Molecular Iodine Promoted Synthesis of New Pyrido[2,3-*d*]pyrimidin-4-ols

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A highly efficient synthesis of novel pyrido[2,3-*d*]pyrimidin-4-ols was developed via an iodine-catalyzed tandem oxidative cyclization under focused microwave irradiation. Pyrido[2,3-*d*]pyrimidin-4-ols were obtained from easily available 2-amino-4-aryl-6-arylnicotinamides and benzylic amines with good to excellent yields.

Keywords iodine catalysis, oxidative cyclization, microwave irradiation, pyrido[2,3-*d*]pyrimidin-4-ol

Introduction

Pyrido[2,3-*d*]pyrimidine ring system is present in a number of biologically active compounds which includes antitumor,[1] antipyretic,[2] analgesic,[3] antihistaminic,[4] PDE4 inhibitor,[5] adenosine kinase inhibitor,[6] tyrosine kinase inhibitor[7] and diuretic[8,9] activities. Although there are a number of well-established methods to prepare pyrido[2,3-*d*]pyrimidine ring system, they mainly depend on the availability of the indispensable metal-catalyzed C—H functionalization and subsequent formation of C—N bonds.[10-12] And toxic or expensive metal catalysts, hazardous oxidants and organic solvents are still involved in most of these systems. The metal residue and environmental pollution are always the main problem with metal-mediated or metal-catalyzed systems.

There are only a few examples on C—H functionalization under transition-metal-free conditions. Recently, Wang *et al.*[13,27] reported an efficient nonmetal catalytic oxidation system by using molecular iodine. Zeng *et al.*[14] reported iodine catalyzed one-pot synthesis of tetrazolo[1,5-*a*]pyrimidine core. He *et al.*[15] described iodine-mediated synthesis of 3*H*-indoles. Mehta *et al.*[16] reported iodine/palladium approaches to the synthesis of polyheterocyclic compounds. Carmen *et al.*[17] reported that pyrido[2,3-*d*]pyrimidin-4-ols show a significant *in vitro* cytotoxicity. Hannah *et al.*[18] found that *β*-keto esters could condens with amidines to give 2,6-substituted pyrimidin-4-ols. Xiao *et al.*[19] reported the HATU-mediated coupling of 4-hydroxyquinazolines with amines. Therefore there is a definite need for catalytic systems that can use green oxidants without metals affording pyrido[2,3-*d*]pyrimidin-4-ol derivatives.

Microwave irradiation have been utilized extensively as a clean source of energy for the synthesis of organic compounds.[20,21] Some important reviews have been published in recent years, covering a large number of microwave induced reactions.[22,23] Herein, we developed a simple and efficient approach to the synthesis of novel 2-phenylpyrido[2,3-*d*]pyrimidin-4-ols with I_2 and TBHP as the catalytic oxidation system. Various 2-phenylpyrido-[2,3-*d*]pyrimidin-4-ols were prepared from 2-amino-4-aryl-6-arylnicotinamides and benzylic amines via a tandem reaction following sp^3 C—H functionalization under metal-free conditions. The reaction was performed in a focused microwave synthesis system so that it was possible to control the temperature, pressure, microwave power and reaction times easily and with high degree of reproducibility.

Results and discussion

In order to synthesize 5-aryl-2-phenyl-7-arylpyrido-[2,3-*d*]pyrimidin-4-ols, various 2-amino-4-aryl-6-arylnicotinamides were employed as starting material to develop a cluster of new compounds and the key intermediate according to a known procedure.[24,25] Initially, when 2-amino-4,6-diphenylnicotinamide (**1a**, 1 mmol) was treated with benzylic amine (2 mmol), iodine (0.05 mmol) and pyridine, and aqueous *tert*-butyl hydroperoxide (TBHP) (2 mmol) under focused microwave irradiation at 90 ℃, 10 W for 8 min, 55% of **2a** was obtained (Table 1, Entry 1). In the absence of pyridine, the reaction can give a higher yield (Table 1, Entry 2). Without iodine, no product was observed (Table 1, Entry 3). Then other environmental benign oxidants, such

