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Regiocontroled S_NAr and Palladium Cross-Coupling Reactions of 2,4,7-Trichloropyrido[3,2-*d*]pyrimidine

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An efficient and original synthesis of various 2,4,7-trisubstituted pyrido[3,2-*d*]pyrimidines is reported. The first access to and the chemical interest of 2,4,7-trichloropyrido[3,2-*d*]pyrimidine is described. Double arylations and S_NAr reactions occurred selectively at the C4 and C2 positions of 2,4,7-trichloropyrido[3,2-*d*]pyrimidine. The reactions at the C7 position were achieved under microwave irradiation in a few minutes. A one-step synthesis of a 2,4,7-tris(aminated) derivative was achieved as a highly efficient alternative.

Introduction

The pyridopyrimidine scaffold has generated a great number of biologically active compounds, and has recently been used to design effective and original drugs, including an MEK inhibitor,[1] a bacterial topoisomerase inhibitor,[2] an HCV inhibitor,[3] a p38 MAP kinase inhibitor,[4] glucocerebrosidase inhibitors,[5] and antimalarial[6] and cytotoxic agents.[7]

A recent review surveyed the efforts undertaken to build and functionalize this heterocyclic skeleton. Most substituents are introduced in advance of or during heterocycle generation.[8] In the general pyridopyrimidine field, the [3,2-*d*] regioisomer is the least well described because of its difficult and costly synthesis. Over the past decade, the regioselectivity of substitution reactions of polyhaloheteroaromatics has been extensively studied.[9]

At the beginning of our research, we reported an original synthesis of 2,4-dichloro derivative **2** (Table 1), and used it in sequential or one-pot reactions, substituting first at the C4 position and then at C2.[10] We then used our methodology to modulate the biological activity of reference molecules, and to synthesize original drug-like molecules, mainly using original heterocyclic skeletons and previously unknown synthetic sequences.[11] As important representative examples of inhibitors of CDK and GSK3 kinases are polyarylated and/or polyaminated,[12] we designed a flexible method to synthesize such compounds from the novel 2,4,7-trichloropyrido[3,2-*d*]pyrimidine (**3**). At the 2-, 4- and 7-positions, tris(arylation) remains unknown, and one patent reports two tris(aminated) structures.[13]

We report herein the preparation of novel trichloro derivative **3** and its regioselective functionalization by reactions of two different classes. Several (het)arylations and aminations were achieved in the order C4, then C2, then C7 to give compounds of types **I** and **II** (Figure 1). Complete discrimination between the chlorinated positions was observed in each reaction, and a single-step strategy for tris(amination) was also developed.

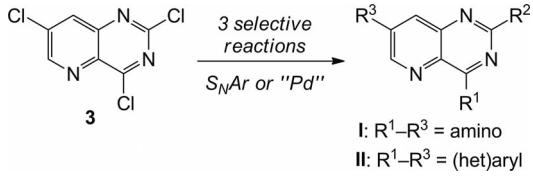

Figure 1. General strategy.

Results and Discussion

Selective chlorination of heterocycles in the position β to a nitrogen atom has been observed with [1,10]phenanthroline,[14] quinoline,[15] 1,6-naphthyridine,[16] and 7-bromo-2*H*-isoquinolin-1-one;[17] but to the best of our knowledge, the direct trichlorination of pyrido[3,2-*d*]pyrimidine in a single step has not yet been described. The sole reported trichlorinated [3,2-*d*]pyridopyrimidine is methyl 2,4,8-trichloropyrido[3,2-*d*]pyrimidine-6-carboxylate, which was used recently by Quattropani et al.[18]

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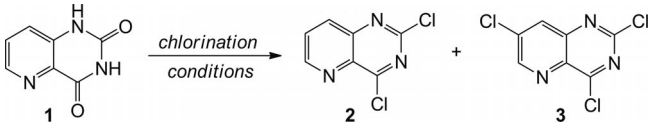
During the multigram synthesis of **2**, we observed the formation of the trichloro derivative **3** in a very low 2% yield (Table 1, Entry 1). Prolonging the reaction time to 24 h gave no significant effect. Fortunately, switching from thermal activation to microwave irradiation at 160 °C for 2 h improved the yield of **3** to 39% (Table 1, Entry 3). Increasing the amount of PCl_5 to 6.0 equiv. provided 2,4,7-trichloropyrido[3,2-*d*]pyrimidine (**3**) in 62% isolated yield, with no trace of any other compound (Table 1, Entry 4). It is noteworthy that the $POCl_3/PCl_5$ system is required for the formation of **3**. When either reagent was used alone, only starting material was detected.

Table 1. Trichlorination of compound **1**.



Entry	Chlorination system (equiv.)	*T* [°C]	Time [h]	Yield[a] [%] **2**	**3**
1	$POCl_3/PCl_5$ (4.0)	130[b]	6	58	2
2	$POCl_3/PCl_5$ (4.0)	130[b]	24	49	5
3	$POCl_3/PCl_5$ (4.0)	160 (MW)[c]	2	20	39
4	$POCl_3/PCl_5$ (6.0)	160 (MW)[c]	2	n.d.[d]	62

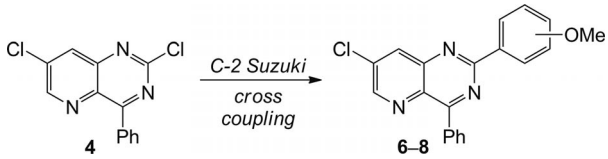
[a] Isolated yields. [b] The reaction was performed in a sealed tube under thermal conditions. [c] Microwave irradiation. [d] Not detected.

Tris[(het)arylation] of 2,4,7-Trichloropyrido[3,2-*d*]pyrimidine

Having obtained the trichloro derivative **3**, we first performed regioselective arylation at C4. Using a near stoichiometric amount of phenylboronic acid in the presence of potassium carbonate and $Pd(PPh_3)_4$ (5 mol-%) in toluene at 100 °C, we observed complete consumption of **3** and the formation of the monophenyl derivative **4** in a good 77% yield (Scheme 1). The small amount of diarylated by-product **5** (2%) that was subsequently formed was separated by flash chromatography.

We then envisioned an arylation at the C2 position without any effect on the chlorine atom at C7. The best conditions were obtained by adding ethanol as co-solvent and using sodium carbonate as base (Table 2). The three (methoxyphenyl)boronic acids reacted with **4** in a few hours to give the bis(arylated) compounds **6**–**8** in good yields. Complete C2 vs. C7 regioselectivity was obtained, and no obvious steric effect of the 2-methoxy group was observed.

Table 2. Selective C2 arylations of compound **4**.



Entry	C2 substitution	Compound	Time [h]	Yield[a,b] [%]
1	2-$MeOC_6H_4$	**6**	5	84
2	3-$MeOC_6H_4$	**7**	4	81
3	4-$MeOC_6H_4$	**8**	5	83

[a] Reaction conditions: $ArB(OH)_2$ (1.05 equiv.), Na_2CO_3 (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol-%), toluene/EtOH (2:1), 100 °C. [b] Isolated yields.

The structures of compounds **4** and **8**, resulting from triple 2,4,7 and double 2,7 chlorine differentiation, respectively, were clearly elucidated by single-crystal X-ray crystallography. The two ORTEP representations in Figure 2 clearly show the positions of the chlorine atoms and the aryl insertions.

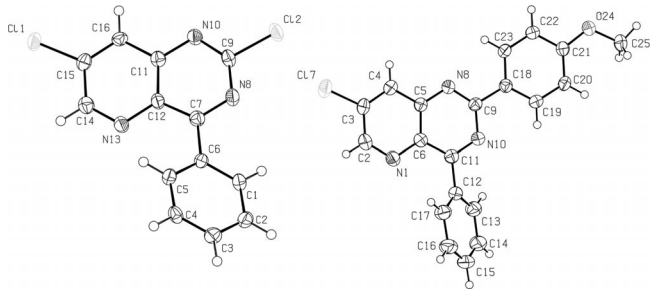
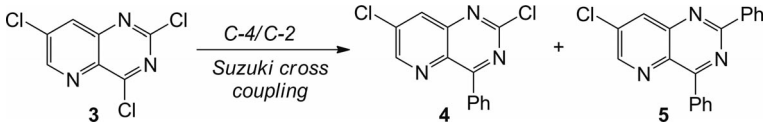


Figure 2. ORTEP views of compound **4** (left) and **8** (right).

