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Original article

Synthesis and biological evaluation of *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines and their pyrido and pyrazino analogues as Ser/Thr kinase inhibitors

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ABSTRACT

A useful and rapid access to libraries of *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines and their pyrido and pyrazino analogues was designed and optimized for the first time *via* microwave-accelerated condensation and Dimroth rearrangement of the starting anilines with *N*′-(2-cyanoaryl)-*N*,*N*-dimethylformimidamides obtained by reaction of thiophene precursors with dimethylformamide dimethylacetal. The inhibitory potency of the final products against five protein kinases (CDK5/p25, CK1δ/ε, GSK3α/β, DYRK1A and CLK1) was estimated. *N*-arylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine series of compounds (**4a**–**j**) turned out to be particularly promising for the development of new pharmacological inhibitors of CK1 and CLK1 kinases.

1. Introduction

Kinases are one of the largest families of the genome. More than 500 kinases play an important role in the regulation of various cellular processes. These enzymes are involved in all major diseases, including cancer, neurodegenerative disorders and cardiovascular diseases. Our research groups are mainly invested in the synthesis of C,N,S- or C,N,O-containing heterocyclic precursors of bioactive molecules able to modulate the activity of kinases in signal transduction [1,2]. In the course of our work, the synthesis of 4-anilinopyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines was described for the first time *via* a microwave-accelerated Dimroth rearrangement [3,4]. In the same time we envisioned to apply this chemical method to the synthesis of various benzo-, pyrido- and pyrazinothieno[3,2-*d*]pyrimidines derivatives, themselves substituted in position 4 of the pyrimidine ring by an aromatic amine. These target compounds were conceived as 6,5,6-tricyclic homologues of the basic 4-aminoquinazoline pharmacophore which is present in approximately 80% of ATP-competitive kinases inhibitors that have received approval for the treatment of cancer [5].

The use of microwave-assisted dielectric heating to perform organic reactions is gaining an increasing popularity in process chemistry [6]. In recent applications of the thermal-dependent Dimroth rearrangement published in the literature, it was demonstrated that the strong heating due to specific molecule–microwave interactions was particularly suitable for the synthesis of the target compounds [6]. This paper describes the development of a simple and reliable method that allows the preparation of a library of new thieno[3,2-*d*]pyrimidines for which interesting kinase inhibitory activities were observed. The main part of the chemistry described in this paper was realized under microwaves in a combinatorial chemistry approach. The evaluation of kinase inhibition of the products obtained was realized on Ser/Thr kinases (CDK5, GSK3, DYRK1A, CLK1 and CK1) chosen for their strong implication in various regulation processes, especially Alzheimer's disease [7].

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2. Chemistry

The target molecules we studied were benzo[*b*]thieno[3,2-*d*]pyrimidines (**3**) and their pyrido (**4** and **5**) and pyrazino analogues (**6**) substituted in position 4 of the pyrimidine ring by an aromatic amine. The retrosynthetic pathway depicted in Scheme 1 started from 3-aminobenzothiophene-2-carbonitrile (**1a**) and aminothienoazinecarbonitriles **1b**–**d** which could be transformed into their corresponding *N*,*N*-dimethylformamidine derivatives **2a**–**d**. The next step consisted in nucleophilic attack of the intermediate amidines by aromatic amines to give the expected tricyclic compounds **3**–**6** *via* a Dimroth rearrangement [4]. A literature survey revealed that the synthesis of such derivatives had not been previously described. Usually the described route required synthesis of pyrimidin-4-one derivatives which reacted with thionyl chloride, phosphoryl chloride or oxalyl chloride to afford 4-chloro-substituted pyrimidine derivatives before transformation into the expected products after nucleophilic substitution using various aromatic amines [8].

2.1. Synthesis of the starting 3-aminoarylthiophene-2-carbonitriles (*1a–d*)

The benzothiophene **1a** and thienoazine precursors (**1b**, **1d**) were obtained by methods already described in the literature (compounds **1a** [9], **1b** [10] and **1d** [8b]). Compound **1c** was synthesized by adaptation of the method used for its benzo analogue **1a** [11] (Scheme 2).

3-Amino-2-benzo[*b*]thiophene-2-carbonitrile (**1a**) was prepared by treatment of 2-nitrobenzonitrile (**7**) with 3-mercaptopropionitrile and aqueous potassium hydroxide in DMF at 0 °C. Ring closure of the cyanomethyl thioether intermediate (not isolated) was performed by addition of the alkylating agent, in the presence of potassium hydroxide (KOH), to give the expected product with a very good yield (89%) [9].

3-Aminothieno[2,3-*b*]pyridine-2-carbonitrile (**1b**) was obtained by a previously described procedure [10]. Condensation of 2-chloronicotinonitrile (**8**) with thiourea in ethanol at 120 °C under microwaves (sealed tubes) for 45 min gave the intermediate 2-mercaptonicotinonitrile or its tautomeric form **9** (drawn in Scheme 2) which was stirred for 4 h at room temperature, in the presence of chloroacetonitrile and potassium carbonate to give the final product **1b** with a good overall yield (57% for the two steps). In order to obtain 3-aminothieno[3,2-*b*]pyridine-2-carbonitrile (**1c**) by transferring the methodology used for the synthesis of compound **1a**, it was first necessary to provide 3-nitropyridine-2-carbonitrile (**12**) as starting material. For this purpose, 3-nitropyridine-2-amine (**10**) was converted to 2-bromo-3-nitropyridine (**11**), without isolating the corresponding diazonium salt, by one-pot transformation using bromodimethylsulfonium bromide generated *in situ* [12]. In this reaction, a diazonium salt was formed from an aromatic amine, by the addition of nitrite salt (KNO_2) and hydrogen bromide, while at the same time an activated bromide nucleophile was prepared readily *in situ* from hydrogen bromide and dimethylsulfoxide. Thus, the transformation of an amine group to halogen group in aromatic compound may occur in a single-step process.

In the next step, reaction of **11** with copper (I) cyanide afforded 3-nitropyridine-2-carbonitrile (**12**) with 68% yield [13].

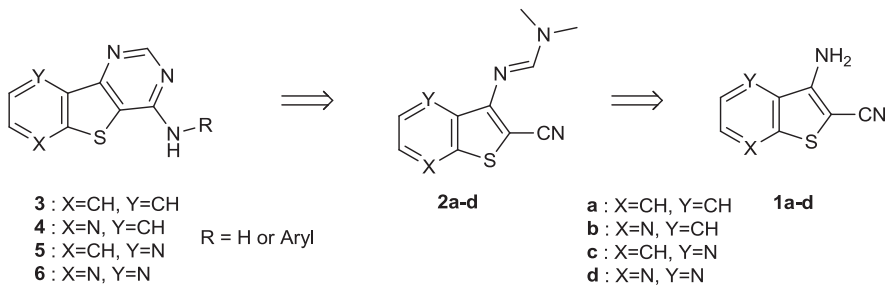
Finally, commercially available pyrazine-2-carbonitrile (**13**) reacted with sulfuryl chloride in toluene and *N*,*N*-dimethylformamide, as co-solvent, at room temperature to afford 3-chloropyrazine-2-carbonitrile (**14**) with moderate yield [14]. 7-Aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1d**) was prepared by reaction between compound **14** and sodium hydrosulfide. The resulting thiol cyclised in the presence of bromoacetonitrile and potassium carbonate, as a base, to give the thienopyrazine **1d** [8b].

2.2. Synthesis of N,N-dimethylformimidamides (*2a–d*)

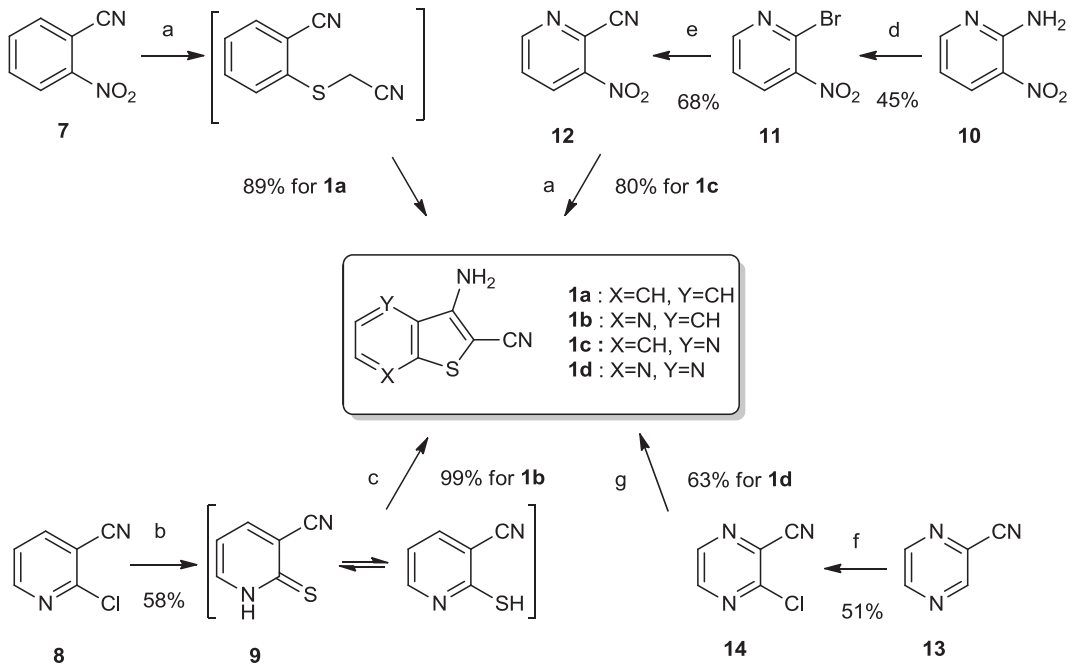
With starting compounds **1a**–**b** now available, the second step in the synthesis consisted of formation of *N*,*N*-dimethylformimidamide intermediates **2a**–**d**. It was realized by the reaction of cyanoenamines **1a**–**d** with *N*,*N*-dimethylformamide dimethylacetal (DMF–DMA). After various attempts to optimize the reaction parameters (time, temperature and applied microwave power), the expected products **2a**–**d** were obtained with good to excellent yields (79–99%) after short times of irradiation (15–30 min) at 70–90 °C. Note that microwave heating was realized at atmospheric pressure in a controlled multimode cavity and not in pressurized vials as often described in various processes [4d,15]. Concerning the technical aspect, the choice of a reactor able to work at atmospheric pressure was guided by our previous experience in microwave-assisted heterocyclic synthesis, especially in the chemistry of quinazolines [4a,16]. Open vessel microwave experiments have some advantages, such as the possibility of easier scale-up and to apply usual laboratory glassware. Our choice was also guided by a recent work describing the tendency of pressure to accumulate when DMF–DMA was heated into pressurized vials, especially under microwaves [17]. Irradiation wattage at 800 W was enough to efficiently reach the programmed temperature. This parameter was mainly monitored *via* a contactless-infrared pyrometer which was calibrated in control experiments with a fibre-optic contact thermometer.

2.3. Synthesis of benzo (*3*), pyrido (*4* and *5*) and pyrazino (*6*) thieno[3,2-d]pyrimidin-4-amine derivatives

Before introducing a substituted amino group on the skeleton of the targeted products, synthesis of the unsubstituted thieno[3,2-*d*]pyrimidin-4-amine derivatives (**3a**, **4a**, **5a** and **6a**) was realized in good yield by strong heating of intermediate formimidamides **2a**–**d** in the presence of formamide which played the dual role of



Scheme 1. Envisioned synthesis of the target benzo[*b*]thieno[3,2-*d*]pyrimidines (**3**) and their pyrido (**4** and **5**) and pyrazino analogues (**6**).



