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SYNTHESIS OF 6,7-DIHYDRO-5*H*-THIOPYRANO[2,3-*d*]PYRIMIDIN-5-ONE DERIVATIVES STARTING WITH 4,6-DICHLORO-2-(METHYLSULFANYL)PYRIMIDINE

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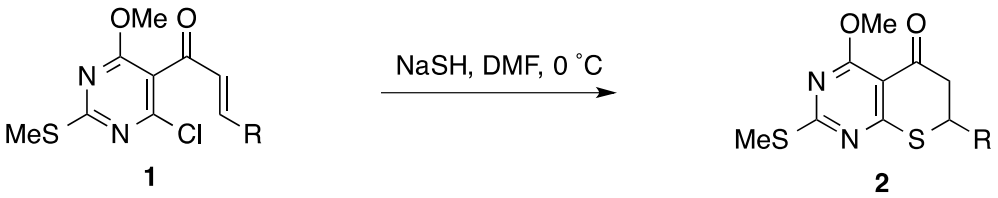
Abstract – An efficient synthesis of 7-substituted 6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives from readily available 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) has been developed. Thus, this starting material is converted to the corresponding 1-(4-chloro-6-methoxy(or dialkylamino)pyrimidin-5-yl)alk-2-en-1-ones by using easily operational sequences. These enones are then treated with sodium hydrogensulfide under mild conditions to afford the desired products in satisfactory yields.

There have been few reports on the preparation of 6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives in the literature. The synthesis of 7-aryl-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives by condensation of 1-(4-sulfanylpyrimidin-5-yl)ethanones with aromatic aldehydes in ethanol has been demonstrated by El-Bahaie in 1990.[1] This is the only practical synthesis of 6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives so far. In 2004, El-Emam and co-workers reported that a compound with the 5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one structure exhibited antiviral activity.[2] Accordingly, we become interested in developing a new and facile method for the general preparation of

this class of heterocycles. We recently demonstrated that 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) is a versatile starting materials for the preparation of various pyrimidine-fused heterocyclic compounds.[3] As continuation of these studies, we report here an efficient method to synthesize 7-substituted 4-methoxy(or dialkylamino)-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-ones (**2**) or (**6**) by the reaction of 1-[4-chloro-6-methoxy(or dialkylamino)-2-(methylsulfanyl)pyrimidin-5-yl]alk-2-en-1-ones (**1**) or (**5**), respectively, with sodium hydrogensulfide under mild conditions.

The synthesis of 4-methoxy-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives (**2**) from 1-[4-chloro-6-methoxypyrimidin-4-yl]alk-2-en-1-one derivatives (**1**) is outlined in Scheme 1. The reaction of **1**, prepared from DCSMP as reported previously,[3g] with sodium hydrogensulfide could be successfully conducted in DMF at 0 ˚C, and after usual workup and subsequent purification by recrystallization or column chromatography on silica gel, the desired products (**2**) were obtained in generally good yields as compiled in Table 1.



Scheme 1

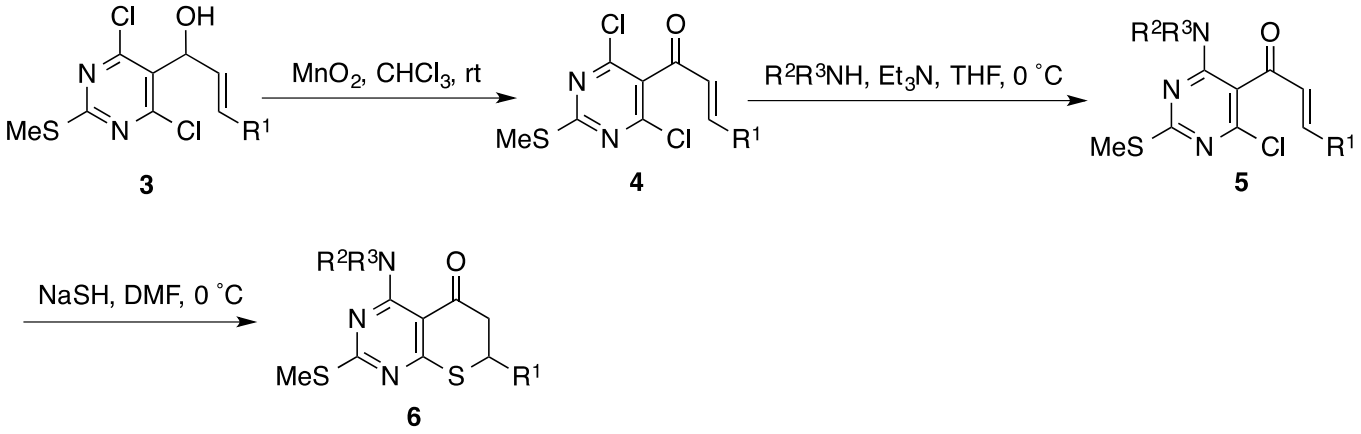
Table 1. Preparation of 6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives (**2**)

