Supplementary Information

Development of Highly Effective Three-component Cytoprotective Adjuncts for Cisplatin Cancer Treatment: Synthesis and In Vivo Evaluation in S180-bearing Mice

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1. Experimental

1.1. General

All the synthetic reactions were carried out under N_2 protection (1 bar). ^1H spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers in D_2O with tetramethylsilane as an internal standard. IR spectra were recorded with a Perkin-Elmer 983 instrument. FAB/MS was determined on VG-ZAB-MS and TOF-MS was recorded on MDS SCIEX QSTAR. Melting points were measured on a XT5 hot stage microscope (Beijing key electro-optic factory). All L-amino acids and α-D-glucose were purchased from China Biochemical Corp. TLC plates were prepared with Qingdao silica gel GF254. Column chromatography was conducted with Qingdao silica gel H60 or Sephadex-LH20. All solvents were distilled and dried before use. Optical rotations were measured on a Jasco P-1020 Polarimeter at 20 ºC. The statistical analysis of all the biological data was carried out by ANOVA test, $p<0.05$ is considered significant.

1.2 Chemical synthesis

1.2.1 General procedure for preparing *N*-(2,3,4,5,6-pentahydroxyhexyl)-*L*-amino acids (2a-s)

To a solution of NaOH (10 mmol) in 3 mL of methanol/water (1:1) was added L-amino acid **1a-s** (10 mmol) at room temperature. The mixture was stirred for 20 min and amino acid was completely dissolved. D-glucose (1.80 g, 10 mmol) was then added, and the resulting mixture was heated at 50 - 60 °C for 5 h under N_2 protection. The reaction solution was then cooled down to room temperature, and $NaBH_4$ (1.62 g, 30 mmol) was added, and stirred for another 96 h. The reaction mixture was then cooled to 0 °C and adjusted to pH 2.5 by aq. HCl (37%). The resulting precipitate was removed by filtration and the filtrate was partially concentrated to 0.5 mL under vacuum. To the concentrated solution was added 2.5 mL of ethanol, the resulting precipitates were removed by filtration and the filtrate was concentrated again. This procedure was repeated for 5 times and the final filtrate was dissolved in 10 mL of water. The solution was loaded on an acidic ion exchange column and eluted with 3% aqueous *N*-methylmorpholine solution to give the title compounds **2a-s** as colorless powder after lyophilization. Any water remaining in the synthetic products, including crystal water in the recrystalized products, was removed by drying the substances at 80 °C for 48 h under vacuum. The dried samples were used in obtaining all physical chemical (including elemental analyses) data as well as biological data

1.2.1.1. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-aspartic acid (2a)

Yield: 15%. Mp: 171 - 173 °C (wax-like product*). $[\alpha]^{20}_D$ = -20.0 (c = 2.3, H_2O), ESI/MS (m/e) 298 $[M + H]^+$, IR (KBr) 3569, 3366, 3233, 2894, 2367, 1730,

1617, 1559, 1397, 1175, 1087, 826, 676, 610. Anal Calcd for $C_{10}H_{19}NO_9$: C 44.40, H 6.44, N 4.71; Found: C 44.58, H 6.30, N 4.86.

1.2.1.2. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-glutamic acid (2b)

Yield: 21%. Mp: 151 - 153 °C(94 °C*). $[\alpha]^{20}_D$ = -45.0 (c = 2.1, H_2O), ESI/MS (m/e) 312 $[M + H]^+$, IR (KBr) 3407, 3352, 3094, 2967, 2916, 1617, 1400, 1354, 1080, 1041, 741, 675, 534. Anal Calcd for $C_{11}H_{21}NO_9$: C 42.44, H 6.80, N 4.50; Found: C 42.60, H 6.95, N 4.38.

1.2.1.3. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-threonine (2c)

Yield: 25%. Mp: 195 - 197 °C (219 °C*). $[\alpha]^{20}_D$ = -19.0 (c = 2.2, H_2O), ESI/MS (m/e) 284 $[M + H]^+$, IR (KBr) 3421, 2975, 2939, 1612, 1571, 1415, 1385, 1084, 1045, 841, 756, 731. 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.

1.2.1.4. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-tyrosine (2d)

Yield: 21%. Mp: 239 - 240 °C (resin-like product*). $[\alpha]^{20}_D$ = -50.0 (c = 2.0, H_2O), ESI/MS (m/e) 346 $[M + H]^+$, IR (KBr) 3353, 3307, 3085, 2968, 2916, 1605, 1560, 1458, 1400, 1354, 1080, 1041, 742, 675, 534. Anal Calcd for $C_{15}H_{23}NO_8$: C 52.17, H 6.71, N 4.06; Found: C 52.33, H 6.90, N 3.95.

1.2.1.5. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-serine (2e)

Yield: 24%. Mp: 195 - 197 °C (resin form*). $[\alpha]^{20}_D$ = -31.0 (c = 2.1, H_2O), ESI/MS (m/e) 270 $[M + H]^+$, IR (KBr) 3222, 2941, 2901, 1621, 1565, 1424, 1337, 1093, 1040, 706. Anal Calcd for $C_9H_{19}NO_8$: C 40.15, H 7.11, N 5.20; Found: C 40.01, H 6.98, N 5.37.

1.2.1.6. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-asparagine (2f)

Yield: 23%. Mp: 240 - 241 °C. $[\alpha]^{20}_{D}$ = -20.0 (c = 2.2, H_2O), ESI/MS (m/e) 297 $[M + H]^+$, IR (KBr) 3407, 3353, 3095, 2968, 2916, 1687, 1400, 1354, 1080, 1041, 742, 675, 534. Anal Calcd for $C_{10}H_{20}N_2O_8$: C 40.54, H 6.80, N 9.46; Found: C 40.68, H 6.95, N 9.33.

1.2.1.7. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-glutamine (2g)

Yield: 18%. Mp: 251 - 253 °C. $[\alpha]^{20}_{D}$ = -23.0 (c = 2.3, H_2O), ESI/MS (m/e) 311 $[M + H]^+$, IR (KBr) 3402, 3350, 3088, 2968, 2917, 1685, 1405, 1352, 1084, 1040, 743, 698. Anal Calcd for $C_{11}H_{22}N_2O_8$: C 42.58, H 7.15, N 9.03; Found: C 42.68, H 6.95, N 9.33.

1.2.1.8. *N*-(2,3,4,5,6-Pentahydroxyhexyl)glycine (2h)

Yield: 36%. Mp: 182 - 183 °C (172 - 177 °C*). $[\alpha]^{20}_{D}$ = -40.0 (c = 2.3, H_2O), ESI/MS (m/e) 240 $[M + H]^+$, IR (KBr) 3532, 3242, 2963, 2897, 2365, 1627, 1561, 1402, 1378, 1061, 1037, 848, 691, 579. Anal Calcd for $C_8H_{17}NO_7$: C 40.17, H 7.16, N 5.86; Found: C 40.00, H 6.99, N 5.71.

1.2.1.9. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-cysteine (2i)

Yield: 45%. Mp: 171 - 172 °C(resin-like product*). $[\alpha]^{20}_{D}$ = -33.0 (c = 2.1, H_2O), ESI/MS (m/e) 286 $[M + H]^+$, IR (KBr) 3275, 2975, 2936, 1607, 1567, 1417, 1391, 1082, 1036, 695, 632. Anal Calcd for $C_9H_{19}NO_7S$: C 37.89, H 6.71, N 4.91; Found: C 38.04, H 6.55, N 4.76.

1.2.1.10. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-methionine (2j)

Yield: 41%. Mp: 197 - 199 °C. $[\alpha]^{20}_{D}$ = -57.0 (c = 2.0, H_2O), ESI/MS (m/e) 314 $[M + H]^+$, IR (KBr) 3464, 3431, 3291, 3117, 2930, 2340, 1601, 1554, 1433, 1398, 1089, 849, 692. Anal Calcd for $C_{10}H_{21}NO_7S$: C 40.12, H 7.07, N 4.68; Found: C 40.00, H 6.93, N 4.83.