Scheme 2. Reagents and conditions: a) $HSCH_2CH_2CN$, KOH/DMF, 0 °C, 15 min then $BrCH_2CN$, 0 °C, 2 h; b) thiourea, ethanol, 120 °C (μW), 45 min; c) $ClCH_2CN$, K_2CO_3, acetone, r.t., 4 h; d) KNO_2, CuBr, HBr 48%, DMSO, 35 °C, 4 h; e) CuCN, fusion 150 °C, 2 h; f) SO_2Cl_2, toluene-DMF, r.t., 5 h; g) NaHS, r.t., 3 h then $BrCH_2CN$, K_2CO_3, acetone, r.t., 3 h.

solvent and reactant (Scheme 3) [18]. Its temperature-dependent ability to generate ammonia synthon and its intrinsic properties of heating under microwave irradiation (its loss dissipation factor, tan δ, is greater than 0.5) [19] were combined in a comfortable process constituting a safe alternative to the extreme conditions usually described in the literature [20].

The last part of the synthesis consisted of heating the formimidamide derivatives **2a**–**d** with various anilines in the presence of acetic acid which serves as a relatively good solvent for heating under microwaves (tan $\delta = 0.174$ at 2.45 GHz [19]) and also initiates the reaction. The starting mixture was irradiated at 400 W in a multimode cavity. After 3 min, the temperature at which the solvent could be refluxed (118 °C) was reached (this time, called "the ramp period", is not added to the reaction time described in Table 1). The evolution of all reactions was followed by thin-layer chromatography and the reaction times given correspond to a complete disappearance of the starting material (Table 1). A library of thirty-six thieno[3,2-*d*]pyrimidin-4-amine derivatives was rapidly prepared *via* Dimroth translocation of the endocyclic and exocyclic nitrogen atoms present in the pyrimidine moiety [4a,9]. This process led to the thermodynamically stable 4-anilino-substituted isomers of the final products (**3**, **4**, **5** and **6**) (Scheme 3).

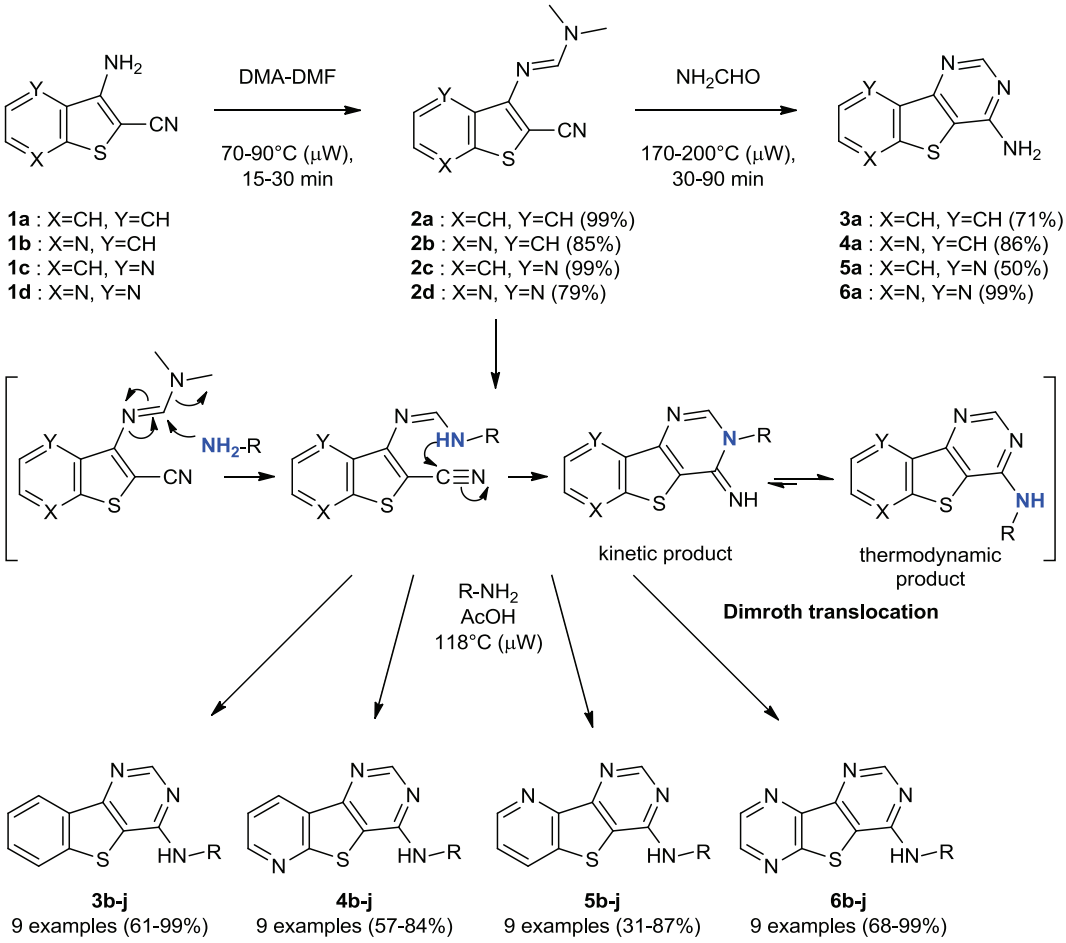
Obviously, as described in previous works [3,9], kinetics and yield of the reaction depended on the nucleophilicity of starting aniline, as well as the presence of electron-withdrawing groups on benzene ring. Steric hindrance due to the position of the substituents may also play a role and caused an increase of reaction time. Table 1 provided us interesting structure-reactivity information, concerning heating time and resulting from pyridine nitrogen atom position on starting compounds such as **2b** and **2c**. The presence of a nitrogen atom on the same side as a sulphur atom for fused heterocyclic ring **2b** induced a sharp increase in time of heating necessary to complete the reaction. On the contrary, the presence of a nitrogen atom opposite to the sulphur atom (*e.g.* **2c**) induced shorter heating times, comparable to those obtained with the benzene derivative **2a**. Finally introducing two nitrogen atoms, the opposite effects discussed above were cancelled since the synthesis of pyrazine derivatives **6b**–**j** from formimidamide **2d** was achieved with the shorter times.

3. Biological activities

The final products were tested on five different *in vitro* kinase assays (CDK5/p25 (cyclin-dependent kinase), CK1δ/ε (casein kinase 1), GSK3α/β (Glycogen Synthase Kinase 3), DYRK1A (dual specificity, tyrosine phosphorylation regulated kinase) and CLK1 (cdc2-like kinase 1)) to evaluate their inhibition potency. Results given in Table 2 demonstrated that the compounds prepared in this paper are definitively inactive against GSK3. Except for compound **3a** (entry 1) for which a micromolar IC_{50} value (5.2 μM) was observed, none of the tricyclic derivatives have shown any affinity against CDK5/p25. On a general aspect, the nine 4-anilino-substituted derivatives **3b**–**j** series were completely inactive on the tested kinases. Note that among the four families of tested molecules, thieno[3,2-*d*]pyrimidin-4-amine derivatives (**3a**, **4a**, **5a** and **6a**) were judged relatively active (in the micromolar range) against three kinases (CDK5, CK1 and DYRK1A for **3a**; CK1, CLK1 and DYRK1A for **4a** and **5a**) or one kinase (CK1 for **6a**).

Concerning compounds **5a**–**j** and **6a**–**j** (entries 21–40) the main part of their activity was linked to CK1 inhibition with eight products (**5a**, **5b**, **5f** and **5j**; **6a**, **6b**, **6e** and **6j**) which exhibited an inhibitory activity in the micromolar and submicromolar ranges ($7.8\ \mu M < IC_{50} < 0.12\ \mu M$). For compounds of **5a**–**j** series, affinity for kinases was sometimes centred on DYRK1A (products **5a**, **5d**, **5i** and **5j**: $7.3\ \mu M < IC_{50} < 3.7\ \mu M$).

The most promising results were obtained with products from the **4a**–**j** series, which showed a rather good inhibition of both CK1 and CLK1 kinases with submicromolar IC_{50} values for most of them. Among these compounds, **4a** and **4i** (entries 11 and 19) can be considered as the most active products with submicromolar IC_{50} values for two of the three kinases (CKI, CLK1 and DYRK1A). The values obtained for **4a** are particularly interesting, especially towards CK1 (31 nM) and CLK1 (680 nM). However **4a** and **4i** are also the least selective products.



Scheme 3. Synthesis of compounds **2a**–**d** and thieno[3,2-*d*]pyrimidine derivatives (**3a**–**j**, **4a**–**j**, **5a**–**j** and **6a**–**j**); for reaction times and yields see Table 1.

It may be noted that derivative **4i** is the one of the forty molecules prepared in this study that had submicromolar affinity (IC_{50} = 890 nM) for the DYRK1A kinase. Looking more closely at results of the **4a**–**d** series, we observed three products of interest: **4b**, **4c** and **4g** (entries 12, 13 and 17), with submicromolar IC_{50} values ranging from 180 nM (**4b**) to 520 nM (**4c**) for CK1. These molecules also showed micromolar IC_{50} values between 2.1 μM (**4i**) and 4.5 μM (**4b**) for CLK1. These three compounds showed no affinity for DYRK1A.

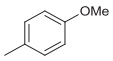
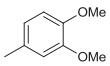
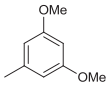
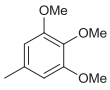
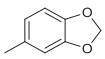
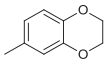
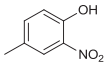
In view of these results it is difficult to define any role for the various substituents of the amine located at position 4 of pyridine ring. It is interesting to note that the presence of two methyl ether groups in the *meta* position of the amine on the aromatic ring (compounds **4e** and **4f**, entries 15 and 16) induced a loss of affinity for all kinases. On the contrary, the presence of two adjacent OMe groups in *meta* and *para* positions (**4d**, entry 14), abolished the inhibitory activity on CK1 in favour of DYRK1A without lowering it to a submicromolar level.

CK1 is a Ser/Thr protein kinase family consisting of multiple isoforms which are highly homologous within their kinase domains. Recently, several studies have highlighted the important role of CK1 in neurodegenerative diseases, especially in tauopathies such as Alzheimer disease (AD) [21]. As the involvement of CK1 in cell regulation and neurodegenerative diseases pathogenesis has recently been identified, there has been little work regarding inhibitors of this family of protein kinases [22]. CLK1 is one of the four isoforms of the cdc2-like kinase family. It was described that inhibitors of CLK1 could prove to be useful agents in disease phenotypes characterized by abnormal splicing. In this sense CLK inhibitors may alter the splicing of microtubule-associated protein tau implicated in AD and Parkinson diseases. In this respect, our tricyclic 6,5,6-heterocyclic derivatives constitute a promising source of inspiration for the synthesis of novel bioactive molecules. The factors governing their dual activity towards CK1 and CLK1 will be investigated.

4. Conclusion

The synthesis of a library of novel *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines and their pyrido and pyrazino analogues was realized under microwaves *via* a Dimroth rearrangement. Good control of the reaction parameters allowed efficient heating of the reaction mixture, resulting in a shorter reaction time and very good yields. On the chemical aspect this article is a further example illustrating how microwave heating can be a very powerful tool for medicinal chemists. The inhibitory potency of the final products against five kinases was evaluated. Among all prepared compounds, three of them turned out to be interesting. *N*-Arylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine series of compounds (**4a**–**j**) is particularly promising for the development of new inhibitors of CK1 and CLK1 kinases. The most effective compounds towards these two kinase families are the pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines **4b**, **4c** and **4g** which showed interesting selectivity towards CK1 and CLK1 kinases over the other tested kinases. These results are the starting point of a larger project within our group, in the hope to lead to the discovery of novel kinase inhibitors.