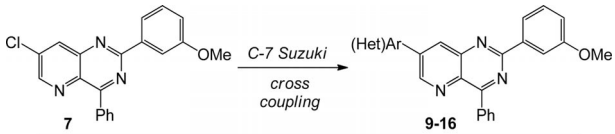
Some conformational differences were observed between compounds **4** and **8**. Firstly, the rms deviation of the pyridopyrimidine bicycles have similar values (0.06 Å and 0.02 Å, respectively). But a slight torsion of the bicycle for compound **4** was observed, with deviations from the least-squares plane of around 0.1 Å for atoms C-7, N-13 and C-11 [–0.109(5), 0.094(5), –0.094(3) Å, respectively]. Secondly, the angles between these planes and the benzene groups were found to be 28.9(2)° and 45.8(1)° for the respective compounds. In addition, for compound **8**, the angle between the bicycle and the methoxyphenyl substituent shows a quasi-planar geometry with a value of 2.4(1) (see Table S1 in the Supporting Information).

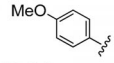
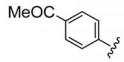
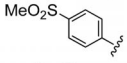


Scheme 1. Selective C4 arylation of **3**. Reaction conditions: $ArB(OH)_2$ (1.05 equiv.), K_2CO_3 (1.5 equiv.), $Pd(PPh_3)_4$ (5.0 mol-%), toluene, 100, 2 h, 77% (**4**), 2% (**5**).

By starting from **7**, the last (het)arylations were first attempted in the presence of a slight excess of boronic acid and K_2CO_3 (Na_2CO_3 gave lower yields) as base (Table 3).

Table 3. Heteroarylation of compound **7**.



Entry	(Het)Ar	Compound	Time	Yield[a,b] [%]
1a		**9**	12 h	95[c]
1b			5 min	94
2		**10**	5 min	97
3		**11**	10 min	97
4		**12**	15 min	98
5		**13**	10 min	97
6		**14**	10 min	88
7		**15**	5 min	96
8		**16**	5 min	67

[a] Isolated yields. [b] Reaction conditions: $(Het)ArB(OH)_2$ (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol-%), toluene/EtOH (2:1), microwave irradiation, 150 °C. [c] Reaction conditions: $(Het)ArB(OH)_2$ (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol-%), toluene/EtOH (2:1), 100 °C.

After 12 h, the trisubstituted derivative **9** was isolated in a best yield of 95%. To diminish the reaction time, microwave irradiation was used. After only 5 min at 150 °C, complete reaction was observed, and purification afforded **9** in a similar yield (Table 3, Entries 1a,b).

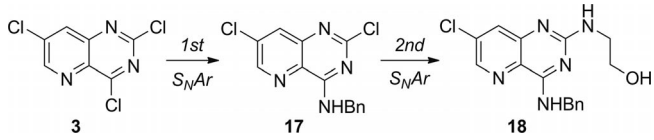
We then used aryl-, naphthyl-, furyl-, pyridinyl-, thienyl- and (benzothienyl)boronic acids to synthesise the corresponding desired compounds in excellent yields. Generally, a slight increase in the reaction time to 10 (Table 3, Entries 3, 5, 6) or 15 min (Table 3, Entry 4) was required for complete reaction to be reached. A decrease in yield was observed in only one case (Table 3, Entry 8), which was mainly due to difficulties during the purification of compound **16**.

In summary, this method enabled us to discriminate between the three chlorine atoms of 2,4,7-trichloro[3,2-*d*]pyrimidine (**3**) using highly efficient successive Suzuki cross-coupling reactions, which were carried out successively in the sequence C4, C2 and finally C7.

Tris(amination) of 2,4,7-Trichloropyrido[3,2-*d*]pyrimidine

In the light of this step-by-step discrimination, the versatility of **3** as a building block was next explored through a wide range of S_NAr and Pd-catalyzed *N*-arylations in order to synthesise unknown C2-monoaminated, 2,4-bis(aminated) and finally 2,4,7-tris(aminated) pyrido[3,2-*d*]pyrimidines.

By applying a sequential route, compound **3** was treated first with a stoichiometric amount of benzylamine in the presence of Et_3N in THF at room temperature. C4 amination occurred after a few hours, and compound **17** was isolated in 90% yield (Scheme 2). The second reaction required thermal activation (refluxing dioxane) and the presence of a slight excess of nucleophilic agent to achieve the C2 chlorine displacement by an S_NAr mechanism. Compound **18** was isolated after 12 h in a high 92% yield (Scheme 2), indicating that the S_NAr reactions tolerate base-sensitive functionalities (NH, OH).



Scheme 2. Regioselective double amination of **3** by sequential S_NAr reactions. Reaction conditions: 1st S_NAr: Et_3N (1.05 equiv.), THF, room temp., 4 h, 90%; 2nd S_NAr: ethanolamine (1.2 equiv.), Et_3N (2.0 equiv.), 1,4-dioxane, reflux, 12 h, 92%.

During the first step, no trace of bis(amination), and during the second step, no trace of tris(amination) was observed, emphasizing the lack of reactivity of the 7-Cl vs. 2-Cl and of the 2-Cl vs. 4-Cl atoms. In order to formally establish the regioselectivity of the first S_NAr reaction at the C4 position, an X-ray analysis of the monoaminated derivative **17** was performed. The ORTEP representation (Figure 3) confirms the C4 amination.

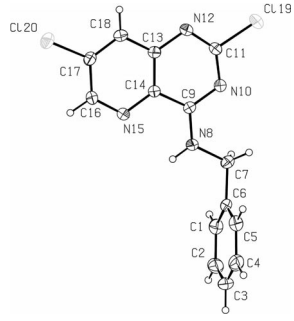
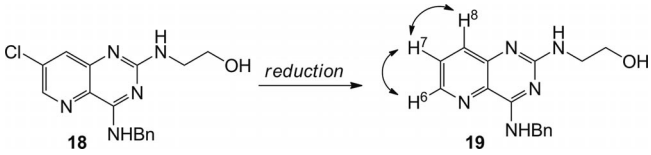


Figure 3. ORTEP view of compound **17**.

The structural conformation of compound **17** could be compared to that of compound **4**. The bicycle shows a torsion for compound **4**, whereas it is very close to planar for compound **17** (the latter compound having an rms deviation of 0.01 Å). This is due to less steric hindrance for this latter compound due to the presence of the linker between the pyridopyrimidine core and the phenyl group. For this reason, and also due to a hydrogen bond of the chelate type (see Table S2 in the Supporting Information) between N8-H and N15, the two planes defined by bicycle and phenyl moieties are angled at 89.6(1)°.

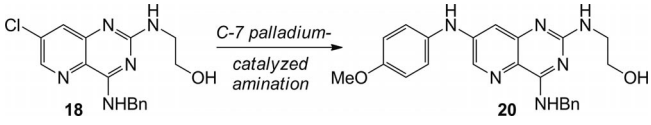
In addition, the C–Cl bond of **18** was reduced under microwave-assisted palladium dechlorination (Scheme 3). The ^{1}H and COSY NMR spectra of product **19** clearly indicate the presence of three adjacent pyridinyl H atoms. This supplementary analysis confirms the regioselectivity of the second nucleophilic attack on C2.



Scheme 3. Dechlorination of compound **18**. Reaction conditions: HCO_2H (2.0 equiv.), Et_3N (3.0 equiv.), $Pd(OAc)_2$ (10 mol-%), Xantphos (20 mol-%), THF, 150 °C under microwave irradiation, 15 min, 57%.

To perform the C7 amination of compound **18**, we decided to study the Pd-catalyzed *N*-arylation as an alternative route, because the starting material was fully recovered from the S_NAr reactions. Our initial experiment focused on the C–N bond formation between compound **18** and *p*-anisidine (Table 4) under Buchwald conditions,[19] which had been used in our previous report. Thus, by using $Pd(OAc)_2$/Xantphos as a catalytic system with K_2CO_3 in refluxing 1,4-dioxane,[20] the target compound **20** was isolated in a modest 49% yield after 24 h (Table 4, Entry 1).

Table 4. *N*-Arylation of compound **18** with *p*-anisidine.



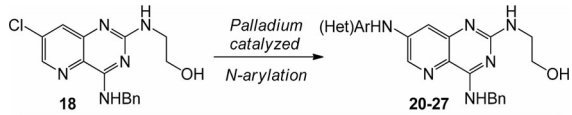
Entry	Catalytic system[a]	Base (equiv.)	Temp. Activating mode	Time	Yield[a,b] [%]
1	$Pd(OAc)_2$/ Xantphos	K_2CO_3 (20.0)	reflux thermal	24 h	49
2	$Pd(OAc)_2$/ Xantphos	K_2CO_3 (20.0)	140 °C MW	40 min	68
3	$Pd(OAc)_2$/ Xantphos	K_2CO_3 (2.0)	140 °C MW	50 min	72
4	$Pd(OAc)_2$/ Xantphos	Cs_2CO_3 (2.0)	140 °C MW	1 h	70
5	none	K_2CO_3 (2.0)	140 °C MW	2 h	n.d.[c]

[a] Isolated yields. [b] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv.), Xantphos (0.2 equiv.), 1,4-dioxane, *p*-anisidine (1.2 equiv.). [c] Not detected; compound **18** was fully recovered.