1.2.1.11. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-alanine (2k)

Yield: 30%. Mp 201 - 202 °C, $[\alpha]^{20}_{D}$ = -20.0 (c = 2.3, H_2O), ESI/MS (m/e) 254 $[M + H]^+$, IR (KBr) 3420, 3273, 2973, 2905, 1622, 1587, 1424, 1400, 1083, 1038, 704, 668. Anal Calcd for $C_9H_{19}NO_7$: C 42.68, H 7.56, N 5.53; Found: C 42.86, H 7.72, N 5.70.

1.2.1.12. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-phenylalanine (2l)

Yield: 24%. Mp 205 - 207 °C, $[\alpha]^{20}_{D}$ = -60.0 (c = 2.1, H_2O), ESI/MS (m/e) 330 $[M + H]^+$, IR (KBr) 3423, 3271, 2975, 2902, 1621, 1586, 1426, 1402, 1086, 1035, 706, 665. Anal Calcd for $C_{15}H_{23}NO_7$: C 54.70, H 7.04, N 4.25; Found: C 54.88, H 7.19, N 4.09.

1.2.1.13. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-leucine (2m)

Yield: 53%. Mp: 207 - 208 °C. $[\alpha]^{20}_{D}$ = -40.0 (c = 2.2, H_2O), ESI/MS (m/e) 296 $[M + H]^+$, IR (KBr) 3365, 3097, 2962, 2924, 1616, 1432, 1374, 1294, 1083, 1044, 761, 677. Anal Calcd for $C_{12}H_{25}NO_7$: C 48.80, H 8.53, N 4.74; Found: C 48.73, H 8.39, N 4.92.

1.2.1.14. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-isoleucine (2n)

Yield: 42%. Mp: 228 - 230 °C. $[\alpha]^{20}_{D}$ = -12.8 (c = 2.4, H_2O), ESI/MS (m/e) 296 $[M + H]^+$, IR (KBr) 3365, 3097, 2962, 2924, 1616, 1432, 1374, 1294, 1083, 1044,

761, 677. Anal Calcd for $C_{12}H_{25}NO_7$: C 48.80, H 8.53, N 4.74; Found: C 48.95, H 8.76, N 4.56.

1.2.1.15. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-tryptophane (2o)

Yield: 22%. Mp: 206 - 207°C. $[\alpha]^{20}_D$ = 10.0 (c = 2.1, H_2O), ESI/MS (m/e) 369 $[M + H]^+$, IR (KBr) 3407, 3353, 3095, 2968, 2916, 1617, 1400, 1354, 1080, 1041, 742, 675, 534. Anal Calcd for $C_{17}H_{24}N_2O_7$: C 55.43, H 6.57, N 7.60; Found: C 55.25, H 6.39, N 7.76.

1.2.1.16. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-valine (2p)

Yield: 19%. Mp 216 - 217 °C, $[\alpha]^{20}_D$ = -35.0 (c = 2.2, H_2O), ESI/MS (m/e) 282 $[M + H]^+$, IR (KBr) 3339, 3186, 2972, 2940, 2362, 1603, 1551, 1421, 1318, 1080, 1035, 825, 695, 617. Anal Calcd for $C_{11}H_{23}NO_7$: C 46.97, H 8.24, N 4.98; Found: C46.98, H 8.22, N 4.96.

1.2.1.17. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-lysine (2q)

Yield: 27%. Mp: 147 - 148 °C (wax-like product*). $[\alpha]^{20}_D$ = -40.0 (c = 2.3, H_2O), ESI/MS (m/e) 497 $[M + H]^+$, IR (KBr) 3567, 3370, 3231, 2921, 2884, 1728, 1610, 1558, 1455, 1175, 1057, 1023, 829, 792, 614. Anal Calcd for $C_{18}H_{37}N_2NaO_{12}$: C, 43.54; H, 7.51; N, 5.64; Found: C 43.60, H 7.52, N 5.66.

1.2.1.18. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-arginine (2r)

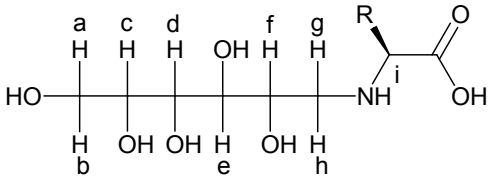
Yield: 28%. Mp: 186 - 188 °C (light-yellow resin*). $[\alpha]^{20}_D$ = -65.0 (c = 2.1, H_2O), ESI/MS (m/e) 339 $[M + H]^+$, IR (KBr) 3437, 3150, 2925, 2882, 1642, 1510, 1396, 1078, 1026, 905. Anal Calcd for $C_{12}H_{26}N_4O_7$: C 42.60, H 7.75, N 16.56; Found: C 42.46, H 7.51, N 16.73.

1.2.1.19. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*L*-histidine (2s)

Yield: 28%. Mp: 233 - 235 °C (brownish resin*). $[\alpha]^{20}_{D}$ = -130.0 (c = 2.2, H_2O), ESI/MS (m/e) 320 $[M + H]^+$, IR (KBr) 3443, 3337, 3125, 2910, 1618, 1448, 1398, 1112, 1057, 1016, 957, 620. Anal Calcd for $C_{12}H_{21}N_3O_7$: C 45.14, H 6.63, N 13.16; Found: C 45.46, H 6.67, N 13.23.

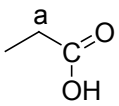
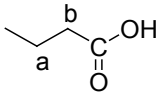
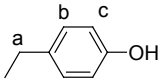
* The melting points in the brackets were from Heins et al., US Patent 4,032,676, June 28, 1977. The ^{1}H NMR signals of **2a-s** were assigned in Table 1.

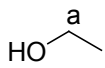
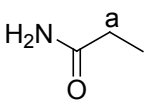
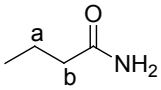
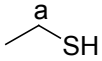
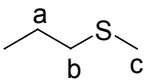
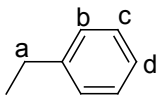
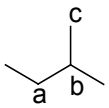
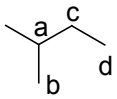
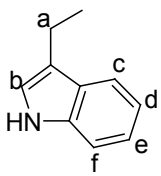
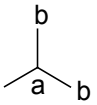
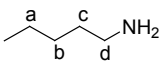
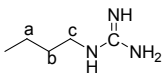
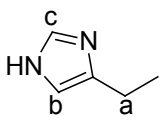
Table 1 ^{1}H NMR signals of **2a-s**



