α-Alkyl Substituted Pirinixic Acid Derivatives as Potent Dual Agonists of the Peroxisome Proliferator Activated Receptor alpha and gamma

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Supplemental Data

2-[4-Chloro-6-(2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-propionic acid 5. mp = 176 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 1.56 (d, 3H, S-CHC*H*$_3$, *J* = 7.2 Hz), 2.19 (s, 3H, Ph-2-C*H*$_3$), 2.39 (s, 3H, Ph-3-C*H*$_3$), 4.38 (q (br), 1H, S-C*H*), 6.28 (s, 1H, Pyr-5-*H*), 7.19-7.25 (m, 3H, Ph-4,5,6-*H*), 9.65 (s (br), 1H, N*H*), 12.90 (s (br), 1H, COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 13.97 (Ph-2-*C*H$_3$), 17.88 (Ph-3-*C*H$_3$), 20.09 (S-CH*C*H$_3$), 42.07 (S-*C*H), 98.75 (Pyr-5-*C*), 124.01 (Ph-6-*C*), 125.75 (Ph-4-*C*), 127.89 (Ph-5-*C*), 132.33 (Ph-2-*C*), 135.58 (Ph-3-*C*), 137.66 (Ph-1-*C*), 157.62 (Pyr-4-*C*), 162.27 (Pyr-2-*C*), 169.60 (Pyr-6-*C*), 172.86 (*C*OOH). MS (ESI–): *m/e* = 335.9 (M – 1). Anal. ($C_{15}H_{16}ClN_3O_2S$) C, H, N: Calc. C 53.33, H 4.77, N 12.44; Found C 53.31, H 4.59; N 12.17.

2-[4-Chloro-6-(2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-butyric acid 6. mp = 178 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 0.99 (t (br), 3H, S-CHCH$_2$C*H*$_3$), 1.79-1.96 (m, 2H, S-CHC*H*$_2$CH$_3$), 2.15 (s, 3H, Ph-2-C*H*$_3$), 2.36 (s, 3H, Ph-3-C*H*$_3$), 4.27-4.33 (m, 1H, S-C*H*), 6.29 (s, 1H, Pyr-5-*H*), 7.19-7.22 (m, 3H, Ph-4,5,6-*H*), 9.60 (s (br), 1H, N*H*), 12.93 (s (br), 1H, COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 11.31 (Ph-2-*C*H$_3$), 14.01 (S-CHCH$_2$*C*H$_3$), 20.08 (Ph-3-*C*H$_3$), 25.32 (S-CH*C*H$_2$CH$_3$), 48.49 (S-*C*H), 98.87 (Pyr-5-*C*), 124.01 (Ph-6-*C*), 125.74 (Ph-4-*C*), 127.88 (Ph-5-*C*), 132.39 (Ph-2-*C*), 135.62 (Ph-3-*C*), 137.68 (Ph-1-*C*), 157.76 (Pyr-

4-*C*), 162.19 (Pyr-2-*C*), 169.65 (Pyr-6-*C*), 172.27 (*C*OOH). MS (ESI–): *m/e* = 350.0 (M – 1). Anal. ($C_{16}H_{18}ClN_3O_2S$) C, H, N: Calc. C 54.62, H 5.16, N 11.94; Found C 54.81, H 5.23; N 11.68.

2-[4-Chloro-6-(2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-pentanoic acid 7. mp = 166-167 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 0.93 (t, 3H, C*H*$_3$ (*n*-Pr), *J* = 7.2 Hz), 1.26-1.30 (m, 2H, S-CHCH$_2$C*H*$_2$), 1.74-1.96 (m, 2H, S-CHC*H*$_2$CH$_2$), 2.17 (s, 3H, Ph-2-C*H*$_3$), 2.38 (s, 3H, Ph-3-C*H*$_3$), 4.34 (m, 1H, S-C*H*), 6.32 (s, 1H, Pyr-5-*H*), 7.20-7.24 (m, 3H, Ph-4,5,6-*H*), 9.63 (s (br), 1H, N*H*), 12.94 (s (br), 1H, COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 13.42 (Ph-2-*C*H$_3$), 14.01 (*C*H$_3$ (*n*-Pr)), 19.81 (S-CHCH$_2$*C*H$_2$), 20.07 (Ph-3-*C*H$_3$), 34.01 (S-CH*C*H$_2$CH$_2$), 46.70 (S-*C*H), 98.91 (Pyr-5-*C*), 124.02 (Ph-6-*C*), 125.71 (Ph-4-*C*), 127.88 (Ph-5-*C*), 132.42 (Ph-2-*C*), 135.62 (Ph-3-*C*), 137.62 (Ph-1-*C*), 157.73 (Pyr-4-*C*), 162.20 (Pyr-2-*C*), 169.64 (Pyr-6-*C*), 172.50 (*C*OOH). MS (ESI–): *m/e* = 364.1 (M – 1). Anal. ($C_{17}H_{20}ClN_3O_2S$) C, H, N: Calc. C 55.81, H 5.51, N 11.48; Found C 55.79, H 5.58; N 11.32.

