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Synthesis, characterisation and in vitro evaluation of palladium(II) iminophosphine complexes for anticancer activity

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Abstract Palladium(II) complexes have been obtained from the reactions of the iminophosphine ligands, (**L1**–**L7**), respectively, with [$PdCl_2$(COD)] and [PdMeCl(COD)] in CH_2Cl_2 at room temperature. The palladium(II) complexes were characterised using elemental analysis, electro spray ionisation–mass spectrometry (ESI–MS), NMR (^{1}H and ^{31}P), IR spectroscopy and X-ray diffraction studies. Single-crystal X-ray diffraction analysis for complexes **2**, **7** and **8** revealed that the complexes exhibited a slightly distorted square planar geometry. In vitro cytotoxic study results show that the palladium complexes exhibit moderate activity and block the proliferation of WHCO1 cells with an IC_{50} range of 19.02–45.27 μM, and IC_{50} range of 10.03–68.54 μM for the KYSE450 cell lines.

Introduction

During recent years, there has been a growing interest in the chemistry of ligands with both 'hard' nitrogen and 'soft' phosphorus donor atoms [1–3]. Metal complexes with N and P donor atoms display a variety of coordination possibilities beyond those of P–P or N–N ligands [4]. The hard ligand components can readily dissociate from a soft metal centre generating a vacant site on the metal ion for substrate binding. These ligands show a particular behaviour in binding to soft metal centres such as palladium(II) and platinum(II) that make their complexes good precursors in catalytic processes [5–8]. Among the most studied ligands with this characteristic are the pyridylphosphines and iminophosphines which have been widely reported in complexes with ruthenium [9], palladium [10], rhodium [11] and iridium [12]. In the last 3 decades, the interest towards platinum(II) and palladium(II) complexes containing *N* and *S* donor ligands has increased, resulting in the development of metal-based drugs exhibiting high anticancer activity together with reduced toxicity, compared with cisplatin and analogous compounds [13].

The development of palladium anticancer drugs has not been promising, probably because their design has been based on structure–activity considerations generated from platinum antitumor drugs. Bearing in mind that Pd(II) complexes are about 105 times more reactive than their Pt(II) analogues, the low antitumoral activity of Pd compounds has been attributed to very rapid hydrolysis of the leaving groups that dissociate readily in solution, leading to reactive species far from their pharmacological targets [14]. Palladium is a suitable candidate for metallodrugs because it displays structural properties similar to those of platinum and also exhibits promising cytotoxicity.

As part of our continuing interest in the synthesis of transition metal complexes of biological molecules, we have investigated the coordination behaviour of iminophosphines towards palladium(II), with a view to develop new transition metal pharmaceuticals. This paper describes the synthesis, structural characterisation and preliminary biological activity of palladium iminophosphine complexes.

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Experimental

All manipulations were carried out under an atmosphere of nitrogen or argon using standard Schlenk techniques. All other glassware was thoroughly dried at 210 °C for at least 4 h prior to use. [$PdCl_2$(COD)], [PdMeCl(COD)], complexes **1**, **2** and ligands **L1**–**L7** were prepared according to known literature procedures [15–17]. Melting points were determined on a Kofler hotstage microscope (Reichart Thermovar) and are uncorrected. Microanalysis data were obtained using a Carlo Erba EA1108 elemental analyser. Infrared spectra were recorded on a Perkin-Elmer 1000 FT–IR spectrometer, as KBr discs for solids. All data are given in wavenumbers (cm^{-1}). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Unity-400 instrument. Mass spectra (EI) were recorded using a JEOL-MATE(II) GC–MS instrument. X-ray intensity data were collected on a Nonius Kappa-CCD diffractometer with 1.5 kW graphite monochromated Mo-Kα radiation.

MTT assay

Thousand five hundred cells were seeded per well in 90 µl DMEM in 96 well plates. Cells were incubated for 24 h, then, test samples were plated at a range of concentrations in 10 µl media, with a final concentration of 0.2 % DMSO. After 48 h of incubation, the cells were observed under a phase contrast microscope and the general appearance of the cells together with confluency status and presence of precipitate if any was recorded.

Ten microlitres of MTT reagent was added per well at the end of the experiment, and the plates incubated for 4 h at 37 °C. Hundred microlitres of solubilisation solution was then added to each well, and plates were incubated at 37 °C overnight. After 16 h, the plates were read at 595 nm on an Anthos microplate reader 2001.

