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# Novel Cis- and Trans-Configured Bis(oxime)platinum(II) Complexes: Synthesis, Characterization, and Cytotoxic Activity

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Novel cis- and trans-configured bis(oxime)platinum(II) complexes have been synthesized and characterized by elemental analyses, IR, electrospray ionization mass spectrometry, multinuclear ($^{1}$H, $^{13}$C, and $^{195}$Pt) NMR spectroscopy, and, in five cases, by X-ray diffraction. Their cytotoxicity was studied in the cisplatin-sensitive CH1 cell line as well as in inherently cisplatin-resistant SW480 cancer cells. Remarkably, every single dihalidobis(oxime)platinum(II) complex (with either a cis or trans configuration) shows a comparable cytotoxic potency in both cell lines, indicating a capacity of overcoming cisplatin resistance. Particularly strong cytotoxicities were observed in the case of *trans*-$[PtCl_2(R_2C{=}NOH)_2]$ (R = Me, *n*-Pr, *i*-Pr) with $IC_{50}$ values in the high nanomolar concentration range in both CH1 and SW480 cancer cells. These complexes are as potent as cisplatin in CH1 cells and up to 20 times more potent than cisplatin in SW480 cells. In comparison to transplatin, the novel compounds are up to 90 (CH1) and 120 times (SW480) more cytotoxic. The previously reported observation that the trans geometry yields a more active complex in the case of $[PtCl_2(Me_2C{=}NOH)_2]$ could be confirmed for at least two structural analogues.

## Introduction

Over 40 years have passed since the serendipitous discovery of the biological activity of cisplatin,[1] which has become one of the most used anticancer drugs today. Since then, great efforts have been concentrated on the development of novel platinum drugs possessing therapeutic properties comparable to those of cisplatin but showing reduced side effects along with a broader spectrum of activity.[2−4] The search for ever new drug candidates among the complexes complying with the classical structure−activity relationships[5,6] led to the achievements of carboplatin and oxaliplatin but then seemed to become gradually exhausted. Therefore, nowadays more investigators turn their attention toward nonclassic structures[7−11] that may help to overcome the drawbacks of platinum-based chemotherapy. Moreover, the development of platinum compounds being structurally different from cisplatin and forming different types of Pt-DNA adducts may lead to a drug with a spectrum of clinical activity different from those of classic platinum drugs.

For decades, trans-configured platinum complexes attracted little interest because of the classic structure−activity relationships according to Cleare and Hoeschele,[5,6] based on cisplatin/transplatin and their analogues. The presence of two monodentate or one bidentate exchangeable ligand(s) (leaving groups) coordinated in cis geometry was declared a requirement for antitumor activity. The significantly lower cytotoxicity of transplatin compared to that of cisplatin in vitro as well as its inactivity in vivo has been ascribed to its disfavored chelation reactions with DNA due to the trans-standing leaving groups. Consequently, the formation of 1,2-intrastrand cross-links, the predominant DNA adducts formed by cisplatin and believed to account for its cytotoxic activity, is greatly hindered.[12] It was shown that transplatin-DNA adducts are more rapidly repaired and cannot be

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recognized by the high-mobility group proteins HMG1, recognizing specifically 1,2-intrastrand cross-links and shielding them from repair. Moreover, the higher reactivity of transplatin compared to that of cisplatin may favor its deactivation, resulting in the lack of anticancer activity.

In the past few years, some exceptions from the classic rules have been reported. Several classes of trans complexes exhibiting higher cytotoxicity than or at least equal to that of the corresponding cis isomer are (i) platinum(II)[13−16]/platinum(IV)[17] complexes with pyridine-like ligands, (ii) platinum(II) complexes with iminoether ligands,[18−21] (iii) platinum(II) complexes with nonplanar heterocyclic ligands, such as piperidine or piperazine,[22−25] (iv) platinum(II)[26−28]/platinum(IV)[29,30] complexes with aliphatic amines, (v) platinum(II) carboxylato complexes with planar amines,[31,32] azole and isopropylamine,[33] azole and ammine ligands,[34] (vi) platinum(II) complexes containing various phosphoric groups,[35,36] and (vii) platinum(II) complexes with acetimine ligands.[37] Interestingly, most of the listed complexes are similarly or even more cytotoxic than cisplatin and all of them proved to be non-cross-resistant to cisplatin in cellular models of acquired cisplatin resistance. Furthermore, for the first four of the above-mentioned classes, the antitumor activity was confirmed in an in vivo model. Moreover, some of the complexes even displayed a lack of cross-resistance to cisplatin in vivo.[20,29]

Very recently, a new intriguing class of trans-configured platinum compounds exhibiting antitumor activity was reported. Almost simultaneously two independent groups of researcher published the fascinating results of in vitro biological investigations for two acetoxime-containing platinum(II) complexes, namely, *trans*-[$PtCl_2(Me_2C{=}NOH)(NH_2$-$CH(CH_3)_2)$][38] as well as *trans*-[$PtCl_2(Me_2C{=}NOH)_2$].[39] According to these investigations, the former complex, but not its cis isomer, causes cell death by apoptosis, even though the overall cytotoxicity was found to be higher for the cis-configured complex. Differently, *trans*-[$PtCl_2(Me_2C{=}NOH)_2$] was found to be 16 times more cytotoxic than its cis isomer and as cytotoxic as cisplatin in cisplatin-sensitive ovarian carcinoma cells (CH1). Moreover, it appeared to be 15 times more cytotoxic than both cisplatin and its cis isomer in intrinsically cisplatin-resistant colon carcinoma cells (SW480).

In this context, it is worthwhile mentioning that oximes are attractive ligands in view of their potential to act as donors or acceptors for hydrogen bonds or even serve as weak acids ($pK_a$ 3−8),[40] which could play an important role in the binding of platinum compounds to DNA.[41] In addition, the biological relevance of oximes appreciably favors their use as ligands for potential metal-based drugs, which may yield increased cytotoxicity by virtue of synergistic effects between the platinum center and the coordinated oxime. For instance, it was reported that oxime complexes and other species bearing the oxime functional group caused biological effects such as endothelium-independent relaxation in blood vessels,[42] an increase in the targeting of specific nuclear bases of DNA,[43] and oxidative DNA cleavage.[44]

On the basis of the promising results obtained with *trans*-[$PtCl_2(Me_2C{=}NOH)_2$] and with the aim to establish structure−activity relationships, we report on a series of novel dihalidobis(oxime)platinum(II) complexes, i.e., *trans*-[$PtX_2(R_2C{=}NOH)_2$] (X = Cl, Br, I; R = Me, Et, *n*-Pr, *i*-Pr), of which at least two exhibit higher cytotoxicity than the corresponding cis species in both CH1 and SW480 cells. Moreover, the corresponding cis/trans couples of

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$[Pt(NH_3)_2(R_2C{=}NOH)_2](NO_3)_2$ (R = Me, Et, *n*-Pr) were synthesized and investigated. In accordance with the classic structure−activity relationships, stating that platinum complexes with four nitrogen donor ligands are devoid of cytotoxicity, the $IC_{50}$ values of the diamminebis(oxime) series were proven to be very high.

## Experimental Section

Solvents were obtained from commercial sources and used as received. Acetone oxime was purchased from Fluka, while 3-pentanone, 4-heptanone, and 2,4-dimethyl-3-pentanone for the synthesis of the corresponding oximes were obtained from Aldrich. The complexes *cis*- and *trans*-$[PtBr_2(Me_2C{=}NOH)]$,[53] *cis*-$[PtI_2(NH_3)_2]$[54], and *trans*-$[PtCl_2(NH_3)_2]$[55] were prepared according to the published methods. For thin-layer chromatography (TLC), Merck UV 254 $SiO_2$ plates were used. Fluka silica gel 60 (220−440 mesh) was used for column chromatography. C, H, and N elemental analyses were carried out by the Microanalytical Laboratory of the University of Vienna and are within ±0.4% of the calculated values, confirming their ≥95% purity. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. Electrospray ionization mass spectrometry (ESI-MS) spectra were obtained with a Bruker Esquire 3000 instrument. Mid-infrared (MIR; 4000−400 $cm^{-1}$) spectra were recorded with a Perkin-Elmer Fourier transform infrared (FTIR) instrument in KBr pellets. $^1H$, $^{13}C$, and $^{195}Pt$ NMR spectra were measured with a Bruker Avance III 500 MHz NMR spectrometer at 500.32 ($^1H$), 125.81 ($^{13}C$), and 107.55 MHz ($^{195}Pt$), correspondingly, at 298 K. $^{195}Pt$ chemical shifts are given relative to external $K_2[PtCl_4]$, and the half-height line width is given in parentheses.

