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SYNTHESIS OF 7-ALKYL-6-AMINO-7*H*-PYRROLO[2,3-*d*]-PYRIMIDINE-6-CARBONITRILES BY THE COPPER-CATALYZED REACTION OF 4-(ALKYLAMINO)-5-IODOPYRIMIDINES WITH PROPANEDINITRILE

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Abstract – A convenient sequence for the first general preparation of 6-aminopyrrolo[2,3-*d*]pyrimidine-5-carbonitrile derivatives has been developed. Thus, treatment of 4-chloro-6-methoxypyrimidines with lithium diisopropylamide in THF at –78 °C lithiated the 5-position to generate 4-chloro-5-lithio-6-methoxypyrimidines, which were allowed to react with iodine to give 4-chloro-5-iodo-6-methoxypyrimidines in good yields. Substitution of the 4-chloro group of these compounds with primary amines in the presence of triethylamine in refluxing THF afforded 4-(alkylamino)-5-iodo-6-methoxypyrimidines. The reaction of these aminated compounds with propanedinitrile (malononitrile) in the presence of a catalytic amount of copper(I) iodide and excess potassium carbonate in dimethyl sulfoxide at 100 °C provided 7-alkyl-6-amino-4-methoxypyrrolo[2,3-*d*]pyrimidine-5-carbonitriles in moderate yields.

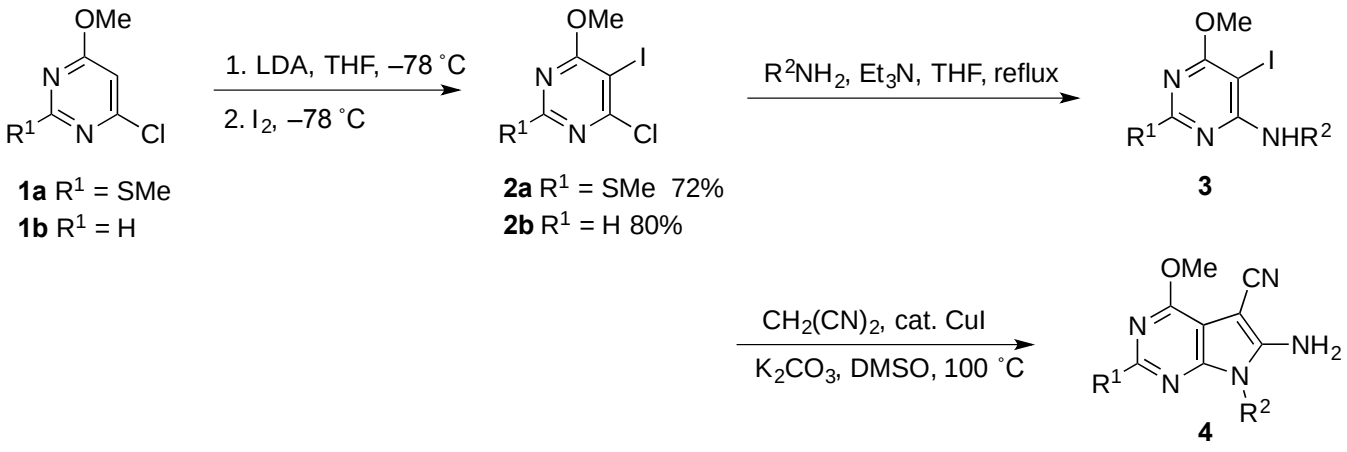
INTRODUCTION

Pyrrolo[2,3-*d*]pyrimidine derivatives have attracted considerable attention of medicinal and synthetic chemists, because they have been reported to exhibit a variety of notable biological activities. Therefore,

