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A practical one-pot procedure for the synthesis of pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones by a tandem aza-Wittig/heterocumulene-mediated annulation strategy

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Abstract—A simple one-pot and efficient method is described for the synthesis of pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinone derivatives **6** via a tandem aza-Wittig/heterocumulene-mediated annulation process. The iminophosphorane **3** reacted with aryl isocyanates, followed by heterocyclization on addition of secondary amines to give the corresponding guanidine intermediates **5**, which were cyclized in the presence of a catalytic amount of potassium carbonate to tricyclic compounds **6**. Similarly, iminophosphorane **3** reacts with phenols, thiophenol, or ROH to give 2-aryl(alkyl)oxy(thio)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinone derivatives **7** in good yields. The corresponding carbodiimide **4c** and guanidine-type intermediate compounds **5** could be isolated and characterized, thus confirming the suggested reaction pathway. However, two isomeric pyrazinothienopyrimidinones **8** and **9** may be produced in the reaction of iminophosphorane **3** with aromatic isocyanates and subsequent reaction with primary amines in the presence of a catalytic amount of potassium carbonate. The effects of the nucleophiles and isocyanates on the regioselectivity of the cyclization have been investigated.

1. Introduction

The development of efficient and mild methods for heterocyclic compound synthesis represents a broad area of organic chemistry.[1] Structures containing such units often play an essential role because of their biological activity, particularly in cancer and virus researches.[2] Among these heterocycles, thienopyrimidine derivatives are an important class of heterocyclic compounds in pharmaceutical discovery research.[3] Also, some derivatives of thienodipyrimidines have been synthesized and some of them show good antitumor activity.[4]

Whereas pyridine annelated sulfur-containing heterocycles have been studied extensively,[5] comparatively little is known about aza-analogue systems in which an *S*-heterocycle is fused to a pyrazine nucleus. 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 and antihistaminic activities.[6] In a search of the literature it is surprising that their isosteres pyrazinothienopyrimidines, moreover isosteres of quinoxalinepyrimidines, have been practically ignored.[7]

Following this research line and in continuation of our work on the studies on *S*- and *N*-heterocyclic compounds, we describe here a convenient approach to substituted pyrazinothienopyrimidinone derivatives **I** as isosteres of pharmaceutically relevant pyridothienopyrimidines[8] as well as their use as appropriate 1,10-phenanthroline-like ligands toward transition metals (Fig. 1). Derivatives **I** are of considerable interest as potential biologically active compounds or pharmaceuticals.

In the development of strategies for the preparation of heterocycles the aza-Wittig reaction has proved to be exceptionally useful and great progress has been made in the field of heterocyclic compounds by the aza-Wittig methodology.

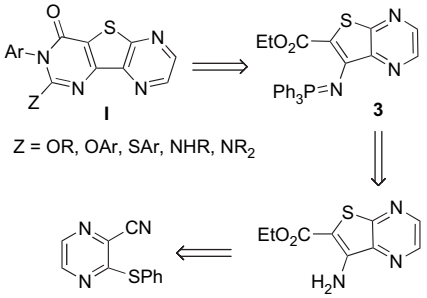

Figure 1. Retrosynthetic pathway for synthesis of the pyrazinothienopyrimidinone derivatives **I**.

Keywords: Pyrazinothienopyrimidinone; Aza-Wittig; Heterocumulene.
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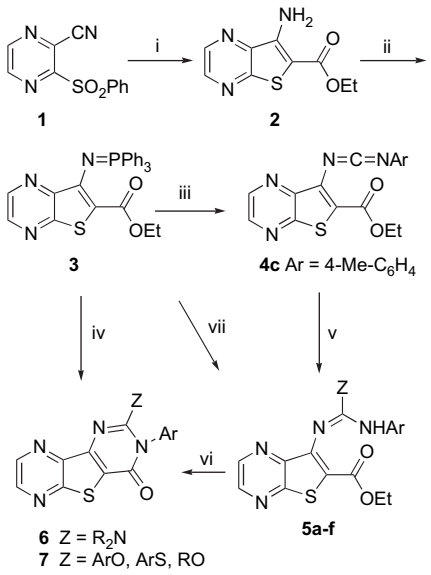
Both inter- and intramolecular version of the aza-Wittig reaction has assumed increasing importance for the specific construction of many heterocyclic compounds, in particular nitrogen heterocyclic compounds.[9] The intramolecular aza-Wittig reaction is a powerful tool for the synthesis of five–seven membered nitrogen heterocycles[10] and the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition, or heterocyclization, the tandem aza-Wittig, and cyclization sequence has been utilized for the synthesis of many important nitrogen heterocycles.[11]

Heteroaryliminophosphoranes, derived from *C*-aminoheterocycles, have proved to be very versatile building blocks for the construction of fused heterocondensed systems.[12] In our ongoing efforts to synthesize biologically active compounds as potential therapeutic agents based on heterocyclization reactions of azahexatriene compounds, we have previously published the synthesis of fused pyrimidines based on the tandem aza-Wittig heterocumulene-mediated annulation strategy.[13] As a continuation of our work on the aza-Wittig-type methodology, we report here a simple, general, and effective strategy for the preparation of substituted derivatives of the pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine ring system employing *N*-heteroaryl iminophosphoranes as a conveniently accessible precursor. Pyrimidothienopyrazines were obtained in a one-pot reaction of the corresponding iminophosphorane of heteroaromatic β-enamino ester **2** with isocyanates, followed by heterocyclization on addition of nucleophilic reagents HZ. Dihydropyrimido-annulation occurs via a heterocumulene moiety, available from the reaction of the iminophosphorane and an isocyanate, which on addition of the corresponding nucleophile undergoes ring closure by nucleophilic attack of the adjacent *Z* group to give a six-membered heterocyclic ring.

2. Preparation of pyrazino[2′,3′:4,5]thieno[3,2-*d*]-pyrimidinones

The starting compound for the aza-Wittig reaction and heterocyclization sequence was prepared from the readily available ethyl 3-aminothieno[2,3-*b*]pyrazine-2-carboxylate **2**. The synthesis of a set of pyrazinothienopyrimidinone derivatives **6** and **7** is depicted in Scheme 1.

The initial reaction of 3-benzenesulfonylpyrazine-2-carbonitrile **1**[14] with ethyl 2-mercaptoacetate, in the presence of an equimolecular amount of sodium carbonate, gave an excellent yield (97%) of pyrazine carboxylate **2**. The key iminophosphorane **3** was obtained, in 97% yield, by a modified Kirsanov reaction of the β-enamino ester **2** with in situ generated dichlorotriphenylphosphorane using a hexachloroethane–triphenylphosphine–triethylamine reagent system.[15] Reaction of iminophosphorane **3** with several aromatic isocyanates, followed by heterocyclization on addition of secondary amines in the presence of a catalytic amount of K_2CO_3, resulted in the formation of triphenylphosphine oxide and the corresponding triheterocyclic pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)ones **6a–j** directly in excellent yields (85–98%). Aniline also reacted directly with the iminophosphorane **3** and phenylisocyanate to afford **6k** in 86% yield. The mechanism for these conversions involves an initial



Scheme 1. Reagents and conditions: (i) $HSCH_2CO_2Et$, Na_2CO_3, EtOH, reflux; (ii) C_2Cl_6, PPh_3, NEt_3, toluene, 100 °C, sealed tube; (iii) 4-MeC_6H_4NCO, THF, room temperature; (iv) ArNCO, THF (1–2 h, room temperature), HZ (5 h, room temperature), K_2CO_3, or NaOR (1 h, reflux); (v) secondary amine, THF, room temperature; (vi) K_2CO_3, acetone, reflux; (vii) ArNCO, THF (1–2 h, room temperature), HZ (5 h, room temperature).

aza-Wittig reaction between the iminophosphorane and the isocyanate to give the highly reactive carbodiimide intermediates which, in turn, were conveniently converted by a one-pot procedure into the corresponding heterocycles **6**, via initial addition of an amine to the carbodiimide cumulenic system followed by intramolecular hetero conjugate addition annulation, by simply heating in acetone in the presence of catalytic K_2CO_3. The results are listed in Table 1. Similarly, iminophosphorane **3** reacted with isocyanates and phenol, thiophenol, substituted phenols, or ROH in the presence of catalytic K_2CO_3 or Na^+RO^- to give the 2-aryl(alkyl)oxy(thioxy)pyrazinothienopyrimidinones **7** in satisfactory to good yields (65–85%).

