Tetrahedron 64 (2008) 11136–11143

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient one-pot three-step domino synthesis of substituted bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones)

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ARTICLE INFO

Article history:
Received 1 September 2008
Received in revised form 19 September 2008
Accepted 19 September 2008
Available online 1 October 2008

Keywords:
Nitrogen heterocycles
Domino reactions
Aza-Wittig reaction
Pyrazinothienopyrimidine

ABSTRACT

A convenient and efficient one-pot three-step domino approach to bis(pyrazinothienopyrimidinones) from ethyl 3-(triphenylphosphoranylideneamino)-thieno[2,3-*b*]pyrazine-6-carboxylate **1** has been developed. In this method, treatment of phosphazene **1** with a mixture of isocyanates, nitrogen, sulfur, and oxygen bis(nucleophiles) and K_2CO_3 in refluxing THF regioselectively furnishes the corresponding bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones) in satisfactory to good yields. This methodology is highly versatile and efficient for the generation of these functionalized bis(triheterocyclic) compounds that are not readily available by other synthetic methods.

1. Introduction

Nitrogen-containing heterocyclic molecules occur in many natural products, and are also found in fine chemicals and biologically active pharmaceuticals vital for enhancing the quality of life.[1] These structures represent a class of molecules that act as ligands for various biological receptors with a high degree of binding affinity. In this context, an increasing important area of ligand design involves the synthesis and study of new bridging ligands[2] and their use as chelating ligands.[3]

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps, and the possibility of designing a 'one-pot' sequence for the construction of complex molecules is a major driving force for new synthetic methodologies.[4] Tandem reactions are efficient strategies in organic synthesis, since they enable multiple transformations via a series of cascade reactions. Consequently, they have found wide application in the preparation of complex molecules. For example, several interesting nitrogen-containing natural products have been synthesized using tandem, domino, and cascade reactions.[5]

On the other hand, heteroaromatic nitrogen ligands have been the focus of much work especially for their extended applications in several important research and technological fields. The vast majority of heteroaromatic nitrogen ligands covers solely pyridine-based structures, which appears as a serious limitation to the strong potential coordinating properties of other heteroaromatic structures. In this context, an increasing important area of ligand design involves the synthesis and study of new bridging ligands and their use as chelating ligands.

Staudinger–Wittig/heterocumulene-mediated annelation processes have been utilized for the synthesis of nitrogen heterocycles.[6] In the context of our ongoing studies on fused nitrogen-containing heterocyclic construction,[7] we wish to report a simple and efficient one-pot three-step domino process, involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization, for the preparation of bis(pyrazinothienopyrimidinone) derivatives **5** and **6** as isosteres of pharmaceutically relevant pyridothienopyrimidines as well as their use as appropriate 1,10-phenantroline-like ligands toward transition metals. We envisioned that the employment consecutively of an aryl or alkyl isocyanate and a bifunctional reactant containing both nucleophilic sites in such a reaction as depicted in Scheme 1 would result in the formation of bis(*N*-heterocycles) compounds.

The syntheses presented in this paper rely on the following reactions: (a) reaction of Staudinger ylide with isocyanate to afford a carbodiimide, (b) addition of a bisnucleophile to the carbodiimide to generate a bis amidine, and (c) lactamization of the latter with neighboring ethyl ester group to deliver fused pyrimidones. Although all the three steps are well-known the reactions are carried out in a one-pot operation leading to complex molecules. This three-step synthesis in a one-pot process is economically and environmentally very advantageous by the simplicity of procedure,

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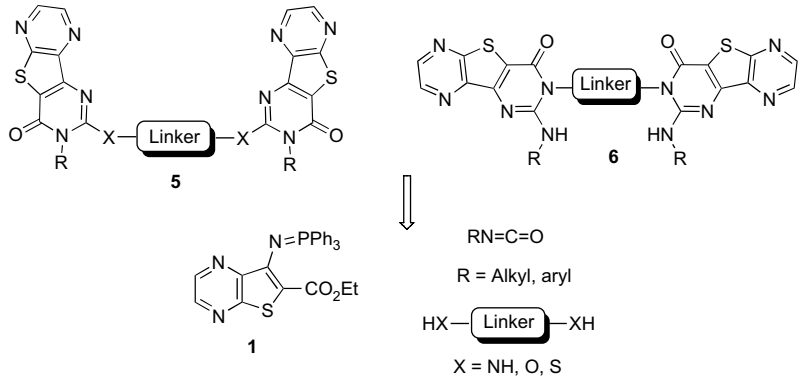
doi:10.1016/j.tet.2008.09.067



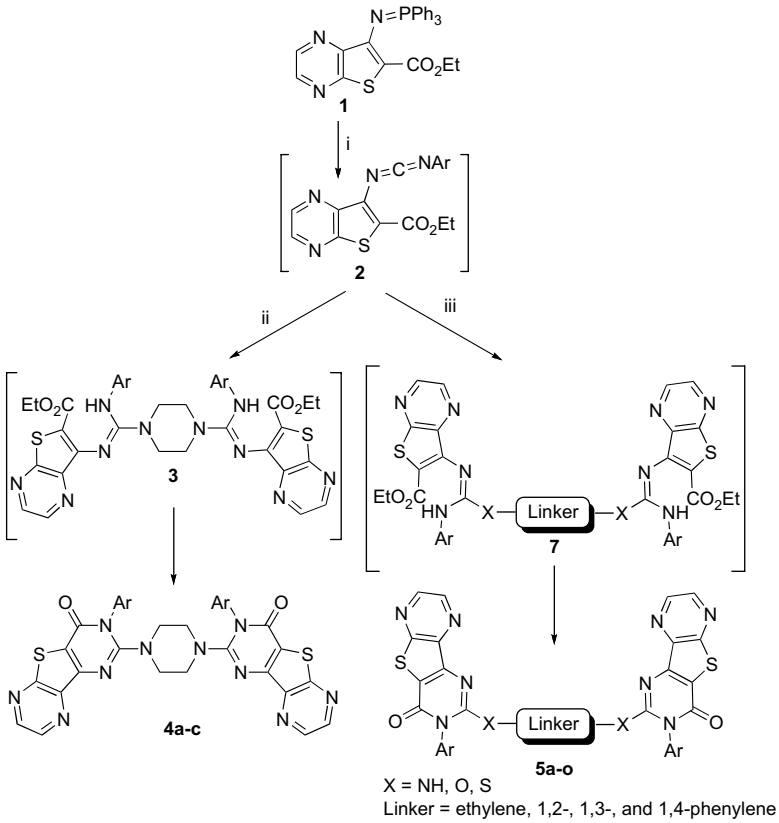
Scheme 1. Retrosynthetic analysis for the synthesis of bis(pyrazinothienopyrimidinones) **5** an **6**.

reduction of isolation and purification steps, time, costs, and waste production.

