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Synthesis and cytostatic activity of Pt(II) complexes of intramolecularly coordinated phosphine and stibine ligands

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The intramolecularly coordinated phosphine and stibine ligands L^1PPh_2 (1), L^2PPh_2 (2) and L^2SbPh_2 (3) containing Y,C,Y-chelating ligands, $L^1 = 2,6\text{-}(^tBuOCH_2)_2C_6H_4^-$ and $L^2 = 2,6\text{-}(Me_2NCH_2)_2C_6H_4^-$, were prepared and characterized. The treatment of these ligands 1–3 with $PtCl_2$ yielded complexes *trans*-{[2,6-$(^tBuOCH_2)_2C_6H_3$]PPh_2}$_2PtCl_2$ (4), *cis*-{[2,6-$(Me_2NCH_2)_2C_6H_3$]PPh_2}$PtCl_2$ (5), and *cis*-{[2,6-$(Me_2NCH_2)_2C_6H_3$]$SbPh_2$}$PtCl_2$ (6) as the result of different ability of the starting compounds 1–3 to complex platinum centre. Compounds 1–6 were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy and electrospray ionization mass spectrometry, and molecular structures of 3–6 were determined by X-ray diffraction analysis. The substitution reactions of complexes 4–6 were also studied. The reaction of 5 and 6 with NaI yielded complexes {[2,6-$(Me_2NCH_2)_2C_6H_3$]PPh_2}PtI_2 (7) and {[2,6-$(Me_2NCH_2)_2C_6H_3$]$SbPh_2$}PtI_2 (8), while the same reaction of 4 with NaI did not proceed. As the compounds 7 and 8 structurally resemble cisplatin, complex {{[2-(Me_2NCH_2)-6-$(Me_2NHCH_2)C_6H_3$]PPh_2}$PtCl_2$}$^+Cl^-$ (9) was prepared as water-soluble platinum complex. The cytotoxic effect of complex 9 was evaluated on human T-lymphocytic leukemia cells MOLT-4 ($IC_{50} = 27.6 \pm 1.8$ μmol l^{-1}) and human promyelocytic leukemia HL-60 ($IC_{50} = 55.9 \pm 4.9$ μmol l^{-1}). Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: Y,C,Y-ligands; platinum; chelates; biological tests; cytotoxic study

Introduction

The discovery of cisplatin established a crucial role of platinum compounds in modern anticancer chemistry. Despite the fact that cisplatin is one of the most effective and frequently used cytostatic, its use is limited by induction of tumor resistance and undesirable side effects, namely nephrotoxicity and neurotoxicity.[1] Many molecular mechanisms underlie the sensitivity of tumor cells to cisplatin and undesirable formation of resistant clones. These include loss of p53, inability to activate apoptosis, increased DNA repair, and increased expression or mutations of H-ras. Thus novel modifications of cisplatin are constantly researched in an effort to minimize resistance development and undesirable side effects of currently used derivatives while maintaining potent antitumor activity. However, although the thousands of compounds were tested, only a few platinum complexes have been successfully used clinically.[2]

Most of the prepared platinum compounds share some common structural features such as the presence of two NLG (non-leaving groups, typically nitrogen ligands) and two LG (leaving groups, e.g. halides or carboxylates) in the *cis* position.[3] This configuration allows bidentate coordination to nucleobases of the DNA double helix,[4] and modifications of new active molecules have mostly focused on closely related systems. Recent studies also suggested that the substitution of the original donors in cisplatin by phosphorus atoms has not been investigated extensively. Structural and biological studies of platinum complexes bearing phosphine ligands instead of the two ammonia ligands were initiated by Longato *et al.*[5] and, subsequently, related phosphine platinum compounds were also studied by others.[6] The lack of investigation in the field of biological activities of platinum phosphine complexes probably arises from general acceptance that they are devoid of antiproliferative activity.[7] This is, however, often due to their poor solubility. In this field, the studies of Romerosa, Bergamini or Osella *et al.* showed that platinum phosphine-containing complexes exhibit antiproliferative properties at selected cell lines *in vitro*.[8] These results showed that studies of variable phosphine-based platinum complexes represent a significant topic and, especially, the design of water-soluble complexes will be of high importance. Among the variety of prepared phosphine ligands, the donor atom functionalized phosphines, so called 'hemi-labile' ligands, are of much interest since they combine characteristics of high basicity and steric bulkiness.[9] These ligands pose a variety of coordination modes in the transition metal complexes; the bidentate or tridentate chelate rings containing

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metal-O bonds derived from elimination of methyl groups.[10] The corresponding P-N chelating ligands are widely used in the chemistry of transition metals. In general, the discussed functionalized phosphines form six- and five-membered metal-donor rings as the result of *P*∩*N* chelation to the transition metal centre.[11] We have recently reported the synthesis of palladium complexes bearing phosphine ligands L^1PPh_2 (**1**) and L^2PPh_2 (**2**) (L^1 is 2,6-(^{t}BuOCH$_2$)$_2$C$_6$H$_4^-$ and L^2 is 2,6-(Me$_2$NCH$_2$)$_2$C$_6$H$_4^-$), where both phosphine ligands coordinated the palladium centre in a different fashion.[12] To extend our studies, we have further synthesized intramolecularly coordinated stibine ligand L^2SbPh_2 (**3**). The ligands **1–3** contain both a different central atom M and donor atom Y and were tested as potential hemilabile ligands for platinum atom, where (*M*∩*Y*) chelation should form six-membered platinum-donor rings.

In the course of our systematic studies on the coordination behavior of ligands **1–3**, here we report the synthesis of the corresponding platinum complexes *trans*-{[2,6-(^{t}BuOCH$_2$)$_2$C$_6$H$_3$]PPh$_2$}$_2$PtCl$_2$ (**4**), {[2,6-(Me$_2$NCH$_2$)$_2$C$_6$H$_3$]PPh$_2$}PtCl$_2$ (**5**) and {[2,6-(Me$_2$NCH$_2$)$_2$C$_6$H$_3$]SbPh$_2$}PtCl$_2$ (**6**) as the result of the different ability of ligands **1–3** to coordinate platinum atom (Chart 1). Substitution reactions of complexes **4–6** were also studied. The reaction of **5** and **6** with NaI yielded complexes {[2,6-(Me$_2$NCH$_2$)$_2$C$_6$H$_3$]PPh$_2$}PtI$_2$ (**7**) and {[2,6-(Me$_2$NCH$_2$)$_2$C$_6$H$_3$]SbPh$_2$}PtI$_2$ (**8**), while the same reaction of **4** with NaI did not proceed. All compounds were characterized by multinuclear NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS), and molecular structures of **3–7** were determined by X-ray diffraction analysis.