The participation of carbodiimide **4** as an intermediate in this process has been confirmed experimentally: the treatment of iminophosphorane **3** with *p*-tolylisocyanate in dry THF resulted in a conversion of the former into ethyl 3-(*p*-tolylimino-methyleneamino)thieno[2,3-*b*]pyrazine-6-carboxylate **4c**. Likewise, reaction of iminophosphorane **3** with aryl isocyanates and secondary amines at room temperature resulted in the formation of triphenylphosphine oxide and

Table 1. 2-Dialkylaminopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6a–6k**

Compd	Ar	Z	Yield (%)	Mp (°C)
6a	C_6H_5	NEt_2	92	215–216
6b	4-CH_3O–C_6H_4	NEt_2	90	194–196
6c	4-CH_3–C_6H_4	NEt_2	91	185–187
6d	4-Cl–C_6H_4	NEt_2	94	230–231
6e	4-NO_2–C_6H_4	NEt_2	93	224–225
6f	4-Cl–C_6H_4	Morpholino	86	232–233
6g	C_6H_5	Morpholino	98	289–290
6h	C_6H_5	Thiomorpholino	85	292–293
6i	C_6H_5	Pyrrolidino	90	244–245
6j	C_6H_5	Piperidino	85	220–221
6k	C_6H_5	C_6H_5NH	86	254–255

the corresponding guanidine-type intermediate derivatives **5a–5f** in good yields (70–85%) (Table 2). It is clear that compounds **5** are the key intermediates for the processes. In the presence of anhydrous potassium carbonate, the separated **5a–f** underwent intramolecular heterocyclization across the electrophilic ester functionality to give the fused pyrimidines **6**. Direct cyclization of the initially formed carbodiimide via a 1,3-OMe migration followed by electrocyclization (Wamhoff's pyrimido annelation)[16] was not observed.

Similarly, iminophosphorane **3** reacted with isocyanates and phenol, thiophenol, substituted phenols, or ROH in the presence of catalytic K_2CO_3 or Na^+RO^- to give the 2-aryl(alkyl)-oxy(thioxy)pyrazinothienopyrimidinones **7** in satisfactory to good yields (65–85%). The one-pot formation of aryloxy- and arylthioxy pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **7** (Table 3) was carried out by the reaction of iminophosphorane **3** with phenylisocyanate, followed by heterocyclization on addition of phenols or thiophenols in the presence of catalytic potassium carbonate. 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. Meanwhile, 4-ethoxy- or 4-methoxy-pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one **7f** or **7g** was obtained in satisfactory yield when the reaction took place in the presence of catalytic sodium ethoxide or sodium methoxide, respectively. The formation of **7** can be also rationalized in terms of an initial nucleophilic addition of phenoxide, thiophenoxide, or alkoxide to the carbodiimide **4** to give the intermediate **5**, which cyclizes to affords **7** (Scheme 1).

Carbodiimide compound **4c**, guanidine compounds **5a–5f**, and fused 2-substituted pyrimidinones **6** and **7** were characterized from their microanalyses, spectroscopic, and mass spectrometric data. The EI-mass spectra show the expected molecular ion peaks in moderate to high intensity and the fragmentation pattern is in accord with the proposed structure. The IR spectra of the guanidine-type intermediates **5a–5f** showed a strong absorption at ν=3280–3320 cm^{-1} attributed to the NH group, while in the ^1H NMR spectra, the NH proton appears at 5.70–6.13 ppm as a broad singlet, in addition to the set of signals due to the ethoxy group. Also, the ^{13}C NMR spectra showed signals between 14.3–14.5 and 60.7–61.4 ppm due to the ethoxy groups. After heterocyclization, the spectra of pyrazinothienopyrimidones **6** and **7** did not include those type of signals.

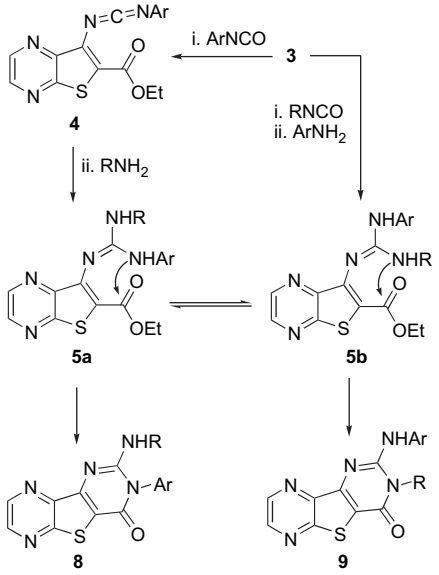
Table 2. Guanidine-type intermediate compounds **5a–5f**

Compd	Ar	Z	Time (h)	Yield (%)	Mp (°C)
5a	C_6H_5	NEt_2	3	70	106–107
5b	4-CH_3O–C_6H_4	NEt_2	4	85	194–195
5c	4-CH_3–C_6H_4	NEt_2	5	84	194–195
5d	4-Cl–C_6H_4	NEt_2	4	75	155–156
5e	4-NO_2–C_6H_4	NEt_2	1	80	182–183
5f	4-Cl–C_6H_4	Morpholino	4	70	160–161

Table 3. 2-Aryl(alkyl)oxypyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **7a–7g**

Compd	Ar	Z	Yield (%)	Mp (°C)
7a	C_6H_5	C_6H_5O	68	232–234
7b	C_6H_5	C_6H_5S	85	226–227
7c	C_6H_5	4-NO_2–C_6H_4O	78	143–145
7d	C_6H_5	4-$(CH_3)_3C$–C_6H_4O	67	228–230
7e	C_6H_5	4-Benzyloxy-C_6H_4O	70	203–205
7f	C_6H_5	EtO	65	202–204
7g	C_6H_5	MeO	72	204–206

Two isomeric pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones **8** and **9** may be produced in the reaction of iminophosphorane **3** with primary amines via a guanidine-type intermediate **5**. In addition, these isomeric pyrazinothienopyrimidones, **8** and **9**, may be produced in the treatment of the heteroaryl-imino-phosphorane **3** with ArNCO/RNH_2 or RNCO/$ArNH_2$ (Scheme 2).



Scheme 2.

We decided to explore the effects of the structural variations on isocyanates and primary amines in the ratio of the formation of compounds **8** and **9**. First, a comparative study of the one-pot procedure for the cyclization of **3** was carried out with phenylisocyanate and substituted primary amines. The ratio of **8**:**9** compounds is strongly influenced by the alkyl substituent at the primary amine. The general conditions in Scheme 1 are used and the results are listed in Table 4. The results showed that the selectivity of the reaction was found markedly dependent on the nature of the primary amine employed. A helpful generalization is that whenever

Table 4. Selectivity and yields in the reaction of **3** with phenylisocyanate and primary amines

Entry	Compd	R	Ar	Yield (%)[a]	Mp (°C)
1	**8a**	*n*-Butyl	C_6H_5	57	197–198
2	**9a**	*n*-Butyl	C_6H_5	19	99–101
3	**8b**	Benzyl	C_6H_5	55	113–115
4	**9b**	Benzyl	C_6H_5	44	175–176
5	**8c**	*iso*-Propyl	C_6H_5	80	228–230
6	**9c**	*iso*-Propyl	C_6H_5	0	
7	**8d**	Cyclohexyl	C_6H_5	95	208–210
8	**9d**	Cyclohexyl	C_6H_5	0	
9	**8e**	*tert*-Butyl	C_6H_5	82	231–232
10	**9e**	*tert*-Butyl	C_6H_5	0	

[a] Unoptimized yield of analytically pure isolated product.

the primary amines are heavily substituted, that is, R=*iso*-propyl, *tert*-butyl, or cyclohexyl, these reactions afforded only **8**, compound **9** not being formed (Table 4, entries 5–10). However, when the primary amine is less hindered, e.g., R=*n*-butyl or R=benzyl, the selectivity is less satisfactory, affording a 75:25 and 55:45 ratios of **8**:**9** compounds, respectively, ratios determined by ^{1}H NMR analysis of the mixture of reaction (Table 4, entries 1–4).

The most important factor in the formation of products **8** and **9** can be ascribed mainly to the large difference in cyclization rates due to the steric hindrance around the Ph and R groups.[13,17] Although the carbodiimide **4** is mainly coplanar due to the resonance effect, it is immediately obvious that the amine would approach essentially by the opposite direction of the COOEt group due to the steric hindrance to form the guanidine-type intermediate **5a** (Scheme 2). However, **5a** may convert to **5b** through C–N single bond rotation and this offers the opportunity that both guanidine-type intermediates, **5a** and **5b**, are suitable to cyclize: **5a** for the arylamine group and **5b** by the alkylamino group to form **8** and **9**, respectively. Steric hindrance between alkyl group and ester group would explain the regioselectivity of the reaction. Thus, the bulkier R group could rationalize the only formation of the final products **8c**–**8e** (Table 4, entries 5, 7, and 9). In these cases, the initially formed **5a** more easily undergoes cyclization to give **8** than to divert to **5b** to give **9**, due the greater steric hindrance between the iso-propyl, cyclohexyl, or *tert*-butyl group and the ester group in the guanidine-type intermediate **5b**. However, with *n*-butyl or benzylamine, the minor steric hindrance between the alkyl group and the ester group may convert more easily **5a** to **5b** with subsequent cyclization of **5a** and **5b** by the arylamino or alkylamino group, respectively, to yield a mixture of the pyrazinothienopyrimidines **8a/9a** and **8b/9b** (Table 4, entries 1–4).

Though steric effects are of greatest importance in governing the relative ratios between compounds **8** and **9** and may determine, which product is formed in these processes, it is also noteworthy that there are other electronic effects that are of importance on the selectivity of the cyclization reaction. In this manner, in an effort to explore the electronic effects on the selectivity of the reaction, at the same time, to achieve diversity in terms of substitution, aryl isocyanates bearing electron-withdrawing or electron-releasing group were also subjected to the reaction conditions with iminophosphorane **3** and primary amines. To the best of our knowledge, no precedent has been reported in this way.

