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Acetonimine and 4-Imino-2-methylpentan-2-amino Platinum(II) Complexes: Synthesis and in Vitro Antitumor Activity

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The reaction of [Pt(dmba)(PPh_3)Cl] [where dmba = N,C-chelating 2-(dimethylaminomethyl)phenyl] with aqueous ammonia in acetone in the presence of $AgClO_4$ gives the acetonimine complex [Pt(dmba)(PPh_3)(NH=CMe_2)]ClO_4 (**1**). The reaction of [Pt(dmba)(DMSO)Cl] with aqueous ammonia in acetone in the presence of $AgClO_4$ gives a mixture of [Pt(dmba)(NH=CMe_2)$_2$]ClO_4 (**2**) and [Pt(dmba)(imam)]ClO_4 (**3a**) (where imam = 4-imino-2-methylpentan-2-amino). [Pt(dmba)(DMSO)Cl] reacts with [Ag(NH=CMe_2)$_2$]ClO_4 in a 1:1 molar ratio to give [Pt(dmba)(DMSO)(NH=CMe_2)]ClO_4 (**4**). The reaction of [Pt(dmba)(DMSO)Cl] with 20% aqueous ammonia in acetone at 70 °C in the presence of KOH gives [Pt(dmba)(CH_2COMe)(NH=CMe_2)] (**5**), whereas the reaction of [Pt(dmba)(DMSO)Cl] with 20% aqueous ammonia in acetone in the absence of KOH gives [Pt(dmba)(imam)]Cl (**3b**). The reaction of [NBu_4]$_2$[$Pt_2(C_6F_5)_4(\mu$-Cl)$_2$] with [Ag(NH=CMe_2)$_2$]ClO_4 in a 1:2 molar ratio produces *cis*-[Pt(C_6F_5)$_2$(NH=CMe_2)$_2$] (**6**). The crystal structures of **1** · 2Me_2CO, **2**, **3a**, **5**, and **6** have been determined. Values of IC_{50} were calculated for the new platinum complexes against a panel of human tumor cell lines representative of ovarian (A2780 and A2780*cis*R) and breast cancers (T47D). At 48 h incubation time complexes **1**, **4**, and **5** show very low resistance factors against an A2780 cell line which has acquired resistance to cisplatin. **1**, **4**, and **5** were more active than cisplatin in T47D (up to 30-fold in some cases). The DNA adduct formation of **1**, **4**, and **5** was followed by circular dichroism and electrophoretic mobility.

Introduction

With metallopharmaceuticals playing a significant role in therapeutic and diagnostic medicine, the discovery and development of new metallodrugs remain an ever-growing area of research in medicinal inorganic chemistry.[1] Cisplatin, carboplatin, and oxaliplatin are at present the only metal-based anticancer agents in worldwide clinical use. The metal complexes are used in about 50% of all tumor therapies and display a remarkable therapeutic activity in a series of solid tumors. Nevertheless, severe dose-limiting side effects and intrinsic or acquired resistance are the main drawbacks associated with this kind of therapy.[2]

Acetonimine (Me_2C=NH) can be prepared from acetone and ammonia at high temperature and pressure and with the use of a catalyst.[3,4] However, acetonimine is unstable, even at room temperature, decomposing readily to give acetonine (2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine) and NH_3.[5] Its difficult synthesis[3,4] and handling may account for the scarcity of acetonimine complexes of transition metals reported so far (Mo, W, Cr,[6−8] Ni,[9] Ru,[10,11] Os,[12] Au,[13,14] Pd,[15] Pt,[16,17] Ag, and Rh[18−20]), none of which has been obtained using acetonimine itself.

The synthesis of the cis and trans isomers of the acetonimine platinum [PtX_2(NH=CMe_2)$_2$] and [PtX_2(NH=CMe_2)(NH_3)] (X = Cl, I) has been recently reported by Natile et al.[16] These complexes display a tumor cell growth inhibitory potency similar to that of the corresponding Pt(II) complexes with iminoethers (Pt−N(H)=C(OR)R′),[21−24] in addition the ability to circumvent (either partially or completely) cisplatin

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resistance.[16] Ketimines and iminoethers are very similar (sp^2-hybridization of the nitrogen atom like in pyridine, a proton still bound to nitrogen like in secondary aliphatic amines, the ligand extending in a plane with the steric bulk localized only on one side of the donor atom), the main advantage of symmetrical ketimines (like acetonimine), with respect to iminoethers, being the lack of geometric isomerism about the C═N double bond.

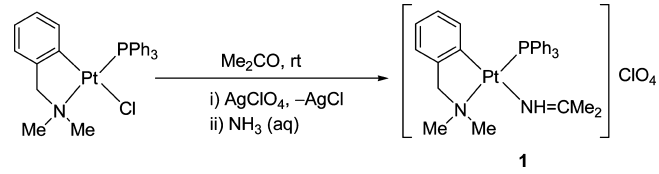
In view of the general interest in acetonimine as ligand,[6−20] in the present study, our initial aim was to synthesize platinum organometallic complexes derived from the N,C-chelating 2-(dimethylaminomethyl)phenyl (dmba) and pentafluorophenyl C_6F_5 groups with the acetonimine ligand. To the best of our knowledge,[25] the complexes herein reported represent the first examples of 4-imino-2-methylpentan-2-amino (imam) platinum complexes and the first platinum complexes containing acetonimine and a σ-metal carbon bond.

Values of IC_{50} were calculated for the new platinum complexes against a panel of human tumor cell lines representative of ovarian (A2780 and A2780*cis*R) and breast cancers (T47D, cisplatin resistant). At 48 h incubation time complex **1** was about 30-fold more active than cisplatin in T47D. Complexes **1**, **4**, and **5** show very low resistance factors against an A2780 cell line which has acquired resistance to cisplatin.

Results and Discussion

Dmba Complexes. The acetonimine dmba complex **1** [where dmba = N,C-chelating 2-(dimethylaminomethyl)phenyl] has been prepared in high yield from the corresponding chloroplatinum complex [Pt(dmba)(PPh_3)Cl][26] by reaction with 20% aqueous ammonia in acetone at room temperature (Scheme 1).

Scheme 1



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Complex **1** is a white air-stable solid that decomposes on heating above 200 °C in a dynamic N_2 atmosphere. Its acetone solution shows a conductance value corresponding to 1:1 electrolytes (Λ_M = 130 S cm^2 mol^{-1}).[27] An IR band is observed at approximately 1096 which is assigned to the ν_3 mode of free perchlorate (T_d symmetry). The observation of an additional band at approximately 622 cm^{-1} for the ν_4 mode confirms the presence of free perchlorate.[28] The NH stretching mode for the complex is found in the 3200 cm^{-1} region, and the C═N vibration is at approximately 1650 cm^{-1}. The ^{1}H NMR spectrum of complex **1** at room temperature shows that both the *N*-methyl and the CH_2 groups of the dmba are diastereotopic, two separate signals being observed for the former and an AB quartet for the latter (some broadening being observed); ^{195}Pt satellites are observed as shoulders for the *N*-methyl protons. The rather bulky PPh_3 ligand hinders the rotation of the acetonimine ligand about the Pt−N bond, breaking the symmetry of the platinum coordination plane. In complex **1** the PPh_3-trans-to-NMe_2 ligand arrangement in the starting product[26] is preserved, after chlorine abstraction and acetonimine coordination, as can be inferred from the small, but significant, coupling constants $^4J_{P-H}$ (ranging from 2.4 to 3.4 Hz) of the NMe_2 and the CH_2N protons with the phosphorus atom.[29] The ^{1}H NMR spectrum of **1** exhibits also a NH proton resonance as a broad singlet in the region of 10 ppm and reveals the inequivalence of the Me groups of the imine ligands, arising from restricted rotation around the C═N bond at room temperature: a singlet at δ 2.18 for the methyl group trans to NH and a doublet ($^4J_{HH}$ = 1.2 Hz) at δ 1.70 ppm for the methyl group cis to NH with respect to the azomethine double bond (^{195}Pt satellites are observed as shoulders for the resonance at δ 2.18). A NOESY experiment performed on complex **1** has confirmed this assignment. A much stronger crosspeak was observed between the more shielded methyl and the iminic proton, clearly indicating that the more shielded methyl is cis to the iminic proton with respect to the azomethine double bond. Therefore the criterion of bigger coupling between methyl group and iminic proton trans to