Despite compounds **5–8** structurally resembling cisplatin, they are poorly soluble in water, which is the crucial problem for their biological testing. For this reason, the compound {{[2-(Me$_2$NCH$_2$)-6-(Me$_2$NHCH$_2$)C$_6$H$_3$]PPh$_2$}PtCl$_2$}$^+$Cl$^-$ (**9**) was prepared as water-soluble platinum complex. Complex **9** was tested for cytostatic activity. The cytotoxic effect of complex **9** was evaluated on human T-lymphocytic leukemia cells MOLT-4 ($IC_{50} = 27.6 \pm 1.8$ μmol L^{-1}) and human promyelocytic leukemia HL-60 ($IC_{50} = 55.9 \pm 4.9$ μmol L^{-1}).

Results and Discussion

The starting phosphine ligands L^1PPh_2 (**1**) and L^2PPh_2 (**2**) were prepared by the treatment of the appropriate lithium salt with chlorodiphenylphosphine (Scheme 1).[12] The corresponding stibine L^2SbPh_2 (**3**) was prepared by a two-step procedure using precursor L^2SbCl_2,[13] which was reacted with phenyl lithium, leading to the desired **3**. Compound **3** was characterized with the help of ESI-MS, ^{1}H and ^{13}C NMR spectroscopy and using single-crystal X-ray analysis.

The molecular structure of **3** as an ORTEP drawing is depicted in Fig. 1 together with the selected bond distances and angles. The crystal data and structure refinement are given in Table 1.

The central antimony atom is located in a trigonal pyramidal array formed by the carbon atoms C(1), C(13) and C(19), which is slightly distorted by two weak N → Sb intramolecular interactions (the Sb1–N1 bond length is 2.934(3) Å and Sb1–N2 is 2.937(3) Å, respectively). Both nitrogen atoms are coordinated mutually in *cis* fashion (the bonding angle N(1)–Sb(1)–N(2) is 117.19°).

Reaction of 2 equiv. of **1** with $PtCl_2$ yielded complex *trans*-{[2,6-(^{t}BuOCH$_2$)$_2$C$_6$H$_3$]PPh$_2$}$_2$PtCl$_2$ (**4**) (equation (1) and Chart 1):

$$2L^1PPh_2 + PtCl_2 \rightarrow trans - \left[L^1PPh_2\right]_2PtCl_2 \qquad (1)$$

The ^{31}P NMR of **4** showed a signal at 14.7 ppm, shifted downfield compared with **1** (−20.4 ppm), with coupling constant ^1J (^{31}P, ^{195}Pt) = 2622 Hz, confirming coordination of **1** to the central Pt atom. The ^{1}H NMR spectrum of **4** at 300 K contains a sharp resonance of methylene CH_2O groups at δ 4.42 ppm. In addition, the ^{1}H and ^{13}C NMR spectra revealed one set of sharp signals over the whole temperature range (300–210 K) suggesting both free rotation of uncoordinated CH$_2$O^{t}Bu arms and a symmetrical arrangement around the central Pt atom in **4**. ESI-MS of **4** showed the presence of the specific ion at *m/z* 1157 $[M + Na]^+$. The structure of **4** was determined by X-ray diffraction techniques. The ORTEP drawing is depicted in Fig. 2 together with the selected bond distances and angles. The crystal data and structure refinement are given in Table 1.

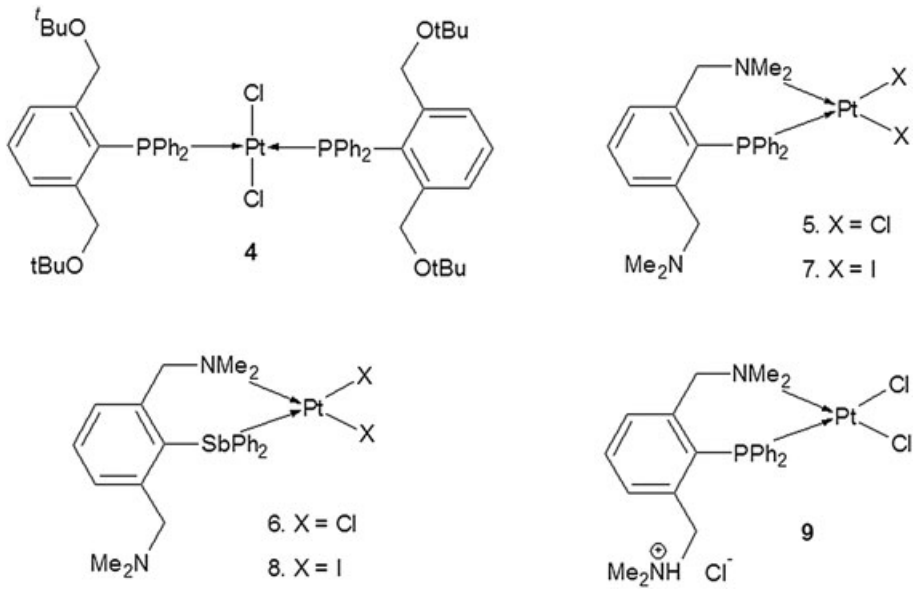
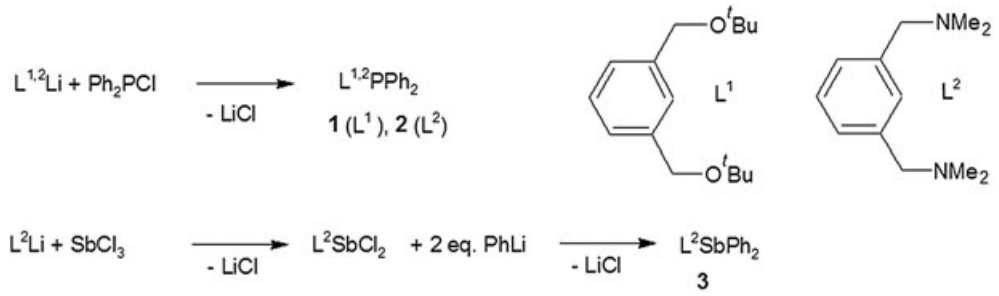


Chart 1. Schematic representation of prepared compounds 4 - 9



Scheme 1. Preparation of starting phosphine and stibine ligands **1–3** bearing Y,C,Y-chelates L^1 and L^2.

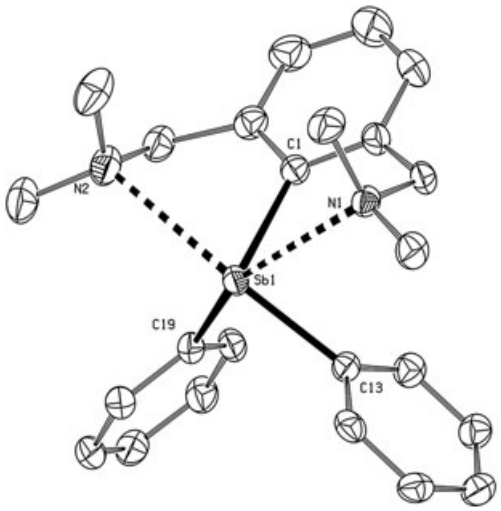


Figure 1. Molecular structure of compound **3**.

