Journal of Coordination Chemistry

ISSN: 0095-8972 (Print) 1029-0389 (Online) Journal homepage: http://www.tandfonline.com/loi/gcoo20

New chiral α-ketoimine-Pd(II) complexes and their anticancer activity

Daniela Gutiérrez, Sylvain Bernès, Guadalupe Hernández, Oscar Portillo, Gloria E. Moreno, Manju Sharma, Pankaj Sharma & René Gutiérrez

To cite this article: Daniela Gutiérrez, Sylvain Bernès, Guadalupe Hernández, Oscar Portillo, Gloria E. Moreno, Manju Sharma, Pankaj Sharma & René Gutiérrez (2015) New chiral α-ketoimine-Pd(II) complexes and their anticancer activity, Journal of Coordination Chemistry, 68:21, 3805-3813, DOI: 10.1080/00958972.2015.1084618

To link to this article: http://dx.doi.org/10.1080/00958972.2015.1084618

Accepted author version posted online: 25 Aug 2015.
Published online: 15 Sep 2015.

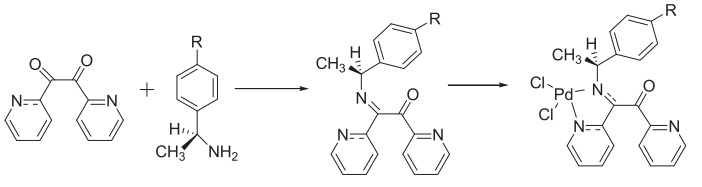
Journal of Coordination Chemistry, 2015
Vol. 68, No. 21, 3805–3813, http://dx.doi.org/10.1080/00958972.2015.1084618

New chiral α-ketoimine-Pd(II) complexes and their anticancer activity

DANIELA GUTIÉRREZ†, SYLVAIN BERNÈS‡, GUADALUPE HERNÁNDEZ†, OSCAR PORTILLO†, GLORIA E. MORENO†, MANJU SHARMA§, PANKAJ SHARMA¶ and RENÉ GUTIÉRREZ*†

†Lab. Síntesis de Complejos. Fac. Ciencias Químicas, Universidad Autónoma de Puebla, Puebla, Mexico
‡Instituto de Física Luis Rivera Terrazas, BUAP, Puebla, Mexico
§Ingeniería Bioquímica, Instituto Tecnológico Superior de Atlixco, Atlixco, Mexico
¶Instituto de Química-UNAM, Circuito exterior, Cd. Universitaria, Coyoacán, México, DF, Mexico

(*Received 28 May 2015; accepted 10 August 2015*)



Optically pure α-ketoimines were obtained under solvent-free conditions starting from 2,2′-pyridil and (*S*)-(−)-1-phenylethylamine and (*S*)-(−)-1-(4-methylphenyl)ethylamine, respectively. These new chiral ketoimines were then complexed with palladium yielding new optically pure mono-Pd complexes **3A**–**B**. The compounds have been characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopies along with MS-FAB^{+} spectrometry. The crystal and molecular structure of **3A** has been fully confirmed by single-crystal X-ray studies. *In vitro* studies of **3A**–**B** display growth inhibition against leukemia (K-562 CML), colon cancer (HCT-15), breast cancer (MCF-7), central nervous system (U-251 Glio), and prostate cancer (PC-3) cancer cell lines.

Keywords: Anticancer activity; Chiral α-ketoimines; Pd complexes

1. Introduction

Interest in palladium(II) complexes stems mainly from their structural diversity along with all-encompassing and far-reaching applications as, *inter alia*, catalysts in organic synthesis, and as antitumor drugs [1–21]. Along this latter line, since the discovery of the tumor-inhibiting of [*cis*-$PtCl_2(NH_3)_2$] (*cisplatin*) by Rosenberg *et al.* [22], the complex has been in