2. Results and discussion

We first tested the reaction of ethyl 3-(triphenylphosphoranylideneamino)-thieno[2,3-*b*]pyrazine-6-carboxylate **1**[8] with phenyl isocyanate (Scheme 2). The reaction proceeded smoothly in THF at room temperature. After consumption of the starting materials in 1 h, as monitored by TLC, piperazine was added to the reaction mixture. We found that in order to facilitate the intramolecular annulation it was necessary the presence of a catalytic amount of a base, and the best results were obtained employing catalytic K_2CO_3 that assisted the cyclization reaction to afford 1,4-bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-2(4*H*)-yl]piperazine **4a** in a 73% yield (entry 1, Table 1). Pyrimido-annulation occurs via a heterocumulene moiety, available from the reaction of the phosphazene **1** and phenyl isocyanate, which, in turn, was conveniently converted, by a one-pot domino procedure, into the corresponding fused bis(heterocycle) system **4**, via initial double nucleophilic addition of piperazine to the carbodiimide cumulenic system **2** to give the bis(guanidine) intermediate **3**, followed by intramolecular hetero conjugate addition annulation in the presence of anhydrous potassium carbonate (Scheme 2).

We envisioned that the present domino protocol might be applied for the preparation of **4b** and **4c** when 4-methyl- or 4-nitrophenyl isocyanate instead of phenyl isocyanate is used as one of the components (Table 1, entries 2 and 3). As demonstrated in Table 1, the reaction is practically irrespective of the fact whether the substituents on the benzene were electron-withdrawing or



Scheme 2. Reagents and conditions: (i) ArNCO, THF (3 h, rt). (ii) Piperazine and K_2CO_3 (1 h, reflux). (iii) Bisnucleophilic reagent: HX–Linker–XH, K_2CO_3, reflux, 1–2 h.

Table 1
Bispyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4a–c**

Entry	Compd	Ar	Yield (%)	Mp (°C)
1	**4a**	C_6H_5	73	>300
2	**4b**	4-CH_3–C_6H_4	52	>300
3	**4c**	4-NO_2–C_6H_4	51	>300

Table 2
2-Dialkylaminopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **5a–l**

Entry	Compd	X	Linker	Ar	Yield (%)	Mp (°C)
1	**5a**	S	CH_2CH_2	C_6H_5	81	>300
2	**5b**	S	1,3-C_6H_4	C_6H_5	77	>300
3	**5c**	S	1,4-C_6H_4	C_6H_5	80	>300
4	**5d**	O	1,3-C_6H_4	C_6H_5	75	200–201
5	**5e**	O	1,4-C_6H_4	C_6H_5	78	>300
6	**5f**	NH	$CH_2CH_2CH_2$	C_6H_5	74	265–267
7	**5g**	NH	$CH_2CH_2CH_2$	4-CH_3–C_6H_5	69	150–152
8	**5h**	NH	CH_2CHCH_3	C_6H_5	57	218–220
9	**5i**	NH	1,2-C_6H_4	C_6H_5	56	225–227
10	**5j**	NH	1,2-C_6H_4	4-CH_3-C_6H_5	40	176–177
11	**5k**	NH	1,2-C_6H_4	4-NO_2-C_6H_5	36	>300
12	**5l**	NH	1,3-C_6H_4	C_6H_5	72	259–260[a]
13	**5m**	NH	1,4-C_6H_4	C_6H_5	79	203–205
14	**5n**	NH	4,4′-$(C_6H_4)_2$	C_6H_5	79	>300
15	**5o**	NH	2,6-C_6H_3N	C_6H_5	53	270–272[a]

[a] Decomposition.

electron-releasing. Thus, replacing the phenyl in isocyanate with tolyl or 4-nitrophenyl had a negligible effect on the enhancement of reaction efficiency. This can be attributed to the greater steric hindrance of substituted phenyl groups.

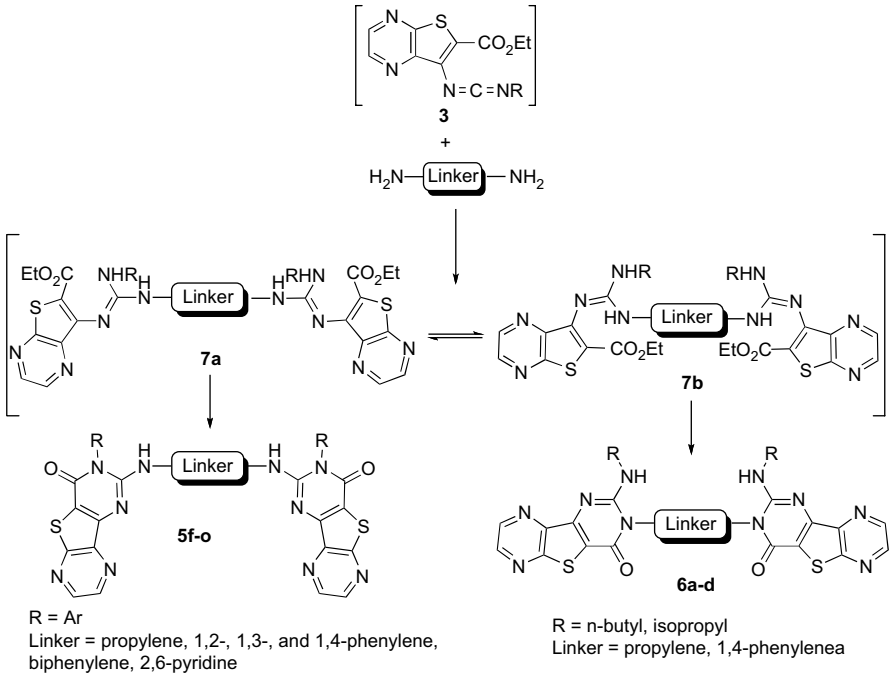
Encouraged by the aforementioned results and with the suitable reaction conditions in hand, we next tested the feasibility of the protocol using various nitrogen, sulfur, and oxygen bis(nucleophiles). Fortunately, this one-pot procedure provided a straightforward synthetic route to the pyrazinothienopyrimidine core structure, but also generated a set of functionalized molecules that are not readily available by other synthetic methods. Therefore, as shown in Table 2, the phosphazene **1** was converted into the bis-(pyrazinothienopyrimidinones) **5a–c** by a domino reaction sequence similar to that shown in Scheme 2 employing phenyl isocyanate and α,ω-dithiols. In compounds **5a–c**, two pyrazinothienopyrimidine rings are linked via their respective C2 carbon atoms by an ethylene, 1,3-phenylene, or 1,4-phenylene dithioether chain (Table 2, entries 1–3). Bis(heterocycles) **5d** and **5e**, in which the two pyrazinothienopyrimidinones are linked by a 1,3-phenylene or 1,4-phenylene diether, were prepared by a similar sequence of reactions (Table 2, entries 4 and 5).

