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Synthesis, structure, and *in vitro* cytotoxicity of organoplatinum(II) complexes containing aryl olefins and quinolines

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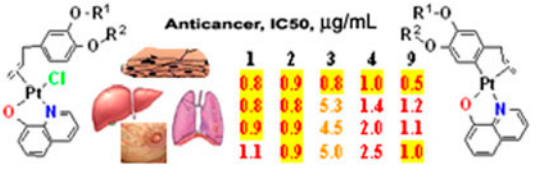

Ten new organoplatinum(II) complexes, [PtCl(Saf)(8-OQ)] (**1**), [Pt(Saf-1H)(8-OQ)] (**2**), [PtCl(Meug)(8-OQ)] (**3**), [Pt(Meug-1H)(8-OQ)] (**4**), [PtCl(Meteug)(8-OQ)] (**5**), [PtCl(Meteug)(Q)] (**6**), [Pt(Meteug)(Q-COO)] (**7**), [Pt(Eteug-1H)(Q)] (**8**), [Pt(Eteug-1H)(8-OQ)] (**9**), and [Pt(Eteug-1H)(Q-COO)] (**10**) (where Saf = safrole, Meug = methyleugenol, Meteug = methyl eugenoxyacetate, Eteug = ethyl eugenoxyacetate, Q = quinoline, 8-OQ = 8-hydroxyquinolinate, and Q-COO = quinolin-2-carboxylate), were synthesized and characterized by spectroscopic methods. The position of N and O donors of quinoline ligands in comparison with the ethylenic double bond and the aromatic C5 of the aryl olefins in platinum(II) coordination sphere of **1–10** was determined using their NOESY spectra and confirmed by single-crystal X-ray diffraction of **10**. Complexes **1**, **2**, **3**, **4,** and **9** exhibit impressive activities on four human cancer cell lines KB, Hep-G2, Lu, and MCF7 with IC_{50} = 1.4–9.6 µM. Complexes **1**, **2**, **4,** and **9** gave better antitumor activity than cisplatin against examined cell lines.

Keywords: Platinum(II) complex; Platinacycle; Safrole; Eugenol; 8-Hydroxyquinoline; Anticancer complex

1. Introduction

Platinum-based drugs, notably cisplatin, carboplatin, and oxaliplatin, have dominated the treatment of various cancers by chemical agents. However, these drugs cause serious side effects [1]; moreover, clinical utility of cisplatin and the second-generation platinum drugs is limited to a relatively narrow range of tumors, because of primary resistance and the

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development of resistance secondary to the initial treatment [2, 3]. Hence, unconventional platinum(II) complexes with different organic ligands were designed as a strategy to overcome resistance to cisplatin and its analogs [4, 5].

Studies over the last three decades have shown that the range of platinum complexes with useful cytotoxicity and antitumor activity is not strictly limited to structural analogs of cisplatin. Most of the well-known platinum anticancer complexes have amines as ligands. Platinum coordination compounds comprising at least one amine ligand and use of such compounds in the treatment of cancer were described [5–8]. Lippard and co-workers describe that *cis*-[Pt(NH_3)$_2$(Phenanthridine)Cl]NO_3, termed phenanthriplatin, was 7–40 times more active than cisplatin in an initial screen of human cancer cells from a variety of organs [5]. Some complexes of platinum(II) with natural compounds are synthesized and their antitumor and antiviral activities have been demonstrated [8, 9]. Several classes of *trans* platinum complexes have been characterized, showing favorable cytotoxicity against cancer cells, especially cisplatin-resistant cells [10]. In particular, unexpected organoplatinum(II) complexes with one normal and one cyclometalated 2-phenylpyridine ligand were discovered that exhibited high antitumor efficacy against cisplatin-resistant mouse sarcoma 180 (S-180cisR) cell lines [11].

Some time ago, we focused our attention to several natural arylolefins from vegetable essential oils that, owing to their structure, could act as good substrate in order to prepare heterocyclic compounds and metallacyclic complexes. For example, safrole (in sassafras oil) and methyleugenol (in lemongrass, tarragon oils) were introduced into the coordination sphere of Pt(II). Then, under mild reaction conditions these aryl olefin ligands were deprotonated to form new platinacycles [12–14]. It is interesting that many of these organoplatinum (II) complexes exhibit significant inhibitory activities on human cancer cells, in which the complexes containing heterocyclic amines have high activity (IC_{50} = 2.5–5.0 μg mL^{-1}).

Herein we report the synthesis, structure, and cytotoxicity of several organoplatinum(II) complexes containing safrole or derivatives of eugenol and some quinolines.

2. Experimental

2.1. *General and instrumental*

Elemental analysis: Pt was analyzed according to the weight method [15], and C and H were analyzed on a LECO CHNS model 932 elemental analyzer. IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr disks from 400 to 4000 cm^{-1}. NMR spectra were recorded on a Bruker AVANCE 500 MHz at 298–300 K, with TMS as the internal standard in a suitable solvent (tables 1–3). The *in vitro* cytotoxicities were tested at the Experimental Biological Laboratory – Institute of Chemistry of Natural Compounds (in Hanoi), according to the method described [16]. IC_{50} values were calculated based on OD values taken on an Elisa instrument at 515–540 nm. Single-crystal X-ray diffraction is recorded on an Agilent SuperNova diffractometer (mirror-monochromated MoKα radiation, $\lambda = 0.71073$ Å) at 100 K with the absorption correction applied using CrysAlisPro [17]. Using OLEX2 [18], the structure was solved by direct methods (SHELXS) [19] and refined by full-matrix least squares based on F^2 using SHELXL [19]. All non-hydrogen atoms were refined anisotropically. Hydrogens were located in calculated positions and refined in the riding mode with $U_{iso} = 1.2U_{eq}$(C) (1.5 times for methyl groups).