IC_{50} data analysis

The resulting dose–response curve was analysed by non-linear regression analysis [nonlinear regression (sigmoidal dose–response with variable slope)] using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) to yield an IC_{50} value which is specific for the compound against that particular cell line. The formula used is as follows:

$$Y = \frac{(\text{top} - \text{bottom})}{\text{bottom} + 1 + 10^{(\log \text{IC50} - X) \times \text{hillslope}}}$$

where Y is the absorbance reading, X is the concentration of the compound, top is the maximum absorbance, bottom is the minimum absorbance (also the absorbance of the medium blank) and the hillslope is the gradient of the curve.

Each experiment was repeated at least three times.

General procedure for the preparation of palladium(II) dichloride complexes (**1**–**7**)

To a solution of the appropriate ligand (**L1**–**L7**) in dry CH_2Cl_2 (10 ml) was added an equimolar amount of [$PdCl_2$(COD)] dissolved in dry CH_2Cl_2 (10 ml). The reaction was allowed to stir at room temperature for 4 h before reducing the solvent to ca 5 ml and precipitating the products using hexane. The products were filtered off, washed with Et_2O and dried under vacuum.

*Complex **1***

Yellow crystalline solid. Yield 70 %. m.p.: 158–160 °C. $C_{22}H_{22}Cl_2NPd$: Found: C, 51.69 %; H, 4.12 %; N, 2.72 %. Calcd. C, 51.94 %; H, 4.36 %; N, 2.75 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1632(s). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H 8.85 (s, 1H, H_a) 7.89 (m, 3H, ArH) 7.66 (dd, 4H, $J = 6.3$ Hz, $J = 7.9$ Hz, ArH) 7.55 (ddd, 7H, $J = 2.0$ Hz, $J = 5.2$ Hz, $J = 8.5$ Hz, ArH) 2.95 (dddd, 2H, $J = 5.4$ Hz, $J = 8.3$ Hz, $J = 13.8$ Hz, $J = 16.7$ Hz, H_b) 1.18 (m, 2H, H_c) 0.53 (t, 3H, $J = 7.3$ Hz, H_d) ^{31}P NMR: δ 30.85 (s). EI–MS: *m/z* 437.30 $[M–2Cl]^+$.

*Complex **2***

Yellow powder. Yield 82 %. m.p. 168–170 °C. $C_{22}H_{22}Cl_2NPPd$: Found: C, 51.79 %; H, 4.12 %; N, 2.52 %. Calcd. C, 51.94 %; H, 4.36 %; N, 2.75 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1630(s). ^{1}H NMR: (dmso-d_6) δ_H 8.02 (s, 1H) 7.72 (m, 2H, ArH) 7.51 (m, 11H, ArH) 6.94 (ddd, 1H, $J = 0.5$ Hz, $J = 7.7$ Hz, $J = 10.6$ Hz, Ar) 5.57 (dtd, 1H, $J = 0.6$ Hz, $J = 6.4$ Hz, $J = 13.0$ Hz) 1.16 (d, 6H, $J = 6.6$ Hz). ^{31}P NMR: δ 31.62 (s). EI–MS: *m/z* 474.68 $[M–Cl]^+$.

*Complex **3***

Yellow crystalline powder. Yield 75 %. m.p. 200–202 °C. $C_{31}H_{32}Cl_2NPPd$: Found: C, 59.19 %; H 5.12 %; N 2.42 %. Calcd. C, 59.39 %; H, 5.15 %; N 2.23 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1624(s). ^{1}H NMR: (dmso-d_6) δ_H 8.74 (s, 1H, HC = N) 7.58 (m, 14H ArH) 7.16 (m, 7.16, 4H, ArH) 1.19 (d, 6H, $J = 6.7$ Hz, $–CH_3$) 0.77 (t, 6H, $J = 6.3$ Hz, $–CH_3$). ^{13}C NMR: (dmso-d_6) δ 169.31, 135.28, 133.94 (d, $J_{CP} = 11.0$ Hz), 132.89, 129.74 (d, $J_{CP} = 11.8$ Hz), 128.90, 123.80, 28.73, 27.99, 24.31, 23.42. ^{31}P NMR: δ 33.34 (s). EI–MS: *m/z* 591.44 $[M–Cl]^+$.

