

SUPPLEMENTARY MATERIAL TO
**Synthesis and biological evaluation of novel urea and thiourea
derivatives of valaciclovir**

VENKATA RAMANA KATLA¹, RASHEED SYED¹, MADHAVA GOLLA¹,
ADAM SHAIK² and NAGA RAJU CHAMARTHI^{1*}

¹Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502, India and

²Department of Biochemistry, Sree Vidyaniketan P.G College, Tirupati - 517 502, India

J. Serb. Chem. Soc. 79 (3) (2014) 283–289

ANALYTIC AND SPECTRAL DATA FOR COMPOUNDS **3a–j**

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 3-methyl-2-
-[[[(phenylamino)thioxomethyl]amino]butanoate (**3a**). Yield: 82 %; m.p. 144–146
°C; Anal. Calcd. for C₂₀H₂₅N₇O₄S: C, 52.27; H, 5.48; N, 21.34 %. Found: C,
52.29, H, 5.42; N, 21.25 %; IR (KBr, cm⁻¹): 3412 (N–H), 3138 (NH₂), 1183
(C=S), 724 (C–S); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 10.8 (1H, s, N–H),
8.21 (1H, s, Ar-H), 7.86 (2H, s, NH₂), 7.68–6.94 (5H, *m*, Ar-H), 5.24 (2H, *t*, *J* =
= 7.6 Hz, CH₂), 5.18 (2H, *t*, *J* = 6.8 Hz, CH₂), 4.58 (2H, *s*, CH₂), 4.20 (1H, *s*,
NH-Ar), 3.41 (1H, *s*, NH–C=S), 2.84 (1H, *d*, *J* = 5.2 Hz, H-16), 1.64–1.48 (1H,
m (CH–(CH₃)₂), 1.24 (6H, *d*, *J* = 5.6 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz,
DMSO-*d*₆, δ / ppm): 166.8 (C₂₀ of C=S), 159.8 (C₁₅ of C=O), 158.2 (C₄ of
HN–C=O), 152.4 (C₆), 146.2, 142.4, 136.2, 128.2, 126.8, 126.4, 124.6, 126.2,
118.6, 67.4, 65.2 (C₁₆), 64.2, 61.2, 32.4, 19.4, 18.5; MS (*m/z*): 459 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-[[[(4-fluoro-
phenyl)amino]thioxomethyl]amino]-3-methylbutanoate (**3b**). Yield: 80 %; m.p.
150–152 °C; Anal. Calcd. for C₂₀H₂₄N₇O₄S: C, 50.31; H, 5.07; N, 20.53 %.
Found: C, 50.25, H, 5.01; N, 20.48 %; IR (KBr, cm⁻¹): 3416 (N–H), 3118 (NH₂),
1188 (C=S), 728 (C–S); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 11.2 (1H, *s*,
N–H), 8.12 (1H, *s*, Ar-H), 8.02 (2H, *s*, NH₂), 7.62–6.92 (4H, *m*, Ar-H), 5.12 (2H,
t, *J* = 7.4 Hz, CH₂), 4.96 (2H, *t*, *J* = 7.4 Hz, CH₂), 4.32 (2H, *s*, CH₂), 4.16 (1H, *s*,
NH-Ar), 3.21 (1H, *s*, NH–C=S), 2.04 (1H, *d*, *J* = 4.6 Hz, H-16), 1.92–1.82 (1H,
m (CH–(CH₃)₂), 1.12 (6H, *d*, *J* = 5.2 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz,
DMSO-*d*₆, δ / ppm): 168.2 (C₂₀ of C=S), 159.2 (C₁₅ of C=O), 156.2 (C₄ of
HN–C=O), 153.8 (C₆), 144.2, 139.6, 135.4, 129.2, 128.6, 127.5, 127.2, 125.4,
116.4, 66.8, 65.7, 65.4 (C₁₆), 60.6, 33.6, 19.6, 19.2; MS (*m/z*): 477 M⁺.

