Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 2034–2041

Efficient one-pot preparation of bis(pyrazino[2′,3′:4,5]thieno-[3,2-*d*]pyrimidin-4-yl)benzenes based on an aza–Wittig/mediated annulation strategy

Gerardo Blanco, José M. Quintela* and Carlos Peinador*

Departamento de Química Fundamental, Facultad de Ciencias, Universidad de A Coruña, 15071 A Coruña, Spain

Received 17 November 2006; revised 12 December 2006; accepted 15 December 2006
Available online 20 December 2006

Abstract—Aza–Wittig mediated annulation provides a highly facile and straightforward one-pot strategy for the synthesis of bis(pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)benzenes **5** and **7**. A tandem aza–Wittig reaction of iminophosphorane **2** with 1,4- or 1,3-phenylene diisocyanate, followed by intramolecular heteroconjugate addition annulation after addition of a nucleophilic reagent (amine, phenol, thiophenol or ROH), in presence of catalytic K_2CO_3 or NaOR, gives selectively the functionalized bis(pyrazinothienopyrimidinones) **5** and **7**.

1. Introduction

Nitrogen or sulfur-containing heterocycles have received a great deal of interest in the medicinal, agricultural, and material sciences and this justifies continuing efforts in the development of new efficient and mild synthetic strategies.[1] The presence of a fused pyrimidine scaffold in the framework of various pharmacologically active compounds continues to spur synthetic efforts regarding their acquisition.[2] Structures containing such units often play an essential role because of their biological activity, particularly in cancer and virus research.[3] Among these heterocycles, thienopyrimidine derivatives are an important class of heterocyclic compounds in pharmaceutical discovery research.[4] Anti-inflammatory, antiallergic, antibacterial, and antifungal activities, have been described for these compounds,[5] whereas others exhibited good anticonvulsant and angiotensin II or H_1 receptor antagonistic activities,[6] and some of them show good antitumor activity.[7]

Whereas pyridine annelated sulfur-containing heterocycles have been studied extensively,[8] surprisingly, aza-analogue compounds incorporating an *S*-heterocycle fused to a pyrazine nucleus have remained relatively rare. Among the diazines, the pyrazine ring system is important, and substituted pyrazine motifs are often to be found in compounds with applications as anti-cancer agents, including currently marketed drugs[9] and those recently reported.[10] Pyrazine ring is present in marine metabolites, which exhibit mild cytotoxicity against certain human cancer cells,[11] and it is also present in other biologically active natural products.[12]

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.[13] 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.[14]

During the last years we reported the synthesis of substituted heterocycles containing the pyridothienopyrimidine and pyridazinothienopyrimidine skeletons with the aim of finding compounds with anti-inflammatory, antihistaminic, and anti-cancer activities.[15] It is surprising that their isosters pyrazinothienopyrimidines, moreover isosters of quinoxalinepyrimidines, have been practically ignored.[16] Besides, we have interested in the synthesis and study of new heterocyclic ligands and their use in coordination and metallosupramolecular chemistry.[17] We previously reported the synthesis of fused pyrimidines based on the tandem aza–Wittig heterocumulene-mediated annulation strategy.[18]

In this work, we describe, as part of a program of investigation the biosignificant pyrimidine and pyrazine nuclei, a novel, highly efficient, and regioselective synthesis of

Keywords: Aza–Wittig reaction; Heterocumulene; Iminophosphoranes; Bis(pyrazinothienopyrimidinones).
* Corresponding authors. Tel.: +34 981 167000; fax: +34 981 167065; e-mail addresses: jqqoqf@udc.es; capeveqo@udc.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.049

substituted bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)benzenes **I** and **II**, which of considerable interest as potential biologically active compounds or pharmaceuticals as isosters of pharmaceutically relevant pyridothienopyrimidines, as well as in their use as appropriate phenanthroline-like ligands. The focus of our research presented here is on the strategy to synthesize these compounds via a one-pot aza–Wittig reaction of ethoxycarbonyliminophosphorane **2** with 1,3-phenylene- or 1,4-phenylene diisocyanate and subsequent reaction with various nucleophiles under mild conditions (Fig. 1).

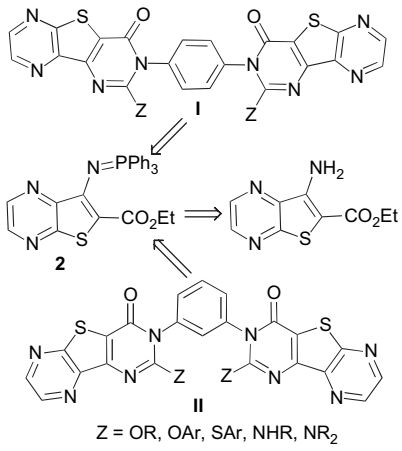


Figure 1. Retrosynthetic pathway for synthesis of the bis(pyrazinothieno-pyrimidinyl)benzenes **I** and **II**.

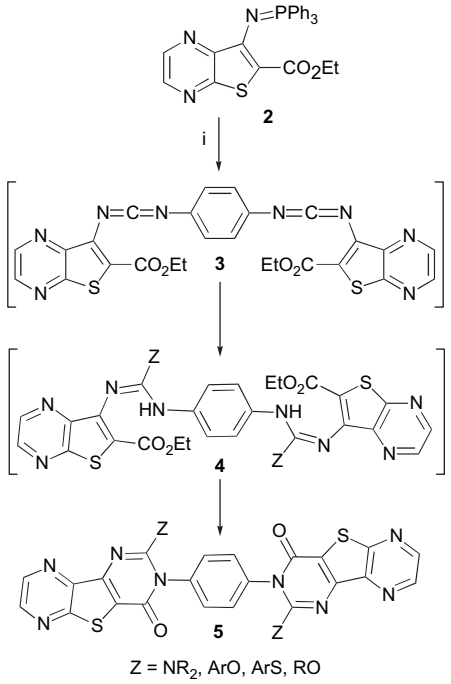
2. Results and discussion

It is well known that iminophosphoranes (λ^5-phosphazenes, phosphine imines) are excellent sources for the construction of imine carbon–nitrogen double bonds through an aza–Wittig reaction in very mild reaction conditions,[19] and over the past 20 years great progress has been made in the field of heterocyclic synthesis by the aza–Wittig methodology.[20] Especially for synthetic strategy of fused heterocycles and biologically important heterocyclic natural products, the aza–Wittig reaction is served as an excellent method. The key intermediate iminophosphoranes can be prepared either by the Staudinger reaction from organic azides[21] or by Kirsanov reaction from primary amines.[22]

Substituted bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)benzenes **5** and **7** were obtained in a one-pot reaction of the corresponding iminophosphorane of heteroaromatic β-enamino ester **2** with 1,4-phenylene or 1,3-phenylene diisocyanate, followed by heterocyclization on addition of nucleophilic reagents. Our approach is centered on the aza–Wittig reaction of iminophosphorane with bis(heterocumulenes) to give a 1,3,5-bis(hexatriene) moiety containing a nitrogen atom at one end and cumulated double bond at the other, which subsequently undergoes double pyrimido annulation by addition of nucleophiles.

