Polyhedron 85 (2015) 685–689

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Antiproliferative activity of platinum(II) complexes containing triphenylphosphine: Correlation between structure and biological activity

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ARTICLE INFO

Article history:
Received 1 August 2014
Accepted 2 October 2014
Available online 12 October 2014

Keywords:
Platinum(II) complexes
Triphenylphosphine
Antiproliferative activity
Structure–activity relationship
Dialkylamino ligands

ABSTRACT

A series of neutral complexes of platinum(II) of general formula $[PtCl_2L(PPh_3)]$ [L = $Et_2NC(Me)NH$, $SOMe_2$, CO, Et_2NH, $(HOCH_2CH_2)_2NH$, Bz_2NH, N-morpholine] was prepared starting from suitable precursors. The syntheses and spectroscopic characterizations of the two new complexes *trans*-$[PtCl_2$(N-morpholine)$(PPh_3)]$ and *cis*-$[PtCl_2(SOMe_2)(PPh_3)]$ are described as well as their X-ray structures. The antiproliferative activity of all the available compounds was tested *in vitro* against HeLa, H460 and A549 human tumor cell lines. A brief discussion regarding the structure–activity correlation is presented.

1. Introduction

In the continuous search for new platinum based anticancer drugs [1] following the discovery of *cis*-$[PtCl_2(NH_3)_2]$ (*cis*-platinum) activity [2], many efforts are oriented to overcome drug-resistance phenomena [3] and serious collateral effects [4] shown by this still widely used anticancer agent. While the mechanism of action of *cis*-platinum has been deeply investigated [5], much less is known about *cis*-platinum analogues. In this context, the building of new libraries of platinum complexes along with the availability of data correlating the structure of derivatives with their activity can be of great help.

Among the many platinum(II) derivatives tested over the last decades, a growing number of phosphine containing complexes have shown promising antiproliferative properties [6], being in some cases [6c,e] active towards *cis*-platinum resistant tumoral cells. In the course of our studies on platinum(II) derivatives, [7,8] we have recently developed convenient synthetic procedures for the preparation of complexes bearing triphenylphosphine [7] $[PtCl_2L(PPh_3)]$ [Chart 1, L = $Et_2NC(Me)NH$ (**1**), $SOMe_2$ (**2**), CO (**3**), Et_2NH (**4**), $(HOCH_2CH_2)_2NH$ (**5**), Bz_2NH (**6**), N-morpholine (**7**)].

In a previous work [9] we have reported interesting antiproliferative activity on human tumor cell lines for derivatives **4**–**6** and, for the most active complex **5**, we obtained experimental evidence for its capacity to affect mitochondrial functions [9]. With the aim of getting some information about the role of free hydroxyl groups in the noteworthy antiproliferative activity shown by **5**, *trans*-$[PtCl_2$(N-morpholino)$(PPh_3)]$ (Chart 1, **7**) was prepared; indeed, this complex, where oxygen in the amine ligand is still present, can be formally obtained from **5** by elimination of a molecule of H_2O, followed by cyclization; although the reactivities of terminal primary hydroxyl groups and dialkylethers can be quite different, in both cases the oxygen atom can be involved in coordination to metals and/or hydrogen bonding, thus the comparison between the biological activities shown *in vitro* by **5** and **7** seemed interesting. Moreover, a model compound containing PPh_3 and dimethylsulfoxide (DMSO) ligands was prepared (Chart 1, **2**). As a matter of fact, given the coordinating character of DMSO, when phosphine complexes are dissolved in this solvent for the biological tests *in vitro*, substitution equilibria cannot be excluded *a priori*; small amounts of **2** could then form and affect the observed biological activity [10]. We report here the synthesis, the characterization and the X-ray structures of *cis*-$[PtCl_2(SOMe_2)(PPh_3)]$ (Chart 1, **2**), and *trans*-$[PtCl_2$(N-morpholino)$(PPh_3)]$ (Chart 1, **7**) and, for all the available Pt complexes shown in the Chart 1, the *in vitro* antiproliferative activity towards HeLa, H460 and A549 human tumor cell lines.

