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# SYNTHESIS OF 7-AMINO-5,8-DIHYDROPYRIDO[2,3-*d*]PYRIMIDINE-6-CARBONITRILE DERIVATIVES BASED ON THE REACTION OF 4-CHLORO-5-LITHIO-6-METHOXYPYRIMIDINES WITH 2-(ARYLMETHYLIDENE)PROPANEDINITRILES

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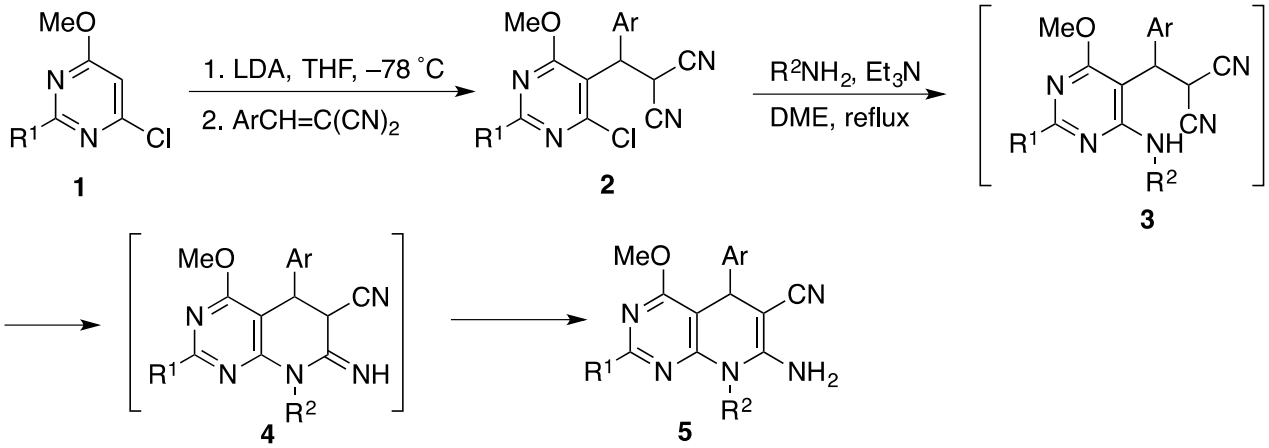
**Abstract** – This paper describes a simple and efficient method for the preparation of 7-amino-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives starting from readily available and inexpensive chemicals. Thus, the reaction of 4-chloro-5-lithio-6-methoxypyrimidines, generated by the treatment of 4-chloro-6-methoxypyrimidines with LDA, with 2-(arylmethylidene)propanedinitriles in THF at –78 ˚C provided the corresponding conjugate addition products, 2-[aryl(4-chloropyrimidin-5-yl)methyl]propanedinitrile derivatives, in fair to good yields. These adducts were then treated with alkylamines in refluxing 1,2-dimethoxyethane (DME) in the presence of triethylamine to result in the formation of the desired products in moderate to fair yields.

The pyrido[2,3-*d*]pyrimidine structure have received much attention, because it is a constitute of a number of biologically important molecules.[1] Some 5,8-dihydropyrido[2,3-*d*]pyrimidine derivatives have also been reported to exhibit biological activities.[2] However, no procedures for the general synthesis of this class of molecules have been reported so far. Therefore, there is a need for development of a simple and versatile method for preparing 5,8-dihydropyrido[2,3-*d*]pyrimidine derivatives. In this paper, we wish to report a convenient method for the preparation of 8-alkyl-7-amino-5-aryl-5,8-dihydropyrido[2,3-

*d*]pyrimidine-6-carbonitriles (**5**). We have found that the reaction of 4-chloro-5-lithio-6-methoxypyrimidines, generated from 4-chloro-6-methoxypyrimidines (**1**), with 2-(arylmethylidene)propanedinitriles gives 2-[aryl(4-chloropyrimidin-5-yl)methyl]propanedinitrile derivatives (**2**), which on treatment with alkylamines gave the desired products. Few general methods have been reported for the synthesis of this type of 5,8-dihydropyrido[2,3-*d*]pyrimidine derivatives,[3] though a general preparation of similar 2,7-diamino-5-aryl-4-oxo-3,4,5,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles have recently been reported.[4]

