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Synthesis and biological evaluation of *N*-aryl-7-methoxybenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines and their *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine analogues as dual inhibitors of CLK1 and DYRK1A kinases

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ABSTRACT

Novel *N*-aryl-7-methoxybenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines (**1**) and their *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine analogues (**2**) were designed and prepared for the first time *via* microwave-accelerated multi-step synthesis. Various anilines were condensed with *N*′-(2-cyanaryl)-*N*,*N*-dimethylformimidamide intermediates obtained by reaction of 3-amino-6-methoxybenzofuran-2-carbonitrile (**3**) and 3-amino-6-methoxybenzothiophene-2-carbonitrile (**4**) 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. Compounds (**2a**–**z**) turned out to be particularly promising for the development of new pharmacological dual inhibitors of CLK1 and DYRK1A kinases.

1. Introduction

Harmine [1] is a β-carboline alkaloid identified as potent inhibitor of dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A, IC_{50} = 80 nM *in vitro*), a kinase implicated in Down Syndrome (DS) and Alzheimer's disease (AD) [2]. Other members of the DYRK family are also inhibited to a lesser extent (DYRK2 IC_{50} = 900 nM and DYRK3 IC_{50} = 800 nM). These eukaryotic kinases belong to a larger family known as the CMGC group of proline/arginine directed serine/threonine kinases. Cyclin-dependent kinases (CDKs), glycogen synthase kinases (GSKs), and CDC2-like kinases (CLKs) are also members of the CMGC group. These enzymes are involved in many major diseases, including cancer and neurodegenerative disorders [3].

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 [4,5]. Inspired by the 6,5,6-fused tricyclic skeleton of harmine molecule, we envisioned to prepare various *N*-aryl-7-methoxybenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines (**1**) and their *N*-arylbenzo[*b*]thieno [3,2-*d*]pyrimidine analogues (**2**), themselves substituted in position 4 of the pyrimidine ring by an aromatic amine (Scheme 1). A literature survey revealed that the synthesis and biological evaluation of such derivatives had not been previously described.

This paper describes the development of a simple and reliable method that allows the preparation of a library of new benzofuro- and benzothieno[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 microwave irradiation in a combinatorial chemistry approach. The evaluation of kinase inhibition of the products obtained was performed on Ser/Thr kinases

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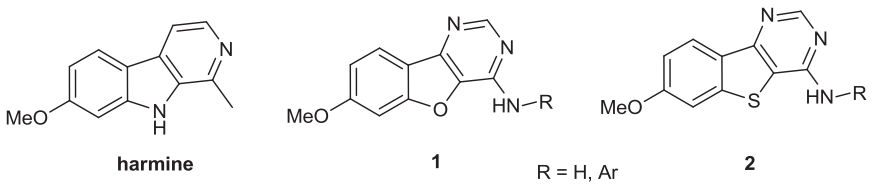


Scheme 1. Structural analogy between harmine and the target compounds **1** and **2**.

(CDK5, GSK3, DYRK1A, CLK1 and CK1) chosen for their strong implication in various regulation processes, especially AD [3].

2. Chemistry

The target molecules we studied were 7-methoxylbenzo[*b*]furo[3,2-*d*]pyrimidines (**1**) and their benzo[*b*]thieno[3,2-*d*]pyrimidines analogues (**2**) substituted in position 4 of the pyrimidine ring by a primary or an aromatic amine. The retrosynthetic pathway depicted in Scheme 2 started from 3-amino-6-methoxybenzofuran-2-carbonitrile (**3**) and 3-amino-6-methoxybenzothiophene-2-carbonitrile (**4**) which could be transformed into their corresponding *N*,*N*-dimethylformamidine derivatives **5** and **6**. The next step consisted in nucleophilic attack of the intermediate amidines by ammonia or aromatic amines to give the expected tricyclic compounds **1**–**2** *via* a thermal-sensitive Dimroth rearrangement. This fast and convenient procedure was recently explored for a general access to pyrimidine-condensed heterocyclic compounds which can be useful for the design of novel bioactive compounds [6].

2.1. Synthesis of the starting 3-amino-6-methoxybenzofuran-2-carbonitrile (*3*) and 3-amino-6-methoxybenzo[b]thiophene-2-carbonitrile (*4*)

The 6-methoxybenzofurane derivative (**3**) was obtained in two steps using a methodology previously described for the synthesis of 3-aminofuro[3,2-*b*]pyridine-2-carbonitriles [7]. Subsequently, 2,4-dimethoxybenzonitrile was treated with 1-decanethiol at 110 °C in dimethylformamide to give the 2-hydroxy-4-methoxybenzonitrile intermediate (**7**) in a very good yield of 96% [8]. O-Alkylation of phenol derivative (**7**) and ring closure of the corresponding cyanomethylether intermediate (not isolated) were performed in the presence of potassium carbonate (K_2CO_3) as base. The target product (**3**) was obtained in good yield (79%) (Scheme 3).

Synthesis of 3-amino-6-methoxybenzo[*b*]thiophene-2-carbonitrile (**4**) started by treatment of commercially available 4-bromo-3-nitroanisole with copper (I) cyanide (CuCN) in anhydrous dimethylformamide (DMF) [9]. Treatment of the resulting 4-methoxy-2-nitrobenzonitrile (**8**) with 3-mercaptopropionitrile [10] in the presence of aqueous potassium hydroxide in DMF at 0 °C was followed by dropwise addition of bromoacetonitrile. Ring closure of the cyanomethylthioether intermediate (not isolated) gave the expected product **4** in moderate yield (55%) (Scheme 4) [11].

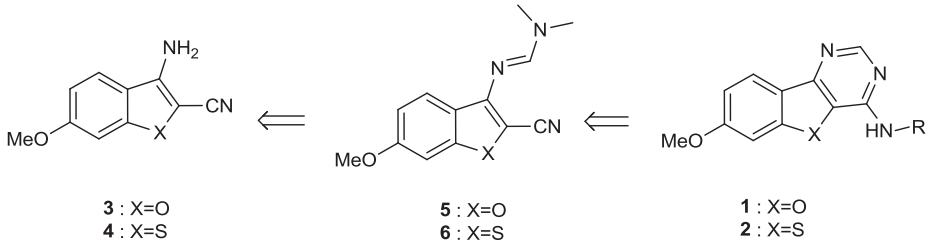
2.2. Synthesis of N,N-dimethylformimidamides (*5* and *6*)

With starting enaminonitriles **3** and **4** now available, the second step in the synthesis consisted in formation of *N*,*N*-dimethylformimidamide intermediates **5** and **6**. It was realized by the reaction of **3** and **4** with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA). After various attempts to optimize the reaction parameters (time, temperature and applied microwave power), the expected products **5** and **6** were obtained with excellent yields (99%) after 30 min irradiation at 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 [12]. Open vessel microwave experiments have some advantages, such as the possibility of easier scale-up and of using standard laboratory glassware. 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.

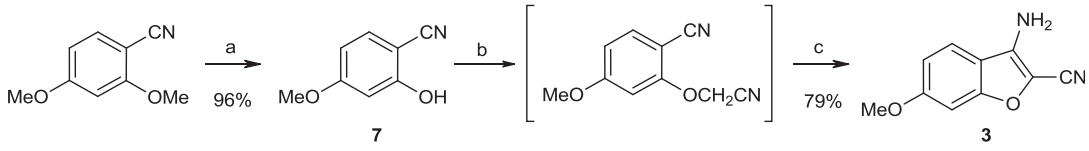
2.3. Synthesis of N-aryl-7-methoxybenzo[b]furo[3,2-d]pyrimidin-4-amines (*1* series) and N-aryl-7-methoxybenzo[b]thieno[3,2-d] pyrimidin-4-amine derivatives (*2* series)

Before introducing a substituted amino group on the skeleton of the targeted products, synthesis of the unsubstituted 4-amino derivatives (**1a** and **2a**) was realized in good yields (84–85%) by strong heating (170 °C for 30 min) of intermediate formimidamides **3** and **4** in the presence of formamide which played the dual role of solvent and reactant [13]. 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) [14] were combined in a comfortable process constituting a safe alternative to the extreme conditions usually described in the literature (Scheme 5) [15].

The synthesis of the 4-anilino-substituted derivatives (**1b**–**z** and **2b**–**z**) consisted of heating the formimidamide derivatives **3** and **4** with various anilines in the presence of acetic acid which served as a relatively good solvent for heating under microwaves



Scheme 2. Retrosynthetic pathway to generate benzofuro[3,2-*d*]pyrimidine (**1**) and benzothieno[3,2-*d*]pyrimidine (**2**) derivatives.



Scheme 3. Synthesis of 3-amino-6-methoxybenzofuran-2-carbonitrile (**3**). Reagents and conditions: a) 1-decanethiol, *t*-BuOK, DMF, 110 °C, 1 h; b) $BrCH_2CN$, K_2CO_3/DMF, r.t., 1.5 h; c) 80 °C, 16 h.

(tan δ = 0.174 at 2.45 GHz [14]) and also initiated 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", was not added to the reaction time described in Table 1). The evolution of all reactions was monitored by thin-layer chromatography and the reaction times given corresponded to a complete disappearance of the starting material (Table 1). A list of anilines was established, based on the Topliss schemes [16], in the hope to maximize the chances of synthesizing the most potent compounds as early as possible. Twenty-five derivatives of each family (**1b**–**z** and **2b**–**z**) were rapidly obtained *via* Dimroth translocation of the endocyclic and exocyclic nitrogen atoms present in the pyrimidine moiety [6]. This process led to the thermodynamically stable 4-anilino-substituted isomers of the final products (Scheme 5).

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 [17–19]. All compounds were first tested at a final concentration of 10 μM. Compounds showing less than 50% inhibition were considered as inactive (IC_{50} > 10 μM). Compounds displaying more than 50% inhibition at 10 μM were next tested over a wide range of concentrations (usually 0.01–10 μM), and IC_{50} values were determined from the dose–response curves (Sigma-Plot). Harmine (entry 27 in Tables 2 and 3) is a β-carboline alkaloid known to be a potent inhibitor of DYRK1A [1,20]. It was also tested as positive control and its IC_{50} value was compared with those obtained for the compounds under study.

Results given in Tables 2 and 3 demonstrated that none of the tricyclic derivatives prepared in this work showed any affinity against CDK5/p25 and GSK3. On a general aspect, the benzofuro[3,2-*d*]pyrimidine and benzothieno[3,2-*d*]pyrimidine derivatives (**1b**–**z** and **2b**–**z**) were completely inactive on the casein kinase 1 (CK1), except for compounds **1a** (entry 1 in Table 2) and **2u** (entry 21 in Table 3) for which micromolar IC_{50} values (1.9 and 3.9 μM, respectively) were observed. On this point of view, **1a** showed a similar activity on CK1 than harmine (1.5 μM).

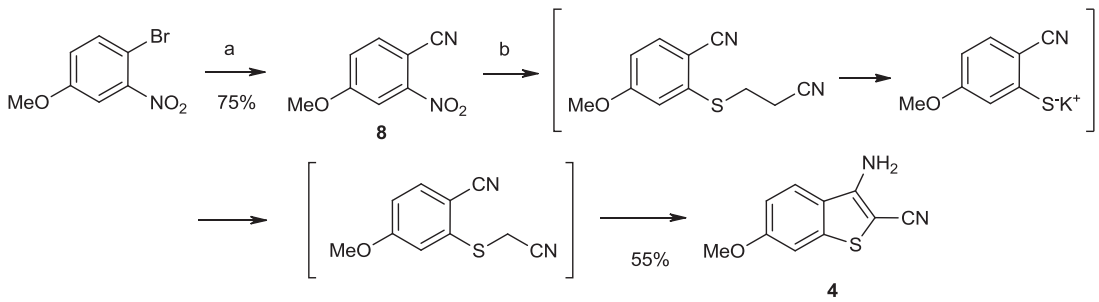
Note that among the two families of tested molecules, four benzofuro[3,2-*d*]pyrimidine derivatives (**1a**, **1e**, **1i** and **1o**) were judged relatively active (in the micromolar range) against two kinases (CLK1 and DYRK1A) or one kinase (DYRK1A for **1r**). Compound **1a** (entry 1 in Table 2) was the only product able to inhibit three kinases in the micromolar (CK1 and DYRK1A) or submicromolar range (CLK1). This result suggests that *N*-arylation of the amine in position 4 of the pyrimidine part of the molecules may provide inhibitory activity towards CLK1 and DYRK1A.