2.2. *Preparation*

2.2.1. [PtCl(Saf)(8-OQ)] (1). To a solution of K[$PtCl_3$(Saf)] (200 mg, 0.4 mmol, previously prepared [12], Saf = Safrole, 4-allyl-1,2-methylenedioxybenzene) in 10 mL ethanol/water (3 : 1 by volume), a solution of 8-hydroxyquinoline (8-HOQ, 58 mg, 0.4 mmol) in 4 mL ethanol was slowly added and stirred at room temperature for 2 h. The resulting deep-yellow precipitate was collected, washed with a solution of 0.1 N HCl, water, cold ethanol, and dried in a vacuum at 50 °C for 2 h. The yield was 162 mg (76%). Anal. Calcd for [$PtC_{19}H_{16}NO_3Cl$] (%): Pt, 36.34; C, 42.51; H, 3.00. Found: Pt, 36.61; C, 42.23; H, 3.21. IR, cm^{-1}: 3062, 2930, 2884 (ν_{CH}); 1574, 1502, 1486 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^{1}H NMR: see table 1. ^{13}C NMR (in d_6-acetone), δ, ppm: 146.03 (C1); 148.70 (C2); 110.04 (C3); 132.08 (C4); 122.74 (C5); 108.98 (C6); 101.80 (C7); 39.80 (C8); 98.41 (C9); 69.30 (C10); 146.63 (C12); 122.19 (C13); 142.58 (C14); 114.89 (C15); 115.32 (C16); 131.47 (C17); 169.21 (C18); 147.21 (C19); 133.67 (C20).

2.2.2. [Pt(Saf-1H)(8-OQ)] (2). To a mixture of [Pt_2Cl_2(Saf-1H)$_2$] (392 mg, 0.5 mmol, previously prepared [12]) and 15 mL acetone, a solution of 8-hydroxyquinoline (8-HOQ, 145 mg, 1 mmol) in 5 mL ethanol was slowly added and stirred at room temperature for 2 h. The resulting solution was evaporated to 10 mL. A deep-yellow precipitate was collected by filtration, washed with cold ethanol and recrystallized from ethanol/water 3/1 by volume. The yield was 334 mg (67%). Anal. Calcd for [$PtC_{19}H_{15}NO_3$] (%): Pt, 39.98; C, 45.60; H, 3.02. Found: Pt, 40.26; C, 45.33; H, 3.23. IR, cm^{-1}: 3050, 2889 (ν_{CH}); 1579, 1499, 1455 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^{1}H NMR: see table 1. ^{13}C NMR (in d_6-acetone), δ, ppm: 144.10 (C1); 146.76 (C2); 105.77 (C3); 143.20 (C4); 129.28 (C5); 112.68 (C6); 100.63 (C7); 38.39 (C8); 79.79 (C9); 56.34 (C10); 146.08 (C12); 122.83 (C13); 139.54 (C14); 114.60 (C15); 116.39 (C16); 129.28 (C17); 169.65 (C18); 144.38 (C19); 131.87 (C20).

2.2.3. [PtCl(Meug)(8-OQ)] (3). To a solution of K[$PtCl_3$(Meug)] (260 mg, 0.5 mmol, previously prepared [13], Meug = methyleugenol, 4-allyl-1,2-dimethoxybenzene) in 15 mL ethanol/water (2 : 1 by volume), a solution of 8-hydroxyquinoline (8-HOQ, 73 mg, 0.5 mmol) in 4 mL ethanol was slowly added and stirred at room temperature for an hour. The resulting red precipitate was collected, washed with a solution of 0.1 N HCl, water, cold ethanol, and dried in a vacuum at 50 °C for 2 h. The yield was 224 mg (81%). Anal. Calcd for [$PtC_{20}H_{20}NO_3Cl$] (%): Pt, 35.28; C, 43.45; H, 3.65. Found: Pt, 35.55; C, 43.19; H, 3.38. IR, cm^{-1}: 3067, 2940, 2848 (ν_{CH}); 1575, 1498, 1464 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^{1}H NMR: see table 1. ^{13}C NMR (in d_6-acetone), δ, ppm: 146.65 (C1); 149.08 (C2); 113.91 (C3); 132.08 (C4); 122.15 (C5); 113.04 (C6); 56.06 (C7a); 55.55 (C7b); 38.69 (C8); 99.35 (C9); 68.76 (C10); 146.06 (C12); 121.63 (C13); 142.54 (C14); 114.87 (C15); 131.48 (C16); 115.37 (C17); 169.28 (C18); 150.27 (C19); 132.40 (C20).

2.2.4. [Pt(Meug-1H)(8-OQ)] (4). To a mixture of [Pt_2Cl_2(Meug-1H)$_2$] (408 mg, 0.5 mmol, previously prepared [13]) in 40 mL acetone/water (4/1 by volume), a solution of 8-hydroxyquinoline (8-HOQ, 145 mg, 1 mmol) in 10 mL acetone/water (4/1 by volume) was slowly added and stirred at room temperature for an hour. A red precipitate was filtered, washed with ethanol, and recrystallized from acetone/water 5/1 by volume. The yield was 418 mg

(81%). Anal. Calcd for [$PtC_{20}H_{19}NO_3$] (%): Pt, 37.77; C, 46.51; H, 3.71. Found: Pt, 38.05; C, 45.25; H, 3.46. IR, cm^{-1}: 3065, 2994, 2831 (ν_{CH}); 1574, 1494, 1458 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^1H NMR: see table 1. ^{13}C NMR (in d_6-acetone), δ, ppm: 146.66 (C1); 149.17 (C2); 110.21 (C3); 143.14 (C4); 128.47 (C5); 117.45 (C6); 56.36 (C7a); 56.17 (C7b); 38.17 (C8); 80.30 (C9); 56.47 (C10); 146.07 (C12); 122.85 (C13); 139.50 (C14); 114.59 (C15); 131.45 (C16); 115.38 (C17); 169.70 (C18); 144.32 (C19); 131.88 (C20).

