SUPPORTING INFORMATION

Dual-acting antitumor Pt(IV) prodrugs of kiteplatin with dichloroacetate axial ligands.

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Characterization of *cis,trans,cis*-[Pt(OXA)(OH)$_2$(*cis*-1,4-DACH)] (5).

The ESI-MS spectrum of compound **5** showed a peak at *m/z* = 470.03 corresponding to [**5**+K]$^+$ and the experimental isotopic pattern of the peak was in good agreement with the theoretical one (data not shown). The ^{1}H NMR of compound **5** in DMSO-d$_6$ is reported in Figure S1. The singlet, with Pt satellites ($^2J_{H\text{-}Pt}$ = 68.9 Hz), located at 6.71 ppm was assigned to the aminic protons of coordinated *cis*-1,4-DACH. The singlet, with Pt satellites ($^3J_{Pt\text{-}H}$ = 74.04 Hz), appearing at 2.91 ppm was assigned to the methynic groups of coordinated DACH while two multiplets located at 1.97 and 1.50 ppm were assigned to the methylenic protons of *cis*-1,4 DACH. Finally the singlet at 0.77 ppm, integrating for two protons, was assigned to the OH residues coordinated in axial positions.

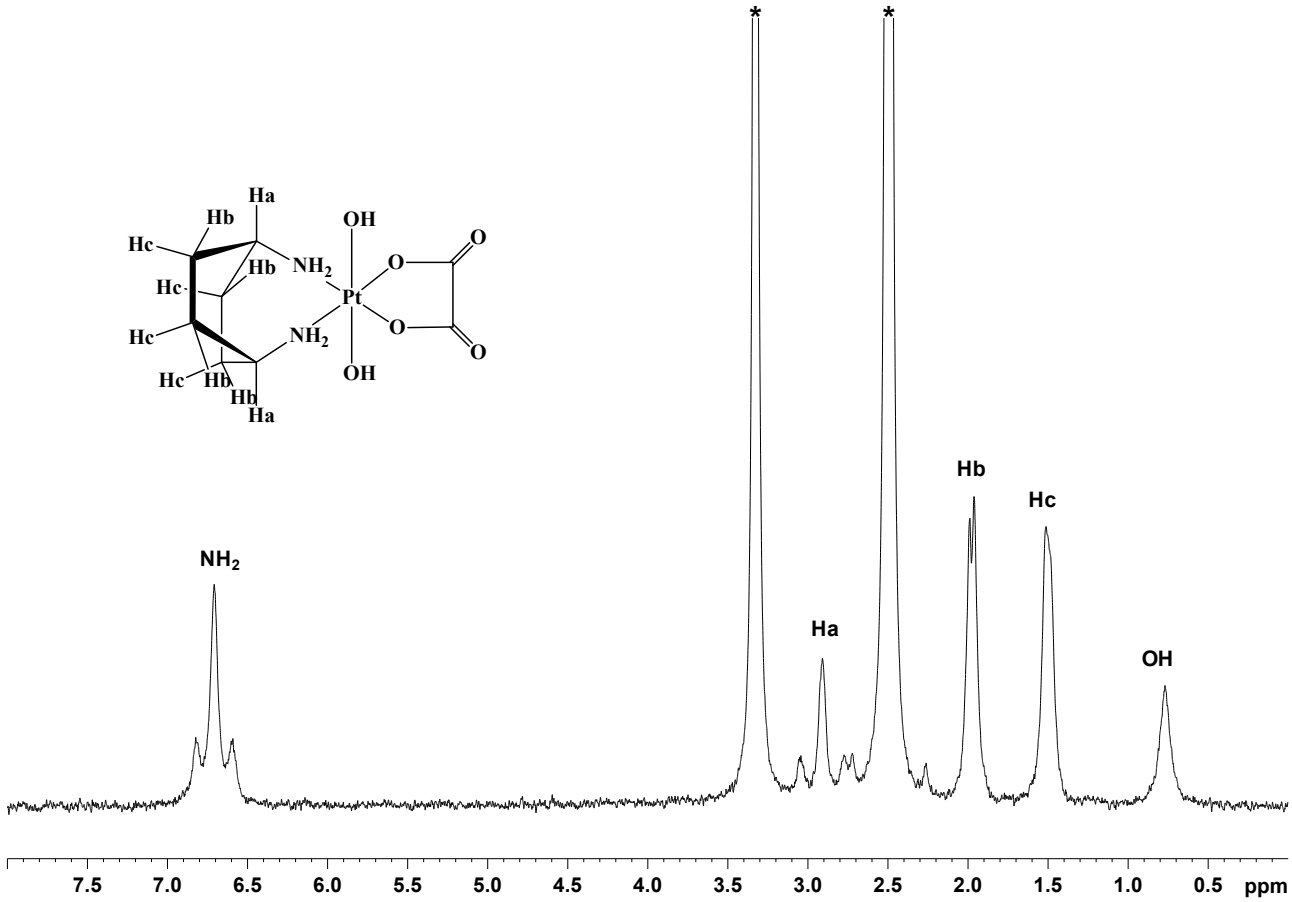


