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Convenient synthesis of 2,4-disubstituted pyrido[2,3-*d*]pyrimidines via regioselective palladium-catalyzed reactions

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ABSTRACT

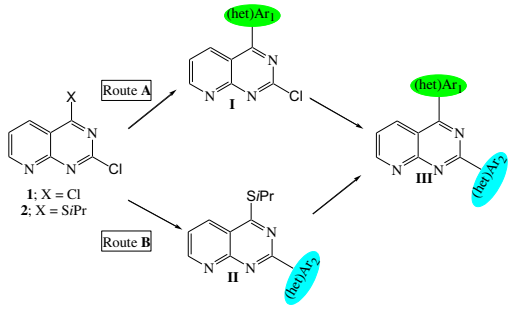
A novel and effective route for the synthesis of 2,4-disubstituted pyrido[2,3-*d*]pyrimidines **III** is reported starting from the corresponding 2,4-dichloropyridopyrimidine **1** through regioselective functionalization palladium-catalyzed C–C coupling reactions, by two successive palladium-catalyzed reactions involving an original regioselective chlorine discrimination. Alternatively, type **III** compounds were elaborated from **2** by C-2 chlorine further displacement of the C-4 isopropylsulfanyl group, which acted as a temporary C-4 protecting group. Further Suzuki–Miyaura cross-coupling reactions led to C-2 and C-4 disubstituted compounds.

1. Introduction

Palladium-catalyzed cross-coupling reactions represent a powerful method for the formation of highly substituted heterocycles.[1] The regioselective functionalization of polyhalogenated heteroaromatics in such reactions has been extensively studied and can provide a versatile means for the synthesis of libraries containing functionalized substituents in specific positions of the heterocyclic scaffold.[2]

The pyridopyrimidine scaffold is present in a great number of biologically active drugs, e.g., PDGF, EGFR, DMFR, P38 MAP kinase,[3] P13 kinase,[4] tyrosine kinase,[5] adenosine kinase,[6,7] cyclin-dependent kinase inhibitors,[8,9] and pro-apoptotic agents.[10] Hence, the synthesis of pyridopyrimidine derivatives provides an interesting challenge in medicinal chemistry.

In connection with our research program focusing on the preparation of new therapeutic agents, our group previously reported an example of the selective bifunctionalization of pyrido[2,3-*d*]pyrimidines in positions 2 and 4[11] and has recently developed original strategies to design 2,4-disubstituted pyrido[3,2-*d*]pyrimidines.[12] Encouraged by these results, we decided to extend this methodology to the synthesis of isomeric position 2,4-di(het)aryl-pyrido[2,3-*d*]pyrimidines via regioselective cross-coupling reactions. In the present paper, we describe the selective and sequential palladium-catalyzed reactions used to prepare compounds **III** from **1** and **2** (Scheme 1).



Scheme 1. Routes **A** and **B** to design derivatives **I**–**III**.

As shown in Scheme 1 we first performed a chlorine discrimination on **1** leading first to 4-(het)Ar$_1$-2-chloro derivatives **I** followed by dissymmetric 2,4-di(het)aryl compounds **III**. As an alternative, two different het(aryl) were introduced on **III** via derivatives **II** by sequential release of the 2-chlorine atom prior to the 4-Si-Pr group, which acted as a C-2 temporary protective group during palladium-catalyzed reactions. These two interesting,

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convergent and efficient synthetic pathways offer numerous dissymmetric 2,4-di(het)aryl-pyrido[2,3-*d*]pyrimidines.

2. Results and discussion

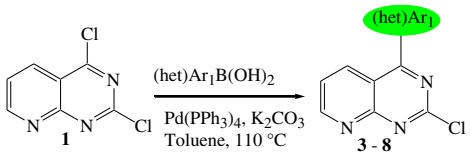
The first synthetic route **A** was achieved from 2,4-dichloropyrido[2,3-*d*]pyrimidine **1**, prepared from 2-aminonicotinic acid according to the procedure described in the literature.[11]

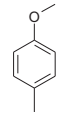
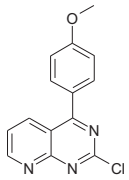
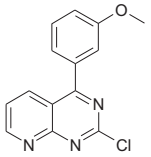
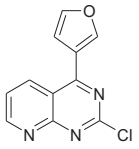
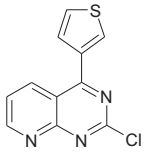
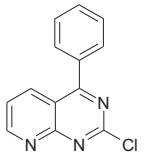
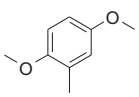
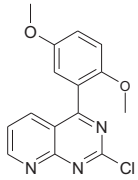
The Suzuki–Miyaura cross-coupling reactions were first performed with a slight excess of boronic acid and only 0.05 mol % of $Pd(PPh_3)_4$ and K_2CO_3 (1.5 equiv) in toluene at 110 °C. After 2–4 h, the regioselective C-4 arylation occurred, and derivatives of type **I** were isolated in 69–83% yields (Table 1). On the basis of proportions implemented by Wipf et al.,[2] and Tikad et al.[12b] we have used a near stoichiometric amount of boronic acid and 2,4-dichloropyrido[2,3-*d*]pyrimidine **1**, under these conditions no trace of bisubstituted compound was observed, indicating the lack of reactivity of the 2-Cl versus the 4-Cl atom.

The C-4 arylations via Suzuki reaction were similarly performed and led to type **I** products (Table 1, entries 1–6) in very good yields (69–83%) starting from phenyl-, hetaryl-, and arylboronic acids with the aromatic ring substituted by electron-donating groups. However, when using pyridinylboronic acid and arylboronic acids functionalized by electron-withdrawing groups (NO_2, CN), only starting material was recovered.

