Development of a series of flurbiprofen and zaltoprofen platinum(IV) complexes with anti-metastasis competence targeting COX-2, PD-L1 and DNA

Zuojie Li, Linming Li, Wenhuan Zhao, Bin Sun, Zhifang Liu, Min Liu, Jun Han, Zhengping Wang, Dacheng Li and Qingpeng Wang*

*a. Institute of Biopharmaceutical Research, Liaocheng University, Liaocheng 252059, P.R. China. E-mail: lywqpj@126.com (Q. Wang).
b. Liaocheng High-Tech Biotechnology Co., Ltd. Liaocheng 252059, P.R. China.
c. Frontier Biotechnologies Inc., Nanjing 210000, P.R. China.
d. Shandong Provincial Key Laboratory of Chemical Energy Storage and Novel Cell Technology, Liaocheng University, Liaocheng 252059, P.R. China.

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1. The synthetic route of flurbiprofen and zaltoprofen platinum(IV) complexes

![Synthetic route diagram]

**Scheme S1** Synthetic route for flurbiprofen and zaltoprofen platinum(IV) complexes 1-9.

2. The antitumor activities *in vivo*

To compare the antitumor activities of NSAIDs platinum(IV) complexes extensively, platinum(IV) complexes 1-10 with ketoprofen and loxoprofen ligands listed in our previous work \(^{S1}\) (signed as \(J1-J10\) in this manuscript) and complexes 1-9 bearing flurbiprofen, zaltoprofen in this work were tested at the same time both *in vitro* and *in vivo* with same control groups. The MTT results were given in Table 1 with cisplatin and oxaliplatin as reference drugs. Meanwhile, the antitumor activities for complexes 1, 2, 5, 6, J1, J7, J9, cisplatin and oxaliplatin *in vivo* against CT26 tumors were shown in Figure S1 and Figure 3, the antitumor activities *in vivo* against 4T1 tumors were shown in Figure S2 and Figure 4, and the anti-metastasis properties against 4T1 breast carcinoma tumors *in vivo* were shown in Figure S6 and Figure 5.
Figure S1 *In vivo* antitumor activities to CT-26 tumors in BALB/c mice ($n = 6$). (a) Schematic illustration of the experimental design. (b) Survival analysis of mice during the treatment of 1, 2, 5, 6, cisplatin and oxaliplatin. (c) Images of tumors treated by 1, 2, oxaliplatin and blank. (d) Images of tumors treated by 5, 6, oxaliplatin and blank. Figure 3d is a combination of images (c) and (d). (e) Full images of tumors treated by 1, 2, 5, 6, J1, J7 (VII), J9 and oxaliplatin and blank. Reprinted with permission from Li et al., *J. Med. Chem.*, 2021, 64, 17920. Copyright 2021 American Chemical Society S1.

Figure S2 *In vivo* antitumor activities to 4T1 tumors in BALB/c mice ($n = 5$). (a) Schematic illustration of the experimental design. (b) Full images of tumors treated by drugs 1, 2, J7 (VII), cisplatin and oxaliplatin and blank. Reprinted with permission from Li et al., *J. Med. Chem.*, 2021, 64, 17920. Copyright 2021 American Chemical Society S1.
Figure S3 H&E staining of liver, spleen and kidney from mice treated by complexes 1, 2, 5, 6 and oxaliplatin and saline.

Figure S4 H&E staining of tumor tissues from mice treated by complexes 1, 2, 5, 6 and oxaliplatin and saline.

Figure S5 Platinum accumulation in tumors tissues treated by complexes 1, 2 and oxaliplatin.
Figure S6 Pulmonary metastasis inhibition of compounds 1, 2, VII(J7) cisplatin and oxaliplatin against 4T1 breast carcinoma tumors in vivo (n = 5). (a) Schematic illustration of the experimental design. (b) Full images of lungs from each group at the end of the experiment. Reprinted with permission from Li et al., *J. Med. Chem.*, 2021, **64**, 17920. Copyright 2021 American Chemical Society.

3. Metastasis inhibitory activities *in vitro*

![Wound closure images](image)

Figure S7 Migration inhibition to 4T1 cells of complex 2 (2 μM), cisplatin (10 μM) and oxaliplatin (10 μM) *in vitro*. The untreated group was set as blank. The extent of wound healing was observed at 0, 12, and 24 h. (a) Representative images; (b) Analysis of wound closure.
4. The reduction potential and DNA binding properties

**Figure S8** HPLC spectra of compound 2 in different media incubated at 37 °C. (a) Compound 2 (0.5 mM) in PBS; (b) Compound 2 (0.5 mM) in RPMI 1640; (c) Compound 2 (0.25 mM) in RPMI 1640 with AsA (1 mM); (d) Solution of compound 2 (0.25 mM) in RPMI 1640 with AsA (1 mM) and 5'-GMP (3 mM) incubated for 24 h; (e) The formation of platinated GMP (Pt-GMP) \(^{S2}\).

**Figure S9** Stability of complex 2 in whole blood incubated at 37 °C.
5. $^1$H NMR, $^{13}$C NMR and MS spectra

$^1$H NMR spectrum for complex 1

$^{13}$C NMR spectrum for complex 1
$^{13}$C NMR spectrum for complex 2

MS spectrum for complex 2
$^1$H NMR spectrum for complex 3

$^{13}$C NMR spectrum for complex 3
MS spectrum for complex 3

* Peaks 3.07 ppm (q) and 1.19 ppm (t) are ascribed to Et₂O.

¹H NMR spectrum for complex 4
Peaks 19.73 ppm and 63.21 ppm are ascribed to Et₂O.

$^{13}$C NMR spectrum for complex 4

MS spectrum for complex 4
$^1$H NMR spectrum for complex 5

$^{13}$C NMR spectrum for complex 5
MS spectrum for complex 5

^1^H NMR spectrum for complex 6
$^{13}$C NMR spectrum for complex 6

MS spectrum for complex 6
$^1$H NMR spectrum for complex 7

$^{13}$C NMR spectrum for complex 7
MS spectrum for complex 7

$^1$H NMR spectrum for complex 8
$^{13}$C NMR spectrum for complex 8

MS spectrum for complex 8
$^1$H NMR spectrum for complex 9

$^{13}$C NMR spectrum for complex 9
Reference