**Synthesis of Ligands.** 3-Pentanone oxime, 4-heptanone oxime, and 2,4-dimethyl-3-pentanone oxime were synthesized by known procedures[45−47] with some modifications: the corresponding ketones were treated with hydroxylamine hydrochloride in a $MeOH/H_2O$ mixture (1:1), while $K_2CO_3$ was used for neutralization. The reaction mixture was stirred at 65−70 °C for 24 h, and then the solvent was removed and the product purified by column chromatography (1:4 ethyl acetate/hexane, first fraction). The yields were 87−92%.

**Synthesis of Complexes. (*SP*-4−2)-Bis(acetone oxime-κ*N*)dibromidoplatinum(II) (2c).** The complex was prepared according to the published method from $K_2[PtCl_4]$ (191 mg, 0.46 mmol), an excess of KBr (274 mg, 2.30 mmol), and 2 equiv of acetoxime (67 mg, 0.92 mmol) in water.[53] Yield: 138 mg (60%). Anal. ($C_6H_{14}N_2Br_2O_2Pt$) C, H, N. IR in KBr (selected bands): *ν* 1656 m ($\nu_{C=N}$) $cm^{-1}$. $^1H$ NMR in $D_2O$: *δ* 2.69 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$) ppm. ESI-$MS^+$ in MeOH: *m*/*z* 524 $[M + Na]^+$, 560 $[M + HCl + Na]^+$.

**(*SP*-4−1)-Bis(acetone oxime-κ*N*)dibromidoplatinum(II) (2t).** The synthesis was performed by thermal isomerization of the corresponding cis complex.[53] **2c** (175 mg, 0.35 mmol) was kept at 140 °C for 6 h; the resulting gray powder was suspended in 2 mL of acetone and filtered through a small amount of $SiO_2$, which was washed three times with 2 mL of acetone. Then the solvent was partially evaporated under reduced pressure, and bright yellow crystals of the product were formed. The crystals were collected, washed with 0.5 mL of acetone, and dried in vacuo. Yield: 35 mg (20%). Anal. ($C_6H_{14}N_2Br_2O_2Pt$) C, H, N. IR in KBr (selected bands): *ν* 1664 m ($\nu_{C=N}$) $cm^{-1}$. $^1H$ NMR in acetone-$d_6$: *δ* 2.62 (s, 3H, $CH_3$), 2.19 (s, 3H, $CH_3$) ppm. ESI-$MS^+$ in MeOH: *m*/*z* 524 $[M + Na]^+$, 560 $[M + HCl + Na]^+$.

**(*SP*-4−2)-Bis(acetone oxime-κ*N*)diiodidoplatinum(II) (3c).** Potassium iodide (406 mg, 2.45 mmol) was added to a solution of $K_2[PtCl_4]$ (203 mg, 0.49 mmol) in 2 mL of $H_2O$, and the mixture was stirred at room temperature for 2 h. After the addition of acetone oxime (72 mg, 0.98 mmol), the reaction mixture was left to stand at the same temperature without stirring for 2 days, and the crystals of **3c** were filtered off, washed twice with 0.5 mL of ice-cold water, and dried in vacuo. Yield: 233 mg (80%). Anal. ($C_6H_{14}N_2I_2O_2Pt$) C, H, N. ESI-$MS^+$ in acetone: *m*/*z* 545 $[M - Me_2C{=}NOH + Na]^+$, 618 $[M + Na]^+$, 634 $[M + K]^+$. ESI-$MS^-$ in acetone: *m*/*z* 521 $[M - Me_2C{=}NOH - H]^-$, 594 $[M - H]^-$. Mp 220 °C (dec). TLC [10:1 (v/v) $CHCl_3/Me_2CO$]: $R_f$ = 0.52. IR in KBr (selected bands): *ν* 3242 s ($\nu_{OH}$), 1653 m ($\nu_{C=N}$) $cm^{-1}$. $^1H$ NMR in acetone-$d_6$: *δ* 2.65 (s, 3H, $CH_3$), 2.19 (s, 3H, $CH_3$) ppm. $^{13}C\{^1H\}$ NMR in acetone-$d_6$: *δ* 164.6 (*C*=N), 24.6 ($CH_3$), 17.9 ($CH_3$) ppm. $^{195}Pt$ NMR in acetone-$d_6$: *δ* −1729 (600 Hz) ppm. Crystals for X-ray study were obtained by slow evaporation of an aqueous solution.

**(*SP*-4−1)-Bis(acetone oxime-κ*N*)diiodidoplatinum(II) (3t).** The powder of **3c** (230 mg, 0.39 mmol) was refluxed in 5 mL of $MeNO_2$ at 95−100 °C for 3 h. A small amount of a brown precipitate was filtered off, and the yellow filtrate was reduced to 1.5 mL at 40 °C using a rotary evaporator, resulting in the precipitation of a yellow solid. The precipitate was collected by filtration, washed twice with 1 mL of $MeNO_2$, and dried in vacuo. Yield: 114 mg (50%). Anal. ($C_6H_{14}N_2I_2O_2Pt$) C, H, N. ESI-$MS^+$ in acetone: *m*/*z* 618 $[M + Na]^+$. Mp 200 °C (dec). TLC [15:1 (v/v) $CHCl_3/Me_2CO$]: $R_f$ = 0.50. IR in KBr (selected bands): *ν* 3329 s ($\nu_{OH}$), 1661 m ($\nu_{C=N}$) $cm^{-1}$. $^1H$ NMR in DMF-$d_7$: *δ* 11.88 (s, br, 1H, O$H^a$), 11.71 (s, br, 1H, O$H^b$), 2.72 (s, 3H, C$H_3{}^b$), 2.68 (s, 3H, C$H_3{}^a$), 2.39 (s, 3H, C$H_3{}^b$), 2.32 (s, 3H, C$H_3{}^a$) ppm. $^{13}C\{^1H\}$ NMR in DMF-$d_7$: *δ* 164.8 (*C*=$N^b$), 162.6 (*C*=$N^a$), 24.87 (C$H_3{}^b$), 24.86 (C$H_3{}^a$), 17.9 (C$H_3{}^b$), 17.5 (C$H_3{}^a$) ppm. $^{195}Pt$ NMR in DMF-$d_7$: *δ* −1800 (320) ppm. Crystals for X-ray study were obtained by slow evaporation of an acetone solution.

**(*SP*-4−2)-Dichloridobis(3-pentanone oxime-κ*N*)platinum(II) (4c) and (*SP*-4−1)-Dichloridobis(3-pentanone oxime-κ*N*)platinum(II) (4t).** 3-Pentanone oxime (113 mg, 1.12 mmol) was added to a solution of $K_2[PtCl_4]$ (239 mg, 0.58 mmol) in 1.5 mL of $H_2O$, and the mixture was stirred at 70 °C for 0.5 h. Then, the reaction mixture was left to stand without stirring at room temperature for 2 days, resulting in the formation of pale-yellow crystals. The precipitate was filtered off, washed twice with 1 mL of ice-cold water, and dried at room temperature in air, whereupon isomers **4c** and **4t** were separated by column chromatography [8:1 (v/v) $CHCl_3/Me_2C{=}O$] and dried in vacuo. Yields: 148 mg (55%) and 108 mg (40%), respectively.

**4c**. Anal. ($C_{10}H_{22}N_2Cl_2O_2Pt$) C, H, N. ESI-$MS^+$ in MeOH: *m*/*z* 491 $[M + Na]^+$, 507 $[M + K]^+$, 533 $[M + Et_2C{=}NOH - Cl]^+$. ESI-$MS^-$ in MeOH: *m*/*z* 330 $[M - Et_2C{=}NOH - HCl - H]^-$, 467 $[M - H]^-$. Mp 153 °C (dec). TLC [7:1 (v/v) $CHCl_3/Me_2CO$]: $R_f$ = 0.46. IR in KBr (selected bands): *ν* 3255 s ($\nu_{OH}$), 1649 m ($\nu_{C=N}$) $cm^{-1}$. $^1H$ NMR in $CDCl_3$: *δ* 9.04 (s, br, 1H, O*H*), 3.18 (q, 2H, $CH_2$, $^3J_{H,H}$ = 7.6 Hz), 3.60 (q, 2H, $CH_2$, $^3J_{H,H}$ = 7.6 Hz), 1.26 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.6 Hz), 1.09 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.6 Hz) ppm. $^{13}C\{^1H\}$ NMR in $CDCl_3$: *δ* 176.2 (*C*=N), 29.8 ($CH_2$), 23.4 ($CH_2$), 10.9 ($CH_3$), 10.3 ($CH_3$) ppm. $^{195}Pt$ NMR in $CDCl_3$: *δ* −441 (380 Hz) ppm. Crystals for X-ray study were obtained by slow evaporation of a chloroform/ethyl acetate solution.

