SYNTHESIS OF 6,7-DIHYDRO-5H-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-5H-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 hydrosulfide under mild conditions to afford the desired products in satisfactory yields.

There have been few reports on the preparation of 6,7-dihydro-5H-thiopyrano[2,3-d]pyrimidin-5-one derivatives in the literature. The synthesis of 7-aryl-6,7-dihydro-5H-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-5H-thiopyrano[2,3-d]pyrimidin-5-one derivatives so far. In 2004, El-Emam and co-workers reported that a compound with the 5H-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 material for the preparation of various pyrimidine-fused heterocyclic compounds.\textsuperscript{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-5H-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-5H-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,\textsuperscript{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](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield/%\textsuperscript{a}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
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<tr>
<td>2</td>
<td>Ph</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>4-CIC\textsubscript{6}H\textsubscript{4}</td>
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<tr>
<td>4</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>84</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yields of isolated products.

4-(Dialkylamino)-6,7-dihydro-5H-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,\textsuperscript{3a} and allowed to react with \(\alpha,\beta\)-unsaturated aldehydes to afford 1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-4-yl]alk-2-en-1-ols (3).\textsuperscript{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-5H-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 hydrosulfide to afford the corresponding desired products (6) in generally good yields as summarized in Table 2 as well.

![Scheme 2](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
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<th>4</th>
<th>Yield/%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R²R³N</th>
<th>5</th>
<th>Yield/%&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>Yield/%&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>4a</td>
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<td>pyrrolidin-1-yl</td>
<td>5a-i</td>
<td>93</td>
<td>6a-i</td>
<td>59</td>
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<tr>
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<td>Ph</td>
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<td>3</td>
<td>3b</td>
<td>Ph</td>
<td>4b</td>
<td>55</td>
<td>Me₂N</td>
<td>5b-i</td>
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<td>83</td>
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<tr>
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<td>3c</td>
<td>4-ClC₆H₄</td>
<td>4c</td>
<td>79</td>
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<tr>
<td>6</td>
<td>3d</td>
<td>4-MeOC₆H₄</td>
<td>4d</td>
<td>80</td>
<td>Et[HO(CH₂)₂]N</td>
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<tr>
<td>7</td>
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<td>4-MeOC₆H₄</td>
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<td>Et[HO(CH₂)₂]N</td>
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<td>90</td>
<td>6d-ii</td>
<td>74</td>
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</tbody>
</table>

<sup>a</sup> Yields of isolated products.

![Scheme 3](image)

The formation of 6,7-dihydro-5H-thiopyran[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 (SNAr). This reaction sequence proceeded relatively smoothly and cleanly at 0 °C. We could not isolate the corresponding thiols produced by protonation of 8. However, possibility that SNAr by sodium hydrosulfide 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-5H-thiopyran[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 hydrosulfide 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. 1H NMR and 13C NMR spectra were recorded in CDCl3 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 PF254. 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 and 3-aryl-1-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ols 3b-d 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-5H-thiopyran[2,3-d]pyrimidin-5-one (2a). A mixture of 1a (0.13 g, 0.50 mmol) and NaSH·nH2O (70% as NaSH, 80 mg, 1.0 mmol) in DMF was stirred at 0 °C for 2 h. Saturated aqueous NH4Cl (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 (Na2SO4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH2Cl2 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); ¹³C 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 C₁₀H₁₃N₂O₂S₂ (M+H): 257.0418. Found: m/z 257.0416. Anal. Calcd for C₁₀H₁₂N₂O₂S₂: 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-5H-thiopyrano[2,3-d]pyrimidin-5-one (2b): a white solid; mp 214–216 °C (hexane/CH₂Cl₂); IR (KBr) 1669, 1601 cm⁻¹; ¹H NMR δ 2.56 (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); ¹³C 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 C₁₅H₁₄N₂O₂S₂ (M): 318.0497. Found: m/z 318.0506. Anal. Calcd for C₁₅H₁₄N₂O₂S₂: 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-5H-thiopyrano[2,3-d]pyrimidin-5-one (2c): a pale-yellow solid; mp 128–130 °C (hexane/CH₂Cl₂); 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); ¹³C 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 C₁₅H₁₃ClN₂O₂S₂ (M): 352.0107. Found: m/z 352.0098. Anal. Calcd for C₁₅H₁₃ClN₂O₂S₂: 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-5H-thiopyrano[2,3-d]pyrimidin-5-one (2d): a yellow solid; mp 119–121 °C (hexane/CH₂Cl₂); 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); ¹³C 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 C₁₆H₁₆N₂O₃S₂ (M): 348.0602. Found: m/z 348.0605. Anal. Calcd for C₁₆H₁₆N₂O₃S₂: 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. ³³ 3a: pale-yellow oil; Rₜ 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); ¹³C NMR δ 14.35, 17.71, 70.54, 126.18, 128.37, 129.97, 160.22, 171.72. HR-MS (ESI). Calcd for C₉H₁₁Cl₂N₂OS (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 CHCl₃ (20 mL) containing activated MnO₂ (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/CH₂Cl₂ 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); ¹³C NMR δ 14.46, 18.81, 125.90, 131.80, 150.06, 157.77, 174.00, 188.98. HR-MS (EI). Calcd for C₉H₈Cl₂N₂O (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/CH₂Cl₂); IR (KBr) 1651, 1622 cm⁻¹; ¹H NMR δ 2.62 (s, 3H), 6.95 (d, J = 16.0 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); ¹³C NMR δ 14.51, 125.83, 126.13, 129.47, 129.98, 132.08, 137.76, 146.69, 157.90, 174.29, 188.72. HR-MS (EI). Calcd for C₁₄H₁₀Cl₂N₂O (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/CH₂Cl₂); 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); ¹³C 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 C₁₄H₉Cl₃N₂O₂S: C, 50.72; H, 3.41; N, 7.89. Found: C, 50.62; H, 3.47; N, 7.83.