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^{1}H-NMR: (300.13 MHz, $(CD_3)_2SO$): δ 0.84 (t, 3H, C*H*$_3$-Octyl, J=6.6Hz); 1.19-1.33 (m, 12H, C*H*$_2$-Octyl); 1.68-1.77 (m, 2H, C*H*$_2$-Octyl); 2.05 (s, 3H, Ph-2-C*H*$_3$); 2.26 (s, 3H, Ph-3-C*H*$_3$); 4.40 (br s, 1H, S-C*H*); 6.21 (br s, 1H, Pyr-5*H*); ; 7.09 (t, 3H, Ph-*H*, J=6.2Hz); 9.49 (s, 1H, -N*H*). ^{13}C-NMR: (75.45 MHz, $(CD_3)_2SO$) δ 13.86 (Ph-2-*C*H$_3$); 13.97 (*C*H$_3$-Octyl); 20.03 (Ph-3-*C*H$_3$); 22.01 (*C*H$_2$-Octyl); 26.36 (*C*H$_2$-Octyl); 28.37 (*C*H$_2$-Octyl); 28.44 (*C*H$_2$-Octyl); 28.64 (*C*H$_2$-Octyl); 31.16 (*C*H$_2$-Octyl); 31.92 (*C*H$_2$-Octyl); 46.93 (S-*C*H); 98.87 (Pyr-*C*$_5$); 123.97 (Ph-*C*$_6$); 125.64 (Ph-*C*$_4$); 127.81 (Ph-*C*$_5$); 132.33 (Ph-*C*$_2$); 135.61 (Ph-*C*$_3$); 137.57 (Ph-*C*$_1$); 157.71 (Pyr-*C*$_4$); 162.15 (Pyr-*C*$_6$); 169.62 (Pyr-*C*$_2$); 172.45 (*C*OOH). MS (ESI +): *m/e* = 435.8 [M+H]$^+$. Anal. ($C_{22}H_{30}ClN_3O_2S$ x 0.4 $C_4H_8O_2$ [471.25]; $C_4H_8O_2$ = ethyl acetate) C, H, N: Calc. C 60.15, H 7.10, N 8.92; Found C 60.21, H 7.06; N 8.80.

[4-Chloro-6-(2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-phenyl-acetic acid 11. mp = 192–200 °C (degradation). ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 2.05 (s, 3H, Ph-2-C*H*$_3$), 2.28 (s, 3H, Ph-3-C*H*$_3$), 5.37 (s, 1H, S-C*H*), 6.20 (s, 1H, Pyr-5-*H*), 7.08-7.17 (m, 3H, N-Ph-4,5,6-*H*), 7.28-7.36 (m, 5H, C-Ph-2,3,4,5,6-*H*), 9.57 (s (br), 1H, N*H*), 13.05 (s (br), 1H,

COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 14.04 (N-Ph-2-*C*H_3), 20.08 (N-Ph-3-*C*H_3), 52.01 (S-*C*H), 98.94 (Pyr-5-*C*), 124.22 (N-Ph-6-*C*), 125.83 (N-Ph-4-*C*), 128.03 (N-Ph-5-*C*), 128.33 (C-Ph-4-*C*), 128.57 (C-Ph-3,5-*C*), 128.88 (C-Ph-2,6-*C*), 132.60 (N-Ph-2-*C*), 135.65 (C-Ph-1-*C*), 136.07 (N-Ph-3-*C*), 137.73 (N-Ph-1-*C*), 157.76 (Pyr-4-*C*), 162.19 (Pyr-2-*C*), 169.31 (Pyr-6-*C*), 170.72 (*C*OOH). MS (ESI–): *m/e* = 398.1 (M – 1). Anal. ($C_{20}H_{18}ClN_3O_2S$) C, H, N: Calc. C 60.07, H 4.54, N 10.51; Found C 59.86, H 4.70; N 10.35.

