Efficient New Synthesis of *N*-Arylbenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines and Their Benzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine Analogues via a Microwave-Assisted Dimroth Rearrangement

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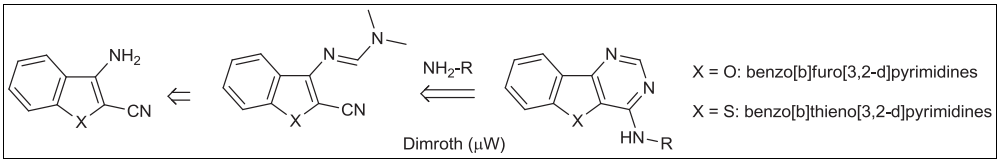

A useful and rapid access to libraries of *N*-arylbenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines (**1**) and their novel benzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine analogues (**2**) was investigated for the first time. Title compounds were obtained via microwave-accelerated condensation and Dimroth rearrangement of suitable anilines with *N*′-(2-cyanaryl)-*N*,*N*-dimethylformimidamides obtained by reaction of benzo[*b*]furane and benzo[*b*]thiophene precursors with *N*,*N*-dimethylformamide dimethyl acetal. This work also demonstrates that well-controlled parameters offer comfortable use of microwave technology and are both safe and beneficial to the environment. Some products obtained in this article exhibit interesting *in vitro* antiproliferative effects.

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INTRODUCTION

Phosphorylation of serine, threonine, and tyrosine residues by cellular protein kinases plays an important role in the regulation of various cellular processes. These enzymes are involved in major human diseases, including cancer, neurodegenerative disorders (Alzheimer and Down Syndrome), diabetes, and cardiovascular diseases. A part of the research activities of our groups concerns the synthesis of heterocyclic moieties containing nitrogen and sulfur atoms as kinase inhibitors [1,2]. Our investment in the search of efficient synthetic procedures allowed us to investigate the possibility to perform in short time and with good yields the synthesis of various tricyclic *N*-arylbenzo[*b*]furo[3,2-*d*] pyrimidin-4-amines and their benzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine analogues (Scheme 1). In comparison with their pyrimido[5,4-*b*]indole isoster and its pyrimido[4,5-*b*]indole isomer, these 6,5,6-fused tricycles were only quite recently studied for their interest as kinases inhibitors [3].

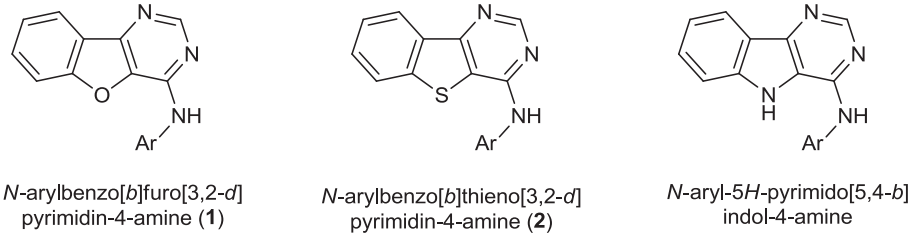
Considering the literature and the scale of research investment in pyrimidine rings associated with various heterocyclic skeletons, it appears that derivatives substituted by an amino group on position 4 of the pyrimidine moiety have received most attention, accounting for a large part for the registered compounds cited in papers and patents [4].

Taking into account all of these facts, we decided to explore the possibility of obtaining a rapid and efficient method for varying the aromatic amines that can be added to these tricyclic homologues of the basic 4-anilinopyrimidine pharmacophore. We decided to adapt the possibilities offered by the Dimroth rearrangement [5,6]. A survey of literature revealed that the synthesis of two examples of benzofuro [3,2-*d*]pyrimidines **1** was only described 30 years ago via this thermally sensitive method [7]. We considered that it would be an interesting challenge to explore microwave-assisted reaction conditions that may allow efficient synthesis of the target molecules for which usual methods require forcing conditions or prolonged reaction times. This article describes the development of a reliable and simple method that allows extending of the list of potential precursors to various bioactive molecules.

RESULTS AND DISCUSSION

The target molecules of our study were benzo[*b*]furo [3,2-*d*]pyrimidines (**1**) and their thieno analogues (**2**) substituted in position 4 of the pyrimidine ring by an aromatic amine. The synthetic routes mainly described in literature [3] included three-step reactions from the starting methyl (or ethyl) 3-aminobenzofurane- or 3-aminobenzothiophene-2-carboxylates. These were cyclized with formamide via Niementowski reaction to give tricyclic benzo[*b*]furo- or benzo[*b*]thieno[3,2-*d*]pyrimidin-4-ones

Scheme 1. General structures of the target benzofuro[3,2-*d*]pyrimidines (**1**) and benzothieno[3,2-*d*]pyrimidines (**2**).



followed by a treatment using thionyl chloride, phosphoryl chloride, or oxalyl chloride to afford 4-chlorobenzo[*b*]furo- or benzo[*b*]thieno[3,2-*d*]pyrimidines. Condensation with a variety of aliphatic and aromatic amines gave the target compounds (see top of Scheme 2).

One of the major drawbacks of these processes is the instability of the very reactive 4-chloro intermediates, which may decompose under storage and sometimes during the long heating times required for completion of the reactions. To overcome this problem and in connection with our work on the application of microwave irradiations in organic and medicinal chemistry, we decided to perform a short synthesis of the expected tricycles via a Dimroth rearrangement (Scheme 3).

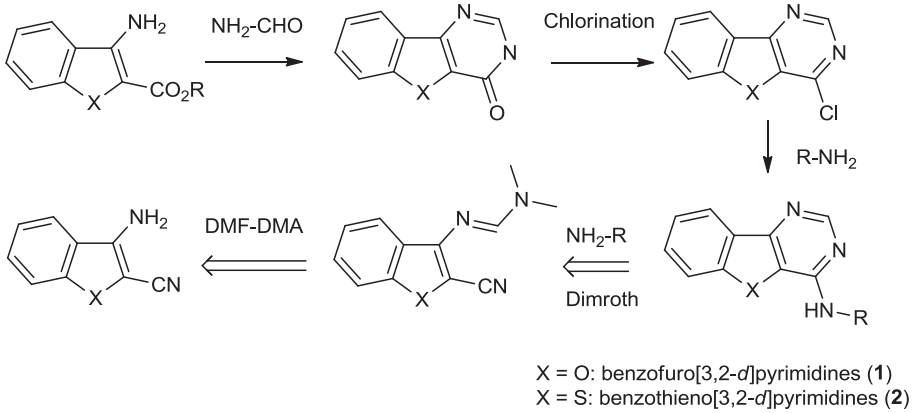
This "ancestral" transformation consists of a translocation of exocyclic and endocyclic heteroatoms present in both five- and six-membered heterocycles [5,6]. As shown in Scheme 3, the reaction generally leads to one of the two possible isomers, and the thermodynamic stability of the final compound is the driving force for its formation. For these reasons, the amount of heat supplied to the starting mixture will influence the final result.

