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Nitric Oxide-releasing Platinum(IV) Prodrug Efficiently Inhibits Proliferation and Metastasis of Cancer Cells

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A dual-functional Pt(IV) prodrug, Pt-furoxan, can release cytotoxic cisplatin and signaling molecule NO upon cellular internalization. NO modulates the cellular response to cisplatin, leading to synergistic anti-proliferation effect and promising anti-metastasis effect both *in vitro* and *in vivo*.

Platinum drugs, such as cisplatin, are widely used in clinic for cancer chemotherapy; they induce apoptosis of tumor cells by cross-linking DNA, hence inhibit proliferation of tumors. The combination with other chemotherapeutic agents, such as paclitaxel, gemcitabine and vinorelbine, can further enhance the drug efficacy of cisplatin.[1] However, recent researches indicate that chemotherapeutic drugs, including platinum-based drugs, could also stimulate metastasis of cancer.[2] Cancer metastasis is responsible for 90% of cancer related patient deaths, especially metastasis of breast cancer.[3] Therefore, exploring the novel platinum drugs with dual-function of anti-proliferation and anti-metastasis is highly desired. Particularly, Pt(IV) prodrugs offer an opportunity to attach bioactive molecules that could modulate the therapeutic function of platinum drugs.[4]

Nitric oxide (NO) is the first found gaseous signaling molecule involved in various physiological and pathological processes.[5] Although low level of NO (100-500nM) is necessary for cell proliferation and metastasis,[6] high level of NO (>500 nM) tends to be cytotoxic and induce apoptosis of cancer cells.[7] Therefore, NO could sensitize tumor chemotherapy.[8] Interestingly, NO is also found to effectively inhibit the migration and invasion of cancer cells, and interfere with hetero-adhesion of cancer cells to vascular endothelium.[9] Gaseous NO is hardly used in therapeutics due to the

instability and inconvenient administration. Therefore, various NO donors have been explored and some of them have been used in clinic, such as nitroglycerin, isosorbide nitrate.[10] The combination of NO donors can improve the therapeutic effect of many antitumor agents, including platinum-based drugs.[11]

Inspired by these findings, we designed anti-metastasis Pt(IV) prodrug by incorporating a furoxan-based NO donor. Furoxan is a reducing-responsive agent; it is stable in a range of temperature and pH conditions;[10] however, it can be activated by reducing agents, such as glutathione (GSH) and cysteine (Cys), leading to the release of NO.[12] Therefore, the resulting platinum complex, Pt-furoxan is stable during the drug administration since platinum(IV) complexes are kinetically more inertness than platinum(II) complexes.[13] Upon cellular internalization, Pt-furoxan can simultaneously release two active components, cisplatin and NO (Scheme S1), as GSH and ascorbic acid exist high level in cancer cells.[14] The cisplatin inhibits the proliferation of cancer cells, while NO prevents the tumor metastasis.

The synthesis of Pt-furoxan is described in Figure S1. Briefly, two intermediates, 3-(hydroxymethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide and c,c,t-[Pt(NH$_3$)$_2$Cl$_2$(OCOCH$_2$CH$_2$COOH)$_2$], were synthesized according to literature.[11d, 15] The ligation of these two compounds was achieved using N,N'-dicyclohexylcarbodiimide (DCC) as dehydrating agent and 4-dimethylaminopyridine (DMAP) as catalyst, which generated the product Pt-furoxan. These compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{195}Pt-NMR and ESI-MS (Figures S2-S8).

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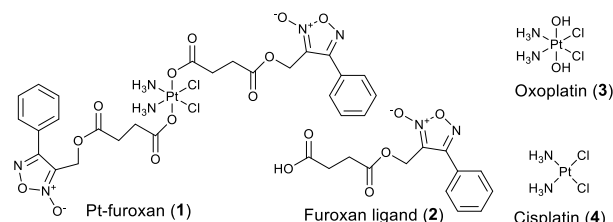
Figure 1. Structures of Pt-furoxan complex, furoxan ligand, oxoplatin and cisplatin.

