Available online at www.sciencedirect.com
SCIENCE DIRECT®
Polyhedron 23 (2004) 2169–2176
POLYHEDRON
www.elsevier.com/locate/poly

Synthesis, characterization, and cytotoxicities of palladium(II) and platinum(II) complexes containing fluorinated pyridinecarboxaldimines

Stephen J. Scales [a], Haiwen Zhang [a], Paul A. Chapman [a], Ciara P. McRory [a], Eric J. Derrah [a], Christopher M. Vogels [a], Mazen T. Saleh [b], Andreas Decken [c], Stephen A. Westcott [a,*]

[a] Department of Chemistry, Mount Allison University, 63C York Street, Sackville, NB, Canada E4L 1G8
[b] Department of Biology and Biochemistry, Mount Allison University, Sackville, NB, Canada E4L 1G7
[c] Department of Chemistry, University of New Brunswick, Fredericton, NB, Canada E3B 5A3

Received 9 May 2004; accepted 9 June 2004
Available online 29 July 2004

Abstract

Condensation of 2-pyridinecarboxaldehyde with several primary amines containing fluorine groups gave the corresponding pyridinecarboxaldimines (N-N′). Addition of these ligands to $[MCl_2(coe)]_2$ (M = Pd, Pt; coe = *cis*-cyclooctene) gave complexes of the type *cis*-MCl_2(N-N′) [Pd (**3**), Pt (**4**)] in moderate to high yields. All palladium and platinum complexes were examined for their potential cytotoxicities against OV2008 (human ovarian carcinoma) and the analogous cisplatin-resistant C13.

Keywords: Pyridinecarboxaldimine; Cytotoxicity; Platinum; Palladium; Fluorine

1. Introduction

Cisplatin, *cis*-$[PtCl_2(NH_3)_2]$ and a few related platinum-based complexes are currently used as anticancer agents against testicular and ovarian malignancies [1–7]. There are several limitations to platinum therapy, however, such as neural and kidney toxicity as well as intrinsic and acquired resistance of tumor cells to the drugs [1]. These complications have provided an incentive for further research into the development of platinum-based complexes with increased solubility and enhanced specificity towards cancer cells. Recent studies have shown that *cis*-amminedichloro(2-methylpyridine)platinum(II) (AMD473 or ZD0473, Fig. 1) shows considerable cytotoxicity in cisplatin-resistant cell lines [8,9]. Steric crowding from the methyl group is believed to decrease the rates of hydrolysis and substitution reactions of AMD473 by effectively shielding the platinum atom and thereby permitting high selectivity in binding to DNA [10]. The primary mechanism of action in these platinum drugs is believed to arise from the metal's interaction with DNA.

We have begun to develop AMD473 analogues by replacing the NH_3 group with a pendant imine group. Previous studies have shown that the platinum complex derived from aniline, **2** (Fig. 1), has shown considerable activity against the hormone independent human mammary carcinoma cell line MDA-MB 231 [11]. Varying the aniline functionality allows us to design compounds with a wide range of physical and chemical properties

* Corresponding author. Tel.: +1-506-364-2351/2372; fax: +1-506-364-2313.
E-mail address: swestcott@mta.ca (S.A. Westcott).

0277-5387/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.poly.2004.06.013

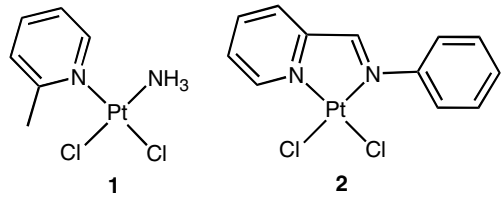


Fig. 1. Structure of AMD473 (**1**) and complex **2**.

that may provide steric congestion around the platinum atom. As well, the use of bidentate ligands prevents trans labilization and undesired displacement of the ligands by sulfur and nitrogen donors in biomolecules, interactions believed responsible for some of the adverse side effects associated with cisplatin [1–3]. We report herein our results on the synthesis and initial cytotoxicity testing of *cis*-dichloro(pyridin-2-ylcarboxaldimine)-palladium(II) and -platinum(II) compounds containing bulky fluorinated aryl groups (Fig. 2).

2. Experimental

2.1. General procedures and methods

Reagents and solvents used were obtained from Aldrich Chemicals. $PdCl_2$ and K_2PtCl_4 were purchased from Precious Metals Online Ltd. and $[PdCl_2(coe)]_2$ and $[PtCl_2(coe)]_2$ were made by established procedures [12]. Pyridinecarboxaldimine ligands were prepared as previously reported [13]. NMR spectra were recorded on a JEOL JNM-GSX270 FT NMR or Varian Mercury Plus 200 NMR spectrometer. ^1H NMR chemical shifts are reported in ppm and are referenced to residual protons in deuterated solvent at 270 and 200 MHz. ^{13}C NMR chemical shifts are referenced to solvent carbon resonances as internal standards at 68 and 50 MHz. ^{19}F NMR chemical shifts are referenced to CF_3CO_2H. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) and overlapping (ov). Infrared spectra were obtained using a Mattson Genesis II FT-IR spectrometer and are reported in cm^{-1}. Melting points were measured uncorrected with a Mel-Temp apparatus. Microanalyses for C, H and N were carried out at Guelph Chemical Laboratories Ltd. (Guelph, Ont.).

2.2. General procedure for the preparation of metal complexes

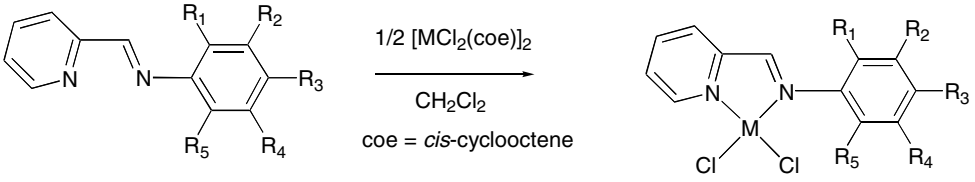
A CH_2Cl_2 (5 ml) solution of ligand (0.55 mmol) was added to the appropriate $[MCl_2(coe)]_2$ (where M = Pd or Pt) (0.25 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred for 5 h at room temperature and the precipitate was collected by suction filtration and washed with CH_2Cl_2 (3×5 ml) to afford the metal complex.