The most promising results were obtained with products from the **2a**–**z** series, which showed a rather good inhibition of both CLK1 and DYRK1A kinases with micromolar or submicromolar IC_{50} values for most of them. Among these compounds, **2j** and **2z** can be considered as the most active products with submicromolar IC_{50} values against the two kinases (entries 10 and 26 in Table 3). The values obtained for **2j** are the most promising towards DYRK1A (500 nM) and CLK1 (680 nM). On an overall aspect, IC_{50} values of the **2a**–**z** series against DYRK1A and CLK1 ranged from 6.8 to 0.50 μM. Therefore, these compounds can be considered as much less active than harmine (0.029 μM and 0.026 μM for DYRK1A and CLK1, respectively).

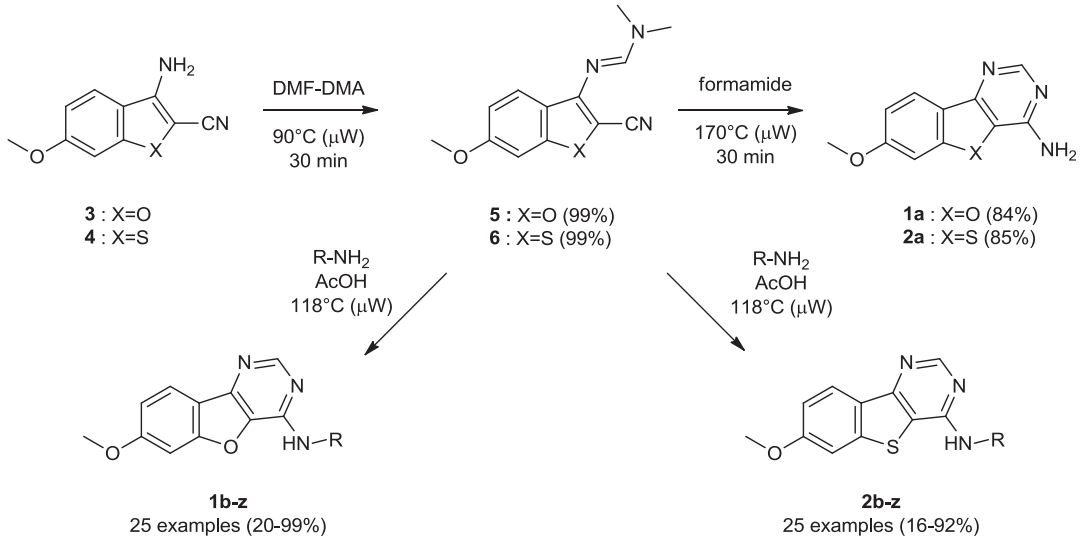
Concerning compounds **2a**–**z** (Table 3) the main part of their activity was linked to DYRK1A with fourteen products (**2d**–**g**, **2j**, **2o**–**r**, **2u**–**x** and **2z**) which exhibited an inhibitory activity in the micromolar and submicromolar ranges (8.1μM < IC_{50} < 0.5 μM). For nine of these fourteen molecules, affinity for kinases was also sometimes centred on CLK1 (products **2f**, **2g**, **2j**, **2o**, **2p**, **2u**, **2v**, **2x** and **2z**: 6.8μM < IC_{50} < 0.68 μM).

Comparison of DYRK1A inhibition of the most active compounds of the two series (**1a**, **1e**, **1i**, **1o** and **1r** in Table 2 and **2f**–**g**, **2j**, **2o**–**r**, **2u**–**x** and **2z** in Table 2) with their analogues (*e.g.* **1e**/**2e**, **1i**/**2i**, etc.) showed that in most cases, benzothieno[3,2-*d*]pyrimidine derivatives (**2**) were more active than their benzofuro[3,2-*d*]pyrimidine congeners except in the case of **1e**/**2e** for which the oxygenated partner (**1e**, 0.88 μM DYRK1A) was more active than its sulfur containing analogue (**2e**, 7.1 μM DYRK1A).

All these results demonstrated that it is difficult to define any role for the various substituents of the amine located at position 4 of the pyridine ring. However, it is interesting to note that the presence of two substituents on the aromatic rings (**2f**, **2g**, **2j**, **2r**, **2u** and **2v** in Table 2) resulted in micromolar and submicromolar affinity for DYRK1A and also for CLK1 in a large number of the



Scheme 4. Synthesis of benzothiophene analogue (**4**). Reagents and conditions: a) CuCN, DMF 160 °C, 2 h; b) $HSCH_2CH_2CN$, KOH/DMF, 0 °C, 15 min then $BrCH_2CN$, 0 °C, 2 h.



Scheme 5. General synthesis of benzofuro[3,2-*d*]pyrimidines (**1a**–**z**) and benzothieno[3,2-*d*]pyrimidine (**2a**–**z**) derivatives.

active products, although the observed affinities were lower for CLK1. On the contrary, the presence of one substituent on the *N*-aryl moiety abolished the inhibitory activity for DYRK1A and all the other kinases tested.

In view of the results of this study, we consider that the tricyclic *N*-aryl-7-methoxybenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine analogues (**2**) constitute a promising source of inspiration for the synthesis of novel bioactive molecules. Synthetic transformations will be envisioned and factors governing their dual activity towards CKL1 and DYRK1A will be further investigated. We are pursuing the SAR study and based on the results and already established co-crystal structures of DYRK1A and CLKs [21], we should be able to establish a precise molecular model of the interaction of our inhibitors with their targets.

4. Conclusion

The synthesis of a library of novel *N*-aryl-7-methoxybenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines (**1**) and their *N*-aryl-7-methoxybenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine analogues (**2**) was realized under microwaves *via* a Dimroth rearrangement. Good control of the reaction parameters allowed efficient heating of the reaction mixture, resulting in short reaction times and good yields. The inhibitory potency of the final products against five kinases was evaluated. Our study demonstrates that *N*-aryl-7-methoxybenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine derivatives are particularly promising for the development of new dual inhibitors of CLK1 and DYRK1A kinases. The most effective compounds towards these two kinase families are the benzothieno[3,2-*d*]pyrimidines **2j** and **2z** which showed interesting submicromolar inhibition and selectivity towards CLK1 and DYRK1A over the other tested kinases. These results are the starting point of a larger program within our group, in the hope to lead to the discovery of novel kinase inhibitors with potential therapeutic application in Alzheimers' disease and Down Syndrome.

5. Experimental section

5.1. Chemistry

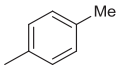
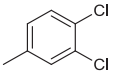
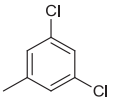
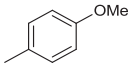
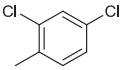
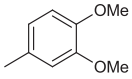
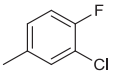
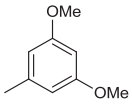
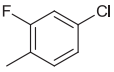
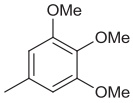
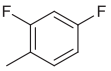
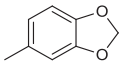
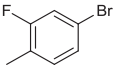
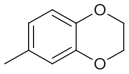
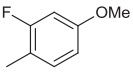
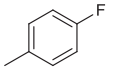
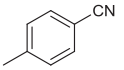
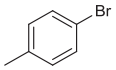
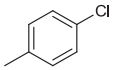
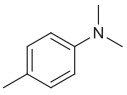
Melting points of powder compounds were measured on an STUART-Advanced apparatus. IR spectra were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker DXP 300 spectrometer at 300, 75 MHz, respectively and a Bruker AVANCE 400 MHz high resolution 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 1^{er} 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 route for the preparation of 3-amino-6-methoxybenzofuran-2-carbonitrile (**3**)

*5.1.1.1. 2-Hydroxy-4-methoxybenzonitrile (**7**).* A mixture of 1-decanethiol (6.41 g, 36.77 mmol) in *N*,*N*-dimethylformamide (50 mL) was cooled to 5–10 °C under nitrogen atmosphere. When the internal temperature was below 10 °C, solid KO*t*Bu (5.16 g, 45.96 mmol) was added in one portion after 10 min, the reaction mass was allowed to warm to 20–25 °C. After 15 min, 2,4-dimethoxybenzonitrile (5.00 g, 30.64 mmol) was added and the reaction was heated to 110 °C for 60 min. TLC analysis (petroleum ether/ethyl acetate 1:1 as mobile phase) showed complete reaction. The mixture was allowed to cool to 20–25 °C and then poured into ice water (150 mL). To the flask was added 1 N HCl dropwise to

Table 1
Synthesis of benzofuro[3,2-*d*]pyrimidine and benzothieno[3,2-*d*]pyrimidine derivatives (**1b**–**z** and **2b**–**z**).[a]

Compound		1		2				1		2	
R		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)			Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
	**b**	20	62	45	67		**o**	120	56	135	68
	**c**	10	99	25	80		**p**	60	64	90	69
	**d**	30	60	45	64		**q**	60	70	120	50
	**e**	45	99	60	55		**r**	60	99	180	77
	**f**	80	99	135	92		**s**	75	73	120	66
	**g**	80	72	135	83		**t**	40	78	90	73
	**h**	80	74	90	84		**u**	60	77	180	73
	**i**	80	65	135	84		**v**	150	67	240	75
	**j**	80	63	135	74		**w**	15	80	25	72
	**k**	90	72	90	73		**x**	90	71	150	67
	**l**	40	61	60	54		**y**	90	55	120	62
	**m**	40	65	30	59		**z**	90	20[c]	215	16[c]
	**n**	40	71	60	61						

[a] Reaction was performed under microwaves (μW) at 400 W, on a 0.5 mmol scale from **5** or **6** with 1 equiv of aniline (MultiSYNTH™ from Milestone S.r.l. Italy).
[b] Yield of isolated product.
[c] Temperature of reaction was increased to 140 °C.

bring the pH to 1 followed by the addition of water (150 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were washed with (2 × 100 mL) saturated brine and dried over Na_2SO_4. The solvent was removed under *vacuum* to give a free flowing solid. To this solid was added 100 mL heptane and stirred for 60 min. The solid obtained was filtered off and washed with 50 mL heptane to give 2-hydroxy-4-methoxybenzonitrile (**7**) as a grey solid (4.39 g, 96%); mp 174–175 °C (lit. [8]: 169–172 °C); IR (KBr) ν_{max} (cm^{-1}): 3213 (OH), 2226 (CN), 1601, 1595, 1514, 1465, 1449, 1435, 1379, 1323, 1277, 1211, 1169, 1103, 1026, 829, 800; ^1H NMR (400 MHz, DMSO-d_6): δ 11.08 (br s, 1H, OH), 7.51 (d, 1H, $J = 8.4$ Hz, H-6), 6.56–6.47 (m, 2H, H-3, H-5), 3.77 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0, 161.9, 134.4, 117.4, 106.7, 101.0, 91.2, 55.5; HRMS *m*/*z* calcd for $C_8H_7NO_2$ 149.0477 [M] found 149.0474.