efforts have been made to develop processes for their preparation.[1] Recently, syntheses and biological activities of several pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile derivatives have been recorded in the literatures.[2] Surprisingly, however, there have been so far few reports on the synthesis of 6-aminopyrrolo[2,3-*d*]pyrimidine-5-carbonitrile derivatives, though Townsend and co-workers have reported that treatment of 4-amino-6-bromopyrrolo[2,3-*d*]pyrimidine-5-carbonitriles with liquid ammonia results in the formation of 4,6-diaminopyrrolo[2,3-*d*]pyrimidine-5-carbonitriles and that these products exhibit antiviral activity and cytotoxicity.[3] However, this method suffered from limited generality and troublesome operations. We, therefore, decided to undertake an investigation of developing a convenient and general method for the preparation of 6-aminopyrrolo[2,3-*d*]pyrimidine-5-carbonitrile derivatives. In the present paper, we wish to describe the results of our investigation, which provide the first general access to this class of molecules. The method is based on the copper-catalyzed reaction[4] of 4-(alkylamino)-5-iodo-6-methoxypyrimidines (**3**), derived from 4-chloro-6-methoxypyrimidines (**1**) by an easy two-step sequence, with propanedinitrile, giving 7-alkyl-6-amino-4-methoxypyrrolo[2,3-*d*]-pyrimidine-5-carbonitriles (**4**).

RESULTS AND DISCUSSION

The method we have developed for the construction of 6-aminopyrrolo[2,3-*d*]pyrimidine-5-carbonitrile skeleton is illustrated in Scheme 1. Initially, compounds **1**, which were easily prepared by mono-methoxy substitution of commercially available 4,6-dichloropyrimidines with sodium methoxide, were lithiated with lithium diisopropylamide in THF,[5,6] and the resulting lithiated products were allowed to react with iodine to give 4-chloro-5-iodo-6-methoxypyrimidines (**2**) in good yields. The chloro atom of **2** was displaced by an N-alkylamino group with primary amines in refluxing THF in the presence of triethylamine to give the corresponding 4-(alkylamino)-5-iodo-6-methoxypyrimidines (**3**) in good yields as compiled in Table 1.



1a R^1 = SMe
1b R^1 = H

2a R^1 = SMe 72%
2b R^1 = H 80%

3

4

Scheme 1

Table 1. Preparation of 6-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles (**4**)

Entry	**1**	R^2	**3**	Yield/%[a]	**4**	Yield/%[a]
1	**1a** (R^1 = SMe)	$PhCH_2$	**3a**	89	**4a**	53
2	**1a**	4-$MeC_6H_4CH_2$	**3b**	74	**4b**	52
3	**1a**	4-$MeOC_6H_4CH_2$	**3c**	95	**4c**	55
4	**1a**	*n*-Bu	**3d**	91	**4d**	51
5	**1a**	*i*-Bu	**3e**	74	**4e**	40
6	**1a**	$C_6H_4(CH_2)_2$	**3f**	90	**4f**	55
7	**1a**	$MeO(CH_2)_2$	**3g**	82	**4g**	54
8	**1b** (R^1 = H)	$PhCH_2$	**3h**	72	**4h**	60
9	**1b**	*n*-Bu	**3i**	87	**4i**	55
10	**1b**	$MeO(CH_2)_2$	**3j**	86	**4j**	59

[a] Yields of isolated products.

When these precursors (**3**) were treated with propanedinitrile in the presence of 10 mol% of copper(I) iodide using potassium carbonate as a base in DMSO at 100 °C, probably replacement of 5-iodo substituent with propanedinitrile followed by attack of 4-nitrogen on one of the two cyano functions of the intermediates proceeded. The desired products (**5**) were obtained, after aqueous workup of the reaction mixture followed by purification of the crude products by column chromatography on silica gel, in generally moderate yields as compiled in Table 1 as well. These results indicate that yields of the products carrying a methylsulfanyl group at the 2-position (Entries 1-7) are slightly lower than those carrying no substituents at the 2-position (Entries 8-10). Somewhat diminished yields were obtained when using isobutyl as an N-substituent, probably due to steric effects (Entry 5). Of solvents investigated DMSO was found to be the best solvent. Using DMF or 1,4-dioxane, reactions proceeded sluggishly and uncleanly to give the desired products much lower yields. Using a greater than 10 mol% of copper(I) iodide gave no yield improvement.