2.2.1. Compound ***3a***

Yield: 80% as an orange solid; m.p. 280–281 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.05 (d, $J = 6$ Hz, 1H, Ar), 8.89 (s, 1H, C(*H*)═N), 8.43 (t of d, $J = 8$, 1 Hz, 1H, Ar), 8.23 (d, $J = 8$ Hz, 1H, Ar), 7.97 (t of d, $J = 6$, 1 Hz, 1H, Ar), 7.48–7.27 (ov m, 4H, Ar); $^{13}C\{^1H\}$ δ: 175.7, 155.9, 154.5 (d, $J_{C-F} = 274$ Hz, *C*F), 150.9, 142.0, 135.6 (d, $J_{C-F} = 12$ Hz), 130.7 (d, $J_{C-F} = 8$ Hz), 130.5, 130.2, 125.7, 124.9 (d, $J_{C-F} = 4$ Hz), 116.4 (d, $J_{C-F} = 20$ Hz); $^{19}F\{^1H\}$ δ: −118.4. IR (nujol): 2949, 2904, 2860, 1581, 1460, 1377, 1250, 1228, 1159, 1101, 955, 798, 771, 739. *Anal*. Calc. for $C_{12}H_9N_2Cl_2FPd$: C, 38.16; H, 2.41; N, 7.42. Found: C, 38.20; H, 2.29; N, 7.13%.

2.2.2. Compound ***3b***

Yield: 76% as an orange solid; m.p. 278–280 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.05 (d, $J = 6$ Hz, 1H, Ar), 8.80 (s, 1H, C(*H*)═N), 8.42 (t, $J = 8$ Hz, 1H, Ar), 8.21 (d, $J = 8$ Hz, 1H, Ar), 7.96 (t, $J = 6$ Hz, 1H, Ar), 7.55–7.47 (m,



a: $R_1 = F$, $R_2 = R_3 = R_4 = R_5 = H$
b: $R_2 = F$, $R_1 = R_3 = R_4 = R_5 = H$
c: $R_3 = F$, $R_1 = R_2 = R_4 = R_5 = H$
d: $R_1 = CF_3$, $R_2 = R_3 = R_4 = R_5 = H$
e: $R_2 = CF_3$, $R_1 = R_3 = R_4 = R_5 = H$
f: $R_3 = CF_3$, $R_1 = R_2 = R_4 = R_5 = H$
g: $R_2 = R_4 = CF_3$, $R_1 = R_3 = R_5 = H$
h: $R_1 = R_2 = R_3 = R_4 = R_5 = F$

3: M = Pd
4: M = Pt

Fig. 2. Synthesis of palladium and platinum complexes **3**–**4**.

1H, Ar), 7.34–7.24 (ov m, 3H, Ar); $^{13}C\{^1H\}$ δ: 174.0, 161.7 (d, J_{C-F} = 245 Hz, *C*F), 156.2, 150.7, 148.8 (d, J_{C-F} = 10 Hz), 141.9, 130.6 (d, J_{C-F} = 9 Hz), 130.3, 129.9, 120.7, 115.9, (d, J_{C-F} = 21 Hz), 112.4 (d, J_{C-F} = 25 Hz); $^{19}F\{^1H\}$ δ: −112.8. IR (nujol): 2951, 2927, 2854, 1591, 1460, 1377, 1360, 1300, 1269, 1252, 1228, 1167, 1138, 980, 897, 856, 796, 771, 723, 692. *Anal*. Calc. for $C_{12}H_9N_2Cl_2FPd$: C, 38.16; H, 2.41; N, 7.42. Found: C, 38.22; H, 2.13; N, 7.25%.

2.2.3. Compound **3c**

Yield: 60% as an orange solid; m.p. 328 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.05 (d, J = 6 Hz, 1H, Ar), 8.75 (s, 1H, C(*H*)═N), 8.40 (t, J = 8 Hz, 1H, Ar), 8.20 (d, J = 8 Hz, 1H, Ar), 7.94 (t, J = 6 Hz, 1H, Ar), 7.51–7.46 (m, 2H, Ar), 7.34–7.28 (m, 2H, Ar); $^{13}C\{^1H\}$ δ: 173.4, 162.2 (d, J_{C-F} = 246 Hz, *C*F), 156.4, 150.6, 143.9 (d, J_{C-F} = 2 Hz), 141.9, 130.1, 129.7, 126.8 (d, J_{C-F} = 9 Hz), 115.6 (d, J_{C-F} = 22 Hz); $^{19}F\{^1H\}$ δ: −113.0. IR (nujol): 3109, 3041, 3016, 2920, 1597, 1579, 1498, 1479, 1308, 1296, 1242, 1228, 1196, 1157, 1103, 960, 850, 806, 795, 768, 579. *Anal*. Calc. for $C_{12}H_9N_2Cl_2FPd$: C, 38.16; H, 2.41; N, 7.42. Found: C, 37.98; H, 2.10; N, 7.10%.

2.2.4. Compound **3d**

Yield: 70% as an orange solid; m.p. 324–326 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.04 (d, J = 6 Hz, 1H, Ar), 8.97 (s, 1H, C(*H*)═N), 8.44 (t of d, J = 8, 1 Hz, 1H, Ar), 8.25 (d, J = 8 Hz, 1H, Ar), 8.01 (t of d, J = 6, 1 Hz, 1H, Ar), 7.82–7.76 (ov m, 2H, Ar), 7.61 (t, J = 8 Hz, 1H, Ar), 7.51 (d, J = 8 Hz, 1H, Ar); $^{13}C\{^1H\}$ δ: 175.2, 155.6, 151.2, 145.3, 142.1, 133.5, 130.6 (2C), 129.0, 126.8 (q, J_{C-F} = 5 Hz), 126.2, 124.5 (q, J_{C-F} = 274 Hz, *C*F_3), 122.2 (q, J_{C-F} = 30 Hz); $^{19}F\{^1H\}$ δ: −55.9. IR (nujol): 3074, 3014, 2952, 2925, 2854, 1593, 1471, 1456, 1319, 1296, 1269, 1203, 1155, 1124, 1055, 1034, 984, 768, 571. *Anal*. Calc. for $C_{13}H_9N_2Cl_2F_3Pd$: C, 36.51; H, 2.13; N, 6.55. Found: C, 36.57; H, 1.98; N, 6.54%.