**4t**. Anal. ($C_{10}H_{22}N_2Cl_2O_2Pt$) C, H, N. ESI-$MS^+$ in MeOH: *m*/*z* 491 $[M + Na]^+$. ESI-$MS^-$ in MeOH: *m*/*z* 330 $[M - Et_2C{=}NOH - HCl - H]^-$, 366 $[M - Et_2C{=}NOH - H]^-$. Mp: 204 °C (dec). TLC [7:1 (v/v) $CHCl_3/Me_2CO$]: $R_f$ = 0.54. IR in KBr (selected bands): $cm^{-1}$: *ν* 3254 s ($\nu_{OH}$), 1658 m ($\nu_{C=N}$). $^1H$ NMR in $CDCl_3$: *δ* 3.10 (q, 2H, $CH_2$, $^3J_{H,H}$ = 7.6 Hz), 2.58 (q, 2H, $CH_2$, $^3J_{H,H}$ = 7.6 Hz), 1.33 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.6 Hz), 1.13 (t, 3H,

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$CH_3$, $^3J_{H,H}$ = 7.6 Hz) ppm. $^{13}C\{^1H\}$ NMR in $CDCl_3$: $\delta$ 176.2 (*C*=N), 29.6 ($CH_2$), 23.5 ($CH_2$), 11.0 ($CH_3$), 10.3 ($CH_3$) ppm. $^{195}Pt$ NMR in $CDCl_3$: $\delta$ −462 (450 Hz) ppm.

**(*SP*-4−1)-Dichloridobis(4-heptanone oxime-$\kappa N$)platinum(II) (5t).** 4-Heptanone oxime (182 mg, 1.41 mmol) was added to a solution of $K_2[PtCl_4]$ (292 mg, 0.70 mmol) in 2 mL of $H_2O$, and the mixture was stirred at 85 °C for 2 h. Then, the heating was switched off, and the reaction mixture was stirred at room temperature for 2 days, resulting in the formation of a large amount of lemon-yellow precipitate. The precipitate was filtered off, washed twice with 1 mL of $H_2O$, and dried at room temperature in air, whereupon it was purified by column chromatography [10:1 (v/v) $CHCl_3$/$Me_2C$=O] and then dried in vacuo. Yield: 240 mg (65%). Anal. ($C_{14}H_{30}N_2Cl_2O_2Pt$) C, H, N. ESI-MS$^+$ in MeOH: *m*/*z* 452 [M − HCl − Cl]$^+$, 525 [M + H]$^+$, 547 [M + Na]$^+$, 584 [M + HCl + Na]$^+$. ESI-MS$^-$ in MeOH: *m*/*z* 358 [M − $Pr_2C$=NOH − HCl − H]$^-$, 394 [M − $Pr_2C$=NOH − H]$^-$. Mp: 173 °C (dec). TLC [10:1 (v/v) $CHCl_3$/$Me_2CO$]: $R_f$ = 0.48. IR in KBr (selected bands): $\nu$ 3299 s ($\nu_{OH}$), 1672 m ($\nu_{C=N}$) cm$^{-1}$. $^1H$ NMR in $CDCl_3$: $\delta$ 7.42 (s, br, 1H, O*H*), 3.04 (m, 2H, $CH_2$), 2.54 (m, 2H, $CH_2$), 1.78 (m, 2H, $CH_3CH_2$), 1.58 (m, 2H, $CH_3CH_2$), 1.12 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.3 Hz), 0.98 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.3 Hz) ppm. $^{13}C\{^1H\}$ NMR in $CDCl_3$: $\delta$ 173.8 (*C*=N), 38.4 ($CH_2$), 32.1 ($CH_2$), 20.2 ($CH_3CH_2$), 19.5 ($CH_3CH_2$), 14.3 ($CH_3$), 13.9 ($CH_3$) ppm. $^{195}Pt$ NMR in $CDCl_3$: $\delta$ −453 (350 Hz) ppm. Crystals for X-ray study were obtained by slow evaporation of a chloroform/ethyl acetate solution.

**(*SP*-4−1)-Dichloridobis(2,4-dimethyl-3-pentanone oxime-$\kappa N$)-platinum(II) (6t).** The synthesis and purification were carried out as described for **4t**, using $K_2[PtCl_4]$ (153 mg, 0.37 mmol) and 2,4-dimethyl-3-pentanone oxime (95 mg, 0.74 mmol). Yield: 104 mg (60%). Anal. ($C_{14}H_{30}N_2Cl_2O_2Pt$) C, H, N. ESI-MS$^+$ in acetone: *m*/*z* 452 [M − HCl − Cl]$^+$, 510 [M − HCl + Na]$^+$, 547 [M + $Pr_2C$=NOH − Cl]$^+$. ESI-MS$^-$ in acetone: *m*/*z* 358 [M − $Pr_2C$=NOH − HCl − H]$^-$, 394 [M − $Pr_2C$=NOH − H]$^-$, 487 [M − HCl − H]$^-$. Mp: 185 °C (dec). TLC [10:1 (v/v) $CHCl_3$/$Me_2CO$]: $R_f$ = 0.45. IR in KBr (selected bands): $\nu$ 3330 s ($\nu_{OH}$), 1662 m ($\nu_{C=N}$) cm$^{-1}$. $^1H$ NMR in $CDCl_3$: $\delta$ 4.28 (m, 2H, 2C*H*), 2.67 (m, 2H, 2C*H*), 1.28 (d, 6H, $2CH_3$, $^3J_{H,H}$ = 6.9 Hz), 1.23 (d, 6H, $2CH_3$, $^3J_{H,H}$ = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR in $CDCl_3$: $\delta$ 180.7 (*C*=N), 37.1 (*C*H), 29.7 (*C*H), 18.9 ($2CH_3$), 18.5 ($2CH_3$) ppm. $^{195}Pt$ NMR in $CDCl_3$: $\delta$ −441 (420 Hz) ppm.

**(*SP*-4−2)-Bis(acetone oxime-$\kappa N$)diammineplatinum(II) Dinitrate (7c).** *cis*-$[PtI_2(NH_3)_2]$ (72 mg, 0.15 mmol) and $AgNO_3$ (51 mg, 0.30 mmol) were suspended in 2 mL of $H_2O$, whereupon the mixture was stirred at room temperature overnight. The yellow precipitate of AgI was filtered off, and acetone oxime (22 mg, 0.30 mmol) was added. After the reaction mixture was stirred at the same temperature for 10 h, the clear colorless solution was reduced to 0.5 mL and 15 mL of acetone was added, inducing the precipitation of a white solid. The precipitate was filtered off, washed with acetone (2 × 1 mL), and dried in vacuo. Yield: 41 mg (55%). Anal. ($C_6H_{20}N_6O_8Pt\cdot H_2O$) C, H, N. ESI-MS$^+$ in $H_2O$/MeOH: *m*/*z* 357 [M − $NH_3$ − $HNO_3$ − $NO_3$]$^+$, 374 [M − $HNO_3$ − $NO_3$]$^+$, 696 [2M − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 713 [2M − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 730 [2M − $NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 747 [2M − $3HNO_3$ − $NO_3$]$^+$. Mp: 147 °C (dec). IR in KBr (selected bands): $\nu$ 3194 s ($\nu_{OH}$), 1666 m ($\nu_{C=N}$) cm$^{-1}$. $^1H$ NMR in $D_2O$: $\delta$ 2.52 (s, 3H, $CH_3$), 2.12 (s, 3H, $CH_3$) ppm. $^{13}C\{^1H\}$ NMR in $D_2O$: $\delta$ 172.5 (*C*=N), 23.8 ($CH_3$), 18.2 ($CH_3$) ppm. $^{195}Pt$ NMR in $D_2O$: $\delta$ −907 (1000 Hz) ppm.

**(*SP*-4−1)-Bis(acetone oxime-$\kappa N$)diammineplatinum(II) Dinitrate (7t).** *trans*-$[PtCl_2(NH_3)_2]$ (81 mg, 0.27 mmol) and $AgNO_3$ (92 mg, 0.54 mmol) were suspended in 2.5 mL of $H_2O$, whereupon the mixture was stirred at 60 °C overnight. The white precipitate of AgCl was filtered off, and acetone oxime (40 mg, 0.54 mmol) was added. After the reaction mixture was stirred at room temperature overnight, the clear yellowish solution was reduced to 0.5 mL and 10 mL of acetone was added, inducing the precipitation of a white solid. The precipitate was filtered off, washed with acetone (2 × 1 mL) and ether (3 mL), and dried in vacuo. Yield: 88 mg (65%). Anal. ($C_6H_{20}N_6O_8Pt$) C, H, N. ESI-MS$^+$ in $H_2O$/MeOH: *m*/*z* 267 [M − $2NH_3$ − $Me_2C$=NOH − $HNO_3$ − $NO_3$]$^+$, 340 [M − $2NH_3$ − $HNO_3$ − $NO_3$]$^+$, 357 [M − $NH_3$ − $HNO_3$ − $NO_3$]$^+$, 374 [M − $HNO_3$ − $NO_3$]$^+$, 639 [2M − $Me_2C$=NOH − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 657 [2M − $Me_2C$=NOH − $NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 696 [2M − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 713 [2M − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 747 [2M − $3HNO_3$ − $NO_3$]$^+$. Mp: 234 °C (dec). IR in KBr (selected bands): $\nu$ 3211 s ($\nu_{OH}$), 1667 m ($\nu_{C=N}$) cm$^{-1}$. $^1H$ NMR in $D_2O$: $\delta$ 4.27 (s, br, 3H, N*H*$_3$), 2.58 (s, 3H, $CH_3$), 2.19 (s, 3H, $CH_3$) ppm. $^{13}C\{^1H\}$ NMR in $D_2O$: $\delta$ 172.2 (*C*=N), 23.4 ($CH_3$), 18.0 ($CH_3$) ppm. $^{195}Pt$ NMR in $D_2O$: $\delta$ −907 (800 Hz) ppm. Crystals for X-ray study were obtained by slow evaporation of an aqueous solution.