Compd.	Ha	Hb	Hc	Hd	He	Hf	Hg	Hh	Hi
2a	3.75 (m, *J* = 3.6 Hz, 1H)	4.15 (m, *J* = 4.6 Hz, 1H)	3.65 (m, *J* = 4.1 Hz, 1H)	3.37 (dd, *J* = 3.5 Hz, *J* = 13.0 Hz, 1H)	3.28 (dd, *J* = 9.0 Hz, *J* = 13.0 Hz, 1H)	3.81 (dd, *J* = 3.0 Hz, *J* = 12.0 Hz, 1H)	4.03 (dd, *J* =5.0 Hz, *J* = 7.0 Hz, 1H)	3.86 (dd, *J* = 3.0 Hz, *J* = 5.0 Hz, 1H)	3.84 (m, *J* = 5.1Hz, 1H)
2b	3.63(m, *J* = 4.0 Hz 1H)	4.12 (m, *J* = 4.4 Hz, 1H)	3.55 (t, *J* = 4.5 Hz, 1H)	3.24(dd, *J* = 3.4 Hz, *J* = 12.7 Hz, 1H)	3.11 (dd, *J* = 8.7 Hz, *J* = 12.8 Hz, 1H)	3.63(m, *J* = 4.0 Hz 1H)	3.82 (dd, *J* = 3.3 Hz, *J* = 5.0 Hz, 1H)	3.77 (dd, *J* = 3.5 Hz, *J* = 12.0 Hz, 1H)	3.72 (m, *J* = 3.4 Hz, 1H)
2c	3.57(d, *J* = 4.7 Hz, 1H)	4.12 (m, *J* = 4.6 Hz, 1H)	3.64 (m, *J* = 4.1 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)	3.26 (dd, *J* = 3.1 Hz, *J* = 13.0 Hz, 1H)	3.12 (dd, *J* = 10.1 Hz, *J* = 13.0 Hz, 1H)	3.64 (m, *J* = 4.1 Hz, 1H)
2d	3.63 (m, *J* = 4.0 Hz, 1H)	4.10 (m, *J* = 4.7 Hz, 1H)	3.63 (m, *J* = 4.0 Hz, 1H)	3.80 (m, *J* = 4.7 Hz, 1H)	3.78 (m, *J* = 3.5 Hz, 1H)	3.73 (m, *J* = 3.5 Hz, 1H)	3.23 (dd, *J* = 3.1 Hz, *J* = 13.0 Hz, 1H)	3.14 (dd, *J* = 3.1 Hz, *J* = 13.0 Hz, 1H)	3.90 (t, *J* = 5.4 Hz, 1H)
2e	3.88 (d, *J* = 5.5 Hz, 1H)	4.12 (m, *J* = 4.6 Hz, 1H)	3.62 (t, *J* = 5.5 Hz, 1H)	3.88 (d, *J* = 5.5 Hz, 1H)	3.75 (dd, *J* = 1.0 Hz, *J* = 3.0 Hz, 1H)	3.82 (dd, *J* = 5.0 Hz, *J* = 12.5 Hz, 1H)	3.26 (dd, *J* = 3.0 Hz, *J* = 13.0 Hz, 1H)	3.14 (dd, *J* = 10.0 Hz, *J* = 13.0 Hz, 1H)	3.80 (t, *J* = 2.5 Hz, 1H)
2f	3.75 (t, *J* = 5.2 Hz, 1H)	4.14 (m, *J* = 4.3 Hz, 1H)	3.67 (m, *J* = 4.0 Hz, 1H)	3.81 (dd, *J* = 3.2 Hz, *J* = 5.2 Hz, 1H)	3.79 (dd, *J* = 3.3 Hz, *J* = 11.7 Hz, 1H)	3.72 (m, *J* = 3.5 Hz, 1H)	3.27 (dd, *J* = 3.4 Hz, *J* = 12.6 Hz, 1H)	3.14 (dd, *J* = 9.1 Hz, *J* = 12.7 Hz, 1H)	3.83 (dd, *J* = 5.1 Hz, *J* = 7.2 Hz, 1H)
2g	3.61 (m, *J* = 4.1 Hz, 1H)	4.10 (m, *J* = 4.4 Hz, 1H)	3.71 (m, *J* = 3.6 Hz, 1H)	3.52 (t, *J* = 5.1 Hz, 1H)	3.78 (dd, *J* = 3.3 Hz, *J* = 5.0 Hz, 1H)	3.74 (dd, *J* = 3.4 Hz, *J* = 11.5 Hz, 1H)	3.26 (dd, *J* = 3.5 Hz, *J* = 12.3 Hz, 1H)	3.12 (dd, *J* = 9.0 Hz, *J* = 12.5 Hz, 1H)	3.80 (dd, *J* = 5.0 Hz, *J* = 7.0 Hz, 1H)
2h	3.65 (d, *J* = 5.2 Hz, 1H)	4.11(m, *J* = 4.5 Hz, 1H)	3.65 (d, *J* = 5.2 Hz, 1H)	3.79 (m, *J* = 5.2 Hz, 1H)	3.76 (m, *J* = 3.6 Hz, 1H)	3.73 (m, *J* = 3.5 Hz, 1H)	3.26 (dd, *J* = 3.5 Hz, *J* = 13.0 Hz, 1H)	3.13 (dd, *J* = 9.5 Hz, *J* = 13.0 Hz, 1H)	3.56 (s, 1H)

2i	3.69 (m, *J* = 4.2 Hz, 1H)	4.16 (m, *J* = 4.6 Hz, 1H)	3.69 (m, *J* = 4.2 Hz, 1H)	3.81 (dd, *J* = 3.0 Hz, *J* = 12.0 Hz, 1H)	3.86 (dd, *J* = 3.0 Hz, *J* = 4.5 Hz, 1H)	3.76 (m, *J* = 4.2 Hz, 1H)	3.27 (dd, *J* = 9.5 Hz, *J* = 13.0 Hz, 1H)	3.16 (dd, *J* = 5.0 Hz, *J* = 18.0 Hz, 1H)	3.97 (t, *J* = 5.0 Hz, 1H)
2j	3.65 (d, *J* = 5.0 Hz, 1H)	4.10 (m, *J* = 4.5 Hz, 1H)	3.50 (t, *J* = 7.0 Hz, 1H)	3.81 (m, *J* = 4.2 Hz, 1H)	3.81 (m, *J* = 4.2 Hz, 1H)	3.76 (m, *J* = 3.5 Hz, 1H)	3.23 (dd, *J* = 3.0 Hz, *J* = 13.0 Hz, 1H)	3.12 (dd, *J* = 10.0 Hz, *J* = 13.0 Hz, 1H)	3.79 (t, *J* = 3.0 Hz, 1H)
2k	3.70 (d, *J* = 5.0 Hz, 1H)	4.14 (m, *J* = 4.3 Hz, 1H)	3.68 (m, *J* = 5.6 Hz, 1H)	3.81 (m, *J* = 5.0 Hz, 1H)	3.81 (m, *J* = 5.0 Hz, 1H)	3.79 (m, *J* = 3.4 Hz, 1H)	3.30 (dd, *J* = 3.4 Hz, *J* = 12.7 Hz, 1H)	3.22 (dd, *J* = 9.2 Hz, *J* = 12.4 Hz, 1H)	3.84 (m, *J* = 5.1 Hz, 1H)
2l	3.66 (m, *J* = 5.4 Hz, 1H)	4.16 (m, *J* = 4.5 Hz, 1H)	3.66 (m, *J* = 5.4 Hz, 1H)	3.84 (m, *J* = 5.2 Hz, 1H)	3.81 (m, *J* = 3.6 Hz, 1H)	3.76 (d, *J* = 4.8 Hz, 1H)	3.28 (dd, *J* = 3.5 Hz, *J* = 12.4 Hz, 1H)	3.16 (dd, *J* = 9.0 Hz, *J* = 12.1 Hz, 1H)	4.07 (m, *J* = 5.3 Hz, 1H)
2m	3.66 (m, *J* = 5.4 Hz, 1H)	4.02 (m, *J* = 4.6 Hz, 1H)	3.66 (m, *J* = 5.4 Hz, 1H)	3.81 (m, *J* = 4.7 Hz, 1H)	3.75 (m, *J* = 5.0 Hz, 1H)	3.68 (t, *J* = 6.0 Hz, 1H)	3.26 (dd, *J* = 3.0 Hz, *J* = 13.0 Hz, 1H)	3.14 (dd, *J* = 10.0 Hz, *J* = 13.0 Hz, 1H)	3.80 (m, *J* = 3.8 Hz, 1H)
2n	3.65 (m, *J* = 5.3 Hz, 1H)	4.04 (m, *J* = 4.5 Hz, 1H)	3.55 (d, *J* = 4.2 Hz, 1H)	3.80 (m, *J* = 3.7 Hz, 1H)	3.77 (m, *J* = 5.1 Hz, 1H)	3.71 (t, *J* = 5.8 Hz, 1H)	3.26 (dd, *J* = 3.2 Hz, *J* = 13.1 Hz, 1H)	3.20 (dd, *J* = 9.8 Hz, *J* = 12.6 Hz, 1H)	3.83 (m, *J* = 4.8 Hz, 1H)
2o	3.71 (d, *J* = 5.3 Hz, 1H)	4.16 (m, *J* = 4.9 Hz, 1H)	3.71 (d, *J* = 5.3 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)	3.27 (dd, *J* = 3.6 Hz, *J* = 12.9 Hz, 1H)	3.20 (dd, *J* = 9.3 Hz, *J* = 12.9 Hz, 1H)	3.90 (t, *J* = 5.0 Hz, 1H)
2p	3.67 (m, *J* = 4.2 Hz, 1H)	4.03 (m, *J* = 4.9 Hz, 1H)	3.67 (m, *J* = 4.2 Hz, 1H)	3.79 (m, *J* = 4.7 Hz, 1H)	3.77 (m, *J* = 3.9 Hz, 1H)	3.65 (dd, *J* = 4.5 Hz, *J* = 16.0 Hz, 1H)	3.22 (dd, *J* = 3.0 Hz, *J* = 13.0 Hz, 1H)	3.13 (dd, *J* = 10.0 Hz, *J* = 13.0 Hz, 1H)	3.80 (m, *J* = 5.1 Hz, 1H)
2q	3.74 (m, *J* = 3.8 Hz, 1H)	4.07 (m, *J* = 4.6 Hz, 1H)	3.67 (m, *J* = 5.0 Hz, 1H)	3.78 (m, *J* = 5.2 Hz, 1H)	3.78 (m, *J* = 5.2 Hz, 1H)	3.60 (d, *J* = 4.5 Hz, 1H)	3.27 (dd, *J* = 3.6 Hz, *J* = 12.6 Hz, 1H)	3.15 (dd, *J* = 9.2 Hz, *J* = 12.4 Hz, 1H)	3.80 (m, *J* = 5.2 Hz, 1H)
2r	3.65 (m, *J* = 5.2 Hz, 1H)	4.08 (m, *J* = 4.9 Hz, 1H)	3.65 (m, *J* = 5.2 Hz, 1H)	3.79 (m, *J* = 5.1 Hz, 1H)	3.76 (m, *J* = 3.9 Hz, 1H)	3.60 (t, *J* = 4.7 Hz, 1H)	3.29 (dd, *J* = 3.3 Hz, *J* = 12.5 Hz, 1H)	3.18 (dd, *J* = 9.0 Hz, *J* = 12.6 Hz, 1H)	3.82 (m, *J* = 5.0 Hz, 1H)
2s	3.66 (m, *J* = 5.1 Hz, 1H)	4.11 (m, *J* = 4.7 Hz, 1H)	3.66 (m, *J* = 5.1 Hz, 1H)	3.84 (m, *J* = 5.1 Hz, 1H)	3.82 (m, *J* = 5.3 Hz, 1H)	3.78 (m, *J* = 4.2 Hz, 1H)	3.26 (dd, *J* = 3.5 Hz, *J* = 12.7 Hz, 1H)	3.17 (dd, *J* = 9.1 Hz, *J* = 12.4 Hz, 1H)	3.91 (t, *J* = 5.3 Hz, 1H)