Armed with the results from Table 4, we examined the scope of the one-pot tandem reaction sequence for phenylisocyanate, 4-nitrophenylisocyanate, and 4-methylisocyanate varying the primary amine. Interesting enough, the results from Table 5 seem to suggest that the selectivity of the reaction is particularly sensitive to electronic effects, as soon as the ratio between compounds **8** and **9** was found to have a pronounced dependence on the relative nucleophilicities of the NHAr groups. Not surprisingly, the effect of nucleophilicity of amine groups on the ratio of the formation of compounds **8c**:**9c**, **8d**:**9d**, and **8e**:**9e** will not be important (Table 5, entries 7–15). In terms of precedent discussion, this high regioselectivity is in agreement with the explanation that the bulkier R group exerts a directing steric effect affording a single cyclized product **8**. However, entries 1–6 show the effect of varying the NHAr group in Scheme 2, allowing us to deduce that their relative nucleophilicity is responsible for these changes in the selectivity of the reaction and will affect the resulting product distribution when *n*-butyl or benzylamine is employed in the one-pot reaction. The most significant difference was observed in the reaction with aryl isocyanates bearing electron-withdrawing groups. Thus, the reaction of **3** with phenylisocyanate/*n*-butylamine or phenylisocyanate/benzylamine proceeded giving the corresponding compounds **8**:**9** in high yields, but little selectivity was observed (Table 5, entries 1 and 4), whereas, in contrast to this, the use of 4-nitrophenylisocyanate/*n*-butylamine and 4-nitrophenylisocyanate/benzylamine resulted in a dramatic change in the reaction selectivity, so that after the reaction the isomer **9** is present in the reaction mixtures with a 95:5 and 90:10 ratios, respectively, ratios determined by NMR spectroscopy (Table 5, entries 2 and 5). One can assume that the powerful electron-withdrawing nitro group decreases the electron density on nitrogen and it reduces strongly the nucleophilicity of the NHAr group. Then, the initially formed guanidine-type intermediate **5a** does not undergo cyclization to give **8** but then could divert conveniently to **5b** making the cyclization mainly by the most reactive butyl or benzylamine (Scheme 2). Moreover, for a comparison of the method, reaction of iminophosphorane **3** with isocyanates bearing electron-releasing groups was carried out. In this reaction the electron-releasing alkyl groups increase the electron density on nitrogen and the initially formed **5a** more easily supports cyclization to give **8** than to divert to **5b** to give **9**. In this manner, the *p*-tolylisocyanate gave a very high **8**-selectivity compared to that of phenylisocyanate (Table 5, entries 3 and 6). Last, the nucleophilicity dependence of the NHR group on the selectivity of the reaction was examined with phenylisocyanate/*p*-nitroaniline or *p*-nitrophenylisocyanate/aniline. As can be seen, in agreement with our previous results, we found that the reaction proceeded in high yield and with complete regioselectivity. In this case, guanidine intermediates **5a** and **5b** (Scheme 2) are the same sterically hindered making the cyclization to progress only by the strong nucleophilic amine

Table 5. Selectivity and yields in the reaction of **3** with ArCNO and primary amines

Entry	R	Ar	**8**/**9**[a]	Yield of isolated products (%)	
1	*n*-Butyl	C_6H_5	70:30	**8a**: 57	**9a**: 19
2	*n*-Butyl	4-NO_2–C_6H_4	5:95		**9a$_1$**: 82
3	*n*-Butyl	4-CH_3–C_6H_4	95:5	**8a$_2$**: 89	
4	Benzyl	C_6H_5	55:45	**8b**: 55	**9b**: 44
5	Benzyl	4-NO_2–C_6H_4	10:90		**9b$_1$**: 85
6	Benzyl	4-CH_3–C_6H_4	90:10	**8b$_2$**: 82	
7	*iso*-Propyl	C_6H_5	100:0	**8c**: 75	
8	*iso*-Propyl	4-NO_2–C_6H_4	95:5	**8c$_1$**: 81	
9	*iso*-Propyl	4-CH_3–C_6H_4	100:0	**8c$_2$**: 98	
10	Cyclohexyl	C_6H_5	100:0	**8d**: 95	
11	Cyclohexyl	4-NO_2–C_6H_4	100:0	**8d$_1$**: 84	
12	Cyclohexyl	4-CH_3–C_6H_4	100:0	**8d$_2$**: 88	
13	*tert*-Butyl	C_6H_5	100:0	**8e**: 82	
14	*tert*-Butyl	4-NO_2–C_6H_4	100:0	**8e$_1$**: 93	
15	*tert*-Butyl	4-CH_3–C_6H_4	100:0	**8e$_2$**: 85	
16	Phenyl	4-NO_2–C_6H_4	100:0	**8f**: 98	

[a] Ratios determined by ^{1}H NMR analysis of the mixture of compounds **8**/**9**. We were not able to separate the isomers **8a$_1$**, **8b$_1$**, **9a$_2$**, **9b$_2$**, and **9c$_1$**.

group to obtain **8f** (Table 5, entry 16; Ar=phenyl, R=4-nitrophenyl in Scheme 2) in excellent yield with total selectivity.

Compounds **8** and **9** were characterized from their spectral data, and the comparison of ^{1}H NMR spectra between **8** and **9** led us to confirm the structure of products without difficulty. In particular, in the ^{1}H NMR spectra of **8**, the corresponding proton of NH displays a characteristic triplet or doublet multiplicity due to coupling with the methylene or methine protons adjacent to the nitrogen atom. Its chemical shift is 3.91–4.73, more shielded than the one in PhNH of **9**.[18] For example, the ^{1}H NMR spectrum of **8a** shows the signals of NH at 4.27 as a triplet and NCH_2 at 3.52–3.63 as a multiplet. When the sample was treated with D_2O, its NCH_2 showed the signal as a triplet with disappearance of signals of NH absorption, which suggests the existence of an NHBu group in **8a**. The ^{1}H NMR spectrum of compound **9a** did not include the characteristic triplet corresponding to NH–Bu proton, but shows the NCH_2 signal at 4.29 as triplet and a new singlet signal at δ=6.66 due to the NHPh group, confirming the selective formation of pyrimido compounds **9** in this case. We were able to obtain suitable crystals of compounds **8** and **9** for X-ray study, which corroborated our earlier assignments (see Section 4). For example, Figures 2 and 3 show the molecular structure of compounds **8a** and **9a$_1$**, respectively. Interestingly, the results revealed a nearly coplanar disposition of the NHR group, in **8a**, and the NHAr group, in **9a$_1$**, with the three heterocyclic rings of the pyrazinothienopyrimidine system, whereas the angle between the NAr group in **8a** (NR in **9a$_1$**) and the triheterocyclic fused ring is approximately of 90°.

In summary, one-pot aza-Wittig/Heterocumulene-mediated annulation methodology provides an efficient protocol for preparing the functionalized pyrazino[2′,3′:4,4]thieno[3,2-*d*]pyrimidinone derivatives, with variable substituents at the pyrimidine ring, from the ethyl 3-(triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazine-6-carboxylate. The one-pot sequence can be extended to secondary amines, phenols, thiophenols, or ROH. In the case of primary amines, a highly regioselective cyclization has been observed and explored. Some advantages, such as the readily available reagents, one-pot procedure in high yields, mild reaction conditions, easy control of regioselectivity, and straightforward product isolation, make this annulation strategy attractive and practical for these previously unreported pyrazinothienopyrimidinones of considerable interest as potential biologically active compounds as well as pharmaceuticals.

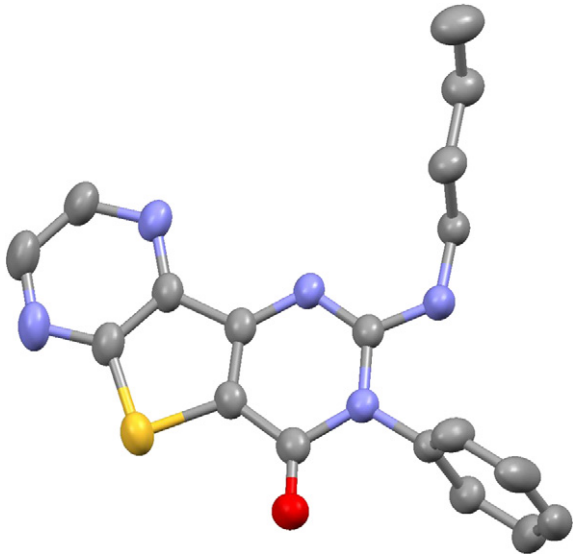


Figure 2. X-ray structure of compound **8a** (30% thermal probability ellipsoids). Hydrogen atoms have been omitted for clarity.

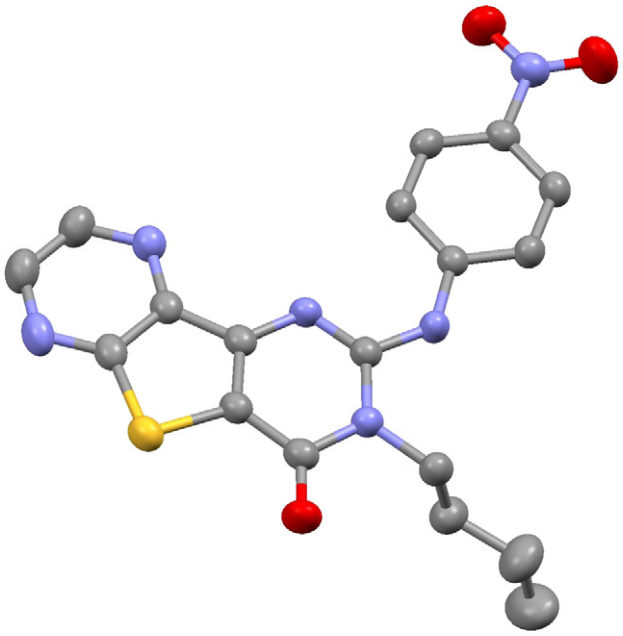


Figure 3. X-ray structure of compound **9a$_1$** (50% thermal probability ellipsoids). Hydrogen atoms have been omitted for clarity.

