.6, 156.9, 158.2, 161.1.

MS (FAB): *m*/*z* (%) = 333 [(M + H)$^+$, 70].

Anal. Calcd for $C_{14}H_{16}N_6S_2$: C, 50.58; H, 4.85; N, 25.28; S, 19.29. Found: C, 50.43; H, 4.65; N, 25.17; S, 19.75.

7-{[(Dimethylamino)(4-methylpiperidin-1-yl)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitrile (4d)
Yellow solid.

IR (KBr): 2921, 2847, 2792, 2180, 1730, 1522, 1347, 1157 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.32 Hz, 3 H), 1.25–1.34 (m, 2 H), 1.78–1.86 (m, 3 H), 3.04–3.28 (m, 2 H), 3.28 (s, 6 H), 4.67–4.73 (m, 2 H), 8.61 (d, *J* = 2.3 Hz, 1 H), 8.77 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 29.6, 31.3, 34.1, 37.3, 46.8, 104.9, 141.8, 143.8, 144.6, 155.1, 157.0, 158.4, 161.2.

MS (FAB): *m*/*z* (%) = 329 [(M + H)$^+$, 100].

Anal. Calcd for $C_{16}H_{20}N_6S$: C, 58.51; H, 6.14; N, 25.59; S, 9.76. Found: C, 58.75; H, 6.36; N, 25.44; S, 9.45.

7-{[(4-Bromophenylamino)(dimethylamino)methylene]amino}thieno[2,3-*b*]pyrazine-6-carbonitrile (4e)
Garnet solid.

IR (KBr): 3279, 2928, 2166, 1615, 1547, 1441, 1391, 1169 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.36 (s, 6 H), 6.63 (s, 1 H, NH), 7.56 (d, *J* = 8.8 Hz, 2 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 8.70 (d, *J* = 2.3 Hz, 1 H), 8.86 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.9, 105.4, 117.0, 123.3, 129.0, 131.1, 132.1, 137.5, 142.4, 144.4, 155.3, 157.6, 161.8, 168.0.

MS (FAB): *m*/*z* (%) = 403 [(M + H)$^+$, 60], 401 (58), 322 (45).

Anal. Calcd for $C_{16}H_{13}BrN_6S$: C, 47.89; H, 3.27; N, 20.94; S, 7.99. Found: C, 47.31; H, 3.03; N, 21.12; S, 7.65.

4-Substituted 2-(Dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines 5; General Procedure
To a soln of **3** (0.10 g, 0.37 mmol) in THF (15 mL) was added gradually the appropriate nucleophile (0.44 mmol). The mixture was heated at reflux temperature until **3** had disappeared (TLC monitoring). The soln was concentrated to dryness, and the residual material was purified by column chromatography or recrystallized.

2-(Dimethylamino)-4-ethoxypyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5a)
Yellow solid.

IR (KBr): 2986, 2933, 2792, 1583, 1528, 1408, 1334 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (t, *J* = 7.1 Hz, 3 H), 3.36 (s, 6 H), 4.63 (q, *J* = 7.1 Hz, 2 H), 8.65 (d, *J* = 2.3 Hz, 1 H), 8.79 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 37.5, 62.7, 106.0, 141.7, 143.9, 164.0.

MS (FAB): *m*/*z* (%) = 276 [(M + H)$^+$, 100].

Anal. Calcd for $C_{12}H_{13}N_5OS$: C, 52.35; H, 4.76; N, 25.44; S, 11.65. Found: C, 52.66; H, 4.34; N, 25.12; S, 11.25.

4-(Butylamino)-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5b)
Yellow solid.

IR (KBr): 2958, 2857, 1591, 1560, 1524, 1396, 1335, 1229 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45–1.52 (m, 3 H), 1.64–1.75 (m, 4 H), 3.30 (s, 6 H), 3.61–3.71 (m, 2 H), 4.70 (br s, 1 H, NH, exchangeable with D_2O), 8.60 (d, *J* = 2.3 Hz, 1 H), 8.77 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 20.1, 37.4, 40.8, 105.0, 141.8, 143.5, 145.1, 153.4, 157.0, 157.4, 161.9.

