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TWO-STEP SYNTHESIS OF 5-HYDROXY-5,7-DIHYDRO-6*H*-PYRROLO[2,3-*d*]PYRIMIDIN-6-ONE DERIVATIVES FROM 4-CHLORO-6-METHOXY-2-(METHYLSULFANYL)PYRIMIDINE

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Abstract – We report a facile two-step procedure that allows the synthesis of the title fused heterocyclic derivatives from 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine, readily available from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP). The first step is the lithiation at the 5-position of the starting material with lithium diisopropylamide (LDA) and the reaction of the resulting lithium compound with α-keto esters to give the corresponding 2-hydroxy-2-(pyrimidin-5-yl)carboxylic acid ester derivatives. In the second step, these are treated with primary aliphatic amines in the presence of triethylamine to afford the desired products.

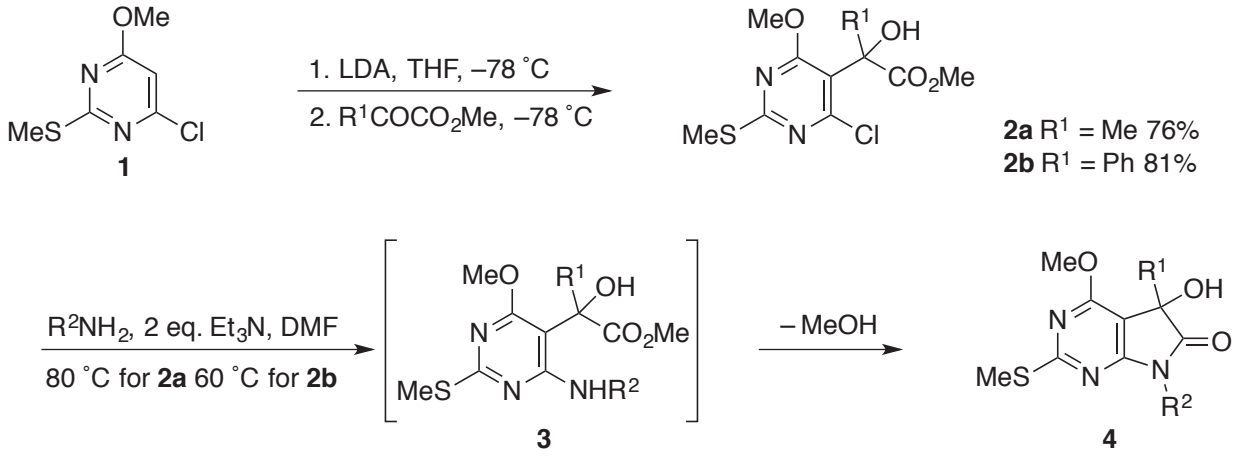
INTRODUCTION

5,7-Dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one derivatives have recently be attracted considerable attention because of their wide variety of biological activities.[1,2] While this structure has usually been constructed using oxidation of pyrrolo[2,3-*d*]pyrimidine derivatives,[2a,3a] some other efficient methods for the syntheses of this class of heterocycles have recently been reported.[3b,c] On the other hand, we have previously reported syntheses of pyrimidine-fused heterocyclic derivatives starting from 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (**1**), readily available from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP).[4] As part of these studies, we herein wish to report a two-step route

to a new 5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one system, 5-hydroxy-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one derivatives (**4**). As the first step, the method involves the reaction of 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine, generated by the treatment of **1** with lithium diisopropylamide (LDA), with α-keto esters leading to the formation of the corresponding 2-hydroxy-2-(4-chloropyrimidin-5-yl)carboxylic acid ester derivatives (**2**). The second step creates the pyrrolidinone ring system by the reaction with aliphatic primary amines.

RESULTS AND DISCUSSION

Our two-step procedure used successfully for the preparation of **4** from **1** was conducted as illustrated in Scheme 1. Compound (**1**) was readily lithiated with LDA in THF at –78 ˚C to generate the 5-lithio derivative as described previously,[4] and afforded good yields of the corresponding 2-hydroxy-2-(4-chloropyrimidin-5-yl)carboxylic acid ester derivatives (**2**) after addition of α-keto esters, such as methyl 2-oxopropanoate (methyl pyruvate) or methyl 2-oxo-2-phenylacetate, and the subsequent aqueous workup.