The starting compound for the aza–Wittig reaction heterocyclization sequence was prepared, in 97% yield, from the readily available ethyl 3-aminothieno[2,3-*b*]pyrazine-2-carboxylate **1**[23] by a modified Kirsanov reaction of the β-enamino ester **1** with in situ generated dichlorotriphenylphosphorane, using a hexachloroethane–triphenylphosphine–triethylamine reagent system.[24]

First, as shown in Scheme 1, we carried out the reaction of 1,4-phenylene diisocyanate with 2 equiv of iminophosphorane **2**, followed by heterocyclization on addition of secondary amines in the presence of a catalytic amount of K_2CO_3. Then, it was found that the aza–Wittig/heterocumulene-mediated-type reaction proceeded and resulted in the formation of triphenylphosphine oxide and the correspondingly substituted bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)benzenes **5a–d** in very good yields (85–95%). Pyrimido annulation occurs via a highly reactive bis(heterocumulene) intermediate **3**. Addition of a secondary amine to the highly reactive cumulenic system followed by intramolecular hetero-conjugate addition annulation gives the final products via guanidine-type intermediates **4**. The results obtained are listed in Table 1.



Scheme 1. Reagents and conditions: (i) (1) 1,4-$C_6H_4(NCO)_2$, THF (5 h, rt) and (2) HZ (5 h, rt), K_2CO_3 or NaOR (0.5 h, reflux).

Table 1. Bispyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones **5a–k**

Compd	Z	Yield[a] (%)	Mp (°C)
5a	Morpholino	92	>300
5b	Thiomorpholino	95	>300
5c	Piperidino	90	>300
5d	NEt_2	85	>300
5e	C_6H_5O	85	>300
5f	4-$C(CH_3)_3C_6H_4O$	83	230 dec
5g	4-$NO_2C_6H_4O$	86	230 dec
5h	C_6H_5S	91	>300
5i	EtO	80	290 dec
5j	MeO	83	290 dec
5k	*n*-Butyl	97	290 dec

[a] Isolated yields based on iminophosphorane **2**.

The one-pot formation of aryloxy- and arylthioxybispyrazinothienopyrimidinones **5e–h** was carried out by reaction of iminophosphorane **3** with 1,4-phenylene diisocyanate, followed by heterocyclization on addition of phenols or thiophenols in the presence of catalytic potassium carbonate. The reaction is practically insensitive to the presence or absence of substituents on the phenols and, irrespective of the fact whether the substituents on the phenols were electron-withdrawing or electron-releasing groups, the cyclization was completed smoothly at room temperature, the yield of the isolated products being higher than 83%. Similarly, 1,4-bis(2-ethoxy- or 1,4-bis(2-methoxy-4-oxopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3-yl)benzenes **5i** and **5j** were obtained in good yields when the reaction took place in the presence of catalytic sodium ethoxide or sodium methoxide, respectively. The formation of **5e–j** can be rationalized in terms of an initial nucleophilic addition of phenoxide, thiophenoxide or alkoxide to the carbodiimide **3** to give the intermediate **4**, which cyclizes to affords **5** (Scheme 1).

The participation of carbodiimide **3** and the corresponding guanidine-type compound **4** as intermediates in this process has been confirmed experimentally.[18] In the presence of anhydrous potassium carbonate or sodium alkoxide **4** underwent intramolecular heterocyclization across the electrophilic ester functionality to give the fused pyrimidinones **5**.

Two isomeric bispyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones **5** and **6** may be produced in the reaction of iminophosphorane **2** with primary amines via a guanidine-type intermediate **4** (Scheme 2). However, it is interesting to note that the reaction of 1,4-phenylene diisocyanate with 2 equiv of iminophosphorane **3** followed by addition of an primary amine, as *n*-butylamine, is regioselective to afford only **5k** in very good yield (97%), compound **6** not being formed. These selectivity results can probably be explained by the large difference in cyclization rates due the steric hindrance around the ethoxycarbonyl and the *n*-butyl groups.[25]

The structure of the prepared compounds **5** was initially deduced from ^{1}H and ^{13}C NMR spectroscopic data and then confirmed unambiguously by an X-ray crystallographic study carried out for the derivative **5k**. Mass and spectroscopic data are in good agreement with the proposed structures. The FAB-mass spectra show the expected ion peaks and the fragmentation pattern is in accord with the proposed structures. It is worth noting that the four aromatic protons on the benzene ring are identical and do not couple with each other (the signals attributable to the 4-H benzene protons are found between δ=7.50–7.93, as a singlet, in the ^{1}H NMR spectra), which suggests identical neighbors for all the protons on the benzene ring in compounds **5**. In particular, the ^{1}H NMR spectra of compound **5k** show the signals of NH at 5.20, as a triplet, due to coupling with the methylene protons adjacent to the nitrogen atom, and NCH_2 at 3.60–3.70, as a multiplet, which suggests the existence of NHBu group in **5k**. Moreover, when the sample was treated with deuterated water, its NCH_2 showed the signal as triplet with disappearance of signals of NH absorption. Finally, an X-ray study of compound **5k** corroborated our earlier assignments. According to the crystal data the benzene ring adopts a nearly anticoplanar disposition with the three heterocyclic rings of the pyrazinothienopyrimidine system. Thus, the *anti*-periplanar conformation, with the two *n*-butyl substituents are opposite to each other, leads to a more stable conformation (Fig. 2).