*Corresponding author. E-mail: rajuchamarthi10@gmail.com

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl {[(4-chlorophenyl)amino]thioxomethyl}amino-3-methylbutanoate (**3c**). Yield: 79 %; m.p. 148–150 °C; Anal. Calcd. for C₂₀H₂₄ClN₇O₄S: C, 48.63; H, 4.90; N, 19.85 %. Found: C, 48.71, H, 4.83; N, 19.68 %; IR (KBr, cm⁻¹): 3422 (N–H), 3130 (NH₂), 1194 (C=S), 732 (C–S); ¹H-NMR (500 MHz DMSO-*d*₆, δ / ppm): 11.6 (1H, s, N–H), 8.32 (1H, s, Ar-H), 7.64–6.82 (4H, *m*, Ar-H), 7.54 (2H, s, NH₂), 5.24 (2H, *t*, *J* = 7.6 Hz, CH₂), 4.82 (2H, *t*, *J* = 6.9 Hz, CH₂), 4.32 (1H, s, NH-Ar), 4.28 (2H, s, CH₂), 4.2 (1H, s, NH–C=S), 2.42 (1H, *d*, *J* = 4.6 Hz, H-16), 1.42–1.34 (1H, *m* (CH–(CH₃)₂), 1.22 (6H, *d*, *J* = 5.4 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz DMSO-*d*₆, δ / ppm): 174.6 (C₂₀ of C=S), 171.6 (C₁₅ of C=O), 154.2 (C₆), 152.5 (C₄ of HN–C=O), 145.6, 141.5, 135.4, 129.2, 128.6, 127.5, 127.2, 125.4, 118.2, 69.2, 67.2 (C₁₆), 66.4, 61.5, 31.4, 19.7, 19.4; MS (*m/z*): 493 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 3-methyl-2-[[[(4-nitrophenyl)amino]thioxomethyl]amino]butanoate (**3d**). Yield: 78 %; m.p. 128–130 °C; Anal. Calcd. for C₂₀H₂₄N₈O₆S: C, 47.61; H, 4.79; N, 22.21 %. Found: C, 47.56, H, 4.75; N, 22.17 %; IR (KBr, cm⁻¹): 3428 (N–H), 3116 (NH₂), 1206 (C=S), 738 (C–S); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 11.4 (1H, s, N–H), 8.42 (1H, s, Ar-H), 7.72 (2H, s, NH₂), 7.52–6.88 (4H, *m*, Ar-H), 5.18 (2H, *t*, *J* = 7.1 Hz, CH₂), 4.64 (2H, *t*, *J* = 6.4 Hz, CH₂), 4.62 (1H, s, NH–C=S), 4.56 (1H, s, NH-Ar), 4.32 (2H, s, CH₂), 2.26 (1H, *d*, *J* = 4.6 Hz, H-16), 1.42–1.26 (1H, *m* (CH–(CH₃)₂), 1.08 (6H, *d*, *J* = 5.2 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz DMSO-*d*₆, δ / ppm): 182.4 (C₂₀ of C=S), 172.4 (C₁₅ of C=O), 155.4 (C₆), 151.6 (C₄ of HN–C=O), 146.2, 140.4, 136.2, 128.7, 128.4, 128.2, 128.0, 127.4, 117.4, 68.6, 67.2, 66.2 (C₁₆), 63.7, 30.6, 19.5, 19.2; MS (*m/z*): 504 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-[[[(3-bromophenyl)amino]thioxomethyl]amino]-3-methylbutanoate (**3e**). Yield: 76 %; m.p. 110–112 °C; Anal. Calcd. for C₂₀H₂₄BrN₇O₄S: C, 44.61; H, 4.49; N, 18.21 %. Found: C, 44.51; H, 4.36; N, 18.32 %; IR (KBr, cm⁻¹): 3426 (N–H), 3112 (NH₂), 1198 (C=S), 720 (C–S); ¹H-NMR (500 MHz DMSO-*d*₆, δ / ppm): 10.9 (1H, s, N–H), 8.28 (1H, s, Ar-H), 7.84 (2H, s, NH₂), 7.32–6.94 (4H, *m*, Ar-H), 5.24 (2H, *t*, *J* = 7.6 Hz, CH₂), 4.82 (1H, s, NH–C=S), 4.46 (2H, *t*, *J* = 6.4 Hz, CH₂), 4.32 (1H, s, NH-Ar), 4.12 (2H, s, CH₂), 2.12 (1H, *d*, *J* = 5.8 Hz, H-16), 1.42–1.24 (1H, *m* (CH–(CH₃)₂), 1.14 (6H, *d*, *J* = 6.4 Hz, (CH–(CH₃)₂); ¹³C-NMR (125 MHz DMSO-*d*₆, δ / ppm): 172.8 (C₂₀ of C=S), 171.6 (C₁₅ of C=O), 157.2 (C₆), 152.4 (C₄ of HN–C=O), 147.6, 138.6, 137.4, 127.6, 127.2, 126.8, 126.4, 124.6, 116.8, 69.2, 68.4, 65.4 (C₁₆), 65.2, 31.2, 18.9, 18.6; MS (*m/z*): 537 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-[3-(4-bromophenyl)ureido]-3-methylbutanoate (**3f**). Yield: 77 %; m.p. 118–120 °C; Anal. Calcd. for C₂₀H₂₄BrN₇O₅: C, 45.99; H, 4.63; N, 15.30 %. Found: C, 45.86; H, 4.52; N, 15.26 %; IR (KBr, cm⁻¹): 3432 (N–H), 3109 (NH₂), 1656 (C=O), 1070 (C–O); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 11.2 (1H, s, N–H), 8.36 (1H, s,

