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Synthesis and *In Vitro* Antitumour Activity of $PtCl_2$ Complexes of Pyridine- and Quinoline-amine and -imine Ligands and of Carbocyclic Ethylenediamine Ligands

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Abstract

$PtCl_2$ complexes of pyridine- and quinoline-amine and -imine ligands and of carbocyclic ethylenediamine ligands were prepared and characterized. Their antitumor activity was tested with respect to the hormone independent human mammary carcinoma cell line MDA-MB 231. The inhibition of the cell proliferation and the [^{3}H]-thymidine incorporation was measured. Depending on the substituent patterns, the activities of the complexes in the present study range from inactive to highly active. The best ED_{50}-values approach the ED_{50} of cisplatin.

Introduction

In a previous paper we described the synthesis of optically active pyridineimines and pyridineamines and their application as ligands for Rh and Pt catalysts in the enantioselective hydrosilylation of acetophenone [1]. 8 of these known imines and amines (the ligands in **1g, h, l, m; 2g, l, m; 3g**), another 18 new imines and amines (the ligands in **1–4**) and 4 related amines (the ligands in **5–8**) were used to prepare Pt(II) complexes, the antitumor activity of which was tested towards the MDA-MB 231 cell line [2, 3]. The recent publication of a patent [4] containing two pyridineamines as ligands in Pt(II) complexes prompts us to report our results [2, 3].

Synthesis of Ligands and Pt Complexes

The $PtCl_2$ complexes prepared in the present study are shown in Scheme 1. The ligands for complexes **1** and **3** were obtained by Schiff base condensation of the corresponding 2-pyridine- or 2-quinoline carbonyl compounds with primary amines [1]. By $NaBH_4$ reduction these imines were converted to the amines used as ligands for complexes **2** and **4**. The ligands for complexes **5** and **8** were commercial products**, whereas the ligands for complexes **6** and **7** were prepared from the corresponding α-amino acid via the route α-amino acid ester, α-amino acid amide and $LiAlH_4$ reduction thereof, as published previously [5, 6].

The primary amines used for the synthesis of complexes of the type **g–m** (Scheme 1) were optically pure and (S)-configurated. In the $NaBH_4$ reduction of imine ligands of type **l** and **m**, a new asymmetric center at the carbon atom α to the heterocyclic ring is formed. These amines **l** and **m** were applied as the diastereomer mixtures obtained in the reduction [1]. The other amine ligands for complexes **1–8** were used as racemic mixtures. All these ligands were converted to their $PtCl_2$ complexes **1–8** by adaptation of known procedures [5, 6]. In the $PtCl_2$ complexes **2f** and **5**, the Cl^- ligands were replaced by the hydroxymalonate ion via the $AgNO_3$ method [6].

Properties, Analytical and Spectral Characterization

The yields, physical properties of amine ligands and their spectral and analytical characterization are given in Tables I and II. The Pt complexes **1–8** are white or yellow solids, insoluble in water and only sparingly soluble in DMF, DMSO, and $CHCl_3$. Their properties, analytical data and ^{1}H NMR parameters are summarized in Tables III–VI. Most of the Pt complexes exhibit the molecular ion in the mass spectrum when the field desorption technique is applied (Tables III and V).

In the IR spectra of the imine complexes **1** and **3**, the ν(C=N) bands are located between 1610 and

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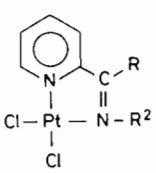

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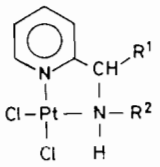

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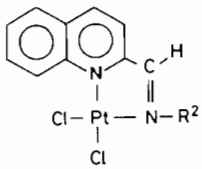

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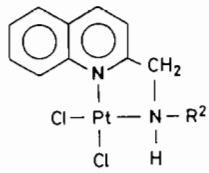

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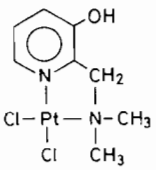
	a	b	c	d	e	f	g	h	i
R^1	H	H	H	H	H	H	H	H	H
R^2	H	Me	Ph	n-Bu	t-Bu	CH_2Ph	(S)-CHMePh	(S)-$CHMeC_6H_{11}$	(S)-CH(COOMe)CH_2Ph

	j	k	l	m
R^1	H	H	Me	Ph
R^2	(S)-CH(COOMe)$CH_2C_6H_4$-4-OH	(S)-CH(COOMe)$CH_2C_8H_6N$[a]	(S)-CHMePh	(S)-CHMePh

[a]Tryptophane derivative.