*5.1.1.2. 3-Amino-6-methoxybenzofuran-2-carbonitrile (**3**).* To a suspension of 2-hydroxy-4-methoxybenzonitrile (3.50 g, 23.46 mmol) and K_2CO_3 (8.11 g, 58.66 mmol) in DMF (80 mL) bromoacetonitrile (1.80 mL, 25.81 mmol) was added at room temperature and the

Table 2
Kinase activity of benzofuro[3,2-*d*]pyrimidine derivatives (**1a**–**z**).[a]

Entry	Compound	CDK5	CK1	CLK1	DYRK1A	GSK3
1	**1a**	>10	**1.9**	**0.41**	**1.1**	>10
2	**1b**	>10	>10	>10	>10	>10
3	**1c**	>10	>10	>10	>10	>10
4	**1d**	>10	>10	>10	>10	>10
5	**1e**	>10	>10	**1.5**	**0.88**	>10
6	**1f**	>10	>10	>10	>10	>10
7	**1g**	>10	>10	>10	>10	>10
8	**1h**	>10	>10	>10	>10	>10
9	**1i**	>10	>10	**2**	**2.8**	>10
10	**1j**	>10	>10	>10	>10	>10
11	**1k**	>10	>10	>10	>10	>10
12	**1l**	>10	>10	>10	>10	>10
13	**1m**	>10	>10	>10	>10	>10
14	**1n**	>10	>10	>10	>10	>10
15	**1o**	>10	>10	**4.2**	**3.2**	>10
16	**1p**	>10	>10	>10	>10	>10
17	**1q**	>10	>10	>10	>10	>10
18	**1r**	>10	>10	>10	**3.1**	>10
19	**1s**	>10	>10	>10	>10	>10
20	**1t**	>10	>10	>10	>10	>10
21	**1u**	>10	>10	>10	>10	>10
22	**1v**	>10	>10	>10	>10	>10
23	**1w**	>10	>10	>10	>10	>10
24	**1x**	>10	>10	>10	>10	>10
25	**1y**	>10	>10	>10	>10	>10
26	**1z**	>10	>10	>10	>10	>10
27	Harmine	>10	**1.5**	**0.026**	**0.029**	>10

Values in bold represents the most significant data in the table.
[a] IC_{50} values are reported in μM.

mixture was stirred at room temperature for 1.5 h. The reaction mixture was then heated at 80 °C for 16 h. The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with brine, then dried, and evaporated to give a pale brown powder which was purified with silica gel column chromatography using diethylether/petroleum ether (5:5, v/v). The desired product (**3**) was isolated as a white powder (3.49 g, 79%); mp 173–174 °C; IR (KBr) ν_{max} (cm^{-1}): 3447 (NH_2), 3358 (NH_2), 3223, 2191 (CN), 1643, 1620, 1605, 1570, 1500, 1448, 1435, 1406, 1285, 1200, 1148, 1103, 1014, 945, 813; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, 1H, J = 8.8 Hz, H-4), 7.09 (d, 1H, J = 1.6 Hz, H-7), 6.95 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-5), 6.62 (br s, 2H, NH_2), 3.85 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.5, 155.9, 143.0, 121.8, 115.0, 114.1, 112.6, 106.4, 95.9, 55.9; MS (ESI) m/z (%): 189.1 (100) $[M + H]^+$. Anal. calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 64.05; H, 4.30; N, 14.94.

Table 3
Kinase activity of benzothieno[3,2-*d*]pyrimidine derivatives (**2a**–**z**).[a]

Entry	Compound	CDK5	CK1	CLK1	DYRK1A	GSK3
1	**2a**	>10	>10	>10	>10	>10
2	**2b**	>10	>10	>10	>10	>10
3	**2c**	>10	>10	>10	>10	>10
4	**2d**	>10	>10	>10	**6.1**	>10
5	**2e**	>10	>10	>10	**7.1**	>10
6	**2f**	>10	>10	**2.8**	**0.93**	>10
7	**2g**	>10	>10	**5.1**	**3.9**	>10
8	**2h**	>10	>10	>10	>10	>10
9	**2i**	>10	>10	>10	>10	>10
10	**2j**	>10	>10	**0.68**	**0.5**	>10
11	**2k**	>10	>10	>10	>10	>10
12	**2l**	>10	>10	>10	>10	>10
13	**2m**	>10	>10	>10	>10	>10
14	**2n**	>10	>10	>10	>10	>10
15	**2o**	>10	>10	**3.1**	**0.61**	>10
16	**2p**	>10	>10	**6.1**	**2**	>10
17	**2q**	>10	>10	>10	**8.1**	>10
18	**2r**	>10	>10	>10	**1.6**	>10
19	**2s**	>10	>10	>10	>10	>10
20	**2t**	>10	>10	>10	>10	>10
21	**2u**	>10	**3.9**	**1.6**	**0.93**	>10
22	**2v**	>10	>10	**2.3**	**0.71**	>10
23	**2w**	>10	>10	>10	**0.71**	>10
24	**2x**	>10	>10	**6.8**	**2.6**	>10
25	**2y**	>10	>10	>10	>10	>10
26	**2z**	>10	>10	**0.79**	**0.66**	>10
27	Harmine	>10	**1.5**	**0.026**	**0.029**	>10

Values in bold represents the most significant data in the table.
[a] IC_{50} values are reported in μM.

*5.1.2. Synthetic route for the preparation of 3-amino-6-methoxybenzothiophene-2-carbonitrile (**4**)*

*5.1.2.1. 4-Methoxy-2-nitrobenzonitrile (**8**).* 3-Nitro-4-bromoanisole (5.00 g, 21.54 mmol) was dissolved in anhydrous DMF and CuCN (2.89 g, 32.32 mmol) was added. The mixture was heated at 160 °C for 2 h. After cooling it was poured into crushed ice and a precipitate was formed, which was filtered and dried under vacuum. The greenish solid obtained was dissolved in $CHCl_3$ and the solution was filtered. The solvent removal of the filtrate gave a yellow solid (2.88 g, 75%); mp 129–130 °C (lit. [9]: 129–131 °C); IR (KBr) ν_{max} (cm^{-1}): 3103, 2230 (CN), 1616, 1529, 1500, 1443, 1348, 1311, 1285, 1248, 1188, 1067, 1020, 899, 840, 808; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.79 (m, 2H, H-3 and H-6), 7.28 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.0 Hz, H-5), 3.99 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 150.1, 136.6, 119.9, 115.2, 111.1, 99.4, 56.5; MS (ESI) m/z (%): 179.1 (100) $[M + H]^+$. Anal. calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.11; H, 3.40; N, 15.75.

*5.1.2.2. 3-Amino-6-methoxybenzo[b]thiophene-2-carbonitrile (**4**).* A solution of potassium hydroxide (2.36 g, 42.10 mmol) in water (8 mL) was added dropwise to a stirred and cold solution (ice bath) containing 4-methoxy-2-nitrobenzonitrile (2.50 g, 14.03 mmol) and 3-mercaptopropionitrile (1.47 g, 16.84 mmol) in DMF (30 mL). The cold mixture was stirred for 15 min and bromoacetonitrile (1.47 mL, 21.05 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 dichloromethane/petroleum ether (5:5, v/v). The desired product (**4**) was isolated as a white powder (1.58 g, 55%); mp 145–148 °C; IR (KBr) ν_{max} (cm^{-1}): 3445 (NH_2), 3333 (NH_2), 3233, 2187 (CN), 1632, 1599, 1572, 1528, 1487, 1427, 1415, 1385, 1340, 1273, 1246, 1200, 1182, 1049, 1018, 891, 837, 823, 812; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, 1H, J = 8.8 Hz, H-4), 7.48 (d, 1H, J = 1.6 Hz, H-7), 7.09–7.06 (m, 3H, H-5 and NH_2), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 152.4, 141.2, 124.1, 123.9, 116.7, 114.7, 105.7, 70.5, 55.8; MS (ESI) m/z (%): 205.1 (100) $[M + H]^+$. Anal. calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72. Found: C, 59.03; H, 3.97; N, 13.76.

*5.1.3. General procedure for the synthesis of N,N-dimethylformimidamides derivatives (**5** and **6**)*

A mixture of starting cyanoenamine (1.0 g) and *N*,*N*-dimethylformamide dimethylacetal (5 mL) was irradiated at 90 °C (800 W). On completion, the solution was cooled to room temperature and the mixture was extracted with ethyl acetate. The organic layers were washed with cold water, dried over Na_2SO_4, filtered and evaporated in *vacuo*. A purification by column chromatography over silica gel using dichloromethane/petroleum ether (5:5, v/v) as the eluent gave the desired compounds **5** and **6**.

*5.1.3.1. (E)-N′-(2-Cyano-6-methoxybenzofuran-3-yl)-N,N-dimethylformimidamide (**5**).* White powder (1.21 g; 99%) obtained from 3-amino-6-methoxybenzofuran-2-carbonitrile (**3**) after 30 min of irradiation; mp 104–105 °C; IR (KBr) ν_{max} (cm^{-1}): 2206 (CN), 1608, 1584, 1564, 1553, 1427, 1372, 1278, 1255, 1195, 1152, 1105, 1091, 1063, 1026, 951, 939, 828, 816; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.27

(s, 1H, NCHN), 7.73 (d, 1H, $J = 8.8$ Hz, H-4), 7.18 (d, 1H, $J = 2.1$ Hz, H-7), 6.95 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.8$ Hz, H-5), 3.83 (s, 3H, OCH_3), 3.11 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 156.3, 156.1, 146.1, 122.1, 115.5, 114.3, 113.9, 113.4, 95.9, 55.7, 33.9 (2C); HRMS calcd for $C_{13}H_{14}N_3O_2$ $[M + H]^+$ 244.1086 found 244.1081.

*5.1.3.2. (E)-N′-(2-Cyano-6-methoxybenzothiophen-3-yl)-N,N-dimethylformimidamide (**6**).* White powder (1.26 g; 99%) obtained from 3-amino-5-methoxybenzo[*b*]thiophene-2-carbonitrile (**4**) after 30 min of irradiation; mp 116–117 °C; IR (KBr) ν_{max} (cm^{-1}): 2191 (CN), 1621, 1597, 1489, 1472, 1423, 1412, 1396, 1374, 1257, 1242, 1113, 1058, 1022, 989, 879, 838, 823; ^1H NMR (300 MHz, DMSO-d_6): δ 8.14 (s, 1H, NCHN), 7.70 (d, 1H, $J = 8.8$ Hz, H-4), 7.53 (d, 1H, $J = 1.9$ Hz, H-7), 7.05 (dd, 1H, $J_1 = 1.9$ Hz, $J_2 = 8.8$ Hz, H-5), 3.84 (s, 3H, OCH_3), 3.11 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.2, 157.0, 155.9, 140.7, 127.7, 124.4, 116.6, 115.3, 105.4, 83.2, 55.7, 34.1 (2C); HRMS calcd for $C_{13}H_{14}N_3OS$ $[M + H]^+$ 260.0858 found 260.0854.

*5.1.4. General procedure for the synthesis of furo or thieno[3,2-d] pyrimidin-4-amine derivatives (**1a** and **2a**)*

A mixture of formamide (2 mL) and *N,N*-dimethylformimidamide derivatives (**5** or **6**) (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 to 0:100, v/v) as the eluent to give the desired compounds (**1a** and **2a**).

*5.1.4.1. 7-Methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1a**).* White powder (0.072 g, 84%); obtained from (*E*)-*N*′-(2-cyano-6-methoxybenzofuran-3-yl)-*N,N*-dimethylformimidamide (**5**) after 30 min of irradiation at 170 °C; mp 281–282 °C; IR (KBr) ν_{max} (cm^{-1}): 3119, 1655, 1629, 1606, 1495, 1402, 1293, 1270, 1183, 1135, 1095, 1045, 962, 930, 822, 815, 780; ^1H NMR (300 MHz, DMSO-d_6): δ 8.35 (s, 1H, H-2), 7.93 (d, 1H, $J = 8.8$ Hz, H-9), 7.43 (br s, 2H, NH_2), 7.29 (d, 1H, $J = 1.6$ Hz, H-6), 7.07 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.6, 157.3, 153.4, 149.6, 145.7, 133.9, 121.7, 115.2, 112.7, 96.8, 55.9; HRMS calcd for $C_{11}H_{10}N_3O_2$ $[M + H]^+$ 216.0773 found 216.0765.