*Complex **4***

Yellow powder. Yield 76 %. m.p.: 200–202 °C. $C_{26}H_{22}Cl_2NPPd$: Found: C, 56.26 %; H 3.72 %; N, 2.72 %. Calcd. C,

56.09 %; H, 3.98 %; N, 2.52 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1627(s). ^{1}H-NMR: (400 MHz, d_6-dmso) δ_H 7.81 (m, 1H) 7.63 (m, 1H) 7.49 (m, 1H) 7.09 (m, 1H) 7.08 (m, 1H) 6.91 (dd, 1H, $J = 4.6$ Hz, $J = 10.9$ Hz) 6.49 (dd, 1H, J 1.1 Hz, $J = 8.1$ Hz) 4.22 (t, 2H, $J = 12.6$ Hz). ^{31}P NMR: δ 34.11 (s).

Complex ***5***

Yellow powder. Yield 70 % yield m.p.: 210–212 °C. $C_{25}H_{21}N_2PPd$: Found: C, 53.69 %; H 3.92 %; N 4.92 %. Calcd. C, 53.84 %; H, 3.80 %; N 5.02 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1626(s). ^{1}H-NMR: (400 MHz, d_6-dmso) δ_H 8.82 (s, 1H, H_a) 8.66 (d, 1H, $J = 2.3$ Hz, H_g) 8.49 (d, 1H, $J = 3.8$ Hz, H_f), 8.34 (s, 1H, H_a) 7.91 (dd, 1H, $J = 4.1$ Hz, $J = 7.3$ Hz, H_e) 7.68 (m, 2H, ArH) 7.55 (dd, 4H, $J = 6.7$ Hz, $J = 8.3$ Hz, ArH) 7.43 (m, 4H, ArH) 7.14 (m, 1H, H_d) 5.45 (s, 2H, H_b) ^{31}P NMR: δ 37.4 (s). EI–MS: *m/z* 557.75 $[M]^+$.

Complex ***6***

Yellow powder. Yield 78 %. m.p.: 200–202 °C. $C_{24}H_{20}Cl_2NOPPd$: Found: C, 52.59 %; H, 3.42 %; N, 2.72 %. Calcd. C, 52.72 %; H, 3.69 %; N, 2.56 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1630(s). ^{1}H-NMR: (400 MHz, d_6-dmso) 8.72 (s, 1H, H_a) 7.98–8.08 (m, 1H, ArH) 7.75(t, 1H, $J = 1.5$ Hz, $J = 7.7$ Hz, ArH) 7.58 (m, 2H, ArH) 7.45 (td, 4H, $J = 2.9$ Hz, 4.8 Hz, ArH) 7.05 (dd, 1H, $J = 8.1$ Hz, $J = 1.8$ Hz, H_f) 7.24 (m, 5H, ArH) 6.55 (d, 1H, $J = 2.9$ Hz, H_e) 6.38 (dd, 1H, $J = 2.9$ Hz, H_d) 5.78 (t, 1H, $J = 1.5$ Hz, $J = 7.7$ Hz, ArH) 5.56 (s, 2H, H_b) ^{31}P NMR: δ 32.3(s). EI–MS: *m/z* 546.71 $[M]^+$.

Complex ***7***

Orange crystalline powder. Yield 65 %. m.p. 234–235 °C. $C_{24}H_{20}Cl_2NPPdS$: Found: C, 51.48 %; H, 3.32 %; N, 2.72 %, S, 5.86. Calcd. C, 51.22 %; H, 3.58 %; N, 2.49 %, S, 5.70 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1628(s). ^{1}H NMR: (dmso-d_6) δ_H 8.80 (s, 1H) 8.03–7.92 (m, 2H, ArH) 7.86–7.93 (m, 1H, ArH) 7.74 (m, 1H, ArH) 7.52–7.60 (m, 2H, ArH) 7.40 (td, 4H, $J = 4.9$ Hz, $J = 2.9$ Hz, ArH) 7.18 (dd, 4H, $J = 7.8$ Hz, $J = 4.9$ Hz, ArH) 6.99–7.07 (m, 2H) 6.90 (dd, 1H, $J = 2.9$ Hz, $J = 2.0$ Hz) 5.66 (s, 2H). ^{31}P NMR: δ 31.8(s). EI–MS: *m/z* 562.73 $[M]^+$.

General procedure for the preparation of palladium(II) chloromethyl complexes (**8–11**)

To the appropriate ligand (**L4–L7**) in dry CH_2Cl_2 (10 ml) was added [PdMeCl(COD)] also in dry CH_2Cl_2 (10 ml) in an equimolar amount. The reaction was allowed to stir at room temperature for ca 2 h before reducing the solvent to ca 5 ml and precipitating out the products with hexane, filtering under gravity and washing the precipitate with dry Et_2O and drying under vacuum for 4 h.