An X-ray analysis performed with compound **3** formally established the regioselectivity of arylation in position C-4 of the 2,4-dichloropyrido[2,3-*d*]pyrimidine (Fig. 1).

Table 1
Selective Suzuki reactions on **1**



Entry	(het)Ar_1	Products		Yields[a] (time)
1			**3**	83% (2 h)
2			**4**	80% (3 h)
3			**5**	81% (2 h)
4			**6**	83% (2 h)
5			**7**	81% (2 h)
6			**8**	69% (4 h)

[a] Yields are given for isolated products.

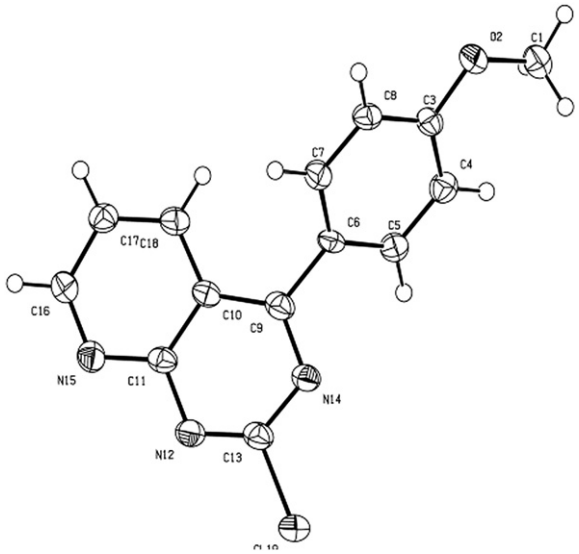


Fig. 1. ORTEP view of compound **3**.

In the next step we explored the reactivity of compounds **3**–**8** through Suzuki cross-coupling. All the reactions required 1.2 equiv of boronic acid and only 5 mol % of catalyst, and 2.0 equiv of Na_2CO_3 in a mixture of toluene/ethanol (6/2 mL) at 110 °C.

The reactions were stopped when the starting material completely disappeared. The second aryl or hetaryl was successfully introduced by C-2 chlorine displacement and the expected products **9**–**18** were obtained after purification by flash silica gel chromatography. The isolated products yields oscillated between 61% and 86% for a fixed reaction time of only a few hours (Table 2).

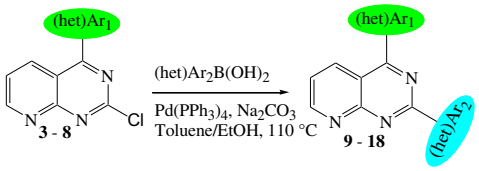
The influence of cosolvent on the Suzuki cross-coupling reaction has been previously reported in the literature.[13] Herein, the high efficiency of the EtOH cosolvent may be due to the increased solubility of the reagents.[14]

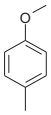
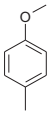
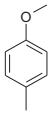
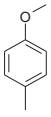
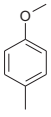
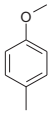
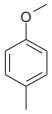
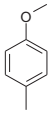
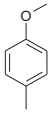
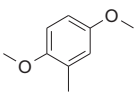
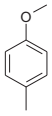
The structure of compound **17** was clearly elucidated by X-ray analysis (Fig. 2).

In the route **B**, the idea was based on the protection of the C-4 position by the isopropylsulfanyl group. Hence, thioether **2** was readily accessed by treatment of 2,4-dichloropyrido[2,3-*d*]-pyrimidine **1** with 1.05 equiv of isopropyl mercaptan and sodium hydride in tetrahydrofuran.[12a]

Substitution occurred exclusively at the electrophilic C-4 position. Subsequent regioselective C-2 arylation of **1** proceeded in very good yields with most arylboronic acids in the presence of 5 mol % of $Pd(PPh_3)_4$ in a mixture of 1,2-dimethoxyethane/water (6/2 mL) at 75 °C.

Table 2
Synthesis of type **III** compounds from type **I**



Entry	(het)Ar$_1$	(het)Ar$_2$	Products	Yields[a] (time)
1			**9**	83% (2 h)
2			**10**	80% (2 h)
3			**11**	71% (2 h)
4			**12**	73% (3 h)
5			**13**	76% (2 h)
6			**14**	73% (3 h)
7			**15**	61% (3 h)
8			**16**	86% (2 h)
9			**17**	70% (2 h)
10			**18**	71% (2 h)

[a] Yields are given for isolated products.

The yields of isolated products ranged between 79% and 83%. The substitution of the starting material by the *S*-isopropyl group did not affect the yield of the coupling reactions, which were very homogeneous (Table 3, entries 1–4).

To access type **III** compounds from type **II** compounds, the second palladium cross-coupling reaction required the presence of copper(I) cofactors. On the basis of the coupling conditions reported by Liebeskind et al.[15] and on our knowledge,[16] we applied this strategy to our electron deficient pyridopyrimidines **19**–**22**.

Suzuki related conditions were also first carried out with a slight excess of (het)arylboronic acid with 2.2 equiv of 2-thiophene copper(I) carboxylate.[17] Each reaction required only 5 mol % of $Pd(PPh_3)_4$ and THF at 50 °C (Table 4).

Interestingly, the cross-coupling reaction using copper(I) as a cofactor was rapidly carried out, and all products were isolated in good yields (71–86%) (Table 4, entries 1–4). These results show the efficiency of the reaction pathway.

