Novel Clioquinol and it Analogous Platinum Complexes: Importance, Role of the Halogen Substitution and the Hydroxyl Group of the Ligand

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General Methods

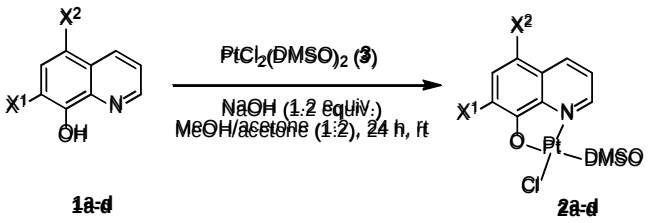
NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, 75 and 64.5 MHz for ^{1}H, ^{13}C and ^{195}Pt, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR; CD_2Cl_2: 5.32 ppm for ^{1}H NMR, 53.84 for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode. ^{195}Pt NMR spectra were obtained with chemical shifts reported in ppm downfield relative to the external reference 1.0 M Na_2PtCl_6 in D_2O. Melting points were measured using a Gallenkamp apparatus in open capillary tubes.

Materials

All reagents and materials were purchased from commercial sources and used without further purification. The *cis*-$PtCl_2(DMSO)_2$ complex was synthesized according to literature procedure.[1,2]

Experimental procedures and characterization

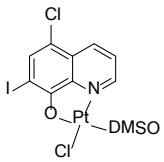
General Procedure for the synthesis of compounds 2a-d.



To a solution of NaOH (0.56 mmol) in 0.3 ml of MeOH was added the corresponding ligand **1a-e** (0.47 mmol) and the resulting suspension was stirred until the ligand was completely dissolved, obtaining a green-yellow solution. Then, a suspension of

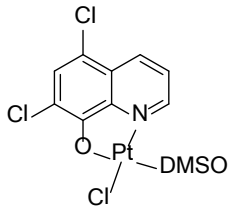
cis-$PtCl_2(DMSO)_2$ (0.45 mmol) in 0.6 ml of acetone was added. A yellow suspension is rapidly observed. The reaction was maintained for 24 h at rt and the solid product is then filtered, washed with cold water and ether, and vacuum dried during 24-48 h.

[PtCl(5-Cl-7-I-quin)(dmso)] (2a)



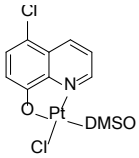
The product was obtained following the general procedure as a yellow solid (86% yield) withouth further purification. MP (°C): 195.5-196.5 (decom.). **^{1}H NMR (300 MHz, CD_2Cl_2)** δ 9.55 (dd, *J* = 5.5, 1.1 Hz, 1H), 8.71 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.01 (s, 1H), 7.62 (dd, *J* = 8.5, 5.5, 1H), 3.63 (s, 6 H). **^{13}C NMR (75 MHz, CD_2Cl_2)** δ 166.6, 149.5, 138.6, 137.7, 137.6, 128.7, 122.8, 117.4, 81.8, 46.7. **^{195}Pt NMR (64.5 MHz, CD_2Cl_2)** δ: -2737.0. **HRMS (ESI$^+$):** calcd for $C_{11}H_{11}Cl_2INO_2PtS$ (M+H): 613.8582; found: 613.8505. **ESI-MS:** m/z 634.8 $[M+Na^+]^+$**,** 612.8 $[M^+]$**. Anal. calcd. for** $C_{11}H_{10}Cl_2INO_2PtS$: C, 21.55; H, 1.64; N, 2.28; found: C, 22.04; H, 1.85; N, 2.39.

[PtCl(5,7-Cl_2-quin)(dmso)] (2b)



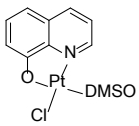
The product was obtained following the general procedure as a yellow solid (77% yield) withouth further purification. MP (°C) 236.5-238.5 (decom.). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.11 (d, *J* = 4.6 Hz, 1H), 8.67 (d, *J* = 9.1 Hz, 1H), 7.67-7.61 (m, 2H), 3.66 (s, 6 H). Due to the low solubility of the complex **^{13}C NMR** and **^{195}Pt NMR** spectra were not possible to acquire. **HRMS (MALDI)** calcd for $C_{11}H_{11}Cl_3NO_2PtS$ (M+H): 521.9117; found: 521.9164. **FAB-MS:** m/z 521.9 $[M+H^+]^+$**. Anal. calcd. for** $C_{11}H_{10}Cl_3NO_2PtS$: C, 25.32; H, 1.93; N, 2.68; found: C, 25.42; H, 2.04; N, 2.55.