3. Experimental

3.1. General

NMR spectra were recorded at 200 or 300 MHz for ^{1}H and 50 or 75 MHz for ^{13}C. Chemical shifts are reported in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded as potassium bromide disks. Melting points were obtained on a capillary melting point apparatus and are uncorrected. All reagents used were commercial grade chemicals from freshly opened containers. Microanalyses for C, H, N, and S were performed by the elemental analyses general service of the University of A Coruña.

3.1.1. Ethyl 3-aminothieno[2,3-*b*]pyrazine-2-carboxylate (2). To a solution of 3-benzenesulfonylpyrazine-2-carbonitrile **1**[14] (2.00 g, 8.2 mmol) in EtOH/THF (5:1, v/v) (120 mL) was added Na_2CO_3 (1.06 g, 10 mmol) and the resultant reaction mixture was stirred at reflux temperature for 1 h. After cooling at room temperature, was extracted with dichloromethane (3×200 mL) and the organic extracts were combined and dried over sodium sulfate. The methylene dichloride solution was concentrated to dryness, and the residual material was recrystallized from ethanol to give **2** (1.80 g, 97%); mp 120–121 °C (lit.[7a] mp 114–116 °C).

3.1.2. Ethyl 3-(triphenylphosphoranylideneamino)-thieno[2,3-*b*]pyrazine-6-carboxylate (3). To a mixture of

2 (1.00 g, 6.65 mmol), triphenylphosphine (2.62 g, 10 mmol), and hexachloroethane (1.37 g, 10 mmol) in dry toluene (40 mL), triethylamine (2.4 mL, 16.50 mmol) was added dropwise. The reaction mixture was heated at 100 °C in a sealed tube for 48 h. After cooling, the precipitate obtained was filtered off, washed with water, and recrystallized from ethanol, to give **3** (2.00 g, 97%) as a yellow solid: mp 174–176 °C; IR (KBr) ν 1690 (C═O), 1175 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (t, J=7.1 Hz, 3H), 4.44 (q, J=7.1 Hz, 2H), 7.35–7.54 (m, 15H), 8.58 (d, J=2.4 Hz, 1H), 8.62 (d, J=2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 60.4, 128.0, 128.3, 131.2, 131.3, 132.7, 132.9, 133.5, 138.5, 138.8, 142.5, 144.9, 148.3, 155.2, 163.9. ^{31}P NMR (81 MHz, $CDCl_3$) δ 7.37; MS (EI) m/z 483 (M^+, 55), 410 (58). Anal. Calcd for $C_{27}H_{22}N_3O_2PS$: C, 67.07; H, 4.59; N, 8.69; S, 6.63. Found: C, 67.13; H, 4.51; N, 8.57; S, 6.80.

3.1.3. Ethyl 3-(*p*-tolylimino-methylenamino)thieno[2,3-*b*]pyrazine-6-carboxylate (4c). To a solution of **3** (0.15 g, 0.31 mmol) in THF (3 mL) was added *p*-tolylisocyanate (0.05 g, 0.37 mmol) and the mixture was stirred at room temperature for 3–5 h. The solvent was evaporated and the solid obtained was purified by flash chromatography using hexane/CH_2Cl_2 (1:1; v/v) as eluent. Yield 53%; yellow solid; mp 105–106 °C; IR (KBr) ν 2140 (C═N), 1710 (C═O), 1580, 1570, 1505 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, J=7.3 Hz, 3H), 2.35 (s, 3H), 4.45 (q, J=7.3 Hz, 2H), 7.06–7.29 (m, 4H), 8.71 (d, J=2.4 Hz, 1H), 8.66 (d, J=2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 21.0, 62.0, 122.2, 124.6, 129.5, 130.0, 131.6, 133.7, 135.0, 135.8, 142.3, 144.0, 154.3, 161.5. Anal. Calcd for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56; S, 9.48. Found: C, 60.53; H, 4.31; N, 16.46; S, 9.31.

3.1.4. Ethyl thieno[2,3-*b*]pyrazine-6-carboxylates (5). The appropriate isocyanate (0.37 mmol) was added to a solution of iminophosphorane **3** (0.15 g, 0.31 mol) in THF (3 mL). The mixture was stirred at room temperature for 1–2 h until the iminophosphorane had disappeared (TLC monitored) and it was therefore treated with an appropriate amine (0.37 mmol). The resultant solution was stirred at room temperature for 1–5 h. The solvent was evaporated, ether (5 mL) was added, and the mixture was stirred at room temperature for 0.5 h. The solid formed was filtered off and purified by crystallization from ethanol or flash chromatography to give the corresponding compounds **5**.

3.1.5. Ethyl 2-(*N*′,*N*′-diethyl-*N*″-phenylguanidino)-thieno[2,3-*b*]pyrazine-6-carboxylate (5a). Yield 70%; yellow solid; mp 106–107 °C; IR (KBr) ν 3320 (NH), 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J=7.3 Hz, 6H), 1.38 (t, J=7.3 Hz, 3H), 3.59 (q, J=7.3 Hz, 4H), 4.35 (q, J=7.3 Hz, 2H), 6.59–6.70 (m, 3H), 6.78–6.89 (m, 3H), 8.47 (d, J=2.2 Hz, 1H), 8.61 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 14.5, 43.1, 60.7, 119.3, 122.1, 128.3, 129.2, 141.3, 142.8, 145.0, 152.7, 155.1, 163.0. MS (EI) m/z 397 (M^+, 24), 324 (58). Anal. Calcd for $C_{20}H_{23}N_5O_2S$: C, 60.43; H, 5.83; N, 17.62; S, 8.07. Found: C, 60.33; H, 6.01; N, 17.56; S, 8.22.

3.1.6. Ethyl 2-[*N*′,*N*′-diethyl-*N*″-(4-methoxyphenyl)guanidino]thieno[2,3-*b*]pyrazine-6-carboxylate (5b). Yield 85%; yellow solid; mp 194–195 °C; IR (KBr) ν 3320 (NH), 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J=6.8 Hz, 6H), 1.39 (t, J=6.8 Hz, 3H), 3.56 (q, J=6.8 Hz, 4H), 3.58 (s, 3H), 4.35 (q, J=6.8 Hz, 2H), 6.35–6.45 (m, 3H), 6.66–6.70 (m, 2H), 8.47 (d, J=2.4 Hz, 1H), 8.60 (d, J=2.4 Hz, 1H); MS (EI) m/z 427 (M^+, 20), 354 (60), 203 (100). Anal. Calcd for $C_{21}H_{25}N_5O_3S$: C, 59.00; H, 5.89; N, 16.38; S, 7.50; Found: C, 58.93; H, 5.71; N, 16.51; S, 7.72.

3.1.7. Ethyl 2-[*N*′,*N*′-diethyl-*N*″(4-methylphenyl)guanidino]thieno[2,3-*b*]pyrazine-6-carboxylate (5c). Yield 84%; yellow solid; mp 194–195 °C; IR (KBr) ν 3320 (NH), 1635; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, J=7.3 Hz, 6H), 1.39 (t, J=7.3 Hz, 3H), 2.15 (s, 3H), 3.57 (q, J=7.3 Hz, 4H), 4.35 (q, J=7.3 Hz, 2H), 6.50 (br, 1H), 6.60–6.67 (m, 4H), 6.78–6.89 (m, 3H), 8.47 (d, J=2.2 Hz, 1H), 8.61 (d, J=2.2 Hz, 1H). Anal. Calcd for $C_{21}H_{25}N_5O_2S$: C, 61.29; H, 6.12; N, 17.02; S, 7.79. Found: C, 61.44; H, 6.00; N, 17.16; S, 7.62.

3.1.8. Ethyl 2-[*N*′,*N*′-diethyl-*N*″-(4-chlorophenyl)guanidino]thieno[2,3-*b*]pyrazine-6-carboxylate (5d). Yield 75%; yellow solid; mp 155–156 °C; IR (KBr) ν 3280 (NH), 1710 (C═O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, J=7.3 Hz, 6H), 1.39 (t, J=7.3 Hz, 3H), 3.57 (q, J=7.3 Hz, 4H), 4.35 (q, J=7.3 Hz, 2H), 5.70 (br, 1H), 6.66 (s, 2H), 6.81–6.85 (m, 2H), 8.51 (d, J=2.4 Hz, 1H), 8.62 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 14.4, 43.1, 60.9, 120.2, 126.8, 128.3, 139.1, 141.4, 143.1, 148.2, 152.6, 155.2; MS (EI) m/z 433/431 (M^+, 11/28), 358 (39). Anal. Calcd for $C_{20}H_{22}ClN_5O_2S$: C, 55.61; H, 5.13; Cl, 8.21; N, 16.21; S, 7.42. Found: C, 55.43; H, 5.21; Cl, 8.34; N, 16.39; S, 7.25.

