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α-Diimine homologues of cisplatin: synthesis, speciation in DMSO/water and cytotoxicity†

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The Pt(II) α-diimine complexes [$PtCl_2\{\kappa^2N$-(HCNR)$_2$}] (R = C_6H_{11}, **1**; 4-$C_6H_{10}OH$, **2**; 4-$C_6H_4CH_3$, **3**; 4-C_6H_4OH, **4**) and [$PtCl_2\{\kappa^2N$-$(CH_3CNOH)_2$}] (**5**) were prepared in 60–81% yields from the 1 : 1 molar reactions of *cis*-[$PtCl_2(DMSO)_2$] with the appropriate α-diimine, [HCN(R)]$_2$ (R = C_6H_{11}, **L1**; 4-$C_6H_{10}OH$, **L2**; 4-C_6H_4Me, **L3**; 4-C_6H_4OH, **L4**), or dimethylglyoxime ($dmgH_2$), in acetone at reflux. The reaction of *cis*-[$PtCl_2(DMSO)_2$] with two molar equivalents of $dmgH_2$ and NEt_3 in methanol at reflux afforded the bis-dimethylglyoximato compound [$Pt\{\kappa^2N,N'$-(ON=C(CH_3)C(CH_3)=NOH)}$_2$], [Pt(dmgH)$_2$], as an insoluble material, in 97% yield. The oxalato derivative [$Pt(\kappa^2O$-$C_2O_4)\{\kappa^2N$-(HCN(C_6H_{11}))$_2$}], **6**, was obtained from the sequential treatment of **1** with $AgNO_3$ and $Na_2C_2O_4$, in 61% yield. Attempts to functionalize **4** *via* esterification of the hydroxyl groups with aspirin (aspCO_2H) led to [$PtCl_2\{\kappa^2N$-(HCN(4-C_6H_4OCO-asp))$_2$}], **7**, in an admixture with **4**. All the products were characterized by elemental analysis, and IR and multinuclear NMR spectroscopy, and the molecular structures of **4**·THF and **5** were elucidated by single crystal X-ray diffraction. NMR spectroscopic studies in DMSO or DMSO/water/NaCl evidenced the substantial stability of **1–2** at 37 °C over 72 hours, whereas **3–5** released their *N*,*N*-ligand. The cytotoxic activity of **1**, **2** and **6** was assessed on cisplatin sensitive and cisplatin resistant human ovarian carcinomas (A2780 and A2780cisR) and non-tumorigenic human embryonic kidney (HEK-293) cells. Compound **1** is moderately cytotoxic, whereas **2** and **6** did not display appreciable antiproliferative activity.

Introduction

The serendipitous discovery of the anticancer properties of *cis*-diamminedichloridoplatinum(II) (cisplatin) dates back 50 years, and represented a breakthrough in cancer chemotherapy.[1] Cisplatin was the first metal-based drug to be approved worldwide for the treatment of cancers, and two other similar compounds followed, namely oxaliplatin and carboplatin (Fig. 1a).[2] Three additional Pt(II) complexes have been adopted in specific countries, *i.e.* nedaplatin, lobaplatin and heptaplatin (Fig. 1b). These successes triggered the investigation of many other types of platinum complexes[3] to further broaden their application,[4] and also inspired the study of complexes based on different transition metals.[5] Over the past decades, interest in the anticancer properties of Pt complexes has spread beyond "classical" structure–activity relationships[6] that predicted the best activity for *cis*-[$PtX_2(RNH_2)_2$] compounds carrying primary amines as ligands (X_2 = chlorides or *O*,*O*-chelate ligand). A plethora of Pt(II) coordination complexes differing in the nature of the nitrogen donors have been developed and tested for their anticancer efficacy.[3b,7] In general, it has been demonstrated that the modification of the *N*-ligands has a profound impact on the biological activity and the pharmacological behaviour of Pt complexes.[7c,8]

Concerning *cis*-[$PtX_2(N,N)$] complexes featuring a bidentate non-diamine nitrogen donor ligand (*N*,*N*′), *in vivo* and/or *in vitro* anticancer activity has been ascertained with aromatic or mixed aromatic-aliphatic ligands such as dipyrido[3,2-*a*:2′,3′-*c*]phenazine, dipyridylmethane, 1,10-phenanthroline-5,6-dione, 4-alkylamino-1,2,5-oxadiazoles and bis(2-chloroethyl)pyridylmethylamine.[9] On the other hand, less positive results were observed with 2,2′-bipyridine and (2-pyridyl)benzoimidazole type ligands.[10] Besides, various organometallic species of general formula *cis*-[$PtR_2(N,N)$] (R = alkyl or aryl group) exhibit moderate cytotoxic activities.[11]

α-Diimines, also called 1,4-diaza-1,3-dienes,[12] are versatile chelating ligands widely employed in coordination chemistry,[13]

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† Electronic supplementary information (ESI) available: Views of H-bonding in X-ray structures; synthesis and characterization of starting compounds; details of stability studies in aqueous medium; IR and NMR spectra. CCDC 1851425 (**4**·**THF**) and 1851426 (**5**) contain the supplementary crystallographic data for the X-ray studies reported. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8nj04195d

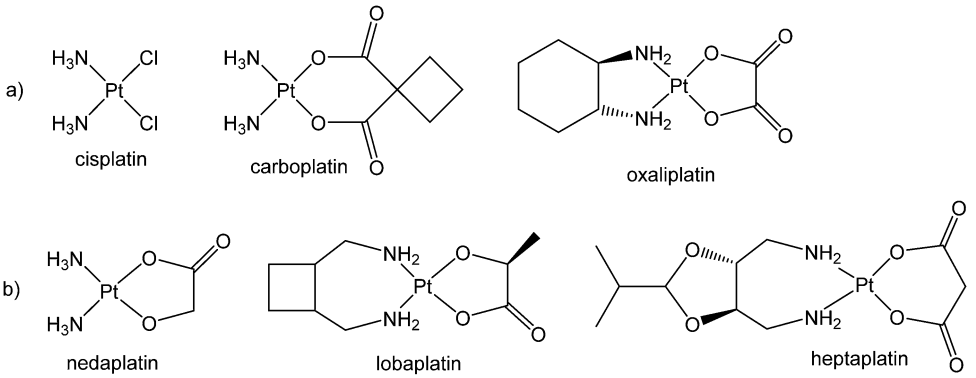


Fig. 1 Platinum-based drugs currently used in the treatment of cancer (a) worldwide; (b) in specific countries.

