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N-Heterocyclic Carbene-Amine Pt(II) Complexes, a New Chemical Space for the Development of Platinum-Based Anticancer Drugs

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N-Heterocyclic carbene (NHC) platinum complexes have been highlighted as a promising and original platform for building new cytotoxic drugs of the cisplatin series. Mixed NHC-amine Pt^{II} complexes have been prepared via a facile and modular two step sequence leading to *trans*-configured square planar species. They have been characterized by spectroscopic methods and X-ray diffraction studies. Their efficiency against both cisplatin sensitive (CEM and H460) and resistant (A2780/DDP, CH1/DDP, and SK-OV-3) cell lines has been demonstrated by in vitro experiments.

Introduction

Cisplatin[1] is one of the most commonly prescribed chemotherapeutic drugs, used either as a single agent in treating head and neck, testicular, ovarian, and small cell lung cancers or in conjunction with other therapeutic regimens, including radiation therapy. However, its clinical application is limited by toxicity issues, mainly ototoxicity and nephrotoxicity, or by acquired and/or intrinsic resistance mechanisms, decreased influx or increased efflux of drug, glutathion or metallothionein conjugation, DNA repair, or skipping lesions during DNA replication.[2] To overcome these limitations, intensive research efforts have been engaged over the past 30 years. This led to the clinical development of cisplatin analogues such as oxaliplatin and carboplatin, widely used for treating colorectal cancers and ovarian tumors, respectively. However, these compounds still display side effects, such as peripheral neuropathy or myelosuppression.[3] To date, a new generation of molecularly targeted drugs is eagerly expected whose rational design would proceed from elucidation of tumor resistance mechanisms.[4] In this context, it becomes desirable to develop a new series of platinum complexes displaying highly modular scaffolds, easily adaptable to drug design. Our original design reported here was to consider N-heterocyclic carbenes (NHC[a])[5] as carrier ligands for cytotoxic platinum complexes. NHCs perfectly fit prerequisites for efficient drug design and fast optimization, since they are readily accessible in few steps and their substituents can be widely varied, thus allowing an easy fine-tuning of both the physicochemical properties and the reactivity in biological medium of the final NHC platinum complexes. Despite extensive studies on NHC complexes in organometallic chemistry and catalysis, only a restricted array of biomedical applications have been reported so far for silver, gold, palladium, copper, ruthenium, and rhodium derivatives, mainly for antimicrobial and antitumor purposes.[6,7]

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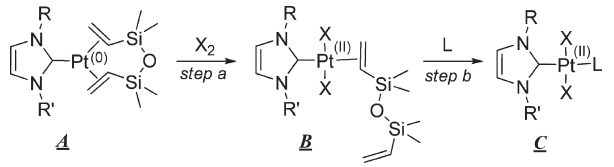
[a] Abbreviations: NHC, N-heterocyclic carbene; dvtms, 1,3-divinyltetramethyldisiloxane; DDP, cis-diamminedichloroplatinum(II).

Scheme 1. Synthetic Approach to Pt^{II} Derivatives from $Pt^{(0)}$-(NHC) Complexes



A *B* *C*

To the best of our knowledge, no platinum NHC complexes displaying anticancer activities have been reported to date. We describe here a versatile synthetic approach to a series of easily tunable (NHC)(amine)Pt^{II} complexes that display high levels of cytotoxic activity against both cisplatin sensitive and resistant cell lines.[8]

Results and Discussion

Synthesis and Characterization of Platinum Compounds. Driven by the aim of screening (NHC)Pt^{II} complexes as cytotoxic agents, we specifically targeted Pt^{II} complexes of the general formula (NHC)$PtLX_2$ (**C** in Scheme 1) which combine a NHC ligand with a second neutral two-electron donor (L) and halide ligands (X). Platinum complexes **C** are structurally related to cisplatin in the sense that they display two strongly bonded carrier ligands and two labile halide groups, X. Platinum complexes **C** are more specifically related to the "*trans* subclass" of platinum antitumor agents, characterized by the trans relative geometry of their strongly bonded ligands, which were reported first by Natile's group.[9,10]

Our synthetic approach to complexes **C** starts from the well-known Pt^0(NHC)(dvtms) complexes **A** (dvtms = divinyltetramethyldisiloxane), introduced by Markó a few years ago as hydrosilylation catalysts.[11] They represent so far the largest and most easily available family of platinum carbene derivatives. We therefore anticipated that complexes **A** might be suitable precursors to complexes **C** via a simple two step sequence involving an oxidative addition reaction (step a in Scheme 1) and subsequent replacement of the olefinic ligand of **B**[13c] by selected L-ligands (step b).

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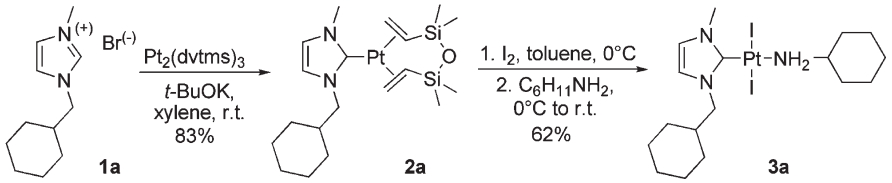
Scheme 2. Synthesis of Mixed NHC-amine Platinum Diiodide **3a**



In the course of this work, iodine was found to be a suitable reagent for the oxidation of the Pt(0) complexes **A** into the corresponding Pt(II) derivatives[12] and amines were used as the preferred L-type ligands, since biological applications were targeted here. In parallel studies, the same strategy has been applied to the synthesis of mixed NHC-phosphine platinum(II) complexes for catalytic purposes.[13]

The two-step synthetic procedure is typified in Scheme 2 by the synthesis of diiodo(imidazolylidene)(cyclohexylamine)-platinum complex **3a**. At first, Pt^0(NHC)(dvtms) complex **2a** was prepared in 83% yield from its corresponding imidazolium salt **1a** using Karstedt catalyst [Pt_2(dvtms)$_3$], according to the Markó's method.[11c] Complex **2a** was then reacted in toluene with iodine and cyclohexylamine successively. The expected mixed NHC−amine complex **3a** was thus obtained in 62% yield.

Complex **3a** was obtained as a single isomer. Unambiguous structural assignment has been done by NMR spectroscopy and X-ray diffraction studies. Single crystals of **3a** have been grown from a $CHCl_3$ solution. The solid state structure, shown in Figure 1, reveals a square planar coordination at the platinum center, with a *trans* relative geometry of the two iodide ligands. The stereochemical outcome of these reactions contrasts with the selective formation of the *cis* isomers of (NHC)Pt(PPh_3)I_2 complexes, when using triphenylphosphine as the L-type ligand in analogous reaction sequences.[13c] The preferred geometry of the final product apparently relates to the nature of the L-ligand involved in the olefin-to-ligand substitution step,[14] with a *trans* arrangement being preferred in the case of amines.