The use of microwave irradiation and a decrease of the amount of base to 2 equiv. provided **20** in the best 72% yield (Table 4, Entries 2–3). Any change of base resulted in a less efficient reaction, and in the absence of the catalytic system, only starting material was observed; therefore, the possibility of nucleophilic attack at C7 may be excluded (Table 4, Entries 4 and 5).

The scope and limitations of the C7 reactions were found by using various amines (Table 5). Only a few minutes were necessary to achieve the reactions of **18** with (het)arylamines, and compounds **20**–**27** were isolated in good yields (Table 5, Entries 1–8). All the reactions led to a complete conversion of the starting material into a single product, but difficulties with purification lowered the isolated yields.

Table 5. *N*-Arylation of compound **18** with various amines.



Entry	Amines	Compound[c]	Time [min]	Yield[a] [%]
1	MeO, NH_2	**20**	50	72
2	MeO, NH_2	**21**	50	76
3	MeO, MeO, NH_2	**22**	50	71
4	O, NH_2	**23**	60	78
5	N, N, NH_2	**24**	60	73
6	N, N, N, NH_2	**25**	60	81
7	N, NH_2	**26**	60	64
8	N, NH_2	**27**	60	77

[a] Isolated yields. [b] Compound **18** was recovered. [c] Reaction conditions: (Het)ArNH_2 (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (0.1 equiv.), Xantphos (0.2 equiv.), 140 °C, microwave irradiation.

One-Pot Reaction of 2,4,7-Trichloropyrido[3,2-*d*]pyrimidine

Small differences in reaction conditions were found to increase efficiency and selectivity during the tris(arylations). Despite varying the reaction conditions, such as the nature of the base, the solvent, and the activation mode (thermal reaction/microwave irradiation), we were unable to find experimental conditions for successful one-pot tris(arylations).

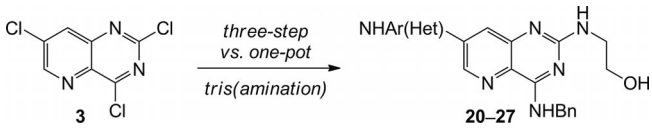
In the case of tris(aminated) pyrido[3,2-*d*]pyrimidines, the larger difference between the reactivity of the three chlorine atoms prompted us to attempt an unprecedented one-pot synthesis of these substrates by tandem double S_NAr/Buchwald *N*-arylation.

After a careful screening of experimental conditions, we found that the first two reactions could be achieved in dioxane in the presence of an excess of triethylamine in a sealed vial. The first S_NAr was achieved at room temperature in the presence of a stoichiometric amount of $BnNH_2$ to preserve the C4 regioselectivity. After complete disappearance of **3** (observed in 5 min), ethanolamine was added, and the reaction mixture was placed under microwave irradiation at 140 °C until the disappearance of intermediate **17** was observed. The completion of the second amination at C2 occurred after 1 h, and led to the in situ formation of **18**.

After cooling, a Buchwald pre-mix [i.e., *p*-anisidine, K_2CO_3, $Pd(OAc)_2$ and Xantphos] was added to the vial. The cross-coupling reaction was activated under microwave irradiation at 140 °C for an additional 1 h. After a single purification step, the expected 2,4,7-tris(triaminated) derivative **20** was isolated in 64% yield.

This new green one-pot tris(amination) methodology diminished the global reaction time and afforded **20** in fairly good yield after a single purification. Having developed such an innovative alternative method, we were now able to apply the procedure to the synthesis of compounds **21**–**27**. As shown in Table 6, the target 2,4,7-trisubstituted pyrido[3,2-*d*]pyrimidines **21**–**27** were isolated in similarly good yields (64–72%), whatever the aniline or the heterocyclic amine used, and whatever the method chosen.

Table 6. Triple amination of compound **3** by a one-pot double S_NAr/Buchwald sequence.



Entry	Compound	Global yield[a] [%]	
		Three steps	One pot[b]
1	**20**	60	64
2	**21**	63	75
3	**22**	59	68
4	**23**	64	70
5	**24**	60	71
6	**25**	67	67
7	**26**	53	72
8	**27**	64	69

[a] Isolated yields. [b] Reaction conditions: 1st S_NAr: $BnNH_2$ (1.0 equiv.), Et_3N (3.0 equiv.), 1,4-dioxane, room temp., 5 min; 2nd S_NAr: ethanolamine (5.0 equiv.), 140 °C, microwave irradiation, 1 h, then (het)$ArNH_2$ (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (0.1 equiv.), Xantphos (0.2 equiv.), 140 °C, microwave irradiation, 1 h.

Conclusions

In this paper, we have described the first access to 2,4,7-trichloropyrido[3,2-*d*]pyrimidine **3** and its use to build two 2,4,7-tris(het)aryl- and -aminopyrido[3,2-*d*]pyrimidine libraries using a novel and highly efficient strategy. Arylations were performed selectively by fine-tuning of the experimental conditions.

The first two aminations were S_NAr reactions and occurred selectively at the C4 and then at the C2 positions of **3**. The chlorine atom at C7 was substituted during (het)arylations, (het)aryl aminations and reduction by using palladium catalysis and microwave irradiation. A one-pot tris(amination) including a double S_NAr reaction and a microwave-assisted Buchwald reaction completed this unprecedented work. With this robust route leading to **3**, and regioselective conditions for the chlorine substitution, we have opened an interesting method that may be used to design new active drugs, in particular protein kinase inhibitors.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded with a 250 MHz or a 400 MHz spectrometer by using $CDCl_3$ or [D_6]-DMSO as the solvent. The chemical shifts are reported in parts per million (δ scale), and all coupling constant (J) values are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). IR spectra were recorded with an FTIR spectrometer with a diamond ATR accessory by using the thin-film method. HRMS data were recorded with a mass spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. Reactions were monitored by TLC on silica [alu-plates (0.2 mm)]. Spots were visualized by UV light at 254 and 356 nm. Column chromatography was performed by using silica gel 60 (0.063–0.200 mm). Microwave irradiation was carried out in sealed 2–5 mL vessels placed in a Biotage Initiator system by using a standard absorbance level (300 W maximum power). The temperature was measured externally by an IR probe that determined the temperature on the surface of the vial and could be read directly from the instrument screen. The reaction time was measured from when the reaction mixture reached the stated temperature for temperature-controlled experiments. Pressure was measured by a non-invasive sensor integrated into the cavity lid.

2,4,7-Trichloropyrido[3,2-*d*]pyrimidine (3): A suspension of 1*H*,3*H*-pyrido[3,2-*d*]pyrimidine-2,4-dione (**1**) (1.0 g, 6.13 mmol) in a mixture of $POCl_3$ (10 mL) and PCl_5 (7.65 g, 36.7 mmol) was heated in a sealed vial under microwave irradiation at 160 °C. After 2 h, excess $POCl_3$ was removed under reduced pressure, and the crude residue was dissolved in CH_2Cl_2 (20 mL) at 0 °C. The crude mixture was poured into an iced-water bath (20 mL) with vigorous stirring, and the organic layer was extracted with CH_2Cl_2 (20 mL). After drying with $MgSO_4$, filtration, and removal of the volatiles under reduced pressure, the residue was purified by flash chromatography using silica gel (petroleum ether/CH_2Cl_2, 40:60) to afford **3** (891 mg, 62%) as a white solid. M.p. 165–166 °C. IR (ATR Diamond): $\tilde{\nu}$ = 3048, 2167, 1579, 1531, 1430, 1324, 1253, 1136, 1001, 872 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.2 Hz, 1 H, 8-H), 9.03 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2 (CH), 135.1 (Cq), 138.5 (Cq), 148.8 (Cq), 152.7 (CH), 157.0 (Cq), 166.0 (Cq) ppm. HRMS (EI-MS$^+$): calcd. for $C_7H_2{}^{35}Cl_3N_3$ $[M]^+$ 232.9314; found 232.9323.