Figure S1: ^{1}H NMR (300 MHz) spectrum of **5** in DMSO-d$_6$. The asterisks indicate residual solvent peaks.

Characterization of *cis,trans,cis*-[Pt(OXA)(DCA)$_2$(*cis*-1,4-DACH)] (6).

The ESI-MS spectrum showed a peak at *m/z* = 650.93 corresponding to [**6**-H]$^-$ and the experimental isotopic pattern of the peak was in good agreement with the theoretical one (data not shown). The ^{1}H NMR of compound **6** in DMSO-d$_6$ is reported in Figure S2. The singlet, with Pt satellites ($^2J_{H\text{-}Pt}$= 59 Hz), located at 7.69 ppm was assigned to the aminic protons of coordinated *cis*-1,4-DACH. This signal is 0.23 ppm upfield with respect to the analogous signal of compound **3** and its shielding could be due to the presence of the *cis* oxalate ligand. The singlet located at 6.53 ppm was assigned to the methynic protons of coordinated dichloroacetate. The singlet, with Pt satellites ($^2J_{H\text{-}Pt}$= 67.12 Hz), integrating for two protons and the multiplet integrating for eight protons falling at 2.98 and 1.72 ppm, respectively, were assigned to the methynic and methylenic protons of coordinated DACH.