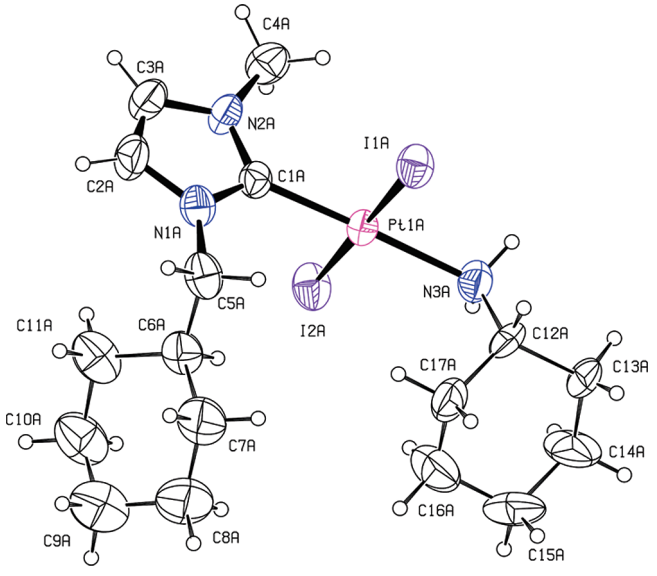


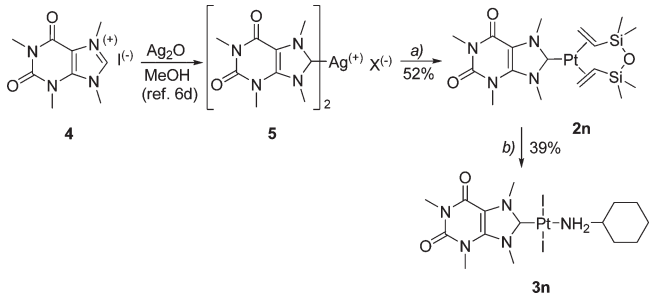
Figure 1. ORTEP view of complex **3a**. Displacement ellipsoids are drawn at the 30% probability level. One conformer is shown arbitrarily with one set of disorder cyclohexane substituents (narrow lines) for clarity. Selected averaged bond distances (Å): Pt(1)−C(1) 1.967(8), Pt(1)−N(3) 2.118(6), Pt(1)−I(1) 2.5932(7), Pt(1)−I(2) 2.5997(7). Bond angles (deg): C(1)−Pt(1)−N(3) 178.4(3), C(1)−Pt−I(1) 90.4(2), I(1)−Pt−I(2) 178.44(2).

The synthetic strategy displayed in Scheme 2 has been applied to the synthesis of a variety of mixed NHC-amine platinum diiodides, starting from the corresponding Pt(0) complexes **2** (X = CH, R^3 = H; **2b**, R^1 = Me, R^2 = CH_2-Ph;[11c] **2c**, $R^1 = R^2 = C_6H_{11}$;[11c] **2d**, $R^1 = R^2 = CH_2Ph$; **2e**, $R^1 = R^2$ = Me;[11c] **2f**, R^1 = Me, R^2 = 4-CF_3−C_6H_4−CH_2; **2g**, NHC = 1,3-dimethylbenzoimidazolylidene; **2h**, X = CPh, R^3 = Ph, $R^1 = R^2$ = Me;[11c] **2i**, X = N, R^3 = H, R^1 = Me, R^2 = Ph). Representative compounds and nonoptimized yields are listed in Table 1.

Satisfactory yields have been obtained with various types of amines, including primary amines such as cyclohexyl- (**3b**−**d**, **3f**, **3i**, **3j**), benzyl- (**3e**), or norbornylamine (**3g**), secondary amines (morpholine, **3l**), as well as ammonia (**3k**) and pyridine (**3m**). Modulations of the carbene moiety were successfully carried out; imidazolylidenes with alkyl or arylalkyl substituents on the nitrogen atoms (**3b**−**g**), benzoimidazolylidenes (**3h**), as well as 4,5-diaryl substituted imidazolylidenes (**3i**) have been incorporated. Also, triazolylidenes (X = N) have been used as ancillary ligands instead of imidazolylidenes, as in **3j**.

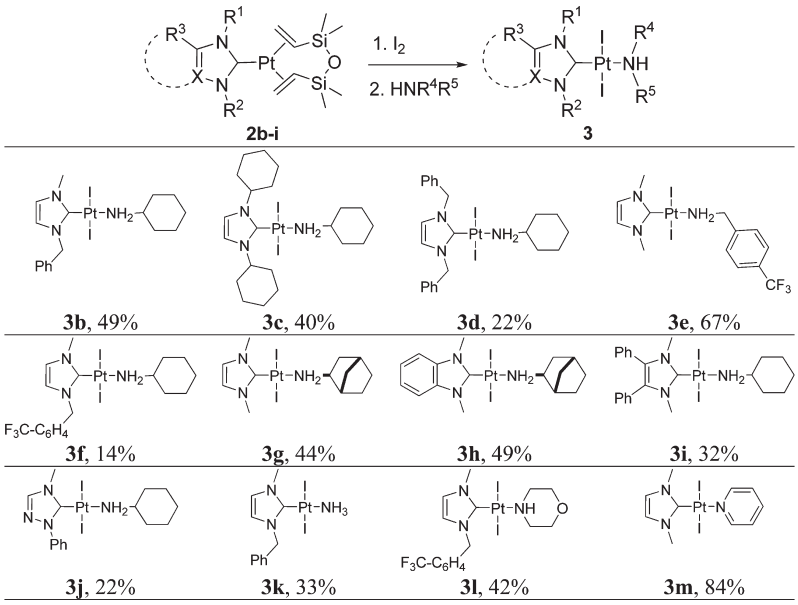
In order to investigate the scope and limitations of the above synthetic approach, we then considered imidazolylidenes of increasing structural complexity. Thus, for instance, a caffeine-derived NHC has been envisioned as an example of purine-based carbenes, a class of ligands already used in organometallic complexes for catalytic[15] and biomedical applications.[6d,6f,16] Methylated caffeine, **4**,[15a] served as starting material for the synthesis of the highly functionalized imidazolylidene complex **3n** (Scheme 3). In this case, the procedure for the synthesis of (NHC)Pt^0(dvtms) complex **2n** makes use of intermediate silver imidazolylidene complex, **5**,[6d] as carbene transfer reagent.[17] The oxidative addition step takes place in the usual conditions, leading to **3n** in 39% yield, at up to 2 g scale.

Scheme 3. Synthesis of the Tetramethylxantin-8-ylidene Pt^{II} Complex **3n**[a]



[a] (a) Pt_2(dvtms)$_3$, xylene/dmf, room temp, 16 h; (b) I_2, 0 °C, toluene, then $C_6H_{11}NH_2$, room temp overnight.

Table 1. Mixed NHC-amine Complexes **3**[a]



[a] Representative examples and yields for reactions performed at a 0.2−0.5 mmol scale, in the conditions described in Scheme 2.

The X-ray crystal structure of complex **3n** is depicted in Figure 2. The structural features of **3n**, regarding trans arrangement of the iodide ligands, bond distances and angles, closely resemble those of complex **3a** (Figure 1).

Another example of highly functionalized NHC platinum-(II) complex, amenable through the aforementioned synthetic approach, consists in the glucopyranose derived imidazolylidene complex **3o** (Scheme 4). The NHC platinum-(dvtms) complex **2o** has been prepared by transmetalation from the corresponding NHC silver complex[18] generated in situ. It has been submitted to oxidative addition of iodine in the presence of cyclohexylamine to produce the targeted complex **3o** in 31% yield.