2.2.5. [PtCl(Meteug)(8-OQ)] (5). This complex was prepared starting from 289 mg (0.5 mmol) K[Pt(Meteug)Cl_3] (previously prepared [13]), 73 mg (0.5 mmol) 8-hydroxyquinoline (8-HOQ) according to the procedure for preparation of **3**. The yield was 210 mg (70%), yellow crystals. Anal. Calcd for [$PtC_{22}H_{22}ClNO_5$] (%): Pt, 31.93; C, 43.25; H, 3.63. Found: Pt, 32.19; C, 43.02; H, 3.46. IR (cm^{-1}): 3062, 2949, 2850 (ν_{CH}); 1764 ($\nu_{C=O}$); 1591, 1507, 1462 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^1H NMR: see table 2. ^{13}C NMR has not been recorded for lack of solubility.

2.2.6. [PtCl(Meteug-1H)(Q)] (6). This complex was prepared starting from 188 mg (0.2 mmol) [Pt_2(Meteug-1H)$_2Cl_2$], 0.4 mmol quinoline (Q) according to the procedure for preparation of **4**. The yield was 160 mg (67%), white crystals. Anal. Calcd for [$PtC_{22}H_{22}NO_4Cl$] (%): Pt, 32.79; C, 44.41; H, 3.73. Found: Pt, 33.04; C, 44.15; H, 3.58. IR, cm^{-1}: 3070, 3000, 2926, 2855 (ν_{CH}); 1764 ($\nu_{C=O}$); 1585, 1500 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^1H NMR: see table 2. ^{13}C NMR has not been recorded for lack of solubility.

2.2.7. [Pt(Meteug-1H)(Q-COO)] (7). To a mixture of [Pt_2(Meteug-1H)$_2Cl_2$] (188 mg, 0.2 mmol), ethanol (5 mL) and water (5 mL) was added a solution of quinaldinic acid (Q-COOH, 0.4 mmol in 4 mL of ethanol/water 1 : 1 by volume). The reaction mixture was stirred at room temperature for 3 h, and then cooled to 0 °C. The solid compound obtained was isolated by filtration, washed with ethanol, and recrystallized from ethanol/acetone 3/1 by volume. The yield was 205 mg (85%), yellow crystals. Anal. Calcd for [$PtC_{23}H_{21}NO_6$] (%): Pt, 32.38; C, 45.85; H, 3.51. Found: Pt, 32.58; C, 45.56; H, 3.25. IR, cm^{-1}: 3029, 2937, 2850 (ν_{CH}); 1753 (ester $\nu_{C=O}$); 1664 (carboxylate $\nu_{C=O}$); 1605, 1570, 1484 ((aromat. $\nu_{C=C}$, $\nu_{C=N}$)). ^1H NMR: see table 2. ^{13}C NMR has not been recorded for lack of solubility.

2.2.8. [PtCl(Eteug-1H)(Q)] (8). This complex was prepared starting from 192 mg (0.2 mmol) [Pt_2(Eteug-1H)$_2Cl_2$], 0.4 mmol quinoline (Q) according to the procedure for preparation of **2**. The yield was 199 mg (82%), white crystals from acetone/ethanol 1 : 2 by volume. Anal. Calcd for [$PtC_{23}H_{24}NO_4Cl$] (%): Pt, 32.03; C, 45.36; H, 3.97. Found: Pt, 32.31; C, 45.03; H, 4.18. IR, cm^{-1}: 3089, 2977, 2834 (ν_{CH}); 1750 ($\nu_{C=O}$); 1582, 1510, 1480 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^1H NMR: see table 3. ^{13}C NMR has not been recorded for lack of solubility.

2.2.9. [Pt(Eteug-1H)(Q-O)] (9). This complex was prepared starting from 192 mg (0.2 mmol) [Pt_2(Eteug-1H)$_2Cl_2$], 0.4 mmol 8-hydroxyquinoline (Q-OH) according to the procedure for preparation of **8**. The yield was 176 mg (75%), yellow crystals from acetone/ethanol 1 : 1 by volume. Anal. Calcd for [$PtC_{23}H_{23}NO_5$] (%): Pt, 33.15; C, 46.94; H, 3.94.

Found: Pt, 33.45; C, 46.69; H, 3.72. IR, cm^{-1}: 3053, 2974, 2825 (ν_{CH}); 1753 ($\nu_{C=O}$); 1580, 1504, 1469 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^{1}H NMR: see table 3. ^{13}C NMR (in d_6-acetone), δ, ppm: 145.05 (C1); 149.60 (C2); 110.71 (C3); 145.14 (C4); 128.70 (C5); 120.34 (C6); 67.85 (C7a); 56.56 (C7b); 61.18 (C7c); 14.63 (C7d); 38.22 (C8); 80.16 (C9); 56.33 (C10); 146.05 (C12); 122.83 (C13); 139.52 (C14); 114.58 (C15); 131.47 (C16); 115.34 (C17); 169.77 (C18); 143.50 (C19); 132.05 (C20); 170.01 (C=O).