Complex ***8***

Pale orange powder. Yield 85 %. m.p.: 168–170 °C. $C_{27}H_{25}ClNPPd$: Found: C, 60.72 %; H, 4.51 %; N, 2.81 %. Calcd. C, 60.46 %; H, 4.70 %; N, 2.61 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1628(s). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H 8.81 (s, 1H, H_a) 7.91 (dd, 1H, $J = 4.3$ Hz, $J = 46.3$ Hz, ArH) 7.83 (t, $J = 7.6$ Hz, ArH) 7.69 (t, 1H, $J = 7.4$ Hz, ArH) 7.56 (m, 2H, ArH) 7.45 (dt, 4H, $J = 2.3$ Hz, 7.6 Hz, ArH) 7.29 (m, 1H, ArH) 7.18 (m, 8H, ArH) 7.09 (dd, 1H, $J = 7.7$ Hz, $J = 10.5$ Hz, ArH) 5.10 (s, 2H, H_b) 0.18 (d, 3H, $J = 1.2$ Hz, CH_3). ^{31}P NMR: δ 38.5 (s). EI–MS: *m/z* 521.75 $[M–CH_3]^+$.

Complex ***9***

Pale yellow powder. Yield 85 %. m.p.: 178–180 °C. $C_{26}H_{24}ClN_2PPd$: Found: C, 58.19 %; H, 4.12 %; N, 5.54 %. Calcd. C, 58.12 %; H, 4.50 %; N, 5.21 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1628(s). ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 8.80 (d, 1H, $J = 1.6$ Hz, H_f) 8.63 (s, 1H, H_a) 8.47 (dd, 1H, $J = 1.6$ Hz, $J = 4.8$ Hz, H_g) 7.88 (ddd, 1H, $J = 1.3$ Hz, $J = 4.1$ Hz, $J = 7.6$ Hz, ArH) 7.66 (m, 2H, ArH) 7.79 (tt, 1H, $J = 1.4$ Hz, $J = 7.6$ Hz, ArH) 7.52 (m, 2H, ArH) 7.39 (ddd, 4H, $J = 2.0$ Hz, $J = 5.1$ Hz, $J = 7.3$ Hz, ArH) 5.41 (s, 2H, H_b) 7.11 (m, 6H) 0.26 (d, 3H, $J = 3.3$ Hz, CH_3). ^{31}P NMR: δ 37.4 (s) EI–MS: *m/z* 537.13 $[M]^+$.

Complex ***10***

Yellow powder. Yield 75 %. m.p.: 195–196 °C. $C_{25}H_{23}ClNOPPd$: Found: C, 57.19 %; H, 4.12 %; N, 2.72 %. Calc. C, 57.07 %; H, 4.40 %; N, 2.66 %. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1631(s). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H 8.65 (s, 1H, H_a) 7.86 (ddd, 1H, $J = 1.2$ Hz, $J = 4.1$ Hz, $J = 7.4$ Hz, ArH) 7.77 (t, 1H, $J = 7.5$ Hz, ArH) 7.66 (t, 1H, $J = 7.5$ Hz, ArH) 7.51 (m, 6H, ArH) 7.34 (m, 4H, ArH) 7.18 (m, 1H, H_f) 6.43 (m, 1H, H_d) 5.39 (s, 2H, H_b) 0.23 (d, 3H, $J = 3.2$ Hz, CH_3). ^{31}P NMR: δ 37.6 (s). EI–MS: *m/z* 526.03 $[M]^+$.

Complex ***11***

Pale yellow powder. Yield 80 %. m.p.: 186–188 °C. $C_{25}H_{23}ClNPPdS$: Found: C, 55.19 %; H, 4.08 %; N, 2.38 %; S, 6.05. Calcd. C, 55.36 %; H, 4.27 %; N, 2.58 %; S, 5.91. IR($\upsilon_{C=N}$, imine: cm^{-1}): −1629(s). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H 8.76 (s, 1H, H_a) 7.87 (m, 1H) 7.80

(t, 1H, $J = 7.5$ Hz) 7.69 (t, 1H, $J = 7.5$ Hz, H_f) 7.54 (dd, 2H, $J = 6.5$ Hz, $J = 8.2$ Hz, ArH) 7.44 (m, 5H, ArH) 7.17 (td, 5H, $J = 6.1$ Hz, $J = 12.2$ Hz, ArH) 7.07 (d, 1H, $J = 2.4$ Hz, H_e) 6.96 (dd, 1H, $J = 3.5$ Hz, $J = 5.1$ Hz, H_d) 5.57 (s, 2H, H_b) 0.25 (d, 3H, $J = 3.3$ Hz, CH_3) ^{31}P NMR: δ 37.6 (s). EI–MS: *m/z* 531.8 $[M–CH_3]^+$.