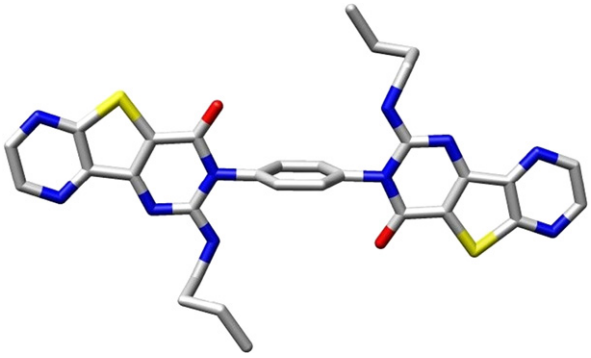
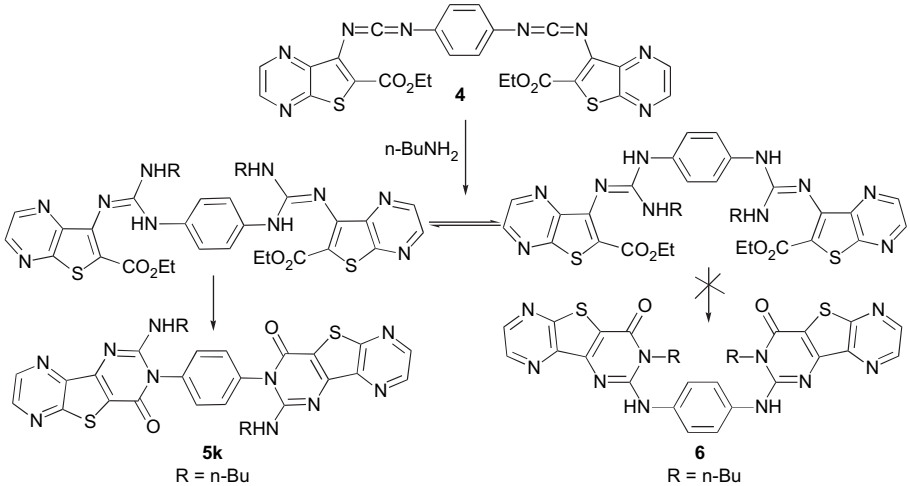
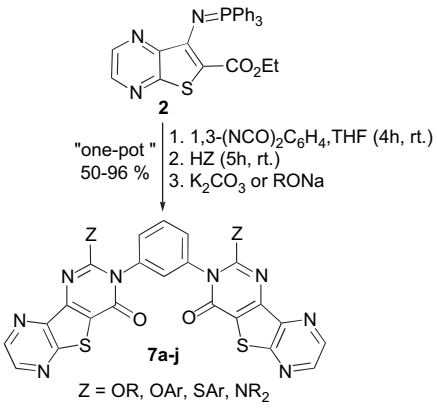


Figure 2. Crystal structure of compound **5k**. Solvent molecules and hydrogen atoms have been omitted for clarity.



Scheme 2.

We next considered the possibility of extending this design strategy to the preparation of 1,3-bis(pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4-yl)benzenes **7**. Thus, we reacted 1,3-phenylene diisocyanate with heteroaryl iminophosphorane **2**, under similar reaction conditions, which furnished new compounds **7** (Scheme 3). As summarized in Table 2, isolated yields ranged from moderate to excellent (50–96%). Once again all new compounds showed spectroscopic and characterization data in accord with the proposed structures.



Scheme 3.

Table 2. Bispyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones **7a–j**

Compd	Z	Yield[a] (%)	Mp (°C)
7a	Morpholino	71	>300
7b	Thiomorpholino	96	>300
7c	Piperidino	71	217–219
7d	NEt_2	92	280–282
7e	C_6H_5O	72	>300
7f	$4\text{-}C(CH_3)_3C_6H_4O$	52	>300
7g	$4\text{-}NO_2C_6H_4O$	50	>300
7h	C_6H_5S	82	>300
7i	EtO	55	230–232
7j	MeO	57	275–277 dec

[a] Isolated yields based on iminophosphorane **2**.

3. Conclusions

In summary, the present study demonstrates that the tandem aza–Wittig-heterocumulene-mediated annulation strategy affords a facile, efficient, and general one-pot route to previously unreported 1,4- and 1,3-bis(pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4-yl)benzenes **5** and **7**, respectively. This one-pot procedure offers an attractive procedure for the generation of these compounds and can be extended to secondary amines, phenols, thiophenols or ROH. In the case of primary amines a regioselective cyclization has been observed. Bis-triheterocyclic compounds **5a–k** and **7a–j** can be useful compounds in medicinal chemistry since the pyrazino, pyrimido, and thiophene moieties display a broad range of biological activities and have been widely used as pharmaceuticals. Moreover, compounds **5** and **7** can be of interest as ligands containing two tridentate binding domains arranged in a ‘angular’ or ‘stepped-parallel’ manner.[26] Studies are currently underway employing these ligands as synthons in coordination and metallosupramolecular chemistry.

4. Experimental section

4.1. General

NMR spectra were recorded at 200 or 300 MHz for ^1H and 50 or 75 MHz for ^{13}C. Chemical shifts are reported in parts per million (δ) relative to an internal Me_4Si. IR spectra were recorded as potassium bromide disks. Melting points were obtained on a Bibby SMP3 apparatus and are uncorrected. Mass spectra were obtained on a VG-QUATTRO spectrometer. All reagents used were commercial grade chemicals from freshly opened containers. The Silica gel 60 F_{254} used for analytical thin layer chromatography was purchased from Merck. Microanalyses for C, H, N, and S were performed by the elemental analyses general service of the University of A Coruña. ^{13}C NMR spectra of **5b**,**c**,**e–k**, and **7e**,**h** could not be obtained due to low solubility in ordinary solvents.

4.2. General procedure for the synthesis of pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (5a–d and k)

To a solution of iminophosphorane **3** (0.10 g, 0.21 mmol) in dry THF (6 mL) was added 1,4-phenylene diisocyanate (0.02 g, 0.10 mmol) at room temperature. The mixture was stirred at room temperature for 3–5 h until the iminophosphorane had disappeared (TLC monitored) and it was therefore treated with an appropriate secondary amine (0.25 mmol). The resultant solution was stirred at room temperature for 5 h. The solvent was evaporated and the residue was solved in acetone (5 mL), a catalytic amount of K_2CO_3 was added, and the mixture was refluxed for 2 h. After cooling, the precipitate obtained was filtered off, washed with water and acetone, and purified by flash chromatography on silica gel using CH_2Cl_2/EtOAc (85:15, v/v) as an eluent.