Scheme 1

Transformation of **2** into the desired products (**4**) was accomplished by treating with aliphatic primary amines in DMF in the presence of triethylamine under heating. Thus, compound (**2a**) was allowed to react with amines in the presence of two equivalents of triethylamine at 80 ˚C to afforded the corresponding 7-substituted 5-hydroxy-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one derivatives (**4a–4f**) in satisfactory yields, as compiled in Table 1 (Entries 1–6). The reactions of **2b** with amines were first carried out under the same conditions for those using **2a**, but provided the corresponding desired products (**4g–4i**) only in low yields (*ca*. 20%) along with considerably quantities of structurally undefined by-products. Fortunately, we found later that the reactions at 60 ˚C gave reasonable yields of the desired products, though rather extended reaction times were required (Entries 7–9). It is notable that all attempts

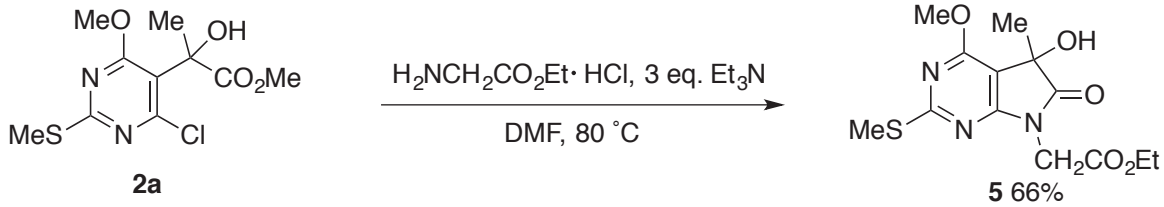
at obtaining 7-aryl-5-hydroxy-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one derivatives by the reaction of **2a** with aromatic amines are unsuccessful. For example, the reaction of **2a** with benzenamine under the same conditions for the preparation of **4a-4f** did not proceed at all. Heating of **2a** with 3 equivalents of 4-methoxybenzenamine without any solvents at 80 ˚C resulted in the formation of a considerably complex mixture of products.

Table 1. Preparation of 5-hydroxy-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones (**4**)

Entry	**2**	R^2 in R^2NH_2	**4**	Yield/%[a]
1	**2a** (R^1 = Me)	Bn	**4a**	65
2	**2a**	4-$MeOC_6H_4CH_2$	**4b**	72
3	**2a**	$C_6H_5(CH_2)_2$	**4c**	79
4	**2a**	prop-2-yn-1-yl	**4d**	77
5	**2a**	$MeO(CH_2)_2$	**4e**	71
6	**2a**	$HO(CH_2)_2O(CH_2)_2$	**4f**	60
7	**2b** (R^1 = Ph)	4-$MeOC_6H_4CH_2$	**4g**	79
8	**2b**	3,4-$(MeO)_2C_6H_3(CH_2)_2$	**4h**	77
9	**2b**	*n*-Bu	**4i**	70

[a] Yields of isolated products.

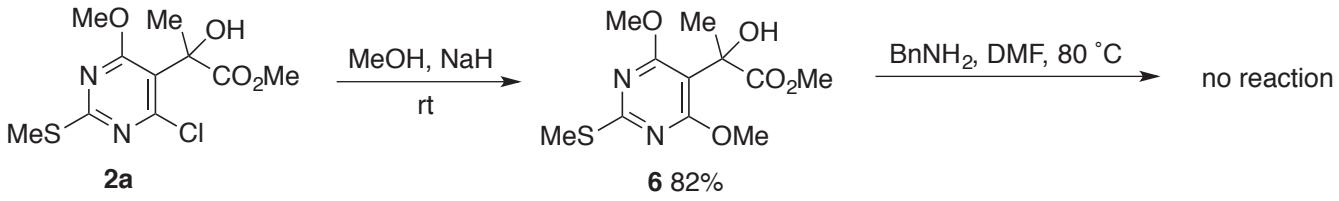
It should be noted that glycine ethyl ester hydrochloride was also usable in the present procedure, as depicted in Scheme 2. Treatment of **2a** with glycine ethyl ester hydrochloride in the presence of three equivalents of triethylamine under the same conditions as described for the preparation of **4a-4f** yielded the desired product **5** in a yield comparable to those of **4a-4f**.