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http://dx.doi.org/10.1016/j.poly.2014.10.001
0277-5387/

2. Materials and methods

2.1. General

All manipulations were performed under a dinitrogen atmosphere, if not otherwise stated. Solvents and liquid reagents were dried according to reported procedures [11]. ^{1}H, ^{13}C, ^{31}P and ^{195}Pt NMR spectra were recorded with a Bruker "Avance DRX400" spectrometer, in $CDCl_3$ solution if not otherwise stated. Chemical shifts were measured in ppm (δ) from TMS by residual solvent peaks for ^{1}H and ^{13}C, from aqueous (D_2O) H_3PO_4 (85%) for ^{31}P and from aqueous (D_2O) hexachloroplatinic acid for ^{195}Pt. A sealed capillary containing C_6D_6 was introduced in the NMR tube to lock the spectrometer to the deuterium signal when non-deuterated solvents were used. FTIR spectra in solid phase were recorded with a Perkin-Elmer "Spectrum One" spectrometer, equipped with an ATR accessory. Elemental analyses (C, H, N) were performed at Dipartimento di Scienze e Tecnologie Chimiche, Università di Udine. *cis*-[$PtCl_2$(NCMe)(PPh_3)] [7a], *cis*-[$PtCl_2(Et_2NC(Me)NH)(PPh_3)$] (**1** [7b]), *cis*-[$PtCl_2(CO)(PPh_3)$] (**3** [7b]), *trans*-[$PtCl_2(Et_2NH)(PPh_3)$] (**4** [7b]), *trans*-[$PtCl_2\{(HOCH_2CH_2)_2NH\}(PPh_3)$] (**5** [9]) and *trans*-[$PtCl_2$(-$Bz_2NH)(PPh_3)$] (**6** [9]) were prepared according to reported procedures.

2.2. Synthesis of cis-[$PtCl_2(SOMe_2)(PPh_3)$] (**2**)

cis-[$PtCl_2(NCCH_3)(PPh_3)$] (0.176 g; 3.1×10^{-4} mol) was dissolved in dimethylsulfoxide (DMSO, 3.0 mL). ^{31}P NMR spectroscopy on a sample of the solution showed the complete conversion of the precursor into a unique product (18.15 ppm, $^{1}J_{P-Pt}$ = 3772 Hz). Colorless crystals separated out from DMSO solution upon addition of ethanol (5.0 mL), were recovered by filtration, washed with ethanol (2.0 mL) and dried (0.136 g, 72% yield). Single crystals were selected for X-ray structure determination: *cis* configuration as well as S-coordination were confirmed. Elemental *Anal.* Calc. for $C_{20}H_{21}Cl_2OPSPt$: C, 39.6; H, 3.5. Found: C, 38.9; H, 3.3%. IR (ATR): 3058, 3000, 2916, 1145 cm^{-1}; ^{1}H NMR: 7.75–7.33 (m, 15 H, H_{arom}), 3.30 ppm (s, 6H, $SOCH_3$, $^{3}J_{H-Pt}$ = 18 - Hz);^{31}P NMR: 16.18 ppm, $^{1}J_{P-Pt}$ = 3720 Hz; ^{195}Pt NMR −3902 ppm $^{1}J_{P-Pt}$ = 3720 Hz; ^{13}C NMR: 134.4 (d, *J* = 10.2 Hz), 131.5, 128.2 (d, *J* = 60.0 Hz), 128.2 (d, *J* = 11.7 Hz), 46.0.