Entry	**1**	R	**2**	Yield/%[a]
1	**1a**	Me	**2a**	87
2	**1b**	Ph	**2b**	89
3	**1c**	4-ClC_6H_4	**2c**	78
4	**1d**	4-$MeOC_6H_4$	**2d**	84

[a] Yields of isolated products.

4-(Dialkylamino)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives (**6**) were prepared as shown in Scheme 2. As described previously, DCSMP was lithiated at the 5-position with lithium diisopropylamide,[3a] and allowed to react with α,β-unsaturated aldehydes to afford 1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-4-yl]alk-2-en-1-ols (**3**).[3i] Oxidation of these alkenols with activated manganese(IV) oxide in chloroform at room temperature yielded 1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-4-yl]alk-2-en-1-ones (**4**) in good yields as listed in Table 2. Unfortunately, however, attempts to obtain 4-chloro-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-ones by treating compounds (**4**) with sodium hydrogensulfide under the same conditions as described for

the preparation of **2** failed to result in the formation of rather complex mixtures of the products. So, compounds (**4**) were transformed into 1-[4-chloro-6-(dialkylamino)-2-(methylsulfanyl)pyrimidin-4-yl]alk-2-en-1-ones (**5**) in good yields (see Table 2) on treatment with secondary amines in THF in the presence of triethylamine at 0 ˚C. Compounds (**5**) were then allowed to react with sodium hydrogensulfide to afford the corresponding desired products (**6**) in generally good yields as summarized in Table 2 as well.

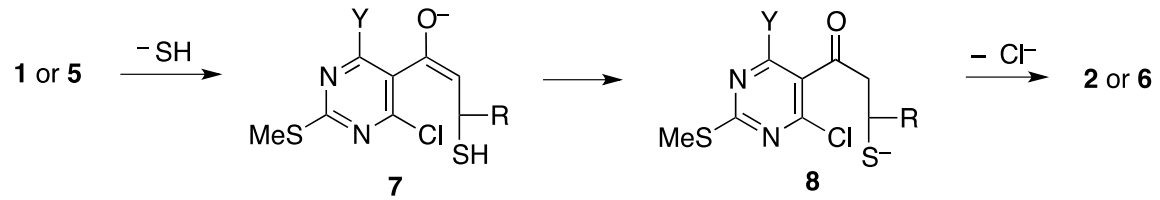


Scheme 2

Table 2. Preparation of 6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives (**6**)

Entry	**3**	R^1	**4**	Yield/%[a]	R^2R^3N	**5**	Yield/%[a]	**6**	Yield/%[a]
1	**3a**	Me	**4a**	71	pyrrolidin-1-yl	**5a-i**	93	**6a-i**	59
2					piperidin-1-yl	**5a-ii**	82	**6a-ii**	64
3	**3b**	Ph	**4b**	55	Me_2N	**5b-i**	72	**6b-i**	76
4					pyrrolidin-1-yl	**5b-ii**	85	**6b-ii**	83
5	**3c**	4-ClC_6H_4	**4c**	79	morpholin-4-yl	**5c-i**	75	**6c-i**	71
6					$Et[HO(CH_2)_2]N$	**5c-ii**	77	**6c-ii**	74
7	**3d**	4-$MeOC_6H_4$	**4d**	80	Me_2N	**5d-i**	76	**6d-i**	87
8					$[MeO(CH_2)_2]_2N$	**5d-ii**	90	**6d-ii**	74

[a] Yields of isolated products.



Scheme 3

The formation of 6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives (**2**) or (**6**) from **1** or **5**, respectively, probably involves the initial formation of the enolate intermediate (**7**) by conjugate addition of sulfanyl anion to the enone moiety of **1** or **5**, as illustrated in Scheme 3. This intermediate undergoes

proton transfer to generate the thiolate intermediate (**8**), which yields **2** or **6** by intramolecular aromatic nucleophilic substitution (S_NAr). This reaction sequence proceeded relative smoothly and cleanly at 0 ˚C. We could not isolate the corresponding thiols produced by protonation of **8**. However, possibility that S_NAr by sodium hydrogensulfide at first followed by intramolecular conjugate addition to afford **2** or **6** may be excluded, because no chemical species, which can promote the conjugate addition, are not generated.

