Synthesis and structure of organoplatinum(II) complexes containing aryl olefins and 8-hydroxyquinolines

Journal:	<i>Journal of Coordination Chemistry</i>
Manuscript ID	GCOO-2018-0484.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	Hong Hai, Le; Hanoi National University of Education, Chemistry Ngoc Vinh, Nguyen; Hanoi National University of Education tuyen, luu; Hanoi National University of Education meervelt, luc; KU Leuven Belgium Da, Tran; Hanoi National University of Education, Chemistry
Keywords:	Platinum(II) complex, Organoplatinum, Safrole, Eugenol, 8-Hydroxyquinolines
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
HAI39.cif	

SCHOLARONE™
Manuscripts

Synthesis and structure of organoplatinum(II) complexes containing aryl olefins and 8-hydroxyquinolines

Le Thi Hong Hai, Nguyen Thi Ngoc Vinh, Tran Thi Da, Luc Van Meervelt

Synthesis and structure of organoplatinum(II) complexes containing aryl olefins and 8-hydroxyquinolines

Le Thi Hong Hai¹, Nguyen Thi Ngoc Vinh¹, Luu Thi Tuyen¹, Luc Van Meervelt², Tran Thi Da¹

¹*Department of Chemistry, Hanoi National University of Education, 136 Xuan Thuy, Hanoi, Vietnam.*

²*Biomolecular Architecture, Chemistry Department KU Leuven, Celestijnenlaan 200F box 2404, B-3001 Leuven, Belgium.*

Abstract

Twelve new organoplatinum(II) complexes: [PtCl(Saf)(2-Me-8-OquiN)] (**1**), [PtCl(Saf)(5,7-Cl₂-8-OquiN)] (**2**), [PtCl(Saf)(5,7-Cl₂-2-Me-8-OquiN)] (**3**), [PtCl(Meteug)(5,7-Cl₂-8-OquiN)] (**4**), [PtCl(Meteug)(5,7-Cl₂-2-Me-8-OquiN)] (**5**), [Pt(Saf-1H)(2-Me-8-OquiN)] (**6**), [Pt(Saf-1H)(5,7-Cl₂-8-OquiN)] (**7**), [Pt(Saf-1H)(5,7-Cl₂-2-Me-8-OquiN)] (**8**), [Pt(Eteug-1H)(2-Me-8-OquiN)] (**9**), [Pt(Eteug-1H)(2-OHC-8-OquiN)] (**10**), [Pt(Eteug-1H)(5,7-Cl₂-8-OquiN)] (**11**), and [Pt(Eteug-1H)(5,7-Cl₂-2-Me-8-OquiN)] (**12**) (Saf: Safrole, Meteug: Methyl eugenoxycetate, Saf-1H: Deprotonated safrole, Eteug-1H: Deprotonated ethyl eugenoxycetate, OquiN: substituted quinolin-8-olate) were synthesized. These complexes were characterized by elemental analyses, IR, ¹H NMR, for several also by NOESY, MS spectra and single crystal X-ray diffraction. It is shown that in **1-5** the Pt(II) atom is surrounded by a Cl atom and the ethylenic double bond of the aryl olefin, and by N and O atoms of the 8-OquiN, its donor N is in *trans*-position in comparison with the ethylenic double bond. In **6-12** the Pt(II) atom is surrounded by an aromatic C atom and the ethylenic C=C double bond of the aryl olefin, and by N and O atoms of the 8-OquiN resulting in a slightly distorted square-planar coordination environment, the donor N is in *cis*-position in comparison with the ethylenic double bond. Complex **7** exhibits high activities on human cancer cells KB, Hep-G2, Lu and MCF-7 with IC₅₀ values of 4.2, 2.7, 4.3 and 3.6 μM, respectively.

Keywords: Platinum(II) complex, Organoplatinum, Safrole, Eugenol, 8-Hydroxyquinolines.

1. Introduction

Recent years have witnessed an unprecedented progress in biological applications of metal coordination compounds of biologically active ligands because of their key role in clinical

therapy. Platinum complexes are particularly suitable for this purpose. Interest in platinum complexes containing biological active natural compounds is increasing. Complexes of platinum(II) with caffeine [1], β -carboline alkaloids [2], theophylline [3], oleanolic acid [4], propyl gallate [5], hydroxyquinolines [6, 7] and so forth, were synthesized and their antitumor and antiviral activities have been demonstrated.

Our idea was to design new organoplatinum(II) anticancer compounds containing aryl olefins which already exert biological properties expecting synergistic effects. Thus, for the first time, methyleugenol (4-allyl-1,2-dimethoxybenzene, from a number of plants such as *Cinnamomum cordatum*, lemongrass, star anise...), safrole (4-allyl-1,2-methylenedioxybenzene, the main component of sassafras oil), eugenol (4-allyl-2-methoxyphenol, a phenolic major component of a number of medicinal plants such as clove and tulsi), and some alkyl eugenoxycetates were introduced into the coordination entity of platinum(II) [8, 9, 10, 11, respectively], then the obtained key compounds were transformed into organoplatinum complexes comprising these aryl olefins or chelating aryl olefins and various amines. It was shown that many synthesized complexes exhibit impressive high *in vitro* cytotoxicity on four human cancer cell lines KB, Hep-G2, Lu, MCF7 with $IC_{50} = 0.4-9.6 \mu M$. Some complexes gave better antitumor activity than cisplatin against examined cell lines [10, 12 – 15].

In the current study we have continued this line of research, focusing on the synthesis, characterization of a series of organoplatinum(II) complexes containing safrole (Saf) as well as methyl eugenoxycetate (Meteug) or ethyl eugenoxycetate (Eteug), all of them differing in the bidentate quinolin-8-olates (OquiN). In addition, several 8-hydroxyquinolines are already known for their antimicrobial and antiprotozoal activity and many of them are or were used in clinical practice [16]. Their biological activity is often ascribed to their ability to bind di- and trivalent transition metal ions such as copper(II), zinc(II), and iron(III) [17].

2. Experimental

2.1. General and instrumentation

Elemental analysis: Pt was analyzed according to the weight method [18], C and H were analyzed on a LECO CHNS model 932 elemental analyzer. The IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs in the range 400 - 4000 cm^{-1} . The NMR spectra were recorded on a Bruker AVANCE 500 MHz, all at 298-300 K, with TMS as the internal standard in suitable solvents (Tables 2-3). MS spectra were recorded on a LC-MSD-Trap-SL instrument. The *in vitro* cytotoxicity were tested at the Experimental Biological Laboratory – Institute of Chemistry of Natural Compounds (in Hanoi), according

to the method described in reference [19], IC_{50} values were calculated based on OD values taken on an Elisa instrument at 515-540 nm.

2.2. X-ray diffraction analysis

Single-crystal X-ray diffraction were collected at 293K on an Agilent Super Nova diffractometer equipped with an Eos CCD detector, using $MoK\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The images were interpreted and integrated with CrysAlisPRO [20] and the implemented absorption correction was applied. Using Olex2 [21], the structure was solved with the ShelXS [22] structure solution program using Direct Methods and refined with the ShelXL [23] refinement package using full-matrix least squares minimization on F^2 . Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in the calculated positions. A summary of crystal data and refinement details is given in Table 1.

Table 1. Crystal data and refinement details for crystal structures of complex **9**.