*Corresponding author. Email: jrgutie@correo.buap.mx

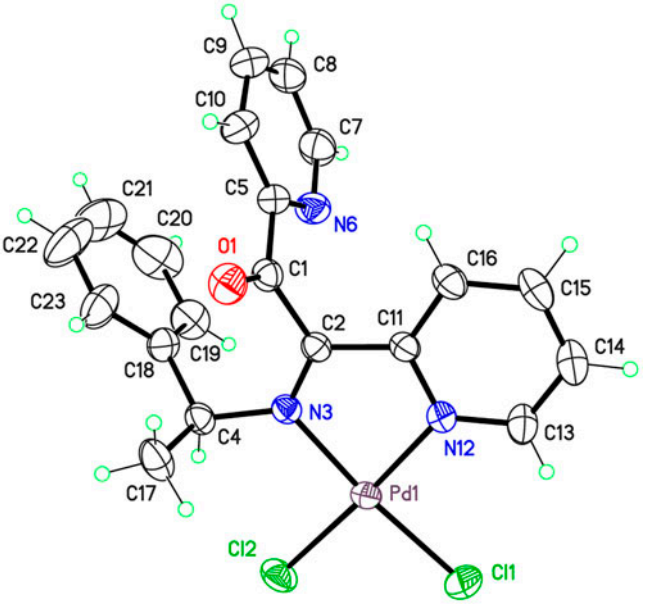
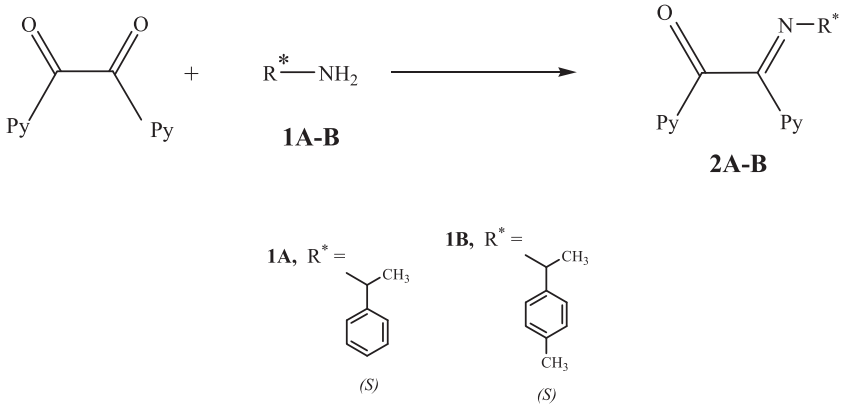


Figure 1. *ORTEP*-like view of **3a** with displacement ellipsoids at the 30% probability level.

widespread use, one of the most effective and successful drugs to treat a variety of human solid tumors. Nevertheless, cisplatin and other second-generation platinum drugs have major drawbacks such as severe tissue toxicity including nephrotoxicity, neurotoxicity, and ototoxicity, the presence of, or acquisition of, resistance to the treatment, and low water solubility, as salient limitations [1]. Therefore, the search for safer platinum complexes continues and also, in this regard, an alternative issue is using palladium on the basis of the structural and thermodynamic analogy between platinum(II) and palladium(II) complexes. It is reasonable to consider platinum as a better option than palladium due to their ligand exchange kinetics considering that the hydrolysis of leaving ligands is much faster than in corresponding platinum complexes. Nevertheless, a variety of palladium-containing compounds have been synthesized and tested for their anticancer activity [1(a) and (e), 23, 24]. Most attention has been aimed at synthesizing complexes derived from a wide-ranging assortment of functionalized ligands and, as a part of an ongoing project centered into the preparation of new chiral Pd complexes, we are currently focusing our efforts on the synthesis of such compounds derived from enantiopure α-diimines [25] and α-ketoimines owing to their attractive features as potential catalysts and bioactive compounds. In this regard, we report herein our results concerning the preparation of the mononuclear Pd(II) complexes **3A–B**, derived from the chiral α-ketoimines of 2,2′-pyridil (see scheme 1), their characterization, and anticancer activities.

2. Results and discussion

The chiral α-ketoimines **2A–B** were synthesized in almost quantitative yields under microwave irradiation in solvent-free conditions starting from (*S*)-(−)-1-phenylethylamine and



Scheme 1. Chiral α-ketoimines **2A–B** derived from 2,2′-pyridil.

