Supporting Information for

**Albumin-encapsulated nanoparticles of naproxen platinum(IV) complexes with inflammation inhibitory competence displaying effective antitumor activities *in vitro* and *in vivo***

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**1. Synthetic procedures**



**Figure S1** Structures of naproxen platinum(IV) compounds **1−2**, oxoplatins **O1-O2**.

**1.1 Preparation of compound O1:**

A suspension of oxaliplatin (1.0 g, 2.5 mmol) in distilled water 30 mL was stirred at room temperature. Then H2O2 (30%) 50 mL was added dropwise. The mixture was kept stirring for 4 h at 60 °C. Then the resultant mixture was recrystallized at 4 °C. Crude product as solid was obtained after filtration. Then recrystallization in water afforded pure oxoplatin **O1** as white solid (0.82 g, 76%).

**1.2 Preparation of compound O2:**

A suspension of cisplatin (1.0 g, 3.3 mmol) in distilled water 30 mL was stirred at room temperature. Then H2O2 (30%) 50 mL was added drop wise. The mixture was kept stirring for 4 h at 60 °C. Then the resultant mixture was recrystallized at 4 °C. Crude product as yellow solid was obtained after filtration. Then recrystallization in water afforded pure compound **O2** as yellow crystals (0.91 g, 82%).

**2. The particle size and zeta potential of nanoparticles**

**Table S1** The effects of ratio for compound **1**:BSA on the size, PDI and Zeta potential of the nanoparticles (pH = 7.4, T = 4 °C)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **1**:BSA | **1** | BSA | Size (nm) | PDI | Zeta Potential (mV) |
| 2.0:1 | 5 mg, 5.85 μmol | 194.3 mg, 2.92 μmol | 368.4±15.0 | 0.46±0.04 | -25.1±0.5 |
| 3.5:1 | 5 mg, 5.85 μmol | 111.0 mg, 1.67 μmol | 278.6±6.5 | 0.32±0.03 | -29.5±0.3 |
| 5.0:1 | 5 mg, 5.85 μmol | 77.7 mg, 1.17 μmol | 299.7±15.2 | 0.49±0.04 | -23.7±0.3 |
| 7.5:1 | 5 mg, 5.85 μmol | 51.8 mg, 0.78 μmol | 319.6±4.1 | 0.40±0.01 | -19.4±0.8 |

**Table S2** The effects of ratio for compound **2**:BSA on the size, PDI and Zeta potential of the nanoparticles (pH = 7.4, T = 4 °C)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **2**:BSA | **2** | BSA | Size (nm) | PDI | Zeta Potential (mV) |
| 2.0:1 | 5 mg, 6.60 μmol | 219.1 mg, 3.30 μmol | 392.9±25.6 | 0.42±0.03 | -10.8±0.3 |
| 3.5:1 | 5 mg, 6.60 μmol | 125.2 mg, 1.88 μmol | 356.3±2.4 | 0.41±0.01 | -25.4±0.6 |
| 5.0:1 | 5 mg, 6.60 μmol | 87.6 mg, 1.32 μmol | 270.2±1.5 | 0.30±0.02 | -22.8±0.8 |
| 7.5:1 | 5 mg, 6.60 μmol | 58.4 mg, 0.88 μmol | 345.1±4.2 | 0.51±0.02 | -16.8±0.7 |

**Table S3**. The particle size, PDI and the zeta potential of **1-NPs** (3.5:1) during storage of 30 days under conditions pH = 7.4, T = 4 °C (n=3)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time(Day) | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 1 | 280.2 | 6.5 | 0.44 | 0.04 | -23.7 | 0.3 |
| 3 | 278.1 | 7.2 | 0.38 | 0.05 | -25.7 | 0.8 |
| 5 | 287.2 | 5.6 | 0.42 | 0.05 | -24.7 | 0.2 |
| 7 | 296.6 | 14.0 | 0.59 | 0.02 | -26.5 | 0.3 |
| 16 | 264.9 | 3.5 | 0.38 | 0.02 | -28.1 | 0.1 |
| 22 | 299.7 | 15.2 | 0.49 | 0.04 | -29.5 | 0.3 |
| 27 | 238.3 | 0.9 | 0.35 | 0.02 | -30.5 | 0.9 |
| 30 | 266.0 | 16.7 | 0.37 | 0.01 | -31.1 | 1.2 |