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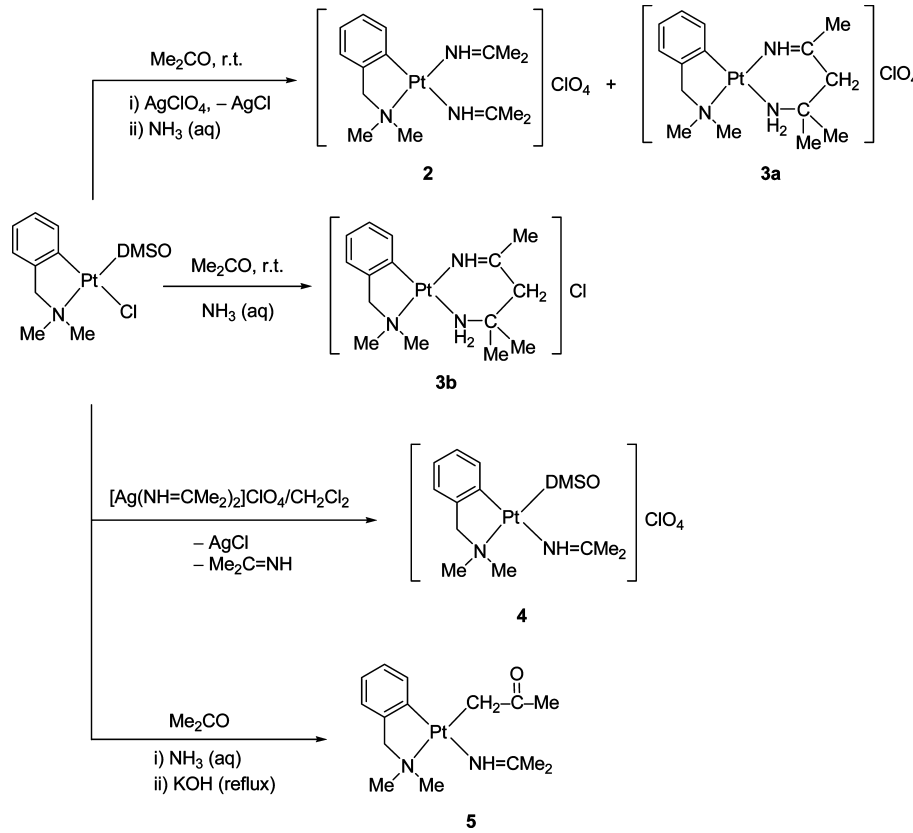
Scheme 2



one another can be misleading in the case of acetonimine complexes of platinum(II), as suggested previously by Natile et al.[16,30] A unique resonance (doublet $J_{Pt-P} = 4100$ Hz) is observed in the ^{195}Pt NMR spectrum of complex **1** at δ −4063.

When we reacted [Pt(dmba)(DMSO)Cl][26] with 20% aqueous ammonia in acetone at room temperature for 4 h in the presence of $AgClO_4$, a mixture of $[Pt(dmba)(NH{=}CMe_2)_2]ClO_4$ (**2**) and $[Pt(dmba)(imam)]ClO_4$ (**3a**) in a 5:2 ratio (Scheme 2), which contains the imam ligand (*N*,*N*-NH=C(Me)CH_2C(Me)$_2$$NH_2$ = 4-imino-2-methylpentan-2-amino) was obtained. To the best our knowledge no imam platinum complexes have been previously reported in the literature.[25] Upon heating a solution of **2** + **3a** (**5**:**2**) at 70 °C in a Carius tube for 24 h, no changes have been observed.

When [Pt(dmba)(DMSO)Cl] was treated with 20% aqueous ammonia in acetone at room temperature for 24 h, [Pt(dmba)(imam)]Cl (**3b**) is obtained (Scheme 2). The formation of complexes [Rh(Cp*)Cl(imam)]Cl and $[Rh(Cp^*)Cl(imam)]ClO_4$ by an intramolecular aldol-type self-condensation of two acetonimine ligands, promoted by gentle heating or by the addition of various ligands, has been recently reported.[19]

The NH stretching modes for **3b** are found in the 3250−3150 cm^{-1} range. The ^{1}H NMR spectrum of complex **3b** shows the presence of the dmba ligand, and the observation of the NCH_2 and NMe_2 proton signals as singlets suggests that the inversion of the configuration at the PtCCCN chelate ring is faster than the NMR time scale at room temperature.[31,32] The assignments given in the Experimental Section for complex **3b** were supported by the pertinent heteronuclear (^{1}H−^{13}C) COSY spectra.

The acetonimine complex **4** has been prepared in high yield from the corresponding chloroplatinum complex [Pt(dmba)(DMSO)Cl] by reaction with the transmetalating agent[18] $[Ag(NH{=}CMe_2)_2]^+$ in a 1:1 molar ratio in dichloromethane (Scheme 2). The precipitation of AgCl produces two free acetonimine ligands, one of which occupies a vacant position at the Pt center. Again, as observed in complex **1**, the rather bulky DMSO ligand hinders the rotation of the acetonimine ligand about the Pt−N bond, breaking the symmetry of the platinum coordination plane as observed in the ^{1}H NMR.

When [Pt(dmba)(Cl)(DMSO)] is heated with 20% aqueous ammonia in acetone at 70 °C for 1 h in the presence of KOH, complex **5** is obtained (Scheme 2). Complex **5** is a white air-stable solid that decomposes on heating above 150 °C in a dynamic N_2 atmosphere. It is also stable at room temperature in organic solvent solutions. The analytical data are consistent with the proposed formula. The FAB mass spectrum shows a peak at $m/z = 443$ ($[Pt(dmba)(CH_2COMe)(NH{=}CMe_2)]^+$, 18%). The NH stretching mode for complex **5** is found in the 3220 cm^{-1} region and the C=N vibration at approximately 1660 cm^{-1}. The IR spectrum shows also

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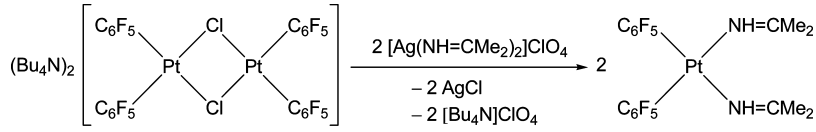
Scheme 3



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one band, assignable to ν(C═O), in the region of 1630 cm^{-1}, which is similar to that reported for terminal acetonyl platinum(II)[33,34] and palladium(II)[31,35] complexes. The singlet signals observed in the ^{1}H NMR spectrum of **5** at δ 2.59 and 1.92 are assignable to the methylene and methyl protons of the acetonyl ligand, respectively (coupling to ^{195}Pt is observed for these two signals). Further, in contrast with what happened for complexes **1** and **4**, a unique singlet resonance for the N—Me groups and a singlet resonance for the CH_2 protons of bonded $C_6H_4CH_2NMe_2$ are observed (coupling to ^{195}Pt is also observed) as a result of the free rotation of the acetonimine ligand about the Pt—N bond in the presence of the sterically less demanding acetonyl ligand. In accord with the structure of the related palladium complex [Pd(dmba)(*t*-BuNC){$CH_2C(O)CH_3$}],[31] a $MeCOCH_2$-trans-to-NMe_2 ligand geometry for monomer **5** is proposed. Proton NOE difference spectra confirmed this suggestion. This structure was also confirmed by X-ray diffraction (vide infra). The ^{1}H NMR spectrum of **5** exhibits also a NH proton resonance as a broad singlet in the region of 10 ppm.

Complex *cis*-[Pt(C$_6$F$_5$)$_2$(NH═CMe$_2$)$_2$]. The reaction of *cis*-[NBu_4]$_2$[$Pt_2(C_6F_5)_4(\mu$-Cl)$_2$][36] and [Ag(NH═CMe_2)$_2$]$^+$ in a 1:2 molar ratio produces the neutral bis(acetonimine) complex *cis*-[Pt(C$_6$F$_5$)$_2$(NH═CMe_2)$_2$] (**6**) in high yield (Scheme 3). The reaction takes place without isomerization.

The IR spectrum of complex **6** shows the characteristic absorptions of the C_6F_5 group (1630 m, 1490 vs, 1050 s, and 950 vs cm^{-1})[37] and a split band at approximately 800 cm^{-1} assigned to the *cis*-Pt(C$_6$F$_5$)$_2$ moiety.[38,39] The ^{19}F NMR spectrum of **6** shows the expected three signals for two equivalent C_6F_5 rings with relative intensities of $2F_o$:$1F_p$:$2F_m$. The ^{1}H NMR spectrum of **6** exhibits a singlet at δ 2.37 and a doublet ($^4J_{HH}$ = 1.4 Hz) at δ 2.12 ppm for the methyl groups of the acetonimine ligands. Again, the signal at higher field has greater coupling with the iminic proton (Pt satellites are observed as shoulders for the signal at lower field).

Crystal Structures of 1·2Me$_2$CO, 2, 3a, 5, and 6. All the structures display some common features. Thus, in all cases, the Pt atom is in a distorted square planar environment; the mean deviations from planarity for the Pt atom and its four immediate neighbors is ≤0.05 Å except for **6** (0.06 Å).

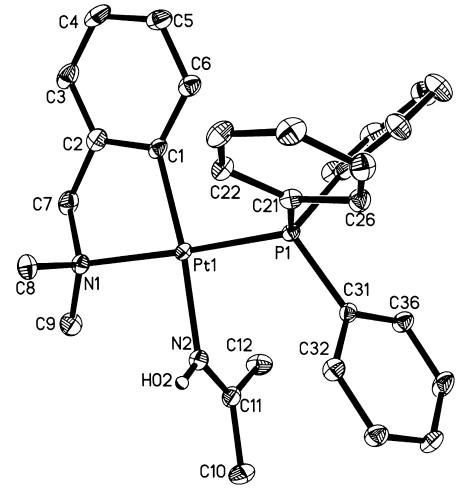

Figure 1. ORTEP representation (50% probability) of **1**·2Me$_2$CO. Selected bond lengths (Å) and angles (deg): Pt(1)—C(1) = 2.022(2), Pt(1)—N(2) = 2.091(2), Pt(1)—N(1) = 2.1370(19), Pt(1)—P(1) = 2.2301(6), C(1)—Pt(1)—N(2) = 173.12(8), C(1)—Pt(1)—N(1) = 82.04(8), N(2)—Pt(1)—N(1) = 91.18(7), C(1)—Pt(1)—P(1) = 95.37(7), N(2)—Pt(1)—P(1) = 91.49(5), N(1)—Pt(1)—P(1) = 174.92(5). Hydrogen bonds (Å) and angles (deg): H(02)···O(3) = 2.21(3), N(2)···O(3) = 3.050(3), N(2)—H(02)···O(3) = 177(3), H(9B)···O(2) = 2.54, C(9)···O(2) = 3.498(3), C(9)—H(9B)···O(2) 164.4, C(10)···O(2)#1 = 2.53, C(10)··· O(2)#1 = 3.384(3), C(10)—H(10B)··· O(2)#1 = 145.4 (symmetry transformations used to generate equivalent atoms: #1, $-x+1$, $-y+1$, $-z+1$).