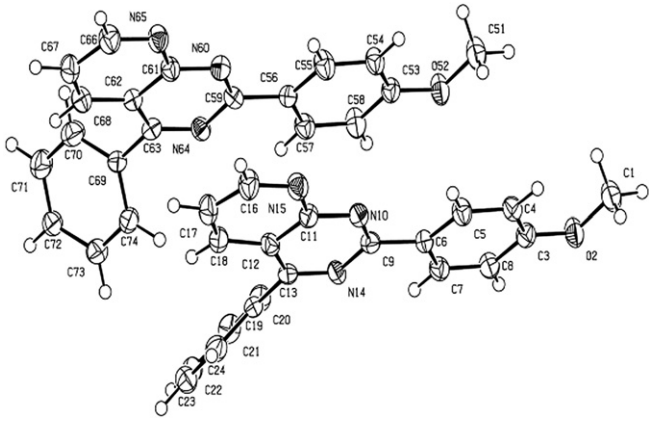
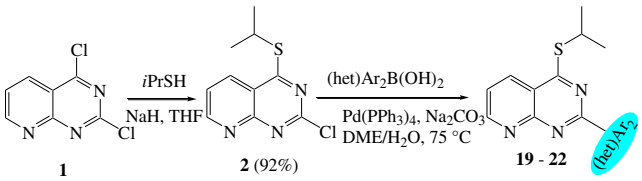
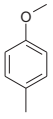
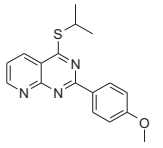
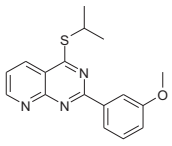
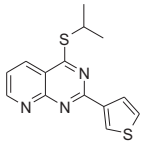
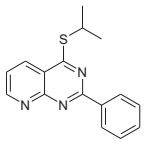


Fig. 2. ORTEP view of compound **17**.

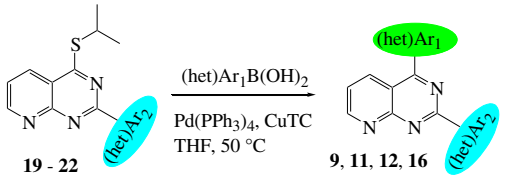
Table 3
Synthesis of type **II** compounds from **2**

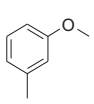
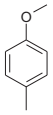
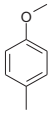
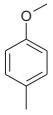
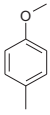


Entry	(het)Ar$_2$	Products	Yields[a] (time)
1		 **19**	83% (2 h)
2		 **20**	79% (3 h)
3		 **21**	81% (3 h)
4		 **22**	81% (3 h)

[a] Yields are given for isolated products.

Table 4
Synthesis of type **III** compounds from type **II**



Entry	(het)Ar$_2$	(het)Ar$_1$	Products	Yields[a] (time)
1			**9**	75% (1 h)
2			**11**	71% (1 h)
3			**12**	75% (2 h)
4			**16**	86% (1 h)

[a] Yields are given for isolated products.

3. Conclusion

In this report, we developed two efficient palladium-catalyzed routes **A** and **B** to design new and rare dissymmetrical 2,4-bis(het)aryl-pyrido[2,3-*d*]pyrimidines.

Suzuki reactions were accurately adapted to perform each step with high selectivity and originality. In the first route **A**, we showed that the first (het)arylation occurred selectively in the C-4 position of the 2,4-dichloropyrido[2,3-*d*]pyrimidine **1**. The two chlorine atoms could be fully discriminated. The second route **B** involved two sequential (het)aryl transfers from the 2-chloro-4-isopropylsulfanyl-pyrido[2,3-*d*]pyrimidine **2** by palladium insertion first on the C–Cl bond and then on the C–S bond.

This simple and efficient sequential coupling route to highly substituted pyrido[2,3-*d*]pyrimidines enables the orchestration of regioselective palladium-catalyzed cross-coupling reactions for the preparation of focused libraries of biologically active compounds.

4. Experimental section

4.1. General remarks and methods

4.1.1. Instrumentation and materials. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (400 MHz ^{1}H, 62.89 MHz ^{13}C) using tetramethylsilane as the internal standard, multiplicities were determined by the DEPT 135 equivalence, chemical shifts were reported in parts per million (ppm, δ units). Coupling constants were reported in units of hertz (Hz) if applicable. Infrared (IR) spectra were obtained on Perkin–Elmer Paragon 1000 PC FT-IR. Infrared spectra recorded using an ATR-Ge equipment. Low-resolution mass spectra (MS) were recorded on a Perkin–Elmer SCIEX API 3000 spectrometer. Exact mass were performed in CRMPO, Rennes and Orleans, France. Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed on silica gel 60 (40–63 mesh). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F$_{254}$ precoated plates. Visualization was made with ultraviolet light. Reactions requiring anhydrous conditions were performed under argon. All solvents were freshly distilled under argon prior to use. Chemicals products were obtained from the following sources: Aldrich and Acros organics. Copper(I) thiophene-2-carboxylate was prepared from procedure described in the literature.[18]

The data of **3** and **17** were collected with an R-Axis Rapid Rigaku MSC and the data of **17** were collected with a CAD4 Enraf Nonius diffractometer, both using the Cu Kα radiation and a graphite monochromator. On the R-axis, all reflections were used for unit cell refinement whereas 25 reflections were used with the CAD4. The program PLATON[19] was used for analysis and drawing figures. The structures were solved by direct methods and refined using SHELX 97 suite of programs[20] integrated in WinGX 1.80 version.[21] The positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. The non-H atoms were refined with anisotropic temperature parameters. H atoms were included for structure factor calculations but not refined.