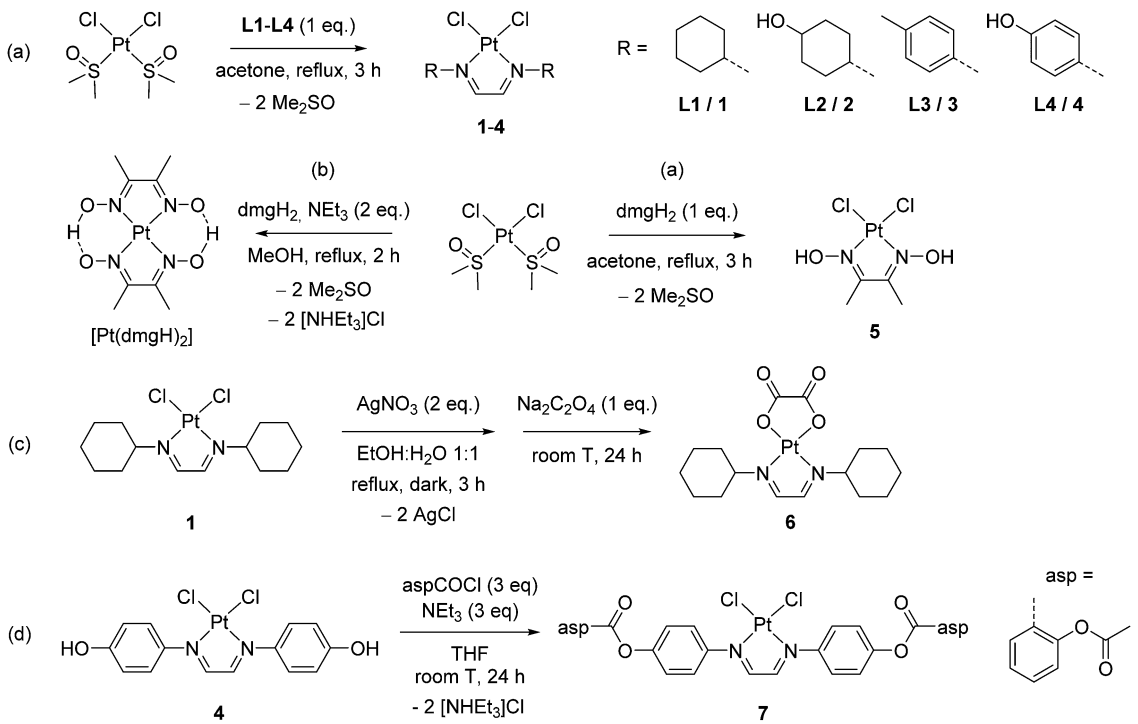
and the steric and electronic properties of the resulting complexes can be finely tuned by an accurate choice of the substituents on the N═CC═N skeleton.[14] A variety of mononuclear *cis*-[$PtCl_2$(κ^2*N*-α-diimine)] species have been synthesized using different synthetic strategies: (a) two-step reaction from the Zeise's salt, K[$PtCl_3$(η^2-C_2H_4)];[15] (b) direct addition to $PtCl_2$;[15c,16] (c) substitution of two neutral, labile ligands in *cis*-[$PtCl_2$($NCPh)_2$][15c,17] or *cis*-[$PtCl_2$($DMSO)_2$].[18] To the best of our knowledge, α-diimine homologues of cisplatin have not been evaluated for their anticancer potential and, in general, biological studies on α-diimine platinum compounds are rare.[19]

We have recently reported that the incorporation of α-diimines in ruthenium(II) arene compounds of formula [(η^6-*p*-cymene)RuCl{κ^2*N*-$(HCNR)_2$}]NO_3 results in unusually strong Ru–Cl binding, and some of the compounds display a potent cytotoxic activity *in vitro*.[20] Herein, we describe the synthesis and the extensive characterization of a series of cisplatin-like *cis*-[$PtCl_2$(α-diimine)] complexes and an oxaliplatin-like derivative, investigating also the potential of a hydroxo-substituted α-diimine to be modified with a bioactive group. The speciation of the complexes in DMSO/water and preliminary cytotoxicity results are discussed.

Results and discussion

1. Synthesis and characterization of the complexes

The platinum(II) α-diimine complexes **1–5** were synthesized in good to high yields (74–92%) by allowing *cis*-[$PtCl_2$(κS-$DMSO)_2$] to react with the appropriate α-diimine (**L1–L4** and $dmgH_2$) in acetone at reflux (Scheme 1a). The oxaliplatin-like derivative **6**



Scheme 1 Synthesis of Pt(II) α-diimine complexes **1–6** (a and c), [Pt($dmgH)_2$] (b) and of the aspirin derivative [$PtCl_2${κ^2*N*-(HCN(4-$C_6H_4OCOasp)$)$_2$}] **7** (d).

Table 1 Selected spectroscopic data for compounds **1–6** and related α-diimine ligands

Compound	IR: $\tilde{\nu}^a$/cm^{-1}			^{1}H NMR: δ^e/ppm				^{13}C{^{1}H} NMR: δ^f/ppm		^{195}Pt{^{1}H} NMR: δ^f/ppm
	ν(O–H)	ν(C═N)^b ($\Delta_{coord}\nu^c$)	ν(Pt–Cl)^d	δ(OH)	δ(HC═N) ($\Delta_{coord}\delta^c$)	$^3J_{HPt}$/Hz	δ(N–CH) ($\Delta_{coord}\delta^c$)	δ(C═N) ($\Delta_{coord}\delta^c$)	δ(N–C) ($\Delta_{coord}\delta^c$)	
L1^g	—	1622s	—	—	7.88	—	3.19	160.9	69.8	—
1	—	1560m (−62)	340s, 329s-sh	—	8.66 (*+0.78*)	102	4.39 (*+1.20*)	167.5 (*+6.6*)	65.7 (*−4.1*)	−2223
6	—	1551m (−71)	—	—	8.79 (*+0.91*)	99	3.86 (*+0.67*)	n.d.	n.d.	n.d.
L2^g	3399m, 3332m	1625s	—	4.49	7.88	—	3.15	156.0	68.0	—
2	3587w-sh, 3477m-br	1557m (−68)	332s	4.68	8.68 (*+0.80*)	102	4.39 (*+1.24*)	167.5 (*+11.5*)	68.0 (*0*)	−2224
L3^g	—	1611m	—	—	8.41	—	—	160.1	148.7	—
3	—	1601m (−10)	345s, 337s	—	8.80 (*+0.39*)	86	—	170.3 (*+10.2*)	146.5 (*−2.2*)	−2102
L4^g	3300–3000w-br	1607s	—	7.20	8.36	—	—	157.7	142.9	—
4^h	3325m, 3211m, 3193m	1604m-sh (−3)	351m, 333m	7.53	8.76 (*+0.40*)	88	—	168.0 (*+10.3*)	141.3 (*−1.6*)	−2094
7	—	1605s/1592s	—	—	9.02	89	—	n.d.	n.d.	n.d.
dmgH$_2$	3290m-sh, 3200m-br	1643s^i	—	10.5	—	—	1.97^j	154.3	9.50^j	—
5	3326m, 3305w-sh, 3254m, 3241m	1594m (−49)	347m-sh, 330m	10.6 br.	—	—	2.20^j (*+0.23*)	161.3 (*+7.0*)	14.1^j (*−4.6*)	−2466
[Pt(dmgH)$_2$]	3410w-br, 3254w-sh	1543s (−100)	—	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
[PtCl$_2$(DMSO)$_2$]	—	—	334s, 309s^k	—	—	—	—	—	—	−3444

^{a} Solid state IR data. ^{b} Antisymmetric stretching of N═CC═N.[46] ^{c} Wavenumber or chemical shift difference upon coordination: $\Delta_{coord}X = X(Pt–L)–X(L)$. ^{d} Antisymmetric and symmetric stretching of the $PtCl_2$ unit. ^{e} ^{1}H NMR data in DMSO-d$_6$ for **L1**/**1**/**6**, **L2**/**2** and *cis*-[PtCl$_2$(κ*S*-DMSO)$_2$]; in CDCl$_3$/CD$_2$Cl$_2$ for **L3**/**3**; in CD$_3$CN for **L4**/**4** and **7**; in acetone-d$_6$ for **L5**/**5**. ^{f} ^{13}C and ^{195}Pt NMR data in DMSO-d$_6$ for **1**, **L2**/**2**; in DMF/C$_6$D$_6$ for **L1**, **L3**/**3**, **L4**/**4** and dmgH$_2$/**5**. ^{g} IR data and some ^{1}H/^{13}C NMR data from the literature.[16,24] ^{h} IR data refer to the solvent-free product. ^{i} Raman band absent in the IR spectrum.[47] ^{j} Related to the CH$_3$ group. ^{k} From the literature.[41] n.d.: not detected due to low solubility.

was obtained from **1** in 69% yield, upon sequential treatment with silver nitrate and sodium oxalate (Scheme 1c).