The cation of **1**·2Me$_2$CO is depicted in Figure 1. Coordination at platinum is approximately square planar, although the angles around platinum deviate from 90° due to the bite of the cyclometallated ligand. The C(1)—Pt—N(1) angle of 82.04(8) is within the normal range for such dmba metal complexes.[39—45] The PPh_3 ligand is trans to the nitrogen donor, displaying no tendency to occupy the position trans to the σ-bound orthoplatinated aryl group.[46] The cyclometallated ring is puckered with the nitrogen atom significantly out of the plane defined by the platinum and carbon atoms, a feature which is quite commonly observed in cyclometallated dmba complexes.[39,42—44] In the crystal, the perchlorate anion is bridging four complex cations through N—H···O

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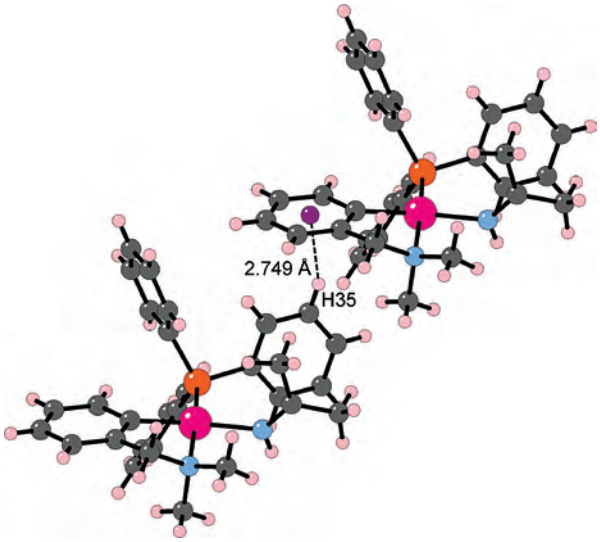

Figure 2. View of the C−H/π interactions in complex **1**·2Me_2CO.

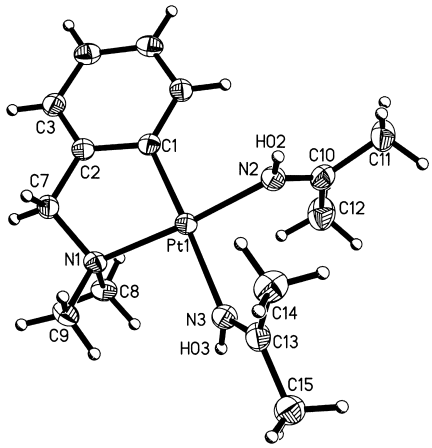

Figure 3. ORTEP representation (50% probability) of **2**. Selected bond lengths (Å) and angles (deg): Pt(1)−C(1) = 1.990(3), Pt(1)−N(2) = 2.006(3), Pt(1)−N(1) = 2.072(3), Pt(1)−N(3) = 2.116(3), C(1)−Pt(1)−N(2) = 92.18(12), C(1)−Pt(1)−N(1) = 82.65(12), N(2)−Pt(1)−N(1) = 174.73(10), C(1)−Pt(1)−N(3) = 174.43(11), N(2)−Pt(1)−N(3) = 91.02(11), N(1)−Pt(1)−N(3) = 94.06(11). Hydrogen bonds (Å) and angles (deg): H(02)···O(3)#1 = 2.18(4), N(2)···O(3)#1 = 3.006(4), N(2)−H(02)···O(3)#1 = 171(4), H(03)···O(2) = 2.42(4), N(3)···O(2) = 3.219(4), N(3)−H(03)···O(2) = 155(4), H(11B)···O(4)#2 = 2.51, C(11)···O(4)#2 = 3.397(5), C(11)−H(11B)···O(4)#2 = 150.9, H(15A)···O(1) = 2.47, C(15)···O(1) = 3.442(5), C(15)−H(15A)···O(1) = 170.6 (symmetry transformations used to generate equivalent atoms: #1, $x + 1$, $y - 1$, z; #2, $-x + 1$, $-y + 1$, $-z$).

and C−H···O bonds in which the NH, CH_3, and CH groups are involved. Figure 2 shows intermolecular CH/π interactions,[47] the distance H35···centroid (C1C2C3C4C5C6) being 2.749 Å.

Figure 3 shows the X-ray structure of the cationic complex of **2**. The Pt−N(3) (acetonimine) distance (2.116 Å) trans to the carbon atom is longer than the Pt−N(2) (acetonimine) distance (2.006 Å), due to higher trans-influence of the C atom than that of the N atom (dmba, sp^3). The imino ligands are planar, and the relative orientation of the acetonimine ligands is head to tail (HL). Both acetonimine ligands show C═N bond lengths (1.281(5) and 1.277(5) Å). In the crystal, the perchlorate anion is bridging five complex cations

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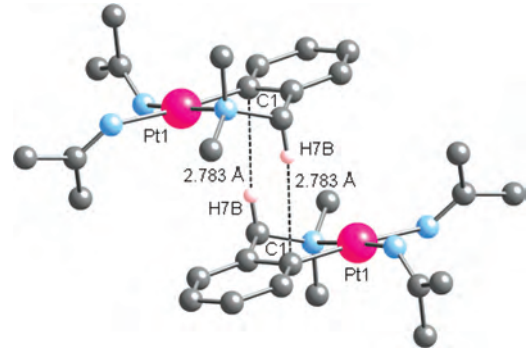

Figure 4. View of the C−H/π interactions in complex **2**.

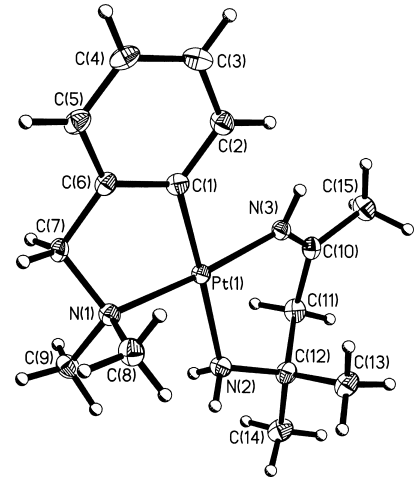

Figure 5. ORTEP representation (50% probability) of **3a**. Selected bond lengths (Å) and angles (deg): Pt(1)−N(3) = 2.002(2), Pt(1)−C(1) = 2.002(3), Pt(1)−N(1) = 2.085(2), Pt(1)−N(2) = 2.157(2), N(3)−Pt(1)−C(1) = 92.83(11), N(3)−Pt(1)−N(1) = 175.12(10), C(1)−Pt(1)−N(1) = 82.30(11), N(3)−Pt(1)−N(2) = 89.86(10), C(1)−Pt(1)−N(2) = 177.30(11), N(1)−Pt(1)−N(2) = 95.01(10). Hydrogen bonds (Å) and angles (deg): H(02B)···O(3) = 2.32(3), N(2)···O(3) = 3.159(4), N(2)−H(02B)···O(3) = 153(3), H(02A)···O(1)#1 = 2.13(3), N(2)···O(1)#1 = 3.030(4), N(2)−H(02A)···O(1)#1 = 172(4), H(03)···O(2)#2 = 2.40(3), N(3)···O(2)#2 = 3.105(3), N(3)−H(03)···O(2)#2 = 133(3), H(7B)···O(2)#3 = 2.56, C(7)···O(2)#3 = 3.515(4), C(7)−H(7B)···O(2)#3 = 161.1, H(9A)···O(3) = 2.42, C(9)···O(3) = 3.395(4), C(9)−H(9A)···O(3) = 171.8, H(11B)···O(2)#1 = 2.47, C(11)···O(2)#1 = 3.438(4), C(11)−H(11B)···O(2)#1 = 166.2, H(13C)···O(1) = 2.56, C(13)···O(1) = 3.480(4), C(13)−H(13C)···O(1) = 155.6 (symmetry transformations used to generate equivalent atoms: #1, $-x + 1$, $y - 1/2$, $-z + 1$; #2, x, y, $z + 1$; #3, $-x + 2$, $y - 1/2$, $-z + 1$).

through N−H···O and C−H···O bonds in which the NH, CH_3, and CH groups are involved and also π interactions (O1···C10 contact of 3.197 Å). Additionally, CH/π interactions[47] are observed (Figure 4).