The reaction of 5-iodo-6-methoxy-2-(methylsulfanyl)-4-[(phenylmethyl)amino]pyrimidine (**3a**) with ethyl cyanoacetate under the same conditions as described above, expecting the formation of ethyl 6-amino-4-methoxy-7-(phenylmethyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxylate, was also investigated. Unfortunately, however, it resulted in the formation of a considerably complicated mixture, of which ^{1}H NMR spectrum showed only a small quantity of the desired product along with some structurally undefined byproducts.

In summary, the results reported above demonstrate that a convenient three-step sequence for the preparation of pyrrolo[2,3-*d*]pyrimidine having amino and cyano groups at the 6- and 5-positions,

respectively, which starts with commercially available starting materials and is based on the copper-catalyzed reaction of 4-(alkylamino)-5-iodopyrimidines with propanedinitrile, has been developed. The products have potential as precursors for further synthetic elaborations. Further investigations are under way to apply the key reaction of the present sequence in the synthesis of related heterocycles of biological interest.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded 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. 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 reported method.[5] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

General Procedure for the Preparation of 4-Chloro-5-iodo-6-methoxypyrimidines (2). 4-Chloro-5-iodo-6-methoxy-2-(methylsulfanyl)pyrimidine (2a). To a stirred solution of LDA (7.5 mmol), generated from *n*-BuLi and *i*-Pr_2NH by the standard method, in THF (12 mL) was added a solution of **1a** (0.95 g, 5.0 mmol) in THF (4 mL) dropwise. After 1.5 h, a solution of I_2 (1.9 g, 7.5 mmol) in THF (4 mL) was added and stirring was continued for an additional 30 min before aqueous 5% $Na_2S_2O_3$ (25 mL) was added. The mixture was warmed to rt and extracted with AcOEt (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane to give **2a** (1.1 g, 72%); a white solid; mp 105–107 °C (hexane); IR (KBr) 1534, 1508, 1370, 1307, 1261, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 4.04 (s, 3H). Anal. Calcd for $C_6H_6ClIN_2OS$: C, 22.77; H, 1.91; N, 8.85. Found: C, 22.67; H, 1.95; N, 8.83.

4-Chloro-5-iodo-6-methoxypyrimidine (2b): a white solid; mp 87–89 °C (hexane); IR (KBr) 1539, 1399, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 3H), 8.44 (s, 1H). Anal. Calcd for $C_5H_4ClIN_2O$: C, 22.21; H, 1.49; N, 10.36. Found: C, 22.60; H, 1.51; N, 10.24.

Typical Procedure for the Preparation of 4-Amino-5-iodo-6-methoxypyrimidines (3). 5-Iodo-6-methoxy-2-methylsulfanyl-4-[(phenylmethyl)amino]pyrimidine (3a). A mixture of **2a** (0.34 g, 1.1

mmol), $PhCH_2NH_2$ (0.11 g, 1.1 mmol), and Et_3N (0.16 g, 1.7 mmol) in THF (4 mL) was heated at reflux temperature under stirring until TLC analyses (silica gel; AcOEt–hexane 1:5) had revealed complete consumption of **2a** (ca. 6 h). After cooling to rt, Et_2O (25 mL) was added and the precipitate was filtered off. The filtrate was concentrated by evaporation and purified by column chromatography on silica gel (AcOEt–hexane 1:10) to afford **3a** (0.37 g, 89%); a white solid; mp 80–82 °C (hexane–CH_2Cl_2); IR (KBr) 3404, 1566, 1542, 1361, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.96 (s, 3H), 4.71 (d, J = 4.9 Hz, 2H), 5.56 (br s, 1H), 7.27–7.36 (m, 5H). Anal. Calcd for $C_{13}H_{14}IN_3OS$: C, 40.32; H, 3.64; N, 10.85. Found: C, 40.15; H, 3.68; N, 10.84.