In conclusion, we have demonstrated that 7-substituted 4-methoxy(or dialkylamino)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one derivatives can be produced by treating the respective 1-[4-chloro-6-methoxy(or dialkylamino)pyrimidin-4-yl]alk-2-en-1-one derivatives with sodium hydrogensulfide under mild conditions with good yields. As the present synthetic method starts with a readily available compound, DCSMP, and is operationally simple, it may find some value in organic synthesis. We are currently investigating further utilization of this pyrimidine derivative for the preparation of other useful pyrimidine-fused heterocycles.

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 Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (ESI and DART, positive) or a JEOL JMS-T100GCV (EI, TOF; 70eV) spectrometer. Elemental analyses were performed with an Elementar 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. 1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]alk-2-en-1-ones **1**[3g] and 3-aryl-1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ols **3b-d**[3i] were prepared according to the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Thiopyranopyrimidinones (2) and (6). 4-Methoxy-7-methyl-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (2a). A mixture of **1a** (0.13 g, 0.50 mmol) and $NaSH{\bullet}nH_2O$ (70% as NaSH, 80 mg, 1.0 mmol) in DMF was stirred at 0 ˚C for 2 h. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to afford **2a** (0.11

g, 87%); a pale-yellow solid; mp 128–130 ˚C; IR (KBr) 1671 cm^{-1}; ^1H NMR δ 1.45 (d, *J* = 6.9 Hz, 3H), 2.56 (s, 3H), 2.76 (dd, *J* = 16.0, 11.5 Hz, 1H), 2.97 (dd, *J* = 16.0, 3.8 Hz, 1H), 3.58–3.65 (m, 1H), 4.07 (s, 3H); ^{13}C NMR δ 14.22, 20.23, 34.20, 47.71, 54.92, 108.22, 166.41, 174.58, 175.12, 191.37. HR-MS (DART). Calcd for $C_{10}H_{13}N_2O_2S_2$ (M+H): 257.0418. Found: *m/z* 257.0416. Anal. Calcd for $C_{10}H_{12}N_2O_2S_2$: C, 46.85; H, 4.72; N, 10.93. Found: C, 46.73; H, 4.71; N, 10.82.

4-Methoxy-2-(methylsulfanyl)-7-phenyl-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (2b): a white solid; mp 214–216 ˚C (hexane/CH_2Cl_2); IR (KBr) 1669, 1601 cm^{-1}; ^1H NMR δ 2.55 (s, 3H), 3.12 (dd, *J* = 15.5, 2.9 Hz, 1H), 3.28 (dd, *J* = 15.5, 12.6 Hz, 1H), 4.08 (s, 3H), 4.71 (dd, *J* = 12.6, 2.9 Hz, 1H), 7.32–7.40 (m, 5H); ^{13}C NMR δ 14.23, 43.20, 46.88, 54.95, 108.32, 127.39, 128.64, 129.11, 137.29, 166.58, 174.79, 175.18, 190.92. HR-MS (EI). Calcd for $C_{15}H_{14}N_2O_2S_2$ (M): 318.0497. Found: *m/z* 318.0506. Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80; S, 20.14. Found: C, 56.30; H, 4.34; N, 8.89; S, 20.42.

7-(4-Chlorophenyl)-4-methoxy-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (2c): a pale-yellow solid; mp 128–130 ˚C (hexane/CH_2Cl_2); IR (KBr) 1676 cm^{-1}; ^1H NMR δ 2.56 (s, 3H), 3.11 (dd, *J* = 16.0, 3.4 Hz, 1H), 3.24 (dd, *J* = 16.0, 12.6 Hz, 1H), 4.09 (s, 3H), 4.68 (dd, *J* = 12.6, 3.4 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.26, 42.50, 46.72, 55.02, 108.32, 128.78, 129.32, 134.55, 135.84, 166.58, 174.77, 174.99, 190.51. HR-MS (EI). Calcd for $C_{15}H_{13}ClN_2O_2S_2$ (M): 352.0107. Found: *m/z* 352.0098. Anal. Calcd for $C_{15}H_{13}ClN_2O_2S_2$: C, 51.06; H, 3.71; N, 7.94. Found: C, 50.85; H, 3.90; N, 7.86.