A drawing of the cationic complex of **3a** is shown in Figure 5. The platinum atom is located in a slightly distorted square-planar environment, surrounded by the C and N atoms of the cyclometallated dmba ligand and the N atoms of the imam ligand. The six-membered Pt−N(3)−C(10)−C(11)−C(12)−N(2) chelate ring adopts a screw-boat conformation with the C(12) and the C(11) atoms lying 0.37 Å below and 0.36 Å above the plane, respectively, of the other four atoms. The Pt−N(2) (amine) distance (2.157(2) Å) trans to the carbon atom is longer than the Pt−N(3) (imine) (2.002(2) Å) due to higher trans influence of the C. In the crystal, the perchlorate anion is bridging four complex cations through N−H···O and C−H···O bonds in which the NH, NH_2, CH_3,

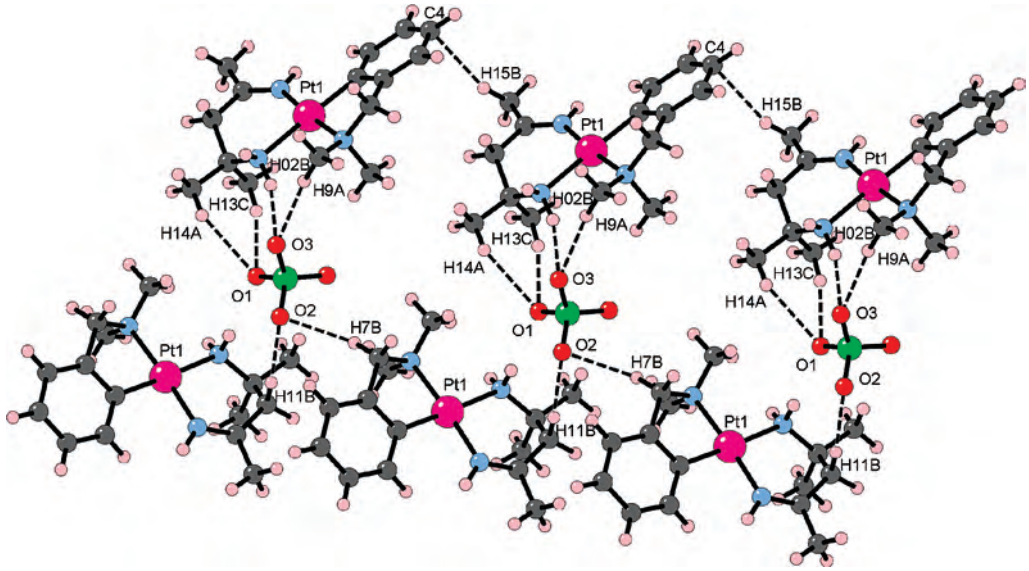

Figure 6. Hydrogen bonds and C−H/π interactions for **3a**.

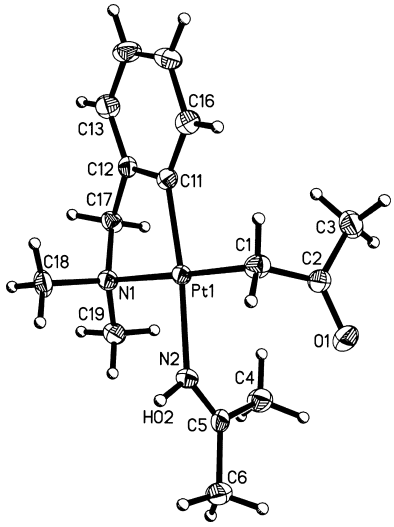

Figure 7. ORTEP representation (50% probability) of one of the three independent molecules of complex **5**. Selected bond lengths (Å) and angles (deg): Pt(1)−C(11) = 1.997(5), Pt(1)−C(1) = 2.078(5), Pt(1)−N(2) = 2.097(4), Pt(1)−N(1) = 2.134(4), C(11)−Pt(1)−C(1) = 96.5(2), C(11)−Pt(1)−N(2) = 174.72(17), C(1)−Pt(1)−N(2) = 86.75(18), C(11)−Pt(1)−N(1) = 82.06(18), C(1)−Pt(1)−N(1) = 178.02(18), N(2)−Pt(1)−N(1) = 94.59(15).

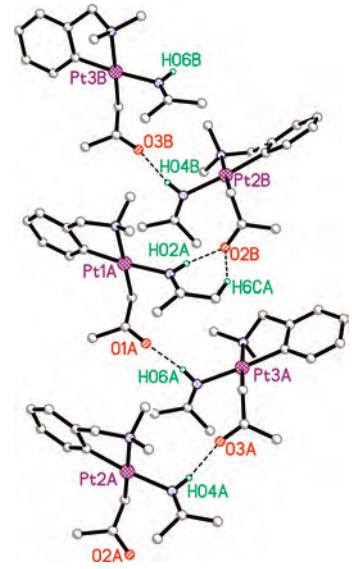

Figure 8. Schematic showing the chain formed by hydrogen bonding in complex **5**.

Table 1. Hydrogen Bonds for Complex **5** [Å and deg][a]

D−H···A	*d*(D−H)	*d*(H···A)	d(D···A)	<(DHA)
N(4)−H(04)···O(3)	0.90(4)	2.00(4)	2.877(5)	165(5)
N(2)−H(02)···O(2)#1	0.90(4)	2.08(4)	2.973(5)	170(5)
N(6)−H(06)···O(1)#2	0.90(4)	1.98(4)	2.873(5)	169(5)
C(6)−H(6C)···O(2)#1	0.98	2.51	3.346(7)	143.3

[a] Symmetry transformations used to generate equivalent atoms: #1, $x - 1/2, -y + 1/2, z + 1/2$; #2, $-x + 1, -y + 1, -z + 1$.

and CH_2 groups are involved. Intermolecular CH/π interactions[47] are also observed (Figure 6).

The crystal structure of compound **5** shows three independent molecules in the asymmetric unit. The structure of the first molecule of the unit cell is shown in Figure 7. Coordination at platinum is approximately square planar, although the angles around platinum deviate from 90° due to the bite of the cyclometallated ligand. The C(1)−Pt−N(1) angle of 82.06(18) is within the normal range for such dmba metal complexes.[39−44] A $MeCOCH_2$-trans-to-NMe_2 ligand geometry for monomer **5** is observed, displaying the acetonyl group (which has a strong trans influence) no tendency to occupy the position trans to the σ-bound orthoplatinated aryl group.[46] The imino ligand is planar and rotated with respect to the coordination plane by approximately 84.7°. The C=N bond distance [1.277(6) Å] is in the range found for the other structurally characterized acetonimine complexes (1.25−1.30 Å).[25] The length of the carbon−oxygen double bond [1.242(6) Å] is longer than that found in other palladium− or platinum−enolate complexes.[31,33,35] The enolate ligand is nearly perpendicular to the mean coordination plane (dihedral angle 78.91°). As can be seen in Figure 8 and Table 1 in the crystal the NH hydrogen atoms of the acetonimine and the O atom of the acetonyl group are involved in intermolecular N−H···O hydrogen bonds leading to hydrogen-bonded zigzag chains.

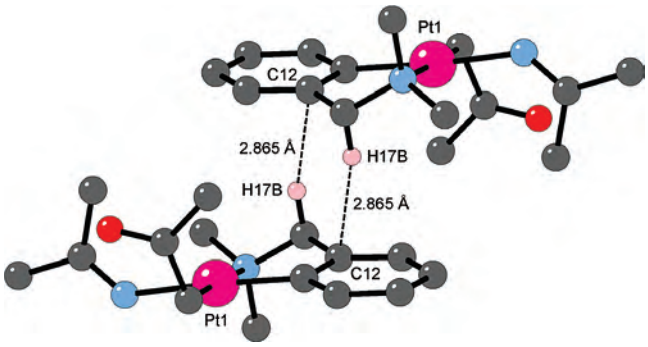

Figure 9. View of the C−H/π interactions in complex **5**.

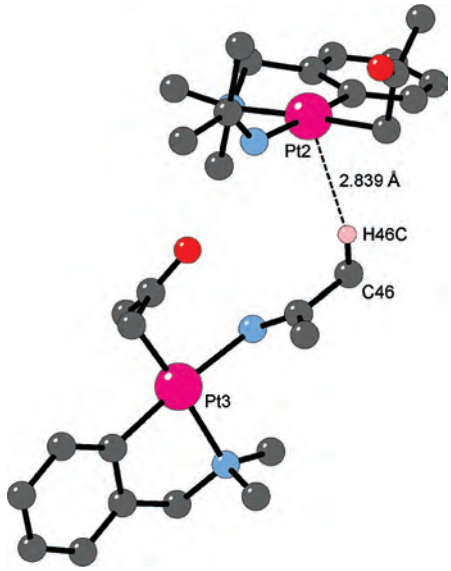

Figure 10. View of the C−H···Pt interaction in complex **5**.

On the other hand, H46C of the acetonimine ligand of molecule **3** is close to the platinum atom of molecule **2**, with a Pt(2)···H(46C) distance of 2.839 Å and a Pt(2)···H(46C)-C(46) angle of 162.3°, which indicates the presence of an anagostic C−H···Pt interaction is observed (Figure 9).[48,49] Intermolecular CH/π interactions[47] are also observed (Figure 10).