**Table S4**. The particle size, PDI and the zeta potential of **1-NPs** (3.5:1) during storage of 7 days under conditions pH = 7.4, T = 25 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 0 h | 304.47 | 4.24 | 0.34 | 0.02 | -38.07 | 0.09 |
| 12 h | 330.53 | 5.12 | 0.36 | 0.02 | -37.30 | 0.45 |
| 1 d | 313.07 | 2.22 | 0.40 | 0.06 | -38.67 | 0.69 |
| 2 d | 304.03 | 4.10 | 0.39 | 0.00 | -32.77 | 1.26 |
| 3 d | 284.13 | 1.44 | 0.37 | 0.01 | -22.03 | 1.22 |
| 4 d | 311.87 | 22.06 | 0.62 | 0.08 | -13.97 | 0.53 |
| 5 d | 338.70 | 15.58 | 0.50 | 0.02 | -12.63 | 0.52 |
| 6 d | 540.10 | 8.64 | 0.59 | 0.03 | -9.81 | 0.71 |
| 7 d | 513.07 | 18.05 | 0.77 | 0.03 | -9.41 | 0.24 |

**Table S5**. The particle size, PDI and the zeta potential of **1-NPs** (3.5:1) during storage of 7 days under conditions pH = 7.4, T = 37 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 0 h | 268.80 | 1.98 | 0.38 | 0.01 | -24.90 | 1.23 |
| 2 h | 277.50 | 8.82 | 0.44 | 0.07 | -27.37 | 0.90 |
| 3 h | 268.97 | 7.36 | 0.42 | 0.03 | -27.20 | 0.57 |
| 4 h | 269.83 | 9.60 | 0.37 | 0.02 | -27.93 | 1.41 |
| 8 h | 267.13 | 5.38 | 0.43 | 0.03 | -28.10 | 0.64 |
| 12 h | 252.60 | 17.56 | 0.49 | 0.05 | -29.30 | 0.71 |
| 24 h | 273.50 | 4.53 | 0.39 | 0.03 | -28.13 | 0.12 |
| 2 d | 270.17 | 14.66 | 0.41 | 0.02 | -22.43 | 0.54 |
| 3 d | 268.43 | 33.49 | 0.45 | 0.01 | -24.13 | 0.46 |
| 4 d | 324.27 | 8.03 | 0.58 | 0.04 | -14.20 | 0.22 |
| 5 d | 678.47 | 83.48 | 0.62 | 0.07 | -5.22 | 1.27 |
| 6 d | 649.87 | 65.74 | 0.75 | 0.05 | -9.58 | 0.52 |
| 7 d | 680.73 | 66.51 | 0.73 | 0.20 | -8.47 | 0.96 |

**Table S6**. The particle size, PDI and the zeta potential of **1-NPs** (3.5:1) during storage of 7 days under conditions pH = 6.4, T = 4 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time(Day) | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 1 d | 285.2 | 10.4 | 0.32 | 0.02 | -28.9 | 0.5 |
| 3 d | 280.1 | 5.8 | 0.37 | 0.03 | -29.7 | 0.6 |
| 5 d | 285.2 | 6.6 | 0.41 | 0.03 | -26.4 | 0.4 |
| 7 d | 273.6 | 7.9 | 0.49 | 0.05 | -22.0 | 0.8 |

