Synthesis, Structural Characterization and Biological Screening of Heteroleptic Palladium(II) Complexes

Hizbullah Khan, Amin Badshah, Muhammad Said, Ghulam Murtaza, Muhammad Sirajuddin, Jamil Ahmad, Ian S. Butler

PII: S0020-1693(16)30106-2
DOI: http://dx.doi.org/10.1016/j.ica.2016.03.014
Reference: ICA 16949

To appear in: *Inorganica Chimica Acta*

Received Date: 13 October 2015
Revised Date: 9 March 2016
Accepted Date: 10 March 2016

Please cite this article as: H. Khan, A. Badshah, M. Said, G. Murtaza, M. Sirajuddin, J. Ahmad, I.S. Butler, Synthesis, Structural Characterization and Biological Screening of Heteroleptic Palladium(II) Complexes, *Inorganica Chimica Acta* (2016), doi: http://dx.doi.org/10.1016/j.ica.2016.03.014

Synthesis, Structural Characterization and Biological Screening of Heteroleptic Palladium(II) Complexes

Hizbullah Khan[1,2*], Amin Badshah[2*], Muhammad Said[3], Ghulam Murtaza[2], Muhammad Sirajuddin[1], Jamil Ahmad[4], Ian S. Butler[5]

[1]Department of Chemistry, University of Science and Technology, Bannu 28100, Khyber Pakhtunkhwa, Pakistan

[2]Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

[3]Department of Chemistry, Abdul Wali Khan University, Mardan 23200, Pakistan

[4]Department of Chemistry, Hazara University, Mansehra 21120, Pakistan

[5]Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

Email: hizbmarwat@yahoo.com; aminbadshah@yahoo.com

Abstract

Heteroleptic palladium(II) complexes of the type formula [(DTC)(Pd)(PR_3)Cl], where DTC = bis(2-ethylhexyl)dithiocarbamate (**1,8,9,10**), bis(2-methoxyethyl)dithiocarbamate (**2**), di-*n*-decyldithiocarbamate (**3,6**), di-*n*-hexyldithiocarbamate (**4,7**), bis(2-methylbutyl)dithiocarbamte (**5**); PR_3 = diphenyl-*t*-butylphosphine (**1**), diphenyl-*n*-propylphosphine (**2**), triphenylphosphine (**3,4,5,10**), diphenyl-*p*-tolylphosphine (**6,7,8**), diphenylbenzylphosphine (**9**); have been synthesized and characterized by FTIR, Raman, multinuclear and multinuclear NMR (^{1}H, ^{13}C, ^{31}P) spectroscopy and elemental analyses. The structures of complexes (**1** and **2**) were determined by single-crystal X-ray diffraction. The geometries around the metal centres are pseudo square-planar. The new complexes exhibit moderate anticancer and antibacterial activity.

Key words: Heteroleptic palladium(II) complexes; single crystal; XRD analysis; anticancer activity; antibacterial activity; Spectroscopy

1.1 Introduction

Since the discovery of the antitumor activity of *cisplatin* in 1969, extensive research has been performed on the antitumor potential of platinum(II) and palladium(II) complexes [1]. There has been particular interest in the study of palladium (II) complexes because they behave similarly to platinum(II) complexes but with faster kinetics[2]. Hydrolysis of palladium(II) complexes is very rapid leading to reactive species that are unable to reach their pharmacological targets. Moreover, some *cis*-palladium(II) complexes transform into the in active *trans*derivatives. The stabilization of Pd(II) complexes by strongly coordinating ligands and an appropriate leaving group has been explored as a synthetic technique for the synthesis of antitumor palladium(II) complexes[3],[4],[5]. Thus various compounds containing bidentate ligands (N-N, P-P, or mixed N-O, N-S)[6], [7], monodentate bulky ligands[8], and organometallic derivatives have been synthesized. Some new 9-aminoacridine palladium(II) complexes exhibit about 30-fold more antitumor activity against the HL-60 human tumor cell line than does *cisplatin* [9].

Because palladium(II) chemistry is similar to that of platinum(II), it was speculated that palladium(II) complexes may exhibit antitumor activity with fewer side effects [10]. Palladium(II) complexes are expected to have less kidney toxicity than does *cisplatin*, which results from binding of the sulfhydryl group of kidney tubule protein [11]. Genova et al. have reported that Pd(II) complexes demonstrated significant activity against acyclovir-resistant viruses R-100 (HSV 1) and PU (HS V 2) and negatively influence the expression of key structural HSV-1 proteins (VP 23, gH, and gG/gD) hereby simultaneously suppressing virus entry, trans activation of the virus genome, capsid assembly, and cell-to-cell spread of infectious HSV progeny [12].

Dithiocarbamates have received considerable attention recently owing to their ability to act as bidentate ligands. Metal dithiocarbamates are currently used as lubricants, antioxidants, accelerators for rubber vulcanization[13], and in biological applications[14]. Dithiocarbamates derived from secondary amines have also been extensively studied because of their interesting electrochemical and optical properties[15]

The synthesis of other metal-containing drugs, such as organometallic complexes[16] of iron[17], iridium[18], copper[19], rhodium[20], ruthenium[21], gold[22] and titanium[23] has also

attracted much interest. More recently, heterometallic[24] complexes have been synthesized which demonstrate the synergic effect of two different metals with known antitumor activity. A series of Pd(II) complexes with a benzene alkyl dicarboxylate chain has been prepared in an attempt to determine the effect of carbon chain length. The four complexes prepared exhibited cytotoxic specificity and significant cancer cell inhibitory rates. Studies of the complexes have shown that there is a substantial correlation between the carbon chain length and the DNA binding properties and cytotoxicity- the longer the carbon chain length, the higher the efficiency of DNA-binding and the greater the cytotoxicity[25].

In this article, we report the syntheses, characterization and biological activities of ten mixed ligand dithiocarbamate and organophosphine palladium(II) complexes.

1.2 Experimental section

All the experiments were carried out at reflux temperature and normal pressure. The chemicals, palladium chloride (Sigma-Aldrich), 2-ethylhexylamine (Sigma-Aldrich), diphenyl-*t*-butylphosphine (Alfa Aesar), 2-methoxyethylamine (Alfa Aesar), diphenyl-*n*-propylphosphine (Alfa Aesar), di-*n*-decylamine (Sigma-Aldrich), triphenylphosphine (Alfa Aesar), di-*n*-hexylamine (Alfa Aesar), bis(2-methylbutyl)amine (Alfa Aesar), diphenyl-*p*-tolylphosphine (Alfa Aesar), bis(2-ethylhexyl)amine (Alfa Aesar), diphenylbenzylphosphine (Alfa Aesar), and hydrochloric acid (Sigma-Aldrich) were purchased from Sigma-Aldrich and Alfa Aesar and ere used without further purification. The solvents used were dried and purified by standard methods. All the dithiocarbamates used and their salts have been reported previously in the literature and were prepared by the methods indicated[26].