2.2.5. Compound **3e**

Yield: 65% as an orange solid; m.p. 346–348 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.06 (d, J = 6 Hz, 1H, Ar), 8.85 (s, 1H, C(*H*)═N), 8.42 (t, J = 8 Hz, 1H, Ar), 8.23 (d, J = 8 Hz, 1H, Ar), 7.97 (t, J = 6 Hz, 1H, Ar), 7.85 (s, 1H, Ar), 7.80 (m, 1H, Ar), 7.77–7.68 (ov m, 2H, Ar); $^{13}C\{^1H\}$ δ: 175.0, 156.8, 151.3, 148.2, 142.5, 130.8, 130.5 (2C), 129.9 (q, J_{C-F} = 32 Hz), 129.4, 128.7 (q, J_{C-F} = 274 Hz, *C*F_3), 126.1 (q, J_{C-F} = 4 Hz), 122.0 (q, J_{C-F} = 4 Hz); $^{19}F\{^1H\}$ δ: −61.0. IR (nujol): 3074, 3014, 2953, 2854, 1593, 1450, 1362, 1329, 1238, 1184, 1159, 1117, 1068, 808, 773, 700, 658. *Anal*. Calc. for $C_{13}H_9N_2Cl_2F_3Pd$: C, 36.51; H, 2.13; N, 6.55. Found: C, 36.23; H, 2.11; N, 6.33%.

2.2.6. Compound **3f**

Yield: 65% as an orange solid; m.p. 301–302 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.06 (d, J = 6 Hz, 1H, Ar), 8.83 (s, 1H, C(*H*)═N), 8.42 (t of d, J = 8, 1 Hz, 1H, Ar), 8.22 (d, J = 8 Hz, 1H, Ar), 7.97 (t of d, J = 6, 1 Hz, 1H, Ar), 7.87 (d, J = 8 Hz, 2H, Ar), 7.63 (d, J = 8 Hz, 2H, Ar); $^{13}C\{^1H\}$ δ: 174.4, 156.3, 150.7, 150.4, 142.0, 130.4, 130.0, 129.1 (q, J_{C-F} = 35 Hz), 126.0 (q, J_{C-F} = 4 Hz), 125.6, 124.5 (q, J_{C-F} = 274 Hz, *C*F_3); $^{19}F\{^1H\}$ δ: −60.8. IR (nujol): 3074, 2870, 1460, 1377, 1186, 1169, 1107, 966, 854, 766, 721, 607. *Anal*. Calc. for $C_{13}H_9N_2Cl_2F_3Pd$: C, 36.51; H, 2.13; N, 6.55. Found: C, 36.66; H, 1.97; N, 6.45%.

2.2.7. Compound **3g**

Yield: 60% as an orange solid; m.p. 358–360 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.07 (d, J = 6 Hz, 1H, Ar), 8.98 (s, 1H, C(*H*)═N), 8.45 (t of d, J = 8, 1 Hz, 1H, Ar), 8.27 (d, J = 8 Hz, 1H, Ar), 8.24 (s, 1H, Ar), 8.19 (s, 2H, Ar), 8.00 (t of d, J = 6, 1 Hz, 1H, Ar); $^{13}C\{^1H\}$ δ: 175.7, 156.1, 150.9, 148.2, 142.1, 130.8, 130.6 (q, J_{C-F} = 34 Hz), 130.3, 126.1, 123.5 (q, J_{C-F} = 274 Hz, *C*F_3), 122.6 (q, J_{C-F} = 4 Hz); $^{19}F\{^1H\}$ δ: −61.2. IR (nujol): 3107, 3020, 2951, 2922, 2854, 1371, 1358, 1292, 1279, 1242, 1184, 1174, 1126, 970, 901, 881, 777, 702, 683. *Anal*. Calc. for $C_{14}H_8N_2Cl_2F_6Pd$: C, 33.92; H, 1.63; N, 5.65. Found: C, 33.50; H, 1.39; N, 5.43%.

2.2.8. Compound **3h**

Yield: 65% as an orange solid; m.p. 288 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.21 (s, 1H, C(*H*)═N), 9.04 (d, J = 6 Hz, 1H, Ar), 8.46 (t, J = 8 Hz, 1H, Ar), 8.34 (d, J = 8 Hz, 1H, Ar), 8.06 (t, J = 6 Hz, 1H, Ar); $^{19}F\{^1H\}$ δ: −145.4 (d, J_{F-F} = 19 Hz), −154.2 (t, J_{F-F} = 19 Hz), −162.8 (t, J_{F-F} = 9 Hz). IR (nujol): 3095, 3016, 2951, 2924, 2856, 1591, 1512, 1470, 1433, 1352, 1294, 1221, 1103, 1009, 995, 960, 885, 793, 781. *Anal*. Calc. for $C_{12}H_5N_2Cl_2F_5Pd$: C, 32.06; H, 1.12; N, 6.23. Found: C, 31.91; H, 0.83; N, 5.99%.

2.2.9. Compound **4a**

Yield: 65% as an orange solid; m.p. 282 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^1H δ: 9.51 (s, J_{H-Pt} = 92 Hz, 1H, C(*H*)═N), 9.47 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 40 Hz, 1H, Ar), 8.47 (t, J_{H-H} = 8 Hz, 1H, Ar), 8.25 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.04 (t, J_{H-H} = 6 Hz, 1H, Ar), 7.50–7.31 (ov m, 4H, Ar); $^{13}C\{^1H\}$ δ: 175.4, 157.1, 154.9 (d, J_{C-F} = 250 Hz, *C*F), 149.8, 141.4, 135.4 (d, J_{C-F} = 12 Hz), 131.1 (d, J_{C-F} = 8 Hz), 130.8 (2C), 126.5, 124.9 (d, J_{C-F} = 4 Hz), 116.5 (d, J_{C-F} = 20 Hz); $^{19}F\{^1H\}$ δ: −120.0. IR (nujol): 2941, 2902, 2860, 1589, 1558, 1493, 1456, 1377, 1348, 1300, 1250, 1228, 1159, 1101, 937, 856, 800, 766, 739,

667, 596. *Anal.* Calc. for $C_{12}H_9N_2Cl_2FPt$: C, 30.91; H, 1.95; N, 6.01. Found: C, 30.44; H, 1.73; N, 5.68%.