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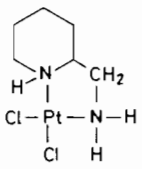

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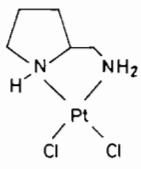

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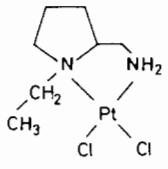

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Scheme 1.

TABLE I. Melting Points, Molecular Ions, and Elemental Analyses of Selected 2-Pyridyl- and 2-Quinolinylmethylamines

Ligand of	Formula (molecular weight)	Melting point (°C) $[M]^+$ [a]	Analyses (calc. (found))		
			C	H	N
2c	$C_{12}H_{12}N_2$	48–49	78.23	6.57	15.20
	(184.23)	184	(78.10)	(6.53)	(15.36)
2f	$C_{13}H_{14}N_2$	yellow oil	78.76	7.12	14.12
	(198.26)	198	(78.33)	(7.08)	(14.10)
2g	$C_{14}H_{14}N_2$	yellow oil	79.21	7.60	13.20
	(212.3)		(78.79)	(7.43)	(13.40)
2h	$C_{14}H_{22}N_2$	yellow oil	77.02	10.16	12.82
	(218.33)		(76.74)	(10.32)	(12.53)
2i	$C_{16}H_{18}N_2O_2$	45–47	71.09	6.71	10.36
	(270.30)	270	(73.31)	(6.81)	(10.63)
4e	$C_{14}H_{18}N_2$	yellow oil	78.47	8.47	13.07
	(214.30)		(78.75)	(8.41)	(13.00)
6·HCl	$C_6H_{15}ClN_2$	yellow oil	47.84	10.04	
	(150.65)		(47.90)	(10.19)	
7·2HCl	$C_5H_{14}Cl_2N_2$	100–102	34.70	8.14	16.18
	(173.07)	100[b]	(34.50)	(7.86)	(15.99)

[a]Molecular ion, low resolution mass spectrometer. [b]M^+-2HCl, field desorption mass spectrometry in H_2O.

1630 cm^{-1}. Compared to the uncoordinated imine, they are lowered by 30–50 cm^{-1} [2]. Characteristic ν(PtCl) bands between 300 and 350 cm^{-1} appear in the KBr spectra of complexes **1**–**8** [2, 6]. These bands are absent in the derivatives of **2f** and **5** in which the Cl-ligands are replaced by hydroxymalonate, the ν(C=O) bands of which are found between 1645 and 1675 cm^{-1} [3].

TABLE II. ^{1}H NMR Parameters of Selected 2-Pyridyl- and 2-Quinolinyl-methylamines (60 MHz; $CDCl_3$, i-TMS, 297 K)

Ligand of	pyH [3]	pyH [4]	pyH [5]	pyH [6]	py-CH_2	N–H	Other protons
2c	7.7(m)	7.5(m)	[a]	8.5(m)	4.7(s)	2.15(s)	aryl H 6.5–7.4
2e	7.6(m)	7.45(m)	7.15(m)	8.5(m)	3.90(s)	1.75(s)	t-C_4H_9 1.2(s)
2f	[a]	[a]	[a]	8.5(m)	3.90(s)	2.2(s)	N–CH_2 3.8(s); arylH 6.9–7.6;
2g	[a]	[a]	[a]	8.4(m)	3.72(s)	2.2(s)	$CHCH_3$ 1.35(d); $CHCH_3$ 3.75(q); arylH 6.9–7.7
2h	7.7(m)	7.5(m)	7.2(m)	8.4(m)	3.9(s)	1.9(s)	$CHCH_3$ 1.0(d); $CHCH_3$ 2.3–2.7(m); cyclohexyl 0.8–2.0
2k	[a]	[a]	[a]	[a]	3.25(s)	2.6 (broad)	OCH_3 3.6(s); $CHCH_2$ 1.45(m); $CHCH_2$ 2.4–4 0; C_8H_6N 6.7–7.7
4e	8.1(m)	7.6(m)	–	–	4.10(s)	2.0(s)	t-C_4H_9 1.25(s)
4g	7.9(m)	[a]	–	–	3.9(s)	2.55(s)	$CHCH_3$ 1.4(d); $CHCH_3$ 3.8(q); arylH 7.1–8.1

[a]In the range of the protons of the arene.