This reaction sequence demonstrates the feasibility of incorporating a saccharide group into the targeted (NHC)Pt^{II} complexes **3** and opens up a way for modulation of physicochemical properties, such as solubility and lipophilicity, and/or targeted delivery in biological systems. Similarly, instead of a saccharide, it could be easily envisioned to attach onto the carbene moiety of the (NHC)Pt^{II} complexes **3**, either directly or through a linker, any biovector useful for active drug targeting and delivery (DTD methodology).[19] Thus, attachment of estrogens, or ligands of estrogen receptor, and attachment of folic acid, or ligands of folate receptor, would help specific delivery to ER(+) and FR(+) tumors, respectively.

Besides modulations of the carbene and amine units, a few other structural variations have been carried out on complexes **3**. Especially, since the leaving group ability of the anionic ligand is known to control the potency of cisplatin and analogues, we embarked on the synthesis of (NHC)Pt^{II} complexes bearing various X-type ligands. This could be achieved by one of two following methods: oxidation of Pt^0 complexes **2** using bromine instead of iodine, or ligand exchange reactions on preformed (NHC)Pt diiodide complexes, **3**. As depicted in Scheme 5, on the one hand, the dibromide complex **7** could be isolated from reaction of the (NHC)Pt^0(dvtms) complex **2f** with bromine and cyclohexylamine, successively. On the other hand, iodide ligands of

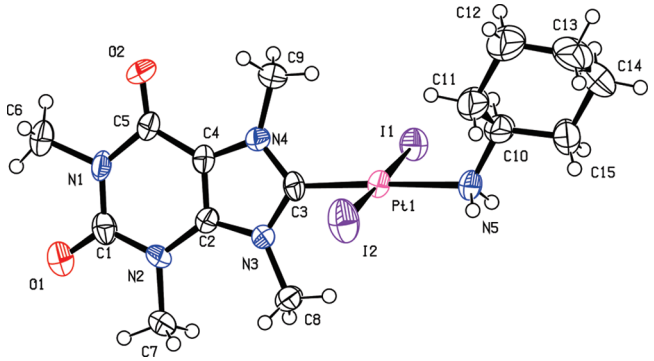


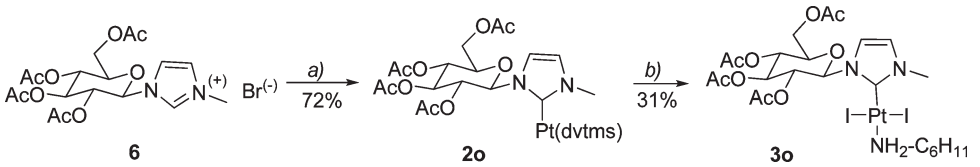
Figure 2. Ortep view of complex **3n**. Displacement ellipsoids are drawn at the 50% probability level. The chloroform molecule has been omitted for clarity. Selected bond distances (Å): Pt(1)−C(3) 1.986(10), Pt(1)−N(5) 2.129(8), Pt(1)−I(1) 2.5945(10), Pt(1)−I(2) 2.5915(11). Bond angles (deg): C(3)−Pt(1)−N(5) 177.6(4), C(3)−Pt(1)−I(1) 91.0(3), I(1)−Pt(1)−I(2) 178.63(3).

complex **3f** could be removed by treatment with silver nitrate in dichloromethane, which induces precipitation of silver iodide and formation of the corresponding *trans*-dinitrato complex **8**. In both cases, only poor yields were obtained, mainly due to tricky purification.

In summary, the examples above illustrate the wide scope and versatility of our synthetic approach to (NHC)Pt^{II} complexes which is intended to open a new chemical space for potentially cytotoxic compounds. Thus, the cytotoxic properties of these novel cisplatin analogues have been investigated in the preliminary studies reported here.

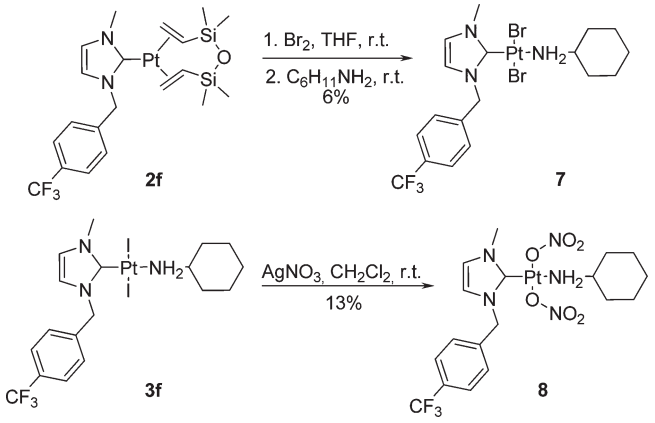
Evaluation of in Vitro Cytotoxic Activities. To assess the anticancer potential of the targeted, newly synthesized complexes **3**, **7**, and **8**, their cytotoxic properties have been evaluated, at first, in vitro on leukemia CCRF-CEM and lung NCI-H460 human cancer cell lines, selected as representative cisplatin-sensitive models of liquid and solid tumors, respectively. Antiproliferative activities of a series of (NHC)Pt^{II} complexes are reported in Figure 3 and Table 2.

Scheme 4. Synthesis of the (2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)imidazolylidene Pt^{II} Complex **3o**[a]



[a] (a) (1) Ag_2O, acetone, room temp, 2 h; (2) $Pt_2(dvtms)_3$, xylene, room temp, 16 h; (b) I_2, 0 °C, toluene, then $C_6H_{11}NH_2$, room temp overnight.

Scheme 5. Variations of the X-Type Ligands in (NHC)(amine)-PtX_2 Complexes



The cytotoxic activities of cisplatin and oxaliplatin are also reported in the graphic for comparison purposes.

The majority of complexes **3** exhibits cytotoxic activities at a micromolar range. On CEM T leukemia cells, measured IC_{50} values of complexes **3** are in the 0.6−2.7 μM range, generally significantly lower than for cisplatin itself (3.0 μM) under similar experimental conditions. Complexes **3b**, **3f**, **3h**, **3i**, **3l**, and **3d** also outperform cisplatin against H460 lung cancer cells. Other $(NHC)Pt^{II}$ complexes have been prepared in the same series that have been prepared that do not display cytotoxic activity,[22] underlying the need for further structure−activity analysis to determine accurate relationships related to carbene and/or amine ligands. On the basis of a comparison of compounds **3l**, **7**, and **8**, iodide ligands might represent an optimal compromise of reactivity toward nucleophiles to efficiently target DNA in tumor cells.

It is worthwhile noting here that complexes **3** display a trans geometry with respect to platinum atom. *Trans*-configured complexes have been postulated as inactive in initial anticancer research and thus neglected until after the pioneering works done by the teams of Farell[20a] and Natile.[9] Their potential interest is now widely recognized,[10a] owing to their ability to form different DNA−platinum adducts, less recognized by DNA-repair machinery, and hence to reduce cross-resistance with respect to cisplatin. Common trans-platinum derivatives displaying significant in vitro antitumor activity include complexes of planar aromatic amines (e.g., pyridine, quinoline, etc.[20]) and heterocyclic derivatives (piperidine, piperazine, and others[21]).