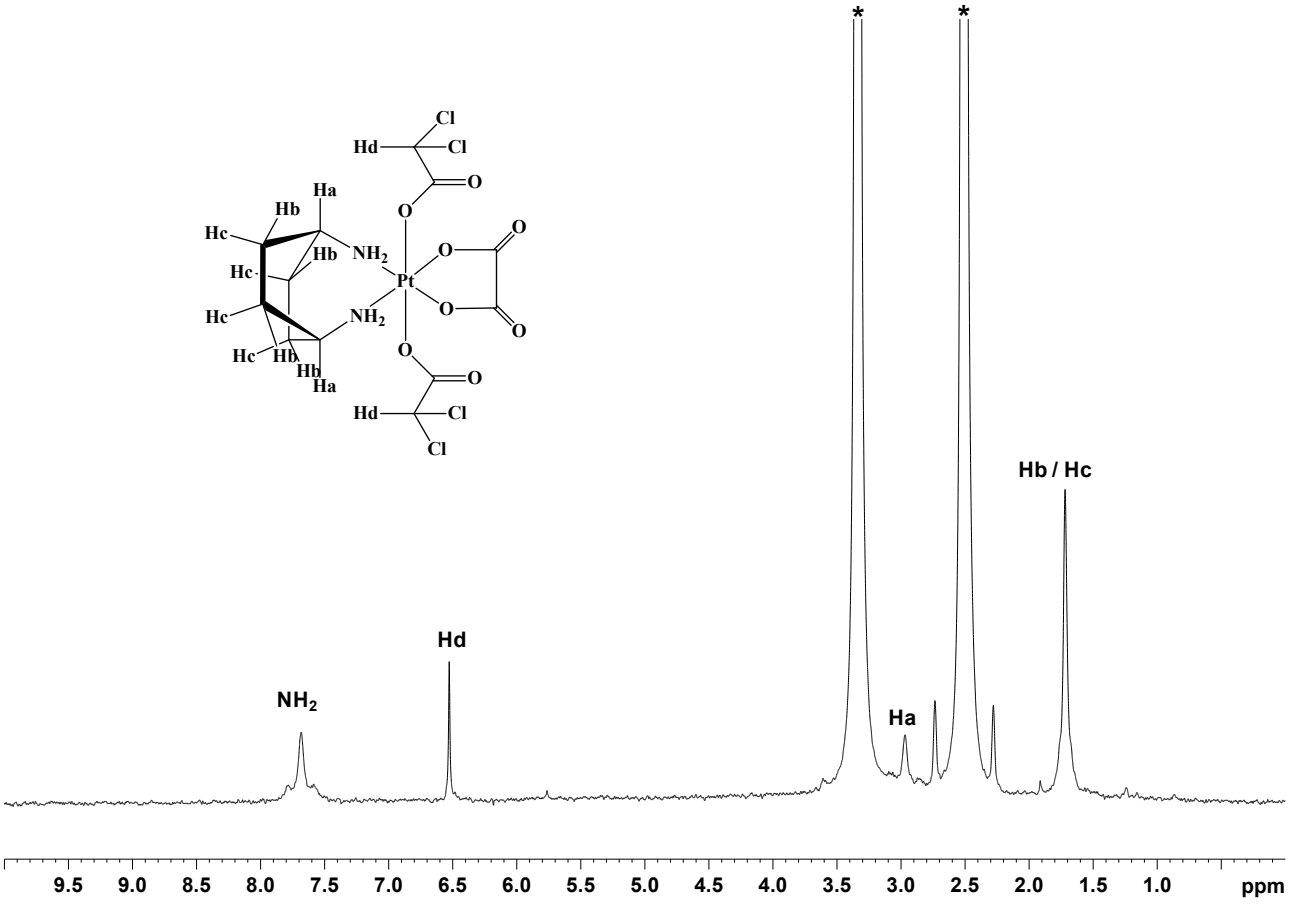


Figure S2: ^{1}H NMR (300 MHz) spectrum of **6** in DMSO-d$_6$. The asterisks indicate residual solvent peaks.

Reduction of *cis,trans,cis*-[$PtCl_2(OH)_2$(*cis*-1,4-DACH)] (2) with ascorbic acid