The crystal structure of compound **6** shows two independent molecules in the asymmetric unit with the platinum atoms in slightly distorted square planar geometries. In the first molecule (Figure 11) the angle between the two C_6F_5 rings is 89.37(9)°, and the imino ligands are planar and mutually perpendicular (86.34(1)°). The relative orientation of the acetonimine ligands is head to head (HH), contrary to that observed for complex **2**. The C=N bond distances [1.274(3) and 1.277(3) Å] are in the range found for the other structurally characterized acetonimine complexes (1.25−1.30 Å).[25] The Pt−N distances (2.0647−2.074 Å) lie within the range reported in complexes containing the $\{Pt(C_6F_5)_2N_2\}$ moiety such as $[Pt(C_6F_5)_2(pz\cdots H\cdots pz]$ (pz = pyrazolate)[50] and *cis*-$[Pt(C_6F_5)_2(HmtpO)_2]$ (HmtpO = 4,7-dihydro-5-methyl-7-oxo[1,2,4]triazolo[1,5-*a*]pyrimidine).[44]

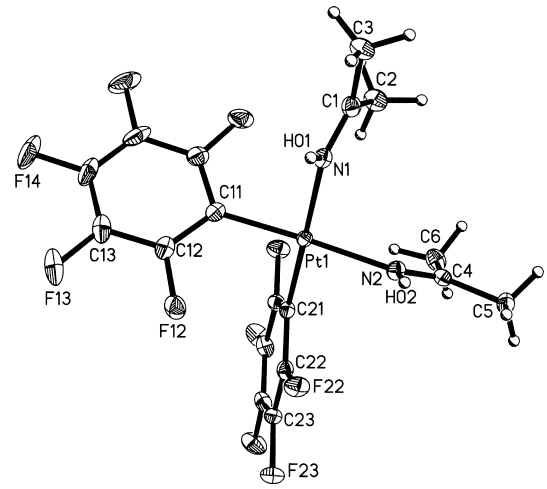

Figure 11. ORTEP representation (50% probability) of one of the two independent molecules of **6**. Selected bond lengths (Å) and angles (deg): Pt(1)−C(21) = 2.006(2), Pt(1)−C(11) = 2.008(2), Pt(1)−N(1) = 2.0673(19), Pt(1)−N(2) = 2.0747(19), C(21)−Pt(1)−C(11) = 89.37(9), C(21)−Pt(1)−N(1) = 178.07(8), C(11)−Pt(1)−N(1) = 89.72(8), C(21)−Pt(1)−N(2) = 92.23(8), C(11)−Pt(1)−N(2) = 173.49(8), N(1)−Pt(1)−N(2) = 88.87(7).

Table 2. Hydrogen Bonds for Complex **6** (Å and deg)[a]

D−H···A	*d*(D−H)	*d*(H···A)	*d*(D···A)	<(DHA)
C(36)−H(36A)···F(46)#1	0.98	2.48	3.279(3)	138.7
N(4)−H(04)···F(56)#1	0.89(3)	2.40(3)	3.055(2)	131(2)
N(3)−H(03)···F(16)#2	0.80(3)	2.47(3)	3.241(2)	162(3)
C(5)−H(5A)···F(12)#3	0.98	2.40	3.331(3)	159.3
N(1)−H(01)···F(22)#3	0.81(3)	2.29(3)	2.871(2)	129(3)

[a] Symmetry transformations used to generate equivalent atoms: #1, $-x+1, -y+1, -z+1$; #2, $-x+1/2, y+1/2, -z+1/2$; #3, $-x, -y, -z+1$.

In the crystal, a rather complex three-dimensional macromolecular network structure is observed built up by extensive hydrogen bonding, which involves the NH groups or the C−H[51−56] of the acetimino ligands and the *ortho*- or *para*-fluorine atoms of the pentafluorophenyl rings neighboring molecules (Table 2). There is also a intermolecular contact F15···F55 (Figure 12). The influence of these fluorine-based interactions seems to be a relevant, noncasual phenomenon to be taken into account in crystal engineering.[44,52,56] F15 is also involved in intermolecular C−F···π_F interactions (F15···C55, 2.982 Å; F15···C56, 3.156 Å, Figure 12).[44,52,56] Other intermolecular interaction contact observed is of the type C−F···$\pi_{acetonimine}$ (*F*23···C4, 3.157 Å).

Biological Assays. Circular Dichroism Spectroscopy. The circular dichroism (CD) spectra of calf thymus DNA alone and incubated with the acetonimine platinum(II) compounds **1**, **4**, and **5** at 37 °C for 24 h at several molar ratios were recorded.

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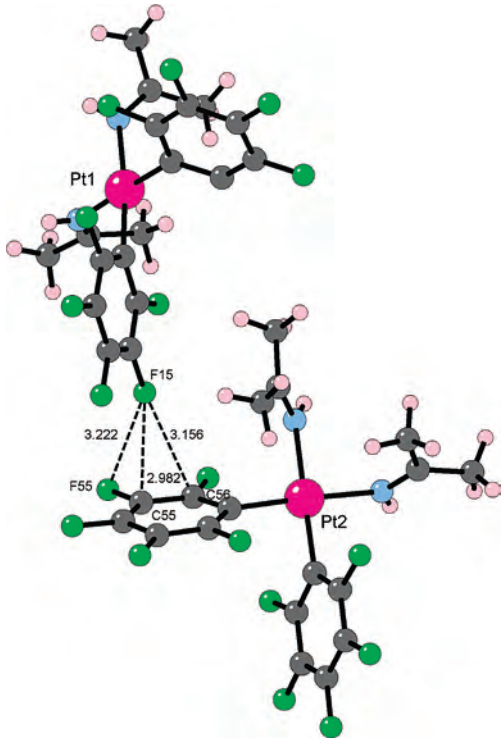

Figure 12. Intermolecular F···F and C−F···π_F interactions in **6**.

The changes in ellipticity and wavelength caused by the new platinum(II) compounds **1** and **4** are significant (Figure 13). Complex **1** reduces the ellipticity of the positive and negative band with increasing values of r_i. An upshift in the λ_{max} (batochromic effect) is also observed. These results suggest modifications in the secondary structure of DNA caused by complexes **1** and **4**, clearly indicating the transformation from the DNA B form to the DNA C form, with increasing winding of the DNA helix by rotation of the bases.[57−60]

Gel Electrophoresis of Compound-pB*R*322 Complexes. The influence of the compounds on the tertiary structure of DNA was determined by their ability to modify the electrophoretic mobility of the covalently closed circular (ccc) and open (oc) forms of pB*R*322 plasmid DNA. The complexes **1, 4**, and **5** were incubated at the molar ratio r_i = 0.50 with pB*R*322 plasmid DNA at 37 °C for 24 h. Representative gel obtained for the Pt complexes **1**, **4**, and **5** are shown in Figure 14. The behavior of the gel electrophoretic mobility of both forms, ccc and oc, of pB*R*322 plasmid and DNA:cisplatin adducts is consistent with previous reports.[61] When the pB*R*322 was incubated with the platinum compound **1** (lane 2) a single footprinting for both forms, ccc and oc, coalescent form, was observed. A similar pattern has been found previously in some others dmba phosphine platinum complexes.[39,44] On the other hand, complexes **4** and **5** (lanes 3 and 4, respectively) delayed the mobility of the ccc form.

The behavior observed for the electrophoretic mobility for the platinum complexes indicates that some conformational changes occurred. This means that the degree of superhelicity of the DNA molecules has been altered.

Cytotoxicity Studies. Values of IC_{50} were evaluated for complexes **1**, **4**, and **5** and cisplatin against a panel of human tumor cell lines representative of ovarian (A2780 and A2780*cis*R) and breast cancers (T47D, cisplatin resistant). A2780*cis*R encompasses all of the known major mechanisms of resistance to cisplatin: reduced drug transport,[62] enhanced DNA repair/tolerance,[63] and elevated GSH levels.[64] Table 3 shows the IC_{50} values and the resistance factors (RF) of the new platinum complexes. The ability of complexes **1, 4**, and **5** to circumvent cisplatin acquired resistance was determined from the resistance factor (RF), defined as the ratio of IC_{50} resistant line to IC_{50} parent line. An RF of <2 was considered to denote noncross-resistance.[65] Especially noteworthy are the very low resistance factors (RF) of these new complexes at 48 h (RF = 1.2−1.4) indicating efficient circumvention of cisplatin resistance (Table 3).

On the other hand, at 48 h incubation time complexes **1, 4**, and **5** were more active than cisplatin in T47D (up to 30-fold in the case of complex **1**).

Complexes **3b** and **6** show no good response against these lines, probably because the formation of a Pt—N7 covalent bond with a guanine base is more difficult for these complexes, as the bidentate ligand (for **3b**) or the two acetonimine ligands (for **6**) occupy two sites of binding in the coordination sphere of platinum(II).

Experimental Section

Instrumental Measurements. The C, H, and N analyses were performed with a Carlo Erba model EA 1108 microanalyzer. Decomposition temperatures were determined with a SDT 2960 simultaneous DSC-TGA of TA instrument at a heating rate of 5 °C min^{-1} and the solid samples under nitrogen flow (100 mL min^{-1}). The ^{1}H, ^{13}C, ^{31}P, ^{19}F, and ^{195}Pt NMR spectra were recorded on a Bruker AC 200E, Bruker AC 300E, or Bruker AV 400 spectrometer, using $SiMe_4$, H_3PO_4, $CFCl_3$, and $Na_2[PtCl_6]$ as standards. Infrared spectra were recorded on a Perkin-Elmer 1430 spectrophotometer using Nujol mulls between polyethylene sheets. Mass spectra (positive-ion FAB) were recorded on a V.G. AutoSpecE spectrometer and measured using 3-nitrobenzyl alcohol as the dispersing matrix.