Formula	$C_{24}H_{25}NO_3Pt$	$V (\text{\AA}^3)$	1061.78(5)
Formula weight	602.54	Z	2
Crystal size (mm)	0.25 x 0.2 x 0.2	$\rho_{\text{calc}} (\text{g/cm}^3)$	1.885
Radiation	$Mo K\alpha (\lambda=0.71073)$	$\mu (\text{mm}^{-1})$	6.644
Temperature (K)	293.4(6)	$F(000)$	588.0
Crystal system	triclinic	2θ value ($^\circ$)	5.222-52.763
Space group	$P-1$	Reflections collected	21675
$a (\text{\AA})$	9.3398(3)	Independent reflections	4316
$b (\text{\AA})$	10.3892(3)	R_{int}	0.0376
$c (\text{\AA})$	11.4404(3)	Data/restraints/parameters	4316/0/283
$\alpha (^\circ)$	92.004(2)	$R[F^2 > 2\sigma(F^2)], wR(F^2)$	0.0163, 0.0365
$\beta (^\circ)$	104.825(2)	Goodness-of-fit on F^2	1.074
$\gamma (^\circ)$	97.310(2)	Largest diff. peak, hole ($e \text{\AA}^{-3}$)	0.43, -0.58

2.3. Preparation of complexes 1-5

The preparation of $K[Pt(\text{Saf})Cl_3]$, $K[Pt(\text{Meteug})Cl_3]$, (here ‘Saf’ and ‘Meteug’ are safrole and methyl eugenoxacetate, respectively, Fig 1) were previously described in [9, 11].

To a solution of $K[Pt(\text{Saf})Cl_3]$ (201 mg, 0.4 mmol) or $K[Pt(\text{Meteug})Cl_3]$ (208 mg, 0.4 mmol) in 15 mL ethanol/water (4:1 by volume) an 8-hydroxyquinoline (0.4 mmol) in 15 mL ethanol or ethanol/water (4:1 by volume) was slowly added and stirred at room temperature for 1 - 2 hours. The mixture was then left at room temperature or refrigerated for several hours. The resulting precipitate was collected, washed with ethanol/water (1:1 by volume) and dried.

2.3.1. [PtCl(Saf)(2-methyl-8-O-quinoline)] (1, (η²-5-allyl-1,3-benzodioxole)chlorido(2-methylquinolin-8-olato-κ²N,O)-platinum(II))

The yield was 159 mg (72%), yellow powder. Anal. Calc. For [C₂₀H₁₈ClNO₃Pt]: C, 43.60; H, 3.29; Pt, 35.41. Found: 43.28; H, 3.48; Pt, 35.70. IR (cm⁻¹): 3057, 2976, 2857 (νCH); 1600, 1553, 1490 (ν C=C/C=N). For ¹H NMR see Table 2.

2.3.2. [PtCl(Saf)(5,7-dichloro-8-O-quinoline)] (2, (η²-5-allyl-1,3-benzodioxole)chlorido(5,7-dichloroquinolin-8-olato-κ²N,O)-platinum(II))

The yield was 181 mg (75%), yellow powder. Anal. Calc. For [C₁₉H₁₄Cl₃NO₃Pt]: C, 37.67; H, 2.33; Pt, 32.20. Found: C, 37.35; H, 2.53; Pt, 32.45. IR (cm⁻¹): 3050, 2980, 2899 (νCH); 1595, 1563, 1493 (ν C=C/C=N). For ¹H NMR see Table 2.

2.3.3. [PtCl(Saf)(5,7-dichloro-2-methyl-8-O-quinoline)] (3, (η²-5-allyl-1,3-benzodioxole)chlorido(5,7-dichloro-2-methylquinolin-8-olato-κ²N,O)-platinum(II))

The yield was 173 mg (70%), yellow powder. Anal. Calc. For [C₂₀H₁₆Cl₃NO₃Pt]: C, 38.76; H, 2.60; Pt, 31.48. Found: C, 38.47; H, 2.82; Pt, 31.75. IR (cm⁻¹): 3060, 2985, 2898 (νCH); 1600, 1554, 1501 (ν C=C/C=N). For ¹H NMR see Table 2. ~~ESI-MS-MS~~: 653.7/100% ([M+Cl]⁻); ~~+MS~~: 583.9/100% ([M-Cl]⁺), 620.5/15% ([M+H]⁺).

Table 2. ¹H NMR signals of complexes 1-3 and 6-8, δ (ppm), J (Hz).

	1/CDCl ₃	2/CDCl ₃	3/CDCl ₃	6/CDCl ₃	7/CDCl ₃	8/CDCl ₃
H1a	5.91 s	5.91 s	5.91 s	5.84 d; ² J 1	5.85 d; ² J 1	5.86 d; ² J 1
H1a'	5.91 s	5.91 s	5.91 s	5.87 d; ² J 1	5.88 d; ² J 1	5.89 d; ² J 1
H3	6.84 s	6.83 d; ⁴ J 1.5	6.83 s	6.61 s	6.61 s	6.60 s
H5	6.79 d; ³ J 7.5	6.78 dd; ³ J 8; ⁴ J 1.5	6.78 d; ³ J 7.5	-	-	-
H6	6.72 d; ³ J 7.5	6.71 d; ³ J 8	6.72 d; ³ J 7.5	7.23 s	7.18 s; ³ J _{PtH} 35	7.27 s; ³ J _{PtH} ov.
H7a	3.21 br.	3.33 dd; ² J 15; ³ J 8	3.22 dd; ² J 15; ³ J 7	2.82 d; ² J 17; ³ J _{PtH} 95	2.85 d; ² J 17; ³ J _{PtH} 95	2.81 d; ² J 17; ³ J _{PtH} 95
H7b	3.57 br.	3.63 dd; ² J 15; ³ J 6	3.56 d; ² J 15	3.74 dd; ² J 17; ³ J 6.5	3.69 dd; ² J 17; ³ J 6	3.71 dd; ² J 17; ³ J 6
H8	5.65 m; ² J _{PtH} 70	5.75 m; ² J _{PtH} 70	5.73 m; ² J _{PtH} 70	4.98 m; ² J _{PtH} 75	4.78 m; ² J _{PtH} 75	5.01 m; ² J _{PtH} 75
H9cis	4.78 d; ³ J 7; ² J _{PtH} 70	4.92 d; ³ J 8; ² J _{PtH} 70	4.87 d; ³ J 8; ² J _{PtH} 70	4.35 d; ³ J 7.5; ² J _{PtH} 75	4.07 d; ³ J 8; ² J _{PtH} 75	4.38 d; ³ J 8; ² J _{PtH} 75
H9trans	4.75 d; ³ J 14; ² J _{PtH} 70	4.88 d; ³ J 15; ² J _{PtH} 70	4.86 d; ³ J 13; ² J _{PtH} 70	3.72 d; ³ J 13; ² J _{PtH} 75	3.93 d; ³ J 13; ² J _{PtH} 75	3.83 d; ³ J 13; ² J _{PtH} 75
H12	-	9.16 dd; ³ J 5.5; ⁴ J 1.5	-	-	8.15 d; ³ J 5	-

H12a	3.17 s	-	3.19 s	2.67 s	-	2.69 s
H13	7.31 d; 3J 8.5	7.68 dd; 3J 8.5; 3J 5.5	7.42 d; 3J 8.5	7.24 d; 3J 8.5	7.56 dd; 3J 8.5; 3J 5	7.33 d; 3J 8.5
H14	8.22 d; 3J 8.5	8.75 dd; 3J 8.5; 4J 1.5	8.56 d; 3J 8.5;	8.15 d; 3J 8.5	8.66 d; 3J 8.5	8.49 d; 3J 8.5
H15	6.96 d; 3J 7.5	-	-	7.20 d; 3J 8	-	-
H16	7.33 t; 3J 7.5	7.64 s	7.54 s	7.46 t; 3J 8	7.74 s	7.65 s
H17	6.96 d; 3J 7.5	-	-	7.00 d; 3J 8	-	-

2.3.4. [PtCl(Meteug)(5,7-dichloro-8-O-quinoline)] (4, chlorido(5,7-dichloroquinolin-8-olato- κ^2N,O){4-methoxycarbonylmethoxy-3-methoxy-1-[(2,3- η)-prop-2-en-1-yl]benzene}platinum(II))

The yield was 207 mg (76%), yellow powder. Anal. Calc. For [C₂₂H₂₀Cl₃NO₅Pt]: C, 38.87; H, 2.97; Pt, 28.69. Found: C, 39.05; H, 3.15; Pt, 28.37. IR (cm⁻¹): 3080, 3005 2952, 2828 (vCH); 1731 (v C=O); 1593, 1564, 1515 (v C=C/C=N). For ¹H NMR see Table 3. ~~ESI-MS~~ ~~MS~~: 713.8/40% ([M+Cl]⁻); ~~+MS~~: 643.9/100% ([M-Cl]⁺), 680.7/50% ([M+H]⁺).