**Table S7**. The particle size, PDI and the zeta potential of **1-NPs** (3.5:1) during storage of 7 days under conditions pH = 6.4, T = 37 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | Size(nm) |  | PDI |  | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 0 h | 282.57 | 6.06 | 0.42 | 0.04 | -24.60 | 1.31 |
| 2 h | 282.97 | 10.20 | 0.41 | 0.01 | -28.30 | 0.45 |
| 3 h | 262.47 | 5.39 | 0.36 | 0.05 | -28.90 | 0.50 |
| 4 h | 267.97 | 6.86 | 0.39 | 0.02 | -28.93 | 0.45 |
| 8 h | 265.57 | 0.48 | 0.37 | 0.02 | -28.27 | 0.90 |
| 12 h | 269.13 | 10.58 | 0.38 | 0.01 | -30.13 | 0.97 |
| 24 h | 263.80 | 6.87 | 0.38 | 0.00 | -22.63 | 1.39 |
| 2 d | 2013.00 | 288.67 | 0.38 | 0.07 | -5.37 | 0.33 |
| 3 d | 2582.33 | 126.41 | 0.87 | 0.13 | -9.59 | 0.58 |
| 4 d | 1439.67 | 64.60 | 0.68 | 0.03 | -13.47 | 0.76 |
| 5 d | 1305.00 | 99.26 | 0.80 | 0.04 | -14.10 | 0.71 |
| 6 d | 1203.00 | 27.43 | 0.50 | 0.12 | -12.80 | 0.163299 |
| 7 d | 1270.00 | 69.46 | 0.50 | 0.08 | -10.53 | 0.980929 |

**Table S8**. The particle size, PDI and the zeta potential of **2-NPs** (5.0:1) during storage of 30 days under conditions pH = 7.4, T = 4 °C (n=3)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time(Day) | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 1 | 273.1 | 1.5 | 0.273 | 0.028 | -22.8 | 0.8 |
| 3 | 287.9 | 9.8 | 0.303 | 0.028 | -25.8 | 1.8 |
| 5 | 259.2 | 8.0 | 0.244 | 0.018 | -23.8 | 0.1 |
| 7 | 274.1 | 3.1 | 0.267 | 0.026 | -25.7 | 0.6 |
| 16 | 286.1 | 2.4 | 0.410 | 0.053 | -11.4 | 0.2 |
| 22 | 285.6 | 4.5 | 0.383 | 0.024 | -20.1 | 0.2 |
| 27 | 303.4 | 12.8 | 0.430 | 0.016 | -16.9 | 3.8 |
| 30 | 297.1 | 4.9 | 0.464 | 0.046 | -12.5 | 0.1 |

**Table S9**. The particle size, PDI and the zeta potential of **2-NPs** (5.0:1) during storage of 7 days under conditions pH = 7.4, T = 25 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 0 h | 292.10 | 8.41 | 0.58 | 0.01 | -38.70 | 1.51 |
| 12 h | 282.27 | 4.27 | 0.43 | 0.04 | -36.10 | 0.22 |
| 24 h | 287.53 | 3.27 | 0.42 | 0.02 | -36.37 | 0.45 |
| 2 d | 272.70 | 4.93 | 0.42 | 0.03 | -34.33 | 1.21 |
| 3 d | 275.50 | 5.80 | 0.42 | 0.05 | -32.67 | 0.93 |
| 4 d | 270.97 | 9.07 | 0.52 | 0.11 | -30.06 | 1.48 |
| 5 d | 223.60 | 11.79 | 0.51 | 0.07 | -36.60 | 0.33 |
| 6 d | 364.67 | 39.38 | 0.57 | 0.05 | -8.88 | 0.46 |
| 7 d | 395.10 | 20.22 | 0.51 | 0.02 | -7.44 | 0.27 |