Table 1
Synthesis of thieno[3,2-*d*]pyrimidine derivatives (**3b**–**j**, **4b**–**j**, **5b**–**j** and **6b**–**j**).[a]

Compound		**3**		**4**		**5**		**6**	
R		Time (min)	(Yield) (%)[b]	Time (min)	(Yield) (%)[b]	Time (min)	(Yield) (%)[b]	Time (min)	(Yield) (%)[b]
	**b**	15	(77)	30	(69)	15	(87)	5	(88)
	**c**	20	(61)	30	(57)	15	(66)	10	(99)
	**d**	20	(99)	30	(58)	15	(75)	10	(96)
	**e**	30	(84)	50	(73)	20	(65)	10	(96)
	**f**	15	(80)	30	(79)	15	(78)	10	(99)
	**g**	30	(68)	180	(67)	45	(31)	20	(79)
	**h**	30	(84)	90	(84)	30	(59)	20	(76)
	**i**	210	(76)	300	(60)	120	(55)	90	(78)
	**j**	30	(66)	135	(71)	30	(62)	30	(68)

[a] Reaction were performed under microwaves (μW) at 400 W, on a 0.5 mmol scale from **2a**–**d** with 1 equiv. of aniline (MultiSYNTH™ from Milestone S.r.l. Italy).
[b] Yield of isolated product.

5. Experimental section

5.1. Chemistry

Melting points of powder compounds were measured on a STUART-Advanced apparatus. IR spectra were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker DXP 300 spectrometer at 300, 75 MHz, respectively and a Bruker AVANCE 400 MHz high resolution NMR spectrometer at 400, 100 MHz, respectively. Multiplicities were abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin layer plates. Column chromatography was carried out on silica gel Merck 60 (70–230 mesh ASTM). Elemental analyses were found within ±0.4% of the theoretical values. Mass spectra were performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters ZQ 2000 and a Waters LCP 1er XR spectrometer.

Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. RotoSYNTH™ (Milestone S.r.l. Italy) is a multi-mode cavity with a microwave power delivery system ranging from 0 to 1200 W. The temperatures of the reactions were mainly monitored *via* contactless infrared pyrometer which was calibrated in control experiments with a fibre-optic contact thermometer protected in a Teflon coated ceramic well inserted directly in the reaction mixture. Open vessel experiments were carried out in a 100–250 mL round bottom flask fitted with a reflux condenser. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature and power profiles were monitored in both cases through the EASY-Control software provided by the manufacturer.

5.1.1. Synthetic routes for the preparation of 3-aminoarylthiophene-2-carbonitriles (*1a*–*d*)

*5.1.1.1. Synthesis of 3-amino-2-cyanobenzo[b]thiophene (**1a**).* A solution of potassium hydroxide (3.8 g, 67.7 mmol) in water (12 mL) was added dropwise under vigorous magnetic stirring to a cooled (ice bath) solution of 2-nitrobenzonitrile **7** (3.40 g, 22.9 mmol) and 3-mercaptopropionitrile (2.40 g, 27.5 mmol) in DMF (45 mL). The cold mixture was stirred for 15 min and bromoacetonitrile (2.30 mL, 33.0 mmol) was added dropwise. After 2 h at 0 °C, the mixture was poured into ice water. The crude product was collected by filtration and purified with silica gel column chromatography using 100% dichloromethane. The desired product (**1a**) was isolated as a white powder (3.56 g, 89%); mp 156–157 °C (lit. [11]: 155–156 °C); IR (KBr) ν_{max} (cm^{-1}): 3319, 2210 (CN), 1644, 1571, 1532, 1467, 1432, 1399, 1326, 1270, 1198, 1150, 1132, 1059, 1022, 754, 721, 680, 644; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.58 (td, J_1 = 0.6 Hz, J_2 = 7.6 Hz, 1H), 7.48 (td, J_1 = 0.6 Hz, J_2 = 7.7 Hz, 1H), 7.18 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.4, 139.1, 130.4, 128.8, 128.7, 124.7, 123.3, 123.0, 116.4; MS (ESI) m/z (%): 174.9 [(M + H)$^+$, 100].

*5.1.1.2. Synthesis of 3-aminothieno[2,3-b]pyridine-2-carbonitrile (**1b**)*

*5.1.1.2.1. 2-Mercaptonicotinonitrile (**9**).* To a mixture of 2-chloro-3-cyanopyridine (1.0 g, 7.25 mmol) in ethanol (15 mL) was added thiourea (0.551 g, 7.25 mmol) in a sealed tube. The solution was irradiated at 120 °C (800 W) for 45 min. The solution was cooled to room temperature and the mixture was filtered off and washed

Table 2
Kinase activity of thieno[3,2-*d*]pyrimidine derivatives **3a**–**j**, **4a**–**j**, **5a**–**j** and **6a**–**j**.[a]

Entry	Compounds	CDK5	CK1	CLK1	DYRK1A	GSK3
1	**3a**	**5.2**	**0.79**	n.t.[b]	**5.1**	>10
2	**3b**	>10	>10	n.t.	>10	>10
3	**3c**	>10	>10	n.t.	>10	>10
4	**3d**	>10	>10	n.t.	**3.7**	>10
5	**3e**	>10	>10	n.t.	>10	>10
6	**3f**	>10	>10	n.t.	>10	>10
7	**3g**	>10	>10	n.t.	>10	>10
8	**3h**	>10	>10	n.t.	>10	>10
9	**3i**	>10	>10	n.t.	>10	>10
10	**3j**	>10	>10	n.t.	>10	>10
11	**4a**	>10	**0.031**	**0.68**	**2.8**	>10
12	**4b**	>10	**0.18**	**4.5**	>10	>10
13	**4c**	>10	**0.52**	**3.3**	>10	>10
14	**4d**	>10	>10	**3.4**	**2.9**	>10
15	**4e**	>10	>10	>10	>10	>10
16	**4f**	>10	>10	>10	>10	>10
17	**4g**	>10	**0.44**	**2.2**	>10	>10
18	**4h**	>10	>10	>10	>10	>10
19	**4i**	>10	**0.28**	**2.1**	**0.89**	>10
20	**4j**	>10	>10	>10	>10	>10
21	**5a**	>10	**1.8**	**5.2**	**6.0**	>10
22	**5b**	>10	**1.6**	>10	>10	>10
23	**5c**	>10	>10	>10	>10	>10
24	**5d**	>10	>10	>10	**3.7**	>10
25	**5e**	>10	>10	>10	>10	>10
26	**5f**	>10	**4.1**	>10	>10	>10
27	**5g**	>10	>10	>10	>10	>10
28	**5h**	>10	>10	>10	>10	>10
29	**5i**	>10	11	>10	**7.3**	>10
30	**5j**	>10	**0.12**	>10	**5.8**	>10
31	**6a**	>10	**2.4**	n.t.	>10	>10
32	**6b**	>10	**5.0**	n.t.	>10	>10
33	**6c**	>10	>10	n.t.	>10	>10
34	**6d**	>10	>10	n.t.	>10	>10
35	**6e**	>10	**7.8**	n.t.	>10	>10
36	**6f**	>10	>10	n.t.	>10	>10
37	**6g**	>10	>10	n.t.	>10	>10
38	**6h**	>10	>10	n.t.	>10	>10
39	**6i**	>10	>10	n.t.	>10	>10
40	**6j**	>10	**1.4**	n.t.	>10	>10

Values in bold shows interesting micromolar or submicromolar values in the table.
[a] IC_{50} values are reported in μM.
[b] n.t.: not tested.

with ethanol. The crude solid was purified by column chromatography over silica gel using dichloromethane/petroleum ether (5:5, v/v) as the eluent to give 2-mercaptonicotinonitrile (**9**) as a yellow powder (0.552 g, 58%); mp 249–250 °C (lit. [10]: 248–250 °C); IR (KBr) ν_{max} (cm^{-1}): 2871, 2226 (CN), 1584, 1489, 1440, 1318, 1236, 1173, 1159, 1079, 1059, 1033, 982, 968, 854, 813, 775, 712; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-4), 7.95 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 6.67 (dd, 1H, $J_1 = 7$ Hz, $J_2 = 8$ Hz, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.2 (C-2), 145.5 (C-6), 142.7 (C-4), 116.8 (CN), 116.6 (C-3), 112.4 (C-5); HRMS calcd for $C_6H_5N_2S$ $[M + H]^+$ 137.0173 found 137.0171.

*5.1.1.2.2. 3-Aminothieno[2,3-b]pyridine-2-carbonitrile (**1b**).* To a mixture of 2-mercaptonicotinonitrile (**9**) (0.500 g, 3.67 mmol) in acetone (30 mL) was added successively chloroacetonitrile (0.280 g, 3.67 mmol) and potassium carbonate (0.560 g, 4.01 mmol). The solution was stirred at room temperature for 4 h. The solution was then filtered and evaporated under *vacuo*. The crude solid was purified by column chromatography over silica gel using dichloromethane/petroleum ether (5:5, v/v) as the eluent to give 3-Aminothieno[2,3-*b*]pyridine-2-carbonitrile (**1b**) as a yellow powder (0.635 g, 99%); mp 219–220 °C (lit. [10]: 215–216 °C); IR (KBr) ν_{max} (cm^{-1}): 3135, 2201 (CN), 1661, 1638, 1586, 1577, 1569, 1536, 1527, 1410, 1391, 1378, 1262, 1202, 1074, 859, 797, 743; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.72 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-4), 8.50 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.53 (dd, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-5), 7.36 (s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.5 (C-3*a*), 150.9 (C-5), 150.4 (C-1), 131.3 (C-7), 124.2 (C-7*a*), 119.9 (C-6), 115.7 (*C*N), 71.2 (C-2); HRMS calcd for $C_8H_6N_3S$ $[M + H]^+$ 176.0282 found 176.0276.

*5.1.1.3. Synthesis of 3-aminothieno[3,2-b]pyridine-2-carbonitrile (**1c**)*

*5.1.1.3.1. 2-Bromo-3-nitropyridine (**11**).* A solution of 48% aq. HBr (3.60 mL, 32.0 mmol) dissolved in DMSO (35 mL) was added dropwise to a solution of 3-nitropyridine-2-amine **10**, (1.0 g, 7.19 mmol) in a mixture of 35 mL of DMSO, KNO_2 (2.45 g, 28.75 mmol) and CuBr (0.206 g, 1.44 mmol) at 35 °C with stirring. The added mixture was stirred at 35 °C for 4 h and then transferred to a solution of K_2CO_3 (7 g) in 100 mL of ice water. The reaction mixture was then taken up in diethyl ether, and the ethereal extracts were washed with water and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product. The crude product was purified by silica gel chromatography (eluent: 100% dichloromethane) to give 2-bromo-3-nitropyridine **11** as a beige powder (0.662 g, 45%). *Rf* = 0.75 (dichloromethane); mp 121–122 °C (lit. [12]: 123–124 °C); IR (KBr) ν_{max} (cm^{-1}): 3042 (νCH_{ar}), 1578 and 1562 (νC=C), 1524 ($\nu_{as}NO_2$), 1350 (ν_{sy} NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 4.8$ Hz, H-6), 8.54 (dd, 1H, $J_1 = 1.6$ Hz, $J_3 = 8.0$ Hz, H-4), 7.79 (dd, 1H, $J_2 = 4.8$ Hz, $J_3 = 8.0$ Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.26 (C-6), 147.08 (C-3), 134.48 (C-4), 132.08 (C-2), 124.44 (C-5); MS (ESI) *m/z* (%): 202.9 (100) $[M + H]^+$, 204.9 (100) $[M + H + 2]^+$. Anal. calcd for $C_5H_3BrN_2O_2$: C, 29.58; H, 1.49; N, 13.80. Found: C, 29.63; H, 1.50; N, 13.83.