Taking into account all these parameters, the retrosynthetic pathway chosen involved the synthesis of intermediate *N*,*N*-dimethylformamidine derivatives obtained by transformation of the starting 3-aminobenzo[*b*]furane- or 3-aminobenzo[*b*]thiophene-2-carbonitrile in the presence of dimethylformamide dimethyl acetal (DMF-DMA) under microwaves (Scheme 2).

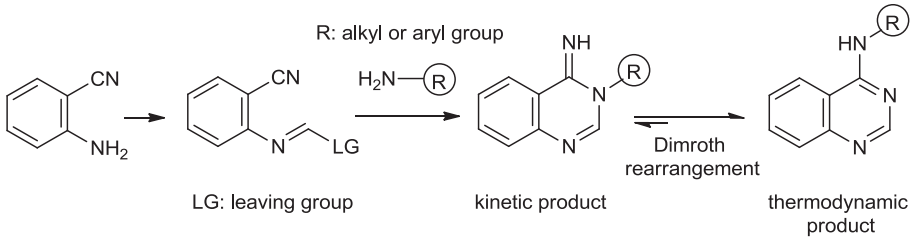
The two benzofurane and benzothiophene precursors (**3** and **4**) were obtained by methods previously described in the literature [8–10]. Subsequently, 3-amino-2-cyanobenzofurane **3** was prepared by treatment of 2-hydroxybenzonitrile with bromoacetonitrile in dimethylformamide. Ring closure of the cyanomethyl ether intermediate (not isolated) was performed in the presence of potassium carbonate (K_2CO_3) as base, which gave the target product in a good yield (63%) (Scheme 4) [8]. Its thiophenic analogue **4** was obtained in a similar procedure from 2-nitrobenzonitrile, 3-mercaptopropionitrile [9], and aqueous potassium hydroxide in DMF at 0°C, followed by addition of the alkylating agent. In this case, the cyanomethyl thioether intermediate was cyclized in the presence of potassium hydroxide (KOH) to the expected product in a very good yield (89%) [10] (Scheme 4).

Our study started with the synthesis of the *N*′-(2-cyanobenzofuran-3-yl)-*N*,*N*-dimethylformimidamide **5** and *N*′-(2-cyanobenzothiophen-3-yl)-*N*,*N*-dimethylformimidamide **6**. After optimization of the microwave conditions by varying reaction time, power input, temperature, and pressure, we were able to obtain in 15 min the expected *N*,*N*-dimethylformimidamides (**5** and **6**) in quantitative yields (99% after purification) (Scheme 5). Some comments can

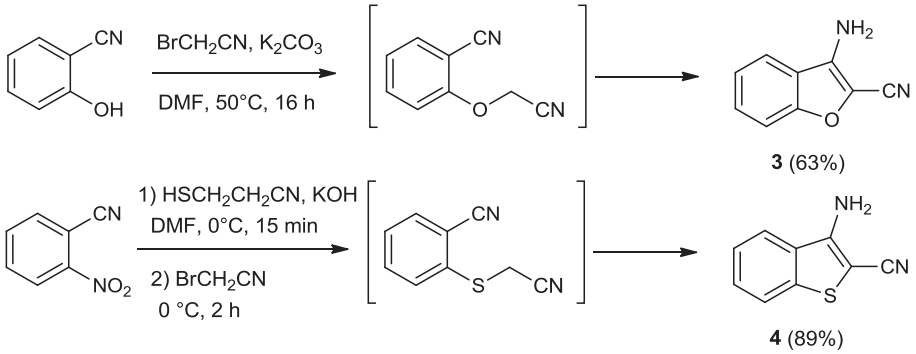
Scheme 2. Usual three-step pathway [3] and our retrosynthetic pathway of the target benzo[*b*]furo[3,2-*d*]pyrimidines (**1**) and benzo[*b*]thieno[3,2-*d*]pyrimidines (**2**).



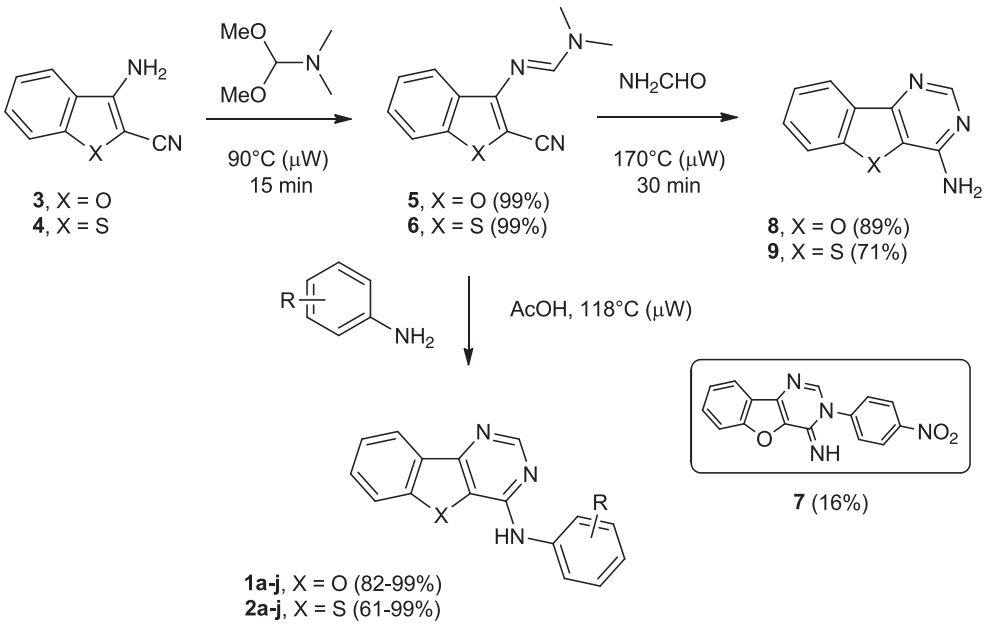
Scheme 3. General pathway of the Dimroth translocation, in the case of quinazolines from anthranilonitriles [5].