3.1.9. Ethyl 2-[*N*′,*N*′-diethyl-*N*″-(4-nitrophenylguanidino]thieno[2,3-*b*]pyrazine-6-carboxylate (5e). Yield 80%; yellow solid; mp 182–183 °C; IR (KBr) ν 3280 (NH), 1680 (C═O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$,) δ 1.30 (t, J=7.3 Hz, 6H), 1.40 (t, J=7.3 Hz, 3H), 3.58 (q, J=7.3 Hz, 4H), 4.37 (q, J=7.3 Hz, 2H), 6.63 (br, 3H), 7.75 (d, J=9.1, 2H), 8.53 (d, J=2.2 Hz, 1H), 8.64 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 14.3, 43.4, 61.4, 117.8, 124.6, 140.9, 141.6, 143.4, 149.7, 154.9, 163.4; MS (EI) m/z 442 (M^+, 14), 413 (5), 369 (53), 220 (100). Anal. Calcd for $C_{20}H_{22}N_6O_4S$: C, 54.29; H, 5.01; N, 18.99; S, 7.25. Found: C, 54.43; H, 5.19; N, 18.79; S, 7.13.

3.1.10. Ethyl 2-[(4-chlorophenylamino)-morpholin-1-yl-methyleneamino]thieno[2,3-*b*]pyrazine-6-carboxylate (5f). Yield 70%; yellow solid; mp 160–161 °C; IR (KBr) ν 3300 (NH), 1700 (C═O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (t, J=7.3 Hz, 3H), 3.51–3.62 (m, 4H), 3.66–3.77 (m, 4H), 4.35 (q, J=7.3 Hz, 2H), 6.13 (br, 1H), 6.86–7.01 (m, 4H), 8.54 (d, J=2.2 Hz, 1H), 8.63 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 47.2, 61.2, 66.4, 120.6, 127.5, 128.7, 138.9, 141.7, 143.3, 152.3, 155.2, 162.8; MS (EI) m/z 447/445 (M^+, 8/21), 372 (24). Anal. Calcd for $C_{20}H_{20}ClN_5O_3S$: C, 53.87; H, 4.52; Cl, 7.95; N, 15.71; S, 7.19. Found: C, 53.97; H, 4.61; Cl, 8.14; N, 15.59; S, 7.05.

3.2. General procedure for the synthesis of 2-dialkylylamino-3-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one 6a–6k

To a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in dry THF (3 mL) was added the appropriate isocyanate (0.37 mmol) at room temperature. The mixture was stirred at room temperature for 1–2 h until the iminophosphorane had disappeared (TLC monitored) and it was therefore treated with an appropriate secondary amine or aniline (0.37 mmol). The resultant solution was stirred at room temperature for 1–5 h. The solvent was evaporated, the residue was treated with a catalytic amount of K_2CO_3, acetone (3 mL) was added, and the mixture was refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel eluting with a hexanes/ethyl acetate gradient from 5 to 40% ethyl acetate to give **6** as a yellow solid.

3.2.1. 2-Diethylamino-3-*N*-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6a). Yield 92%; mp 215–216 °C; IR (KBr) ν 1685 (C=O), 1530 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, 6H, J=7.3 Hz, 6H), 3.25 (q, J=7.3 Hz, 4H), 7.35–7.58 (m, 5H), 8.69 (d, J=2.2 Hz, 1H), 8.85 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 45.3, 128.5, 128.6, 129.2, 137.6, 142.5, 143.8, 148.9, 158.0, 158.7, 159.9; MS (EI) *m*/*z* 351 (M$^+$, 20), 322 (100). Anal. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.43; H, 4.81; N, 20.06; S, 9.31.

3.2.2. 2-Diethylamino-3-*N*-(4-methoxyphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6b). Yield 90%; mp 194–196 °C; IR (KBr) ν 1690 (C=O), 1525 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 6H), 3.26 (q, J=7.3 Hz, 4H), 3.87 (s, 3H), 7.03–7.29 (m, 4H), 8.68 (d, J=2.4 Hz, 1H), 8.84 (d, J=2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6, 45.3, 55.5, 114.5, 118.3, 129.5, 130.1, 142.4, 143.8, 144.2, 148.9, 158.3, 158.6, 159.4, 160.2; MS (EI) *m*/*z* 381 (M$^+$, 13), 352 (46). Anal. Calcd for $C_{19}H_{19}N_5O_2S$: C, 59.82; H, 5.02; N, 18.36; S, 8.41. Found: C, 60.03; H, 5.01; N, 18.26; S, 8.31.

3.2.3. 2-Diethylamino-3-*N*-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6c). Yield 91%; mp 185–187 °C; IR (KBr) ν 1670 (C=O), 1520 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (t, J=6.8 Hz, 6H), 2.43 (s, 3H), 3.26 (q, J=6.8 Hz, 4H), 7.25–7.33 (m, 4H), 8.68 (d, J=2.4 Hz, 1H), 8.84 (d, J=2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6, 21.2, 45.3, 128.2, 129.9, 134.9, 138.5, 142.4, 143.8, 144.1, 148.9, 158.2, 158.7, 160.1; MS (EI) *m*/*z* 365 (M$^+$, 22), 336 (100). Anal. Calcd for $C_{19}H_{19}N_5OS$: C, 62.44; H, 5.24; N, 19.16; S, 8.77. Found: C, 62.63; H, 5.21; N, 19.26; S, 8.61.

3.2.4. 2-Diethylamino-3-*N*-(4-chlorophenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6d). Yield 94%; mp 230–231 °C; IR (KBr) ν 1680 (C=O), 1530 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, J=6.8 Hz, 6H), 3.25 (q, J=6.8 Hz, 4H), 7.30–7.52 (m, 4H), 8.70 (d, J=2.4 Hz, 1H), 8.85 (d, J=2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 45.3, 118.5, 129.5, 129.9, 134.5, 135.9, 142.4, 142.6, 144.0, 149.0, 157.8, 158.7, 159.9; MS (EI) *m*/*z* 387/385 (M$^+$, 7/20), 356 (100). Anal. Calcd for $C_{18}H_{16}ClN_5OS$: C, 56.03; H, 4.18; Cl, 9.19; N, 18.15; S, 8.31. Found: C, 56.14; H, 4.21; Cl, 9.33; N, 17.99; S, 8.51.

3.2.5. 2-Diethylamino-3-*N*-(4-nitrophenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6e). Yield 93%; mp 224–225 °C; IR (KBr) ν 1670 (C=O), 1520 cm^{-1}; ^{1}H NMR (200 MHZ, $CDCl_3$) δ 0.98 (t, J=7.3 Hz, 6H), 3.25 (q, J=7.3 Hz, 4H), 7.63, 8.41 (m, 4H), 8.72 (d, J=2.2 Hz, 1H), 8.88 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 45.2, 124.5, 142.8, 143.1, 143.8, 144.2, 147.2, 149.1, 157.2, 158.7, 159.2; MS (EI) *m*/*z* 396 (M$^+$, 39), 367 (85). Anal. Calcd for $C_{18}H_{16}N_6O_3S$: C, 54.54; H, 4.07; N, 21.20; S, 8.09. Found: C, 54.73; H, 4.01; N, 20.26; S, 8.24.

3.2.6. 3-*N*-(4-Chlorophenyl)-2-(4-morpholinyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6f). Yield 86%; mp 232–233 °C; IR (KBr) ν 1670 (C=O), 1520 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.23–3.32 (m, 4H), 3.50–3.54 (m, 4H), 7.40, 7.54 (m, 4H), 8.72 (d, J=2.2 Hz, 1H), 8.87 (d, J=2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.4, 65.8, 120.0, 129.5, 129.7, 134.8, 135.1, 142.7, 143.7, 144.2, 148.5, 157.4, 158.5, 159.1; MS (EI) *m*/*z* 401/399 (M$^+$, 36/100), 313 (57). Anal. Calcd for $C_{18}H_{14}ClN_5O_2S$: C, 54.07; H, 3.53; Cl, 8.87; N, 17.51; S, 8.02. Found: C, 54.13; H, 3.41; Cl, 9.08; N, 17.46; S, 7.91.

3.2.7. 2-(4-Morpholinyl)-3-*N*-phenylpyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6g). Yield 98%; mp 289–290 °C; IR (KBr) ν 1701 (C=O), 1520, 1490, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26–3.36 (m, 4H), 3.40–3.50 (m, 4H), 7.41–7.62 (m, 5H), 8.71 (d, J=2.4 Hz, 1H), 8.86 (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.4, 65.8, 119.9, 128.4, 128.9, 129.3, 136.7, 142.6, 144.0, 148.5, 157.6, 158.5, 159.3; MS (EI) *m*/*z* 365 (M$^+$, 5), 279 (10), 77 (100). Anal. Calcd for $C_{18}H_{15}N_5O_2S$: C, 59.16; H, 4.14; N, 19.17; S, 8.78. Found: C, 58.97; H, 4.20; N, 19.01; S, 8.62.