2.2.10. [Pt(Eteug-1H)(Q-COO)] (10). This complex was prepared starting from 192 mg (0.2 mmol) $[Pt_2(Eteug\text{-}1H)_2Cl_2]$, 0.4 mmol quinaldinic acid (Q-COOH) according to the procedure for preparation of **7**. The yield was 200 mg (81%), yellow crystals from ethanol/acetone 3 : 1 by volume. Anal. Calcd for $[PtC_{24}H_{23}NO_6]$ (%): Pt, 31.64; C, 46.76; H, 3.76. Found: Pt, 31.35; C, 46.39; H, 4.14. IR, cm^{-1}: 3050, 2965, 2866 (ν_{CH}); 1753 (ester $\nu_{C=O}$); 1656 (carboxylate $\nu_{C=O}$); 1600, 1567, 1490, 1455 (aromat. $\nu_{C=C}$, $\nu_{C=N}$). ^{1}H NMR: see table 3. ^{13}C NMR has not been recorded for lack of solubility.

Crystal data for $C_{24}H_{23}NO_6Pt$ (M = 616.52): monoclinic, space group $P2_1/n$ (no. 14), a = 8.4184(4) Å, b = 17.3263(16) Å, c = 14.6435(3) Å, β = 102.267(3)°, V = 2087.1(2) Å^3, Z = 4, T = 99.99(10) K, μ(Mo Kα) = 6.766 mm^{-1}, $Dcalc$ = 1.968 g mm^{-3}, 42,682 reflections measured ($5.48 \le 2\Theta \le 52.74$), 4274 unique ($R_{int}$ = 0.0303) which were used in all calculations. The final R_1 was 0.0155 (>2sigma(I)), and wR_2 was 0.0329 (all data). Largest difference peak/hole = 0.60/−0.39 e Å^{-3}. The deposition number: CCDC 1057363.

3. Results and discussion

Four aryl olefins of natural origin used for formation of C-Pt bonds in the title complexes are presented in figure 1. They are safrole (Saf), methyl eugenol (Meug), methyl eugenoxyacetate (Meteug), and ethyl eugenoxyacetate (Eteug).

The replacement of ethylene in Zeise's salt with the aryl olefins (Arol) gave complexes of formula $K[PtCl_3(Arol)]$, which may be readily transformed to dinuclear chelate ring complexes of formula $[Pt_2Cl_2(Arol\text{-}1H)_2]$ (here (Arol-1H) is the chelating aryl olefin) [12, 13]. Reaction of these starting complexes and monodentate or bidentate quinolines such as quinoline (Q), 8-hydroxyquinoline (8-HOQ), and quinaldinic acid (Q-COOH) afforded **1–10** as shown in figure 2 (see also tables 1–3).

The absorption bands in IR spectra of **1–10** are in accord with the coordinated aryl olefins and the quinolines (see Experimental section). In addition, the absence of a band at

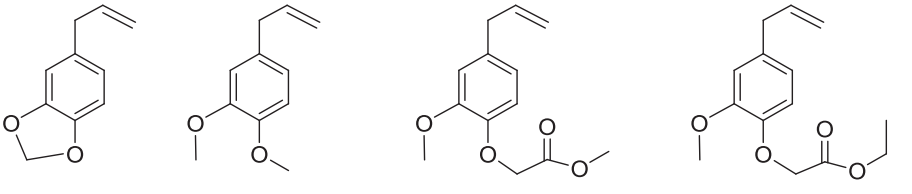


Figure 1. Four aryl olefins used for the formation of C-Pt bonds.

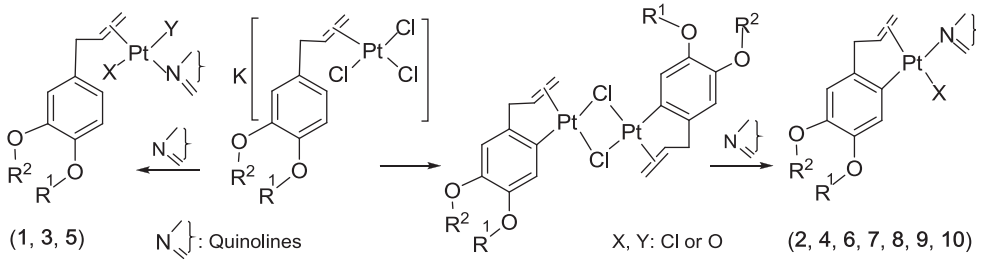


Figure 2. Reaction scheme for synthesis of **1–10**.

Table 1. ^{1}H NMR signals of **1–4**, δ (ppm), J (Hz).

Compd.	(1)	(2)	(3)	(4)
Sol.	$(CD_3)_2CO$	$(CD_3)_2CO$	$(CD_3)_2CO$	$(CD_3)_2CO$
H3	6.98 d; ^4J 1;	6.60 s	7.10 d; ^4J 1.5;	6.69 s
H5	6.90 dd; ^3J 8; ^4J 1	–	6.95 dd; ^3J 8; ^4J 1.5	–
H6	6.72 d; ^3J 8	7.06 s; $^3J_{PtH}$ 40	6.83 d; ^3J 8	7.12 s
H7a/7b	5.91 s/5.91 s	5.83 s/5.83 s	3.72 s/3.45 s	3.81 s/3.71 s
H8a	3.29 dd; ^2J 15; ^3J 7; $^3J_{PtH}$ unr.(*)	2.84 d; ^2J 17; $^3J_{PtH}$ 85	3.26 dd; ^2J 15; ^3J 6; $^3J_{PtH}$ unr.	2.82 d; ^2J 17; $^3J_{PtH}$ unr.
H8b	3.66 dd; ^2J 15; ^3J 7	3.61 dd; ^2J 17; ^3J 6	3.59 dd; ^2J 15; ^3J 8	3.63 dd; ^2J 17; ^3J 6
H9	5.58 m; $^2J_{PtH}$ 75	4.86 m; $^2J_{PtH}$ 75	5.61 m; $^2J_{PtH}$ 70	4.87 m; $^2J_{PtH}$ 75
t-H10	4.77 d; ^3J 15; $^2J_{PtH}$ 65	3.70 d; ^3J 14; $^2J_{PtH}$ 65	4.75 d; ^3J 14; $^2J_{PtH}$ 67	3.68 d; ^3J 13
c-H10	4.75 d; ^3J 8; $^2J_{PtH}$ 65	4.23 d; ^3J 8; $^2J_{PtH}$ 66	4.72 d; ^3J 8; $^2J_{PtH}$ 67	4.24 d; ^3J 8; $^2J_{PtH}$ 70
H12	9.07 dd; ^3J 5; ^4J 1; $^3J_{PtH}$ 40	8.43 d; ^3J 5; $^3J_{PtH}$ unr.	9.06 dd; ^3J 5; ^4J 1; $^3J_{PtH}$ 40	8.46 dd; ^3J 5; ^4J 1; $^3J_{PtH}$ 40
H13	7.83 dd; ^3J 5; ^3J 8	7.62 dd; ^3J 5; ^3J 8	7.82 dd; ^3J 5; ^3J 8	7.64 dd; ^3J 5; ^3J 8
H14	8.75 dd; ^3J 8; ^4J 1	8.52 d; ^3J 8	8.75 dd; ^3J 8; ^4J 1	8.52 dd; ^3J 8; ^4J 1
H15	7.23 d; ^3J 8	7.15 d; ^3J 8	7.23 d;^3J 8	7.16 d; ^3J 8
H16	7.49 t; ^3J 8	7.55 t; ^3J 8	7.50 t; ^3J 8	7.56 t; ^3J 8
H17	7.03 d; ^3J 8	7.10 d; ^3J 8	7.05 d; ^3J 8	7.11 d; ^3J 8