(*S*)-(−)-1-(4-methylphenyl)ethylamine with 2,2′-pyridil, respectively (see scheme 1). The formation of the α-ketoimine compound was followed by TLC analysis and ^{1}H NMR spectroscopy. Compounds **2A–B** have similar ^{1}H NMR spectra in $CDCl_3$. A characteristic feature of the ^{1}H NMR spectra for **2A** and **2B** are the methyne protons which appeared as quartets centered at 4.6 and 4.4 ppm for **2A** for **2B**, respectively, with J_{HH} coupling constant of 6.9 Hz for the former and 6.6 Hz for the latter. The methyl protons of the chiral carbon are one doublet centered at 1.55 and 1.58 ppm for **2A** and **2B**, respectively, also with J_{HH} coupling constant of 6.9 Hz for the former and 6.6 Hz for the latter, and for **2B** the distinctive feature being the methyl group in the *para* position at 2.19 ppm. The IR spectrum of **2A–B** in KBr revealed the C=N stretch at 1625 and 1613 cm^{-1}, respectively. Mass spectra for **2A–B** displayed the molecular ion peaks at *m/z* 315 and 329, respectively, matching the expected molecular weights in each case.

Treatment according to the previously reported procedure [26] led to formation of the corresponding complexes, **3A–B**, and their structures were partly established by spectroscopic analysis. The complexes are apparently air stable in solid and in solution, with no evidence of decomposition even after exposure of the solutions to air for several days.

Complexes **3A–B**, isolated as clear orange solids in 78 and 69% yield, respectively, were given structure **3** based on their spectroscopic features. The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3A** shown at 8.4–6.6 ppm multiple signals (11 H) owing to the aromatic rings, and downfield at 6.4 ppm the distinctive quartet assigned to the proton belonging to the chiral center, whereas at 1.9 ppm the doublet is ascribed to the methyl group. The molecular weight of the complex was observed at *m/z* 493 by EI mode suggesting a mononuclear complex. This fact was unequivocally established by single-crystal X-ray diffraction (table 1) and the molecular structure is given in figure 1. For **3B**, almost identical spectroscopic data were obtained (see Experimental section), the only difference being the additional signal owing to the methyl group in the *para* position for the benzene ring of the ligand, and the distinctive features being the position of the signals in NMR for the proton of the chiral entity. Attempts to grow crystals of **3B** suitable for X-ray crystallography failed.

Table 1. Crystal data for **3A**.

Compound	**3A**: [$PdCl_2$(**2A**)]
Empirical formula	$C_{20}H_{17}Cl_2N_3OPd$
Formula weight	492.66
Color, habit	Orange, prism
Crystal size (mm)	0.60 × 0.50 × 0.38
Space group	$P4_1$
$a = b$ (Å)	8.7111(8)
c (Å)	27.1870(16)
Unit-cell volume (Å^3)	2063.0(4)
Z, Z'	4, 1
ρ_{calcd} (g cm^{-3})	1.586
2θ range (°)	4–60
Reflns. collected	5279
Independent reflns. (R_{int})	3192 (0.026)
Transm. factors	0.228–0.296
Final R [$I \geq 2\sigma(I)$] R_1, wR_2	0.027, 0.063
Final R (all data) R_1, wR_2	0.031, 0.065
Goodness-of-fit on F^2	1.025
Data/restraints/parameters	3192/1/246
Largest peak/hole (eÅ^{-3})	0.377/−0.423

2.1. *Solid-state structure*

The optical purity of crystallized **3A** is confirmed by the space group $P4_1$. The asymmetric unit contains one [$PdCl_2$(**2A**)] complex, in general position (figure 1), and the Pd^{II} displays the expected square-planar coordination geometry, universally observed for [$Pd^{II}Cl_2L$] compounds in which L is a bidentate ligand. The main distortion from an ideal geometry arises from the bite angle formed by the bidentate **2A**, N3–Pd1–N12 = 80.52(12)°. In spite of this distortion, the metal should present hybridization very close to dsp^2, since the coordination geometry is perfectly planar: the sum of *cis* angles around Pd1 is 360°.