*5.1.1.3.2. 3-Nitropyridine-2-carbonitrile (**12**).* 2-Bromo-3-nitropyridine **11** (0.500 g, 2.46 mmol) was mixed with copper (I) cyanide (0.450 g, 5.02 mmol) in a 50 mL round-bottom flask. The flask was slowly heated in an oil bath. When the temperature reached 150 °C (takes 2 h), the reaction mass began to turn black. The mixture was cooled to room temperature and reaction mass were treated with hot acetone (100 mL). The resulting mixture was filtered, and the mother liquor evaporated to dryness to yield the crude title compound as a dark brown solid. This solid was purified by column chromatography (eluent: 100% dichloromethane) to give 3-nitropyridine-2-carbonitrile **12** as a white powder (0.250 g, 68%). *Rf* = 0.54 (dichloromethane); mp 74–75 °C (lit. [23]: 75–78 °C); IR (KBr) ν_{max} (cm^{-1}): 3091 (νCH_{ar}), 2160 (νCN), 1600 and 1566 (νC=C), 1531 ($\nu_{as}NO_2$), 1348 (ν_{sy} NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 4.8$ Hz, H-6), 8.83 (dd, 1H, $J_1 = 1.2$ Hz, $J_3 = 8.4$ Hz, H-4), 8.08 (dd, 1H, $J_2 = 4.8$ Hz, $J_3 = 8.4$ Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.90 (C-6), 146.95 (C-3), 134.08 (C-4), 128.64 (C-5), 127.69 (C-2), 115.20 (CN); MS (ESI) *m/z* (%): 150.1 (100) $[M + H]^+$. Anal. calcd for $C_6H_3N_3O_2$: C, 48.33; H, 2.03; N, 28.18. Found: C, 48.51; H, 2.04; N, 28.22.

*5.1.1.3.3. 3-Aminothieno[3,2-b]pyridine-2-carbonitrile (**1c**).* A solution of potassium hydroxide (1.06 g, 18.9 mmol) in water (3.2 mL) was added dropwise to a stirred and cold solution (ice bath) containing 3-nitropyridine-2-carbonitrile **12** (0.950 g, 6.37 mmol) and 3-mercaptopropionitrile (0.670 g, 7.66 mmol) in DMF (12 mL). The cold mixture was stirred for 15 min and bromoacetonitrile (0.64 mL, 9.18 mmol) was added dropwise. After 1 h at 0 °C, the mixture was poured into ice water. The crude product was collected by filtration and purified with silica gel column chromatography using 100% dichloromethane to give 3-aminothieno[3,2-*b*]pyridine-2-carbonitrile **1c** as a beige powder (0.893 g, 80%). *Rf* = 0.12 (dichloromethane); mp 198–200 °C; IR (KBr) ν_{max} (cm^{-1}): 3385, 3307, 3217 and 3189 (νNH_2), 2193 (νCN), 1630 and 1532 (νC=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (dd, 1H, $J_1 = 1.4$ Hz, $J_2 = 4.6$ Hz, H-5), 8.46 (dd, 1H, $J_1 = 1.4$ Hz, $J_3 = 8.4$ Hz, H-7), 7.62 (dd, 1H, $J_2 = 4.6$ Hz, $J_3 = 8.4$ Hz, H-6), 7.16 (br s, 2H, NH_2);

13C NMR (100 MHz, DMSO-d_6): δ 150.95 (CH), 147.50 (CH), 145.25 (C), 133.71 (C), 132.11 (CH), 123.19 (CH), 115.52 (CN), 74.95 (C); MS (ESI) m/z (%): 176.1 (100) $[M + H]^+$. Anal. calcd for $C_8H_5N_3S$: C, 54.84; H, 2.88; N, 23.98. Found: C, 55.01; H, 2.89; N, 24.07.

*5.1.1.4. Synthesis of 7-aminothieno[2,3-b]pyrazine-6-carbonitrile (**1d**)*

*5.1.1.4.1. 3-Chloropyrazine-2-carbonitrile (**14**).* To a solution of pyrazine-2-carbonitrile **13** (6.90 g, 65.65 mmol) in toluene (48 mL) and DMF (5 mL) was added sulfuryl chloride (21.2 mL, 260.8 mmol) over 10 min. The reaction mixture was stirred for 30 min in an ice bath, then allowed to warm up to room temperature gradually, after which it was stirred for 5 h. The toluene layer was decanted, and the reddish oil residue was extracted three times with diethyl ether. The combined toluene and ether layers were quenched with ice water and cooled in an ice bath. The combined layers were then neutralized with solid $NaHCO_3$, then separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to afford the title compound. The crude product was purified by silica gel chromatography (eluent: 100% dichloromethane) to give 3-chloropyrazine-2-carbonitrile **14** as a white powder (4.7 g, 51%). $Rf = 0.76$ (dichloromethane); mp 44–46 °C (lit. [14]: 47–48 °C); IR (KBr) ν_{max} (cm^{-1}): 3088 (νCH_{ar}), 2242 (νCN), 1377 (νC=C), 1087 (νC-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (d, 1H, $J = 2.4$ Hz, H-6), 8.88 (d, 1H, $J = 2.4$ Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.67 (C-3), 147.97 (C-5), 144.26 (C-6), 129.87 (C-2), 114.66 (CN); MS (ESI) m/z (%): 140.3 (100) $[M + H]^+$, 142.3 (40) $[M + H + 2]^+$. Anal. calcd for $C_5H_2ClN_3$: C, 43.04; H, 1.44; N, 30.11. Found: C, 43.18; H, 1.45; N, 30.16.

*5.1.1.4.2. 7-Aminothieno[2,3-b]pyrazine-6-carbonitrile (**1d**).* To a solution of 3-chloropyrazine-2-carbonitrile **14** (4.60 g, 32.96 mmol) in EtOH (120 mL) was added NaSH (3.94 g, 42.79 mmol), and the mixture was stirred at room temperature for 3 h (TLC monitoring). EtOH was evaporated under reduced pressure, and the residue was dissolved in H_2O and 2 M HCl was carefully added to neutralize the suspension. After evaporation of the solvent, the residue was dissolved in acetone (48 mL) and $ClCH_2CN$ (2.29 mL, 32.96 mmol), K_2CO_3 (4.55 g, 32.96 mmol), and a catalytic amount of KI were added. The resulting mixture was stirred at room temperature for 3 h, and then the resulting residue was separated by filtration and washed with acetone (3 × 30 mL). The filtrate was evaporated under reduced pressure, the resulting residue was dissolved in THF (240 mL), piperidine (3.26 mL, 32.96 mmol) was added, and the mixture was stirred at reflux for 5 h. After cooling, the solution was concentrated to dryness, and the residual material was purified by column chromatography (eluent: 100% dichloromethane) to give 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile **1d** as a yellow powder (3.66 g, 63%); $Rf = 0.18$ (dichloromethane); mp 205–207 °C (lit. [8b]: 205–206 °C); IR (KBr) ν_{max} (cm^{-1}): 3383, 3329, 3231 and 3204 (νNH_2), 2197 (νCN), 1643, 1566 and 1529 (νC=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (d, 1H, $J = 2.4$ Hz), 8.84 (d, 1H, $J = 2.4$ Hz), 7.45 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.55 (C), 149.15 (C), 145.26 (CH), 142.36 (CH), 139.76 (C), 115.37 (CN), 74.27 (C); MS (ESI) m/z (%): 177.0 (100) $[M + H]^+$. Anal. Calcd for $C_7H_4N_4S$: C, 47.72; H, 2.29; N, 31.80; S, 18.20. Found: C, 47.84; H, 2.30; N, 31.86.

*5.1.2. General procedure for the synthesis of N,N-dimethylformimidamides derivatives (**2a**–**d**)*

A mixture of starting cyanoenamine **1a**–**d** (0.5 g) and dimethylformamide dimethylacetal (4 mL) was irradiated at 70 °C (**1d**) or 90 °C (800 W) (**1a**–**c**) for 15 min (**1a** and **1d**) or 30 min (**1b** and **1c**). On completion, the solution was cooled to room temperature and crude products were extracted with ethyl acetate. The organic layers were washed with cold water, dried over Na_2SO_4, filtered and evaporated *in vacuo*. Purification by column chromatography over silica gel using dichloromethane/petroleum ether (5:5, v/v) as the eluent gave the desired compounds **2a**–**d**.

*5.1.2.1. (E)-N′-(2-Cyanobenzo[b]thiophen-3-yl)-N,N-dimethylformimidamide (**2a**).* Yellow powder (0.655 g; 99%) obtained from 3-aminobenzothiophene-2-carbonitrile (**1a**) after 15 min of irradiation; mp 88–89 °C; IR (KBr) ν_{max} (cm^{-1}): 2196 (CN), 1614, 1591, 1558, 1501, 1481, 1462, 1438, 1427, 1415, 1371, 1314, 111, 1043, 972, 768, 732, 663; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.18 (s, 1H, NC*H*N), 7.98 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-7), 7.85 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-4), 7.59 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-6), 7.47 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-5), 3.12 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.2 (C-3*a*), 156.0 (*N*CN), 138.7 (C-7*a*), 134.1 (C-1), 128.5 (C-5), 125.1 (C-6), 123.6 (C-7), 123.2 (C-4), 116.4 (C-2), 85.8 (*C*N), 34.1 ($N(CH_3)_2$); HRMS calcd for $C_{12}H_{11}N_3S$ $[M + H]^+$ 230.0752 found 230.0749.

*5.1.2.2. (E)-N′-(2-Cyanothieno[2,3-b]pyridin-3-yl)-N,N-dimethylformimidamide (**2b**).* White fibres (0.554 g; 85%) obtained from 3-aminothieno[2,3-*b*]pyridine-2-carbonitrile (**1b**) after 30 min of irradiation; mp 113–114 °C; IR (KBr) ν_{max} (cm^{-1}): 2197 (CN), 1617, 1577, 1555, 1477, 1468, 1437, 1411, 1380, 1261, 1190, 1111, 1040, 1021, 980, 919, 862, 811, 759, 753; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.76 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-5), 8.24 (s, 1H, NC*H*N), 8.23 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.53 (dd, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-5), 3.14 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.3 (C-3*a*), 156.3 (*N*CN), 155.3 (C-1), 150.9 (C-5), 132.1 (C-7), 127.8 (C-7*a*), 120.7 (C-6), 115.8(*C*N), 85.1 (C-2), 34.2 ($N(CH_3)_2$); HRMS calcd for $C_{11}H_{11}N_4S$ $[M + H]^+$ 231.0704 found 231.0708.

*5.1.2.3. (E)-N′-(2-Cyanothieno[3,2-b]pyridin-3-yl)-N,N-dimethylformimidamide (**2c**).* Yellow fibres (0.657 g; 99%) obtained from 3-aminothieno[3,2-*b*]pyridine-2-carbonitrile (**1c**) after 30 min of irradiation; mp 120–121 °C; IR (KBr) ν_{max} (cm^{-1}): 2199 (CN), 1600, 1545, 1508, 1432, 1394, 1368, 1288, 1264, 1237, 1165, 1151, 1114, 1089, 1075, 1059, 872, 783, 663, 635; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (s, 1H, NC*H*N), 8.73 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-5), 8.46 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-4), 7.53 (dd, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-6), 3.11 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.9 (*N*CN), 154.5 (C-1), 148.0 (C-6), 147.3 (C-7*a*), 134.0 (C-3*a*), 132.3 (C-4), 122.5 (C-5), 115.8(*C*N), 92.8 (C-2), 33.4 ($N(CH_3)_2$); HRMS calcd for $C_{11}H_{11}N_4S$ $[M + H]^+$ 231.0704 found 231.0704.