4.2. General procedures

*4.2.1. General procedure for synthesis of **2**.* A solution of compound **1**, the desired nucleophile (1.0 equiv) and NaH (1.05 equiv) in dry THF at 0 °C was stirred under Argon for 12 h. After fully disappearance of the starting material, dried from THF, water was added. After three extractions (CH_2Cl_2), the combined organic layers were dried with $MgSO_4$, filtered and dried under reduced pressure. The crude residue was next purified by flash chromatography. This procedure was used for the synthesis of compounds **2.**

*4.2.2. General procedure A: synthesis of 2-chloro-4-(het)aryl-pyrido [2,3-d]pyrimidine (**I**) via Suzuki cross-coupling reaction.* To a argon degassed solution of 2,4-dichloropyrido[2,3-*d*]pyrimidine **1** (100 mg, 0.5 mmol) in toluene (6 mL) were successively added the desired (het)aryl boronic acid (1.05 equiv), potassium carbonate (1.5 equiv), and Pd(PPh$_3$)$_4$ (29 mg, 0.05 equiv). The reaction mixture was heated at 110 °C under vigorous stirring for the desired time. After complete disappearance of **1**, water (10 mL) was added. After extraction with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography to afford compounds of type **I**.

4.2.3. General procedure B. Compounds **III** were obtained via a Suzuki reaction from **I** (0.5 mmol) by modification of the procedure A and also using (het)aryl boronic acid (1.2 equiv), Na_2CO_3 (1.5 equiv), and Pd(PPh$_3$)$_4$ (0.05 equiv) in a mixture of toluene/EtOH (3/1) at 110 °C. After complete disappearance of **I**, water (10 mL) and CH_2Cl_2 (10 mL) were added. After extraction with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography to afford compounds of type **III**.

*4.2.4. General procedure C: synthesis of 2-(het)aryl-4-isopropyl-sulfanylpyrido[2,3-d]pyrimidine (**II**).* To a solution containing **2** (0.5 mmol) in a mixture of DME/H_2O (3/1) were successively added the desired (het)aryl boronic acid (1.2 equiv), sodium carbonate (2.0 equiv), and Pd(PPh$_3$)$_4$ (0.05 equiv). The reaction mixture was heated at 75 °C under vigorous stirring for the desired time. After complete disappearance of **2**, water (10 mL) and CH_2Cl_2 (10 mL) were added. After extraction with CH_2Cl_2 (3×10 mL), the combined organic

layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography to afford compounds of type **II**.

*4.2.5. General procedure D: synthesis of compounds type (**III**) via a Suzuki cross-coupling reaction in the presence of CuTC.* A solution containing 2-(het)aryl-4-isopropylsulfanylpyrido[2,3-*d*]pyrimidine **II** (0.35 mmol), the (het)aryl boronic acid (2.2 equiv), CuTC (2.2 equiv), and $Pd(PPh_3)_4$ (0.05 equiv) in dry THF (6 mL) was flushed with argon for 15 min. The brown suspension was stirred under argon at 50 °C for 3 h. After complete disappearance of starting material **II**, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2×10 mL). The solvent was evaporated under reduced pressure the residue was next purified by flash chromatography to give the attempted products of type **III**.

4.3. Experimental data

*4.3.1. 4-Isopropylsulfanylpyrido[2,3-d]pyrimidine **2**.* Compound **2** was isolated after flash chromatography (PE/EtOAc: 8/2) as a white solid. IR (ATR-Ge, cm^{-1}) ν 1556, 1475, 1438, 1366, 1244, 1011, 841, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, 6H, J=8.0 Hz, 2×CH_3), 4.33 (m, 1H, J=4.0, 8.0 Hz, CH), 7.50 (dd, 2H, J=4.0, 8.0 Hz, H_{Ar}), 8.38 (dd, 1H, J=4.0, 8.0 Hz, H_5), 9.14 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.73 (2×CH_3), 36.76 (CH), 117.29 (Cq), 122.68 (CH), 133.54 (CH), 157.66 (Cq), 158.19 (CH), 159.63 (Cq), 176.81 (Cq).

*4.3.2. 2-Chloro-4-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine **3**.* Compound **3** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 116–118 °C; IR (ATR-Ge, cm^{-1}) ν 1536, 1478, 1452, 1262, 1019, 895, 769, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 7.11 (d, 2H, J=8.0 Hz, H_{Ar}), 7.58 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.79 (d, 2H, J=8.0 Hz, H_{Ar}), 8.55 (d, 1H, J=8.0 Hz, H_5), 9.25 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.73 (CH_3), 114.69 (2×CH), 116.51 (Cq), 123.28 (CH), 127.61 (Cq), 132.38 (2×CH), 137.15 (CH), 158.44 (CH), 160.54 (Cq), 162.55 (2×Cq), 172.50 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{14}H_{10}N_3OCl$: 271.0514, found: 271.0512.

*4.3.3. 2-Chloro-4-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine **4**.* Compound **4** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 121–122 °C; IR (ATR-Ge, cm^{-1}) ν 1554, 1488, 1432, 1259, 1042, 895, 769, 663; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 7.15 (d, 1H, J=8.0 Hz, H_{Ar}), 7.28 (m, , 2H, J=4.0, 8.0 Hz, H_{Ar}), 7.49 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.59 (dd, 1H, J=4.0, 8.0 Hz, H_{Ar}), 8.53 (d, 1H, J=8.0 Hz, H_5), 9.25 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.56 (OCH_3),115.4 (CH), 116.57 (Cq), 117.09 (CH), 122.63 (CH), 123.39 (CH), 130.01 (CH), 136.12 (Cq), 136.97 (CH), 158.6 (CH), 160.02 (Cq), 160.19 (Cq), 160.33 (Cq), 172.93 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{14}H_{10}N_3OCl$: 271.0514, found: 271.0511.