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/CH₂Cl₂); 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); ¹³C 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 C₁₅H₁₂Cl₂N₂O₂S: 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 Et₃N (0.12 g, 1.2 mmol) at 0 °C was added pyrrolidine (89 mg, 1.2 mmol) dropwise. After 20 min, H₂O (20 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H₂O (3 × 10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH₂Cl₂ 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); ¹³C 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 C₁₃H₁₆ClN₃OS (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/CH₂Cl₂); 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); ¹³C 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 C₁₄H₁₈ClN₃OS (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/CH₂Cl₂); 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); ¹³C 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 C₁₆H₁₆ClN₃OS (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/CH₂Cl₂); 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); ¹³C 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 C₁₈H₁₈ClN₃OS: 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/CH₂Cl₂); 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); ¹³C NMR δ 14.17, 47.67, 66.30, 111.05, 127.42, 129.44, 129.84, 132.26, 137.42, 145.10, 15.11, 160.57, 171.71, 192.65. Anal. Calcd for C₁₈H₁₇ClN₃O₂S: 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; Rₐ 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); ¹³C NMR δ 12.27, 14.02, 45.69, 50.93, 60.37, 111.05, 127.42, 129.88, 131.03, 132.29, 137.35, 145.42, 156.57, 160.01, 193.07. HR-MS (ESI). Calcd for C₁₈H₁₉ClN₃NaO₂S (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/CH₂Cl₂); 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); ¹³C NMR δ 14.09, 40.24, 55.43, 110.21, 114.51, 125.95, 126.59, 130.54,
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\(^{-1}\); \(^1\)H NMR \( \delta \) 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 \( \delta \) 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\(_3\)O\(_4\)S (M+H): 452.1431. Found: \( \text{m/z} \) 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\(_2\)Cl\(_2\)); IR (KBr) 1646 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 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 \( \delta \) 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\(_3\)O\(_2\)S (M): 295.0813. Found: \( \text{m/z} \) 295.0827. Anal. Calcd for C\(_{13}\)H\(_{17}\)N\(_3\)O\(_2\)S: 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\(_2\)Cl\(_2\)); IR (KBr) 1648 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 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 \( \delta \) 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\(_3\)O\(_2\)S (M): 309.0970. Found: \( \text{m/z} \) 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\(_2\)Cl\(_2\)); IR (KBr) 1644 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 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 \( \delta \) 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\(_3\)O\(_2\)S (M): 331.0813. Found: \( \text{m/z} \) 333.0828. Anal. Calcd for C\(_{16}\)H\(_{17}\)N\(_3\)O\(_2\)S: 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\(_2\)Cl\(_2\)); IR (KBr) 1654 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 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 \( \delta \) 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$_{16}$H$_{19}$N$_3$O$_2$S$_2$ (M): 357.0970. Found: m/z 357.0959. Anal. Calcd for C$_{18}$H$_{19}$N$_3$O$_2$S$_2$: 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$_2$Cl$_2$); IR (KBr) 1640 cm$^{-1}$; $^1$H 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$_{19}$ClN$_3$O$_2$S$_2$ (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$_2$Cl$_2$); IR (KBr) 3409, 1647 cm$^{-1}$; $^1$H 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$_3$O$_2$S$_2$ (M+Na): 432.0583. Found: m/z 432.0580. Anal. Calcd for C$_{18}$H$_{20}$ClN$_3$O$_2$S$_2$: 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$_2$Cl$_2$); IR (KBr) 1641, 1610 cm$^{-1}$; $^1$H 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$_3$O$_2$S$_2$: C, 56.49; H, 4.92; 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$_3$O$_4$S$_2$ (M+H): 450.1521. Found: m/z 450.1517.

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