*5.1.2.4. (E)-N′-(6-Cyanothieno[2,3-b]pyrazin-7-yl)-N,N-dimethylformimidamide (**2d**).* Yellow powder (0.519 g; 79%) obtained from 7-aminothieno[2,3-*b*]pyrazine-6-carbonitrile (**1d**) after 30 min of irradiation; mp 134–135 °C; IR (KBr) ν_{max} (cm^{-1}): 2201 (CN), 1616, 1547, 1506, 1412, 1384, 1355, 1335, 1325, 1183, 1112, 1077, 1059, 1047, 972, 872, 785; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.87 (s, 1H, NC*H*N), 8.86 (d, 1H, $J = 2$ Hz, H-5), 8.80 (d, 1H, $J = 2$ Hz, H-6), 3.14 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.0 (*N*CN), 154.4 (C-3*a*), 152.7 (C-1), 144.2 (C-5), 142.9 (C-6), 141.8 (C-7*a*), 115.1 (*C*N), 92.0 (C-2), 33.6 ($N(CH_3)_2$); HRMS calcd for $C_{10}H_{10}N_5S$ $[M + H]^+$ 232.0657 found 232.0646.

*5.1.3. General procedure for the synthesis of thieno[3,2-d]pyrimidin-4-amine derivatives (**3a**, **4a**, **5a** and **6a**)*

A mixture of formamide (2 mL) and *N*,*N*-dimethylformimidamide derivatives (**2a**–**d**) (0.1 g) was irradiated (200 W). On completion (followed by GC–MS chromatography), the reaction

was cooled to room temperature and water was added. The solid was filtered off, washed with water and dried. The crude solid was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (100:0–0:100, v/v) as the eluent to give the desired compounds (**3a**, **4a**, **5a** and **6a**).

*5.1.3.1. Benzo[b]thieno[3,2-d]pyrimidin-4-amine (**3a**).* Brown powder (0.062 g, 71%); obtained from (*E*)-*N*′-(2-cyanobenzo[*b*]thiophen-3-yl)-*N*,*N*-dimethylformimidamide **2a** after 90 min of irradiation at 170 °C; mp 301–302 °C (lit. [9]: 280 °C) IR (KBr) ν_{max}(cm^{-1}): 3298, 3117, 1666, 1572, 1523, 1435, 1403, 1344, 1315, 1277, 1142, 1062, 1030, 958, 938, 812, 787, 740, 719, 674, 651, 609; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (s, 1H, H-2), 8.30 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.14 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-8), 7.68 (td, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-7), 7.57 (s, 2H, NH_2), 7.57 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.6 (C-4), 155.5 (C-5*a*), 155.1 (C-2), 140.5 (C-4*a*), 133.9 (C-9*a*), 129.4 (C-7), 125.1 (C-8), 123.7 (C-9*b*), 123.0 (C-9), 113.3 (C-6); HRMS calcd for $C_{10}H_8N_3S$ $[M + H]^+$ 202.0439 found 202.0427.

*5.1.3.2. Pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4a**).* Yellow powder (0.075 g, 86%) obtained from (*E*)-*N*′-(2-cyanothieno[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide (**2b**) after 30 min of irradiation at 200 °C; mp > 320 °C; IR (KBr) ν_{max}(cm^{-1}): 3111, 1671, 1573, 1557, 1525, 1403, 1379, 1347, 1285, 1274, 1253, 1235, 1071, 1031, 818, 810, 772, 747, 733; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.83 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.64 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 8.56 (s, 1H, H-2), 7.68 (s, 2H, NH_2), 7.64 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2, 158.4, 155.5, 153.3, 151.5, 131.4, 127.7, 120.8, 112.4; HRMS calcd for $C_9H_7N_4S$ $[M + H]^+$ 203.0391 found 203.0381.

*5.1.3.3. Pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5a**).* Yellow powder (0.044 g, 50%) obtained from (*E*)-*N*′-(2-cyanothieno[3,2-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide **2c** after 30 min of irradiation at 200 °C; mp > 320 °C; IR (KBr) ν_{max}(cm^{-1}): 3114, 1661, 1577, 1563, 1519, 1471, 1391, 1341, 1312, 1294, 1271, 1142, 1062, 1016, 952, 822, 754; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.85 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.66 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 8.59 (s, 1H, H-2), 7.73 (s, 2H, NH_2), 7.64 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.9, 155.6, 154.1, 149.4, 147.9, 134.6, 132.4, 123.2, 115.4; HRMS calcd for $C_9H_7N_4S$ $[M + H]^+$ 203.0391 found 203.0396.

*5.1.3.4. Pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6a**).* Grey powder (0.087 g, 99%) obtained from (*E*)-*N*′-(6-cyanothieno[2,3-*b*]pyrazin-7-yl)-*N*,*N*-dimethylformimidamide (**2d**) after 30 min of irradiation at 180 °C; mp > 320 °C; IR (KBr) ν_{max} (cm^{-1}): 3111, 1665, 1572, 1538, 1361, 1338, 1282, 1227, 1198, 1169, 1076, 1025, 852, 835, 799, 767; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96 (d, 1H, $J = 2$ Hz, H-7), 8.87 (d, 1H, $J = 2$ Hz, H-8), 8.63 (s, 1H, H-2), 7.88 (s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 156.3, 156.0, 151.8, 145.1, 143.8, 143.0, 114.8; HRMS calcd for $C_8H_6N_5S$ $[M + H]^+$ 204.0344 found 204.0334.

*5.1.4. General procedures for the synthesis of thieno[3,2-d]pyrimidine derivatives (**3b–j**, **4b–j**, **5b–j** and **6b–j**)*

*5.1.4.1. Synthesis of N-arylbenzo[b]thieno[3,2-d]pyrimidin-4-amines (**3b–j**).* A mixture of (*E*)-*N*′-(2-cyanobenzo[*b*]thiophen-3-yl)-*N*,*N*-dimethylformimidamide (**2a**, 0.1 g, 0.43 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) was irradiated at 118 °C (400 W). On completion (followed by thin-layer chromatography), the reaction was cooled to room temperature and water was added. The solid was filtered off, washed with water and dried. The crude solid was purified by column chromatography over silica gel using a gradient of petroleum ether/ethyl acetate (100:0–0:100, v/v) as the eluent to give the desired compounds (**3b–j**).

*5.1.4.1.1. N-Phenylbenzo[b]thieno[3,2-d]pyrimidin-4-amine (**3b**).* Yield: 77%; white powder; mp 272–273 °C; IR (KBr) ν_{max} (cm^{-1}): 1610, 1561, 1531, 1495, 1472, 1453, 1432, 1382, 1313, 1297, 1259, 1251, 1227, 1056, 759, 744, 723, 709, 688, 617; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 1H, N*H*), 8.74 (s, 1H, H-2), 8.35 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.19 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.80 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-ar), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.61 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.42 (td, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-ar), 7.12 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2 (C-4), 155.4 (C-2), 154.4 (C-5*a*), 139.7 (C-4*a*), 138.4 (C-11), 133.6 (C-7), 129.8 (C-8), 128.5 (C-13), 125.4 (C-9), 123.8 (C-14), 123.7 (C-9*a*), 123.0 (C-6), 122.4 (C-12), 115.1 (C-9*b*); HRMS calcd for $C_{16}H_{12}N_3S$ $[M + H]^+$ 278.0752 found 278.0759.

*5.1.4.1.2. N-(4-Methoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (**3c**).* Yield: 61%; yellow powder; mp 221–222 °C; IR (KBr) ν_{max} (cm^{-1}): 1599, 1571, 1560, 1504, 1473, 1451, 1435, 1415, 1251, 1228, 1172, 1059, 1030, 831, 749, 733, 726, 711, 697, 626; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.64 (s, 1H, N*H*), 8.66 (s, 1H, H-2), 8.33 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.15 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.69–7.58 (m, 3H, H-ar and H-7), 6.98 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-ar), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2 (C-4), 156.0 (C-2), 154.5 (C-5*a*), 150.2 (C-14), 139.7 (C-4*a*), 133.6 (C-7), 131.3 (C-11), 129.7 (C-8), 125.3 (C-9), 125.1 (C-13), 123.6 (C-9*a*), 123.0 (C-6), 114.5 (C-9*b*), 113.7 (C-12), 55.2 (OCH_3); HRMS calcd for $C_{17}H_{14}N_3OS$ $[M + H]^+$ 308.0858 found 308.0846.

*5.1.4.1.3. N-(3,4-Dimethoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (**3d**).* Yield: 99%; grey powder; mp 203–204 °C; IR (KBr) ν_{max} (cm^{-1}): 1574, 1562, 1509, 1503, 1469, 1453, 1445, 1434, 1401, 1266, 1247, 1231, 1201, 1143, 1053, 1020, 978, 744, 730; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.63 (s, 1H, N*H*), 8.69 (s, 1H, H-2), 8.34 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.15 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.70 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.64 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.30 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 6.98 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0 (C-4), 155.8 (C-2), 154.5 (C-5*a*), 148.4 (C-13), 145.9 (C-14), 139.8 (C-4*a*), 133.6 (C-7), 131.7 (C-11), 129.7 (C-8), 125.3 (C-9), 123.6 (C-9*a*), 123.0 (C-6), 115.8 (C-15), 114.6 (C-9*b*), 111.6 (C-16), 108.4 (C-12) 55.7 (OCH_3), 55.5 (OCH_3); HRMS calcd for $C_{18}H_{16}N_3O_2S$ $[M + H]^+$ 338.0963 found 338.0956.

*5.1.4.1.4. N-(3,5-Dimethoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (**3e**).* Yield: 84%; grey powder; mp 194–195 °C; IR (KBr) ν_{max} (cm^{-1}): 1584, 1568, 1533, 1513, 1487, 1463, 1441, 1415, 1194, 1146, 1064, 1009, 821, 744, 712, 669, 620, 595, 441; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, N*H*), 8.78 (s, 1H, H-2), 8.36 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.20 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.73 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.64 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.13 (s, 2H, H-ar), 6.30 (s, 1H, H-ar), 3.76 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0 (C-4), 155.8 (C-2), 154.5 (C-5*a*), 148.4 (C-13), 145.9 (C-14), 139.8 (C-4*a*), 133.6 (C-7), 131.7 (C-11), 129.7 (C-8), 125.3 (C-9), 123.6 (C-9*a*), 123.0 (C-6), 115.8 (C-9*b*), 114.6 (C-15), 111.6 (C-16), 108.4 (C-12) 55.7 (OCH_3), 55.5 (OCH_3); HRMS calcd for $C_{18}H_{16}N_3O_2S$ $[M + H]^+$ 338.0963 found 338.0956.

*5.1.4.1.5. N-(3,4,5-Trimethoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (**3f**).* Yield: 80%; white powder; mp 198–199 °C; IR (KBr) ν_{max} (cm^{-1}): 1551, 1500, 1458, 1438, 1426, 1413, 1242, 1228, 1124, 1056, 1008, 1001, 747, 728, 708, 675, 631, 595, 520; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, N*H*), 8.74 (s, 1H, H-2), 8.36 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.19 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.61 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.21 (s, 2H, H-ar), 3.80 (s, 6H, (OCH_3)$_2$), 3.68 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.1 (C-4), 155.7 (C-2), 154.6 (C-5*a*),

152.5 (C-13), 139.7 (C-4*a*), 134.8 (C-14), 134.0 (C-11), 133.6 (C-7), 129.8 (C-8), 125.4 (C-9), 123.6 (C-9*a*), 123.0 (C-6), 115.0 (C-9*b*), 100.5 (C-12), 60.1 ((OCH_3)$_2$), 55.8 (OCH_3); HRMS calcd for $C_{19}H_{18}N_3O_3S$ $[M + H]^+$ 368.1069 found 368.1060.