Compd.	R	Ha	Hb	Hc	Hd	He	Hf
2a		3.08 (dd, *J* = 5.0 Hz, *J* = 18.0 Hz, 1H)	3.01 (dd, *J* = 7.0 Hz, *J* = 18.0 Hz, 1H)				
2b		2.00 (m, *J* = 4.8 Hz, 2H)	2.26 (d, *J* = 5.0 Hz, 2H)				
2c		3.95 (d, *J* = 4.5 Hz, 1H)	1.24 (d, *J* = 4.7 Hz, 3H)				
2d		3.00 (d, *J* = 4.5 Hz, 2H)	7.02 (d, *J* = 7.0 Hz, 2H)	6.78 (d, *J* = 7.1 Hz, 2H)			

2e		3.66 (m, *J* = 4.0 Hz, 2H)					
2f		2.58 (d, *J* = 5.2 Hz, 2H)					
2g		2.00 (m, *J* = 5.0 Hz, 1H)	2.02 (m, *J* = 5.3 Hz, 1H)	2.24 (t, *J* = 5.0 Hz, 2H)			
2h		3.56 (s, 1H)					
2i		3.08 (d, *J* = 5.0 Hz, 2H)					
2j		2.09 (m, 2H)	2.55 (t, *J* = 4.2 Hz, 2H)	2.13 (s, 3H)			
2k		1.26 (d, *J* = 5.6 Hz, 3H)					
2l		2.93 (d, *J* = 5.3 Hz, 2H)	7.14 (d, *J* = 7.4 Hz, 2H)	7.22 (t, *J* = 7.6 Hz, 2H)	7.10 (t, *J* = 7.5 Hz, 1H)		
2m		1.70 (m, *J* = 3.7 Hz, 2H)	1.72 (m, *J* = 4.1 Hz, 1H)	0.95 (dd, *J* = 3.0 Hz, *J* = 6.0 Hz, 6H)			
2n		2.35 (m, *J* = 4.2 Hz, 1H)	1.10 (d, *J* = 3.6 Hz, 3H)	1.33 (m, *J* = 3.7 Hz, 2H)	0.92 (dd, *J* = 3.2 Hz, *J* = 6.3 Hz, 3H)		
2o		2.93 (d, *J* = 4.9 Hz, 2H)	6.92 (s, 1H)	7.16 (t, *J* = 7.8 Hz, 1H)	7.14 (t, *J* = 7.7 Hz, 1H)	7.20 (d, *J* = 7.5 Hz, 1H)	7.22 (d, *J* = 7.5 Hz, 1H)
2p		2.38 (m, *J* = 4.6 Hz, 1H)	1.05 (dd, *J* = 7.0 Hz, *J* = 16.0 Hz, 6H)				
2q		1.68 (m, *J* = 4.4 Hz, 2H)	1.32 (m, *J* = 4.7 Hz, 2H)	1.57 (m, *J* = 4.9 Hz, 2H)	2.70 (t, *J* = 4.9 Hz, 2H)		
2r		1.66 (m, *J* = 4.6 Hz, 2H)	1.56 (m, *J* = 4.8 Hz, 2H)	2.68 (t, *J* = 4.7 Hz, 2H)			
2s		2.88 (d, *J* = 5.3 Hz, 2H)	6.81 (s, 1H)	7.46 (s, 1H)			

1.2.2 General procedure for preparing *N*-(2,3,4,5,6-pentahydroxyhexyl)-*N*-dithiocarbamate amino acid disodium (3a-s)

To the suspension of *N*-(2,3,4,5,6-pentahydroxyhexyl)-amino acid **2a-s** (1.0 mmol) in 7 mL of water at 0 ºC were added NaOH (140 mg, 4.0 mmol), CS_2 (304 mg, 4.0 mmol), and 0.4 mL of dioxane. The reaction mixture was stirred at 0ºC for 24 h. The reaction mixture was then filtered and the filtrate was concentrated under vacuum. The resulting residue was recrystallized in aqueous acetone to give the title compou-nds **3a-s** as yellow powder. Any water remaining in the synthetic products, including crystal water in the recrystalized products, was removed by drying the substances at 80 °C for 48 h under vacuum. The dried samples were used in obtaining biological data.

1.2.2.1. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-aspartic acid trisodium (3a)

Yield: 86%. Mp: 90 - 91 °C. $[\alpha]^{20}_{D}$ = -8.6 (c = 2.8, H_2O), ESI/MS (m/e) 418 [M + H]$^+$, IR (KBr) 3346, 2950, 2894, 1730, 1602, 1548, 1395,1290, 1210, 1079, 830, 690. Anal Calcd for $C_{11}H_{16}NNa_3O_9S_2$: C, 30.07; H, 3.67; N, 3.19; Found: C, 30.30; H, 3.81; N, 2.99.

1.2.2.2. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-glutamic acid trisodium (3b)

Yield: 97%. Mp: 87 - 88 °C. $[\alpha]^{20}_{D}$ = -1.3 (c = 2.8, H_2O), ESI-MS (m/e) 455 [M + H]$^+$, IR (KBr) 3329, 3051, 2967, 2912, 1720, 1624, 1594, 1410, 1394, 1352, 1092,

1061, 852, 664, 528. Anal Calcd for $C_{12}H_{18}NNa_3O_9S_2$: C 31.79, H 4.00, N 3.09; Found: C 31.61, H 4.17, N 3.32.

1.2.2.3. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-threonine disodium (3c)

Yield: 91%. Mp: 86 - 87 °C $[\alpha]^{20}_D$ = -32.3 (c = 2.8, H_2O), ESI-MS (m/e) 406 $[M + H]^+$. IR (KBr) 3356, 2952, 2831, 1726, 1616, 1571, 1465, 1382, 1230, 1195, 1080, 1045, 861, 721. Anal Calcd for $C_{11}H_{19}NNa_2O_8S_2$: C, 32.75; H, 4.75; N, 3.47; Found: C, 32.53; H, 4.61; N, 3.72.