MS (FAB): *m*/*z* (%) = 303 [(M + H)$^+$, 100].

Anal. Calcd for $C_{14}H_{18}N_6S$: C, 55.61; H, 6.00; N, 27.79; S, 10.60. Found: C, 55.32; H, 6.23; N, 27.51; S, 10.94.

4-(Diethylamino)-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5c)
White solid.

IR (KBr): 3041, 2975, 2929, 1537, 1352, 1080 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.0 Hz, 6 H), 3.38 (s, 6 H), 3.80 (q, *J* = 7.0 Hz, 4 H), 8.63 (d, *J* = 2.3 Hz, 1 H), 8.79 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 37.3, 43.6, 126.3, 141.8, 143.8, 144.5, 154.8, 157.1, 157.3, 161.2.

MS (FAB): *m*/*z* (%) = 303 [(M + H)$^+$, 100].

Anal. Calcd for $C_{14}H_{18}N_6S$: C, 55.61; H, 6.00; N, 27.79; S, 10.60. Found: C, 55.44; H, 6.18; N, 27.94; S, 10.44.

2-(Dimethylamino)-4-mercaptopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5d)
Yellow solid.

IR (KBr): 3066, 2927, 2796, 1657, 1489, 1407, 1148, 989 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.34 (s, 6 H), 8.89 (d, *J* = 2.3 Hz, 1 H), 8.96 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.3, 55.4, 60.2, 120.1, 143.4, 143.7, 146.7, 155.8, 158.2, 158.4, 160.9.

MS (FAB): *m*/*z* (%) = 264 [(M + H)$^+$, 20], 219 (10), 176 (30).

Anal. Calcd for $C_{10}H_9N_5S_2$: C, 45.61; H, 3.44; N, 26.59; S, 24.35. Found: C, 45.56; H, 3.32; N, 26.67; S, 24.45.

2-(Dimethylamino)-4-phenoxypyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5e)
Yellow solid.

IR (KBr): 3046, 2925, 1693, 1581, 1545, 1405, 788 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.14 (s, 6 H), 7.28–7.33 (m, 3 H), 7.42–7.47 (m, 2 H), 8.68 (d, *J* = 2.3 Hz, 1 H), 8.82 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (FAB): *m*/*z* (%) = 323 [(M + H)$^+$, 85], 191 (70), 136 (68).

Anal. Calcd for $C_{16}H_{13}N_5OS$: C, 59.43; H, 4.05; N, 21.61; S, 9.92. Found: C, 59.11; H, 4.32; N, 21.90; S, 9.75.

2-(Dimethylamino)-4-(phenylthio)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5f)
Orange solid.

IR (KBr): 2920, 2851, 1676, 1646, 1516, 1162 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 6 H), 7.46–7.48 (m, 3 H), 7.67–7.71 (m, 2 H), 8.67 (d, *J* = 2.3 Hz, 1 H), 8.79 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1, 127.1, 129.0, 129.7, 136.0, 142.0, 144.6, 153.9, 160.6.

MS (FAB): *m*/*z* (%) = 340 [(M + H)$^+$, 100].

Anal. Calcd $C_{16}H_{13}N_5S_2$: C, 56.61; H, 3.86; N, 20.63; S, 18.89. Found: C, 56.83; H, 3.76; N, 20.42; S, 18.99.

2-(Dimethylamino)-4-(pyrrolidin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5g)
White solid.

IR (KBr): 3051, 2937, 2856, 1556, 1535, 1400, 1208 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.04–2.07 (m, 4 H), 3.27 (s, 6 H), 3.88–3.91 (m, 4 H), 8.59 (d, *J* = 2.3 Hz, 1 H), 8.76 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 37.2, 47.5, 105.1, 141.6, 143.4, 144.5, 154.1, 156.6, 157.3, 161.4.