The reactions of Staudinger ylide **1** with phenyl isocyanate and 1,3-propylenediamine or 1,2-diaminopropane provided only bis(heterocycles) **5f–h** (Table 2, entries 6–8), in which the two pyrazinothienopyrimidine rings are linked via their respective C2 carbon atoms by a 1,3-propylene or 1,2-propylene chain, with total selectivity. Compounds were characterized from their spectral data, and the study of ^{1}H NMR spectra led us to confirm the structure of products without difficulty. In particular, in the ^{1}H NMR spectra of **5h**, the protons of the NH groups display a characteristic triplet or doublet multiplicity depending on the coupling with the methylene or methine protons adjacent to the nitrogen atom. Its chemical shift is 4.31 and 5.13, more shielded than the one in PhNH of compounds **6**.[8] For example, the ^{1}H NMR spectrum of **5f** shows the signal of NH at 4.31 as a triplet and NCH_2 at 3.72 as a quartet. When the sample was treated with D_2O, its NCH_2 showed the signal as a triplet with disappearance of signals of NH absorption.

Likewise, reaction of phosphazene **1** with phenyl isocyanate and aromatic primary diamines as 1,2-, 1,3-, or 1,4-phenylenediamine, benzidine, or 2,6-diaminopyridine is regioselective and resulted only in the formation of triphenylphosphine oxide and the corresponding bis(heterocyclic) compounds **5i–o** (Table 2, entries 9–15), with the two pyrazinothienopyrimidinone systems linked by a 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, biphenylene, or 2,6-pyridinediamine chain. Steric hindrance seems to be a limitation to the reaction, as the reaction with 1,2-phenylenediamine and substituted aryl isocyanates only afforded low yields of the corresponding bis(pyrazinothienopyrimidines) **5j** and **5k** (entries 10 and 11, Table 2).

It is interesting to note that the reaction of Staudinger ylide **1** with alkyl isocyanates, as *n*-butyl or isopropyl isocyanate, followed by addition of an primary diamine, as 1,3-propylenediamine or phenylenediamines, is also regioselective but affords only bis(pyrazinothienopyrimidinones) **6a–d** in moderate yields, isomeric compounds **5** not being formed (Scheme 3, Table 3). Moreover, more time was needed for the reaction to proceed satisfactorily. Thus, Staudinger–Wittig reaction of phosphazene **1** with isopropyl isocyanate and 1,3-propanediamine, in tetrahydrofuran solution at reflux temperature for 5 h, gave bis(pyrazinothienopyrimidine) **6a** in 78% yield (entry 1, Table 3), whose formation was confirmed by their spectroscopic data. In particular, the ^{1}H NMR spectra of compound **6a** show the signals of NH at 5.45, as a doublet, due to coupling with the methine proton adjacent to the nitrogen atom, and NCH at 4.66–4.76, as a multiplet, which suggest the existence of ^{i}PrNH group in **6a**. Moreover, its NCH_2 showed the signal at 4.26 (J=7.1 Hz), as triplet, and the central methylene protons on the propylene moiety at 2.26 (J=7.1 Hz), as a quintuplet, in concordance with the proposed structure. However, steric hindrance seems to be a limitation to the intramolecular cyclization, as the reaction with 1,4- or 1,2-phenylenediamine afforded a mixture of the bis (pyrazinothienopyrimidines) **6b–d** and the corresponding pyrazino [2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **8b–d** (Scheme 4). Moreover, more time was needed for the reaction to proceed satisfactorily: 9 h were necessary for **6b**, 10 h for **6c**, and 14 h were needed for **6d**. Thus, we found that bis(pyrazinothienopyrimidines) **6b–d** were isolated and fully identified by treating phosphazene **1** with *n*-butyl or isopropyl isocyanate and 1,4- or 1,2-phenylenediamine. The tetrahydrofuran solutions containing phosphazene **1**, alkyl isocyanate, and the appropriate phenylenediamine were heated at reflux temperature up to total disappearance of phosphazene. Column chromatography of the final reaction mixtures obtained from this treatment allowed the isolation of pure coupling bis(heterocycles) **6b–d** in not very good yields. Isopropyl or *n*-butylaminopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **8b–d** were also isolated from the reaction mixtures (entries 2–4, Table 3). The sequential treatment, in the same reaction flask, of a tetrahydrofuran solution of phosphazene **1** with the amino derivatives **8b–d** and isopropyl isocyanate or *n*-butyl isocyanate led to the corresponding linked bis(heterocycles) **6b–d** in 55–70% yield after heating at reflux temperature for 8 h.

Mass and spectroscopic data of the prepared compounds **6** are in good agreement with the proposed structures. The IR spectra of compounds **6** reveal, for example, N–H and C=O absorption bands between 3434–2922 and 1690–1646 cm^{-1}, respectively. The four aromatic protons on the benzene ring of **6b** and **6c** are identical and do not couple with each other. These signals are found at 7.67 for **6b** and 7.66 for **6c** as a singlet, which suggest identical neighbors for all the protons on the benzene ring in compounds **6b**,**c**. In particular, the ^{1}H NMR spectra of compound **6c** show the signals of NH at 5.37, as a doublet, due to coupling with the methine proton adjacent to the nitrogen atom, and NCH at 4.62–4.70, as a multiplet, which suggest the existence of NH-isopropyl group in **6c**, in concordance with the proposed structure. Indeed, consistently with that observed in the spectroscopic and crystal data of bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)benzene **6b**, also obtained by a tandem aza-Wittig reaction of phosphazene **1** with 1,4-



Scheme 3. Bispyrazinothienopyrimidinones **5f–o** and **6a–d**.

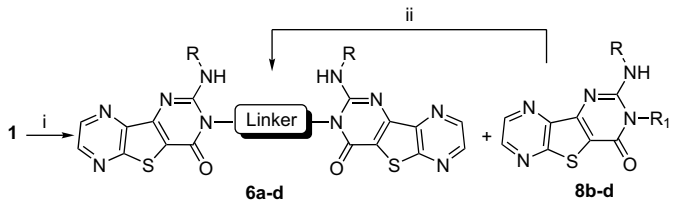
Table 3
2-Dialkylaminopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6a–d**

Entry	Compd	R	Linker	R^1	Yield (%)	Mp (°C)
1	**6a**	^{i}Pr	$(CH_2)_3$		78	>300
	8a	^{i}Pr		$CH_2CH_2NH_2$	0	
2	**6b**[a]	^{n}Bu	1,4-C_6H_4		37	290[b]
	8b	^{n}Bu		4-NH_2–C_6H_4	60	231–233
3	**6c**	^{i}Pr	1,4-C_6H_4		41	>300
	8c	^{i}Pr		4-NH_2–C_6H_4	52	266–267[b]
4	**6d**	^{i}Pr	1,2-C_6H_4		33	>300
	8d	^{i}Pr		2-NH_2–C_6H_4	28	250–252[b]

[a] Compound **6a** has also been obtained by an alternate method.[6i]
[b] Decomposition.

phenylene diisocyanate followed by intramolecular hetero conjugate addition annulation after addition of *n*-butylamine as we previously reported,[8] with the same compound **6b** prepared using the present protocol, the structure of compounds **6** was unambiguously confirmed.