1.2.2.4. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-tyrosine disodium (3d)

Yield: 90%. Mp: 103 - 105 °C. $[\alpha]^{20}_D$ = -17.6 (c = 2.2, H_2O), ESI-MS (m/e) 490 $[M + H]^+$. IR (KBr) 3302, 3055, 2972, 2863, 1600, 1498, 1402, 1362,1200, 1152, 1081, 1041, 768, 680. Anal Calcd for $C_{16}H_{20}NNa_3O_8S_2$: C, 39.43; H, 4.14; N, 2.87; Found: C, 39.22; H, 4.00; N, 3.11.

1.2.2.5. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-serine disodium (3e)

Yield: 90%. Mp: 103 - 105 °C. $[\alpha]^{20}_D$ = -36.4 (c = 2.5, H_2O), ESI-MS (m/e) 390 $[M + H]^+$. IR (KBr) 3390, 2940, 2860, 1610, 1550, 1420, 1355, 1220, 1148, 1063, 730. Anal Calcd for $C_{10}H_{17}NNa_2O_9S_2$: C, 30.85; H, 4.40; N, 3.60; Found: C, 31.04; H, 4.55; N, 3.83.

1.2.2.6. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-asparagine disodium (3f)

Yield: 88%. Mp: 93 - 95 °C. $[\alpha]^{20}_{D}$ = -9.9 (c = 2.5, H_2O), ESI-MS (m/e) 418 [M + H]$^+$. IR (KBr) 3382, 2952, 2826, 1687,1605,1460, 1402, 1352, 1206, 1072, 793, 650. Anal Calcd for $C_{11}H_{18}N_2Na_2O_8S_2$: C, 31.73; H, 4.36; N, 6.73; Found: C, 31.51; H, 4.20; N, 6.95.

1.2.2.7. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-glutamine disodium (3g)

Yield: 85%. Mp: 89 - 91 °C. $[\alpha]^{20}_{D}$ = -10.7 (c = 1.3, H_2O), ESI-MS (m/e) 431 [M + H]$^+$. IR (KBr) 3368, 3052, 2964, 2845, 1615, 1402, 1360, 1203, 1146, 1079, 1002, 752, 685. Anal Calcd for $C_{12}H_{20}N_2Na_2O_8S_2$: C, 33.49; H, 4.68; N, 6.51; Found: C, 33.68; H, 4.84; N, 6.76.

1.2.2.8. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-glycine disodium (5h)

Yield: 84%. Mp: 95 - 97 °C. $[\alpha]^{20}_{D}$ = -20.9 (c = 4.3, H_2O), ESI-MS (m/e) 360 [M + H]$^+$. IR (KBr) 3374, 2921, 2885, 2365, 1600, 1456, 1381, 1381, 1310, 1212, 1173, 1080, 969, 870, 717. Anal Calcd for $C_9H_{15}NNa_2O_7S_2$: C, 30.08; H, 4.21; N, 3.90; Found: C, 30.26; H, 4.35; N, 3.71.

1.2.2.9. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-cysteine disodium (3i)

Yield: 88%. Mp: 87 - 89 °C. $[\alpha]^{20}_{D}$ = -23.4 (c = 2.6, H_2O), ESI-MS (m/e) 407 [M + H]$^+$. IR (KBr) 3346, 2950, 2836, 1604, 1560, 1420, 1385, 1210, 1084, 1032, 749, 650. Anal Calcd for $C_{10}H_{17}NNa_2O_7S_3$: C 29.63, H 4.23, N 3.45; Found: C 29.42, H 4.09, N 3.64.

1.2.2.10. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-methionine disodium (3j)

Yield: 90%. Mp: 99 - 101 °C. $[\alpha]^{20}_{D}$ = -0.8 (c = 2.9, H_2O), ESI-MS (m/e) 435 $[M + H]^+$. IR (KBr) 3398, 3017, 2930, 2840, 1706, 1608, 1557, 1440, 1372, 1092, 850, 762, 682. Anal Calcd for $C_{12}H_{21}NNa_2O_7S_3$: C, 33.25; H, 4.88; N, 3.23; Found: C, 33.64; H, 4.73; N, 3.45.

1.2.2.11. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-alanine disodium (3k)

Yield: 94%. Mp: 93 - 94 °C. $[\alpha]^{20}_{D}$ = -24.4 (c = 2.6, H_2O), ESI-MS (m/e) 374 $[M+H]^+$. IR (KBr) 3315, 2927, 2829, 1590, 1420, 1396, 1365, 1302, 1257, 1176, 1075, 1011, 957, 762, 648. Anal Calcd for $C_{10}H_{17}NNa_2O_7S_2$: C 32.17, H 4.59, N 3.75; Found: C 32.00, H 4.43, N 3.52.

1.2.2.12. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-phenylalanine disodium (3l)

Yield: 84%. Mp: 103 - 104 °C. $[\alpha]^{20}_{D}$ = -37.2 (c = 2.9, H_2O), ESI-MS (m/e) 450 $[M + H]^+$. IR (KBr) 3373, 2969, 2835, 1703, 1618, 1595, 1435, 1401, 1382, 1263, 1086, 1026, 785, 682. Anal Calcd for $C_{16}H_{21}NNa_2O_7S_2$: C 42.76, H 4.71, N 3.12; Found: C 42.97, H 4.88, N 3.35.

1.2.2.13. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-leucine disodium (3m)

Yield: 93%. Mp: 113 - 114 °C. $[\alpha]^{20}_{D}$ = -8.9 (c = 3.2, H_2O), ESI-MS (m/e) 417 $[M + H]^+$. IR (KBr) 3382, 2962, 2841, 1612, 1440, 1382, 1364, 1294, 1146, 1083,

1030, 770, 642. Anal Calcd for $C_{13}H_{23}NNa_2O_7S_2$: C 37.58, H 5.58, N 3.37; Found: C 37.36, H 5.42, N 3.59.

1.2.2.14. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-isoleucine disodium (3n)

Yield: 88%. Mp: 109 - 111 °C. $[\alpha]^{20}_D$ = -9.2 (c = 2.6, H_2O), ESI-MS (m/e) 416 $[M + H]^+$. IR (KBr) 3331, 2954, 2860, 1602, 1434, 1375, 1320, 1286, 1152, 1064, 1025, 789, 633. Anal Calcd for $C_{13}H_{23}NNa_2O_7S_2$: C 37.58, H 5.58, N 3.37; Found: C 37.39, H 5.41, N 3.61.

1.2.2.15. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-tryptophan disodium (3o)

Yield: 89%. Mp: 106 - 108 °C. $[\alpha]^{20}_D$ = -24.3 (c = 2.8, H_2O), ESI-MS (m/e) 490 $[M + H]^+$. IR (KBr) 3360, 2968, 2852, 1602, 1560, 1452, 1400, 1374, 1070, 1052, 750, 669. Anal Calcd for $C_{18}H_{22}N_2Na_2O_7S_2$: C 44.26, H 4.54, N 5.73; Found: C 44.04, H 4.38, N 5.51.

1.2.2.16. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-valine disodium (3p)

Yield: 91%. Mp: 90 - 92 °C. $[\alpha]^{20}_D$ = -46.6 (c = 2.4, H_2O), ESI-MS (m/e) 403 $[M + H]^+$. IR (KBr) 3303, 2952, 2836, 1695, 1602, 1550, 1419, 1395, 1362 1303, 1087, 1039, 827, 741, 617. Anal Calcd for $C_{12}H_{21}NNa_2O_7S_2$: C 35.91, H 5.27, N 3.49; Found: C 35.70, H 5.11, N 3.72.

1.2.2.17. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-lysine disodium (3q)

Yield: 78%. Mp: 82 - 84 °C. $[\alpha]^{20}_{D}$ = -3.5 (c = 1.7, H_2O), ESI-MS (m/e) 694 $[M + H]^+$. IR (KBr) 3389, 2962, 2852, 1716, 1608, 1560, 1435, 1382, 1216, 1170, 1069, 1013, 803, 782, 659. Anal Calcd for $C_{20}H_{35}N_2Na_3O_{12}S_4$: C 34.68, H 5.09, N 4.04; Found: C 34.90, H 5.25, N 4.27.

