

ELECTRONIC SUPPLEMENTARY MATERIALS

New Oxaliplatin-Pyrophosphato Analogs with Improved In Vitro Cytotoxicity.

Alessandra Barbanente,¹ Rosa Maria Iacobazzi,² Amalia Azzariti,² James D. Hoeschele,³ Nunzio Denora,⁴ Paride Papadia,⁵ Concetta Pacifico,¹ Giovanni Natile,¹ Nicola Margiotta.^{1,*}

¹Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Via E. Orabona 4, 70125 Bari, Italy.

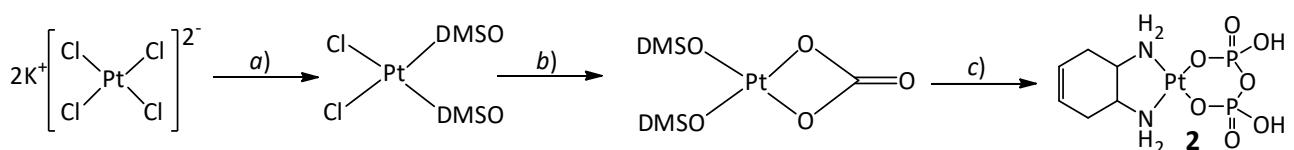
²Experimental Pharmacology Laboratory, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy.

³Department of Chemistry, Eastern Michigan University, 48197 Ypsilanti, Michigan, United States.

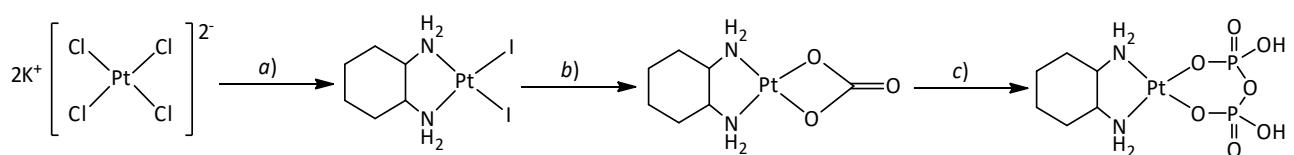
⁴Dipartimento di Farmacia-Scienze del Farmaco, Università degli Studi di Bari Aldo Moro, Via E. Orabona 4, 70125 Bari, Italy;

⁵Department of Biological and Environmental Sciences and Technologies (DiSTeBA), University of Salento, Prov.le Lecce-Monteroni, Centro Ecotekne, 73100 Lecce, Italy.

*Correspondence: nicola.margiotta@uniba.it; Tel.: +39 080 5442759



Scheme S1. *a)* water, dimethyl sulfoxide, room temperature, dark, 24 h; *b)* water, Ag_2CO_3 , 40 °C, 2 h; *c)* water, pH=8, *trans*-1,2-diamino-cyclohexene (DACHEX), sodium pyrophosphate decahydrate, 55 °C, 18 h.



Scheme S2. *a)* water, excess KI (6 fold), 1*R*,2*R*-diamino-cyclohexane (DACH), room temperature, 3 h; *b)* water, Ag_2CO_3 , 40 °C, 2 h; *c)* water, pH=8, sodium pyrophosphate decahydrate, 55 °C, 3.5 h.

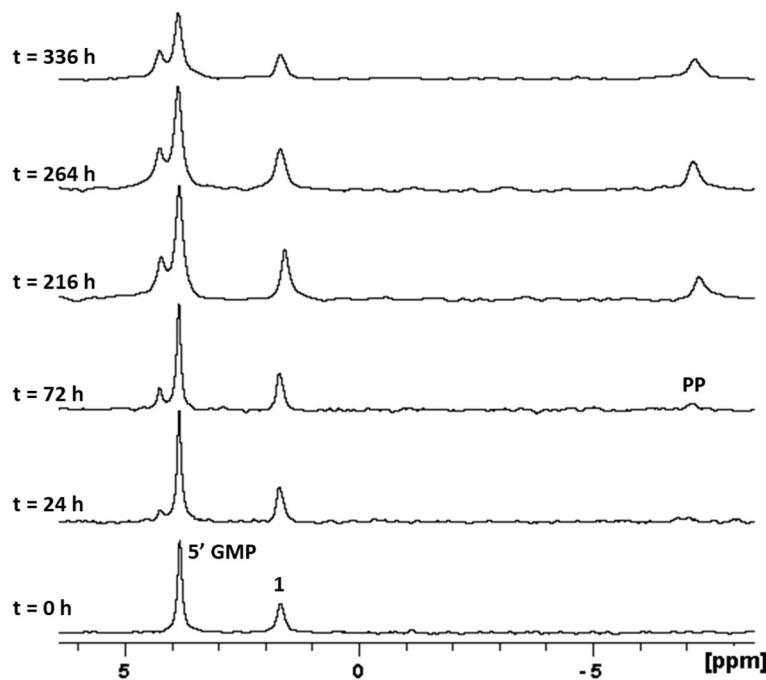


Figure S1. ^{31}P NMR spectra at different time intervals of **1** (5 mM) in the presence of 5'-GMP (12.5 mM) at $\text{pH}^* = 7.4$ (D_2O , 50 mM HEPES buffer), 4 mM NaCl, and 37 °C.