4.2.1. 1,4-Bis(2-(4-morpholinyl)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5a). Yield (92%); mp >300 °C; IR (KBr) ν 1691 (CO), 1649, 1634, 1630, 1537, 1513, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.30–3.40 (m, 8H), 3.54–3.63 (m, 8H), 7.67 (s, 4H), 8.75 (d, J=2.3 Hz, 2H), 8.90 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.6, 65.8, 129.4, 136.9, 142.9, 143.8, 144.3, 148.7, 157.4, 158.6, 159.1, 162.2; MS (FAB$^+$) m/z 653 (MH$^+$, 40); Anal. Calcd for $C_{30}H_{24}N_{10}O_4S_2$: C, 55.20; H, 3.71; N, 21.46; S, 9.83. Found: C, 55.41; H, 3.67; N, 21.34; S, 10.03.

4.2.2. 1,4-Bis(4-oxo-2-(4-thiomorpholinyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5b). Yield (95%); mp >300 °C; IR (KBr) ν 1678 (CO), 1537, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40–2.55 (m, 8H), 3.55–3.65 (m, 8H), 7.64 (s, 4H), 8.74 (d, J= 2.3 Hz, 2H), 8.89 (d, J=2.3 Hz, 2H); MS (FAB$^+$) m/z 685 (MH$^+$, 28); Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_4$: C, 52.61; H, 3.53; N, 20.45; S, 18.73. Found: C, 52.52; H, 3.39; N, 20.39; S, 18.56.

4.2.3. 1,4-Bis(4-oxo-2-(1-piperidinyl)pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5c). Yield (90%); mp >300 °C; IR (KBr) ν 1680 (CO), 1537, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.48 (m, 8H), 1.49–1.55 (m, 4H), 3.29–3.38 (m, 8H), 7.63 (s, 4H), 8.72 (d, J=2.3 Hz, 2H), 8.87 (d, J=2.3 Hz, 2H); MS (FAB^+) m/z 649 (MH^+, 19), 281 (30); Anal. Calcd for $C_{32}H_{28}N_{10}O_2S_2$: C, 59.24; H, 4.35; N, 21.59; S, 9.89. Found: C, 59.11; H, 4.26; N, 21.42; S, 9.76.

4.2.4. 1,4-Bis(2-diethylamino-4-oxopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5d). Yield (85%); mp >300 °C; IR (KBr) ν 1677 (CO), 1540, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, J=7.1 Hz, 12H), 3.32 (q, J=7.1 Hz, 8H), 7.58 (s, 4H), 8.71 (d, J=2.3 Hz, 2H), 8.88 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 45.5, 129.6, 137.5, 142.7, 144.0, 144.1, 149.1, 157.8, 158.7, 159.8; MS (FAB^+) m/z 625 (MH^+, 5); Anal. Calcd for $C_{30}H_{28}N_{10}O_2S_2$: C, 57.68; H, 4.52; N, 22.42; S, 10.27. Found: C, 57.53; H, 4.37; N, 22.38; S, 10.15.

4.2.5. 1,4-Bis(2-*n*-butylamino-4-oxopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5k). Yield (97%); mp 290 °C dec; IR (KBr) ν 2956, 2933 (NH), 1677 (CO), 1562, 1522, 1509, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J=7.3 Hz, 6H), 1.28–1.44 (m, 4H), 1.49–1.73 (m, 4H), 3.60–3.70 (m, 4H), 5.20 (t, J=5.3 Hz, 2H), 7.67 (s, 4H), 8.72 (d, J=2.3 Hz, 2H), 8.88 (d, J=2.3 Hz, 2H); MS (FAB^+) m/z 625 (MH^+, 100); Anal. Calcd for $C_{30}H_{28}N_{10}O_2S_2$: C, 57.68; H, 4.52; N, 22.42; S, 10.27. Found: C, 57.73; H, 4.31; N, 22.60; S, 10.11.

4.3. Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (5e–h)

To a solution of iminophosphorane **3** (0.10 g, 0.21 mmol) in dry THF (6 mL) was added 1,4-phenylene diisocyanate (0.02 g, 0.10 mmol) at room temperature. The mixture was stirred at room temperature for 4–5 h until the iminophosphorane had disappeared (TLC monitored) and after was treated with an appropriate substituted phenol or thiophenol (0.25 mmol), a catalytic amount of K_2CO_3 was added and the resultant solution was refluxed for 8 h. After cooling, the precipitate obtained was filtered off, washed water and THF, and purified by flash chromatography on silica gel with a solvent gradient of EtOAc in CH_2Cl_2 (10–50%) as an eluent. Compound **5h** could not be purified because of their insolubility in ordinary solvents.

4.3.1. 1,4-Bis(4-oxo-2-phenoxypyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5e). Yield (85%); mp >300 °C; IR (KBr) ν 1683 (CO), 1598, 1568, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.65 (m, 10H), 7.93 (s, 4H), 8.87 (d, J=2.3 Hz, 2H), 8.89 (d, J=2.3 Hz, 2H); MS (FAB^+) m/z 667 (MH^+, 37); 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, 61.36; H, 2.81; N, 16.75; S, 9.54.

4.3.2. 1,4-Bis(2-(4-*tert*-butylphenoxy)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5f). Yield (83%); mp 230 °C dec; IR (KBr) ν 1698 (CO), 1568, 1544, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 18H), 7.16–7.22 (m, 4H), 7.40–7.47 (m, 4H), 7.67 (s, 4H), 8.71 (d, J=2.3 Hz, 2H), 8.82 (d, J=2.3 Hz, 2H); MS (FAB^+) m/z 779 (MH^+, 30); Anal. Calcd for $C_{42}H_{34}N_8O_4S_2$: C, 64.76; H, 4.40; N, 14.39; S, 8.23. Found: C, 64.56; H, 4.34; N, 14.57; S, 8.05.

4.3.3. 1,4-Bis(2-(4-nitrophenoxy)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5g). Yield (86%); mp 230 °C dec; IR (KBr) ν 1694 (CO), 1615, 1590, 1568, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.52 (m, 4H), 7.72 (s, 4H), 8.38–8.83 (m, 4H), 8.75 (d, J=2.2 Hz, 2H), 8.86 (d, J=2.2 Hz, 2H); MS (FAB^+) m/z 757 (MH^+, 5); Anal. Calcd for $C_{34}H_{16}N_{10}O_8S_2$: C, 53.97; H, 2.13; N, 18.51; S, 8.48. Found: C, 54.06; H, 2.24; N, 18.57; S, 8.35.