*5.1.4.2. 7-Methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2a**).* White powder (0.074 g, 85%); obtained from (*E*)-*N*′-(2-cyano-6-methoxybenzothiophen-3-yl)-*N,N*-dimethylformimidamide (**6**) after 30 min of irradiation at 170 °C; mp 277–278 °C; IR (KBr) ν_{max} (cm^{-1}): 3064, 1564, 1518, 1493, 1476, 1457, 1443, 1433, 1287, 1263, 1232, 1031, 880, 834, 823, 781, 730; ^1H NMR (300 MHz, DMSO-d_6): δ 8.47 (s, 1H, H-2), 8.14 (d, 1H, $J = 8.8$ Hz, H-9), 7.72 (d, 1H, $J = 1.6$ Hz, H-6), 7.45 (br s, 2H, NH_2), 7.15 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 3.89 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.7, 158.2, 155.5, 115.1, 141.6, 127.2, 123.8, 114.8, 111.8, 106.2, 55.7; HRMS calcd for $C_{11}H_{10}N_3OS$ $[M + H]^+$ 232.0545 found 232.0556.

*5.1.5. General procedures for the synthesis of furo or thieno[3,2-d] pyrimidine derivatives (**1b–z** and **2b–z**)*

*5.1.5.1. Synthesis of N-aryl-7-methoxybenzofuro[3,2-d]pyrimidin-4-amines (**1b–z**).* A mixture of (*E*)-*N*′-(2-cyano-5-methoxybenzofuran-3-yl)-*N,N*-dimethylformimidamide (**5**) (0.1 g, 0.38 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 to 0:100, v/v) as the eluent to give the desired compounds (**1b–z**).

*5.1.5.1.1. 7-Methoxy-N-phenylbenzofuro[3,2-d]pyrimidin-4-amine (**1b**).* Yield: 62%; white powder; mp 222–223 °C; IR (KBr) ν_{max} (cm^{-1}): 1620, 1592, 1497, 1472, 1448, 1433, 1301, 1284, 1241, 1145, 1139, 1085, 1030, 823; ^1H NMR (300 MHz, DMSO-d_6): δ 10.04 (s, 1H, NH), 8.60 (s, 1H, H-2), 8.03 (d, 1H, $J = 8.8$ Hz, H-9), 7.90 (dd, 2H, $J_1 = 1.0$ Hz, $J_2 = 8.4$ Hz, H-ar), 7.38 (td, 2H, $J_1 = 1.0$ Hz, $J_2 = 8.4$ Hz, H-ar), 7.35 (d, 1H, $J = 1.6$ Hz, H-6), 7.16 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 7.07 (td, 1H, $J_1 = 1.0$ Hz, $J_2 = 8.4$ Hz, H-ar), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.0, 157.5, 152.8, 146.3, 145.8, 139.3, 134.3, 128.5 (2C), 122.9, 121.9, 120.7 (2C), 115.1, 113.0, 96.9, 56.0; HRMS calcd for $C_{17}H_{14}N_3O_2$ $[M + H]^+$ 292.1086 found 292.1072.

*5.1.5.1.2. 7-Methoxy-N-(p-tolyl)benzofuro[3,2-d]pyrimidin-4-amine (**1c**).* Yield: 99%; white powder; mp 206–207 °C; IR (KBr) ν_{max} (cm^{-1}): 1634, 1623, 1615, 1586, 1509, 1495, 1478, 1436, 1405, 1333, 1306, 1229, 1138, 1082, 1015, 967, 820; ^1H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1H, NH), 8.56 (s, 1H, H-2), 8.00 (d, 1H, $J = 8.8$ Hz, H-9), 7.76 (d, 2H, $J = 8.4$ Hz, H-ar), 7.32 (d, 1H, $J = 1.6$ Hz, H-6), 7.16 (d, 2H, $J = 8.4$ Hz, H-ar), 7.12 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 3.92 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.9, 157.5, 152.9, 145.8, 136.7, 134.4, 131.8, 131.1, 128.9 (2C), 121.9, 120.8 (2C), 115.1, 112.9, 96.9, 56.0, 20.5; HRMS calcd for $C_{18}H_{16}N_3O_2$ $[M + H]^+$ 306.1243 found 306.1245.

*5.1.5.1.3. 7-Methoxy-N-(m-tolyl)benzofuro[3,2-d]pyrimidin-4-amine (**1d**).* Yield: 60%; white powder; mp 200–201 °C; IR (KBr) ν_{max} (cm^{-1}): 1620, 1596, 1469, 1455, 1433, 1332, 1299, 1281, 1268, 1238, 1136, 1020, 825; ^1H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1H, NH), 8.59 (s, 1H, H-2), 8.02 (d, 1H, $J = 8.8$ Hz, H-9), 7.77 (s, 1H, H-ar), 7.70 (d, 1H, $J = 8.4$ Hz, H-ar), 7.33 (d, 1H, $J = 1.6$ Hz, H-6), 7.16 (td, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.4$ Hz, H-ar), 7.14 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 6.92 (d, 1H, $J = 8.0$ Hz, H-ar), 3.93 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.0, 157.5, 152.9, 146.3, 145.8, 139.2, 137.7, 134.3, 128.4, 123.6, 121.9, 121.2, 118.0, 115.1, 113.0, 96.9, 56.0, 21.3; HRMS calcd for $C_{18}H_{16}N_3O_2$ $[M + H]^+$ 306.1243 found 306.1247.

*5.1.5.1.4. 7-Methoxy-N-(4-methoxyphenyl)benzofuro[3,2-d]pyrimidin-4-amine (**1e**).* Yield: 99%; purple powder; mp 224–225 °C; IR (KBr) ν_{max} (cm^{-1}): 1620, 1591, 1508, 1494, 1474, 1466, 1453, 1441, 1434, 1411, 1397, 1333, 1295, 1264, 1241, 1135, 1086, 968, 819; ^1H NMR (300 MHz, DMSO-d_6): δ 9.87 (s, 1H, NH), 8.53 (s, 1H, H-2), 8.00 (d, 1H, $J = 8.8$ Hz, H-9), 7.74 (d, 2H, $J = 9.0$ Hz, H-ar), 7.31 (d, 1H, $J = 1.6$ Hz, H-6), 7.13 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 6.95 (d, 2H, $J = 9.0$ Hz, H-ar), 3.93 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 157.4, 155.3, 152.9, 146.0, 145.9, 134.2, 132.1, 122.7 (2C), 121.8, 115.1, 113.7 (2C), 112.9, 96.9, 56.0, 55.2; HRMS calcd for $C_{18}H_{16}N_3O_3$ $[M + H]^+$ 322.1192 found 322.1192.

*5.1.5.1.5. 7-Methoxy-N-(3,4-dimethoxyphenyl)benzofuro[3,2-d] pyrimidin-4-amine (**1f**).* Yield: 99%; purple powder; mp 182–183 °C; IR (KBr) ν_{max} (cm^{-1}): 1635, 1621, 1590, 1507, 1466, 1442, 1427, 1402, 1363, 1299, 1256, 1238, 1227, 1199, 1135, 1091, 1024, 987, 839, 805; ^1H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H, NH), 8.55 (s, 1H, H-2), 7.99 (d, 1H, $J = 8.8$ Hz, H-9), 7.53 (d, 1H, $J = 1.7$ Hz, H-ar), 7.43 (dd, 1H, $J_1 = 1.7$ Hz, $J_2 = 8.7$ Hz, H-ar), 7.31 (d, 1H, $J = 1.6$ Hz, H-6), 7.13 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, H-8), 6.95 (d, 1H, $J = 8.7$ Hz, H-ar), 3.93 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 157.4, 152.9, 148.4, 145.9, 144.9, 134.2, 132.6, 121.8 (2C), 115.1, 113.0, 112.9, 111.9, 106.4, 96.8, 55.9, 55.7, 55.4; HRMS calcd for $C_{19}H_{18}N_3O_4$ $[M + H]^+$ 352.1297 found 352.1298.

*5.1.5.1.6. 7-Methoxy-N-(3,5-dimethoxyphenyl)benzofuro[3,2-d] pyrimidin-4-amine (**1g**).* Yield: 72%; grey powder; mp 172–173 °C; IR (KBr) ν_{max} (cm^{-1}): 1598, 1573, 1483, 1451, 1434, 1415, 1248, 1238,

1203, 1191, 1153, 1132, 1090, 1070, 1055, 1026, 944, 827, 821; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.63 (s, 1H, H-2), 8.02 (d, 1H, J = 8.8 Hz, H-8), 7.32 (d, 1H, J = 1.6 Hz, H-6), 7.24 (d, 2H, J = 2.1 Hz, H-ar), 7.14 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-9), 6.25 (t, 1H, J = 2.1 Hz, H-ar), 3.94 (s, 3H, OCH_3), 3.76 (s, 6H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.0, 160.4 (2C), 157.5, 152.8, 146.3, 145.6, 141.0, 134.3, 121.9, 115.0, 113.0, 98.9 (2C), 96.9, 94.5, 56.0, 55.1 (2C); HRMS calcd for $C_{19}H_{18}N_3O_4$ $[M + H]^+$ 352.1297 found 352.1295.

*5.1.5.1.7. 7-Methoxy-N-(3,4,5-trimethoxyphenyl)benzofuro[3,2-d] pyrimidin-4-amine (**1h**).* Yield: 74%; grey powder; mp 203–204 °C; IR (KBr) ν_{max} (cm^{-1}): 1638, 1625, 1592, 1508, 1451, 1430, 1413, 1237, 1125, 1086, 1028, 1009, 998, 830, 819; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.98 (s, 1H, NH), 8.60 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.32 (d, 1H, J = 1.6 Hz, H-6), 7.31 (s, 2H, H-ar), 7.14 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.93 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3), 3.66 (s, 3H; OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.0, 157.5, 152.9, 152.5 (2C), 146.2, 145.7, 135.4, 134.3, 133.3, 121.9, 115.1, 113.0, 98.7 (2C), 96.9, 60.1, 56.0, 55.8 (2C); HRMS calcd for $C_{20}H_{20}N_3O_5$ $[M + H]^+$ 382.1403 found 382.1395.

*5.1.5.1.8. N-(Benzo[d][1,3]dioxol-5-yl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1i**).* Yield: 65%; black powder; mp 233–234 °C; IR (KBr) ν_{max} (cm^{-1}): 1649, 1631, 1608, 1500, 1488, 1475, 1450, 1435, 1329, 1274, 1241, 1192, 1145, 1085, 1036, 1027, 936, 832, 800; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.91 (s, 1H, NH), 8.55 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.54 (d, 1H, J = 2.2 Hz, H-ar), 7.32 (d, 1H, J = 1.6 Hz, H-6), 7.28 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.4 Hz, H-ar), 7.13 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 6.92 (d, 1H, J = 8.4 Hz, H-ar), 6.02 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.9, 157.4, 152.9, 146.9, 146.0, 145.8, 142.9, 134.2, 133.4, 121.9, 115.1, 113.8, 112.9, 107.9, 103.2, 101.0, 96.9, 56.0; HRMS calcd for $C_{18}H_{14}N_3O_4$ $[M + H]^+$ 336.0984 found 336.0978.

*5.1.5.1.9. N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1j**).* Yield: 63%; purple powder; mp 213–214 °C; IR (KBr) ν_{max} (cm^{-1}): 1647, 1624, 1597, 1497, 1472, 1450, 1445, 1298, 1283, 1241, 1204, 1140, 1067, 1025, 845, 838, 821, 807; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H, NH), 8.55 (s, 1H, H-2), 8.00 (d, 1H, J = 8.8 Hz, H-9), 7.50 (d, 1H, J = 1.8 Hz, H-ar), 7.31 (d, 1H, J = 1.6 Hz, H-6), 7.29 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.6 Hz, H-ar), 7.14 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 6.84 (d, 1H, J = 8.6 Hz, H-ar), 4.25 (br s, 4H, CH_2), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.9, 157.4, 152.9, 145.9, 145.8, 142.8, 139.3, 134.2, 132.8, 121.8, 116.6, 115.1, 114.1, 112.9, 110.0, 96.9, 64.2, 63.9, 55.9; HRMS calcd for $C_{19}H_{16}N_3O_4$ $[M + H]^+$ 350.1141 found 350.1132.