**Table S10**. The particle size, PDI and the zeta potential of **2-NPs** (5.0:1) during storage of 7 days under conditions pH = 7.4, T = 37 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 0 h | 266.13 | 7.61 | 0.59 | 0.08 | -39.40 | 1.10 |
| 2 h | 230.00 | 1.39 | 0.43 | 0.05 | -42.17 | 1.44 |
| 3 h | 260.07 | 6.24 | 0.50 | 0.07 | -41.40 | 0.73 |
| 4 h | 268.30 | 10.71 | 0.53 | 0.06 | -42.13 | 1.58 |
| 8 h | 254.30 | 2.38 | 0.39 | 0.03 | -42.27 | 0.45 |
| 12 h | 259.27 | 6.46 | 0.35 | 0.02 | -40.70 | 0.67 |
| 24 h | 246.03 | 13.15 | 0.42 | 0.06 | -42.97 | 2.11 |
| 2 d | 278.73 | 11.45 | 0.41 | 0.06 | -42.93 | 0.90 |
| 3 d | 236.73 | 7.33 | 0.38 | 0.01 | -32.60 | 2.02 |
| 4 d | 274.27 | 17.08 | 0.65 | 0.04 | -33.70 | 1.08 |
| 5 d | 268.70 | 22.87 | 0.79 | 0.04 | -8.62 | 0.43 |
| 6 d | 365.33 | 10.60 | 0.84 | 0.11 | -8.09 | 1.57 |
| 7 d | 439.77 | 48.34 | 0.73 | 0.02 | -6.94 | 1.20 |

**Table S11**. The particle size, PDI and the zeta potential of **2-NPs** (5.0:1) during storage of 7 days under conditions pH = 6.4, T = 4 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time(Day) | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 1 d | 257.1 | 3.6 | 0.320 | 0.013 | -28.9 | 0.5 |
| 3 d | 246.7 | 4.5 | 0.311 | 0.032 | -29.7 | 0.9 |
| 5 d | 234.5 | 7.3 | 0.256 | 0.024 | -32.3 | 0.3 |
| 7 d | 248.6 | 5.7 | 0.283 | 0.016 | -22.4 | 0.5 |

**Table S12**. The particle size, PDI and the zeta potential of **2-NPs** (5.0:1) during storage of 7 days under conditions pH = 6.4, T = 37 °C (n=3)



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | Size(nm) | | PDI | | Zeta potential (mV) | |
| Average | SD | Average | SD | Average | SD |
| 0 h | 242.43 | 5.90 | 0.39 | 0.04 | -31.60 | 1.15 |
| 2 h | 275.33 | 17.15 | 0.43 | 0.04 | -34.43 | 1.04 |
| 3 h | 254.57 | 50.78 | 0.46 | 0.02 | -36.40 | 0.80 |
| 4 h | 278.03 | 4.05 | 0.57 | 0.07 | -34.70 | 0.54 |
| 8 h | 251.47 | 4.25 | 0.43 | 0.02 | -33.70 | 0.37 |
| 12 h | 276.47 | 15.18 | 0.37 | 0.01 | -38.80 | 1.31 |
| 24 h | 264.47 | 12.41 | 0.47 | 0.02 | -36.43 | 0.74 |
| 2 d | 295.40 | 5.91 | 0.43 | 0.05 | -36.00 | 0.50 |
| 3 d | 467.47 | 6.11 | 0.45 | 0.07 | -17.67 | 0.61 |
| 4 d | 543.00 | 27.53 | 0.74 | 0.03 | -9.57 | 0.44 |
| 5 d | 683.30 | 38.37 | 0.80 | 0.08 | -6.34 | 0.55 |
| 6 d | 737.20 | 26.38 | 0.85 | 0.09 | -5.63 | 1.81 |
| 7 d | 1115.00 | 94.05 | 0.69 | 0.21 | -5.57 | 0.70 |



**Figure S2** Fluorescence spectrum of BSA in the absence and presence of the platinum(IV) complexes (A) **1** and (B) **2** (*λ*ex = 280 nm, T = 298 K). a-d: *c*(BSA) = 4.0 μM, *c*(complex**)** = 0.0, 8.0, 14.0, 20.0 μM; e: fluorescence spectrum of free complex, *c*(complex)= 20.0 μM.