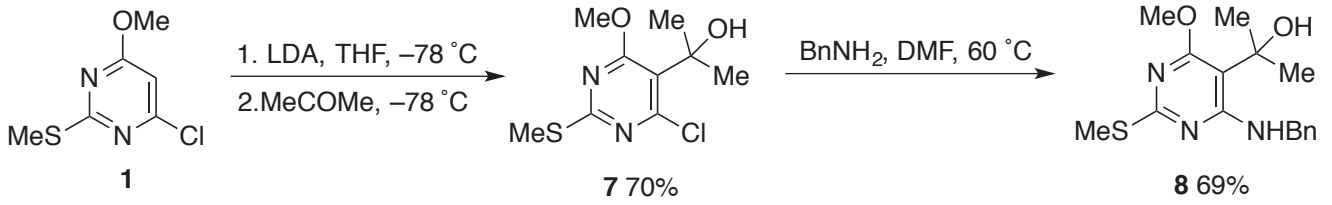
Scheme 2

In each case, the replacement of the chloro substituent of **2** by an alkylamino group, followed by lactamization of the resulting alkylamino ester intermediate (**3**), appears to lead to the formation of **4**. The spot due to **3** could not be observed by TLC analyses during the reaction. It reveals that the rate-determining step is the first replacement step and the following ring closure occurs immediately. In order to confirm this assumption we carried out the following reactions. As shown in Scheme 3, compound (**2a**) was transformed into methyl 2-[4,6-dimethoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (**6**), of which treatment with phenylmethanamine in DMF at 80 ˚C resulted in an almost quantitative recovery of **6** (Scheme 3). On the other hand, 2-[4-chloro-6-methoxy-

2-(methylsulfanyl)pyrimidin-5-yl]propan-2-ol (**7**) was prepared by the reaction of 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine with acetone and allowed to react with phenylmethanamine in DMF. The replacement of the chloro group by the (phenylmethyl)amino group proceeded smoothly only at 60 ˚C to give 2-[6-methoxy-2-(methylsulfanyl)-4-[(phenylmethyl)amino]pyrimidin-5-yl]propan-2-ol (**8**) in a reasonable yield, as illustrated in Scheme 4.



Scheme 3



Scheme 4

In conclusion, a new strategy has been developed for the preparation of 7-alkyl-5-hydroxy-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one derivatives, which are of potential interest from a biological point of view, using the reaction of 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine with α-keto esters followed by the treatment with aliphatic primary amines. This is the first preparation of 5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones bearing a hydroxyl group at the 5-position and the method may be of value in synthesis because of the ready availability of the starting materials and the simple operations. Since the 2-methylsulfanyl and the 4-methoxy groups in the products (**4**) are replaceable with other functional groups and the 5-hydroxy group is usable for further functionalization, the present synthesis may provide many other pharmacophores. Further study on the synthesis of pyrimidine-fused heterocycles utilizing the reaction of this lithium compound with other electrophiles followed by ring closure is under investigation in our laboratory.

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. ^{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 Exative 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-methoxy-2-(methylsulfanyl)pyrimidine (**1**) was prepared according to the reported method.[4] *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-(Pyrimidin-5-yl)-2-hydroxyalkanoates (2). Methyl 2-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (2a). To a stirred solution of LDA (2.0 mmol), generated by the standard method from *n*-BuLi and *i*-Pr_2NH, in THF (6 mL) at –78 ˚C was added a solution of **1** (0.38 g, 2.0 mmol) in THF (4 mL) dropwise. After 1 h, $MeCOCO_2Me$ (0.20 g, 2.0 mmol) was added and stirring was continued for an additional 10 min at the same temperature before addition of aqueous NH_4Cl (20 mL). The mixture was warmed to rt and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:6) to give **2a** (0.44 g, 76%); a white solid; mp 59–62 ˚C (hexane/CH_2Cl_2); IR (KBr) 3486, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H), 2.55 (s, 3H), 3.78 (s, 3H), 3.90 (s, 1H), 4.01 (s, 3H). Anal. Calcd for $C_{10}H_{13}ClN_2O_4S$: C, 41.03; H, 4.48; N, 9.57. Found: C, 40.82; H, 4.56; N, 9.53.

Methyl 2-[4-Chloro-4-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxy-2-phenylacetate (2b): a white solid; mp 116–118 ˚C (hexane/CH_2Cl_2); IR (KBr) 3493, 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.75 (s, 3H), 3.92 (s, 3H), 4.51 (s, 1H), 7.30–7.35 (m, 3H), 7.53 (dd, *J* = 7.6, 1.5 Hz, 2H). Anal. Calcd for $C_{15}H_{15}ClN_2O_4S$: C, 50.78; H, 4.26; N, 7.90. Found: C, 50.78; H, 4.22; N, 7.83.