2.3.5. [PtCl(Meteug)(5,7-dichloro-2-methyl-8-O-quinoline)] (5, chlorido(5,7-dichloro-2-methylquinolin-8-olato- κ^2N,O){4-methoxycarbonylmethoxy-3-methoxy-1-[(2,3- η)-prop-2-en-1-yl]benzene}platinum(II))

The yield was 180 mg (65%), yellow powder. Anal. Calc. For [C₂₃H₂₂Cl₃NO₅Pt]: C, 39.81; H, 3.20; Pt, 28.11. Found: C, 40.12; H, 3.05; Pt, 28.27. IR (cm⁻¹): 3076, 2953, 2858 (vCH); 1757 (v C=O); 1595, 1586, 1554, 1514 (v C=C/C=N). For ¹H NMR see Table 3. ~~MSESI-MS~~: 727.8/100% ([M+Cl]⁻); ~~+MS~~: 657.9/100% ([M-Cl]⁺), 693.8/30% ([M+H]⁺).

2.4. Preparation of complexes 6-12

The preparation of [Pt₂Cl₂(Saf-1H)₂] and [Pt₂Cl₂(Eteug-1H)₂] ('Saf-1H' and 'Eteug-1H' are deprotonated safrole and deprotonated ethyl eugenoxycetate, respectively, Fig 1) were previously described in [9, 11].

To a mixture of [Pt₂Cl₂(Saf-1H)₂] (157 mg, 0.2 mmol) or [Pt₂Cl₂(Eteug-1H)₂] (192 mg, 0.2 mmol) in 12 mL acetone/ethanol (5:1 by volume) an 8-hydroxyquinoline (0.4 mmol) in 10 mL acetone or acetone/ethanol (5:1 by volume) was slowly added and stirred at room temperature for 1 - 2 hours. The resulting solution was kept at room temperature for several hours. The precipitate was collected, washed with ethanol and dried.

2.4.1. [Pt(Saf-1H)(2-methyl-8-O-quinoline)] (6, (η^2 -5-allyl-1,3-benzodioxole- κC^6)(2-methylquinolin-8-olato- $\kappa^2 N, O$)-platinum(II))

The yield was 154 mg (75%), yellow powder. Anal. Calc. For [C₂₀H₁₇NO₃Pt]: C, 46.70; H, 3.33; Pt, 37.92. Found: C, 46.42; H, 3.12; Pt, 38.21. IR (cm⁻¹): 2977, 2876, 2830 (νCH); 1598, 1564, 1507 (ν C=C/C=N). For ¹H NMR see Table 2.

2.4.2. [Pt(Saf-1H)(5,7-dichloro-8-O-quinoline)] (7, (η^2 -5-allyl-1,3-benzodioxole- κC^6)(5,7-dichloroquinolin-8-olato- $\kappa^2 N, O$)-platinum(II))

The yield was 155 mg (68%), dark yellow powder. Anal. Calc. For [C₁₉H₁₃Cl₂NO₃Pt]: C, 40.09; H, 2.30; Pt, 34.27. Found: C, 39.83; H, 2.52; Pt, 34.53. IR (cm⁻¹): 3055, 2970, 2894 (νCH); 1588, 1562, 1496 (ν C=C/C=N). For ¹H NMR see Table 2.

2.4.3. [Pt(Saf-1H)(5,7-dichloro-2-methyl-8-O-quinoline)] (8, (η^2 -5-allyl-1,3-benzodioxole- κC^6)(2-methyl-5,7-dichloroquinolin-8-olato- $\kappa^2 N, O$)-platinum(II))

The yield was 168 mg (72%), yellow powder. Anal. Calc. For [C₂₀H₁₅Cl₂NO₃Pt]: C, 41.18; H, 2.59; Pt, 33.44. Found: C, 39.90; H, 2.30; Pt, 33.72. IR (cm⁻¹): 3060, 2978, 2887 (νCH); 1603, 1582, 1551, 1502 (ν C=C/C=N). For ¹H NMR see Table 2. ~~ESI-MS-MS~~: 619.8/100% ([M+Cl]⁻); ~~MS~~: 583.9/100% ([M+H]⁺).

2.4.4. [Pt(Eteug-1H)(2-methyl-8-O-quinoline)] (9, {4-ethoxycarbonylmethoxy-3-methoxy-1-[(2,3- η)-prop-2-en-1-yl]phenyl- κC^6 }(2-methylquinolin-8-olato- $\kappa^2 N, O$)-platinum(II))

The yield was 161 mg (67%), yellow powder. Anal. Calc. For [C₂₄H₂₅NO₅Pt]: C, 47.84; H, 4.18; Pt, 32.38. Found: C, 48.15; H, 4.03; Pt, 32.12. IR (cm⁻¹): 3051, 2944, 2843 (νCH); 1717 (ν C=O); 1557, 1501, 1459 (ν C=C/C=N). For ¹H NMR see Table 3. Yellow crystals suitable for X-ray diffraction were obtained by slow evaporation within 24 h from a saturated acetone-ethanol mixture (6:1 by volume) solution at room temperature.

Table 3. ¹H NMR signals of complexes **4**, **5** and **9-12**, δ (ppm), J (Hz).

	4 / CDCl ₃	5 / CDCl ₃	9 /Me ₂ CO	10 / CDCl ₃	11 / Me ₂ CO	12 /CDCl ₃
H1a	4.63 s	4.63 s	4.57 d; ² J 16 4.58 d; ² J 16	4.76 s 4.76 s	4.66 s 4.66 s	4.78d; ² J 16 4.79d; ² J 16
H1b	3.77 s	3.77 s	4.18 q; ³ J 7 4.19 q; ³ J 7	4.31 q; ³ J 7 4.32 q; ³ J 7	4.24 q; ³ J 7 4.26 q; ³ J 7	4.28 q; ³ J 7 4.29 q; ³ J 7
H1c	-	-	1.23 t; ³ J 7	1.33 t; ³ J 7	1.28 t; ³ J 7	1.31 t; ³ J 7