2,7-Dichloro-4-phenylpyrido[3,2-*d*]pyrimidine (4): Compound **3** (2.14 g, 9.13 mmol) was dissolved in anhydrous toluene (7 mL) under argon. Phenylboronic acid (1.17 g, 9.596 mmol, 1.05 equiv.), K_2CO_3 (1.989 g, 14.394 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (527 mg, 0.457 mmol, 0.05 equiv.) were successively added, and the reaction mixture was heated at 100 °C for 2 h. After cooling, water (30 mL) was added, and extractions were performed with CH_2Cl_2 (2× 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography using silica gel (petroleum ether/CH_2Cl_2, 90:10) to afford **4** (1.942 g, 77%) as a white solid. M.p. 140–141 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.62 (m, 3 H, H_{Ph}), 8.29 (d, J = 2.2 Hz, 1 H, 8-H), 8.36–8.40 (m, 2 H, H_{Ph}), 8.97 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.5 (2 CH), 132.1 (3 CH), 134.1 (CH), 134.4 (Cq), 135.6 (Cq), 136.7 (Cq), 149.6 (Cq), 151.2 (CH), 158.7 (Cq), 169.6 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3043, 2167, 1584, 1527, 1439, 1268, 1124, 1080, 933, 852 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{13}H_8{}^{35}Cl_2N_3$ $[M + 1]^+$ 276.0095; found 276.0098.

7-Chloro-2,4-diphenylpyrido[3,2-*d*]pyrimidine (5): Compound **5** (58 mg, 2%) was isolated as a yellow solid as a by-product during

the synthesis of **4**. M.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.63 (m, 6 H, H_{Ph}), 8.38 (d, J = 2.2 Hz, 1 H, 8-H), 8.44–8.48 (m, 2 H, H_{Ph}), 8.68–8.72 (m, 2 H, H_{Ph}), 8.90 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.4 (2 CH), 128.8 (2 CH), 129.1 (2 CH), 131.1 (CH), 131.4 (CH), 131.8 (2 CH), 135.2 (CH), 135.5 (Cq), 136.0 (Cq), 136.2 (Cq), 137.4 (Cq), 148.5 (Cq), 150.2 (CH), 161.8 (Cq), 166.6 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3043, 2167, 1584, 1527, 1439, 1268, 1124, 1080, 933, 852 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{19}H_{13}{}^{35}ClN_3$ [M + 1]$^+$ 318.0798; found 318.0799.

7-Chloro-2-(2-methoxyphenyl)-4-phenylpyrido[3,2-*d*]pyrimidine (6): A solution of 2,7-dichloro-4-phenylpyrido[3,2-*d*]pyrimidine (**4**) (100 mg, 362 µmol) in toluene (6 mL) and EtOH (3 mL) was degassed and placed under argon, and (2-methoxyphenyl)boronic acid (58 mg, 380 µmol, 1.05 equiv.), Na_2CO_3 (77 mg, 724 µmol, 2 equiv.), and $Pd(PPh_3)_4$ (21 mg, 18 µmol, 0.05 equiv.) were successively added. The reaction mixture was heated at 100 °C with vigorous stirring. After 5 h, the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (EtOAc/petroleum ether, 5:95) to afford compound **6** (84%) as a yellow solid. M.p. 116–117 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, OCH_3), 7.07–7.15 (m, 2 H, H_{Ar}), 7.44–7.51 (m, 1 H, H_{Ar}), 7.54–7.58 (m, 3 H, H_{Ph}), 7.93 (dd, J = 1.7, J = 7.5 Hz, 1 H, H_{Ar}), 8.36–8.40 (m, 2 H, H_{Ph}), 8.43 (d, J = 2.4 Hz, 1 H, 8-H), 8.95 (d, J = 2.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 56.2 (CH_3), 112.4 (CH), 120.9 (CH), 128.3 (2 CH), 128.4 (Cq), 131.0 (CH), 131.5 (CH), 131.8 (2 CH), 132.2 (CH), 135.2 (CH), 135.4 (Cq), 135.5 (Cq), 136.1 (Cq), 148.1 (Cq), 150.5 (CH), 158.2 (Cq), 163.5 (Cq), 166.7 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3068, 2267, 1584, 1538, 1445, 1379, 1292, 1113, 1077, 887 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{20}H_{15}{}^{35}ClN_3O$ [M + 1]$^+$ 348.0904; found 348.0900.

7-Chloro-2-(3-methoxyphenyl)-4-phenylpyrido[3,2-*d*]pyrimidine (7): Compound **7** was obtained as described for **6** by using (3-methoxyphenyl)boronic acid in 4 h. Flash chromatography by using silica gel (petroleum ether/EtOAc, 98:2) afforded compound **7** (81%) as a yellow solid. M.p. 112–113 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 7.06 (ddd, J = 0.8, J = 2.6, J = 8.2 Hz, 1 H, H_{Ar}), 7.42 (t, J = 8.0 Hz, 1 H, H_{Ar}), 7.55–7.58 (m, 3 H, H_{Ph}), 8.20 (dd, J = 1.6, J = 2.6 Hz, 1 H, H_{Ar}), 8.25 (d, J = 8.0 Hz, 1 H, H_{Ar}), 8.32 (d, J = 2.4 Hz, 1 H, 8-H), 8.40–8.44 (m, 2 H, H_{Ph}), 8.85 (d, J = 2.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.5 (CH_3), 113.8 (CH), 117.5 (CH), 121.6 (CH), 128.3 (2 CH), 129.7 (CH), 131.1 (CH), 131.8 (2 CH), 135.1 (CH), 135.4 (Cq), 135.9 (Cq), 136.1 (Cq), 138.7 (Cq), 148.3 (Cq), 150.1 (CH), 160.0 (Cq), 161.5 (Cq), 166.4 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3053, 2828, 1589, 1536, 1456, 1334, 1248, 1179, 1047, 836 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{20}H_{15}{}^{35}ClN_3O$ [M + 1]$^+$ 348.0904; found 348.0905.

7-Chloro-2-(4-methoxyphenyl)-4-phenylpyrido[3,2-*d*]pyrimidine (8): Compound **8** was obtained as described for **6** by using (4-methoxyphenyl)boronic acid in 5 h. Flash chromatography by using silica gel (petroleum ether/EtOAc, 95:5) afforded compound **8** (83%) as a yellow solid. M.p. 193–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, OCH_3), 7.03 (d, J = 9.0 Hz, 2 H, H_{Ar}), 7.57–7.59 (m, 3 H, H_{Ph}), 8.32 (d, J = 2.4 Hz, 1 H, 8-H), 8.41–8.44 (m, 2 H, H_{Ph}), 8.64 (d, J = 9.0 Hz, 2 H, H_{Ar}), 8.84 (d, J = 2.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (CH_3), 114.1 (2 CH), 128.3 (2 CH), 130.1 (Cq), 130.9 (2 CH), 131.0 (CH), 131.8 (2 CH), 134.9 (CH), 135.4 (Cq), 135.8 (Cq), 136.3 (Cq), 148.6 (Cq), 149.6 (CH), 161.6 (Cq), 162.5 (Cq), 166.5 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3053, 2167, 1604, 1538, 1443, 1317, 1249, 1164, 1027, 846 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{20}H_{15}{}^{35}ClN_3O$ [M + 1]$^+$ 348.0904; found 348.0908.

2-(3-Methoxyphenyl)-7-(4-methoxyphenyl)-4-phenylpyrido[3,2-*d*]-pyrimidine (9): Under argon, in a sealed vial, compound **7** (70 mg, 0.201 mmol) was dissolved in a mixture of toluene/EtOH (1.4/0.7 mL), and (4-methoxyphenyl)boronic acid (37 mg, 0.241 mmol, 1.2 equiv.), K_2CO_3 (56 mg, 0.402 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (12 mg, 10 µmol, 0.05 equiv.) were successively added. The reaction mixture was heated under microwave irradiation at 150 °C for 5 min. After cooling, water (15 mL) was added, and extractions were performed with CH_2Cl_2 (2× 15 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the volatiles were removed under reduced pressure. The crude residue was purified by flash chromatography by using silica gel (petroleum ether/CH_2Cl_2, 80:20) to afford **9** (79 mg, 94%) as a yellow solid. M.p. 147–148 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.92–6.98 (m, 3 H, H_{Ar}), 7.34 (t, J = 8.0 Hz, 1 H, H_{Ar}), 7.46–7.50 (m, 3 H, H_{Ph}), 7.59 (d, J = 8.8 Hz, 2 H, H_{Ar}), 8.16–8.18 (m, 1 H, H_{Ar}), 8.21 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.32 (d, J = 2.3 Hz, 1 H, 8-H), 8.38–8.42 (m, 2 H, H_{Ph}), 9.11 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.5 (CH_3), 55.5 (CH_3), 113.7 (CH), 114.9 (2 CH), 117.1 (CH), 121.5 (CH), 128.2 (2 CH), 128.6 (Cq), 128.8 (2 CH), 129.7 (CH), 130.7 (CH), 131.8 (2 CH), 132.2 (CH), 136.4 (Cq), 136.6 (Cq), 139.3 (Cq), 139.8 (Cq), 148.3 (Cq), 150.2 (CH), 160.0 (Cq), 160.7 (Cq), 160.9 (Cq), 165.9 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3002, 2828, 1604, 1543, 1451, 1333, 1230, 1169, 1021, 836 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{27}H_{22}N_3O_2$ [M + 1]$^+$ 420.1712; found 420.1717.