The preparation of **5** from **1** was conducted according to the sequence illustrated in Scheme 1. Thus, compounds (**1**), easily obtained from commercially available 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) and 4,6-dichloropyrimidine, were treated with LDA in THF at –78 ˚C as described previously[5] to generate 4-chloro-5-lithio-6-methoxypyrimidines, which were then allowed to react with 2-(arylmethylidene)propanedinitriles. Conjugate addition proceeded smoothly to afford, after aqueous workup and the subsequent purification by column chromatography on silica gel, 2-[aryl(4-chloropyrimidin-5-yl)methyl]propanedinitrile derivatives (**2**) in fair to good yields, as compiled in Table 1. The results show that in the case of using the substrate with $R^1$ = H (**1b**), the corresponding adduct (**2e**) was produced in a higher yield (Entry 9) than those of using the substrate with $R^1$ = SMe (**1a**) (Entries 1 and 6-8).




**Scheme 1**

The precursors (**2**), thus obtained, were then treated with a range of alkylamines in refluxing DME to afford the corresponding desired products (**5**). The formation of **5** involves a sequential substitution of the 4-chloro group with an alkylamino group forming the intermediates (**3**) and the subsequent ring closure by the attack of alkylamino nitrogen on the carbon atom of one of the two-cyano groups, followed by tautomerization of the imino nitrile structure (**4**) to the enamino nitrile structure, as shown in Scheme 1. This sequence took *ca*. 5 h to reach to completion. The products were isolated by aqueous workup

followed by column chromatography on silica gel. As shown in Table 1, the yields of **5** are generally moderate-to-fair. However, the yields of the products from **2e** (Entries 9 and 10) were somewhat lower than those from **2a-d**, likely due to the absence of a substituent at the 2-position; Nucleophilic species in the reaction mixtures may attack on this position of the products, the intermediates, and/or the starting materials during the reactions. The reaction of **2a** with phenylmethanamine in DMF at 80 ˚C was examined expecting improvement of the yield. It proceeded much rapidly than that in DME. Unfortunately, however, it resulted in the formation of a somewhat complicated mixture of products. The isolated yield of the product **5a-i** was 52%, which is somewhat lower than that using DME (Entry 1). The reaction in DME using excess phenylmethanamine was also undertaken, but it gave a similar result.

Table 1. Preparation of 7-amino-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitriles (**5**)

| Entry | **1** | Ar | **2** | Yield/%[a] | $R^2$ | **5** | Yield/%[a] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** ($R^1$ = SMe) | Ph | **2a** | 68 | $PhCH_2$ | **5a-i** | 60 |
| 2 | | | | | 4-$ClC_6H_4CH_2$ | **5a-ii** | 63 |
| 3 | | | | | *n*-Bu | **5a-iii** | 60 |
| 4 | | | | | $Ph(CH_2)_2$ | **5a-iv** | 60 |
| 5 | | | | | $MeO(CH_2)_2$ | **5a-v** | 62 |
| 6 | **1a** | 4-$MeC_6H_4$ | **2b** | 66 | $Ph(CH_2)_2$ | **5b** | 60 |
| 7 | **1a** | 4-$ClC_6H_4$ | **2c** | 63 | 4-$MeOC_6H_4CH_2$ | **5c** | 70 |
| 8 | **1a** | 4-$MeOC_6H_4$ | **2d** | 64 | 4-$MeC_6H_4CH_2$ | **5d** | 65 |
| 9 | **1b** ($R^1$ = H) | Ph | **2e** | 82 | $PhCH_2$ | **5e-i** | 46 |
| 10 | | | | | *n*-Bu | **5e-ii** | 48 |

[a] Yields of isolated products.

To explore the scope of the present method, compound (**2a**) was allowed to react with aromatic amines, such as benzenamine and 4-methoxybenzenamine, under the same conditions as described above. Unfortunately, however, the reactions proved to be very reluctant, and the extended reaction time resulted in the formation of small quantities of structurally undefined products and significant amounts of **2a** remained unchanged. This result is presumably ascribed to lower nucleophilicity of aromatic amines compared to that of aliphatic amines.

In conclusion, the forgoing results demonstrate that a facile general method for the synthesis of a new type of 5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives, bearing an amino group at the 7-position and a cyano group at the 6-position, by the reaction of 2-[aryl(4-chloropyrimidin-5-yl)methyl]propanedinitrile derivatives, derived from 4-chloro-6-methoxypyrimidines and 2-(arylmethylidene)propanedinitriles, with aliphatic primary amines has been developed. These products are of interest as not only pharmacophores but also versatile building blocks that could potentially be used to synthesize more structurally complex molecules as they carry an enamino nitrile unit. Further work on exploiting the utility of 4-chloro-6-methoxypyrimidines in heterocycle synthesis is ongoing.

## EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr discs with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. $^1$H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. $^{13}$C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. Elemental analyses were performed with an Elemental Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 $PF_{254}$. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

**Starting Materials.** 4-Chloro-6-methoxypyrimidines (**1**) were prepared according to the procedure previously reported by us.[5] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

**Typical Procedure for the Preparation of 2-[Aryl(4-chloro-6-methoxypyrimidin-5-yl)methyl]propanedinitriles (2). 2-{[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl](phenyl)methyl}propanedinitrile** (**2a).** To a stirred solution of LDA (1.8 mmol), generated by the standard method from *i*-$Pr_2NH$ and *n*-BuLi, in THF (6 mL) at –78 ˚C was added a solution of **1a** (0.29 g, 1.5 mmol) in THF (1.5 mL) dropwise. After 90 min, a solution of $PhCH{=}C(CN)_2$ (0.23 g, 1.5 mmol) in THF (1.5 mL) was added dropwise and stirring was continued for an additional 10 min before saturated aqueous $NH_4Cl$ (20 mL) was added. The mixture was warmed to rt and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated by evaporation to give a residue, of which purification by column chromatography on silica gel gave **2a** (0.35 g, 68%); a pale-yellow solid; mp 57–59 ˚C (hexane); IR 2257, 1563 cm$^{-1}$; $^1$H NMR δ 2.54 (s, 3H), 4.14 (s, 3H), 5.01 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 7.34–7.45 (m, 5H). Anal. Calcd for $C_{16}H_{13}ClN_4OS$: C, 55.73; H, 3.80; N, 16.25. Found: C, 55.62; H, 4.01; N, 16.24.

**2-{[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl](4-methylphenyl)methyl}propanedinitrile (2b):** a pale-yellow solid; mp 129–131 ˚C (hexane/$CH_2Cl_2$); IR 2258, 1567 cm$^{-1}$; $^1$H NMR δ 2.33 (s, 3H), 2.54 (s, 3H), 4.13 (s, 3H), 4.98 (d, *J* = 11.5 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H). Anal. Calcd for $C_{17}H_{15}ClN_4OS$: C, 56.90; H, 4.21; N, 15.61. Found: C, 56.87; H, 4.19; N, 15.67.

**2-{[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl](4-chlorophenyl)methyl}propanedinitrile** (**2c):** a pale-yellow solid; mp 149–152 ˚C (hexane/$CH_2Cl_2$); IR 2257, 1563 cm$^{-1}$; $^1$H NMR δ 2.55 (s, 3H), 4.14 (s, 3H), 4.96 (d, *J* = 11.5 Hz, 1H), 5.03 (d, *J* = 11.5 Hz, 1H), 7.32 (d, *J* = 9.2 Hz, 2H), 7.35 (d, *J* =

9.2 Hz, 2H). Anal. Calcd for $C_{16}H_{12}Cl_2N_4OS$: C, 50.67; H, 3.19; N, 14.77. Found: C, 50.42; H, 3.20; N, 14.49.

**2-{[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl](4-methoxyphenyl)methyl}propanedinitrile (2d):** a pale-yellow solid; mp 80–83 ˚C (hexane/$CH_2Cl_2$); IR 2258, 1611, 1562 $cm^{-1}$; $^1H$ NMR δ 2.56 (s, 3H), 3.79 (s, 3H), 4.14 (s, 3H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 6.88 (d, *J* = 9.2 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 2H). Anal. Calcd for $C_{17}H_{15}ClN_4O_2S$: C, 54.47; H, 4.03; N, 14.95. Found: C, 54.25; H, 4.16; N, 14.85.

**2-[(4-Chloro-6-methoxypyrimidin-5-yl)(phenyl)methyl]propanedinitrile (2e):** a pale-yellow solid; mp 122–124 ˚C (hexane/$CH_2Cl_2$); IR 2255, 1543 $cm^{-1}$; $^1H$ NMR δ 4.18 (s, 3H), 5.06 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 7.37–7.47 (m, 5H), 8.55 (s, 1H). Anal. Calcd for $C_{15}H_{11}ClN_4O$: C, 60.31; H, 3.71; N, 18.76. Found: C, 60.06; H, 3.75; N, 18.63.