*5.1.4.1.6. N-(Benzo[d][1,3]dioxol-5-yl)benzo[4,5]thieno[3,2-d]pyrimidin-4-amine (**3g**).* Yield: 68%; brown powder; mp 237–238 °C; IR (KBr) ν_{max} (cm^{-1}): 1571, 1500, 1485, 1472, 1453, 1436, 1393, 1264, 1236, 1186, 1034, 1020, 936, 853, 803, 745, 715, 709, 597, 570, 421; ^1H NMR (300 MHz, DMSO-d_6): δ 9.65 (s, 1H, N*H*), 8.69 (s, 1H, H-2), 8.34 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.17 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.71 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.63 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.37 (d, 1H, $J = 2$ Hz, H-ar), 7.12 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.97 (d, 1H, $J = 8$ Hz, H-ar), 6.06 (s, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.1 (C-4), 155.7 (C-2), 154.4 (C-5*a*), 147.0 (C-13), 144.0 (C-14), 139.7 (C-4*a*), 133.6 (C-7), 132.6 (C-11), 129.7 (C-8), 125.3 (C-9), 123.6 (C-9*a*), 123.0 (C-6), 116.4 (C-16), 114.6 (C-9*b*), 107.8 (C-15), 105.4 (C-12), 101.2 (C-18); HRMS calcd for $C_{17}H_{12}N_3O_2S$ $[M + H]^+$ 322.0650 found 322.0640.

*5.1.4.1.7. N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)benzo[4,5]thieno[3,2-d]pyrimidin-4-amine (**3h**).* Yield: 84%; grey powder; mp 254–255 °C; IR (KBr) ν_{max} (cm^{-1}): 1573, 1563, 1534, 1495, 1472, 1451, 1435, 1420, 1308, 1283, 1203, 1168, 1068, 1059, 862, 745, 730, 709, 576, 421; ^1H NMR (300 MHz, DMSO-d_6): δ 9.59 (s, 1H, N*H*), 8.69 (s, 1H, H-2), 8.34 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.17 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.71 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.63 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.34 (d, 1H, $J = 2$ Hz, H-ar), 7.16 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.87 (d, 1H, $J = 8$ Hz, H-ar), 4.26 (br. s, 4H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0 (C-4), 155.5 (C-2), 154.4 (C-5*a*), 142.7 (C-13), 140.1 (C-14), 139.7 (C-4*a*), 133.6 (C-7), 132.0 (C-11), 129.7 (C-8), 125.3 (C-9), 123.6 (C-9*a*), 123.0 (C-6), 116.6 (C-16), 116.2 (C-15), 114.6 (C-9*b*), 112.1 (C-12), 64.1 (C-18), 64.2 (C-19); HRMS calcd for $C_{18}H_{14}N_3O_2S$ $[M + H]^+$ 336.0807 found 336.0801.

*5.1.4.1.8. N-(4-bromo-2-fluorophenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (**3i**).* Yield: 76%; yellow powder; mp 201–202 °C; IR (KBr) ν_{max} (cm^{-1}): 3417, 1683, 1597, 1562, 1524, 1508, 1469, 1444, 1429, 1411, 1273, 1249, 1180, 1105, 1053, 959, 862, 855, 818, 740, 726, 708; ^1H NMR (300 MHz, DMSO-d_6): δ 9.81 (s, 1H, N*H*), 8.66 (s, 1H, H-2), 8.37 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.20 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.75–7.47 (m, 5H, H-ar, H-8 and H-7), ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.8 (C-4), 154.5 (C-2), 152.3 (C-5*a*), 148.3 (C-12), 146.2 (C-15), 142.6 (C-11), 139.9 (C-4*a*), 133.4 (C-7), 129.8 (C-8), 127.7 (C-13), 125.5 (C-9), 123.8 (C-9*a*), 123.2 (C-6), 119.7 (C-16), 119.1 (C-14), 114.7 (C-9*b*); HRMS calcd for $C_{16}H_{10}N_3SBrF$ $[M + H]^+$ 373.9763 found 373.9773.

*5.1.4.1.9. 4-(Benzo[4,5]thieno[3,2-d]pyrimidin-4-ylamino)-2-nitrophenol (**3j**).* Yield: 66%; red powder; mp 256–257 °C; IR (KBr) ν_{max} (cm^{-1}): 3360, 1529, 1503, 1473, 1449, 1434, 1328, 1312, 1235, 1216, 1171, 1135, 1056, 969, 825, 753, 708, 684, 576, 555, 425; ^1H NMR (300 MHz, DMSO-d_6): δ 10.86 (s, 1H, O*H*), 9.87 (s, 1H, N*H*), 8.75 (s, 1H, H-2), 8.44 (d, 1H, $J = 2$ Hz, H-ar), 8.37 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.21 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.97 (d, 1H, $J = 8$ Hz, H-15), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.64 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.18 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.1 (C-4), 155.2 (C-2), 154.3 (C-5*a*), 139.7 (C-4*a*), 139.7 (C-14), 135.7 (C-13), 133.6 (C-7), 131.8 (C-11), 130.5 (C-16), 129.9 (C-8), 125.4 (C-9), 123.7 (C-9*a*), 123.0 (C-6), 119.3 (C-15), 118.2 (C-12), 114.6 (C-9*b*); HRMS calcd for $C_{16}H_{11}N_4O_3S$ $[M + H]^+$ 339.0552 found 339.0547.

*5.1.4.2. Synthesis of N-arylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amines (**4b**–**j**).* A mixture of (*E*)-*N*′-(2-cyanothieno[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide (**2b**, 0.1 g, 0.43 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) was irradiated at 118 °C (400 W). On completion (followed by thin-layer chromatography), the reaction was cooled to room temperature and water was added. The solid was filtered off, washed with water and dried. The crude solid was purified by column chromatography over silica gel using a gradient of petroleum ether/ethyl acetate (100:0–0:100, v/v) as the eluent to give the desired compounds (**4b**–**j**).

*5.1.4.2.1. N-Phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4b**).* Yield: 69%; white powder; mp 310–311 °C; IR (KBr) ν_{max} (cm^{-1}): 1611, 1569, 1557, 1528, 1495, 1473, 1455, 1437, 1392, 1374, 1296, 1255, 1144, 1058, 773, 760, 749, 731, 725; ^1H NMR (300 MHz, DMSO-d_6): δ 9.84 (s, 1H, N*H*), 8.85 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.75 (s, 1H, H-2), 8.68 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.79 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 7.66 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.42 (td, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 7.16 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 155.2, 154.7, 153.9, 151.8, 138.7, 131.5, 128.6 (2C), 127.5, 124.0, 122.4 (2C), 121.0, 114.3; HRMS calcd for $C_{15}H_{11}N_4S$ $[M + H]^+$ 279.0704 found 279.0708.

*5.1.4.2.2. N-(4-Methoxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4c**).* Yield: 57%; gold powder; mp 257–258 °C; IR (KBr) ν_{max}(cm^{-1}): 1559, 1502, 1473, 1451, 1411, 1378, 1245, 1233, 1212, 1179, 1055, 1036, 1023, 832, 823, 814, 770, 748, 739, 721; ^1H NMR (300 MHz, DMSO-d_6): δ 9.73 (s, 1H, N*H*), 8.85 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.69 (s, 1H, H-2), 8.67 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.66 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.63 (d, 2H, $J = 9$ Hz, H-ar), 6.99 (d, 2H, $J = 9$ Hz, H-ar), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.4, 156.3, 115.6, 154.9, 153.7, 151.7, 131.4, 131.1, 127.7, 125.0 (2C), 120.9 (2C), 113.8, 113.6, 55.2; HRMS calcd for $C_{16}H_{13}N_4OS$ $[M + H]^+$ 309.0810 found 309.0821.

*5.1.4.2.3. N-(3,4-Dimethoxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4d**).* Yield: 58%; gold powder; mp 237–238 °C; IR (KBr) ν_{max} (cm^{-1}): 1574, 1559, 1505, 1456, 1417, 1374, 1279, 1252, 1226, 1200, 1145, 1023, 981, 863, 807, 774, 765, 751, 739, 722; ^1H NMR (300 MHz, DMSO-d_6): δ 9.72 (s, 1H, N*H*), 8.84 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.72 (s, 1H, H-2), 8.67 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.65 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.34–7.31 (m, 2H, H-ar), 6.99 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.4, 155.6, 154.8, 153.7, 151.7, 148.4, 145.9, 131.5, 131.4, 127.4, 120.9, 115.5, 113.7, 111.6, 108.3, 55.7, 55.5; HRMS calcd for $C_{17}H_{15}N_4O_2S$ $[M + H]^+$ 339.0916 found 339.0914.

*5.1.4.2.4. N-(3,5-Dimethoxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4e**).* Yield: 73%; white powder; mp 214–215 °C; IR (KBr) ν_{max} (cm^{-1}): 1617, 1581, 1557, 1528, 1483, 1468, 1457, 1422, 1373, 1158, 1148, 1139, 1076, 1061, 833, 818, 812, 770, 731; ^1H NMR (300 MHz, DMSO-d_6): δ 9.76 (s, 1H, N*H*), 8.86 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.72 (s, 1H, H-2), 8.69 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.68 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.14 (d, 2H, $J = 1$ Hz, H-ar), 6.30 (t, 1H, $J = 1$ Hz, H-ar), 3.71 (s, 6H, (OCH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 160.3 (2C), 155.1, 154.6, 154.0, 151.9, 140.5, 131.5, 127.4, 121.0, 114.5, 100.3 (2C), 95.7, 55.2 (2C); HRMS calcd for $C_{17}H_{15}N_4O_2S$ $[M + H]^+$ 339.0916 found 339.0914.

*5.1.4.2.5. N-(3,4,5-Trimethoxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4f**).* Yield: 79%; yellow powder; mp 200–201 °C; IR (KBr) ν_{max} (cm^{-1}): 1577, 1502, 1457, 1430, 1411, 1182, 1118, 1082, 1009, 990, 840, 823, 746, 729; ^1H NMR (300 MHz, DMSO-d_6): δ 9.76 (s, 1H, N*H*), 8.86 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.78 (s, 1H, H-2), 8.69 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.67 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.22 (s, 2H, H-ar), 3.80 (s, 6H, (OCH_3)$_2$), 3.68 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 155.3, 154.7, 153.8, 152.5 (2C), 151.8, 134.6, 134.1, 131.5, 127.4, 121.0, 114.1, 100.5 (2C), 60.1, 55.8 (2C); HRMS calcd for $C_{18}H_{17}N_4O_3S$ $[M + H]^+$ 369.1021 found 369.1007.

*5.1.4.2.6. N-(Benzo[d][1,3]dioxol-5-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4g**).* Yield: 67%; brown powder; mp 292–

293 °C; IR (KBr) ν_{max} (cm^{-1}): 1590, 1533, 1520, 1498, 1486, 1470, 1454, 1376, 1234, 1203, 1034, 937, 833, 812, 798, 780, 768, 744, 729; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.74 (s, 1H, N*H*), 8.84 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.71 (s, 1H, H-2), 8.66 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.66 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.38 (d, 1H, $J = 2$ Hz, H-ar), 7.13 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.95 (d, 1H, $J = 8$ Hz, H-ar), 6.06 (s, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 155.5, 154.8, 153.8, 151.7, 147.0, 144.1, 132.4, 131.4, 127.4, 121.0, 116.4, 113.7, 107.8, 105.3, 101.2; HRMS calcd for $C_{16}H_{11}N_4O_2S$ $[M + H]^+$ 323.0603 found 323.0588.