*4.3.4. 2-Chloro-4-(3-furyl)pyrido[2,3-d]pyrimidine **5**.* Compound **5** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 146–147 °C; IR (ATR-Ge, cm^{-1}) ν 1567, 1523, 1475, 1444, 1278, 1162, 1046, 991, 834, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H, H_{Het}), 7.62 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.65 (dd, 1H, J=4.0, 8.0 Hz, H_{Het}), 8.19 (d, 1H, J=4.0 Hz, H_{Het}), 8.68 (d, 1H, J=8.0 Hz, H_5), 9.26 (d, 1H, J=4.0, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 111.03 (2×CH), 122.94 (Cq), 123.62 (Cq), 135.64 (CH), 144.72 (CH), 145.76 (CH), 158.70 (CH), 160.18 (Cq), 160.72 (Cq), 165.34 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{11}H_6N_3OCl$: 231.0199, found: 231.0209.

*4.3.5. 2-Chloro-4-(3-thienyl)pyrido[2,3-d]pyrimidine **6**.* Compound **6** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 158–159 °C; IR (ATR-Ge, cm^{-1}) ν 3376, 2963, 1582, 1463, 1320, 1275, 1096, 926, 866, 798; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1H, J=8.0 Hz, H_{Het}), 7.62 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.66 (d, 1H, J=8.0 Hz, H_{Het}), 8.03 (d, 1H, J=4.0 Hz, H_{Het}), 8.69 (d, 1H, J=8.0 Hz, H_5), 9.27 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 116.55 (Cq), 123.60 (CH), 127.59 (CH), 128.86 (CH), 130.91 (CH), 136.52 (CH), 136.96 (Cq), 158.66 (CH), 160.46 (Cq), 160.68 (Cq), 167.40 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{11}H_6N_3ClS$: 246.9971, found: 246.9978.

*4.3.6. 2-Chloro-4-phenylpyrido[2,3-d]pyrimidine **7**.* Compound **7** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 143–144 °C; IR (ATR-Ge, cm^{-1}) ν 1523, 1465, 1279, 1135, 884, 811, 761, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 4H, J=4.0, 8.0 Hz, H_{Ar}, H_6), 7.77 (dd, 2H, J=4.0, 8.0 Hz, H_{Ar}), 8.52 (d, 1H, J=8.0 Hz, H_5), 9.26 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 116.68 (Cq), 123.55 (CH), 129.15 (2×CH), 130.37 (2×CH), 131.46 (CH), 135.06 (CH), 137.08 (Cq), 158.71 (CH), 160.34 (Cq), 160.50 (Cq), 173.23 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{13}H_8N_3Cl$: 241.0407, found: 241.0413.

*4.3.7. 2-Chloro-4-(2,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidine **8**.* Compound **8** was isolated after flash chromatography (DCM 100%) as a yellow solid. Mp 127–128 °C; IR (ATR-Ge, cm^{-1}) ν 1576, 1489, 1464, 1273, 1043, 889, 776, 692; ^1H NMR (250 MHz, $CDCl_3$) δ 3.71 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.62 (d, 1H, J=2.5 Hz, H_{Ar}), 6.72 (dd, 1H, J=2.5,7.5 Hz, H_{Ar}), 7.52 (dd, 2H, J=2.5, 7.5 Hz, H_{Ar}, H_6), 8.17 (d, 1H, J=7.5 Hz, H_5), 9.21 (d, 1H, J=2.5 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.52 (CH_3), 55.58 (CH_3), 114.54 (CH), 116.34 (Cq), 118.14 (CH), 123.13 (Cq), 129.11 (Cq), 129.46 (CH), 132.23 (CH), 136.34 (CH), 138.94 (Cq), 158.29 (CH), 160.38 (Cq), 162.4 (Cq), 172.16 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{13}H_8N_3Cl$: 303.0408, found: 303.0415.

*4.3.8. 2-(3-Methoxyphenyl)-4-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine **9**.* Compound **9** was isolated after flash chromatography (DCM/PE: 9/1) as a yellow solid. Mp 119–120 °C; IR (ATR-Ge, cm^{-1}) ν 1611, 1552, 1469, 1457, 1361, 1255, 1038, 821, 747, 692; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 6H, CH_3), 7.13 (d, 2H, J=8.0 Hz, H_{Ar}), 7.44 (t, 2H, J=8.0 Hz, H_{Ar}), 7.44 (dd, 2H, J=4.0, 8.0 Hz, H_6), 7.87 (d, 2H, J=8.0 Hz, H_{Ar}), 8.37 (s, 1H, H_{Ar}), 8.42 (d, 1H, J=8.0 Hz, H_{Ar}), 8.53 (d, 1H, J=8.0 Hz, H_5), 9.23 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.53 (2×CH_3), 113.29 (CH), 114.30 (2×CH), 116.38 (Cq), 118.16 (CH), 121.97 (CH), 122.25 (CH), 129.11 (Cq), 129.46 (CH), 132.02 (2×CH), 136.55 (CH), 138.93 (Cq), 157.4 (CH), 159.94 (2×Cq), 161.78 (Cq), 163.17 (Cq), 169.36 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{21}H_{17}N_3O_2$: 344.1399, found: 344.1402.