In line with our initial goal to find new cytotoxics for cisplatin resistant cells, we then evaluated the activity of selected complexes **3** toward cisplatin resistant cells. We selected three ovarian cell lines that are representative of at least two different cisplatin resistance mechanisms, i.e., glutathione induced resistance (SK-OV-3) and specific acquired resistance to platinum drugs (CH1/DDP or A2780/DDP). Results are reported in Figure 4 and Table 3.

Our hypothesis is that the imidazole-derived NHC complexes disclosed here operate with the same mechanism of action as other active trans-coordinated complexes and thus should be highly active on cell lines with acquired resistance to cis-coordinated platinum drugs. As expected on the basis of our hypothesis, unlike the reference cis-metallodrugs cisplatin and oxaliplatin, representative complexes **3** display high cytotoxicity against human ovarian A2780/DDP cells, with IC_{50} values in the range 1.2−1.8 μM, and against CH1/DDP cells, with IC_{50} values in the range 2.1−2.4 μM, irrespective of modulations of the NHC scaffold.

Two of the complexes studied, **3d** and **3f**, are also significantly more potent than cisplatin against SK-OV-3 cells, with IC_{50} of 2.8 and 2.6 μM, vs 6.1 μM for cisplatin.

These initial studies clearly demonstrate the promising potential of this new family of $(NHC)Pt^{II}$ complexes as anticancer drugs.

Conclusion

In summary, this study affords a potent and innovative new chemical platform for cytotoxic drugs of the platinum(II) series, based on NHC ligands. It demonstrates the potential anticancer activity of $(NHC)PtI_2$(amine) complexes and therefore implements a range of ligand pairs affording

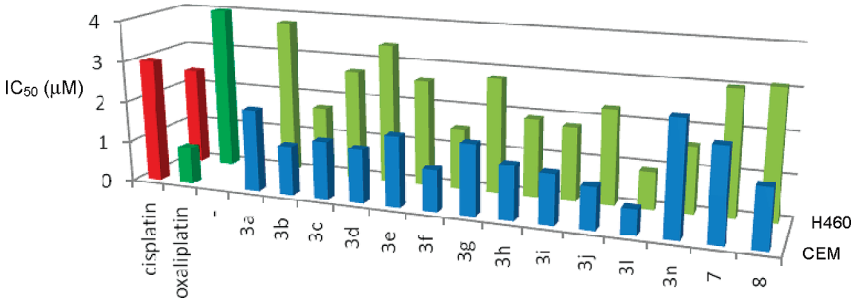


Figure 3. In vitro cytotoxic activity of platinum complexes in CCRF-CEM T leukemia cells (front series) and NCI-H460 lung cancer cells (back series) (IC_{50}, μM). See also Table 2.

Table 2. In Vitro Cytotoxic Activity of Platinum Complexes in CEM and H460 Cell Lines (IC_{50}, μM)

	cisplatin	oxaliplatin	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
CEM[a]	3 ± 0.4	0.9± 0.3	2.0 ± 0.5	1.2 ± 0.2	1.4 ± 0.2	1.3 ± 0.3	1.7 ± 0.1	1.0 ± 0.3
H460[b]	2.4 ± 0.3	4 ± 0.5	3.8 ± 1.0	1.7 ± 0.4	2.7 ± 0.8	3.4 ± 0.3	2.6 ± 0.5	1.5 ± 0.1
	3g	**3h**	**3i**	**3j**	**3l**	**3n**	**7**	**8**
CEM[a]	1.7 ± 0.2	1.3 ± 0.3	1.2 ± 0.1	1.0 ± 0.1	0.6 ± 0.1	2.7 ± 1.0	2.2 ± 0.3	1.4 ±0.4
H460[b]	2.8 ± 0.9	1.9 ± 0.3	1.8 ± 0.3	2.3 ± 0.4	0.9 ± 0.1	1.6 ± 0.1	3.0 ± 0.1	3.1 ± 1.1

[a] CCRF-CEM, T leukemia cells. [b] NCI-H460, lung cancer cells.

Table 3. In Vitro Cytotoxic Activity of Trans-platinum Complexes **3** toward Cisplatin Resistant Cell Lines (IC_{50}, μM)

	cisplatin	oxaliplatin	**3a**	**3b**	**3d**	**3f**	**3h**	**3n**
A2780/DDP[a]	> 10	17.3 ± 2.0	1.2 ± 0.2	1.8 ±0.3	1.2 ± 0.4	1.1 ± 0.2	1.8 ± 0.2	1.4 ± 0.3
CH1/DDP[a]	> 10	6.2± 1.0	2.0 ± 0.3	2.4 ± 0.3			2.4 ± 0.3	2.1 ± 0.3
SKOV3[a]	6.1 ± 0.8	> 10	5.3 ± 1.0	6.5 ± 0.4	2.8 ± 0.8	2.6 ± 0.4	7.0 ± 1.0	> 10

[a] Human ovarian cancer cells.

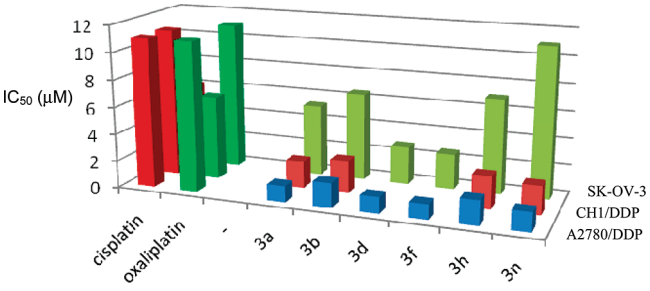


Figure 4. In vitro cytotoxic activity of platinum complexes toward cisplatin resistant, human ovarian cancer cells (IC_{50}, μM). See also Table 3.

platinum complexes whose antitumor properties are associated with a trans geometry. We also demonstrate that the (NHC)Pt^{II} unit is an easily available, highly tunable structure, potentially amenable to tumor-specific drug targeting and/or delivery approach, via a specific design of its carbene group, for instance. (NHC)PtI_2(amine) complexes warrant further preclinical evaluation: identification of their main DNA adducts, their stability with regard to plasma nucleophiles such as glutathione, their metabolic stability and pharmacokinetics, stability in plasma, and their in vivo effects in animal models.

Experimental Section

General Procedures. The (NHC)Pt^0(dvtms) complexes **2** were prepared according to the reported procedures.[8,11,13] The synthesis of **2a** is described hereafter as a representative procedure. Chromatographic separations were performed on silica gel columns. Purity of complexes **3** has been ascertained to be > 95% by either elemental analysis or LC/MS on an AQUITY BECH C18 column, eluted with H_2O/MeCN/1% HCO_2H gradients.