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as *t*-BuOOBu-*t*, aqueous H_2O_2, and oxygen, were also examined, but only aqueous H_2O_2 can generate a trace amount of the product (Table 1, Entry 4). No better result was observed when various solvents were introduced to the reaction (Table 1, Entries 5—8). Raising the reaction temperature to 100 ℃ can increase the reaction yield to 78%. Further raising the reaction temperature cannot enhance the reaction yield obviously (Table 1, Entry 10). After the ratios of iodine, benzylic amine, and TBHP were optimized, the reaction yield was improved to 90% (Table 1, Entries 11—17). Therefore, the optimal reaction conditions is, the mixture of 2-amino-4,6-diphenylnicotinamide (**1a**, 1 mmol) and benzylic amine (2.5 mmol) was heated at 100 ℃ for 8 min with iodine (0.10 mmol) as catalyst and TBHP (2 mmol) as oxidant (Table 1, Entry 16).

Subsequently, we investigated the scope of the reaction substrates under the optimized conditions, as shown in Table 2. The introduction of electron-withdrawing group (such as Br, Cl, F) and electron-donating group (such as CH_3, CH_3O) to the phenyl ring of 2-amino-4-aryl-6-arylnicotinamides affected the reaction slightly. However, when the phenyl ring of benzylic amine was replaced with aliphatic amine such as ethylamine, the desired product was not obtained and we isolated the starting material.

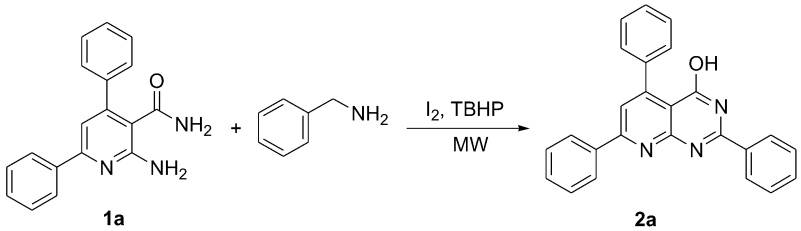
The analysis of the structure of the product **2a** after D_2O exchange experiment by ^{1}H NMR revealed that the peak at δ 12.54 disappeared, which could be attributed to the replacement of hydrogen atom of hydroxyl group of the product **2a** by deuterium atom of D_2O. Besides, the IR spectrum of the product **2a** showed a peak at 3444 cm^{-1}, which further confirmed the presence of the OH in the product **2a**.

A tentative mechanism was proposed in Scheme 1. First, intermediate **I** can be generated from 2-amino-4,6-diphenylnicotinamide (**1a**) and benzylic amine. Subsequently, **I** is oxidized to intermediate **III** via sp^3 C—H functionalization under the reaction conditions.[26] Then intermediate **III** is converted to the pyrido[2,3-*d*]-pyrimidin-4-ol (**2**) product after intramolecular cyclization and further oxidization in tandem process.[13,27]

Conclusion

In summary, a practical and efficient synthesis of novel pyrido[2,3-*d*]pyrimidin-4-ols was described via an iodine-catalyzed tandem process. Various pyrido[2,3-*d*]-pyrimidin-4-ols were rapiddly obtained from easily available 2-amino-4-aryl-6-arylnicotinamide and benzylic

Table 1 Optimization of the reaction conditions for 2-phenylpyrido[2,3-*d*]pyrimidin-4-ol (**2a**)[a]