(*) unr: unresoluble.

1640 cm^{-1} from the C=C double bond of allyl group in the non-coordinated aryl olefins (figure 1) indicates the allyl group coordinates in an η^2 manner. The absence of a strong broadened band of the OH group in spectra of **1–5**, **7**, **9,** and **10** indicates that the OH of 8-hydroxyquinoline and of quinaldinic acid are deprotonated.

The assignment of the ^{1}H NMR and ^{13}C NMR signals is based on their chemical shifts and spin–spin splitting patterns. For the ambiguous cases NOESY, HSQC, and HMBC were also used. For example in the NOESY spectrum of **2**, the singlet at 6.60 ppm gives a cross peak with H8a, whereas the singlet at 7.06 ppm does not give a cross peak. Therefore, the first singlet was assigned to H3, and the second was assigned to H6 (see figure 3). The ^{1}H

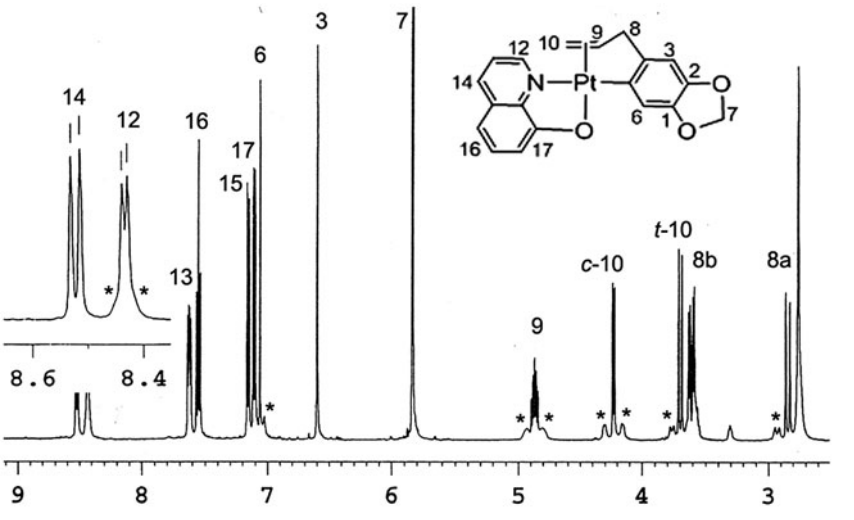


Figure 3. The ^{195}Pt satellites indicated with * in ^{1}H NMR of **2**.

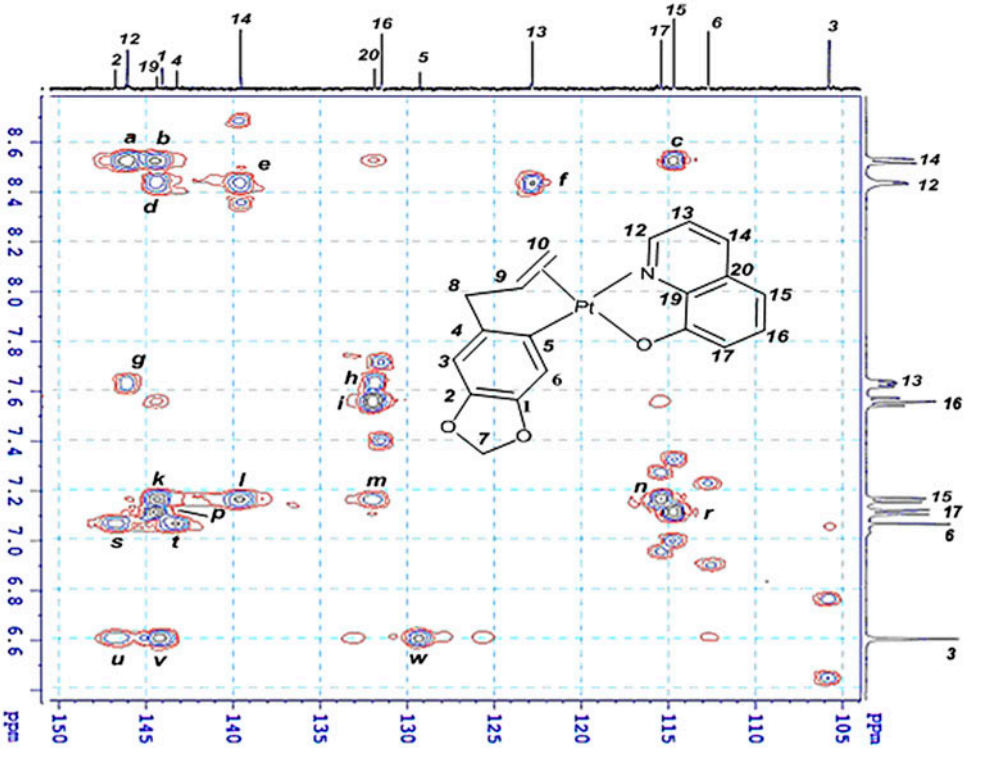


Figure 4. Partial HMBC spectrum of **2**.