The key feature for **2A** is its conformation, which should fit the square-planar coordination of the metal and the steric requirements for the three aromatic rings. The α-ketoimine core is bent, with a torsion angle O1=C1–C2=N3 of 72.1(5)°. Such a *gauche* conformation is by far the less common for X-ray-characterized α-ketoimines. A scan of the CSD (v 5.36, with all updates) [27] shows that for more than 3000 retrieved organic molecules including that fragment, *cis* ($\tau = 0$) and *trans* ($\tau = 180°$) conformers are clearly preferred, compared to any other conformation. In the case of **2A**, the observed *gauche* conformer is an obvious consequence of the substitution of vicinal C1 and C2 by pyridil rings and the conjugation of imine and carbonyl double bonds with these aromatic systems. The same conformation was described for free 2,2′-pyridil, with $\tau = 78.6°$ [28], and other non-planar conformations have been observed in related small molecules, for instance in benzil, which crystallizes as an *anti*clinal conformer ($\tau = 107.3°$) [29]. The conformation of **2A** in the Pd^{II} complex allows the conjugation of the imine bond C2=N3 with the pyridil ring containing N12, and therefore the formation of the planar palladacycle Pd1–N3–C2–C11–N12 required by the $PdCl_2$ fragment. Once N3 and N12 are coordinated to the metal, other potential donors in the ligand, O1 and N6, are no longer available for coordination. Finally, the chiral moiety centered on C4 adopts a position avoiding steric hindrance between the methyl group and the α-ketoimine system, and favors significant $\pi\cdots\pi$ interaction between the phenyl ring C18–C23 and the non-coordinating pyridil ring C5–C10: these rings are arranged almost parallel [dihedral angle between mean planes: 24.8(3)°] and the centroid-to-centroid

Table 2. IC_{50} ($\mu molL^{-1}$) values of **3A–B** and cisplatin against U251 (CNS), PC-3 (prostate), K562 (leukemia), HCT-15 (colon), and MCF-7 (breast) human cancer cells.

Complex	U251 (CNS)	PC-3 (Prostate)	K562 (Leukemia)	HCT-15 (Colon)	MCF-7 (Breast)
3A	37 ± 1	29 ± 1	>100	31 ± 1	22 ± 1
3B	48 ± 1	45 ± 1	>100	36 ± 1	30 ± 1
Cisplatin	N. D.	10.5 ± 0.05	3 ± 1	5 ± 1	2.5 ± 0.6

N. D.: Not determined.

separation is rather short, 3.76 Å. Surprisingly, **3A** seems to be the first X-ray-characterized transition metal complex bearing a pyridil-substituted α-ketoimine ligand.

In the crystal, molecules interact through weak hydrogen bonds involving the carbonyl group C1=O1 as acceptor, to form chains in the [0 0 1] direction, along the 4_1 screw axis.

2.2. *Anticancer results*

IC_{50} values (μM) of **3A–B** and cisplatin against U251 (CNS), PC-3 (prostate), K562 (leukemia), HCT-15 (colon), and MCF-7 (breast) human cancer cells are displayed in table 2. The data show that both **3A–B** do not show cytotoxicity toward K562 (leukemia) cell lines. Complexes **3A** and **3B** have a IC_{50} value lower than 100 $\mu molL^{-1}$ against U251 (CNS), PC-3 (prostate), HCT-15 (colon), and MCF-7 (breast) cancer cells as salient features, with **3A** performing slightly better for all cell lines, i.e. complex **3A** shows moderate activity against U251 (CNS), and PC-3 cell lines ($IC_{50} = 37 \pm 1$ and 29 ± 1 $\mu molL^{-1}$, respectively), while **3B** displays an $IC_{50} = 48 \pm 1$ and 45 ± 1 $\mu molL^{-1}$, respectively. Both complexes show better activity toward HCT15 (colon) and MCF-7 (breast) cell lines: **3A** shows values of = 3 ± 1 and 22 ± 1, respectively, while **3B** exhibits $IC_{50} = 36 \pm 1$ and 30 ± 1, respectively. These complexes display, in general, similar cytotoxicity as shown by chiral benzyl α-ketoimine Pd(II) complexes, reported earlier by our group [26]. These complexes show much better cytotoxicity than related chiral dimine palladium complexes [25]. These studies indicate that the nature of the aromatic rings have an effect in the coordination mode of the metal and consequently in their cytotoxicity, but the IC_{50} values do not show a definite correlation and as these studies are based on a limited series of complexes, a point of convergence cannot be established yet.

