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Expanding the Arsenal of Pt^{IV} Anticancer Agents; Multi-action Pt^{IV} Anticancer Agents with Bioactive Ligands Possessing Hydroxyl Functional Group.

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Dedicated to the late Prof. J. Katzhendler for his mentorship, inspiration and friendship.

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Abstract

Most multi-action Pt^{IV} prodrugs have bioactive ligands containing carboxylates. This is probably due to the ease of carboxylating the OH axial ligands and because following reduction, the active form of the agent is released. A major challenge is to expand the arsenal of bioactive ligands to include those without carboxylates. We describe a general approach for synthesis of Pt^{IV} prodrugs that release in their native form, molecules with OH groups. We linked the OH groups of gemcitabine (Gem), paclitaxel, and estramustine (EM) to the Pt^{IV} derivative of cisplatin by a carbonate bridge. Following reduction, the axial ligands lost CO_2, rapidly generating the active drugs. In contrast, succinate linked drugs did not readily release the free drugs. The carbonate bridged *ctc*-[$Pt(NH_3)_2$(PhB)(Gem-Carb)Cl_2] was significantly more cytotoxic than the succinate bridged *ctc*-[$Pt(NH_3)_2$(PhB)(Gem-Suc)Cl_2]. In vivo data show that carbonate-bridged compound was more potent and less toxic than gemcitabine, cisplatin and co-administration pf cisplatin and gemcitabine.

10.1002/anie.201910014

Despite advances in the treatment of cancer, square planar Pt^{II} complexes such as cisplatin, carboplatin and oxaliplatin (Figure 1) are widely used to treat several forms of cancer, alone or in combination with other drugs.[1,2] They are administered intravenously and after entering the cancer cell, the cis-$[Pt(Am)_2]^{2+}$ binds to two adjacent guanines on the same DNA strand, distorting its structure and triggering cellular responses that result in apoptosis.[3,4] Pt drugs suffer from two major problems: the ability of the tumors to acquire resistance to the drugs and dose-limiting side effects.[5,6,7] To overcome resistance to a given drug, and diminish side effects, clinicians treat patients with a combination of drugs that have different cellular targets and different modes of action.[8,9,10]

Octahedral multi-action Pt^{IV} complexes are used as prodrugs to overcome resistance.[11] They are usually prepared by oxidizing the square planar Pt^{II} drugs with H_2O_2 and subsequent modification of the axial hydroxido ligands. Pt^{IV} complexes are particularity suitable as prodrugs because they are stable outside the cancer cell and activated by reduction inside the cell. The reduction severs the bonds between the platinum and the axial ligands, regenerating the original Pt^{II} drug and releasing the two axial ligands (Figure 1). The axial ligands of Pt^{IV} complexes can be utilized as: lipophilic moieties that enhance passive cellular uptake; tumor targeting agents; or linkers to polymers, nanoparticles, proteins or other delivery agents.[12,13,14] In addition, they can be bioactive agents such as approved drugs, enzyme inhibitors, pathway activators or suppressors, epigenetic modifiers, antimetabolites etc. that attack different cellular targets and work in synergy with Pt^{II} drugs to overcome resistance.[15,16,17]