[PtCl(5-Cl-quin)(dmso)] (2c)



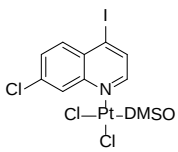
The product was obtained following the general procedure as a yellow-orange solid (77% yield) without further purification. MP (°C) 226.0-228.0 (decom.). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.46 (d, *J* = 4.5 Hz, 1H), 8.70 (dd, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.53 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 3.64 (s, 6 H). Due to the low solubility of the complex, **^{13}C NMR** spectrum was not possible to acquire. **^{195}Pt NMR (64.5 MHz, $CDCl_3$)** δ: -2763.1. **HRMS (MALDI)** calcd for $C_{11}H_{11}Cl_2NO_2PtSNa$ ($M+Na^+$): 509.9409; found: 509.9396. **FAB-MS:** m/z 486.9 $[M+H^+]^+$, 452.0 $[M-Cl]^+$**. Anal. calcd. for** $C_{11}H_{11}Cl_2NO_2PtS$: C, 27.11; H, 2.28; N, 2.87; found: C, 26.80; H, 2.28; N, 2.70.

[PtCl(quin)(dmso)] (2d)



The product was obtained following the general procedure as a yellow-orange solid (78% yield) without further purification. MP (°C) 197.0-198.0 (decom.). **^{1}H NMR (300 MHz, CD_2Cl_2)** δ 9.41 (dd, *J* = 10.7, 1.2 Hz, 1H), 8.38 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.58-7.40 (m, 2H), 7.02-7.06 (m, 2H), 3.61 (s, 6H). **^{13}C NMR (75 MHz, CD_2Cl_2)** δ 148.6, 148.3, 140.3, 140.2, 131.5, 131.0, 121.7, 115.6, 114.6. 46.6. **^{195}Pt NMR (64.5 MHz, CD_2Cl_2)** δ: -2760.7. **HRMS (FAB^+):** calcd for $C_{11}H_{12}ClNO_2PtS$ (M^+): 452.9915; found: 452.9928. **FAB-MS:** m/z 453.0 $[M+H^+]^+$, 417.0 $[M-Cl]^+$**. Anal. calcd. for** $C_{11}H_{12}ClNO_2PtS$: C, 29.18; H, 2.67; N, 3.09; found: C, 29.00; H, 2.67; N, 2.94.

[$Pt(Cl)_2$(4-I-7-Cl-quinoline)(dmso)] (5)



To a suspension of *c*-$PtCl_2(DMSO)_2$ (0.45 mmol) in 0.6 ml of acetone was added a suspension of ligand **4** (0.47 mmol) in 0.3 ml of MeOH. The resultant pale yellow suspension was stirred for 24 h at rt and the formed solid was then filtered, washed with cold water and ether, and vacuum

dried during 24-48 h. The product was obtained as a pale yellow solid (94% yield) without further purification. MP (°C) 201.5-202.2 (decom.). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.35 (d, *J* = 1.4 Hz, 1H), 8.64 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.70 (dd, *J* = 8.9, 1.8 Hz, 1H), 3.55 (s, 6H). Due to the low solubility of the complex, **^{13}C NMR** spectrum was not possible to acquire. **^{195}Pt NMR (64.5 MHz, $CDCl_3$)** δ: -3029.3. **FAB-MS:** m/z 633.6 $[M+H^+]^+$, 597.6 $[M-Cl]^+$**. Anal. calcd. for** $C_{11}H_{11}Cl_3INOPtS$: C, 20.85; H, 1.75; N, 2.21; found: C, 20.69; H, 1.79; N, 2.11.

Biological evaluation

Determination of the antiproliferative activity against different tumor cell lines.