H2a	3.69 s	3.66 s	3.69 s	3.84 s	3.76 s	3.83 s
H3	6.90 s	6.89 s	6.67 s	6.70 s	6.74 s	6.66 s
H5	6.86 d; 3J_8	6.86 d; 3J_8	-	-	-	-
H6	6.75 d; 3J_8	6.75 d; 3J_8	7.13 s; $^3J_{\text{PtH}} 35$	7.20 s; $^3J_{\text{PtH}} 35$	7.11 s; $^3J_{\text{PtH}} 35$	7.25 s; $^3J_{\text{PtH}} 35$
H7a	3.33 dd; $^2J_{15}; ^3J_7$	3.15 m; ov.	2.68 ov.	2.87 d; $^2J_{17}$; $^3J_{\text{PtH}} 95$	2.86 d; $^2J_{17}$; $^3J_{\text{PtH}} 95$	2.80 d; $^2J_{17}$; $^3J_{\text{PtH}} 95$
H7b	3.63 dd; $^2J_{15}; ^3J_7$	3.62 m; ov.	3.59 dd; $^2J_7; ^3J_6$	3.79 dd; $^2J_{17}; ^3J_6$	3.67 dd; $^2J_7; ^3J_6$	3.73 dd; $^2J_{17}; ^3J_6$
H8	5.78 m; $^2J_{\text{PtH}} 70$	5.77 m; $^2J_{\text{PtH}} 70$	5.02 m; $^2J_{\text{PtH}} 75$	5.03 m; $^2J_{\text{PtH}} 75$	5.01 m; $^2J_{\text{PtH}} 75$	5.00 m; $^2J_{\text{PtH}} 75$
H9 _{cis}	4.92 d; 3J_8 $^2J_{\text{PtH}} 70$	4.89 d; 3J_8 $^2J_{\text{PtH}} 70$	4.44 d; $^3J_{7.5}$; $^2J_{\text{PtH}} 75$	4.27 d; $^3J_{6.5}$; $^2J_{\text{PtH}} 75$	4.36 d; $^3J_{7.5}$; $^2J_{\text{PtH}} 75$	4.40 d; $^3J_{7.5}$
H9 _{trans}	4.89 d; $^3J_{14}$ $^2J_{\text{PtH}} 70$	4.87 d; $^3J_{14}$ $^2J_{\text{PtH}} 70$	3.53 d; $^3J_{13}$; $^2J_{\text{PtH}} 75$	3.83 d; $^3J_{13.5}$	3.83 d; $^3J_{13.5}$; $^2J_{\text{PtH}} 75$	3.85 d; $^3J_{14}$
H12	9.14 d; 3J_5	-	-	-	8.62 d; 3J_5	-
H12a	-	3.17 s	2.68 s	9.81 s	-	2.69 s
H13	7.68 dd; $^3J_{8.5}; ^3J_5$	7.42 d; $^3J_{8.5}$	7.42 d; $^3J_{8.5}$	8.01 d; $^3J_{8.5}$	7.84 dd; $^3J_{8.5}; ^3J_5$	7.35 d; $^3J_{8.5}$
H14	8.75 d; $^3J_{8.5}$	8.56 d; $^3J_{8.5}$	8.29 d; $^3J_{8.5}$	8.43 d; $^3J_{8.5}$	8.75 d; $^3J_{8.5}$	8.49 d; $^3J_{8.5}$
H15	-	-	7.01 dd; $^3J_8; ^4J_1$	7.12 d; 3J_8	-	-
H16	7.64 s	7.54 s	7.38 t; 3J_8	7.69 t; 3J_8	7.81 s	7.66 s
H17	-	-	6.98 dd; $^3J_{7.5}; ^4J_1$	6.29 dd; $^3J_{7.5}; ^4J_1$	-	-

2.4.5. [Pt(Eteug-1H)(2-formyl-8-O-quinoline)] (10, {4-ethoxycarbonylmethoxy-3-methoxy-1-[(2,3- η)-prop-2-en-1-yl]phenyl- κC^6 }(quinoline-2-carbaldehyde-8-olato- $\kappa^2 N, O$)-platinum(II))

The yield was 158 mg (64%), brown powder. Anal. Calc. For [C₂₄H₂₃NO₆Pt]: C, 46.76; H, 3.76; Pt, 31.64. Found: C, 47.02; H, 3.51; Pt, 31.93. IR (cm⁻¹): 3055, 2931, 2840 (vCH); 1755, 1697 (v C=O); 1589, 1555, 1454 (v C=C/C=N). For ¹H NMR see Table 3. ~~MS~~ESI-MS: 650.9/100% ([M+Cl]⁻); ~~MS~~: 616.9/80% ([M+H]⁺).

2.4.6. [Pt(Eteug-1H)(5,7-dichloro-8-O-quinoline)] (11, {4-ethoxycarbonylmethoxy-3-methoxy-1-[(2,3- η)-prop-2-en-1-yl]phenyl- κC^6 }(5,7-dichloroquinolin-8-olato- $\kappa^2 N, O$)-platinum(II))

The yield was 195 mg (74%), brown powder. Anal. Calc. For [C₂₃H₂₁Cl₂NO₅Pt]: C, 42.02; H, 3.22; Pt, 29.67. Found: C, 42.30; H, 3.01; Pt, 29.89. IR (cm⁻¹): 3080, 2919, 2837 (vCH); 1748 (v C=O); 1562, 1483, 1443 (v C=C/C=N). For ¹H NMR see Table 3.

2.4.7. [Pt(Eteug-1H)(5,7-dichloro-2-methyl-8-O-quinoline)] (12, {4-ethoxycarbonylmethoxy-3-methoxy-1-[(2,3-η)-prop-2-en-1-yl]phenyl-κC⁶} (2-methyl-5,7-dichloroquinolin-8-olato-κ²N,O)-platinum(II))

The yield was 175 mg (65%), yellow powder. Anal. Calc. For [C₂₄H₂₃Cl₂NO₅Pt]: C, 42.93; H, 3.45; Pt, 29.05. Found: C, 43.18; H, 3.20; Pt, 28.81. IR (cm⁻¹): 3065, 2984, 2933, 2835 (νCH); 1755 (ν C=O); 1590, 1573, 1548, 1499 (ν C=C/C=N). For ¹H NMR see Table 3. ~~MS~~^{ESI-MS}: 705.9/100% ([M+Cl]⁻); ~~MS~~⁺: 671.9/100% ([M+H]⁺).

3. Results and discussion

Four previously prepared [9, 11] organoplatinum(II) complexes used for the synthesis of the title complexes are K[Pt(Saf)Cl₃], K[Pt(Meteug)Cl₃], [Pt₂Cl₂(Saf-1H)₂] and [Pt₂Cl₂(Eteug-1H)₂], here 'Saf-1H' and 'Eteug-1H' are deprotonated safrole and deprotonated ethyl eugenoxacetate, respectively. Their structures are presented in Fig. 1.

Figure 1. Starting organoplatinum(II) complexes.

3.1. Synthesis and structure of complexes 1-5

Treatment of K[Pt(Saf)Cl₃] or K[Pt(Meteug)Cl₃] with 8-hydroxyquinolines (HOQuiN) in suitable solvents (see Experimental) gave complexes [PtCl(Saf)(OquiN)] (1, 2, 3) and [PtCl(Meteug)(OquiN)] (4, 5). Complexes 1-5 (Fig. 2) easily precipitate from reaction mixture because they are neutral and have large hydrophobic residues.

Figure 2. Structure of complexes **1-5** (the numeration on these structures is specifically used for NMR analysis).

In IR spectra of **1-5** (see Experimental) the absence of a band at about 1630 cm^{-1} from the C=C double bond of allyl group in non-coordinated aryl olefin indicates that the allyl group coordinates in an η^2 -manner. The absence of a strong absorption band at about 3400 cm^{-1} from the OH group of 8-hydroxyquinolines suggests that this OH group was deprotonated.

In the negative mode ESI MS of **3**, **4** and **5** there are pseudomolecular $[M+Cl]^-$ peaks with relative intensity of 100, 40 and 100%, respectively. In the positive mode ESI MS all of their pseudomolecular $[M-Cl]^+$ peaks have relative intensity of 100%, while their $[M+H]^+$ peaks have relative intensity of 15, 50 and 30%, respectively. These are explained with the following reaction scheme.

The assignment of the 1H NMR signals of examined complexes is based on their chemical shift, spin-spin splitting patterns and intensities. For the ambiguous cases the NOESY spectra were also used. For example, the singlet of H2a at 3.69 ppm in complex **4** is distinguished from the near singlet of H1b at 3.77 ppm by the fact that H2a has a NOESY cross peak with H3 while H1b has not. The 1H NMR signals of **1-3** are listed in Table 2, and those of **4** and **5** are in Table 3.

