Electronic Supplementary Material (ESI) for Metallomics

Supplementary Information

Novel potassium N-[(2S,3R,4R,5R)-2,3,4,5,6-Pentahydroxylhex-1-yl]-L-amino acid dichloroplatinates(II) with high anti-tumor activity and low side reaction

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Contents

N-[(2S,3R,4R,5R)-2,3,4,5,6-Pentahydroxylhex-1-yl]-L-threonine (4a)

Yield: 25%, colorless powders, Mp 195 - 197 °C. $[\alpha]_D^{20}$=-19.0 (c 2.0, H_2O). IR (KBr): 3421, 2975, 2939, 1612, 1571, 1415, 1385, 1084, 1045, 841, 756, 731. ESI-MS (m/e): 284 $[M + H]^+$; ^1H NMR (D_2O): δ = 4.12 (m, *J* = 4.6 Hz, 1H), 3.95 (d, *J* = 4.5 Hz, 1H), 3.81 (m, *J* = 4.5 Hz, 1H), 3.80 (m, *J* = 3.4 Hz, 1H), 3.75 (m, *J* = 3.6 Hz, 1H), 3.64 (m, *J* = 4.1 Hz, 2H), 3.57 (d, *J* = 4.7 Hz, 1H), 3.26 (dd, *J* = 3.1 Hz, *J* = 13.0 Hz, 1H), 3.12 (dd, *J* = 10.1 Hz, *J* = 13.0 Hz, 1H), 1.24 (d, *J* = 4.7 Hz, 3H). Anal Calcd for $C_{10}H_{21}NO_8$: C 42.40, H 7.47, N 4.94; Found: C 42.57, H 7.64, N 4.77.

N-[(2S,3R,4R,5R)-2,3,4,5,6-Pentahydroxylhex-1-yl]-L-tryptophane (4b)

Yield: 22%, colorless powders, Mp 206 - 207 °C. $[\alpha]_D^{25}$ = 10.0 (c 2.0, H_2O). IR (KBr): 3407, 3353, 3095, 2968, 2916, 1617, 1400, 1354, 1080, 1041, 742, 675, 534. ESI-MS (m/e): 369 $[M + H]^+$; ^1H NMR (D_2O): δ = 7.22 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.92 (s, 1H), 4.16 (m, *J* = 4.9 Hz, 1H), 3.90 (t, *J* = 5.0 Hz, 1H), 3.85 (m, *J* = 5.2 Hz, 1H), 3.83 (m, *J* = 5.3 Hz, 1H), 3.77 (m, *J* = 3.9 Hz, 1H), 3.71 (d, *J* = 5.3 Hz, 2H), 3.27 (dd, *J* = 3.6 Hz, *J* = 12.9 Hz, 1H), 3.20 (dd, *J* = 9.3 Hz, *J* = 12.9 Hz, 1H), 2.93 (d, *J* = 4.9 Hz, 2H). Anal Calcd for $C_{17}H_{24}N_2O_7$: C 55.43, H 6.57, N 7.60; Found: C55.25, H 6.39, N 7.76.

N-[(2S,3R,4R,5R)-2,3,4,5,6-Pentahydroxylhex-1-yl]-L-arginine (4c)

Yield: 28%, colorless powders, Mp 186 - 187 °C. $[\alpha]_D^{20}$= -65.0 (c 2.0, H_2O). IR (KBr): 3437, 3150, 2925, 2882, 1642, 1510, 1396, 1078, 1026, 905. ESI-MS (m/e): 339 $[M + H]^+$; ^1H NMR (D_2O): δ = 4.08 (m, *J* = 4.9 Hz, 1H), 3.82(m, *J* = 5.0 Hz, 1H), 3.79 (m, *J* = 5.1 Hz, 1H), 3.76 (m, *J* = 3.9 Hz, 1H), 3.65 (m, *J* = 5.2 Hz, 2H), 3.60 (t, *J* = 4.7 Hz, 1H), 3.29 (dd, *J* = 3.3 Hz, *J* = 12.5Hz, 1H), 3.18 (dd, *J* = 9.0 Hz, *J* = 12.6 Hz, 1H), 2.68 (t, *J* = 4.7 Hz, 2H), 1.66 (m, *J* = 4.6 Hz, 2H), 1.56 (m, *J* = 4.8 Hz, 2H). Anal Calcd for $C_{12}H_{26}N_4O_7$: C 42.60, H 7.75, N 16.56; Found: C 42.46, H 7.51, N 16.73.