7-(4-Acetylphenyl)-2-(3-methoxyphenyl)-4-phenylpyrido[3,2-*d*]pyrimidine (10): Compound **10** was obtained as described for **9** by using (4-acetylphenyl)boronic acid in 5 min. Flash chromatography by using silica gel (petroleum ether/EtOAc, 85:15) afforded compound **10** (97%) as a yellow solid. M.p. 133–134 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.92–6.98 (m, 3 H, H_{Ar}), 7.34 (t, J = 8.0 Hz, 1 H, H_{Ar}), 7.46–7.50 (m, 3 H, H_{Ph}), 7.59 (d, J = 8.8 Hz, 2 H, H_{Ar}), 8.16–8.18 (m, 1 H, H_{Ar}), 8.21 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.32 (d, J = 2.3 Hz, 1 H, 8-H), 8.38–8.42 (m, 2 H, H_{Ph}), 9.11 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 26.7 (CH_3), 55.4 (CH_3), 113.7 (CH), 117.1 (CH), 121.4 (CH), 127.7 (2 CH), 128.2 (2 CH), 129.3 (2 CH), 129.6 (CH), 130.9 (CH), 131.8 (2 CH), 133.9 (CH), 136.3 (Cq), 137.0 (Cq), 137.2 (Cq), 138.7 (Cq), 138.9 (Cq), 140.5 (Cq), 147.8 (Cq), 149.6 (CH), 159.9 (Cq), 160.9 (Cq), 165.8 (Cq), 197.3 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 2935, 1681, 1604, 1536, 1454, 1340, 1265, 1047, 908, 830 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{28}H_{22}N_3O_2$ [M + 1]$^+$ 432.1712; found 432.1709.

2-(3-Methoxyphenyl)-7-(4-methylsulfonyl)-4-phenylpyrido[3,2-*d*]pyrimidine (11): Compound **11** was obtained as described for **9** by using [4-(methylsulfonyl)phenyl]boronic acid in 10 min. Flash chromatography by using silica gel (petroleum ether/EtOAc, 80:20) afforded compound **11** (97%) as a yellow solid. M.p. 215–216 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.33 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 7.14 (dd, J = 2.5, J = 8.1 Hz, 1 H, H_{Ar}), 7.49 (t, J = 8.0 Hz, 1 H, H_{Ar}), 7.60–7.64 (m, 3 H, H_{Ph}), 8.09–8.13 (m, 3 H, H_{Ar}), 8.21 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.28 (d, J = 8.4 Hz, 2 H, H_{Ar}), 8.43–8.47 (m, 2 H, H_{Ph}), 8.78 (d, J = 2.2 Hz, 1 H, 8-H), 9.46 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 43.4 (CH_3), 55.2 (CH_3), 113.3 (CH), 116.9 (CH), 120.8 (CH), 127.8 (2 CH), 128.1 (2 CH), 128.8 (2 CH), 129.9 (CH), 130.8 (CH), 131.6 (2 CH), 134.0 (CH), 135.9 (Cq), 136.6 (Cq), 138.0 (Cq), 138.4 (Cq), 140.4 (Cq), 141.3 (Cq), 147.4 (Cq), 150.6 (CH), 159.7 (Cq), 159.8 (Cq), 165.5 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 2920, 1594, 1535,

1460, 1301, 1225, 1148, 1034, 956, 852 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{27}H_{22}N_3O_3S$ [M + 1]$^+$ 468.1382; found 468.1384.

2-(3-Methoxyphenyl)-7-(2-naphthyl)-4-phenylpyrido[3,2-*d*]pyrimidine (12): Compound **12** was obtained as described for **9** by using 2-naphthylboronic acid in 15 min. Flash chromatography by using silica gel (petroleum ether/CH_2Cl_2, 80:20) afforded compound **12** (98%) as a yellow solid. M.p. 166–167 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 6.95 (dd, J = 2.6, J = 8.1 Hz, 1 H, H_{Ar}), 7.33 (t, J = 8.0 Hz, 1 H, H_{Ar}), 7.40–7.43 (m, 2 H, H_{Naph}), 7.47–7.50 (m, 3 H, H_{Ph}), 7.68–7.86 (m, 4 H, H_{Naph}), 8.06 (s, 1 H, H_{Naph}), 8.16–8.17 (m, 1 H, H_{Ar}), 8.22 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.40–8.45 (m, 3 H, H_{Ph} and 8-H), 9.23 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.5 (CH_3), 113.7 (CH), 117.2 (CH), 121.6 (CH), 124.8 (CH), 126.9 (CH), 127.1 (CH), 127.2 (CH), 127.8 (CH), 128.2 (2 CH), 128.6 (CH), 129.4 (CH), 129.7 (CH), 130.8 (CH), 131.9 (2 CH), 133.4 (Cq), 133.5 (CH), 133.6 (Cq), 136.6 (Cq), 136.8 (Cq), 139.2 (Cq), 140.1 (Cq), 148.2 (Cq), 150.4 (CH), 160.0 (2Cq), 160.9 (Cq), 166.0 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3063, 2833, 1584, 1532, 1445, 1338, 1276, 1220, 1046, 826 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{30}H_{22}N_3O$ [M + 1]$^+$ 440.1763; found 440.1766.

7-(2-Furyl)-2-(3-methoxyphenyl)-4-phenylpyrido[3,2-*d*]pyrimidine (13): Compound **13** was obtained as described for **9** by using 2-furylboronic acid in 10 min. Flash chromatography by using silica gel (petroleum ether/CH_2Cl_2, 80:20) afforded compound **13** (97%) as a yellow solid. M.p. 131–132 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.48 (dd, J = 1.8, J = 3.4 Hz, 1 H, H_{Het}), 6.90 (d, J = 3.4 Hz, 1 H, H_{Het}), 6.97 (dd, J = 1.9, J = 8.1 Hz, 1 H, H_{Ar}), 7.34 (t, J = 8.0 Hz, 1 H, H_{Ar}), 7.47–7.52 (m, 4 H, H_{Ph} and H_{Het}), 8.15–8.17 (m, 1 H, H_{Ar}), 8.21 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.35–8.40 (m, 3 H, H_{Ph} and 8-H), 9.16 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.6 (CH_3), 109.7 (CH), 112.5 (CH), 113.7 (CH), 117.2 (CH), 121.6 (CH), 128.2 (2 CH), 128.9 (CH), 129.7 (CH), 130.1 (Cq), 130.8 (CH), 131.8 (2 CH), 136.4 (Cq), 136.5 (Cq), 139.2 (Cq), 144.7 (CH), 147.4 (CH), 148.3 (Cq), 150.2 (Cq), 160.0 (Cq), 161.1 (Cq), 165.9 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 2956, 1599, 1531, 1451, 1340, 1229, 1176, 1034, 897, 825 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{24}H_{18}N_3O_2$ [M + 1]$^+$ 380.1399; found 380.1416.

2-(3-Methoxyphenyl)-4-phenyl-7-(3-pyridyl)pyrido[3,2-*d*]pyrimidine (14). Compound **14** was obtained as described for **9** by using 3-pyridylboronic acid in 10 min. Flash chromatography by using silica gel (CH_2Cl_2/MeOH, 99.5:0.5) afforded compound **14** (88%) as a yellow solid. M.p. 134–135 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 7.05 (ddd, J = 0.9, J = 2.6, J = 8.2 Hz, 1 H, H_{Ar}), 7.39–7.48 (m, 2 H, H_{Ar} and H_{Pyr}), 7.57–7.60 (m, 3 H, H_{Ph}), 8.02 (d, J = 7.9 Hz, 1 H, H_{Pyr}), 8.22–8.24 (m, 1 H, H_{Ar}), 8.28 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.47–8.52 (m, 3 H, H_{Ph} and 8-H), 8.75 (br., 1 H, H_{Pyr}), 9.04 (br., 1 H, H_{Pyr}), 9.18 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.5 (CH_3), 113.7 (CH), 117.3 (CH), 121.5 (CH), 128.3 (2 CH), 129.7 (CH), 130.9 (CH), 131.8 (2 CH), 134.0 (CH), 134.8 (CH), 136.3 (Cq), 137.1 (Cq), 137.2 (Cq), 138.9 (Cq), 147.9 (Cq), 148.5 (CH), 149.5 (2 CH), 150.3 (CH), 160.0 (2Cq), 161.1 (Cq), 166.2 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3048, 2162, 1589, 1533, 1453, 1394, 1341, 1230, 1026, 841 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{25}H_{19}N_4O$ [M + 1]$^+$ 391.1559; found 391.1565.