3.2.8. 3-*N*-Phenyl-2-(4-thiomorpholinyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6h). Yield 85%; mp 292–293 °C; IR (KBr) ν 1702 (C=O), 1530, 1449, 1383 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30–2.40 (m, 4H), 3.50–3.70 (m, 4H), 7.30–7.65 (m, 5H), 8.71 (d, J=2.4 Hz, 1H), 8.86 (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 51.9, 120.1, 128.7, 128.8, 129.4, 137.0, 142.6, 144.1, 148.4, 158.4, 159.4; MS (EI) *m*/*z* 397 (M$^+$, 4), 279 (25), 203 (15). Anal. Calcd for $C_{18}H_{15}N_5OS_2$: C, 56.67; H, 3.96; N, 18.36; S, 16.81. Found: C, 56.43; H, 4.03; N, 18.36; S, 16.77.

3.2.9. 3-*N*-Phenyl-2-(1-pyrrolidinyl)pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6i). Yield 90%; mp 244–245 °C; IR (KBr) ν 1703 (C=O), 1570, 1443, 1348 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70–1.82 (m, 4H), 3.16–3.25 (m, 4H), 7.35–7.57 (m, 5H), 8.66 (d, J=2.4 Hz, 1H), 8.81 (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 50.6, 128.7, 129.2, 137.2, 142.2, 143.8, 144.2, 150.0, 155.3, 158.9, 159.7; MS (EI) *m*/*z* 349 (M$^+$, 20), 294 (13), 77 (100). Anal. Calcd for $C_{18}H_{15}N_5OS$: C, 61.87; H, 4.33; N, 20.04; S, 9.18. Found: C, 61.73; H, 4.34; N, 19.91; S, 9.07.

3.2.10. 3-*N*-Phenyl-2-(1-piperidinyl)pyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6j). Yield 85%; mp 220–221 °C; IR (KBr) ν 1700 (C=O), 1602, 1547, 1520, 1390 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.50 (m, 6H), 3.10–3.40 (m, 4H), 7.30–7.56 (m, 5H), 8.66 (d, J=2.4 Hz, 1H), 8.82 (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 24.8, 50.4, 119.2, 128.4, 128.5, 129.1, 137.4, 142.5, 143.9, 144.0, 148.8, 158.6, 158.7, 159.6; MS (EI) m/z 363 (M^+, 20). Anal. Calcd for $C_{19}H_{17}N_5OS$: C, 62.79; H, 4.71; N, 19.27; S, 8.82. Found: C, 62.63; H, 4.63; N, 19.16; S, 8.78.

3.2.11. 2-Phenyl-3-*N*-phenylaminopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6k). Yield 86%; mp 254–255 °C; IR (KBr) ν 3404 (NH), 1682 (C=O), 1595, 1556, 1537, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 1H), 7.08–7.13 (m, 1H), 7.31–7.37 (m, 2H), 7.47–7.57 (m, 4H), 7.59–7.71 (m, 3H), 8.65 (d, J=2.3 Hz, 1H), 8.79 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.2, 120.8, 124.4, 128.8, 129.0, 130.6, 131.0, 133.7, 137.2, 142.4, 143.8, 149.3, 150.3, 158.3, 158.4; MS (EI) m/z 371 (M^+, 55). Anal. Calcd for $C_{20}H_{13}N_5OS$: C, 64.68; H, 3.53; N, 18.86; S, 8.63. Found: C, 64.49; H, 3.53; N, 18.66; S, 8.65.

3.3. General procedure for the synthesis of 3-aryloxy-2-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one 7a–7e

To a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in dry THF (3 mL) was added phenylisocyanate (0.37 mmol) at room temperature. The mixture was stirred at room temperature for 1–2 h until the iminophosphorane had disappeared (TLC monitored) and after treating with an appropriate substituted phenol or thiophenol (0.37 mmol), a catalytic amount of K_2CO_3 was added and the resultant solution was refluxed for 1 h. The solvent was evaporated under reduced pressure, the solid residue was treated with ether (5 mL), and the mixture was stirred at room temperature for 0.5 h. The solid formed was filtered off and purified by chromatography on silica gel eluting with a dichloromethane/ethyl acetate gradient from 10 to 30% ethyl acetate to give **7** as a yellow solid.

3.3.1. 3-*N*-Phenyl-2-phenoxypyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (7a). Yield 68%; mp 232–234 °C; IR (KBr) ν 1687 (C=O), 1600, 1564, 1534, 1505, 1487 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.32 (m, 3H), 7.37–7.50 (m, 4H), 7.51–7.65 (m, 3H), 8.69 (d, J=2.1 Hz, 1H), 8.80 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.0, 126.3, 127.9, 129.5, 129.7, 129.8, 142.8, 144.1; MS (FAB) m/z 373 (MH^+, 98), 279 (13). Anal. Calcd for $C_{20}H_{12}N_4O_2S$: C, 64.50; H, 3.25; N, 15.04; S, 8.61. Found: C, 64.42; H, 3.11; N, 14.95; S, 8.56.

3.3.2. 3-*N*-Phenyl-2-phenylthiopyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (7b). Yield 85%; mp 226–227 °C; IR (KBr) ν 1677 (C=O), 1516, 1493, 1340, 1233, 1182 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.55 (m, 5H), 7.57–7.70 (m, 5H), 8.65 (d, J=2.2 Hz, 1H), 8.76 (d, J=2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.8, 128.9, 129.4, 130.1, 130.2, 130.6, 135.4, 143.0, 143.9; MS (FAB) m/z 389 (MH^+, 100), 279 (16). Anal. Calcd for $C_{20}H_{12}N_4OS_2$: C, 61.84; H, 3.11; N, 14.42; S, 16.51. Found: C, 61.72; H, 2.99; N, 14.39; S, 16.45.

3.3.3. 2-(4-Nitrophenoxy)-3-*N*-phenylpyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (7c). Yield 78%; mp 143–145 °C; IR (KBr) ν 1699 (C=O), 1569, 1538, 1524, 1487, 1345, 1260, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.49 (m, 4H), 7.53–7.65 (m, 3H), 8.28–8.50 (m, 2H), 8.72 (d, J=2.3 Hz, 1H), 8.82 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.9, 125.6, 127.8, 129.8, 129.9, 133.9, 143.1, 144.3; MS (FAB) m/z 418 (MH^+, 50), 371 (19), 279 (100). Anal. Calcd for $C_{20}H_{11}N_5O_4S$: C, 57.55; H, 2.66; N, 16.78; S, 7.68. Found: C, 57.45; H, 2.82; N, 16.73; S, 7.52.

3.3.4. 3-(4-*tert*-Butylphenoxy)-2-*N*-phenylpyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (7d). Yield 67%; mp 228–230 °C; IR (KBr) ν 1690 (C=O), 1567, 1542, 1503, 1354, 1268, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 7.13–7.16 (m, 2H), 7.40–7.45 (m, 4H), 7.50–7.63 (m, 3H), 8.70 (d, J=2.1 Hz, 1H), 8.81 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 120.3, 127.7, 126.7, 127.9, 129.4, 134.5, 142.8, 144.1; MS (EI) m/z 348 (M^+, 45), 294 (43). Anal. Calcd for $C_{24}H_{20}N_4O_2S$: C, 67.27; H, 4.70; N, 13.07; S, 7.48. Found: C, 67.11; H, 4.53; N, 12.95; S, 7.33.

3.3.5. 3-(4-Benzyloxyphenoxy)-2-*N*-phenylpyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (7e). Yield 70%; mp 203–205 °C; IR (KBr) ν 1660 (C=O), 1568, 1547, 1535, 1520, 1497, 1446, 1354, 1195 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2H), 6.90–7.20 (m, 4H), 7.25–7.80 (m, 10H), 8.69 (d, J=2.1 Hz, 1H), 8.81 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.4, 115.7, 122.0, 127.5, 127.9, 128.1, 128.6, 129.5, 129.7, 142.8, 144.0; MS (FAB) m/z 479 (MH^+, 24), 279 (52). Anal. Calcd for $C_{27}H_{18}N_4O_3S$: C, 67.77; H, 3.79; N, 11.71; S, 6.70. Found: C, 67.52; H, 3.61; N, 11.65; S, 6.58.

3.3.6. 3-Alkoxy-2-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]-pyrimidin-4(3*H*)-one 7f and 7g. To a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in THF (3 mL) was added the appropriate isocyanate (0.37 mmol) at room temperature. The mixture was stirred at room temperature for 1–2 h until the iminophosphorane had disappeared (TLC monitored). The solvent was evaporated, ROH (4 mL) was added to dissolve the solid, and then NaOR (0.40 mmol) was added and the resultant mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel eluting with a dichloromethane/ethyl acetate 90:10 (v/v).

Compound **7f**: yield 65%; yellow solid; mp 202–204 °C; IR (KBr) ν 1692 (C=O), 1563, 1541, 1515, 1373, 1335, 1196 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J=7.1 Hz, 3H), 4.65 (q, J=7.1 Hz, 2H), 7.28–7.33 (m, 2H), 7.48–7.60 (m, 3H), 8.73 (d, J=2.3 Hz, 1H), 8.88 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 66.0, 127.9, 129.2, 129.4, 142.7, 144.1; MS (EI) m/z 324 (M^+, 44). Anal. Calcd for $C_{16}H_{12}N_4O_2S$: C, 59.25; H, 3.73; N, 17.27; S, 9.89. Found: C, 59.13; H, 3.61; N, 17.12; S, 9.79.