Synthesis of (NHC)Pt(dvtms) Complexes. Representative Procedure: [(1-(Cyclohexylmethyl)-3-methylimidazol-2-ylidene)(1,3-divinyl-1,1,3,3-tetramethyldisiloxane)]platinum (2a). (a) 1-Cyclohexylmethyl-3-methylimidazolium bromide **1a** was obtained in quantitative yield by reaction of 1-methylimidazole (0.9 mL, 10.8 mmol) and cyclohexylmethyl bromide (1.7 mL, 11.9 mmol) in toluene at 100 °C for 16 h. After evaporation of the solvents, the crude product was recrystallized in ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0−1.9 (11H), 4.13 (s, 3H, NMe), 4.15 (d, 2H, CH_2), 7.26 (s, 1H, *CH*=CH), 7.42 (s, 1H, CH=*CH*), 10.48 (s, 1H, NCH). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 25.41 (CH_2), 25.90 (CH_2), 30.17 (CH_2), 36.96 (NMe), 38.62 (CH), 56.15 (CH_2N), 122.29 (CH), 123.28 (CH), 138.29 (NCH). (b) The imidazolium salt **1a** (0.15 g, 0.6 mmol) was added to a xylene solution of Pt_2(dvtms)$_3$ (Karstedt's catalyst, ~2% Pt in xylene, 6 mL, 0.6 mmol of "Pt"). *t*-BuOK (0.09 g, 0.80 mmol) was then added at 0 °C, and the mixture was stirred at room temperature overnight. Complex **2a** was obtained in 83% yield (0.30 g) after purification by column chromatography with a heptane/ethyl acetate 9:1 mixture as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.26 (s, 6H, SiMe), 0.33 (s, 6H, SiMe), 0.8−0.9 (m, 2H), 1.1−1.2 (m, 3H), 1.5−2.0 (m, 10H), 2.21 (d, J = 9.9 Hz, $^2J_{H-Pt}$ = 52 Hz, 2H, CHSi), 3.50 (s, 3H, NMe), 3.68 (m, 2H, CH_2N), 6.97 (br, 2H, CH=CH). ^{13}C NMR (75,48 MHz, $CDCl_3$): δ −1.65 (SiMe), 1.64 (SiMe), 25.82 (CH_2), 26.44 (CH_2), 30.68 (CH_2), 34.04 (CHSi), 36.97 (NMe), 38.21 (CH), 40.21 (CH_2), 56.26 (CH_2N), 121.60 (CH).

Synthesis of (Amino)(NHC)PtI_2 Complexes 3a−m. Typical Procedure: *trans*-Diiodo(*N*-cyclohexylamine)(1-(cyclohexylmethyl)-3-methylimidazol-2-ylidene)platinum (3a). A solution of I_2 (130 mg, 0.5 mmol) in toluene (30 mL) was added at 0 °C to a solution of complex **2a** (280 mg, 0.5 mmol) in 20 mL of toluene under argon. Cyclohexylamine (60 μL, 0.5 mmol) was then added at 0 °C to the resulting mixture. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the final product was purified by chromatography with a heptane/ethyl acetate 9:1 mixture as the eluent. Yield: 62% (230 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.0−1.4 (12H, CH_2), 1.6−1.9 (m, 8H, CH_2), 2.30 (m, 2H, CH_2), 2.55 (m, 1H, CH), 2.92 (br, 2H, NH_2), 3.26 (m, 1H, CH), 3.86 (s, 3H, NMe), 4.07 (d, 2H, ^3J = 7.5 Hz, CH_2N), 6.74 (s, 1H, CH=CH), 6.77 (s, 1H, CH=CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 24.85 (CH_2), 25.33 (CH_2), 25.56 (CH_2), 26.36 (CH_2), 30.74 (CH_2), 35.92 (CH_2), 37.16 (CH), 38.27 (NMe), 54.91 (CH), 57.45 (CH_2), 121.08 (CH=CH), 121.66 (CH=CH), 138.95 (C). Anal. Calcd for $C_{17}H_{31}I_2N_3Pt$: C, 28.11; H, 4.30; N, 5.79. Found: C, 28.12; H, 4.11; N, 5.59. Crystals suitable for X-ray diffraction studies were obtained from a $CHCl_3$ solution.

***trans*-Diiodo(cyclohexylamine)(1-benzyl-3-methylimidazol-2-ylidene)platinum, (3b).** Complex **3b** was obtained in 49% yield (70 mg) from (1-benzyl-3-methylimidazol-2-ylidene)Pt^0(dvtms) complex (**2b**)[11c] (110 mg, 0.2 mmol), I_2 (50 mg, 0.2 mmol), and cyclohexylamine (25 μL, 0.22 mmol). The final product was purified by chromatography with a heptane/ethyl acetate 9:1 mixture as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1−1.9 (8H), 2.28 (m, 2H, CH_2), 2.93 (br, 2H, NH_2), 3.25 (m, 1H, CH), 3.89 (s, 3H, NMe), 5.59 (s, 2H, CH_2N), 6.56 (d, 1H, ^3J = 3 Hz, CH=CH), 6.77 (d, 1H, ^3J = 3 Hz, CH=CH), 7.3−7.5 (5H, Ph). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 24.81 (CH_2), 25.28 (CH_2), 35.88 (CH_2), 38.08 (CH_3N), 54.29 (CH_2N), 54.82 (CH), 119.84 (CH=CH), 122.19 (CH=CH), 128.28 (CH), 128.77 (CH), 129.05 (CH), 135.37 (C), 139.77 (C). Anal. Calcd for $C_{17}H_{25}I_2N_3Pt$: C, 28.35; H, 3.50; N, 5.83. Found: C, 28.83; H, 3.31; N, 5.75.

***trans*-Diiodo(*N*-cyclohexylamine)(1,3-dicyclohexylimidazol-2-ylidene)platinum (3c).** Complex **3c** was obtained in 40% yield (100 mg) from (1,3-dicyclohexylimidazol-2-ylidene)Pt^0(dvtms), **2c** (200 mg, 0.32 mmol), I_2 (90 mg, 0.35 mmol), and cyclohexylamine (40 μL, 0.35 mmol). The final product was purified by chromatography with a heptane/toluene 4:6 mixture and recrystallized from a dichloromethane−heptane mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.1−1.5 (15H), 1.63 (m, 1H), 1.7−1.8 (4H), 1.88 (m, 4H), 2.31 (m, 6H), 2.92 (br, 2H, NH_2), 3.28 (m, 1H, NCH), 5.20 (m, 2H, NCH), 6.82 (s, 2H, CH=CH). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 24.82 (CH_2), 25.34 (CH_2), 25.41 (CH_2), 25.67 (CH_2), 32.93 (CH_2), 35.93 (CH_2), 54.93 (CH), 59.30 (CH), 117.09 (CH=CH), 135.97 (C). HRMS (^{195}Pt) calcd for $C_{21}H_{37}I_2N_3Pt$.Na: 803.0622. Found: 803.0658.

***trans*-Diiodo(*N*-cyclohexylamine)(1,3-dibenzylimidazol-2-ylidene)platinum (3d).** Complex **3d** was obtained in 22% yield (90 mg) from (1,3-dibenzylimidazol-2-ylidene)Pt^0(dvtms), **2d** (325 mg, 0.52 mmol), I_2 (131 mg, 0.52 mmol), and cyclohexylamine (51 μL, 0.52 mmol). The final product was purified by chromatography with a cyclohexane/toluene 97:3 to 95:5 mixture as the eluent and recrystallized from 5 mL of diisopropyl ether. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, 1H), 1.20 (q, 2H), 1.32 (q, 2H), 1.62 (d, 1H), 1.75 (d,2H), 2.28 (d, 2H), 2.98 (m, 2H, NH_2), 3.28 (m, 1H), 5.62 (s, 4H, CH_2N), 6.53 (s, 2H, CH=CH), 7.38 (m, 6H, Ph), 7.48 (d, 4H, Ph). Anal. Calcd for $C_{23}H_{28}I_2N_3Pt$: C, 34.73; H, 3.55; N, 5.28. Found: C, 34.76; H, 3.44; N, 5.26.