4.3.4. 1,4-Bis(4-oxo-2-phenylthiopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5h). Yield (91%); mp >300 °C dec; IR (KBr) ν 1689 (CO), 1516, 1505, 1488, 1474 cm^{-1}; ^1H NMR and ^{13}C NMR spectra could not be obtained due to low solubility in ordinary solvents; MS (FAB^+) m/z 669 (MH^+, 5).

4.4. Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (5i and j)

To a solution of iminophosphorane **3** (0.10 g, 0.21 mmol) in dry THF (6 mL) was added 1,4-phenylene diisocyanate (0.02 g, 0.10 mmol) at room temperature. The mixture was stirred at room temperature for 5 h until the iminophosphorane had disappeared (TLC monitored). The solvent was evaporated, ROH (6 mL) was added to dissolve the solid and then NaOR (0.25 mmol) was added and the resultant mixture was stirred at room temperature for 8 h. The precipitate obtained was filtered off, washed water and THF, and purified by flash chromatography on silica gel using CH_2Cl_2/EtOAc (75:25, v/v) as an eluent.

4.4.1. 1,4-Bis(2-ethoxy-4-oxopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5i). Yield (80%); mp 290 °C dec; IR (KBr) ν 1687 (CO), 1568, 1544, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J=7.0 Hz, 6H), 4.70 (q, J=7.0 Hz, 4H), 7.50 (s, 4H), 8.75 (d, J=2.1 Hz, 2H), 8.89 (d, J=2.1 Hz, 2H); MS (FAB^+) m/z 571 (MH^+, 100); Anal. Calcd for $C_{26}H_{18}N_8O_4S_2$: C, 54.73; H, 3.18; N, 19.64; S, 11.24. Found: C, 54.53; H, 3.00; N, 19.56; S, 11.18.

4.4.2. 1,4-Bis(2-methoxy-4-oxopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (5j). Yield (83%); mp 290 °C dec; IR (KBr) ν 1683 (CO), 1573, 1543, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 6H), 7.51 (s, 4H), 8.76 (d, J=2.2 Hz, 2H), 8.90 (d, J=2.2 Hz, 2H); MS (FAB^+) m/z 543 (MH^+, 100); Anal. Calcd for $C_{24}H_{14}N_8O_4S_2$: C, 53.13; H, 2.60; N, 20.65; S, 11.82. Found: C, 52.96; H, 2.47; N, 20.48; S, 11.65.

4.5. Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (7a–d)

To a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in dry THF (3 mL) was added 1,3-phenylene diisocyanate (0.37 mmol) at room temperature. The mixture was stirred at room temperature for 1–5 h until the iminophosphorane had

disappeared (TLC monitored) and it was therefore treated with an appropriate secondary amine. The resultant solution was stirred at room temperature for 5 h. The solvent was evaporated and the residue was solved in acetone (3 mL), a catalytic amount of K_2CO_3 was added, the mixture was refluxed for 0.5 h. The solvent was removed under reduced pressure, and the solid obtained was purified by flash chromatography on silica gel using CH_2Cl_2/EtOAc (75:25, v/v) as an eluent.

4.5.1. 1,3-Bis(2-(4-morpholinyl)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7a). Yield (71%); mp >300 °C; IR (KBr) ν 1697 (CO), 1534, 1530, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.30–3.70 (m, 16H), 7.45–7.50 (m, 2H), 7.70–7.79 (m, 2H), 8.74 (d, J=2.3 Hz, 2H), 8.89 (d, J=2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.7, 65.9, 119.6, 127.8, 130.1, 131.5, 137.3, 142.9, 143.8, 144.3, 148.8, 157.5, 158.5, 159.3; MS (FAB^+) m/z 653 (MH^+, 100); Anal. Calcd for $C_{30}H_{24}N_{10}O_4S_2$: C, 55.20; H, 3.71; N, 21.46; S, 9.83. Found: C, 55.20; H, 3.76; N, 21.32; S, 9.70.

4.5.2. 1,3-Bis(4-oxo-2-(4-thiomorpholinyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7b). Yield (92%); mp >300 °C; IR (KBr) ν 1694 (CO), 1550, 1536, 1532, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30–2.60 (m, 8H), 3.70–3.75 (m, 8H), 7.37–7.42 (m, 2H), 7.70–7.73 (m, 1H), 7.74–7.79 (m, 1H), 8.74 (d, J=2.3 Hz, 2H), 8.89 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 52.2, 119.7, 127.9, 130.3, 132.5, 137.7, 142.9, 143.7, 144.3, 148.8, 158.2, 158.5, 159.4; MS (FAB^+) m/z 685 (MH^+, 25); Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_4$: C, 52.61; H, 3.53; N, 20.45; S, 18.73. Found: C, 52.47; H, 3.75; N, 20.40; S, 18.80.

4.5.3. 1,3-Bis(4-oxo-2-(1-piperidinyl)pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7c). Yield (72%); mp 217–219 °C; IR (KBr) ν 1687 (CO), 1537, 1532, 1524, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.40 (m, 4H), 1.40–1.55 (m, 8H), 3.30–3.45 (m, 8H), 7.37–7.45 (m, 2H), 7.65–7.75 (m, 2H), 8.71 (d, J=2.3 Hz, 2H), 8.87 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 24.9, 50.7, 127.5, 129.7, 131.6, 131.7, 137.9, 142.6, 143.9, 144.0, 149.1, 158.5, 159.6; MS (FAB^+) m/z 649 (MH^+, 100); Anal. Calcd for $C_{32}H_{28}N_{10}O_2S_2$: C, 59.24; H, 4.35; N, 21.59; S, 9.89. Found: C, 59.37; H, 4.31; N, 21.44; S, 9.87.

4.5.4. 1,3-Bis(2-diethylamino-4-oxopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7d). Yield (52%); mp 280–282 °C; IR (KBr) ν 1696 (CO), 1539, 1521, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00–1.07 (m, 12H), 3.20–3.51 (m, 8H), 7.33–7.38 (m, 2H), 7.62–7.68 (m, 1H), 7.70–7.72 (m, 1H), 8.71 (d, J=2.3 Hz, 2H), 8.87 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 45.4, 127.7, 129.9, 131.6, 138.2, 142.6, 144.0, 144.1, 149.2, 157.7, 158.6, 159.8; MS (FAB^+) m/z 625 (MH^+, 100); Anal. Calcd for $C_{30}H_{28}N_{10}O_2S_2$: C, 57.68; H, 4.52; N, 22.42; S, 10.27. Found: C, 57.62; H, 4.50; N, 22.31; S, 10.28.