The NO release from Pt-furoxan in PBS was investigated by Griess assay in the presence of cysteine (Figure S9-10). In

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agreement with literatures,[15-16] the free furoxan ligand (**2**) alone was rather stable and no detectable NO release was observed in 72 h. In comparison, 73.8% NO release was observed from **2** in the presence of cysteine in 72 h (Figure 2A), confirming the thiol-trigged NO release of the furoxan ligand. Pt-furoxan yielded 35.0% NO release in the same condition. The lower NO release in the Pt complex could be associated with its bulky structure and the less hydrophilicity; this NO release rate is comparable to the furoxan derivatives.[15]

The NO release from Pt-furoxan in cells was analyzed by fluorescence imaging using a NO probe DAF-FM DA. Weak fluorescence was observed in the cells incubated with DAF-FM DA, showing the low concentration of intrinsic NO on cells (Figure 2B).[17] By comparison, the treatment of Pt-furoxan clearly enhanced the fluorescence in cells, indication the release of NO from Pt-furoxan in cells (Figure 2B). Pt-furoxan itself did not show fluorescence (Figure S11). In addition, flow cytometry measurement was applied on the cells treated with DAF-FM DA. The result confirmed that Pt-furoxan led to more NO release in cells than oxoplatin or its mixture with free **2** (Figure 2C). It is worth noting that higher NO release was observed from Pt-furoxan than from free ligand **2** in cells, although **2** caused more NO-release in solution based on Greiss assay. This difference is probably due to the different cellular uptake of two compounds. On the other hand, the reduction and activation of Pt-furoxan by ascorbic acid was assessed by DNA platination assay (Figure S12).
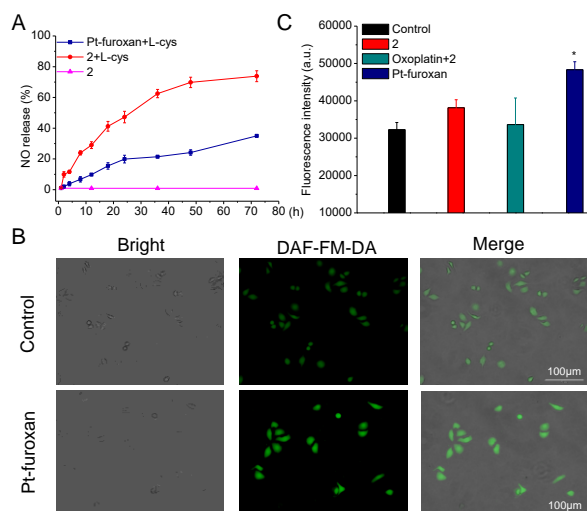

Figure 2. NO release from Pt-furoxan *in vitro*. (A) Time dependent NO release from Pt-furoxan (250 μM) and furoxan (500 μM) in the presence or absence of L-cysteine (5 mM) at 37°C. (B) Fluorescence imaging of NO in HepG2 cells. HepG2 cells were co-incubated with 5 μM of Pt-furoxan for 24 h, stained with DAF-FM-DA probe and observed using fluorescence microscope. (C) NO released from Pt-furoxan, furoxan and its mixture with oxoplatin in HepG2 cells. HepG2 cells were co-incubated with 5 μM of these platinum complexes (the mole ratio of platinum/2 = 1:2 in mixture, or 10 μM of **2**) for 24 h, stained with DAF-FM-DA probe and measured using flow cytometry. *$p < 0.05$, **$p < 0.01$.

The *in vitro* cytotoxicity of Pt-furoxan was evaluated using MTT assay on five human cancer cells (hepatocellular carcinoma HepG2, cervical cancer HeLa, lung carcinoma A549, ovarian cancer A2780 and breast carcinoma MCF-7 cells) and mouse breast cancer 4T1 cells (Table S1). The half maximal inhibitory concentrations (IC$_{50}$) indicate that Pt-furoxan is

more potent than cisplatin to all tumor cells. Encouragingly, two breast cancer cells (MCF-7 and 4T1) exhibited significantly higher sensitivity to Pt-furoxan than to cisplatin (15.6 and 19.4 folds decrease of IC$_{50}$, respectively). The free ligand **2** showed only marginal cytotoxicity (Figure S13); while the simple mixture of **2** did not enhance the cytotoxicity of oxoplatin.