TABLE III. Melting Points, Molecular Ions, Elemental Analyses, and Yields of Selected 2-Pyridineimine–$PtCl_2$ Complexes

Compound	Formula (melting point (°C))	Molecular ion (M^+)[a]	Analyses (calc. (found))			Yield (%)
			C	H	N	
1c	$C_{12}H_{10}Cl_2N_2Pt$ (>250)	448.12 446	32.16 (32.10)	2.25 (2.25)	6.25 (6.25)	41
1g	$C_{14}H_{14}Cl_2N_2Pt$ (130–135)	476.18 474	35.31 (35.34)	2.96 (2.86)	5.88 (5.89)	73
1h	$C_{14}H_{20}Cl_2N_2Pt$ (190–196)	482.22 480	34.87 (34.48)	4.18 (4.08)	5.81 (5.64)	34
1i	$C_{16}H_{16}Cl_2N_2O_2Pt$ (210)	534.21 532	35.97 (36.02)	3.02 (3.03)	5.24 (5.30)	73

[a]Field desorption, DMF solution, with reference to ^{194}Pt.

TABLE IV. ^{1}H NMR Parameters of Selected 2-Pyridineimine–$PtCl_2$ Complexes (250 MHz; i-TMS, 297 K)

Complex	pyH [3]	pyH [4]	pyH [5]	pyH [6]	py-CH	Other protons
1c[a]	8.39(m)	8.55(m)	8.09(m)	9.65(m)	9.46(s)	7.38–7.60(m; 5H, arylH)
1g[b]	7.91(m)	8.11(m)	7.66(m)	9.62(m)	8.61(s)	1.91(d, 6.94 Hz; 3H, $CHCH_3$); 6.35(q; 1H, $CHCH_3$), 7.33–7.51(m; 5H, arylH)
1h[b]	8.12(m)	8.20(m)	7.68(m)	9.67(m)	8.77(s)	0.96–2.16(m; 11H, C_6H_{11}), 1.44(d, 6.81 Hz; 3H, $CHCH_3$), 4.94(m; 1H, $CHCH_3$)
1i[b]	[c]	8.14(m)	9.66(m)	9.74(m)	8.44(s)	3.37–3.74(m; 3H, Ø–CH_2–CH), 3.80(s; 3H, OCH_3), 7.17–7.33(m; 5H, arylH)

[a]DMF-d_7. [b]$CDCl_3$. [c]Obscured by other signals.

In Vitro Antitumor Tests

Complexes **1–8** of scheme 1 have been tested *in vitro* with the hormone independent human mammary carcinoma cell line MDA-MB 231 [2, 7]. In these series of tests, between three and six different concentrations were used. The inhibition of the cell proliferation and of the [^{3}H]-thymidine incorporation was measured as described [7]. The ED_{50} values obtained are summarized in Table VII for both measurements.

It is amazing that complexes of type **1–8** show a high antitumor activity because it is known that substituents at the N atoms in chelate ligands, occupying two *cis* positions at the Pt atom, tend to reduce the activity [8–10]. Compounds of type **6–8** contain ethylenediamine ligands with one

TABLE V. Formula, Melting Points, Molecular Ions, Elemental Analyses, and Yields of the 2-Pyridine and 2-Quinolineamine–$PtCl_2$ Complexes