**(*SP*-4−2)-Diamminebis(3-pentanone oxime-$\kappa N$)platinum(II) Dinitrate (8c).** *cis*-$[PtI_2(NH_3)_2]$ (109 mg, 0.23 mmol) and $AgNO_3$ (77 mg, 0.45 mmol) were suspended in 2 mL of $H_2O$, whereupon the mixture was stirred at room temperature overnight. The yellow precipitate of AgI was filtered off, and 3-pentanone oxime (50 $\mu$L, 0.45 mmol) in 2 mL of THF was added. After the reaction mixture was stirred at the same temperature for 2 days, the solvent was removed and the crude product was dried in vacuo. Then, the white solid was suspended in 10 mL of acetone, filtered off, washed with acetone (2 × 1 mL), and dried in vacuo. Yield: 53 mg (42%). Anal. ($C_{10}H_{28}N_6O_8Pt$) C, H, N. ESI-MS$^+$ in $H_2O$/MeOH: *m*/*z* 396 [M − $2NH_3$ − $HNO_3$ − $NO_3$]$^+$, 413 [M − $NH_3$ − $HNO_3$ − $NO_3$]$^+$, 430 [M − $HNO_3$ − $NO_3$]$^+$, 606 [2M − $2Et_2C$=NOH − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 690 [2M − $Et_2C$=NOH − $4NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 724 [2M − $Et_2C$=NOH − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 808 [2M − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 825 [2M − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 843 [2M − $NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 859 [2M − $3HNO_3$ − $NO_3$]$^+$. Mp: 158 °C (dec). IR in KBr (selected bands): $\nu$ 3194 s ($\nu_{OH}$), 1666 m ($\nu_{C=N}$) cm$^{-1}$. $^1H$ NMR in $D_2O$: $\delta$ 3.00 (m, 2H, $CH_2$), 2.53 (m, 2H, $CH_2$), 1.12 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.6 Hz), 0.99 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.6 Hz) ppm. $^{13}C\{^1H\}$ NMR in $D_2O$: $\delta$ 178.9 (*C*=N), 29.5 ($CH_2$), 22.9 ($CH_2$), 9.9 ($CH_3$), 9.3 ($CH_3$) ppm. $^{195}Pt$ NMR in $D_2O$: $\delta$ −897 (1050 Hz) ppm.

**(*SP*-4−1)-Diamminebis(pentanone oxime-$\kappa N$)platinum(II) Dinitrate (8t).** *trans*-$[PtCl_2(NH_3)_2]$ (105 mg, 0.35 mmol) and $AgNO_3$ (118 mg, 0.70 mmol) were suspended in 4 mL of $H_2O$, whereupon the mixture was stirred at 60 °C overnight. The white precipitate of AgCl was filtered off, and 3-pentanone oxime (77 $\mu$L, 0.70 mmol) in 2 mL of THF was added. After the reaction mixture was stirred at room temperature overnight, the solvent was removed and the yellowish solid was suspended in 10 mL of acetone; the precipitate was then filtered off, washed with acetone (2 × 1 mL) and diethyl ether (3 mL), and dried in vacuo. Yield: 54 mg (45%). Anal. ($C_{10}H_{28}N_6O_8Pt$) C, H, N. ESI-MS$^+$ in $H_2O$/MeOH: *m*/*z* 396 [M − $2NH_3$ − $HNO_3$ − $NO_3$]$^+$, 413 [M − $NH_3$ − $HNO_3$ − $NO_3$]$^+$, 430 [M − $HNO_3$ − $NO_3$]$^+$, 724 [2M − $Et_2C$=NOH − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 808 [2M − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 859 [2M −$3HNO_3$ − $NO_3$]$^+$. Mp: 213 °C (dec). IR in KBr (selected bands): $\nu$ 3270 s ($\nu_{OH}$), 1645 m ($\nu_{C=N}$) cm$^{-1}$. $^1H$ NMR in $D_2O$: $\delta$ 4.30 (s, br, 3H, N*H*$_3$), 3.02 (m, br, 2H, $CH_2$), 2.58 (m, br, 2H, $CH_2$), 1.17 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.7 Hz), 1.03 (t, 3H, $CH_3$, $^3J_{H,H}$ = 7.6 Hz) ppm. $^{13}C\{^1H\}$ NMR in $D_2O$: $\delta$ 180.2 (*C*=N), 29.3 ($CH_2$), 23.0 ($CH_2$), 10.0 ($CH_3$), 9.3 ($CH_3$) ppm. $^{195}Pt$ NMR in $D_2O$: $\delta$ −914 (1500 Hz) ppm.

**(*SP*-4−2)-Diamminebis(4-heptanone oxime-$\kappa N$)platinum(II) dinitrate (9c).** The synthesis was carried out as described for **7c**, using 203 mg (0.42 mmol) of *cis*-$[PtI_2(NH_3)_2]$, 143 mg (0.84 mmol) of $AgNO_3$, and 122 $\mu$L (0.84 mmol) of 4-heptanone oxime. Yield: 39 mg (15%). Anal. ($C_{14}H_{36}N_6O_8Pt\cdot H_2O$) C, H, N. ESI-MS$^+$ in $H_2O$/MeOH: *m*/*z* 340 [M − $NH_3$ − *n*-$Pr_2C$=NOH − $HNO_3$ − $NO_3$]$^+$, 452 [M − $2NH_3$ − $HNO_3$ − $NO_3$]$^+$, 470 [M − $NH_3$ − $HNO_3$ − $NO_3$]$^+$, 486 [M − $HNO_3$ − $NO_3$]$^+$, 774 [2M − *n*-$Pr_2C$=NOH − $4NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 791

**Table 1.** Crystal Data and Details of Data Collection for **3c**, **3t**, **4c**, **5t**, and **7t**

| | **3c** | **3t** | **4c** | **5t** | **7t** |
|---|---|---|---|---|---|
| empirical formula | $C_6H_{14}I_2N_2O_2Pt$ | $C_6H_{14}I_2N_2O_2Pt$ | $C_{10}H_{22}Cl_2N_2O_2Pt$ | $C_{14}H_{30}Cl_2N_2O_2Pt$ | $C_6H_{20}N_6O_8Pt$ |
| fw | 595.08 | 595.08 | 468.29 | 524.39 | 499.37 |
| space group | $P2_1/c$ | $P2_12_12_1$ | $P\bar{1}$ | *Pnma* | $P\bar{1}$ |
| *a*, Å | 7.9315(2) | 9.0055(4) | 9.1808(2) | 8.0268(6) | 6.3713(4) |
| *b*, Å | 17.4453(5) | 9.0841(3) | 9.4940(3) | 16.3958(13) | 7.6065(5) |
| *c*, Å | 9.6186(2) | 16.5477(5) | 9.5723(3) | 14.4299(12) | 8.4282(6) |
| $\lambda$, deg | | | 79.582(3) | | 91.570(4) |
| $\beta$, deg | 101.752(2) | | 79.141(2) | | 105.325(4) |
| $\gamma$, deg | | | 72.957(2) | | 101.662(3) |
| *V*, Å$^3$ | 1303.00(6) | 1353.72(9) | 776.38(4) | 1899.1(3) | 384.39(4) |
| *Z* | 4 | 4 | 2 | 4 | 1 |
| α, Å | 0.710 73 | 0.710 73 | 0.710 73 | 0.710 73 | 0.710 73 |
| $\rho_{calcd}$, g cm$^{-3}$ | 3.033 | 2.920 | 2.003 | 1.834 | 2.157 |
| crystal size, mm | 0.25 × 0.10 × 0.08 | 0.12 × 0.05 × 0.03 | 0.21 × 0.15 × 0.08 | 0.20 × 0.06 × 0.06 | 0.21 × 0.12 × 0.10 |
| *T*, K | 100 | 100 | 100 | 100 | 100 |
| $\mu$, cm$^{-1}$ | 154.85 | 149.05 | 93.74 | 76.75 | 91.73 |
| R1[a] | 0.0250 | 0.0144 | 0.0174 | 0.0187 | 0.0195 |
| wR2[b] | 0.0543 | 0.0309 | 0.0354 | 0.0400 | 0.0385 |
| GOF[c] | 1.034 | 0.990 | 1.010 | 0.989 | 1.000 |

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$. [c] $GOF = \{\sum[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$, where *n* is the number of reflections and *p* is the total number of parameters refined.