2.2.10. Compound **4b**

Yield: 81% as an orange solid; m.p. 286 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.48 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 47 Hz, 1H, Ar), 9.40 (s, J_{H-Pt} = 91 Hz, 1H, C(*H*)═N), 8.45 (t, J_{H-H} = 8 Hz, 1H, Ar), 8.24 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.01 (t, J_{H-H} = 6 Hz, 1H, Ar), 7.60–7.52 (m, 1H, Ar), 7.40–7.29 (ov m, 3H, Ar); ^{13}C{^{1}H} δ: 174.0, 161.8 (d, J_{C-F} = 247 Hz, *C*F), 157.5, 149.7, 148.7 (d, J_{C-F} = 10 Hz), 141.3, 130.7, 130.5, 130.4, 121.2 (d, J_{C-F} = 3 Hz), 116.2 (d, J_{C-F} = 21 Hz), 112.7 (d, J_{C-F} = 25 Hz); ^{19}F{^{1}H} δ: −112.7. IR (nujol): 2931, 2912, 2856, 1593, 1460, 1377, 1358, 1300, 1269, 1252, 1230, 1138, 984, 897, 858, 796, 769, 694. *Anal.* Calc. for $C_{12}H_9N_2Cl_2FPt$: C, 30.91; H, 1.95; N, 6.01. Found: C, 31.27; H, 1.65; N 6.00%.

2.2.11. Compound **4c**

Yield: 85% as an orange solid; m.p. 327 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.47 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 40 Hz, 1H, Ar), 9.34 (s, J_{H-Pt} = 93 Hz, 1H, C(*H*)═N), 8.45 (t of d, J_{H-H} = 8, 1 Hz, 1H, Ar), 8.23 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.00 (t of d, J_{H-H} = 6, 1 Hz, 1H, Ar), 7.56–7.51 (ov m, 2H, Ar), 7.39–7.33 (ov m, 2H, Ar); ^{13}C{^{1}H} δ: 172.8, 161.8 (d, J_{C-F} = 250 Hz, *C*F), 157.1, 149.1, 143.3 (d, J_{C-F} = 2 Hz), 140.7, 129.8, 129.7, 126.6 (d, J_{C-F} = 9 Hz), 115.0 (d, J_{C-F} = 23 Hz); ^{19}F{^{1}H} δ: −112.7. IR (nujol): 2951, 2939, 2914, 2852, 1462, 1377, 1298, 1244, 1228, 1157, 1101, 1059, 1039, 972, 947, 932, 920, 850, 806, 766, 752, 586. *Anal.* Calc. for $C_{12}H_9N_2Cl_2FPt$: C, 30.91; H, 1.95; N, 6.01. Found: C, 30.75; H, 1.69; N, 5.72%.

2.2.12. Compound **4d**

Yield: 75% as an orange solid; m.p. 315 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.59 (s, J_{H-Pt} = 90 Hz, 1H, C(*H*)═N), 9.48 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 40 Hz, 1H, Ar), 8.48 (t, J_{H-H} = 8 Hz, 1H, Ar), 8.30 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.06 (t, J_{H-H} = 6 Hz, 1H, Ar), 7.88–7.79 (ov m, 2H, Ar), 7.67 (t, J_{H-H} = 8 Hz, 1H, Ar), 7.54 (d, J_{H-H} = 8 Hz, 1H, Ar); ^{13}C{^{1}H} δ: 174.9, 163.2, 156.9, 150.1, 141.5, 133.4, 131.1, 130.9, 129.4, 127.1, 126.9 (q, J_{C-F} = 5 Hz), 125.0 (q, J_{C-F} = 274 Hz, *C*F$_3$), 122.9 (q, J_{C-F} = 30 Hz); ^{19}F{^{1}H} δ: −56.2. IR (nujol): 2945, 2902, 2868, 1560, 1460, 1377, 1317, 1306, 1271, 1234, 1201, 1163, 1124, 1055, 1032, 968, 781, 762, 723, 596. *Anal.* Calc. for $C_{13}H_9N_2Cl_2F_3Pt$: C, 30.24; H, 1.76; N, 5.43. Found: C, 29.81; H, 1.69; N, 5.25%.

2.2.13. Compound **4e**

Yield: 65% as an orange solid; m.p. 336 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.48 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 40 Hz, 1H, Ar), 9.45 (s, J_{H-Pt} = 88 Hz, 1H, C(*H*)═N), 8.47 (t of d, J_{H-H} = 8, 1 Hz, 1H, Ar), 8.26 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.02 (t of d, J_{H-H} = 6, 1 Hz, 1H, Ar), 7.90 (s, 1H, Ar), 7.85–7.75 (ov m, 3H, Ar); ^{13}C{^{1}H} δ: 174.5, 157.6, 149.7, 147.6, 141.4, 130.6, 130.5, 130.2 (q, J_{C-F} = 31 Hz), 130.0, 129.2, 128.3 (q, J_{C-F} = 274 Hz, *C*F$_3$), 126.0 (q, J_{C-F} = 4 Hz), 121.9 (q, J_{C-F} = 4 Hz); ^{19}F{^{1}H} δ: −61.0. IR (nujol): 2943, 2910, 2860, 1460, 1377, 1327, 1240, 1182, 1161, 1117, 1066, 941, 808, 771, 700, 660, 596. *Anal.* Calc. for $C_{13}H_9N_2Cl_2F_3Pt$: C, 30.24; H, 1.76; N, 5.43. Found: C, 30.20; H, 1.50; N, 5.43%.