X-ray crystal structure determination

Crystals suitable for single-crystal X-ray diffraction for complexes **2**, **7** and **8** were obtained by slow evaporation of a dmso-d_6-CH_2Cl_2 solution of the complex at room temperature. All X-ray intensity data were collected on a Nonius Kappa-CCD diffractometer with 1.5 kW graphite monochromated Mo-Kα radiation.

The structures were solved by direct methods using SHELXS-97 and refined employing full-matrix least squares with the programme SHELXL-97 refining on F^2. Packing diagrams were produced using the programme PovRay and graphic interface X-seed [18]. Crystallographic data for the structure determinations are listed in Table 1.

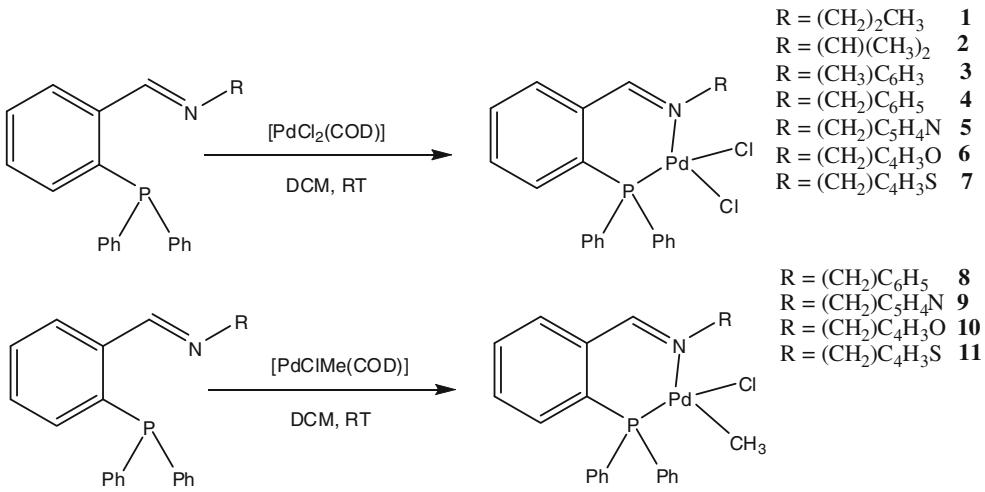
Results and discussion

Treatment of the iminophosphine ligands (**L1**–**L7**), with $[PdCl_2(COD)]$ in CH_2Cl_2 at room temperature afforded the palladium iminophosphine complexes **1**–**7**, respectively, and palladium methylchloride complexes **8**–**11** were obtained from the reaction of ligands (**L4**–**L7**) (Scheme 1).

The reaction was allowed to stir in dry CH_2Cl_2 at room temperature for 8 h. The solvent was reduced and product precipitated out with Et_2O. Further precipitation was achieved by allowing the products to crystallize slowly at −16 °C giving pale yellow/orange crystals in reasonable yields. These palladium methylchloride complexes are much more soluble than the palladium dichloride complexes.

Table 1 Crystal data and structure refinement parameters for complexes **2**, **7** and **8**

Compound	**2**	**7**	**8**
Empirical formular	$C_{24}H_{28}Cl_2NOPPdS$	$C_{24}H_{20}Cl_2NPPdS$	$C_{27}H_{25}ClNPPd$
Formular weight	586.81	562.74	536.30
T/K	173(2)	173(2)	173(2)
λ/Å	0.71073	0.71073	0.7103
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	*P1*	*P 21/n*	*P 21/n*
Crystal colour and shape	Yellow, plate	Orange, needle	Orange, needle
a	8.9935(2)	9.8892(5)	10.0147(8)
b	10.0413(2)	21.6512(12)	21.8935(18)
c	13.9439(3)	10.7050(6)	10.7478
α(deg)	91.189(10)	90	90
β(deg)	97.957(10)	94.7860(10)	94.192(2)
γ(deg)	94.869(10)	90	90
V(Å^3)	1241.93(5))	2284.1(2)	2350.2(3)
Z	2	4	4
$Density_{calc}$(mg/ml)	1.569	1.637	1.516
Absorption coefficient (mm^{-1})	1.128	1.220	0.986
F(000)	596	1128.0	1088
Crystal size (mm)	0.05 × 0.1 × 0.20	0.10 × 0.26 × 0.46	0.03 × 0.12 × 0.13
Theta range for data collection (deg)	3.0–28.7	1.9–30.7	2.1–28.3
Limiting indices	$-12 \le h \le 12$, $-13 \le k \le 13$, $-18 \le 1 \le 18$	$-14 \le h \le 14$, $-31 \le k \le 31$, $-15 \le 1 \le 15$	$-13 \le h \le 13$, $-29 \le k \le 29$, $-14 \le 1 \le 13$
Reflections collected/unique	45019/6342 [R(int) = 0.057]	50973/7032 [R(int) = 0.021]	32545/5809 [R(int) = 0.043]
Completeness of theta max. and min. transmission	28.66 (99.2 %)	30.670 (99.5 %)	28.25 (99.6 %)
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restraints/parameters	6342/0/284	7032/0/271	6590/8/270
Goodness-of-fit on F^2	1.059	1.061	1.031