4-Methoxy-7-(4-methoxyphenyl)-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (2d): a yellow solid; mp 119–121 ˚C (hexane/CH_2Cl_2); IR (KBr) 1678, 1610 cm^{-1}; ^1H NMR δ 2.56 (s, 3H), 3.10 (dd, *J* = 15.2, 3.0 Hz, 1H), 3.26 (dd, *J* = 15.2, 13.0 Hz, 1H), 3.81 (s, 3H), 4.09 (s, 3H), 4.67 (dd, *J* = 13.0, 3.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 14.26, 42.69, 47.13, 54.99, 55.30, 108.30, 114.41, 128.59, 129.12, 159.67, 166.59, 174.75, 175.34, 191.25. HR-MS (EI). Calcd for $C_{16}H_{16}N_2O_3S_2$ (M): 348.0602. Found: *m/z* 348.0605. Anal. Calcd for $C_{16}H_{16}N_2O_3S_2$: C, 55.15; H, 4.63; N, 8.04; S, 18.40. Found: C, 54.81; H, 4.50; N, 7.95; S, 18.35.

1-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]but-2-en-1-ol (3a). This compound was prepared from **1** and crotonaldehyde as described for the preparation of **3b-d**.[3i] **3a:** pale-yellow oil; R_f 0.31 (AcOEt/hexane 1:5); IR (neat) 3397, 1666 cm^{-1}; ^1H NMR δ 1.74 (d, *J* = 6.3 Hz, 3H), 2.57 (s, 3H), 2.61 (d, *J* = 5.8 Hz, 1H), 5.72 (dd, *J* = 6.9, 5.8 Hz, 1H), 5.80 (dq, *J* = 15.5, 6.3 Hz, 1H), 5.87 (ddd, *J* = 15.5, 6.9, 1.7 Hz, 1H); ^{13}C NMR δ 14.35, 17.71, 70.54, 126.18, 128.37, 129.97, 160.22, 171.72. HR-MS (ESI). Calcd for $C_9H_{11}Cl_2N_2OS$ (M+H): 264.9964. Found: *m/z* 264.9969.

Typical Procedure for the Oxidation of 3 to 4. 1-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]but-2-en-1-one (4a). A mixture of **3a** (2.0 g, 7.7 mmol) in $CHCl_3$ (20 mL) containing activated MnO_2 (6.7 g, 77 mmol) was stirred overnight at rt. After filtration of the mixture under reduced pressure, the filtrate was concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to afford **4a** (1.4 g, 71%); a yellow solid; mp 82–84 ˚C; IR (KBr) 1666, 1636 cm^{-1}; ^1H NMR δ 2.02 (dd, *J* = 6.9, 1.7 Hz, 3H), 2.60 (s, 3H), 6.37 (dd, *J* = 16.0, 1.7 Hz, 1H), 6.72 (dq, *J* = 16.0, 6.9 Hz, 1H); ^{13}C NMR δ 14.46, 18.81, 125.90, 131.80, 150.06, 157.77, 174.00, 188.98. HR-MS (EI). Calcd for $C_9H_8Cl_2N_2OS$ (M): 261.9742. Found: *m/z* 261.9734.

1-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-one (4b): a white solid; mp 129–131 ˚C (hexane/CH_2Cl_2); IR (KBr) 1651, 1622 cm^{-1}; ^1H NMR δ 2.62 (s, 3H), 6.95 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 16.0 Hz, 1H), 7.42–7.46 (m, 3H), 7.58 (dd, *J* = 8.0, 1.7 Hz, 2H); ^{13}C NMR δ 14.51, 125.83, 126.00, 128.89, 129.17, 131.71, 133.65, 148.41, 157.98, 174.20, 189.00. HR-MS (EI). Calcd for $C_{14}H_{10}Cl_2N_2OS$ (M): 323.9891. Found: *m/z* 323.9906.

3-(4-Chlorophenyl)-1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]prop-2-en-1-one (4c): a pale-yellow solid; mp 133–134 ˚C (hexane/CH_2Cl_2); IR (KBr) 1647, 1622 cm^{-1}; ^1H NMR δ 2.62 (s, 3H), 6.92 (d, *J* = 16.6 Hz, 1H), 7.34 (d, *J* = 16.6 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.50, 125.82, 126.13, 129.47, 129.98, 132.08, 137.76, 146.69, 157.90, 174.29, 188.72. HR-MS (EI). Calcd for $C_{14}H_9Cl_3N_2OS$ (M): 357.9501. Found: *m/z* 357.9491.