2.3. Synthesis of trans-[$PtCl_2$(N-morpholino)(PPh_3)] (**7**)

A solution of *cis*-[$PtCl_2$(NCMe)(PPh_3)] (0.215 g, 3.77×10^{-4} mol) in MeCN (10.0 mL) was refluxed under stirring and treated with a solution of morpholine in the same solvent ([morpholine]/[Pt] = 1.2 M ratio). The mixture was stirred until the maximum conversion of the precursor was observed (^{31}P NMR, 1.5 h). Acetonitrile was removed under vacuum and the residue after being dissolved in the minimum amount of 1,2-dichloroethane (5.0 mL) was crystallized by addition of heptane (7.0 mL). Bright yellow crystals were recovered by filtration, washed with heptane and dried under vacuum (0.116 g, 50% yield). A small sample was recrystallized by slow diffusion of pentane vapors into a chloroform solution of the complex and single crystals were selected for the X-ray structure determination. Elemental *Anal.* Calc. for $C_{22}H_{24}Cl_2NOPPt$: C, 42.9; H, 3.9; N, 2.3. Found: C, 42.9; H, 3.6; N, 2.3%. IR (ATR): 3197, 1481, 1433, 1098, 1070 cm^{-1}; ^{1}H NMR: 7.80–7.35 (m, 15H, H_{arom}), 3.97–3.93 (m, 3H, NH+NC*H*H), 3.68–3.59 (m, 4H, OCH_2), 3.15–3.10 (m, 2H, NCH*H*); ^{31}P NMR: 4.75, $^{1}J_{P-Pt}$ = 3542 Hz; ^{195} Pt NMR: −3663, $^{1}J_{Pt-P}$ = 3542 Hz; ^{13}C NMR: 134.7 (d, $^{3}J_{C-P}$ = 10 Hz), 130.9, 128.5 (d, $^{1}J_{C-P}$ = 64 Hz), 127.9 (d, $^{2}J_{C-P}$ = 11 Hz), 67.9, 48.6.

2.4. Inhibition growth assay

HeLa (cervix adenocarcinoma), H460 (large cell lung carcinoma), A549 (non-small cell lung cancer) were grown in Nutrient Mixture F-12 [HAM] (Sigma Chemical Co.), RPMI 1640 (Sigma Chemical Co.) supplemented with 2.38 g/L Hepes, 0.11 g/L pyruvate sodium, 2.5 g/L glucose and Nutrient Mixture F-12-K (Sigma Chemical Co.), respectively. 10% Heat-inactivated fetal calf serum (Invitrogen), 100 U/mL penicillin, 100 μg/mL streptomycin, and 0.25 μg/mL amphotericin B (Sigma Chemical Co.) were added to the media. The cells were cultured at 37 °C in a moist atmosphere of 5% carbon dioxide in air. H-460 and A-549 cells ($3–4 \times 10^4$) were seeded into each well of a 24-well cell culture plate. After incubation for 24 h, various concentrations of the test agents were added to the complete medium and cells were incubated for a further 72 h. HeLa cells ($3–4 \times 10^4$) were seeded into each well of a 24-well cell culture plate. After incubation for 24 h, the medium was replaced with an equal volume of fresh medium, and various