Potassium N-[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxylhex-1-yl]-L-threonine dichrolo-platinate (II) (5a)

Yield: 83%, yellow powders, Mp 210 - 212 °C, $[a]_D^{20}$= -38.4 (c 1.6, H_2O). IR (KBr): 3428, 2926, 1645, 1385, 1323, 1080, 870. ESI-MS (m/e): 589 $[M + H]^+$; ^1H NMR (D_2O): δ = 4.22 (t, *J* = 6.5 Hz1H), 3.90 (dd, J = 3.0 Hz, , *J* = 8.0 Hz, 1H), 3.80 (dd, *J* = 2.0 Hz, *J* = 5.5 Hz, 1H), 3.78 (dd, *J* = 2.0 Hz, *J* = 5.0 Hz, 1H), 3.67 (m, *J* = 3.0 Hz, 2H), 3.65 (m, *J* = 6.5 Hz 1H), 3.28 (d, *J* = 8.0 Hz, 1H), 3.20 (dd, *J* = 2.5 Hz, *J* = 13.5 Hz, 1H), 3.07 (dd, *J* = 10.0 Hz, *J* = 13.5 Hz, 1H), 1.38 (d, *J* = 6.0 Hz, 3H). Anal Calcd for $C_{10}H_{20}Cl_2KNO_8Pt$: C, 20.45; H, 3.43; N, 2.38; Found: C, 20.24; H, 3.30; N, 2.64.

Potassium N-[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxylhex-1-yl]-L-tryptophane dichrolo-platinate (II) (5b)

Yield: 89%, yellow powders, Mp 226 - 229 °C. $[a]_D^{20}$= -15.3 (c 1.7, H_2O). IR (KBr): 3459, 3364, 2973, 2887, 1702, 1605, 1512, 1404, 1369, 1217, 1078, 775. ESI-MS (m/e): 671 $[M + H]^+$; ^1H NMR (D_2O): δ = 7.21 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.12 (t, *J* = 6.5 Hz, 1H), 6.89 (s, 1H), 4.10 (m, *J* = 5.0 Hz, 1H), 3.83 (t, *J* = 5.0 Hz, 1H), 3.79 (m, *J* = 5.5 Hz, 1H), 3.74 (m, *J* = 5.0 Hz, 1H), 3.70 (m, *J* = 4.5 Hz, 1H), 3.66 (d, *J* = 5.0 Hz, 2H), 3.24 (dd, *J* = 4.0 Hz, *J* = 11.0 Hz, 1H), 3.10 (dd, *J* = 9.0 Hz, *J* = 10.5 Hz, 1H), 2.86 (d, *J* = 5.0 Hz, 2H). Anal Calcd for $C_{17}H_{23}Cl_2KN_2O_7Pt$: C, 30.36; H, 3.45; N, 4.17; Found: C, 30.14; H, 3.31; N, 4.41.

Potassium N-[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxylhex-1-yl]-L-arginine dichrolo-platinate (II) (5c)

Yield: 88%, yellow powders, Mp 209 - 211 °C. $[a]_D^{20}$ = -83.7 (c 2.3, H_2O). IR (KBr): 3491, 3209, 2958, 2868, 1685, 1556, 1416, 1202, 1082, 903. ESI-MS (m/e): 643 $[M + H]^+$; ^1H NMR (D_2O): δ = 4.06 (m, *J* = 4.5 Hz, 1H), 3.91 (m, *J* = 5.0 Hz, 1H), 3.80 (m, *J* = 4.5 Hz, 1H), 3.76 (dd, *J* = 5.0 Hz, *J* = 6.5 Hz, 1H), 3.72 (m, *J* = 5.5 Hz, 1H), 3.65 (m, *J* = 4.5 Hz, 2H), 3.32 (m, *J* = 7.0 Hz, 1H), 3.18 (dd, *J* = 6.0 Hz, *J* = 11.0 Hz, 1H) 2.62 (t, *J* = 4.5 Hz, 2H), 1.63 (m, *J* = 4.0 Hz, 2H), 1.52 (m, *J* = 4.5 Hz, 2H). Anal Calcd for $C_{12}H_{25}C_{l2}KN_4O_7Pt$: C, 22.43; H, 3.92; N, 8.72; Found: C, 22.21; H, 3.80; N, 8.50.