3. Summary

The synthesis and characterization of two chiral ketoimines and their Pd(II) complexes are reported. The crystal and molecular structure for **3A** has been determined by single-crystal X-ray studies. Molecular structure shows that asymmetric unit contains one [$PdCl_2$(**2A**)] complex, and the Pd^{II} metal presents a square-planar coordination geometry, where ligand **2A** acts as a bidentate ligand. Anticancer activity of both the complexes has also been determined. The data show that both **3A–B** do not show cytotoxicity toward K562 (leukemia) cell lines, with **3A** performing slightly better for all cell lines. These complexes show a similar cytotoxicity as shown by benzyl α-ketoimine Pd(II) complexes and better cytotoxicity than related chiral dimine palladium complexes reported earlier by us. Work is in

progress with other optically pure α-ketoimines to increase the scope and fine-tuning the cytotoxic activity by varying the functional groups.

4. Experimental

4.1. *General methods*

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400S spectrometer using $CDCl_3$ as solvent and TMS as internal reference. IR spectra were performed on a Perkin-Elmer 283 B or 1420 spectrometer. The FAB spectra were obtained on a JEOL JMS-SX 102A mass spectrometer operated at an accelerating voltage of 10 kV. Samples were desorbed from a nitrobenzyl alcohol matrix using 6 keV xenon atoms. The electronic impact (EI) ionization mass spectra were acquired on a JEOL JMS-AX505 HA mass spectrometer operated in the positive ion mode. The acquisition conditions were ion source temperature 230°C, ionization energy 70 eV, emission current 0.14 μA, and ionization current 100 μA. Mass measurements in FAB are performed at 10,000 resolution using electrical field scans and the polyethylene glycol ions as reference material. Melting points were measured using a Mel-Temp II apparatus and are uncorrected. Elemental analyses were recorded from a Euro EA elemental analyzer. Reagents were obtained from commercial suppliers and used as received.

4.2. *Synthesis of chiral α-ketoimines 2A–B*

2,2′-Pyridil (1 g, 4.7 mmol) was allowed to react with the chiral amine in equimolar amounts, *i.e.* with (*S*)-(−)-1-phenylethylamine (0.56 g, 4.7 mmol) and (*S*)-(−)-1-(4-methylphenyl)ethylamine (0.64 g, 4.7 mmol), respectively, under focused microwave irradiation at 400 W during 15 min in solvent-free conditions. The products obtained were characterized by spectroscopic techniques and were used without purification.

***N-(S)*-(−)-(phenylethyl)pyridil-pyridilidenamine (2A).** Yield (97%), orange powder, mp = 158 °C. FT-IR (KBr): 1692.7 (C=O), 1625.5 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.182 (m, 13 H, Ar), 4.64 (q, 1H, *H*–C*), *J* = 6.9 Hz., 1.55 (d, 3H, H_3C–C*), *J* = 6.9 Hz. ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.5 (*C*=O), 164.8 (*C*=N), 149.2, 148.2, 142.9, 137.1, 136.9, 136,3, 128.4, 127.4, 126.6, 124.3, 121.6, 120.7, 61.9 (H*C**), 22.1 (CH_3–C*). MS-EI *m/z* = 315 (M^+). $[\alpha]^{25}_D = -14.2$ (*c* = 0.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.13; H, 5.33; N, 12.92.

***N-(S)*-(−)-(4-methyl-1-phenylethyl)pyridyl-pyridilidenamine (2B).** Yield (93%), yellow oil. FT-IR (KBr): 1685.5 (C=O), 1613.8 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62–7.12 (m, 12 H, Ar), 4.40 (q, 1H, *H*–C*), *J* = 6.6 Hz., 2.19 (s, 3H, H_3C–Ph), 1.58 (d, 3H, H_3C–C*), *J* = 6.6 Hz. ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9 (*C*=O), 165.0 (*C*=N), 153.7, 151.6, 149.4, 148.3, 139.9, 137.2, 136.5, 129.6, 128.5, 128.2, 126.5, 124.4, 122.2, 61.9 (H*C**), 50.9 (CH_3), 21.3 (CH_3–C*). MS-EI *m/z* = 329 (M^+). $[\alpha]^{25}_D = -35.6$ (*c* = 0.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.44; H, 5.75; N, 12.62.