MS (FAB): *m*/*z* (%) = 301 [(M + H)$^+$, 100].

Anal. Calcd for $C_{14}H_{16}N_6S$: C, 55.98; H, 5.37; N, 27.98; S, 10.67. Found: C, 55.93; H, 5.33; N, 27.79; S, 10.95.

2-(Dimethylamino)-4-(morpholin-4-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5h)
Yellow solid.

IR (KBr): 2888, 1643, 1537, 1170, 1070 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.31 (s, 6 H), 3.89 (t, *J* = 4.8 Hz, 4 H), 3.91 (t, *J* = 4.8 Hz, 4 H), 8.64 (d, *J* = 2.3 Hz, 1 H), 8.80 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.4, 46.6, 66.7, 142.1, 144.1, 155.6, 157.0, 158.9, 161.2.

MS (FAB): *m*/*z* (%) = 317 [(M + H)$^+$, 100].

Anal. Calcd for $C_{14}H_{16}N_6OS$: C, 53.15; H, 5.10; N, 26.56; S, 10.13. Found: C, 53.34; H, 5.11; N, 26.23; S, 10.15.

2-(Dimethylamino)-4-(thiomorpholin-4-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5i)
Yellow solid.

IR (KBr): 3048, 2987, 2849, 1552, 1398, 1175 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 (d, *J* = 5.0 Hz, 4 H), 3.34 (s, 6 H), 4.25 (d, *J* = 5.0 Hz, 4 H), 8.63 (d, *J* = 2.3 Hz, 1 H), 8.79 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 37.4, 49.9, 66.7, 104.7, 142.1, 144.5, 155.6, 157.0, 158.9, 161.2.

MS (FAB): *m*/*z* (%) = 333 [(M + H)$^+$, 100], 259 (15), 149 (29).

Anal. Calcd for $C_{14}H_{16}N_6S_2$: C, 50.58; H, 4.85; N, 25.28; S, 19.29. Found. C, 50.66; H, 4.83; N, 25.46; S, 19.05.

2-(Dimethylamino)-4-(4-methylpiperidin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5j)
Yellow solid.

IR (KBr): 3040, 2952, 2856, 1535, 1383, 1115, 943 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.38 Hz, 3 H), 1.24–1.37 (m, 2 H), 1.76–1.80 (m, 3 H), 3.02–3.12 (m, 2 H), 3.27 (s, 6 H), 4.65–4.71 (m, 2 H), 8.59 (d, *J* = 2.3 Hz, 1 H), 8.76 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 31.3, 34.1, 46.7, 104.8, 141.8, 143.8, 144.6, 155.1, 156.9, 158.3, 161.2.

MS (FAB): *m*/*z* (%) = 329 [(M + H)$^+$, 100].

Anal. Calcd for $C_{16}H_{20}N_6S$: C, 58.51; H, 6.14; N, 25.59; S, 9.76. Found: C, 58.75; H, 6.45; N, 25.37; S, 9.43.

2-(Dimethylamino)-4-(4-methylpiperazin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5k)
White solid.

IR (KBr): 3051, 2848, 2761, 1523, 1175, 965 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 2.58 (t, *J* = 4.80 Hz, 4 H), 3.29 (s, 6 H), 3.96 (t, *J* = 4.80 Hz, 4 H), 8.62 (d, *J* = 2.3 Hz, 1 H), 8.78 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.4, 46.0, 46.1, 54.9, 104.8, 141.9, 144.0, 144.6, 155.4, 157.0, 158.6, 161.1.

MS (FAB): *m*/*z* (%) = 330 [(M + H)$^+$, 100], 259 (42).