[4-Chloro-6-(2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-naphtalen-1-yl-acetic acid 12. mp = 150 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 2.08 (s, 3H, Ph-2-C*H*$_3$), 2.27 (s, 3H, Ph-3-C*H*$_3$), 6.16 (s, 1H, S-C*H*), 6.25 (s, 1H, Pyr-5-*H*), 7.11-7.15 (m, 3H, Ph-4,5,6-*H*), 7.43-7.46 (m, 2H, Naph-2,3-*H*), 7.53-7.56 (m, 2H, Naph-6,7-*H*), 7.88-7.97 (m, 3H, Naph-4,5,8-*H*), 9.60 (s (br), 1H, N*H*), 13.15 (s (br), 1H, COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 13.98 (Ph-2-*C*H_3), 20.01 (Ph-3-*C*H_3), 49.00 (S-*C*H), 99.01 (Pyr-5-*C*), 123.19 (Ph-6-*C*), 124.00 (Ph-4-*C*), 125.40 (Naph-8-*C*), 125.77 (Naph-6-*C*), 126.01 (Naph-7-*C*), 126.67 (Ph-5-*C*), 126.81 (Naph-4-*C*), 127.94 (Naph-2-*C*), 128.71 (Naph-3-*C*), 128.78 (Naph-5-*C*), 130.37 (Ph-2-*C*), 131.88 (Naph-8a-*C*), 132.49 (Naph-4a-*C*), 133.52 (Naph-1-*C*), 135.57 (Ph-3-*C*), 137.67 (Ph-1-*C*), 157.82 (Pyr-4-*C*), 162.16 (Pyr-2-*C*), 169.32 (Pyr-6-*C*), 171.04 (*C*OOH). MS (ESI+): *m/e* = 450.1 (M + 1). Anal. ($C_{24}H_{20}ClN_3O_2S \times 0.4\ C_4H_8O_2$ [520.45]; $C_4H_8O_2$ = ethyl acetate) C, H, N: Calc. C 62.77, H 5.10, N 8.07; Found C 62.44, H 4.81; N 8.19.

[4-Chloro-6-(4-bromo-2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-acetic acid 14. mp = 181 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 2.28 (s, 3H, Ph-2-C*H*$_3$), 2.50 (s, 3H, Ph-3-C*H*$_3$), 3.63 (s, 2H, S-C*H*$_2$), 6.33 (s (br), 1H, Pyr-5-*H*), 7.28 (d, 1H, Ph-6-*H*, *J* = 8.6 Hz), 7.57 (d, 1H, Ph-5-*H*, *J* = 8.6 Hz), 9.63 (s (br), 1H, N*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 15.62 (Ph-2-*C*H_3), 19.98 (Ph-3-*C*H_3), 38.02 (S-*C*H_2), 98.23 (Pyr-5-*C*), 121.58 (Ph-3-*C*), 125.35 (Ph-6-*C*), 129.58 (Ph-5-*C*), 134.46 (Ph-2-*C*), 135.77 (Ph-4-*C*), 136.57 (Ph-1-*C*), 157.65 (Pyr-4-*C*), 161.70 (Pyr-2-*C*), 169.54 (Pyr-6-*C*), 172.75 (*C*O). MS (ESI–): *m/e* = 401.9 (M(^{37}Cl) – 1). Anal. ($C_{14}H_{13}BrClN_3O_2S \times 2\ H_2O$ [440.54]) C, H, N: Calc. C 38.17, H 3.94, N 9.54; Found C 38.33, H 3.52; N 8.70.