The apoptosis induced by platinum complexes was analyzed using flow cytometry. After treatment of platinum complexes for 24 h or 48 h, cells were stained with annexin V-FITC and propidium iodide (PI). The results showed that Pt-furoxan caused significantly higher apoptosis than cisplatin or oxoplatin; while the mixture of free ligand **2** demonstrated only marginal effect on apoptosis induced by cisplatin or oxoplatin (Figure S14A). Moreover, Pt-furoxan decreased mitochondrial membrane potential (Δψm) more significantly than free ligand **2**, cisplatin, oxoplatin or the mixture of **2** (Figure S15), indicating that Pt-furoxan induces cell apoptosis while disrupting mitochondrial membrane. In addition, flow cytometry measurement confirmed that Pt-furoxan S-phase cell cycle arrest was similar to cisplatin, in agreement with the DNA damage induced cell apoptosis by platinum complexes (Figure S14B). These data indicate that the enhanced apoptosis caused by Pt-furoxan attributed to the high cytotoxicity of the compound.
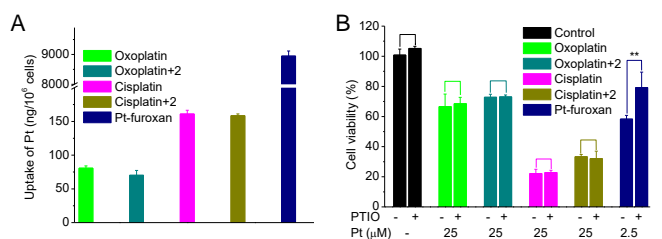

Figure 3. (A) Cellular accumulation of platinum complexes. Platinum in HepG2 cells were measured using ICP-MS after 4 h treatment of 100 μM platinum complexes. (D) Effects of PTIO on the anti-proliferation of HepG2 cells. After pre-treatment of HepG2 cells with 300 μM of PTIO for 1 h, the cells were treated with 2.5 μM Pt-furoxan or 25 μM other platinum complexes. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Two molar equivalents of **2** was used alone or in the mixture of all assays.

To explore the mechanism of enhanced cytotoxicity of Pt-furoxan, the cellular accumulation of Pt-furoxan and the effect of NO release were further investigated. The platinum accumulation was evaluated by measuring platinum in cells using ICP-MS after incubation of cells with different platinum agents for 4 h. The result showed that the accumulation of Pt-furoxan in cells was significantly higher than that of cisplatin (Figure 3A), indicating the covalent conjugation of **2** to Pt(IV) complex in favor of internalization of **2** and oxoplatin by cells. The high cellular accumulation could be associated with the prominent cytotoxicity of Pt-furoxan.

To verify the effect of NO release on the cytotoxicity of Pt-furoxan, cells were pretreated with 300 μM NO scavenger PTIO for 1 h before drug treatment. The pretreatment of PTIO increased cell viability by 35.9% in the Pt-furoxan group, whereas no effect was observed on the viability of cells treated with other compounds (Figure 3B). These findings indicate that the NO released from Pt-furoxan indeed

contributes, at least partially, to its enhanced cytotoxicity to tumor cells.

Since NO is able to inhibit the motility of cancer cells, the anti-metastasis effect of Pt-furoxan was evaluated with wound-healing assay on highly metastatic 4T1 cells. The photographic imaging showed that the gap on the monolayer cells gradually recovered with time in 24 h to 48 h, showing the migration of the cells. Pt-furoxan clearly inhibited the cell migration, whereas cisplatin, oxoplatin and its mixture with **2** showed negligible effect (Figure 4A). Moreover, the pretreatment of PTIO restored the cell migration that was inhibited by Pt-furoxan (Figure S16), indicating that the NO release contributed to the anti-metastasis effect of Pt-furoxan.

It has been reported that NO could down-regulates MMP, the enzyme promoting metastasis of cancer cells.[18] To exploring the mechanism of anti-metastasis of Pt-furoxan, the activity of MMP2 and MMP9 were analyzed using gelatin zymography. Pt-furoxan significantly inhibited the activity of MMP 9 and MMP2，while other platinum complexes and their mixture with compound **2** did not alter the function of MMPs (Figure S17B). This observation suggests that inhibition of MMP9 and MMP2 is associated with the anti-metastasis function of Pt-furoxan.
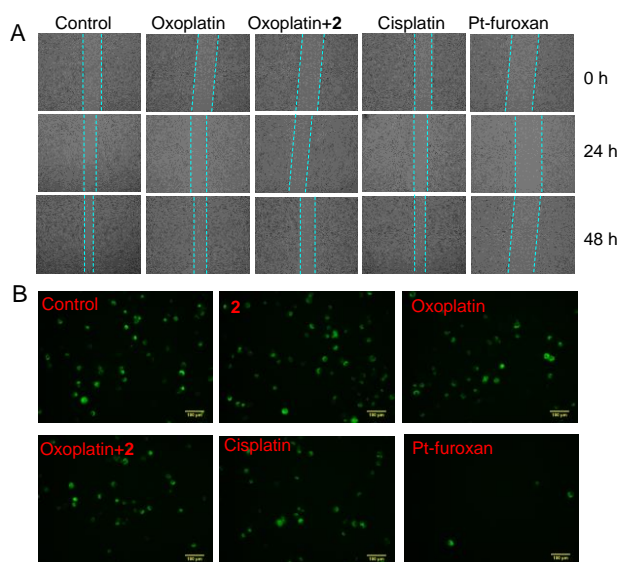