Anal. Calcd for $C_{15}H_{19}N_7S$: C, 54.69; H, 5.81; N, 29.76; S, 9.73. Found: C, 54, 74; H, 5.99; N, 29.82; S, 9.45.

4-[(4-Bromophenyl)amino]-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5l)
Garnet solid.

IR (KBr): 3016, 2920, 1693, 1373, 1237, 1104 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.30 (s, 6 H), 6.50 (s, 1 H, NH, exchangeable with D_2O), 7.50–7.65 (m, 4 H), 8.66 (d, *J* = 2.3 Hz, 1 H), 8.82 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7, 123.1, 131.9, 142.2, 144.1, 155.1.

MS (FAB): *m*/*z* (%) = 403 (95), 401 [(M + H)$^+$, 100].

Anal. Calcd for $C_{16}H_{13}BrN_6S$: C, 47.89; H, 3.27; N, 30.94. S, 7.99. Found: C, 47.99; H, 3.11; N, 30.59; S, 8.20.

4-Substituted 2-(Dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines 5m–p; General Procedure
To a soln of **3** (0.10 g, 0.37 mmol) in anhyd toluene (5 mL) were added the appropriate boronic acid (0.56 mmol), K_2CO_3 (64 mg, 0.47 mmol), and $Pd(PPh_3)_4$ (11 mg, 0.0094 mmol). The mixture was heated at 100 °C under argon until **3** had disappeared (TLC monitoring). After cooling, the resulting precipitate was filtered off, the soln was concentrated to dryness, and the residual material was purified by column chromatography.

2-(Dimethylamino)-4-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5m)
White solid.

IR (KBr): 2851, 2793, 2193, 1584, 1505, 1444, 1337 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.43 (s, 6 H), 7.58–7.61 (m, 3 H), 8.17–8.20 (m, 2 H), 8.70 (d, *J* = 2.3 Hz, 1 H), 8.85 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 37.6, 128.4, 128.9, 130.8, 137.6, 142.1, 144.3, 144.7, 156.3, 159.3, 161.1, 161.8.

MS (FAB): *m*/*z* (%) = 308 [(M + H)$^+$, 100].

Anal. Calcd for $C_{16}H_{13}N_5S$: C, 62.52; H, 4.26; N, 22.78; S, 10.43. Found: C, 62.66; H, 4.20; N, 22.99; S, 10.15.

2-(Dimethylamino)-4-(4-methoxyphenyl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5n)
White solid.

IR (KBr): 3013, 2927, 1608, 1463, 1405, 1265, 1172, 838 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.35 (s, 6 H), 3.76 (s, 3 H), 6.76–6.78 (m, 4 H), 8.71 (d, *J* = 2.3 Hz, 1 H), 8.84 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.5, 55.4, 114.3, 130.1, 142.1, 144.6, 146.0, 161.8.

MS (FAB): *m*/*z* (%) = 338 [(M + H)$^+$, 100].

Anal. Calcd for $C_{17}H_{15}N_5OS$: C, 60.52; H, 4.48; N, 20.76; O, 4.74; S, 9.50. Found: C, 60.19; H, 4.41; N, 20.72; S, 9.75.

4-(4-Chlorophenyl)-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5o)
White solid.

IR (KBr): 3053, 2960, 1557, 1525, 1404, 1337, 1172, 762 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.43 (s, 6 H), 7.53–7.55 (m, 2 H), 8.04–8.16 (m, 2 H), 8.72 (d, *J* = 2.3 Hz, 1 H), 8.86 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.6, 126.4, 128.6, 130.1, 130.8, 135.1, 139.4, 142.2, 144.1, 144.9, 156.6, 159.6, 161.7.

MS (FAB): *m*/*z* (%) = 345 (37), 342 [(M + H)$^+$, 100].

Anal. Calcd $C_{16}H_{12}ClN_5S$: C, 56.22; H, 3.54; N, 10.37; S, 9.38. Found: C, 56.01; H, 3.84; N, 10.44; S, 9.55.