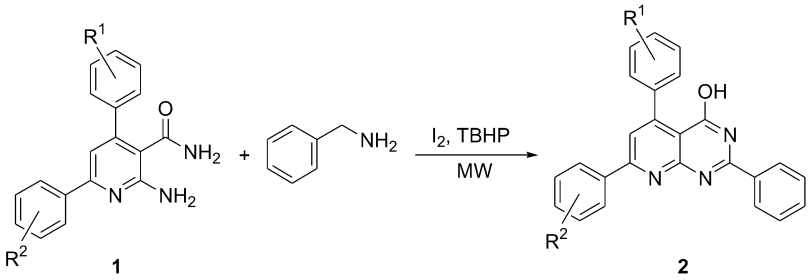


1a **2a**

Entry	I_2/mmol	$BnNH_2$/mmol	TBHP/mmol	Solvent	*T*/℃	Yield/%
1[b]	0.05	2	2		90	55
2	0.05	2	2		90	62
3		2	2		90	0
4[c]	0.05	2			90	12
5	0.05	2	2	MeCN	90	20
6	0.05	2	2	H_2O	90	18
7	0.05	2	2	*t*-BuOH	90	15
8	0.05	2	2	1,4-dioxane	90	20
9	0.05	2	2		100	78
10	0.05	2	2		110	78
11	0.05	1.5	2		100	70
12	0.05	2.5	2		100	80
13	0.05	3	2		100	80
14	0.05	2.5	1.5		100	75
15	0.05	2.5	2.5		100	76
16	0.10	2.5	2		100	90
17	0.20	2.5	2		100	85

[a] Reaction conditions: the mixture of **1a** (1 mmol), $BnNH_2$, I_2 and TBHP was focused under microwave irradiation at 10 W for 8 min. [b] Pyridine (0.05 mmol) was added. [c] 30% of aqueous H_2O_2 was used as oxidant and 0.5 mL of solvent was added.

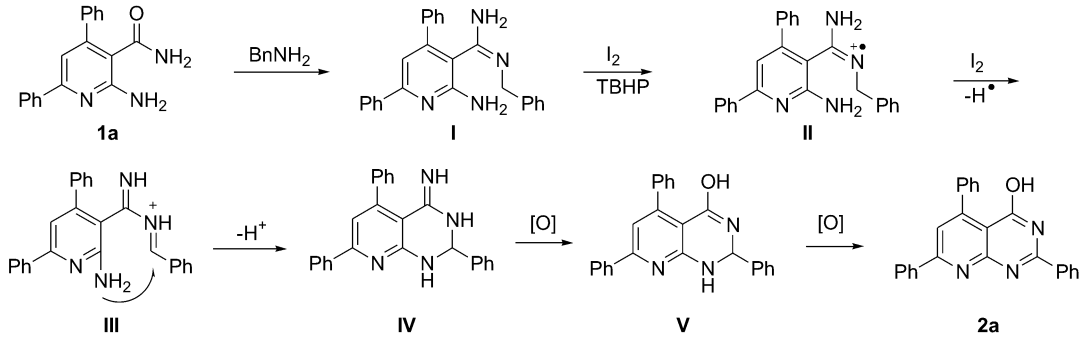
Table 2 Synthesis of 5-aryl-2-phenyl-7-arylpyrido[2,3-*d*]pyrimidin-4-ols **2a**—**2m** under MWI[a]



Entry	R^1	R^2	Product **2**	Isolated yield/%
1	H	H	**2a**	90
2	4-Br	H	**2b**	93
3	4-Cl	H	**2c**	90
4	4-CH_3	H	**2d**	83
5	4-CH_3O	H	**2e**	80
6	4-F	H	**2f**	90
7	2-CH_3O	H	**2g**	78
8	H	4-Br	**2h**	88
9	4-CH_3	4-Br	**2i**	80
10	4-Cl	4-Br	**2j**	85
11	4-F	4-Br	**2k**	85
12	4-Br	4-Br	**2l**	87
13	4-CH_3O	4-Br	**2m**	80

[a] Reaction condition: 2-amino-4-aryl-6-arylnicotinamides **1** (1 mmol), $BnNH_2$ (2.5 mmol), I_2 (0.10 mmol) and TBHP (2 mmol), focused microwave irradiation at 100 ℃, 8 min, 10 W.

Scheme 1 Proposed mechanism of the tandem reaction



amines under focused microwave irradiation. The reaction did not involve any metal salt, excluding the residue of a metal ion in the products.