1-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methoxyphenyl)prop-2-en-1-one (4d): a yellow solid; mp 138–139 ˚C (hexane/CH_2Cl_2); IR (KBr) 1636, 1620 cm^{-1}; ^1H NMR δ 2.62 (s, 3H), 3.86 (s, 3H), 6.83 (d, *J* = 16.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 16.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.48, 55.47, 114.60, 123.48, 126.14, 126.25, 130.84, 148.46, 157.95, 162.59, 173.87, 188.88. Anal. Calcd for $C_{15}H_{12}Cl_2N_2O_2S$: C, 50.72; H, 3.41; N, 7.89. Found: C, 50.62; H, 3.47; N, 7.83.

Typical Procedure for the Dialkylamination of 4 Affording 5. 1-[4-Chloro-2-(methylsulfanyl)-6-(pyrrolidin-1-yl)pyrimidin-5-yl]but-2-en-1-one (5a-i). To a stirred solution of **4a** (0.32 g, 1.2 mmol) in DMF (6 mL) containing Et_3N (0.12 g, 1.2 mmol) at 0 ˚C was added pyrrolidine (89 mg, 1.2 mmol) dropwise. After 20 min, H_2O (20 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to afford **5a-i** (0.33 g, 93%); a yellow solid; mp 86–87 ˚C; IR (KBr) 1652, 1621, 1630 cm^{-1}; ^1H NMR δ 1.89–1.91 (m, 4H), 1.98 (dd, *J* = 6.9, 1.7 Hz, 3H), 2.51 (s, 3H), 3.42 (br, 4H), 6.43 (dq, *J* = 15.5 Hz, 1.7 Hz, 1H), 6.76 (dq, *J* = 15.5 Hz, 6.9 Hz, 1H); ^{13}C NMR δ 13.99, 18.53, 25.20, 49.01, 109.80, 134.37, 148.33, 155.75, 157.27, 170.88, 193.73. HR-MS (EI). Calcd for $C_{13}H_{16}ClN_3OS$ (M): 297.0703. Found: *m/z* 297.0712.

1-[4-Chloro-2-(methylsulfanyl)-6-(piperidin-1-yl)pyrimidin-5-yl]but-2-en-1-one (5a-ii): a yellow solid; mp 100–101 ˚C (hexane/CH_2Cl_2); IR (KBr) 1649 cm^{-1}; ^1H NMR δ 1.53–1.66 (m, 6H), 1.98 (dd, *J* = 6.9, 1.1 Hz, 3H), 2.50 (s, 3H), 3.49–3.51 (m, 4H), 6.36 (dq, *J* = 15.5, 1.1 Hz, 1H), 6.81 (dq, *J* = 15.5, 6.9 Hz, 1H); ^{13}C NMR δ 14.09, 18.49, 24.29, 25.47, 48.53, 110.65, 132.98, 147.44, 156.65, 160.11, 170.97, 193.26. HR-MS (EI). Calcd for $C_{14}H_{18}ClN_3OS$ (M): 311.0873. Found: *m/z* 311.0859.

1-[4-Chloro-6-(dimethylamino)-2-(methylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-one (5b-i): a yellow solid; mp 98–99 ˚C (hexane/CH_2Cl_2); IR (KBr) 1630 cm^{-1}; ^1H NMR δ 2.54 (s, 3H), 3.07 (s, 6H), 7.05 (d, *J* = 16.6 Hz, 1H), 7.42–7.44 (m, 3H), 7.47 (d, *J* = 16.6 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.7 Hz, 2H); ^{13}C NMR δ 14.10, 40.33, 110.17, 128.14, 128.68, 129.08, 131.18, 134.02, 146.35, 156.54, 160.30, 170.97, 193.33. HR-MS (EI). Calcd for $C_{16}H_{16}ClN_3OS$ (M): 333.0703. Found: *m/z* 333.0709.