These selectivity results can probable be explained by the large difference in cyclization rates due to steric hindrance around the ethoxy carbonyl and the *n*-butyl or isopropyl groups on the guanidine-type intermediate (Scheme 3). It seems immediately obvious that each amine group would approach to the carbodiimide **2** essentially by the opposite direction of the carboxylate group, due to the steric hindrance, to form the bisamidine **7a**. However, **7a** may convert to **7b** through C–N single bond rotation and this offers the opportunity that both bisamidine intermediates, **7a** and **7b**, are suitable to cyclize: **7a** for the NHR group and **7b** by the NH-linked group to form **5** and **6**, respectively. Steric hindrance between R and ester groups would explain the regioselectivity of the reaction. The greater steric hindrance between the isopropyl or *n*-butyl group and the ethoxy carbonyl group in the bisamidine **7a** may convert easily **7a** to **7b** through C–N single bond rotation with subsequent cyclization to afford bis(pyrazinothienopyrimidinones) **6a–d**. Consequently, the regioselectivity of the reaction seems strongly influenced by the steric hindrance between R and ester groups. The isolation of compounds **8b–d** of the reaction mixtures could be explained by steric hindrance of the bulkier alkyl group and could help to explain the regioselectivity of the reaction.



Scheme 4. Synthesis of bis(pyrazinothienopyrimidinones) **6a–d**. Reagents and conditions: (i) RNCO, THF, rt, 3 h; then bisnucleophilic reagent, K_2CO_3, reflux, 10 h. (ii) Phosphazene (**1**), alkyl isocyanate, THF, rt, 1 h; then, **8b–d**, reflux, 8 h.

3. Conclusions

In conclusion, we have established a new strategy for the synthesis of bis(pyrazinothienopyrimidine) derivatives based on the domino interaction of phosphazene **1** with isocyanates and bifunctional nucleophiles. This one-pot procedure by a tandem aza-Wittig-heterocumulene-mediated annulation offers an attractive synthetic route for the generation of these functionalized bis-(triheterocyclic) compounds that are not readily available by other synthetic methods, and can be extended to secondary amines, phenols, or thiophenols. In the case of primary diamines a regioselective cyclization has been observed strongly influenced by the steric hindrance between R and ester groups. The easy availability of starting material, simple and convenient synthetic procedure, and formation of functionalized bis(pyrazinothienopyrimidines) render this method very useful in synthetic and coordination chemistry, as well as in medicinal chemistry.

4. Experimental section

4.1. General

All reagents were commercial grade chemicals from freshly opened containers. Merck 60 F_{254} foils were used for thin layer chromatography 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) or a Bruker Avance 500 (500 MHz and 125 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$ as solvent, and the chemical shifts are expressed in parts per million relative to TMS at δ=0.00 for ^1H and to $CDCl_3$ at δ=77.1 for ^{13}C. IR spectra were recorded as potassium bromide disks on a Bruker VECTOR 22 spectrophotometer. FAB spectrometric experiments were carried out in a VG Trio instrument. 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.

4.2. General procedure for the synthesis of functionalized bis(pyrazinothienopyrimidines) 4 and 5

To a solution of phosphazene **1** (0.15 g, 0.31 mmol) in dry THF (5 mL) was added the appropriate isocyanate (0.31 mmol). The mixture was stirred at room temperature for 1–2 h until the phosphazene had disappeared (TLC monitored) and it was therefore treated with piperazine or the corresponding appropriate bisnucleophilic reagent (0.16 mmol) and a catalytic amount of K_2CO_3. The resultant mixture was refluxed for 3–8 h. After cooling to room temperature, the yellow precipitate was collected by filtration and washed with water (2×3 mL) and THF (2×3 mL) or the solvent was removed under reduced pressure. The resultant material was subjected to chromatography on silica gel eluting with a dichloromethane/ethyl acetate gradient from 10 to 90% ethyl acetate to give compounds **4** or **5** as yellow solids.

*4.2.1. 1,4-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]piperazine (**4a**)*

Yield 73%; mp >300 °C; IR (KBr) ν=1682 (C=O), 1518, 1452, 1361, 1259 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=3.09 (s, 8H, NCH_2), 7.35–7.41 (m, 4H, H–Ar), 7.45–7.56 (m, 6H, H–Ar), 8.72 (d, J=2.3 Hz, 2H, H-6), 8.86 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=48.1, 120.6, 128.3, 129.2, 129.5, 136.4, 142.7, 143.8, 144.2, 148.2, 157.7, 158.6, 159.2 ppm. MS (FAB) m/z 643 [$(MH)^+$, 50]. Anal. Calcd for $C_{32}H_{22}N_{10}O_2S_2$: C, 59.80; H, 3.45; N, 21.79; S, 9.98. Found: C, 59.67; H, 3.29; N, 21.74; S, 10.36.

*4.2.2. 1,4-Bis[3-(4-methylphenyl)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-2(4H)-yl]piperazine (**4b**)*

Yield 52%; mp >300 °C; IR (KBr) ν=1674 (C=O), 1588, 1523, 1506, 1449, 1425, 1373, 1239 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=2.44 (s, 6H, CH_3), 3.11 (s, 8H, NCH_2), 7.21–7.37 (m, 8H, H–Ar), 8.71 (d, J=2.3 Hz, 2H, H-6), 8.84 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.4, 48.2, 120.6, 128.0, 130.2, 133.4, 139.3, 142.7, 143.8, 144.2, 148.1, 157.9, 158.6, 159.4 ppm. MS (FAB) m/z 671 [$(MH)^+$, 15]. Anal. Calcd for $C_{34}H_{26}N_{10}O_2S_2$: C, 60.88; H, 3.91; N, 20.88; S, 9.56. Found: C, 60.72; H, 3.65; N, 20.57; S, 9.35.