Compound **1** was previously reported from a different synthetic route,[21] whereas **2–6** are unprecedented.[22] All the products have been fully characterized by analytical and spectroscopic methods; selected IR and NMR spectroscopic data of **1–6** are compiled in Table 1 (it has to be noted that IR and ^{13}C/^{195}Pt NMR spectroscopic data are generally missing in the literature for this family of compounds). The IR spectra, in the solid state, display a medium-strong band in the 1550–1660 cm^{-1} region, accounting for the C═N moieties, appearing at lower wavenumbers compared to the respective non-coordinated α-diimine. The absorptions related to the Pt–Cl ligands are observed in the range 329–351 cm^{-1}. The ^{1}H and ^{13}C NMR resonances of the α-diimine backbone undergo significant deshielding upon coordination, conversely the ^{13}C resonance of the *N*-bound substituent carbon is shifted upfield. The C*H*═N protons in **1–4** and **6** show satellite peaks due to the coupling with the ^{195}Pt nucleus, the coupling constant value being around 100 Hz. In contrast, the ^{1}H-decoupled ^{195}Pt NMR spectra of **1–5** consist of a single resonance in the region −2094 to −2466 ppm. More specifically, the ^{195}Pt NMR chemical shift of [PtCl$_2$(α-diimine)] compounds depends on the *N*-substituent on the α-diimine: it is found around −2200 ppm for *N*-alkyl groups (**1**, **2**), around −2100 ppm for *N*-aryl groups (**3**, **4**), in agreement with what previously reported for related [PtX$_2$(N^N)] complexes,[15c,23] and at −2466 ppm for the dimethylglyoxime derivative (**5**).

The presence of two hydroxyl groups in **4** results in a marked tendency to form intermolecular H bonds, therefore this compound is obtained as its acetone–solvato complex **4**·(**Me$_2$CO**)$_n$ (see ESI† for details). Acetone can be then removed either by suspending the solid in refluxing CH_2Cl_2 or by heating it at 110 °C under vacuum. Crystals of **4**·**THF** suitable for X-ray analysis were recovered from THF/diethyl ether, and X-ray quality crystals of **5** were obtained from DMF/^{i}PrOH.

Views of the X-ray structures of **4**·**THF** and **5** are shown in Fig. 2 and 3, with salient bonding parameters compiled in Tables S1 and S2 (ESI†). The Pt(II) centres have the expected square-planar geometry, with the major deviation being due to the small N(1)–Pt(1)–N(2) bite angle [79.6(4) and 77.5(3)° for **4** and **5**, respectively] of the *N*,*N*-chelate. Comparable geometries were previously found in related PtX$_2$(*N*^*N*) complexes.[15b,c,16,17] The OH groups within **L4** and dmgH$_2$ ligands are involved in intermolecular H-bonds that, in the case of **4**·**THF**, include also the O-atom of the THF solvate. The resulting networks and the most relevant H-bonds parameters are summarized in Fig. S1, S2 and Tables S3, S4 (ESI†).

The bis-dimethylglyoximato complex [Pt(dmgH)$_2$] was recovered, in near-quantitative yield, as an intractable material from the 1 : 2 molar reaction of *cis*-[PtCl$_2$(κ*S*-DMSO)$_2$] with dmgH$_2$, in methanol in the presence of triethylamine (Scheme 1b).

A promising strategy to optimize the anticancer activity of metal complexes consists in the inclusion of bioactive organic

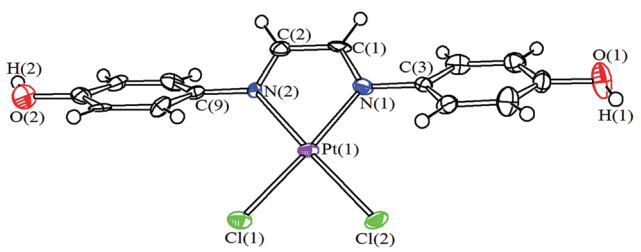


Fig. 2 Molecular structure of **4** (THF molecule not shown). Displacement ellipsoids are at the 50% probability level.

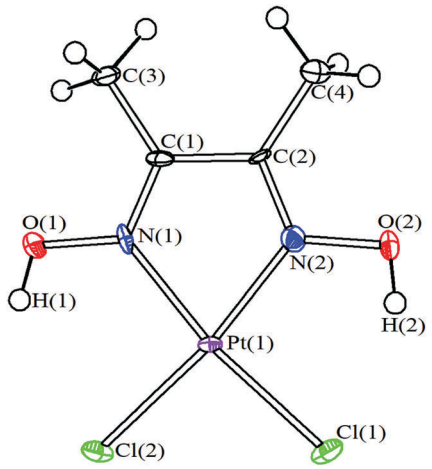


Fig. 3 Molecular structure of **5**. Displacement ellipsoids are at the 50% probability level.

fragments, aimed to favour the interaction of the resulting compounds with specific targets overexpressed or uniquely expressed in cancer cells.[25] A variety of bioactive carboxylic acids have been tethered directly to the Pt(IV) centre as monodentate carboxylato ligands, providing an improved anticancer action.[3b,26] Conversely, the introduction of bioactive groups in Pt(II) complexes by linking them to suitable ligands already coordinated to the metal centre has been explored to a lesser extent.[27]

In principle, the OH groups of α-diimine ligands **L2**, **L4** and $dmgH_2$ could be functionalized *via* esterification with bioactive carboxylic acids. However, the α-diimine moiety does not generally tolerate the required reaction conditions, thus modification of *N*-aryl substituents is usually performed prior to generation of the imine group.[28] In analogy with our recent study on α-diimine ruthenium complexes,[20] we investigated the possibility of modifying the **L2** and **L4** ligands by direct esterification on the respective Pt complexes **2** and **4**. Aspirin was selected as a viable candidate, since it possesses anticancer properties,[29] and it has been previously demonstrated that its incorporation into Pt(IV) complexes can provide a synergism resulting in enhanced cytotoxicity and activity against the primary tumour *in vivo*.[30]

The reaction of **4** with aspirin acyl chloride (aspCOCl) was conducted in THF, in the presence of triethylamine. Compound **7** was obtained after work-up as the prevalent component of an inseparable mixture with the precursor, **4** (Scheme 1d). The ^{1}H NMR resonance for the imine proton in **7** is observed at 9.0 ppm, deshielded ($\Delta\delta$ = +0.3 ppm) with respect to the precursor **4**. In the solid-state IR spectrum, C=O stretching absorptions due to the ester groups of **7** were found in the 1760–1730 cm^{-1} region. Notably, **2** was completely unreactive under analogous conditions (aspCOCl/NEt_3 in CH_2Cl_2 or DMF solution) and could be recovered at the end of the reaction.