NMR spectra were recorded on Mercury 200 MHz and Bruker 300 MHz spectrometers. ^{1}H NMR (300.13 MHz): $CDCl_3$ (7.26 from $SiMe_4$). ^{13}C NMR (75.47 MHz), internal standard TMS; ^{31}P NMR (121.49 MHz): $CDCl_3$. The splitting of proton resonances are shown as, s = singlet, d = doublet, t = triplet and m = multiplet (showing a complex pattern). IR spectra were recorded on a Nicolet 6700 FT-IR instrument in the range of 4000-400 cm^{-1} and Raman spectra (± 1 cm^{-1}) were measured with an InVia Renishaw spectrometer, using argon ion (514.5 nm) and near infrared

diode (785 nm) lasers. Wire 2.0 software was used for the Raman data acquisition and spectra manipulations. The elemental analyses were conducted on a LECO-183 CHNS analyzer. Melting points were measured on Stuart SMP10 apparatus and are uncorrected.

1.2.1 General synthesis of mixed ligand dithiocarbamate-organophosphine palladium(II) complexes 1-10

The heteroleptic Pd(II) complexes were prepared in two steps. In the first step, the Pd(II)-organophosphine complex was prepared by dissolving $PdCl_2$ in methanol, along with 3-4 drops of concentrated hydrochloric acid. The desired organophosphine was dissolved in dry acetone and reacted with $PdCl_2$ solution in 2:1 molar ratio. The reaction mixture was refluxed for 1 h and the solid product was filtered off. In the second step, the dichloromethane solution of Pd-organophosphine was reacted with dithiocarbamic acid or the potassium salt of the dithiocarbamate ligand in 1:1 molar ration under reflux conditions, for 6 h. The resulting golden yellow solid product was obtained by rotary evaporation. The solid product was recrystallized in conical flask in 20 mL dichloromethane and *n*-hexane in a 4:1 by volume ratio. Golden yellow crystals of complexes **1** and **2** were obtained by slow evaporation at room temperature and pressure, while the other complexes did not crystallize.

1.2.2 [Pd(bis(2-ethylhexyl)dithiocarbamate)($PPh_2C(CH_3)_3$)Cl] (1)

Quantities used were: 0.21g (0.59 mmol) bis(2-ehtylhexyl)dithiocarbamic acid, 0.39g (0.59 mmol) Pd-phosphine complex. Yield: 0.28 g (69%). M. p.:147-148 °C. MW = 700.76. FT-IR (powder, cm^{-1}): 3043 υ(C-H, aromatic), 2981, 2922 υ(C-H, aliphatic), 1514 υ(C=N), 1096 υ(SCS). Raman (powder, cm^{-1}): 260 υ(Pd-P), 296 υ(Pd-Cl), 416 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.78,(t, 3H, $CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-,$^3J_{H-H}$= 7.2 Hz)0.86 (t, 3H,$CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-,$^3J_{H-H}$= 7.2 Hz), 1.12-1.23 (m, 12H,$CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-),1.69-1.75 (m, 4H, $CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 1.82-1.89 (m, 2H, $CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-) 3.55, 3.50 (d,4H, $CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 1.45 (s, 9H, $C(CH_3)_3$), 7.41-7.91 (m, 10H, Ar-***H***).^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm:135.5, 134.9, 130.3, 127.7 (Ar***C***), 53.1, 52.7 ($CH_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 37.4, 37.3

($CH_3(CH_2)_3$***C***$H(CH_2CH_3)CH_2$-), 35.5, 35.3 ($CH_3CH_2CH_2$***C***$H_2CH(CH_2CH_3)CH_2$-), 30.3, 30.4 (CH_3CH_2***C***$H_2CH_2CH(CH_2CH_3)CH_2$-), 30.1, 30.0 ($CH_3(CH_2)_3CH($***C***$H_2CH_3)CH_2$-), 29.5 (***C***$(CH_3)_3$), 28.5 (C(***C***$H_3)_3$), 23.8, 23.7 (CH_3***C***$H_2CH_2CH_2CH(CH_2CH_3)CH_2$-), 14.1, 14.0 (***C***$H_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 10.6, 10.5 ($CH_3(CH_2)_3CH(CH_2$***C***$H_3)CH_2$-), 208.6 (S***C***S),. ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 45.1. Elemental analysis, % Calculated (Found) for$C_{33}H_{53}ClNPPdS_2$: C, 56.56 (56.60); H, 7.62 (7.65); N, 2.00 (1.99); S, 9.15 (9.16).

1.2.3 [Pd(bis(2-methoxyethyl)dithiocarbamate)(PPh_2-*n*-propyl)Cl] (2)

Quantities used were: 0.03 g (0.12 mmol) potassium salt of bis-2-methoxyethyldithiocarbamate, 0.08g (0.12 mmol) Pd-phosphine complex. Yield: 0.05 g (63 %). M. p.: 177-178 °C. MW = 578.46. FT-IR (powder, cm^{-1}): 3050 υ(C-H, aromatic), 2935, 2886 υ(C-H, aliphatic), 1517υ(C⎓N), 1089 υ(SCS). Raman (powder, cm^{-1}): 200 υ(Pd-P), 299 υ(Pd-Cl), 413 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 3.29, (s, 3H, C***H***$_3OCH_2CH_2$-), 3.30 (s, 3H, C***H***$_3OCH_2CH_2$-), 3.86 (t, 2H, CH_3OC***H***$_2CH_2$-, $^3J_{H\text{-}H}$= 5.1 Hz), 3.98 (t, 2H, CH_3OC***H***$_2CH_2$-, $^3J_{H\text{-}H}$= 5.1 Hz), 3.51 (t, 2H, CH_3OCH_2C***H***$_2$-,$^3J_{H\text{-}H}$= 5.1 Hz), 3.61 (t, 2H, CH_3OCH_2C***H***$_2$-,$^3J_{H\text{-}H}$= 5.1 Hz), 1.03 (t, 2H, C***H***$_3CH_2CH_2$-, $^3J_{H\text{-}H}$= 7.2 Hz), 1.58-1.78 (m, CH_3C***H***$_2CH_2$-), 2.47 (t, 2H, CH_3CH_2C***H***$_2$-, $^3J_{H\text{-}H}$= 7.2 Hz), 7.26-7.69 (m, 10H, Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 59.0, 59.1 (***C***$H_3OCH_2CH_2$-), 69.9, 70.0 (CH_3O***C***H_2CH_2-), 50.2, 50.5 (CH_3OCH_2***C***H_2-), 15.7 (***C***$H_3CH_2CH_2$-), 18.3 (CH_3***C***H_2CH_2-), 28.0 (d, CH_3CH_2***C***H_2-,$^2J_{C\text{-}P}$= 109.8 Hz), 206.6 (S***C***S).^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 23.9. Elemental analysis, % Calculated (Found) for $C_{22}H_{31}ClNO_2PPdS_2$: C, 45.68 (45.72); H, 5.40 (5.43); N, 2.42 (2.40); S, 11.09 (11.11).