All starting materials were commercially available research-grade chemicals and used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), fetal calf serum (FCS) from Gibco (Grand Island, NY), trichloroacetic acid (TCA) and glutamine from Merck (Darmstadt, Germany), and penicillin G, streptomycin, DMSO and sulforhodamine B (SRB) from Sigma (St Louis, MO). Cells culture and plating: Human solid tumor cell lines HBL-100, HeLa, SW1573 and WiDr were used in this study. These cell lines were a kind gift from Prof. G. J. Peters (VU Medical Center, Amsterdam, The Netherlands). Cells were mantained in 25 cm^2 culture flasks in RPMI 1640 supplemented with 5% heat inactivated fetal calf serum and 2 mM L-glutamine in a 37 °C, 5% CO_2, 95% humidified air incubator. Exponentially growing cells were trypsinized and re-suspended in antibiotic containing medium (100 units penicillin G and 0.1 mg of

streptomycin per mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 µL per well at densities of 10,000 (HBL-100 and SW1573), 15,000 (HeLa), and 20,000 (WiDr) cells per well, based on their doubling times. Chemosensitivity testing: Compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (0.25% v/v, negative control). Each agent was tested in triplicate at different dilutions in the range of 1–100 µM. The drug treatment was started on day 1 after plating and drug incubation times were 48 h. Then, cells were precipitated with 25 µL ice-cold TCA (50% w/v) and fixed for 60 min at 4 ^{o}C. Then the SRB assay was performed. The optical density (OD) of each well was measured at 492 nm, using BioTek's PowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium.

Table S-1 Antiproliferative Activity (GI_{50}, µM) of 2a-d, 5 and CDDP in Human Solid Tumor Cells.[a]

Entry	Complex	HBL-100	HeLa	SW1573	WiDr
1	**2a**	1.9 (±0.4)	14.0 (±2.7)	1.9 (±0.3)	14.0 (±8.0)
2	**2b**	21 (±0.8)	2.7 (±0.05)	7.3 (±0.8)	28.0 (±5.4)
3	**2c**	6.6 (±2.8)	2.1 (±0.4)	3.6 (±0.5)	15.0 (±0.2)
4	**2d**	4.4 (±0.2)	1.8 (±0.3)	3.3 (±0.5)	6.0 (±0.2)
5	**5**	27.0(±.078)	20.0(±1.3)	54.0(±3.6)	53.0(±2.7)
6	CDDP	1.9 (±0. 2)	2.0 (±0.3)	3.0(±0.4)	26.0 (±5.3)

[a]Data were collected after 48 h of exposure to the drugs. Values are given in µM (between brackets is the standard deviation) and are the means of 3-5 experiments.

Stability Assays

The stability of the compounds **2d** and **5** was performed in saline solution (0.9% NaCl). 1 mL of 250 µM test compound in saline solution (stock solution: 0.5 mM in CH_3OH and DMSO, for compounds **2d** and **5**, respectively) was incubated at 37 ^oC in Eppendorf tubes. At five selected time point (as indicated in Fig. 1) 100 µL aliquots were withdrawn from the Eppendorf tube, 200 µL of MeOH was added and the mixture was incubated on ice for 10 min. Afterwards, the samples were centrifugated at 5,000 rpm for 10 min at room temperature and the supernatant was analyzed in triplicated by RP-HPLC analysis on an Agilent 1200 system using Kromasil C18 reverse phase column: flow rate, 1 mL/min; detection, UV 228 nm; isocratic solvent system A/B (acetonitrile/water), 30:70 or 70:30 for **2d** and **5**, respectively. The disappearance of the compound over time was expressed as remaining percentage compared to the initial concentration.

DNA binding studies, conditions and interaction of pBR322 with cisplatin and complex 2d.[3]

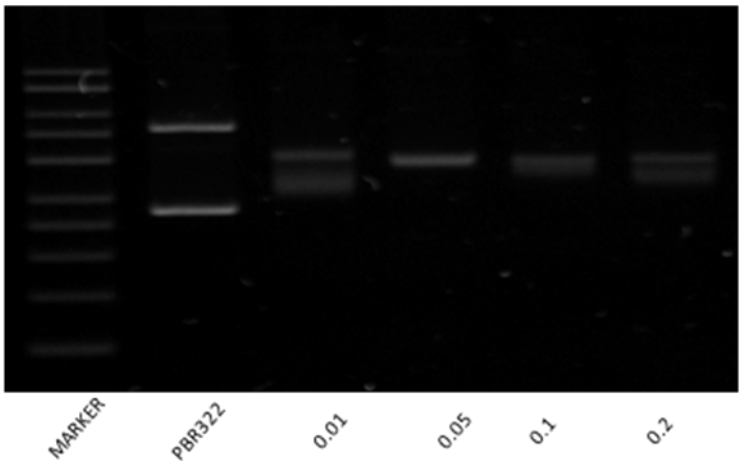


Figure S-1. Interaction of cis-platin with pBR322. Details: Agarose gel electrophoresis of pBR322 plasmid treated with cisplatin. Lane 1: Marker and lane 2: DNA of control plasmid. Plasmid DNA incubated at r_i = 0.01, 0.05, 0.1 and 0.2 with complex cisplatin

(lines 3 to 6) oc = open circular DNA form (first form from the top); ccc =covalently closed circular DNA form (second form from the top).