**Typical Procedure for the Preparation of 7-Amino-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitriles (5). 7-Amino-4-methoxy-2-methylsulfanyl-5-phenyl-8-phenylmethyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5a-i).** A solution of **2a** (0.16 g, 0.46 mmol) and $BnNH_2$ (49 mg, 0.46 mmol) in DME (3 mL) containing $Et_3N$ (93 mg, 0.92mmol) was heated at reflux temperature for 5 h. After cooling to 0 ˚C, the precipitate was filtered off under reduced pressure and the filtrated was concentrated by evaporation. The residue was purified by column chromatography on silica gel to afford **5a-i** (0.11 g, 60%); a pale-yellow solid; mp 178–180 ˚C (hexane/$CH_2Cl_2$); IR 3457, 3332, 2181, 1649, 1603 $cm^{-1}$; $^1H$ NMR δ 2.38 (s, 3H), 3.89 (s, 3H), 4.22 (br s, 2H), 4.78 (s, 1H), 5.03 (d, *J* = 16.6 Hz, 1H), 5.66 (d, *J* = 16.6 Hz, 1H), 7.17–7.39 (m, 10H); $^{13}C$ NMR δ 14.13, 36.19, 46.62, 54.37, 63.25, 97.12, 121.16, 126.28, 126.93, 126.98, 128.06, 128.53, 129.29, 136.89, 144.51, 152.40, 155.27, 166.64, 169.17. HR MS. Calcd for $C_{23}H_{22}N_5OS$ (M+H): 416.1545. Found: *m/z* 416.1538. Anal. Calcd for $C_{23}H_{21}N_5OS$: C, 66.48; H, 5.09; N, 16.85. Found: C, 66.35; H, 5.07; N, 16.87.

**7-Amino-8-[(4-chlorophenyl)methyl]-4-methoxy-2-methylsulfanyl-5-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5a-ii):** a pale-yellow solid; mp 213–216 ˚C (hexane/$CH_2Cl_2$); IR 3424, 3346, 2178, 1667, 1636, 1604 $cm^{-1}$; $^1H$ NMR δ 2.31 (s, 3H), 3.82 (s, 3H), 4.14 (br s, 2H), 4.96 (d, *J* = 16.1 Hz, 1H), 5.49 (d, *J* = 16.1 Hz, 1H); 4.70 (s, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 7.12–7.21 (m, 5H), 7.27 (d, *J* = 8.4 Hz, 2H); $^{13}C$ NMR δ 14.11, 36.14, 46.06, 54.39, 63.67, 87.15, 120.84, 126.92, 126.99, 127.78, 128.54, 129.38, 133.91, 135.37, 144.31, 152.07, 155.11, 166.61, 169.27. HR-MS. Calcd for $C_{23}H_{21}ClN_5OS$ (M+H): 450.1155. Found: *m/z* 450.1140. Anal. Calcd for $C_{23}H_{20}ClN_5OS$: C, 61.39; H, 4.48; N, 15.56. Found: C, 61.17; H, 4.67; N, 15.40.

**7-Amino-8-butyl-4-methoxy-2-methylsulfanyl-5-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carb-onitrile (5a-iii):** a pale-yellow solid; mp 155–157 ˚C (hexane/$CH_2Cl_2$); IR 3449, 3340, 2168, 1637, 1603 $cm^{-1}$; $^1H$ NMR δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.38–1.42 (m, 2H), 1.54–1.58 (m, 1H), 1.78–1.83 (m, 1H), 2.50

(s, 3H), 3.85 (s, 3H), 3.90–3.96 (m, 1H), 4.09–4.11 (m, 1H), 4.39 (br s, 2H), 4.72 (s, 1H), 7.15 (d, $J$ = 7.5 Hz, 2H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.25 (t, $J$ = 7.5 Hz, 2H); $^{13}$C NMR δ 13.79, 141.11, 20.08, 31.02, 36.05, 42.65, 54.22, 62.51, 97.11, 121.54, 126.82, 126.91, 128.43, 144.73, 151.86, 155.05, 166.50, 168.75. HR-MS. Calcd for $C_{20}H_{24}N_5OS$ (M+H): 382.1701. Found: *m/z* 382.1698. Anal. Calcd for $C_{20}H_{23}N_5OS$: C, 62.97; H, 6.08; N, 18.36. Found: C, 62.80; H, 6.11; N, 18.11.