1.2.4 [Pd(di-*n*-decyldithiocarbamate)(PPh_3)Cl] (3)

Quantities used were: 0.04g (0.10 mmol) potassium salt of di-n-decyldithiocarbamate, 0.08g (0.10 mmol) Pd-phosphine complex. Yield: 0.06 g (71 %). M. p.: 183-184 °C. MW = 776.85. FT-IR (powder, cm^{-1}): 3053 υ(C-H, aromatic), 2922, 2850 υ(C-H, aliphatic), 1510 υ(C⎓N), 1097 υ(SCS). Raman (powder, cm^{-1}): 206 υ(Pd-P), 298 υ(Pd-Cl), 413 υ(Pd-S). ^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.88 (t, 3H, C***H***$_3(CH_2)_8CH_2$-, $^3J_{H\text{-}H}$= 7.0 Hz), 0.80 (t, 3H, C***H***$_3(CH_2)_8CH_2$-, $^3J_{H\text{-}H}$= 7.0 Hz), 2.46 (t, 2H, NC***H***$_2$-, $^3J_{H\text{-}H}$= 7.0 Hz), 2.61 (t, 2H, NC***H***$_2$-, $^3J_{H\text{-}H}$= 7.0 Hz), 1.23-1.63 (m, 32H, $CH_3(C$***H***$_2)_8CH_2$-), 7.18-7.71 (m, 15H, Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm:

14.0, 14.2 (***C***$H_3(CH_2)_8CH_2$-), 49.1, 49.9 (N***C***H_2-), 26.6, 27.1, 29.1, 29.2 29.3, 29.5, 31.8, 31.9 (-(***C***$H_2)_8$-), 128.4, 128.5, 132.0, 136.1 (Ar-***C***), 206.8 (S***C***S).^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 21.5. Elemental analysis, % Calculated (Found) for$C_{39}H_{57}ClNPPdS_2$: C, 60.30 (60.28); H, 7.40 (7.38); N, 1.80 (1.81); S, 8.26 (8.23).

1.2.5 [Pd(di-*n*-hexyldithiocarbamate)(PPh_3)Cl] (4)

Quantities used were: 0.04 g (0.13 mmol) potassium salt of di-*n*-hexyldithiocarbamate, 0.09 g (0.13 mmol) Pd-phosphine complex. Yield: 0.06 g (73 %). M. p.: 190-191 °C. MW = 664.6. FT-IR (powder, cm^{-1}): 3040 υ(C-H, aromatic), 2975, 2930 υ(C-H, aliphatic), 1511 υ(C═N), 1096 υ(SCS). Raman (powder, cm^{-1}):218 υ(Pd-P), 311 υ(Pd-Cl), 388 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.79 (t, 3H, C***H***$_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 7.2 Hz), 0.85 (t, 3H, C***H***$_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 7.2 Hz),1.15-1.24 (m, 16H, $CH_3(CH_2)_4CH_2$-),2.56 (t, 2H, $CH_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 7.1 Hz), 2.59 (t, 2H, $CH_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 7.1 Hz), 7.29-7.67 (m, 15H, Ar-***H***).^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 14.0, 14.3 (***C***$H_3(CH_2)_4CH_2$-), 22.4, 22.7 (CH_3***C***$H_2CH_2CH_2CH_2CH_2$-), 26.1, 26.3 ($CH_3CH_2CH_2$***C***$H_2CH_2CH_2$-), 27.0, 27.2 ($CH_3CH_2CH_2CH_2$***C***H_2CH_2-), 31.1, 31.3(CH_3CH_2***C***$H_2CH_2CH_2CH_2CH_2$-), 49.3, 50.1 ($CH_3CH_2CH_2CH_2CH_2$***C***H_2-), 206.4 (S***C***S). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 30.0. Elemental analysis, % Calculated (Found) for $C_{31}H_{41}ClNPPdS_2$: C, 56.02 (56.11); H, 6.22 (6.20); N, 2.11 (2.10); S, 9.65 (9.67).

1.2.6 [Pd(bis(2-methylbutyl)dithiocarbamte)(PPh_3)Cl] (5)

Quantities used were: 0.06g (0.22 mmol) of potassium salt of bis(2-methybutyl)dithiocarbamate, 0.16 g (0.22 mmol) of palladium triphenylphosphine complex. Yield: 0.11 g (76 %) M. p.: 201-202 °C. MW = 636.59. FT-IR (powder, cm^{-1}): 3072 υ(C-H, aromatic), 2957, 2925υ(C-H, aliphatic), 1526υ(C═N), 1093 υ(SCS).Raman (powder, cm^{-1}): 238 υ(Pd-P), 293 υ(Pd-Cl), 430 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.82 (t, 3H, C***H***$_3CH_2CH(CH_3)CH_2$-, $^3J_{H-H}$= 5.3 Hz), 0.86 (t, 3H, C***H***$_3CH_2CH(CH_3)CH_2$-, $^3J_{H-H}$= 5.3 Hz), 0.93, 1.06 (d, 6H, CH_3CH_2CH(C***H***$_3$)CH_2-), 1.50 (m, 4H, CH_3C***H***$_2CH(CH_3)CH_2$-), 1.61 (m, 2H, CH_3CH_2C***H***$(CH_3)CH_2$-), 3.45, 3.62 (d, 4H, $CH_3CH_2CH(CH_3)$C***H***$_2$-), 7.26-7.70 (m, 15H, Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 22.3, 22.4 (***C***$H_3CH_2CH(CH_3)CH_2$-), 26.0, 26.1 (CH_3CH_2CH(***C***H_3)CH_2-), 30.8, 30.9 (CH_3***C***$H_2CH(CH_3)CH_2$-), 35.7, 35.8 (CH_3CH_2***C***$H(CH_3)CH_2$-), 47.7, 47.9 ($CH_3CH_2CH(CH_3)$***C***H_2-

), 207.0 (S***C***S). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 30.1. Elemental analysis, % Calculated (Found) for$C_{29}H_{37}ClNPPdS_2$: C, 54.72 (54.68); H, 5.86 (5.87); N, 2.20 (2.21); S, 10.07 (10.04).