Table S1 Platinum in the organs of the mice receiving **5a-c** [a]

Compd.	Spleen	Kidney	Liver	Brain	Heart
Cisplatin	6.03 ± 1.37	12.31 ± 3.97	11.81 ± 2.35	0.86 ± 0.25	1.67 ± 0.49
Oxaplatin	4.02 ± 0.95	5.56 ± 1.15	9.64 ± 1.55	0.49 ± 0.11	1.06 ± 0.27
5a	4.05 ± 1.06	4.86 ± 1.30 [c]	9.06 ± 1.15	0.19 ± 0.08 [b]	0.51 ± 0.22 [b]
5b	2.25 ± 0.36 [b]	3.56 ± 0.42 [b]	6.06 ± 1.05 [b]	0.08 ± 0.01 [b]	0.11 ± 0.02 [b]
5c	3.65 ± 0.93 [c]	8.23 ± 1.58 [c]	8.29 ± 1.18 [c]	0.43 ± 0.10 [c]	1.22 ± 0.22 [c]

a) Organ platinum is represented by $\bar{x}$ ±SD μg platinum per g of organ; Dose of cisplatin, oxaliplatin and **5a-c**: 1.67 μmol/kg; n = 10; b) Compare to cisplatin and oxaliplatin $p<0.01$; c) Compare to cisplatin $p<0.01$.

Table S2 Platinum in blood, bone and tumor of the mice receiving **5a-c** [a]

Compd.	Blood platinum	Femur platinum	Tumor platinum
Cisplatin	6.31 ± 1.10	19.12 ± 2.92	8.74 ± 2.23
Oxaplatin	5.64 ± 1.56	16.84 ± 2.19	7.04 ± 1.12
5a	3.37 ± 1.06 [d]	5.74 ± 1.31 [b]	7.45 ± 1.31
5b	1.38 ± 0.53 [b]	5.01 ± 1.74 [b]	8.87 ± 1.08 [c]
5c	1.30 ± 0.34 [b]	5.72 ± 0.92 [b]	5.84 ± 0.89 [d]

a) Bone or tumor platinum is represented by $\bar{x}$ ± SD μg platinum per g of bone or tumor; Blood platinum is represented by $\bar{x}$ ± SD μg platinum per mL of blood; NS (normal saline) = vehicle; Dose of cisplatin, oxaliplatin and **5a-c**: 1.67 μmol/kg; n=10; b) Compared to cisplatin and oxaliplatin $p<0.01$; c) Compared to oxaliplatin $p<0.05$; d) Compared to cisplatin $p<0.01$.

Table S3 Platinum in the urine and feces of the mice receiving **5a-c** [a]

Compd.	Urine platinum	Fecal platinum
Cisplatin	26.93 ± 3.93	6.34 ± 2.64
Oxaliplatin	122.39 ± 9.36	15.28 ± 2.95
5a	119.68 ± 5.84 [c]	31.41 ± 4.56 [b]
5b	163.60 ± 8.58 [b]	37.01 ± 4.13 [b]
5c	138.38 ± 7.82 [b]	28.05 ± 5.94 [b]

a) Urinary and fecal platinum is represented by $\bar{x}$ ± SD μg platinum per g of urine and fecas, n = 10; Dose of cisplatin, oxaliplatin and **5a-c**: 1.67 μmol/kg; b) Compared to cisplatin and oxaliplatin $p<0.01$; c) Compared to cisplatin $p<0.01$.