[2M − *n*-$Pr_2C$=NOH − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 808 [2M − *n*-$Pr_2C$=NOH − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 920 [2M − $3NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 937 [2M − $2NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 955 [2M − $NH_3$ − $3HNO_3$ − $NO_3$]$^+$, 972 [2M − $3HNO_3$ − $NO_3$]$^+$. Mp: 155 °C (dec). IR in KBr (selected bands): *ν* 3316 s ($\nu_{OH}$), 1645 m ($\nu_{C=N}$) cm$^{-1}$. $^1$H NMR in $D_2O$: $\delta$ 2.94 (t, 2H, C$H_2$, $^3J_{H,H}$ = 8.0 Hz), 2.51 (t, br, 2H, C$H_2$), 1.55 (m, br, 2H, $CH_3CH_2$), 1.45 (m, br, 2H, $CH_3CH_2$), 0.96 (t, 3H, C$H_3$, $^3J_{H,H}$ = 7.4 Hz), 0.84 (t, 3H, C$H_3$, $^3J_{H,H}$ = 7.2 Hz) ppm. $^{13}$C{$^1$H} NMR in $D_2O$: $\delta$ 177.8 (*C*=N), 38.3 (*C*$H_2$), 31.7 (*C*$H_2$), 19.5 ($CH_3$*C*$H_2$), 18.9 ($CH_3$-*C*$H_2$), 13.34 (*C*$H_3$), 13.32 (*C*$H_3$) ppm. $^{195}$Pt NMR in $D_2O$: $\delta$ −882 (1050 Hz) ppm.

**(*SP*-4−1)-Diamminebis(4-heptanone oxime-*κN*)platinum(II) Dinitrate (9t).** *trans*-[$PtCl_2(NH_3)_2$] (200 mg, 0.67 mmol) and $AgNO_3$ (227 mg, 1.34 mmol) were suspended in 5 mL of $H_2O$, whereupon the mixture was stirred at 60 °C overnight. The white precipitate of AgCl was filtered off, and 4-heptanone oxime (173 mg, 1.34 mmol) in 1 mL of THF was added. After the reaction mixture was stirred at room temperature for 3 days, the yellowish solution was filtered from a small amount of a gray precipitate. Then the solvent was removed, and the solid was suspended in 10 mL of acetone; the white precipitate was filtered off and washed with acetone (2 × 1 mL) and ether (3 mL). After that, the solid was suspended in 5 mL of EtOH, filtered off, and then washed three times with 1 mL of EtOH. The filtrates were combined, the volume was reduced to 0.5 mL, and 5 mL of $Et_2O$ was added, inducing the precipitation of a white solid. After filtration, the product was washed with 0.5 mL of $Et_2O$ and dried in vacuo. Yield: 123 mg (30%). Anal. ($C_{14}H_{36}N_6O_8Pt\cdot H_2O$) C, H, N. ESI-MS$^+$ in $H_2O$/MeOH: *m*/*z* 452 [M − $2NH_3$ − $HNO_3$ − $NO_3$]$^+$, 469 [M − $NH_3$ − $HNO_3$ − $NO_3$]$^+$, 486 [M − $HNO_3$ − $NO_3$]$^+$. Mp: 211 °C (dec). IR in KBr (selected bands): *ν* 3202 s ($\nu_{OH}$), 1657 m ($\nu_{C=N}$) cm$^{-1}$. $^1$H NMR in $D_2O$: $\delta$ 4.30 (s, br, 3H, N$H_3$), 2.96 (s, br, 2H, C$H_2$), 2.56 (t, 2H, C$H_2$, $^3J_{H,H}$ = 8.0 Hz), 1.63 (m, br, 2H, $CH_3CH_2$), 1.49 (m, br, 2H, $CH_3CH_2$), 1.00 (t, 3H, C$H_3$, $^3J_{H,H}$ = 7.3 Hz), 0.87 (t, 3H, C$H_3$, $^3J_{H,H}$ = 7.4 Hz) ppm. $^{13}$C{$^1$H} NMR in $D_2O$: $\delta$ 178.2 (*C*=N), 38.1 (*C*$H_2$), 31.8 (*C*$H_2$), 19.6 ($CH_3CH_2$), 18.9 ($CH_3CH_2$), 13.4 (*C*$H_3$), 13.2 (*C*$H_3$) ppm. $^{195}$Pt NMR in $D_2O$: $\delta$ −906, −914 (950 Hz) ppm.

**Crystallographic Structure Determination.** X-ray diffraction measurements were performed with a Bruker X8 APEX II CCD diffractometer at 100 K. Single crystals were positioned at 40, 40, 40, 40, 40, and 35 mm from the detector, and 930, 2109, 1575, 804, and 1869 frames were measured, each for 5, 30, 30, 50, and 3 s over 1° scan width for **3c**, **3t**, **4c**, **5t**, and **7t**, respectively. The data were processed using the *SAINT* software package.[48] Crystal data, data collection parameters, and structure refinement details for **3c**, **3t**, **4c**, **5t**, and **7t** are given in Table 1. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at calculated positions and refined as riding atoms in the subsequent least-squares model refinements. The isotropic thermal parameters were estimated to be 1.2 times the values of the equivalent isotropic thermal parameters of the non-hydrogen atoms to which the hydrogen atoms were bonded. *SHELXS-97*[49] was used for structure solution and *SHELXL-97*[50] for refinement, molecular diagrams were produced with ORTEP,[51] and appropriate scattering factors were used.[52]

**Cell Lines and Culture Conditions.** Human CH1 (ovarian carcinoma) and SW480 (colon carcinoma) cells were kindly provided by Lloyd R. Kelland (CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, U.K.) and Brigitte Marian (Institute of Cancer Research, Department of Medicine I, Medical University of Vienna, Austria), respectively. Cells were grown in 75 cm$^2$ culture flasks (Iwaki/Asahi Technoglass, Gyouda, Japan) as adherent monolayer cultures in a complete culture medium, i.e., a minimal essential medium (MEM) supplemented with 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, and 4 mM L-glutamine (all purchased from Sigma-Aldrich, Vienna, Austria). Cultures were maintained at 37 °C in a humidified atmosphere containing 5% $CO_2$ and 95% air.

**Cytotoxicity Tests in Cancer Cell Lines.** Cytotoxicity was determined by means of a colorimetric microculture assay [MTT

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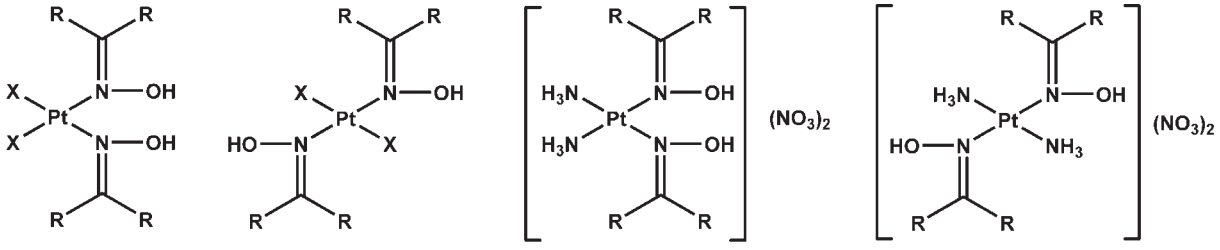

**1c** X = Cl, R = Me
**2c** X = Br, R = Me
**3c** X = I, R = Me
**4c** X = Cl, R = Et

**1t** X = Cl, R = Me
**2t** X = Br, R = Me
**3t** X = I, R = Me
**4t** X = Cl, R = Et
**5t** X = Cl, R = *n*-Pr
**6t** X = Cl, R = *i*-Pr

**7c** R = Me
**8c** R = Et
**9c** R = *n*-Pr

**7t** R = Me
**8t** R = Et
**9t** R = *n*-Pr

**Figure 1.** Platinum(II) oxime complexes under investigation.

assay, MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide]. For this purpose, CH1 and SW480 cells were harvested from culture flasks by trypsinization and seeded in 100 $\mu$L aliquots in MEM supplemented with 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, 4 mM L-glutamine, and 1% nonessential amino acids (100×) (all purchased from Sigma-Aldrich) into 96-well microculture plates (Iwaki/Asahi Technoglass, Gyouda, Japan) in cell densities of $1.5 \times 10^3$ and $2.5 \times 10^3$ cells well$^{-1}$, respectively, in order to ensure exponential growth of untreated controls throughout drug exposure. For 24 h, cells were allowed to settle and resume exponential growth, followed by the addition of dilutions of the test compounds in aliquots of 100 $\mu$L well$^{-1}$ in the same medium. Only for the less water-soluble compounds **5t** and **6t**, stock solutions had to be prepared in a dimethyl sulfoxide (DMSO)/$H_2O$ mixture (the stability of the compounds in a DMSO solution was proven by $^1$H NMR spectroscopy). The DMSO content in the actually tested dilutions did not exceed 0.5%. After continuous exposure for 96 h, drug solutions were replaced by a 130 $\mu$L well$^{-1}$ RPMI 1640 culture medium (supplemented with 10% heat-inactivated fetal bovine serum and 4 mM L-glutamine) plus 20 $\mu$L well$^{-1}$ MTT solution in phosphate-buffered saline (5 mg mL$^{-1}$). After incubation for 4 h, the medium/MTT mixtures were removed, and the formazan crystals formed by viable cells were dissolved in 150 $\mu$L of DMSO per well. Optical densities at 550 nm were measured with a microplate reader (Tecan Spectra Classic), using a reference wavelength of 690 nm to correct for unspecific absorption. The quantity of vital cells was expressed in terms of $T/C$ values by comparison to untreated control microcultures, and 50% inhibitory concentrations ($IC_{50}$) were calculated from concentration−effect curves by interpolation. Evaluation is based on means from at least three independent experiments, each comprising three replicates per concentration level.