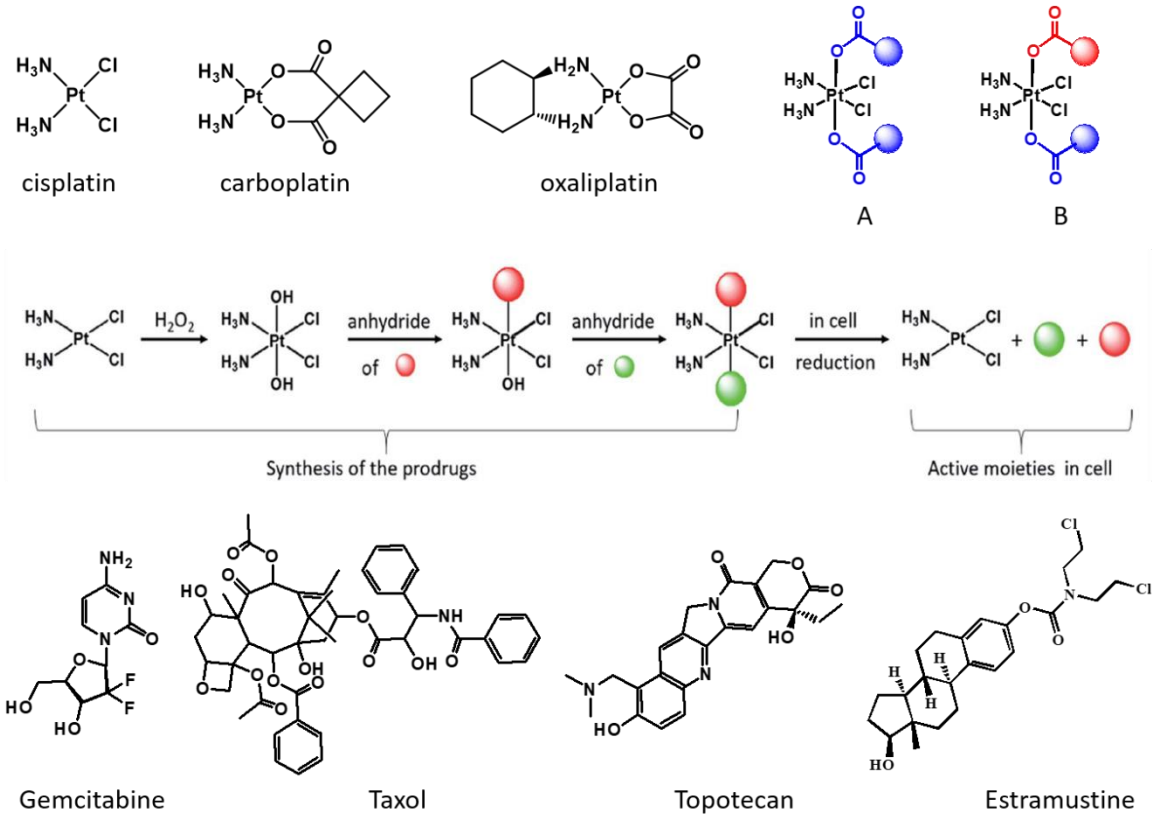

Figure 1 – (top row)-the FDA approved Pt^{II} drugs: cisplatin, carboplatin and oxaliplatin. and dual-action (A) and triple-action (B) Pt^{IV} prodrugs. (middle row)- synthesis and mode of action of Pt^{IV} prodrugs and four anticancer drugs with no carboxylates (bottom row).

10.1002/anie.201910014

The nature of the linkage between the ligand and the axial hydroxido of Pt^{IV} (carboxylate, carbamate, ether or carbonate) is not usually important when conjugating Pt^{IV} to lipophilic moieties, targeting agents or delivery systems. In contrast, it is important for multi-action Pt^{IV} prodrugs that should release the bioactive moieties from the axial positions, in their active form. This implies that the axial oxygen (Pt-OR) should be an integral part of the bioactive molecule, or be part of a linker that can readily release the active drug. Most multi-action Pt^{IV} prodrugs, have bioactive moieties possessing a carboxyl group (Figure 1 A, B), probably because following reduction, the active form of the agent is released.

Drugs such as taxol, doxorubicin, 5-fluoruracil, gemcitabine, topotecan or irinotecan are given in combination with platinum drugs in the clinic.[18,19,20] They have no carboxylates, but have either hydroxy or amine groups (Figure 1 – bottom row).

Therefore, a major challenge is the synthesis of multi-action Pt^{IV} complexes with FDA approved drugs that have no carboxylates. Attempts were made to conjugate OH bearing bioactive molecules to Pt^{IV}. Since no effective protocols exist for direct conjugation of OH bearing moecules to the axial positions of Pt^{IV}, ester or ether linkers were used to conjugate estrogens,[21] combretastatin- A4,[22] 7-hydroxy coumarin or wagonin[23], NBDHEX,[24] etc to Pt^{IV} (Figure 2). Due to the relative stabilities of the ether and ester bonds, the active moieties are not released rapidly following reduction.