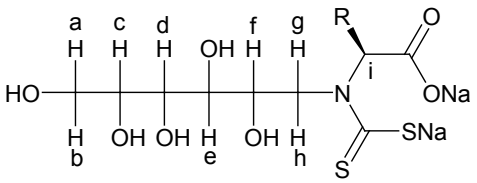
1.2.2.18. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-arginine disodium (3r)

Yield: 88%. Mp: 95 - 97 °C. $[\alpha]^{20}_{D}$ = -18.7 (c = 2.3, H_2O), ESI-MS (m/e) 460 $[M + H]^+$. IR (KBr) 3369, 2945, 2856, 1706, 1630, 1503, 1386, 1238, 1104, 1075, 1016, 905, 759. Anal Calcd for $C_{13}H_{24}N_4Na_2O_7S_2$: C 34.06, H 5.28, N 12.22; Found: C 33.87, H 5.13, N 12.01.

1.2.2.19. *N*-(2,3,4,5,6-Pentahydroxyhexyl)-*N*-dithiocarbamate-*L*-histidine disodium (3s)

Yield: 84%. Mp: 106 - 108 °C. $[\alpha]^{20}_{D}$ = -13.9 (c = 2.7, H_2O), ESI-MS (m/e) 441 $[M + H]^+$. IR (KBr) 3443, 3337, 3125, 2910, 1618, 1448, 1398, 1112, 1057, 1016, 957, 620. Anal Calcd for $C_{13}H_{19}N_3Na_2O_7S_2$: C 35.53, H 4.36, N 9.56; Found: C 35.75, H 4.51, N 9.79. The ^{1}H NMR signals of **3a-s** were assigned in Table 2.

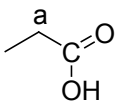
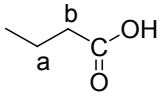
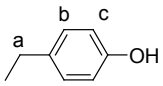
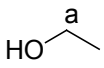
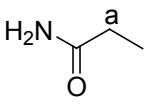
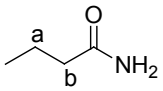
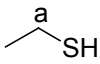
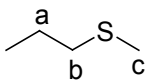
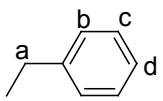
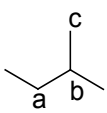
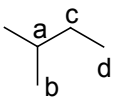
Table 2 ^{1}H NMR signals of **3a-s**

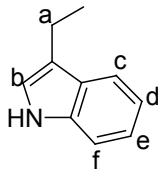
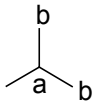
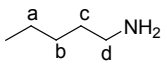
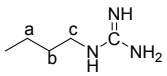
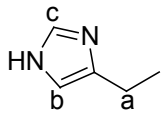


Compd	Ha	Hb	Hc	Hd	He	Hf	Hg	Hh	Hi

3a	3.59 (m, *J* = 4.0 Hz, 1H)	4.10 (m, *J* = 4.5 Hz, 1H)	3.59 (m, *J* = 4.0 Hz, 1H)	3.80 (m, *J* = 4.5 Hz, *J* = 3.5 Hz, 1H)	3.76 (m, *J* = 12.5 Hz, *J* = 3.0 Hz, 1H)	3.71 (m, *J* = 3.5 Hz, 1H)	3.34 (dd, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H)	3.20 (dd, *J* = 13.0 Hz, *J* = 9.0 Hz, 1H)	3.94 (m, *J* = 7.5 Hz, *J* = 4.5 Hz, 1H)
3b	3.15 (d, *J* = 9.5 Hz, 1H)	3.88 (m, *J* = 7.0 Hz 1H)	3.51 (m, *J* = 3.5 Hz, 1H)	3.15 (d, *J* = 9.5 Hz, 1H)	3.88 (m, *J* = 7.0 Hz 1H)	3.38 (m, *J* = 5.0 Hz, 1H)	3.70 (dd, *J* = 5.0 Hz, *J* = 3.0 Hz, 1H)	3.60 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1H)	3.41 (m, *J* = 5.5 Hz, 1H)
3c	3.67 (m, *J* = 3.0 Hz, 1H)	4.39 (m, *J* = 8.0 Hz, 1H)	3.64 (m, *J* = 3.5 Hz, 1H)	3.84 (dd, *J* = 11.5 Hz, *J* = 3.5 Hz, 1H)	3.84 (dd, *J* = 11.5 Hz, *J* = 3.5 Hz, 1H)	3.28 (d, *J* = 4.0 Hz, 1H)	3.20 (dd, *J* = 13.5, *J* = 3.5 Hz, 1H)	3.10 (dd, *J* = 10.5 Hz, *J* = 3.5 Hz, 1H)	3.79 (m, *J* = 4.5 Hz, 1H)
3d	3.53 (m, *J* = 4.0 Hz, 1H)	4.01 (m, *J* = 4.5 Hz, 1H)	3.53 (m, *J* = 4.0 Hz, 1H)	3.82 (m, *J* = 5.0 Hz, 1H)	3.67 (m, *J* = 3.5 Hz, 1H)	3.60 (m, *J* = 3.5 Hz, 1H)	3.23 (dd, *J* = 3.5 Hz, *J* = 12.5 Hz, 1H)	3.08 (dd, *J* = 12.5 Hz, *J* = 3.5 Hz, 1H)	3.74 (m, *J* = 4.5 Hz, 1H)
3e	3.48 (t, *J* = 5.5 Hz, 1H)	4.08 (m, *J* = 5.0 Hz, 1H)	3.80 (m, *J* = 4.5 Hz, 1H)	3.72 (dd, *J* = 12.0 Hz, *J* = 5.5 Hz, 1H)	3.67 (m, *J* = 2.5 Hz, 1H)	3.60 (dd, *J* = 5.0 Hz, *J* = 3.0 Hz, 1H)	3.20 (dd, *J* = 12.0 Hz, *J* = 4.0 Hz, 1H)	3.08 (dd, *J* = 12.5 Hz, *J* = 5.0 Hz, 1H)	3.80 (m, *J* = 4.5 Hz, 1H)
3f	3.59 (m, *J* = 3.5 Hz, 1H)	3.98 (m, *J* = 3.5 Hz, 1H)	3.52 (m, *J* = 4.0 Hz, 1H)	3.72 (dd, *J* = 5.0 Hz, *J* = 3.5 Hz, 1H)	3.68 (dd, *J* = 11.0 Hz, *J* = 2.5 Hz, 1H)	3.62 (t, *J* = 4.5 Hz, 1H)	3.22 (dd, *J* = 12.0 Hz, *J* = 3.5 Hz, 1H),	3.10 (dd, *J* = 12.5 Hz, *J* = 8.5 Hz, 1H)	3.76 (dd, *J* = 7.0 Hz, *J* = 5.0 Hz, 1H),
3g	3.38 (m, *J* = 3.5 Hz, 1H)	3.92 (m, *J* = 5.0 Hz, 1H)	3.34 (m, *J* = 4.0 Hz, 1H)	3.59 (m, *J* = 5.0 Hz, *J* = 4.0 Hz, 1H)	3.51 (m, *J* = 12.0 Hz, *J* = 3.5 Hz, 1H)	3.22 (t, *J* = 5.1 Hz, 1H)	3.26 (dd, *J* = 12.0 Hz, *J* = 3.5 Hz, 1H)	3.12 (dd, *J* = 12.5 Hz, *J* = 9.0 Hz, 1H)	3.68 (dd, *J* = 5.0 Hz, *J* = 9.0 Hz, 1H)
3h	3.70 (d, *J* = 6.0 Hz, 1H)	4.28 (m, *J* = 5.0 Hz, 1H)	3.70 (d, *J* = 6.0 Hz, 1H)	3.91 (m, *J* = 8.5 Hz, 1H)	3.86 (m, *J* = 5.0 Hz, 1H)	3.76 (m, *J* = 3.0 Hz, 1H)	3.46 (dd, *J* = 12.0 Hz, *J* = 4.0 Hz, 1H)	3.22 (dd, *J* = 12.0 Hz, *J* = 9.0 Hz, 1H)	3.66 (s, 1H)
3i	3.49 (m, *J* = 4.5 Hz, 1H)	4.06 (m, *J* = 4.0 Hz, 1H)	3.49 (m, *J* = 4.5 Hz, 1H)	3.67 (dd, *J* = 5.0Hz, *J* = 3.5Hz, 1H)	3.64 (dd, *J* = 12.0Hz, *J*= 4.0Hz, 1H)	3.56 (m, *J* = 4.5 Hz, 1H)	3.29 (dd, *J* = 12.5 Hz, *J* = 5.5 Hz, 1H)	3.20 (m, *J* = 18.0 Hz, *J* = 4.5 Hz, 1H)	3.98 (m, *J* = 5.0 Hz, 1H)
3j	3.50 (d, *J* = 5.0 Hz, 1H)	4.02 (m, *J* = 4.5 Hz, 1H)	3.46 (m, *J* = 6.5 Hz, 1H)	3.80 (m, *J* = 4.0 Hz, 1H)	3.65 (m, *J* = 3.5 Hz, 1H)	3.56 (m, *J* = 3.5 Hz, 1H)	3.26 (dd, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H)	3.12 (dd, *J* = 12.5 Hz, *J* = 8.5 Hz, 1H)	3.80 (m, *J* = 4.0 Hz, 1H)
3k	3.64 (m, *J* = 5.0 Hz, 1H)	3.92 (m, *J* = 3.5 Hz, 1H)	3.68 (d, *J* = 5.0 Hz, 1H)	3.82 (m, *J* = 4.5 Hz, 1H)	3.80 (m, *J* = 3.5 Hz, 1H)	3.68 (d, *J* = 5.0 Hz, 1H)	3.14 (dd, *J* = 12.5 Hz, *J* = 3.5 Hz, 1H)	2.90 (dd, *J* = 12.5 Hz, *J* = 9.0 Hz, 1H)	3.83 (m, *J* = 5.0 Hz, 1H)
3l	3.56 (d, *J* = 7.0 Hz, 1H)	3.94 (m, *J* = 8.5 Hz, 1H)	3.66 (d, *J* = 6.0 Hz, 1H)	3.76 (m, *J* = 4.0 Hz, 1H)	3.71 (m, *J* = 3.0 Hz, 1H)	3.66 (d, *J* = 6.0 Hz, 1H)	3.48 (dd, *J* = 6.5 Hz, *J* = 3.0 Hz, 1H)	3.18 (dd, *J* = 9.0 Hz, *J* = 4.5 Hz, 1H)	3.83 (m, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H)
3m	3.65 (m, *J* = 5.5 Hz, 1H)	4.06 (m, *J* = 5.0 Hz, 1H)	3.65 (m, *J* = 5.5 Hz, 1H)	3.81 (m, *J* = 5.0 Hz, 1H)	3.80 (m, *J* = 4.0 Hz, 1H)	3.68 (t, *J* = 6.0 Hz, 1H)	3.24 (m, *J* = 13.0 Hz, *J* = 2.5 Hz, 1H)	3.10 (m, *J* = 13.0 Hz, *J* = 6.0 Hz, 1H)	3.75 (m, *J* = 5.0 Hz, 1H)
3n	3.64 (m, *J* = 5.5 Hz, 1H)	4.02 (m, *J* = 5.0 Hz, 1H)	3.64 (m, *J* = 5.5 Hz, 1H)	3.78 (m, *J* = 4.0 Hz, 1H)	3.74 (m, *J* = 5.0 Hz, 1H)	3.67 (t, *J* = 6.0 Hz, 1H)	3.26 (m, *J* = 13.0 Hz, *J* = 2.5 Hz, 1H)	3.11 (m, *J* = 13.0 Hz, *J* = 6.0 Hz, 1H)	3.80 (m, *J* = 5.0 Hz, 1H)
3o	3.62 (d, *J* = 4.5 Hz, 1H)	4.12 (m, *J* = 5.0 Hz, 1H)	3.62 (d, *J* = 4.5 Hz, 1H)	3.80 (m, *J* = 5.0 Hz, 1H)	3.76 (m, *J* = 5.0 Hz, 1H)	3.70 (m, *J* = 4.0 Hz, 1H)	3.22 (dd, *J* = 12.5 Hz, *J* = 4.0 Hz, 1H),	3.12 (dd, *J* = 9.3 Hz, *J* = 12.9 Hz, 1H)	3.83 (m, *J* = 5.0 Hz, 1H)
3p	3.67 (m, *J* = 4.0 Hz, 1H)	4.08 (m, *J* = 5.0 Hz, 1H)	3.58 (dd, *J* = 4.5 Hz, *J* = 16.0 Hz, 1H)	3.76 (m, *J* = 4.5 Hz, 1H)	3.74 (m, *J* = 4.0 Hz, 1H)	3.67 (m, *J* = 4.0 Hz, 1H)	3.20 (dd, *J* = 3.0 Hz, *J* = 13.0 Hz, 1H)	3.14 (dd, *J* = 10.0 Hz, *J* = 13.0 Hz, 1H)	3.79 (m, *J* = 5.0 Hz, 1H)