Ar-H), 7.62 (2H, s, NH₂), 7.46–6.87 (4H, m, Ar-H), 5.12 (2H, t, *J* = 7.1 Hz, CH₂), 4.64 (1H, s, NH–C=S), 4.32 (2H, t, *J* = 6.2 Hz, CH₂), 4.26 (1H, s, NH–Ar), 4.06 (2H, s, CH₂), 2.24 (1H, d, *J* = 6.4 Hz, H-16), 1.36–1.24 (1H, m (CH–(CH₃)₂), 1.22 (6H, d, *J* = 4.6 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz, DMSO-*d*₆, δ / ppm): 169.2 (C₁₅ of C=O), 158.4 (C₆), 151.6 (C₄ of HN–C=O), 148.4 (C₂₀ of C=O), 145.8, 137.5, 136.2, 128.2, 127.9, 127.6, 126.8, 123.8, 118.2, 69.5, 68.4, 66.5 (C₁₆), 64.8, 30.6, 19.4, 18.8; MS (*m/z*): 521 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-[3-(4-fluorophenyl)ureido]-3-methylbutanoate (**3g**). Yield: 81 %; m.p. 106–108 °C; Anal. Calcd. for C₂₀H₂₄FN₇O₅: C, 52.06; H, 5.24; N, 21.25 %. Found: C, 52.01, H, 5.17; N, 21.18 %; IR (KBr, cm⁻¹): 3440 (N–H), 3152 (NH₂), 1648 (C=O), 1035 (C–O); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 12.4 (1H, s, N–H), 8.02 (1H, s, Ar-H), 7.92–6.74 (4H, m, Ar-H), 7.76 (2H, s, NH₂), 5.64 (2H, t, *J* = 7.2 Hz, CH₂), 4.86 (1H, s, NH–C=S), 4.36 (1H, s, NH–Ar), 4.28 (2H, t, *J* = 6.1 Hz, CH₂), 4.12 (2H, s, CH₂), 2.12 (1H, d, *J* = 5.6 Hz, H-16), 1.82–1.64 (1H, m (CH–(CH₃)₂), 1.38 (6H, d, *J* = 6.8 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz, DMSO-*d*₆, δ / ppm): 170.4 (C₁₅ of C=O), 157.2 (C₆), 153.4 (C₄ of HN–C=O), 152.6 (C₂₀ of C=O), 146.4, 139.8, 139.4, 127.2, 126.6, 125.8, 125.2, 124.6, 117.5, 68.2, 67.6, 67.2, 65.2, (C₁₆), 31.6, 19.8, 19.4; MS (*m/z*): 461 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-[3-(3,4-dichlorophenyl)ureido]-3-methylbutanoate (**3h**). Yield: 75 %; m.p. 102–104 °C; Anal. Calcd. for C₂₀H₂₃Cl₂N₇O₅: C, 46.89; H, 4.52; N, 19.14 %. Found: C, 46.80, H, 4.46; N, 19.10 %; IR (KBr, cm⁻¹): 3438 (N–H), 3112 (NH₂), 1652 (C=O), 1074 (C–O); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 12.2 (1H, s, N–H), 8.12 (1H, s, Ar-H), 7.94–6.84 (3H, m, Ar-H), 7.62 (2H, s, NH₂), 5.52 (2H, t, *J* = 7.8 Hz, CH₂), 4.74 (1H, s, NH–C=S), 4.32 (2H, t, *J* = 6.3 Hz, CH₂), 4.28 (1H, s, NH–Ar), 4.14 (2H, s, CH₂), 2.22 (1H, d, *J* = 5.6 Hz, H-16), 1.86–1.64 (1H, m (CH–(CH₃)₂), 1.26 (6H, d, *J* = 6.2 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz, DMSO-*d*₆, δ / ppm): 171.5 (C₁₅ of C=O), 158.4 (C₆), 155.6 (C₄ of C=O), 150.8 (C₂₀ of C=O), 148.2, 138.2, 136.8, 127.4, 126.8, 126.6, 126.2, 125.8, 118.2, 69.2, 67.4, 66.4 (C₁₆), 62.6, 19.6, 32.4, 19.2; MS (*m/z*): 512 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-[3-(3-chloro-4-fluorophenyl)ureido]-3-methylbutanoate (**3i**). Yield: 72 %; m.p. 100–102 °C; Anal. Calcd. for C₂₀H₂₃ClFN₇O₅: C, 48.44; H, 4.67; N, 19.77 %. Found: C, 48.39, H, 4.58; N, 19.72 %; IR (KBr, cm⁻¹): 3442 (N–H), 3132 (NH₂), 1668 (C=O), 1035 (C–O); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 11.9 (1H, s, N–H), 8.24 (1H, s, Ar-H), 7.86–6.92 (3H, m, Ar-H), 7.74 (2H, s, NH₂), 5.42 (2H, t, *J* = 7.6 Hz, CH₂), 4.62 (1H, s, NH–C=S), 4.46 (2H, t, *J* = 6.4 Hz, CH₂), 4.16 (1H, s, NH–Ar), 4.24 (2H, s, CH₂), 2.34 (1H, d, *J* = 5.7 Hz, H-16), 1.91–1.74 (1H, m (CH–(CH₃)₂), 1.34 (6H, d, *J* = 5.2 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz, DMSO-*d*₆, δ / ppm): 172.4 (C₁₅ of C=O), 159.6 (C₆), 156.2 (C₄ of HN–C=O),