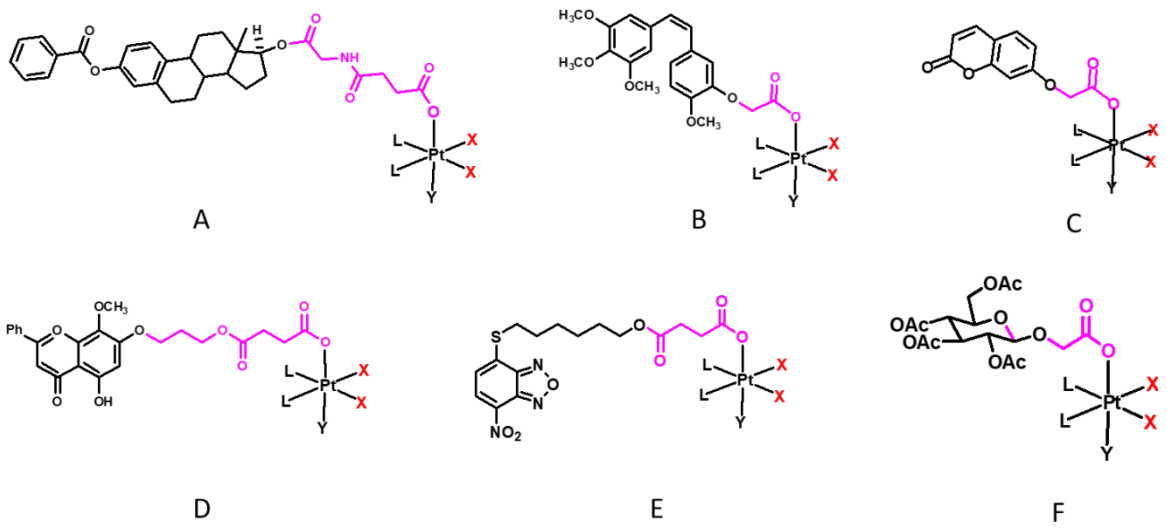

Figure 2 – Pt^{IV} prodrugs to which OH containing bioactive ligands were attach by forming an ester link to the OH (A & E) or via an ether linkage (B, C, D & F)

We developed a new conceptual approach to attain this goal. It is based on reports that carbonic acid monoesters are unstable and decompose to alcohols and CO_2.[25] If we form a carbonate bridge linking the axial OH of Pt^{IV} and the OH of the bioactive moiety, reduction of the Pt^{IV} will generate an unstable carbonic acid monoester that will rapidly release the active moiety.

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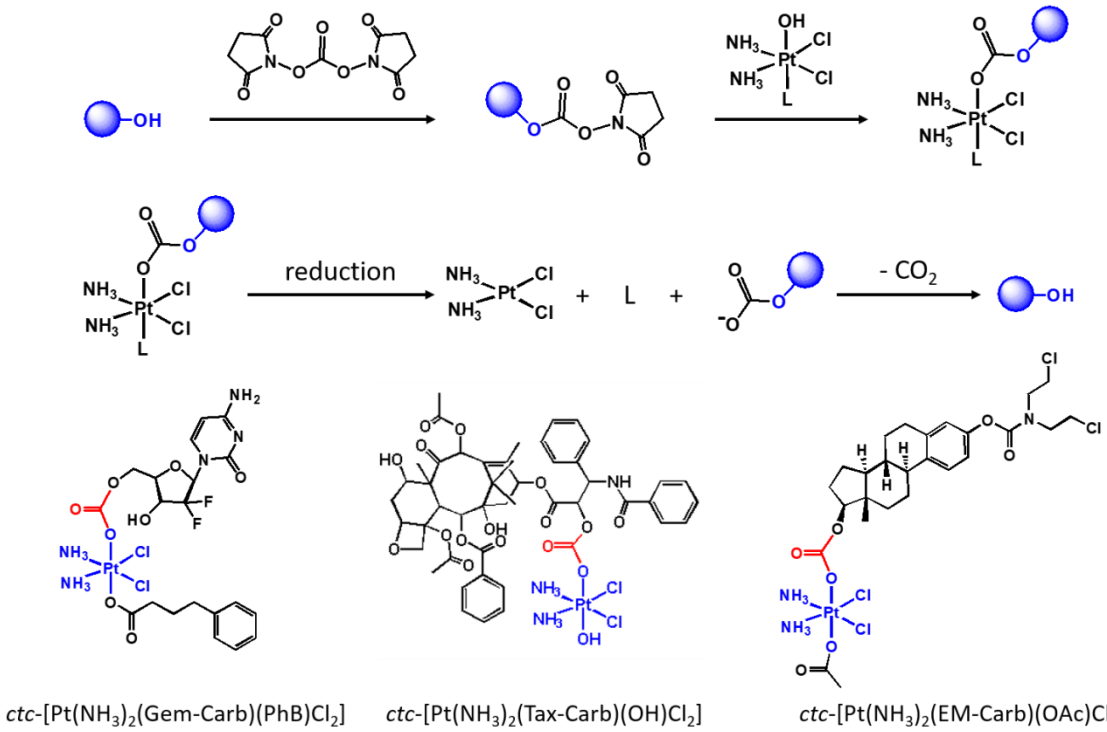