1.2.7 [Pd(di-*n*-decyldithiocarbamate)(PPh_2-*p*-tolyl)Cl] (6)

Quantities used were: 0.04 g (0.10 mmol) potassium salt of di-n-decyldithiocarbamate, 0.08g (0.10 mmol) Pd-phosphine complex. Yield: 0.06 g (70%). M. p.:160-161 °C. MW = 790.88. FT-IR (powder, cm^{-1}): 3053 υ(C-H, aromatic), 2922, 2850 υ(C-H, aliphatic), 1510 υ(C═N), 1097υ(SCS). Raman (powder, cm^{-1}): 206 υ(Pd-P), 298 υ(Pd-Cl), 413 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.88 (t, 3H, C***H***$_3(CH_2)_8CH_2$-, $^3J_{H-H}$= 7.0 Hz), 0.83 (t, 3H, C***H***$_3(CH_2)_8CH_2$-, $^3J_{H-H}$= 7.0 Hz) 2.46 (t, 2H, NC***H***$_2$-, $^3J_{H-H}$= 7.0 Hz), 2.61 (t, 2H, NC***H***$_2$-, $^3J_{H-H}$= 7.0 Hz), 2.65 (t, 2H, NC***H***$_2$-, $^3J_{H-H}$= 7.0 Hz),1.23-1.63 (m, 32H, $CH_3(CH_2)_8CH_2$-), 2.38 (s, 3H, Ph-C***H***$_3$), 7.18-7.71 (m, 14H,Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 14.0, 14.1 ***C***$H_3(CH_2)_8CH_2$-), 49.1, 49.8 (N***C***H_2-), 26.6, 27.1, 29.1, 29.2, 29.3, 29.5, 31.8, 31.9 (-(***C***$H_2)_8$-), 21.5 (Ph-***C***H_3), 206.5 (S***C***S). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 27.0. Elemental analysis, % Calculated (Found) for $C_{40}H_{59}ClNPPdS_2$: C, 60.75 (60.79); H, 7.52 (7.54); N, 1.77 (1.76); S, 8.11 (8.15).

1.2.8 [Pd(di-*n*-hexyldithiocarbamate)(PPh_2-*p*-tolyl)Cl] (7)

Quantities used were: 0.07 g potassium salt of di-*n*-hexyldithiocarbamate, 0.17 g of palladium diphenyl-*p*-tolyl phosphine complex. Yield: 0.11g (68 %).M. p.: 230-231 °C. MW = 678.67. FT-IR (powder, cm^{-1}):3050 υ(C-H, aromatic), 2923, 2850 υ(C-H, aliphatic), 1510 υ(C═N), 1097 υ(SCS).Raman (powder, cm^{-1}): 206 υ(Pd-P), 298 υ(Pd-Cl), 413 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.86 (t, 3H, C***H***$_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 8.0 Hz), 0.83 (t, 3H, C***H***$_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 8.0 Hz), 1.23-2.38 (m, 16H, $CH_3(CH_2)_4CH_2$-, 3.46 (t, 2H, $CH_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 7.1 Hz), 3.61 (t, 2H, $CH_3(CH_2)_4CH_2$-, $^3J_{H-H}$= 7.1 Hz), 2.36 (s, 3H, Ph-C***H***$_3$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 13.7,13.9 (***C***$H_3(CH_2)_4CH_2$-), 21.5 (Ph-***C***H_3), 22.4, 22.6 (CH_3***C***$H_2CH_2CH_2CH_2CH_2$-), 26.2, 26.5 ($CH_3CH_2CH_2$***C***$H_2CH_2CH_2$-), 27.0, 27.4 ($CH_3CH_2CH_2CH_2$***C***H_2CH_2-), 31.3, 31.5 (CH_3CH_2***C***$H_2CH_2CH_2CH_2$-), 49.3, 49.8 ($CH_3CH_2CH_2CH_2CH_2$***C***H_2-), 206.3 (S***C***S).^{31}P NMR

(121.49 MHz, $CDCl_3$) δ-ppm: 27.0. Elemental analysis, % Calculated (Found) for$C_{32}H_{43}ClNPPdS_2$: C, 56.63 (56.60); H, 6.39 (6.41); N, 2.06 (2.05); S, 9.45 (9.47).

1.2.9 [Pd(bis(2-ethylhexyl)dithiocarbamate)(PPh_2-*p*-tolyl)Cl] (8)

Quantities used were: 0.17g (0.48 mmol) bis(2-ehtylhexyl)dithiocarbamic acid, 0.35g (0.48 mmol) Pd-phosphine complex. Yield: 0.27 g (76%). M. p.:197-198 °C. MW = 734.77. FT-IR (powder, cm^{-1}): 3040 υ(C-H, aromatic), 2971, 2922 υ(C-H, aliphatic), 1510 υ(C═N), 1096 υ(SCS). Raman (powder, cm^{-1}): 223 υ(Pd-P), 312 υ(Pd-Cl), 391 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm:0.83 (t, 3H, C***H***$_3(CH_2)_3CH(CH_2CH_3)CH_2$-, $^3J_{H-H}$= 7.2 Hz), 0.88 (t, 3H, $CH_3(CH_2)_3CH(CH_2C$***H***$_3)CH_2$-, $^3J_{H-H}$= 7.2 Hz), 1.16-1.30 (m, 12H, $CH_3(C$***H***$_2)_3CH(CH_2CH_3)CH_2$-), 1.70-1.77 (m, 4H, $CH_3(CH_2)_3CH(C$***H***$_2CH_3)CH_2$-), 1.83-1.90 (m, 2H, $CH_3(CH_2)_3C$***H***$(CH_2CH_3)CH_2$-),3.56 (d, 2H, $CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-, $^2J_{H-H}$= 7.1 Hz), 3.60 (d, 2H, $CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-, $^2J_{H-H}$= 7.1 Hz), 2.36 (s, 3H, Ph-C***H***$_3$), 7.18-7.71 (m, 14H, Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 10.5,10.6 (***C***$H_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 14.0,14.1 ($CH_3(CH_2)_3CH(CH_2$***C***$H_3)CH_2$-), 22.9, 23.7, 28.4, 30.4 ($CH_3($***C***$H_2)_3CH($***C***$H_2CH_3)CH_2$-), 37.4, 37.6 ($CH_3(CH_2)_3$***C***$H(CH_2CH_3)CH_2$-), 52.7,52.9 ($CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-), 21.5 (Ph-***C***$H_3$), 127.8, 128.3, 128.8 129.3, 130.3, 134.4, 135.0, 140.8 (Ar-***C***), 207.7 (S***C***S). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 23.8. Elemental analysis, % Calculated (Found) for $C_{36}H_{51}ClNOPPdS_2$: C, 57.59 (57.65); H, 6.85 (6.87); N, 1.87 (1.88); S, 8.54 (8.57).