1-[4-Chloro-2-(methylsulfanyl)-6-(pyrrolidin-1-yl)pyrimidin-5-yl]-3-phenylprop-2-en-1-one (5b-ii): a yellow solid; mp 134–135 ˚C (hexane/CH_2Cl_2); IR (KBr) 1634 cm^{-1}; ^1H NMR δ 1.88–1.92 (m, 4H), 2.53 (s, 3H), 3.44 (br s, 4H), 7.04 (d, *J* = 16.6 Hz, 1H), 7.40–7.46 (m, 4H), 7.56–7.59 (m, 2H); ^{13}C NMR δ 14.04, 25.16, 49.19, 109.89, 128.49, 128.66, 129.04, 131.14, 133.98, 146.89, 155.87, 157.34, 171.04, 193.50. Anal. Calcd for $C_{18}H_{18}ClN_3OS$: C, 60.08; H, 5.04; N, 11.68. Found: C, 59.83; H, 5.03; N, 11.83.

1-[4-Chloro-2-(methylsulfanyl)-6-(morpholin-4-yl)pyrimidin-5-yl]-3-(4-chlorophenyl)prop-2-en-1-one (5c-i): a yellow solid; mp 149–150 ˚C (hexane/CH_2Cl_2); IR (KBr) 1647, 1629 cm^{-1}; ^1H NMR δ 2.53 (s, 3H), 3.58 (t, *J* = 4.6 Hz, 4H), 3.68 (t, *J* = 4.6 Hz, 4H), 6.97 (d, *J* = 16.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 16.0 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.17, 47.67, 66.30, 111.05, 127.42, 129.44, 129.84, 132.26, 137.42, 145.10, 157.11, 160.57, 171.71, 192.65. Anal. Calcd for $C_{18}H_{17}Cl_2N_3O_2S$: C, 52.69; H, 4.18; N, 10.24. Found: C, 52.37; H, 4.22; N, 10.09.

1-[4-Chloro-6-[ethyl(2-hydroxyethyl)amino]-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-chlorophenyl)-prop-2-en-1-one (5c-ii): a yellow viscous oil; R_f 0.12 (AcOEt/hexane 1:2); IR (neat) 3421, 1644, 1625 cm^{-1}; ^1H NMR δ 1.13 (t, *J* = 6.9 Hz, 3H), 2.52 (s, 3H), 2.96 (br, 1H), 3.42 (q, *J* = 6.9 Hz, 2H), 3.66 (t, *J* = 5.2 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 6.99 (d, *J* = 16.0 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 16.0 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 12.27, 14.02, 45.69, 50.93, 60.37, 110.31, 128.01, 129.38, 129.88, 131.03, 132.29, 137.35, 145.42, 156.57, 160.01, 193.07. HR-MS (ESI). Calcd for $C_{18}H_{19}Cl_2N_3NaO_2S$ (M+Na): 434.0473. Found: *m/z* 434.0469.

1-[4-Chloro-6-(dimethylamino)-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methoxyphenyl)prop-2-en-1-one (5d-i): a yellow solid; mp 131–132 ˚C (hexane/CH_2Cl_2); IR (KBr) 1633 cm^{-1}; ^1H NMR δ 2.54 (s, 3H), 3.07 (s, 6H), 3.86 (s, 3H), 6.92 (d, *J* = 15.4 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 15.4 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.09, 40.24, 55.43, 110.21, 114.51, 125.95, 126.59, 130.54,

146.75, 156.44, 160.16, 162.16, 170.69, 193.42. Anal. Calcd for $C_{17}H_{18}ClN_3O_2S$: C, 56.12; H, 4.99; N, 11.55. Found: C, 54.74; H, 4.94; N, 11.18.

1-{4-[Bis(2-methoxyethyl)amino]-6-chloro-2-(methylsulfanyl)pyrimidin-5-yl}-3-(4-methoxyphenyl)-prop-2-en-1-one (5d-ii): a yellow oil; R_f 0.28 (AcOEt/hexane 1:2); IR (neat) 1640 cm^{-1}; ^1H NMR δ 2.51 (s, 3H), 3.28 (s, 6H), 3.52 (t, *J* = 5.2 Hz, 4H), 3.72 (t, *J* = 5.2 Hz, 4H), 3.86 (s, 3H), 6.87 (d, *J* = 16.0 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 16.0 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.01, 50.27, 55.41, 58.86, 70.25, 110.47, 114.50, 125.59, 126.54, 130.61, 147.16, 156.64, 159.36, 162.22, 170.59, 193.32. HR-MS (ESI). Calcd for $C_{21}H_{27}ClN_3O_4S$ (M+H): 452.1431. Found: *m/z* 452.1420.