*5.1.5.1.10. N-(4-Fluorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1k**).* Yield: 72%; white powder; mp 250–251 °C; IR (KBr) ν_{max} (cm^{-1}): 1639, 1621, 1598, 1507, 1493, 1482, 1449, 1436, 1305, 1295, 1239, 1208, 1138, 1085, 838, 812; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H, NH), 8.57 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.88 (d, 2H, J = 8.7 Hz, H-ar), 7.33 (d, 1H, J = 1.6 Hz, H-6), 7.20–7.16 (m, 2H, H-ar), 7.14 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.0, 157.5, 152.8, 146.3, 145.7, 135.6, 135.5, 134.2, 122.6, 122.4, 121.9, 115.3, 115.0, 114.9, 113.0, 96.9, 56.0; HRMS calcd for $C_{17}H_{13}N_3O_2F$ $[M + H]^+$ 310.0992 found 310.0988.

*5.1.5.1.11. N-(4-Bromophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1l**).* Yield: 61%; white powder; mp 254–255 °C; IR (KBr) ν_{max} (cm^{-1}): 1621, 1579, 1563, 1513, 1473, 1436, 1399, 1362, 1301, 1284, 1273, 1237, 1224, 1143, 1094, 1072, 1033, 1008, 968, 807; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H, NH), 8.62 (s, 1H, H-2), 8.03 (d, 1H, J = 8.8 Hz, H-9), 7.91 (d, 2H, J = 8.9 Hz, H-ar), 7.55 (d, 2H, J = 8.9 Hz, H-ar), 7.34 (d, 1H, J = 1.6 Hz, H-6), 7.15 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.6, 152.7, 146.6, 145.4, 138.8, 134.3, 131.3 (2C), 122.3 (2C), 122.0, 115.0, 114.3, 113.0, 96.9, 56.0; HRMS calcd for $C_{17}H_{13}N_3O_2Br$ $[M + H]^+$ 370.0191 found 370.0197.

*5.1.5.1.12. N-(4-Chlorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1m**).* Yield: 65%; white powder; mp 253–254 °C; IR (KBr) ν_{max} (cm^{-1}): 1622, 1583, 1515, 1491, 1473, 1435, 1402, 1363, 1302, 1241, 1224, 1144, 1085, 1035, 1013, 968, 852, 821, 810; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.19 (s, 1H, NH), 8.62 (s, 1H, H-2), 8.03 (d, 1H, J = 8.8 Hz, H-9), 7.96 (d, 2H, J = 9.0 Hz, H-ar), 7.43 (d, 2H, J = 9.0 Hz, H-ar), 7.34 (d, 1H, J = 1.6 Hz, H-6), 7.15 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.6, 152.8, 146.5, 145.4, 138.4, 134.3, 128.4 (2C), 126.4, 121.9 (2C), 115.0, 113.0, 106.8, 96.9, 56.0; HRMS calcd for $C_{17}H_{13}N_3O_2Cl$ $[M + H]^+$ 326.0696 found 326.0706.

*5.1.5.1.13. N-(3-Chlorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1n**).* Yield: 71%; white powder; mp 220–221 °C; IR (KBr) ν_{max} (cm^{-1}): 1634, 1620, 1602, 1578, 1566, 1519, 1476, 1471, 1445, 1435, 1419, 1357, 1331, 1288, 1239, 1138, 1093, 1082, 971, 878, 834, 822; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.24 (s, 1H, NH), 8.66 (s, 1H, H-2), 8.16 (s, 1H, H-ar), 8.03 (d, 1H, J = 8.8 Hz, H-9), 7.84 (d, 1H, J = 7.6 Hz, H-ar), 7.39 (td, 1H, J_1 = 7.6 Hz, J_2 = 8.0 Hz, H-ar), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.16 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 7.15 (d, 1H, J = 8.0 Hz, H-ar), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.6, 152.7, 146.7, 145.3, 141.0, 134.3, 132.9, 130.2, 122.3, 122.0, 119.6, 118.7, 114.9, 113.0, 96.9, 56.0; HRMS calcd for $C_{17}H_{13}N_3O_2Cl$ $[M + H]^+$ 326.0696 found 326.0699.

*5.1.5.1.14. N-(2-Chlorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1o**).* Yield: 56%; white powder; mp 182–183 °C; IR (KBr) ν_{max} (cm^{-1}): 1615, 1591, 1462, 1444, 1430, 1384, 1332, 1304, 1292, 1279, 1259, 1134, 1084, 1019, 930, 826, 785; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, NH), 8.47 (s, 1H, H-2), 8.03 (d, 1H, J = 8.8 Hz, H-9), 7.67 (dd, 1H, J_1 = 1.4 Hz, J_2 = 7.9 Hz, H-ar), 7.58 (dd, 1H, J_1 = 1.4 Hz, J_2 = 7.8 Hz, H-ar), 7.42 (td, 1H, J_1 = 1.4 Hz, J_2 = 7.8 Hz, H-ar), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.32 (td, 1H, J_1 = 1.4 Hz, J_2 = 7.9 Hz, H-ar), 7.12 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.7, 153.0, 146.8, 146.6, 136.4, 134.2, 129.9, 129.7, 128.3, 127.6, 127.2, 121.9, 114.8, 113.2, 96.9, 56.0; HRMS calcd for $C_{17}H_{13}N_3O_2Cl$ $[M + H]^+$ 326.0696 found 326.0690.

*5.1.5.1.15. N-(3,4-Dichlorophenyl)-7-methoxybenzofuro[3,2-d] pyrimidin-4-amine (**1p**).* Yield: 64%; white powder; mp 249–250 °C; IR (KBr) ν_{max} (cm^{-1}): 1635, 1622, 1598, 1580, 1559, 1509, 1468, 1401, 1359, 1302, 1284, 1273, 1138, 1130, 1093, 1025, 973, 867, 841, 813, 803; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.34 (s, 1H, NH), 8.68 (s, 1H, H-2), 8.36 (d, 1H, J = 2.5 Hz, H-ar), 8.03 (d, 1H, J = 8.8 Hz, H-9), 7.90 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.9 Hz, H-ar), 7.62 (d, 1H, J = 8.9 Hz, H-ar), 7.33 (d, 1H, J = 1.6 Hz, H-6), 7.15 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 157.7, 152.7, 146.8, 145.1, 139.7, 134.3, 130.7, 130.4, 123.9, 122.0, 121.2, 120.2, 114.9, 113.1, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2Cl_2$ $[M + H]^+$ 360.0307 found 360.0312.

*5.1.5.1.16. N-(3,5-Dichlorophenyl)-7-methoxybenzofuro[3,2-d] pyrimidin-4-amine (**1q**).* Yield: 70%; white powder; mp 234–235 °C; IR (KBr) ν_{max} (cm^{-1}): 1625, 1576, 1560, 1472, 1449, 1440, 1407, 1394, 1332, 1086, 1025, 985, 847, 822, 815, 809; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1H, NH), 8.72 (s, 1H, H-2), 8.11 (d, 2H, J = 1.8 Hz, H-ar), 8.05 (d, 1H, J = 8.8 Hz, H-9), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.27 (t, 1H, J = 1.8 Hz, H-ar), 7.17 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.95 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.3, 157.7, 152.6, 147.0, 144.9, 142.0, 134.3, 133.8 (2C), 122.0, 121.5, 118.0 (2C), 114.8, 113.1, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2Cl_2$ $[M + H]^+$ 360.0307 found 360.0303.

*5.1.5.1.17. N-(2,4-Dichlorophenyl)-7-methoxybenzofuro[3,2-d] pyrimidin-4-amine (**1r**).* Yield: 99%; yellow powder; mp 206–207 °C; IR (KBr) ν_{max} (cm^{-1}): 1623, 1514, 1498, 1455, 1403, 1332, 1305, 1240, 1138, 1082, 1048, 1021, 970, 870, 828, 818, 812; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.78 (s, 1H, NH), 8.49 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.75 (d, 1H, J = 2.4 Hz, H-ar), 7.70 (d, 1H,

J = 8.6 Hz, H-ar), 7.49 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.6 Hz, H-ar), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.13 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.8, 152.9, 147.0, 146.3, 134.7, 134.2, 130.8, 130.4, 129.4, 129.1, 127.7, 121.9, 114.7, 113.3, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2Cl_2$ $[M + H]^+$ 360.0307 found 360.0309.

*5.1.5.1.18. N-(3-Chloro-4-fluorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1s**).* Yield: 73%; white powder; mp 229–230 °C; IR (KBr) ν_{max} (cm^{-1}): 1638, 1622, 1437, 1472, 1436, 1400, 1360, 1303, 1281, 1256, 1235, 1204, 1138, 1091, 1030, 976, 870, 856, 809; ^1H NMR (300 MHz, DMSO-d_6): δ 10.23 (s, 1H, NH), 8.64 (s, 1H, H-2), 8.25 (dd, 1H, J_1 = 2.6 Hz, J_2 = 6.8 Hz, H-ar), 8.02 (d, 1H, J = 8.8 Hz, H-9), 7.87–7.83 (m, 1H, H-ar), 7.43 (t, 1H, J = 9.2 Hz, H-ar), 7.33 (d, 1H, J = 1.6 Hz, H-6), 7.15 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.6, 152.7, 146.6, 145.3, 136.7, 134.2, 122.0, 121.6, 120.7, 119.0, 118.7, 116.8, 114.9, 113.1, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2FCl$ $[M + H]^+$ 344.0602 found 344.0592.

*5.1.5.1.19. N-(4-Chloro-2-fluorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1t**).* Yield: 78%; white powder; mp 243–244 °C; IR (KBr) ν_{max} (cm^{-1}): 1618, 1588, 1484, 1471, 1430, 1415, 1332, 1307, 1290, 1262, 1134, 1118, 1078, 1021, 851, 833, 819, 807; ^1H NMR (300 MHz, DMSO-d_6): δ 9.90 (s, 1H, NH), 8.50 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.65 (t, 1H, J = 8.6 Hz, H-ar), 7.57 (dd, 1H, J_1 = 1.8 Hz, J_2 = 9.2 Hz, H-ar), 7.37–7.32 (m, 2H, H-ar and H-6), 7.13 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 157.8, 154.5, 152.9, 146.9, 146.0, 134.3, 129.6, 128.2, 125.3, 124.6, 122.0, 116.7, 114.7, 113.3, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2FCl$ $[M + H]^+$ 344.0602 found 344.0604.

*5.1.5.1.20. N-(2,4-Difluorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1u**).* Yield: 77%; white powder; mp 246–247 °C; IR (KBr) ν_{max} (cm^{-1}): 1629, 1611, 1518, 1490, 1471, 1429, 1332, 1308, 1287, 1260, 1134, 1083, 1019, 960, 843, 829, 823, 809; ^1H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 1H, NH), 8.47 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.63–7.60 (m, 1H, H-ar), 7.41–7.35 (m, 1H, H-ar), 7.34 (d, 1H, J = 1.6 Hz, H-6), 7.18–7.15 (m, 1H, H-ar), 7.12 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 157.7, 153.0, 146.7, 146.5, 134.2, 128.9, 128.8, 122.4, 122.0, 114.7, 113.2, 111.4, 104.8, 104.1, 96.8, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2F_2$ $[M + H]^+$ 328.0898 found 328.0901.

*5.1.5.1.21. N-(4-Bromo-2-fluorophenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1v**).* Yield: 67%; yellow powder; mp 240–241 °C; IR (KBr) ν_{max} (cm^{-1}): 1618, 1584, 1513, 1481, 1470, 1430, 1408, 1391, 1334, 1306, 1291, 1262, 1236, 1191, 1135, 1118, 1084, 1073, 1020, 877, 850, 833, 819, 804; ^1H NMR (300 MHz, DMSO-d_6): δ 9.86 (s, 1H, NH), 8.51 (s, 1H, H-2), 8.01 (d, 1H, J = 8.8 Hz, H-9), 7.65 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.4 Hz, H-ar), 7.59 (d, 1H, J = 8.4 Hz, H-ar), 7.45 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.4 Hz, H-ar), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.13 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 157.8, 152.9, 147.0, 145.9, 134.4, 128.4, 127.4, 125.8, 122.0, 119.4, 119.1, 117.2, 114.7, 113.2, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3O_2FBr$ $[M + H]^+$ 388.0097 found 388.0085.