Scheme 4. Synthesis of benzofurane and benzothiophene precursors **3** and **4**.



Scheme 5. Microwave-assisted (μw) syntheses of benzo[*b*]furo- and benzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines; for reaction times and yields, see Table 1.



be made in comparison with previous works on various anthranilonitrile derivatives [5]. In the case of 2-aminobenzofuran-3-carbonitrile (**3**) and 2-aminobenzothiophene-3-carbonitrile **4**, the temperature used for a rapid and convenient production of compounds **5** and **6** must be increased from 70°C to 90°C, and the time of the synthesis of 10 min was also extended for an average irradiation time of 15 min (instead of 5 min for anthranilonitriles). The microwave heating was performed at atmospheric pressure in order to avoid hydrolysis of the final product or generation of by-products, which can occur when heating for too long or if microwave heating is combined with high pressure [5g].

The second step of the synthesis consisted of heating different anilines with **5** or **6** in the presence of acetic acid (AcOH). The choice of AcOH was guided by the fact that this carboxylic acid is a good solvent for heating under microwaves ($\tan \delta = 0.174$ at 2.45 GHz) [11]. The reactions were monitored by thin-layer chromatography to obtain the required reaction for a complete disappearance of the starting material (Table 1).

After various trials to optimize reaction parameters (time, temperature, and microwave power) and starting from **5**, we were able to obtain, in short times, excellent yields (87–99%) of the expected *N*-arylbenzo[*b*]furo[3,2-*d*] pyrimidin-4-amines (**1a–j**) (Scheme 5).

It should be noticed that the quantity of amine (1 equiv only) introduced into the reaction vial must be monitored. When an excess of aniline was used in the reaction mixture, the condensation of a part of the starting aromatic amine with acetic acid was observed and gave the corresponding acetamide derivatives as by-products [5g]. As described in various applications of this rearrangement, reaction time and yields depend on the nucleophilicity of the aniline and also on steric hindrance of the substituents [5,6]. The presence of large atoms or groups on the *ortho*-position of the aromatic amine (e.g., 4-bromo-2-fluoroaniline in Table 1) involved an increase of reaction time and slight decrease of the yields. Heating at higher temperatures in order to compensate this effect did not give the expected compound.

No traces of 3-arylbenzo[*b*]furo[3,2-*d*]pyrimidin-4-imine isomers (e.g., **7** in Scheme 5) were detected, except when the condensed aniline was substituted by a strong electron withdrawing group such as a nitro group. In that case, we observed initial condensation of the amine and ring closure into the 4-imino-isomer (**7** in Scheme 5), but the microwave heating was not sufficient to allow this kinetic intermediate to rearrange into the thermodynamic product substituted in position 4.

Table 1

Synthesis of *N*-arylbenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines (**1a–j**) and *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines (**2a–j**).

R	Product	Time (min)	Yield (%)[a]	Product	Time (min)	Yield (%)
	**1a**	5	99	**2a**	15	77
	**1b**	5	99	**2b**	20	61
	**1c**	5	98	**2c**	20	99
	**1d**	90	88	**2d**	210	76
	**1e**	15	82	**2e**	45	81
	**1f**	10	97	**2f**	30	84
	**1g**	5	77	**2g**	15	80
	**1h**	15	94	**2h**	30	68
	**1i**	10	98	**2i**	30	84
	**1j**	15	89	**2j**	30	66

Reactions were performed under microwave (μw) at 400 W on a 0.5-mmol scale from **3** or **4** with 1 equiv of aniline (MultiSYNTH™ from Milestone S.r.l. Italy).
[a]Yield of isolated product.

A library of novel *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines (**2a–j**) was prepared using similar experimental conditions and substituted anilines. We observed that the average time of the reactions needed to be at least three times increased compared with the corresponding benzofurane analogues. The most important observation was the slight decrease of the yields obtained for sulfur five-membered heterocycles (**2a–j**, Table 1). In this case, the nucleophilicity of condensed aniline was not the limiting factor. Long irradiation time seemed to overcome the difficulty for starting attack of aniline on the carbon of *N*,*N*-dimethylformimidamide **6**. Microwave irradiation at higher temperatures (180°C) decreased slightly the reaction times, but it involved diminished yields.

The last part of this work concerns the synthesis of benzo[*b*]furo[3,2-*d*]pyrimidin-4-amine (**8**) [7] and benzo[*b*]thieno[3,2-*d*]pyrimidin-4-amine **9** as sulfur analogue [12]. The synthesis of such compounds was realized in good yields by using high microwave heating to decompose formamide as material for introduction of nitrogen atoms in heterocyclic rings (Scheme 5) [13].

In this process, the use of dimethylformimidamides **5** and **6** showed to be an attractive method that allowed a short reaction time (30 min) associated to a convenient temperature of 170°C to avoid the *in situ* hydrogen cyanide formation, which is traditionally produced by thermal decomposition of formamide at higher temperatures (200–220°C) [14,15]. Considering these facts, we confirmed that our method constitutes an interesting and safe alternative to the harsh conditions usually described in the literature [3].

In a preliminary experiment, the antiproliferative effect of molecules (**1a–e**) and (**2a–e**), each one tested at three concentrations (0.001, 0.1, and 10 μ*M*), was studied on Caco-2 and HT-29 cells during 24, 48, and 72 h (**1e** and **2a** were not soluble in the conditions used). Proliferation of Caco-2 and HT-29 cells was not modified with molecules **1a–d** and **2b** (data not shown). Table 2 describes the results of the two promising compounds (**2c** and **2d**). Compounds **2c** and **2d** showed any effect on HT-29 proliferation (data not shown), whereas a weak inhibitory effect was observed in Caco-2 cells.

Indeed, a slight but significant proliferation inhibition of the Caco-2 colon cancer cells was noticed after 24 h of treatment with 0.1 or 10.0 μ*M* of compound (**2c**) (about 10% and 15% inhibition, respectively, $p < 0.05$) (Table 2). This inhibitory effect on Caco-2 proliferation was no longer observed after 24 h incubation. As assessed by MTT assays, compound **2d** inhibited Caco-2 cell growth at 10 μ*M* after 24 h of treatment (15% inhibition approximately), and a quite similar inhibitory effect (about 20%) was observed at 0.1 μ*M* after 72 h incubation (Table 2). Concentration below 0.1 μ*M* did not affect Caco-2 cell growth compared with untreated cells (data not shown). In comparison, the positive control, LY294002 (50 μ*M*), inhibited Caco-2 cell growth at 24, 48, and 72 h with an inhibitory effect of 20%, 35%, and 47%, respectively.