4.3. *Synthesis of 3A–B*

A solution of benzene (30 mL) containing the ligand (1 mmol), i.e. **2A** (315 mg, 1 mmol) and **2B** (329 mg, 1 mmol) along with $Pd(COD)Cl_2$ (285 mg, 1 mmol) was stirred for 2 h and a precipitate was formed almost instantaneously. The solid was filtered and washed with $AcOEt/CH_2Cl_2$ (1:1). Crystals were formed after 1–2 days.

Complex 3A. Yield (78%), orange crystals, mp = 208°C. FT-IR(KBr): 1701 (C=O), 1589 (C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.48–6.69 (m, 13H, Ar), 6.40 (q, 1H, *H*–C*), 1.95 (d, 3H, H_3C–C*). ^{13}C NMR ($CDCl_3$/TMS): δ 150.8, 148.5, 139.1, 136.5, 131.0, 128.5, 128.2, 127.4, 127.1, 126.2, 122.6, 64.0 (H*C*), 18.7 (*C*H_3–C*). MS-EI *m/z* = 493 M^+. $[\alpha]^{25}_D$ = +20.6 (*c* = 0.1, CH_3Cl_3). Anal. Calcd for $C_{20}H_{17}Cl_2N_3OPd$: C, 48.76; H, 3.48; N, 8.53. Found: C, 48.69; H, 3.45; N, 8.50.

Complex 3B. Yield (69%), light orange powder, mp = 243 °C. FT-IR(KBr): 1715 (C=O), 1611(C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.86–6.24 (m, 12H), 6.46 (q, 1H, *H*–C*), 2.24 (s, 3H, H_3C–Ph), 1.95 (d, 3H, H_3C–C*). ^{13}C NMR ($CDCl_3$/TMS): δ 148.6, 145.1, 139.7, 135.1, 132.3, 129.7, 128.2, 127.7, 127.3, 126.5, 121.5, 61.8 (H*C*), 52.4 (*C*H_3), 20.3 (*C*H_3–C*). MS-EI *m/z* = 508 M^+. $[\alpha]^{25}_D$ = +67.8 (*c* = 0.1, CH_3Cl_3). Anal. Calcd for $C_{21}H_{19}Cl_2N_3OPd$: C, 49.78; H, 3.78; N, 8.29. Found: C, 49.21; H, 3.65; N, 8.19.

4.4. *Crystallographic study*

Diffraction data for **3A** (table 1) were collected at room temperature with a Siemens P4 diffractometer (Mo *Kα* radiation) using standard procedures [30], and the structure was solved and refined using *SHELX* programs [31]. A small coverage of Friedel pairs afforded a refined Flack parameter consistent with the expected enantiomer *S*–C4 for **2A**. In the final cycles, all hydrogens were refined as riding to their carrier carbons, with bond lengths fixed to 0.93 (aromatic CH), 0.96 (methyl CH_3), or 0.98 Å (methine CH), and calculated isotropic displacement parameters. A cif file including intensity data has been deposited with reference CCDC 1401876.

4.5. *Assay for anticancer activity*

Colon cancer (HCT-15), cancer breast (MCF-7), leukemia (K-562 CML), central nervous system (U-251 Glio), and prostate cancer (PC-3) cell lines were supplied by the National Cancer Institute (USA). Cytotoxicities of the tumors cells with the test compounds were determined using the protein-binding dye sulforhodamine B (SRB) in microculture assay to measure cell viability and cell growth, as described in the literature [32]. The cell lines were cultured in RPMI-1640 supplemented with 10% fetal bovine serum, 2 mM L glutamine, 100 IU mL^{-1} penicillin G, 100 μg mL^{-1} streptomycin sulfate, and 0.25 μg mL^{-1} amphotericin B (Gibco). They were maintained at 37 °C in a 5% CO_2 atmosphere with 95% humidity. For the assay, cells were detached with 0.1% trypsin-EDTA to make single-cell suspension, and viable cells were counted using a haemocytometer and diluted with medium to give 5×10^4 cell/mL (K562, MCF-7), 7.5×10^4 cell/well (U251, PC-3) and 10×10^4 cell/well (HCT-15). About 100 μL/well of these cells suspension were seeded in