2. Speciation of the complexes in DMSO/water and cytotoxicity studies

Compounds **1–6** are insoluble in water, thus cytotoxicity tests were performed by pre-dissolving the complexes in DMSO.[31]

Table 2 Fraction of starting material in DMSO-d_6 or DMSO-d_6/D_2O/NaCl (in parentheses) at 37 °C as a function of time. % values are based on the integration of the ^{1}H NMR spectra and correspond to identified compounds only

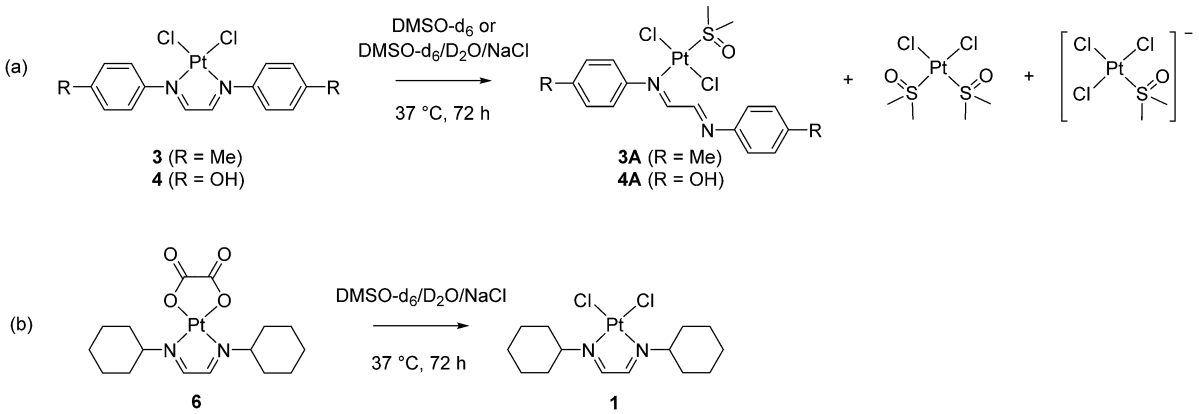
	% (^{1}H NMR)		
Compound	0[a] h	17 h	72 h
1	100 (100)	—	96 (100)
2	100 (100)	—	96 (100)
3	55 (74)	0 (<1)	0 (0)
4	26 (43)	6 (6)	4 (4)
5	13 (11)	10	4 (4)
6	100 (100)	100 (13)	100 (14)

[a] NMR spectra were recorded shortly after dissolution (t < 10 min).

In view of the biological studies, the behaviour of **1–6** in DMSO-d_6 and in a DMSO-d_6/D_2O 9 : 1 v/v mixture was investigated by NMR spectroscopy at 37 °C over 72 hours (see ESI† for details). NaCl was added to the DMSO-d_6/D_2O solution in a concentration resembling that present in the medium used for the *in vitro* tests (0.11 M). Complexes **1** and **2**, containing cyclohexyl *N*-substituents, are substantially stable in both DMSO and DMSO/water/NaCl solutions (Table 2). Solvolysis of the chloride ligands was not observed; this was confirmed in a separate experiment for **1** (chloride abstraction with silver triflate followed by NMR analysis of the product in the DMSO-d_6 and DMSO-d_6/D_2O/NaCl solutions, see ESI†). Such behaviour contrasts to that of cisplatin, which reacts with DMSO[32] and for which the cleavage of Pt–Cl bonds once inside the cell is an essential activation step.[33] The higher stability of the Pt–Cl bonding in **1** and **2**, with respect to the diamine analogues, is presumably ascribable to the electron withdrawing properties of the α-diimine co-ligand.[20]

In the *N*-aryl substituted complexes **3** and **4** and the dimethylglyoximato complex **5**, the binding between platinum and the α-diimine ligand is weaker, the latter being significantly dissociated shortly after dissolution and almost completely released after 72 hours (Table 2). Progressive substitution of the α-diimine ligand by DMSO and Cl^- is in agreement with previous findings[15d] and was clearly recognized by the formation of $[PtCl_2(DMSO)_2]$ and $[PtCl_3(DMSO)]^-$ from **3** and **4** (Scheme 2a). Analogous to the related cyclohexyl species **1-2**, compound **6** is stable in DMSO-d_6, but it undergoes nearly quantitative release of the oxalato ligand in the presence of NaCl, thus partially converting into **1** (Scheme 2b). Such behaviour resembles that of oxaliplatin (stability in DMSO-d_6, slow oxalate/chloride exchange in Cl^--containing aqueous media).[32,34]

As **3–5** rapidly decompose in media relevant to the cytotoxicity tests, they were not studied further. Instead, **1**, **2** and **6** were assessed for their antiproliferative activity against cisplatin sensitive and cisplatin resistant human ovarian carcinomas (A2780 and A2780cisR) and non-tumorigenic human embryonic kidney (HEK-293) cell lines (Table 3). Cisplatin, the α-diimines **L1** and **L2**, and $dmgH_2$ were also evaluated as controls. Ligands **L1** and **L2** are not cytotoxic, whereas **1** exhibits a moderate cytotoxicity against all the tested cell lines but does not display selectivity towards tumoral cells. In contrast, **2** and **6** were inactive on all the investigated cell lines. It should be noted that the α-diimine **L1**,



Scheme 2 Platinum derivatives determined by NMR spectroscopy formed in DMSO-d_6 and DMSO-d_6/D_2O/NaCl solutions of compounds **3**, **4** and **6** at 37 °C.

Table 3 IC_{50} values (μM) determined for selected ligands and complexes and relevant platinum complexes on human ovarian (A2780 and A2780cisR) cancer cells and human embryonic kidney (HEK-293) cells at 72 hours. Values are given as the mean ± SD

Compound	A2780	A2780cisR	HEK-293
L1[20]	>200	>200	>200
L2[20]	>200	>200	>200
$dmgH_2$	>200	>200	>200
1	55 ± 6	86 ± 10	29 ± 4
2	>200	>200	>200
6	>200	>200	>200
$PtCl_2(\kappa_2N\text{-}NH_2CH_2CH_2NH_2)$	5.62[36]		
$PtCl_2(\kappa_2N\text{-}NMe_2CH_2CH_2NMe_2)$	64.7[36]		
Cisplatin	2.3 ± 0.6	31 ± 3	8.4 ± 0.9

albeit not cytotoxic itself, was also found to be the most efficient, among a series of analogous compounds, in providing anti-proliferative activity to the $[(\eta^6\text{-}p\text{-cymene})RuCl]^+$ frame.[20] The lack of cytotoxicity of **2** and **6** and the moderate cytotoxicity of **1**, notably lower than cisplatin and related $PtCl_2$(1,2-diamine) complexes (Table 3), can probably be attributed to the rather strong Pt–Cl bonds resulting from α-diimine coordination,[35] preventing binding to potential biological targets such as DNA.

Conclusions

Few platinum(II) complexes are currently employed as metal based drugs in cancer chemotherapy protocols, and many related compounds have been investigated for their anticancer potential. Surprisingly, Pt(II) α-diimine complexes have not been included in these studies so far, in spite of the fact that α-diimines are robust and versatile ligands, widely used in coordination chemistry. Herein, we have presented the preparation and the characterization of a series of α-diimine homologues of cisplatin and oxaliplatin. Despite the bidentate coordination mode,[37] the α-diimine ligand may undergo fast dissociation in aqueous environment, a feature that is strongly dependent on the *N*-substituents. The most stable complexes have been assessed for their cytotoxic activity towards human ovarian cancer cells and non-tumorigenic cells. In general, the complexes are essentially inactive, apart from one exception. This outcome may be related to the overall electron withdrawing properties of the α-diimine ligand, disfavouring the Pt–Cl bond cleavage which is considered an essential pre-activation step for related drugs.