Considering the results obtained on HT29 cells with compounds **2c** and **2d**, we have not tested the molecule **2e** on these cells. In Caco-2 cells, it seems that molecule **2e** inhibited cell proliferation at a concentration of 10 μ*M* in a time-dependent manner: 24% growth inhibition at 48 h and 35% growth inhibition at 72 h (proliferation of $76.0 \pm 3.8\%$ and $64.8 \pm 1.4\%$, respectively, compared with solvent control). Concentrations of 0.1 μ*M* and 1 n*M* inhibited slightly Caco-2 proliferation at 72 h: about 9% and 6% inhibition, respectively (proliferation of $91.4 \pm 0.9\%$ and $93.6 \pm 0.5\%$, respectively, compared with solvent control).

It is well known that HT-29 and Caco-2 colorectal cancer cell lines contain different p53 mutations [16]. TP53 plays an important role in regulating cell survival. Mutation inducing a loss of p53 function could explain that molecules have proliferation effect on Caco-2 cells but not on HT-29. Compounds **2c** and **2d** showed a weak inhibitory effect on Caco-2 cells at concentration of 10 μ*M*; this effect appears to be transient, whereas compound **2e** at 10 μ*M* seems to inhibit proliferation in a time-dependent manner. Compared with other compounds tested (data not

Table 2

Proliferation of Caco-2 cells (mean ± SD in percentage) treated with compounds **2c** and **2d** after 24, 48, and 72 h treatment.

	Time of treatment (h)		
Drug concentrations (μ*M*)	24	48	72
LY294002 (50)	78.0 ± 5.2*	64.8 ± 3.1*	53.5 ± 7.4*
2c (10)	86.4 ± 6.7*	100.0 ± 14.7	86.1 ± 12.0
2c (0.1)	91.5 ± 7.2*	103.3 ± 10.6	90.8 ± 9.3
2d (10)	83.4 ± 11.3*	96.7 ± 13.5	85.1 ± 24.0
2d (0.1)	88.1 ± 13.7	98.9 ± 9.0	76.5 ± 17.8*

LY294002 was used as a positive control for growth inhibition.
*$p < 0.05$.

shown), these compounds have structure that seems to interfere with proliferation signaling.

CONCLUSION

The synthesis of a library of *N*-arylbenzo[*b*]furo[3,2-*d*] pyrimidin-4-amines was realized for the first time under microwaves via an accelerated Dimroth rearrangement from the corresponding 3-amino-2-cyanobenzofurane precursor. Good control of the reaction parameters offer comfortable use of microwave technology with safe and environmental benefits. It allowed an efficient heating of the reaction mixture, resulting in short time of reaction and very good yields. This very useful and rapid procedure was also successfully applied to the synthesis of novel *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines analogues taking into account the necessity to add more heat to the reaction mixture. The information given in this article is a further example that microwave heating can be a very powerful tool for chemists. Further investigations extending the families of heterocyclic precursors and the nature of the aromatic amines are underway in the hope to increase the interesting *in vitro* antiproliferative effects observed.

EXPERIMENTAL

All reactions were monitored by thin-layer chromatography with silica gel 60 F254 precoated aluminum plates (0.25mm). Melting points of solid compounds were measured on an Electrothermal IA 9000 melting point apparatus (compounds **3** and **4**) or a STUART apparatus advanced SMP3 with a precision of ±0.5°C (compounds **1**, **2**, **5–9**) and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum 100 Series FTIR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Absorption bands are given in cm^{-1}.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on an AVANCE 400 MHz spectrometer (compounds **3** and **4**) or on a Bruker DXP 300 spectrometer at 300, 75, and 282 MHz respectively (compounds **1**, **2**, **5–9**). Abbreviations used for peak multiplicities are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet and br (broad). Coupling constants *J* are given in hertz (Hz), and chemical shifts are given in parts per million (δ) and calibrated with DMSO-d_6 or D_2O (residual solvent signals). Mass spectra analysis was performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters ZQ 2000 and Waters LCP 1^{er} XR spectrometers.

Microwave experiments were conducted in two commercial microwave reactors especially designed for synthetic chemistry. Start SYNTH (Milestone S.r.l. Italy) is a multimode cavity with a microwave power delivery system ranging from 0 to 1200 W. Open vessel experiments were carried out in a 250-mL round bottom flask fitted with a reflux condenser. The temperature was monitored via a fiber-optic contact thermometer protected in a Teflon-coated ceramic well inserted directly in the reaction mixture or via contact-less infrared pyrometer. 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, pressure, and power profiles were monitored in both cases through the EASY-Control software provided by the manufacturer.

Multi SYNTH (Milestone S.r.l. Italy) is a novel dedicated microwave system for synthetic applications. It allows a fast reaction optimization, providing high energy density in a single-mode such as configuration and an efficient scale-up (maximum working volume 300 mL) through parallel synthesis in a multimode configuration. The instrument features a special shaking system that ensures high homogeneity of the reaction mixtures. It is equipped with an indirect pressure control through precalibrated springs at the bottom of the vessel shields and with both contact-less infrared pyrometer (IRT) and fiber-optic contact thermometer (FO) for accurate temperature measurement. It is noteworthy that the IRT can be calibrated directly on the temperature read by the FO to ensure the highest accuracy and reproducibility.

3-Amino-2-cyanobenzo[b]furane (3). To a suspension of 2-hydroxybenzonitrile (4.00 g, 33.6 mmol) and K_2CO_3 (10.21 g, 73.9 mmol) in DMF (80 mL), bromoacetonitrile (2.57 mL, 36.9 mmol) was added at room temperature with stirring. The reaction mixture was heated at 50°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 by chromatography on silica gel using dichloromethane as eluent. The desired product (**3**) was isolated as a white powder (3.35 g, 63%); mp 160–161°C (lit. [8]: 162–163°C); IR (KBr) ν_{max} (cm^{-1}): 3445, 3356, 2199 (CN), 1637, 1619, 1607, 1584, 1489, 1449, 1419, 1337, 1251, 1156, 1106, 1008, 885, 848, 761, 735, 648; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, $J = 7.6$ Hz, 1H), 7.49–7.57 (m, 2H), 7.34 (td, $J_1 = 1.2$ Hz, $J_2 = 7.9$ Hz, 1H), 6.70 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.3, 142.6, 129.3, 122.8, 121.5, 121.1, 114.6, 112.0, 106.5; MS (ESI) *m/z* (%): 158.9 [$(M+H)^+$, 100].