*4.3.9. 2,4-Bis(4-methoxyphenyl)pyrido[2,3-d]pyrimidine **10**.* Compound **10** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 127–128 °C; IR (ATR-Ge, cm^{-1}) ν 1582, 1463, 1320, 1275, 1096, 926, 866, 798; ^1H NMR (250 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.09 (dd, 1H, J=4.0, 8.0 Hz, H_{Ar}), 7.12 (d, 2H, J=8.0 Hz, H_{Ar}), 7.43 (t, 1H, J=8.0 Hz, H_{Ar}), 7.49 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.87 (d, 2H, J=8.0 Hz, H_{Ar}), 8.37 (d, 1H, J=4.0 Hz, H_{Ar}), 8.42 (d, 1H, J=8.0 Hz, H_5), 8.52 (dd, 1H, J=4.0, 8.0 Hz, H_{Ar}), 9.23 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.66 (CH_3), 55.70 (CH_3), 113.43 (CH), 114.42 (2×CH), 116.48 (Cq), 118.28 (CH), 122.09 (CH), 122.37 (CH), 129.35 (Cq), 129.60 (CH), 132.15 (2×CH), 136.68 (CH), 139.07 (Cq), 157.53 (CH), 160.09 (Cq), 160.12 (Cq), 161.81 (Cq), 163.29 (Cq), 169.48 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{21}H_{17}N_3O_2$: 344.1399, found: 344.1396.

*4.3.10. 4-(4-Methoxyphenyl)-2-(3-thienyl)pyrido[2,3-d]pyrimidine **11**.* Compound **11** was isolated after flash chromatography (DCM/PE: 9/1) as a white solid. Mp 179–180 °C; IR (ATR-Ge, cm^{-1}) ν 1600, 1525, 1423, 1371, 1322, 1214, 950, 752; ^1H NMR (250 MHz, $CDCl_3$) δ 3.91 (s, 3H, OCH_3), 7.10 (d, 2H, J=8.0 Hz, H_{Ar}), 7.39 (d, 1H, J=8.0 Hz,

H_{Het}), 7.44 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.82 (d, 2H, J=8.0 Hz, H_{Ar}), 8.18 (d, 1H, J=4.0 Hz, H_{Het}), 8.46 (d, 1H, J=8.0 Hz, H_5), 8.60 (dd, 1H, J=4.0, 8.0 Hz, H_{Het}), 9.17 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.62 (CH_3), 114.37 (2×CH), 116.18 (Cq), 122.08 (CH), 126.02 (CH), 128.31 (CH), 129.08 (Cq), 130.06 (CH), 132.02 (2×CH), 136.62 (CH), 141.93 (Cq), 157.42 (CH), 160.09 (Cq), 160.58 (Cq), 161.83 (Cq), 169.63 (Cq); HRMS (EIMS): m/z calcd for $C_{18}H_{13}N_3OS$: 320.0858, found: 320.0855.

4.3.11. 2-Phenyl-4-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine ***12***. Compound **12** was isolated after flash chromatography (DCM/PE: 9/1) as a white solid. Mp 122–123 °C; IR (ATR-Ge, cm^{-1}) ν 1582, 1463, 1320, 1275, 1096, 926, 866, 798; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.94 (s, 3H, OCH_3), 7.14 (d, J=7.5 Hz, 2H, H_{Ar}), 7.52 (m, 4H, J=2.5, 7.5 Hz, H_{Ar}, H_6), 7.88 (dd, 2H, J=2.5, 7.5 Hz, H_{Ar}), 8.53 (d, 1H, J=7.5 Hz, H_5), 8.82 (dd, 2H, J=2.5, 7.5 Hz, H_{Ar}), 9.23 (d, 1H, J=2.5 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.68 (CH_3), 114.45 (2×CH), 116.44 (Cq), 122.35 (CH), 128.65 (2×CH), 129.32 (Cq), 129.40 (2×CH), 131.40 (CH), 132.15 (2×CH), 136.66 (CH), 137.60 (Cq), 157.56 (CH), 160.20 (Cq), 161.90 (Cq), 163.51 (Cq), 169.58 (Cq); HRMS (EIMS): m/z calcd for $C_{20}H_{15}N_3O$: 314.1287, found: 314.1288.

4.3.12. 2-(4-Methoxyphenyl)-4-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine ***13***. Compound **13** was isolated after flash chromatography (DCM/PE: 9/1) as a white solid. Mp 131–132 °C; IR (ATR-Ge, cm^{-1}) ν 1579, 1469, 1352, 1275, 1011, 942, 834, 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 7.01 (d, 2H, J=8.0 Hz, H_{Ar}), 7.11 (d, 1H, J=8.0 Hz, H_{Ar}), 7.36 (m, 2H, J=4.0, 8.0 Hz, H_{Ar}), 7.42 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.47 (dd, 1H, J=4, 8 Hz, H_{Ar}), 8.42 (d, 1H, J=8.0 Hz, H_5), 8.75 (d, 2H, J=8.0 Hz, H_{Ar}), 9.09 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.45 (CH_3), 55.58 (CH_3), 113.93 (2×CH), 115.71 (CH), 116.02 (CH), 116.09 (Cq), 122.00 (CH), 122.64 (CH), 129.80 (CH), 130.04 (Cq), 131.14 (2×CH), 136.48 (CH), 138.04 (Cq), 157.58 (CH), 159.93 (Cq), 159.97 (Cq), 162.51 (Cq), 163.26 (Cq), 169.76 (Cq); HRMS (EIMS): m/z calcd for $C_{21}H_{17}N_3O_2$: 344.1399, found: 314.1403.