7-Methyl-2-(methylsulfanyl)-4-(pyrrolidin-1-yl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (6a-i): a pale-yellow solid; mp 128–129 ˚C (hexane/CH_2Cl_2); IR (KBr) 1646 cm^{-1}; ^1H NMR δ 1.44 (d, *J* = 6.9 Hz, 3H), 1.76–1.82 (m, 1H), 1.97–2.05 (m, 3H), 2.49 (s, 3H), 2.67 (dd, *J* = 18.3, 12.0 Hz, 1H), 2.79–2.82 (m, 1H), 2.91 (dd, *J* = 18.3, 3.4 Hz, 1H), 3.45 (br, 1H), 3.56–3.61 (m, 1H), 3.78–3.81 (m, 2H); ^{13}C NMR δ 14.11, 19.33, 24.04, 26.33, 34.74, 48.88, 106.33, 157.45, 171.42, 173.94, 190.87. HR-MS (EI). Calcd for $C_{13}H_{17}N_3OS_2$ (M): 295.0813. Found: *m/z* 295.0827. Anal. Calcd for $C_{13}H_{17}N_3OS_2$: C, 52.85; H, 5.80; N, 14.22; S, 21.70. Found: C, 52.86; H, 5.67; N, 14.18; S, 21.69.

7-Methyl-2-(methylsulfanyl)-4-(piperidin-1-yl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (6a-ii): pale-yellow solid; mp 109–110 ˚C (hexane/CH_2Cl_2); IR (KBr) 1648 cm^{-1}; ^1H NMR δ 1.43 (d, *J* = 6.9 Hz, 3H), 1.62–1.70 (m, 6H), 2.47 (s, 3H), 2.65 (dd, *J* = 17.7, 12.0 Hz, 1H), 2.89 (dd, *J* = 17.7, 2.9 Hz, 1H), 3.93 (br s, 2H), 3.54–3.58 (m, 1H), 3.75 (br, 2H); ^{13}C NMR δ 14.21, 19.22 (2 overlapped Cs), 24.16, 25.95, 33.93, 48.60, 105.53, 159.60, 171.92, 175.30, 190.81. HR-MS (EI). Calcd for $C_{14}H_{19}N_3OS_2$ (M): 309.0970. Found: *m/z* 309.0960.

4-(Dimethylamino)-2-(methylsulfanyl)-7-phenyl-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (6b-i): a yellow solid; mp 176–178 ˚C (hexane/CH_2Cl_2); IR (KBr) 1644 cm^{-1}; ^1H NMR δ 2.50 (s, 3H), 2.88–3.26 (m, 8H), 4.66 (dd, *J* = 12.6, 3.4 Hz, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR δ 14.19, 20.84, 43.40, 47.46, 105.58, 127.61, 128.39, 128.97, 137.24, 160.37, 171.75, 174.57, 190.12. HR-MS (EI). Calcd for $C_{16}H_{17}N_3OS_2$ (M): 331.0813. Found: *m/z* 333.0828. Anal. Calcd for $C_{16}H_{17}N_3OS_2$: C, 57.98; H, 5.17; N, 12.68; S, 19.35. Found: C, 57.60; H, 5.05; N, 12.79; S, 19.28.

2-(Methylsulfanyl)-7-phenyl-4-(pyrrolidin-1-yl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (6b-ii): a yellow solid; mp 175–176 ˚C (hexane/CH_2Cl_2); IR (KBr) 1654 cm^{-1}; ^1H NMR δ 1.74–2.05 (m, 4H), 2.49 (s, 3H), 2.79–2.83 (m, 1H), 3.12 (dd, *J* = 17.7, 2.9 Hz, 1H), 3.24 (dd, *J* = 17.7, 12.6 Hz, 1H), 3.49–3.55 (m, 1H), 3.76–3.82 (m, 2H), 4.67 (dd, *J* = 12.6, 2.9 Hz, 1H), 7.30–7.47 (m, 5H); ^{13}C NMR δ 14.15, 24.03, 26.32, 43.82, 47.65, 49.03, 51.97, 106.24, 127.61, 128.37, 128.95, 137.31, 157.47, 171.65,

173.82, 190.23. HR-MS (EI). Calcd for $C_{18}H_{19}N_3OS_2$ (M): 357.0970. Found: *m/z* 357.0959. Anal. Calcd for $C_{18}H_{19}N_3OS_2$: C, 60.48; H, 5.36; N, 11.75. Found: C, 60.28; H, 5.22; N, 12.03.