Materials. The starting complexes $[Bu_4N]_2[Pt_2(C_6F_5)_4(\mu\text{-}Cl)_2]$,[36] [Pt(dmba)Cl(L)] (L = PPh_3 and DMSO),[26] and [Ag(NH=CMe$_2$)]-

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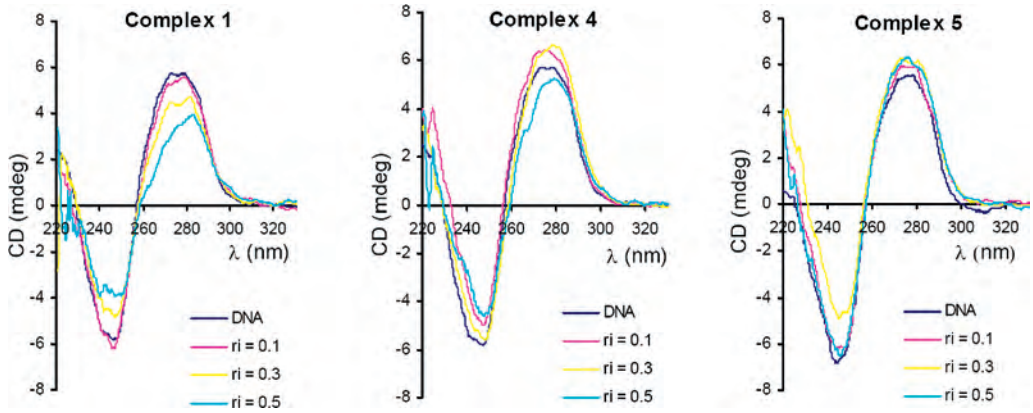

Figure 13. Circular dichroism spectra of DNA and DNA incubated with complex **1**, complex **4**, and complex **5** at different r_i.

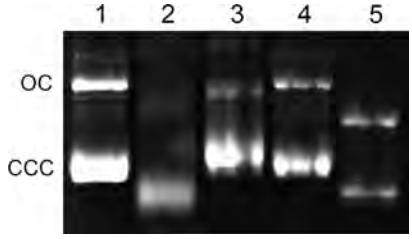

Figure 14. Modification of the gel electrophoretic mobility of pB*R*322 plasmid incubated with the new platinum compounds: lane 1, pBR; lane 2, **1**; lane 3, **4**; lane 4, **5**; lane 5, pBR-cisplatin.

Table 3. IC_{50} (μM) and resistance factors for Cisplatin and Complexes **1**, **4**, and **5**

complex	T47D 48 h	A2780 48 h	A2780*cis*R 48 h (RF)[a]
1	1.2	0.85	1.2 (1.4)
4	3.1	0.77	1.0 (1.3)
5	14	1.7	2.0 (1.2)
cisplatin	37	0.85	1.1 (12.9)

[a] The numbers in parentheses are the resistance factors RF (IC_{50} resistant/IC_{50} sensitive).

ClO_4[18] were prepared by procedures described elsewhere. Solvents were dried by the usual methods. The sodium salt of calf thymus DNA, EDTA (ethylenediaminotetracetic acid), and Tris-HCl (tris(hydroxymethyl)-aminomethane-hydrochloride) used in the circular dichroism (CD) study were obtained from Sigma-Aldrich (Madrid, Spain); HEPES (*N*-(2-hydroxyethyl)piperazine-*N*′-ethanesulfonic acid) was obtained from ICN (Madrid, Spain), and pB*R*322 plasmid DNA was obtained from Boehringer-Mannheim (Mannheim, Germany).

Warning! *Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great caution.*

Preparation of Complex [Pt(dmba)(NH═CMe$_2$)(PPh$_3$)](ClO$_4$) (1). $AgClO_4$ (49.8 mg, 0.24 mmol) was added to an acetone (20 mL) solution of [Pt(dmba)(Cl)(PPh_3)] (150 mg, 0.24 mmol). After the resulting suspension was stirred at room temperature in the darkness for 30 min, it was filtered through Celite, and NH_3 (443 μL of 20% aqueous NH_3, 4.8 mmol) was added. The solution was stirred at room temperature for 4 h, and the solvent was evaporated to dryness. The residue was treated with acetone and ether to give a white precipitate that was filtered off and air-dried.

Data for Complex 1. Yield: 99 mg, 83%. Anal. Calcd for $C_{30}H_{34}ClN_2O_4PPt$: C, 48.17; H, 4.58; N, 3.74. Found: C, 47.92; H, 4.71; N, 3.75. Mp: 254 °C (dec). Λ_M: 130 S cm^2 mol^{-1}. IR (Nujol, cm^{-1}): ν(NH) 3236, ν(C═N) 1660. ^{1}H NMR (acetone-d_6): δ(SiMe$_4$) 9.92 (br, 1H, NH), 7.76 (m, 6H, PPh_3), 7.51 (m, 9H, PPh_3), 7.10 (dd, 1H, aromatic of dmba, J_{HH} = 7.5 Hz, J_{HH} = 0.6 Hz), 6.83 (vtd, 1H, aromatic of dmba, J_{HH} = 7.5 Hz, J_{HH} = 1.2 Hz), 6.47 (dd, 1H, aromatic of dmba, J_{HH} = 7.5 Hz, J_{HP} = 2.7 Hz, J_{HPt} = 43 Hz), 6.32 (vtd, 1H, aromatic of dmba, J_{HH} = 7.5 Hz, J_{HH} = 1.2 Hz), 4.29 (dd, 1H, C*H*$_2$N, J_{HH} = 13.5 Hz, J_{HP} = 2.4 Hz), 4.21 (dd, 1H, C*H*$_2$N, J_{HH} = 13.5 Hz, J_{HP} = 3.43 Hz), 2.92 (d, 3H, N*Me*$_2$, J_{HP} = 2.7 Hz, J_{HPt} = 12 Hz), 2.89 (d, 3H, N*Me*$_2$, J_{HP} = 3.0 Hz, Pt satellites are observed as shoulders), 2.18 (s, 3H, C*Me*$_2$, *trans*-CH_3 to NH, Pt satellites are observed as shoulders), 1.70 (d, 3H, C*Me*$_2$, *cis*-CH_3 to NH, J_{HH} = 1.2 Hz). ^{13}C{^{1}H} (acetone-d_6): δ(SiMe$_4$) 187.2 (C═N), 149.6 (s, aromatic C of dmba), 139.2 (d, aromatic CH of dmba, J_{CP} = 6.5 Hz), 137.0 (d, aromatic C of dmba, J_{CP} = 7.2 Hz), 135.9 (d, *ortho*-C PPh_3, J_{CP} = 11.2 Hz), 132.4 (d, *para*-C PPh_3, J_{CP} = 2.6 Hz), 130.1 (d, *ipso*-C PPh_3, J_{CP} = 61.3 Hz), 129.5 (d, *meta*-C PPh_3, J_{CP} = 11.1 Hz), 125.7 (d, aromatic CH dmba, J_{CP} = 2.5 Hz), 125.0 (aromatic *C*H dmba), 122.7 (aromatic *C*H dmba), 73.9 (*C*H$_2$NMe$_2$), 51.5 (N*Me*$_2$), 28.4 (HN═C*Me*$_2$), 27.9 (HN═C*Me*$_2$). ^{31}P NMR (acetone-d_6): δ(H_3PO_4) 21.3 (s, J_{PtP} = 4100 Hz). ^{195}Pt NMR (acetone-d_6): δ($Na_2[PtCl_6]$) −4063 (d, J_{Pt-P} = 4100 Hz). Positive-ion FAB mass spectrum: *m*/*z* 648 ([Pt(dmba)(PPh_3)(HN═CMe$_2$)]$^+$, 24%).

Reaction of [Pt(dmba)(Cl)(DMSO)] with AgClO$_4$ and NH$_3$ in Acetone. $AgClO_4$ (70.5 mg, 0.34 mmol) was added to an acetone (20 mL) solution of [Pt(dmba)(Cl)(DMSO)] (150 mg, 0.34 mmol). After the resulting suspension was stirred at room temperature in the darkness for 30 min, it was filtered through Celite, and NH_3 (628 μL of 20% aqueous NH_3, 6.8 mmol) was added. The solution was stirred at room temperature for 4 h, and the solvent was evaporated to dryness. The residue was treated with acetone and ether to give a white precipitate that was filtered off and air-dried. A mixture of complexes [Pt(dmba)(NH═CMe$_2$)$_2$]ClO_4 (**2**) and [Pt(dmba){NHC-(Me)CH$_2$C(Me$_2$)NH$_2$}]ClO_4 (**3a**) was obtained in a 5:2 ratio.

Data for Complex 2. ^{1}H NMR (acetone-d_6): δ(SiMe$_4$) 10.34 (br, 1H, N*H*), 10.12 (br, 1H, N*H*), 7.10−6.72 (m, 4H, aromatics of dmba), 4.03 (s, 2H, C*H*$_2$, J_{PtH} = 41.7 Hz), 2.84 (s, 6H, N*Me*$_2$, J_{PtH} = 35.7 Hz), 2.48 (d, 3H, C*Me*, *trans*-CH_3 to NH, J_{HH} = 0.6 Hz, Pt satellites are observed as shoulders), 2.38 (d, 3H, C*Me*, *trans*-CH_3 to NH, J_{HH} = 0.9 Hz, Pt satellites are observed as shoulders), 2.34 (d, 3H, C*Me*, *cis*-CH_3 to NH, J_{HH} = 1.5 Hz), 2.25 (d, 3H, C*Me*, *cis*-CH_3 to NH, J_{HH} = 1.5 Hz).

Data for Complex 3a. ^{1}H NMR (acetone-d_6): δ(SiMe$_4$) 10.17 (br, 1H, N*H*), 7.13−6.95 (m, 4H, aromatics of dmba), 4.52 (br s, 2H, N*H*$_2$, Pt satellites are observed as shoulders), 4.05 (s, 2H, C*H*$_2$N, J_{PtH} = 42 Hz), 2.90 (s, 6H, N*Me*$_2$, J_{PtH} = 34.8 Hz), 2.71 (s, 2H, CC*H*$_2$ of imam ligand, Pt satellites are observed as shoulders), 2.42 (d, 3H, C*Me*, J_{HH} = 1.5 Hz), 1.47 (s, 6H, C*Me*$_2$).