Scheme 1 Synthesis of palladium dichloride complexes

The ligands show a distinctive stretching frequency, ν(C=N) at between 1,629 and 1,636 cm^{-1} which agrees with previously reported values for iminophosphine ligands [19]. Upon complexation, the peaks shift to lower frequencies than in the ligands at 1,624–1,630 cm^{-1}. This is due to increased electron density on the metal upon coordination of the imine moiety to the metal centre.

The ^{1}H NMR spectra of complexes **8–11** showed imine protons in the region δ 8.63–8.81 ppm. The observed upfield shifts of 0.21–0.28 ppm with respect to the free ligands further confirmed coordination of the imine nitrogen to the metal centre. A downfield shift of δ 0.18–0.25 ppm was also observed for the methylene signals, due to the coordination of the adjacent imine nitrogen thereby deshielding these protons. No significant chemical shifts were observed for the olefinic signals of the furyl and the thiophenyl with respect to those of the free ligands, suggesting that these groups did not participate in bonding with the metal centre. The ^{31}P NMR spectra of complexes **8–11** showed the expected downfield shift to δ 37.4–38.5 ppm with respect to the free ligands which appeared at δ −13.2 to −13.9 ppm, due to coordination of the phosphine moiety to the palladium metal centre.

Table 2 Selected bond distances and angles for the palladium complex **2**

Bond distances (Å)		Bond angles(°)	
Pd(1)-Cl(2)	2.3838(6)	Cl(2)-Pd(1)-Cl(3)	90.74(2)
Pd(1)-Cl(3)	2.2826(6)	Cl(2)-Pd(1)-P(4)	172.6(2)
Pd(1)-N(24)	2.0726(17)	Cl(2)-Pd(1)-N(24)	91.07(5)
Pd(1)-P(4)	2.2189(6)	Cl(3)-Pd(1)-P(4)	92.31(2)
P(4)-C(11)	1.811(2)	Cl(3)-Pd(1)-N(24)	177.29(5)
P(4)-C(17)	1.820(2)	P(4)-Pd(1)-N(24)	86.13(5)
N(24)-C(23)	1.268(3)		

The appearance of one signal in the ^{31}P NMR spectra also suggests that only one species had been formed.

Structural description of complexes 2, 7 and 8

The selected bond lengths and angles for complexes **2** [25], **7** and **8** [26] are summarised in Tables 2, 3 and 4. Their molecular structures are shown in Figs. 1, 2 and 3.

Table 3 Selected bond distances and angles for the palladium complex **7**

Bond distances (Å)		Bond angles(°)	
Pd(1)-Cl(2)	2.149(3)	Cl(2)-Pd(1)-Cl(3)	88.82(8)
Pd(1)-Cl(3)	2.3930(12)	Cl(2)-Pd(1)-P(4)	91.49(8)
Pd(1)-P(4)	2.1904(9)	Cl(2)-Pd(1)-N(24)	174.37(11)
Pd(1)-N(24)	2.135(3)	Cl(3)-Pd(1)-P(4)	176.40(4)
P (4)-C(5)	1.820(3)	P(4)-Pd(1)-N(24)	86.38(9)
P(4)-C(11)	1.812(3)	Pd(1)-P(4)-C(5)	111.55(11)
P(4)-C(17)	1.823(3)	Pd(1)-P(4)-C(11)	120.74(11)
N(24)-C(23)	1.276(5)	Pd(1)-P(4)-C(17)	109.32(11)