5-Iodo-6-methyl-4-[(4-methylphenyl)methyl]amino-2-(methylsulfanyl)pyrimidine (3b): a white solid; mp 85–87 °C (hexane–CH_2Cl_2); IR (KBr) 3418, 1583, 1544, 1363 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.48 (s, 3H), 3.97 (s, 3H), 4.66 (d, J = 6.1 Hz, 2H), 5.51 (br s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 2H). Anal. Calcd for $C_{14}H_{16}IN_3OS$: C, 41.91; H, 4.02; N, 10.47. Found: C, 41.80; H, 4.07; N, 10.45.

5-Iodo-6-methoxy-4-{[(4-methoxyphenyl)methyl]amino}-2-(methylsulfanyl)pyrimidine (3c): a yellow oil; R_f 0.30 (AcOEt–hexane 1:10); IR (neat) 3403, 1612, 1567, 1543, 1361 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.80 (s, 3H), 3.96 (s, 3H), 4.63 (d, J = 4.9 Hz, 2H), 5.47 (br s, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{14}H_{16}IN_3O_2S$: C, 40.30; H, 3.87; N, 10.07. Found: C, 40.26; H, 3.96; N, 10.01.

4-Butylamino-5-iodo-6-methoxy-2-(methylsulfanyl)pyrimidine (3d): a yellow oil; R_f 0.43 (CH_2Cl_2–hexane 1:10); IR (neat) 3409, 1574, 1362 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3H), 1.40 (sext, J = 7.6 Hz, 2H), 1.57 (quint, J = 7.6 Hz, 2H), 2.51 (s, 3H), 3.49 (q, J = 7.6 Hz, 2H), 3.95 (s, 3H), 5.21 (br s, 1H). Anal. Calcd for $C_{10}H_{16}IN_3OS$: C, 34.00; H, 4.57; N, 11.90. Found: C, 33.71; H, 4.61; N, 11.64.

5-Iodo-6-methoxy-4-(2-methylpropylamino)-2-(methylsulfanyl)pyrimidine (3e): a yellow oil; R_f 0.52 ($CHCl_3$–hexane 1:3); IR (neat) 3397, 1576, 1361 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, J = 6.1 Hz, 6H), 1.86–1.94 (m, 1H), 2.50 (s, 3H), 3.32 (t, J = 6.1 Hz, 2H), 3.95 (s, 3H), 5.31 (br s, 1H). Anal. Calcd for $C_{10}H_{16}IN_3OS$: C, 34.00; H, 4.57; N, 11.90. Found: C, 34.03; H, 4.71; N, 11.73.

5-Iodo-6-methoxy-2-methylsulfanyl-4-[(2-phenylethyl)amino]pyrimidine (3f): a yellow oil; R_f 0.33 ($CHCl_3$–hexane 1:10); IR (neat) 3340, 1570, 1361 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.53 (s, 3H), 2.90 (t, J = 6.9 Hz, 2H), 3.73 (q, J = 6.9 Hz, 2H), 3.96 (s, 3H), 5.27 (br s, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H). Anal. Calcd for $C_{14}H_{16}IN_3OS$: C, 41.91; H, 4.02; N, 10.47. Found: C, 41.88; H, 4.03; N, 10.46.

5-Iodo-6-methoxy-4-(2-methoxyethylamino)-2-(methylsulfanyl)pyrimidine (3g): a white solid; mp 122–124 °C (hexane–CH_2Cl_2); IR (KBr) 3341, 1575, 1353 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.51 (s,

3H), 3.40 (s, 3H), 3.55 (t, J = 5.4 Hz, 2H), 3.68 (q, J = 5.4 Hz, 2H), 3.96 (s, 3H), 5.57 (br s, 1H). Anal. Calcd for $C_9H_{14}IN_3O_2S$: C, 30.43; H, 3.97; N, 11.83. Found: C, 30.38; H, 4.04; N, 11.83.