7-(3-Benzothienyl)-2-(3-methoxyphenyl)-4-phenylpyrido[3,2-*d*]pyrimidine (15): Compound **15** was obtained as described for **9** by using 3-benzothienylboronic acid in 5 min. Flash chromatography by using silica gel (CH_2Cl_2/MeOH, 99.5:0.5) afforded compound **15** (96%) as a yellow solid. M.p. 112–113 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 7.09 (ddd, J = 0.9, J = 2.6, J = 8.2 Hz, 1 H, H_{Ar}), 7.43–7.51 (m, 3 H, H_{Ar} and H_{Het}), 7.61–7.64 (m, 3 H, H_{Ph}), 7.70 (s, 1 H, H_{Het}), 7.95–7.99 (m, 1 H, H_{Het}), 8.04–8.08 (m, 1 H, H_{Het}), 8.30–8.32 (m, 1 H, H_{Ar}), 8.36 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.54–8.58 (m, 3 H, H_{Ph} and 8-H), 9.24 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.5 (CH_3), 113.7 (CH), 117.2 (CH), 121.6 (CH), 122.4 (CH), 123.3 (CH), 125.2 (2 CH), 126.8 (CH), 128.3 (2 CH), 129.7 (CH), 130.9 (CH), 131.9 (2 CH), 133.2 (Cq), 134.8 (CH), 135.7 (Cq), 136.5 (Cq), 136.9 (Cq), 137.0 (Cq), 139.2 (Cq), 140.9 (Cq), 148.2 (Cq), 151.2 (CH), 160.0 (Cq), 161.0 (Cq), 166.2 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 2920, 1599, 1538, 1505, 1448, 1334, 1226, 1039, 908, 831 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{28}H_{20}N_3OS$ [M + 1]$^+$ 446.1327; found 446.1329.

2-(3-Methoxyphenyl)-4-phenyl-7-(2-thienyl)pyrido[3,2-*d*]pyrimidine (16): Compound **16** was obtained as described for **9** by using 2-thienylboronic acid in 5 min. Flash chromatography by using silica gel (CH_2Cl_2/MeOH, 99.5:0.5) afforded compound **16** (67%) as a yellow solid. M.p. 140–141 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.98 (dd, J = 2.0, J = 8.2 Hz, 1 H, H_{Ar}), 7.09 (dd, J = 3.7, J = 5.0 Hz, 1 H, H_{Het}), 7.32–7.39 (m, 2 H, H_{Ar} and H_{Het}), 7.46–7.52 (m, 4 H, H_{Ph} and H_{Het}), 8.15–8.17 (m, 1 H, H_{Ar}), 8.21 (d, J = 7.8 Hz, 1 H, H_{Ar}), 8.35 (d, J = 2.3 Hz, 1 H, 8-H), 8.37–8.41 (m, 2 H, H_{Ph}), 9.17 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.6 (CH_3), 113.7 (CH), 117.3 (CH), 121.6 (CH), 126.3 (CH), 128.1 (CH), 128.3 (2 CH), 128.9 (CH), 129.7 (CH), 130.8 (CH), 130.9 (CH), 131.8 (2 CH), 133.9 (Cq), 136.5 (Cq), 136.7 (Cq), 139.2 (Cq), 139.3 (Cq), 148.3 (Cq), 148.8 (CH), 160.1 (Cq), 161.2 (Cq), 165.9 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3073, 2203, 1599, 1537, 1452, 1335, 1274, 1218, 1042, 894 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{24}H_{18}N_3OS$ [M + 1]$^+$ 396.1171; found 396.1181.

4-(Benzylamino)-2,7-dichloropyrido[3,2-*d*]pyrimidine (17): A solution of compound **3** (2.0 g, 8.53 mmol), benzylamine (914 mg, 8.53 mmol, 1 equiv.) and triethylamine (863 mg, 7.76 mmol, 1.05 equiv.) in dry THF (100 mL) was stirred at room temperature for 4 h. The solvent was evaporated, and water (20 mL) was added. The organic material was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated under vacuum. Flash chromatography by using silica gel (petroleum ether/CH_2Cl_2, 1:1) afforded product **17** (2.341 g, 90%) as a white solid. M.p. 169–171 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 4.85 (d, J = 5.8 Hz, 2 H, CH_2), 7.33–7.39 (m, 5 H, H_{Ph}), 7.48 (br., 1 H, NH), 8.00 (d, J = 2.1 Hz, 1 H, 8-H), 8.56 (d, J = 2.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 45.3 (CH_2), 128.1 (CH), 128.2 (2 CH), 128.8 (Cq), 129.1 (2 CH), 133.6 (CH), 136.3 (Cq), 136.9 (Cq), 146.1 (Cq), 147.8 (CH), 159.7 (Cq), 160.4 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3036, 2156, 1601, 1572, 1524, 1438, 1297, 1130, 1045, 880 cm^{-1}. HRMS (EI-MS^+): calcd. for $C_{14}H_{11}{}^{35}Cl_2N_4$ [M + 1]$^+$ 305.0361; found 305.0365.

4-(Benzylamino)-7-chloro-2-[(2-hydroxyethyl)amino]pyrido[3,2-*d*]-pyrimidine (18): A solution of compound **17** (1.5 g, 4.91 mmol), ethanolamine (360 mg, 5.90 mmol, 1.2 equiv.) and Et_3N (994 mg, 9.83 mmol, 2 equiv.) in dry 1,4-dioxane (100 mL) was heated at reflux for 12 h. After cooling, the volatiles were evaporated, and water (20 mL) was added. The organic material was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated under vacuum. Flash chromatography by using silica gel (MeOH/CH_2Cl_2, 5:95) afforded product **18** (1.489 g, 92%) as a yellow solid. M.p. 106–107 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.57–3.63 (m, 2 H,

CH_2), 3.81–3.84 (m, 2 H, CH_2), 4.58 (br., 1 H, OH), 4.71 (d, J = 5.9 Hz, 1 H, CH_2Ph), 5.74 (br., 1 H, NH), 7.26–7.35 (m, 6 H, H_{Ph} and NH), 7.63 (d, J = 2.0 Hz, 1 H, 8-H), 8.16 (d, J = 2.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 44.6 (CH_2), 44.9 (CH_2), 63.7 (CH_2), 127.3 (Cq), 127.7 (2 CH), 127.8 (2 CH), 128.8 (CH), 130.6 (CH), 135.5 (Cq), 137.9 (Cq), 142.3 (CH), 146.5 (Cq), 159.6 (Cq), 160.9 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3406, 2843, 1609, 1568, 1515, 1445, 1312, 1159, 1067, 893 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{16}H_{17}{}^{35}ClN_5O$ [M + 1]$^+$ 330.1122; found 330.1107.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]pyrido[3,2-*d*]pyrimidine (19): Compound **18** (100 mg, 0.303 mmol) was dissolved in dry THF (2 mL), and Et_3N (92 mg, 0.91 mmol, 3 equiv.) and formic acid (28 mg, 0.606 mmol, 2 equiv.) were successively added. After 5 min of stirring at room temperature, $Pd(OAc)_2$ (7 mg, 30.3 µmol, 0.1 equiv.) and Xantphos (35 mg, 60.6 µmol, 0.2 equiv.) were added, and the reaction mixture was heated at 150 °C under microwave irradiation for 15 min. After cooling, the volatiles were evaporated, and water (20 mL) was added. The organic material was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated under vacuum. Flash chromatography by using silica gel (EtOAc/MeOH, 95:5) afforded product **19** (51 mg, 57%) as a white solid. M.p. 87–88 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.59–3.64 (m, 2 H, CH_2), 3.82–3.86 (m, 2 H, CH_2), 4.74 (d, J = 5.9 Hz, 1 H, CH_2Ph), 5.79 (br., 1 H, NH), 7.26–7.36 (m, 6 H, H_{Ph} and NH), 7.42 (dd, J = 4.2, J = 8.5 Hz, 1 H, H^7), 7.68 (dd, J = 1.4, J = 8.5 Hz, 1 H, 8-H), 8.29 (dd, J = 1.4, J = 4.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 44.4 (CH_2), 44.8 (CH_2), 63.3 (CH_2), 127.4 (CH), 127.6 (CH), 127.7 (2 CH), 128.6 (2 CH), 129.0 (Cq), 132.0 (CH), 138.1 (Cq), 143.1 (CH), 145.8 (Cq), 159.7 (Cq), 160.1 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3247, 2930, 1604, 1563, 1507, 1415, 1323, 1118, 1056, 821 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{16}H_{18}N_5O$ [M + 1]$^+$ 296.1511; found 296.1504.