4-(Biphenyl-4-yl)-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (5p)
IR (KBr): 3036, 2920, 2850, 2352, 1554, 1403, 1169, 766 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.45 (s, 6 H), 7.42–7.53 (m, 3 H), 7.72 (d, *J* = 7.7 Hz, 2 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.28 (d, *J* = 8.4 Hz, 2 H), 8.72 (d, *J* = 2.3 Hz, 1 H), 8.86 (d, *J* = 2.3 Hz, 1 H).

^{13}C RMN (75 MHz, $CDCl_3$): δ = 37.6, 127.2, 127.6, 127.9, 128.9, 136.4, 140.2, 142.1, 143.7, 144.3, 144.8, 156.3, 160.7, 161.8.

MS (FAB): *m*/*z* (%) = 384 [(M + H)$^+$, 20], 345 (15), 191 (70).

Anal. Calcd for $C_{22}H_{17}N_5S$: C, 68.91; H, 4.47; N, 18.26; S, 8.36. Found: C, 68.81; H, 4.37; N, 18.37; S, 8.45.

Bis[pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines] 6a–d and Compounds 7–9; General Procedure
To a soln of **3** (0.20 g, 0.74 mmol) in THF (25 mL) were added the appropriate bis(nucleophile) (0.32 mmol) and a catalytic amount of K_2CO_3. The mixture was heated at reflux temperature until **3** had disappeared (TLC monitoring). The soln was concentrated to dryness, and the residual material was purified by column chromatography or recrystallized.

1,4-Bis[2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl]piperazine (6a)
Yellow solid.

IR (KBr): 2988, 2895, 2856, 1561, 1538, 1457, 1238 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.63–2.65 (s, 8 H), 3.34 (s, 12 H), 8.92 (d, *J* = 2.3 Hz, 2 H), 8.99 (d, *J* = 2.3 Hz, 2 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (ESI): *m*/*z* = 545.

Anal. Calcd for $C_{24}H_{24}N_{12}S_2$: C, 52.95; H, 4.44; N, 30.86; S, 11.77. Found: C, 52.76; H, 4.12; N, 30.78; S, 11.97.

1,4-Bis{[2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl]sulfanyl}benzene (6b)
IR (KBr): 2911, 2845, 1612, 1508, 1398, 1156, 788 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.35 (s, 12 H), 8.30 (s, 4 H), 8.65 (d, *J* = 2.3 Hz, 2 H), 8.68 (d, *J* = 2.3 Hz, 2 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (FAB): *m*/*z* (%) = 601 [(M + H)$^+$, 60].

Anal. Calcd for $C_{26}H_{20}N_{10}S_4$: C, 51.98; H, 3.36; N, 23.31; S, 21.35. Found: C, 51.65; H, 3.40; N, 23.50; S, 21.45.

1,4-Bis{[2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl]amino}benzene (6c)
Yellow solid.

IR (KBr): 2963, 2865, 1640, 1493, 1359, 1164, 955 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.37 (s, 12 H), 6.89 (s, 2 H, NH, exchangeable with D_2O), 8.49 (s, 4 H), 8.73 (d, *J* = 2.3 Hz, 2 H), 8.76 (d, *J* = 2.3 Hz, 2 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (ESI): *m*/*z* = 567.

Anal. Calcd for $C_{26}H_{22}N_{12}S_2$: C, 55.11; H, 3.91; N, 29.66; S, 11.32. Found: C, 55.36; H, 4.02; N, 29.45; S, 11.07.

***N,N′*-Bis[2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl]propane-1,3-diamine (6d)**
Yellow solid.

IR (KBr): 3270, 2923, 2194, 1583, 1559, 1400, 1341, 1167 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.22–1.26 (m, 2 H), 3.35 (s, 12 H), 3.73–3.75 (m, 4 H), 6.98 (br s, 2 H, NH, exchangeable with D_2O), 8.78 (d, *J* = 2.3 Hz, 2 H), 8.84 (d, *J* = 2.3 Hz, 2 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (FAB): *m*/*z* (%) = 533 [(M + H)$^+$, 30], 345 (15), 192 (100).