Figure 3 – The synthetic route for conjugating the OH group of a ligand to the axial position of Pt^{IV} via a carbonate linkage (top); the release and activation of the bioactive ligand (middle); and the three Pt^{IV} multi-action prodrugs with gemcitabine, taxol and estramustine.

To test our hypothesis, we synthesized three Pt^{IV} derivatives of cisplatin with carbonate bridging the platinum and OH groups of the drugs. The synthetic strategy appears in Figure 3. The OH group of the ligand is activated with DSC, [bis(2,5-dioxopyrrolidin-1-yl)carbonate], and then reacted with the axial OH of the Pt^{IV} to form the carbonate link. To the best of our knowledge, there are very few reports on Pt^{IV} complexes with carbonate axial ligands, and no description of this synthetic approach.[26] We chose three anticancer drugs that have cellular targets different from cisplatin: gemcitabine (Gem); an antimetabolite,[27] Paclitaxel (Taxol); acts on the tubulin-microtubule system[28] and estramustine (EM); acts on the tubulin-microtubule system and on the DNA (Figure 3).

The synthesis is described in in Figure 3. Detailed procedures are provided in the supplementary material. All compounds were purified by preparative HPLC and characterized by ^{195}Pt and ^{1}H NMR, and ESI-MS. Purity was verified by elemental analysis.

To test whether the reduction of the carbonate linked molecules leads to the release of the drugs, we exposed *ctc*-[$Pt(NH_3)_2$(Gem-Carb)$(PhB)Cl_2$], *ctc*-[$Pt(NH_3)_2$(Tax-Carb)$(OH)Cl_2$] and *ctc*-[$Pt(NH_3)_2$(EM-Carb)$(OAc)Cl_2$] to an excess of ascorbic acid at 37°C in phosphate buffer (pH=7.0) and monitored the reduction by HPLC. The reduction of *ctc*-[$Pt(NH_3)_2$(Tax-Carb)$(OH)Cl_2$] was monitored by ^{1}H NMR.

10.1002/anie.201910014

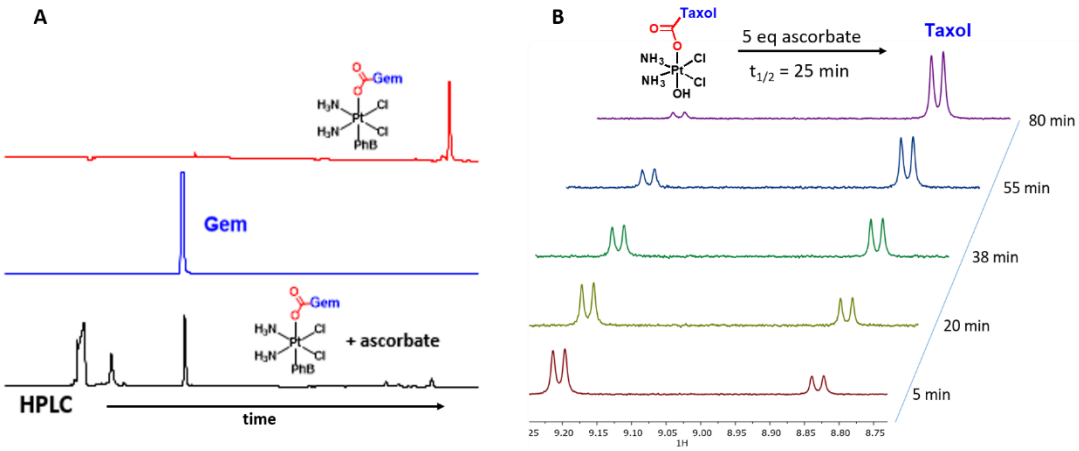

Figure 4 – A) HPLC chromatograms of *ctc*-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$] – top, Gem (middle) and the reaction mixture of *ctc*-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$] with 10 eq of ascorbate after 2 h. B) ^{1}H NMR spectra of the reduction of *ctc*-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$] with 5 eq of ascorbate, monitoring the amide proton of taxol.