Table 4 Selected bond distances and angles for the palladium complex **8**

Bond distances (Å)		Bond angles(°)	
Pd(1)-Cl(2)	2.4035(9)	Cl(2)-Pd(1)-P(4)	178.09(8)
Pd(1)-P(4)	2.1940(7)	Cl(2)-Pd(1)-N(24)	94.38(8)
Pd(1)-N(24)	2.151(2)	Cl(2)-Pd(1)-C(3)	88.10(6)
Pd(1)-C(3)	2.1232(19)	P(4)-Pd(1)-N(24)	86.76(6)
P (4)-C(5)	1.821(3)	P(4)-Pd(1)-N(24)	86.38(9)
P(4)-C(11)	1.824(3)	Pd(1)-P(4)-C(5)	111.55(11)
N(24)-C(23)	1.280(4)	Pd(1)-P(4)-C(17)	109.32(11)
N(24)-C(25)	1.486(4)		

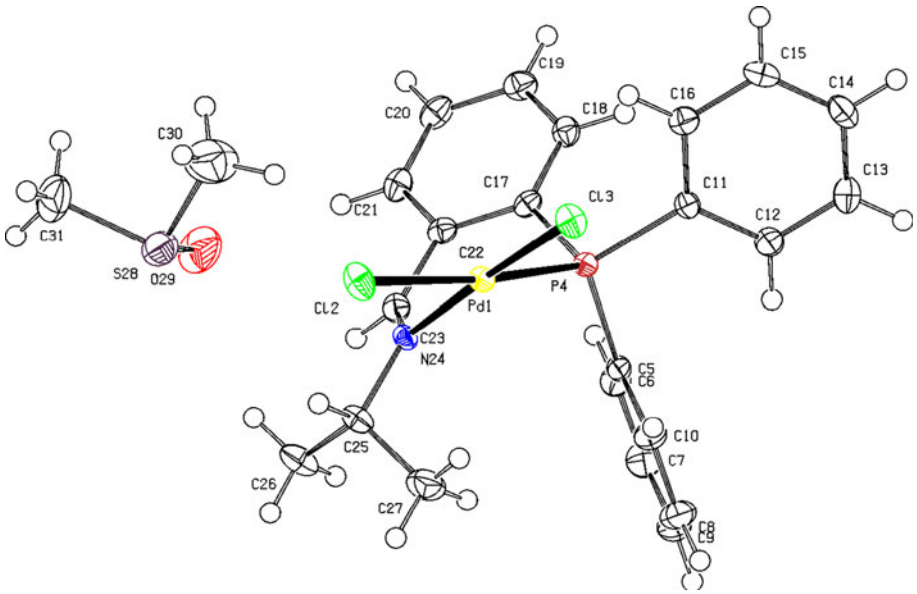


Fig. 1 Molecular structure of complex **2**. All non-hydrogen atoms were presented with ellipsoidal model with probability level 40 %. The asymmetric unit contains the organometallic compound and a DMSO solvent molecule

The coordination around the palladium is slightly distorted from the ideal square planar geometry. The main distortion is the NPdP bite angle of 86.13(5)° similar to other palladium complexes with iminophosphines [20]. The Pd–P distance (2.2189(6) Å) is within the expected range and the length of the carbon–nitrogen double bond is also within the expected range.

The molecular structure revealed a slightly distorted square planar geometry around the palladium metal centre. The ligand was shown to bind in the expected K^2–P^N fashion with a bite angle P(4)-Pd(1)-N(24) of 86.38(9)°. The angle deviated slightly from the expected 90°, presumably due to the strain imposed by the six-membered chelate ring P(4)-C(17)-C(22)-C(23)-N(24)-Pd(1). This reduction in the bite angle was compensated for by an increase in the Cl(2)-Pd(1)-P(4) angle of 91.49(8)°. This deviation of the bite angle from 90° has been observed for similar complexes with iminophosphines [20–22].

The Pd–P distances of 2.1940(7) Å are within the expected range and close to the values determined for the monohalide complex [PdMeCl(L)] (2.1925(9) Å and in the dihalide complexes of the same ligand studied by Coleman et al. [23, 24]. The Pd–N distances are similar to those found for Pd(II) complexes in the same series. The methyl group is *trans* to the nitrogen atom of the ligand. The torsion angle Pd(1)-P(4)-C(17)-C(22) = 39.9(2) Å indicates that the $=CHC_6H_4$- unit lies above the PdMeCl(P,N) plane.