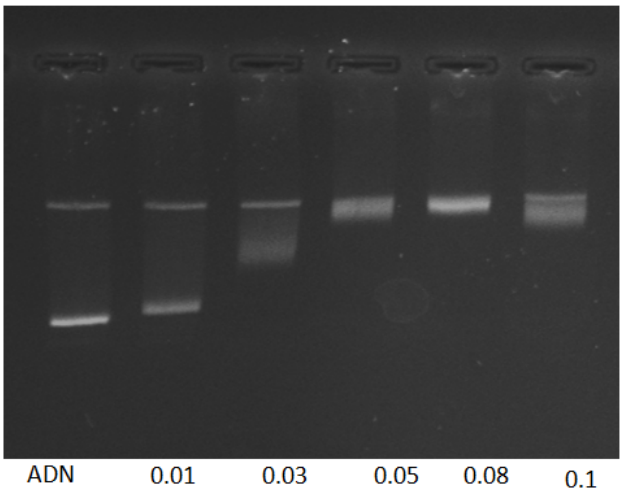


Figure S-2. Interaction of **2d** with pBR322. Details: Agarose gel electrophoresis of pBR322 plasmid treated with **2d**. Lane 1: DNA of control plasmid. Plasmid DNA incubated at r_i = 0.01, 0.03, 0.05, .0.08, and 0.1 with complex **2d** (lines 2 to 6).

The DNA binding studies were done in a total volume of 20 μL using pBR322 plasmid DNA that was purchased from GeneCust-thermo scientific. The DNA aliquots containing 8 μL of DNA-pBR322 (10 ng/mL stock) in 10 mM Tris-HCl (pH 7.6) and 1 mM EDTA were incubated with the platinum compounds at several ri (Pt/nucleotides molar ratio) values (0.01 to 0.2) using the corresponding amount of platinum from either 10 μM or 50 μM stock solution (the stock solutions were prepared from the compound solution in DMSO (1 mg/mL) and water until reaching the desired concentration). The samples were incubated at 37 ºC for 24 h, after which time 2 μL of a loading dye containing 50% glycerol, 0.25% bromophenol blue and 0.25% xylene cyanol was added. The total of the sample (20 μL) was loaded in the wells of a 0.8% agarose gel. Electrophoresis was carried out for a period of 2.5 h at approximately 50 V. After electrophoresis the gel was immersed in 800 mL of Millipore water containing 64 μL from a 10 mg/mL stock solution of ethidium bromide for 30 min. to stain the DNA.[3]

X-ray ORTEP and data of compound 2a

X-ray structure determination for compound 2a.

Crystals of compound **2a** were mounted at low temperature in inert oil on a glass fiber. Data were collected on a Bruker X8 APPEX II CCD-based diffractometer, equipped with a graphite monochromated MoKα (radiation source (λ = 0.71073 Å).

The crystal data, data collection, structural solution, and refinement parameters for the complexes are summarized in Table 1. Data were integrated using SAINT[4] and an absorption correction was performed with the program SADABS.[5] The structures were solved by direct methods using SHELXTL,[6] and refined by full-matrix least-squares methods based on F^2. All non-hydrogen atoms were refined with anisotropic thermal parameters. All H atoms were computed and refined with an overall isotropic temperature factor using a riding model.

Table S-1. Selected bond lengths [Å] and angles [°] for complex 2a.

		Bond lengths (Å)	
Entry	**Atoms**	Molecule 1	Molecule 2
1	Pt(1)-N(1)	2.022(4)	2.035(5)
2	Pt(1)-O(1)	2.029(4)	2.023(4)
3	Pt(1)-S(1)	2.195(1)	2.206(1)
4	Pt(1)-Cl(1)	2.302(1)	2.294(2)
		Angles (°)	
		Molecule 1	Molecule 2
5	N(1)-Pt(1)-O(1)	81.8(2)	81.7(2)
6	N(1)-Pt(1)-S(1)	98.6(1)	99.7(1)
7	O(1)-Pt(1)-S(1)	177.0(1)	177.3(1)
8	N(1)-Pt(1)-Cl(1)	172.0(1)	170.9(1)
9	O(1)-Pt(1)-Cl(1)	90.2(1)	89.2(1)
10	S(1)-Pt(1)-Cl(1)	89.4(1)	89.4(1)