Figure 4. *In vitro* anti-metastasis assay. (A) The effect of platinum complexes on migration of cancer cells measured using scratch test. 4T1 cells were pre-incubated for 24 h or 48 h with 2 μM platinum complexes. (B) The effect of compounds on adhesion of 4T1 cells (green) to HUVECs measured using fluorescence microscope. Co-incubation of Rhodamine 123-labeled 4T1 cells with HUVECs pre-treated with IL-1β (1 ng/ml) in presence of 5 μM of these platinum complexes for 2 h. Two molar equivalents of **2** was used alone or in the mixture in all assays.

Adhesion of tumor cells to vascular endothelial cells is an important step for tumor invasion and metastasis. To verify the effect of Pt-furoxan on adhesion of tumor cells, a fluorescence-based assay was conducted on human umbilical vein endothelial cells (HUVECs). HUVECs seeded on plate were pretreated with IL-1β and then co-cultured with 4T1 cells that stained with Rhodamine 123. After co-incubation for 1 h, the free 4T1 cells were washed out and the cells adhered to HUVECs were counted under a fluorescence microscope. The observation of Rhodamine-stained 4T1 cells on the plate

clearly indicates the adhesion of 4T1 cells to HUVECs, which is consistent with the high metastasis of 4T1 cells. The treatment of cisplatin, oxoplatin or the mixture of oxoplatin and **2** marginally reduced the adhesion of 4T1 cells on the plate (Figure 4B, Figure S17A). By comparison, only a few 4T1 cells were observed on the plate after Pt-furoxan treatment. This result clearly indicates that Pt-furoxan is able to inhibit the IL-1β-induced adhesion of tumor cells to vascular endothelial cells, which is consistent with the anti-metastasis effect of Pt-furoxan.

The *in vivo* antitumor and anti-metastasis activities of Pt-furoxan were evaluated on 4T1 tumor bearing mice. The growth and pulmonary metastasis of breast cancer were measured. Pt-furoxan and testing compounds were administered via intravenous injection. The tumor growth curves showed that Pt-furoxan exerted higher antitumor effect than cisplatin; even half Pt dosage of Pt-furoxan inhibited the tumor growth more effectively than cisplatin (Figure 5A). The tumor weight and imaging at the end of the treatment confirmed this result (Figure 5B, 5D, and S18). Moreover, H&E stain showed that Pt-furoxan caused apoptosis of tumor in a dose-dependent manner (Figure S19). Consistent with the tumor inhibition result, even half platinum dosage of Pt-furoxan induced more intensive apoptosis than cisplatin or the mixture of oxoplatin with furoxan **2**. These results confirmed the high *in vivo* antitumor potency of Pt-furoxan.
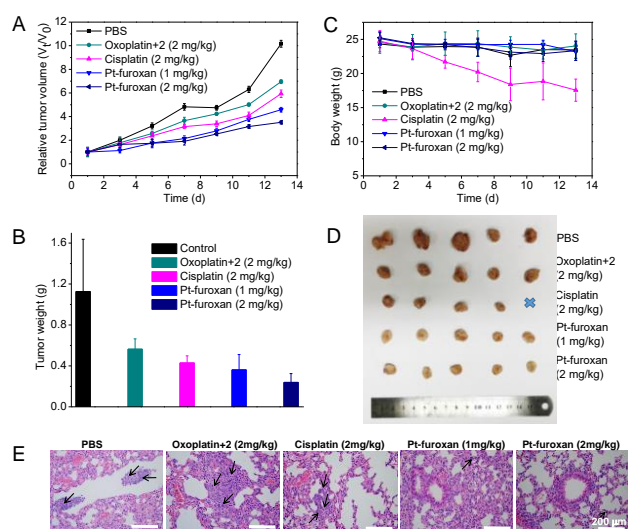

Figure 5. *In vivo* antitumor activity and anti-metastasis assays on 4T1 tumor bearing mice. (A) The relative tumor volume during treatments. (B) The tumor weight in each group at the end of the experiment. (C) The body weight of mice during the treatments. (D) The images of tumor at the end of the experiment. X denotes a mouse died during the treatment. (E) Representative histopathologic examination of the lungs at the end of the experiment. The metastatic tumors in the lungs are marked with black arrows. Balb/c mice-bearing 4T1 tumors were injected through the tail vein with PBS, the mixture of oxoplatin+2 (2 mg Pt/kg body weight, two molar equivalents of 2 was used in the mixture), cisplatin (2 mg/kg, Pt/body weight) and Pt-furoxan (1 mg/kg or 2 mg/kg, Pt/body weight), (n = 5). PBS was used as a control. Mice were treated every-other-day 6 times. Error bars denote standard deviations.