Experimental section

IR spectra were measured for KBr discs using a Digilab Merlin FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Mercury plus 400 MHz spectrometer in DMSO with TMS as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz in DMSO with TMS as an internal standard using a Mercury plus 400 MHz spectrometer. HRMS was recorded on a Bruker Daltonics APEXII 47e FT-ICR spectrometer.

Microwave reactions were conducted using a CEM Focused Microwave™ Synthesis System (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. The pressure control system uses a load cell for an indirect measurement of the reaction vessel contents. The load cell is connected to a 10 mL vessel and senses changes in the external deflection of the septa on top of the sealed pressure vessel. The sensor housing incorporates a capture and release mechanism to secure the reaction in the cavity. Pressure is programmable from 0 to 2.1×10^6 Pa. The temperature control system uses a non-contact, infrared sensor to measure temperature. It is located below

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the microwave cavity floor and measures the temperature on the bottom of the vessel. The sensor is vessel volume independent and is used in a feedback loop with the on-board computer to control the temperature rise rate and control point of the vessel contents. Temperature is programmable from 25—250 ℃. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Typical procedure for the synthesis of 5-aryl-2-phenyl-7-arylpyrido[2,3-*d*]pyrimidin-4-ols 2a—2m

In a 10 mL glass tube were placed 2-amino-4-aryl-6-arylnicotinamide **1** (1 mmol), benzylic amine (2.5 mmol), iodine (0.10 mmol), TBHP (2 mmol) and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 10 W was used, the temperature being ramped from room temperature to 100 ℃. Once 100 ℃ was reached, the reaction mixture was held at this temperature for 8 min. After cooling the mixture to room temperature, the reaction vessel was opened and the contents poured into a flask. Then ethanol was added and the mixture was filtered and recrystallized from DMF and ethanol.

2,5,7-Triphenylpyrido[2,3-*d*]pyrimidin-4-ol (2a) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.54 (s, 1H), 8.33—8.25 (m, 4H), 7.81 (s, 1H), 7.64—7.53 (m, 7H), 7.51—7.44 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.8, 160.3, 160.1, 155.7, 153.1, 139.4, 137.4, 132.3, 131.9, 130.5, 128.9, 128.8, 128.6, 128.1, 127.8, 127.6, 127.4, 120.8, 112.2; FT-IR (KBr) v: 3444, 3193, 3051, 2955, 1670, 1572, 1543, 1492, 1389, 768, 693 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}N_3O$ $[M+H]^+$ 376.1400, found 376.1416.

5-(4-Bromophenyl)-2,7-diphenylpyrido[2,3-*d*]pyrimidin-4-ol (2b) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.55 (s, 1H), 8.34—8.26 (m, 4H), 7.82 (s, 1H), 7.65—7.54 (m, 6H), 7.42 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.9, 160.4, 160.3, 155.8, 153.2, 139.6, 137.6, 132.4, 132.3, 130.6, 128.9, 128.8, 128.7, 128.3, 127.9, 127.8, 127.5, 120.8, 112.3; FT-IR (KBr) v: 3446, 3183, 3061, 2955, 1670, 1572, 1543, 1492, 1389, 1176, 772 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{16}BrN_3O$ $[M+H]^+$ 454.0560, found 454.0569.

5-(4-Chlorophenyl)-2,7-diphenylpyrido[2,3-*d*]pyrimidin-4-ol (2c) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.57 (s, 1H), 8.36—8.27 (m, 4H), 7.83 (s, 1H), 7.68—7.57 (m, 6H), 7.45 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.1, 160.6, 160.4, 155.8, 153.3, 139.7, 137.6, 132.5, 132.3, 130.7, 129.2, 128.8, 128.7, 128.4, 127.9, 127.8, 127.5, 120.9, 112.5; FT-IR (KBr) v: 3448, 3186, 3070, 2956, 1672, 1575, 1544, 1500, 1389, 1179, 776 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{16}ClN_3O$ $[M+H]^+$ 410.1047, found 410.1054.