Compound **7g**: yield 72%; yellow solid; mp 204–206 °C; IR (KBr) ν 1693 (C=O), 1569, 1543, 1517, 1487, 1449, 1353, 1265, 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (s, 3H), 7.25–7.35 (m, 2H), 7.45–7.65 (m, 3H), 8.73 (d, J=2.3 Hz, 1H), 8.88 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.8, 127.9, 129.3, 129.5, 134.3, 142.7, 143.6, 144.1, 147.7, 156.8, 158.3, 158.7; MS (FAB) m/z 311 (MH^+, 68). Anal. Calcd for $C_{15}H_{10}N_4O_2S$: C, 58.05; H, 3.25; N, 18.05; S, 10.33. Found: C, 57.93; H, 3.38; N, 18.12; S, 10.19.

3.4. General procedure for the synthesis of pyrazinothienopyrimidinones 8 and 9

The appropriate isocyanate (phenyl-, 4-nitrophenyl-, or 4-methylphenylisocyanate) (0.37 mmol) was added to a solution of iminophosphorane **3** (0.15 g, 0.31 mmol) in THF (3 mL) at room temperature. The mixture was stirred at room temperature for 1–2 h until the iminophosphorane had disappeared (TLC monitored) and it was then treated with the appropriate primary amine (0.37 mmol). The resultant solution was stirred at room temperature for 5 h. The solvent was evaporated, the solid residue was treated with a catalytic amount of K_2CO_3, acetone (3 mL) was added, and the mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel eluting with a hexanes/ethyl acetate gradient from 5 to 40% ethyl acetate to give **8/9** as a yellow solid.

3.4.1. 2-*n*-Butylamino-3-*N*-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (8a). Yield 57%; mp 197–198 °C; IR (KBr) ν 3435 (NH), 1676 (C=O), 1589, 1564, 1548, 1530, 1523, 1486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7.3 Hz, 3H), 1.20–1.35 (m, 2H), 1.42–1.56 (m, 2H), 3.52–3.63 (m, 2H), 4.27 (t, J=5.0 Hz, 1H, NH), 7.32–7.40 (m, 2H), 7.53–7.69 (m, 3H), 8.67 (d, J=2.3 Hz, 1H), 8.81 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 19.9, 31.1, 40.0, 128.6, 130.6, 130.8, 134.0, 142.2, 143.7, 144.0, 150.2, 153.5, 158.5, 158.6; MS (EI) m/z 351 (M^+, 25), 294 (85). Anal. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.37; H, 4.95; N, 19.92; S, 8.92.

3.4.2. 3-*N*-*n*-Butyl-2-phenylaminopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (9a). Yield 19%; mp 99–101 °C dec; IR (KBr) ν 3354 (NH), 1674 (C=O), 1657, 1537, 1523, 1494, 1472, 1456, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J=7.3 Hz, 3H), 1.45–1.60 (m, 2H), 1.80–1.95 (m, 2H), 4.29 (t, J=7.7 Hz, 2H), 6.66 (s, 1H, NH), 7.14–7.23 (m, 1H), 7.40–7.50 (m, 2H), 7.63–7.72 (d, 2H), 8.79 (d, J=2.3 Hz, 1H), 8.86 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.3, 29.8, 41.9, 121.6, 124.8, 129.3, 137.8, 142.4, 143.8, 150.6, 158.7; MS (EI) m/z 351 (M^+, 25), 294 (45). Anal. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.34; H, 4.99; N, 19.83; S, 8.95.

3.4.3. 2-Benzylamino-3-*N*-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (8b). Yield 55%; mp 113–115 °C; IR (KBr) ν 3249 (NH), 1681 (C=O), 1552, 1522, 1493, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (t, J=5.3 Hz, 1H, NH), 4.83 (d, J=5.3 Hz, 2H), 7.20–7.35 (m, 5H), 7.35–7.45 (m, 2H), 7.50–7.70 (m, 3H), 8.69 (d, J=2.3 Hz, 1H), 8.83 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.3, 127.4, 127.7, 128.6, 128.8, 130.5, 130.9, 133.9, 137.5, 142.3, 143.9, 150.1, 153.4, 158.6, 158.7; MS (EI) m/z 385 (M^+, 5), 279 (3), 106 (25), 91 (100). Anal. Calcd for $C_{21}H_{15}N_5OS$: C, 65.44; H, 3.92; N, 18.17; S, 8.32; Found: C, 65.30; H, 4.01; N, 18.07; S, 8.16.

3.4.4. 3-*N*-Benzyl-2-phenylaminopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (9b). Yield 44%; mp 175–176 °C; IR (KBr) ν 3311 (NH), 1655 (C=O), 1595, 1536, 1461, 1455, 1446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (s, 2H), 6.73 (s, 1H, NH), 7.05–7.15 (m, 1H), 7.30–7.55 (m, 9H), 8.66 (d, J=2.3 Hz, 1H), 8.76 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.5, 121.0, 124.5, 126.8, 129.0, 129.1, 129.8, 134.0, 137.6, 142.4, 143.9, 149.2, 150.9, 158.7, 159.1; MS (EI) m/z 385 (M^+, 25), 294 (15). Anal. Calcd for $C_{21}H_{15}N_5OS$: C, 65.44; H, 3.92; N, 18.17; S, 8.32. Found: C, 65.33; H, 4.01; N, 18.05; S, 8.15.

3.4.5. 2-Isopropylamino-3-*N*-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (8c). Yield 80%; mp 228–230 °C; IR (KBr) ν 3416 (NH), 1679 (C=O), 1545, 1522, 1508, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J=6.5 Hz, 6H), 4.11 (d, J=7.7 Hz, 1H, NH), 4.47–4.62 (m, 1H), 7.33–7.35 (m, 2H), 7.54–7.65 (m, 3H), 8.65 (d, J=2.3 Hz, 1H), 8.80 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 44.0, 115.2, 128.6, 130.2, 130.8, 134.0, 142.2, 143.7, 144.1, 150.2, 152.7, 158.5, 158.7; MS (EI) m/z 337 (M^+, 40), 294 (100). Anal. Calcd for $C_{17}H_{15}N_5OS$: C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.48; H, 4.55; N, 20.56; S, 9.41.

3.4.6. 2-Cyclohexylylamino-3-*N*-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (8d). Yield 95%; mp 208–210 °C; IR (KBr) ν 3271 (NH), 1685 (C=O), 1532, 1517, 1487, 1479, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00–1.13 (m, 3H), 1.31–1.49 (m, 5H), 1.88–1.92 (m, 2H), 4.20–4.28 (m, 2H), 7.30–7.32 (m, 2H), 7.47–7.60 (m, 3H), 8.59 (d, J=2.3 Hz, 1H), 8.75 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 25.2, 32.4, 49.6, 114.9, 128.4, 130.1, 130.6, 133.9, 142.0, 143.5, 143.8, 150.1, 152.6, 158.3, 158.5; MS (EI) m/z 377 (M^+, 10), 294 (95). Anal. Calcd for $C_{20}H_{19}N_5OS$: C, 63.64; H, 5.07; N, 18.55; S, 8.49; Found: C, 63.56; H, 4.97; N, 18.49; S, 8.47.

3.4.7. 2-*tert*-Butylamino-3-*N*-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (8e). Yield 82%; mp 231–232 °C; IR (KBr) ν 3432 (NH), 1683 (C=O), 1561, 1545, 1521, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 4.12 (s, 1H, NH), 7.33–7.37 (m, 2H), 7.61–7.64 (m, 3H), 8.66 (d, J=2.3 Hz, 1H), 8.85 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 53.2, 128.6, 130.3, 130.9, 143.6, 145.0; MS (EI) m/z 351 (M^+, 5), 294 (30). Anal. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.49; H, 4.73; N, 20.06; S, 9.25.

3.4.8. 3-*N*-*n*-Butyl-2-(4-nitrophenylamino)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($9a_1$). Yield 82%; mp 234–235 °C; IR (KBr) ν 3423 (NH), 1676

(C=O), 1538, 1502, 1404 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.3 Hz, 3H), 1.48–1.63 (m, 2H), 1.80–1.96 (m, 2H), 4.34 (t, J=7.7 Hz, 2H), 7.03 (s, 1H, NH), 7.30–7.37 (m, 2H), 7.87–7.99 (m, 2H), 8.71 (d, J=2.3 Hz, 1H), 8.84 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.2, 30.1, 42.1, 120.1, 125.3, 142.7, 143.5, 144.2, 158.3; MS (EI) m/z 396 (M^+, 15), 339 (25). Anal. Calcd for $C_{18}H_{16}N_6O_3S$: C, 54.54; H, 4.07; N, 21.20; S, 8.09. Found: C, 54.31; H, 4.21; N, 21.45; S, 8.14.

3.4.9. 2-*n*-Butylamino-3-*N*-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8a_2$). Yield 89%; mp 163–165 °C; IR (KBr) ν 3256 (NH), 1611 (C=O), 1562, 1524, 1509, 1480, 1464, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7.3 Hz, 3H), 1.22–1.34 (m, 2H), 1.44–1.54 (m, 2H), 2.45 (s, 3H), 3.53–3.60 (m, 2H), 4.35 (t, J=5.1 Hz, 1H, NH), 7.21–7.23 (m, 2H), 7.39–7.42 (m, 2H), 8.65 (d, J=2.3 Hz, 1H), 8.80 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 19.9, 21.3, 31.1, 42.0, 115.3, 128.2, 131.2, 131.5, 140.5, 142.1, 143.7, 144.1, 150.1, 153.6, 158.5, 158.7; MS (EI) m/z 365 (M^+, 10), 308 (30). Anal. Calcd for $C_{19}H_{19}N_5OS$: C, 62.44; H, 5.24; N, 19.16; S, 8.77. Found: C, 62.51; H, 5.39; N, 19.02; S, 8.75.