The evidences for the coordination of the allyl group with Pt(II) in an η^2 -manner are: i) The resonances of ethylenic protons (H8, H9_{cis}, H9_{trans}) shift upfield in comparison to those of non-coordinated allyl group and are accompanied by two ^{195}Pt satellites with the distance between them, $^2J_{PtH}$, 70Hz (Tables 2 and 3); ii) Two protons H7 give rise to two separate signals (denoted H7a and H7b, usually in form a doublet of doublets, Fig. 3) while for non-coordinated allyl group they give only one doublet. This is expected since upon coordination to Pt(II), atom C8 becomes a chiral center and thus H7a and H7b become diastereotopic.

In 1H NMR of **1-5**, except the signal of moist water in $CDCl_3$ at 1.5 ppm there is not any HO-signal of used 8-hydroxyquinolines. The resonances of 2-methyl group of the coordinated 2-methylquinolin-8-olates (H12a of **1**, **3** and **5** at 3.17, 3.19 and 3.17 ppm) largely shift

downfield in comparison to those of non-coordinated 2-methyl-8-hydroxyquinolines (at about 2.5 ppm). These support the coordination of the chelating quinolin-8-olates with Pt(II).

In NOESY spectrum of **3** (Fig. 3) there is not any cross peak between all protons of the chelating OquiN including methyl proton H12a and the protons of methyl eugenoxacetate. In the spectrum there are cross peak *a* shown the proximity of H12a to H13 and cross peak *b* shown the proximity of H9_{cis} and H9_{trans} to H8. That is to say, the donor N of the chelating OquiN and the ethylenic double bond C8=C9 are not at *cis*-positions but at *trans*-positions to one another in the coordination sphere of Pt(II).

Figure 3. NOESY spectrum of complex **3**.

3.2. Synthesis and structure of complexes 6-12

Interaction of [Pt₂Cl₂(Saf-1H)₂] or [Pt₂Cl₂(Eteug-1H)₂] with 8-hydroxyquinolines (HOquiN) in acetone/ethanol/chloroform (see Experimental) afforded complexes [Pt(Saf-1H)(OquiN)] (**6**, **7**, **8**, Fig. 4) and [Pt(Eteug-1H)(OquiN)] (**9**-**12**, Fig. 5).

Figure 4. Structure of complexes **6-8**.

Figure 5. Structure of complexes **9-12** (the numeration on these structures is specifically used for NMR analysis).

The IR spectra of **6-8** and **9-12** are similar to those of **1-3** and **4-5** respectively (see 3.1). Although there is no Cl^- ligand in complexes **8**, **10**, and **12**, in their negative mode ESI MS there are pseudomolecular $[\text{M}+\text{Cl}]^-$ peaks with relative intensity of 100%. In the positive mode ESI MS of **8**, **10**, and **12** pseudomolecular $[\text{M}+\text{H}]^+$ peaks have relative intensity of 15, 50 and 30%, respectively. These are associated with the following reaction scheme.

The evidences for the coordination of the allyl group with $\text{Pt}(\text{II})$ in **6-12** are similar to those for **1-5** (Tables 2 and 3). For complexes **6-12**, the phenyl group gives rise to two signals: H3 and H6. The H6-singlet is distinguished from the H3-singlet by ^{195}Pt satellites with a $^3J_{\text{PtH}}$ value of 35 Hz (Table 2 and 3, Fig. 6). This value is comparable in magnitude to $^3J_{\text{PtH}}$ in analogous platinum(II) complexes [11, 12, 14] and twice smaller than $^2J_{\text{PtH}}$ (70-75 Hz), indicating that the phenyl group is bound with $\text{Pt}(\text{II})$ by σ -(C5-Pt)-bond as shown in Fig. 4 and 5. The ^1H NMR signals of **6-8** are listed in Table 2, and those of **9-12** are in Table 3. The NOESY spectrum of **8** is presented in Fig. 6.

In Fig. 6 the cross peaks *a* and *b* shown the spatial proximity of H12a to H9_{cis} and to H8. This indicates that the donor N of the chelating ‘OquiN’ is at *cis*-positions to the ethylenic

double bond C8=C9 and the latter is almost perpendicular to the coordination plane of Pt(II), i.e. perpendicular to the plane of the chelating OquiN. Besides, there are the cross peaks which shown the proximity of H12a to H13 (the cross peak *c*), H7a and H7b to H3 (the cross peaks *d* and *e*), and so forth.

Figure 6. NOESY spectrum of complex **8**.

It is known that the interaction of $[\text{Pt}_2(\text{C}_2\text{H}_4)_2\text{Cl}_4]$ and amines (Am) gives *trans*- $[\text{Pt}(\text{C}_2\text{H}_4)(\text{Am})\text{Cl}_2]$, as ethylene has a large *trans* effect. The formation of **1-5** obeys the *trans*-effect (i.e. donor N and ethylenic double bond are at *trans*-positions to one another), whilst in the interaction of $[\text{Pt}_2\text{Cl}_2(\text{Saf-1H})_2]$ or $[\text{Pt}_2\text{Cl}_2(\text{Eteug-1H})_2]$ with 8-hydroxyquinolines (HOquiN) donor N was not introduced *trans* to the ethylenic double bond of the allyl group but were *trans* to C5 of the phenyl group to form complexes **6-12** (Fig. 4 and 5). We suggest that this selectivity is controlled by steric effects rather than by the *trans* effect.

It is interesting to note some anomalies in the ^1H NMR spectra of the examined complexes (Tables 2 and 3). First, for **6-12**, the chemical shift of H7a (2.7-2.9 ppm) is largely decreased in comparison with those of H7b (3.6-3.8 ppm). Second, for **1-3**, two methylene protons H1a and H1a' are equivalent, while for **6-8** they are non equivalent (Table 2). Third, the chemical shift of 2-methyl protons of OquiN ligand (H12a) in **6**, **8**, **9** and **12** (2.67-2.69 ppm) is much smaller than those in **1**, **3** and **5** (3.17-3.19 ppm).

The first and the second observations are related to the formation of a non-coplanar platinacycle from the allyl, phenyl groups and the Pt(II) as seen from Fig. 4, 5 and 7. For **6-12** this cyclization causes a steric compressed Pt(C7-C8-C9)-system increasing the spatial difference between H7a and 7b. For **6-8** this cyclization causes some deformation of the five-membered 1,3-dioxole ring making its two methylene protons become non-equivalent. In addition, it is surprising that for **9-12** two methylene protons H1a and H1a' as well as H1b and H1b' are non-equivalent (Table 3). It is possible that -OCH₂COOCH₂CH₃ as bulky group hinders the rotations around its single C-O bonds. The third one involves the spatial proximity of H12a to the double bond C8=C9 in **6, 8, 9** and **12**. As a result, the methyl protons H12a fall into the shielded region of the double bond C8=C9 and therefore they resonate at relative high field (see also Fig. 7).

3.3. Crystal structure of complex **9**

The molecular structure of complex **9** determined by single-crystal X-ray diffraction is shown in Fig. 7 (a different numbering scheme is used than in Fig. 5). The Pt(II) atom is surrounded by an aromatic C atom and the C=C double bond of the ethyl eugenoxacetate ligand, and by the N and O atoms of the 8-oxyquinoline, resulting in a slightly distorted square-planar coordination environment and the N and O atoms are in *trans* positions (the *trans* angle C14-Pt1-N2 is 169.80(9)°). The best planes through both aromatic rings make an angle of 41.41 (10)°. In general, these confirm the solution structure of the examined complexes.

It is noted that for platinum(II) complexes containing natural aryl olefin and monodentate amine, the single-crystal X-ray diffraction data were reported in several works [11, 13, 15]. For platinum(II) complexes containing natural aryl olefin and didentate amine, the positions of N and O donors in platinum(II) coordination sphere was usually determined by NMR data [10, 13], in the present paper these position were determined by both NMR and the single-crystal X-ray diffraction investigations.