## Results and Discussion

Recently, we reported on the intriguing biological properties of an isomeric couple *cis*/*trans*-[$PtCl_2$($Me_2C$=NOH)$_2$] (**1c**/**1t**).[39] In order to establish and learn more about their structure−activity relationships, a series of novel oximeplatinum(II) analogues were prepared: (i) cis/trans couples of [$PtX_2$($Me_2C$=NOH)$_2$], where X = Br (**2c**/**2t**)[53] or I (**3c**/**3t**), with the aim of understanding the role of the ionic leaving ligands and the configuration of the complexes for their cytotoxic properties, (ii) [$PtCl_2$($R_2C$=NOH)$_2$], where R = Et (**4c**/**4t**), *n*-Pr (**5t**), and *i*-Pr (**6t**), to elucidate the influence of increased lipophilicity and/or steric hindrance, and (iii) complexes of the type [$Pt(NH_3)_2$($R_2C$=NOH)$_2$]($NO_3$)$_2$, where R = Me (**7c**/**7t**), Et (**8c**/**8t**), and *n*-Pr (**9c**/**9t**), which were anticipated to be inactive (Figure 1).

**Synthesis and Characterization of Dihalidobis(oxime)-platinum(II) Complexes.** Synthesis of the target *cis*-diiodidoplatinum(II) complex **3c** was carried out in analogy to corresponding dibromido species **2c**.[53] The reaction between $K_2[PtI_4]$, obtained in situ by the addition of KI to an aqueous solution of $K_2[PtCl_4]$, and acetoxime proceeded in an aqueous solution at room temperature and led to precipitation of **3c**. Corresponding trans isomer **3t** was obtained via thermal isomerization of **3c** in a $MeNO_2$ solution at 95−100 °C for 3 h. The preparation of dichlorido species **4c** and **4t**−**6t** was performed by a one-step reaction of $K_2[PtCl_4]$ and 2 equiv of the corresponding oxime in an aqueous solution at 75−85 °C; a higher temperature was needed to increase the solubility of the oximes in water. The formation of a cis/trans isomeric mixture was observed exclusively in the case of the *n*-pentanone oxime complex (**4c**/**4t**), and these isomers could be separated by column chromatography. The reactions with *n*-heptanone oxime as well as with 2,4-dimethyl-3-pentanone oxime resulted, because of steric reasons, solely in isomerically pure trans compounds **5t** and **6t**, respectively. The final products were obtained as pale-yellow solids and were isolated in moderate to good yields (40−65%).

Complexes **3c**, **4c**, and **3t**−**6t** were characterized by C, H, and N elemental analyses, $^1$H, $^{13}C\{^1H\}$, and $^{195}$Pt NMR and IR spectroscopy, ESI-MS, and also X-ray crystallography (for **3c**, **3t**, **4c**, and **5t**). All compounds gave satisfactory C, H, and N elemental analyses. ESI-MS spectra displayed the fragments $[M + Na]^+$ and $[M + K]^+$ in the positive mode as well as $[M - \text{oxime} - H]^-$ and $[M - H]^-$ in the negative mode, having isotopic patterns that were in good agreement with the calculated ones. The IR spectra of **3c**, **4c**, and **3t**−**6t** showed strong-intensity $\nu_{OH}$ (3242−3330 cm$^{-1}$) and medium-intensity $\nu_{C=N}$ (1649−1672 cm$^{-1}$) stretching vibrations. Interestingly, only in the case of the trans-configured complex **3t**, displaying sterically demanding iodido ligands, two sets of $CH_3$ signals were detected in the $^1$H NMR spectrum. This circumstance is explainable by a hindered rotation of the oxime ligands around the Pt−N bonds as proven via

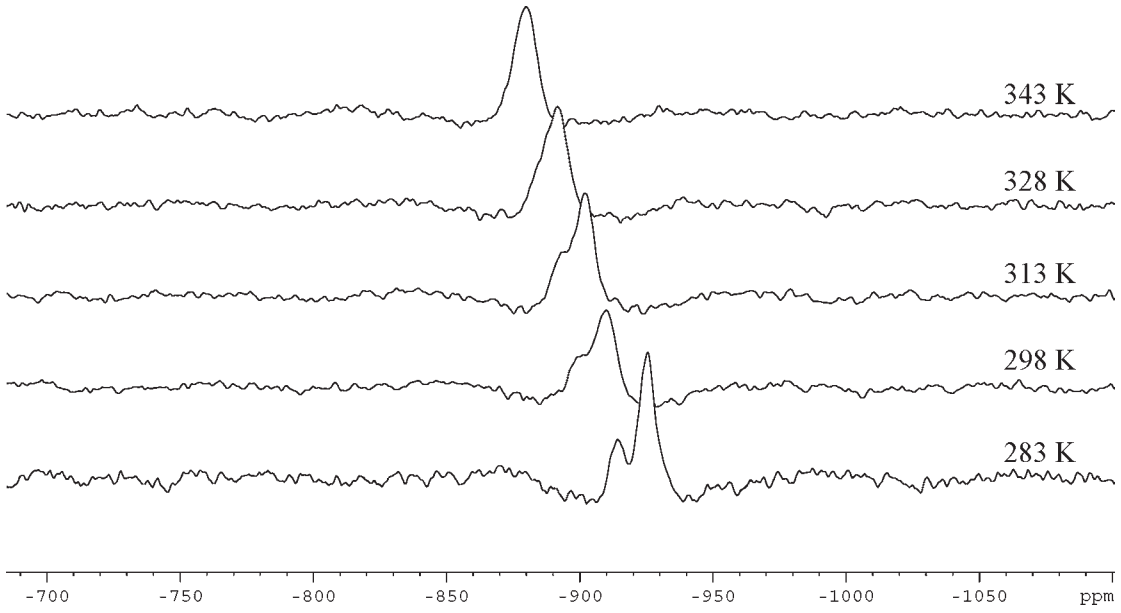


**Figure 2.** Temperature-dependent $^{195}$Pt NMR spectra of **9t** (the region between −1100 and −700 ppm is shown). At low temperatures, the rotation of the ligands is slowed down, resulting in a splitting of the platinum resonances.

the acquisition of $^1$H NMR spectra at different temperatures (278−335 K; Figure S1 in the Supporting Information).

**Synthesis and Characterization of Diamminebis(oxime)platinum(II) Dinitrate Complexes.** For the preparation of *cis*- and *trans*-$[Pt(NH_3)_2(R_2C{=}NOH)_2](NO_3)_2$ (**7c**/**7t**−**9c**/**9t**), the well-known *cis*-$[PtI_2(NH_3)_2]$[54] and *trans*-$[PtCl_2(NH_3)_2]$[55] complexes were used as starting materials. First, halide abstraction of the starting complex by using $AgNO_3$ was carried out in an aqueous solution at room temperature in the case of the cis species and at 60 °C for the corresponding trans-configured complexes. The elevated temperature in the latter case was necessary for the second chlorido ligand to be abstracted[31] after the first chloride was already exchanged by a water molecule (aqua ligands are known for their extremely weak trans effect[56]). After the formed AgX (X = Cl, I) precipitate was filtered off, 2 equiv of the corresponding oxime was added to the in situ generated *cis*/*trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ species, leading to the formation of the desired complexes (**7c**/**7t**−**9c**/**9t**). The compounds were obtained in moderate to good yields (15−65%) via either precipitation (**7c**, **7t**, and **9c**; the addition of acetone to the aqueous solution) or solvent removal and suspension in acetone (**8c**, **8t**, and **9t**).