Anal. Calcd for $C_{23}H_{24}N_{12}S_2$: C, 51.86; H, 4.54; N, 31.56; S, 12.04. Found: C, 51.78; H, 4.67; N, 31.23; S, 12.32.

4-[(4′-Aminobiphenyl-4-yl)amino]-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (7)
Yellow solid.

IR (KBr): 3042, 2539, 1585, 1490, 1167, 817 cm^{-1}.

^1H NMR (3000 MHz, DMSO-d_6): δ = 3.23 (s, 6 H), 7.11–7.15 (m, 4 H), 7.64–7.68 (m, 2 H), 7.94–7.97 (m, 2 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.87 (d, *J* = 2.3 Hz, 1 H), 9.69 (s, 1 H, NH, exchangeable with D_2O).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (FAB): *m*/*z* (%) = 414 [(M + H)$^+$, 45], 276 (35).

Anal. Calcd for $C_{22}H_{19}N_7S$: C, 63.90; H, 4.63; N, 23.71; S, 7.75. Found: C, 63.80; H, 4.54; N, 24.04; S, 7.62.

4-(5-Amino-1-naphthylamino)-2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (8)
Yellow solid.

IR (KBr): 3347, 2920, 2851, 1681, 1528, 1373, 774 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.09 (s, 6 H), 5.84 (s, 2 H, NH_2, exchangeable with D_2O), 6.85 (d, *J* = 7.1 Hz, 1 H), 7.17–7.22 (m, 1 H), 7.44 (d, *J* = 7.4 Hz, 1 H), 7.50 (d, *J* = 7.1 Hz, 1 H), 7.93–7.97 (m, 1 H), 8.12 (d, *J* = 7.4 Hz, 1 H), 8.72 (d, *J* = 2.3 Hz, 1 H), 8.82 (d, *J* = 2.3 Hz, 1 H), 9.72 (s, 1 H, NH, exchangeable with D_2O).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.1, 104.4, 108.3, 111.1, 122.3, 123.3, 123.9, 126.0, 127.6, 132.4, 133.8, 142.6, 143.9, 145.0, 145.6, 154.6, 157.6, 158.1, 161.6.

MS (FAB): *m*/*z* (%) = 388 [(M + H)$^+$, 50], 276 (100).

Anal. Calcd for $C_{20}H_{17}N_7S$: C, 62.00; H, 4.42; N, 25.30; S, 8.28. Found: C, 61.97; H, 4.75; N, 25.21; S, 8.07.

N,N′-Bis[2-(dimethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl]tris(2-aminoethyl)amine (9)
Yellow solid.

IR (KBr): 3290, 3167, 2960, 2176, 1588, 1446, 1384, 1323, 1064 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.63 (br s, 2 H, NH_2, exchangeable with D_2O), 2.43 (t, *J* = 5.9 Hz, 4 H), 2.55 (t, *J* = 5.6 Hz, 2 H), 2.70–2.83 (m, 2 H), 2.89–2.95 (m, 4 H), 3.24 (s, 12 H), 6.50 (t, *J* = 4.1 Hz, 2 H, NH, exchangeable with D_2O), 8.48 (d, *J* = 2.3 Hz, 2 H), 8.69 (d, *J* = 2.3 Hz, 2 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (FAB): *m*/*z* (%) = 605 [(M + H)$^+$, 30).

Anal. Calcd for $C_{26}H_{32}N_{14}S_2$: C, 51.64; H, 5.33; N, 32.43; S, 10.60. Found: C, 51.52; H, 5.47; N, 32.64; S, 10.37.