4.3.13. 4-(3-Furyl)-2-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine ***14***. Compound **14** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 129–130 °C; IR (ATR-Ge, cm^{-1}) ν 1591, 1472, 1334, 1288, 1046, 922, 862, 771; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.91 (s, 3H, OCH_3), 7.01 (d, 2H, J=7.5 Hz, H_{Ar}), 7.16 (d, 1H, J=2.5 Hz, H_{Het}), 7.51 (dd, 1H, J=2.5, 7.5 Hz, H_6), 7.68 (d, 1H, J=2.5 Hz, H_{Het}), 8.19 (s, 1H, H_{Het}), 8.63 (d, 1H, J=7.5 Hz, H_5), 8.76 (d, 2H, J=7.5 Hz, H_{Ar}), 9.22 (d, 1H, J=2.5 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.57 (CH_3), 111.35 (2×CH), 114.04 (CH), 116.07 (Cq), 122.18 (CH), 124.17 (Cq), 130.08 (2×CH), 131.14 (Cq), 135.26 (CH), 144.21 (CH), 144.74 (CH), 157.70 (CH), 159.99 (Cq), 162.35 (Cq), 162.63 (Cq), 163.62 (Cq); HRMS (EIMS): m/z calcd for $C_{18}H_{13}N_3O_2$: 304.0721, found: 304.0724.

4.3.14. 4-(3-Furyl)-2-(3-thienyl)pyrido[2,3-d]pyrimidine ***15***. Compound **15** was isolated after flash chromatography (DCM/PE: 9/1) as a white solid. Mp 172–173 °C; IR (ATR-Ge, cm^{-1}) ν 1595, 1436, 1337, 1283, 1086, 962, 882, 796; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H, J=4.0 Hz, H_{Het}), 7.42 (d, 1H, J=8.0 Hz, H_{Het}), 7.51 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.67 (d, 1H, J=4.0 Hz, H_{Het}), 8.18 (d, 2H, J=4.0 Hz, H_{Het}), 8.62 (m, 2H, J=4.0, 8.0 Hz, H_{Het}, H_5), 9.22 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 111.29 (CH), 116.20 (Cq), 122.42 (CH), 123.94 (Cq), 126.15 (CH), 128.27 (CH), 130.13 (CH), 135.26 (CH), 141.76 (Cq), 144.25 (CH), 144.79 (CH), 157.77 (CH), 159.91 (Cq), 160.92 (Cq), 162.64 (Cq); HRMS (EIMS): m/z calcd for $C_{18}H_{13}N_3OS$: 280.0545, found: 280.0549.

4.3.15. 2-(4-Methoxyphenyl)-4-(3-thienyl)pyrido[2,3-d]pyrimidine ***16***. Compound **16** was isolated after flash chromatography (DCM 100%) as a white solid. Mp 133–134 °C; IR (ATR-Ge, cm^{-1}) ν 1601, 1473, 1332, 1221, 1113, 962, 878, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 7.03 (d, 1H, J=8.0 Hz, H_{Ar}), 7.47 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.56 (d, 1H, J=4.0 Hz, H_{Het}), 7.73 (d, 1H, J=4.0 Hz, H_{Het}), 7.99 (d, 1H, J=4.0 Hz, H_{Het}), 8.61 (d, 1H, J=8.0 Hz, H_5), 8.75 (d, 2H, J=8.0 Hz, H_{Ar}), 9.19 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.53 (OCH_3), 114.00 (2×CH), 116.10 (Cq), 122.16 (CH), 126.87 (CH), 129.12 (CH), 129.33 (CH), 130.09 (Cq), 131.13 (2×CH), 136.02 (CH), 138.67 (Cq), 157.61 (CH), 160.15 (Cq), 162.58 (Cq), 163.48 (Cq), 164.50 (Cq); HRMS (EIMS): m/z calcd for $C_{18}H_{13}N_3OS$: 320.0858, found: 320.0867.

4.3.16. 4-Phenyl-2-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine ***17***. Compound **17** was isolated after flash chromatography (DCM/PE: 9/1) as a white solid. Mp 120–121 °C; IR (ATR-Ge, cm^{-1}) ν 1579, 1451, 1349, 1291, 1084, 934, 832, 792; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 7.02 (d, J=8.0 Hz, 2H, H_{Ar}), 7.42 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.60 (dd, 3H, J=4.0, 8.0 Hz, H_{Ar}), 7.83 (m, 2H, J=4.0, 8.0 Hz, H_{Ar}), 8.41 (d, 1H, J=8.0 Hz, H_5), 8.76 (d, 2H, J=8.0 Hz, H_{Ar}), 9.18 (d, 1H, J=4 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.48 (OCH_3), 113.96 (2×CH), 116.10 (Cq), 122.02 (CH), 128.83 (2×CH), 130.10 (Cq), 130.27 (2×CH), 130.52 (CH), 131.16 (2×CH), 136.49 (CH), 136.80 (Cq), 157.58 (CH), 160.03 (Cq), 162.53 (Cq), 163.33 (Cq), 169.95 (Cq); HRMS (EIMS): m/z calcd for $C_{20}H_{15}N_3O$: 314.1293, found: 314.1294.

4.3.17. 4-(2,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine ***18***. Compound **18** was isolated after flash chromatography (DCM/PE: 9/1) as a yellow solid. Mp 144–145 °C; IR (ATR-Ge, cm^{-1}) ν 1589, 1477, 1343, 1292, 1082, 950, 853, 775; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.67 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.03 (d, 3H, J=7.5 Hz, H_{Ar}), 7.08 (d, 1H, J=7.5 Hz, H_{Ar}), 7.12 (s, 1H, H_{Ar}), 7.39 (dd, 1H, J=2.5, 7.5 Hz, H_6), 8.07 (d, 1H, J=7.5 Hz, H_5), 8.76 (d, 2H, J=7.5 Hz, H_{Ar}), 9.16 (dd, 1H, J=2.5 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.67 (OCH_3), 55.75 (OCH_3), 56.79 (OCH_3), 113.52 (CH), 114.51 (2×CH), 116.57 (Cq), 118.37 (CH), 122.46 (CH), 129.34 (Cq), 129.69 (CH), 132.24 (2×CH), 136.71 (CH), 139.16 (Cq), 157.62 (CH), 160.18 (Cq), 160.21 (2×Cq), 161.98 (Cq), 163.38 (Cq), 169.57 (Cq); HRMS (EIMS): m/z calcd for $C_{22}H_{19}N_3O_3$: 374.1299, found: 374.1304.