2.2.14. Compound **4f**

Yield: 85% as an orange solid; m.p. 300 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.48 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 40 Hz, 1H, Ar), 9.43 (s, J_{H-Pt} = 97 Hz, 1H, C(*H*)═N), 8.47 (t of d, J_{H-H} = 8, 1 Hz, 1H, Ar), 8.26 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.03 (t of d, J_{H-H} = 6, 1 Hz, 1H, Ar), 7.92 (d, J_{H-H} = 8 Hz, 2H, Ar), 7.68 (d, J_{H-H} = 8 Hz, 2H, Ar); ^{13}C{^{1}H} δ: 174.4, 157.5, 149.7, 149.5, 141.3, 130.6, 130.5, 130.2 (q, J_{C-F} = 31 Hz), 126.5 (q, J_{C-F} = 274 Hz, *C*F$_3$), 126.0 (2C); ^{19}F{^{1}H} δ: −60.8. IR (nujol): 2958, 2939, 2883, 1416, 1325, 1201, 1111, 1066, 856, 825, 808, 760, 731, 700, 685, 669, 606, 596, 515. *Anal.* Calc. for $C_{13}H_9N_2Cl_2F_3Pt$: C, 30.24; H, 1.76; N, 5.43. Found: C, 29.98; H, 1.42; N, 5.22%.

2.2.15. Compound **4g**

Yield: 60% as an orange solid; m.p. 338 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.59 (s, J_{H-Pt} = 85 Hz, 1H, C(*H*)═N), 9.49 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 40 Hz, 1H, Ar), 8.49 (t, J_{H-H} = 8 Hz, 1H, Ar), 8.31 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.27 (s, 1H, Ar), 8.25 (s, 2H, Ar), 8.05 (t, J_{H-H} = 6 Hz, 1H, Ar); ^{13}C{^{1}H} δ: 175.6, 157.4, 149.9, 148.1, 141.5, 130.9, 130.6 (q, J_{C-F} = 34 Hz), 130.4, 126.5, 123.5 (q, J = 274 Hz, *C*F$_3$), 123.1 (q, J_{C-F} = 4 Hz); ^{19}F{^{1}H} δ: −61.2. IR (nujol): 2935, 2904, 2870, 1460, 1377, 1290, 1173, 1126, 974, 900, 847, 773. *Anal.* Calc. for $C_{14}H_8N_2Cl_2F_6Pt$: C, 28.77; H, 1.38; N, 4.80. Found: C, 28.57; H, 1.16; N, 4.57%.

2.2.16. Compound **4h**

Yield: 60% as an orange solid; m.p. 302 °C (decomposition). Spectroscopic NMR data (in DMSO-d_6): ^{1}H δ: 9.85 (s, J_{H-Pt} = 82 Hz, 1H, C(*H*)═N), 9.47 (d, J_{H-H} = 6 Hz, J_{H-Pt} = 38 Hz, 1H, Ar), 8.50 (t, J_{H-H} = 8 Hz, 1H, Ar), 8.40 (d, J_{H-H} = 8 Hz, 1H, Ar), 8.14 (t, J_{H-H} = 6 Hz, 1H, Ar); ^{19}F{^{1}H} δ: −145.9 (d, J = 19 Hz), −153.6 (t, J = 19 Hz), −162.6 (t, J = 19 Hz). IR (nujol): 3041, 3016, 2960, 2939, 2864, 1512, 1471, 1433, 1350, 1292, 1223, 1105, 1026, 1011, 993, 939, 887, 779, 667. *Anal.* Calc. for $C_{12}H_5N_2Cl_2F_5Pt$: C, 26.77; H, 0.94; N, 5.21. Found: C, 26.53; H, 0.75; N, 5.15%.

2.3. X-ray crystallography

Crystals of **3d**·**DMF** were grown from a saturated DMF solution at 20 °C. Single crystals were coated with Paratone-N oil, mounted using a glass fibre and frozen in the cold stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and θ scans with a scan width of 0.3° and 10 s exposure time. The detector distance was 4 cm. The data were reduced [14] and corrected for absorption [15]. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 [16]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in Fourier difference maps and refined isotropically.

2.4. Cell culture

OV2008 (human ovarian carcinoma) and the analogous cisplatin-resistant cell line C13 were a generous gift from Dr. Barbara C. Vanderhyden of the Centre for Cancer Therapeutics, Ottawa Regional Cancer Centre, Ont., Canada. Both cell lines were cultured in complete RPMI-1640 medium with L-glutamine, supplemented with 5% fetal bovine serum, penicillin (50 units/ml) and streptomycin (50 mg/ml). Cells were incubated in a humidified atmosphere of 5% CO_2 at 37 °C and were subcultured twice weekly using trypsin–EDTA.

2.5. Cell growth inhibition assay

Cells were seeded in 96-well plates at a concentration of $0.1–1.0 \times 10^4$ cells/well in 200 μl of complete media and incubated for 24 h at 37 °C in a 5% CO_2 atmosphere to allow for cell adhesion. Stock solutions (15 mM) of the compounds made in DMSO were filter sterilized, then diluted to 10 mM in phosphate-buffered saline (PBS, 0.02 M phosphate, 0.11 M NaCl, pH 7.0, sterile). The 10 mM solutions were diluted to 50 μM and 1.4 mM in complete media for treatment against OV2008 and C13 cell lines, respectively, where 20 μl of compound solutions were added to 180 μl of fresh medium in wells to give final concentrations of 5 μM against OV2008 and 140 μM for C13. All assays were performed in two independent sets of quadruplicate tests. Control groups containing no drug were run in each assay, along with standards of cisplatin and a previously studied *cis*-dichloro(pyridin-2-ylcarboxaldimine)platinum(II) complex (**2**) [11].

Following 48 h of exposure, each well was carefully rinsed with 200 μl PBS buffer. MTT solution (50 μl, 1 mg/ml ddH_2O) along with 200 μl of fresh, complete media were added to each well, and plates were incubated for 45 min. Following incubation, the medium was removed and the purple formazan precipitate in each well was solubilized in 200 μl DMSO. Absorbances were measured using a VersaMax tunable microplate reader (Molecular Devices) at 570 nm. Reduction of cell proliferation was determined as a fraction of the absorbance values for each drug treatment (T) to the mean absorbance of the no-drug control (C), and calculated using the expression $1 - T/C \times 100\%$. Data from the separate trials were combined using a t test ($P < 0.05$).