96-well microtiter plates and incubated to allow for cell attachment. After 24 h, the cells were treated with logarithmic concentrations of the test products and the positive control, doxorubicin. They were initially dissolved in DMSO (40 mM) and further diluted in medium to produce five concentration test solutions (100, 31, 10, 3.1, and 1 μM). About 100 μL of each test solution with the compound to evaluate were added to each well. After 48 h, adherent cell cultures were fixed *in situ* by adding 50 μL of cold 50% (wt/vol) trichloroacetic acid (TCA) and incubated for 60 min at 4 °C. The supernatant was discarded and the plates were washed three times with water and air dried. Cultures fixed with TCA were stained for 30 min with 100 μL of SRB solution (0.4% wt/vol in 1% acetic acid). Unbound SRB was removed by four washes with 1% acetic acid and protein-bound dye was extracted with 10-mM unbuffered tris base (tris[hydroxymethyl]aminomethane), and the optical densities were read on an automated spectrophotometric plate reader at a single wavelength of 515 nm. The IC_{50} (concentrations required to inhibit cell growth by 50%) were calculated according to the protocol previously established. Mean and standard error (SE) of the three independent experiments for each selected concentration of the studied compound were determined.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] See e.g. (a) A.R. Kapdi, I.J.S. Fairlamb. Chem. Soc. Rev., **43**, 4751 (2014); (b) A.D. Ryabov. In *Palladacycles: Synthesis, Characterization and Applications: Cyclopalladated Compounds as Enzyme Prototypes and Anticancer Drugs*, J. Dupont, M. Pfeffer (Eds.), pp. 307–340, Wiley-VCH, Weinheim (2008); (c) N. Cutillas, G.S. Yellol, C. de Haro, C. Vicente, V. Rodriguez, J. Ruiz. Coord. Chem. Rev., **257**, 2784 (2013); (d) E. Gao, C.Liu, M. Zhu, H. Lin, Q.Wu, L. Liu. Anticancer Agents Med. Chem., **9**, 356 (2009); (e) A.C.F. Caires. Anticancer Agents Med. Chem., **7**, 484 (2007); (f) A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis. *Coord. Chem. Rev.*, **253**, 1384 (2009); (g) A.S. Abu-Surrah, M. Kettunen. Curr. Med. Chem., **13**, 1337 (2006); (h) G. Zhao, H. Lin. *Curr. Med. Chem.*, **5**, 137 (2005).
[2] R.A. de Souza, A. Stevanato, O. Treu-Filho, A.V.G. Netto, A.E. Mauro, E.E. Castellano, I.Z. Carlos, F.R. Pavan, C.Q.F. Leite. *Eur. J. Med. Chem.*, **45**, 4863 (2010).
[3] F. Ari, N. Aztopal, C. Icsel, V.T. Yilmaz, E. Guney, O. Buyukgungor, E. Ulukaya. *Bioorg. Med. Chem.*, **21**, 6427 (2013).
[4] E. Budzisz, M. Miernicka, I.-P. Lorenz, P. Mayer, E. Balcerczak, U. Krajewska, M. Rozalski. *Eur. J. Med. Chem.*, **45**, 2613 (2010).
[5] R.A. Haque, A.W. Salman, S. Budagumpi, A.A. Abdullah, A.M.S.A. Majid. *Metallomics*, **5**, 760 (2013).
[6] A.M. Krause-Heuer, P. Leverett, A. Bolhuis, J.R. Aldrich-Wright. *Aust. J. Chem.*, **65**, 860 (2012).
[7] H. Varbanov, A. Bakalova, R. Buyukliev, G. Momekov, R. Baykushev. *Transition Met. Chem.*, **35**, 457 (2010).
[8] B.B. Zmejkovski, G.N. Kaluđerović, S. Gómez-Ruiz, Ž. Žižak, D. Steinborn, H. Schmidt, R. Paschke, Z.D. Juranić, T.J. Sabo. *Eur. Med. Chem.*, **44**, 3452 (2009).
[9] E. Ulukaya, F. Ari, K. Dimas, E.I. Ikitimur, E. Guney, V.T. Yilmaz. *Eur. J. Med. Chem.*, **46**, 4957 (2011).
[10] M.D. Coskun, F. Ari, A.Y. Oral, M. Sarimahmut, H.M. Kutlu, V.T. Yilmaz, E. Ulukaya. *Bioorg. Med. Chem.*, **21**, 4698 (2013).
[11] M. Tanaka, H. Kataoka, M. Mabuchi, S. Sakuma, S. Takahashi, R. Tujii, H. Akashi, H. Ohi, S. Yano, A. Morita, T. Joh. *Anticancer Res.*, **31**, 763 (2011).
[12] H. Khan, A. Badshah, M. Said, G. Murtaza, J. Ahmad, B.J. Jean-Claude, M. Todorova, I.S. Butler. *Appl. Organomet. Chem.*, **27**, 387 (2013).
[13] P. Kalaivani, R. Prabhakaran, E. Ramachandran, F. Dallemer, G. Paramaguru, R. Renganathan, P. Poornima, V.V. Padma, K. Natarajan. *Dalton Trans.*, **41**, 2486 (2012).