5-Iodo-6-methoxy-4-[(phenylmethyl)amino]pyrimidine (3h): a yellow oil; R_f 0.28 (AcOEt–hexane 1:10); IR (neat) 3404, 1679, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.73 (d, J = 5.7 Hz, 2H), 5.61 (br s, 1H), 7.29 (t, J = 6.9 Hz, 1H), 7.32–7.38 (m, 4H), 8.17 (s, 1H). Anal. Calcd for $C_{12}H_{12}IN_3O$: C, 42.25; H, 3.55; N, 12.32. Found: C, 42.18; H, 3.69; N, 12.17.

4-(Butylamino)-5-iodo-6-methoxypyrimidine (3i): a yellow oil; R_f 0.56 (AcOEt–hexane 1:5); IR (neat) 3408, 1583, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3H), 1.42 (sext, J = 7.6 Hz, 2H), 1.62 (quint, J = 7.6 Hz, 2H), 3.49 (q, J = 7.6 Hz, 2H), 3.98 (s, 3H), 5.27 (br s, 1H), 8.14 (s, 1H). Anal. Calcd for $C_9H_{14}IN_3O$: C, 35.20; H, 4.59; N, 13.68. Found: C, 35.10; H, 4.71; N, 13.42.

5-Iodo-6-methoxy-4-[(2-methoxyethyl)amino]pyrimidine (3j): colorless crystals; mp 49–51 °C (hexane–$CHCl_3$); IR (KBr) 3407, 1583, 1465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.57 (t, J = 5.4 Hz, 2H), 3.69 (q, J = 5.4 Hz, 2H), 3.98 (s, 3H), 5.65 (br s, 1H), 8.13 (s, 1H). Anal. Calcd for $C_8H_{12}IN_3O_2$: C, 31.09; H, 3.91; N, 13.59. Found: C, 30.96; H, 4.17; N, 13.62.

Typical Procedure for the Preparation of 6-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles (4). 6-Amino-4-methoxy-2-methylsulfanyl-7-(phenylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitril e (4a). A mixture of **3a** (0.12 g, 0.37 mmol), $CH_2(CN)_2$ (50 mg, 0.75 mmol) in DMSO (3 mL) containing CuI (14 mg, 0.074 mmol) and K_2CO_3 (0.21 g, 1.5 mmol) was heated at 100 °C under stirring until TLC analyses (silica gel; AcOEt–hexane 1:1) had revealed complete consumption of **3a**. After cooling to rt, 25% ammonia solution, water (10 mL each), and AcOEt (20 mL) were added. The precipitate was removed by filtration through a Celite pad and the layers were separated. The aqueous layer was extracted with AcOEt (2 × 10 mL). The combined extracts were washed with water (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:10) to afford **4a** (65 mg, 53%); a pale-yellow solid; mp 193–195 °C (hexane–$CHCl_3$); IR (KBr) 3442, 3315, 2205, 1645, 1603, 1566 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H), 4.11 (s, 3H), 4.42 (br s, 2H), 5.32 (s, 2H), 7.19 (d, J = 6.9 Hz, 2H), 7.34–7.39 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 13.77, 43.68, 53.81, 57.19, 99.50, 116.84, 127.16, 127.62, 128.68, 136.29, 150.76, 152.40, 158.99, 160.42. HR-MS. Calcd for $C_{16}H_{16}N_5OS$ (M+H): 326.1075. Found: *m/z* 326.1073. Anal. Calcd for $C_{16}H_{15}N_5OS$: C, 59.06; H, 4.65; N, 21.52. Found: C, 59.00; H, 4.82; N, 21.49.