3. Results and discussion

3.1. Synthesis and structure

The addition of a primary amine to commercially available 2-pyridinecarboxaldehyde to afford the corresponding pyridinecarboxaldimine ligand is a well-known route to a versatile class of bidentate ligands [17–27]. Variation of the amine therefore allows for the facile design of ligands and subsequent metal complexes with different physical and chemical properties. In this study, the metal complexes **3**–**4** (Fig. 2) were prepared by addition of the pyridin-2-ylcarboxaldimine ligands to CH_2Cl_2 solutions of $[MCl_2(coe)]_2$ (M = Pd, Pt; coe = *cis*-cyclooctene) [12,13]. Palladium complexes were also prepared because of recent interest for their anticancer potential. Compounds of the type $[Pd(en)Cl_2]$ and [Pd(en)L] (en = ethylenediamine; L = malonato, methylmalonato, dimethylmalonato and 1,1-cyclobutanedicarboxylato) were recently shown to bind to DNA in a manner similar to that proposed for cisplatin [28].

Complexes containing fluorine groups are of particular interest as substitution of hydrocarbon fragments with C–F moieties can dramatically alter the properties of biologically active compounds and can influence the metabolism and distribution of drug molecules in the body [29–31]. For instance, substitution of fluorine on the aromatic ring of the neurotransmitter norepinephrine produces large differences in its adrenergic activities [32].

In this study, complexes **3**–**4** have been characterized by a number of physical methods, including multinuclear NMR spectroscopy. A significant downfield shift in the ^1H NMR is observed for the imine sp^2 proton upon coordination of the ligand to the metal center. For instance, the singlet at δ 8.59 ppm for the free ligand derived from 2-pyridinecarboxaldehyde and 4-fluoroaniline shifts to 9.34 ppm in complex **4c**. Platinum satellites are also observed for this resonance (J_{H-Pt} = 93 Hz) upon complexation of the ligand to the metal. Similar trends are observed for the pyridine hydrogen α to the nitrogen atom as the chemical shift changes from δ 8.71 to 9.47 ppm (J_{H-Pt} = 40 Hz). The ^{19}F NMR spectra for compounds **3**–**4** are similar to analogous palladium and platinum complexes containing fluorinated imines [33–36]. For instance, three distinct resonances appear

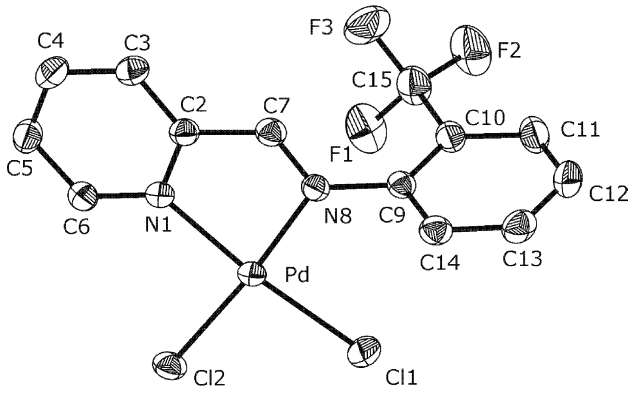


Fig. 3. A view of molecule **3d·DMF**, with displacement ellipsoids drawn at the 30% probability level. H atoms and the molecule of DMF have been omitted for clarity.

in the aromatic region for complexes **3**, **4h**, derived from pentafluoroaniline, and coupling constants are in the expected range for analogous compounds [37]. It is interesting to note, however, that metal complexes **3**, **4h** were unstable in DMSO and decomposed after ca. 12 h to give a number of unidentified products, precluding the acquisition of ^{13}C NMR data. As late metals are known to activate the C–F bond in related pentafluoropyridine [38], it is plausible that compounds **3**, **4h** are also decomposing via a similar mechanism [39,40].

Complex **3d·DMF** has also been characterized by an X-ray diffraction study (Fig. 3). Crystallographic data are given in Table 1 and selected bond lengths and angles provided in Table 2. The nitrogen–palladium bonds of 2.0296(15) Å (pyridine) and 2.0181(16) Å (imine) are similar to those reported in other imine palladium systems [41–43]. The imine C(7)–N(8) distance of 1.286(2) Å is in the range of accepted carbon–nitrogen double bonds [44]. Interesting, the aromatic ring on the imine nitrogen is almost perpendicular to the N(1)–Pd–N(8) plane (83.4°), a trend that is observed in related diimine platinum systems [45]. Indeed, this structural feature has been used to create active and selective catalyst precursors for the polymerization of α-olefins, where *ortho* substitution of the aniline group with bulky groups is believed to shield and stabilize the metal center. The structure of the related $[PtCl_2(R\text{-pea})]$ (pea = 1,(2-pyridyl)ethylamine) has been reported recently [46], where the methyl group of the backbone lies in an equatorial plane and results in a close contact between it and the pyridine, which would otherwise not be present if the methyl group were in the axial position. In the case of **3d·DMF**, a closest contact of Pd with F is 3.387 Å, where the trifluoromethyl group is canted over the plane of the metal center. This observation suggests that complexes with CF_3 groups in the *ortho* position of the imine aryl ring may shield the metal atom in a similar way to AMD473.

Table 1
Crystallographic data collection parameters for **3d·DMF**

Complex	**3d·DMF**
Formula	$C_{16}H_{16}Cl_2F_3N_3OPd$
Formula weight	500.62
Crystal system	triclinic
Space group	$P\bar{1}$
a (Å)	7.9624(5)
b (Å)	9.4425(5)
c (Å)	12.8704(7)
α (°)	77.022(1)
β (°)	76.213(1)
γ (°)	89.263(1)
V (Å^3)	914.93(9)
Z	2
D_{calc} (Mg m^{-3})	1.817
Crystal size (mm^3)	$0.375 \times 0.30 \times 0.15$
T (K)	173(1)
Radiation	Mo Kα ($\lambda = 0.71073$)
μ (mm^{-1})	1.346
Total reflections	7377
Total unique reflections	4769
Number of variables	299
R_{int}	0.0244
θ Range (°)	2.22–30.00
Largest difference peak/hole (e Å^{-3})	0.918/−0.2828
S (Goodness-of-fit) on F^2	1.063
R_1[a] ($I > 2\sigma(I)$)	0.0272
wR_2[b] (all data)	0.0703

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$.

[b] $wR_2 = (\sum[w(F_o^2 - F_c^2)^2/\sum[F_o^4]])^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (0.0354 \times P)^2 + (0.2668 * P)]$, where $P = (\max(F_o^2, 0) + 2 \times F_c^2)/3$.