1.2.10 [Pd(bis(2-ethylhexyl)dithiocarbamate)(PPh_2(benzyl))Cl] (9)

Quantities used were: 0.15 g (0.42 mmol) of potassium salt of bis(2-ethylhexyl)dithiocarbamate, 0.31 g (0.42 mmol) of palladium benzyldiphenyl phosphine complex. Yield: 0.25 g (81 %). M. p.: 203-204 °C. MW = 734.77. FT-IR (powder, cm^{-1}): 3040 υ(C-H, aromatic), 2975, 2930 υ(C-H, aliphatic), 1511 υ(C═N), 1096 υ(SCS).Raman (powder, cm^{-1}):218 υ(Pd-P), 311 υ(Pd-Cl), 388 υ(Pd-S). ^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.78 (t, 3H, C***H***$_3(CH_2)_3CH(CH_2CH_3)CH_2$-, $^3J_{H-H}$= 7.2 Hz), 0.86 (t, 3H, $CH_3(CH_2)_3CH(CH_2C$***H***$_3)CH_2$-, $^3J_{H-H}$= 7.2 Hz), 1.15-1.24 (m, 12H, $CH_3(C$***H***$_2)_3CH(CH_2CH_3)CH_2$-), 1.53-1.69 (m, 4H, $CH_3(CH_2)_3CH(C$***H***$_2CH_3)CH_2$-), 1.81-1.89 (m, 2H, $CH_3(CH_2)_3C$***H***$(CH_2CH_3)CH_2$-), 3.93 (d, 4H, $CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-, $^3J_{H-H}$= 7.0 Hz), 4.01 (d, 2H, Ph-C***H***$_2$-, $^3J_{H-H}$= 7.0 Hz), 7.17-7.52 (m, 15H, Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$)

δ-ppm: 10.5 (***C***$H_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 14.0 ($CH_3(CH_2)_3CH(CH_2$***C***$H_3)CH_2$-), 22.9, 23.8 28.4, 30.6 (CH_3(***C***$H_2)_3CH($***C***$H_2CH_3)CH_2$-), 32.9 (d, Ph-***C***H_2-, $^2J_{C\text{-}P}[^{13}C, ^{31}P]$), 37.4 ($CH_3(CH_2)_3$***C***$H(CH_2CH_3)CH_2$-), 52.7 ($CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-), 207.1 (S***C***S). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 27.0. Elemental analysis, % Calculated (Found) for $C_{36}H_{51}ClNPPdS_2$: C, 58.85 (58.80); H, 7.00 (7.02); N, 1.91 (1.90); S, 8.73 (8.75).

1.2.11 [Pd(bis(2-ethylhexylhexyl)dithiocarbamate)(PPh_3)Cl] (10)

Quantities used were: 0.20g (0.56 mmol) bis(2-ehtylhexyl)dithiocarbamic acid, 0.39g (0.56 mmol) Pd-phosphine complex. Yield: 0.32 g (80%). M. p.:290-291 °C (decompose). MW = 720.75. FT-IR (powder, cm^{-1}): 3040 υ(C-H, aromatic), 2975, 2930 υ(C-H, aliphatic), 1511 υ(C ═N), 1096 υ(SCS). Raman (powder, cm^{-1}): 218 υ(Pd-P), 311 υ(Pd-Cl), 388 υ(Pd-S).^{1}H NMR (300 MHz, $CDCl_3$) δ-ppm: 0.79 (t, 3H, C***H***$_3(CH_2)_3CH(CH_2CH_3)CH_2$-, $^3J_{H\text{-}H}$= 7.2 Hz),0.81 (t, 3H, C***H***$_3(CH_2)_3CH(CH_2CH_3)CH_2$-, $^3J_{H\text{-}H}$= 7.2 Hz), 0.84 (t, 3H, $CH_3(CH_2)_3CH(CH_2C$***H***$_3)CH_2$-, $^3J_{H\text{-}H}$= 7.2 Hz), 0.82 (t, 3H, $CH_3(CH_2)_3CH(CH_2C$***H***$_3)CH_2$-, $^3J_{H\text{-}H}$= 7.2 Hz), 1.17-1.24 (m, 12H, $CH_3(C$***H***$_2)_3CH(CH_2CH_3)CH_2$-), 1.54-1.68 (m, 4H, $CH_3(CH_2)_3CH(C$***H***$_2CH_3)CH_2$-), 1.80-1.89 (m, 2H, $CH_3(CH_2)_3C$***H***$(CH_2CH_3)CH_2$-), 3.91 (d, 2H, $CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-, $^3J_{H\text{-}H}$= 7.0 Hz), 3.94 (d, 2H, $CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-, $^3J_{H\text{-}H}$= 7.0 Hz), 7.29-7.67 (m, 15H, Ar-***H***). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ-ppm: 10.4, 10.6 (***C***$H_3(CH_2)_3CH(CH_2CH_3)CH_2$-), 14.1, 14.2 ($CH_3(CH_2)_3CH(CH_2$***C***$H_3)CH_2$-), 22.9, 23.6 28.3, 30.6 (CH_3(***C***$H_2)_3CH($***C***$H_2CH_3)CH_2$-), 37.6, 37.7 ($CH_3(CH_2)_3$***C***$H(CH_2CH_3)CH_2$-), 52.7, 52.9 ($CH_3(CH_2)_3CH(CH_2CH_3)C$***H***$_2$-), 128.4, 130.7 132.1, 134.4 (Ar-***C***),207.1 (S***C***S). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ-ppm: 30.2. Elemental analysis: % Calculated (Found) for $C_{35}H_{49}ClNPPdS_2$: C, 58.32 (58.25); H, 6.85 (6.84); N, 1.94 (1.95); S, 8.90 (8.92).

1.3 Structural studies of complexes 1 and 2

The needle shaped golden yellow crystals of the complexes **1** and **2** were developed in dichloromethane and n-hexane in the volume ratio of 2:1 respectively. The crystals were mounted on a glass fibre with the help of epoxy glue. The measurements were made at 293 K on a STOE IPDS image plate detector diffractometer equipped with graphite mono-chromated MoKα radiation. The cell parameters, data collection and data integration were performed with

the help of; S1TOE X-AREA [27]. The structures of the complexes were solved and refined by using SHELXS-97 and SHELXL-97 (Sheldrick, 1997) and all the non-hydrogen atoms were refined anisotropically, with the hydrogen atoms were placed at the idealized positions. The two A level alerts in the CIF file of the complex **1** can be ignored, as these don't disturb the geometry around the metal centre.

*1.4 A*nti-bacterial assays

The antibacterial potential of the synthesized mixed ligand metal complexes was tested against some Gram positive and Gram negative bacterial strains.