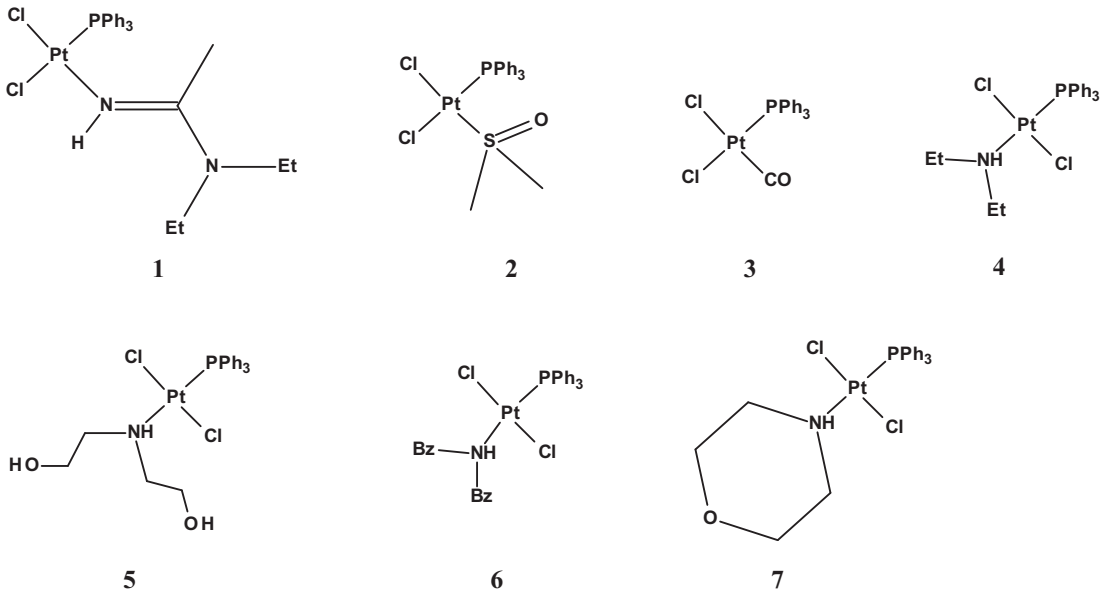

Chart 1. Platinum complexes tested in the present work.

concentrations of the test complex were added. The cells were then incubated in standard conditions for a further 72 h.

A trypan blue assay was performed to determine cell viability. Cytotoxicity data were expressed as GI_{50} values, i.e., the concentration of the test agent inducing 50% reduction in cell number compared with control cultures.

2.5. X-ray structure determination

The X-ray single-crystal data of the compounds **2** and **7** were collected on a Bruker-AXS SMART-Breeze CCD diffractometer at room-temperature. The crystallographic data, the conditions used for the intensity data collection and some features of the structure refinements are listed in Table 1. The intensities of 99% of reflections of the Ewald sphere with a θ_{max} = 29.5° and 30°, respectively, were collected with a mean redundancy of about 4. Data processing, Lorentz-polarization and absorption corrections were performed using SMART, SAINT and the SADABS computer programs [12]. The structures were solved by direct methods and refined by full-matrix least-squares methods on F^2, using the SHELXTL [13] program package. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from difference Fourier maps, assigned with isotropic displacement factors and included in the final refinement cycles by use of geometrical constraints. Some other utilities contained in the WINGX suite [14] were also used. Some reliability factors of the structure refinement are reported in Table 1.

3. Results and discussion

3.1. Synthesis of the complexes 1–7

The platinum(II) derivatives prepared and tested in this study are reported in Chart 1. All the complexes are characterized by the presence of a triphenylphosphine and two chloride ligands, while the other ligand is varied in the nature and in the relative position. Complex **1** [7b] was prepared by low temperature (−30 °C) addition reaction of diethylamine on *cis*-[$PtCl_2(PPh_3$)(NCMe)] [7a]. Compounds **2**, **3** and **4** [7b], **5** and **6** [9] and **7** were prepared by substitution reactions of *cis*-[$PtCl_2(PPh_3)$(NCMe)] [7a] with the suitable nucleophile under appropriate experimental conditions. In particular, in the case of DMSO derivative **2**, crystals of the product were obtained from a DMSO solution of the precursor, upon addition of ethanol. S-coordination to platinum could be inferred by the ipsochromic shift of the S=O stretching observed in the IR spectrum (1145 versus 1050 cm^{-1} in the free ligand) [15], as well as by the downfield shift of the CH_3 carbon signal in the ^{13}C NMR spectrum carried out in $CDCl_3$ (46.0 versus 41.0 ppm for the free ligand in the same solvent) [16]. This hypothesis was confirmed by X-ray diffraction studies on single crystals of **2**, that also showed the *cis* configuration of the complex (Fig. 1).

