Supporting Material

for

Synthesis of novel analogs of thieno[2,3-d] pyrimidin-4(3H)-ones as selective inhibitors of cancer cell growth

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Synthesis

The general procedure for synthesis of the 2,3-disubstituted thieno[2,3-d]pyrimidin-4(3H)-ones was published previously [SynOpen 2018, 02, 207]. The compounds were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200–300 mesh). Melting points were determined on a Buchi B-540 apparatus and uncorrected. NMR spectra were recorded with a Varian 400 MHz or a 600MHz NMR spectrometer in CDCl$_3$ or DMSO-$d_6$, using TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded on UHPLC-Q-Orbitrap-MS. The purities of compounds were confirmed by HPLC (Ulitmate 3000, Thermo Scientific) to be over than 95%. Analytic data of compounds 4, 5, 9, 11, 14, 16, 17, 20, and 22 were presented below, other compounds was reported previously [SynOpen 2018, 02, 207].

3-benzyl-2-(3,4-bis(trifluoromethyl)phenyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (compound 4)

Yield 56%, white solid; m.p. 161-163 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$7.93 (s, 1H), 7.66 (s, 2H), 7.25 – 7.20 (m, 3H), 6.88 – 6.80 (m, 2H), 5.19 (s, 2H), 3.12 (t, $J$ = 5.8 Hz, 2H), 2.84 (t, $J$ = 4.8 Hz, 2H), 1.99-1.95 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.08, 158.60, 152.55, 136.93, 136.22, 135.69, 132.25, 132.23, 131.91, 129.10 (2 × CH), 128.68, 128.65, 128.00 (CH), 126.60 (2× CH), 124.14, 123.70, 121.86, 121.43, 48.31 (CH$_2$Ph), 25.78 (CH$_2$), 25.53 (CH$_2$). HR-ESI-MS: 509.11038 [M+H]$^+$ (calc.: 509.11223)

3-benzyl-2-(thiophen-2-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (compound 5)

Yield 68%, yellow solid; m.p. 185-187 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49-7.43 (m, 1H), 7.31 (t, $J$ = 7.2 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.17-7.13 (m, 1H), 7.10 (d, $J$ = 7.3 Hz, 2H), 7.01-6.95 (m, 1H), 5.48 (s, 2H), 3.04 (t, $J$ = 5.9 Hz, 2H), 2.80 (t, $J$ = 5.8 Hz, 2H), 1.95-1.79 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.73, 158.88, 149.67, 136.90, 136.68, 134.69, 131.97, 129.54, 129.46, 129.01, 127.51, 127.49, 126.14, 121.03, 48.98 (CH$_2$Ph), 25.71 (CH$_2$), 25.50 (CH$_2$), 23.08 (CH$_2$), 22.41 (CH$_2$). HR-ESI-MS: 379.09183 [M+H]$^+$ (calc.: 379.09388)

2-(3-chlorophenyl)-3-(4-hydroxyphenethyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (compound 9)

Yield 56%, yellow solid ;m.p. 238-240 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.24 (s, 1H), 8.31 (s, 1H), 7.61 (d, $J$ = 7.8 Hz, 1H), 7.51 (t, $J$ = 7.7 Hz, 1H), 7.41 (d, $J$ = 8.0 Hz, 2H), 6.59 (s, 4H), 3.95 (t, $J$ = 7.2 Hz, 2H), 2.97 (t, $J$ = 6.0 Hz, 2H), 2.78 (t, $J$ = 5.4 Hz, 2H), 2.70 (t, $J$ = 7.6 Hz, 2H), 1.87-1.76 (m, 4H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 160.50, 157.52, 156.05, 154.12, 136.75, 133.27, 133.07, 130.89, 130.20, 129.63, 129.32 (2×CH), 127.89, 127.75, 126.71, 120.70, 115.30 (2×CH), 47.11 (NCH$_3$), 32.84
3-benzyl-2-(furan-2-yl)-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (compound 11)