General Procedure for the Preparation of 5-Hydroxy-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones (4). A mixture of **2** (1.0 mmol) and an amine (1.0 mmol) in DMF (4 mL) containing Et_3N (0.20 g, 2.0 mmol) was heated at the temperature indicated in Scheme 1 until most of the starting material had disappeared (TLC on SiO_2; about 3 h for **2a** and 20 h for **2b**). After cooling to rt, H_2O (30 mL) was added and the mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with water (2 × 20 mL) and then brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **4**.

5-Hydroxy-4-methoxy-5-methyl-2-(methylsulfanyl)-7-(phenylmethyl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4a): a white solid; mp 160–161 ˚C (hexane/CH_2Cl_2); IR (KBr) 3379, 1726, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H), 2.54 (s, 3H), 2.88 (s, 1H), 4.02 (s, 3H), 4.87 (s, 2H), 7.25 (t, *J* = 6.9 Hz, 1H), 7.29 (t, *J* = 6.9 Hz, 2H), 7.40 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.57, 42.98,

54.10, 72.87, 99.31, 127.79, 128.47, 128.57, 135.98, 163.32, 164.00, 173.05, 178.09. HR-MS. Calcd for $C_{16}H_{18}N_3O_3S$ (M+H): 332.1069. Found: *m*/*z* 332.1061. Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68. Found: C, 57.64; H, 5.20; N, 12.53.

5-Hydroxy-4-methoxy-7-(4-methoxyphenylmethyl)-5-methyl-2-(methylsulfanyl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4b): a white solid; mp 127–129 ˚C (hexane/CH_2Cl_2); IR (KBr) 3340, 1729, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3H), 2.53 (s, 1H), 2.57 (s, 3H), 3.77 (s, 3H), 4.02 (s, 3H), 4.81 (s, 2H), 6.82 (d, *J* = 6.9 Hz, 2H), 7.36 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.33, 22.52, 42.41, 54.10, 55.20, 72.84, 99.50, 113.88, 128.19, 130.03, 159.14, 163.26, 163.99, 172.96, 178.04. HR MS. Calcd for $C_{17}H_{20}N_3O_4S$ (M+H): 362.1175. Found: *m*/*z* 362.1167. Anal. Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.40; H, 5.32; N, 11.57.

5-Hydroxy-4-methoxy-5-methyl-2-(methylsulfanyl)-7-(2-phenylethyl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4c): a white solid; mp 127–131 ˚C (hexane/CH_2Cl_2); IR (KBr) 3407, 1727, 1607 cm^{-1}; ^1H NMR $CDCl_3$) δ 1.54 (s, 3H), 2.56 (s, 3H), 2.89 (s, 1H), 3.01 (t, *J* = 7.6 Hz, 2H), 3.91–4.01 (m, 2H), 4.03 (s, 3H), 7.17–7.20 (m, 3H), 7.26 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.25, 22.46, 33.63, 40.49, 54.04, 72.71, 99.21, 126.60, 128.42, 128.91, 137.82, 163.20, 164.10, 172.93, 178.09. HR-MS. Calcd for $C_{17}H_{20}N_3O_3S$ (M+H): 346.1225. Found: *m*/*z* 346.1216. Anal. Calcd for $C_{17}H_{19}N_3O_3S$: C, 59.11; H, 5.54; N, 12.17. Found: C, 58.73; H, 5.61; N, 11.96.

5-Hydroxy-4-methoxy-5-methyl-2-(methylsulfanyl)-7-(prop-2-yn-1-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4d): a white solid; mp 162–164 ˚C (hexane/CH_2Cl_2); IR (KBr) 3340, 3277, 1721, 1607 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.37 (s, 3H), 2.49 (s, 3H), 3.16 (br s, 1H), 3.91 (s, 3H), 4.30 (dd, *J* = 16.3, 3.1 Hz, 1H), 4.34 (dd, *J* = 16.3, 3.1 Hz, 1H), 6.07 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.69, 21.54, 28.09, 53.89, 71.59, 73.89, 78.04, 100.60, 162.68, 162.70, 171.26, 177.16. HR-MS. Calcd for $C_{12}H_{14}N_3O_3S$ (M+H): 280.0756. Found: *m*/*z* 280.0749. Anal. Calcd for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 14.99. Found: C, 51.55; H, 4.39; N, 14.99.