Experimental section

(1) Materials and methods

$K_2[PtCl_4]$ (99.9%) and dimethylglyoxime ($dmgH_2$) were purchased from Alfa Aesar, and other reagents and solvents were obtained from Alfa Aesar, Sigma Aldrich or TCI Europe, and were of the highest purity available. Aspirin ($aspCO_2H$, acetylsalicylic acid) was stored under N_2. The ligands *N*,*N*′-bis(cyclohexyl)-ethylenediimine (**L1**),[38] *N*,*N*′-bis(4-hydroxycyclohexyl)ethylene-diimine (**L2**),[20] *N*,*N*′-bis(4-methylphenyl)ethylenediimine (**L3**)[39] and *N*,*N*′-bis(4-hydroxyphenyl)ethylenediimine (**L4**)[20,39] and aspirin acyl chloride ($aspCOCl$)[25a,40] were prepared according to literature methods. Compound *cis*-$[PtCl_2(\kappa S\text{-DMSO})_2]$ was prepared by a slight modification of the published procedure (see ESI†).[41] The synthesis of **7** was carried out under a N_2 atmosphere, using standard Schlenk techniques in THF distilled over CaH_2. All the other operations were carried out in air and all isolated Pt complexes are air- and moisture-stable in the solid-state. NMR spectra were recorded at 298 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. Chemical shifts (expressed in parts per million) are referenced to the residual solvent peaks (^1H, ^{13}C)[42] or to external standards (^{19}F to $CFCl_3$, ^{195}Pt to 1.2 M Na_2PtCl_6 in D_2O). A sealed capillary tube containing C_6D_6 was used for NMR measurements in non-deuterated DMF solutions (indicated as DMF/C_6D_6). NMR spectra were assigned with the assistance of DEPT-135 and ^1H–^{13}C (*gs*-HSQC and *gs*-HMBC) correlation experiments.[43] Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer (650–4000 cm^{-1} region, UATR sampling accessory) or with a Perkin Elmer Spectrum 100 FT-IR spectrometer (250–650 cm^{-1} region, CsI tablets) and were processed with Spectragryph software.[44] IR assignments related to stretching vibrations of the $\{PtCl_2\}$ group[19,45] and N═CC═N group in α-diimine[46] and $dmgH_2$[47]

ligands were based on the literature. Carbon, hydrogen and nitrogen analyses were performed on a Vario MICRO cube instrument (Elementar). The chloride content in **5** was determined with $AgNO_3$ potentiometric titration on a solution prepared by dissolution of the solid sample in aqueous KOH and heated at boiling temperature for 72 hours, followed by cooling to room temperature and addition of HNO_3 up to neutralization.

(2) Synthesis and characterization of Pt complexes

$[PtCl_2\{\kappa^2N\text{-}(HCN(C_6H_{11}))_2\}]$, 1 (Chart 1). A suspension of *cis*-$[PtCl_2(\kappa S\text{-DMSO})_2]$ (174 mg, 0.412 mmol) and **L1** (92 mg, 0.42 mmol) in acetone (10 mL) was stirred at reflux. After 3 hours, the reaction mixture (orange solid + yellow solution) was cooled to room temperature and filtered. The solid was washed with acetone (1 mL), Et_2O and dried under vacuum (50 °C). Yield: 184 mg, 92%. Preparation of the title compound from **L1** and $K[PtCl_3(\eta^2\text{-}C_2H_4)]\cdot H_2O$ (60% yield) was previously described.[21] Compound **1** is soluble in DMSO and DMF, poorly soluble in other polar organic solvents (acetone, MeOH, EtOH, CH_2Cl_2, $CHCl_3$, THF and CH_3NO_2), insoluble in water and Et_2O. Anal. calcd for $C_{14}H_{24}Cl_2N_2Pt$: C, 34.57; H, 4.97; N, 5.76. Found: C, 34.5; H, 4.98; N, 5.7. IR (solid state): $\tilde{\nu}/cm^{-1}$ = 3083w, 3070w, 2954m-sh, 2929s-sh, 2922s, 2854s, 2793w, 2656w, 1560m ($\nu_{C=N}$), 1465w, 1454m, 1445m, 1408w, 1380w, 1352w, 1334m-sh, 1328m, 1311m, 1305m-sh, 1299m-sh, 1290m, 1263m, 1256m, 1189w, 1146w, 1100s, 1081m, 1054w, 1024m, 1014m-sh, 992m, 960w, 938w, 922w, 896s, 851w-sh, 844s, 816w, 793w, 770m, 698w, 674w, 598w, 525w, 520w, 512w, 581w, 437w, 428w, 370w, 340s (ν_{Pt-Cl}), 329s-sh (ν_{Pt-Cl}), 311w. ^1H NMR (DMSO-d_6): δ/ppm = 8.66 (s + satellites, $^3J_{HPt}$ = 102 Hz, 2H, C1-H), 4.39 (t, $^3J_{HH}$ = 11.2 Hz, 2H, C2-H), 2.11 (d, J = 10.2 Hz, 4H, C3-H), 1.80 (d, J = 13.0 Hz, 4H, C4-H), 1.65 (d, J = 12.7 Hz, 2H, C5-H), 1.44 (q, J = 11.9 Hz, 4H, C3-H′), 1.31 (q, J = 12.8 Hz, 4H, C4-H′), 1.20–1.08 (m, 2H, C5-H′). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ/ppm = 167.5 (C1), 65.7 (C2), 32.6 (C3), 25.1 (C4), 24.9 (C5). $^{195}Pt\{^1H\}$ NMR (DMSO-d_6): δ/ppm = −2223.

$[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_{10}OH))_2\}]$, 2 (Chart 2). The title compound was prepared as described for **1**, using *cis*-$[PtCl_2(\kappa S\text{-DMSO})_2]$ (173 mg, 0.410 mmol), **L2** (103 mg, 0.408 mmol) and acetone (10 mL). Yellow solid, yield: 169 mg, 80%. Compound **2** is soluble in DMF and hot DMSO, poorly soluble in MeCN, MeOH, EtOH, CH_2Cl_2, $CHCl_3$, insoluble in water and Et_2O. Anal. calcd for $C_{14}H_{24}Cl_2N_2O_2Pt$: C, 32.44; H, 4.67; N, 5.40. Found: C, 32.31; H, 4.72; N, 5.48. IR (solid state): $\tilde{\nu}/cm^{-1}$ = 3587w-sh (ν_{O-H}), 3477m-br (ν_{O-H}), 3080w, 2934m, 2862m, 1557m ($\nu_{C=N}$), 1454m, 1442m, 1410m, 1367m, 1336m, 1322m, 1296m-sh, 1286m, 1259w, 1237w, 1200m, 1141w, 1128w-sh, 1096s, 1071s, 1055s, 1043s-sh, 1017m, 999w, 965s, 949w, 905s, 887w, 848s, 835w, 820m, 799w, 777w, 721w, 608w, 599w, 556w, 522w, 459w, 457w, 332s (ν_{Pt-Cl}). ^1H NMR (DMSO-d_6): δ/ppm = 8.68 (s + satellites, $^3J_{HPt}$ = 102 Hz, 2H, C1-H), 4.65 (d, $^3J_{HH}$ = 4.4 Hz, 2H, OH), 4.39 (t, $^3J_{HH}$ = 10.0 Hz, 2H, C2-H), 3.47–3.37 (m, 2H, C5-H), 2.07 (d, J = 11.2 Hz, 4H, C3-H), 1.90 (d, J = 10.8 Hz, 4H, C4-H), 1.56 (q, J = 11.6 Hz, 4H, C3-H′), 1.25 (q, J = 11.8 Hz, 4H, C4-H′). No change in the ^1H NMR spectrum was observed after 24 hours at room temperature. $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ/ppm = 167.5 (C1), 68.0 (C5), 65.1 (C2), 34.0 (C4), 30.5 (C3). $^{195}Pt\{^1H\}$ NMR (DMSO-d_6): δ/ppm = −2224.

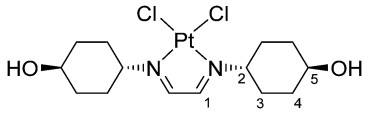


Chart 2 Structure of **2** (numbering refers to C atoms).