After 2 h, the peak of *ctc*-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$] vanished, and a new peak with the same retention time and the same ESI-MS as Gem appears, indicating complete reduction of *ctc*-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$] and full release of Gem (Figure 4A). The HPLC data for the reduction of *ctc*-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$] with 20 eq of ascorbate is depicted in Figure S35. We incubated *ctc*-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$] with 5 eq of ascorbate and the reduction was followed by ^{1}H NMR. The NH proton in *ctc*-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$] resonates at ~ 9.2 ppm and in free taxol at ~ 8.85 ppm. The reduction of *ctc*-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$] with the concurrent growth of Taxol is depicted in Figure 4B with a half-life of 25 min. No intermediates were observed, confirming rapid decarboxylation. Similar results were obtained for the reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Carb)(OAc)Cl$_2$] (Figure 5A).

OH containing bioactive molecules can be conjugated to Pt^{IV} prodrugs via a succinate bridge (Figure 3A, 3E). Following reduction, the succinated-drug is released. To obtain the free drug, the ester bond to the succinate has to be severed by hydrolysis or by esterases. We prepared *ctc*-[Pt(NH$_3$)$_2$(Gem-Suc)(PhB)Cl$_2$] and *ctc*-[Pt(NH$_3$)$_2$(EM-Suc)(OAc)Cl$_2$], the Pt^{IV} succinate-linked analogs of *ctc*-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$] and *ctc*-[Pt(NH$_3$)$_2$(EM-Carb)(OAc)Cl$_2$] and monitored their reduction, and the release of Gem-Suc (Figure S36) or EM-Suc by HPLC (Figure 5B).

One hour after reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Carb)(OAc)Cl$_2$] began, free EM is observed, and after 8 h reduction was nearly complete with concurrent release of EM (RT=28.1 min. -Figure 5A). In contrast, reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Suc)(OAc)Cl$_2$] yielded only the EM-succinate conjugate (RT=28.9 min), and even after 79 h no free EM was observed (Figure 5B). The $t_{1/2}$ for the reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Carb)(OAc)Cl$_2$] is 2.2 h and for the reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Suc)(OAc)Cl$_2$] is 6 h (Figure S37).

Free EM can be generated from *ctc*-[Pt(NH$_3$)$_2$(EM-Suc)(OAc)Cl$_2$] only by hydrolysis of the ester link to the succinate. Since the reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Suc)(OAc)Cl$_2$] was nearly complete after 30 h and no EM was observed after 79 h, the rate determining step for the release of EM is the ester hydrolysis. To confirm this, we prepared the EM-succinate conjugate and monitored the hydrolysis of the ester bond ($t_{1/2}$ 15 d -Figure S41).