The molecular structure of complex **2** is shown in Fig. 1 and its more relevant geometric parameters are listed in Table 2. The metal shows the usual square planar coordination typical of Pt(II) derivatives (max dev. 0.11 Å by Cl(2)). The chlorine atoms occupy two *cis* positions being in *trans* to the phosphine ligand and to the sulfoxide ligand. The sulfoxide oxygen is pointed towards the phosphine and roughly lies on the Pt coordination plane. The disposition is very similar to that found in *cis*-[dichloro(3,6-dihydro-1,2-oxazine)(dimethylsulfoxide)platinum(II)] [17] or in *cis*-[dichloro(cyclopentylamine)(S-dimethylsulfoxide-)platinum(II)] [18], where the phosphino ligand is substituted by the oxazino or by the cyclopentylamino ones. With respect to these compounds, however, the two Pt—Cl bonds in **2** differ more in length. That opposite to the phosphine, consistently with the known structures of *cis*-[dichloro*bis*(triphenylphosphine)platinum(II)] [19], is 2.35 Å long, while that opposite to the sulfoxide is 2.29 Å long. This last value represents the lowest limit for the Pt—Cl bond length range in *cis*-dichlorodimethylsulfoxide structures [mean value 2.308(2) Å] according to a survey on the Cambridge Structural Data Base. [20].

The preparation of *trans*-[$PtCl_2$(N-morpholino)(PPh_3)] (**7**) was carried out by addition of a slight excess of morpholine to a refluxing acetonitrile solution of *cis*-[$PtCl_2$(NCMe)(PPh_3)]. As already observed in the case of diethylamine, [7b] under these conditions, a fast *cis* to *trans* isomerization of the precursor occurs, followed by nitrile substitution by the secondary amine. The complex was

Table 1
Crystal data and structure refinement parameters for compounds **2** and **7**.

Formula	$C_{20}H_{21}Cl_2OPPtS$	$C_{22}H_{24}Cl_2NOPPt$
Formula weight	606.39	615.38
T (K)	296(2)	296(2)
Color	colorless	colorless
Crystal system	triclinic	triclinic
Space group	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)
a (Å)	10.3041(1)	11.3705(6)
b (Å)	10.5610(2)	14.1820(7)
c (Å)	12.5185(2)	16.0292(8)
α (°)	95.706(1)	73.375(2)
β (°)	108.445(1)	71.462(2)
γ (°)	118.791(1)	71.462(2)
V (Å^3)	1079.35(3)	2273.5(2)
Z	2	4
μ (mm^{-1})	6.906	6.490
F(000)	584	1192
D_{calc} (g cm^{-3})	1.861	1.798
λ(Mo Kα) (Å)	0.71073	0.71073
θ (°)	2.29–29.50	2.09–30.07
Reflection collected/unique	22139/5989	47322/13171
Absorption correction	multi-scan	multi-scan
R_{int}	0.0348	0.0175
Parameters refined	237	505
R_1 [$I > 2\sigma(I)$]	0.0269	0.0202
wR_2 (all data)	0.0444	0.0450
Goodness-of-fit (GOF) on F^2	0.969	1.026

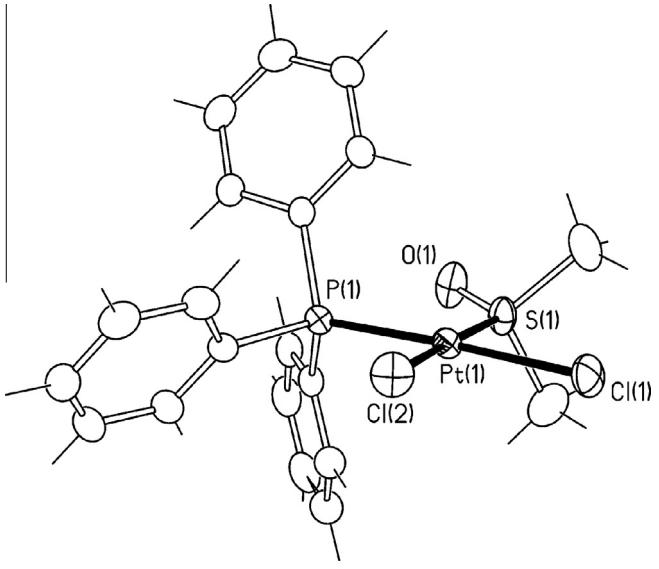

Fig. 1. View of the molecular structure of *cis*-[$PtCl_2(SOMe_2)(PPh_3)$] (**2**). Thermal ellipsoids are at 30% probability.