General Procedure A Leading to the Tris(aminated) Derivatives 20–27 from 18: In a sealed vial, compound **18** (0.2 mmol scale, 1.0 equiv.) and the required amine (2.0 equiv.) were dissolved in anhydrous dioxane (2 mL). K_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (0.1 equiv.) and Xantphos (0.2 equiv.) were successively added, and the reaction mixture was heated under microwave irradiation at 140 °C. After cooling, the solvent was evaporated, water (10 mL) was added, and extractions were performed with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography by using silica gel to afford the 2,4,7-tris(aminated) derivatives **20**–**27**.

General Procedure B Leading to the Tris(aminated) Derivatives 20–27 from 3: Under argon, in a sealed vial, compound **3** (0.3 mmol scale, 1.0 equiv.), triethylamine (3.0 equiv.) and benzylamine (1.0 equiv.) were dissolved in dry dioxane (2 mL). After 5 min of stirring, ethanolamine (5.0 equiv.) was introduced prior to heating the vial at 140 °C under microwave irradiation for 1 h. After cooling, a Buchwald pre-mix containing the required amine (1.2 equiv.), K_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (0.1 equiv.) and Xantphos (0.2 equiv.) was added. The resulting suspension was placed under microwave irradiation at 140 °C for 1 h. After cooling, the same purification as described in general procedure A led to the 2,4,7-tris(aminated) derivatives **20**–**27**.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]-7-[(4-methoxyphenyl)-amino]pyrido[3,2-*d*]pyrimidine (20): Compound **20** was obtained after flash chromatography by using silica gel (CH_2Cl_2/MeOH, 95:5) as a yellow solid in 72% yield by using general procedure A and in 64% yield by using general procedure B. M.p. 126–127 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.57–3.61 (m, 2 H, CH_2), 3.80–3.83 (m, 5 H, CH_2 et OCH_3), 4.73 (d, J = 5.9 Hz, 2 H, CH_2Ph), 5.48 (br., 1 H, OH), 5.84 (br., 1 H, NH), 6.88–6.94 (m, 3 H, H_{Ar} and 8-H), 7.06 (br., 1 H, NH), 7.14 (d, J = 8.9 Hz, 2 H, H_{Ar}), 7.29–7.37 (m, 5 H, H_{Ph}), 7.93 (d, J = 2.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 43.0 (CH_2), 43.5 (CH_2), 55.1 (CH_3), 60.4 (CH_2), 107.8 (CH), 114.6 (2 CH), 120.6 (Cq), 122.4 (2 CH), 126.3 (CH), 127.1 (2 CH), 127.8 (2 CH), 133.7 (Cq), 134.6 (CH), 139.5 (Cq), 145.4 (Cq), 146.8 (Cq), 155.2 (Cq), 158.8 (Cq), 159.1 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3247, 2926, 1564, 1503, 1454, 1414, 1326, 1237, 1175, 1028, 816 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{23}H_{25}N_6O_2$ [M + 1]$^+$ 417.2039; found 417.2033.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]-7-[(3-methoxyphenyl)-amino]pyrido[3,2-*d*]pyrimidine (21): Compound **21** was obtained after flash chromatography by using silica gel (EtOAc/MeOH, 95:5) as a yellow solid in 76% yield by using general procedure A and in 75% yield by using general procedure B. M.p. 110–111 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.33–3.37 (m, 2 H, CH_2), 3.47–3.52 (m, 2 H, CH_2), 3.75 (s, 3 H, OCH_3), 4.65 (d, J = 6.3 Hz, 2 H, CH_2Ph), 6.50 (t, J = 6.3 Hz, 1 H, NH), 6.58 (dd, J = 2.0, J = 8.1 Hz, 1 H, H_{Ar}), 6.71–6.73 (m, 1 H, H_{Ar}), 6.80 (d, J = 8.1 Hz, 1 H, H_{Ar}), 7.06 (d, J = 2.0 Hz, 1 H, H_{Ar}), 7.18–7.39 (m, 6 H, H_{Ph} and 8-H), 8.09 (d, J = 2.4 Hz, 1 H, 6-H), 8.27 (br., 1 H, NH), 8.75 (br., 1 H, NH) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 42.9 (CH_2), 43.5 (CH_2), 54.7 (CH_3), 60.4 (CH_2), 104.8 (CH), 107.2 (CH), 110.9 (CH), 111.1 (CH), 121.6 (Cq), 126.2 (CH), 127.1 (2 CH), 127.7 (2 CH), 129.7 (CH), 135.1 (CH), 139.5 (Cq), 142.6 (Cq), 143.5 (Cq), 147.4 (Cq), 158.8 (Cq), 159.6 (Cq), 160.1 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3252, 2930, 2290, 1568, 1490, 1320, 1230, 1152, 1048, 846 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{23}H_{25}N_6O_2$ [M + 1]$^+$ 417.2039; found 417.2042.

4-(Benzylamino)-7-[(3,4-dimethoxyphenyl)amino]-2-[(2-hydroxyethyl)amino]pyrido[3,2-*d*]pyrimidine (22): Compound **22** was obtained after flash chromatography by using silica gel (EtOAc/MeOH, 99.5:0.5) as a yellow solid in 71% yield by using general procedure A and in 68% yield by using general procedure B. M.p. 149–150 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.56 (br., 2 H, CH_2), 3.77–3.82 (m, 5 H, CH_2 and OCH_3), 3.85 (s, 3 H, OCH_3), 4.69 (d, J = 5.9 Hz, 2 H, CH_2Ph), 5.58 (br., 1 H, NH), 6.30 (br., 1 H, NH), 6.69–6.81 (m, 3 H, H_{Ph} and H_{Ar}), 6.97 (d, J = 2.4 Hz, 1 H, 8-H), 7.06 (t, J = 5.9 Hz, 1 H, NH), 7.29–7.34 (m, 5 H, H_{Ph} and H_{Ar}), 7.92 (d, J = 2.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 44.5 (CH_2), 45.3 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 64.8 (CH_2), 107.1 (CH), 110.3 (CH), 112.1 (CH), 114.6 (CH), 121.9 (Cq), 127.5 (CH), 127.8 (2 CH), 128.8 (2 CH), 133.3 (Cq), 135.2 (CH), 138.5 (Cq), 145.7 (Cq), 146.3 (Cq), 146.9 (Cq), 149.8 (Cq), 159.5 (Cq), 160.9 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3837, 1585, 1504, 1504, 1449, 1235, 1172, 1058, 800, 733 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{24}H_{27}N_6O_3$ [M + 1]$^+$ 447.2145; found 447.2146.

7-[(4-Acetylphenyl)amino]-4-(benzylamino)-2-[(2-hydroxyethyl)amino]-pyrido[3,2-*d*]pyrimidine (23): Compound **23** was obtained after flash chromatography by using silica gel (CH_2Cl_2/MeOH, 99.5:0.5) as a yellow solid in 78% yield by using general procedure A and in 70% yield by using general procedure B. M.p. 125–126 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 2.50 (s, 3 H, CH_3), 3.33–3.39 (m, 2 H, CH_2), 3.48–3.50 (m, 2 H, CH_2), 4.66 (d, J = 6.3 Hz, 2 H, CH_2Ph), 4.93 (br., 1 H, OH), 6.59 (t, J = 6.3 Hz, 1 H, NH), 7.19–7.40 (m, 8 H, H_{Ph}, H_{Ar} and 8-H), 7.92 (d, J = 8.6 Hz, 1 H, H_{Ar}), 8.17 (d, J = 2.4 Hz, 1 H, 6-H), 8.36 (br., 1 H, NH), 9.26 (br., 1 H, NH) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 25.6 (CH_3), 43.1 (CH_2), 43.5 (CH_2), 60.2 (CH_2), 116.0 (CH), 126.3 (CH), 127.2

