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Synthesis, characterization and cytotoxicity of a new palladium(II) complex with a coumarin-derived ligand. Crystal structure of 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one-palladium(II) complex

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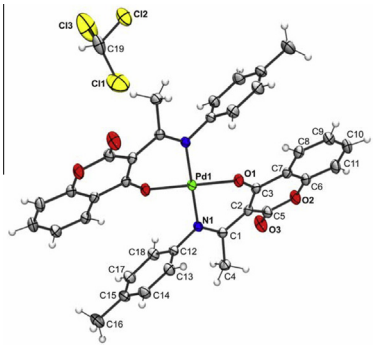
HIGHLIGHTS

- Synthesis of a new palladium(II) complex with coumarine-derived ligand.
- Crystal structure of palladium(II) complex.
- Cytotoxicity of obtained compounds.

GRAPHICAL ABSTRACT



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ABSTRACT

The new coumarine derivative, 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one, and corresponding palladium(II) complex have been synthesized and characterized by microanalysis, infrared, ^{1}H and ^{13}C NMR spectroscopy. The proposed structure of the complex was confirmed on the basis of an X-ray structural study. *In vitro* antitumor activity for the ligand and complex was investigated.

1. Introduction

After the Rosenberg's discovery of the cisplatin antitumor activity [1], the scientists synthesized a lot of platinum-based drugs that could be less toxic to healthy tissue [2] and overcome the resistance to cisplatin [3]. The toxic side-effects of the cisplatin limit the doses that can be applied to patients [4].

Palladium(II) complexes have also been a subject of wide examination due to their structural analogy with platinum(II) complexes. However, initial results were not very encouraging because the palladium(II) complexes generally showed lower antitumor activity than cisplatin. This could be explained by the more labile nature of the palladium(II) complexes in comparison to the corresponding platinum(II) complexes [5]. However, some of

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palladium(II) complexes exerted higher antitumor activity in comparison with cisplatin and carboplatin. Budzisz et al. found that palladium(II) complex with 4-hydroxy-3-(1-iminoethyl)-2*H*-chromen-2-one was 7800 times more active than carboplatin [6].

Coumarine and its derivatives are natural compounds with spasmolitic, antiarrhytmic, cardiotonic and photodynamic properties [7]. Weber et al. [8] tested coumarine and its major metabolite 7-hydroxycoumarin against several human tumor cell lines (Caco-2 colorectal carcinoma, Hep-G2 hepatoma and CCRF-CEM lymphoblastoma). Egan et al. [9] investigated cytostatic and cytotoxic nature of 8-nitro-7-hydroxycoumarin against both human (K-562 and HL-60) and animal cell lines grown *in vitro*. Also, coumarin and its 4-hydroxy and 7-hydroxy derivatives were tested against P-815 and P-388 tumor cells *in vitro* [10]. Metal complexes with coumarine derivatives showed significant anticoagulant [11,12] and antitumor activity [13,7]. Also, some cerium(III), zirconium(IV), copper(II), zinc(II), bismuth(III) and cadmium(II) were significantly cytotoxic *in vitro* [14,15].

Herein we described the synthesis and characterization of the 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one and corresponding palladium(II) complex. The crystal structure of 4-Hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one-palladium(II) complex was also reported. In addition, antitumor activities of both 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one and corresponding palladium(II) complex were tested.

2. Experimental

2.1. Materials and methods

All applied chemicals and reagents were of the highest purity available and purchased from the Sigma–Aldrich Chemical Company (St. Louis, MO), Difco and Merck Laboratory Supplies (Darmstadt, Germany).

Infrared spectra were recorded by a Perkin–Elmer Spectrum One FT-IR spectrometer using the KBr pellet technique (4000–400 cm^{-1}). ^1H and ^{13}C NMR spectra were recorded by a Varian Gemini-2000 (200 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Elemental microanalyses for C, H and N were performed by standard methods by a Vario EL *III* C, H, N Elemental Analyzer. The microwave assisted reaction was carried out in the MICROSYNTH Microwave Synthesis System (Milestone Inc. 25 Controls Dr. Shelton), the microwaves were generated by magnetron at the frequency of 2450 MHz having an output energy range of 100–500 W. Melting point of ligand was determined by using Kofler-hot stage apparatus.

2.2. Chemical synthesis

Chemical synthesis of ligand 4-hydroxy-3-(1-(*p*-tolylimino) ethyl)-2*H*-chromen-2-one was published earlier [16].