Table 2
Selected bond lengths (Å) and angles (°) for **3d·DMF**

Pd–N(8)	2.0181(16)
Pd–N(1)	2.0296(15)
Pd–Cl(1)	2.2663(5)
Pd–Cl(2)	2.2841(5)
N(1)–C(6)	1.327(2)
N(1)–C(2)	1.357(2)
C(7)–N(8)	1.286(2)
N(8)–C(9)	1.424(2)
C(15)–F(2)	1.325(2)
C(15)–F(1)	1.334(3)
C(15)–F(3)	1.341(3)
N(8)–Pd–N(1)	80.39(6)
N(8)–Pd–Cl(1)	93.28(5)
N(1)–Pd–Cl(1)	173.64(4)
N(8)–Pd–Cl(2)	174.97(4)
N(1)–Pd–Cl(2)	94.66(5)
Cl(1)–Pd–Cl(2)	91.673(19)
C(6)–N(1)–C(2)	118.60(17)
C(6)–N(1)–Pd	128.69(14)
C(2)–N(1)–Pd	112.68(12)
F(2)–C(15)–F(1)	106.7(2)
F(2)–C(15)–F(3)	106.8(2)
F(1)–C(15)–F(3)	105.64(19)
F(2)–C(15)–C(10)	112.02(18)
F(1)–C(15)–C(10)	112.97(19)
F(3)–C(15)–C(10)	112.2(2)

3.2. Cytotoxic activity

We have tested the cytotoxic activity of all the new palladium and platinum complexes against both cisplatin-sensitive and cisplatin-resistant human ovarian cells (Table 3), OV2008 and C13, respectively, at concentrations corresponding to cisplatin's IC_{50} value against either cell line [47–49]. While marginal activity was observed for palladium complexes against cisplatin-sensitive cells OV2008, most of the analogous platinum complexes showed significantly less activity. Indeed, the platinum complexes **4a** and **4h**, which contain a F group in the α position showed no activity against the cisplatin-sensitive cell line. In contrast, however, is the observation that **4d**, with a bulky CF_3 group in the α position, showed considerable activity against OV2008 while **4e** showed no activity with the CF_3 group in the *meta* position. More remarkable is that almost all palladium and platinum complexes displayed substantial activity against cisplatin-resistant cell lines C13. Only compound **4a** does not show any significant activity. Compound **3d**, with the CF_3 group in the *ortho* position of the aryl group, was significantly more active than its platinum analogue **4d**. The platinum compounds **4e** and 4**g** contain a CF_3 moiety in the *meta* position and show enhanced activities towards C13 as compared to OV2008. Interestingly, increased activities were observed for both metal complexes when the CF_3 group was bound in the *para* position (complexes **3f** and **4f** show the greatest activity against C13). While these initial studies have shown that some compounds show promise against the cisplatin-resistant cell line, further in vitro studies are needed to address the structure activity relationships in these complexes in order to design a potent drug candidate.

Table 3
Percent reduction of cell proliferation of cisplatin-sensitive (OV2008) and cisplatin-resistant (C13) cancer cells to compounds at 5 and 140 μM, respectively ($n = 8$; ±SD)

Compound	OV2008	C13
cisplatin	44 ± 11	41 ± 8
2	21 ± 3	37 ± 8
3a	25 ± 11	78 ± 8
3b	21 ± 7	31 ± 9
3c	28 ± 12	31 ± 7
3d	28 ± 10	79 ± 11
3e	20 ± 11	29 ± 16
3f	24 ± 12	83 ± 15
3g	23 ± 10	39 ± 15
3h	25 ± 8	56 ± 13
4a	0	4 ± 4
4b	10 ± 16	83 ± 4
4c	26 ± 5	78 ± 7
4d	70 ± 14	28 ± 13
4e	0	81 ± 6
4f	45 ± 12	96 ± 2
4g	12 ± 9	87 ± 9
4h	0	35 ± 12

4. Conclusion

Pyridinecarboxaldimines derived from the condensation of 2-pyridinecarboxaldehyde and fluorine-containing amines have been prepared in high yields and used as ligands for palladium and platinum salts. The resulting metal complexes have shown considerable cytotoxicity against the OV2008 (human ovarian carcinoma) cisplatin-resistant C13 cell line. Future work in this area will continue to develop bulkier metal complexes containing highly fluorinated groups.

Acknowledgements

Thanks are gratefully extended to the Research Corporation (Cottrell College Science Award), NSERC, Canada Research Chair/Canadian Foundation for Innovation/Atlantic Innovation Fund programs and Mount Allison University for financial support. We also thank Roger Smith, Dan Durant and Barbie Sears (MAU) for expert technical assistance, Dr. Barbara C. Vanderhyden of the Centre for Cancer Therapeutics (Ottawa Regional Cancer Centre, Ont., Canada) for providing us with the OV2008 and C13 cell lines, and anonymous reviewers for helpful comments.

Appendix A. Supplementary material

Full crystallographic data in CIF format have been deposited with The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-366033; e-mail: deposit@ccdc.cam.ac.uk or www: http//www.ccdc.cam.ac.uk) and are available on request, quoting deposition number 237107 for compound **3d·DMF**. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.poly.2004.06.013.

References

[1] E.R. Jamieson, S.J. Lippard, Chem. Rev. 99 (1999) 2467.
[2] J. Reedijk, Chem. Rev. 99 (1999) 2499.
[3] E. Wong, C.M. Giandomenico, Chem. Rev. 99 (1999) 2451.
[4] H. Rauter, R.D. Domencio, E. Menta, A. Oliva, Y. Qu, N. Farrell, Inorg. Chem. 36 (1997) 3919.
[5] Y.-P. Ho, S.C.F. Au-Yeung, K.K.W. To, Med. Res. Rev. 23 (2003) 633.
[6] N. Poklar, D.S. Pilch, S.J. Lippard, E.A. Redding, S.U. Dunham, K.J. Breslauer, Proc. Natl. Acad. Sci. USA 93 (1996) 7606.