*4.2.3. 1,4-Bis[3-(4-nitrophenyl)-4-oxopyrazino[2′,3′:4,5]thieno-[3,2-d]pyrimidin-2(4H)-yl]piperazine (**4c**)*

Yield 51%; mp >300 °C; IR (KBr) ν=1677 (C=O), 1522, 1507, 1488, 1457, 1438, 1375, 1347, 1260 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=3.00 (s, 8H, NCH_2), 7.87–7.91 (m, 4H, H–Ar), 8.41–8.45 (m, 4H, H–Ar), 8.91 (d, J=2.3 Hz, 2H, H-6), 9.01 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) m/z 733 [$(MH)^+$, 40]. Anal. Calcd for $C_{32}H_{20}N_{12}O_6S_2$: C, 52.46; H, 2.75; N, 22.94; S, 8.75. Found: C, 52.68; H, 2.58; N, 22.69; S, 8.57.

*4.2.4. 1,2-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]ethane disulfide (**5a**)*

Yield 81%; mp >300 °C; IR (KBr) ν=1678 (C=O), 1511, 1487, 1342, 1291 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=3.57 (s, 4H, CH_2), 7.46–7.50 (m, 2H, H–Ar), 7.59–7.65 (m, 8H, H–Ar), 8.79 (d, J=2.3 Hz, 2H, H-6), 8.85 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) m/z 651 [$(MH)^+$, 10]. Anal. Calcd for $C_{30}H_{18}N_8O_2S_4$: C, 55.37; H, 2.79; N, 17.22; S, 19.71. Found: C, 55.69; H, 2.95; N, 17.63; S, 19.50.

*4.2.5. 1,3-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]benzene disulfide (**5b**)*

Yield 77%; mp >300 °C; IR (KBr) ν=1674 (C=O), 1515, 1489, 1233 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=7.60–7.70 (m, 10H, H–Ar), 7.72–7.79 (m, 3H, H–Ar), 7.99 (s, 1H, H–Ar), 8.83 (d, J=2.3 Hz, 2H, H-6), 8.87 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=122.4, 129.6, 130.3, 130.8, 131.0, 136.0, 136.7, 141.1, 143.2, 144.2, 145.4, 148.4, 157.1, 158.2, 161.4 ppm. MS (FAB) m/z 699 [$(MH)^+$, 25]. Anal. Calcd for $C_{34}H_{18}N_8O_2S_4$: C, 58.44; H, 2.60; N, 16.03; S, 18.35. Found: C, 58.16; H, 2.22; N, 16.28; S, 18.72.

*4.2.6. 1,4-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]benzene disulfide (**5c**)*

Yield 80%; mp >300 °C; IR (KBr) ν=1675 (C=O), 1525, 1517, 1493, 1234 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=7.64–7.70 (m, 10H, H–Ar), 7.74 (s, 4H, H–Ar), 8.84 (d, J=2.3 Hz, 2H, H-6), 8.87 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) m/z 699 [$(MH)^+$, 10]. Anal. Calcd for $C_{34}H_{18}N_8O_2S_4$: C, 58.44; H, 2.60; N, 16.03; S, 18.35. Found: C, 58.18; H, 2.37; N, 15.81; S, 18.60.

*4.2.7. 1,3-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yloxy]benzene (**5d**)*

Yield 75%; mp 200–201 °C; IR (KBr) ν=1691 (C=O), 1565, 1538, 1477, 1454, 1341, 1258 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=7.13 (d, J=2.3 Hz, 2H, H–Ar), 7.16 (d, J=2.3 Hz, 2H, H–Ar), 7.25 (t, J=2.3 Hz, 1H, H–Ar), 7.40–7.48 (m, 5H, H–Ar), 7.52–7.63 (m, 6H, H–Ar), 8.68 (d, J=2.3 Hz, 2H, H-6), 8.75 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=114.2, 119.0, 121.8, 127.8, 129.6, 129.8, 130.3, 134.2, 142.8, 143.4, 144.1, 147.3, 152.3, 155.1, 157.7, 158.1, 158.6 ppm. MS (FAB) m/z 667 [$(MH)^+$, 25]. Anal. Calcd for $C_{34}H_{18}N_8O_4S_2$: C, 61.25; H, 2.72; N, 16.81; S, 9.62. Found: C, 61.08; H, 2.53; N, 16.65; S, 9.44.

*4.2.8. 1,4-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yloxy]benzene (**5e**)*

Yield 78%; mp >300 °C; IR (KBr) ν=1683 (C=O), 1567, 1542, 1488, 1341, 1265 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=7.41 (s, 4H, H–Ar), 7.51–7.57 (t, J=7.8 Hz, 2H, H–Ar), 7.59–7.64 (t, J=7.8 Hz, 4H, H–Ar), 7.66–7.71 (d, J=7.7 Hz, 4H, H–Ar), 8.87 (d, J=2.3 Hz, 2H, H-6), 8.91 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=120.5, 123.3, 128.8, 129.7, 129.9, 135.2, 143.3, 144.1, 145.4, 147.8, 149.8, 156.4, 157.1, 158.9 ppm. MS (FAB) m/z 667 [$(MH)^+$, 20]. Anal. Calcd for $C_{34}H_{18}N_8O_4S_2$: C, 61.25; H, 2.72; N, 16.81; S, 9.62. Found: C, 61.07; H, 2.97; N, 16.52; S, 9.44.

*4.2.9. N,N′-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]-1,3-propanediamine (**5f**)*

Yield 74%; mp 265–267 °C; IR (KBr) ν=3305 (N–H), 1674 (C=O), 1549, 1519, 1440, 1339, 1311 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=1.70 (quintet, J=6.0 Hz, 2H, NCH_2CH_2), 3.72 (q, J=6.0 Hz, 4H, NCH_2), 4.31 (t, J=6.0 Hz, 2H, NH, exchangeable with D_2O), 7.55–7.71 (m, 10H, H–Ar), 8.60 (d, J=2.3 Hz, 2H, H-6), 8.66 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C

NMR (75 MHz, $CDCl_3$) δ=29.7, 37.6, 115.0, 129.1, 129.5, 130.3, 130.9, 134.4, 142.4, 143.4, 143.9, 149.5, 153.7, 158.2, 158.3 ppm. MS (FAB) m/z 631 [$(MH)^+$, 50]. Anal. Calcd for $C_{31}H_{22}N_{10}O_2S_2$: C, 59.03; H, 3.52; N, 22.21; S, 10.17. Found: C, 58.92; H, 3.38; N, 22.19; S, 10.07.