4-Chloropyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (10)
To an ice-cooled soln of **1** (0.90 g, 5.10 mmol) in HCl–AcOH (1:1, 100 mL) was added dropwise a soln $NaNO_2$ (0.70 g, 10.20 mmol) in H_2O (5 mL). The mixture was stirred at the same temperature for 2 h, and then poured into H_2O (75 mL). The resulting solid was filtered off, washed with H_2O (pH 7), and subjected to chromatography (silica gel, CH_2Cl_2) to give **10** (0.97 g, 86%) as yellow crystals; mp 182–183 °C.

IR (KBr): 1535, 1512, 1309, 1070, 1045, 866, 822, 439 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.96 (d, *J* = 2.3 Hz, 1 H), 9.14 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): 132.4, 141.9, 144.8, 147.1, 149.6, 154.4, 157.8.

MS (FAB): *m*/*z* (%) = 225 (17), 223 [(M + H)$^+$, 50], 188 (36), 159 (100), 132 (11).

Anal. Calcd for $C_7H_2ClN_5S$: C, 37.60; H, 0.90; N, 31.31; S, 14.34. Found: C, 37.12; H, 0.58; N, 31.13; S, 14.65.

4-Substituted Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazines 11; General Procedure
To a soln of **10** (0.15 g, 0.67 mmol) in THF (15 mL) was added gradually the appropriate nucleophile (1.60 mmol). The mixture was stirred at reflux temperature until **10** had disappeared (TLC monitoring). The precipitated solid was filtered off, washed with THF, and purified by column chromatography (silica gel) or recrystallized.

4-Ethoxypyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11a)
Yellow solid.

IR (KBr): 3056, 2983, 2936, 1548, 1522, 1330 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (t, *J* = 7.1 Hz, 3 H), 4.95 (q, *J* = 7.1 Hz, 2 H), 8.85 (d, *J* = 2.3 Hz, 1 H), 9.03 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 65.5, 120.0, 142.5, 143.9, 145.9, 157.6, 160.2.

MS (FAB): *m*/*z* (%) = 234 [(M + H)$^+$, 100], 206 (7).

Anal. Calcd for $C_9H_7N_5OS$: C, 46.34; H, 3.02; N, 30.03; S, 12.32. Found: C, 46.11; H, 3.50; N, 29.75; S, 12.12.

4-(Diethylamino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11b)
White solid.

IR (KBr): 3060, 2974, 2931, 2868, 1560, 1489, 1151 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 6.8 Hz, 6 H), 3.96 (q, *J* = 6.8 Hz, 4 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.98 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 44.1, 99.9, 143.7, 145.5, 152.4, 156.1.

MS (FAB): *m*/*z* (%) = 261 [(M + H)$^+$, 100], 233 (21).

Anal. Calcd for $C_{11}H_{12}N_6S$: C, 50.75; H, 4.65; N, 32.28; S, 12.32. Found: C, 50.97; H, 4.44; N, 32.12; S, 12.47.

4-(Pyrrolidin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11c)
Yellow solid.

IR (KBr): 3052, 2964, 2872, 1564, 1520, 1317, 1163 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.16–2.19 (m, 4 H), 3.98–4.05 (m, 4 H), 8.74 (d, *J* = 2.3 Hz, 1 H), 8.93 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.9, 46.0, 54.7, 115.7, 142.8, 143.8, 145.7, 147.6, 153.0, 156.0.

MS (FAB): *m*/*z* = 259 [(M + H)$^+$, 100], 231 (17), 136 (18).

Anal. Calcd for $C_{11}H_{10}N_6S$: C, 51.15; H, 3.90; N, 32.54; S, 12.41. Found: C, 51.53; H, 3.77; N, 32.59; S, 12.11.

4-(Piperidin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11d)
White solid.

IR (KBr): 3053, 3000, 2940, 2856, 1552, 1488, 1354 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 6 H), 4.10 (s, 4 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.97 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 26.1, 47.6, 115.5, 143.7, 145.5, 147.5, 152.8, 156.0.