The coordination number of Pt(II) is four with mutually *trans* monodentate phosphines **1** and chlorine atom Cl1 and Cl1a as demonstrated by bonding angles of P1–Pt1–P2 (180°) and Cl1–Pt1–Cl1a (180°) in **4**. The P1–Pt1–Cl1 and P1a–Pt1–Cl1 angles are 85.53(6)° and 94.47(6)°, respectively, leading to a slight distortion from the square planar geometry around the metal centre. The Pt–P bond distance in **4** is 2.3264(16) Å and is similar to those observed in phosphine and phosphite complexes of Pt(II) (2.2–2.4Å).[14] The lengths of Pt–O (range of 4.202(8)–4.647(5) Å) bond lengths suggest there are no contacts in **4** between Pt and O atoms leaving the phosphine ligand in a monodentate fashion.

Reaction of 2 equiv. of **2** with $PtCl_2$ was monitored by ^{31}P NMR spectroscopy and revealed the presence of a new signal at δ −2.5 ppm together with a signal of the starting **2** at δ −17.6 ppm in 1:1 ratio. Modification of stoichiometry to 1:1 (2/$PtCl_2$) yielded the compound {[2,6-$(Me_2NCH_2)_2C_6H_3$]PPh_2}$PtCl_2$ (**5**) as the only product (equation **2** and Chart 1):

$$\underset{2}{L^2PPh_2} + PtCl_2 \rightarrow \quad \underset{5}{cis - [L^2PPh_2]_2PtCl_2} \qquad (2)$$

The ^{31}P NMR of **5** showed the signal at δ −2.5 ppm, shifted downfield when compared with **2** (−17.6 ppm), with coupling constant $^1J(^{31}P, ^{195}Pt) = 4021$ Hz. The ^1H NMR spectrum of **5** measured at 300 K contained a broad signal at δ 2.31 ppm for CH_2N and at δ 1.81 ppm for CH_3 groups of the ligand L^2. The ^1H NMR spectrum of **5** measured at 210 K revealed an AB spin system (δ_A 2.23, δ_B 2.36) with J_{AB} being 12 Hz and an AX spin system at δ_A 3.38 ppm and δ_X 4.17 ppm for CH_2N groups and three signals at δ 1.78, 2.88 and 3.27 ppm, respectively, in a 2:1:1 ratio for the CH_3 groups of the ligand L^2. This pattern indicates that **5** in solution possesses two magnetically non-equivalent CH_2NMe_2 moieties. This is in accordance with the measured solid state structure (see below). The ESI-MS analysis of **5** revealed the presence of specific ions at *m/z* 677 $[M + Cl]^-$. The molecular structure of **5** was also confirmed by X-ray diffraction techniques. The ORTEP drawing is depicted in Fig. 3 together with the selected bond distances and angles. The crystal data and structure refinement are given in Table 1.

The phosphine **2**-bearing nitrogen atom behaves as a P∩N chelate in **5**. The coordination number of Pt(II) is four with mutually *cis* arrangement of phosphorus and nitrogen atoms of the η^2-coordinated phosphine **2** and chlorine atoms Cl1 and Cl2 in **5**. The values of N1–Pt1–P1 (95.32(18)°) and Cl1–Pt1–Cl2 (86.95(9)°) angles define the distortion of ideal square-planar geometry resulting from the ring strain of the six-membered metallacycle Pt1–P1–C1–C2–C3–N1. The Pt1–P1 bond distance in **5** of 2.2328(19) Å is similar to those observed in phosphine complexes of Pt(II).[14] The value of Pt1–N1 bond being 2.068(7) Å defines a strong coordination of the nitrogen atom to platinum and is comparable to those found in similar monomeric N-coordinated Pt complexes (range 2.073–2.155 Å).[15]

The treatment of **3** with $PtCl_2$ produced *cis*-{[2,6-$(Me_2NCH_2)_2C_6H_3$]$SbPh_2$}$PtCl_2$ (**6**) (equation **3** and Chart 1):

$$\underset{3}{L^2SbPh_2} + PtCl_2 \rightarrow \quad \underset{6}{cis - [L^2SbPh_2]_2PtCl_2} \qquad (3)$$

Compound **6** was characterized with the help of ESI-MS, ^1H and ^{13}C NMR spectroscopy and using single-crystal X-ray analysis. The ^1H NMR spectrum of **6** at 300 K revealed two AX spin systems at δ_A 2.63 ppm and δ_X 3.43 ppm and at δ_A 3.97 ppm and δ_X 4.20 ppm for CH_2N groups, and three signals at δ 1.60, 2.82 and 3.33 ppm, respectively, in mutual 2:1:1 integral ratio for the CH_3 groups of the ligand L^2. This pattern indicates that the solution structure of **6** is analogous to the phosphorus analogue **5** (see below). ESI-MS revealed the presence of specific ions at *m/z* 770 $[M + K]^+$, *m/z* 754 $[M + Na]^+$ and *m/z* 696 $[M - Cl]^+$.

The structure of **6** was determined by X-ray diffraction techniques. The ORTEP drawing is depicted in Fig. 4 together with the selected bond distances and angles. The crystal data and structure refinement are given in Table 1.

The square planar geometry of the Pt(II) atom in **6** is formed by two chlorine atoms, the Sb(1) atom and the N(1) atom, showing that the ligand behaves as an Sb∩N chelate. The nitrogen and antimony atoms and both chlorine atoms are mutually placed in *cis* positions, as demonstrated by the bonding angles of Sb1–Pt1–N1