**Figure S3** UV-vis spectra of BSA with and without compounds (A) **1** and (B) **2**: (a) absorption spectrum of BSA, *c*(BSA) = 10 μM; (b) absorption spectrum of compound-BSA (2:1), *c*(BSA) = 10 μM, *c*(compound) = 20 μM; (c) absorption spectrum of compound, *c*(compound) = 20 μM; (d) subtraction spectrum of absorption spectrum of compound-BSA complex (a) and compound **1/2** (c). Inset: the curve (a) and (d) for the wavelength ranging from 250 to 300 nm.

**3. Organ weight indexes and biochemical indexes**





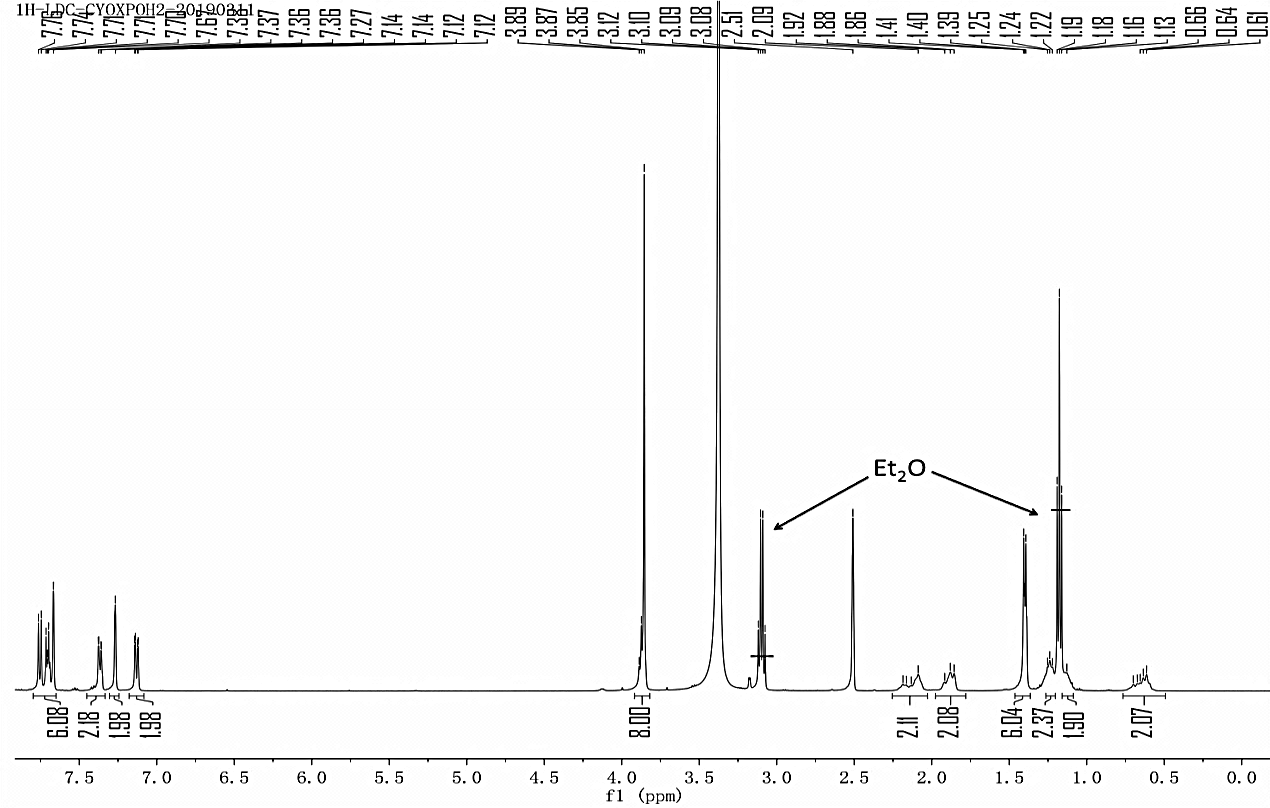
**Figure S4** Organ weight indexes of heart (A), liver (B), spleen (C), lung (D) and kidney (E) (organ weight/body weight). Results are presented as the mean ± SD.