$[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4CH_3))_2\}]$, 3 (Chart 3). The title compound was prepared as described for **1**, using *cis*-$[PtCl_2(\kappa S\text{-DMSO})_2]$ (50 mg, 0.12 mmol), **L3** (29 mg, 0.12 mmol) and acetone (5 mL). Purple-red solid, yield: 44 mg, 74%. Analogous reaction with excess of **L3** (3 eq.) afforded the title compound in a lower yield (23%). Compound **3** is soluble in DMF, in DMSO with rapid degradation (see Table S7, ESI†), poorly soluble in CH_2Cl_2, insoluble in acetone, THF, $CHCl_3$, MeOH, toluene, Et_2O and water. Anal. calcd for $C_{16}H_{16}Cl_2N_2Pt$: C, 38.26, H, 3.21, N, 5.58. Found: C, 38.33, H, 3.25, N, 5.48. IR (solid state): $\tilde{\nu}/cm^{-1}$ = 3116w, 3050m, 3004w, 2975w, 2947w, 1920w, 1885w, 1809w, 1758w, 1713w, 1662w, 1601m ($\nu_{C=N}$), 1580w, 1558w, 1500m-sh, 1482s, 1445m, 1377w, 1353m, 1313w, 1299w, 1279w, 1215w, 1181m, 1175m-sh, 1121w-sh, 1109m, 1055w, 1035w, 1019m, 973w, 943m, 886m, 873w, 831m-sh, 819s, 781m, 710m, 641w, 592w, 578m, 545m-sh, 540m, 491w, 480w, 445m, 430w, 416w, 345s (ν_{Pt-Cl}), 337s (ν_{Pt-Cl}), 310w. ^1H NMR (CD_2Cl_2): δ/ppm = 8.80 (s + satellites, $^3J_{HPt}$ = 87 Hz, 2H), 7.45 (d, $^3J_{HH}$ = 8.3 Hz, 4H, C3-H), 7.33 (d, $^3J_{HH}$ = 8.2 Hz, 4H, C4-H), 2.45 (s, 6H, C6-H). $^{13}C\{^1H\}$ (DMF/C_6D_6): δ/ppm = 170.3 (C1), 146.5 (C2), 144.7 (C5), 129.5 (C4), 125.5 (C3), 21.3 (C6). $^{195}Pt\{^1H\}$ NMR (DMF/C_6D_6): δ/ppm = −2102.

$[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OH))_2\}]$, 4 (Chart 4). A suspension of *cis*-$[PtCl_2(\kappa S\text{-DMSO})_2]$ (118 mg, 0.278 mmol) and **L4** (67 mg, 0.28 mmol) in acetone (10 mL) was stirred at reflux for 2 hours. During this time, the mixture progressively turned to dark red with precipitation of a purple red solid, **$4\cdot(Me_2CO)_n$** (see ESI† for details). The suspension was centrifuged (10′ × 5000 rpm) and cooled to −20 °C. Next, the dark red solution was removed and the solid was washed with acetone (2 × 2 mL; separated by centrifugation) then suspended in refluxing CH_2Cl_2 (10 mL). After for 1.5 hours, the suspension was filtered and the resulting purple red solid was washed with CH_2Cl_2 and dried under vacuum (110 °C, 1 h). Yield: 114 mg, 81%. Alternatively, acetone can be removed from **$4\cdot(Me_2CO)_n$** by heating the solid at 110 °C under vacuum. The thermal treatment requires

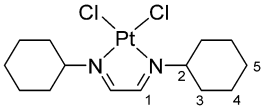


Chart 1 Structure of **1** (numbering refers to C atoms).

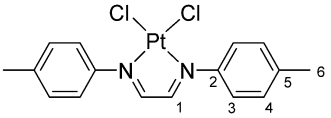


Chart 3 Structure of **3** (numbering refers to C atoms).

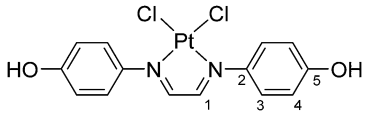


Chart 4 Structure of **4** (numbering refers to C atoms).

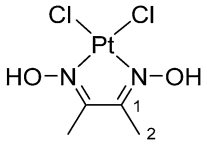


Chart 5 Structure of **5** (numbering refers to C atoms).

6–10 hours to completion, yielding a purple red solid with a distinct IR spectrum (Fig. S10, ESI†). Compound **4** is soluble in DMF, hot MeOH, in DMSO with rapid degradation (see Table S8, ESI†), moderately soluble in MeOH, poorly soluble in MeCN, EtOH, acetone, THF and CH_3NO_2; insoluble in $CHCl_3$, CH_2Cl_2, Et_2O, EtOAc and water. X-ray quality orange crystals of **4·THF** were obtained from a THF solution layered with Et_2O and settled aside at −20 °C. Anal. calcd for $C_{14}H_{12}Cl_2N_2O_2Pt$: C, 33.21; H, 2.39; N, 5.53. Found: C, 33.28; H, 2.43; N, 5.57. IR (solid state): $\tilde{\nu}$/cm^{-1} = 3325m (ν_{O-H}), 3211m (ν_{O-H}), 3193m (ν_{O-H}), 3192m-sh, 3046w, 1604m-sh ($\nu_{C=N}$), 1593m-sh, 1587m, 1551m, 1504m, 1473m, 1455s, 1374m, 1358m, 1301w, 1277m-sh, 1259m-sh, 1247s, 1236s, 1224s, 1168m, 1109m, 1058w, 1012w, 950w, 944w-sh, 927w, 895w, 876w, 824s, 809m-sh, 796w-sh, 717w, 674w-sh, 667m, 643w, 590m-sh, 583m, 541m, 495m, 468w, 441m, 416w, 398w, 351m (ν_{Pt-Cl}), 333m (ν_{Pt-Cl}), 289w. IR (solid state; thermal treatment): $\tilde{\nu}$/cm^{-1} = 3457m (ν_{O-H}), 3375m (ν_{O-H}), 3063w, 3030w, 2976w, 1604m ($\nu_{C=N}$), 1591m ($\nu_{C=N}$), 1572w, 1501s, 1450m, 1431w, 1363w, 1349w, 1318w, 1271m, 1264m, 1238m, 1211s, 1172s, 1162s-sh, 1100m, 1050w, 1012w, 968w, 942w, 928w, 882w-sh, 871w, 833s, 805m-sh, 723w, 671w. ^{1}H NMR (CD_3CN): δ/ppm = 8.76 (s + satellites, $^3J_{HPt}$ = 88 Hz, 2H, C1-H), 7.53 (s, 2H, OH), 7.42 (d, $^3J_{HH}$ = 8.8 Hz, 4H, C3-H), 6.91 (d, $^3J_{HH}$ = 8.8 Hz, 4H, C4-H). ^{1}H NMR (CD_3OD): δ/ppm = 8.83 (s + satellites, $^3J_{HPt}$ = 90 Hz, 2H, C1-H), 7.45 (d, $^3J_{HH}$ = 8.8 Hz, 4H, C3-H), 6.86 (d, $^3J_{HH}$ = 8.8 Hz, 4H). No changes in the ^{1}H NMR spectra (CD_3CN, CD_3OD) were observed after 24 hours at room temperature. ^{13}C{^{1}H} NMR (CD_3OD): δ/ppm = 167.4 (C1), 161.0 (C5), 141.8 (C2), 127.4 (C3), 115.8 (C4). ^{13}C{^{1}H} NMR (DMF/C_6D_6): δ/ppm = 168.0 (C1), 160.7 (C5), 141.3 (C2), 127.5 (C3), 115.6 (C4). ^{195}Pt{^{1}H} NMR (DMF/C_6D_6): δ/ppm = −2094.