3-Amino-2-cyanobenzo[b]thiophene (4). 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 (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 (**4**) was isolated as a white powder (3.56 g, 89%); mp 156–157°C (lit. [10]: 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].

(E)-N′-(2-Cyanobenzo[b]furan-3-yl)-N,N-dimethylformimidamide (5). A mixture of 3-aminobenzofurane-2-carbonitrile (**3**) (0.5 g, 3.16 mmol) and DMF DMA (4.4 mL, 31.60 mmol) was irradiated at 90°C (800 W) for 15 min. The final solution was cooled to room temperature, and cold water was added. The solid was filtered off, washed with cold water, and dried over magnesium sulfate. Purification by column chromatography over silica gel using dichloromethane/petroleum ether (5:5, v/v) as the eluent gave the desired compound (**5**) as a pale yellow powder

(671 mg; 99%); mp 107–108°C; IR (KBr) ν_{max} (cm^{-1}): 2210 (CN), 1623, 1588, 1568, 1447, 1435, 1384, 1334, 1244, 1192, 1165, 1115, 1095, 1067, 1021, 936, 742, 672, 661; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (s, 1H, NC*H*N), 7.88 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-7), 7.55 (m, 2H, J_1 = 1 Hz, J_2 = 2 Hz, H-5 and H-6), 7.36 (td, 1H, J_1 = 2 Hz, J_2 = 7 Hz, H-4), 3.13 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2 (N*C*N), 154.7 (C-3*a*), 145.9 (C-1), 128.8 (C-2), 123.6 (C-5), 122.6 (C-7*a*), 121.8 (C-6), 114.6 (*C*N), 113.9 (C-7), 112.2 (C-4), 33.9 (N(*C*H_3)$_2$); HRMS calcd for $C_{12}H_{11}N_3O$ $[M+H]^+$ 214.0980, found 214.0972.

(E)-N′-(2-Cyanobenzo[b]thiophen-3-yl)-N,N-dimethylformimidamide (6). A mixture of 3-aminobenzothiophen-2-carbonitrile (**4**) (0.5 g; 2.87 mmol) and DMF DMA (3.9 mL; 28.70 mmol) was irradiated at 90°C (800 W) for 15 min. 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. Purification by column chromatography over silica gel using dichloromethane/petroleum ether (5:5, v/v) as the eluent gave the desired compound (**6**) as a yellow powder (655 mg; 99%); 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*C*N), 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(*C*H_3)$_2$); HRMS calcd for $C_{12}H_{11}N_3S$ $[M+H]^+$ 230.0752, found 230.0749.

General procedure for the synthesis of *N*-arylbenzo[*b*]furo[3,2-*d*]pyrimidin-4-amines (1a–j). A mixture of (*E*)-*N*′-(2-cyanobenzo[*b*]furan-3-yl)-*N*,*N*-dimethylformimidamide **5** (0.1 g, 0.47 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 stepwise gradient of petroleum ether/ethyl acetate (100:0 to 0:100, v/v) as the eluent to give the desired compounds.

***N*-Phenylbenzo[b]furo[3,2-d]pyrimidin-4-amine (1a).** Yield: 99%; pale yellow powder; mp 201−202°C (lit. [11]: 190°C); IR (KBr) ν_{max} (cm^{-1}): 3457, 1585, 1566, 1513, 1477, 1437, 1406, 1360, 1308, 1279, 1273, 1158, 1133, 969, 743, 734, 684, 647, 617; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H, N*H*), 8.66 (s, 1H, H-2), 8.17 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-9), 7.94 (dd, 2H, J_1 = 2 Hz, J_2 = 8 Hz, H-ar), 7.86 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-8), 7.75 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-7), 7.54 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-6), 7.48 (td, 2H, J_1 = 2 Hz, J_2 = 8 Hz, H-ar), 7.09 (td, 1H, J_1 = 2 Hz, J_2 = 8 Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.8 (C-4), 152.9 (C-2), 146.5 (C-5*a*), 145.9 (C-4*a*), 139.2 (C-11), 134.7 (C-7), 130.5 (C-8), 128.6 (C-13), 124.2 (C-9), 123.0 (C-14), 122.2 (C-9*a*), 121.4 (C-6), 120.7 (C-12), 112.7 (C-9*b*); HRMS calcd for $C_{16}H_{12}N_3O$ $[M+H]^+$ 262.0980, found 262.0968.

***N*-(4-Methoxyphenyl)benzo[b]furo[3,2-d]pyrimidin-4-amine (1b).** Yield: 99%; brown powder; mp 158–159°C; IR (KBr) ν_{max} (cm^{-1}): 3446, 1634, 1612, 1589, 1506, 1489, 1417, 1307, 1295, 1251, 1229, 1200, 1158, 1146, 1134, 1090, 1040, 971, 814, 743, 693; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.02 (s, 1H, N*H*), 8.59 (s, 1H, H-2), 8.13 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-9), 7.85–7.70 (m, 4H, H-ar, H-8 and H-7), 7.52 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-6), 6.95 (td, 2H, J_1 = 2 Hz, J_2 = 8 Hz, H-ar), 3.76 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.7 (C-4), 155.4 (C-14), 153.0 (C-2), 146.6 (C-5*a*), 145.4 (C-4*a*), 134.6 (C-7), 132.0 (C-11), 130.3 (C-8), 124.1 (C-9), 122.6 (C-13), 122.3 (C-9*a*), 121.3 (C-6), 113.8 (C-12), 112.7 (C-9*b*), 55.2 (O*C*H_3); HRMS calcd for $C_{17}H_{14}N_3O_2$ $[M+H]^+$ 292.1086, found 292.1073.

***N*-(3,4-Dimethoxyphenyl)benzo[b]furo[3,2-d]pyrimidin-4-amine (1c).** Yield: 98%; gray powder; mp 173–174°C; IR (KBr) ν_{max} (cm^{-1}): 3448, 2828, 1637, 1509, 1481, 1450, 1423, 1268, 1233, 1201, 1173, 1141, 1034, 987, 838, 830, 778, 761, 748, 700, 611; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.05 (s, 1H, N*H*), 8.66 (s, 1H, H-2), 8.19 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-9), 7.89 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-6), 7.77 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-7), 7.63–7.52 (m, 3H, H-ar and H-8), 7.01 (dd, 1H, J_1 = 1 Hz, J_2 = 8 Hz, H-ar), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.7 (C-4), 153.0 (C-2), 148.4 (C-13), 146.6 (C-5*a*), 145.4 (C-4*a*), 144.9 (C-14), 134.7 (C-7), 132.5 (C-11), 130.3 (C-8), 124.2 (C-9), 122.3 (C-9*a*), 121.3 (C-6), 113.0 (C-15), 112.6 (C-9*b*), 111.9 (C-16), 106.3 (C-12), 55.7 (O*C*H_3), 55.4 (O*C*H_3); HRMS calcd for $C_{18}H_{16}N_3O_3$ $[M+H]^+$ 322.1192, found 322.1183.