Compound	Formula (melting point (°C))	Molecular ion $[M]^+$ [a]	Analyses (calc. (found))			Yield (%)
			C	H	N	
2a	$C_6H_8Cl_2N_2Pt$	374.04	19.27	2.16	7.49	90
	c	372	(19.31)	(2.17)	(7.46)	
2c	$C_{12}H_{12}Cl_2N_2Pt$	450.14	32.02	2.69	6.22	52
	c	488	(31.23)	(2.50)	(6.03)	
2e	$C_{10}H_{16}Cl_2N_2Pt$	430.15	27.92	3.75	6.51	81
	c	428	(27.68)	(3.71)	(6.41)	
2f	$C_{13}H_{14}Cl_2N_2Pt$	464.17	33.64	3.04	6.03	46
	c	462	(33.55)	(2.99)	(6.05)	
2g	$C_{14}H_{16}Cl_2N_2Pt$	478.19	35.16	3.37	5.86	76
	242	476	(35.15)	(3.37)	(5.84)	
2h	$C_{14}H_{21}Cl_2N_2Pt$	484.31	34.72	4.58	5.78	66
	c		(34.73)	(4.56)	(5.95)	
2i	$C_{16}H_{18}Cl_2N_2O_2Pt$	536.23	35.84	3.38	5.22	58
	139		(35.68)	(3.36)	(4.87)	
2j	$C_{16}H_{18}Cl_2N_2O_3Pt$	552.23	34.80	3.29	5.07	66
	215	514[b]	(34.74)	(3.32)	(4.94)	
2k	$C_{18}H_{19}Cl_2N_3O_2Pt$	575.26	37.73	3.32	7.33	39
	38	537[b]	(38.60)	(3.63)	(7.38)	
2l	$C_{15}H_{18}Cl_2N_2Pt$	491.23	36.68	3.69	5.69	78
	234	490	(37.28)	(3.59)	(5.37)	
2m	$C_{20}H_{20}Cl_2N_2Pt$	554.29	43.34	3.64	5.05	81
	75–79	552	(43.36)	(3.68)	(4.98)	
4e	$C_{14}H_{18}Cl_2N_2Pt$	480.21	35.02	3.78	5.83	43
	c	478	(34.95)	(3.79)	(5.74)	
4g	$C_{18}H_{18}Cl_2N_2Pt$	528.25	40.93	3.43	5.30	48
	c	526	(40.18)	(4.06)	(5.85)	
5	$C_8H_{12}Cl_2N_2OPt$	418.09	22.98	2.89	6.70	82
	c	–	(22.63)	(2.94)	(6.57)	

[a]Field desorption mass spectrometry in DMF solution with reference to ^{194}Pt. [b]M^+ – HCl. [c]Melting points >250 °C. [d]M^+ + DMF.

TABLE VI. ^1H NMR Parameter of the 2-Pyridine and 2-Quinolineamine–$PtCl_2$ Complexes (250 MHz, DMF-d_7* or $CDCl_3$**, i-TMS, 296 K)

Complex	pyH [3]	pyH [4]	pyH [5]	pyH [6]	pyCHR	NH	Other protons
2a*	7.73(m)	8.19(m)	7.54(m)	9.25(m)	4.37(t; 6.0 Hz)	6.24[c]	
2c*	7.92(m)	8.32(m)	7.66(m)	9.24(m)	4.86 (AB)[d]	9.31[c]	7.21–7.27(m; 5H, aryl H)
2e**	7.47(m)	7.89(m)	7.26(m)	9.17(m)	4.29(d, 17.1 Hz)	6.60[c]	1.32(s; 9H, t-C_4H_9)
2f*	[b]	8.12(m)	7.46(m)	9.15(m)	4.20(AB) [e]	9.14[c]	4.36(ABX, J_{AB} = 13.39 Hz, J_{AX} = 2.83 Hz, J_{BX} = 3.53 Hz; 2H, ϕCH_2) 7.34–7.38 aryl H
2g**	[a]	[a]	[a]	8.96(m)	3.8 - 5.4(m; 2H)[f]	6.80[c]	1.80(d) + 1.87(d) ($CHCH_3$)[f], 4.41(m) + 4.82(m) ($CHCH_3$)[f]
2h*	7.77(m)	8.21(m)	7.44(m)	9.22(m)	4.48(AB)[g]	6.53[c]	0.92–2.06(m; 11H, C_6H_{11}), 1.29(d, 6.83 Hz; 3H, $CHCH_3$)
2l**	7.55(m)	7.86(m)	[a]	9.17(m)	4.22(m)	5.34[c]	1.81(d) + 1.89(d) + 1.98(d) + 2.06(d) (6.8 Hz; $CHCH_3$)[h], 4.22(m) ($CHCH_3$), 7.01–7.33 aryl H
2m*	[a]	[b]	[a]	9.09(m)	4.65(m)	5.86(s)	1.84(d) + 1.99(d) (6.97 Hz; $CHCH_3$)[i] 7.27–7.59 aryl H

(continued on facing page)