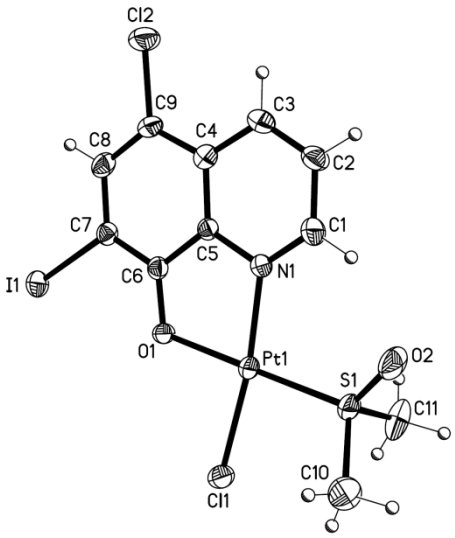


Figure S-3. ORTEP of structure **2a**.

Table 1. Crystal data and structure refinement for complex **2a**.

Complex	**2a**
Empirical formula	$C_{22}H_{20}Cl_4I_2N_2O_4Pt_2S_2$
Mw	1226.30
Temperature (K)	230 (2)
Wavelength (Å)	0.71073
Cryst. Syst.	Monoclinic
Space group	$P2_1/c$
a (Å)	7.234(1)
b (Å)	20.564(1)
c (Å)	20.220(1)
α (deg)	90
β (deg)	92.986(1)
γ (deg)	90
Volume (Å^3)	3003.6(3)
Z	8
Density (calcd) (g/cm^3)	2.712
Abs. coeff (mm^{-1})	11.888
F(000)	2240
Crystal size (mm^3)	0.431 × 0.273 × 0.222
Index ranges	$-7 \leq h \leq 8$

	$-25 \leq k \leq 25$ $-24 \leq l \leq 24$
Reflections collected	20653
Independent reflections	5695 [*R*(int) 0.0368]
Observed reflections	4837
No. of data/restraints/params.	5695 / 0 / 347
Goodness-of-fit on F^2	1.017
Final *R* indices [I > 2σ (I)]	R1 = 0.0283 wR2 = 0.0595
Largest diff peak hole ($eÅ^{-3}$)	0.891 and –1.112

Table 2. Bond lengths [A] and angles [°].

Pt(1)-N(1)	2.022(4)
Pt(1)-O(1)	2.029(4)
Pt(1)-S(1)	2.1946(15)
Pt(1)-Cl(1)	2.3024(15)
I(1)-C(7)	2.094(5)
Cl(2)-C(9)	1.738(6)
S(1)-O(2)	1.455(5)
S(1)-C(10)	1.746(8)
S(1)-C(11)	1.761(8)
O(1)-C(6)	1.317(6)
N(1)-C(1)	1.320(7)
N(1)-C(5)	1.374(6)
C(1)-C(2)	1.382(8)
C(2)-C(3)	1.353(9)
C(3)-C(4)	1.414(8)
C(4)-C(9)	1.403(8)
C(4)-C(5)	1.415(8)
C(5)-C(6)	1.421(7)
C(6)-C(7)	1.378(7)
C(7)-C(8)	1.399(8)
C(8)-C(9)	1.373(8)
Pt(1A)-O(1A)	2.023(4)
Pt(1A)-N(1A)	2.035(5)
Pt(1A)-S(1A)	2.2062(14)
Pt(1A)-Cl(1A)	2.2944(16)
I(1A)-C(7A)	2.079(7)
Cl(2A)-C(9A)	1.744(6)
S(1A)-O(2A)	1.473(4)
S(1A)-C(11A)	1.766(6)