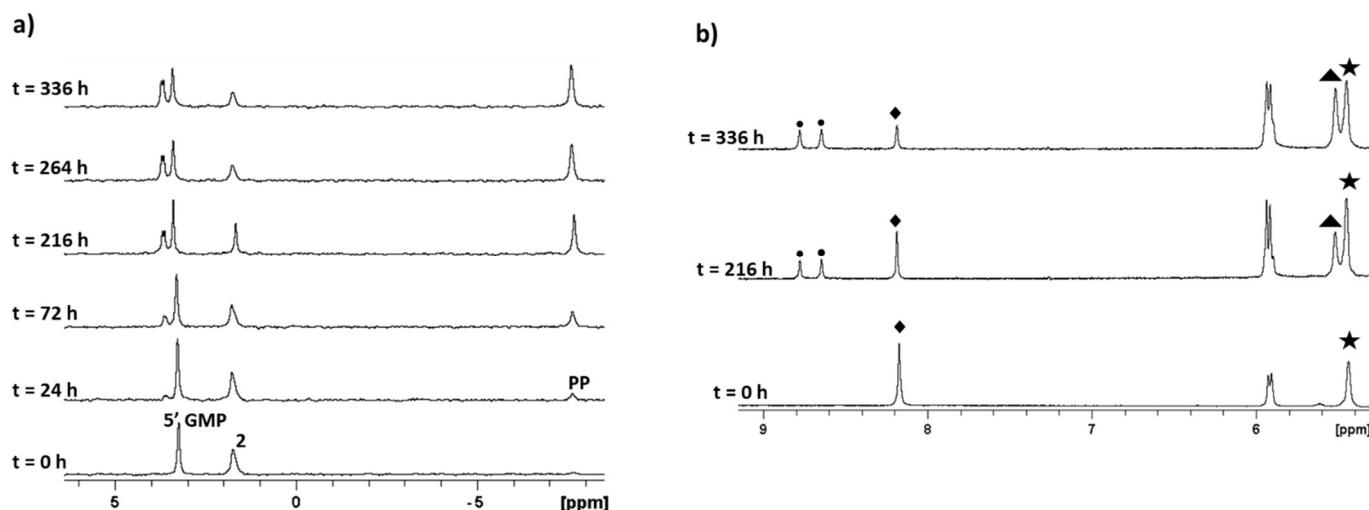


Figure S2. a) ^{31}P NMR spectra at different time intervals of **2** (5 mM) in the presence of 5'-GMP (12.5 mM) at $\text{pH}^* = 7.4$ (D_2O , 50 mM HEPES buffer), 4 mM NaCl, and 37 °C. b) ^1H NMR spectra at different time intervals of **2** (5 mM) in the presence of 5'-GMP (12.5 mM) at $\text{pH}^* = 7.4$ (D_2O , 50 mM HEPES buffer), 4 mM NaCl, and 37 °C.

Table S1. *In vitro* cytotoxicity^a

Compounds	IC_{50} (μM) \pm S.D.				
	HCT116	PC3	OV2008	MDAMB231	Average
1	21 \pm 2	29 \pm 3	15 \pm 2	26 \pm 3	23 \pm 3
2	20 \pm 2	100 \pm 6	30 \pm 3	39 \pm 4	47 \pm 6
3	19 \pm 4	100 \pm 8	29 \pm 5	91 \pm 5	60 \pm 8
4	44 \pm 3	100 \pm 5	46 \pm 5	100 \pm 7	72 \pm 7
CDDP	9 \pm 2	9 \pm 3	4 \pm 1	2 \pm 1	6 \pm 3
OXP	72 \pm 5	100 \pm 5	54 \pm 4	93 \pm 6	80 \pm 6

^aCells ($3\text{--}5\cdot10^3$ cells per mL) were treated for 72 h with increasing concentrations of the tested compounds. Cytotoxicity was assessed by the MTT test. IC_{50} values were calculated by the four parameter logistic model ($p < 0.05$). S.D. = standard deviation. OXP = oxaliplatin, CDDP = cisplatin.