10.1002/anie.201910014

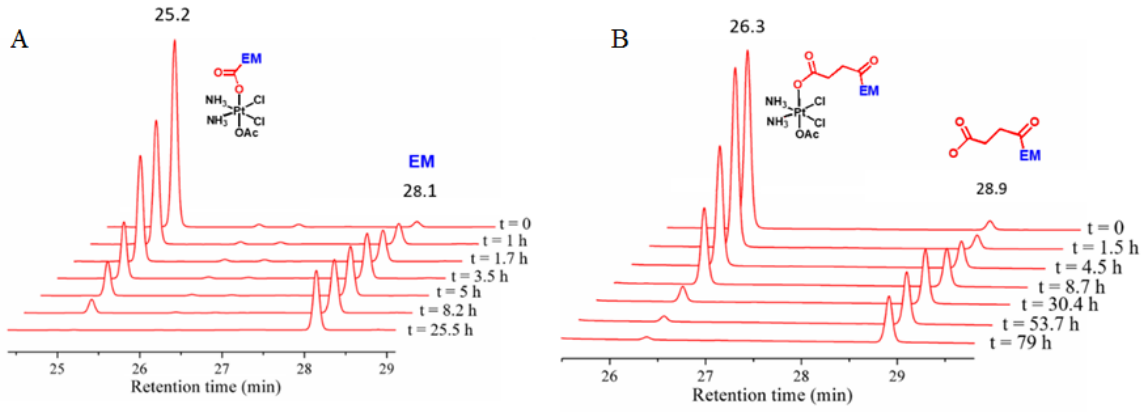

Figure 5 – The reduction of *ctc*-[Pt(NH$_3$)$_2$(EM-Carb)(OAc)Cl$_2$] compared to the reduction and hydrolysis of the ester linked *ctc*-[Pt(NH$_3$)$_2$(EM-Suc)(OAc)Cl$_2$].

We combined Gem and taxol with cisplatin because they are potent anticancer drugs, used in the clinic with platinum drugs.[29] Preliminary cytotoxicity data against ovarian cancer cells (A2780) and the cisplatin resistant line (A2780cisR) appear in Table 1.

Table 1- in vitro cytotoxicity data for a 72 h incubation of the compounds with the ovarian cancer cell lines (A2780 and A2780cisR -left) and the in vivo efficacy study of cisPt(Gem)(PhB) on the Lewis lung cancer murine model.

	In vitro IC$_{50}$ (μM)		**In vivo efficacy LLC**		
compound	Cancer cell lines		Daily dose (mg kg^{-1})	tumor weight (g)	Inhibition of tumor growth (%)
	A2780	**A2780cisR**			
ctc-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$]	0.004±0.002	0.0059±0.00004	ND[a]	ND[a]	ND[a]
Taxol	0.0022±0.001	0.003±0.00006	NDa	ND	ND[a]
ctc-[Pt(NH$_3$)$_2$(Gem-Suc)(PhB)Cl$_2$]	0.063 ±0.01	0.066 ±0.002	ND[a]	ND[a]	ND[a]
ctc-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$]	0.005±0.0005	0.014±0.001	20	0.032±0.003	92
cisplatin	0.924±0.05	16.25±3.14	3	0.040±0.01	90
gemcitabine	0.002±0.001	0.005±0.001	60	0.08±0.2	80
cisplatin+gemcitabine (1:1)	0.0031±0.0002	0.0121±0.0001	60+3	0.058±0.03	86
control			none	0.41±0.1	
[a]ND = Not determined					

Taxol is much more potent than cisplatin and *ctc*-[Pt(NH$_3$)$_2$(Tax-Carb)(OH)Cl$_2$] is only slightly less potent than taxol. Gemcitabine is significantly more cytotoxic than cisplatin and also somewhat more potent than *ctc*-[Pt(NH$_3$)$_2$(Gem-Carb)(PhB)Cl$_2$] and *ctc*-[Pt(NH$_3$)$_2$(Gem-

Suc)(PhB)Cl_2]. The triple-action *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] and *ctc*-[Pt(NH_3)$_2$(Gem-Suc)(PhB)Cl_2] have IC_{50} values in the low nM range, significantly more potent than cisplatin. Interestingly, the nature of the linkage between the Gem and the Pt^{IV} has a large effect on cytotoxicity. *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2], with the carbonate linkages is about 12- and 5-fold more potent than its analog with the succinate bridge in A2780 and A2780cisR respectively. The reasons for these differences are currently under investigation.

In vitro cytotoxicity does not predict the ability of the compound to reach the tumor and to kill cancer cells. Moreover, it provides no information on the toxicity of the compounds. Therefore, we carried out preliminary in vivo studies comparing cisplatin, gemcitabine, *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] and co-treatment with cisplatin and gemcitabine in the murine Lewis Lung Carcinoma (LLC) solid tumor model. Seven days after tumor inoculation the tumor-bearing mice were randomized into vehicle control and treatment groups. Control mice received the vehicle (0.5% DMSO (v/v) and 99.5% of a saline solution (v/v)), whereas treated groups received daily doses of *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] (20 mg kg^{-1} in vehicle solution, orally) gemcitabine (60 mg kg^{-1} in 0.9% saline solution, iv) or cisplatin (3 mg kg^{-1} in saline solution, iv). The tumor growth was evaluated at day 15, and the results are summarized in Tables 1 and S1. Changes in the body weights were monitored every two days (Figure S43).