TABLE VI. *(continued)*

Complex	pyH [3]	pyH [4]	pyH [5]	pyH [6]	pyCHR	NH	Other protons
4e*	–	–	–	–	4.55(m)	6.2[c]	1.24(s) + 1.42(s) (t-C_4H_9)[f], 7.41–8.31(m; 5H, quinoline), 9.43(m; 1H, quinoline)
4g**	–	–	–	–	4.28(m)		0.9–2.0(m; $CHCH_3$)[f], 7.06–9.43(m; 6H, quinoline H)
5*		7.54(m)	7.38(m)	8.56(m)	4.42(m)		2.83(s; 6H, $N(CH_3)_2$)

[a]In the range of the arene protons. [b]Obscured by solvent signals. [c]Broad. [d]J_{AB} = 16.75 Hz, J_{AX} = 6.53 Hz, J_{BX} = 1.38 Hz. [e]J_{AB} = 16.59 Hz, J_{AX} = 5.93 Hz, J_{BX} = 8.44 Hz. [f]Diastereomer ratio 1:1. [g]J_{AB} = 16.88 Hz, J_{AX} = 6.77 Hz, J_{BX} = 2.91 Hz. [h]Diastereomer ratio 2:3. [i]Diastereomer ratio 2:1.

TABLE VII. ED_{50}-values in mol/l for the Inhibition of the Cell Proliferation and the [^{3}H]-thymidine Incorporation in MDA-MB 231-cells by the Complexes **1–8** of Scheme 1

Number	Complex	Cell number	[^{3}H]-thymidine incorporation
1	**2a**[a]	3.0×10^{-6}	3.0×10^{-6}
2	**2c**[a]	2.6×10^{-5}	8.2×10^{-6}
3	**2e**[a]	inactive	inactive
4	**2f**[b]	2.3×10^{-6}	1.6×10^{-6}
5	**2g**[b]	1.8×10^{-6}	2.1×10^{-6}
6	**2h**[a]	2.8×10^{-6}	3.3×10^{-6}
7	**2i**[a]	inactive	inactive
8	**2j**[a]	inactive	inactive
9	**2k**[a]	inactive	inactive
10	**2l**[a]	7.0×10^{-6}	6.3×10^{-6}
11	**2m**[a]	1.4×10^{-6}	1.4×10^{-6}
12	**1c**[a]	$>1 \times 10^{-5}$	$>1 \times 10^{-5}$
13	**1g**[a]	1.8×10^{-5}	7.4×10^{-6}
14	**1h**[a]	4.8×10^{-6}	3.8×10^{-6}
15	**1i**[a]	3.9×10^{-5}	7.3×10^{-6}
16	**4e**[a]	inactive	inactive
17	**4g**[a]	1.9×10^{-5}	6.6×10^{-6}
18	**5**[a]	inactive	inactive
19	**6**[a]	3.5×10^{-6}	3.4×10^{-6}
20	**7**[a]	3.5×10^{-6}	1.4×10^{-6}
21	**8**[a]	4.6×10^{-6}	2.7×10^{-6}
22	cisplatin	3.0×10^{-7}	4.0×10^{-7}

[a]One serie of tests. [b]Average of two series of tests.

or two substituents at one of the nitrogen atoms. Compounds **2**, **4**, and **5** are pyridine or quinoline derivatives with one or two additional substituents at the imine nitrogen atom. For two such compounds, namely **2a** and the corresponding NMe derivative, antitumour activity was reported in a recent patent [4]. It is even more surprising that pyridine and quinoline imines of type **1** and **3** show appreciable inhibition in the two test systems used [2].

11 pyridineamine complexes of type **2** have been tested. A phenyl substituent reduced the activity in **2c** compared to **2a** and a t-butyl substituent in **2e** made the complex completely inactive (Table VII no. 1–3). With a benzyl or (S)-1-phenylethyl substituent, however, the activity of the complexes was increased (no. 4, 5). The $PtCl_2$ complex derived from a ligand containing the (R)-1-phenylethyl substituent gave the same ED_{50}-values as the (S)-1-phenylethyl derivative **2g**. The cyclohexyl complex showed an activity similar to the unsubstituted compound **2a** (no. 1, 6). The aminoacid derivatives **2i**, **2j**, **2k** all were inactive (no. 7–9). The complex obtained by replacement of the Cl ligands in **2f** by the hydroxymalonate ion was inactive in the cell proliferation test. ED_{50} for the inhibition of the [^{3}H]-thymidine incorporation had the high value 4.6×10^{-5} mol/l.