***trans*-Diiodo(4-(trifluoromethyl)benzylamine)(1,3-dimethylimidazol-2-ylidene)platinum (3e).** Complex **3e** was obtained in 67% yield (201 mg) from (1,3-dimethylimidazol-2-ylidene)Pt^0-(dvtms), **2e** (200 mg, 0.42 mmol), I_2 (106 mg, 0.42 mmol), and 4-(trifluoromethyl)benzylamine (60 μL, 0.42 mmol). The final product was purified by chromatography with a cyclohexane/toluene 95:5 to 90:10 mixture as the eluent and recrystallized from 2 mL of isopropyl ether. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.9 (m, 2 H), 3.85 (s, 6 H, NMe), 4.23 (m, 2 H, NCH_2), 6.81 (s, 2 H, CH=CH), 7.53 (d, J = 8.1 Hz, 2 H, Ph), 7.66 (d, J = 8.1 Hz, 2 H, Ph).

***trans*-Diiodo(*N*-cyclohexylamine)(1-(4-trifluoromethylbenzyl)-3-methylimidazol-2-ylidene)platinum (3f).** **3f** was obtained in 14% yield (40 mg) from (1-(4-trifluoromethylbenzyl)-3-methylimidazol-2-ylidene)Pt^0(dvtms) complex (**2f**), I_2 (0.09 g, 0.39 mmol) and cyclohexylamine (42.4 μL, 0.39 mmol). The final product was purified by chromatography with a cyclohexane/ethyl acetate 85:15 mixture as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, 1H), 1.26 (q, 2H), 1.38 (q, 2H), 1.78 (d, 1H), 1.82 (d, 2H), 2.32 (d, 2H), 2.98 (d, 2H), 3.30 (m, 1H), 3.98 (s, 3H, NMe), 5.73 (s, 2H, NCH_2), 6.65 (d, 1H, CH=CH), 6.88 (d, 1H, CH=CH), 7.62 (d, 2H, Ph), 7.69 (d, 2H, Ph).

***trans*-Diiodo(*N*-*exo*-2-norbornylamine)(1,3-dimethylimidazol-2-ylidene)platinum (3g).** Complex **3g** was obtained in 44% yield (188 mg) from (1,3-dimethylimidazol-2-ylidene)Pt^0(dvtms), **2e** (310 mg, 0.65 mmol), I_2 (167 mg, 0.65 mmol), and *exo*-norbornylamine (72 μL, 0.65 mmol). The final product was purified by chromatography with a cyclohexane/toluene 85:15 mixture as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (m, 1 H), 1.25 (m, 2 H), 1.42−1.60 (m, 3 H), 1.73 (m, 1 H), 1.78 (m, 1 H), 2.33 (t, J = 4.6 Hz, 1 H), 2.44 (d, J = 4.6 Hz, 1 H), 2.88 (m, 2 H), 3.44 (m, 1H) 3.85 (s, 6 H, NMe) 6.79 (s, 2 H, CH=CH).

***trans*-Diiodo(*N*-*exo*-2-norbornylamine)(1,3-dimethylbenzoimidazol-2-ylidene)platinum (3h).** Complex **3h** was obtained in 49% yield (207 mg) from (1,3-dimethylbenzoimidazol-2-ylidene)Pt^0-(dvtms), **2g** (316 mg, 0.60 mmol), I_2 (67 mg, 0.60 mmol), and exonorbornylamine (152 μL, 0.60 mmol). The final product was purified by chromatography with a cyclohexane/toluene 90:10 mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (m, 1 H), 1.27 (m, 2 H), 1.42−1.64 (m, 3 H), 1.76 (m, 1 H), 1.85 (m, 1 H), 2.37 (t, J = 4.6 Hz, 1 H), 2.48 (d, J = 4.6 Hz, 1 H), 2.91−3.13 (br, 2 H), 3.51 (m, 1 H), 4.08 (s, 6 H, NMe), 7.23−7.29 (m, 2 H), 7.30−7.37 (m, 2 H).

***trans*-Diiodo(*N*-cyclohexylamine)(4,5-diphenyl-1,3-dimethylimidazol-2-ylidene)platinum (3i).** Complex **3i** was obtained in 32% yield (76 mg) from (4,5-diphenyl-1,3-dimethylimidazol-2-ylidene)Pt^0(dvtms), **2h** (190 mg, 0.30 mmol), I_2 (77 mg, 0.30 mmol), and cyclohexylamine (35 μL, 0.30 mmol). The final product was purified by chromatography with a cyclohexane/toluene 95:5 to 90:10 mixture and recrystallized from 2 mL of isopropyl ether. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, 1H), 1.30 (q, 2H), 1.40 (q, 2H), 1.70 (d, 1H), 1.85 (d, 2H), 2.38 (d, 2H), 2.98 (m, 2H), 3.35 (m, 1H), 3.35 (s, 6H, NMe), 7.22 (m, 4H, Ph), 7.38 (m, 6H, Ph). Anal. Calcd for $C_{23}H_{28}I_2N_3Pt$: C, 34.73; H, 3.55; I, 31.91; N, 5.28. Found: C, 34.79; H, 3.54; I, 31.98; N, 5.30.

***trans*-Diiodo(*N*-cyclohexylamine)(1-phenyl-4-methyl-1,2,4-triazol-5-ylidene)platinum (3j). 3j** was obtained in 22% yield (20 mg) from (1-phenyl-4-methyl-1,2,4-triazol-5-ylidene)Pt^0(dvtms) complex (**2i**) (70 mg, 0.13 mmol), I_2 (40 mg, 0.14 mmol), and cyclohexylamine (22 μL, 0.19 mmol). The final product was purified by chromatography with heptane/ethyl acetate 85:15 mixture. Yield: 22% (20 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.0−1.3 (5H, CH_2), 1.62 (m, 1H, CH_2), 1.74 (m, 2H, CH_2), 2.19 (m, 2H, CH_2), 2.97 (br, 2H, NH_2), 3.17 (m, 1H, NCH), 3.99 (s, 6H, NMe), 7.3−7.5 (3H, Ph), 8.03 (s, 1H, NCHN), 8.19 (m, 2H, Ph). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 24.76 (CH_2), 25.21 (CH_2), 35.68 (NMe), 55.16 (NCH), 125.29 (CH), 128.46 (CH), 128.75 (CH Ph), 143.19 (NCHN). HRMS (^{195}Pt) calcd for $C_{15}H_{22}I_2N_4Pt\cdot$Na: 729.9479. Found: 729.9509.

***trans*-Diiodo(ammonia)(1-benzyl-3-methylimidazol-2-ylidene)-platinum (3k). 3k** was obtained in 33% yield (360 mg) from (1-benzyl-3-methylimidazol-2-ylidene)Pt^0(dvtms), **2b** (830 mg, 1.5 mmol), I_2 (380 mg, 1.5 mmol), and ammonia (141 μL, 2.25 mmol). The final product was purified by chromatography with an heptane/ethyl acetate 7:3 mixture as the eluent and recrystallization from a chloroform/heptane mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (br, 3H, NH_3), 3.90 (s, 3H, NMe), 5.61 (s, 2H, CH_2N), 6.58 (d, 1H, ^3J = 2 Hz, CH), 6.79 (d, 1H, ^3J = 2 Hz, CH), 7.3−7.5 (m, 5H, Ph). Anal. Calcd for $C_{11}H_{15}I_2N_3Pt$: C, 20.70; H, 2.37; N, 6.58. Found: C, 20.71; H, 2.35; N, 6.31.