NMR signals of **1–10** are listed in tables 1–3. The ^{13}C NMR signals of **2** were assigned using its HMBC spectrum as in figure 4.

The signal at 146.76 ppm has cross peaks *s* with H6 and *u* with H3, and thus, it is assigned to C2. The signal at 146.08 ppm gives cross peaks *a* with H14 and *g* with H13, and thus, it belongs to C12. The signal at 144.38 ppm has the cross peaks *b* with H14, *d* with H12, *k* with H15 and *p* with H17, and thus, it belongs to C19. The signal at 144.10 ppm has the cross peak *v* with H3, and thus, it is assigned to C1. The signal at 143.20 ppm has the cross peak *t* with H6, and thus, it is assigned to C4. The signal at 131.87 ppm has the cross peaks *h* with H13, *i* with H16 and *m* with H15, and thus, it belongs to C20. Similarly, all carbon signals of the compound were assigned. The ^{13}C NMR signals of examined compounds are listed in the experimental part.

Coordination of the C=C bond of the allyl group with Pt in **1–10** is proved as following: For the non-coordinated aryl olefins, the two H8 protons give a doublet at 3.22 ppm with $^{3}J = 6.5$ Hz, but in the spectra of the examined complexes, there are two separated signals (usually in form of two doublets with $^{2}J = 15–17$ Hz) for H8a and H8b (figure 3). This is expected since upon coordination to Pt(II), C9 becomes a chiral center and H8a and H8b become diastereotopic. The ^{195}Pt satellites from H9, *cis*-H10, and *trans*-H10 in many compounds are clear (indicated with * in figure 3) with the distance between them, $^{2}J_{PtH}$, 65–75 Hz. For non-coordinated aryl olefins, the signals of C9 and C10 lie in sp^2-carbon region (greater than 120 ppm), whereas for **1–4** and **9**, the signals of C9 are 80.16–99.35 ppm and C10 56.33–69.30 ppm. These indicate that the allyl group of aryl olefins in **1–10** are η^2-coordinated olefin.

The loss of the signal of H5 and the appearance of the ^{195}Pt satellites for H6 in ^{1}H NMR spectra of **2**, **4,** and **6–10** (tables 1–3, figure 3) are convincing evidence for the formation of Pt-C5 linkage in these complexes.

The appearance of the ^{195}Pt satellites for H12 in ^{1}H NMR spectra of **1–6**, **8,** and **9** shows the coordination of quinoline N with Pt. For **1**, **3**, **4,** and **5,** the ^{195}Pt satellites for H12 of quinolines are clear so the distance between them was measured ($^{3}J_{PtH} = 40$ Hz). For other compounds, the ^{195}Pt satellites for H12 are overlapping or unresolved (figure 3, tables 1–3) so $^{3}J_{PtH}$ was not estimated.

In order to determine the configuration of the reported complexes, with respect to the position of N and O donors of quinoline ligands in the coordination sphere of Pt, their NOESY spectra were studied. For example, in the spectrum of **4** (figure 5), the cross peaks *a* and *b* between H9 and *cis*-H10, and between H12 and H9 show that N of 8-hydroxyquinolinate is *cis* to the ethylenic double bond, *i.e.,* is at *trans*-position in comparison with C5 of the phenyl group. In the NOESY spectrum of **4,** there are also other cross peaks, for instance, the cross peaks between H7a and H6, between H7b and H3, and between H3 and H8a, *etc*. All these cross peaks suggest the spatial structure of **4** as in figure 5.

The NOESY spectra of the other compounds were also analyzed. In the spectra of **2**, **4**, **6**, **8,** and **9,** the protons H9 and *cis*-H10 give two cross peaks with H12 of the quinoline ligand. In the spectra of **7** and **10,** H9 and *cis*-H10 give two cross peaks with H18 of the quinaldinate ligand. These indicate that in **2**, **4**, **6**, **7**, **8**, **9,** and **10,** the quinoline N is *trans* to C5 of the phenyl group as shown in tables 1–3. In spectra of **1**, **3,** and **5,** there are no cross peaks between H9 or *cis*-H10 and H12 of the 8-hydroxyquinolinate ligand, indicating that in **1**, **3,** and **5,** the quinoline N is *trans* to the ethylenic double bond as shown in tables 1 and 2.