Reaction of condensation of 3-acetyl-4-hydroxychromene-2-one **1** with p-tolylamine **2** was successfully performed by two different methods (conventional and microwave method).

Conventional method: Mixture of 3-acetyl-4-hydroxy-chromene-2-one **1** (0.01 mol, 2.0418 g), p-tolylamine **2** (0.01 mol, 1.0715 g) and catalytic amount of *p*-toluene sulfonic acid in anhydrous toluene (50 mL) was heated with azeotropic removal of water in the period of 10–12 h. Progress of reaction was monitored by TLC (toluene: acetone = 7:3). At the end of reaction, solvent was removed under reduced pressure. The solid products were filtered, dried, purified via column chromatography (benzene: acetone = 8:2) to give compound **3** (see Scheme 1). Yield: 2.1412 g (73%).

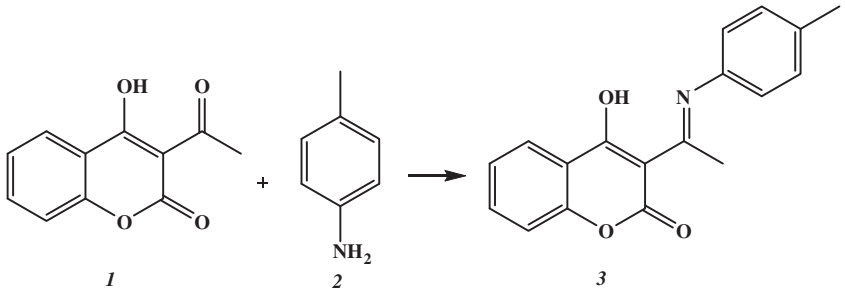
Microwave method: Catalytic amount of *p*-toluene sulfonic acid was added to 50 mL toluene solution of equimolar amounts (0.01 mol) of 3-acetyl-4-hydroxy-chromene-2-one **1** and *p*-tolylamine **2**. The mixture was heated under microwave for 3 min. After cooling, the solvent was removed, and then the obtained solid was filtered and recrystallized from methanol. Yield 2.7865 g (95%).

4-Hydroxy-3-(1-(p-tolylimino)ethyl)-2H-chromen-2-one (**3**): *Anal.* Calcd. for $C_{18}H_{15}NO_3$ (Mr = 293.32): C, 73.71; H, 5.15; N, 4.78; found: C, 73.72; H, 5.12; N, 4.79. M.P. 147–149 °C. IR (KBr, cm^{-1}): 3421 (OH), 3073 (=CH)ar, 2985, 2922 and 2852 (CH_3), 1709 (lactone C=O), 1611 (imino C=N), 1597, 1569, 1513 and 1483 (C=C)ar. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (s, 3H, CH_3—C4″), 2.69 (s, 3H, CH_3—C=N), 7.09–7.65 (ABq, 4H, *J* = 8.43 Hz, $C_{2''}$, $_{3''}$, $_{5''}$, $_{6''}$—H), 7.3 (m, 1H, C_6—H), 7.4 (dd, 1H, *J* = 8.3 Hz, *J* = 1.1 Hz, C_8—H), 7.6 (dd, 1H, *J* = 7.8 Hz, *J* = 1.7 Hz, C_5—H), 7.7 (m, 1H, C-7-H), 16.07 (bs, 1H, C_4—OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6 (CH_3—C4″), 20.8 (CH_3—C=N), 97.3 (C_3), 116.6 (C_{10}), 116.8 (C_8), 119.3 (C_5), 119.9 ($C_{2''}$, $C_{6''}$), 125.9 (C_6), 129.3 (C_7), 129.9 ($C_{4''}$), 131.7 ($C_{3''}$, $C_{5''}$), 138.4 ($C_{1''}$), 163.5 (C_2), 152.4 (C_9), 180.4 (C_4), 180.5 ($C_{1'}$).