Table 1. Crystal data and structure refinement for **3–7**

	3	4	5	6	7
Empirical formula	$C_{24}H_{29}N_2Sb$	$C_{56}H_{70}Cl_2O_4P_2Pt \times 2(C_4H_8O) \times CH_2Cl_2$	$C_{24}H_{29}Cl_2N_2PPt \times (CHCl_3) \times C_6H_{14}$	$C_{24}H_{29}Cl_2N_2SbPt \times 3(CHCl_3)$	$C_{24}H_{29}I_2N_2PPt \times CHCl_3 \times C_3H_6O$
Color	Colorless	Colorless	Colorless	Yellowish	Colorless
Crystal system	Triclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P\ -1$	$P\ 2_1/c$	$P\ 2_1/c$	$P\ bca$	$P\ 2_1/c$
a (Å)	9.6171(10)	13.1400(6)	8.9420(5)	20.0540(14)	12.0100(13)
b (Å)	11.1900(4)	20.501(2)	12.6541(14)	16.8370(16)	9.4380(10)
c (Å)	11.5619(6)	12.4221(10)	26.479(3)	22.375(2)	28.617(2)
α (°)	106.298(6)	90	90	90	90
β (°)	106.938(7)	111.915(6)	95.403(7)	90	98.543(10)
γ (°)	96.409(9)	90	90	90	90
Z	2	2	4	8	4
μ (mm^{-1})	1.245	2.451	5.233	5.215	6.624
D_x (Mg m^{-3})	1.389	1.461	1.888	1.919	2.076
Crystal size (mm)	0.52 × 0.39 × 0.35	0.66 × 0.28 × 0.14	0.31 × 0.09 × 0.09	0.28 × 0.21 × 0.17	0.22 × 0.20 × 0.15
Crystal shape	Block	Needle	Needle	Block	Block
θ range (°)	1–27.5	1–27.5	1–27.5	1–27.5	1–27.5
T_{min}, T_{max}	0.673, 0.814[a]	0.425, 0.744[a]	0.388, 0.678[a]	0.297, 0.541[a]	0.347, 0.578[a]
No. of reflections measured	22 704	28 676	27 441	52 444	28 429
No. of unique reflections; R_{int}	4 749, 0.0974	5 149, 0.1023	4 998, 0.1297	6 258, 0.0901	6 227, 0.0662
No. of observed ref. [$I > 2\sigma(I)$]	5 102	6 789	6 600	8 641	7 307
No. of parameters	244	277	271	379	307
Final R[b] [$I > 2\sigma(I)$]	0.0372	0.0558	0.0568	0.0382	0.0531
$wR2$[b] (all data)	0.1066	0.1304	0.1444	0.1020	0.1302

[a]Correction by SORTAV program.
[b]Definitions: $R(F) = \Sigma\ ||F_o| - ||F_c||/\Sigma\ |F_o|$, $wR2 = [\Sigma\ (w(F_o^2 - F_c^2)^2)/\Sigma\ (w(F_o^2)^2)]^{1/2}$, $S = [\Sigma\ (w(F_o^2 - F_c^2)^2)/(N_{reflns} - N_{params})]^{1/2}$.

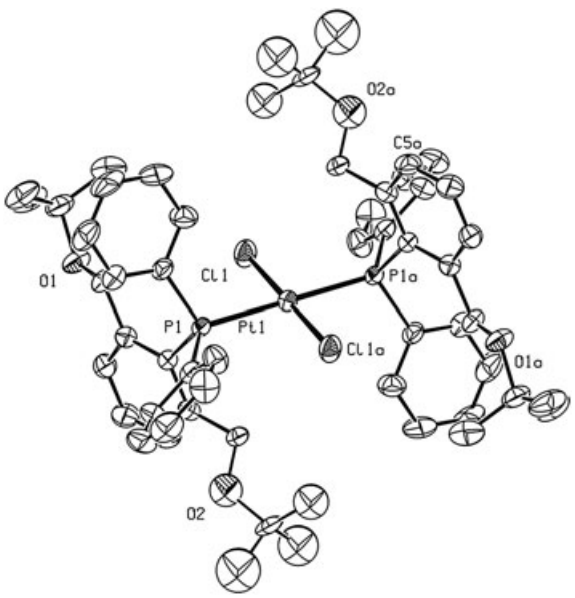


Figure 2. Molecular structure of **4**. Thermal ellipsoids are drawn with 50% probability. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): Pt1–Cl1 2.3031(15), Pt1–P1 2.3264(15), Cl1–Pt1–Cl1a 180.00(8), Cl1–Pt1–P1 85.54(5), Cl1a–Pt1–P1 95.46(5), P1–Pd1–P1a 180.00(5).

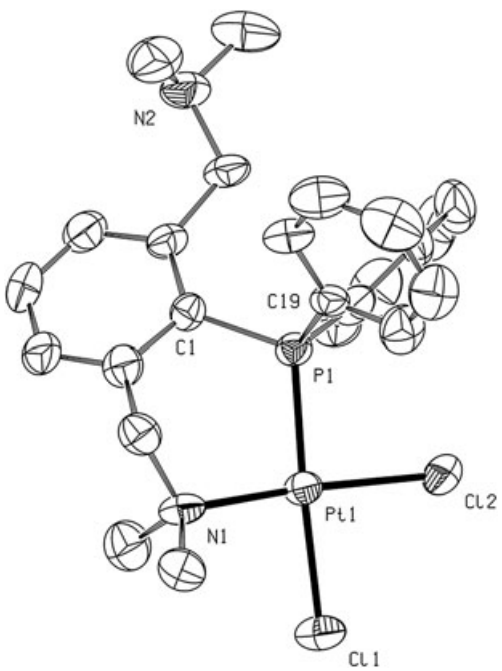


Figure 3. Molecular structure of **5**. Thermal ellipsoids are drawn with 50% probability. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): Pt1–N1 2.068(7), Pt1–P1 2.2328(19), Pt1–Cl2 2.302(2), Pt1–Cl1 2.368(2), N1–Pt1–P1 95.32(18), N1–Pt1–Cl2 173.69(18), P1–Pt1–Cl2 88.59 (8), N1–Pt1–Cl1 89.68(18), P1–Pt1–Cl1 172.36(7), Cl1–Pt1-Cl2 86.95(9).

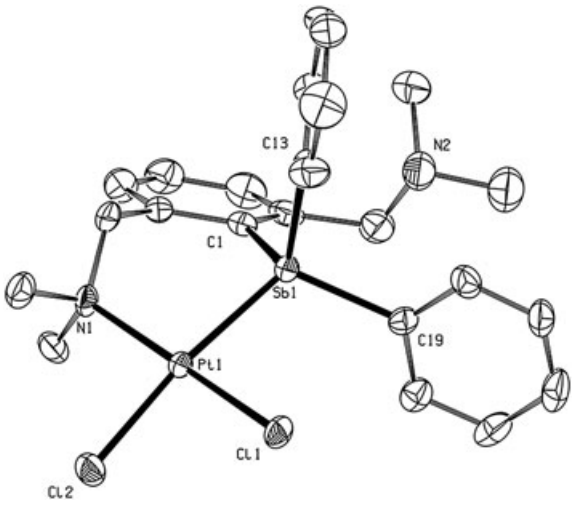


Figure 4. Molecular structure of **6**. Thermal ellipsoids are drawn with 50% probability. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): Pt1–N1 2.096(5), Pt1–Sb1 2.4935(5), Pt1–Cl2 2.3618(15), Pt1–Cl1 2.2983(15), N1–Pt1–Sb1 93.77(13), N1–Pt1–Cl1 90.51 (14), Sb1–Pt1–Cl1 88.35(4), N1–Pt1-Cl1 174.97(14), Sb1–Pt1–Cl2 171.85 (4), Cl1–Pt1–Cl2 87.95(6).