4.6. Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (7e–h)

To a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in dry THF (3 mL) was added 1,3-phenylene diisocyanate (0.37 mmol) at room temperature. The mixture was stirred at room temperature for 1–5 h until the iminophosphorane had disappeared (TLC monitored) and it was therefore treated with an appropriate secondary amine. The resultant solution was stirred at room temperature for 5 h. The solvent was evaporated and the residue was solved in acetone (3 mL), a catalytic amount of K_2CO_3 was added, the mixture was refluxed for 0.5 h. The solvent was removed under reduced pressure, and the solid obtained was purified by flash chromatography on silica gel with a solvent gradient of EtOAc in CH_2Cl_2 (10–60%) as an eluent. Compound **7h** could not be purified because of its insolubility in ordinary solvents.

4.6.1. 1,3-Bis(4-oxo-2-phenoxypyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7e). Yield (50%); mp >300 °C; IR (KBr) ν 1701 (CO), 1566, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00–7.50 (m, 10H), 7.60–7.70 (m, 3H), 7.80–7.85 (m, 1H), 8.71 (d, J=2.3 Hz, 2H), 8.81 (d, J=2.3 Hz, 2H); MS (FAB^+) m/z 667 (MH^+, 100); 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, 2.57; N, 17.00; S, 9.61.

4.6.2. 1,3-Bis(2-(4-*tert*-butylphenoxy)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7f). Yield (40%); mp >300 °C; IR (KBr) ν 1688 (CO), 1573, 1564, 1543, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 18H), 6.95–7.15 (m, 2H), 7.30–7.55 (m, 5H), 7.60–7.70 (m, 4H), 7.79–7.83 (m, 1H), 8.73 (d, J=2.3 Hz, 2H), 8.84 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 120.3, 121.3, 126.7, 128.3, 129.2, 130.6, 135.4, 142.9, 143.5, 144.2, 147.6, 149.1, 149.3, 155.2, 158.3, 158.4; MS (FAB^+) m/z 779 (MH^+, 100); Anal. Calcd for $C_{42}H_{34}N_8O_4S_2$: C, 64.76; H, 4.40; N, 14.39; S, 8.23. Found: C, 64.67; H, 4.29; N, 14.20; S, 8.16.

4.6.3. 1,3-Bis(2-(4-nitrophenoxy)-4-oxopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7g). Yield (50%); mp >300 °C; IR (KBr) ν 1699 (CO), 1569, 1541, 1521, 1487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.65 (m, 4H), 7.65–7.73 (m, 3H), 7.86–7.91 (m, 1H), 8.32–8.42 (m, 4H), 8.77 (d, J=2.3 Hz, 2H), 8.87 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.6, 121.1, 125.7, 126.2, 128.4, 129.5, 131.1, 135.0, 143.1, 143.3, 144.7, 145.7, 147.1, 153.9, 155.8, 158.3; MS (FAB^+) m/z 757 (MH^+, 15), 341 (25); Anal. Calcd for $C_{34}H_{16}N_{10}O_8S_2$: C, 53.97; H, 2.13; N, 18.51; S, 8.48. Found: C, 54.08; H, 2.27; N, 18.60; S, 8.61.

4.6.4. 1,3-Bis(4-oxo-2-phenylthiopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7h). Yield (82%); mp >300 °C; IR (KBr) ν 1692 (CO), 1545, 1515, 1493, 1482 cm^{-1}; ^1H NMR and ^{13}C NMR spectra could not be obtained due to low solubility in ordinary solvents; MS (FAB^+) m/z 699 (MH^+, 15).

4.7. Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (7i and j)

To a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in dry THF (3 mL) was added 1,3-phenylene diisocyanate (0.37 mmol) at room temperature. The mixture was stirred

at room temperature for 1–5 h until the iminophosphorane had disappeared (TLC monitored) and it was therefore treated with an appropriate secondary amine. The resultant solution was stirred at room temperature for 5 h. The solvent was evaporated and the residue was solved in acetone (3 mL), a catalytic amount of K_2CO_3 was added, the mixture was refluxed for 0.5 h. The solvent was removed under reduced pressure, and the solid obtained was purified by flash chromatography using CH_2Cl_2/$AcOEt_2$ (75:25, v/v) as an eluent.

4.7.1. 1,3-Bis(2-ethoxy-4-oxopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7i). Yield (55%); mp 230–232 °C dec; IR (KBr) ν 1695 (CO), 1683, 1568, 1543, 1540, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J=7.0 Hz, 6H), 4.69 (q, J=7.0 Hz, 4H), 7.32–7.35 (m, 1H), 7.45–7.50 (m, 2H), 7.70–7.77 (m, 1H), 8.74 (d, J=2.3 Hz, 2H), 8.88 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 66.4, 128.4, 128.6, 129.0, 130.1, 132.0, 132.2, 135.2, 142.8, 143.6, 144.2, 156.0, 158.3; MS (FAB$^+$) *m*/*z* 571 (MH^+, 45), 279 (100); Anal. Calcd for $C_{26}H_{18}N_8O_4S_2$: C, 54.73; H, 3.18; N, 19.64; S, 11.24. Found: C, 55.02; H, 3.20; N, 19.51; S, 11.28.

4.7.2. 1,3-Bis(2-methoxy-4-oxopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-3(4*H*)-yl)benzene (7j). Yield (55%); mp 275–277 °C dec; IR (KBr) ν 1689 (CO), 1571, 1544, 1521, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 6H), 7.36–7.38 (m, 1H), 7.50–7.54 (m, 2H), 7.75–7.79 (m, 1H), 8.77 (d, J=2.3 Hz, 2H), 8.92 (d, J=2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2, 120.3, 128.4, 129.2, 130.4, 135.1, 142.9, 143.6, 144.3, 147.9, 156.5, 158.4, 158.6; MS (FAB$^+$) *m*/*z* 543 (MH^+, 60); Anal. Calcd for $C_{24}H_{14}N_8O_4S_2$: C, 53.13; H, 2.60; N, 20.65; S, 11.82. Found: C, 53.08; H, 2.59; N, 20.65; S, 11.69.

5. Crystallographic material

Crystallographic data (excluding structural factors) for **5k** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication number CCDC 627137. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 33603 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The authors are grateful to MCyT (Spain, Grant BQU2003-00574) and the Xunta de Galicia (Spain, Grant PGI-DIT04P-XIC10307PN) for financial support. G.B. acknowledges a predoctoral fellowship from the University of A Coruña.