***trans*-Diiodo(*N*-morpholine)[1-(4-trifluoromethylbenzyl)-3-methylimidazol-2-ylidene]platinum (3l). 3l** was obtained in 42% yield (260 mg) from (1-(4-trifluoromethylbenzyl)-3-methylimidazol-2-ylidene)Pt^0(dvtms), **2f** (500 mg, 0.80 mmol), I_2 (214 mg, 0.84 mmol), and morpholine (77 μL, 0.88 mmol) in THF. The final product was purified by chromatography with a heptane/ethyl acetate 85:15 mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.96 (d, J = 12.5 Hz, 2 H), 3.21−3.52 (m, 1 H), 3.51−3.74 (m, 4 H), 3.87 (d, J = 9.6 Hz, 2 H), 3.94 (s, 3 H, NMe), 5.71 (s, 2 H), 6.64 (s, 1 H, CH=CH), 6.89 (s, 1 H, CH=CH), 7.55−7.64 (m, 2 H, Ar), 7.65−7.74 (m, 2 H, Ar)

***trans*-Diiodo(pyridine)(1,3-dimethylimidazol-2-ylidene)platinum (3m). 3m** was obtained in 84% yield (400 mg) from (1,3-dimethylimidazol-2-ylidene)Pt^0(dvtms), **2e** (300 mg, 0.68 mmol), I_2 (170 mg, 0.68 mmol), and pyridine (55 μL, 0.68 mmol). The final product was purified by chromatography with a heptane/ethyl acetate 7:3 mixture as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 6H, NMe), 6.83 (s, 2H,CH=CH), 7.33 (m, 2H, CH), 7.73 (m, 1H, CH), 9.04 (m, 2H, CH). ^{13}C NMR (75.48 MHz, $CDCl_3$, 20 °C): δ [ppm] = 38.2 (NMe), 121.8 (CH), 124.9 (CH), 137.4 (CH), 153.7 (CH). Anal. Calcd for $C_{10}H_{13}I_2N_3Pt$: C, 12.53; H, 2.10; N, 7.31. Found: C, 12.67; H, 2.11; N, 7.11. Crystals suitable for X-ray diffraction studies were obtained from a $CHCl_3$ solution.

***trans*-Diiodo(*N*-cyclohexylamine)(1,3,7,9-tetramethylxanthin-8-ylidene)platinum (3n).** (a) The NHC silver complex **5** (4.1 g, 6.8 mmol) in DMF (240 mL) was reacted with a xylene solution of the Karstedt's catalyst (136 mL, ~2% Pt, 13.6 mmol of "Pt") at room temperature for 16 h. After evaporation of the solvents, the residue was filtered on Clarcel and then separated by column chromatography with heptane/ethyl acetate 7:3 to 1:1 gradient. The (1,3,7,9-tetramethylxanthin-8-ylidene)Pt^0(dvtms) complex **2n** was obtained in 52% yield (4.2 g).

(b) A solution of I_2 (0.60 g, 2.4 mmol) in toluene (170 mL) was added at 0 °C to a solution of **2n** (1.3 g, 2.2 mmol) in toluene

(90 mL). Cyclohexylamine (0.27 mL, 2.4 mmol) was then added at 0 °C to the resulting mixture. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the final product was purified by chromatography with a heptane/ethyl acetate 7:3 mixture. Yield: 39% (0.70 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.1−1.4 (5H, CH_2), 1.65 (m, 1H, CH_2), 1.79 (m, 2H, CH_2), 2.27 (m, 2H, CH2), 3.0 (br, 2H, NH_2), 3.26 (m, 1H, CH), 3.38 (s, 3H, NMe), 3.78 (s, 3H, NMe), 4.21 (s, 3H, NMe), 4.32 (s, 3H, NMe). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 24.79 (CH_2), 25.22 (CH_2), 28.52 (NMe), 32.00 (NMe), 35.85 (CH_2), 37.09 (NMe), 38.73 (NMe), 55.09 (CH), 109.87 (C), 139.33 (C), 150.04 (CO), 150.52 (CO), 152.87 (C). HRMS (^{195}Pt) calcd for $C_{15}H_{25}I_2N_5O_2Pt\cdot Na$: 778.9643. Found: 778.9643. Crystals suitable for X-ray diffraction studies were obtained from a $CHCl_3$ solution.

***trans*-Diiodo(cyclohexylamine)(1-methyl-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)imidazol-2-ylidene)platinum (3o).** (a) Ag_2O (54 mg, 0.23 mmol) was added to a solution of imidazolium **6** (50 mg, 0.09 mmol) in acetone (1 mL), and the mixture was stirred at room temperature for 2 h. The insoluble solids were removed by filtration through Celite.[18] The crude mixture was added to a xylene solution of the Karstedt catalyst (∼1 M, 0.9 mL, 0.09 mmol of Pt). After the mixture was stirred for 16 h at room temperature and after evaporation of the solvents, chromatography with heptane/ethyl acetate 7:3 as the eluent afforded complex **2o** (52 mg, 72% yield). (b) A solution of I_2 (40 mg, 0.17 mmol) in toluene (14 mL) was added at 0 °C to **2o** (0.12 g, 0.15 mmol) in 7 mL of toluene. Cyclohexylamine (14 μL, 0.23 mmol) was then added at 0 °C, and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the final product was purified by chromatography with a gradient mixture of heptane/ethyl acetate (from7:3 to 6:4). Yield: 31% (40 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0−1.5 (5H), 1.64 (m, 1H), 1.81 (m, 2H), 2.03 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.3 (br, 2H), 3.0 (br, 2H), 3.28 (m, 1H), 3.86 (s, 3H, NMe), 4.00 (m, 1H), 4.16 (m, 1H), 4.28 (dd, J = 12.6 Hz, J = 4.8 Hz, 1H), 5.19 (m, 1H), 5.46 (m, 2H), 6.70 (m, 1H), 6.84 (d, J = 2.4 Hz, 1H, CH=CH), 7.06 (d, J = 2.4 Hz, 1H, CH=CH). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 20.54 (Me), 20.58 (Me), 20.99 (Me),21.49 (Me), 24.78 (CH2), 25.25 (CH_2), 35.82 (CH_2), 35.93 (CH_2), 38.46 (Me), 54.95 (CH),61.68 (CH_2), 68.11 (CH), 69.25 (CH), 73.50 (CH), 74.51 (CH), 85.28 (CH), 117.95 (CH),123.07 (CH), 169.57 (C), 169.89 (C), 170.71 (C). HRMS (^{195}Pt) calcd for $C_{24}H_{37}I_2N_3O_9Pt\cdot Na$: 983.0165. Found: 983.0165.