4.2.10. N,N′-Bis[3-(4-methylphenyl)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-2(4H)-yl]-1,3-propanediamine (**5g**)

Yield 69%; mp 150–152 °C; IR (KBr) ν=3340 (N–H), 1677 (C═O), 1553, 1520, 1505, 1435, 1338 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=1.71 (quintet, 2H, J=6.0 Hz, NCH_2CH_2), 2.48 (s, 6H, CH_3), 3.73 (q, J=6.0 Hz, 4H, NCH_2), 4.33 (t, J=6.0 Hz, 2H, NH, exchangeable with D_2O), 7.43–7.49 (m, 4H, H–Ar), 7.52–7.56 (m, 4H, H–Ar), 8.61 (d, J=2.3 Hz, 2H, H-6), 8.67 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.5, 29.8, 31.0, 119.2, 128.1, 128.7, 130.4, 131.7, 139.4, 140.7, 142.4, 142.6, 143.9, 144.9, 153.8 ppm. MS (FAB) m/z 659 [$(MH)^+$, 25]. Anal. Calcd for $C_{33}H_{26}N_{10}O_2S_2$: C, 60.17; H, 3.98; N, 21.26; S, 9.74. Found: C, 60.61; H, 3.47; N, 21.78; S, 9.28.

4.2.11. N,N′-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]-1,2-propanediamine (**5h**)

Yield 57%; mp 218–220 °C; IR (KBr) ν=3336 (N–H), 1672 (C═O), 1516, 1339 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=1.19 (d, J=6.6 Hz, 3H, CH_3), 3.68 (dd, J=5.1, 7.4 Hz, 2H, NCH_2), 4.53 (d, J=8.6 Hz, 1H, NH, exchangeable with D_2O), 4.65–4.84 (m, 1H, NCH), 5.13 (t, J=5.1 Hz, 2H, NH, exchangeable with D_2O), 6.90–7.34 (m, 9H, H–Ar), 7.43–7.52 (m, 1H, H–Ar), 8.69 (d, J=2.3 Hz, 1H, H pyrazine), 8.72 (d, J=2.3 Hz, 1H, H-6), 8.79 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ=18.5, 47.1, 48.0, 115.5, 115.6, 127.9, 128.3, 128.6, 128.7, 129.5, 130.1, 130.6, 130.7, 133.4, 133.7, 142.1, 143.8, 143.9, 149.6, 149.7, 153.5, 153.8, 158.3, 158.4, 158.5 ppm. MS (FAB) m/z 631 [$(MH)^+$, 50]. Anal. Calcd for $C_{31}H_{22}N_{10}O_2S_2$: C, 59.03; H, 3.52; N, 22.21; S, 10.17. Found: C, 58.69; H, 3.25; N, 22.49; S, 9.79.

4.2.12. 1,2-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]-1,2-phenylenediamine (**5i**)

Yield 56%; mp 225–227 °C; IR (KBr) ν=3280 (N–H), 1667 (C═O), 1601, 1537, 1518, 1484, 1444, 1337 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=7.12–7.19 (m, 2H, H–Ar), 7.38–7.45 (m, 4H, H–Ar), 7.65–7.74 (m, 6H, H–Ar), 7.85–7.90 (m, 2H, H–Ar), 7.94 (s, 2H, NH, exchangeable with D_2O), 8.66 (d, J=2.3 Hz, 2H, H-6), 8.80 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ=115.9, 121.2, 124.4, 129.1, 131.4, 133.0, 135.2, 137.8, 142.7, 143.5, 144.3, 150.9, 151.2, 158.8, 160.2 ppm. MS (FAB) m/z 665 [$(MH)^+$, 70]. Anal. Calcd for $C_{34}H_{20}N_{10}O_2S_2$: C, 61.43; H, 3.03; N, 21.07; S, 9.65. Found: C, 61.17; H, 3.32; N, 21.21; S, 9.43.

4.2.13. 1,2-Bis[3-(4-methylphenyl)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-2(4H)-yl]-phenylenediamine (**5j**)

Yield 40%; mp 176–177 °C; IR (KBr) ν=3327 (N–H), 1680 (C═O), 1633, 1600, 1518, 1451, 1342 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=2.35 (s, 6H, CH_3), 7.18–7.24 (m, 4H, H–Ar), 7.55–7.60 (m, 4H, H–Ar), 7.63–7.69 (m, 2H, H–Ar), 7.81 (s, 2H, NH, exchangeable with D_2O), 7.84–7.91 (m, 2H, H–Ar), 8.65 (d, J=2.3 Hz, 2H, H-6), 8.79 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.9, 115.6, 121.4, 129.6, 131.4, 133.0, 134.1, 135.1, 142.7, 143.6, 144.3, 151.0, 151.4, 158.8, 160.2 ppm. MS (FAB) m/z 693 [$(MH)^+$, 10]. Anal. Calcd for $C_{36}H_{24}N_{10}O_2S_2$: C, 62.41; H, 3.49; N, 20.22; S, 9.26. Found: C, 62.79; H, 3.28; N, 20.59; S, 9.54.

4.2.14. 1,2-Bis[3-(4-nitrophenyl)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-2(4H)-yl]-phenylenediamine (**5k**)

Yield 36%; mp >300 °C; IR (KBr) ν=3353 (N–H), 1638 (C═O), 1603, 1520, 1452, 1329 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=7.64–7.72 (m, 2H, H–Ar), 7.86–7.97 (m, 6H, H–Ar), 8.28–8.35 (m, 4H, H–Ar), 8.51 (s, 2H, NH, exchangeable with D_2O), 8.72 (d, J=2.3 Hz, 2H, H-6), 8.86 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=117.4, 120.2, 125.1, 131.2, 133.6, 134.8, 143.1, 143.2, 143.4, 143.8, 144.9, 150.0, 150.4, 158.8, 160.3 ppm. MS (FAB) m/z 755 [$(MH)^+$, 15]. Anal. Calcd for $C_{34}H_{18}N_{12}O_6S_2$: C, 54.11; H, 2.40; N, 22.27; S, 8.50. Found: C, 54.52; H, 2.48; N, 22.89; S, 8.76.

4.2.15. 1,3-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]phenylenediamine (**5l**)

Yield 72%; mp 259–260 °C (dec); IR (KBr) ν=3408 (N–H), 1681 (C═O), 1517, 1479, 1434, 1340 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.45 (s, 2H, NH, exchangeable with D_2O), 7.00–7.17 (m, 2H, H–Ar), 7.50–7.58 (m, 5H, H–Ar), 7.67–7.78 (m, 7H, H–Ar), 8.47 (d, J=2.3 Hz, 2H, H-6), 8.56 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=112.8, 113.5, 117.5, 129.0, 129.5, 130.8, 131.2, 133.8, 138.4, 141.8, 143.9, 144.3, 149.3, 150.2, 158.3, 158.6 ppm. MS (FAB) m/z 665 [$(MH)^+$, 15]. Anal. Calcd for $C_{34}H_{20}N_{10}O_2S_2$: C, 61.43; H, 3.03; N, 21.07; S, 9.65. Found: C, 61.26; H, 2.72; N, 21.39; S, 9.43.