[7] E.T. Martins, H. Baruah, J. Kramarczyk, G. Saluta, C.S. Day, G.L. Kucera, U. Bierbach, J. Med. Chem. 44 (2001) 4492.
[8] J.L. Butour, J.-P. Macquet, Eur. J. Biochem. 78 (1977) 455.
[9] K. Neplechová, J. Kašpárková, O. Vrána, O. Nováková, A. Habtemariam, B. Watchman, P.J. Sadler, V. Brabec, Mol. Pharmacol. 56 (1999) 20.
[10] A.C.G. Hotze, Y. Chen, T.W. Hambley, S. Parsons, N.A. Kratochwil, J.A. Parkinson, V.P. Munk, P.J. Sadler, Eur. J. Inorg. Chem. (2002) 1035.
[11] H. Brunner, M. Schmidt, H. Schönenberger, Inorg. Chim. Acta 123 (1986) 201.
[12] S. Otto, A. Roodt, L.I. Elding, J. Chem. Soc., Dalton Trans. (2003) 2519.
[13] L.G. Nikolcheva, C.M. Vogels, R.A. Stefan, H.A. Darwish, S.J. Duffy, R.J. Ireland, A. Decken, R.H.E. Hudson, S.A. Westcott, Can. J. Chem. 81 (2003) 269.
[14] SAINT 6.02, Bruker AXS, Inc., Madison, Wisconsin, USA (1997–1999).
[15] G.M. Sheldrick, SADABS, Bruker AXS, Inc., Madison, WI, USA, 1999.
[16] G.M. Sheldrick, SHELXTL-5.1, Bruker AXS, Inc., Madison, WI, USA, 1997.
[17] P. Krumholz, Inorg. Chem. 4 (1965) 609.
[18] J. Burgess, J. Chem. Soc. (A) (1968) 497.
[19] H. Brunner, B. Reiter, G. Riepl, Chem. Ber. 177 (1984) 1330.
[20] P. Pointeau, H. Patin, A. Mousser, J.-Y. Le Marouille, J. Organomet. Chem. 312 (1986) 263.
[21] G.J.P. Britovsek, G.Y.Y. Woo, N. Assavathorn, J. Organomet. Chem. 679 (2003) 110.
[22] M. Crespo, Polyhedron 15 (1996) 1981.
[23] J.H. Groen, M.J.M. Vlaar, P.W.N.M. van Leeuwen, K. Vrieze, H. Kooijman, A.L. Spek, J. Organomet. Chem. 551 (1998) 67.
[24] M.L. Ferrara, I. Orabona, F. Ruffo, M. Funicello, A. Panunzi, Organometallics 17 (1998) 3832.
[25] S.-J. Kim, N. Yang, D.-H. Kim, S.O. Kang, J. Ko, Organometallics 19 (2000) 4036.
[26] A. Kundu, B.P. Buffin, Organometallics 20 (2001) 3635.
[27] X.–F. He, C.M. Vogels, A. Decken, S.A. Westcott, Polyhedron 23 (2004) 155.
[28] J.M. Tercero, A. Matilla, M.A. Sanjuán, C.F. Moreno, J.D. Martín, J.A. Walmsley, Inorg. Chim. Acta 342 (2003) 77.
[29] B.K. Park, N.R. Kitteringham, P.M. O'Neill, Annu. Rev. Pharmacol. Toxicol. 41 (2001) 443.
[30] Z.-M. Qiu, D.J. Burton, J. Org. Chem. 60 (1995) 5570.
[31] H.L. Bardlow, C.A. VanderWerf, J. Am. Chem. Soc. 70 (1948) 654.
[32] A. Adejare, J.-Y. Nie, D. Hebel, L.E. Brackett, O. Choi, F. Gusovsky, W.L. Padgett, J.W. Daly, C.R. Creveling, K.L. Kirk, J. Med. Chem. 34 (1991) 1063.
[33] M. Crespo, X. Solans, M. Font-Bardía, Organometallics 14 (1995) 355.
[34] J. Albert, J. Granell, R. Moragas, J. Sales, M. Font-Bardía, X. Solans, J. Organomet. Chem. 494 (1995) 95.
[35] O. López, M. Crespo, M. Font-Bardía, X. Solans, Organometallics 16 (1997) 1233.
[36] M. Crespo, M. Font-Bardía, X. Solans, Polyhedron 21 (2002) 105.
[37] C. Crocker, R.J. Goodfellow, J. Gimeno, R. Usón, J. Chem. Soc., Dalton Trans. (1977) 1448.
[38] T. Braun, S. Rothfeld, V. Schorlemer, A. Stammler, H.-G. Stammler, Inorg. Chem. Commun. 6 (2003) 752.
[39] E.F. Murphy, R. Murugavel, H.W. Roesky, Chem. Rev. 97 (1997) 3425.
[40] J.L. Kiplinger, T.G. Richmond, C.E. Osterberg, Chem. Rev. 94 (1994) 373.
[41] A. Bacchi, M. Carcelli, L. Gabba, S. Ianelli, P. Pelagatti, G. Pelizzi, D. Rogolino, Inorg. Chim. Acta 342 (2003) 229.
[42] R. Ares, M. López-Torres, A. Fernández, M.T. Pereira, G. Alberdi, D. Vázquez-García, J.J. Fernández, J.M. Vila, J. Organomet. Chem. 665 (2003) 76.
[43] C. Navarro-Ranninger, I. López-Solera, V.M. González, J.M. Pérez, A. Alvarez-Valdés, A. Martín, P.R. Raithby, J.R. Masaguer, C. Alonso, Inorg. Chem. 35 (1996) 5181.
[44] A.I. Kltaigorodskii, Organic Chemical Crystallography, Consultants Bureau, New York, NY, 1961.
[45] S.D. Ittel, L.K. Johnson, M. Brookhart, Chem. Rev. 100 (2000) 1169.
[46] V.P. Munk, C.I. Diakos, L.T. Ellis, R.R. Fenton, B.A. Messerle, T.W. Hambley, Inorg. Chem. 42 (2003) 3582.
[47] M.S. Robillard, M. Bacac, H. van den Elst, A. Flamigni, G.A. van der Marel, J.H. van Boom, J. Reedijk, J. Comb. Chem. 5 (2003) 821.
[48] A. Trevisan, C. Marzano, P. Cristofori, M.B. Venturini, L. Giovagini, D. Fregona, Arch. Toxicol. 76 (2002) 262.
[49] M.D. Todd, X. Lin, L.F. Stankowski Jr., M. Desai, G.H. Wolfgang, J. Biomol. Screen. 5 (1999) 259.