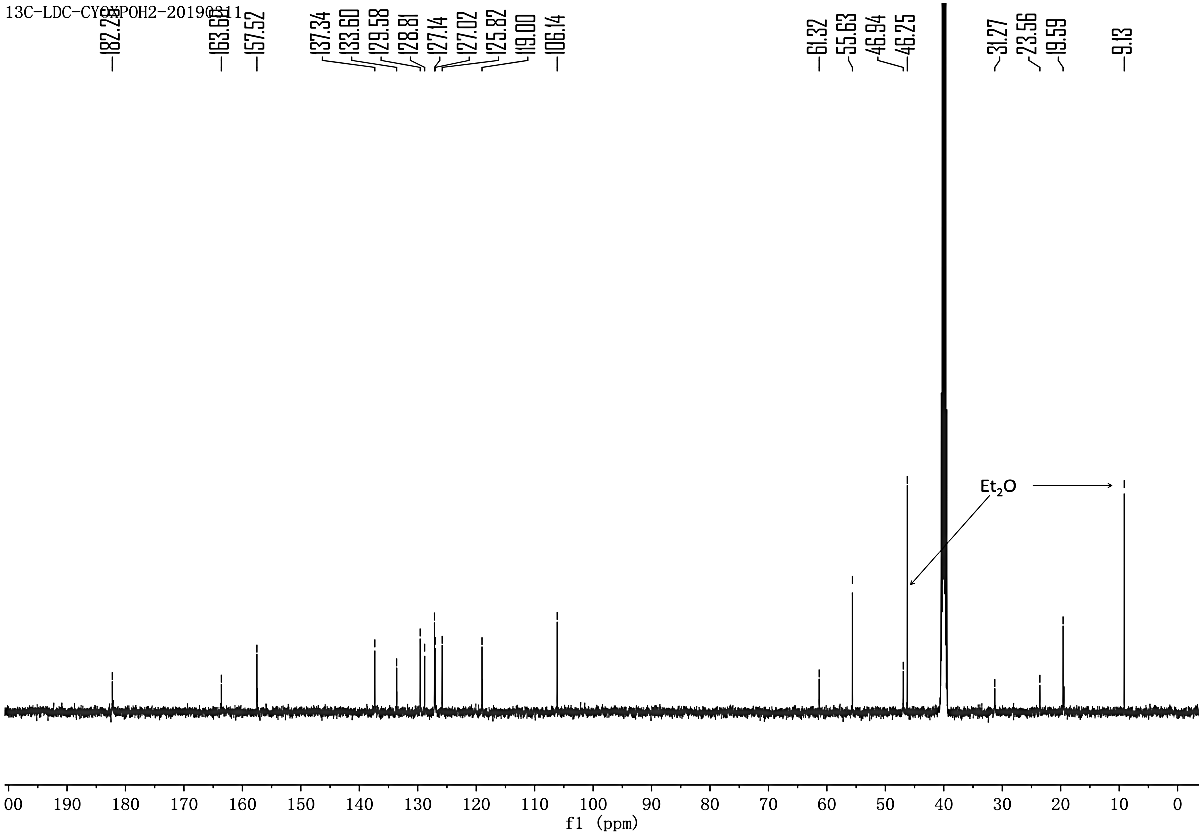
**Figure S5** Serum ALT levels (A), AST levels (B), CRE levels (C) and BUN levels (D) in mice. Results are presented as the mean ± SD (n=6). \**P* < 0.05, \*\**P* < 0.01.