*5.1.5.1.22. N-(2-Fluoro-4-methoxyphenyl)-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1w**).* Yield: 80%; white powder; mp 195–196 °C; IR (KBr) ν_{max} (cm^{-1}): 1634, 1622, 1592, 1524, 1490, 1467, 1428, 1299, 1279, 1260, 1239, 1200, 1135, 1104, 1086, 1026, 829, 824, 813; ^1H NMR (300 MHz, DMSO-d_6): δ 9.62 (s, 1H, NH), 8.43 (s, 1H, H-2), 7.99 (d, 1H, J = 8.8 Hz, H-9), 7.42 (t, 1H, J = 9.0 Hz, H-ar), 7.32 (d, 1H, J = 1.6 Hz, H-6), 7.11 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 6.95 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.0 Hz, H-ar), 6.82 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.0 Hz, H-ar), 3.91 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.0, 159.4, 157.6, 153.1, 147.0, 146.4, 134.2, 128.8, 127.8, 121.9, 118.3, 114.8, 113.1, 109.9, 102.2, 96.8, 56.0, 55.7; HRMS calcd for $C_{18}H_{15}N_3O_3F$ $[M + H]^+$ 340.1097 found 340.1082.

*5.1.5.1.23. 4-[(7-Methoxybenzofuro[3,2-d]pyrimidin-4-yl)amino]benzonitrile (**1x**).* Yield: 71%; white powder; mp > 300 °C; IR (KBr) ν_{max} (cm^{-1}): 2223 (CN), 1628, 1607, 1583, 1517, 1506, 1498, 1475, 1401, 1364, 1304, 1285, 1240, 1176, 1140, 1094, 970, 853, 832, 816; ^1H NMR (300 MHz, DMSO-d_6): δ 10.55 (s, 1H, NH), 8.71 (s, 1H, H-2), 8.17 (d, 2H, J = 8.7 Hz, H-ar), 8.06 (d, 1H, J = 8.8 Hz, H-9), 7.82 (d, 2H, J = 8.7 Hz, H-ar), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.16 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.3, 157.8, 152.6, 147.3, 144.8, 143.9, 134.5, 133.0 (2C), 122.1, 119.8 (2C), 119.3, 114.8, 113.2, 103.8, 97.0, 56.0; HRMS calcd for $C_{18}H_{13}N_4O_2$ $[M + H]^+$ 317.1039 found 317.1044.

*5.1.5.1.24. 7-N-[3-(Trifluoromethyl)phenyl]-7-methoxybenzofuro[3,2-d]pyrimidin-4-amine (**1y**).* Yield: 55%; white powder; mp 193–194 °C; IR (KBr) ν_{max} (cm^{-1}): 1634, 1622, 1607, 1472, 1450, 1327, 1300, 1263, 1160, 1137, 1114, 1093, 1085, 1022, 830; ^1H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H, NH), 8.68 (s, 1H, H-2), 8.42 (d, 1H, J = 1.0 Hz, H-ar), 8.20 (dd, 1H, J_1 = 1.0 Hz, J_2 = 8.5 Hz, H-ar), 8.05 (d, 1H, J = 8.8 Hz, H-9), 7.61 (td, 1H, J_1 = 1.0 Hz, J_2 = 8.5 Hz, H-ar), 7.41 (dd, 1H, J_1 = 1.0 Hz, J_2 = 8.5 Hz, H-ar), 7.35 (d, 1H, J = 1.6 Hz, H-6), 7.15 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 157.7, 152.7, 146.8, 145.3, 140.3, 134.3, 129.7, 129.1, 123.8, 122.0, 118.8, 116.3, 116.2, 114.9, 113.1, 96.9, 56.0; HRMS calcd for $C_{18}H_{13}N_3O_2F_3$ $[M + H]^+$ 360.0960 found 360.0957.

*5.1.5.1.25. N^1-(7-Methoxybenzofuro[3,2-d]pyrimidin-4-yl)-N^4,N^4-dimethylbenzene-1,3-diamine (**1z**).* Yield: 20%; blue powder; mp 243–244 °C; IR (KBr) ν_{max} (cm^{-1}): 1618, 1515, 1493, 1472, 1442, 1436, 1333, 1304, 1286, 1266, 1238, 1136, 1084, 1017, 968, 932, 821, 814; ^1H NMR (300 MHz, DMSO-d_6): δ 9.72 (s, 1H, NH), 8.49 (s, 1H, H-2), 7.99 (d, 1H, J = 8.8 Hz, H-9), 7.62 (d, 2H, J = 9.0 Hz, H-ar), 7.31 (d, 1H, J = 1.6 Hz, H-6), 7.13 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.8 Hz, H-8), 6.77 (d, 2H, J = 9.0 Hz, H-ar), 3.93 (s, 3H, OCH_3), 2.89 (s, 6H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 157.3, 153.0, 147.2, 146.2, 145.6, 134.2, 128.6, 122.7 (2C), 121.8, 115.2, 112.8, 112.6 (2C), 96.9, 55.9, 40.5 (2C); HRMS calcd for $C_{19}H_{19}N_4O_2$ $[M + H]^+$ 335.1508 found 335.1501.

*5.1.5.2. Synthesis of N-aryl-7-methoxybenzothieno[3,2-d]pyrimidin-4-amines (**2b–z**).* A mixture of (*E*)-*N*′-(2-cyano-6-methoxybenzofuran-3-yl)-*N*,*N*-dimethylformimidamide (**6**) (0.1 g, 0.39 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 to 0:100, v/v) as the eluent to give the desired compounds (**2b–z**).

*5.1.5.2.1. 7-Methoxy-N-phenyl-benzothieno[3,2-d]pyrimidin-4-amine (**2b**).* Yield: 67%; white powder; mp 231–232 °C; IR (KBr) ν_{max} (cm^{-1}): 1597, 1562, 1531, 1503, 1496, 1485, 1455, 1439, 1263, 1252, 1229, 1046, 1023, 832, 827, 820; ^1H NMR (300 MHz, DMSO-d_6): δ 9.65 (s, 1H, NH), 8.67 (s, 1H, H-2), 8.23 (d, 1H, J = 8.7 Hz, H-9), 7.77 (m, 3H, H-6 and H-ar), 7.39 (dt, 2H, J_1 = 1.0 Hz, J_2 = 8.0 Hz, H-ar), 7.19 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 7.14 (dt, 1H, J_1 = 1.0 Hz, J_2 = 8.4 Hz, H-ar), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.2, 155.0, 154.3, 141.9, 139.0, 128.5 (2C), 126.9, 123.9, 123.6, 122.3 (2C), 115.1, 113.6, 106.1, 55.8; HRMS calcd for $C_{17}H_{14}N_3OS$ $[M + H]^+$ 308.0858 found 308.0851.

*5.1.5.2.2. 7-Methoxy-N-(p-tolyl)benzothieno[3,2-d]pyrimidin-4-amine (**2c**).* Yield: 80%; white powder; mp 224–225 °C; IR (KBr) ν_{max} (cm^{-1}): 1597, 1562, 1533, 1505, 1485, 1453, 1438, 1429, 1402, 1263, 1249, 1228, 1045, 1022, 820, 813; ^1H NMR (300 MHz, DMSO-d_6): δ 9.59 (s, 1H, NH), 8.64 (s, 1H, H-2), 8.20 (d, 1H, J = 8.7 Hz, H-9), 7.76 (d, 1H, J = 2.1 Hz, H-6), 7.62 (d, 2H, J = 8.3 Hz, H-ar), 7.19

(dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 7.18 (d, 2H, $J = 8.3$ Hz, H-ar), 3.91 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 156.0, 155.1, 154.4, 141.9, 136.2, 132.9, 128.9 (2C), 126.9, 123.8, 122.7 (2C), 115.1, 113.3, 106.1, 55.7, 20.5; HRMS calcd for $C_{18}H_{16}N_3OS$ $[M + H]^+$ 322.1014 found 322.1012.

*5.1.5.2.3. 7-Methoxy-N-(m-tolyl)benzothieno[3,2-d]pyrimidin-4-amine (**2d**).* Yield: 64%; white powder; mp 232–233 °C; IR (KBr) ν_{max} (cm^{-1}): 1596, 1571, 1530, 1508, 1486, 1455, 1439, 1264, 1251, 1230, 1046, 1024, 832, 818; ^1H NMR (300 MHz, DMSO-d_6): δ 9.59 (s, 1H, NH), 8.67 (s, 1H, H-2), 8.22 (d, 1H, $J = 8.7$ Hz, H-9), 7.77 (d, 1H, $J = 2.1$ Hz, H-6), 7.58 (m, 2H, H-ar), 7.27 (td, 1H, $J_1 = 1.0$ Hz, $J_2 = 8.0$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 6.96 (d, 1H, $J = 8.0$ Hz, H-ar), 3.92 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.2, 155.1, 154.4, 141.9, 138.8, 137.7, 128.3, 126.9, 124.4, 123.8, 122.9, 119.6, 115.1, 113.6, 106.1, 55.8, 21.2; HRMS calcd for $C_{18}H_{16}N_3OS$ $[M + H]^+$ 322.1014 found 322.1009.

*5.1.5.2.4. 7-Methoxy-N-(4-methoxyphenyl)benzothieno[3,2-d]pyrimidin-4-amine (**2e**).* Yield: 55%; purple powder; mp 240–241 °C; IR (KBr) ν_{max} (cm^{-1}): 1600, 1570, 1506, 1480, 1446, 1431, 1410, 1245, 1230, 1176, 1140, 1105, 1045, 1034, 1023, 953, 878, 822; ^1H NMR (300 MHz, DMSO-d_6): δ 9.52 (s, 1H, NH), 8.59 (s, 1H, H-2), 8.19 (d, 1H, $J = 8.7$ Hz, H-9), 7.74 (d, 1H, $J = 2.1$ Hz, H-6), 7.57 (d, 2H, $J = 8.8$ Hz, H-ar), 7.16 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 6.96 (d, 2H, $J = 8.8$ Hz, H-ar), 3.90 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 156.2, 156.0, 155.5, 154.5, 141.9, 131.4, 126.9, 125.1 (2C), 123.8, 115.0, 113.7 (2C), 112.9, 106.0, 55.7, 55.2; HRMS calcd for $C_{18}H_{16}N_3O_2S$ $[M + H]^+$ 338.0963 found 338.0961.

*5.1.5.2.5. 7-Methoxy-N-(3,4-dimethoxyphenyl)benzothieno[3,2-d]pyrimidin-4-amine (**2f**).* Yield: 92%; purple powder; mp 218–219 °C; IR (KBr) ν_{max} (cm^{-1}): 1602, 1566, 1505, 1452, 1440, 1429, 1409, 1260, 1239, 1226, 1218, 1164, 1128, 1044, 1024, 1016, 975, 858, 836; ^1H NMR (300 MHz, DMSO-d_6): δ 9.52 (s, 1H, NH), 8.62 (s, 1H, H-2), 8.19 (d, 1H, $J = 8.7$ Hz, H-9), 7.74 (d, 1H, $J = 2.1$ Hz, H-6), 7.28 (m, 2H, H-ar), 7.15 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 6.97 (d, 1H, $J = 8.3$ Hz, H-ar), 3.90 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 156.1, 155.5, 154.4, 148.4, 145.8, 142.0, 131.8, 126.9, 123.8, 115.7, 115.0, 112.9, 111.6, 108.5, 106.0, 55.7 (2C), 55.5; HRMS calcd for $C_{19}H_{18}N_3O_3S$ $[M + H]^+$ 368.1069 found 368.1061.