*5.1.4.2.7. N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4h**).* Yield: 84%; silver powder; mp 294–295 °C; IR (KBr) ν_{max} (cm^{-1}): 1574, 1557, 1530, 1495, 1472, 1452, 1421, 1391, 1374, 1310, 1248, 1235, 1203, 1140, 1069, 1058, 864, 812, 772, 739; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, N*H*), 8.85 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.72 (s, 1H, H-2), 8.67 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.65 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.35 (d, 1H, $J = 2$ Hz, H-ar), 7.17 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.88 (d, 1H, $J = 8$ Hz, H-ar), 4.27 (br. s, 4H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 155.3, 154.8, 153.7, 151.7, 142.8, 140.3, 131.9, 131.4, 127.5, 121.0, 116.6, 116.2, 113.8, 112.1, 64.1, 64.0; HRMS calcd for $C_{17}H_{13}N_4O_2S$ $[M + H]^+$ 337.0759 found 337.0746.

*5.1.4.2.8. N-(4-Bromo-2-fluorophenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (**4i**).* Yield: 60%; white powder; mp 259–260 °C; IR (KBr) ν_{max} (cm^{-1}): 1620, 1596, 1590, 1570, 1558, 1526, 1507, 1483, 1471, 1444, 1412, 1386, 1373, 1280, 1192, 1117, 1057, 873, 849, 770; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.92 (s, 1H, N*H*), 8.87 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.72 (s, 1H, H-2), 8.70 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 7.71–7.66 (m, 2H, H-8 and H-ar), 7.57–7.48 (m, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.4, 158.5, 155.7, 154.9, 154.2, 152.0, 131.7, 129.8, 127.7, 127.3, 125.3, 121.1, 119.6, 118.5, 113.8; HRMS calcd for $C_{15}H_9N_4SBrF$ $[M + H]^+$ 374.9715 found 374.9716.

*5.1.4.2.9. 2-Nitro-4-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-ylamino)phenol (**4j**).* Yield: 71%; orange powder; mp 267–268 °C; IR (KBr) ν_{max} (cm^{-1}): 3202, 1613, 1560, 1533, 1514, 1490, 1475, 1456, 1350, 1324, 1256, 1230, 1164, 1149, 1066, 817, 773, 760, 729; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.87 (s, 1H, O*H*), 9.94 (s, 1H, N*H*), 8.86 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-7), 8.77 (s, 1H, H-2), 8.68 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-9), 8.45 (d, 1H, $J = 2$ Hz, H-ar), 7.98 (d, 1H, $J = 8$ Hz, H-ar), 7.68 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-8), 7.19 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 154.9, 154.6, 153.8, 151.8, 148.7, 135.6, 131.5, 130.6, 129.9, 127.4, 121.0, 119.2, 117.9, 114.2; HRMS calcd for $C_{15}H_{10}N_5O_3S$ $[M + H]^+$ 340.0504 found 340.0492.

*5.1.4.3. Synthesis of N-arylpyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amines (**5b**–**j**).* A mixture of (*E*)-*N*′-(2-cyanothieno[3,2-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide (**2c**, 0.1 g, 0.43 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) was irradiated at 118 °C (400 W). On completion (followed by thin-layer chromatography), the reaction was cooled to room temperature and water was added. The solid was filtered off, washed with water and dried. The crude solid was purified by column chromatography over silica gel using a gradient of petroleum ether/ethyl acetate (100:0–0:100, v/v) as the eluent to give the desired compounds (**5b**–**j**).

*5.1.4.3.1. N-Phenylpyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5b**).* Yield: 87%; yellow powder; mp 285–286 °C; IR (KBr) ν_{max} (cm^{-1}): 1613, 1527, 1511, 1494, 1475, 1452, 1444, 1435, 1394, 1382, 1284, 1217, 1059, 755, 748, 740, 725; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.91 (s, 1H, N*H*), 8.90 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.79 (s, 1H, H-2), 8.72 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.80 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 7.69 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.41 (td, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 7.15 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.7, 154.8, 154.7, 149.1, 148.2, 138.7, 134.9, 132.3, 128.5 (2C), 124.0, 123.5, 122.6 (2C), 117.3; HRMS calcd for $C_{15}H_{11}N_4S$ $[M + H]^+$ 279.0704 found 279.0709.

*5.1.4.3.2. N-(4-Methoxyphenyl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5c**).* Yield: 66%; white powder; mp 272–273 °C; IR (KBr) ν_{max}(cm^{-1}): 1569, 1548, 1512, 1497, 1435, 1388, 1251, 1217, 1186, 1173, 1055, 1028, 830, 818, 808, 779, 756, 719; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.77 (s, 1H, N*H*), 8.87 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.72 (s, 1H, H-2), 8.66 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.66 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.63 (d, 2H, $J = 9$ Hz H-ar), 6.99 (d, 2H, $J = 9$ Hz, H-ar), 3.78 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 156.1, 154.9, 154.6, 149.1, 148.1, 134.8, 132.2, 131.1, 125.2 (2C), 123.4, 116.6, 113.8 (2C), 55.2; HRMS calcd for $C_{16}H_{13}N_4OS$ $[M + H]^+$ 309.0810 found 309.0803.

*5.1.4.3.3. N-(3,4-Dimethoxyphenyl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5d**).* Yield: 75%; white powder; mp 217–218 °C; IR (KBr) ν_{max} (cm^{-1}): 1608, 1580, 1536, 1511, 1449, 1420, 1394, 1270, 1234, 1205, 1167, 1126, 1063, 1024, 988, 808, 789, 775, 748; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.78 (s, 1H, N*H*), 8.86 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.74 (s, 1H, H-2), 8.67 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.66 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.32–7.29 (m, 2H, H-ar), 6.98 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.1, 154.9, 154.6, 149.1, 148.4, 148.1, 146.0, 134.9, 132.2, 131.4, 123.4, 116.6, 115.8, 111.6, 108.5, 55.7, 55.5; HRMS calcd for $C_{17}H_{15}N_4O_2S$ $[M + H]^+$ 339.0916 found 339.0918.

*5.1.4.3.4. N-(3,5-Dimethoxyphenyl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5e**).* Yield: 65%; yellow powder; mp 283–284 °C; IR (KBr) ν_{max} (cm^{-1}): 1609, 1574, 1529, 1472, 1458, 1437, 1418, 1389, 1200, 1148, 1061, 1052, 815, 786, 766, 758, 748, 727; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.88 (s, 1H, N*H*), 8.91 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.75 (s, 1H, H-2), 8.72 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.72 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.13 (d, 2H, $J = 1$ Hz, H-ar), 6.33 (t, 1H, $J = 1$ Hz, H-ar), 3.77 (s, 6H, O(CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3 (2C), 155.7, 154.7, 149.0, 148.2, 140.4, 134.9, 132.3, 130.0, 123.6, 117.4, 100.5 (2C), 95.8, 55.2 (2C); HRMS calcd for $C_{17}H_{15}N_4O_2S$ $[M + H]^+$ 339.0916 found 339.0910.

*5.1.4.3.5. N-(3,4,5-Trimethoxyphenyl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5f**).* Yield: 78%; white powder; mp 249–250 °C; IR (KBr) ν_{max} (cm^{-1}): 1532, 1503, 1459, 1452, 1444, 1414, 1400, 1119, 1014, 992, 824, 781, 748, 732, 671; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 1H, N*H*), 8.89 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.79 (s, 1H, H-2), 8.68 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.68 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.20 (s, 2H, H-ar), 3.80 (s, 6H, (OCH_3)$_2$), 3.68 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.8, 154.8, 154.6, 152.6 (2C), 149.0, 148.2, 134.8, 134.4, 134.2, 132.3, 123.5, 117.0, 100.7 (2C), 60.1, 55.8 (2C); HRMS calcd for $C_{18}H_{17}N_4O_3S$ $[M + H]^+$ 369.1021 found 369.1011.

*5.1.4.3.6. N-(Benzo[d][1,3]dioxol-5-yl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5g**).* Yield: 31%; brown powder; mp 256–257 °C; IR (KBr) ν_{max} (cm^{-1}): 1532, 1499, 1485, 1456, 1392, 1333, 1264, 1237, 1182, 1140, 1058, 1033, 919, 800, 788, 750; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 1H, N*H*), 8.87 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.74 (s, 1H, H-2), 8.69 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.67 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.39 (d, 1H, $J = 2$ Hz, H-ar), 7.15 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.96 (d, 1H, $J = 8$ Hz, H-ar), 6.09 (s, 2H, H-18); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0, 154.9, 154.6, 149.1, 148.1, 147.0, 144.1, 134.9, 132.4, 132.3, 123.4, 116.8, 116.6, 107.8, 105.5, 101.2; HRMS calcd for $C_{16}H_{11}N_4O_2S$ $[M + H]^+$ 323.0603 found 323.0587.

*5.1.4.3.7. N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5h**).* Yield: 59%; yellow powder; mp 299–300 °C; IR (KBr) ν_{max} (cm^{-1}): 1628, 1573, 1498, 1475, 1456, 1447, 1422, 1394, 1311, 1279, 1265, 1199, 1163, 1059, 885, 807, 779, 750, 740; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1H, N*H*), 8.90 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.76 (s, 1H, H-2), 8.72 (dd, 1H,

$J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 7.69 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.36 (d, 1H, $J = 2$ Hz, H-ar), 7.18 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.88 (d, 1H, $J = 8$ Hz, H-ar), 4.27 (br s, 4H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0, 154.1, 153.0, 148.1, 142.8 (2C), 140.5, 135.3, 132.4, 131.6, 123.8, 117.1, 116.6 (2C), 112.5, 64.1, 64.0; HRMS calcd for $C_{17}H_{13}N_4O_2S$ $[M + H]^+$ 337.0759 found 337.0766.

*5.1.4.3.8. N-(4-Bromo-2-fluorophenyl)pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**5i**).* Yield: 55%; white powder; mp 250–251 °C; IR (KBr) ν_{max}(cm^{-1}): 1620, 1529, 1505, 1490, 1475, 1442, 1397, 1384, 1345, 1288, 1263, 1190, 1116, 1058, 873, 814, 786, 752, 728; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.96 (s, 1H, N*H*), 8.90 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.74 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 8.71 (s, 1H, H-2), 7.73–7.70 (m, 2H, H-7 and H-*ar*), 7.59–7.48 (m, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2, 155.0, 148.9, 148.3, 135.0, 132.4, 129.9, 127.7, 125.5, 125.3, 123.7, 119.6, 119.3, 118.6, 116.8; HRMS calcd for $C_{15}H_9N_4SBrF$ $[M + H]^+$ 374.9715 found 374.9712.

*5.1.4.3.9. 2-Nitro-4-(pyrido[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-ylamino)phenol (**5j**).* Yield: 62%; brown powder; mp 280–281 °C; IR (KBr) ν_{max} (cm^{-1}): 1628, 1582, 1536, 1516, 1478, 1456, 1395, 1328, 1300, 1284, 1260, 829, 805, 791, 762, 749, 727; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.93 (s, 1H, O*H*), 10.04 (s, 1H, N*H*), 8.90 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 5$ Hz, H-8), 8.81 (s, 1H, H-2), 8.74 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-6), 8.44 (d, 1H, $J = 2$ Hz, H-ar), 8.00 (d, 1H, $J = 8$ Hz, H-ar), 7.71 (td, 1H, $J_1 = 5$ Hz, $J_2 = 8$ Hz, H-7), 7.20 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6, 154.6, 154.2, 148.8, 148.25, 135.7, 134.9, 132.4, 130.4, 130.2, 123.6, 119.2 (2C), 118.3, 117.2; HRMS calcd for $C_{15}H_{10}N_5O_3S$ $[M + H]^+$ 340.0504 found 340.0501.

*5.1.4.4. Synthesis of N-arylpyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amines (**6b–j**).* A mixture of (*E*)-*N*′-(6-cyanothieno[2,3-*b*]pyrazin-7-yl)-*N*,*N*-dimethylformimidamide (**2d**, 0.1 g, 0.43 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) was irradiated at 118 °C (400 W). On completion (followed by thin-layer chromatography), the reaction was cooled to room temperature and water was added. The solid was filtered off, washed with water and dried. The crude solid was purified by column chromatography over silica gel using a gradient of petroleum ether/ethyl acetate (100:0–0:100, v/v) as the eluent to give the desired compounds (**6b–j**).