***trans*-Dibromo(*N*-cyclohexylamine)[1-(4-trifluoromethylbenzyl)-3-methylimidazol-2-ylidene]platinum 7.** Complex **7** was obtained from **2f** (300 mg, 0.48 mmol) in THF (5 mL) by successive additions of Br_2 (25 μL, 0.48 mmol) in THF (2 mL) and cyclohexylamine (55 μL, 0.48 mmol), according to the general procedure (see synthesis of **3a**). Complex **7** was purified by chromatography with a heptane/ethyl acetate gradient (from 9:1 to 7:3): pale yellow solid, 6% yield (20 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10−1.48 (m, 5H), 1.63−1.73 (m, 1H), 1.75−1.87 (m, 2H), 2.34 (d, J = 13.8 Hz, 2H), 2.78−3.06 (m, 2H), 3.12−3.31 (m, 1H), 4.10 (s, 3H, NMe), 5.85 (s, 2H, NCH_2), 6.69 (s, 1H, CH=CH), 6.89 (s, 1H, CH=CH), 7.57−7.64 (m, 2H, Ar), 7.64−7.71 (m, 2H, Ar).

***trans*-Dinitrato(*N*-cyclohexylamine)[1-(4-trifluoromethylbenzyl)-3-methylimidazol-2-ylidene]platinum (8).** Silver nitrate (36 mg, 0,21 mmol) was added to a CH_2Cl_2 solution (20 mL) of complex **3f** (80 mg, 0,10 mmol), and the mixture was stirred overnight at room temperature. After filtration and evaporation of the solvent, the residue was crystallized from a heptane/ethyl acetate 1:1 mixture to give the dinitrato complex **8** as a colorless solid (9 mg, 13% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14−1.26 (m, 1H) 1.27−1.48 (m, 4 H), 1.67−1.77 (m, 1 H), 1.81−1.90 (m, 2H), 2.30−2.41 (m, 2H), 2.87 (br s, 1H), 3.32−3.44 (m, 2H), 4.21 (s, 3H, NMe), 5.88 (s, 2H, NCH_2), 6.74 (d, J = 2.0 Hz, 1H, CH=CH), 6.94 (d, J = 2.0 Hz, 1H, CH=CH), 7.46 (d, J = 8.1 Hz, 2H, Ar) 7.70 (d, J = 8.1 Hz, 2H, Ar).

Technical Details of the X-ray Structure Determinations. Crystals of **3a** and **3n** obtained from $CHCl_3$ were glued on top of a thin silica rod, and X-ray data were collected on an Enraf-Nonius κCCD diffractometer at room temperature using graphite monochromatized Mo Kα radiation (λ = 0.7107 Å). A crystal of **3a** (**3n**) was positioned at 50 (45) mm from the CCD, and the Bragg peaks were measured using a φ and ω scan strategy optimized by the COLLECT suite[23] once the cell parameters were derived by DENZO (HKL2000 suite)[24] from a preliminary 10° φ-scan. The counting time employed was 20 s (12 s for compound **3n**) per degree of oscillation. Data reduction including a multiscan absorption correction was carried out using SCALEPACK (HKL2000).[24] The structures were solved by the Patterson method (DIRDIF-99)[25] and by subsequent difference Fourier syntheses and refined by full matrix least-squares on F^2 using the SHELX-97 suite.[26] Anisotropic thermal parameters were used for all non-hydrogen atoms, whereas hydrogen atoms, located from difference Fourier maps, were refined as a riding model with $U_{iso} = 1.2U_{eq}$ of the parent atom (1.5 for the methyl hydrogen atoms). The asymmetric unit of **3a** contains two molecules of interest, each of them bearing two cyclohexane groups disordered over two independent positions basically, with refined occupancies of 0.677(13), 0.603(18) (**3a**), 0.69(7), and 0.90(2)(**3n**). Soft restraints to geometric and anisotropic parameters were applied in order to maintain a homogeneous and reasonable behavior for the atoms of cyclohexane groups. The asymmetric unit of **3n** contains one molecule of interest and one chloroform solvent molecule.

X-ray crystal structure analysis of 3a: formula $C_{17}H_{31}I_2N_3Pt$, M_w = 726.34, colorless crystal 0.49 mm × 0.18 mm × 0.15 mm, a = 16.885(2) Å, b = 17.373(2) Å, c = 31.576(5) Å, V = 9263(2) Å^3, D_{calc} = 2.083 Mg·m^{-3}, μ = 2.529 mm^{-1}, Z = 8, orthorhombic, space group *Pbca* (No. 61), λ = 0.7107 Å, T = 292 K, φ and ω scans, 64 545 reflections collected, 7331 independent (R_{int} = 0.0293), 631 refined parameters, R1/wR2 ($I \geq 2\sigma(I)$) = 0.0340/0.0812 and R1/wR2 (all data) = 0.0608/0.0913, maximum (minimum) residual electron density 0.719(−0.971) e·Å^{-3}.

X-ray crystal structure analysis of 3n: formula $C_{15}H_{25}I_2N_5O_2Pt$, $CHCl_3$, M_w = 875.65, yellow crystal 0.40 mm × 0.35 mm × 0.18 mm, a = 14.954(3) Å, b = 10.099(2) Å, c = 17.229(3) Å, β = 94.74(5)°, V = 9263(2) Å^3, D_{calc} = 2.243 Mg·m^{-3}, μ = 8.123 mm^{-1}, Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 0.7107 Å, T = 292 K, φ and ω scans, 26 629 reflections collected, 6195 independent (R_{int} = 0.0571), 266 refined parameters, R1/wR2 ($I \geq 2\sigma(I)$) = 0.0635/0.1784 and R1/wR2 (all data) = 0.0958/0.1992, maximum (minimum) residual electron density 2.667(−2.790) e·Å^{-3}.

Cell Culture. Cells were cultured in a 175 cm^2 tissue culture flask (Falcon Becton Dickinson, Lincoln Park, NJ) in RPMI 1640 (Gibco Laboratories, Grand Island, NY), supplemented with 10% fetal calf serum (FCS) (Gibco Laboratories), 2 mM glutamine (Gibco Laboratories), 1000 IU/mL penicillin, and 100 μg/mL streptomycin (Gibco Laboratories).

Cell Growth Inhibition (CGI) Assay. Exponentially growing cells were cultured in 96-well flat-bottomed plates (Falcon) in quadruplicate at a concentration of 2 × 10^4 cells/well in the complete medium. Cells were cultured for 24 h before compounds were added. The incubation was carried on for 48 h, then pulsed with 1 μCi/well [^{3}H]thymidine ([^{3}H]TdR (Amersham, Les Ullis, France) for 24 h. H460, A2780/DDP, CH1/DDP, SKOV3 cells were then trypsinized and harvested on glass fiber papers, using a Skatron harvester system (Pharmacia-LKB, Piscataway, NJ). Nonadherent CEM cells were harvested without trypsinization. Radioactivity was measured by using a β plate liquid scintillation spectrometer (Pharmacia-LKB).

Results of the CGI assay, performed in triplicate or quadruplicate, were given as IC_{50} defined as the concentration needed to inhibit 50% of cell proliferation. Mean counts per minute were expressed as a percentage of inhibition, referring to the

vehicle-treated cells, allowing the graphic determination of the IC_{50} values.

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Supporting Information Available: NMR data for representative compounds **3** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 753541 (compound **3a**) and 753542 (compound **3n**) contain the supplementary crystallographic data for this paper, which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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