Yield 66%, yellow solid; m.p. 192-194 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55 (s, 1H), 7.29 (d, \(J = 6.9\) Hz, 1H), 7.26 – 7.20 (m, 2H), 7.12 (d, \(J = 7.1\) Hz, 2H), 6.88 – 6.82 (m, 1H), 6.47 (dd, \(J = 3.3, 1.6\) Hz, 1H), 5.57 (s, 2H), 3.36 (t, \(J = 5.5\) Hz, 2H), 2.90 (t, \(J = 5.5\) Hz, 2H), 1.95 – 1.87 (m, 2H), 1.76-1.64 (m, 4H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 160.22, 159.14, 147.02, 145.43, 144.60 (CH), 139.25, 137.67, 136.93, 128.79 (2× CH), 127.42 (CH), 126.46 (2xCH), 121.85, 115.39 (CH), 112.05 (CH), 47.81 (CH\(_2\)Ph), 32.73 (CH\(_2\)), 30.24 (CH\(_2\)), 27.99 (CH\(_2\)), 27.86 (CH\(_2\)), 27.39 (CH\(_2\)). HR-ESI-MS: 377.13141 [M+H]\(^+\) (calc.: 377.13237)

2-(4,5-dimethylthiophen-2-yl)-3-(4-hydroxyphenethyl)-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (compound 14)

Yield 74%, yellow solid; m.p. 186-188 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 9.28 (s, 1H), 7.30 (s, 1H), 6.95 (d, \(J = 8.3\) Hz, 2H), 6.70 (d, \(J = 8.4\) Hz, 2H), 4.30 (t, \(J = 8.0\) Hz, 2H), 3.31 (d, \(J = 5.7\) Hz, 2H), 1.94 – 1.81 (m, 2H), 1.73 – 1.50 (m, 4H). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 159.21, 158.20, 156.02, 148.94, 137.39, 137.33, 136.54, 133.70, 132.35, 130.90, 129.35 (2×CH), 127.89 (CH), 120.24, 115.35 (2×CH), 46.61 (CH\(_2\)N), 33.12 (CH\(_2\)Ph), 31.97 (CH\(_2\)), 29.10 (CH\(_2\)), 27.30 (CH\(_2\)), 27.04 (CH\(_2\)), 26.83 (CH\(_2\)), 13.73 (CH\(_3\)). HR-ESI-MS: 451.14907 [M+H]\(^+\) (calc.: 451.15139)

3-benzyl-2-(4-chlorophenyl)-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (compound 16)

Yield 72%, white solid; m.p. 170-172 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 (d, \(J = 8.4\) Hz, 2H), 7.28-7.20 (m, 5H), 7.01 – 6.90 (m, 2H), 5.23 (s, 1H), 3.39 (t, \(J = 5.4\) Hz, 2H), 2.88 (t, \(J = 5.3\) Hz, 2H), 1.98-1.88 (m, 2H), 1.80-1.66 (m, 4H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 180.05 (NCO), 159.26, 154.43, 138.98, 137.60, 136.76, 136.29, 133.61, 129.70 (2×CH), 128.90 (2×CH), 128.83 (2×CH), 127.61 (CHPh), 126.71 (2×CH), 122.04, 48.59 (CH\(_2\)Ph), 32.75 (CH\(_3\)), 30.21 (CH\(_2\)), 28.02 (CH\(_2\)), 27.90 (CH\(_2\)), 27.45 (CH\(_2\)). HR-ESI-MS: 421.11175 [M+H]\(^+\) (calc.: 421.11414)

3-benzyl-2-(4-fluorophenyl)-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (compound 17)

Yield 61%, white solid; m.p. 146-148 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.19 (m, 5H), 7.05 (t, \(J = 8.5\) Hz, 2H), 6.99 – 6.89 (m, 1H), 5.24 (s, 1H), 3.47 – 3.34 (m, 1H), 2.94 – 2.83 (m, 1H), 1.98 – 1.88 (m,
1H), 1.73 (tt, \( J = 11.4, 5.9 \text{ Hz}, 2\text{H} \)). \(^{13}\text{C} \text{NMR} (100 \text{ MHz, CDCl}_3) \delta 166.55 (\text{NCO}), 158.74, 154.44, 154.44, 140.83, 140.14, 136.63, 136.37, 133.47, 129.77, 128.92 (2\times \text{CH}), 128.83 (2\times \text{CH}), 127.68 (\text{CH}), 126.83 (2\times \text{CH}), 119.14, 48.63 (\text{CH}_2\text{Ph}), 29.86 (\text{CH}_2), 29.15 (\text{CH}_2), 28.23 (\text{CH}_2). \text{HR-ESI-MS}: 405.14217 [\text{M+H}]^+ (\text{calc.: 405.14369})

3-benzyl-5,6-dimethyl-2-(thiophen-2-yl)thieno[2,3-d]pyrimidin-4(3H)-one (compound 20)