3.4.10. 3-*N*-Benzylamino-2-(4-nitrophenylamino)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($9b_1$). Yield 85%; mp 113–115 °C; IR (KBr) ν 3393 (NH), 1676 (C=O), 1610, 1541, 1503, 1464, 1413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 2H), 7.01 (s, 1H, NH), 7.42–7.57 (m, 5H), 7.58–7.65 (m, 2H), 8.21–8.28 (m, 2H), 8.74 (d, J=2.3 Hz, 1H), 8.86 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.8, 119.7, 125.3, 127.0, 130.0, 130.2, 133.7, 142.8, 144.3; MS (EI) m/z 430 (M^+, 10), 279 (3), 91 (20). Anal. Calcd for $C_{21}H_{14}N_6O_3S$: C, 58.60; H, 3.28; N, 19.52; S, 7.45. Found: C, 58.58; H, 3.39; N, 19.43; S, 7.39.

3.4.11. 2-Benzylamino-3-*N*-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8b_2$). Yield 82%; mp 218–220 °C; IR (KBr) ν 3336 (NH), 1685 (C=O), 1553, 1522, 1509, 1452, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.73 (t, J=5.2 Hz, 1H, NH), 4.83 (d, J=5.2 Hz, 2H), 7.20–7.35 (m, 7H), 7.36–7.44 (m, 2H), 8.68 (d, J=2.3 Hz, 1H), 8.81 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 46.2, 115.9, 127.4, 127.6, 128.2, 128.7, 131.0, 131.6, 137.5, 140.7, 142.3, 143.8, 144.1, 150.0, 153.6, 158.6, 158.8; MS (EI) m/z 399 (M^+, 20), 91 (35). Anal. Calcd for $C_{22}H_{17}N_5OS$: C, 66.15; H, 4.29; N, 17.53; S, 8.03. Found: C, 66.24; H, 4.08; N, 17.64; S, 8.17.

3.4.12. 2-Isopropylamino-3-*N*-(4-nitrophenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8c_1$). Yield 81%; mp>300 °C; IR (KBr) ν 3350 (NH), 1685 (C=O), 1545, 1520, 1480, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J=6.5 Hz, 6H), 3.91 (d, J=7.8 Hz, 1H, NH), 4.45–4.70 (m, 1H), 7.58–7.65 (m, 2H), 8.50–8.56 (m, 2H), 8.71 (d, J=2.3 Hz, 1H), 8.86 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 44.5, 115.1, 126.1, 130.4, 139.9, 142.5, 144.1, 148.8, 151.7; MS (EI) m/z 382 (M^+, 63), 339 (100), 324 (17), 203 (33). Anal. Calcd for $C_{17}H_{14}N_6O_3S$: C, 53.40; H, 3.69; N, 21.98; S, 8.39. Found: C, 53.49; H, 3.53; N, 21.76; S, 8.25.

3.4.13. 2-Isopropylamino-3-*N*-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8c_2$). Yield 98%; mp 217–219 °C; IR (KBr) ν 3414 (NH), 1676 (C=O), 1665, 1552, 1547, 1522, 1507, 1482, 1466, 1422, 1409 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J=6.5 Hz, 6H), 2.46 (s, 3H), 4.18 (d, J=7.9 Hz, 1H, NH), 4.45–4.75 (m, 1H), 7.17–7.25 (m, 2H), 7.40–7.45 (m, 2H), 8.65 (d, J=2.3 Hz, 1H), 8.81 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 22.7, 43.9, 115.2, 128.2, 131.2, 132.5, 140.5, 142.2, 143.7, 144.1, 150.2, 152.9, 158.6, 158.8; MS (EI) m/z 351 (M^+, 40), 308 (100), 91 (25). Anal. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.45; H, 4.97; N, 20.03; S, 9.17.

3.4.14. 2-Cyclohexylylamino-3-*N*-(4-nitrophenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8d_1$). Yield 84%; mp 246–248 °C; IR (KBr) ν 3429 (NH), 1690 (C=O), 1547, 1530, 1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06–1.24 (m, 3H), 1.35–1.50 (m, 3H), 1.73–1.92 (m, 2H), 1.99–2.04 (m, 2H), 3.97 (d, J=8.0 Hz, 1H, NH), 4.25–4.38 (m, 1H), 7.57–7.65 (m, 2H), 8.48–8.56 (m, 2H), 8.71 (d, J=2.3 Hz, 1H), 8.86 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.3, 32.8, 50.4, 126.1, 130.4, 140.0, 142.5, 144.1, 148.8, 150.6, 151.7; MS (EI) m/z 422 (M^+, 5), 339 (30), 203 (30), 123 (30), 99 (52). Anal. Calcd for $C_{20}H_{18}N_6O_3S$: C, 56.86; H, 4.29; N, 19.89; S, 7.59. Found: C, 56.69; H, 4.13; N, 19.76; S, 7.46.

3.4.15. 2-Cyclohexylylamino-3-*N*-(4-methylphenyl)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8d_2$). Yield 88%; mp 233–235 °C; IR (KBr) ν 3416 (NH), 1686 (C=O), 1546, 1532, 1520, 1485, 1347 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00–1.23 (m, 3H), 1.36–1.65 (m, 5H), 1.90–2.05 (m, 2H), 2.48 (s, 3H), 4.20–4.35 (m, 2H), 7.19–7.26 (m, 2H), 7.39–7.47 (m, 2H), 8.67 (d, J=2.3 Hz, 1H), 8.82 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 24.2, 25.4, 32.8, 49.9, 115.2, 128.2, 131.3, 131.5, 140.5, 142.2, 143.6, 144.1, 150.2, 153.0, 158.6, 158.9; MS (EI) m/z 391 (M^+, 10), 308 (100). Anal. Calcd for $C_{21}H_{21}N_5OS$: C, 64.43; H, 5.41; N, 17.89; S, 8.19. Found: C, 64.33; H, 5.42; N, 17.69; S, 8.12.

3.4.16. 2-*tert*-Butylamino-3-*N*-(4-nitrophenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8e_1$). Yield 93%; mp 227–229 °C; IR (KBr) ν 3415 (NH), 1690 (C=O), 1596, 1556, 1545, 1523, 1518, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 3.99 (s, 1H, NH), 7.58–7.61 (m, 2H), 7.48–7.51 (m, 2H), 8.68 (d, J=2.3 Hz, 1H), 8.86 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 53.8, 126.0, 130.4, 140.3, 142.6, 143.9, 144.1, 148.7, 150.3, 151.0, 158.4, 158.7; MS (EI) m/z 396 (M^+, 15), 339 (90). Anal. Calcd for $C_{18}H_{16}N_6O_3S$: C, 54.54; H, 4.07; N, 21.20; S, 8.09. Found: C, 54.43; H, 4.19; N, 21.14; S, 8.19.

3.4.17. 2-*tert*-Butylamino-3-*N*-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one ($8e_2$). Yield 85%; mp 224–226 °C; IR (KBr) ν 3428 (NH), 1681 (C=O), 1557, 1545, 1520, 1484, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.43 (s, 3H), 4.29 (s,

1H, NH), 7.18–7.21 (m, 2H), 7.33–7.41 (m, 2H), 8.62 (d, J=2.3 Hz, 1H), 8.81 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 28.8, 53.0, 115.1, 128.1, 131.4, 140.3, 142.2, 143.4, 144.2, 149.8, 152.2, 158.4, 158.9; MS (EI) m/z 365 (M^+, 10), 308 (50). Anal. Calcd for $C_{19}H_{19}N_5OS$: C, 62.44; H, 5.24; N, 19.16; S, 8.77. Found: C, 62.49; H, 5.39; N, 19.13; S, 8.91.

3.4.18. 3-*N*-(4-Nitrophenyl)-2-phenylaminopyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (8f). Yield 98%; mp 254–256 °C; IR (KBr) ν 3380 (NH), 1609 (C=O), 1572, 1542, 1537, 1520, 1503, 1492, 1487, 1455, 1413 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H, NH), 7.49–7.52 (m, 2H), 7.68–7.79 (m, 3H), 7.81–7.84 (m, 2H), 8.24–8.27 (m, 2H), 8.75 (d, J=2.3 Hz, 1H), 8.90 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.7, 125.2, 128.8, 131.2, 131.4, 133.3, 142.9, 143.1, 143.4, 143.6, 144.3, 148.6, 149.0, 158.1, 158.4; MS (EI) m/z 416 (M^+, 100), 370 (20). Anal. Calcd for $C_{20}H_{12}N_6O_3S$: C, 57.69; H, 2.90; N, 20.18; S, 7.70. Found: C, 57.50; H, 2.78; N, 20.33; S, 7.82.

4. Crystallographic material

Crystallographic data (excluding structural factors) for **8a**, **8c$_1$**, and **9a$_1$** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 614690, CCDC 614691, and CCDC 614692 for **8a**, **8c$_1$**, and **9a$_1$**, respectively. 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).

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