Table 2
Selected bond lengths (Å) and angles (°) in **2**.

Pt(1)—Cl(1)	2.3541(8)	Pt(1)—Cl(2)	2.2895(8)
Pt(1)—S(1)	2.2215(8)	Pt(1)—P(1)	2.2624(7)
S(1)—O(1)	1.459(2)		
Cl(1)—Pt(1)—Cl(2)	88.20(3)	Cl(1)—Pt(1)—S(1)	88.03(3)
Cl(2)—Pt(1)—P(1)	92.12(3)	S(1)—Pt(1)—P(1)	90.10(8)
Pt(1)—S(1)—O(1)	118.6(1)		

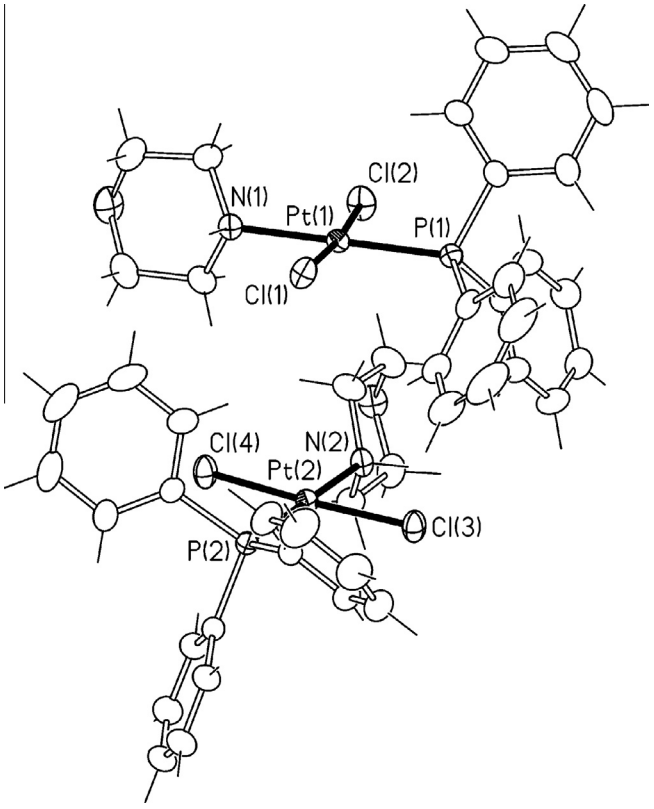

Fig. 2. View of the molecular structure of *trans*-[$PtCl_2$(N-morpholino)(PPh_3)] (**7**). Thermal ellipsoids are at 30% probability.

characterized by spectroscopic analysis and X-ray diffraction studies on single crystals (Fig. 2).

The molecular structure of compound **7** (Fig. 2) is similar to that of *trans*-[dichloro(pyrrolidine)(triethylphosphine)platinum(II)] (PRLPTA) [21] or that of *trans*-[dichloro-((*S*)-1-methylpropylamine) (triphenylphosphine) platinum(II)] (BAPXOG) [22]. Unlike these structures, however, the asymmetric unit of **7** is made by a couple of molecules, as shown in Fig. 2. The two molecules show very similar conformations and may be distinguished by different rotation angles around the P—C bonds of the phosphine phenyl groups. The Pt—Cl bond distances (Table 3) are all similar to the shorter one in compound **2**. The Pt—N distance is slightly longer than that reported for the morpholine complex *trans*-[$PtCl_2$(N-morpholino)(DMSO)] [23] which shows a distance of 2.09 Å.

Table 3
Selected bond lengths (Å) and angles (°) in **7**.