1.4.1 Antibacterial assays

The antibacterial activity of all the synthesized metal complexes has been investigated against five strains of bacteria (*Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumoniae* and *Staphylococcus epidermidis*) by the agar well diffusion method[28]. Imipenem was selected as a standard antibiotic. Four milligrams of the complexes were dissolved in 1 ml of DMSO. Centrifuged pellets of bacteria were taken from 24h old culture containing approximately 10^4–10^6 colony forming unit (CFU) per ml was spread on the surface of Muller Hinton Agar (MHA) plates. Wells were created in medium with the help of a sterile metallic borer and nutrients agar medium were prepared by suspending nutrient agar(Merck) 20 g in one litre of distilled water (pH 7.0), autoclaved and cooled down to 45 °C. Then it was seeded with10 ml of prepared inocula to have 106 CFU/ml. Petri dishes were prepared by pouring 75 ml of seeded nutrients agar. Experimental plates were incubated for 24 h and zones of inhibition (%) were measured and compared with standard antibiotic Imipenem. The bactericidal assays were performed in triplicate and results are shown in Table 1.2.

1.4.2 Anticancer assays

The human lung Fibroblast MRC-5 carcinoma cells were obtained from the American Type Culture Collection. The cells were maintained in Roswell Park Memorial Institute medium supplemented with 10 mM HEPES, 3 mM L-glutamine, 10% FBS and 100 µg/mL penicillin. Prior to the drug treatment, all the assay cells were plated for 24 h. 100 mmol stock solutions of

the synthesized compounds were prepared in DMSO. Nine serial dilutions of the heteroleptic palladium complexes were used to treat the cells.

The MRC-5 carcinoma cells were plated at 5000 cells/well in 96-well flat-bottom microtiter plates. After 24 h incubation, cells were exposed to various concentrations of each compound for five days. The remaining live cells were fixed using 60 μL of cold trichloroacetic acid (50%) for 60 minutes at 276 K , washed with water, stained with 0.4% sulphorhodamine B (SRB) for 5 h at 298 K, rinsed with 1% acetic acid and allowed to dry overnight[29]. The resulting coloured residue was dissolved in 200 μL Tris base (10 mM, pH 10.0) and optical density was recorded at 490 nm using a microplate reader ELx808 (Biotek instruments). The results were analysed by Graph Pad Prism (Graph Pad Software, Inc., San Diego, CA) and the sigmoidal dose response curve was used to determine 50% cell growth inhibitory concentration (IC_{50}). The growth inhibition assay was performed once in triplicate.

1.5 Results and discussion

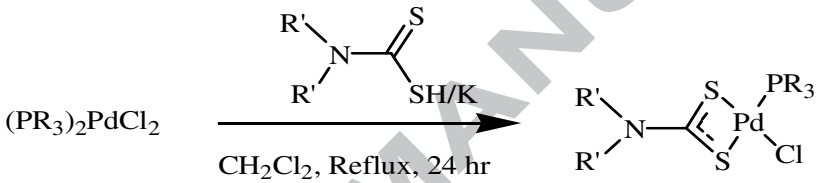
Synthesis and characterization of mixed ligand palladium(II) complexes

The heteroleptic Pd(II) complexes were synthesized by reacting known Pd-phosphine complexes [30] with dithiocarbamate ligands [31] while stirring magnetically and under reflux conditions in dichloromethane (Scheme 1.1). The synthesized compounds are stable at normal conditions of temperature and pressure and soluble in common organic solvents.

The stretching frequencies of $C{=}N$ and $S{=}C{=}S$, were of prime interest in the IR spectra of the mixed ligand palladium(II) complexes. Both of these vibrations can be used to determine the coordination mode of a dithiocarbamate ligand to metal moiety. The presence of a single band in the range of 1089-1097 cm^{-1} due to $\upsilon(S{=}C{=}S)$ is an indication that dithiocarbamate has been coordinated to metal centre in a symmetrical bidentate fashion, otherwise two peaks are observed in this region[30b]. The $C{=}N$ absorption peak is observed in the range of 1510-1526 cm^{-1}, which is intermediate between a single bond C-N (1250-1350 cm^{-1}) and a double bond C=N (1640-1690 cm^{-1}), and a very typical characteristic of dithiocarbamate complexes[32]. The intermediate nature of the C-N bond showed the resonance phenomenon in the dithiocarbamate moiety and

has been confirmed using X-ray crystallography[33]. The disappearance of the S-H peak in the metal complexes suggested the coordination of dithiocarbamate ligand with metal centre.

Raman spectroscopy was mainly used to identify the metal ligand bonds in the far IR region i.e., below 400 cm^{-1}. The most explicit feature in the spectra of all of the complexes was the appearance of a new band in the 388-430 cm^{-1} region, which was absent in the spectra of the free ligands, this band is assigned to the Pd-S[34] stretching mode. The Pd-Cl stretching mode was observed in the 296-312 cm^{-1} range, while the Pd-P stretching mode appeared in the 200-238 cm^{-1}, region for all the complexes. The observation of all of these bands demonstrates complex formation between the Pd(II) moiety and the ligands.



PR_3 = $PPh_2C(CH_3)_3$ (1), PPh_2-n-propyl (2), PPh_3 (3,4,5,10), PPh_2-p-tolyl (6,7,8), PPh_2(benzyl) (9)

R' = 2-ethylhexyl (1,8,9,10), 2-methoxyethyl (2), n-decyl (3,6), n-hexyl (4,7), 2-methylbutyl (5)

Scheme 1.1: Synthesis of heteroleptic palladium(II) complexes

The proton NMR spectra of the synthesized compounds were recorded in $CDCl_3$. The assignments of the proton peaks were made from their multiplicity, chemical shift, intensity pattern and comparison of the integration areas of the protons with the expected composition. The ^1H NMR data show the disappearance of the SH frequency- suggesting coordination of the dithiocarbamate ligand to the metal centre by abstraction of H^+ from the dithiocarbamic acid moiety. Another characteristic feature of the ^1H NMR spectra is the asymmetry in the alkyl groups attached to the nitrogen atom of the dithiocarbamate moiety, caused by restricted rotation around the C-N bond, which is known to have a barrier energy ranging from 65 to 92 $kJ.mol^{-1}$[35]. The restricted rotation around the C-N bond can be attributed to the partial double bond character

in this bond owing to resonance in the dithiocarbamate group. The aromatic protons were observed at 7.18-7.10 ppm. The rest of the proton frequencies in the metal complexes show no distincive changes when compared to the spectra of their precursors. All these observations are in agreement with the previously reported literature for Pd-dithiocarbamate complexes[31a, 36].