The formation of compound **4** from *cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] is solvent- (a) and concentration- (b) sensitive. (a) Other solvents: MeOH, reflux T, 24 hours: mixture of products. $CHCl_3$, reflux T, 24 hours: only *cis*-[$PtCl_2$(κ*S*-DMSO)$_2$], no reaction. CH_2Cl_2, reflux T, 67 hours: *cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] and **4**, 47% conversion (^{1}H NMR, CD_3OD). (b) In acetone, a low amount of **4·(Me2CO)$_n$** as precipitate is collected for diluted mixtures (*cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] < 6 mg mL^{-1}). On the other hand, formation of a by-product (presumably *trans*-[$PtCl_2$(κ*S*-DMSO){κ*N*-(HCN(4-C_6H_4OH))$_2$}], **4A**) is observed for concentrated mixtures (*cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] > 14 mg mL^{-1}). ^{1}H NMR (CD_3OD): δ/ppm = 8.96 (s, 1H), 8.84 (s, 1H), 7.60 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H).

[$PtCl_2${κ^2*N*-(CH_3CNOH)$_2$}], 5 (Chart 5)[22]. The title compound was prepared as described for **1**, using *cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] (88 mg, 0.21 mmol), $dmgH_2$ (24 mg, 0.21 mmol) and acetone (5 mL). Brown solid (yellow colour in solution), yield: 59 mg, 74%. Compound **5** is soluble in DMF, in DMSO with rapid degradation (see Table S9, ESI†), poorly soluble in acetone, CH_3CN and MeOH, insoluble in CH_2Cl_2, ^{i}PrOH, Et_2O and water. Needle-shaped X-ray quality crystals of **5** were obtained from a DMF solution, layered with ^{i}PrOH and settled aside at −20 °C. Anal. calcd for $C_4H_8Cl_2N_2O_2Pt$: C, 12.57; H, 2.11, N, 7.33, Cl, 18.56. Found: C, 12.55; H, 2.07; N, 7.49; Cl, 18.36. IR (solid state): $\tilde{\nu}$/cm^{-1} = 3326m (ν_{O-H}), 3305w-sh (ν_{O-H}), 3254m (ν_{O-H}), 3241m (ν_{O-H}), 2928w, 1645w, 1594m ($\nu_{C=N}$), 1548w, 1421m-sh, 1393s-br, 1372s-br, 1335s-sh, 1261m-sh, 1213s, 1138w, 1095m-sh, 1065s, 1004m, 833w, 742w, 716s, 551m-sh, 553m, 440m-br, 399m, 375 m, 347m-sh (ν_{Pt-Cl}), 330m (ν_{Pt-Cl}), 307w, 250w. ^{1}H NMR (CD_3CN): δ/ppm = 10.2 (s-br, 1.3H, *OH), 2.08 (s, 6H, C2-H). ^{1}H NMR (acetone-d_6): δ/ppm = 10.6 (s-br, 1.4H, *OH), 2.20 (s, 6H, C2-H). *Lower integral due to rapid exchange with residual water. ^{13}C{^{1}H} NMR (acetone-d_6): δ/ppm = 160.1 (C1), 13.7 (C2). ^{13}C{^{1}H} NMR (DMF/C_6D_6): δ/ppm = 161.3 (C1), 14.1 (C2). ^{195}Pt{^{1}H} NMR (DMF/C_6D_6): δ/ppm = −2466.

[Pt{κ^2*N*,*N*′-(ONC(CH_3)C(CH_3)NOH)}$_2$], [Pt(dmgH)$_2$] (Chart 6)[48]. A suspension of *cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] (54 mg, 0.13 mmol) and $dmgH_2$ (30 mg, 0.26 mmol) in MeOH was treated with NEt_3 (40 μL, 0.29 mmol) then heated at reflux. Immediate formation of a yellow colour was observed, slowly turning to green and then dark blue. After 2 hours, the resulting suspension (yellow solution + dark blue solid) was cooled to room temperature and filtered. The solid was thoroughly washed with acetone, Et_2O and dried under vacuum (50 °C). Yield: 53 mg, 97%. Compound [Pt(dmgH)$_2$] is insoluble in DMSO, MeOH, CH_2Cl_2, acetone, MeCN and water. Anal. calcd for $C_8H_{14}N_4O_4Pt$: C, 22.59; H, 3.32; N, 13.17. Found: C, 22.50; H, 3.46; N, 13.29. IR (solid state): $\tilde{\nu}$/cm^{-1} = 3410w-br (ν_{O-H}), 3254w-sh (ν_{O-H}), 2979w, 2947w, 2924w, 2883w, 2738w, 2623m-sh, 2604m, 2531w, 2497m, 1712w, 1543s ($\nu_{C=N}$), 1506m-sh, 1495m, 1480m, 1474m, 1455m-sh, 1444m, 1397m, 1377m, 1367m-sh, 1333m, 1304w-sh, 1256s, 1217m-sh, 1172w, 1133w, 1084s, 1036m, 1008m, 993m, 902m, 851w-sh, 807w, 738s, 543w, 524m, 520m-sh, 416m, 379m, 339w, 268w.

Analogous reaction with excess of $dmgH_2$ (3 eq.) and without NEt_3 gave a brown solid probably composed by a mixture of products (IR spectrum different from both **5** and [Pt(dmgH)$_2$]).

Preparation from $K_2[PtCl_4]$/$dmgH_2$ in a EtOH/H_2O/HCl mixture (90 : 10 : 1 v/v) at 80 °C, as described in the literature,[48b]

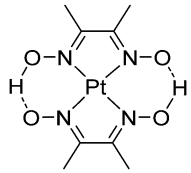


Chart 6 Structure of [Pt(dmgH)$_2$].

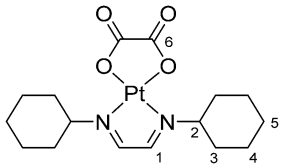


Chart 7 Structure of **6** (numbering refers to C atoms).

was not satisfactory. The resulting dark blue solid was isolated in a lower yield (*ca.* 70%) and its IR spectrum did not match that of $[Pt(dmgH)_2]$.