Yield 71\%, white solid; m.p. 162-164 °C; \(^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 7.46 (d, \( J = 5.1 \text{ Hz}, 1\text{H} \)), 7.32 (t, \( J = 7.3 \text{ Hz}, 2\text{H} \)), 7.29 – 7.23 (m, 1\text{H} \)), 7.15 (d, \( J = 3.7 \text{ Hz}, 1\text{H} \)), 7.10 (d, \( J = 7.3 \text{ Hz}, 2\text{H} \)), 7.01-6.93 (m, 1\text{H} \)), 5.48 (s, 2\text{H} \)), 2.50 (s, 3\text{H} \)), 2.42 (s, 3\text{H} \)). \(^{13}\text{C} \text{NMR} (100 \text{ MHz, CDCl}_3) \delta 161.01, 159.11 (\text{CO}), 149.63, 136.91, 136.65, 131.46, 129.92, 129.51 (\text{CH}), 129.44 (\text{CH}), 129.03 (2\times \text{CH}), 127.51 (\text{CH}), 127.49 (\text{CH}), 126.07 (2\times \text{CH}), 121.82, 49.06 (\text{CH}_2\text{Ph}), 13.36 (\text{CH}_2), 13.23 (\text{CH}_3).

3-(4-hydroxyphenethyl)-5,6-dimethyl-2-phenylthieno[2,3-d]pyrimidin-4(3H)-one (compound 22)

Yield 66\%, white solid; m.p. 251-253 °C; \(^1\text{H} \text{NMR} (400 \text{ MHz, DMSO-d}_6) \delta 9.23 (s, 1\text{H} \)), 7.62 – 7.47 (m, 5\text{H} \)), 6.60 (dd, \( J = 11.7 \text{ Hz}, 4\text{H} \)), 3.98 (t, \( J = 7.7 \text{ Hz}, 2\text{H} \)), 2.70 (t, \( J = 8.1 \text{ Hz}, 2\text{H} \)), 2.48 (s, 3\text{H} \)), 2.41 (s, 3\text{H} \)). \(^{13}\text{C} \text{NMR} (100 \text{ MHz, DMSO-d}_6) \delta 160.00, 157.87, 155.94, 155.47, 134.97, 129.99, 129.69 (\text{CH}), 129.22 (2\times \text{CH}), 128.75, 128.32 (2\times \text{CH}), 127.98 (2\times \text{CH}), 127.83, 121.27, 115.24 (2\times \text{CH}), 46.92 (\text{NCH}_2), 33.03 (\text{CH}_2\text{Ph}), 12.90 (\text{CH}_3), 12.76 (\text{CH}_3). \text{HR-ESI-MS}: 377.12927 [\text{M+H}]^+ (\text{calc.: 377.13237})

NMR spectrum of compounds 4, 5, 9, 11, 14, 16, 17, 20, and 22
1H NMR of compound 4 (CDCl₃, 400 MHz)

13C NMR of compound 4 (CDCl₃, 100 MHz)
$^1$H NMR of compound 5 (CDCl$_3$, 400 MHz)

$^{13}$C NMR of compound 5 (CDCl$_3$, 100 MHz)
H NMR of compound 9 (DMSO-\textit{d}_6, 400 MHz)

$^{13}$C NMR of compound 9 (DMSO-\textit{d}_6, 100 MHz)
$^1$H NMR of compound 11 (CDCl$_3$, 400 MHz)

$^{13}$C NMR of compound 11 (CDCl$_3$, 100 MHz)
H NMR of compound 14 (DMSO-$d_6$, 400 MHz)

$^{13}$C NMR of compound 14 (DMSO-$d_6$, 100 MHz)
$^1$H NMR of compound 16 (CDCl$_3$, 400 MHz)

$^{13}$C NMR of compound 16 (CDCl$_3$, 100 MHz)
$^1$H NMR of compound 17 (CDCl$_3$, 400 MHz)

$^{13}$C NMR of compound 17 (CDCl$_3$, 100 MHz)
$^1$H NMR of compound 20 (CDCl$_3$, 400 MHz)

$^{13}$C NMR of compound 20 (CDCl$_3$, 100 MHz)
$^1$H NMR of compound 22 (DMSO-$d_6$, 400 MHz)

$^{13}$C NMR of compound 22 (DMSO-$d_6$, 100 MHz)