3.4. Biological activities of complexes **7, 9, 11, 12**

Four complexes **7, 9, 11** and **12** were tested for cell *in vitro* cytotoxicity on human cancer cells and the IC₅₀ values are listed in Table 4. [Pt(Saf-1H)(5,7-Cl₂-8-O-quinoline)] (**7**) exhibits high activities on four cell lines *Human epidermic carcinoma* (KB), *Hepatocellular carcinoma* (Hep-G2), *Human lung carcinoma* (Lu), and *Human breast carcinoma* (MCF-7) with IC₅₀ is 4.2, 2.7, 4.3 and 3.6 μM, respectively. The IC₅₀ values in Table 4 and in [12, 13]

shown that the complexes containing safrole or chelating safrole usually give higher cytotoxicity than the complexes containing ethyl eugenooxyacetate.-

Figure 7. Molecular structure of **9**, with atom labelling scheme and displacement ellipsoids drawn at the 50% probability level.

Table 4. The cell *in vitro* cytotoxicity of examined compounds, IC₅₀ (μM).

Cell line	KB	Hep-G2	Lu	MCF-7
[Pt(Saf-1H)(5,7-Cl ₂ -8-O-quinoline)](7)	4.2	2.7	4.3	3.6
[Pt (Eteug-1H)(2-Me-8-O-quinoline)] (9)	> 212	> 212	-	-
[Pt (Eteug-1H)(5,7-Cl ₂ -8-O-quinoline)](11)	121.3	25.3	-	-
[Pt (Eteug-1H)(5,7-Cl ₂ -2-Me-8-O-quinoline)] (12)	16.4	74.8	66.5	22.0
8-HO-quinoline	37.9	43.5	62.9	40.4

4. Conclusions

In this work, twelve new organoplatinum(II) complexes were synthesized from K[Pt(Saf)Cl₃] (Saf: Safrole), K[Pt(Meteug)Cl₃] (Meteug: Methyl eugenoxacetate), [Pt₂Cl₂(Saf-1H)₂] (Saf-1H: Deprotonated safrole), [Pt₂Cl₂(Eteug-1H)₂] (Eteug-1H: Deprotonated ethyl eugenoxacetate) and three substituted 8-hydroxyquinolines (HOquiN). The obtained complexes are: [PtCl(Saf)(2-Me-8-OquiN)] (**1**), [PtCl(Saf)(5,7-Cl₂-8-OquiN)] (**2**), [PtCl(Saf)(5,7-Cl₂-2-Me-8-OquiN)] (**3**), [PtCl(Meteug)(5,7-Cl₂-8-OquiN)] (**4**), [PtCl(Meteug)(5,7-Cl₂-2-Me-8-OquiN)] (**5**), [Pt(Saf-1H)(2-Me-8-OquiN)] (**6**), [Pt(Saf-1H)(5,7-Cl₂-8-OquiN)] (**7**), [Pt(Saf-1H)(5,7-Cl₂-2-Me-8-OquiN)] (**8**), [Pt(Eteug-1H)(2-Me-8-OquiN)] (**9**), [Pt(Eteug-1H)(2-OHC-8-OquiN)] (**10**), [Pt(Eteug-1H)(5,7-Cl₂-8-OquiN)] (**11**), and [Pt(Eteug-1H)(5,7-Cl₂-2-Me-8-OquiN)] (**12**). These complexes were characterized by elemental analyses, IR, ¹H NMR, for several also by MS spectra and single crystal X-ray diffraction. The exhaustive study on these spectra shown that in **1-5** the donor N of the substituted quinolin-8-olates is in *trans*-position, and in **6-12** the donor N is in *cis*-position in comparison with the ethylenic double bond of the allyl group. Four complexes were tested for cell *in vitro* cytotoxicity on human cancer cells. Complex **7** exhibits high activities on human cancer cells KB, Hep-G2, Lu and MCF-7 with IC₅₀ values of 4.2, 2.7, 4.3 and 3.6 μM, respectively.

Acknowledgements

This research is funded by Vietnam Ministry of Education under grant number B 2017-SPH-43. LVM thanks the Hercules Foundation for supporting the purchase of the diffractometer through project AKUL/09/0035.

Appendix A. Supplementary data

CCDC 1856503 contain the supplementary crystallographic data for complexes **9**. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

References

- [1] G. Pneumatikakis, *Inorganica Chimica Acta*, **93**, 5-11 (1984).
- [2] T. ~~alal~~ A.K. Al-Allaf, M. ~~ikdad~~ T. Ayoub, L. ~~uay~~ J. Rashan, *Journal of Inorganic Biochemistry*, **38**, 47-56 (1990).
- [3] A. L. Konovalova, K. I. Yakovlev, A. I. Stetsenko, N. D. Rozhkova, G. K. Gerasimova, T. I. Ivanova, N. S. Kamaletdinov, and V. P. Sinditskii, *Pharmaceutical Chemistry Journal*, **28**, 21-24 (1994).
- [4] L. Fang, M. Feng, F. Chen, X. Liu, H. Shen, J. Zhao, S. Gou, *Bioorganic & Medicinal Chemistry*. **24**, 4611 (2016).
- [5] M. Massoni, J. C. Tenorio Clavijo, L. Colina-Vegas, W. Villarreal, J. S. M. Dias, G. A. F. da Silva, M. Ionta, M. Soares, J. Ellena, A. C. Dorigueto, M. I. F. Barbosa, A. A. Batista, *Polyhedron*, **129**, 214-221 (2017).
- [6] C. M. Santos, S. Cabrera, C. Ríos-Luci, J. M. Padrón, I. L. Solera, A. G. Quiroga, M. A. Medrano, C. Navarro-Ranninger and J. Alemán, *Dalton Trans.*, **42**, 13343-13348 (2013).
- [7] M. D. Živković, J. Kljun, T. Ilic-Tomic, A. Pavic, A. Veselinović, D. D. Manojlović, J. Nikodinovic-Runic and I. TurellInorg. *Inorg.Chem. Front.*, **5**, 39-53 (2018).
- [8] T. T. Da, N. T. T. Minh, N. T. T. Chi, N. H. Dinh. *Polyhedron*, **26**, 3271-**3276** (2007).
- [9] T. T. Da, Y. M. Kim, N. T. T. Chi, L. X. Chien, N. V. Minh, N. H. Dinh. *Organometallics*, **27**, 3611-**3613** (2008).
- [10] N. T. T. Chi, T. T. Da, N. V. Ha, N. H. Dinh, *Journal of Coordination Chemistry*, **70**, 1008-1017 (2017).
- [11] T. T. Da, Y. M. Kim, T. T. C. Mai, N. C. Cuong and N. H. Dinh. *Journal of Coordination Chemistry*, **63**, 473-483 (2010).
- [12] T. T. Da, L. X. Chien, N. T. T. Chi, L. T. H. Hai and N. H. Dinh. *Journal of Coordination Chemistry*, **65**, 131-142 (2012).