An interesting point is the comparison of no. 1, 10, and 11 of Table VII. The corresponding complexes **2a**, **2l**, **2m** differ only in the substituent at the α-position of the pyridine system. **2a** is unsubstituted, **2l** methylsubstituted, and **2m** phenyl-substituted in that position. The antitumor activity dropped in going from **2a** to **2l** but increased appreciably in going to **2m**. Thus, the phenyl derivative **2m** is the most active antitumor agent of the whole series of complexes.

In the series of the imine complexes, the phenyl derivative **1c** was much less active than the corresponding amine derivative **2c** (no. 2, 12) and the (S)-1-phenylethyl complex **1g** was less active than **2g** by a factor of 5 to 10 (no. 13). The cyclohexylimine derivative **1h**, however, exhibited almost the same activity as the corresponding amine complex **2h** (no. 6, 14), and, surprisingly, the imine complex **1i** had an increased activity compared to the amine complex **2i**.

In the quinoline series the t-butyl derivative **4e** was inactive, similar to its pyridine counterpart **2e** (no. 3, 16). The (S)-1-phenylethyl compound **4g** showed a reduced activity with respect to its pyridine analogue **2g** (no. 5, 17).

The hydroxypyridine complex **5** proved to be inactive (no. 18). The same was true for the deriva-

tive, in which its Cl ligands were replaced by the hydroxymalonate ion [3].

The ED_{50}-values for complexes **6**, **7**, and **8** in both tests were between 1.4×10^{-6} and 4.6×10^{-6} mol/l (no. 19–21). It is remarkable that in going from the NH compound **7** to the N-ethyl compound **8** the antitumor activity is only slightly reduced (no. 20, 21).

In contrast to the assumption that only those compounds in which the $-NH_2$ moiety is coordinated to Pt show high antitumor activity, the present study demonstrates that $PtCl_2$ chelate complexes with a wide variety of N substituents are active in antitumor tests and that their activity can be controlled by the choice of substituents.

Experimental

General Procedures

Melting points, uncorrected, were determined on a Büchi SMP-20. IR spectra were recorded on a Beckman spectrometer 4240. ^{1}H NMR spectra were measured on a Varian T60 and a Bruker WM 250 instrument. Mass spectra were obtained on a Finnigan MAT311A using low resolution and field desorption techniques.

Imines and Amines

Imine ligands of the complexes of type **1** and **3** were prepared by condensation of 2-pyridine aldehyde, 2-quinoline aldehyde [10], 2-acetylpyridine, and 2-benzoylpyridine with the corresponding primary amine components as described [1]. Amine ligands of the complexes of type **2** and **4** were obtained from the corresponding imines by $NaBH_4$ reduction [1].

The crude oily imines and amines were dissolved in ether and dried with anhydrous $MgSO_4$. Repeated recrystallization from petrol ether/ether or high vacuum distillation gave the pure imines and amines. The analytical data and ^{1}H NMR parameters of selected 2-pyridyl- and 2-quinolinylmethylamines are given in Tables I and II.

The amine ligands for compounds **6** and **7** were prepared starting from 2-piperidyl carboxyclic acid and L-proline, via their methyl esters, amides, and $LiAlH_4$ reduction as described [5, 6]. Their analytical data are contained in Table I.

L-α-Pyrrolidylmethylamine Dihydrochloride

Yield 60%. IR (KBr): 3000vs,br (ν_{NH}), 1600m, 1575m cm^{-1} (δ_{NH}). ^{1}H NMR (D_2O, standard Na-2.2.3.3-tetradeutero-3-trimethylsilyl-propionate): 1.76–2.43(m; 2H), 2.07–2.19(m; 2H), 3.34–3.51(m, 4H), 3.86–3.98(m; 1H).

2-Piperidylmethylamine Hydrochloride

Yield 43%. IR (KBr): 3360vs,br, 3250vs,br, 3110s,br (ν_{NH}), 2920vs, 2850m (ν_{CH}), 1610s cm^{-1} (δ_{NH}). ^{1}H NMR (DMF-d_7): 1.49–3.09(m; 11H), 5.42(m; 2H), 6.38(m; 1H).

The ligands of complexes **5** and **8** are commercial products.