Table 4. Crystal Structure Determination Details

parameter	**1**·2Me$_2$CO	**2**	**3a**	**5**	**6**
empirical formula	$C_{36}H_{46}ClN_2O_6PPt$	$C_{15}H_{26}ClN_3O_4Pt$	$C_{15}H_{26}ClN_3O_4Pt$	$C_{15}H_{24}N_2OPt$	$C_{18}H_{14}F_{10}N_2Pt$
fw	864.26	542.93	542.93	443.45	643.40
cryst system	triclinic	triclinic	monoclinic	monoclinic	monoclinic
a (Å)	9.5629(4)	9.0918(3)	9.3719(4)	14.0193(6)	9.2445(4)
b (Å)	12.3783(5)	9.5904(4)	10.3163(4)	26.1617(11)	20.1630(11)
c (Å)	16.8813(7)	12.4696(5)	9.6044(4)	14.2020(6)	20.8673(10)
α (deg)	70.351(2)	80.297(2)	90	90	90
β (deg)	77.702(2)	72.744(2)	93.592(2)	112.707(2)	91.291(2)
γ (deg)	85.013(2)	65.489(2)	90	90	90
V (Å^3)	1838.48(13)	943.47(6)	926.76(7)	4805.1(4)	3888.6(3)
temp (K)	100(2)	100(2)	100(2)	100(2)	100(2)
space group	$P\bar{1}$	$P\bar{1}$	$P2_1$	$P2_1/n$	$P2_1/n$
Z	2	2	2	12	8
μ (mm^{-1})	3.978	7.601	7.738	8.755	7.318
reflns collected	21245	10276	9674	52064	44273
independent reflns	8230	3820	3703	9824	8995
R(int)	0.0178	0.0156	0.0156	0.0301	0.0188
R1 [$I > 2\sigma(I)$][a]	0.0199	0.0195	0.0120	0.0298	0.0161
wR$_2$ (all data)[b]	0.0480	0.0487	0.0291	0.0702	0.0386

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum w(F_o^2)^2]^{0.5}$. [b] $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (2F_c^2 + F_o^2)/3$ and *a* and *b* are constants set by the program.

Preparation of Complex [Pt(dmba){NHC(Me)CH$_2$C(Me$_2$)NH$_2$}]-Cl (3b). To a solution of [Pt(dmba)(Cl)(DMSO)] (150 mg, 0.34 mmol) in acetone (20 mL) was added 20% aqueous NH_3 (157 μL, 1.69 mmol). The resulting suspension was stirred at room temperature for 24 h. Then, a white solid was collected by filtration and air-dried.

Data for Complex 3b. Yield: 85 mg, 52%. Anal. Calcd for $C_{15}H_{26}ClN_3Pt$: C, 37.62; H, 5.47; N, 8.77. Found: C, 37.41; H, 5.35; N, 8.79. Mp: 254 °C (dec). IR (Nujol, cm^{-1}): *ν*(NH) 3277, 3159, *ν*(C═N) 1650. ^{1}H NMR (D_2O): *δ*(SiMe$_4$) 7.10−6.81 (m, 4H, aromatics of dmba), 3.91 (s, 2H, C*H*$_2$N, J_{PtH} = 40.2 Hz), 2.78 (s, 6H, N*Me*$_2$, J_{PtH} = 34.5 Hz), 2.45 (s, 2H, CC*H*$_2$ of imam ligand), 2.11 (s, 3H, C*Me*), 1.24 (s, 6H, C*Me*$_2$). ^{13}C{^{1}H} (D_2O): *δ*(SiMe$_4$) 184.4 (C═N), 149.2, 136.4 (aromatic C of dmba), 130.8, 125.0, 124.6, 121.8 (aromatics CH of dmba), 75.0 (CH$_2$N), 51.8 (NMe$_2$), 49.9 (N*C*Me$_2$), 47.3 (*C*H$_2$C), 29.6 (C*Me*), 26.3 (C*Me*$_2$). ^{195}Pt NMR (D_2O): *δ*(Na$_2$[PtCl$_6$]) −3282 (s). Positive-ion FAB mass spectrum: *m*/*z* 443 ([Pt(dmba)(imam)]$^+$, 67%).

Preparation of Complex [Pt(dmba)(NH═CMe$_2$)(DMSO)](ClO$_4$) (4). To a solution of [Pt(dmba)(Cl)(DMSO)] (150 mg, 0.34 mmol) in CH_2Cl_2 (20 mL) was added [Ag(NH═CMe$_2$)$_2$]ClO$_4$ (108.8 mg, 0.34 mmol). AgCl immediately formed. The resulting suspension was stirred for 1 h and then filtered through Celite. The filtrate was then evaporated to dryness. The residue was treated with Et_2O to yield a white solid, which was filtered, washed with Et_2O, and air-dried.

Data for Complex 4. Yield: 162 mg, 85%. Anal. Calcd for $C_{14}H_{25}ClN_2O_5PtS$: C, 29.82; H, 4.47; N, 4.97; S, 5.68. Found: C, 30.10; H, 4.73; N, 4.94; S, 5.44. Mp: 200 °C (dec). Λ_M: 135 S cm^2 mol^{-1}. IR (Nujol, cm^{-1}): *ν*(NH) 3258, *ν*(C═N) 1664. ^{1}H NMR ($CDCl_3$): *δ*(SiMe$_4$) 10.35 (br, 1H, NH), 7.70 (d, 1H, aromatics of dmba, J_{HH} = 6.3 Hz), 7.11 (m, 3H, aromatics of dmba), 4.56 (d, 1H, C*H*$_2$N, J_{HH} = 13.2 Hz), 3.62 (d, 1H, C*H*$_2$N J_{HH} = 13.2 Hz), 3.46 (s, 3H, Me of DMSO, J_{HPt} = 35.7 Hz), 3.13 (s, 3H, Me of DMSO, Pt satellites are observed as shoulders), 2.86 (s, 3H, N*Me*$_2$, J_{HPt} = 31.5 Hz), 2.64 (s, 3H, N*Me*$_2$, J_{HPt} = 39.0 Hz), 2.60 (s, 3H, C*Me*$_2$, *trans*-C*H*$_3$ to NH), 2.38 (d, 3H, C*Me*$_2$, J_{HH} = 1.5 Hz, *cis*-C*H*$_3$ to NH). ^{13}C{^{1}H} (DMSO-*d*$_6$): *δ*(SiMe$_4$) 188.9 (C═N), 148.0, 137.6 (aromatics C of dmba), 134.4, 125.6, 125.1, 122.0 (aromatics CH of dmba), 73.6 (*C*H$_2$NMe$_2$), 51.7 (N*Me*$_2$), 51.2 (N*Me*$_2$), 44.6 (DMSO), 45.5 (DMSO), 28.6 (HN═C*Me*$_2$), 27.7 (HN═C*Me*$_2$). ^{195}Pt NMR (DMSO-*d*$_6$): *δ*(Na$_2$[PtCl$_6$]) −3705 (s). Positive-ion FAB mass spectrum: *m*/*z* 464 ([Pt(dmba)(DMSO)(HN═CMe$_2$)]$^+$, 100%).

Preparation of Complex [Pt(dmba)(NH═CMe$_2$){CH$_2$C(O)CH$_3$}] (5). To a solution of [Pt(dmba)(Cl)(DMSO)] (150 mg, 0.34 mmol) in acetone (20 mL) was added 20% aqueous NH_3 (157 μL, 1.69 mmol). The resulting suspension was stirred at room temperature for 1 h, and a solution of KOH (99 mg, 1.77 mmol) in MeOH (10 mL) was then added. The resulting mixture was stirred at 70 °C for 1 h, and the yellow solution obtained was concentrated to dryness. The residue was then treated with 1:4 Et_2O-hexane and the suspension was filtered off to separate the pale yellow solid **5**, which was washed with hexane and air-dried.

Data for Complex 5. Yield: 80 mg, 53%. Anal. Calcd for $C_{15}H_{24}N_2OPt$: C, 40.63; H, 5.45; N, 6.32. Found: C, 40.55; H, 5.31; N, 6.29. Mp: 156 °C (dec). IR (Nujol, cm^{-1}): *ν*(NH) 3224, *ν*(C═N) 1662, *ν*(C═O) 1634. ^{1}H NMR (acetone-*d*$_6$): *δ*(SiMe$_4$) 9.80 (br, 1H, NH), 7.46 (dd, 1H, aromatic of dmba, J_{HH} = 7.4 Hz, J_{HH} = 1.2 Hz, J_{PtH} = 46.4 Hz), 6.93−6.80 (m, 3H, aromatics of dmba), 3.76 (s, 2H, C*H*$_2$N, J_{PtH} = 25.8 Hz), 2.69 (s, 6H, N*Me*$_2$, J_{PtH} = 22.8 Hz), 2.59 (s, 2H, C*H*$_2$CO, J_{PtH} = 120 Hz), 2.37 (s, 3H, C*Me*$_2$, *trans*-Me to NH, Pt satellites are observed as shoulders), 2.18 (d, 3H, C*Me*$_2$, *cis*-Me to NH, J_{HH} = 1.5 Hz), 1.92 (s, 3H, COC*H*$_3$, J_{PtH} = 18 Hz). ^{13}C{^{1}H} (acetone-*d*$_6$): *δ*(SiMe$_4$) 181.7 (*C*═N), 150.4, 142.4 (aromatic C of dmba), 134.5, 125.3, 122.4, 121.8 (aromatics *C*H of dmba), 73.7 (*C*H$_2$N), 51.3 (N*Me*$_2$), 30.6−29.0 (*C*H$_3$CO and HN═C*Me*$_2$, overlapped with acetone-*d*$_6$ signals), 26.6 (HN═C*Me*$_2$), 19.6 (*C*H$_2$CO). ^{195}Pt NMR (acetone-*d*$_6$): *δ*(Na$_2$[PtCl$_6$]) −3455 (s). Positive-ion FAB mass spectrum: *m*/*z* 443 [Pt(dmba)(NH═CMe$_2$)-{CH$_2$C(O)CH$_3$}]$^+$, 18%).