MS (FAB): *m*/*z* (%) = 273 [(M + H)$^+$, 100], 245 (32), 109 (31).

Anal. Calcd for $C_{12}H_{12}N_6S$: C, 52.95; H, 4.44; N, 30.86; S, 11.77. Found: C, 53.26; H, 4.64; N, 30.50; S, 11.60.

4-(Morpholin-4-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11e)
Yellow solid.

IR (KBr): 3060, 2979, 2922, 2872, 1964, 1666, 1543 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.82–3.85 (m, 4 H), 4.04–4.07 (m, 4 H), 9.00 (d, *J* = 2.3 Hz, 1 H), 9.12 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.2, 36.2, 46.3, 66.3, 116.2, 142.3, 144.8, 147.0, 147.7, 153.6, 156.2, 162.8.

MS (FAB): *m*/*z* (%) = 275 [(M + H)$^+$, 96], 247 (17), 137 (66).

Anal. Calcd for $C_{11}H_{10}N_6OS$: C, 48.17; H, 3.67; N, 30.64; S, 11.69. Found: C, 48.62; H, 3.24; N, 30.45; S, 11.65.

4-(Thiomorpholin-4-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11f)
Orange solid.

IR (KBr): 3010, 2980, 2953, 2878, 1522, 1488, 1282 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.87–2.89 (m, 4 H), 4.37–4.39 (m, 4 H), 9.01 (d, *J* = 2.3 Hz, 1 H), 9.12 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 49.4, 79.1, 79.4, 79.7, 116.3, 142.2, 144.8, 147.0, 147.7, 153.6, 156.2.

MS (FAB): *m*/*z* (%) = 291 [(M + H)$^+$, 100], 263 (14), 136 (32).

Anal. Calcd for $C_{11}H_{10}N_6S_2$: C, 45.50; H, 3.47; N, 28.94; S, 22.09. Found: C, 45.18; H, 3.63; N, 28.94; S, 22.25.

4-(4-Methylpiperidin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11g)
Yellow solid.

IR (KBr): 3001, 2952, 2858, 1556, 1472, 1342, 965 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): 1.02 (s, 3 H), 1.36–1.41 (m, 2 H), 1.91–1.95 (m, 3 H), 3.27–3.36 (m, 2 H), 4.90–4.96 (m, 2 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.99 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): 21.6, 31.1, 34.2, 46.8, 115.6, 143.0, 143.8, 145.6, 147.5, 152.9, 156.0.

EM (FAB): *m*/*z* (%) = 287 [$(M + H)^+$, 80], 137 (72), 107 (25).

Anal. Calcd for $C_{13}H_{14}N_6S$: C, 54.53; H, 4.93; N, 29.35; S, 11.20. Found. C, 54.67; H, 4.79; N, 29.10; S, 11.44.

4-(4-Methylpiperazin-1-yl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazine (11h)
Yellow solid.

IR (KBr): 3009, 2888, 2773, 1549, 1519, 1194, 1142, 996, 847 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 2.64 (t, *J* = 5.0 Hz, 4 H), 4.16 (t, *J* = 5.0 Hz, 4 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.98 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.9, 46.0, 54.7, 115.7, 142.8, 143.8, 145.7, 147.6, 153.0, 156.0.

MS (FAB): *m*/*z* (%) = 288 [$(M + H)^+$, 60].

Anal. Calcd for $C_{12}H_{13}N_7S$: C, 50.16; H, 4.56; N, 34.12; S, 11.16. Found: C, 50.35; H, 4.30; N, 34.01; S, 11.34.

Acknowledgment

This work was supported by Ministerio de Ciencia y Tecnología (Spain) and FEDER (project CTQ2007-63839). A.F.-M. acknowledges predoctoral fellowships from the Xunta de Galicia (Spain).

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