2.2.1. Synthesis of 4-hydroxy-3-(p-tolylimino)ethyl)-2H-chromen-2-one-palladium(II) complex (**C3**)

Complex was obtained by mixing $K_2[PdCl_4]$ (0.25 mmol, 0.0816 g) in 10 cm^3 of water and ligand (0.5 mmol, 0.1467 g) in 10 cm^3 of methanol in molar ratio 1:2. The solution was mixed for 5 h. Within this period, pale yellow precipitates of the complex were obtained, filtered off and air dried. Yield of 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one-palladium(II) (**C3**) 0.1274 g (72%). *Anal.* Calcd. for $C_{36}H_{30}N_2O_6Pd$ (Mr = 693.05): C, 62.39; H, 4.36; N, 4.04; found: C, 62.66; H, 4.50; N, 4.28. IR (KBr, cm^{-1}): 3054 (=CH)ar, 2979, 2923 and 2855 (CH_3), 1705 (lactone C=O), 1607 (imino C=N), 1562, 1480 and 1475 (C=C)ar, 532 (Pd—O), 435 (Pd—N). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.25 (s, 6H, CH_3—C4″), 2.38 (s, 6H, CH_3—C=N), 6.98–7.45 (ABq, 8H, *J* = 8.51 Hz, $C_{2''}$, $_{3''}$, $_{5''}$, $_{6''}$—H), 7.59 (m, 2H, C_6—H), 7.28 (dd, 2H, *J* = 8.33 Hz, *J* = 1.1 Hz, C_8—H), 8.05 (dd, 2H, *J* = 7.83 Hz, *J* = 1.6 Hz, C_5—H), 7.58 (m, 2H, C-7-H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.1 (CH_3—C4″), 24.6 (CH_3—C=N), 105.8 (C_3), 115.2 (C_{10}), 115.8 (C_8), 117.9 (C_5), 122.7 ($C_{2''}$, $C_{6''}$), 124.7 (C_6), 129.8 (C_7), 130.2 ($C_{4''}$), 133.1 ($C_{3''}$, $C_{5''}$), 144.5 ($C_{1''}$), 162.5 (C_2), 152.7 (C_9), 169.8 (C_4), 172.7 ($C_{1'}$).



Scheme 1. Synthesis of the 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one (**3**).

2.3. Structure determination

The crystal of complex **C3** suitable for X-ray measurements was obtained from an oversaturated chloroform solution at 20 °C. A single crystal of complex **C3** was selected and mounted on a glass fiber. Diffraction data were collected using a Oxford Diffraction Gemini S four-circle goniometer equipped with Sapphire CCD detector. The crystal to detector distance was 45.0 mm and graphite monochromated MoKα ($\lambda = 0.71073$ Å) radiation was used for the experiments. The data were reduced using the program CrysAlisPRO [17]. A semiempirical absorption–correction based upon the intensities of equivalent reflections was applied, and the data were corrected for Lorentz, polarization, and background effects. The structure was solved by direct methods using Sir 97 program [18] and refined by full-matrix least-squares procedures on F^2 using SHELXL-97 programs [19] as implemented in the WinGX program suite [20]. The non-H atoms were refined anisotropically. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. At the final stage of the refinement, H atoms from the methyl group were positioned geometrically (C—H = 0.96 Å) and refined using a riding model with fixed isotropic displacement parameters. Crystallographic data and refinement parameters are listed in Table 1. The figures representing molecular structure were made using ORTEP-3 [21] and PLATON [22] programs.

The perspective view of molecular structure of compound 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one-palladium(II) complex (**C3**) is shown in Fig. 1. Fig. 2 presents crystal packing for compound 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one-palladium(II) complex (**C3**). Selected bond lengths are given in Table 2, bond angles are given in Table 3. Torsion angles are given in Table 4.

Table 1
Crystal data and structure refinement for 4-hydroxy-3-(1-(*p*-tolylimino)ethyl)-2*H*-chromen-2-one-palladium(II) complex (**C3**).

Empirical formula	$C_{38}H_{29}Cl_3N_2O_6Pd$
Formula weight	929.74
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	*P-1*
Unit cell dimensions	$a = 10.022(5)$ Å $\alpha = 111.224(5)°$ $b = 10.534(5)$ Å $\beta = 110.920(5)°$ $c = 10.735(5)$ Å $\gamma = 94.812(5)°$
Volume	956.8(8) Å^3
Z	1
Density (calculated)	1.614 Mg/m^3
Absorption coefficient	0.953 mm^{-1}
F(000)	468
Crystal size	0.354 × 0.261 × 0.212 mm^3
Theta range for data collection	3.46–25.00°
Index ranges	$-11 \leqslant h \leqslant 11$, $-12 \leqslant k \leqslant 11$, $-9 \leqslant l \leqslant 12$
Reflections collected	5920
Independent reflections	3358 [*R*(int) = 0.0282]
Completeness to $\theta = 25.00°$	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.99246
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3358/0/279
Goodness-of-fit on F^2	1.032
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0449, *wR*2 = 0.0911
R indices (all data)	*R*1 = 0.0505, *wR*2 = 0.0951
Largest diff. peak and hole	0.614 and −0.741 e Å^{-3}