Preparation of Complex *cis*-[(C$_6$F$_5$)$_2$Pt(NH═CMe$_2$)$_2$] (6). [Ag(NH═CMe$_2$)$_2$]ClO$_4$ (80 mg, 0.248 mmol) was added to a solution of [Bu$_4$N]$_2$[(C$_6$F$_5$)$_4$Pt$_2$(*μ*-Cl)$_2$] (200 mg, 0.124 mmol) in CH_2Cl_2 (20 mL). The resulting suspension was stirred for 30 min and filtered though Celite. The resulting solution was evaporated to dryness, and then Et_2O (30 mL) was added and filtered through florisil to remove the insoluble [Bu$_4$N]ClO$_4$. The clear solution was concentrated (1 mL) and the addition of hexane caused the precipitation of a white solid which was collected by filtration and air-dried.

Data for Complex 6. Yield: 130 mg, 81%. Anal. Calcd for $C_{18}H_{14}F_{10}N_2Pt$: C, 33.60; H, 2.19; N, 4.35. Found: C, 33.61; H, 2.19; N, 4.30. Mp: 252 °C (dec). IR (Nujol, cm^{-1}): *ν*(NH) 3306,

ν(C═N) 1662, ν(Pt−C_6F_5) 806, 796. ^{1}H NMR ($CDCl_3$): δ($SiMe_4$) 8.77 (br, 2H, NH), 2.37 (s, 6H, C*Me*$_2$, *trans*-CH_3 to NH, Pt satellites are observed as shoulders), 2.12 (d, 6H, C*Me*$_2$, *cis*-CH_3 to NH, J_{HH} = 1.4 Hz). ^{19}F ($CDCl_3$): δ($CFCl_3$) −120.6 (m, 4F_o, J_{PtFo} = 470.7 Hz), −162.9 (t, 2F_p, J_{mp} = 20.7 Hz), −164.9 (m, 4F_m). ^{13}C{^{1}H} ($CDCl_3$): δ($SiMe_4$) 184.5 (*C*═N), 29.8 (Me, J_{CPt} = 24.7 Hz), 26.6 (Me, J_{CPt} = 48.4 Hz). ^{195}Pt NMR ($CDCl_3$): δ($Na_2[PtCl_6]$) −3540 (vt, J_{PtF} = 465.4 Hz). Positive-ion FAB mass spectrum: *m*/*z* 643 $(M)^+$ 5%.

X-ray Crystal Structure Analysis. Suitable crystals from **1**·2Me_2CO and **5** were grown from acetone. Crystals of **2** and **3a** were grown from dichloromethane/hexane. Crystals of **6** were grown from dichloromethane/toluene/hexane. The crystal and molecular structures of the compounds **1**·2Me_2CO, **2**, **3a**, **5**, and **6** have been determined by X-ray diffraction studies (Table 4).

Compounds **1**·2Me_2CO, **2**, **3a**, **5**, and **6** were measured on a Bruker Smart Apex diffractometer. Data were collected using monochromated Mo Kα radiation in ω scan mode. Absorption corrections were applied on the basis of multiscans (Program SADABS[66]). All structures were solved by direct methods using SHELX-97[67] and refined anisotropically on F^2. The NH_2 hydrogens were refined freely with SADI, the NH hydrogens were refined freely, the ordered methyl groups were refined using rigid groups (AFIX 137), and the other hydrogens were refined using a riding model.

Special Features. For the compound **1**·2Me_2CO: One of acetone molecules is well resolved, but the other is disordered over two sites with occupation 53:47.

For the compound **3a**: The Flack parameter refined to 0.038(5).

Biological Assays. Circular Dichroism Study. Spectra were recorded at room temperature on an Applied Photophysics Π*-180 spectrometer with a 75 W xenon lamp using a computer for spectral substraction and smooth reduction. The platinum samples (r_i = 0.1, 0.3, 0.5) were prepared by addition of aliquots of each compound, from stock solutions (1 mg/mL, 2% in DMSO), to a solution of calf thymus DNA (Sigma) in TE buffer (20 μg/mL), and incubated for 24 h at 37 °C. As a blank, a solution of each compound in TE buffer (50 mM NaCl, 10 mM Tris-HCl, 0.1 mM EDTA, pH 7.4) was used. Each sample was scanned twice in a range of wavelengths between 220 and 330 nm. The drawn CD spectra are the means of two independent scans. The ellipticity values are given in millidegrees (mdeg).

Electrophoretic Mobility Study. pB*R*322 plasmid DNA of 0.25 μg/μL concentration was used for the experiments. Four microliters of charge maker were added to aliquot parts of 20 μL of the complex: DNA compound containing 0.7 μg of DNA previously incubated at 37 °C for 24 h. The mixtures underwent electrophoresis in agarose gel 1% in 1 × TBE buffer (45 mM Tris-borate, 1 mM EDTA, pH 8.0) for 5 h at 30 V. Gel was subsequently stained in the same buffer containing ethidium bromide (1 μg/mL) for 20 min. The DNA bands were visualized with a Typhoon 9410 Variable Mode Imager (Amersham Biosciences).

Cell Line and Culture. The T-47D human mammary adenocarcinoma cell line used in this study was grown in RPMI-1640 medium supplemented with 10% (v/v) fetal bovine serum (FBS) and 0.2 unit/mL bovine insulin in an atmosphere of 5% CO_2 at 37 °C. The human ovarian carcinoma cell lines (A2780 and A2780*cis*R) used in this study were grown in RPMI 1640 medium supplemented with 10% (v/v) fetal bovine serum (FBS) and 2 mM L-glutamine in an atmosphere of 5% CO_2 at 37 °C.

Cytotoxicity Assay. Cell proliferation was evaluated by assay of crystal violet. T-47D cells plated in 96-well sterile plates at a density of 5 × 10^3 cells/well with 100 μL of medium and were then incubated for 48 h. After attachment to the culture surface the cells were incubated with various concentrations of the compounds tested freshly dissolved in DMSO and diluted in the culture medium (DMSO final concentration 1%) for 48 h at 37 °C. The cells were fixed by adding 10 μL of 11% glutaraldehyde. The plates were stirred for 15 min at room temperature and then washed three to four times with distilled water. The cells were stained with 100 μL of 1% crystal violet. The plate was stirred for 15 min and then washed three to four times with distilled water and dried. One hundred microliters of 10% acetic acid were added, and it was stirred for 15 min at room temperature. Absorbance was measured at 595 nm in a Tecan Ultra Evolution spectrophotometer.

The effects of complexes were expressed as corrected pertentage inhibition values according to the following equation,

$$\% \text{ inhibition} = [1 - (T/C)] \times 100 \quad (1)$$

where *T* is the mean absorbance of the treated cells and *C* the mean absorbance in the controls.

The inhibitory potential of compounds was measured by calculating concentration-percentage inhibition curves, and these curves were adjusted to the following equation:

$$E = E_{max}/[1 + (IC50)/C)^n] \quad (2)$$

were *E* is the percentage inhibition observed, E_{max} is the maximal effects, IC_{50} is the concentration that inhibits 50% of maximal growth, *C* is the concentration of compounds tested, and *n* is the slope of the semilogarithmic dose−response sigmoid curves. This nonlinear fitting was performed using GraphPad Prism 2.01, 1996 software (GraphPad Software Inc.).

For comparison purposes, the cytotoxicity of cisplatin was evaluated under the same experimental conditions. All compounds were tested in two independent studies with triplicate points. The in vitro studies were performed in the USEF platform of the University of Santiago de Compostela (Spain).

Conclusions

This is the first report of the synthesis of imam complexes of platinum. The first organometallic acetonimine platinum complexes have also been prepared. Strong supramolecular interactions are present in all the structures. Complex *cis*-[$Pt(C_6F_5)_2(NH{=}CMe)_2$] (**6**) exhibits a head to head orientation of the acetonimine moieties, whereas the relative orientation of the acetonimine ligands in [$Pt(dmba)(NH{=}CMe_2)_2$]ClO_4 (**2**) is head to tail (HL). Values of IC_{50} were calculated for the complexes **1**, **4**, and **5** against the human tumor cell lines A2780, A2780*cis*R and T47D. At 48 h incubation time complex **1** was about 30-fold more active than cisplatin in T47D. Complexes **1**, **4**, and **5** show very low resistance factors against a A2780 cell line which has acquired resistance to cisplatin. Circular dichroism and electrophoretic mobility indicate interaction of the new platinum complexes with DNA.

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Supporting Information Available: X-ray crystallography data in CIF format for complexes **1**·2acetone, **2**, **3a**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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