The molecular and crystal structure of [Pt(Eteug-1H)(Q-COO)] (**10**) was determined by single-crystal X-ray diffraction. The obtained information confirms the conclusion from the

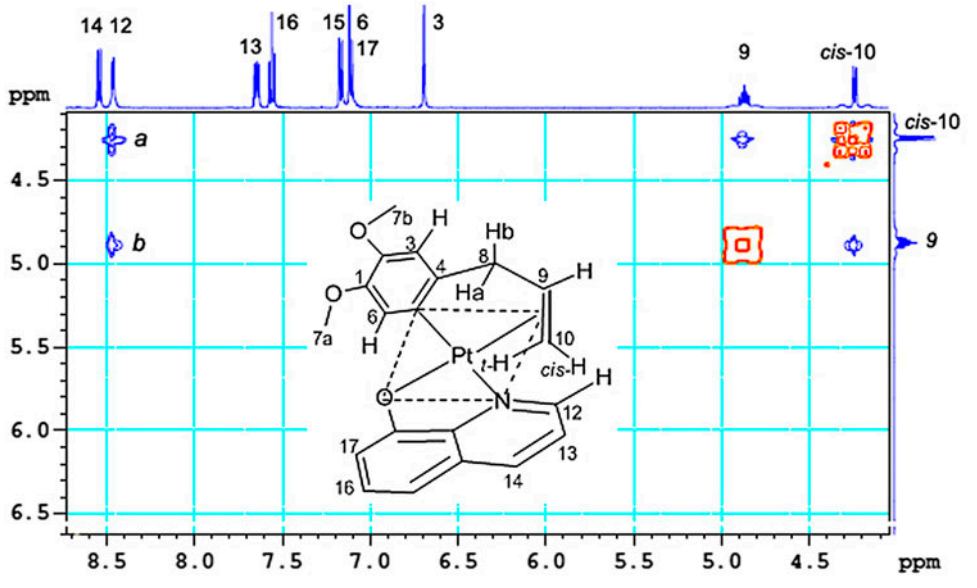
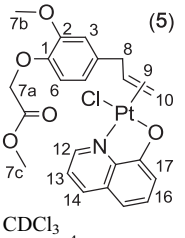
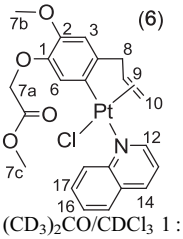
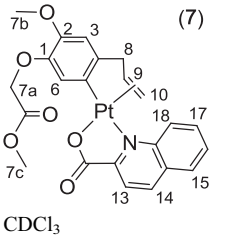


Figure 5. Partial NOESY spectrum of **4**.

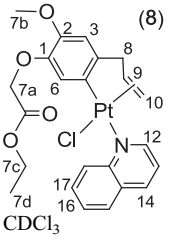
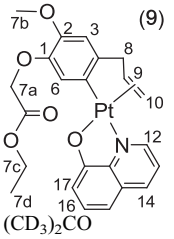
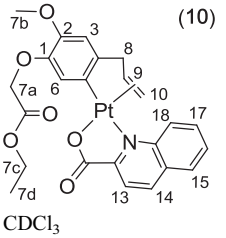
Table 2. ^{1}H NMR signals of **5**, **6** and **7**, δ (ppm), J (Hz).

Compd.	 (5)	 (6)	 (7)
Sol.	$CDCl_3$	$(CD_3)_2CO/CDCl_3$ 1 : 1	$CDCl_3$
H3/ H5	6.95 d; ^{4}J 2/6.84 dd; ^{3}J 8; ^{4}J 2	6.70 s/–	6.68 s/–
H6	6.74 d; ^{3}J 8	7.13 s; $^{3}J_{PtH}$ 40	7.03 s; $^{3}J_{PtH}$ 40
H7a/H7b	4.64 s/ 3.61 s	4.63 s/3.76 s	4.77 s/3.83 s
H7c	3.71 s	3.78 s	3.86 s
H8a	3.29 dd; ^{2}J 15; ^{3}J 7	2.69 d; ^{2}J 17	2.86 d; ^{2}J 17
H8b	3.65 dd; ^{2}J 15; ^{3}J 7	3.75 m	3.84 d; ^{2}J 17
H9	5.69 m; $^{2}J_{PtH}$ 70	4.67 m; $^{2}J_{PtH}$ unr. (*)	5.54 m; $^{2}J_{PtH}$ 75
trans-H10	4.79 d; ^{3}J 14; $^{2}J_{PtH}$ 70	3.86 d; ^{3}J 12;	4.03 d; ^{3}J 14
cis-H10	4.83 d; ^{3}J 8; $^{2}J_{PtH}$ unr.	3.88 d; ^{3}J 6;	4.63 d; ^{3}J 7
H12	9.09 dd; ^{3}J 5; ^{4}J 1; $^{3}J_{PtH}$ 40	9.18 br. (**) s; $^{3}J_{PtH}$ unr.	–
H13	7.57 dd; ^{3}J 5; ^{3}J 8	7.73 m	8.39 d; ^{3}J 8
H14	8.45 dd; ^{3}J 8; ^{4}J 1	8.62 d; ^{3}J 8	8.52 d; ^{3}J 8
H15/H16	7.09 d/7.45 t; ^{3}J 8	8.14 d/7.77 t; ^{3}J 8	8.02 d/7.75 t; ^{3}J 8
H17/ H18	7.07 d; ^{3}J 8/–	8.01 t; ^{3}J 8/9.18 br. s	7.86 t; ^{3}J 8/7.60 d; ^{3}J 8

(*) unr: unresoluble; (**) br. broadened.

analysis of the NOESY spectra. In particular, as seen in figure 6, the N of quinaldinate ligand is *cis* to the ethylenic double bond, the O of the ligand is *trans* to the ethylenic double bond and the proton H12 is in proximity to both H9 and *cis*-H10. The best least-squares planes through both aromatic rings (C5–C10 and N20–C29) make an angle of 34.15(10)°.

Table 3. ^{1}H NMR signals of **8**, **9,** and **10**, δ (ppm), J (Hz).