[14] E.G. Rodrigues, L.S. Silva, D.M. Fausto, M.S. Hayashi, S. Dreher, E.L. Santos, J.B. Pesquero, L.R. Travassos, A.C.F. Caires. *Int. J. Cancer*, **107**, 498 (2003).
[15] F.K. Keter, S.O. Ojwach, O.A. Oyetunji, I.A. Guzei, J. Darkwa. *Inorg. Chim. Acta*, **362**, 2595 (2009).
[16] V.W.R. Moraes, A.C.F. Caires, E.J. Paredes-Gamero, T. Rodrigues. *Cell Death Dis.*, **4**, e658 (2013).
[17] L. Giovagnini, L. Ronconi, D. Aldinucci, D. Lorenzon, S. Sitran, D. Fregona. *J. Med. Chem.*, **48**, 1588 (2005).
[18] D. Kovala-Demertzi, A. Alexandratos, A. Papageorgiou, P.N. Yadav, P. Dalezis, M.A. Demertzis. *Polyhedron*, **27**, 2731 (2008).
[19] T.V. Segapelo, S. Lillywhite, E. Nordlander, M. Haukka, J. Darkwa. *Polyhedron*, **36**, 97 (2012).
[20] D. Plażuk, A. Wieczorek, A. Błauż, B. Rychlik. *MedChemComm*, **3**, 498 (2012).
[21] F. Shaheen, A. Badshah, M. Gielen, C. Gieck, D. de Vos. *Appl. Organomet. Chem.*, **21**, 633 (2007).
[22] B. Rosenberg, L. Van Camp, T. Krigas. *Nature*, **205**, 698 (1965).
[23] S. Cruz, S. Bernès, P. Sharma, R. Vazquez, G. Hernández, R. Portillo, R. Gutiérrez. *Appl. Organomet. Chem.*, **24**, 8 (2010).
[24] L. Li, J. Zhang, L. Ma, Z. Zhang, S. Wang, S. Li, G. Zhou. *J. Coord. Chem.*, **66**, 638 (2013)
[25] J. Vázquez, S. Bernès, P. Sharma, J. Pérez, G. Hernández, A. Tovar, U. Peña, R. Gutiérrez. *Polyhedron*, **30**, 2514 (2011).
[26] M.A. Peláez, T. Ramírez, M. Martínez, P. Sharma, C. Álvarez, R. Gutiérrez. *Z. Anorg. Allg. Chem.*, **630**, 1489 (2004).
[27] C.R. Groom, F.H. Allen. *Angew. Chem. Int. Ed.*, **53**, 662 (2014).
[28] T. Ashida, S. Hirokawa. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, **B26**, 454 (1970).
[29] M. More, G. Odou, J. Lefebvre. *Acta Crystallogr., Sect. B: Struct. Sci* , **B43**, 398 (1987).
[30] *XSCANS (Version 2.31)*, Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA (1996).
[31] G.M. Sheldrick. *Acta Cryst.*, **C71**, 3 (2015).
[32] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd. *J. Nat. Cancer Inst.*, **83**, 757 (1991).