The ^{13}C NMR spectra of the complexes were also recorded in $CDCl_3$. The most important peak in the carbon spectra of all the compounds is the carbon of SCS moiety of the dithiocarbamate ligand. The slight up field shift of this signal can be attributed to the accumulation of electronic density after complexation. It confirms coordination of the dithiocarbamate ligand with the metal centre. The SCS carbon atom in the complexes investigated was observed in the 206.3-208.6 ppm range. Like the proton atoms of the alkyl groups attached to the nitrogen atom of the dithiocarbamate, the carbon atoms of the alkyl groups are also asymmetrical in nature.

^{31}P NMR data were collected for the synthesized complexes in $CDCl_3$ and their precursors. Generally, the ^{31}P frequency shifted considerably downfield after the coordination of the phosphine ligand to metal moiety. The downfield shift of the ^{31}P frequency can be assigned to the flow of electronic density from the phosphorus atom to the palladium centre after the complex formation. The ^{31}P shifts were observed in the range of 21.5-45.1ppm

1.6 Structural studies of complexes 1 and 2

The ball and stick diagrams of compounds **1** and **2** with selected bond lengths and angles are shown in Figures 1.1 and 1.2 respectively. Both complexes crystallize in the P2(1)/c space group. In both complexes, the central atom exhibits similar pseudo square-planar geometry with the dithiocarbamate ligand occupying two adjacent coordination sites while the chloride ion and the tertiary organophosphine ligand dwell in the two remaining sites. The largest deformation from the normal square planar geometry comes from the bidentate ligand (S(1)-Pd-S(2) of 75.05(3)°and 75.37(3)° for **1** and **2**, respectively) which causes the *trans* S-Pd-Cl (166.34(3)° (**1**) and 170.71(4)° (**2**)) and P-Pd-S angles to be 169.14(3)° (**1**) and 170.89(3)° (**2**), smaller than the expected value of 180°. The asymmetry observed in the Pd-S distances (ΔS, 0.0502 Å (**1**) and 0.0777 Å (**2**)) is usual for square planar systems and reflects the *trans* influence of the attached ligands. In both complexes, the Pd-S bond lengths *trans* to the phosphine ligands are longer

(2.3372(8) Å (**1**) and 2.3643(14) Å (**2**) than the Pd-S bond lengths *trans* to the chloride (2.2870(9) Å (**1**) and 2.2854(9) Å (**2**). The largest inconsistency in the Pd-S bond lengths (0.0777 Å) for complex **2** demonstrates the better donating capability of the diphenyl-*n*-propylphosphine than diphenyl-*tert*-butylphosphine ligand. The S-C bond distances (1.709(3), 1.727(3) (**1**) and (1.732(4), 1.715(4) (**2**) are intermediate between single bond, C-S (1.82 Å) and double bond C=S (1.60 Å) distances. In the same way, the C-N bond lengths of 1.323(4)Å for **1** and 1.322(4)Å for **2** are significantly shorter than a normal C-N bond distance (1.47 Å) and longer than a C=N bond length (1.28 Å)[37]. These bond values clearly demonstrate the resonance phenomenon in N-CSS moiety.

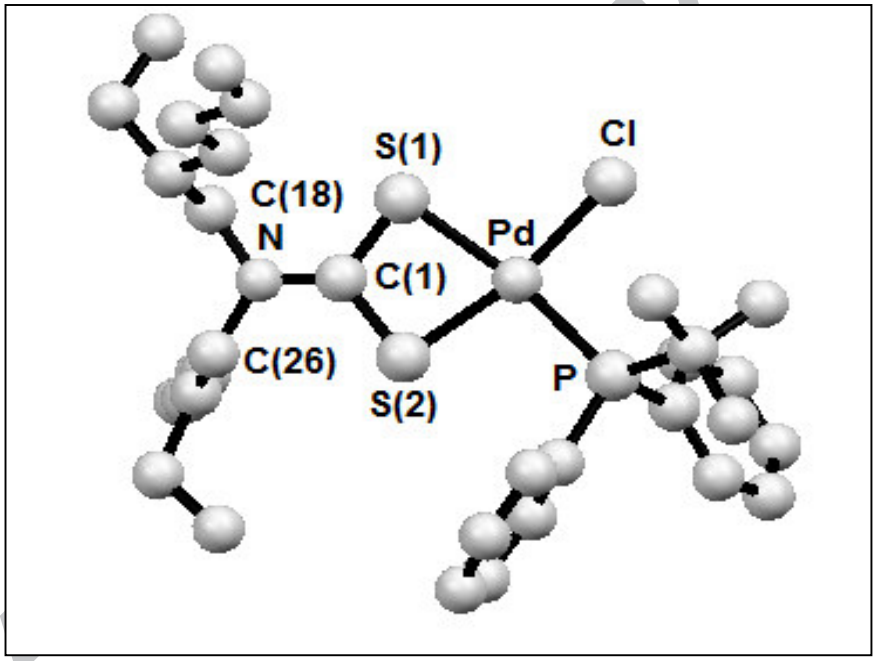


Figure 1.1: The ball and stick diagram (50% probability)of (**1**). The Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): 2.3372(8) (Pd-S, *trans* to organophosphine), 2.2870(9) (Pd-S, *trans* to Cl^-), 0.0502 (ΔS),1.323(4) (C-N); 169.14(3) (P-Pd-S,S

trans to phosphorus atom), 166.34(3) (Cl-Pd-S, S *trans* to chloride ion), 75.05(3) (S-Pd-S), 110.1(2) (S-C-S).

Complex 2

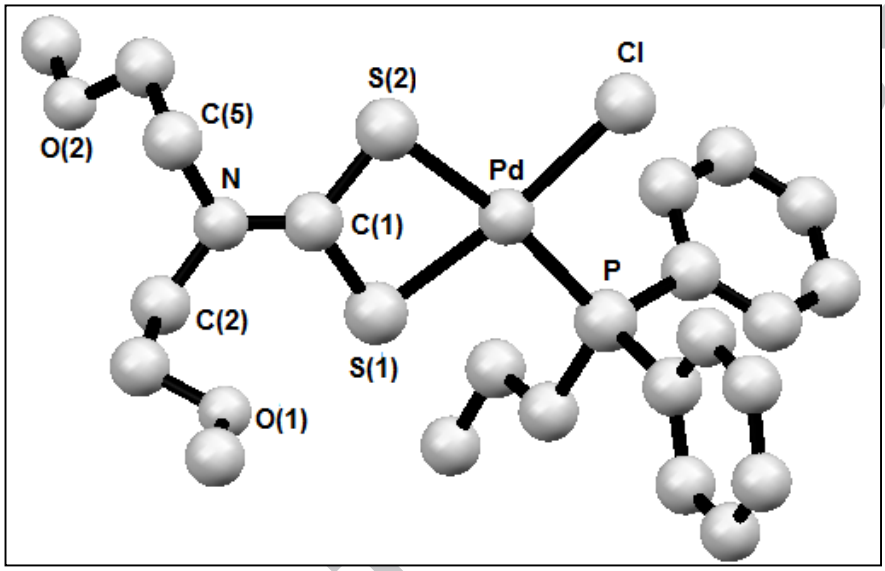


Figure1.2: The ball and stick diagram (50% probability)of (2). Hydrogen atoms have been removed for clarity. Selected bond lengths (Å) and angles (deg): 2.3631(9) (Pd-S, *trans* to organophosphine), 2.2854(9) (Pd-S, *trans* to Cl^-), 0.0777 (ΔS), 1.322(4) (C-N); 170.89(3) (P-Pd-S, S, *trans* to phosphorus atom), 170.71(4) (Cl-Pd-S, S, *trans* to chloride ion), 75.37(3) (S-Pd-S), 111.1(2) (S-C-S).