- [13] T. T. Da, L. T. H. Hai, L. Van Meervelt, N. H. Dinh, *Journal of Coordination Chemistry*, **68**, 3525-3536 (2015).
- [14] T. T. Da, N. T. T. Chi, L. Van Meervelt, P. M. Kimpende and N. H. Dinh, *Polyhedron*, **85**, 104-109 (2015).
- [15] N. T. T. Chi, T. T. Da, K. Robeyns, L. Van Meervelt, T. T. C. Mai, N. D. Dat. and N. H. Dinh. *Polyhedron*, **151**, 330-337 (2018).
16. V. Prachayasittikul, S. Prachayasittikul, S. Ruchirawat, V. Prachayasittiku, *Drug Design, Development and Therapy*, **7**, 1157–1178 (2013).
- [17] C. M. Santos, S. Cabrera, C. Rios-Luci, J. M. Padron, I. L. Solera, A. G. Quiroga, M. A. Medrano, C. Navarro-Ranninger and J. Aleman, *Dalton Trans.*, **42**, 13343-13348 (2013).
- [18] A. D. Ghelman, E. F. Karandasova, L. N. Essen, *Izv. Sectora Platinum, Inst. Obsch. Nheorg. Khim. AN SSSR*, **24**, 68-72 (1949).
- [19] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, JT. Warren, H. Bokesch, S. Kenney, MR. Boyd, *J. National Cancer Institute*, **82**, 1107-1112 (1990).
- [20] CrysAlis PRO. Agilent Technologies UK Ltd, Yarnton, Oxfordshire, England, (2012).
- [21] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, and H. Puschmann, *J. Appl. Cryst.* **42**-(2009), 339-341 (2009).
- [22] G. M. Sheldrick, *Acta Crystallogr.* **A64**, 112-122 (2008).
- [23] G.M. Sheldrick, *Acta Crystallogr.* **C71**, 3-8 (2015).

Table 1. Crystal data and refinement details for crystal structures of complex **9**.

Formula	C ₂₄ H ₂₅ NO ₅ Pt	<i>V</i> (Å ³)	1061.78(5)
Formula weight	602.54	<i>Z</i>	2
Crystal size (mm)	0.25 x 0.2 x 0.2	ρ_{calc} (g/cm ³)	1.885
Radiation	Mo K α (λ =0.71073)	μ (mm ⁻¹)	6.644
Temperature (K)	293.4(6)	<i>F</i> (000)	588.0
Crystal system	triclinic	2θ value (°)	5.222-52.763
Space group	<i>P</i> -1	Reflections collected	21675
<i>a</i> (Å)	9.3398(3)	Independent reflections	4316
<i>b</i> (Å)	10.3892(3)	<i>R</i> _{int}	0.0376
<i>c</i> (Å)	11.4404(3)	Data/restraints/parameters	4316/0/283
α (°)	92.004(2)	$R[F^2 > 2\sigma(F^2)], wR(F^2)$	0.0163, 0.0365
β (°)	104.825(2)	Goodness-of-fit on <i>F</i> ²	1.074
γ (°)	97.310(2)	Largest diff. peak, hole (e Å ⁻³)	0.43, -0.58

Table 2. ^1H NMR signals of complexes **1-3** and **6-8**, δ (ppm), J (Hz).

	1/ CDCl_3	2/ CDCl_3	3/ CDCl_3	6/ CDCl_3	7/ CDCl_3	8/ CDCl_3
H1a	5.91 s	5.91 s	5.91 s	5.84 d; 2J 1	5.85 d; 2J 1	5.86 d; 2J 1
H1a'	5.91 s	5.91 s	5.91 s	5.87 d; 2J 1	5.88 d; 2J 1	5.89 d; 2J 1
H3	6.84 s	6.83 d; 4J 1.5	6.83 s	6.61 s	6.61 s	6.60 s
H5	6.79 d; 3J 7.5	6.78 dd; 3J 8; 4J 1.5	6.78 d; 3J 7.5	-	-	-
H6	6.72 d; 3J 7.5	6.71 d; 3J 8	6.72 d; 3J 7.5	7.23 s	7.18 s; $^3J_{\text{PH}}$ 35	7.27 s; $^3J_{\text{PH}}$ ov.
H7a	3.21 br.	3.33 dd; 2J 15; 3J 8	3.22 dd; 2J 15; 3J 7	2.82 d; 2J 17; $^3J_{\text{PH}}$ 95	2.85 d; 2J 17; $^3J_{\text{PH}}$ 95	2.81 d; 2J 17; $^3J_{\text{PH}}$ 95
H7b	3.57 br.	3.63 dd; 2J 15; 3J 6	3.56 d; 2J 15	3.74 dd; 2J 17; 3J 6.5	3.69 dd; 2J 17; 3J 6	3.71 dd; 2J 17; 3J 6
H8	5.65 m; $^2J_{\text{PH}}$ 70	5.75 m; $^2J_{\text{PH}}$ 70	5.73 m; $^2J_{\text{PH}}$ 70	4.98 m; $^2J_{\text{PH}}$ 75	4.78 m; $^2J_{\text{PH}}$ 75	5.01 m; $^2J_{\text{PH}}$ 75
H9 _{cis}	4.78 d; 3J 7; $^2J_{\text{PH}}$ 70	4.92 d; 3J 8; $^2J_{\text{PH}}$ 70	4.87 d; 3J 8; $^2J_{\text{PH}}$ 70	4.35 d; 3J 7.5; $^2J_{\text{PH}}$ 75	4.07 d; 3J 8; $^2J_{\text{PH}}$ 75	4.38 d; 3J 8; $^2J_{\text{PH}}$ 75
H9 _{trans}	4.75 d; 3J 14; $^2J_{\text{PH}}$ 70	4.88 d; 3J 15; $^2J_{\text{PH}}$ 70	4.86 d; 3J 13; $^2J_{\text{PH}}$ 70	3.72 d; 3J 13; $^2J_{\text{PH}}$ 75	3.93 d; 3J 13; $^2J_{\text{PH}}$ 75	3.83 d; 3J 13; $^2J_{\text{PH}}$ 75
H12	-	9.16 dd; 3J 5.5; 4J 1.5	-	-	8.15 d; 3J 5	-
H12a	3.17 s	-	3.19 s	2.67 s	-	2.69 s
H13	7.31 d; 3J 8.5	7.68 dd; 3J 8.5; 3J 5.5	7.42 d; 3J 8.5	7.24 d; 3J 8.5	7.56 dd; 3J 8.5; 3J 5	7.33 d; 3J 8.5
H14	8.22 d; 3J 8.5	8.75 dd; 3J 8.5; 4J 1.5	8.56 d; 3J 8.5;	8.15 d; 3J 8.5	8.66 d; 3J 8.5	8.49 d; 3J 8.5
H15	6.96 d; 3J 7.5	-	-	7.20 d; 3J 8	-	-
H16	7.33 t; 3J 7.5	7.64 s	7.54 s	7.46 t; 3J 8	7.74 s	7.65 s
H17	6.96 d; 3J 7.5	-	-	7.00 d; 3J 8	-	-

Table 3. ¹H NMR signals of complexes **4**, **5** and **9-12**, δ (ppm), *J* (Hz).