3q	3.48 (d, *J* = 5.0 Hz, 1H)	4.22 (m, *J* = 7.5 Hz, 1H)	3.48 (d, *J* = 5.0 Hz, 1H)	3.68 (m, *J* = 5.0 Hz, 1H)	3.63 (m, *J* = 4.0 Hz, 1H)	3.58 (m, *J* = 4.5 Hz, 1H)	3.20 (dd, *J* = 12.5 Hz, *J* = 3.5 Hz, 1H)	3.03 (dd, *J* = 12.0 Hz, *J* = 9.0 Hz, 1H)	3.70 (m, *J* = 5.0 Hz, 1H)
3r	3.58 (t, *J* = 4.5 Hz, 1H)	4.12 (m, *J* = 5.0 Hz, 1H)	3.62 (m, *J* = 5.0 Hz, 1H)	3.75 (m, *J* = 4.5 Hz, 1H)	3.70 (m, *J* = 4.0 Hz, 1H)	3.62 (m, *J* = 5.0 Hz, 1H)	3.21 (dd, *J* = 12.0 Hz, *J* = 3.5 Hz, 1H)	3.16 (dd, *J* = 12.0 Hz, *J* = 4.5 Hz, 1H)	3.79 (m, *J* =5.0 Hz, 1H)
3s	3.56 (m, *J* = 11.5 Hz, *J* = 4.5 Hz, 1H)	4.28 (dd, *J* = 6.5 Hz, *J* = 2.0 Hz, 1H)	3.56 (m, *J* = 11.5 Hz, *J* = 4.5 Hz, 1H)	3.75 (m, *J* = 5.0 Hz, 1H)	3.70 (m, *J* = 4.0 Hz, 1H)	3.62 (m, *J* = 4.2 Hz, 1H)	3.44 (dd, *J* = 12.5 Hz, *J* = 3.5 Hz, 1H)	2.86 (m, *J* = 12.5 Hz, *J* = 9.0 Hz, 1H)	3.79 (m, *J* = 5.0 Hz, 1H)

Compd	R	Ha	Hb	Hc	Hd	He	Hf
3a		3.01 (dd, *J* = 18.0 Hz, *J* = 5.0 Hz, 1H)	2.92 (dd, *J* = 18.0 Hz, *J* = 7.0 Hz, 1H)				
3b		2.25 (t, *J* = 11.5 Hz, *J* = 9.5 Hz, 2H)	2.01 (m, *J* = 8.0 Hz, 2H)				
3c		1.32 (d, *J* = 6.0 Hz, 3H)	3.76 (m, *J* = 2.0 Hz, 1H)				
3d		7.09 (d, *J* = 7.5 Hz, 2H)	6.86 (d, *J* = 7.5 Hz, 2H)	2.85 (m, *J* = 4.5 Hz, 2H)			
3e		3.54 (m, *J* = 4.0 Hz, 2H)					
3f		2.62 (d, *J* = 5.0 Hz, 2H)					
3g		2.20 (t, *J* = 5.0 Hz, 2H)	2.00 (m, *J* = 5.0 Hz, 1H)	1.97 (m, *J* = 4.5 Hz, 1H)			
3h		3.66 (s, 1H)					
3i		3.14 (d, *J* = 5.0 Hz, 2H)					
3j		2.50 (t, *J* = 4.0 Hz, 2H)	2.12 (m, 2H)	2.08 (s, 3H)			
3k		1.66 (d, *J* = 7.0 Hz, 3H)					
3l		7.32 (m, *J* = 7.5 Hz, 2H)	7.30 (m, *J* = 7.0 Hz 2H)	7.23 (m, *J* = 8.0 Hz, 1H)	2.96 (d, *J* = 5.0 Hz, 2H)		
3m		1.79 (m, *J* = 6.0 Hz, 1H)	1.72 (m, *J* = 7.0 Hz, *J* = 3.5 Hz, 2H)	1.02 (d, *J* = 6.5 Hz, 6H)			
3n		2.32 (m, *J* = 4.5 Hz, 1H)	1.36 (m, *J* = 4.0 Hz, 2H)	1.15 (d, *J* = 3.0 Hz, 3H)	0.95 (dd, *J* = 6.0 Hz, *J* = 3.5 Hz, 3H)		