$[Pt(\kappa^2O\text{-}C_2O_4)\{\kappa^2N\text{-}(HCN(C_6H_{11}))_2\}]$, 6 (Chart 7). A suspension of **1** (76 mg, 0.16 mmol) and $AgNO_3$ (53 mg, 0.31 mmol) in H_2O : EtOH (1 : 1 v/v, 8 mL) was stirred at reflux in the dark for 3 hours. The resulting mixture (colourless solid + orange-red solution) was cooled to room temperature then filtered over celite. The filtrate solution was treated with $Na_2C_2O_4$ (22 mg, 0.16 mmol) and stirred at room temperature for 24 hours then at reflux for 2 hours. The resulting suspension (yellow solid + red solution) was filtered and the solid was washed with water, acetone, Et_2O then dried under vacuum (50 °C). Yield: 54 mg, 69%. Analogous reaction with 1 equivalent of $AgNO_3$ afforded the title compound in 39% yield. Compound **6** is poorly soluble in DMSO, DMF and CH_2Cl_2; insoluble in other polar organic solvents ($CHCl_3$, THF, acetone, MeOH, EtOH, CH_3NO_2) and water. Anal. calcd for $C_{16}H_{24}N_2O_4Pt$: C, 38.17; H, 4.80; N, 5.56. Found: C, 38.02; H, 4.90; N, 5.59. IR (solid state): $\tilde{\nu}$/cm^{-1} = 3112w, 3042w, 2929s, 2920m-sh, 2853m, 1696s ($\nu_{C=O}$), 1676s ($\nu_{C=O}$), 1666s ($\nu_{C=O}$), 1615w, 1551m ($\nu_{C=N}$), 1453w-sh, 1445m, 1409w, 1368s ($\nu_{C=O}$), 1354s ($\nu_{C=O}$), 1336m-sh, 1330m-sh, 1310m, 1289m, 1270w, 1259w, 1244m, 1224m, 1193w, 1108w, 1081w, 1030w, 994w, 966w, 926w, 895m, 873w, 851w, 821w, 808s, 768w, 707w, 570m, 525m, 461m-br, 368w-sh, 357w, 323w, 284m. ^{1}H NMR (CD_2Cl_2): δ/ppm = 8.48 (s + satellites, $^3J_{HPt}$ = 99 Hz, 2H, C1-H), 4.15–3.99 (m, 2H, C2-H), 2.23 (d, J = 10.3 Hz, 4H, C3-H/C4-H), 1.94 (d, J = 11.7 Hz, 4H, C3-H/C4-H), 1.69 (d, J = 12.1 Hz, C5-H); other ^{1}H signals are hidden by H_2O peak and solvent impurities. ^{1}H NMR (DMSO-d_6): δ/ppm = 8.79 (s + satellites, $^3J_{HPt}$ = 99 Hz, 2H, C1-H), 3.90–3.80 (m, 2H, C2-H), 1.97 (d, J = 11.2 Hz, 4H, C3-H/C4-H), 1.83 (d, J = 15.4 Hz, 4H, C3-H/C4-H), 1.81–1.71 (m, 4H, C3-H′/C4-H′), 1.66 (d, J = 11.7 Hz, 2H, C5-H), 1.34 (q, J = 12.5 Hz, 4H, C3-H′/C4-H′), 1.21–1.13 (m, 2H, C5-H′). The low solubility of the product prevented a full NMR characterization, including $^{13}C\{^1H\}$ and $^{195}Pt\{^1H\}$ NMR spectra.

(3) X-ray crystallography

Crystal data and collection details for **4·THF** and **5** are reported in Table 4. Data were recorded on a Bruker APEX II diffractometer equipped with a PHOTON100 detector using Mo-Kα radiation. Data were corrected for Lorentz polarization and absorption effects (empirical absorption correction SADABS).[49] The structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2.[50] Hydrogen atoms bonded to carbon were fixed at calculated positions and refined by a riding model. Hydrogen atoms bonded to oxygen in **4·THF** were preliminarily located in the Fourier map and, then, refined by a riding model. Hydrogen atoms bonded to oxygen in **5** were located in the Fourier map and refined isotropically with O–H distances restrained to 0.84 Å. All non-hydrogen atoms were refined with anisotropic displacement parameters. The structure of **4·THF** presents A and B alerts due to high values for the residual electron density. These maxima are located close to the Pt-atom, in positions which are not realistic for any atom, and they are series termination errors which are common with heavy atoms such as Pt.

Table 4 Crystal data and measurement details for **4·THF** and **5**

	4·THF	**5**
Formula	$C_{18}H_{20}Cl_2N_2O_3Pt$	$C_4H_8Cl_2N_2O_2Pt$
FW	578.35	382.11
T, K	100(2)	100(2)
λ, Å	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1/n$
a, Å	10.5760(4)	9.1298(9)
b, Å	14.2795(6)	6.7916(6)
c, Å	24.2119(10)	14.3444(14)
β, °	90	106.402(2)
Cell volume, Å^3	3656.5(3)	853.24(14)
Z	8	4
D_c, g cm^{-3}	2.101	2.975
μ, mm^{-1}	7.988	17.023
F(000)	2224	696
Crystal size, mm	0.15 × 0.13 × 0.10	0.18 × 0.14 × 0.11
θ limits, °	1.682–25.026	2.378–25.096
Reflections collected	41 664	8075
Independent reflections	3234 [R_{int} = 0.0906]	1506 [R_{int} = 0.0491]
Data/restraints/parameters	3234/178/283	1506/8/108
Goodness on fit on F^2	1.221	1.101
R_1 ($I > 2\sigma(I)$)	0.0653	0.0307
wR_2 (all data)	0.1096	0.0752
Largest diff. peak and hole, e Å^{-3}	1.943/−3.032	2.901/−1.745

(4) Stability studies in DMSO-d_6 and DMSO-d_6/D_2O mixtures

General features. Stock solutions of DMSO-d_6 or DMSO-d_6/D_2O 9 : 1 v/v + NaCl (0.11 M) were used for the following experiments. Dimethyl sulfone (Me_2SO_2, *ca.* 5 mM) was added to each solution as reference for ^{1}H NMR spectra (δ/ppm = 2.97 (s, 6H)).[51] The selected Pt complex (*ca.* 3 mg) was added to the DMSO-d_6 solution (0.55 mL) with vigorous stirring; the resulting solution or suspension was maintained at 37 °C for 72 hours and analyzed by ^{1}H and ^{195}Pt{^{1}H} NMR as a function of time. A parallel experiment was carried out with the DMSO-d_6/D_2O/NaCl mixture. NMR measurements were performed upon brief cooling to room temperature and then the solutions were heated again at 37 °C. In DMSO-d_6:D_2O mixtures, chemical shift were referenced to the residual $(CHD_2)(CD_3)SO$ peak as in pure DMSO-d_6 (δ/ppm = 2.50).[52] Percent values of compounds in solution are based on ^{1}H NMR spectroscopy and refer to identified compounds only (indicated as "% NMR"). Data are reported for each compound in the ESI† (Tables S5–S10); selected data are compiled in Table 2. NMR signals in brackets [ ] indicate a superimposition with signals belonging to other species in the same spectrum.

(5) Cell culture and cytotoxicity studies

The human ovarian carcinoma (A2780 and A2780cisR) cell lines were obtained from the European Collection of Cell Cultures (ECACC). The human embryonic kidney (HEK-293) cell line was obtained from ATCC (Sigma, Switzerland). Penicillin streptomycin, RPMI-1640 GlutaMAX and DMEM GlutaMAX media were obtained from Life Technologies and fetal bovine serum (FBS) was obtained from Pan Biotech. The cells were cultured in RPMI 1640 GlutaMAX (A2780 and A2780cisR) and DMEM GlutaMAX (HEK-293) medium containing 10% heat-inactivated fetal bovine serum and 1% penicillin–streptomycin at 37 °C and CO_2 (5%). The A2780cisR cell line was routinely treated with cisplatin (2 μM) in the media. Cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide).[53] Cells were seeded in flat bottomed 96-well plates as a suspension in prepared medium (100 μL aliquots and approximately 4300 cells per well) and pre-incubated for 24 h. Stock solutions of compounds were prepared in DMSO and diluted in medium. The solutions were sequentially diluted to give a final DMSO concentration of 0.5% and final compound concentration range (0 μM to 500 μM). Cisplatin was tested as a positive control (0 μM to 100 μM). The compounds were added to the pre-incubated 96-well plates in 100 μL aliquots and the plates were incubated for 72 h. MTT (20 μL, 5 mg mL^{-1} in Dulbecco's Phosphate Buffered Saline, DPBS) was added to the cells and the plates were incubated for a further 4 h. The culture medium was aspirated and the purple formazan crystals, formed by the mitochondrial dehydrogenase activity of vital cells, were dissolved in DMSO (100 μL per well). The absorbance of the resulting solutions, directly proportional to the number of surviving cells, was quantified at 590 nm using a SpectroMax M5e multi-mode microplate reader (using SoftMax Pro software (version 6.2.2)). The percentage of surviving cells was calculated from the absorbance of wells corresponding to the untreated control cells. The reported IC_{50} values (Table 3) are based on means from three independent experiments, each comprising four tests per concentration level.

Conflicts of interest

There are no conflicts to declare.

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