*5.1.5.2.6. 7-Methoxy-N-(3,5-dimethoxyphenyl)benzothieno[3,2-d]pyrimidin-4-amine (**2g**).* Yield: 83%; grey powder; mp 201–202 °C; IR (KBr) ν_{max} (cm^{-1}): 1607, 1577, 1532, 1455, 1446, 1435, 1421, 1277, 1226, 1205, 1168, 1151, 1141, 1058, 838, 819; ^1H NMR (300 MHz, DMSO-d_6): δ 9.57 (s, 1H, NH), 8.72 (s, 1H, H-2), 8.22 (d, 1H, $J = 8.7$ Hz, H-9), 7.79 (d, 1H, $J = 2.1$ Hz, H-6), 7.20 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 7.12 (d, 2H, $J = 2.0$ Hz, H-ar), 6.29 (t, 1H, $J = 2.0$ Hz, H-ar), 3.92 (s, 3H, OCH_3), 3.77 (s, 6H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 160.3 (2C), 156.2, 154.9, 154.2, 141.9, 140.8, 126.9, 123.9, 115.1, 113.9, 106.1, 100.2 (2C), 95.4, 55.8, 55.1 (2C); HRMS calcd for $C_{19}H_{18}N_3O_3S$ $[M + H]^+$ 368.1069 found 368.1073.

*5.1.5.2.7. 7-Methoxy-N-(3,4,5-trimethoxyphenyl)benzothieno[3,2-d]pyrimidin-4-amine (**2h**).* Yield: 84%; grey powder; mp 230–231 °C; IR (KBr) ν_{max} (cm^{-1}): 1602, 1578, 1505, 1489, 1456, 1444, 1429, 1408, 1228, 1125, 1051, 1041, 1029, 1001, 827; ^1H NMR (300 MHz, DMSO-d_6): δ 9.57 (s, 1H, NH), 8.68 (s, 1H, H-2), 8.21 (d, 1H, $J = 8.7$ Hz, H-8), 7.77 (d, 1H, $J = 2.1$ Hz, H-6), 7.20 (s, 2H, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-9), 3.92 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3), 3.68 (s, 3H; OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.1, 155.1, 154.3, 152.5 (2C), 141.9, 134.9, 134.0, 126.9, 123.8, 115.1, 113.4, 106.1, 100.5 (2C), 60.1, 55.8 (3C); HRMS calcd for $C_{20}H_{20}N_3O_4S$ $[M + H]^+$ 398.1175 found 398.1169.

*5.1.5.2.8. N-(Benzo[d][1,3]dioxol-5-yl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2i**).* Yield: 84%; grey powder; mp 248–249 °C; IR (KBr) ν_{max} (cm^{-1}): 1583, 1532, 1499, 1479, 1454, 1440, 1329, 1264, 1242, 1228, 1183, 1039, 1016, 921, 857, 833, 802; ^1H NMR (300 MHz, DMSO-d_6): δ 9.55 (s, 1H, NH), 8.63 (s, 1H, H-2), 8.20 (d, 1H, $J = 8.7$ Hz, H-9), 7.75 (d, 1H, $J = 2.1$ Hz, H-6), 7.36 (d, 1H, $J = 1.8$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 7.14 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 8.3$ Hz, H-ar), 6.94 (d, 1H, $J = 8.3$ Hz, H-ar), 6.06 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 156.1, 155.4, 154.4, 147.0, 143.9, 141.9, 132.7, 126.9, 123.8, 116.4, 115.0, 113.1, 107.8, 106.0, 105.4, 101.1, 55.7; HRMS calcd for $C_{18}H_{14}N_3O_3S$ $[M + H]^+$ 352.0756 found 352.0746.

*5.1.5.2.9. N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2j**).* Yield: 74%; purple powder; mp 219–220 °C; IR (KBr) ν_{max} (cm^{-1}): 1599, 1568, 1496, 1451, 1431, 1416, 1309, 1268, 1238, 1228, 1203, 1166, 1068, 1060, 1044, 1023, 880, 862, 817; ^1H NMR (300 MHz, DMSO-d_6): δ 9.48 (s, 1H, NH), 8.63 (s, 1H, H-2), 8.20 (d, 1H, $J = 8.7$ Hz, H-9), 7.75 (d, 1H, $J = 2.1$ Hz, H-6), 7.32 (d, 1H, $J = 2.3$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 7.16 (dd, 1H, $J_1 = 2.3$ Hz, $J_2 = 8.7$ Hz, H-ar), 6.86 (d, 1H, $J = 8.7$ Hz, H-ar), 4.27 (br s, 4H, CH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 156.0, 155.2, 154.4, 142.8, 141.9, 140.1, 132.2, 126.9, 123.8, 116.5, 116.2, 115.0, 113.1, 112.1, 106.1, 64.1, 64.0, 55.7; HRMS calcd for $C_{19}H_{16}N_3O_3S$ $[M + H]^+$ 366.0912 found 366.0906.

*5.1.5.2.10. N-(4-Fluorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2k**).* Yield: 73%; white powder; mp 248–249 °C; IR (KBr) ν_{max} (cm^{-1}): 1571, 1504, 1486, 1451, 1440, 1430, 1402, 1264, 1228, 1210, 1183, 1157, 1043, 1021, 826; ^1H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, NH), 8.66 (s, 1H, H-2), 8.22 (d, 1H, $J = 8.7$ Hz, H-9), 7.80–7.75 (m, 3H, H6 and H-ar), 7.26–7.17 (m, 3H, H-8 and H-ar), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.9, 156.2, 155.0, 154.3, 141.9, 135.2 (2C), 126.9, 124.4, 123.9, 115.2, 115.1, 114.9, 113.4, 106.1, 55.8; HRMS calcd for $C_{17}H_{13}N_3O_2FS$ $[M + H]^+$ 326.0763 found 326.0755.

*5.1.5.2.11. N-(4-Bromophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2l**).* Yield: 54%; white powder; mp 272–273 °C; IR (KBr) ν_{max} (cm^{-1}): 1599, 1559, 1527, 1500, 1481, 1452, 1438, 1392, 1343, 1263, 1250, 1228, 1063, 1044, 1018, 1010, 834, 826, 815; ^1H NMR (300 MHz, DMSO-d_6): δ 9.75 (s, 1H, NH), 8.70 (s, 1H, H-2), 8.22 (d, 1H, $J = 8.7$ Hz, H-9), 7.82 (d, 2H, $J = 7.8$ Hz, H-ar), 7.79 (d, 1H, $J = 2.1$ Hz, H-6), 7.55 (d, 2H, $J = 7.8$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 156.3, 154.6, 154.2, 141.9, 138.6, 131.2 (2C), 126.8, 123.9, 123.7 (2C), 115.2, 115.0, 114.0, 106.2, 55.8; HRMS calcd for $C_{17}H_{13}N_3OSBr$ $[M + H]^+$ 385.9963 found 385.9955.

*5.1.5.2.12. N-(4-Chlorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2m**).* Yield: 59%; white powder; mp 261–262 °C; IR (KBr) ν_{max} (cm^{-1}): 1599, 1560, 1528, 1499, 1483, 1452, 1441, 1428, 1396, 1343, 1264, 1250, 1229, 1173, 1093, 1062, 1044, 1015, 826, 817; ^1H NMR (300 MHz, DMSO-d_6): δ 9.76 (s, 1H, NH), 8.70 (s, 1H, H-2), 8.22 (d, 1H, $J = 8.7$ Hz, H-9), 7.85 (d, 2H, $J = 8.7$ Hz, H-ar), 7.79 (d, 1H, $J = 2.1$ Hz, H-6), 7.43 (d, 2H, $J = 8.7$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 156.3, 154.7, 154.2, 141.9, 138.1, 128.3 (2C), 127.0, 126.9, 123.9, 123.4 (2C), 115.2, 113.9, 106.2, 55.8; HRMS calcd for $C_{17}H_{13}N_3OSCl$ $[M + H]^+$ 342.0468 found 342.0456.

*5.1.5.2.13. N-(3-Chlorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2n**).* Yield: 61%; white powder; mp 278–279 °C; IR (KBr) ν_{max} (cm^{-1}): 1594, 1559, 1529, 1501, 1483, 1475, 1451, 1435, 1415, 1270, 1257, 1249, 1228, 1061, 1044, 1019, 870, 833; ^1H NMR (300 MHz, DMSO-d_6): δ 9.80 (s, 1H, NH), 8.75 (s, 1H, H-2), 8.23 (d, 1H, $J = 8.7$ Hz, H-8), 8.06 (s, 1H, H-ar), 7.80 (d, 1H, $J = 2.1$ Hz, H-6), 7.77 (d, 1H, $J = 8.1$ Hz, H-ar), 7.40 (dt, 1H, $J_1 = 8.1$ Hz, $J_2 = 9.0$ Hz, H-ar), 7.19 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, H-9), 7.15 (d, 1H, $J = 9.0$ Hz, H-ar), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 156.4, 154.6, 154.2, 142.0, 140.8, 132.8, 130.1, 126.8, 123.9, 122.8,

120.9, 119.9, 115.2, 114.1, 106.2, 55.8; HRMS calcd for $C_{17}H_{13}N_3OSCl$ $[M + H]^+$ 342.0468 found 342.0462.

*5.1.5.2.14. N-(2-Chlorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2o**).* Yield: 68%; white powder; mp 202–203 °C; IR (KBr) ν_{max} (cm^{-1}): 1678, 1598, 1565, 1531, 1519, 1454, 1442, 1434, 1421, 1343, 1267, 1252, 1240, 1224, 1052, 1043, 1028; ^1H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, NH), 8.57 (s, 1H, H-2), 8.21 (d, 1H, J = 8.7 Hz, H-9), 7.75 (d, 1H, J = 2.1 Hz, H-6), 7.62–7.59 (m, 2H, H-ar), 7.44–7.39 (m, 2H, H-ar), 7.20 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.6, 154.6, 142.1, 135.2, 131.8, 130.3, 129.7, 128.3, 127.7, 126.7, 124.1, 115.6, 115.0, 112.6, 106.1, 55.7; HRMS calcd for $C_{17}H_{13}N_3OSCl$ $[M + H]^+$ 342.0468 found 342.0453.

*5.1.5.2.15. N-(3,4-Dichlorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2p**).* Yield: 69%; white powder; mp 232–233 °C; IR (KBr) ν_{max} (cm^{-1}): 1721, 1606, 1591, 1561, 1537, 1504, 1475, 1452, 1436, 1396, 1345, 1273, 1246, 1227, 1068, 1055, 1026, 868, 854, 818; ^1H NMR (300 MHz, DMSO-d_6): δ 9.87 (s, 1H, NH), 8.76 (s, 1H, H-2), 8.28 (d, 1H, J = 2.0 Hz, H-ar), 8.22 (d, 1H, J = 8.7 Hz, H-9), 7.85 (dd, 1H, J_1 = 2.0 Hz, J_2 = 9.0 Hz, H-ar), 7.80 (d, 1H, J = 2.1 Hz, H-6), 7.62 (d, 1H, J = 9.0 Hz, H-ar), 7.20 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2, 156.4, 154.3, 154.1, 142.0, 139.6, 130.6, 130.3, 126.8, 124.4, 124.0, 122.4, 121.2, 115.2, 114.3, 106.2, 55.8; HRMS calcd for $C_{17}H_{12}N_3OSCl_2$ $[M + H]^+$ 376.0078 found 376.0073.

*5.1.5.2.16. N-(3,5-Dichlorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2q**).* Yield: 50%; white powder; mp 264–265 °C; IR (KBr) ν_{max} (cm^{-1}): 1589, 1561, 1524, 1502, 1443, 1431, 1403, 1268, 1252, 1230, 1045, 1023, 979, 854, 845, 833, 807; ^1H NMR (300 MHz, DMSO-d_6): δ 9.88 (s, 1H, NH), 8.81 (s, 1H, H-2), 8.23 (d, 1H, J = 8.7 Hz, H-9), 8.07 (d, 2H, J = 1.9 Hz, H-ar), 7.81 (d, 1H, J = 2.1 Hz, H-6), 7.28 (t, 1H, J = 1.9 Hz, H-ar), 7.21 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2, 156.6, 154.2, 154.0, 142.0, 141.9, 133.7 (2C), 126.7, 124.0, 121.9, 118.9 (2C), 115.3, 114.5, 106.2, 55.8; HRMS calcd for $C_{17}H_{12}N_3OSCl_2$ $[M + H]^+$ 376.0078 found 376.0083.