Compd.	 (8)	 (9)	 (10)
Sol.	$CDCl_3$	$(CD_3)_2CO$	$CDCl_3$
H3	6.65 s	6.74 s	6.62 s
H6	7.18 s; $^{3}J_{PtH}$ 40	7.10 s; $^{3}J_{PtH}$ 40	7.02 s; $^{3}J_{PtH}$ 40
H7a/H7b	4.72 s/ 3.81 s	4.65 s/3.77 s	4.72 s/3.82 s
H7c/H7d	4.26 q; ^{3}J 7/1.31 t; ^{3}J 7	4.31 q; ^{3}J 7/1.35 t; ^{3}J 7	4.32 q; ^{3}J 7/1.35 t; ^{3}J 7
H8a	2.62 m;	2.86 d; ^{2}J 17	2.80 d; ^{2}J 17
H8b	3.92 m	3.64 dd; ^{2}J 17; ^{3}J 6	3.77 dd; ^{2}J 17; ^{3}J 6
H9	4.57 m; $^{2}J_{PtH}$ 70	4.88 m; $^{2}J_{PtH}$ 70	5.54 m; $^{2}J_{PtH}$ 70
trans-H10	4.10 m	3.68 d; ^{3}J 13	3.99 d; ^{3}J 13
cis-H10	3.61 m	4.30 d; ^{3}J 7	4.59 d; ^{3}J 7
H12	9.03 m; $^{3}J_{PtH}$ unr.	8.46 dd; ^{3}J 5; ^{4}J 1; $^{3}J_{PtH}$ unr.	–
H13	7.40 m	7.65 dd; ^{3}J 8; ^{3}J 5	8.27 d; ^{3}J 8
H14	8.31 d; ^{3}J 8	8.55 dd; ^{3}J 8; ^{4}J 1	8.44 d; ^{3}J 8
H15 /H16	7.91 m/7.65 t; ^{3}J 8	7.18 d; ^{3}J 8/7.57 t; ^{3}J 8	7.97 d; ^{3}J 8/7.73 t; ^{3}J 8
H17/H18	7.90 m/9.17 br. s	7.10 d; ^{3}J 8/–	7.88 t; ^{3}J 8/7.56 d; ^{3}J 8

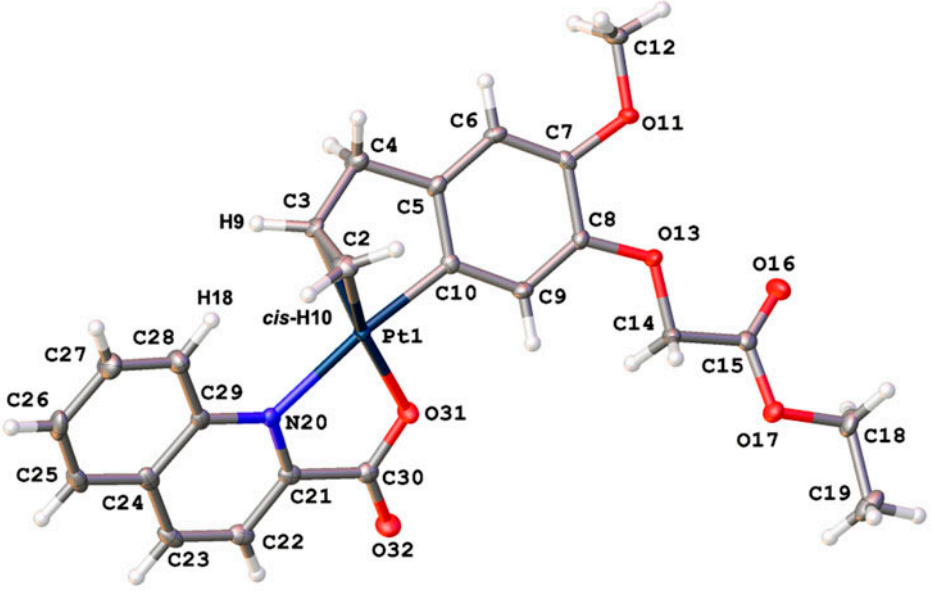


Figure 6. Structure of [Pt(Eteug-1H)(Q-COO)] (**10**) from XRD.

Complexes **1**, **2**, **3**, **4**, **8,** and **9** were assayed for *in vitro* cytotoxicity on human cancer cells KB (*Human epidermic carcinoma*), HepG2 (*Hepatocellular carcinoma*), Lu (*Human lung carcinoma*), and MCF7 (*Human breast carcinoma*). 8-Hydroxyquinoline (8-HOQ) was

Table 4. The *in vitro* cytotoxicity of examined compounds, IC_{50}, μM.

Cell line	**1**	**2**	**3**	**4**	**9**	8-HOQ	**8**	Cisplatin	Others
KB	1.45	1.82	1.39	1.92	0.92	37.89	169.62	2.65 [20]	6.0–22.5 [20]
Hep-G2	1.45	1.64	9.58	2.79	1.97	43.54	148.77	4.0 [21]	3.7–14.4 [21, 22]
Lu	1.79	1.84	8.17	3.89	1.94	62.96	>210.18	–	–
MCF-7	2.09	1.74	9.04	4.86	1.67	40.37	>210.18	3.9 [21]	4.6–16.8 [20, 23]

also tested. The IC_{50} values are listed in table 4 where the data for cisplatin (*cis*-diammine dichloroplatinum(II)) and some other platinum(II) complexes are also cited from the references.

The data in table 4 shows that 8-hydroxyquinolinate containing **1**, **2**, **3**, **4,** and **9** exhibit high activities on four human cancer cell lines while 8-hydroxyquinoline (8-HOQ) displayed lower cytotoxicity toward the examined cell lines. These compounds gave better antitumor activity than cisplatin against KB; **1**, **2**, **4,** and **9** gave better antitumor activity than cisplatin against Hep-G2; **1**, **2,** and **9** gave better antitumor activity than cisplatin against MCF-7.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplementary data

CCDC 1057363 contains the supplementary crystallographic data for **10**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223-336-033; or Email: deposit@ccdc.cam.ac.uk.

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