***N*-(4-Bromo-2-fluorophenyl)benzo[b]furo[3,2-d]pyrimidin-4-amine (1d).** Yield: 88%; pale yellow powder; mp 174–175°C; IR (KBr) ν_{max} (cm^{-1}): 3432, 1632, 1519, 1486, 1473, 1466, 1408, 1395, 1310, 1185, 1142, 1107, 1087, 967, 873, 848, 826, 799, 746, 741; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.02 (s, 1H, N*H*), 8.57 (s, 1H, H-2), 8.15 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-9), 7.84 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-6), 7.78–7.45 (m, 5H, H-ar; H-8 and H-7), ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0 (C-4), 154.5 (C-12), 153.0 (C-2), 146.7 (C-5*a*), 146.4 (C-4*a*), 134.7 (C-7), 130.7 (C-8), 128.6 (C-11), 127.5 (C-15), 124.3 (C-9), 121.9 (C-9*a*), 121.5 (C-6), 119.5 (C-13), 119.2 (C-16), 117.4 (C-14), 112.8 (C-9*b*); HRMS calcd for $C_{16}H_{10}N_3OBrF$ $[M+H]^+$ 357.9991, found 357.9981.

***N*-(3-Chloro-4-fluorophenyl)benzo[b]furo[3,2-d]pyrimidin-4-amine (1e).** Yield: 82%; white powder; mp 221–222°C; IR (KBr) ν_{max} (cm^{-1}): 1635, 1618, 1489, 1414, 1358, 1309, 1266, 1212, 1198, 1092, 976, 817, 794, 746, 692, 577, 564, 502, 435, 428; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H, N*H*), 8.71 (s, 1H, H-2), 8.30 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-9), 8.17 (d, 1H, J_1 = 7 Hz, H-ar), 7.89–7.87 (m, 2H, H-8 and H-ar), 7.78 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-7), 7.53 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-6), 7.41 (td, 2H, J_1 = 1 Hz, J_2 = 8 Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.9 (C-4), 152.8 (C-2), 146.1 (C-5*a*), 146.0 (C-4*a*), 136.6 (C-14), 134.6 (C-7), 130.7 (C-8), 124.3 (C-9), 122.1 (C-9*a*), 121.7 (C-11), 121.5 (C-6), 120.8 (C-13), 118.8 (C-16), 116.9 (C-12), 116.6 (C-15), 112.7 (C-9*b*); HRMS calcd for $C_{16}H_{10}N_3OClF$ $[M+H]^+$ 314.0491, found 314.0496.

***N*-(3,5-Dimethoxyphenyl)benzo[b]furo[3,2-d]pyrimidin-4-amine (1f).** Yield: 97%; creamy powder; mp 206–207°C; IR (KBr) ν_{max} (cm^{-1}): 3451, 1609, 1585, 1566, 1480, 1446, 1424, 1303, 1192, 1161, 1090, 1071, 845, 830, 754, 742, 679, 619, 542, 430; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.10 (s, 1H, N*H*), 8.69 (s, 1H, H-2), 8.15 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-9), 7.86 (dd, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-6), 7.76 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-7), 7.55 (td, 1H, J_1 = 1 Hz, J_2 = 7 Hz, H-8), 7.28 (s, 2H, H-ar), 6.26 (s, 1H, H-ar), 3.76 (s, 6H, (OCH_3)$_2$); ^{13}C NMR (75 MHz,

DMSO-d_6): δ 160.4 (C-13), 155.8 (C-4), 152.8 (C-2), 146.4 (C-5*a*), 145.9 (C-4*a*), 140.9 (C-11), 134.8 (C-7), 130.5 (C-8), 124.3 (C-9), 122.2 (C-9*a*), 121.4 (C-6), 112.7 (C-9*b*), 99.0 (C-12), 94.7 (C-14), 55.1 ((O*C*H$_3$)$_2$); HRMS calcd for $C_{18}H_{16}N_3O_3$ $[M+H]^+$ 322.1192, found 322.1180.

***N*-(3,4,5-Trimethoxyphenyl)benzo[b]furo[3,2-d]pyrimidin-4-amine (1g).** Yield: 77%; pale brown powder; mp 183–184°C; IR (KBr) ν_{max} (cm^{-1}): 3447, 1638, 1585, 1567, 1504, 1473, 1445, 1416, 1231, 1182, 1128, 1090, 999, 805, 736, 627, 609, 594, 574, 528, 422; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.05 (s, 1H, N*H*), 8.67 (s, 1H, H-2), 8.15 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 7.85 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.75 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.56 (td, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-8), 7.39 (s, 2H, H-ar), 3.80 (s, 6H, (OC*H*$_3$)$_2$), 3.66 (s, 3H; OC*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.8 (C-4), 152.9 (C-13), 152.8 (C-2), 146.4 (C-5*a*), 145.7 (C-4*a*), 135.3 (C-15), 134.7 (C-7), 133.5 (C-11), 130.5 (C-8), 124.2 (C-9), 122.2 (C-9*a*), 121.4 (C-6), 112.7 (C-9*b*), 98.7 (C-12), 60.1 (O*C*H$_3$), 55.1 ((O*C*H$_3$)$_2$); HRMS calcd for $C_{19}H_{18}N_3O_4$ $[M+H]^+$ 352.1297, found 352.1297.