2,7-Diphenyl-5-p-tolylpyrido[2,3-*d*]pyrimidin-4-ol (2d) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.70 (s, 1H), 8.47—8.40 (m, 4H), 7.94 (s, 1H), 7.81—7.70 (m, 6H), 7.58 (d, J=8.0 Hz, 2H), 7.41 (d, J=8.0 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.8, 160.2, 160.1, 155.6, 153.2, 137.5, 137.3, 136.4, 132.3, 131.9, 130.4, 128.9, 128.8, 128.7, 128.1, 128.0, 127.6, 120.9, 112.2, 20.9; FT-IR (KBr) v: 3443, 3184, 3069, 2921, 2820, 1672, 1575, 1513, 1445, 1361, 1179, 696 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{19}N_3O$ $[M+H]^+$ 390.1550, found 390.1558.

5-(4-Methoxyphenyl)-2,7-diphenylpyrido[2,3-*d*]pyrimidin-4-ol (2e) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.50 (s, 1H), 8.35—8.26 (m, 4H), 7.81 (s, 1H), 7.65—7.53 (m, 6H), 7.42 (d, J=7.8 Hz, 2H), 7.25 (d, J=7.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.0, 160.6, 160.3, 155.9, 153.3, 139.6, 137.6, 132.4, 132.3, 130.5, 129.2, 128.8, 128.7, 128.5, 127.8, 127.7, 127.5, 120.9, 112.4, 58.9; FT-IR (KBr) v: 3442, 3183, 3067, 2900, 2538, 1672, 1600, 1492, 1445, 1361, 1176, 778 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{19}N_3O_2$ $[M+H]^+$ 406.1510, found 406.1521.

5-(4-Fluorophenyl)-2,7-diphenylpyrido[2,3-*d*]pyrimidin-4-ol (2f) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.56 (s, 1H), 8.32—8.24 (m, 4H), 7.83 (s, 1H), 7.67—7.55 (m, 6H), 7.44 (d, J=8.1 Hz, 2H), 7.27 (d, J=8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 163.3, 161.9, 160.9, 160.4, 160.1, 155.7, 152.1, 137.4, 135.6, 132.3, 132.0, 131.1, 131.0, 130.5, 128.9, 128.7, 128.1, 127.7, 120.9, 114.4, 114.2, 112.3; FT-IR (KBr) v: 3447, 3198, 3070, 2956, 1667, 1573, 1542, 1500, 1387, 1179, 692 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{16}FN_3O$ $[M+H]^+$ 390.1315, found 390.1325.

5-(2-Methoxyphenyl)-2,7-diphenylpyrido[2,3-*d*]pyrimidin-4-ol (2g) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.51 (s, 1H), 8.36—8.27 (m, 4H), 7.82 (s, 1H), 7.66—7.54 (m, 6H), 7.43—7.26 (m, 4H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.1, 160.4, 160.2, 155.9, 153.2, 139.5, 137.4, 132.4, 132.1, 130.5, 129.3, 128.8, 128.7, 128.5, 127.7, 127.6, 127.4, 120.9, 112.4, 57.7; FT-IR (KBr) v: 3443, 3183, 3061, 2930, 2860, 1669, 1600, 1496, 1445, 1364, 1173, 753 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{19}N_3O_2$ $[M+H]^+$ 406.1510, found 406.1521.

7-(4-Bromophenyl)-2,5-diphenylpyrido[2,3-*d*]pyrimidin-4-ol (2h) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.56 (s, 1H), 8.35—8.27 (m, 4H), 7.83 (s, 1H), 7.66—7.46 (m, 10H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.1, 160.6, 160.4, 155.8, 153.3, 140.3, 137.7, 132.5, 132.4, 130.5, 128.9, 128.8, 128.7, 128.5, 127.9, 127.8, 127.5, 121.0, 112.5;. FT-IR (KBr) v: 3450, 3185, 3068, 2955, 1670, 1573, 1543, 1500, 1389, 1178, 776 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{16}BrN_3O$ $[M+H]^+$ 454.0560, found 454.0570.