4.2.16. 1,4-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]phenylenediamine (**5m**)

Yield 79%; mp 203–205 °C; IR (KBr) ν=3052 (N–H), 1681 (C═O), 1499, 1339 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.24 (s, 2H, NH, exchangeable with D_2O), 7.46–7.52 (m, 10H, H–Ar), 7.59 (s, 4H, H–Ar), 8.70 (d, J=2.3 Hz, 2H, H-6), 8.80 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=117.4, 122.2, 128.9, 130.9, 131.2, 133.7, 133.9, 142.4, 143.9, 144.0, 149.4, 150.6, 158.6 ppm. MS (FAB) m/z 665 [$(MH)^+$, 55]. Anal. Calcd for $C_{34}H_{20}N_{10}O_2S_2$: C, 61.43; H, 3.03; N, 21.07; S, 9.65. Found: C, 61.22; H, 2.86; N, 20.89; S, 9.88.

4.2.17. 4,4′-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]biphenylenediamine (**5n**)

Yield 79%; mp >300 °C; IR (KBr) ν=3412 (N–H), 1681 (C═O), 1598, 1537, 1487, 1338 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.37 (s, 2H, NH, exchangeable with D_2O), 7.19–7.25 (m, 2H, H–Ar), 7.43–7.49 (m, 4H, H–Ar), 7.65–7.69 (m, 4H, H–Ar), 7.70–7.73 (m, 4H, H–Ar), 8.02–8.08 (m, 4H, H–Ar), 8.78 (d, J=2.3 Hz, 2H, H-6), 8.92 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=117.4, 121.3, 128.9, 129.4, 129.7, 130.1, 133.9, 137.2, 142.0, 142.7, 143.9, 144.2, 149.5, 150.4, 158.6, 158.7 ppm. MS (FAB) m/z 741 [$(MH)^+$, 40]. Anal. Calcd for $C_{40}H_{24}N_{10}O_2S_2$: C, 64.85; H, 3.27; N, 18.91; S, 8.66. Found: C, 64.42; H, 3.56; N, 18.50; S, 8.45.

4.2.18. 2,6-Bis[4-oxo-3-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-2(4H)-yl]diaminopyridine (**5o**)

Yield 53%; mp 270–272 °C (dec); IR (KBr) ν=3387 (N–H), 1689 (C═O), 1549, 1488, 1455, 1337 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.66 (s, 2H, NH, exchangeable with D_2O), 7.40–7.48 (m, 4H, H–Ar), 7.65–7.74 (m, 6H, H–Ar), 8.03 (t, J=7.7 Hz, 1H, H–Py), 8.51 (d, J=7.7 Hz, 2H, H–Py), 8.75 (d, J=2.3 Hz, 2H, H-6), 8.90 (d, J=2.3 Hz, 2H, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=109.4, 118.5, 128.8, 130.8, 131.2, 133.5, 141.7, 142.8, 143.8, 144.2, 148.9, 149.0, 158.3, 158.6 ppm. MS (FAB) m/z 666 [$(MH)^+$, 20]. Anal. Calcd for $C_{33}H_{19}N_{11}O_2S_2$: C, 59.54; H, 2.88; N, 23.14; S, 9.63. Found: C, 59.79; H, 2.65; N, 23.46; S, 9.82.

4.3. General procedure for the synthesis of functionalized bis(pyrazinothienopyrimidines) 6

To a solution of phosphazene **1** (0.15 g, 0.31 mmol) in dry THF (5 mL) was added the appropriate alkyl isocyanate (0.37 mmol). The mixture was stirred at reflux temperature for 8 h until the phosphazene had disappeared (TLC monitored) and it was therefore treated with the corresponding appropriate bisnucleophilic reagent (0.16 mmol) and a catalytic amount of K_2CO_3. The resultant mixture was refluxed for 5–14 h. After cooling, the solvent was

removed under reduced pressure, and the residue was subjected to chromatography on silica gel eluting with a dichloromethane/ethyl acetate gradient from 0 to 100% ethyl acetate to give compounds **6a–d** and **8b–d** as yellow solids.

4.3.1. 1,3-Bis[2-isopropylamino-4-oxopyrazino[2′,3′:4,5]thieno-[3,2-d]pyrimidin-3(4H)-yl]propane (*6a*)

Eluted with CH_2Cl_2/EtOAc (40:60). Yield 78%; mp >300 °C; IR (KBr) ν=3393 (N–H), 1646 (C=O), 1545, 1489, 1347, 1301 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=1.38 (d, J=6.5 Hz, 12H, CH_3), 2.26 (quintet, J=6.5 Hz, 2H, NCH_2CH_2), 4.26 (t, J=6.5 Hz, 4H, NCH_2), 4.66–4.76 (m, 1H, CH), 5.45 (d, J=7.6 Hz, 2H, NH, exchangeable with D_2O), 8.67 (d, J=2.3 Hz, 2H, H-7), 8.82 (d, J=2.3 Hz, 2H, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=22.8, 26.7, 40.0, 44.6, 114.1, 142.4, 142.8, 144.0, 144.1, 150.5, 152.3, 158.7, 159.6 ppm. MS (FAB) m/z 563 [$(MH)^+$, 35]. Anal. Calcd for $C_{25}H_{26}N_{10}O_2S_2$: C, 53.36; H, 4.66; N, 24.89; S, 11.40. Found: C, 53.62; H, 4.38; N, 25.19; S, 11.27.

4.3.2. 1,4-Bis[2-n-butylamino-4-oxopyrazino[2′,3′:4,5]thieno-[3,2-d]pyrimidin-3(4H)-yl]-benzene (*6b*)

Eluted with CH_2Cl_2/EtOAc (80:20). Yield 37%; mp 290 °C (dec), mp 290 °C (dec).[6i] Its spectroscopic data were identical to those reported in the literature.[6i]

4.3.3. 3-N-(4-Aminophenyl)-2-n-butylaminopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (*8b*)

Eluted with CH_2Cl_2/EtOAc (40:60). Yield 60%; mp 231–233 °C; IR (KBr) ν=3056, 2956 (N–H), 1676 (C=O), 1556, 1514, 1436. ^1H NMR (500 MHz, $CDCl_3$) δ=0.89 (t, J=7.3 Hz, 3H, CH_3), 1.25–1.34 (m, 2H, $NCH_2CH_2CH_2$), 1.46–1.54 (m, 2H, NCH_2CH_2), 3.54–3.60 (dt, J=5.1, 7.1 Hz, 2H, NCH_2), 4.06 (s, 2H, NH_2, exchangeable with D_2O), 4.48 (t, J=5.1 Hz, 1H, NH, exchangeable with D_2O), 6.82–6.86 (m, 2H, H–Ar), 7.05–7.09 (m, 2H, H–Ar), 8.65 (d, J=2.3 Hz, 2H, H-7), 8.81 (d, J=2.3 Hz, 2H, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=13.9, 20.1, 31.3, 42.1, 115.4, 116.6, 123.5, 129.4, 142.3, 143.7, 144.3, 148.3, 150.1, 154.3, 158.7, 159.3 ppm. MS (FAB) m/z 367 [$(MH)^+$, 20]. Anal. Calcd for $C_{18}H_{18}N_6OS$: C, 59.00; H, 4.95; N, 22.93; S, 8.75. Found: C, 59.34; H, 4.71; N, 23.19; S, 8.97.