**4. NMR spectra**

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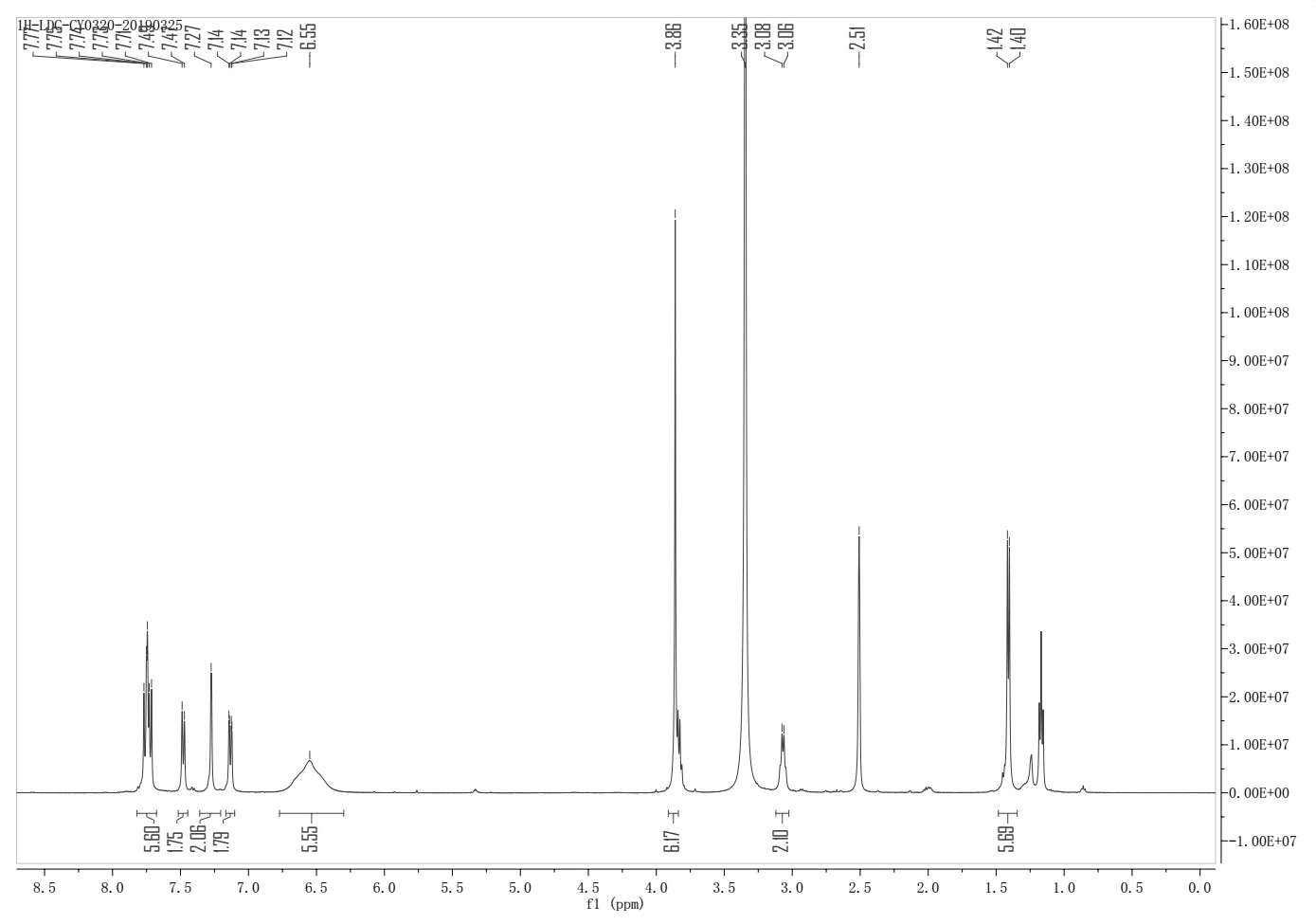
**\*** Signals at 1.19 (t) and 3.08 ppm (q) were ascribed to the peaks of solvent Et2O.