7-(4-Bromophenyl)-2-phenyl-5-p-tolylpyrido[2,3-*d*]pyrimidin-4-ol (2i) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.51 (s, 1H), 8.37—8.28 (m, 4H), 7.82 (s, 1H), 7.66—

7.57 (m, 5H), 7.55 (d, J=7.8 Hz, 2H), 7.45 (d, J=8.1 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 163.1, 161.6, 161.4, 156.8, 154.3, 140.7, 138.6, 133.5, 133.3, 131.7, 130.2, 129.8, 129.7, 129.4, 128.9, 128.8, 128.5, 121.9, 113.5, 22.7; FT-IR (KBr) v: 3448, 3184, 3069, 2921, 2820, 1672, 1575, 1513, 1445, 1361, 1179, 696 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{18}BrN_3O$ $[M+H]^+$ 468.0645, found 468.0657.

7-(4-Bromophenyl)-5-(4-chlorophenyl)-2-phenylpyrido[2,3-*d*]pyrimidin-4-ol (2j) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.59 (s, 1H), 8.38—8.29 (m, 4H), 7.85 (s, 1H), 7.70—7.62 (m, 5H), 7.59 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 164.1, 162.6, 162.4, 157.8, 155.3, 141.7, 139.6, 134.5, 134.3, 132.7, 131.2, 130.8, 130.7, 130.4, 129.9, 129.8, 129.5, 122.9, 114.5; FT-IR (KBr) v: 3452, 3190, 3075, 2959, 1676, 1578, 1544, 1503, 1389, 1182, 778 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{15}BrClN_3O$ $[M+H]^+$ 488.0112, found 488.0100.

7-(4-Bromophenyl)-5-(4-fluorophenyl)-2-phenylpyrido[2,3-*d*]pyrimidin-4-ol (2k) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.55 (s, 1H), 8.34—8.26 (m, 4H), 7.84 (s, 1H), 7.69—7.59 (m, 5H), 7.55 (d, J=8.0 Hz, 2H), 7.48 (d, J=8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 164.3, 162.7, 161.5, 161.0, 160.8, 156.6, 152.9, 137.9, 136.2, 133.3, 133.0, 132.1, 132.0, 131.5, 129.1, 129.0, 128.8, 128.3, 121.7, 115.4, 115.2, 113.0; FT-IR (KBr) v: 3450, 3194, 3073, 2957, 1670, 1575, 1545, 1500, 1385, 1181, 695 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{15}BrFN_3O$ $[M+H]^+$ 472.0383, found 472.0370.

5,7-Bis(4-bromophenyl)-2-phenylpyrido[2,3-*d*]pyrimidin-4-ol (2l) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.57 (s, 1H), 8.37—8.29 (m, 4H), 7.85 (s, 1H), 7.68—7.60 (m, 5H), 7.58 (d, J=8.0 Hz, 2H), 7.48 (d, J=8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.1, 161.4, 161.3, 156.3, 154.2, 139.9, 138.5, 133.4, 133.3, 131.1, 129.6, 129.2, 129.1, 129.0, 128.5, 128.3, 128.1, 121.4, 113.3; FT-IR (KBr) v: 3454, 3188, 3067, 2957, 1676, 1576, 1548, 1497, 1392, 1180, 778 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{15}Br_2N_3O$ $[M+H]^+$ 531.9582, found 531.9597.

7-(4-Bromophenyl)-5-(4-methoxyphenyl)-2-phenylpyrido[2,3-*d*]pyrimidin-4-ol (2m) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.52 (s, 1H), 8.36—8.27 (m, 4H), 7.82 (s, 1H), 7.66—7.59 (m, 5H), 7.56 (d, J=7.8 Hz, 2H), 7.45 (d, J=8.1 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.3, 160.8, 160.5, 156.1, 153.5, 139.8, 137.8, 132.6, 132.5, 130.7, 129.4, 129.0, 128.9, 128.7, 128.0, 127.9, 127.7, 121.2, 112.6, 59.1; FT-IR (KBr) v: 3443, 3185, 3068, 2900, 2541, 1675, 1600, 1496, 1445, 1363, 1178, 778 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{18}BrN_3O_2$ $[M+H]^+$ 484.0582, found 484.0594.

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