Although most potent in vitro, gemcitabine was the least effective in vivo and induced a reduction of tumor growth of about 80%. Oral administration of *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] induced a ca. 92% reduction of the tumor mass compared to the control group, very similar to the result obtained with cisplatin (~90% tumor inhibition). Remarkably, the time course of body weight changes indicated that treatment with *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] induced a body weight loss lower than that induced by cisplatin (Figure S43). Gemcitabine induced a reduction of tumor growth of about 80% and a significant anorexia, with a body weight loss ~20%. Co-treatment with cisplatin+gemcitabine was less effective than *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] in inhibition of tumor growth (86 vs. 92%) but more importantly it was significantly more toxic than *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] resulting in a body weight loss >30%.

In summary, we developed a new approach for conjugating bioactive molecules with OH groups to the axial position of Pt^{IV} such that following reduction of the Pt^{IV}, the bioactive molecule is released in its active form. We accomplished this by using a carbonate as a bridge between the hydroxido axial ligand of Pt^{IV} complexes and OH groups of the bioactive molecules. Following reduction, the carbonated ligands lose CO_2 and rapidly generate the original bioactive molecules with an OH group. This allowed us to prepare multi-action Pt^{IV} derivatives of cisplatin with drugs such as gemcitabine, taxol and estramustine.

C*tc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] was significantly more potent than cisplatin *in vitro* but slightly less potent than gemcitabine and comparable to co-treatment with cisplatin+gemcitabine. Importantly, in the in vivo studies *ctc*-[Pt(NH_3)$_2$(Gem-Carb)(PhB)Cl_2] was more effective and less toxic than the co-treatment with cisplatin and gemcitabine demonstrating in this case the advantage of using multi-action prodrugs as compared to combination therapy.

We believe that this novel approach, paves the way for the design and synthesis of novel classes of multi-action Pt^{IV} anticancer agents with a variety of bioactive moieties that have hydroxyl functional groups that were hitherto unavailable to the medicinal chemists.

While succinates can be used to bridge the bioactive ligands with the Pt^{IV}, we have shown that that the differences in the rates of reduction between Pt^{IV} complexes with carbonate and succinate bridges to the hydroxy groups of the ligands, are not very large, but there is a huge

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difference in the rates of release of the active moiety, due to the slow hydrolysis of the ester bond. Nevertheless, these results may not necessarily reflect the relative rates of release of the bioactive moieties in cells.

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Conflict of interest

The authors have no conflict of interest

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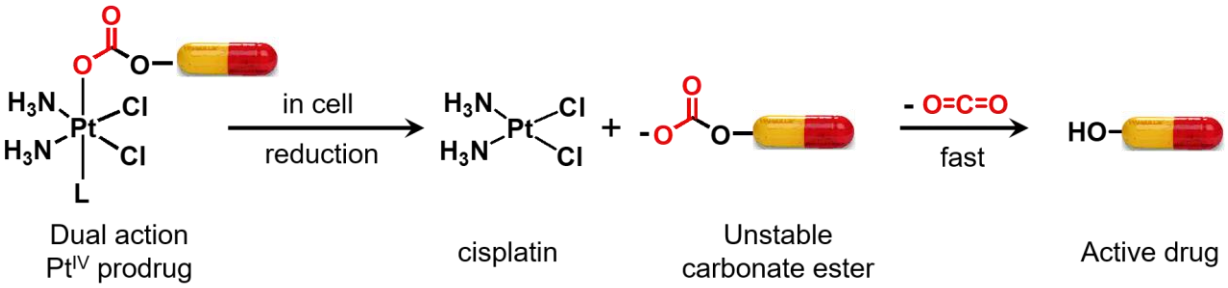
Table of contents



We prepared very potent multi-action Pt^{IV} prodrugs that following reduction release cisplatin and OH containing drugs such as gemcitabine or taxol. Using carbonate to bridge the axial Pt^{IV} OH and the OH of the drug facilitates rapid decarboxylation and release of the active drug.

Keywords:
Anti-cancer
Gemcitabine
Platinum
Prodrug
Taxol