4.3.18. 4-Isopropylsulfanyl-2-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine ***19***. Compound **19** was isolated after flash chromatography (PE/EtOAc: 9/1) as a yellow solid. Mp 123–124 °C; IR (ATR-Ge, cm^{-1}) ν 1636, 1539, 1432, 1382, 1326, 1217, 1012, 867, 749; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.59 (d, 6H, J=8.0 Hz, 2×CH_3), 3.90 (s, 3H, OCH_3), 4.47 (m, 1H, J=4.0, 8.0 Hz, CH), 7.04 (dd, 2H, J=4.0, 8.0 Hz, H_{Ar}), 7.40 (dd, 1H, J=4.0, 8.0 Hz, H_6), 8.36 (d, 1H, J=8.0 Hz, H_5), 8.68 (dd, 2H, J=4.0, 8.0 Hz, H_{Ar}), 9.16 (d, 1H, J=8 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.94 (2×CH_3), 36.02 (CH), 55.56 (CH_3), 114.02 (2×CH), 117.13 (Cq), 121.42 (CH), 130.17 (Cq), 131.04 (2×CH), 133.30 (CH), 157.40 (CH), 157.83 (Cq), 162.15 (Cq), 162.54 (Cq), 173.11 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{17}N_3OS$: 311.1108, found: 311.1105.

4.3.19. 4-Isopropylsulfanyl-2-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine ***20***. Compound **20** was isolated after flash chromatography (PE/EtOAc: 9/1) as a yellow solid. Mp 116–117 °C; IR (ATR-Ge, cm^{-1}) ν 1602, 1533, 1443, 1328, 1254, 1036, 1011, 821, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (d, 6H, J=8.0 Hz, 2×CH_3), 3.89 (s, 3H, OCH_3), 4.43 (m, 1H, J=4.0, 8.0 Hz, CH), 7.15 (d, 1H, J=8.0 Hz , H_{Ar}), 7.28 (m, 2H, J=4.0, 8.0 Hz, H_{Ar}), 7.49 (dd, 1H, J=4.0, 8.0 Hz, H_6), 7.58 (dd, 1H, J=4.0, 8.0 Hz, H_{Ar}), 8.52 (d, 1H, J=8.0 Hz, H_5), 9.25 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.77 (2×CH_3), 35.86 (CH), 55.39 (OCH_3), 113.85 (2×CH), 116.96 (Cq), 121.25 (CH), 130.00 (Cq), 130.87 (2×CH), 133.13 (CH), 157.23 (CH), 157.66 (Cq), 161.98

(Cq), 162.37 (Cq), 172.94 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{17}H_{17}N_3OS$: 311.1092, found: 311.1088.

4.3.20. 4-Isopropylsulfanyl-2-(3-thienyl)pyrido[2,3-d]pyrimidine ***21***. Compound **21** was isolated after flash chromatography (PE/EtOAc: 9/1) as a beige solid. Mp 128–129 °C; IR (ATR-Ge, cm^{-1}) ν 1636, 1539, 1432, 1382, 1326, 1217, 1012, 867, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, 6H, J=8.0 Hz, 2×CH_3), 4.43 (m, 1H, J=4.0, 8.0 Hz, CH_{Ar}), 7.41 (m, 2H, J=4.0, 8.0 Hz, $H_{Het,}$ H_6), 8.11 (d, 1H, J=8.0 Hz, H_{Het}), 8.36 (d, 1H, J=8.0 Hz, H_5), 8.52 (d, 1H, J=4.0 Hz, H_{Het}), 9.12 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.02 (2×CH_3), 36.32 (CH), 113.85 (Cq), 117.42 (Cq), 121.81 (CH), 126.26 (CH), 128.38 (CH), 130.07 (CH), 133.47 (CH), 142.00 (Cq), 157.59 (CH), 159.63 (Cq), 173.61 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{14}H_{13}N_3OS_2$: 288.0629, found: 288.0632.

4.3.21. 4-Isopropylsulfanyl-2-phenylpyrido[2,3-d]pyrimidine ***22***. Compound **22** was isolated after flash chromatography (PE/EtOAc: 9/1) as a beige solid. Mp 113–114 °C; IR (ATR-Ge, cm^{-1}) ν 1549, 1465, 1447, 1379, 1322, 1244, 1009, 851, 714; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, 6H, J=8.0 Hz, 2×CH_3), 4.51 (m, 1H, J=4.0, 8.0 Hz, CH), 7.66 (m, 4H, J=4.0, 8.0 Hz, $H_{Ar,}$ H_6), 7.82 (dd, 2H, J=4.0, 8.0 Hz, H_{Ar}), 8.56 (d, 1H, J=8.0 Hz, H_5), 9.31 (d, 1H, J=4.0 Hz, H_7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.25 (2×CH_3), 36.34 (CH), 117.00 (Cq), 123.87 (CH), 129.47 (2×CH), 130.69 (2×CH), 131.77 (CH), 135.38 (CH), 137.40 (Cq), 159.03 (CH), 160.66 (Cq), 160.82 (Cq), 173.54 (Cq); HRMS (EIMS): *m*/*z* calcd for $C_{16}H_{15}N_3S$: 282.1060, found: 282.1058.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.051.

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