The platinum accumulation in tumor was measured using ICP-MS. The treatment with Pt-furoxan at a dosage of 2 mg Pt/kg (10.26 μmol Pt/kg) resulted in 1.94 μg Pt/g tumor, which is 2.9-fold higher in comparison to the treatment of cisplatin

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(0.66 µg Pt/g tumor) in the same Pt dosage (Figure S20). While the high drug accumulation is consistent with the higher *in vivo* antitumor effect of Pt-furoxan, the half dosage of Pt-furoxan (1.0 mg Pt/kg) led to a similar drug accumulation (0.68 µg Pt/g tumor) relative to cisplatin in a dosage of 2 mg Pt/kg, even though the low dosage of Pt-furoxan demonstrated high antitumor effect than cisplatin. This result reveals that, in addition to drug accumulation in tumor, the function of platinum agents, such as NO releasing of Pt-furoxan in this study, contributes significantly to the antitumor efficacy.

The systemic toxicity of Pt-furoxan was monitored with body weight during the treatment. Pt-furoxan did not alter the growth of mice in both dosages, suggesting the low toxicity of the drug (Figure 5C). By comparison, cisplatin clearly decreased the body weight of mice, and even one mouse died during the treatment of cisplatin. Moreover, to analyze the toxicity of these platinum complexes to major organs, heart, liver, spleen, lung and kidney of mice from drug experimental groups were collected and stained with H&E. Cisplatin clearly caused kidney damage, whereas no obvious damage was observed with the treatment of Pt-furoxan or other platinum agents (Figure S21).

The anti-metastasis effect of Pt-furoxan was also analyzed *in vivo* on the 4T1 breast tumor bearing mice model. After 14-day treatment of these platinum complexes, lung tissues were stained with H&E dying to analyze the pulmonary migration of cancer cells. The results showed that Pt-furoxan detectably inhibited the metastasis of cancer cells to lungs (Figure 5E), in agreement with the *in vitro* results of anti-metastasis assay.

In summary, a novel NO-releasing Pt(IV) complex, Pt-furoxan was designed and synthesized in this work. Pt-furoxan can release cisplatin and NO in cells. While cisplatin causes the apoptosis of tumor cells, the NO released in cells modulates cell response and enhanced the potency of cisplatin. Therefore, Pt-furoxan exhibits synergistic effect on the inhibition of tumor growth. *In vitro* and *in vivo* experiments indicate that Pt-furoxan is more potent than cisplatin. Meanwhile, Pt-furoxan possesses lower systemic toxicity than cisplatin. Moreover, Pt-furoxan effectively inhibits the migration of cancer cells *in vitro* and tumor metastasis in mice model. Further investigations indicate that Pt-furoxan can suppress the activity of MMP9 and MMP2, two key steps of tumor metastasis. In addition, Pt-furoxan efficiently inhibits the adhesion of tumor cells to vascular endothelial cells. These findings indicate that Pt-furoxan possesses dual function of anti-proliferation and anti-metastasis, and exhibits lower systemic toxicity *in vivo*.

Conflicts of interest

There are no conflicts to declare

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Nitric Oxide-releasing Platinum(IV) Prodrug Efficiently Inhibits the Proliferation and Metastasis of Cancer Cells
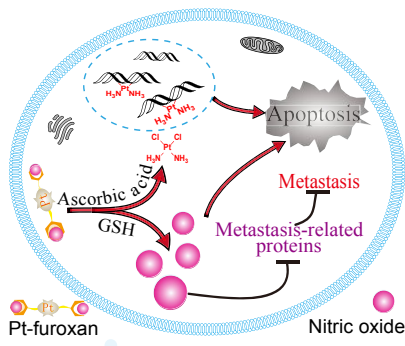
5 Pt-furoxan, a nitric oxide-releasing platinum(IV) prodrug exhibits dual function by releasing cytotoxic cisplatin to induce cell apoptosis, and a signaling molecule NO to inhibit tumor metastasis.