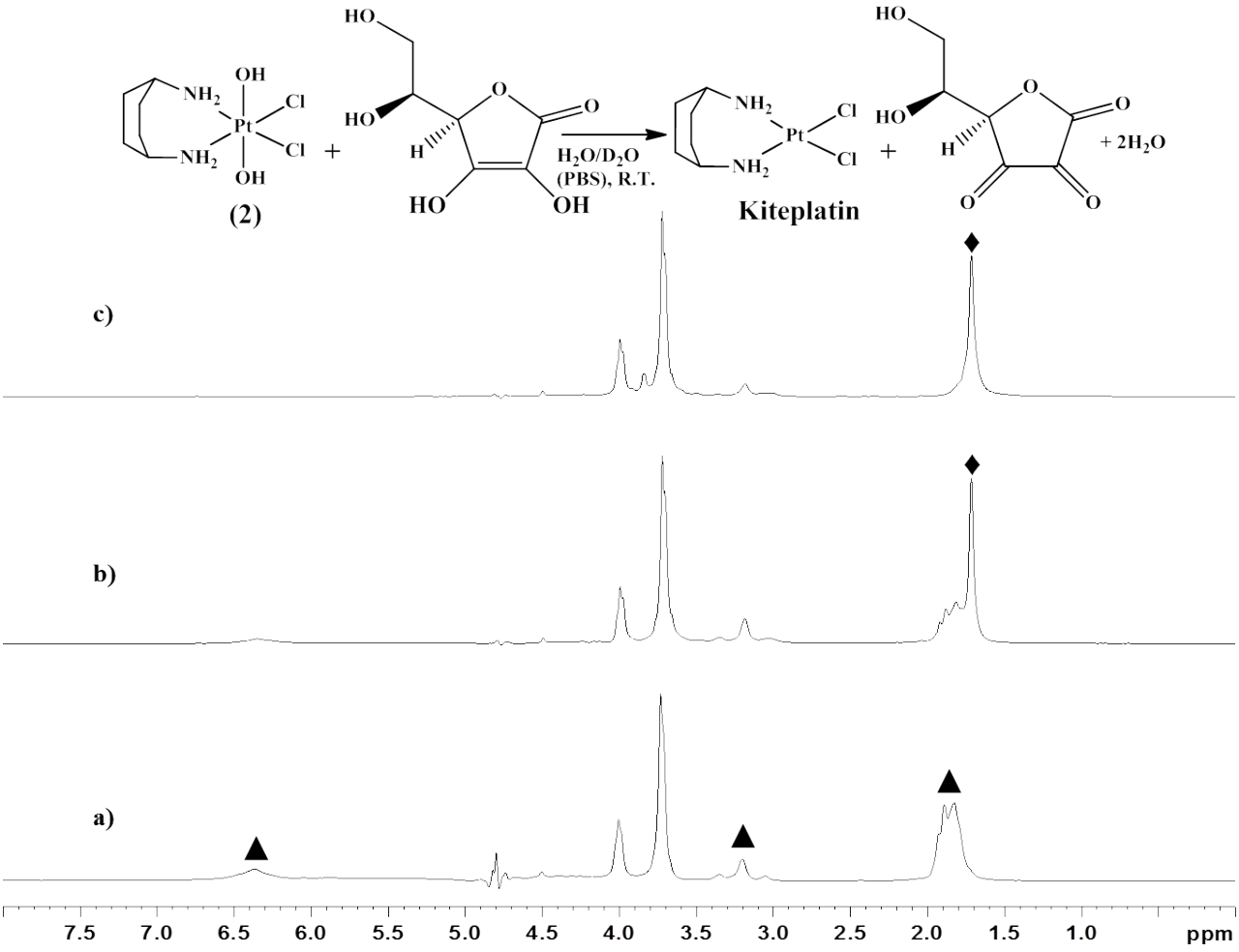


Figure S3: ^{1}H NMR spectra of *cis,trans,cis*-[$PtCl_2(OH)_2$(*cis*-1,4-DACH)] (**2**) treated with ascorbic acid (3-fold molar excess) in deuterated phosphate buffer (H_2O/D_2O, 90/10, v/v; 500 µL, 100 mM NaCl, 200 mM Na_2HPO_4/NaH_2PO_4, pH 7.0) at zero time (**a**), after 50 minutes (**b**), and 3 h (**c**). ▲ indicates the peaks belonging to **2**; ♦ indicates the peak belonging to **1**.

SRB test.

Sulforhodamine B assay was also used to determine the antiproliferative activity of newly synthesized derivatives. Briefly, BxPC3 cells (5×103 per well) were seeded (100 µL) in 96-well microplates. After 24 h, the medium was removed and replaced with fresh medium containing the compound to be studied at the appropriate concentration. Triplicate cultures were established for each treatment. After 72 h, the medium was removed and cells were fixed with 10% cold trichloroacetic acid (TCA) and kept at 4 °C for 2 h, then washed five times with distilled water, and air dried. Cells were subsequently stained with Sulforhodamine B dye for 1 h, then washed with glacial acetic acid five times and air dried. Thereafter, each well was treated with TrisBuffer (150 µL) and plates were gently shaken for 10 min on a mechanical shaker. Cell growth inhibition was evaluated by measuring the absorbance of each well at 540 nm, by using a Bio-Rad 680 microplate reader.