***N*-(Benzo[d][1,3]dioxol-5-yl)benzofuro[3,2-d]pyrimidin-4-amine (1h).** Yield: 94%; brown powder; mp 218–219°C; IR (KBr) ν_{max} (cm^{-1}): 1641, 1609, 1480, 1448, 1262, 1190, 1140, 1035, 927, 845, 789, 782, 748, 697, 648, 634, 600, 571, 502; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.07 (s, 1H, N*H*), 8.62 (s, 1H, H-2), 8.14 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 7.85 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.74 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.58–7.51 (m, 2H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-8 and H-ar), 7.33 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 6.93 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 6.03 (s, 2H, H-18); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.7 (C-4), 152.9 (C-2), 146.9 (C-13), 146.5 (C-5*a*), 145.5 (C-4*a*), 143.0 (C-14), 134.6 (C-7), 133.3 (C-11), 130.4 (C-8), 124.2 (C-9), 122.2 (C-9*a*), 121.4 (C-6), 113.9 (C-16), 112.7 (C-9*b*), 107.9 (C-15), 103.2 (C-12), 101.0 (C-18); HRMS calcd for $C_{17}H_{12}N_3O_3$ $[M+H]^+$ 306.0879, found 306.0888.

***N*-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)benzofuro[3,2-d]pyrimidin-4-amine (1i).** Yield: 98%; pale brown powder; mp 212–213°C; IR (KBr) ν_{max} (cm^{-1}): 1648, 1617, 1501, 1479, 1433, 1416, 1304, 1278, 1265, 1257, 1244, 1200, 1166, 1068, 885, 793, 759, 742, 576, 431; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.00 (s, 1H, N*H*), 8.61 (s, 1H, H-2), 8.14 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 7.85 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.74 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.56–7.52 (m, 2H, $J_1 = 2$ Hz, $J_2 = 8$ Hz, H-8 and H-ar), 7.34 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 6.85 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-ar), 4.25 (br s, 4H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6 (C-4), 152.9 (C-2), 146.4 (C-5*a*), 145.5 (C-4*a*), 142.8 (C-13), 139.4 (C-14), 134.7 (C-7), 132.6 (C-11), 130.4 (C-8), 124.2 (C-9), 122.2 (C-9*a*), 121.3 (C-6), 116.6 (C-15), 114.2 (C-16), 112.7 (C-9*b*), 110.0 (C-12), 64.2 (C-18), 64.0 (C-19); HRMS calcd for $C_{18}H_{14}N_3O_3$ $[M+H]^+$ 320.1035, found 320.1028.

***4*-(Benzofuro[3,2-d]pyrimidin-4-ylamino)-2-nitrophenol (1j).** Yield: 89%; white powder; mp 262–263°C; IR (KBr) ν_{max} (cm^{-1}): 3289, 1643, 1591, 1551, 1518, 1486, 1306, 1269, 1253, 1180, 1151, 1091, 1035, 978, 833, 759, 677, 584, 570, 552; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.31 (s, 1H, N*H*), 8.67 (s, 1H, H-2), 8.66 (d, 1H, $J = 2$ Hz, H-ar), 8.15 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.02 (dd, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-ar), 7.87 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.74 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.54 (td, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.18 (d, 1H, $J = 7$ Hz, H-ar), 6.03 (s, 2H, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.8 (C-4), 152.9 (C-2), 148.3 (C-14), 146.2 (C-5*a*), 145.9 (C-4*a*), 135.7 (C-13), 134.6 (C-7), 131.0 (C-11), 130.5 (C-8), 128.6 (C-16), 124.3 (C-9), 122.1 (C-9*a*), 121.4 (C-6), 119.4 (C-15), 116.3 (C-12), 112.7 (C-9*b*); HRMS calcd for $C_{16}H_{11}N_4O_4$ $[M+H]^+$ 323.0780, found 323.0771.

3-(4-Nitrophenyl)benzo[b]furo[3,2-d]pyrimidin-4(3H)-imine (7). Yield: 16%; white powder; mp 282–283°C; IR (KBr) ν_{max} (cm^{-1}): 1644, 1595, 1567, 1509, 1496, 1411, 1341, 1305, 1241, 1182, 1149, 1093, 970, 863, 853, 831, 745, 706, 660; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82 (s, 1H, H-2), 8.27 (s, 4H, H-ar), 8.20 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 7.90 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-8), 7.77 (td, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-7), 7.56 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9 (C-14), 156.2 (C-4), 152.6 (C-2), 147.1 (C-5*a*), 146.0 (C-4*a*), 145.5 (C-11), 141.4 (C-9*b*), 131.1 (C-7), 124.9 (C-12), 124.5 (C-9*a*), 121.9 (C-8), 121.6 (C-9), 119.4 (C-13), 112.8 (C-6); HRMS calcd for $C_{16}H_{11}N_4O_3$ $[M+H]^+$ 307.0831, found 307.0829.

General procedure for the synthesis of *N*-arylbenzo[*b*]thieno[3,2-*d*]pyrimidin-4-amines (2a–j). A mixture of (*E*)-*N*′-(2-cyanobenzo[*b*]thiophen-3-yl)-*N*,*N*-dimethylformimidamide **6** (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 to 0:100, v/v) as the eluent to give the desired compounds.

***N*-Phenylbenzo[b]thieno[3,2-d]pyrimidin-4-amine (2a).** 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-8), 7.80 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-H-ar), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.61 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 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.

***N*-(4-Methoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (2b).** 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-8), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.69–7.58 (m, 3H, H-ar and H-6), 6.98 (dd, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-ar), 3.79 (s, 3H, OC*H*$_3$); ^{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 (O*C*H$_3$); HRMS calcd for $C_{17}H_{14}N_3OS$ $[M+H]^+$ 308.0858, found 308.0846.

***N*-(3,4-Dimethoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (2c).** Yield: 99%; gray 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-7),

7.64 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.30 (dd, 1H, $J_1 = 1$ 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, OC$\underline{H}_3$), 3.77 (s, 3H, OC$\underline{H}_3$); ^{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 (O$\underline{C}$H$_3$), 55.5 (O$\underline{C}$H$_3$); HRMS calcd for $C_{18}H_{16}N_3O_2S[M+H]^+$ 338.0963, found 338.0956.

***N*-(4-Bromo-2-fluorophenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (2d).** 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; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.81 (s, 1H, N$\underline{H}$), 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.

***N*-(3-Chloro-4-fluorophenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (2e).** Yield: 81%; white powder; mp 241–242°C; IR (KBr) ν_{max} (cm^{-1}): 1614, 1563, 1491, 1473, 1449, 1433, 1396, 1264, 1200, 1057, 962, 879, 809, 779, 746, 728, 710, 692, 574; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.90 (s, 1H, N$\underline{H}$), 8.79 (s, 1H, H-2), 8.38 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 8.22 (d, 1H, $J_1 = 7$ Hz, H-ar), 8.17 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.82–7.72 (m, 2H, H-7 and H-ar), 7.63 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-6), 7.45 (td, 2H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.3 (C-4), 155.0 (C-2), 154.3 (C-5*a*), 139.8 (C-4*a*), 136.3 (C-14), 133.5 (C-7), 130.0 (C-8), 125.5 (C-9), 123.7 (C-9*a*), 123.1 (C-6), 122.3 (C-11), 119.0 (C-13), 118.7 (C-16), 116.8 (C-12), 116.5 (C-15), 115.3 (C-9*b*); HRMS calcd for $C_{16}H_{10}N_3SClF$ $[M+H]^+$ 330.0256, found 330.0250.