1H NMR for Compound **1.[S1]**

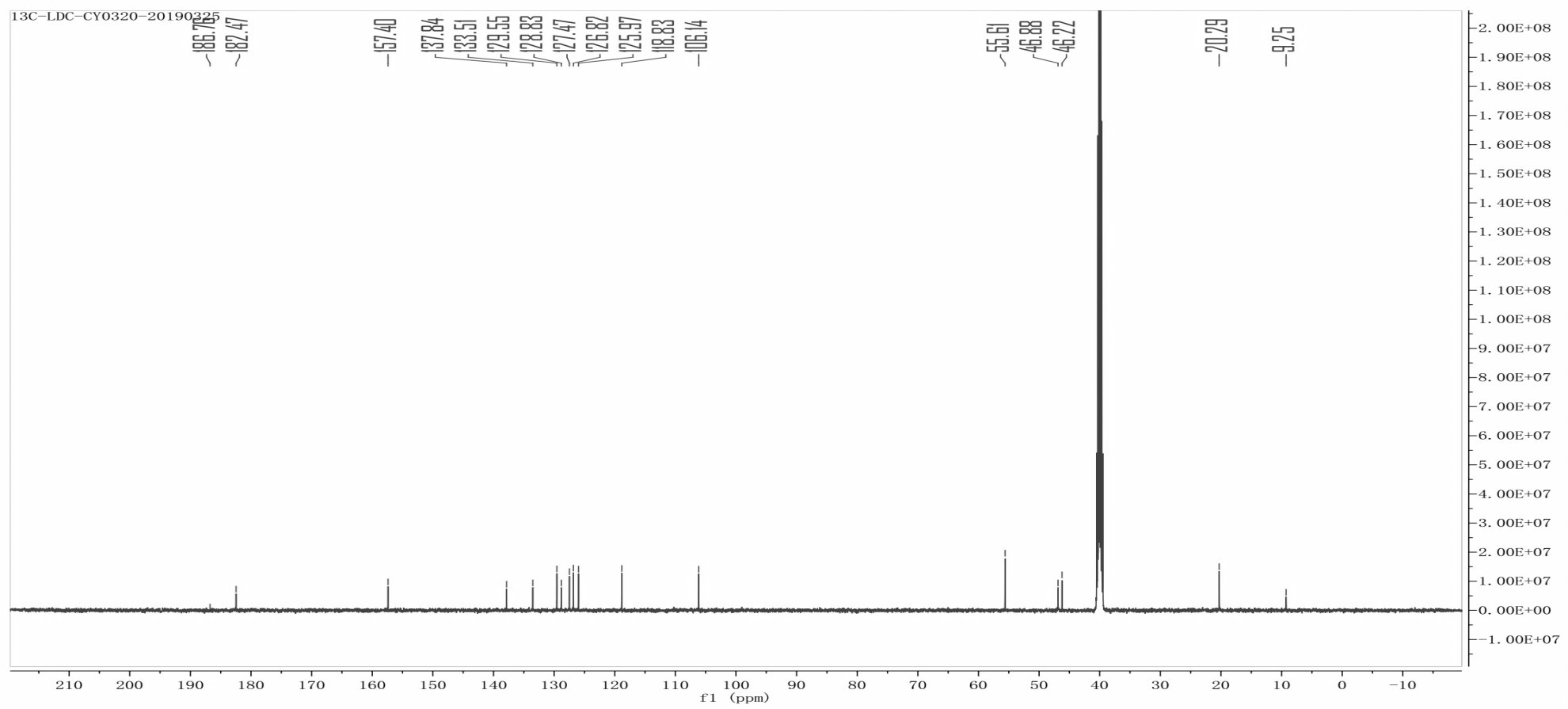
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**\*** Signals at 9 ppm and 46 ppm were ascribed to the peaks of solvent Et2O.

13C NMR for Compound **1.[S1]**



1H NMR for Compound **2.**



13C NMR for Compound **2.**

**References**

[S1] Y. Chen, Q. Wang, Z. Li, Z. Liu, Y. Zhao, J. Zhang, M. Liu, Z. Wang, D. Li, J. Han, Naproxen platinum(IV) hybrids inhibiting cycloxygenases and matrix metalloproteinases and causing DNA damage: synthesis and biological evaluation as antitumor agents in vitro and in vivo. Dalton Trans. 49 (2020) 5192–5204.