	4/ CDCl ₃	5/ CDCl ₃	9/ Me ₂ CO	10/ CDCl ₃	11/ Me ₂ CO	12/ CDCl ₃
H1a	4.63 s	4.63 s	4.57 d; ² <i>J</i> 16 4.58 d; ² <i>J</i> 16	4.76 s 4.76 s	4.66 s 4.66 s	4.78 d; ² <i>J</i> 16 4.79 d; ² <i>J</i> 16
H1b	3.77 s	3.77 s	4.18 q; ³ <i>J</i> 7 4.19 q; ³ <i>J</i> 7	4.31 q; ³ <i>J</i> 7 4.32 q; ³ <i>J</i> 7	4.24 q; ³ <i>J</i> 7 4.26 q; ³ <i>J</i> 7	4.28 q; ³ <i>J</i> 7 4.29 q; ³ <i>J</i> 7
H1c	-	-	1.23 t; ³ <i>J</i> 7	1.33 t; ³ <i>J</i> 7	1.28 t; ³ <i>J</i> 7	1.31 t; ³ <i>J</i> 7
H2a	3.69 s	3.66 s	3.69 s	3.84 s	3.76 s	3.83 s
H3	6.90 s	6.89 s	6.67 s	6.70 s	6.74 s	6.66 s
H5	6.86 d; ³ <i>J</i> 8	6.86 d; ³ <i>J</i> 8	-	-	-	-
H6	6.75 d; ³ <i>J</i> 8	6.75 d; ³ <i>J</i> 8	7.13 s; ³ <i>J</i> _{PtH} 35	7.20 s; ³ <i>J</i> _{PtH} 35	7.11 s; ³ <i>J</i> _{PtH} 35	7.25 s; ³ <i>J</i> _{PtH} 35
H7a	3.33 dd; ² <i>J</i> 15; ³ <i>J</i> 7	3.15 m; ov.	2.68 ov.	2.87 d; ² <i>J</i> 17; ³ <i>J</i> _{PtH} 95	2.86 d; ² <i>J</i> 17; ³ <i>J</i> _{PtH} 95	2.80 d; ² <i>J</i> 17; ³ <i>J</i> _{PtH} 95
H7b	3.63 dd; ² <i>J</i> 15; ³ <i>J</i> 7	3.62 m; ov.	3.59 dd; ² <i>J</i> 7; ³ <i>J</i> 6	3.79 dd; ² <i>J</i> 17; ³ <i>J</i> 6	3.67 dd; ² <i>J</i> 7; ³ <i>J</i> 6	3.73 dd; ² <i>J</i> 17; ³ <i>J</i> 6
H8	5.78 m; ² <i>J</i> _{PtH} 70	5.77 m; ² <i>J</i> _{PtH} 70	5.02 m; ² <i>J</i> _{PtH} 75	5.03 m; ² <i>J</i> _{PtH} 75	5.01 m; ² <i>J</i> _{PtH} 75	5.00 m; ² <i>J</i> _{PtH} 75
H9cis	4.92 d; ³ <i>J</i> 8 ² <i>J</i> _{PtH} 70	4.89 d; ³ <i>J</i> 8 ² <i>J</i> _{PtH} 70	4.44 d; ³ <i>J</i> 7.5; ² <i>J</i> _{PtH} 75	4.27 d; ³ <i>J</i> 6.5; ² <i>J</i> _{PtH} 75	4.36 d; ³ <i>J</i> 7.5; ² <i>J</i> _{PtH} 75	4.40 d; ³ <i>J</i> 7.5
H9trans	4.89 d; ³ <i>J</i> 14 ² <i>J</i> _{PtH} 70	4.87 d; ³ <i>J</i> 14 ² <i>J</i> _{PtH} 70	3.53 d; ³ <i>J</i> 13; ² <i>J</i> _{PtH} 75	3.83 d; ³ <i>J</i> 13.5	3.83 d; ³ <i>J</i> 13.5; ² <i>J</i> _{PtH} 75	3.85 d; ³ <i>J</i> 14
H12	9.14 d; ³ <i>J</i> 5	-	-	-	8.62 d; ³ <i>J</i> 5	-
H12a	-	3.17 s	2.68 s	9.81 s	-	2.69 s
H13	7.68 dd; ³ <i>J</i> 8.5; ³ <i>J</i> 5	7.42 d; ³ <i>J</i> 8.5	7.42 d; ³ <i>J</i> 8.5	8.01 d; ³ <i>J</i> 8.5	7.84 dd; ³ <i>J</i> 8.5; ³ <i>J</i> 5	7.35 d; ³ <i>J</i> 8.5
H14	8.75 d; ³ <i>J</i> 8.5	8.56 d; ³ <i>J</i> 8.5	8.29 d; ³ <i>J</i> 8.5	8.43 d; ³ <i>J</i> 8.5	8.75 d; ³ <i>J</i> 8.5	8.49 d; ³ <i>J</i> 8.5
H15	-	-	7.01 dd; ³ <i>J</i> 8; ⁴ <i>J</i> 1	7.12 d; ³ <i>J</i> 8	-	-
H16	7.64 s	7.54 s	7.38 t; ³ <i>J</i> 8	7.69t; ³ <i>J</i> 8	7.81 s	7.66 s
H17	-	-	6.98 dd; ³ <i>J</i> 7.5; ⁴ <i>J</i> 1	6.29 dd; ³ <i>J</i> 7.5; ⁴ <i>J</i> 1	-	-

Table 4. The cell *in vitro* cytotoxicity of examined compounds, IC₅₀ (μM).

Cell line	KB	Hep-G2	Lu	MCF-7
[Pt (Saf-1H)(5,7-Cl ₂ -8-O-quinoline)] (7)	4.2	2.7	4.3	3.6
[Pt (Eteug-1H)(2-Me-8-O-quinoline)] (9)	> 212	> 212	-	-
[Pt (Eteug-1H)(5,7-Cl ₂ -8-O-quinoline)] (11)	121.3	25.3	-	-
[Pt (Eteug-1H)(5,7-Cl ₂ -2-Me-8-O-quinoline)] (12)	16.4	74.8	66.5	22.0
8-HO-quinoline	37.9	43.5	62.9	40.4

Figure 1. Starting organoplatinum(II) complexes.

Figure 2. Structure of complexes 1-5 (the numeration on these structures is specifically used for NMR analysis).

Figure 3. NOESY spectrum of complex 3.

Figure 4. Structure of complexes 6-8.

Figure 5. Structure of complexes 9-12 (the numeration on these structures is specifically used for NMR analysis).

Figure 6. NOESY spectrum of complex 8.

Figure 7. Molecular structure of 9, with atom labelling scheme and displacement ellipsoids drawn at the 50% probability level.

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) hai39

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: hai39

Bond precision: C-C = 0.0040 Å Wavelength=0.71073

Cell: a=9.3398(3) b=10.3892(3) c=11.4404(3)

 alpha=92.004(2) beta=104.825(2) gamma=97.310(2)

Temperature: 293 K

	Calculated	Reported
Volume	1061.78(5)	1061.78(5)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C24 H25 N O5 Pt	C24 H25 N O5 Pt
Sum formula	C24 H25 N O5 Pt	C24 H25 N O5 Pt
Mr	602.53	602.54
Dx, g cm ⁻³	1.885	1.885
Z	2	2
Mu (mm ⁻¹)	6.644	6.644
F000	588.0	588.0
F000'	584.97	
h,k,lmax	11,12,14	11,12,14
Nref	4321	4316
Tmin,Tmax	0.221,0.265	0.729,1.000
Tmin'	0.174	

Correction method= # Reported T Limits: Tmin=0.729 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.999 Theta(max)= 26.368

R(reflections)= 0.0163(4085) wR2(reflections)= 0.0374(4316)

S = 1.074 Npar= 283

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level C

CRYSC01_ALERT_1_C The word below has not been recognised as a standard identifier.
yellowish

Alert level G

PLAT012_ALERT_1_G	No	_shelx_res_checksum Found in CIF	Please Check
PLAT154_ALERT_1_G	The s.u.'s on the Cell Angles are Equal ..(Note)		0.002 Degree
PLAT199_ALERT_1_G	Reported _cell_measurement_temperature	(K)	293 Check
PLAT200_ALERT_1_G	Reported _diffrn_ambient_temperature	(K)	293 Check
PLAT794_ALERT_5_G	Tentative Bond Valency for Pt1 (II)		2.14 Info
PLAT910_ALERT_3_G	Missing # of FCF Reflection(s) Below Theta(Min).		4 Note
PLAT933_ALERT_2_G	Number of OMIT Records in Embedded .res File ...		2 Note
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.		5 Info

0 **ALERT level A** = Most likely a serious problem - resolve or explain
 0 **ALERT level B** = A potentially serious problem, consider carefully
 1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
 8 **ALERT level G** = General information/check it is not something unexpected

5 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
 2 ALERT type 2 Indicator that the structure model may be wrong or deficient
 1 ALERT type 3 Indicator that the structure quality may be low
 0 ALERT type 4 Improvement, methodology, query or suggestion
 1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 14/07/2018; check.def file version of 05/06/2018

Datablock hai39 - ellipsoid plot