***N*-(3,5-Dimethoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (2f).** Yield: 84%; gray 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$\underline{H}$), 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-7), 7.64 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.13 (s, 2H, H-ar), 6.30 (s, 1H, H-ar), 3.76 (s, 3H, OC$\underline{H}_3$), 3.35 (s, 3H, OC$\underline{H}_3$); ^{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 (O$\underline{C}$H$_3$), 55.5 (O$\underline{C}$H$_3$); HRMS calcd for $C_{18}H_{16}N_3O_2S[M+H]^+$ 338.0963, found 338.0956.

***N*-(3,4,5-Trimethoxyphenyl)benzo[b]thieno[3,2-d]pyrimidin-4-amine (2g).** 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$\underline{H}$), 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-7), 7.61 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 7.21 (s, 2H, H-AR), 3.80 (s, 6H, (OC$\underline{H}_3$)$_2$), 3.68 (s, 3H, OC$\underline{H}_3$); ^{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 ((O$\underline{C}$H$_3$)$_2$), 55.8 (O$\underline{C}$H$_3$); HRMS calcd for $C_{19}H_{18}N_3O_3S[M+H]^+$ 368.1069, found 368.1060.

***N*-(Benzo[d][1,3]dioxol-5-yl)benzo[4,5]thieno[3,2-d]pyrimidin-4-amine (2h).** 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; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.65 (s, 1H, N$\underline{H}$), 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-7), 7.63 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 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.

***N*-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)benzo[4,5]thieno[3,2-d]pyrimidin-4-amine (2i).** Yield: 84%; gray 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; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.59 (s, 1H, N$\underline{H}$), 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-7), 7.63 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 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.

***4*-(Benzo[4,5]thieno[3,2-d]pyrimidin-4-ylamino)-2-nitrophenol (2j).** 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; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.87 (s, 1H, N$\underline{H}$), 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-ar), 7.72 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-7), 7.64 (td, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-8), 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.

Benzo[b]furo[3,2-d]pyrimidin-4-amine (8). Formamide (2 mL) was added to (*E*)-*N*′-(2-cyanobenzo[*b*]furan-3-yl)-*N*,*N*-dimethylformimidamide (**5**) (0.1 g, 0.47 mmol). The mixture was irradiated at 170°C (200W) for 30 min. 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 compound (**8**) (0.076 g, 89%) as a white powder; mp 273–274°C (lit. [7]: 258°C); IR (KBr) ν_{max} (cm^{-1}): 3308, 3124, 1655, 1628, 1598, 1554, 1446, 1418, 1327, 1296, 1274, 1185, 1155, 1097, 1052, 964, 827, 751, 741, 644, 616; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (s, 1H, H-2), 8.09 (dd, 1H, $J_1 = 1$ Hz, $J_2 = 7$ Hz, H-9), 7.78 (dd, 2H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-8), 7.62 (td, 1H, $J_1 = 2$ Hz, $J_2 = 7$ Hz, H-7), 7.57 (s, 2H, N$\underline{H}_2$), 7.49 (td, 1H, $J_1 = 1$ Hz, $J_2 = 8$ Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6 (C-4),

153.5 (C-5*a*), 150.3 (C-2), 145.3 (C-4*a*), 134.3 (C-9*a*), 130.1 (C-7), 123.9 (C-8), 122.3 (C-9*b*), 121.3 (C-9), 113.7 (C-6); HRMS calcd for $C_{10}H_8N_3O$ $[M+H]^+$ 186.0667, found 186.0657.

Benzo[b]thieno [3,2-d]pyrimidin-4-amine (9). Formamide (2 mL) was added to (*E*)-*N*′-(2-cyanobenzo[*b*]thiophen-3-yl)-*N*,*N*-dimethylformimidamide (**6**) (0.1 g, 0.43 mmol). The mixture was irradiated at 170°C (200W) for 90 min. 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 compound (**9**) (0.062 g, 71%) as a brown powder; mp 301–302°C (lit. [12]: 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, 2H, $J_1 = 2$ 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.

General procedure for antiproliferative activity. ***Cell culture.*** Human HT-29 and Caco-2 colorectal adenocarcinoma cells were purchased from American Type Culture Collection (Manassas, VA, USA). HT-29 and Caco-2 colorectal cancer cell lines possess different p53 mutations. HT29 contains mutation at codon 273 resulting in an Arg → His substitution and overproduction of p53, whereas Caco2 contains a deletion and a termination signal at codon 204, which impaired p53 function [16]. The cells were grown in Dulbecco's modified Eagle's medium supplemented with 20% fetal bovine serum (Invitrogen, France), 2 m*M* L-glutamine (Invitrogen) and penicillin (10 U/mL)/streptomycin (10 µg/mL) at 37°C with 5% CO_2 and 90% relative humidity.

MTT proliferation assay. HT-29 and Caco-2 cells were seeded at a density of 8000 cells/well in 96-well microplates. Cells were treated the next day and let to proliferate for 96 h with or without molecules. Compounds **1a–e** and **2a–e** were dissolved in DMSO (Sigma-Aldrich, France) to obtain a concentration of 100 mmol/L and further diluted to the indicated concentrations in medium immediately before performing each experiment. Molecules **1e** and **2a** were not tested because of their poor solubility in solvent. MTT test was carried out daily after treatment (24, 48, or 72 h) as previously described [17]. The final concentration of DMSO in culture medium was maintained at 0.1%. LY294002 (Sigma-Aldrich), a PI3K inhibitor, was used as a positive control for growth inhibition.

Statistical analysis. Data are presented as mean ± SD from at least three independent experiments for molecules **2c** and **2d** and two independent experiments for molecule **2e**. At least six different replicates were conducted for each compound. For molecules **2c** and **2d**, statistical analysis was performed with nonparametric test (Mann–Whitney *U*-test between two groups) using SigmaStat software. Differences were considered statistically significant at a p-value < 0.05. First, the two controls were compared, control without and control with solvent, and no effect of the solvent was seen. Then, the control with the solvent was compared with the treated cells.

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