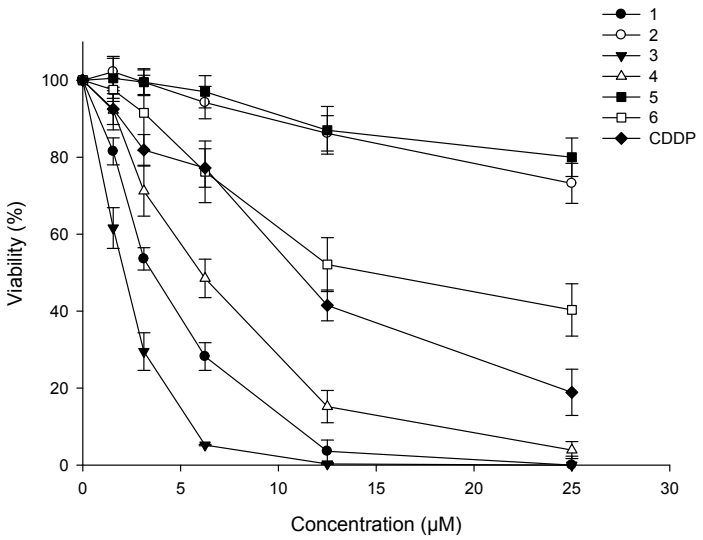
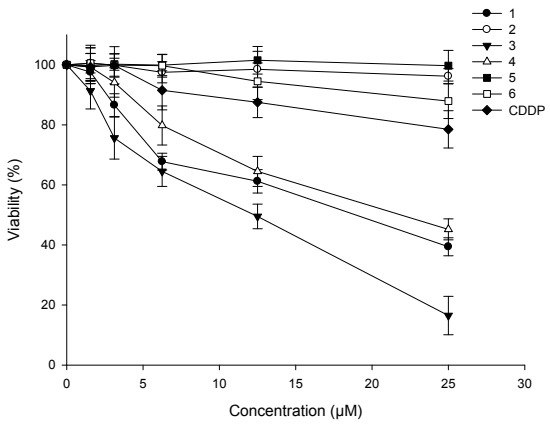


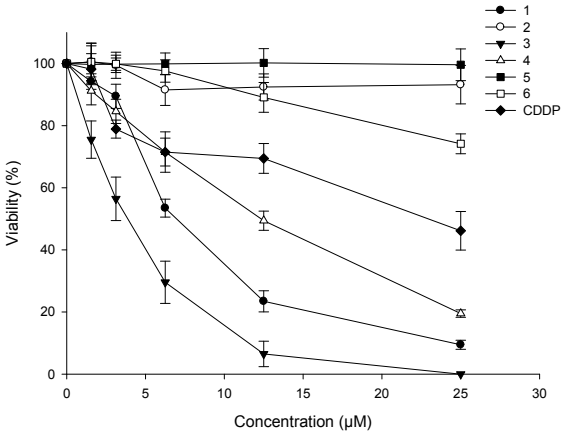
Figure S4. BxPC3 cells (5×10^3 mL^{-1}) were treated for 72 h with increasing concentrations of tested compounds. Cytotoxicity was assessed by SRB test. Data are the means of three independent experiments. Error bars indicate S.D.

Time-course cytotoxicity assays.

A



B



C

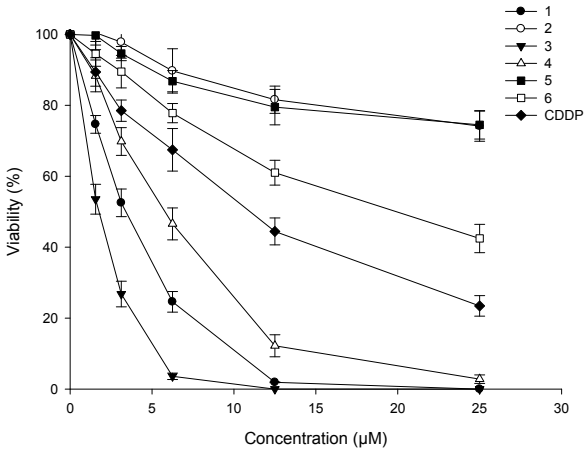


Figure S5. BxPC3 cells (5×10^3 mL^{-1}) were treated for 24 (**A**), 48 (**B**) and 72 (**C**) h with increasing concentrations of tested compounds. Cytotoxicity was assessed by MTT test. Data are the means of three independent experiments. Error bars indicate S.D.