References and notes

1. (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kniesel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302; (b) Turk, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489; (c) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941 and references therein; (d) Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1997**, *14*, 413; (e) Neuschütz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227; (f) Palacios, F.; Gil, M. J.; Martínez, E.; Rodríguez, M. *Tetrahedron Lett.* **1999**, *40*, 2411; (g) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840.
2. (a) Ganjgee, A.; Adair, O.; Queener, S. F. *J. Med. Chem.* **2003**, *46*, 5074 and references cited therein; (b) Ding, M.-W.; Huang, N.-Y.; He, H.-W. *Synthesis* **2005**, 1601 and references cited therein.
3. (a) Wnuk, S. F.; Lewandowska, E.; Companioni, D. R.; García, P. I., Jr.; Secrist, J. A., III. *Org. Biomol. Chem.* **2004**, *2*, 120; (b) Cushman, M.; Sambaiah, T.; Jin, G.; Illarionov, B.; Fischer, M.; Bacher, A. *J. Org. Chem.* **2004**, *69*, 601; (c) Haraguchi, K.; Kubota, Y.; Tanaka, H. *J. Org. Chem.* **2004**, *69*, 1831; (d) Depecker, G.; Patino, N.; Giorgio, C. D.; Terreux, R.; Cabrol-Bass, D.; Bailly, C.; Aubertin, A.-M.; Condom, R. *Org. Biomol. Chem.* **2004**, *2*, 74; (e) Rabow, A. A.; Shoemaker, R. H.; Sausville, E. A.; Covell, D. J. *J. Med. Chem.* **2002**, *45*, 818; (f) Carraro, F.; Naldini, A.; Pucci, A.; Locatelli, G. A.; Maga, G.; Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Brullo, Ch.; Fossa, P.; Menozzi, G.; Mosti, L.; Modugno, M.; Tintori, C.; Menetti, F.; Botta, M. *J. Med. Chem.* **2006**, *49*, 1549 and references cited therein; (g) Koch, U.; Attenni, B.; Malancona, S.; Colarusso, S.; Conte, I.; Di Filippo, M.; Harper, S.; Pacini, B.; Giomini, C.; Thomas, S.; Incitti, I.; Tomei, L.; De Francesco, R.; Altamura, S.; Matassa, V. G.; Narjes, F. *J. Med. Chem.* **2006**, *49*, 1693 and references cited therein; (h) Santana, L.; Teijeira, M.; Uriarte, E.; Balzarini, J.; De Clerq, E. *J. Med. Chem.* **2002**, *37*, 755; (i) De Clerq, E. *J. Clin. Virol.* **2004**, *30*, 115.
4. (a) Shishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. *Eur. J. Med. Chem.* **2000**, *35*, 351; (b) Walter, H. WO 9911631, 1999; *Chem. Abstr.* **1999**, *130*, 237580e; (c) Walter, H. WO 9914202, 1999; *Chem. Abstr.* **1999**, *130*, 252368k; (d) Chambhare, R. V.; Khadse, B. G.; Bobde, A. S.; Bahekar, R. H. *Eur. J. Med. Chem.* **2003**, *38*, 89.
5. (a) Aboulwafa, O. M.; Ismail, K. A.; Koreish, E. A. *Farmaco* **1992**, *47*, 631; (b) See Ref. 4c; *Chem. Abstr.* **1999**, *130*, 252368k; (c) Leitsner, S.; Wagner, G.; Guetschow, M.; Glusa, E. *Pharmazie* **1986**, *41*, 54; (d) Hozien, Z. A.; Atta, F. M.; Hassan, K. M.; Abdel-Wahah, A. A.; Ahmed, S. A. *Synth. Commun.* **1996**, *26*, 3733.
6. (a) See Ref. 4a; (b) Santagati, M.; Modica, M.; Santagati, A.; Russo, F.; Spampinato, S. *Pharmazie* **1996**, *51*, 7.
7. (a) Cheng, C. C. *Structural Aspects of Antineoplastic Agents. A New Approach*; Ellis, G. P., West, G. B., Eds.; Progress in Medicinal Chemistry; Elsevier: Amsterdam, 1988; Vol. 25, pp 35–83; (b) Skelton, V.; Bavetsias, V.; Jackman, A. WO 0050417, 2000; *Chem. Abstr.* **2000**, *133*, 207917q.
8. (a) Jones, G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon: Oxford, 1996; Vol. 5; (b) Friedrichsen, W. *Comprehensive Heterocyclic Chemistry*; Bird, W., Cheeseman, G. W. H., Eds.; Pergamon: Oxford, 1984; p 1002; (c) Jones, G. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2.
9. Baker, D. C.; Hand, E. S.; Plowman, J.; Rampal, J. B.; Safavy, A.; Haugwitz, R. D.; Narayanan, V. L. *Anti-Cancer Drug Des.* **1987**, *2*, 297.
10. For a recent example, see: Burns, C. J.; Wilks, A. F.; Bu, X. Worldwide Patent WO 2005054230, 2005; *Chem. Abstr.* **2005**, *143*, 60004o.

11. Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett.* **2003**, *5*, 2433.
12. (a) Pettit, G. R.; Tan, R.; Xu, J.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 995; (b) Immamura, N.; Nishijima, M.; Takadera, T.; Adachi, K.; Sakai, M.; Sano, H. *J. Antibiot.* **1997**, *50*, 8.
13. (a) Abboto, A.; Bradamante, S.; Facchetti, A.; Pagani, G. A. *J. Org. Chem.* **2002**, *67*, 5753; (b) Wang, S. *Coord. Chem. Rev.* **2001**, *215*, 79; (c) Balzani, V.; Juris, A.; Venturi, M.; Campagna, S.; Serroni, S. *Chem. Rev.* **1996**, *96*, 759; (d) Di Bella, S. *Chem. Soc. Rev.* **2001**, *30*, 355.
14. (a) *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: New York, NY, 2004; (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: New York, NY, 2000; (c) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Prospectives*; VCH: Weinheim, 1995; (d) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853; (e) Steel, P. J. *Acc. Chem. Res.* **2005**, *38*, 243; (f) See Ref. 13c; (g) Steel, P. J. *Coord. Chem. Rev.* **1990**, *106*, 227.
15. (a) Quintela, J. M.; Peinador, C.; González, L. M.; Rioja, I.; Terencio, M. C.; Ubeda, A.; Alcaraz, M. J.; Riguera, R. *J. Med. Chem.* **1999**, *42*, 4720; (b) Quintela, J. M.; González, L.; Devesa, I.; Ferrándiz, M. L.; Alcaraz, M. J.; Riguera, R. *Bioorg. Med. Chem.* **2003**, *11*, 863; (c) Quintela, J. M.; Peinador, C.; González, L.; Iglesias, R.; Paramá, A.; Alvárez, F.; Sanmartín, M.; Riguera, R. *Eur. J. Med. Chem.* **2003**, *38*, 265; (d) Rioja, I.; Ubeda, A.; Terencio, M. C.; Guillén, I.; Riguera, R.; Quintela, J. M.; Peinador, C.; González, L.; Alcaraz, M. J. *Eur. J. Pharmacol.* **2000**, *397*, 207; (e) Quintela, J. M.; Peinador, C.; Veiga, C.; González, L.; Botana, L. M.; Alfonso, A.; Riguera, R. *Bioorg. Med. Chem.* **1998**, *6*, 1911; (f) *Eur. J. Med. Chem.* **1998**, *33*, 887; (g) Peinador, C.; Veiga, M. C.; Ojea, V.; Quintela, J. M. *Heterocycles* **1994**, *38*, 2065; (h) Peinador, C.; Ojea, V.; Quintela, J. M. *J. Heterocycl. Chem.* **1992**, *29*, 1693.
16. To our knowledge, there is only two reports on the pyridothienopyridazine system: (a) Schneller, S. W.; Clough, F. W.; Hardee, L. E. *J. Heterocycl. Chem.* **1975**, *12*, 513; (b) Badr, M. Z. A.; Mahgoub, S. A.; Atta, F. M.; Moustafa, O. S. *J. Indian Chem. Soc.* **1997**, *74*, 30.
17. (a) Chas, M.; Pia, E.; Toba, R.; Peinador, C.; Quintela, J. M. *Inorg. Chem.* **2006**, *45*, 6117; (b) Pia, E.; Toba, R.; Chas, M.; Peinador, C.; Quintela, J. M. *Tetrahedron Lett.* **2006**, *47*, 1953; (c) Chas, M.; Platas-Iglesias, C.; Peinador, C.; Quintela, J. M. *Tetrahedron Lett.* **2006**, *47*, 3119.
18. (a) Vázquez, D.; Peinador, C.; Quintela, J. M. *Tetrahedron* **2004**, *60*, 275; (b) Álvarez-Sarandés, R.; Peinador, C.; Quintela, J. M. *Tetrahedron* **2001**, *57*, 5413; (c) Quintela, J. M.; Álvarez-Sarandés, R.; Peinador, C. *Tetrahedron* **1998**, *54*, 8107; (d) Peinador, C.; Moreira, M. J.; Quintela, J. M. *Tetrahedron* **1994**, *50*, 6705.
19. For some references, see: (a) Molina, P.; Fresneda, P. M.; Delgado, S. *Synthesis* **1999**, 326; (b) Eguchi, E.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.* **1996**, *61*, 7316; (c) Ding, M.-W.; Xu, Sh.-Zh.; Zhao, J.-F. *J. Org. Chem.* **2004**, *69*, 8366; (d) Takahashi, M.; Suga, D. *Synthesis* **1998**, 986; (e) Nitta, M.; Akei, T.; Iino, Y. *J. Org. Chem.* **1994**, *59*, 1309; (f) He, F.; Snider, B. B. *Synlett* **1997**, 483; (g) Csampai, A.; Turos, G.; Kudar, V.; Simon, K.; Oeynhausen, H.; Wamhoff, H.; Sohar, P. *Eur. J. Org. Chem.* **2004**, 717; (h) Zhao, M.-X.; Wang, M.-X.; Yu, C.-Y.; Huang, Z.-T.; Fleet, G. W. J. *J. Org. Chem.* **2004**, *69*, 997; (i) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112; (j) Yadav, J. S.; Srinivas, C. *Tetrahedron* **2003**, *59*, 10325; (k) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690.
20. For reviews on heterocyclic synthesis by the aza–Wittig methodology, see: (a) Eguchi, S. *ARKIVOC* **2005**, *ii*, 98; (b) Eguchi, S. *Top. Heterocycl. Chem.* **2006**, *6*, 113; (c) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1; (d) Eguchi, S.; Okano, T.; Okawa, T. *Recent Res. Dev. Org. Chem.* **1997**, 337; (e) Wamhoff, H.; Richardt, G.; Stölben. *Adv. Heterocycl. Chem.* **1995**, *64*, 159; (f) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; (g) Eguchi, S.; Matshushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209; (h) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353; (i) Gussar, N. I. *Russ. Chem. Rev.* **1991**, *60*, 146.
21. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
22. (a) *Ylides and Imines of Phosphorus*; Johnson, A. W., Kahsa, W. S., Starzewski, K. A. D., Dixon, D. A., Eds.; Wiley: New York, NY, 1993; (b) Taylor, E. C.; Patel, M. *J. Heterocycl. Chem.* **1991**, *28*, 1857.
23. Sato, N.; Matsui, N. *J. Heterocycl. Chem.* **1992**, *29*, 1689.
24. The iminophosphorane synthesis is known as the Appel method, i.e., the modified Kirsanov reaction. Appel, R.; Halstenberg, M. *Organophosphorous Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic: London, 1979; p 378 and often used in recent literatures, for example: (a) See Ref. 18; (b) Okawa, T.; Kawase, M.; Eguchi, S. *Synthesis* **1998**, 1185; (c) Okawa, T.; Eguchi, S. *Tetrahedron* **1998**, *54*, 5853.
25. (a) Blanco, G.; Seguí, N.; Quintela, J. M.; Peinador, C.; Chas, M.; Toba, R. *Tetrahedron* **2006**, *62*, 11124; (b) Wang, H.-Q.; Liu, Z.-J.; Yang, L.-M.; Ding, M.-W. *J. Heterocycl. Chem.* **2004**, *41*, 393; (c) Saito, T.; Tsuda, Y. *Tetrahedron Lett.* **1996**, *37*, 209.
26. (a) D'Alessandro, D. M.; Keene, F. R. *New J. Chem.* **2006**, *30*, 228; (b) Slater, J. W.; Steel, P. J. *Tetrahedron Lett.* **2006**, *47*, 6941.