Complexes **7c**/**7t**−**9c**/**9t** gave satisfactory elemental analyses and expected molecular ion/fragmentation patterns in the ESI-MS spectra. The presence of a broad range of peaks was recognized in the positive mode (see Experimental Section). Complexes **7c**/**7t**−**9c**/**9t** were characterized by IR spectroscopy; characteristic $\nu_{OH}$ (3194−3316 cm$^{-1}$) and $\nu_{C=N}$ (1645−1667 cm$^{-1}$) bands were observed. With respect to the $^1$H NMR spectra in $D_2O$ of the *trans*-$[Pt(NH_3)_2(R_2C{=}NOH)_2](NO_3)_2$ complexes **7t**, **8t**, and **9t**, it is worth mentioning that the proton signals become broader with the increased length of *R*. In turn, in the $^{195}$Pt NMR spectra, the platinum signal of **8t** was broader than that for **7t** (the half-height widths were 1500 and 800 Hz, respectively), turning into two signals (a broad signal with a shoulder) in the case of **9t**, which is most probably the result of a hindered rotation of the sterically demanding ligands. To clarify that fact, $^{195}$Pt (Figure 2) and $^1$H NMR (Figure S2 in the Supporting Information) spectra were measured at different temperatures for **9t**. At 283 K, two platinum signals at −914 and −926 ppm were observed; upon an increase in the temperature to 343 K, only one signal was detected, showing that the complex exists in temperature-dependent conformations.

An analogous behavior was monitored in the proton resonance spectra, measured at the same temperatures (Figure S2 in the Supporting Information). However, for the NMR spectra of the corresponding cis-configured $[Pt(NH_3)_2(R_2C{=}NOH)_2](NO_3)_2$ complexes **7c**, **8c**, and **9c**, no such features were observed.

**X-ray Crystal Structures.** The structures of *cis*-$[PtI_2(Me_2C{=}NOH)_2]$ (**3c**), *trans*-$[PtI_2(Me_2C{=}NOH)_2]$ (**3t**), *cis*-$[PtCl_2(Et_2C{=}NOH)_2]$ (**4c**), *trans*-$[PtCl_2(n\text{-}Pr_2C{=}NOH)_2]$ (**5t**), and *trans*-$[Pt(NH_3)_2(Me_2C{=}NOH)_2](NO_3)_2$ (**7t**) were determined by X-ray diffraction (Table 1 and Figures 3−5). In **3c**, **3t**, **4c**, and **5t**, the metal center is bound by two oximic nitrogen atoms and two halogenido ligands, being in the cis (**3c** and **4c**) or trans (**3t** and **5t**) positions. In **7t**, two ammonia and two oxime ligands are mutually trans. In the coordinated oximes, the C=N bond lengths [1.270(7)−1.292(7) Å] are similar within 3$\sigma$ and correspond to previously reported distances in metal-bound oximes [1.268−1.324 Å].[53,57−60] The platinum atom in the square-planar complex **3t** is slightly displaced out of the

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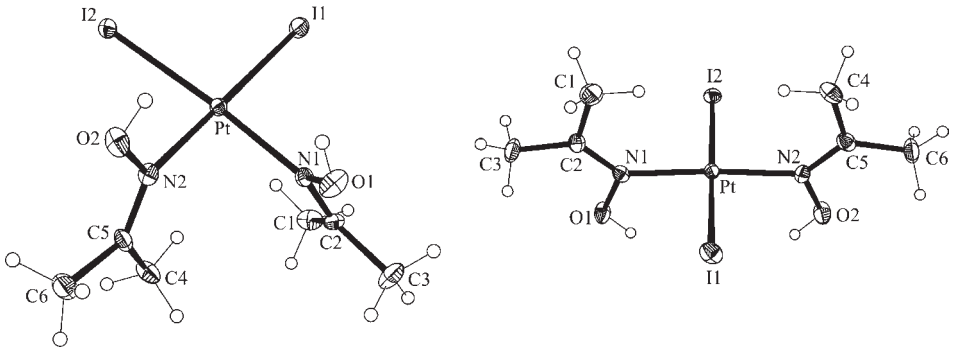


**Figure 3.** ORTEP diagram of **3c** (left) and **3t** (right) displaying thermal ellipsoids at 50% probability. Selected bond lengths (Å) and angles (deg) for **3c**: Pt−N1, 2.041(4); Pt−N2, 2.055(4); Pt−I1, 2.5819(4); Pt−I2, 2.5963(4); N1−C2, 1.292(7); N2−C5, 1.270(7); N1−Pt−N2, 89.03(17); N1−Pt−I1, 90.77(12); N1−Pt−I2, 176.08(12). Selected bond lengths (Å) and angles (deg) for **3t**: Pt−N1, 2.002(3); Pt−N2, 2.007(3); Pt−I1, 2.5938(3); Pt−I2, 2.6104(2); N1−C2, 1.285(4); N2−C5, 1.291(4); N1−Pt−N2, 174.39(11); N1−Pt−I1, 90.69(8); N1−Pt−I2, 89.63(8).

mean plane through N1−I1−N2−I2, by 0.01 Å, whereas in the case of **3c**, it lies ideally within the corresponding N1−I1−N2−I2 plane (Figure 3).

The Pt−I bond distances in complexes **3c** and **3t** were found in the range of 2.5819(4)−2.6104(2) Å. These distances agree well with those of previously published platinum(II) iodide compounds.[61−63] The Pt−N distances in the case of cis-configured **3c** at 2.041(4) and 2.055(4) Å for Pt−N1 and Pt−N2, respectively, are significantly longer than those found in **3t** [Pt−N1, 2.002(3) Å; Pt−N2, 2.007(3) Å] because of the more pronounced trans influence of the coordinated iodide.[56]

In dichloridoplatinum(II) complexes **4c** and **5t** (Figures 4 and 5), deviation of the platinum atom from the mean planes through N1−Cl1−N2−Cl2 and N1−Cl1−N1−I1−Cl2 is not larger than 0.04 Å. The Pt−Cl bond distances in **4c** and **5t** vary from 2.2821(9) to 2.3208(8) Å, which falls into the range of typical Pt−Cl distances.[64,65] The Pt−N1 bond length in **4c** at 2.0049(19) Å is in the expected range for platinum complexes with a cis configuration.[53,57] Of note is the relatively long distance Pt−N2 at 2.0249(19) Å, displaying a 7$\sigma$ difference from the Pt−N1 bond length. The N1−Pt−N2 angle at 92.08(8)° in **4c** is larger than that in **3c** [N1−Pt−N2, 89.03(17)°], depending on the coordinated halogenido ligand (chlorido versus iodido).

The Pt−N1 bond of trans-configured **5t** at 2.006(2) Å is well comparable with Pt−N distances found in **3t** and **7t** at 2.002(3) and 2.006(2) Å, respectively. In contrast, the Pt−N2 distance (coordinated ammine ligand) in **7t** at 2.045(2) Å is significantly longer.

**Cytotoxicity and Structure−Activity Relationships.** The cytotoxic potencies of the halogenido oxime complexes **2c**−**4c** and **2t**−**6t**, as well as the diamminebis(oxime) compounds **7c**/**7t**−**9c**/**9t**, were compared to those of cisplatin and transplatin in the cisplatin-sensitive ovarian carcinoma

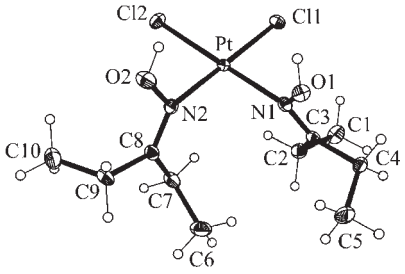


**Figure 4.** ORTEP diagram of **4c** displaying thermal ellipsoids at 50% probability. Selected bond lengths (Å) and angles (deg): Pt−N1, 2.0049(19); Pt−N2, 2.0249(19); Pt−Cl1, 2.2977(6); Pt−Cl2, 2.2957(6); N1−C3, 1.290(3); N2−C8, 1.287(3); N1−Pt−N2, 92.08(8); N1−Pt−Cl1, 88.35(6); N1−Pt−Cl2, 178.14(5).

cell line CH1 and the intrinsically cisplatin-resistant colon carcinoma cell line SW480 by means of the colorimetric MTT assay. $IC_{50}$ values are listed in Table 2. In general, both cell lines are similarly sensitive to the halogenido oxime compounds **2c**−**4c** and **2t**−**6t**, while CH1 cancer cells are considerably more sensitive to the cationic diamminebis(oxime) complexes **7c**−**9c** as well as **7t** and **9t** than SW480 cells; complex **8t** showed no antiproliferative effect at all.

Specific structural modifications of the previously reported *cis*/*trans*-[$PtCl_2(Me_2C{=}NOH)_2$] complexes **1c** and **1t**[39] were made in order to investigate the structure−activity relationships with respect to the effect of (i) the leaving group, (ii) the carbon chain length of coordinated oximes in the case of the chlorido complexes, as well as (iii) an increasing oxime carbon chain length in cationic diamminebis(oxime) complexes.