4.3.4. 1,4-Bis[(2-isopropyl)-4-oxopyrazino[2′,3′:4,5]thieno-[3,2-d]pyrimidin-3(4H)-yl]-benzene (*6c*)

Eluted with CH_2Cl_2/EtOAc (30:70). Yield 41%; mp >300 °C; IR (KBr) ν=2922 (NH), 1690 (C=O), 1545, 1464, 1379 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=1.17 (d, J=6.5 Hz, 12H, CH_3), 4.62–4.70 (m, 2H, CH), 5.37 (d, J=7.6 Hz, 2H, NH, exchangeable with D_2O), 7.66 (s, 4H, H–Ar), 8.71 (d, J=2.3 Hz, 2H, H-7), 8.87 (d, J=2.3 Hz, 2H, H-8) ppm. ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) m/z 597 [$(MH)^+$, 10]. Anal. Calcd for $C_{28}H_{24}N_{10}O_2S_2$: C, 56.36; H, 4.05; N, 23.47; S, 10.75. Found: C, 56.07; H, 3.78; N, 23.79; S, 10.52.

4.3.5. 3-N-(4-Aminophenyl)-2-isopropylaminopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (*8c*)

Eluted with CH_2Cl_2. Yield 52%; mp 266–267 °C (dec); IR (KBr) ν=3408, 3363 (N–H), 1682 (C=O), 1611, 1542, 1517, 1343. ^1H NMR (500 MHz, $CDCl_3$) δ=1.17 (d, J=6.5 Hz, 6H, CH_3), 4.02 (s, 2H, NH_2, NH, exchangeable with D_2O), 4.32 (d, J=8.1 Hz, 1H, NH, exchangeable with D_2O), 4.48–4.62 (m, 1H, CH), 6.80–6.88 (m, 2H, H–Ar), 7.02–7.10 (m, 2H, H–Ar), 8.65 (d, J=2.3 Hz, 2H, H-7), 8.81 (d, J=2.3 Hz, 2H, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=22.8, 43.9, 115.2, 116.6, 123.5, 129.4, 142.2, 143.7, 144.3, 148.2, 150.2, 153.5, 158.7, 159.3 ppm. MS (FAB) m/z 353 [$(MH)^+$, 70]. Anal. Calcd for $C_{17}H_{16}N_6OS$: C, 57.94; H, 4.58; N, 23.85; S, 9.10. Found: C, 57.74; H, 4.79; N, 23.70; S, 8.91.

4.3.6. 1,2-Bis[(2-isopropyl)-4-oxopyrazino[2′,3′:4,5]thieno[3,2-d]-pyrimidin-3(4H)-yl]benzene (*6d*)

Eluted with CH_2Cl_2/EtOAc (20:80). Yield 33%; mp >300 °C; IR (KBr) ν=3434, 3403, 3338 (NH), 1680 (C=O), 1542, 1521, 1455, 1338 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=1.19 (d, J=6.5 Hz, 12H, CH_3), 4.35–4.50 (m, 2H, CH), 5.46 (d, J=7.7 Hz, 2H, NH, exchangeable with D_2O), 7.50–7.58 (m, 2H, H–Ar), 7.81–7.89 (m, 2H, H–Ar), 8.63 (d, J=2.3 Hz, 2H, H-7), 8.78 (d, J=2.3 Hz, 2H, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.5, 22.5, 44.6, 113.5, 131.9, 133.0, 134.1, 142.5, 143.9, 144.2, 151.7, 152.9, 159.0, 159.9 ppm. MS (FAB) m/z 597 [$(MH)^+$, 20]. Anal. Calcd for $C_{28}H_{24}N_{10}O_2S_2$: C, 56.36; H, 4.05; N, 23.47; S, 10.75. Found: C, 55.72; H, 4.42; N, 23.79; S, 11.17.

4.3.7. 3-N-(2-Aminophenyl)-2-isopropylaminopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (*8d*)

Eluted with CH_2Cl_2. Yield 28%; mp 250–252 °C (dec); IR (KBr) ν=3404, 3338 (N–H), 1668 (C=O), 1541, 1520, 1499, 1338. ^1H NMR (500 MHz, $CDCl_3$) δ=1.20 (d, J=6.5 Hz, 6H, CH_3), 3.76 (s, 2H, NH_2, NH, exchangeable with D_2O), 4.42 (d, J=8.1 Hz, 1H, NH, exchangeable with D_2O), 4.50–4.65 (m, 1H, CH), 6.94–7.02 (m, 2H, H–Ar), 7.09–7.16 (m, 1H, H–Ar), 7.33–7.42 (m, 1H, H–Ar), 8.69 (d, J=2.3 Hz, 2H, H-7), 8.85 (d, J=2.3 Hz, 2H, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=22.7, 44.0, 114.8, 117.9, 118.9, 120.2, 129.2, 131.5, 142.3, 143.4, 143.9, 144.1, 150.7, 152.7, 158.3, 158.7 ppm. MS (FAB) m/z 353 [$(MH)^+$, 40]. Anal. Calcd for $C_{17}H_{16}N_6OS$: C, 57.94; H, 4.58; N, 23.85; S, 9.10. Found: C, 57.61; H, 4.29; N, 23.99; S, 8.87.

4.4. General procedure for the synthesis of functionalized bis(pyrazinothienopyrimidines) 6 from derivatives 8b–d

To a solution of phosphazene **1** (0.15 g, 0.31 mmol) in dry THF (5 mL) was added the appropriate alkyl isocyanate (0.31 mmol). The mixture was stirred at reflux temperature for 8 h until the phosphazene had disappeared (TLC monitored) and it was therefore treated with the corresponding appropriate nucleophilic reagents **8b–d** (0.31 mmol) and a catalytic amount of K_2CO_3. The resultant mixture was refluxed for 8 h. After cooling, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography on silica gel eluting with a dichloromethane/ethyl acetate gradient to give **6b** (70% yield), **6c** (66% yield), and **6d** (55% yield) as yellow solids.

Acknowledgements

We gratefully acknowledge financial support from the Xunta de Galicia and Feder (Project PGIDIT06PXIB103224PR).

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