S(1A)-C(10A)	1.769(6)
O(1A)-C(6A)	1.308(7)
N(1A)-C(1A)	1.323(7)
N(1A)-C(5A)	1.387(7)
C(1A)-C(2A)	1.391(9)
C(2A)-C(3A)	1.364(9)
C(3A)-C(4A)	1.409(9)
C(4A)-C(9A)	1.413(8)
C(4A)-C(5A)	1.421(8)
C(5A)-C(6A)	1.407(8)
C(6A)-C(7A)	1.390(8)
C(7A)-C(8A)	1.392(9)
C(8A)-C(9A)	1.369(10)
N(1)-Pt(1)-O(1)	81.81(16)
N(1)-Pt(1)-S(1)	98.58(13)
O(1)-Pt(1)-S(1)	176.98(12)
N(1)-Pt(1)-Cl(1)	172.05(13)
O(1)-Pt(1)-Cl(1)	90.25(10)
S(1)-Pt(1)-Cl(1)	89.37(6)
O(2)-S(1)-C(10)	105.6(4)
O(2)-S(1)-C(11)	107.1(4)
C(10)-S(1)-C(11)	103.8(5)
O(2)-S(1)-Pt(1)	119.50(19)
C(10)-S(1)-Pt(1)	113.5(3)
C(11)-S(1)-Pt(1)	106.0(2)
C(6)-O(1)-Pt(1)	111.9(3)
C(1)-N(1)-C(5)	118.7(5)
C(1)-N(1)-Pt(1)	129.5(4)
C(5)-N(1)-Pt(1)	111.9(3)
N(1)-C(1)-C(2)	122.7(6)
C(3)-C(2)-C(1)	120.2(6)
C(2)-C(3)-C(4)	119.9(6)
C(9)-C(4)-C(3)	126.1(6)
C(9)-C(4)-C(5)	117.2(5)
C(3)-C(4)-C(5)	116.7(5)
N(1)-C(5)-C(4)	121.8(5)
N(1)-C(5)-C(6)	115.4(5)
C(4)-C(5)-C(6)	122.8(5)
O(1)-C(6)-C(7)	124.3(5)
O(1)-C(6)-C(5)	119.1(5)
C(7)-C(6)-C(5)	116.6(5)

C(6)-C(7)-C(8)	121.9(5)
C(6)-C(7)-I(1)	119.7(4)
C(8)-C(7)-I(1)	118.3(4)
C(9)-C(8)-C(7)	120.6(5)
C(8)-C(9)-C(4)	120.9(5)
C(8)-C(9)-Cl(2)	119.9(5)
C(4)-C(9)-Cl(2)	119.2(5)
O(1A)-Pt(1A)-N(1A)	81.70(17)
O(1A)-Pt(1A)-S(1A)	177.28(13)
N(1A)-Pt(1A)-S(1A)	99.67(13)
O(1A)-Pt(1A)-Cl(1A)	89.24(12)
N(1A)-Pt(1A)-Cl(1A)	170.92(13)
S(1A)-Pt(1A)-Cl(1A)	89.40(6)
O(2A)-S(1A)-C(11A)	108.1(3)
O(2A)-S(1A)-C(10A)	107.1(3)
C(11A)-S(1A)-C(10A)	102.2(3)
O(2A)-S(1A)-Pt(1A)	117.87(17)
C(11A)-S(1A)-Pt(1A)	108.1(2)
C(10A)-S(1A)-Pt(1A)	112.3(2)
C(6A)-O(1A)-Pt(1A)	112.6(4)
C(1A)-N(1A)-C(5A)	119.6(5)
C(1A)-N(1A)-Pt(1A)	129.8(4)
C(5A)-N(1A)-Pt(1A)	110.6(4)
N(1A)-C(1A)-C(2A)	122.3(6)
C(3A)-C(2A)-C(1A)	120.1(6)
C(2A)-C(3A)-C(4A)	119.8(6)
C(3A)-C(4A)-C(9A)	125.9(6)
C(3A)-C(4A)-C(5A)	117.9(5)
C(9A)-C(4A)-C(5A)	116.2(6)
N(1A)-C(5A)-C(6A)	116.2(5)
N(1A)-C(5A)-C(4A)	120.4(5)
C(6A)-C(5A)-C(4A)	123.4(5)
O(1A)-C(6A)-C(7A)	124.1(6)
O(1A)-C(6A)-C(5A)	118.9(5)
C(7A)-C(6A)-C(5A)	117.0(6)
C(6A)-C(7A)-C(8A)	121.2(6)
C(6A)-C(7A)-I(1A)	118.9(5)
C(8A)-C(7A)-I(1A)	120.0(5)
C(9A)-C(8A)-C(7A)	121.2(6)
C(8A)-C(9A)-C(4A)	121.1(6)
C(8A)-C(9A)-Cl(2A)	120.4(5)

C(4A)-C(9A)-Cl(2A) 118.5(5)

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