**7-Amino-4-methoxy-2-methylsulfanyl-5-phenyl-8-(2-phenylethyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5a-iv):** a pale-yellow solid; mp 201–203 ˚C (hexane/$CH_2Cl_2$); IR 3480, 3344, 2183, 1646, 1604 cm$^{-1}$; $^1$H NMR δ 2.56 (s, 3H), 3.06–3.17 (m, 2H), 3.79 (br s, 2H), 3.87 (s, 3H), 4.20–4.29 (m, 2H), 4.71 (s, 1H), 7.12 (dd, $J$ = 8.6, 1.7 Hz, 2H), 7.18 (tt, $J$ = 7.4, 1.7 Hz, 1H), 7.22–7.25 (m, 4H), 7.29 (tt, $J$ =7.4, 2.3 Hz, 1H), 7.35 (dd, $J$ = 8.0, 7.4 Hz, 2H); $^{13}$C NMR δ 14.19, 35.24, 36.29, 45.26, 54.22, 63.60, 97.23, 121.31, 126.85, 126.98, 127.25, 128.45, 128.90, 129.16, 138.31, 144.67, 151.95, 155.11, 166.56, 169.08. HR-MS. Calcd for $C_{24}H_{24}N_5OS$ (M+H): 430.1701. Found: *m/z* 430.1689. Anal. Calcd for $C_{24}H_{23}N_5OS$: C, 67.11; H, 5.40; N, 16.30. Found: C, 67.07; H, 5.29; N, 16.29.

**7-Amino-4-methoxy-8-(2-methoxyethyl)-2-methylsulfanyl-5-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimi-dine-6-carbonitrile (5a-v):** a pale-yellow solid; mp 203–205 ˚C (hexane/$CH_2Cl_2$); IR 3397, 3327, 2188, 1656, 1614 cm$^{-1}$; $^1$H NMR δ 2.48 (s, 3H), 3.39 (s, 3H), 3.70–3.72 (m, 1H), 3.80–3.83 (m, 1H), 3.88 (s, 3H), 4.03–4.08 (m, 1H), 4.34–4.37 (m, 1H), 4.74 (s, 1H), 5.21 (br s, 2H), 7.14–7.19 (m, 3H), 7.24 (d, $J$ = 7.4 Hz, 2H); $^{13}$C NMR δ 14.13, 36.14, 44.96, 54.21, 59.15, 62.17, 72.27, 97.50, 121.87, 126.78, 126.85, 128.45, 144.72, 153.71, 155.53, 166.35, 168.57. HR-MS. Calcd for $C_{19}H_{22}N_5O_2S$ (M+H): 384.1494. Found: *m/z* 384.1492. Anal. Calcd for $C_{19}H_{21}N_5O_2S$: C, 59.51; H, 5.52; N, 18.26. Found: C, 59.40; H, 5.59; N, 18.10.

**7-Amino-4-methoxy-5-(4-methylphenyl)-8-(2-phenylethyl)-2-methylsulfanyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5b):** a pale-yellow solid; mp 193–195 ˚C (hexane/AcOEt); IR 3477, 3326, 3227, 2185, 1657, 1610 cm$^{-1}$; $^1$H NMR δ 2.29 (s, 3H), 2.55 (s, 3H), 3.09–3.12 (m, 2H), 3.78 (br s, 2H), 3.87 (s, 3H), 4.22–4.26 (m, 2H), 4.67 (s, 1H), 7.00 (d, $J$ = 8.4 Hz, 2H), 7.05 (d, $J$ = 8.4 Hz, 2H), 7.22 (d, $J$ = 6.9 Hz, 2H), 7.28 (t, $J$ = 7.6 Hz, 1H), 7.35 (dd, $J$ = 7.6, 6.9 Hz, 2H); $^{13}$C NMR δ 14.19, 21.03, 35.27, 35.84, 45.28, 54.23, 63.80, 97.38, 121.32, 126.84, 127.24, 128.91, 129.15 (2 overlapped Cs), 136.40, 138.35, 141.83, 151.78, 155.11, 166.56, 168.88. HR-MS. Calcd for $C_{25}H_{26}N_5OS$ (M+H): 444.1858. Found: *m/z* 444.1848. Anal. Calcd for $C_{25}H_{25}N_5OS$: C, 67.69; H, 5.68; N, 15.79. Found: C, 67.62; H, 5.79; N, 15.73.