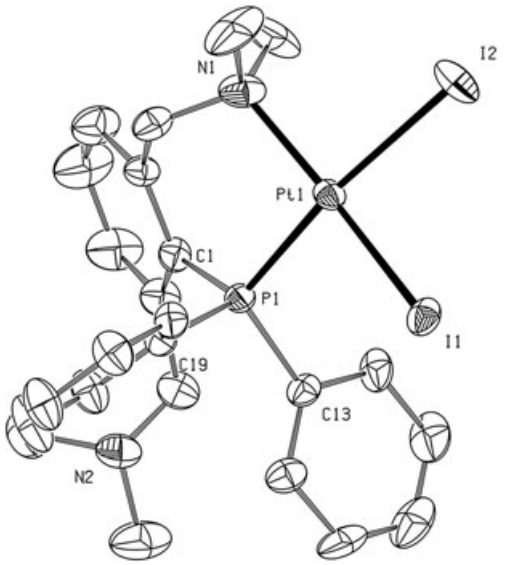


Figure 5. Molecular structure of **7**. Thermal ellipsoids are drawn with 50% probability. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): Pt1–N1 2.121(8), Pt1–P1 2.254(2), Pt1–I1 2.6082(7), Pt1–I2 2.6721(7), N1–Pt1–P1 93.3(2), N1–Pt1–I1 167.4(2), P1–Pt1–I1 89.90(5), N1–Pt1–I2 91.6(2), P1–Pt1–I2 168.94(5), I1–Pt1–I2 87.46(2).

(93.77(13)°) and Cl1–Pt1–Cl2 (87.95(6)°). The value of the Pt1–N1 bond (2.096(5) Å) defines strong coordination of the nitrogen atom to the central platinum atom.[15] The value of Sb1–Pt1 bond length 2.4935(5) Å is comparable to the values established in analogous platinum complexes containing stibine ligands.[16] The value of Sb1–N2 (3.552(6) Å) bond distance indicates that the second nitrogen atom remains out of the coordination sphere of the antimony atom.

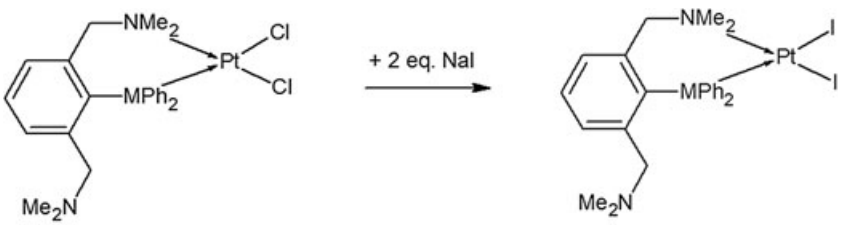
Depending on the ligand used, different coordination arrangements of the central Pt(II) atom were observed. The different geometries of mentioned compounds (*cis* vs. *trans*) also provided different reactivity patterns. While the reaction of **4** with excess of NaI did not provide any new product and no substitution of *trans* chlorides took place, the same reactions of **5** and **6**, having chlorine atoms mutually in the *cis* position, yielded complexes {[2,6-$(Me_2NCH_2)_2C_6H_3$]PPh_2}PtI_2 (**7**) and {[2,6-$(Me_2NCH_2)_2C_6H_3$]$SbPh_2$}PtI_2 (**8**) (Scheme 2 and Chart 1).

These complexes were characterized by the ^{1}H NMR spectroscopy, and the molecular structure of **7** was determined by X-ray diffraction technique (see Fig. 5). All data are, however, rather similar to those found for the chlorine analogues **5** and **6** and established the *cis* arrangement of iodine atoms together with P∩N or Sb∩N chelating character of the phosphine **2** and stibine **3** ligands in platinum complexes **7** and **8**, respectively (see Experimental section).

Solubility in Water and Biological Tests

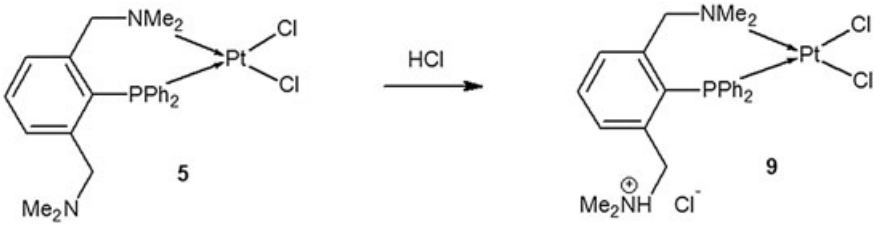
As the compounds **5–8** geometrically resemble cisplatin, practical tests of biological activity were supposed to be done, but compounds were not sufficiently soluble or stable in water. The structural studies, however, showed the presence of a free - uncoordinated NMe_2 moiety in the structures of the discussed complexes. The simple treatment of **5** with HCl provided a water-soluble complex {{[2-(Me_2NCH_2)-6-$(Me_2NHCH_2)C_6H_3$]PPh_2}$PtCl_2$}$^+Cl^-$ (**9**), in which the phosphine **2** still behaves as the P∩N chelating ligand to the central platinum atom, but the protonization of free uncoordinated NMe_2 moiety yielded an ammonium NMe_2H^+ group (Scheme 3). The same reactions of **6–8** with HCl to obtain other water-soluble complexes were unsuccessful.

Complex **9** was characterized by NMR spectroscopy. The ^{31}P NMR spectrum of **9** in D_2O showed a signal at δ −4.0 ppm, similarly to the starting compound **5** (δ −2.5), with coupling constant $^1J(^{31}P, ^{195}Pt) = 4116$ Hz. The ^{1}H NMR spectrum of **9** contains two broad signals of methylene CH_2N groups at δ 4.09 and 4.13 ppm together with two broad signals of methyl NCH_3 groups at δ 2.48 ppm and 2.80 ppm. This hints that both CH_2NMe_2 moieties are non-equivalent in D_2O solution of **9**. The successful protonation of the ligand arm was also proved by the presence of the signal of N*H* moiety at δ 4.23 ppm. The structure of **9** was determined



5: M = P
6: M = Sb
7: M = P
8: M = Sb

Scheme 2. Preparation of complexes **7** and **8**.



Scheme 3. Synthesis of the water-soluble complex **9**, structural analogue of cisplatin.