7-(4-Chlorophenyl)-2-(methylsulfanyl)-4-(morpholin-4-yl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (6c-i): a yellow solid; mp 92–93 ˚C (hexane/CH_2Cl_2); IR (KBr) 1640 cm^{-1}; ^1H NMR δ 2.48 (s, 3H), 3.07 (dd, *J* = 17.7, 2.9 Hz, 1H), 3.18 (dd, *J* = 17.7, 12.0 Hz, 1H), 3.77–3.85 (m, 8H), 4.61 (dd, *J* = 12.0, 2.9 Hz, 1H), 7.35 (s, 4H); ^{13}C NMR δ 14.25, 22.60, 31.53, 42.18, 47.11 (2 overlapped Cs), 66.68, 105.48, 128.92, 129.21, 134.38, 135.52, 159.75, 172.80, 175.23, 189.71. HR-MS (EI). Calcd for $C_{18}H_{18}ClN_3O_2S_2$ (M): 407.0529. Found: *m/z* 407.0537.

7-(4-Chlorophenyl)-4-[ethyl(2-hydroxyethyl)amino]-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano-[2,3-*d*]pyrimidin-5-one (6c-ii): a yellow solid; mp 54–66 ˚C (hexane/CH_2Cl_2); IR (KBr) 3409, 1647 cm^{-1}; ^1H NMR δ 1.22 (t, *J* = 7.4 Hz, 3H), 2.49 (s, 3H), 3.10 (dd, *J* = 17.7, 3.4 Hz, 1H), 3.18 (dd, *J* = 17.7, 12.0 Hz, 1H), 3.40–3.51 (m, 3H), 3.63–3.68 (m, 1H), 3.85 (t, *J* = 5.2 Hz, 2H), 4.00 (br s, 1H), 4.63 (dd, *J* = 12.0, 3.5 Hz, 1H), 7.36 (s, 4H); ^{13}C NMR δ 12.78, 14.15, 42.38, 46.17, 47.10, 50.49, 59.19, 106.50, 128.96, 129.20, 134.38, 135.41, 161.16, 172.62, 174.81, 190.65. HR-MS (ESI). Calcd for $C_{18}H_{20}ClN_3NaO_2S_2$ (M+Na): 432.0583. Found: *m/z* 432.0580. Anal. Calcd for $C_{18}H_{20}ClN_3O_2S_2$: C, 52.74; H, 4.92; N, 10.25. Found: C, 52.51; H, 5.20; N, 10.02.

4-(Dimethylamino)-7-(4-methoxyphenyl)-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano[2,3-*d*]pyrimidin-5-one (6d-i): a yellow solid; mp 137–138 ˚C (hexane/CH_2Cl_2); IR (KBr) 1641, 1610 cm^{-1}; ^1H NMR δ 2.50 (s, 3H), 3.09 (dd, *J* = 17.7, 2.3 Hz, 1H), 3.14 (br s, 6H), 3.21 (dd, *J* = 17.7, 12.6 Hz, 1H), 3.81 (s, 3H), 4.63 (dd, *J* = 12.6, 2.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.19, 20.52, 42.85, 47.62, 55.26, 105.52, 114.26, 128.75, 129.06, 159.47, 160.35, 171.65, 174.69, 190.38. HR-MS (EI). Calcd for $C_{17}H_{19}N_3O_2S_2$ (M): 361.0919. Found: *m/z* 361.0901. Anal. Calcd for $C_{17}H_{19}N_3O_2S_2$: C, 56.49; H, 5.30; N, 11.62. Found: C, 56.22; H, 5.35; N, 11.45.

4-[Bis(2-methoxyethyl)amino]-7-(4-methoxyphenyl)-2-(methylsulfanyl)-6,7-dihydro-5*H*-thiopyrano-[2,3-*d*]pyrimidin-5-one (6d-ii): a yellow viscous oil; R_f 0.33 (AcOEt/hexane 1:1); IR (neat) 1651, 1610 H NMR δ 2.48 (s, 3H), 3.07 (d, *J* = 16.6 Hz, 1H), 3.18 (dd, *J* = 16.6, 12.6 Hz, 1H), 3.34 (s, 6H), 3.65–3.69 (m, 8H), 3.82 (s, 3H), 4.62 (d, *J* = 12.6 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 14.15, 21.04, 42.55, 47.82, 55.27, 58.87, 70.30, 106.26, 114.29, 128.75, 128.92, 159.50, 160.67, 171.77, 174.91, 191.01. HR-MS (ESI). Calcd for $C_{21}H_{28}N_3O_4S_2$ (M+H): 450.1521. Found: *m/z* 450.1517.

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