Pt(1)—Cl(1)	2.2913(7)	Pt(2)—Cl(3)	2.2885(8)
Pt(1)—Cl(2)	2.2969(8)	Pt(2)—Cl(4)	2.2997(8)
Pt(1)—N(1)	2.128(2)	Pt(2)—N(2)	2.129(2)
Pt(1)—P(1)	2.2498(7)	Pt(2)—P(2)	2.2454(7)
P(1)—Pt(1)—Cl(1)	94.60(3)	P(2)—Pt(2)—Cl(3)	96.36(3)
P(1)—Pt(1)—Cl(2)	91.05(3)	P(2)—Pt(2)—Cl(4)	90.03(3)
N(1)—Pt(1)—Cl(1)	84.09(7)	N(2)—Pt(2)—Cl(3)	84.62(7)
N(1)—Pt(1)—Cl(2)	90.25(7)	N(2)—Pt(2)—Cl(4)	88.97(7)
P(1)—Pt(1)—N(1)	178.62(7)	P(2)—Pt(2)—N(2)	178.69(7)
Cl(1)—Pt(1)—Cl(2)	173.99(3)	Cl(3)—Pt(2)—Cl(4)	173.58(3)

Table 4
Cell growth inhibition values in the presence of complexes **1**–**7** and *cis*-platinum (*cis*-Pt) as reference drug.

Complex	Cell line GI_{50} (μM)[a]		
	HeLa	H460	A549
1	7.0 ± 1.2	18.5 ± 4.0	12.1 ± 3.1
2	5.7 ± 1.6	>20	15.3 ± 3.7
3	>20	>20	>20
4[b]	5.1 ± 1.5	6.8 ± 0.6	8.4 ± 0.4
5[b]	0.42 ± 0.06	1.1 ± 0.3	2.3 ± 0.7
6[b]	3.3 ± 1.7	6.6 ± 1.4	7.0 ± 1.2
7	9.7 ± 0.7	4.4 ± 0.3	12.8 ± 0.8
cis-Pt[b]	1.5 ± 0.6	0.76 ± 0.11	1.6 ± 0.7

[a] Mean values ± SD of at least three independent experiments are reported.
[b] See Ref. [9].

3.2. Biological tests and conclusions

The antiproliferative activity of all complexes was evaluated on three human tumor cell lines: HeLa (cervix adenocarcinoma), H460 (large cell lung carcinoma) and A549 (non-small cell lung cancer). The results are reported in Table 4 and are expressed as GI_{50} values, i.e. the concentration (μM) of complex able to cause 50% of cell death with respect to the control culture.

The well-known drug *cis*-platinum was used as reference compound. A notable cytotoxic effect, comparable to that obtained for the reference drug, is exerted by **5** [9], characterized by a *trans* configuration and carrying a *bis*(2-hydroxyethyl)amine ligand coordinated to the platinum. An interesting capacity to inhibit cell growth is also showed by **4** [9], **6** [9] and **7**. Otherwise, *cis* complexes **1** and **2** showed a low antiproliferative capacity, whereas **3** is ineffective under the same experimental conditions. As far as the inactivity of **3** is concerned, we did not collect specific data to explain it, but the high reactivity of platinum(II) carbonyl complexes towards protic nucleophiles [24] such as those found in aqueous cellular media could be the basis for this behavior. It is anyway interesting to note that all complexes able to exert a significant antiproliferative effect are characterized by the *trans* isomery and by the presence of a dialkylamine coordinated to the metal (Chart 1). It has also to be underlined that, despite the structural similarity between **5** and **7**, the cytotoxicity shown by the two complexes is quite different, with **5** significantly more active than **7** (Table 4). These data suggest that the presence of a dialkylamino ligand *trans* to PPh_3 as well as the availability of hydroxyl groups are important for the development of biologically active complexes.

Acknowledgments

The *Ministero dell' Università e della Ricerca Universitaria* (MIUR), *Progetti di Ricerca di Rilevante Interesse Nazionale* (PRIN 2009) is gratefully acknowledged for financial support. Thanks are due to Chimet S.p.A., I-52041 Badia al Pino (Arezzo) for a loan of platinum. L. Dalla Via and A.N. García-Argáez are grateful to the financial support provided by Università degli Studi di Padova – Progetti di Ricerca di Ateneo 2010 – "Attività antitumorale di nuovi composti di coordinazione nel carcinoma del polmone non a piccole cellule (NSCLC)".

Appendix A. Supplementary data

CCDC 950540–950541 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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