Dichloro–Platinum(II) Complexes

Imine complexes 1 and 3

A solution of 1 mmol of the 2-pyridine or 2-quinolineimine ligand in 5 ml 1 N HCl was added to a stirred solution of 1 mmol (415 mg) K_2PtCl_4 in 5 ml of water. While heating the red solution to 50 °C, the orange to yellow solids precipitated. After 3–5 h they were filtered off, washed successively with water and dried in vacuum at 80 °C. In the preparation of **1e** the water-insoluble t-Bu derivative **e** was added to the K_2PtCl_4 solution as a solid [2]. The yields and analytical data of the imine–$PtCl_2$ complexes **1** and **3** are summarized in Table III, ^{1}H NMR parameters in Table IV.

Amine complexes 2 and 4

A solution of 1 mmol of the 2-pyridine or 2-quinolineamine ligand in 6 ml of DMF was added dropwise at room temperature to the orange solution of 1 mmol (415 mg) K_2PtCl_4 in 6 ml of water with stirring, excluding light. After addition of 1 ml DMSO the color gradually turned yellow. Subsequently, the solvent was removed *in vacuo* and the oily residue was treated with water, causing instantaneous precipitation of the yellow solid which was filtered off, washed successively with water and dried in vacuum at 80 °C.

When the preparation of **2f** was carried out in DMF without addition of DMSO, a small quantity of a brown precipitate forming prior to **2f** had to be discarded before the yellow **2f** precipitated from the red solution within 15 h. The yield of **2f** could be raised to 60% by concentrating the solution [3].

The ligands 2-aminomethyl-pyridine* and 2-dimethylaminomethyl-3-hydroxypyridine** are water soluble. For the preparation of the yellow complexes **2a** and **5**, they were added in water solution to the solution of K_2PtCl_4, the pH being adjusted to **6** with 0.5 N NaOH. The solutions were worked up after 30 h.

The yields and analytical data of the amine–$PtCl_2$ complexes **2** and **4** are given in Table V, ^{1}H NMR parameters in Table VI.

The complexes **6**–**8** were prepared according to literature procedures [5, 6].

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Dichloro-(2-piperidylmethylamine)platinum(II) 6

Yellow solid. Yield 63%. Melting.point >250 °C. *Anal.* Calc. for $C_6H_{14}Cl_2N_2Pt$ (380.19): C, 18.96; H, 3.71; N, 7.37%. Found: C, 18.79; H, 3.72; N, 7.31%.

Dichloro-(L-α-pyrrolidylmethylamine)platinum(II) 7

Yellow to green solid. Yield 25%. Melting point >250 °C. Mass spectrum (FD in DMF): m/e = 365 (^{194}Pt). *Anal.* Calc. for $C_5H_{12}Cl_2N_2Pt$ (366.06): C, 16.41; H, 3.30; N, 7.65. Found: C, 16.31; H, 3.08; N, 7.60%.

Dichloro-(2-aminomethyl-1-ethylpyrrolidine)platinum(II) 8

Yellow solid. Yield 68%. Melting point 234–236 °C (decomposition). Mass spectrum (FD in DMF): m/e = 392 (^{194}Pt). *Anal.* Calc. for $C_7H_{16}Cl_2N_2Pt$ (394.11): C, 21.22; H, 4.09; N, 7.10. Found: C, 21.25; H, 4.10; N, 7.11%.

Hydroxymalonato–Platinum(II) Complexes

The $PtCl_2$ complexes **2f** and **5** were reacted with $AgNO_3$ in water solution. After filtration the solution was treated with an equimolar solution of hydroxymalonic acid. The hydroxymalonic acid derivatives of **2f** and **5** are water insoluble. Work-up as described [3, 6].

Hydroxymalonato-(2-pyridylmethyl-benzylamine)-platinum(II)

White solid. Yield 74%. Melting point 230 °C (decomposition). *Anal.* Calc. for $C_{16}H_{16}N_2O_5Pt$ (511.41): C, 37.57; H, 3.16; N, 5.48. Found: C, 36.48; H, 3.53; N, 5.78%.

Hydroxymalonato-(2-dimethylaminomethyl-3-hydroxy-pyridine)platinum(II)

White solid. Yield 74%. Melting point >250 °C. Mass spectrum (FD in DMF): m/e = 463 (^{194}Pt). Anal. Calc. for $C_{11}H_{14}N_2O_5Pt$ (465.25): C, 28.40; H, 3.04; N, 6.02. Found: C, 28.35; H, 3.12; N, 6.03%.

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