5-Hydroxy-4-methoxy-7-(2-methoxyethyl)-5-methyl-2-(methylsulfanyl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4e): a white solid; mp 154–156 ˚C (hexane/CH_2Cl_2); IR (KBr) 3371, 1725, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3H), 2.55 (s, 3H), 3.26 (br, 1H), 3.34 (s, 3H), 3.65–3.69 (m, 2H), 3.90–3.93 (m, 2H), 4.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.22, 22.45, 38.48, 54.00, 58.49, 68.57, 72.69, 99.45, 163.26, 164.15, 172.83, 178.42. HR MS. Calcd for $C_{12}H_{18}N_3O_4S$ (M+H): 300.1018. Found: *m*/*z* 300.1005. Anal. Calcd for $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.72; N, 14.04. Found: C, 47.90; H, 5.75; N, 13.83.

5-Hydroxy-7-[2-(2-hydroxyethoxy)ethyl]-4-methoxy-5-methyl-2-(methylsulfanyl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4f): a white solid; mp 92–93 ˚C (hexane/CH_2Cl_2); IR (KBr) 3419, 1738, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3H), 1.95 (br, 1H), 2.55 (s, 3H), 2.84 (br, 1H), 3.50–3.54 (m, 1H),

3.56–3.63 (m, 3H), 3.76–3.78 (m, 2H), 3.87–3.91 (m, 1H), 3.94–4.00 (m, 1H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.22, 22.78, 39.01, 54.02, 61.55, 67.52, 72.30, 72.57, 99.78, 163.29, 164.08, 172.76, 178.84. HR MS. Calcd for $C_{13}H_{20}N_3O_5S$ (M+H): 330.1123. Found: *m*/*z* 330.1118. Anal. Calcd for $C_{13}H_{19}N_3O_5S$: C, 47.41; H, 5.81; N, 12.76; S, 9.74. Found: C, 47.03; H, 5.61; N, 12.66; S, 9.74.

5-Hydroxy-4-methoxy-7-(4-methoxyphenylmethyl)-2-(methylsulfanyl)-5-phenyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4g): a white solid; mp 147–149 °C (hexane/CH_2Cl_2); IR (KBr) 3419, 1744, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.57 (d, 3H), 3.30 (s, 1H), 3.77 (s, 3H), 3.90 (s, 3H), 4.82 (d, *J* = 14.3 Hz, 1H), 4,86 (d, *J* = 14.3 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.29–7.38 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.34, 42.73, 54.12, 55.22, 77.12, 99.82, 113.93, 125.41, 128.14, 128.56, 128.62, 130.08, 137.98, 159.23, 162.97, 164.67, 173.47, 176.94. HR MS. Calcd for $C_{22}H_{22}N_3O_4S$ (M+H): 424.1331. Found: *m*/*z* 424.1320. Anal. Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.40; H, 5.00; N, 9.92; S, 7.57. Found: C, 62.12; H, 4.79; N, 9.70; S, 7.66.

5-Hydroxy-7-[2-(3,4-dimethoxyphenyl)ethyl]-4-methoxy-2-(methylsulfanyl)-5-phenyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4h): a pale-yellow solid; mp 177–179 °C (hexane/CH_2Cl_2); IR (KBr) 3461, 1743, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 2.97–3.08 (m, 2H), 3.24 (br, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 3.95–4.12 (m, 2H), 6.71–6.73 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.26–7.28 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.27, 32.99, 40.58, 54.08, 55.81, 55.82, 77.05, 99.70, 111.15, 112.02, 121.04, 125.37, 128.45, 128.56, 130.16, 137.88, 147.74, 148.88, 162.85, 164.85, 173.34, 177.09. HR MS. Calcd for $C_{24}H_{26}N_3O_5S$ (M+H): 468.1593. Found: *m*/*z* 468.1586. Anal. Calcd for $C_{24}H_{25}N_3O_5S$: C, 61.65; H, 5.39; N, 8.99; S, 6.86. Found: C, 61.86; H, 5.16; N, 8.67; S, 6.84.