[4-Chloro-6-(4-bromo-3-methyl-phenylamino)-pyrimidin-2-ylsulfanyl]-acetic acid 15. mp = 185-186 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 2.34 (s, 3H, Ph-3-C*H*$_3$), 3.94 (s, 2H, S-C*H*$_2$), 6.50 (s, 1H, Pyr-5-*H*), 7.36 (dd, 1H, Ph-6-*H*, ^4J = 3.8 Hz, ^3J = 13 Hz), 7.48-7.56 (m, 2H, Ph-2,5-*H*), 9.94 (s (br), 1H, N*H*), 12.76 (s (br), 1H, COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 22.52 (Ph-3-*C*H$_3$), 32.96 (S-*C*H$_2$), 101.06 (Pyr-5-*C*), 117.62 (Ph-4-*C*), 119.49 (Ph-6-*C*), 122.33 (Ph-2-*C*), 131.98 (Ph-5-*C*), 137.64 (Ph-3-*C*), 138.07 (Ph-1-*C*), 157.39 (Pyr-4-*C*), 160.35 (Pyr-2-*C*), 169.77 (Pyr-6-*C*), 170.28 (*C*OOH). MS (ESI–): *m/e* = 387.7 (M – 1). Anal. ($C_{13}H_{11}BrClN_3O_2S \times 0.1\ C_4H_8O_2$ [397.49]; $C_4H_8O_2$ = ethyl acetate) C, H, N: Calc. C 40.49, H 2.99, N 10.57; Found C 40.63, H 2.95; N 10.29.

[4-Chloro-6-(4-chloro-2,3-dimethyl-phenylamino)-pyrimidin-2-ylsulfanyl]-acetic acid 16. mp = 189-190 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 2.25 (s, 3H, Ph-2-C*H*$_3$), 2.45 (s, 3H, Ph-3-C*H*$_3$), 3.92 (s, 2H, S-C*H*$_2$), 6.40 (s (br), 1H, Pyr-5-*H*), 7.29 (d, 1H, Ph-6-*H*, *J* = 8.6 Hz), 7.40 (d, 1H, Ph-5-*H*), *J* = 8.6 Hz), 9.63 (s (br), 1H, N*H*), 12.82 (s (br), 1H, COO*H*).

^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 15.37 (Ph-2-*C*H$_3$), 16.97 (Ph-3-*C*H$_3$), 32.88 (S-*C*H$_2$), 99.42 (Pyr-5-*C*), 125.15 (Ph-6-*C*), 126.66 (Ph-5-*C*), 131.18 (Ph-2,4-*C*, superposition), 134.71 (Ph-3-*C*), 135.26 (Ph-1-*C*), 158.05 (Pyr-4-*C*), 162.00 (Pyr-2-*C*), 170.00 (Pyr-6-*C*), 170.12 (*C*OOH). MS (ESI–): *m/e* = 355.9 (M – 1). Anal. ($C_{14}H_{13}Cl_2N_3O_2S$) C, H, N: Calc. C 46.94, H 3.66, N 11.73; Found C 46.83, H 3.63; N 11.54.

[4-Chloro-6-(indan-4-ylamino)-pyrimidin-2-ylsulfanyl]-acetic acid 17. mp = 164-165 °C. ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 2.13 (quin, 2H, Indane-2-*H*, *J* = 7.4 Hz), 2.91 (t, 2H, Indane-3-*H*, *J* = 7.4 Hz), 3.02 (t, 2H, Indane-1-*H*, *J* = 7.4 Hz), 3.99 (s, 2H, S-C*H*$_2$), 6.57 (s, 1H, Pyr-5-*H*), 7.18-7.29 (m, 2H, Indane-5,7-*H*), 7.45-7.49 (m, 1H, Indane-6-*H*), 9.55 (s (br), 1H, N*H*), 12.87 (s (br), 1H, COO*H*). ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 24.55 (Indane-3-*C*), 30.44 (Indane-2-*C*), 32.71 (Indane-1-*C*), 32.85 (S-*C*H$_2$), 99.86 (Pyr-5-*C*), 121.16 (Indane-5,7-*C*, superposition), 126.80 (Indane-6-*C*), 133.79 (Indane-3a-*C*), 137.20 (Indane-7a-*C*), 145.28 (Indane-4-*C*), 157.63 (Pyr-4-*C*), 161.20 (Pyr-2-*C*), 169.88 (Pyr-6-*C*), 169.98 (*C*OOH). MS (ESI–): *m/e* = 333.9 (M – 1). Anal. ($C_{15}H_{14}ClN_3O_2S$) C, H, N: Calc. C 53.65, H 4.20, N 12.51; Found C 53.38, H 4.22; N 12.38.