3o		7.40 (d, *J* = 8.0 Hz, 1H)	7.35 (d, *J* = 7.5 Hz, 1H)	7.30 (t, *J* = 7.0 Hz, 1H)	7.28 (t, *J* = 7.5 Hz, 1H)	6.85 (s, 1H)	2.89 (d, *J* = 4.9 Hz, 2H)
3p		2.38 (m, *J* = 4.5 Hz, 1H)	1.05 (dd, *J* = 7.0 Hz, *J* = 16.0 Hz, 6H)				
3q		2.90 (t, *J* = 4.5 Hz, 2H)	1.83 (m, *J* = 4.0 Hz, 2H)	1.60 (m, *J* = 4.5 Hz, 2H)	1.38 (m, *J* = 4.7 Hz, 2H)		
3r		2.68 (t, *J* = 4.5 Hz, 2H)	1.68 (m, *J* = 5.0 Hz, 2H)	1.55 (m, *J* = 4.5 Hz, 2H)			
3s		7.59 (s, 1H)	7.02 (d, *J* = 5.0 Hz, 1H)	2.62 (m, *J* = 10.0 Hz, *J* = 2.5 Hz, 2H)			

1.3. *In vitro* anti-tumor assays of cisplatin and 3a-s

HeLa cell lines obtained from Peking University Health Science Center were cultivated at 37 °C in a 75-cm^2 flask, which contains 12 mL of RPMI1640 (Gibco Laboratories, Santa Clara, CA, USA) with 10% fetal calf serum (Gibco Laboratories). Penicillin and streptomycin (100 U/mL and 100 μg/mL, respectively) were administered. The cells were incubated in humidified air with 5% CO_2 and grown to a density of 1×10^5 cells/mL. Proliferation of HeLa and HL60 cells was determined by the colorimetric MTT assay as described previously [30, 31]. Briefly, cells were seeded in 100 μL of medium in the 96-well plates (Corning, NY, USA) with a density of 1×10^4 cells/well. In the treatment group, each 6 wells were added 12.5 μL of cisplatin in NS (final concentration: 16 μM) and 12.5 μL of **3a-s** in NS (final concentration: 16 μM). In the positive control group, each 6 wells were added 25 μL of cisplatin (final concentration: 8 μM). In the negative control group, each 6 wells were added 25 μL

of NS. The 96-well plates were incubated for 48 h at 37 °C, centrifuged at 2000 r/min for 10 min and the supernatant was aspirated. To each well, 20 mL aqueous 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT, 5 mg/mL) solution was added. The 96-well plates were incubated at 37°C for another 4 h and the supernatant was aspirated. 100 μL of DMSO was added to each well and the plates were shaken for 8 min. Optical density (OD) at 570 nm (reference at 630 nm) was measured on a 96-well microplate reader (Mode 680, Bio-Rad). All assays were repeated three times. Viability of the cells treated with test compound was deter- mined as: % Cell viability = [(average OD of test compound)/(average OD of control)] × 100.

1.4. *In vivo* anti-cancer assay with cisplatin and 3a-s

Male Kunming mice, purchased from Peking University Health Science Center, were maintained at 21 °C with natural day/night cycle in a conventional animal colony. 10-12 week-old mice were used in the in vivo experiments. S180, a solid sarcoma tumor, was chosen as the tumor model for this study. S180 cells for initiating subcutaneous tumors were obtained from the ascitic fluid in S180-bearing mice. S180 tumors were implanted in mice by subcutaneously injecting 0.2 mL of 0.9% normal saline containing 4×10^6 viable S180 cells under the skin on the right oxter. Twenty-four hours after implantation, the mice were randomly divided into experimental groups. The mice (30) in the positive control groupwere given a daily i.p. injection of 1.667 μmol/kg of cisplatin (Platinol, obtained as a crystalline powder from Qilu pharmaceutical factory, China) in 0.2 mL of 0.9% normal saline for ten consecutive

days. The mice (10) in the negative control group were given a daily i.p injection of 0.2 mL of 0.9% saline for ten consecutive days. The mice (each 10) in the treatment groups were given a daily i.p injection of 1.67 μmol/kg of cisplatin in 0.2 mL of 0.9% saline and 1.67 μmol/kg of each of **3a-s** in 0.2 mL of 0.9% saline for ten consecutive days. On the first day, 2 h after the administration the urine of each group was continually collected for 5 h and the feces of each group were continually collected for 24 h. 24 h after the last drug administration, all mice were weighed and blood was drawn from the eye orbit. The mice were then sacrificed by diethyl ether anesthesia and immediately dissected to provide tumor, liver, kidney, brain, spleen and heart samples.

1.5. Determination of the platinum in tumor, organs, urine, feces and blood of S180-bearing mice

Twenty-four hours after the last administration, all mice were weighed and blood was drawn from the eye orbit. Then the mice were sacrificed by diethyl ether anesthesia, dissected and weighed immediately to obtain the biosamples of the tumor, liver, kidney, brain, spleen, heart and left femur of the S180-bearing mice. All of these biosamples were digested in $HClO_4/HNO_3$ (1/3) on a heating block, dried at 80 °C, re-dissolved in 1% nitric acid, and measured their platinum on a Varian Spectr AA-220 atomic absorption spectrometer (Zeeman graphite furnace).

The sample solution or the standard solution (1.5 mL) was transferred to the autosampler for platinum measurement in a graphite furnace. In the measurement the

conditions, namely Drying Temperature 95 - 120 °C, Ramp 40s, Flow rate of Ar 3.0 L/min, Ashing Temperature 1000 °C, Atomization temperature 2700 °C, Substrate Background on, Lamp Current 10 mA, Wavelength 265.9 nm, Slit Width 0.2 nm, Measure Mode peak height, were used. The standard calibrations (0 μg/L, 45 μg/L, 90 μg/L, 135 μg/L, 180 μg/L, 225 μg/L) were prepared by diluting the stock standard solution (Pt (II) 300 μg/L) with the autosampler. The concentration of the platinum in the sample solution was calculated automatically with the unit, μg per gram of organ (for urine, μg per mL of urine).

1.3.4 Metabolic analysis of platinum complex of 3n in urine, fecal, kidney and tumor samples of mice.

S180 mice were treated with cisplatin and **3n** for ten days as described above. 1 mL of urine sample was collected and extracted with ethyl acetate (3 mL × 4). The ethyl acetate phase was combined and washed with distilled water (5 mL × 4), evaporated under vacuum and the resulting residue was analyzed by reverse-phase HPLC coupled with ESI-MS (Waters, Atlantis HILIC Silica 5μm 4.6 × 150mm, 20 min, 70 - 90% of Methanol/water).

1 gram of the fecal sample was suspended in 5 mL of distilled waster, stirred at room temperature for 1 h and then filtered. The filtrate was extracted with ethyl acetate (3 mL × 4). The combined ethyl acetate phase was washed with distilled waster (5 mL × 4), evaporated under vacuum, and the residue was analyzed by LC-MS.

Kidney and tumor sample of mice were collected. At 4 ºC, 1 gram of the kidney or tumor and 3 mL of distilled water was homogenized, centrifuged at 2000 rpm for 5 min and 3 mL of the supernatant was obtained. The supernatant was extracted with ethyl acetate (3 mL × 4). The combined ethyl acetate phase was washed with distilled waster (5 mL × 4), evaporated under vacuum, and the resulting residue was analyzed by LC-MS.