*5.1.4.4.1. N-Phenylpyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6b**).* Yield: 88%; yellow powder; mp 292–293 °C; IR (KBr) ν_{max} (cm^{-1}): 1623, 1525, 1500, 1488, 1479, 1454, 1438, 1364, 1339, 1253, 1158, 1046, 766, 760, 745, 733, 715; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.01 (s, 1H, N*H*), 9.00 (d, 1H, $J = 2$ Hz, H-7), 8.91 (d, 1H, $J = 2$ Hz, H-8), 8.83 (s, 1H, H-2), 7.80 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 7.43 (td, 2H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 7.18 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.5, 155.5, 155.3, 152.3, 145.4, 143.6, 143.3, 138.4, 128.6 (2C), 124.2, 122.6 (2C), 116.7; HRMS calcd for $C_{14}H_{10}N_5S$ $[M + H]^+$ 280.0657 found 280.0654.

*5.1.4.4.2. N-(4-Methoxyphenyl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6c**).* Yield: 99%; yellow powder; mp 191–192 °C; IR (KBr) ν_{max} (cm^{-1}): 1606, 1571, 1505, 1478, 1451, 1439, 1362, 1244, 1227, 1176, 1156, 1081, 1047, 1023, 830, 763, 748, 724; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.92 (s, 1H, N*H*), 8.99 (d, 1H, $J = 2$ Hz, H-7), 8.89 (d, 1H, $J = 2$ Hz, H-8), 8.76 (s, 1H, H-2), 7.63 (d, 2H, $J = 9$ Hz H-ar), 6.99 (d, 2H, $J = 9$ Hz, H-ar), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 155.9, 155.4, 152.1, 145.2, 143.6, 143.2, 130.9, 128.0, 125.1, 120.5, 116.2, 113.8 (2C), 55.2; HRMS calcd for $C_{15}H_{12}N_5OS$ $[M + H]^+$ 310.0763 found 310.0755.

*5.1.4.4.3. N-(3,4-Dimethoxyphenyl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6d**).* Yield: 96%; gold powder; mp 212–213 °C; IR (KBr) ν_{max} (cm^{-1}): 1661, 1623, 1579, 1519, 1511, 1436, 1263, 1239, 1157, 1139, 1084, 1049, 1028, 996, 855, 786, 771, 745, 729, 704; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.88 (s, 1H, N*H*), 8.98 (d, 1H, $J = 2$ Hz, H-7), 8.88 (d, 1H, $J = 2$ Hz, H-8), 8.78 (s, 1H, H-2), 7.35–7.33 (m, 2H, H-ar), 6.99 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 155.8, 155.4, 152.2, 148.4, 146.1, 145.2, 143.5, 143.2, 131.2, 116.2, 115.6, 111.6, 108.4, 55.7, 55.5; HRMS calcd for $C_{16}H_{14}N_5O_2S$ $[M + H]^+$ 340.0868 found 340.0858.

*5.1.4.4.4. N-(3,5-Dimethoxyphenyl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6e**).* Yield: 96%; yellow powder; mp 249–250 °C; IR (KBr) ν_{max} (cm^{-1}): 1575, 1527, 1458, 1444, 1415, 1357, 1334, 1200, 1145, 1056, 815, 762, 749, 733; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.86 (s, 1H, N*H*), 8.97 (d, 1H, $J = 2$ Hz, H-7), 8.87 (d, 1H, $J = 2$ Hz, H-8), 8.84 (s, 1H, H-2), 7.13 (d, 2H, $J = 1$ Hz, H-ar), 6.31 (t, 1H, $J = 1$ Hz, H-ar), 3.77 (s, 6H, (OCH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3 (2C), 156.4, 155.4, 155.1, 152.3, 145.3, 143.5, 143.2, 140.2, 116.9, 100.4 (2C), 95.9, 55.2 (2C); HRMS calcd for $C_{16}H_{14}N_5O_2S$ $[M + H]^+$ 340.0868 found 340.0860.

*5.1.4.4.5. N-(3,4,5-Trimethoxyphenyl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6f**).* Yield: 99%; yellow powder; mp 245–246 °C; IR (KBr) ν_{max} (cm^{-1}): 1634, 1584, 1504, 1454, 1444, 1431, 1410, 1117, 1085, 983, 840, 825, 761; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.93 (s, 1H, N*H*), 8.99 (d, 1H, $J = 2$ Hz, H-7), 8.91 (d, 1H, $J = 2$ Hz, H-8), 8.84 (s, 1H, H-2), 7.22 (s, 2H, H-ar), 3.81 (s, 6H, (OCH_3)$_2$), 3.68 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 155.6, 155.3, 152.6 (2C), 152.3, 145.4, 143.5, 143.3, 134.3, 133.3, 116.5, 100.6 (2C), 60.1, 55.8 (2C); HRMS calcd for $C_{17}H_{16}N_5O_3S$ $[M + H]^+$ 370.0980 found 370.0977.

*5.1.4.4.6. N-(Benzo[d][1,3]dioxol-5-yl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6g**).* Yield: 79%; orange powder; mp 293–294 °C; IR (KBr) ν_{max} (cm^{-1}): 1595, 1530, 1501, 1486, 1458, 1444, 1267, 1223, 1192, 1159, 1037, 923, 854, 798, 785, 763, 748; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.93 (s, 1H, N*H*), 8.99 (d, 1H, $J = 2$ Hz, H-7), 8.90 (d, 1H, $J = 2$ Hz, H-8), 8.79 (s, 1H, H-2), 7.39 (d, 1H, $J = 2$ Hz, H-ar), 7.15 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.97 (d, 1H, $J = 8$ Hz, H-ar), 6.07 (s, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 155.9, 155.1, 151.8, 147.1, 145.4, 144.4, 143.3, 135.8, 132.0, 116.7, 116.2, 107.9, 105.5, 101.3; HRMS calcd for $C_{15}H_{10}N_5O_2S$ $[M + H]^+$ 324.0555 found 324.0554.

*5.1.4.4.7. N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6h**).* Yield: 76%; yellow powder; mp 255–256 °C; IR (KBr) ν_{max} (cm^{-1}): 1615, 1528, 1495, 1477, 1459, 1450, 1359, 1297, 1244, 1223, 1201, 1065, 1048, 863, 805, 764; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.84 (s, 1H, N*H*), 8.98 (d, 1H, $J = 2$ Hz, H-7), 8.89 (d, 1H, $J = 2$ Hz, H-8), 8.78 (s, 1H, H-2), 7.36 (d, 1H, $J = 2$ Hz, H-ar), 7.17 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar), 6.88 (d, 1H, $J = 8$ Hz, H-ar), 4.27 (br s, 4H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 155.6, 155.3, 152.2, 145.2, 143.5, 143.2, 142.8, 140.5, 131.6, 116.7, 116.3 (2C), 112.2, 64.1, 64.0; HRMS calcd for $C_{16}H_{12}N_5O_2S$ $[M + H]^+$ 338.0712 found 338.0706.

*5.1.4.4.8. N-(4-Bromo-2-fluorophenyl)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-amine (**6i**).* Yield: 78%; yellow powder; mp 262–263 °C; IR (KBr) ν_{max} (cm^{-1}): 1631, 1596, 1530, 1511, 1481, 1449, 1411, 1362, 1337, 1186, 1115, 1046, 869, 854, 838, 763; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.11 (s, 1H, N*H*), 9.02 (d, 1H, $J = 2$ Hz, H-7), 8.92 (d, 1H, $J = 2$ Hz, H-8), 8.77 (s, 1H, H-2), 7.72 (ddd, 1H, $J_1 = 1$ Hz, $J_2 = 2$ Hz, $J_3 = 8$ Hz, H-ar), 7.59–7.49 (m, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.6, 156.0, 155.4, 152.6, 145.5, 143.4, 143.4, 129.8, 127.8, 125.2, 119.7, 119.3, 118.7, 116.2; HRMS calcd for $C_{14}H_8N_5SBrF$ $[M + H]^+$ 375.9668 found 375.9666.

*5.1.4.4.9. 2-Nitro-4-(pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4-ylamino)phenol (**6j**).* Yield: 68%; yellow powder; mp 261–262 °C; IR (KBr) ν_{max} (cm^{-1}): 3205, 1604, 1523, 1505, 1485, 1447, 1359, 1244, 1226, 1154, 1133, 1077, 1050, 835, 801, 763, 752; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.99 (s, 1H, O*H*), 10.11 (s, 1H, N*H*), 9.01 (d, 1H, $J = 2$ Hz, H-7), 8.91 (d, 1H, $J = 2$ Hz, H-8), 8.85 (s, 1H, H-2), 8.45 (d, 1H, $J = 2$ Hz, H-ar), 8.00 (d, 1H, $J = 8$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.4, 155.3, 155.2, 152.3, 148.9,

145.4, 143.5, 143.3, 135.7, 130.2, 130.0, 119.3, 118.3, 116.7; HRMS calcd for $C_{14}H_9N_6O_3S$ $[M + H]^+$ 341.0457 found 341.0456.

5.2. In vitro kinase preparation and assays [23]

5.2.1. Buffers

Buffer A: $MgCl_2$ (10 mM), 1 mM ethylene glycol-bis(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), 1 mM dithiothreitol (DTT), 25 mM Tris–HCl pH 7.5, 50 μg heparin/mL.

Buffer B: β-Glycerophosphate (60 mM), 30 mM p-nitrophenylphosphate, 25 mM 3-(*N*-morpholino)propanesulfonic acid (Mops) (pH 7.2), 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 0.1 mM sodium vanadate.

5.2.2. Kinase preparations and assays

Kinase activities were assayed in buffer A or B, at 30 °C, at a final adenosine triphosphate (ATP) concentration of 15 μM. Blank values were subtracted and activities expressed in % of the maximal activity, i.e., in the absence of inhibitors. Controls were performed with appropriate dilutions of dimethylsulfoxide (DMSO). The GSK-3, CK1, DYRK1A and CLK1 peptide substrates were obtained from Proteogenix (Oberhausbergen, France).

5.2.2.1. CDK5/p25. (Human, recombinant) was prepared as previously described [24]. Its kinase activity was assayed in buffer A, with 1 mg of histone H1/mL, in the presence of 15 μM [γ-^{33}P] ATP (3000 Ci/mmol; 10 mCi/mL) in a final volume of 30 μL. After 30 min incubation at 30 °C, supernatant were spotted onto Whatman P81 phosphocellulose paper, and later, the filters were washed eight times in a solution of 10 mL phosphoric acid/L of water. The wet filters were counted in the presence of 1 mL ACS (Amersham) scintillation fluid.

5.2.2.2. GSK-3α/β. (Porcine brain, native) was assayed, as described for CDK5/p25 but in buffer A and using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQpSEDEEE) (pS stands for phosphorylated serine) [25].

5.2.2.3. CK1δ/ε. (Porcine brain, native) was assayed as described for CDK5/p25 but using the CK1-specific peptide substrate RRKHAAIGpSAYSITA [26].

5.2.2.4. DYRK1A. (Rat, recombinant, expressed in *Escherichia coli* as a glutathione transferase (GST) fusion protein) was purified by affinity chromatography on glutathione-agarose and assayed as described for CDK5/p25 using Woodtide (KKISGRLSPIMTEQ) (1.5 μg/assay) as a substrate.

5.2.2.5. CLK1. (Human, recombinant, expressed in *E. coli* as GST fusion protein) was assayed in buffer A (+0.15 mg BSA/ml) with RS peptide (GRSRSRSRSRSR) (1 μg/assay).

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