2.4. Cells and cell culture

NCI-H460 cell line was purchased from the American Type Culture Collection, Rockville, MD. NCI-H460/R cells were selected originally from NCI-H460 cells and cultured in a medium containing

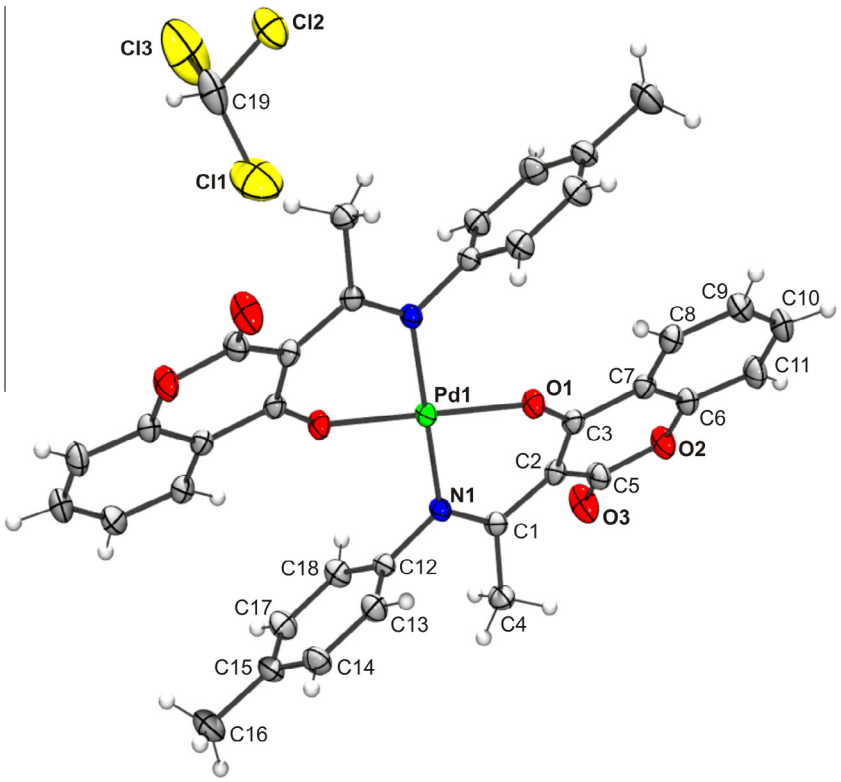


Fig. 1. Molecular structure of the complex with the non-H atom numbering scheme with thermal ellipsoids at 30% probability level. Symmetry transformations used to generate equivalent atoms: $-x, -y, -z+1$.

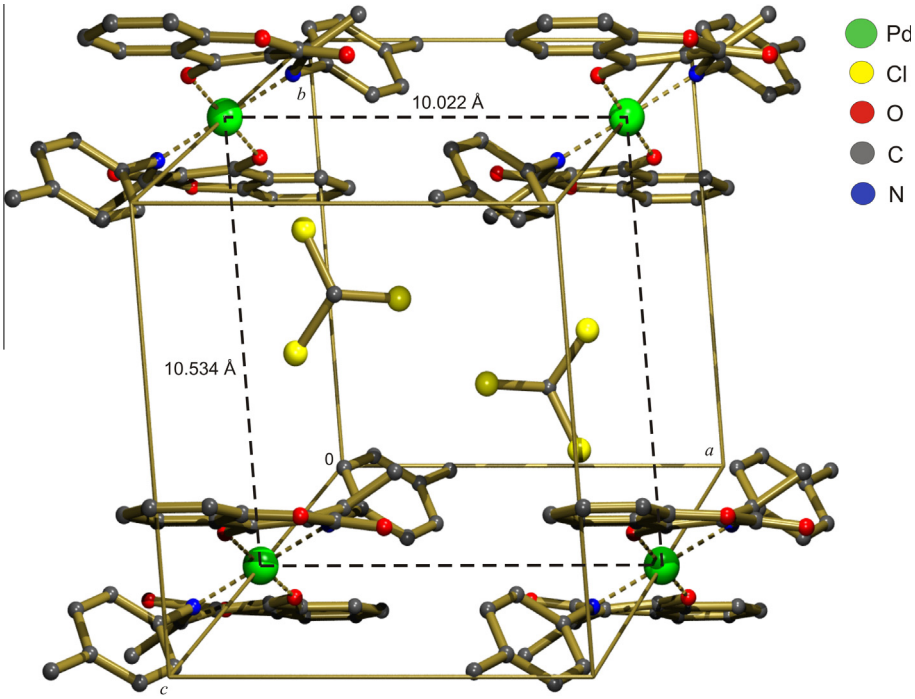


Fig. 2. PLATON drawing showing crystal packing for complex **C3**. H atoms are not shown for clarity.