(CH), 127.8 (CH), 129.6 (Cq), 129.7 (CH), 136.1 (CH), 139.2 (Cq), 141.9 (Cq), 145.9 (Cq), 146.2 (Cq), 158.7 (2Cq), 158.9 (Cq), 195.3 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 1645, 1570, 1511, 1467, 1342, 1287, 1180, 1062, 829, 726 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{24}H_{25}N_6O_2$ [M + 1]$^+$ 429.2039; found 429.2047.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]-7-(2-pyrimidinylamino)-pyrido[3,2-*d*]pyrimidine (24): Compound **24** was obtained after flash chromatography by using silica gel (EtOAc/MeOH, 90:10) as a yellow solid in 73% yield by using general procedure A and in 71% yield by using general procedure B. M.p. 141–142 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.62–3.63 (m, 2 H, CH_2), 3.84–3.88 (m, 2 H, CH_2), 4.54 (br., 1 H, OH), 4.70 (d, J = 5.9 Hz, 2 H, CH_2Ph), 5.86 (br., 1 H, NH), 6.75 (t, J = 4.8 Hz, 1 H, H_{Het}), 7.23 (br., 1 H, NH), 7.27–7.34 (m, 5 H, H_{Ph}), 8.21 (br., 1 H, NH), 8.31 (d, J = 2.3 Hz, 1 H, 8-H), 8.34 (d, J = 2.3 Hz, 1 H, 6-H), 8.42 (d, J = 4.8 Hz, 2 H, H_{Het}) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]-DMSO): δ = 43.0 (CH_2), 43.5 (CH_2), 60.4 (CH_2), 113.1 (CH), 116.3 (CH), 122.8 (Cq), 126.3 (CH), 127.1 (2 CH), 127.8 (2 CH), 136.1 (CH), 139.4 (Cq), 140.0 (Cq), 146.6 (Cq), 157.6 (2 CH), 158.9 (Cq), 159.4 (Cq), 159.5 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3247, 2935, 2290, 1566, 1517, 1407, 1343, 1200, 1051, 882 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{20}H_{21}N_8O$ [M + 1]$^+$ 389.1838; found 389.1841.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]-7-(1,3,5-triazinylamino)-pyrido[3,2-*d*]pyrimidine (25): Compound **25** was obtained after flash chromatography by using silica gel (EtOAc/MeOH/Et$_3$N, 94:5:1) as a yellow solid in 81% yield by using general procedure A and in 67% yield by using general procedure B. M.p. 202–203 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.37–3.41 (m, 2 H, CH_2), 3.50–3.52 (m, 2 H, CH_2), 4.68 (d, J = 5.9 Hz, 2 H, CH_2Ph), 6.71 (br., 1 H, NH), 7.21–7.40 (m, 5 H, H_{Ph}), 8.22 (br., 1 H, 8-H), 8.45 (br., 1 H, NH), 8.56 (d, J = 2.3 Hz, 1 H, 6-H), 8.87 (s, 2 H, H_{Het}), 10.70 (br., 1 H, NH) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 43.0 (CH_2), 43.5 (CH_2), 60.2 (CH_2), 119.5 (CH), 124.1 (Cq), 126.2 (CH), 127.1 (2 CH), 127.7 (2 CH), 136.3 (CH), 138.1 (Cq), 139.2 (Cq), 146.6 (Cq), 158.8 (Cq), 159.6 (Cq), 163.0 (Cq), 165.8 (2 CH) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3416, 2904, 2280, 1619, 1573, 1430, 1307, 1205, 1067, 811 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{19}H_{20}N_9O$ [M + 1]$^+$ 390.1791; found 390.1807.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]-7-(3-quinolinylamino)-pyrido[3,2-*d*]pyrimidine (26): Compound **26** was obtained after flash chromatography by using silica gel (EtOAc/MeOH, 99.5:0.5) as a yellow solid in 64% yield by using general procedure A and in 72% yield by using general procedure B. M.p. 154–155 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.60–3.64 (m, 2 H, CH_2), 3.83–3.85 (m, 2 H, CH_2), 4.75 (d, J = 5.9 Hz, 2 H, CH_2Ph), 5.49 (br., 1 H, OH), 6.42 (br., 1 H, NH), 7.11 (t, J = 5.9 Hz, 1 H, NH), 7.28–7.32 (m, 2 H, H_{Ph}), 7.34–7.40 (m, 4 H, H_{Ph} and H_{Ar}), 7.52 (t, J = 7.0 Hz, 1 H, H_{Ar}), 7.60 (dt, J = 1.4, J = 7.0 Hz, 1 H, H_{Ar}), 7.72 (d, J = 8.0 Hz, 1 H, H_{Ar}), 7.93 (d, J = 2.4 Hz, 1 H, 8-H), 8.05 (d, J = 8.4 Hz, 1 H, H_{Ar}), 8.13 (d, J = 2.4 Hz, 1 H, 6-H), 8.75 (d, J = 2.6 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 43.1 (CH_2), 43.5 (CH_2), 60.1 (CH_2), 118.8 (CH), 121.4 (Cq), 126.3 (CH), 126.51 (CH), 126.54 (2 CH), 126.58 (CH), 127.2 (2 CH), 127.8 (2 CH), 127.9 (Cq), 128.2 (CH), 135.0 (Cq), 135.5 (CH), 139.1 (Cq), 143.2 (Cq), 143.3 (Cq), 145.4 (CH), 158.2 (Cq), 158.7 (2Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3242, 2924, 1645, 1565, 1452, 1345, 1234, 1123, 1046, 826 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{25}H_{24}N_7O$ [M + 1]$^+$ 438.2042; found 438.2044.

4-(Benzylamino)-2-[(2-hydroxyethyl)amino]-7-(6-quinolinylamino)-pyrido[3,2-*d*]pyrimidine (27): Compound **27** was obtained after flash chromatography by using silica gel (EtOAc/MeOH/Et$_3$N, 94:5:1) as a yellow solid in 77% yield by using general procedure A and in 69% yield by using general procedure B. M.p. 203–204 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.35–3.40 (m, 2 H, CH_2), 3.51 (br., 2 H, CH_2), 4.67 (d, J = 6.3 Hz, 2 H, CH_2Ph), 6.67 (br., 1 H, NH), 7.23 (t, J = 7.2 Hz, 1 H, H_{Ar}), 7.29–7.33 (m, 3 H, H_{Ph}), 7.38–7.40 (m, 2 H, H_{Ph}), 7.45 (dd, J = 4.2, J = 8.3 Hz, 1 H, H_{Quin}), 7.62 (dd, J = 2.3, J = 9.0 Hz, 1 H, H_{Quin}), 7.70 (d, J = 2.2 Hz, 1 H, 8-H), 7.98 (d, J = 9.0 Hz, 1 H, H_{Quin}), 8.24 (d, J = 2.2 Hz, 1 H, 6-H), 8.27 (d, J = 8.3 Hz, 1 H, H_{Quin}), 8.31 (br., 1 H, NH), 8.72 (dd, J = 1.4, J = 4.2 Hz, 1 H, H_{Quin}), 9.19 (br., 1 H, NH) ppm. ^{13}C NMR (100 MHz, 80 °C, [D$_6$]DMSO): δ = 43.0 (CH_2), 43.5 (CH_2), 60.3 (CH_2), 111.2 (CH), 111.8 (CH), 121.2 (CH), 121.9 (Cq), 123.6 (CH), 126.3 (CH), 127.1 (2 CH), 127.8 (2 CH), 128.7 (Cq), 129.9 (CH), 134.1 (CH), 135.5 (CH), 139.3 (Cq), 139.5 (Cq), 143.1 (Cq), 144.0 (Cq), 146.6 (Cq), 147.7 (CH), 158.8 (Cq), 159.1 (Cq) ppm. IR (ATR Diamond): $\tilde{\nu}$ = 3427, 2915, 2172, 1614, 1565, 1503, 1382, 1243, 1026, 846 cm^{-1}. HRMS (EI-MS$^+$): calcd. for $C_{25}H_{24}N_7O$ [M + 1]$^+$ 438.2042; found 438.2047.

X-ray Crystallography. Crystallographic details are available in the Supporting Information. CCDC-720326 (for **4**), -720327 (for **8**) and -720333 (for **17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Crystallographic details, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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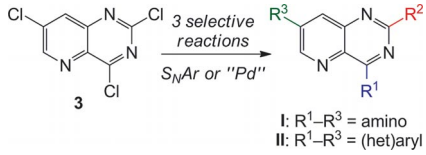
An efficient and original synthesis of 2,4,7-trisubstituted pyrido[3,2-*d*]pyrimidines is reported. Arylations and S_NAr reactions occurred regioselectively at the C4 and C2 positions of 2,4,7-trichloropyrido[3,2-*d*]-pyrimidine. Reactions at the C7 position were achieved under microwave irradiation in a few minutes. A one-step synthesis of a 2,4,7-tris(aminated) derivative was achieved as an efficient alternative.



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Regiocontroled S_NAr and Palladium Cross-Coupling Reactions of 2,4,7-Trichloropyrido[3,2-*d*]pyrimidine

Keywords: Arylation / Aromatic substitution / Cross-coupling / Amination / Heterocycles