152.6 (C₂₀ of C=O), 149.5, 139.7, 139.2, 128.5, 127.7, 126.8, 126.2, 125.2, 119.4, 69.6, 68.2, 67.6 (C₁₆), 63.7, 31.8, 20.2, 19.8; MS (*m/z*): 496 M⁺.

2-[(2-Amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl 2-{3-[4-chloro-3-(trifluoromethyl) phenyl]ureido}-3-methylbutanoate (**3j**). Yield: 74 %; m.p. 122–124 °C; Anal. Calcd. for C₂₁H₂₃ClF₃N₇O₅: C, 46.20; H, 4.25; N, 17.96 %. Found: C, 46.14; H, 4.18; N, 17.89 %; IR (KBr, cm⁻¹): 3448 (N–H), 3142 (NH₂), 1672 (C=O), 1053 (C–O); ¹H-NMR (500 MHz, DMSO-*d*₆, δ / ppm): 12.2 (1H, s, N–H), 8.22 (1H, s, Ar-H), 7.92–6.74 (3H, *m*, Ar-H), 7.58 (2H, s, NH₂), 5.32 (2H, *t*, *J* = 7.4 Hz, CH₂), 4.56 (1H, s, NH–C=S), 4.54 (2H, *t*, *J* = 6.4 Hz, CH₂), 4.36 (2H, s, CH₂), 4.28 (1H, s, NH-Ar), 2.28 (1H, *d*, *J* = 4.4 Hz, H-16), 1.84–1.62 (1H, *m* (CH–(CH₃)₂), 1.26 (6H, *d*, *J* = 6.6 Hz (CH–(CH₃)₂); ¹³C-NMR (125 MHz, DMSO-*d*₆, δ / ppm): 171.6 (C₁₅ of C=O), 157.6 (C₄ of HNC=O), 156.4 (C₆), 151.2 (C₂₀ of C=O), 148.8, 140.8, 139.4, 128.2, 127.9, 126.5, 125.8, 124.8, 118.2, 68.6, 67.4, 66.4 (C₁₆), 62.6, 30.4, 19.8, 19.2; MS (*m/z*): 545 M⁺.