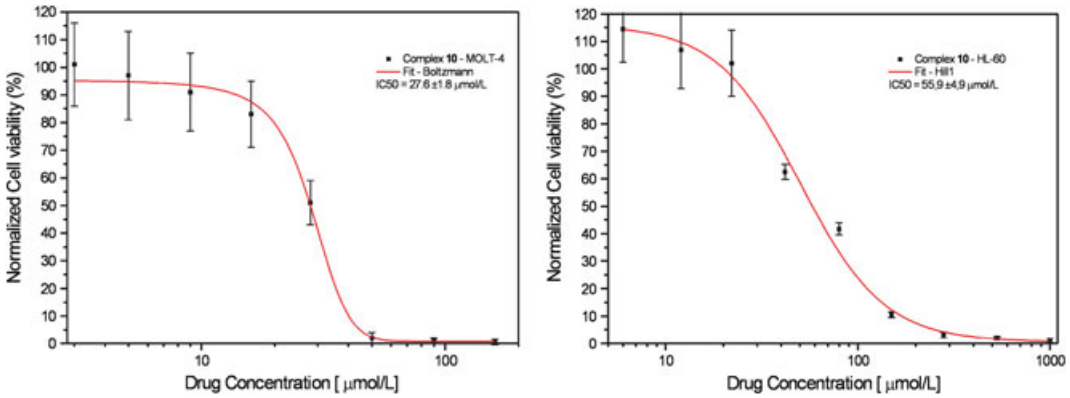


Figure 6. Cytotoxic activity of Pt(II) complex **9** towards T-lymphocytic leukemia cells MOLT-4 and human promyelocytic leukemia HL-60.

by X-ray diffraction techniques. The molecular structure, however, is highly disordered due to the presence of water molecules. The central core of compound **9** was unaffected and well determined (see Fig. S1 in supporting information).

To examine the cytotoxic activity of Pt(II) complex **9**, the standard WST-1 viability assay was used.[17] Cytotoxic effect was evaluated on human T-lymphocytic leukemia cells MOLT-4 and human promyelocytic leukemia HL-60 in exponential grow phase, 24 h after incubation with the cytostatic drugs. Cytotoxicity data were given as IC_{50} values: the concentration of complex required to inhibit the growth of cells by 50% compared with that of a control (see Fig. 6). The results show that complex **9** has antitumor activity on MOLT-4 ($IC_{50} = 27.6 \pm 1.8$ μmol L^{-1}) and on HL-60 ($IC_{50} = 55.9 \pm 4.9$ μmol L^{-1}). Compared with the results for cisplatin (MOLT-4; $IC_{50} = 6.8$ μmol L^{-1}) and (HL-60; $IC_{50} = 8.1$ μmol L^{-1}) complex **9** showed lower toxicity (greater IC_{50} values). It is possible that these ligands may play a partial role in the biological activity.

Experimental

The starting phosphine ligands L^1PPh_2 (**1**), L^2PPh_2 (**2**) and L^2SbCl_2 were synthesized according to the literature.[12,13] Starting with *n*BuLi, chlorodiphenylphosphine, $PtCl_2$ and NaI were purchased from Sigma Aldrich and used as received. All reactions were carried out under argon atmosphere, using standard Schlenk techniques. Solvents were dried by standard methods and distilled prior to use. The ^1H, ^{13}C and ^{31}P NMR spectra were acquired with a Bruker Avance 500 spectrometer in $CDCl_3$ or D_2O. Appropriate chemical shifts were calibrated on ^1H-residual peak of $CHCl_3$ (δ = 7.25 ppm), ^{13}C-residual peak of $CHCl_3$ (δ = 77.23 ppm) and ^{31}P-external H_3PO_4 (δ = 0.00 ppm). ESI mass spectra were recorded in positive mode on an Esquire 3000 ion trap analyzer (Bruker Daltonics) in the range 100–1200 *m/z* and in the negative mode on the Platform quadrupole analyzer in the range 100–800 *m/z*. The samples were dissolved in acetonitrile and analyzed by direct infusion at a flow rate of 1–10 μl min^{-1}.

Preparation of $[2,6\text{-}(Me_2NCH_2)_2C_6H_3]SbPh_2$ (3)

2.14 ml of a solution of phenyllithium (3.86 mmol, 1,8 M solution in dibutyl ether, 10% excess) was added dropwise to the stirred toluene (40 ml) solution of L^2SbCl_2 (0.672 g, 1.75 mmol) at −70°C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The resulting mixture was filtered and the filtrate was evaporated to give yellowish crystals. The crystals were washed with pre-cooled hexane (5 ml, −30°C) to give a pale-yellow solid **3**. Yield: 0.66 g (80%); m.p. 81–84°C. ^1H NMR ($CDCl_3$, 500 MHz, 300 K) δ (ppm): 1.86 (s, 12H, N(CH_3)$_2$); 3.17 (s, 4H, CH_2N) 7.14 (m, 8H, Ar*H*); 7.24 (t, 1H, Ar*H*); 7.61 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 44.4 (CH_3); 65.5 (CH_2N); 127.0, 127.8, 128.3, 129.0, 135.7, 146.9, 147.5 (s, Ar-*C*) C(1) not observed. Positive-ion ESI-MS: *m/z* 389 $[LSbPh]^+$, 100%. Anal. Calc. for $C_{24}H_{29}N_2Sb$ (467.26): C, 61.69; H, 6.26. Found: C, 61.81; H, 6.39%.

Preparation of $\{[2,6\text{-}(^tBuOCH_2)_2C_6H_3]PPh_2\}_2PtCl_2$ (4)

160 mg (0.6 mmol) of $PtCl_2$ was added to the THF (20 ml) solution of 1 (0.65 g; 1.5 mmol) and the suspension was stirred for 4 days. The resulting suspension was filtered and solvent evaporated to a form light-yellow solid, which was washed with hexane (5 ml) to form crystalline material **4**. Yield: 0.61 g (95%); m.p. 205–208°C ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.89 (s, 36H, CH_3) 4.47 (s, 8H, CH_2O) 7.28–7.85 (m, 26H, Ar*H*) ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 27.5 (CH_3) 63.9 ((CH_2O) $^3J(^{13}C, ^{31}P) = 8.8$ Hz) 73.3 ($OCMe_3$) 123.1 (C(1) $^1J(^{13}C, ^{31}P) = 25.0$ Hz) 126.6 (*C*(3,5)) 127.7 (*C*(3′,5′)) 130.3 (*C*(4′)) 130.5 (*C*(4)) 131.9 (*C*(1′) $^1J(^{13}C, ^{31}P) = 22.6$ Hz) 135.8 (*C*(2′,6′) $^2J(^{13}C, ^{31}P) = 12.5$ Hz) 144.0 (*C*(2,6) $^2J(^{13}C, ^{31}P) = 7.5$ Hz); ^{31}P NMR ($CDCl_3$, 145 MHz) δ (ppm):

11.3; positive-ion ESI-MS: *m/z* 1157 $[M+Na]^+$ (100%). Anal. Calc. for $C_{56}H_{70}Cl_2O_4P_2Pt$ (1135.12): C, 63.03; H, 9.30. Found: C, 63.39; H, 9.34%.