Preliminary biological evaluation

The palladium complexes synthesised were evaluated for their cytotoxic activity using the MTT assay to determine

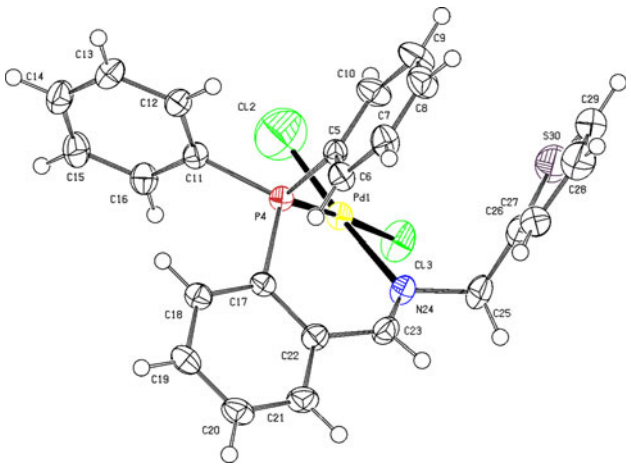


Fig. 2 Molecular structure of complex **7**. All non-hydrogen atoms were presented with ellipsoidal model with probability level 40 %

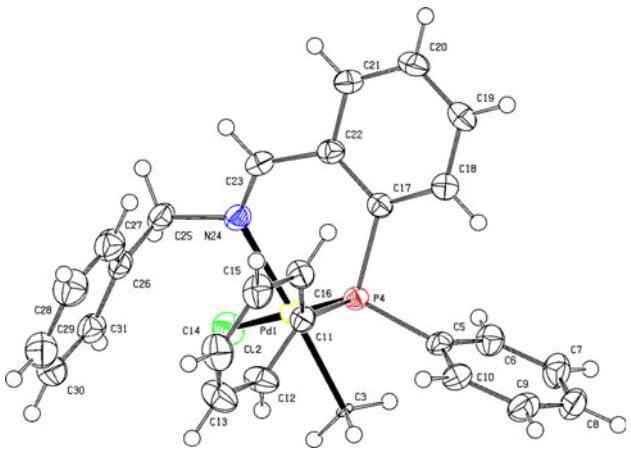


Fig. 3 Molecular structure of **8** showing the atomic numbering scheme. All non-hydrogen atoms were presented with ellipsoidal model with probability level 40 %

IC_{50} values against the oesophageal cancer cell lines WHCO1 and KYSE450 for selected complexes. Dose–response curves for each of the complexes were performed against the cell lines. Each experiment was performed in triplicate.

In vitro anticancer activity

The cytotoxicity of the palladium complexes was examined. In WHCO1 cell lines, complex **2** had the highest activity with an IC_{50} value of 19.02 μM and the least active was complex **10** with an IC_{50} value of 45.27 μM. In comparison with cisplatin which has an IC_{50} of 15–18 μM in WHCO1 cell lines, the palladium complexes described here displayed moderate activity against oesophageal cancer cell lines. In KYSE 450 cells, highest activity was observed with complex **2** with an IC_{50} of 10.03 μM and lowest activity with complex **10** with an IC_{50} of 68.54 μM as shown in Table 5.

The palladium complexes **1** and **2** were the dichlorides which were very soluble in DMSO as compared with the other dichloride complexes **3–7** which were insoluble. Complexes **8–11** were the chloromethyl derivatives and these were very soluble in DMSO. Introduction of a methyl group into the dichloride complexes increased the solubility of the complexes.

Conclusion

Palladium dichloride and methyl chloride complexes have been prepared and characterised using standard spectroscopic and analytical techniques. Single-crystal X-ray diffraction revealed that in complexes **2**, **7** and **8**, there is a slightly distorted square planar geometry around the palladium metal centre and the Pd–P distances are within the expected ranges. Three complexes displayed moderate to good cytotoxicity for the indicated cell lines. Biological activity of some of the palladium(II) complexes could not be determined due to poor solubility. Further investigations are under way to increase the solubility of the palladium complexes and to explore their anticancer activity.

Table 5 Pd(II) complexes evaluated for anticancer activity in WHCO1 and KYSE450 cell lines

Compound	IC_{50} in WHCO1 (μM)	95 % CI	IC_{50} in KYSE450 (μM)	95 % CI
1	26.59	23.79–29.76	15.29	13.81–16.93
2	19.02	15.46–23.42	10.03	8.22–12.23
8	44.14	39.24–49.65	22.38	14.34–34.95
9	39.07	35.45–43.08	59.36	52.30–67.27
10	45.27	31.59–64.88	68.54	54.65–86.03
11	28.50	18.45–44.02	10.99	8.17–14.78

All experiments were done three times and all experimental points within an experiment were done in triplicate

Supplementary materials

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 825329, 841468 and 818609 for complexes **2**, **7** and **8**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, Fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk of www: http://www.ccdc.cam.ac.uk.

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