Table 2
Selected bond lengths (Å) for **C3**.

Pd(1)—O(1)	1.985(2)
Pd(1)—N(1)	2.014(3)
N(1)—C(1)	1.307(4)
N(1)—C(12)	1.440(4)
O(1)—C(3)	1.289(4)
O(2)—C(6)	1.380(5)
O(2)—C(5)	1.382(5)
O(3)—C(5)	1.201(5)
C(2)—C(3)	1.389(5)
C(2)—C(1)	1.456(5)
C(2)—C(5)	1.460(5)
C(7)—C(3)	1.466(5)

Table 3
Selected bond angles (°) for **C3**.

O(1)—Pd(1)—N(1)	88.73(11)
C(3)—O(1)—Pd(1)	121.7(2)
C(1)—N(1)—Pd(1)	125.7(2)
C(12)—N(1)—Pd(1)	114.7(2)
N(1)—C(1)—C(2)	120.8(3)
N(1)—C(1)—C(4)	120.2(3)
C(1)—N(1)—C(12)	119.5(3)
O(1)—C(3)—C(2)	126.1(3)
O(1)—C(3)—C(7)	114.9(3)
C(1)—C(2)—C(5)	117.2(3)
C(2)—C(3)—C(7)	119.0(3)
C(2)—C(1)—C(4)	118.7(3)
C(3)—C(2)—C(1)	122.8(3)
C(3)—C(2)—C(5)	119.9(3)

100 nM doxorubicin [23]. Cells were subcultured at 72 h intervals using 0.25% trypsin/EDTA and seeded into a fresh medium at the following densities: 8000 cells/cm^2 for NCI-H460 and 16,000 cells/cm^2 for NCI-H460/R.

Table 4
Selected torsion angles (°) for **C3**.

N(1)^1—Pd(1)—O(1)—C(3)	143.7(3)
N(1)—Pd(1)—O(1)—C(3)	−36.3(3)
O(1)^1—Pd(1)—N(1)—C(1)	−154.4(3)
O(1)—Pd(1)—N(1)—C(1)	25.6(3)
N(1)^1—Pd(1)—N(1)—C(1)	−123(3)
O(1)^1—Pd(1)—N(1)—C(12)	29.3(3)
O(1)—Pd(1)—N(1)—C(12)	−150.7(3)
N(1)^1—Pd(1)—N(1)—C(12)	61(3)
Pd(1)—N(1)—C(1)—C(2)	−1.3(5)
Pd(1)—N(1)—C(1)—C(4)	−174.9(3)
Pd(1)—O(1)—C(3)—C(2)	24.0(5)

Symmetry transformations used to generate equivalent atoms: 1 −*x*, −*y*, −*z* + 1.

2.4.1. Sulforhodamine B assay (SRB)

Cells grown in 25 cm^2 tissue flasks were trypsinized, seeded into flat-bottomed 96-well tissue culture plates, and incubated overnight. NCI-H460 was seeded at 2000 cells/well, while NCI-H460/R cells were seeded at 4000 cells/well. Treatment with coumarine-derived ligand (1–500 μM) and **C3** (0.01–200 μM) lasted 72 h. The cancer cell growth inhibition was assessed and the cellular proteins were stained with SRB, following a slightly modified protocol [24].

3. Results and discussion

The structure of synthesized complex **C3** was determined by means of spectral (IR, ^{1}H NMR and ^{13}C NMR) and elemental analysis, as well as X-ray diffraction study. In comparison to IR spectral data of ligand **3**, obtained Pd complex showed significant differences. The characteristic band assigned to the OH vibration in ligand **3** was not observed in complex **C3**, which indicated that oxygen from position C-4 of coumarine moiety participated in formation of bond with Pd. This is confirmed by identification of Pd—O stretching vibration at 532 cm^{-1}. The stretching vibration of C=N group in ligand **3** was observed at 1611 cm^{-1}, while in

Pd complex it was shifted to lower frequency (1607 cm^{-1}). The involving of imino nitrogen in coordination with Pd was confirmed by identification of Pd—N band at 434 cm^{-1}. Also, in obtained complex, lactone C=O group was identified at lower energy, showing intensive band at 1705 cm^{-1}.