*5.1.5.2.17. N-(2,4-Dichlorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2r**).* Yield: 77%; yellow powder; mp 238–239 °C; IR (KBr) ν_{max} (cm^{-1}): 1600, 1588, 1558, 1529, 1508, 1455, 1448, 1426, 1279, 1260, 1250, 1232, 1225, 1040, 1012, 839, 827, 822; ^1H NMR (300 MHz, DMSO-d_6): δ 9.72 (s, 1H, NH), 8.57 (s, 1H, H-2), 8.20 (d, 1H, J = 8.7 Hz, H-9), 7.78 (d, 1H, J = 2.1 Hz, H-6), 7.75 (d, 1H, J = 2.8 Hz, H-ar), 7.61 (d, 1H, J = 8.1 Hz, H-ar), 7.52 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.1 Hz, H-ar), 7.18 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 3.89 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.5, 155.9, 154.5, 142.1, 134.6, 132.6, 131.5, 131.2, 129.2, 127.8, 126.6, 123.9, 115.1, 112.8, 106.1, 55.7; HRMS calcd for $C_{17}H_{12}N_3OSCl_2$ $[M + H]^+$ 376.0078 found 376.0087.

*5.1.5.2.18. N-(3-Chloro-4-fluorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2s**).* Yield: 66%; white powder; mp 252–253 °C; IR (KBr) ν_{max} (cm^{-1}): 1600, 1566, 1530, 1496, 1483, 1450, 1439, 1430, 1389, 1342, 1267, 1231, 1211, 1062, 1043, 1018, 870, 835, 827, 815; ^1H NMR (300 MHz, DMSO-d_6): δ 9.79 (s, 1H, NH), 8.73 (s, 1H, H-2), 8.23 (d, 1H, J = 8.7 Hz, H-9), 8.16 (dd, 1H, J_1 = 2.2 Hz, J_2 = 6.6 Hz, H-ar), 7.79–7–76 (m, 2H, H-6 and H-ar), 7.44 (t, 1H, J = 9.2 Hz, H-ar), 7.19 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 156.3, 154.6, 154.2, 141.9, 136.5, 126.8, 123.9, 123.2, 122.1, 118.9, 116.7, 116.4, 115.2, 113.8, 106.2, 55.8; HRMS calcd for $C_{17}H_{12}N_3OFSCl$ $[M + H]^+$ 360.0374 found 360.0388.

*5.1.5.2.19. N-(4-Chloro-2-fluorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2t**).* Yield: 73%; white powder; mp 226–227 °C; IR (KBr) ν_{max} (cm^{-1}): 1618, 1588, 1484, 1471, 1430, 1415, 1332, 1307, 1290, 1262, 1134, 1118, 1078, 1021, 851, 833, 819, 807; ^1H NMR (300 MHz, DMSO-d_6): δ 9.71 (s, 1H, NH), 8.59 (s, 1H, H-2), 8.21 (d, 1H, J = 8.7 Hz, H-9), 7.77 (d, 1H, J = 2.0 Hz, H-6), 7.62–7.52 (m, 2H, H-ar), 7.35 (dd, 1H, J_1 = 1.0 Hz, J_2 = 8.5 Hz, H-ar), 7.18 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.7 Hz, H-8), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 157.8, 154.5, 152.9, 146.9, 146.0, 134.3, 129.6, 128.2, 125.3, 124.6, 122.0, 116.7, 114.7, 113.3, 96.9, 56.0; HRMS calcd for $C_{17}H_{12}N_3OFSCl$ $[M + H]^+$ 360.0374 found 360.0371.

*5.1.5.2.20. N-(2,4-Difluorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2u**).* Yield: 73%; white powder; mp 211–212 °C; IR (KBr) ν_{max} (cm^{-1}): 1602, 1579, 1505, 1485, 1450, 1437, 1425, 1263, 1237, 1136, 1062, 1045, 1025, 969, 950, 836; ^1H NMR (300 MHz, DMSO-d_6): δ 9.63 (s, 1H, NH), 8.56 (s, 1H, H-2), 8.21 (d, 1H, J = 8.8 Hz, H-9), 7.74 (d, 1H, J = 2.1 Hz, H-6), 7.59–7.55 (m, 1H, H-ar), 7.41–7.37 (m, 1H, H-ar), 7.18 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.8 Hz, H-8), 7.17–7.14 (m, 1H, H-ar), 3.89 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 156.3, 155.9, 154.6, 142.0, 130.2, 130.1, 126.7, 123.9, 122.3, 115.1, 112.8, 111.5, 106.2, 104.9, 104.2, 55.7; HRMS calcd for $C_{17}H_{12}N_3OF_2S[M + H]^+$ 344.0669 found 344.0672.

*5.1.5.2.21. N-(4-Bromo-2-fluorophenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2v**).* Yield: 75%; yellow powder; mp 243–244 °C; IR (KBr) ν_{max} (cm^{-1}): 1595, 1566, 1519, 1502, 1474, 1465, 1435, 1425, 1403, 1289, 1261, 1252, 1234, 1190, 1045, 1022, 882, 875, 832, 815; ^1H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H, NH), 8.59 (s, 1H, H-2), 8.21 (d, 1H, J = 8.7 Hz, H-9), 7.77 (d, 1H, J = 2.0 Hz, H-6), 7.68 (dd, 1H, J_1 = 2.0 Hz, J_2 = 10.1 Hz, H-ar), 7.54–7.46 (m, 2H, H-ar), 7.18 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.7 Hz, H-8), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 156.5, 155.6, 155.2, 154.5, 142.3, 130.0, 127.6, 126.7, 125.5, 123.9, 119.8, 119.3, 115.3, 113.4, 106.3, 55.9; HRMS calcd for $C_{17}H_{12}N_3OFSBr$ $[M + H]^+$ 405.9840 found 405.9832.

*5.1.5.2.22. N-(2-Fluoro-4-methoxyphenyl)-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2w**).* Yield: 72%; white powder; mp 249–250 °C; IR (KBr) ν_{max} (cm^{-1}): 1600, 1574, 1508, 1486, 1453, 1441, 1425, 1264, 1238, 1225, 1194, 1155, 1045, 1033, 1023, 946, 844, 832, 823; ^1H NMR (300 MHz, DMSO-d_6): δ 9.44 (s, 1H, NH), 8.54 (s, 1H, H-2), 8.18 (d, 1H, J = 8.7 Hz, H-9), 7.72 (d, 1H, J = 2.1 Hz, H-6), 7.42 (t, 1H, J = 9.2 Hz, H-ar), 7.16 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 6.96 (dd, 1H, J_1 = 1.2 Hz, J_2 = 9.0 Hz, H-ar), 6.85 (dd, 1H, J_1 = 1.2 Hz, J_2 = 9.0 Hz, H-ar), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 159.1, 156.5, 156.2, 154.6, 142.1, 130.4, 126.6, 123.9, 117.9, 115.0, 112.3, 110.1, 106.0, 102.2, 101.9, 55.8, 55.7; HRMS calcd for $C_{18}H_{15}N_3O_2FS$ $[M + H]^+$ 356.0869 found 356.0864.

*5.1.5.2.23. 4-[(7-Methoxybenzothieno[3,2-d]pyrimidin-4-yl)amino]benzonitrile (**2x**).* Yield: 67%; white powder; mp 262–263 °C; IR (KBr) ν_{max} (cm^{-1}): 2217 (CN), 1597, 1555, 1529, 1503, 1448, 1424, 1406, 1371, 1341, 1263, 1226, 1173, 1043, 1014, 955, 841, 827, 820; ^1H NMR (300 MHz, DMSO-d_6): δ 10.06 (s, 1H, NH), 8.80 (s, 1H, H-2), 8.25 (d, 1H, J = 8.7 Hz, H-9), 8.11 (d, 2H, J = 8.6 Hz, H-ar), 7.83–7.81 (m, 3H, H-6 and H-ar), 7.21 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 156.8, 154.2, 154.0, 143.9, 142.1, 132.9 (2C), 126.7, 124.0, 120.8 (2C), 119.3, 115.3, 114.9, 106.2, 104.2, 55.8; HRMS calcd for $C_{18}H_{13}N_4OS$ $[M + H]^+$ 333.0810 found 333.0806.

*5.1.5.2.24. N-[3-(Trifluoromethyl)phenyl]-7-methoxybenzothieno[3,2-d]pyrimidin-4-amine (**2y**).* Yield: 62%; white powder; mp 236–237 °C; IR (KBr) ν_{max} (cm^{-1}): 1578, 1530, 1451, 1439, 1325, 1262, 1231, 1217, 1167, 1137, 1109, 1101, 1060, 1044, 1022, 833; ^1H NMR (300 MHz, DMSO-d_6): δ 9.93 (s, 1H, NH), 8.77 (s, 1H, H-2), 8.29–8.19 (m, 3H, H-9 and H-ar), 7.83 (d, 1H, J = 1.7 Hz, H-6), 7.63 (td, 1H, J_1 = 1.0 Hz, J_2 = 7.8 Hz, H-ar), 7.44 (dd, 1H, J_1 = 1.0 Hz, J_2 = 7.8 Hz, H-ar), 7.22 (dd, 1H, J_1 = 1.7 Hz, J_2 = 8.6 Hz, H-8), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 161.2, 156.5, 154.6, 154.2, 142.0, 140.2, 129.7, 129.4, 126.8, 124.9, 124.0, 117.4, 115.3, 114.2, 106.2, 95.7, 55.8; HRMS calcd for $C_{18}H_{13}N_3OF_3S$ $[M + H]^+$ 376.0731 found 376.0727.

*5.1.5.2.25. N^1-(7-Methoxybenzothieno[3,2-d]pyrimidin-4-yl)-N^4,N^4-dimethylbenzene-1,3-diamine (**2z**).* Yield: 16%; blue powder; mp 233–234 °C; IR (KBr) ν_{max} (cm^{-1}): 1605, 1557, 1524, 1478, 1459, 1426, 1366, 1267, 1224, 1182, 1055, 1032, 853, 811; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38 (s, 1H, NH), 8.56 (s, 1H, H-2), 8.18 (d, 1H, J = 8.7 Hz, H-9), 7.69 (d, 1H, J = 2.1 Hz, H-6), 7.41 (d, 2H, J = 8.9 Hz, H-ar), 7.15 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.7 Hz, H-8), 6.77 (d, 2H, J = 8.9 Hz, H-ar), 3.89 (s, 3H, OCH_3), 2.93 (s, 6H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.7 (2C), 155.9, 154.5, 148.2, 142.1, 127.1, 126.8, 125.8, 123.8 (2C), 114.9, 112.4, 112.2 (2C), 105.9, 55.7, 40.3 (2C); HRMS calcd for $C_{19}H_{19}N_4OS$ $[M + H]^+$ 351.1280 found 351.1274.

5.2. In vitro kinase preparation and assays [17]

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 triplicates in buffer A or B, for 30 min at 30 °C, at a final adenosine triphosphate (ATP) concentration of 15 μM. Blank values were substracted and activities expressed in % of the maximal activity, *i.e.*, in the absence of inhibitors. Controls were performed with appropriate dilutions of dimethylsulfoxide (DMSO). IC_{50} values were calculated from dose–response curves established by Sigma-Plots. The GSK-3, CK1, DYRK1A and CLK1 peptide substrates were obtained from Proteogenix (Oberhausbergen, France).

5.2.2.1. CDK5/p25. CDK5/p25 (Human, recombinant) was prepared as previously described [18]. 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, 25 μL aliquots of supernatant were spotted onto sheets of Whatman P81 phosphocellulose paper, and 20 s later, the filters were washed eight times (for at least 5 min each time) 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. 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) [19].

5.2.2.3. CK1δ/ε. CK1δ/ε (Porcine brain, native) was assayed as described for CDK5/p25 but using the CK1-specific peptide substrate RRKHAAIGpSAYSITA [22].

5.2.2.4. DYRK1A. 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. 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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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.11.030.

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