**7-Amino-5-(4-chlorophenyl)-4-methoxy-8-[(4-methoxyphenyl)methyl]-2-methylsulfanyl-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (5c):** a pale-yellow solid; mp 220–223 ˚C (hexane/$CH_2Cl_2$); IR 3434, 3342, 3239, 2173, 1655, 1607 cm$^{-1}$; $^1$H NMR δ 2.41 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 4.30 (br s, 2H), 4.74 (s, 1H), 4.97 (d, $J$ = 16.0 Hz, 1H), 5.59 (d, $J$ = 16.0 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 2H), 7.09 (d, $J$

= 8.4 Hz, 2H), 7.19 (d, *J* = 9.2 Hz, 2H), 7.22 (d, *J* = 9.2 Hz, 2H); $^{13}$C NMR δ 14.16, 35.82, 46.13, 54.38, 55.34, 62.72, 96.66, 114.70, 120.92, 127.72, 128.39, 128.64 (2 overlapped Cs), 132.62, 143.11, 152.58, 155.21, 159.44, 166.58, 169.49. HR-MS. Calcd for $C_{24}H_{23}ClN_5O_2S$ (M+H): 480.1261. Found: *m/z* 480.1248. Anal. Calcd for $C_{24}H_{22}ClN_5O_2S$: C, 60.06; H, 4.62; N, 14.59. Found: C, 60.00; H, 4.73; N, 14.52.

**7-Amino-4-methoxy-5-(4-methoxyphenyl)-8-[(4-methylphenyl)methyl]-2-methylsulfanyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5d):** a pale-yellow solid; mp 180–183 ˚C (hexane/$CH_2Cl_2$); IR 3454, 3339, 3229, 2178, 1655, 1608 cm$^{-1}$; $^1$H NMR δ 2.36 (s, 3H), 2.40 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 4.23 (br s, 2H), 4.73 (s, 1H), 5.00 (d, *J* =16.0 Hz, 1H), 5.62 (d, *J* = 16.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR δ 14.12, 21.08, 35.41, 46.38, 54.31, 55.20, 63.40, 97.31, 113.83, 121.18, 126.28, 128.02, 129.94, 133.89, 137.03, 137.84, 152.32, 155.18, 158.45, 166.61, 168.97. HR MS. Calcd for $C_{25}H_{26}N_5O_2S$ (M+H): 460.1807. Found: *m/z* 460.1798. Anal. Calcd for $C_{25}H_{25}N_5O_2S$: C, 65.34; H, 5.48; N, 15.24. Found: C, 65.20; H, 5.51; N, 15.18.

**7-Amino-4-methoxy-5-phenyl-8-phenylmethyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5e-i):** a pale-yellow solid; mp 122–124 ˚C (hexane/$CH_2Cl_2$); IR 3462, 3331, 2183, 1648, 1610 cm$^{-1}$; $^1$H NMR δ 3.92 (s, 3H), 4.25 (br s, 2H), 4.86 (s, 1H), 5.06 (d, *J* = 16.6 Hz, 1H), 5.70 (d, *J* = 16.6 Hz, 1H), 7.18–7.29 (m, 7H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 8.40 (s, 1H); $^{13}$C NMR δ 36.37, 46.58, 54.31, 62.91, 101.80, 120.99, 126.15, 127.29 (2 overlapped Cs), 128.12, 128.58, 129.34, 136.61, 144.25, 152.47, 155.44, 155.93, 166.97. HR-MS. Calcd for $C_{22}H_{20}N_5O$ (M+H): 370.1668. Found: *m/z* 370.1652. Anal. Calcd for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.40; H, 5.21; N, 18.71.

**7-Amino-8-butyl-4-methoxy-5-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5e-ii):** a pale-yellow solid; mp 193–196 ˚C (hexane/$CH_2Cl_2$); IR 3396, 3328, 3229, 1651, 1612 cm$^{-1}$; $^1$H NMR δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.39–1.86 (m, 4H), 3.91 (s, 3H), 3.92–3.95 (m, 1H), 4.13–4.19 (m, 1H), 4.43 (br s, 2H), 4.80 (s, 1H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 2H), 8.39 (s, 1H); $^{13}$C NMR δ 13.76, 20.01, 31.02, 36.21, 42.60, 54.17, 62.24, 101.86, 121.46, 125.93, 126.98, 128.50, 144.47, 152.00, 155.22, 155.61, 166.79. HR-MS. Calcd for $C_{19}H_{22}N_5O$ (M+H): 336.1824. Found: *m/z* 336.1829. Anal. Calcd for $C_{19}H_{21}N_5O$: C, 68.04; H, 6.31; N, 20.88. Found: C, 67.80; H, 6.46; N, 20.80.

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