In comparison to the ^1H NMR spectra of obtained complex **C3**, which does not have broadened signal from OH group, the ^1H NMR spectra of ligand **3** C_4—OH proton showed resonance at 16.07 ppm. On the other hand, it is evident that formation of complex influenced decrease of chemical shifts of CH_3—C4″ and CH_3—C=N protons (2.41 ppm and 2.69 ppm, respectively).

The ^{13}C NMR spectral study showed that coordination has strong effect on C-4 carbon, decreasing the chemical shift from 180.4 ppm (in ligand) to 169.8 ppm (in complex). The signal of carbon from methyl group bonded to imino group (CH_3—C=N) was at lower frequency in ligand **3** than in complex **C3** (20.8 ppm and 24.6 ppm, respectively).

3.1. The crystal structure of 4-hydroxy-3-(1-(p-tolylimino)ethyl)-2H-chromen-2-one-palladium(II) complex (*C3*)

The X-ray diffraction study of **C3** (Fig. 1) shows that in the PdL2 molecule two L-ligands chelate to the Pd ion through their N and O donors, giving a four-coordinate Pd(II) center with a *trans*-N2O2 donor set. The coordination geometry at Pd(II) is square-planar, with standard values for the distances from the metal atom to the coordinated atoms [Pd—N1: 2.014(3); Pd—O1: 1.985(2) Å]. The bond angle values of O1—Pd1—N1: 88.73(11) and O1—Pd1—N1 $^1[^1-x, -y, -z+1]$: 91.27(11) around the Pd(II) ion confirms the square-planar coordination geometry. The Pd(II) ion lies in the least-squares plane of the coordinated atoms. While the N1—C1 bond in the six-membered chelate rings possess the character of a localized double bond that deviates only marginally from the ideal value of 1.28 Å, [25] a substantial lengthening of the O1—C3 bond is observed when compared to the localized double O3—C5 bond (Table 2). The distribution of the bond lengths over the fragments C1—C2—C3 indicates significant delocalization of the electron density (Table 2).

The results of Cremer and Pople's ring puckering analysis [26] showed that the six-membered chelate ring could be described in a twist or skew-boat conformation [Pd1—N1—C1—C2—C3—O1: Q_T = 0.470 Å, φ_2 = 165.1°, θ_2 = 108.1°], while the conformation of C2—C3—C7—C6—O2—C5 is almost planar but more precisely can be described as envelope [Q_T = 0.118 Å, φ_2 = 180°, θ_2 = 109°].

The crystal packing is dominantly arranged by Van Der Waals forces. We have not found classic hydrogen bond in intra or inter molecular space (Fig. 2). The distances between Pd atoms in the unit cell are shown in the Fig. 2. Fig. 2 shows that the crystal structure corresponds to a discrete arrangement of PdL2 molecules certainly due to the presence within the unit cell of molecules of solvent of crystallization ($CHCl_3$).

3.2. Cancer cell growth inhibition by novel *C3* complex

Compared to cisplatin as a referent platinum-based anticancer drug, novel palladium(II) complex (**C3**) showed significantly lower growth inhibition effect in NCI-H460 non-small cell carcinoma cell line and its multi-drug resistant P-glycoprotein over-expressing counterpart – NCI-H460/R. The IC50 values for cisplatin were 2.2 and 3.9 μM in NCI-H460 and NCI-H460/R, respectively, whereas the IC50 values for **C3** were 19.4 and 147.2 μM. Coumarine-derived ligand did not decrease the cell growth of both tested cancer cell lines. The obtained results suggest that **C3** anti-cancer effect was significantly suppressed by the presence of multi-drug resistant phenotype in NCI-H460/R cells. The impact of P-glycoprotein transport activity in NCI-H460/R cells must be considered as a reason for resistance to **C3**.

4. Conclusion

The prepared complex (**C3**) has been characterized by elemental analyses, infrared and NMR (^1H and ^{13}C) spectroscopy. The X-ray analysis of the crystal confirmed the Pd(II) coordination with ligand in molar ratio 1:2. The coordination geometry of the Pd(II) ion is square-planar with expected values for Pd—O and Pd—N distances. The investigation of cancer cell growth inhibition showed that ligand **3** did not decrease the cell growth of both tested cancer cell lines, while the corresponding Pd(II) complex showed significantly lower growth inhibition effect than cisplatin.

Supplementary material

CCDC 920512 contains the supplementary crystallographic data for this paper. 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.

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