6-Amino-4-methoxy-7-[(4-methylphenyl)methyl]-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4b): a white solid; mp 241–243 °C (hexane–THF); IR (KBr) 3398, 3334, 2207, 1651, 1602, 1568 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.59 (s, 3H), 4.11 (s, 3H), 4.41 (br s, 2H), 5.27 (s, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.34, 21.11, 44.65, 54.02, 62.53, 99.43, 116.13, 126.93, 130.93, 131.50, 138.49, 149.98, 150.86, 160.52, 162.96. HR-MS. Calcd for

$C_{17}H_{18}N_5OS$ (M+H): 340.1232. Found: *m/z* 340.1205. Anal. Calcd for $C_{17}H_{17}N_5OS$: C, 60.16; H, 5.05; N, 20.63. Found: C, 59.86; H, 5.10; N, 20.54.

6-Amino-4-methoxy-7-[(4-methoxyphenyl)methyl]-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4c): a pale-yellow solid; mp 223–225 °C (hexane–$CHCl_3$); IR (KBr) 3443, 3343, 2199, 1637, 1611, 1567 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.80 (s, 3H), 4.11 (s, 3H), 4.44 (br s, 2H), 5.25 (s, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 13.78, 43.21, 53.91, 55.16, 57.21, 99.57, 114.04, 116.78, 128.30, 128.86, 150.70, 152.26, 158.79, 158.91, 160.40. HR-MS. Calcd for $C_{17}H_{18}N_5O_2S$ (M+H): 356.1181. Found: *m/z* 356.1165. Anal. Calcd for $C_{17}H_{17}N_5O_2S$: C, 57.45; H, 4.82; N, 19.71. Found: C, 57.40; H, 4.89; N, 19.49.

6-Amino-7-butyl-4-methoxy-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4d): a pale-yellow solid; mp 181–183 °C (hexane–THF); IR (KBr) 3405, 3315, 2211, 1648, 1606, 1562 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.6 Hz, 3H), 1.35 (sext, *J* = 7.6 Hz, 2H), 1.73 (quint, *J* = 7.6 Hz, 2H), 2.58 (s, 3H), 4.06 (t, *J* = 7.6 Hz, 2H), 4.09 (s, 3H), 4.59 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 13.52, 13.60, 19.13, 30.10, 40.28, 53.56, 56.84, 99.32, 116.86, 150.63, 152.27, 158.71, 159.95. HR-MS. Calcd for $C_{13}H_{18}N_5OS$ (M+H): 292.1232. Found: *m/z* 292.1235. Anal. Calcd for $C_{13}H_{17}N_5OS$: C, 53.59; H, 5.88; N, 24.04. Found: C, 53.54; H, 6.03; N, 24.13.

6-Amino-4-methoxy-7-(2-methylpropyl)-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4e): a pale-yellow solid; mp 182–184 °C (hexane–$CHCl_3$); IR (KBr) 3418, 3330, 2203, 1658, 1607, 1570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.9 Hz, 6H), 2.15–2.23 (m, 1H), 2.58 (s, 3H), 3.85 (d, *J* = 7.6 Hz, 2H), 4.09 (s, 3H), 4.56 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.30, 20.08, 28.42, 48.73, 53.94, 62.06, 99.31, 116.34, 149.74, 151.07, 160.36, 162.58. HR-MS. Calcd for $C_{13}H_{18}N_5OS$ (M+H): 292.1232. Found: *m/z* 292.1217. Anal. Calcd for $C_{13}H_{17}N_5OS$: C, 53.59; H, 5.88; N, 24.04. Found: C, 53.44; H, 6.06; N, 24.22.