**i. Effect of the Leaving Group.** Substitution of the chlorido ligands in **1c**/**1t** for bromides, yielding **2c**/**2t**, dramatically decreases the cytotoxic potencies by factors of 9−39. These results were expected and can be explained by the lower reactivity of bromido complexes compared to chlorido analogues.[6] Still, the trans isomer **2t** is more cytotoxic than its cis analogue **2c**. However, this trend is not continued in the iodido counterparts. **3c** and **3t** proved to be more cytotoxic than, or at least similarly cytotoxic to the corresponding bromido species **2c** and **2t**, despite a higher stability [hard and soft acids and bases (HSAB) principle]. This might be caused by the higher lipophilicity of **3c** and **3t**, facilitating cellular accumulation of the complexes. Thus, the order of cytotoxicity of

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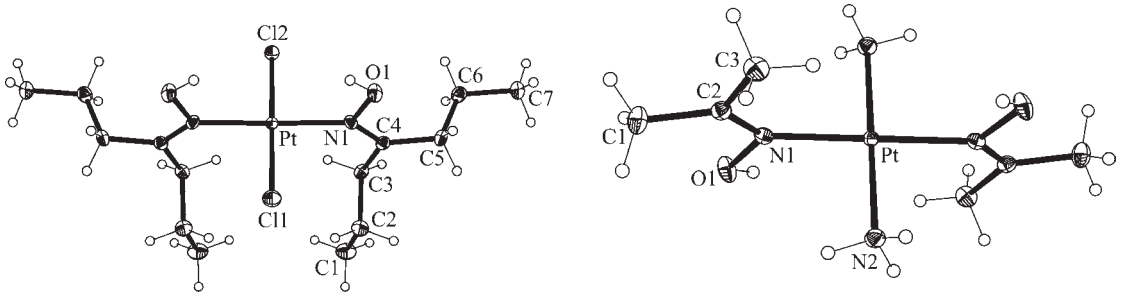


**Figure 5.** ORTEP diagram of **5t** (left) and **7t** (right) displaying thermal ellipsoids at 50% probability. Selected bond lengths (Å) and angles (deg) for **5t**: Pt−N1, 2.006(2); Pt−Cl1, 2.2821(9); Pt−Cl2, 2.3208(8); N1−C4, 1.277(3); N1−Pt−N1#1, 174.82(11); N1−Pt−Cl1, 89.09(6); N1−Pt−Cl2, 90.90(6). Selected bond lengths (Å) and angles (deg) for **7t**: Pt−N1, 2.006(2); Pt−N2, 2.045(2); N1−C2, 1.288(3); N1−Pt−N2, 89.66(9); N1−Pt−N2i1, 90.34(9); N1−Pt−N1i1, 180.0(11).

**Table 2.** Cytotoxicity of Platinum(II) Oxime Complexes in CH1 and SW480 Cancer Cells (Exposure Time 96 h)

| cis configuration | | | trans configuration | | |
|---|---|---|---|---|---|
| | $IC_{50}$, $\mu$M | | | $IC_{50}$, $\mu$M | |
| compound | CH1 | SW480 | compound | CH1 | SW480 |
| **1c** | 2.7 ± 0.7 | 3.4 ± 0.3 | **1t** | 0.17 ± 0.09 | 0.22 ± 0.05 |
| **2c** | 25 ± 4 | 45 ± 6 | **2t** | 6.7 ± 0.2 | 2.5 ± 0.4 |
| **3c** | 1.6 ± 0.2 | 1.8 ± 0.5 | **3t** | 3.0 ± 0.5 | 2.8 ± 0.3 |
| **4c** | 11 ± 1 | 15 ± 1 | **4t** | 1.4 ± 0.3 | 1.9 ± 0.6 |
| | | | **5t** | 0.18 ± 0.03 | 0.16 ± 0.02 |
| | | | **6t** | 0.19 ± 0.03 | 0.21 ± 0.03 |
| **7c** | 21 ± 7 | 567 ± 39 | **7t** | 468 ± 180 | > 1000 |
| **8c** | 717 ± 46 | > 1000 | **8t** | > 1000 | > 1000 |
| **9c** | 162 ± 46 | > 1000 | **9t** | 29 ± 5 | 350 ± 30 |
| cisplatin | 0.14 ± 0.03 | 3.3 ± 0.4 | transplatin | 15 ± 2 | 19 ± 3 |

$[PtX_2(Me_2C{=}NOH)_2]$-type agents is dependent on the halido ligand X as follows: I > Cl > Br (cis geometry) and Cl > I ≥ Br (trans geometry). Contrary to the chlorido (**1c**/**1t**) and bromido (**2c**/**2t**) complexes, the cis isomer **3c** is slightly more cytotoxic than trans-configured **3t**, reversing the structure−activity relationships to a more cis/transplatin-like behavior.

**ii. Effect of the Oxime Carbon Chain in Dichlorido Complexes.** A series of complexes with chlorido ligands and a systematically increased carbon chain of the oxime ligand were investigated. Using *n*-pentanone oxime in **4c**/**4t** instead of acetoxime in **1c**/**1t** resulted in a 4−8.6-fold decrease of cytotoxicity. Remarkably, the trans-configured complex **4t** is 8 times more cytotoxic than **4c**. Further increasing the length of the oxime carbon chain of the trans complexes by either *n*-propyl (**5t**) or isopropyl (**6t**) residues results in similarly enhanced cytotoxicity with $IC_{50}$ values in the high nanomolar concentration range in both the cisplatin-sensitive CH1 and cisplatin-resistant SW480 cells. Hence, the cytotoxicity of the *trans*-$[PtCl_2(R_2C{=}NOH)_2]$-type complexes depends on the residues R as follows: Me ≈ *n*-Pr ≈ *i*-Pr > Et.

**iii. Effect of the Oxime Carbon Chain Length in Cationic Diamminebis(oxime) Complexes.** All six cationic diamminedioxime complexes (**7c**/**7t**−**9c**/**9t**) displayed either a low or a negligible cytotoxicity. This is in accordance with the classic structure−activity relationships, according to which complexes with four nitrogen donor ligands (virtually no leaving groups[66]) or charged compounds (low cellular accumulation but increased renal elimination[6]) are generally considered to be noncytotoxic. The reason for the observed (albeit low) cytotoxicity of **7c** and **9t**, especially in CH1 cells, is yet unclear.

In comparison to cisplatin, the cis-configured halido complexes **1c**−**4c** are considerably (up to 70 times) less potent in the cisplatin-sensitive cell line CH1 but almost completely retain their cytotoxicity in the cisplatin-resistant SW480 cells, as indicated by a comparison of the resistance factors (RF = $IC_{50}$ in the cisplatin-resistant cell line/$IC_{50}$ in the cisplatin-sensitive cell line) of **1c**−**4c** (RF = 1.1−1.8; Table S1 in the Supporting Information) with that of cisplatin (RF = 24).

In the case of *trans*-halido compounds **1t**−**6t**, the resistant factors of 0.4−1.4 show that the complexes are not cross-resistant with cisplatin either. **1t**, **5t**, and **6t** are similarly cytotoxic as cisplatin in CH1 cells and up to 20 times more cytotoxic than cisplatin in SW480 cells. In comparison to transplatin, **1t**−**6t** are up to 90 (CH1) and 120 (SW480) times more cytotoxic.

## Conclusions

A series of novel bis(oxime)platinum(II) complexes with either cis or trans configuration have been synthesized, characterized, and investigated in two human cancer cell lines. Structure−activity relationships could be inferred from these results. The observation that the trans geometry yields a more active complex in the case of the prototypic oxime complex $[PtCl_2(Me_2C{=}NOH)_2]$ could be confirmed for at least two further structural analogues, $[PtBr_2(Me_2C{=}NOH)_2]$ and $[PtCl_2(Et_2C{=}NOH)_2]$. Every single cis- or trans-configured halido bis(oxime) complex showed comparable cytotoxic potency in both cell lines, the cisplatin-sensitive CH1 and the inherently cisplatin-resistant SW480 cancer cells. Particularly high cytotoxicities were revealed for the three trans compounds with chlorido ligands, with $IC_{50}$ values as low as 0.16−0.22 $\mu$M. Given these encouraging results, their mechanism of action should be studied in more detail in order to gain an understanding, which, in turn, may help to optimize their anticancer activity.

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**Supporting Information Available:** Figures with temperature-dependent $^1$H NMR spectra of **3t** and **9t**, tables with resistance factors and elemental analyses of platinum oxime complexes, and X-ray crystallographic data in CIF format for **3c**, **3t**, **4c**, **5t**, and **7t**. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as CCDC 767592−767596 for **4c**, **5t**, **3c**, **3t**, and **7t**, respectively. Copies of data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (deposit@ccdc.com.ac.uk). This material is available free of charge via the Internet at http://pubs.acs.org.