Preparation of {[2,6-(Me_2NCH_2)$_2C_6H_3$]PPh_2}$PtCl_2$ (5)

100 mg (0.3 mmol) of $PtCl_2$ was added to the THF (15 ml) solution of **2** (0.11 g 0.3 mmol) and the suspension was stirred for 5 days. THF was evaporated and solid residuum extracted with 15 ml CH_2Cl_2 and the suspension was stirred for 30 min. After filtration CH_2Cl_2 was evaporated and the solid was washed with hexane (5 ml) to form an orange crystalline material **5**. Yield: 0,17 g (81%); m.p. 120–125°C; ^{1}H NMR ($CDCl_3$, 500 MHz, 210 K) δ (ppm): 1.78 (s, 6H, NCH_3); 2.27 (AB spin system, 2H, CH_2N, δa 2.23 ppm, δb 2.36 ppm) 2.88 (s, 3H, NCH_3); 3.27 (s, 3H, NCH_3); 3.83 (AX spin system, 1H, CH_2N) 4.17 (AX spin system, 1H, CH_2N) 6.94–7.93 (m, 13H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 44.4 (NCH_3); 45.2 (NCH_3); 45.4 (NCH_3); 63.0 (CH_2N); 71.2 ((CH_2N) $^3J(^{13}C, ^{31}P) = 14.5$ Hz) 127.5 (*C*(4′)) 128.4 (*C*(3′,5′) $^3J(^{13}C, ^{31}P) = 4.5$ Hz) 129.2 (*C*(4)) 130.9 (C(1) $^1J(^{13}C, ^{31}P) = 77.8$ Hz) 131.6 (*C*(2′,6′) $^2J(^{13}C, ^{31}P) = 18.1$ Hz) 132.2 (*C*(3) $^3J(^{13}C, ^{31}P) = 2.7$ Hz) 132.8 (*C*(5) $^3J(^{13}C, ^{31}P) = 7.2$ Hz) 133.8 (*C*(1′)) 137.7 (*C*(2) $^2J(^{13}C, ^{31}P) = 15.4$ Hz) 139.5 (*C*(6) $^2J(^{13}C, ^{31}P) = 15.4$ Hz) ^{31}P NMR ($CDCl_3$, 145 MHz) δ (ppm): −2.5; positive-ion ESI-MS: *m/z* 677 $[M+Cl]^-$ (100%). Anal. Calc. for $C_{24}H_{29}Cl_2N_2PPt$ (643.49): C, 39.27; H, 4.64. Found: C, 39.10; H, 4.58%.

Preparation of {[2,6-(Me_2NCH_2)$_2C_6H_3$]$SbPh_2$}$PtCl_2$ (6)

239 mg (0.9 mmol) of $PtCl_2$ was added to the dichlormethane solution (20 ml) of **3** (0.42 g 0.9 mmol) and the suspension was stirred for 24 h. During this period $PtCl_2$ was consumed and the reaction mixture turned to a bright yellow color. Traces of insoluble material were filtered off and the volume of the filtrate was reduced to ~5 ml. Crystallization at −10°C gave compound **6** as yellow crystals, which were decanted from solution and dried *in vacuo*. Yield: 0.43 g (65%); m.p. 173°C-dec.; ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K) δ (ppm): 1.60 (s, 6H, NCH_3); 2.63 (AX spin system, 1H, CH_2N) 2.82 (s, 3H, NCH_3); 3.33 (s, 3H, NCH_3); 3.43 (AX spin system, 1H, CH_2N); 3.97 (AX spin system, 1H, CH_2N) 4.20 ppm (AX spin system, 1H, CH_2N) 7.21–7.48 (m, 11H, Ar*H*); 7.94 (d, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 45.0 (NCH_3); 50.5 (NCH_3); 56.7 (NCH_3); 64.2 (CH_2N); 75.2 (CH_2N) 125.1, 126.7, 128.7, 129.1, 129.9, 130.7, 131.3, 131.6, 133.0, 134.1, 135.8, 136.4, 141.4, 145.7 (Ar-*C*) positive-ion ESI-MS: *m/z* 770 $[M+K]^+$; *m/z* 754 $[M+Na]^+$; *m/z* 696 $[M-Cl]^+$; *m/z* 389 $[LSbPh]^+$, 100%. Anal. Calc. for $C_{24}H_{29}Cl_2N_2SbPt$ (733.26): C, 39.31; H, 3.99. Found: C, 39.10; H, 4.22%.

Preparation of {[2,6-(Me_2NCH_2)$_2C_6H_3$]PPh_2}PtI_2 (7)

0.056 g (0.38 mmol) of NaI in acetone (8 ml) was added dropwise to the dichloromethane (15 ml) solution of **5** (0.071 g 0.16 mmol) and stirred for 24 h. Solvent was evaporated; solid residue was dissolved in dichloromethane and the solution was stirred for 2 h. After filtration, the solvent was evaporated to form orange crystalline material of **7**. Yield: 0.079 g (85%); m.p. 197–199°C; ^{1}H NMR ($CDCl_3$, 500 MHz, 230 K) δ (ppm): 1.83 (s, 6H, NCH_3); 2.39 (AB spin system, 2H, CH_2N, δ_a 2.34 ppm, δ_b 2.43 ppm); 3.04 (s, 3H, NCH_3); 3.46 (s, 3H, NCH_3) 4.31 (AX spin system, 1H, CH_2N) 4.64 (AX spin system, 1H, CH_2N) 7.12–8.19 (m, 13H, Ar*H*); ^{31}P NMR ($CDCl_3$, 145 MHz) δ (ppm): 1.3. Anal. Calc. for $C_{24}H_{29}I_2N_2PPt$ (826.39): C, 41.28; H, 5.04. Found: C, 41.45; H, 5.11%.

Preparation of {[2,6-(Me_2NCH_2)$_2C_6H_3$]$SbPh_2$}PtI_2 (8)

0.056 g (0.38 mmol) of NaI in acetone (15 ml) was added dropwise to the dichloromethane (15ml) solution of **6** (0.120 g 0.13 mmol) and stirred for 24 h. During this period the reaction mixture turned to an orange color. The volume of the reaction mixture was reduced to ~20 ml and filtrated. The filtrate was evaporated to form orange crystalline material of **8**, which was almost insoluble after isolation. Yield: 0.118 g (79%); m.p. 215°C-dec.; ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K) δ (ppm): 1.66 (s, 6H, NCH_3); 3.00 (s, 3H, NCH_3); 2.68 (AX spin system, 1H, CH_2N); 3.46 (AX spin system, 1H, CH_2N) 3.53 (s, 3H, NCH_3); 4.07 (AX spin system, 1H, CH_2N); 4.52 (AX spin system, 1H, CH_2N) 7.37–7.57 (m, 11H, Ar*H*); 8.06 (d, 2H, Ar*H*); positive-ion ESI-MS: *m/z* 788 $[M-I]^+$, (100%); *m/z* 389 $[LSbPh]^+$. Anal. Calc. for $C_{24}H_{29}I_2N_2SbPt$ (916.16): C, 31.46; H, 3.19. Found: C, 31.69; H, 3.42%.