7-Butyl-5-hydroxy-4-methoxy-2-(methylsulfanyl)-5-phenyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (4i): a white solid; mp 129–131 °C (hexane/CH_2Cl_2); IR (KBr) 3437, 1728, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.6 Hz, 3H), 1.35 (sext, *J* = 7.6 Hz, 2H), 1.70 (quint, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 3.30 (s, 1H), 3.74–3.78 (m, 2H), 3.93 (s, 3H), 7.32–7.36 (m, 3H), 7.41 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.61, 14.27, 19.90, 29.78, 39.50, 54.08, 77.00, 99.78, 125.42, 128.58, 128.62, 138.08, 162.93, 165.13, 173.46, 177.20. HR MS. Calcd for $C_{18}H_{22}N_3O_3S$ (M+H): 360.1382. Found: *m*/*z* 360.1375. Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.15; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.01; H, 5.67; N, 11.67; S, 9.04.

Ethyl 2-[5-Hydroxy-4-methoxy-5-methyl-2-(methylsulfanyl)-6-oxo-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]acetate (5). A solution of **2a** (0.16 g, 0.55 mmol) and glycine ethyl ester hydrochloride (77 mg, 0.55 mmol) in DMF (3 mL) containing Et_3N (0.17 g, 1.7 mmol) was heated at 80 °C until most of the starting material had disappeared (TLC on SiO_2, AcOEt/CH_2Cl_2). After cooling to rt, the mixture was worked up and purified as described above for the preparation of **4** to afford **5** (0.12 g, 66%); a white solid; mp 88–89 °C (hexane/CH_2Cl_2); IR (KBr) 3445, 1748, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, *J* =

7.6 Hz, 3H), 1.69 (s, 3H), 2.53 (s, 3H), 3.15 (s, 1H), 4.05 (s, 3H), 4.20 (q, *J* = 7.6 Hz, 2H), 4.45 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.04, 14.19, 22.43, 40.17, 54.12, 61.89, 72.92, 99.45, 163.22, 163.35, 167.21, 172.96, 177.90. HR MS. Calcd for $C_{13}H_{18}N_3O_5S$ (M+H): 328.0967. Found: *m*/*z* 328.0961. Anal. Calcd for $C_{13}H_{17}N_3O_5S$: C, 47.70; H, 5.23; N, 12.84. Found: C, 47.61; H, 5.23; N, 12.65.

Methyl 2-[4,6-Dimethoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (6). To a stirred solution of **2a** (0.27 g, 0.93 mmol) in MeOH (4 mL) at rt was added NaH (60% in mineral oil; 37 mg, 0.93 mmol). After stirring overnight at the same temperature, the precipitate was filtered off under reduced pressure and the filtrate was concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to afford **6** (0.22 g, 82%); a white solid; mp 112–114 ˚C (hexane/CH_2Cl_2); IR (KBr) 3553, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3H), 2.53 (s, 3H), 3.73 (s, 3H), 3.96 (s, 6H), 4.15 (s, 1H). Anal. Calcd for $C_{11}H_{16}N_2O_5S$: C, 45.82; H, 5.59; N, 9.72. Found: C, 45.85; H, 5.39; N, 9.81.

2-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]propan-2-ol (7). After treatment of **1** (0.24 g, 1.3 mmol) with LDA as described for the preparation of **2a**, acetone (73 mg, 1.3 mmol) was added. After 5 min, the mixture was worked up and purified as described for the preparation of **2a** to give **7** (0.22 g, 70%); a white solid; mp 58–60 ˚C (hexane); IR (KBr) 3416, 3370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 6H), 2.54 (s, 3H), 4.07 (s, 3H), 4.16 (s, 1H). Anal. Calcd for $C_9H_{13}ClN_2O_2S$: C, 43.46; H, 5.27; N, 11.26. Found: C, 43.30; H, 5.20; N, 11.16.

2-{6-Methoxy-2-(methylsulfanyl)-4-[(phenylmethyl)amino]pyrimidin-5-yl}propan-2-ol (8). A solution of **7** (99 mg, 0.40 mmol) and $BnNH_2$ (43 mg, 0.40 mmol) in DMF (3 mL) containing Et_3N (41 mg, 0.40 mmol) was heated at 60 ˚C for 3 h under stirring. The mixture was worked up and purified as described for the preparation of **4** to afford **8** (89 mg, 69%); a yellow oil; R_f 0.30 (AcOEt/hexane 1:5); IR (neat) 3364 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 6H), 1.78 (s, 1H), 2.43 (s, 3H), 3.87 (s, 3H), 4.67 (d, *J* = 5.4 Hz, 2H), 7.22–7.31 (m, 5H), 7.90 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.85, 30.41, 45.20, 53.31, 74.25, 99.34, 126.76, 127.36, 128.38, 140.12, 161.10, 164.52, 167.13. Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.05; H, 6.69; N, 13.12.

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