6-Amino-4-methoxy-2-methylsulfanyl-7-(2-phenylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4f): a pale-yellow solid; mp 191–193 °C (hexane–THF); IR (KBr) 3432, 3343, 2207, 1647, 1606, 1571 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.07 (t, *J* = 6.1 Hz, 2H), 3.69 (br s, 2H), 4.10 (s, 3H), 4.26 (t, *J* = 6.1 Hz, 2H), 7.04 (dd, *J* = 7.6, 2.3 Hz, 2H), 7.29–7.32 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 13.61, 33.90, 41.94, 53.60, 56.97, 99.22, 116.94, 126.47, 128.26, 128.86, 137.83, 150.50, 152,17, 158.53, 159.91. HR-MS. Calcd for $C_{17}H_{18}N_5OS$ (M+H): 340.1232. Found: *m/z* 340.1208. Anal. Calcd for $C_{17}H_{17}N_5OS$: C, 60.16; H, 5.05; N, 20.63. Found: C, 60.12; H, 5.08; N, 20.56.

6-Amino-4-methoxy-7-(2-methoxyethyl)-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4g): a pale-yellow solid; mp 236–238 °C (hexane–THF); IR (KBr) 3397, 3329, 2207, 1647, 1608, 1566 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.47 (br s, 2H), 2.49 (s, 3H), 3.19 (s, 3H), 3.56 (t, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 4.20 (t, *J* = 5.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 13.64, 40.22, 53.64, 57.03, 58.04,

68.96, 99.40, 116.82, 150.82, 152.63, 158.80, 159.98. HR-MS. Calcd for $C_{12}H_{16}N_5O_2S$ (M+H): 294.1024. Found: *m/z* 294.1008. Anal. Calcd for $C_{12}H_{15}N_5O_2S$: C, 49.13; H, 5.15; N, 23.87. Found: C, 49.23; H, 5.26; N, 23.74.

6-Amino-4-methoxy-7-(phenylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4h): a pale-yellow solid; mp 241–243 °C (hexane–THF); IR (KBr) 3443, 3301, 3225, 2201, 1643, 1607 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.99 (s, 3H), 5.35 (s, 2H), 7.13 (d, J = 6.9 Hz, 2H), 7.23 (t, J = 6.9 Hz, 1H), 7.29 (t, J = 6.9 Hz, 2H), 7.43 (br s, 2H), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 43.53, 53.63, 57.29, 103.34, 116.66, 126.86, 127.47, 128.60, 136.26, 148.86, 149.81, 152.96, 158.92. HR-MS. Calcd for $C_{15}H_{14}N_5O$ (M+H): 280.1198. Found: *m/z* 280.1178. Anal. Calcd for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.33; H, 4.86; N, 24.85.

6-Amino-7-butyl-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4i): a white solid; mp 181–183 °C (hexane–CH_2Cl_2); IR (KBr) 3407, 3332, 3201, 2206, 1656, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.38 (sext, J = 7.4 Hz, 2H), 1.76 (quint, J = 7.4 Hz, 2H), 4.10 (t, J = 7.4 Hz, 2H), 4.12 (s, 3H), 4.71 (br s, 2H), 8.37 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.59, 19.22, 30.22, 40.41, 53.49, 56.96, 103.14, 116.78, 148.58, 149.72, 152.84, 158.77. HR-MS. Calcd for $C_{12}H_{16}N_5O$ (M+H): 246.1355. Found: *m/z* 246.1336. Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.65; H, 6.14; N, 28.39.

6-Amino-4-methoxy-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (4j): a white solid; mp 186–188 °C (hexane–CH_2Cl_2); IR (KBr) 3393, 3319, 3230, 2215, 1646, 1598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.73 (t, J = 4.6 Hz, 2H), 4.11 (s, 3H), 4.34 (t, J = 4.6 Hz, 2H), 5.38 (br s, 2H), 8.33 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 40.36, 53.55, 57.18, 58.14, 69.07, 103.20, 116.71, 148.60, 149.94, 153.18, 158.82. HR-MS. Calcd for $C_{11}H_{14}N_5O_2$ (M+H): 248.1147. Found: *m/z* 246.1146. Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.17; H, 5.24; N, 28.08.

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