Preparation of {{[2-(Me_2NCH_2)-6-(Me_2NHCH_2)C_6H_3]PPh_2} $PtCl_2$}$^+Cl^-$ (9)

0.14 ml of 35% HCl (1.62 mmol) was added dropwise to the dichloromethane (4 ml) solution of **5** (0.41 g; 0.65 mmol) and the reaction mixture was stirred for the next 20 h. The green formed suspension of product was extracted with 50 ml distilled water and the layers were separated. Slow evaporation of water produced crystalline material identified as **9**. Yield: 0.26 g (61%); m.p. 215–216°C; ^{1}H NMR (D_2O, 400 MHz) δ (ppm): 2.48 (bs, 6H, NHCH_3); 2.80 (bs, 6H, NCH_3); 4.09 (bs, 2H, CH_2NH) 4.13 (bs, 2H, CH_2N) 4.23 (bs, 1H, NHCH$_3$) 7.46–7.70 (m, 13H, Ar*H*); ^{13}C NMR (D_2O, 100 MHz) δ (ppm): 41.9 (NCH_3); 42.0 (NCH_3); 48.4 (NHCH_3); 57.0 (CH_2NH); 69.8 ((CH_2N) $^3J(^{13}C, ^{31}P) = 15.3$ Hz) 122.9 (*C*(4′)) 123.5 (*C*(3′,5′)) 129.6 (*C*(4)) 130.6 (*C*(2′,6′) $^2J(^{13}C, ^{31}P) = 8$ Hz) 132.6 (*C*(1′), $^1J(^{13}C, ^{31}P) = 166$ Hz)) 133.3 (*C*(2) $^2J(^{13}C, ^{31}P) = 11.0$ Hz) 133.6 (*C*(3)) 134.5 (*C*(6) $^nJ(^{13}C, ^{31}P) = 6.0$ Hz) 134.7 (*C*(5)) 141.1 (*C*(1) $^1J(^{13}C, ^{31}P) = 160$ Hz) ^{31}P NMR (D_2O, 161 MHz) δ (ppm): −4.0; $^1J(^{31}P, ^{195}Pt) = 4116$ Hz. Anal. Calc. for $C_{24}H_{31}Cl_3N_2PPt$ (680.96): C, 41.27; H, 4.61. Found: C, 42.33; H, 4.74%.

Crystallography

Crystals suitable for X-ray analyses were grown from hexane (**3**), THF/CH_2Cl_2 (**4**), $CHCl_3$/hexane (**5**); $CHCl_3$ (**6**), $CHCl_3$/acetone (**7**) solutions at +4°C, and compounds **4–7** crystallized as the corresponding solvates **4**x(THF)$_2$xCH_2Cl_2, **5**x($CHCl_3$)xC_6H_{14}, **6**x($CHCl_3$)$_3$ and **7**x$CHCl_3$xC_2H_6O. The X-ray data for colorless crystals of **4–7** were obtained at 150 K using an Oxford Cryostream low-temperature device on a Nonius Kappa CCD diffractometer with MoK_α radiation ($\lambda = 0.71073$ Å), a graphite monochromator, and the ϕ and χ scan modes. Data reductions were performed with DENZO-SMN.[18] The absorption was corrected by integration methods.[19] Structures were solved by direct methods (Sir92) and refined by full matrix least-square based on F^2 (SHELXL97).[20] Hydrogen atoms were mostly localized on a difference Fourier map; however, to ensure uniformity of the treatment of the crystal, all hydrogen atoms were recalculated into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom) or of 1.5 U_{eq} for the methyl moiety with C-H = 0.96, 0.97, and 0.93 Å for methyl, methylene and hydrogen atoms in aromatic ring moiety, respectively. The oxygen atoms as well as one of the disordered *t*-butyl groups in **4** were treated isotropically.

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from the CCDC (E-mail: deposit@ccdc.cam.ac.uk; web: http://www.ccdc.cam.ac.uk). There are disordered solvents in structures of **4**, **5** and **7**. Attempts were made to model these disorders or split it into two positions, but were unsuccessful. PLATON /SQUEZZE was used to correct the data for the presence of disordered solvent.[21] Potential solvent volumes of 673, 800 and 344 ^{3} were found for **4**, **5** and **7**, respectively. 269, 464 and 160 electrons per unit cell of scattering were located in the void. The stoichiometry of solvent was calculated to two THF and one dichlormethane (**4**), four hexane and four chloroform (**5**), two acetone and two chloroform molecules per unit cell of **7**. CCDC 865746 (for **3**), 865748 (for **4**) 865749 (for **5**) 865747 (for **6**) and 865750 (for **7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/data_request/cif).

Cytotoxic Studies

Studies were performed on the human T-lymphocytic leukemia cells MOLT-4 obtained from the American Type Culture Collection (USA) and HL-60 obtained from the European Collection (Porton Down, Salisbury, UK). The cells were cultured in Iscove's modified Dulbecco's medium supplemented with 20% fetal calf serum and 0.05% L-glutamine (all Sigma-Aldrich, USA) in a humidified incubator at 37°C and a controlled 5% CO_2 atmosphere. The cell lines in the maximal range of up to 20 passages were used for this study. Cytotoxicity of compound **9** was evaluated by the WST-1 cell viability test (Roche, Germany) according to the manufacturer's instructions. The assay is based on the reduction of WST-1 (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2*H*-5-tetrazolio]-1,3-benzene disulfonate) by viable cells. The reaction produces a colored soluble formazan salt.[22] The absorbance at 440 nm was measured using a multiplate reader (Tecan Infinite 200). Compound **9** was dissolved in cultivation medium to the desired concentrations. The cells were seeded in a 96-well plate, incubated in 1–1000 μmol l^{-1} solutions of compound **9** for 24 h, then washed in pure media and incubated for 180 min in WST-1 solution. The same cells incubated in the cultivation media only were used as the control. Absorbance data were normalized to 100% cell viability for non-treated cells; half inhibiting concentration (IC_{50}), defined as the concentration of the drug reducing cell viability by 50%, was obtained from the dose–response sigmoid using Origin Pro (version 8, Microcal Software, Inc., Northampton, MA, USA).

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