Table 1.1: Crystal data and structure refinement parameters for complexes 1 and **2**

Compound No.	**1**	**2**
Empirical formula	C_{33} H_{53} Cl N P Pd S_2	C_{22} H_{31} Cl NO_2 P Pd S_2
Formula weight	700.76	578.46
Temperature	296(2) K	200 (2) K
Wavelength	0.71073 Å	1.54178 Å
Diffraction radiation type	MoK\α	CuK\α
Space group	P2(1)/c	P2(1)/c
F(000)	1472.0	1184.0
Index ranges	-16<=h<=16, -23<=k<=29, -17<=l<=12	-16<=h<=16, 0<=k<=12, 0<=l<=23
Unit cell dimensions	a = 12.3536(6) Å α = 90.00° b = 22.0280(9) Å β = 96.970(2)° c = 13.4169(6) Å γ = 90.00°	a = 13.3911(6) Å α = 90.00° b = 10.2874(5) Å β = 103.714(3)° c = 18.7804(9) Å γ = 90.00°
Reflections collected	42458	30349
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2

1.7 Biological activity

1.7.1 Cell cytotoxicity assay

The synthesized compounds **1-10** were assayed for their cytotoxicities against the human lung fibroblast MRC-5 cell line. The IC_{50} values of the compounds are given in the Table 1.1. The

complex **6**, [Pd(di-*n*-decyldithiocarbamate)(PPh_2-*p*-tolyl)Cl] showed the greatest cytotoxicity of the ten complexes. The higher cytotoxicity of complex **6** may be assigned to the higher carbon chain length of the dithiocarbamate ligand. The longer the carbon chain length, the higher the efficiency of the DNA-binding and the greater the cytotoxicity [25]. Compound **3**, which contains the same ligand di-*n*-decyldithiocarbamate ligand also exhibited cytotoxic activity but less than compound **6**. The difference in activity may be due to the variation in the attached organophosphine ligand. In general, the compounds exhibited low to moderate activity.

Table 1.2: Anticancer activity

Samples	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
IC_{50} [mM]±SEM	36.7±2.9	>100	71.5±13.1	>100	81.6±13.1	22.8±2.4	>100	30.8±2.6	>100	65.3±12.5

1.7.2 Antibacterial activity

The synthesized metallodrugs were screened for their antibacterial activity against two Gram positive (*Bacillus subtilis*, *Staphylococcus aureus*) and three Gram negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*). The antibacterial activities are shown in Table 1.2. The antibacterial activities of the synthesized compounds decrease in the order **1>3>10>8>9>2>7>6>4>5**.A regular structure activity relationship cannot be concluded from the available data. Generally, the compounds containing the 2-ethylhexyldithiocarbamate ligand (**1**, **8**, **9**, and **10**) showed higher antibacterial activity. According to chelation theory, the polarity of the metal atom decreases upon complexation and lipophilicity of the metallo drug is increased. The organophosphine ligands also have an important role in the antibacterial activity of compounds. The two compounds, **4** and **5**, which contain triphenylphosphine, exhibit the lowest antibacterial activity; this may be assigned to the electron-withdrawing nature of triphenylphosphine moiety.

Table 1.3: Antibacterial activity (diameter of inhibition zone in mm) of the synthesized complexes

Samples	*Bacillus subtilis* (G +)	*Staphylococcus aureus* (G +)	*Escherichia coli* (G -)	*Klebsiella pneumoniae* (G -)	*Staphylococcus epidermidis* (G -)
1	20 ± 0.21	16 ± 0.32	22 ± 0.33	16 ± 0.46	22 ± 0.16
2	11 ± 0.52	12 ± 0.67	15 ± 0.21	17 ± 0.35	15 ± 0.27
3	21 ± 0.61	19 ± 0.55	18 ± 0.39	17 ± 0.62	18 ± 0.13
4	14 ± 0.51	13 ± 0.69	10 ± 0.47	10 ± 0.16	10 ± 0.23
5	07 ± 0.26	09 ± 0.43	10 ± 0.38	12 ± 0.55	10 ± 0.36
6	11 ± 0.23	10 ± 0.13	12 ± 0.33	13 ± 0.21	12 ± 0.44
7	16 ± 0.23	15 ± 0.43	10 ± 0.71	11 ± 0.63	10 ± 0.32
8	14 ± 0.35	18 ± 0.22	17 ± 0.24	13 ± 0.32	17 ± 0.46
9	15 ± 0.37	16 ± 0.25	16 ± 0.36	15 ± 0.58	16 ± 0.18
(**10**	16 ± 0.21	18 ± 0.42	17 ± 0.39	20 ± 0.28	17 ± 0.33
Reference drug (Imipenem)	25 ± 0.11	26 ± 0.15	32 ± 0.44	35 ± 0.36	35 ± 0.54

1.8 Conclusions

Ten heteroleptic palladium(II) compounds were synthesized and characterized by various spectroscopic techniques. Metal-based compounds, such as these have exhibited promising antitumor and antibacterial activity. All the synthesized complexes were prepared in good yield. The spectroscopic results and single-crystal X-ray diffraction studies for two of the compounds reveal that the compounds have distorted square-planar geometry around the metal moiety. The compounds exhibited moderate antibacterial and antitumor activity.

1.9 Supplementary material

The crystallographic data for the structural analyses of complexes 1 and 2, have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. for 1 is CCDC 1420935 and for complex 2 is CCDC 1420934. Copy of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ1EZ, UK (fax: þ44 1223 336 033; email:deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

1.10 Acknowledgement

Dr Hizbullah Khan is highly grateful to Higher Education Commission (HEC) of Pakistan for providing PhD scholarship under the "5000 Indigenous PhD Scholarships Programme", at Quaid-i-Azam University Islamabad and six months scholarship under the programme of International Research Support Initiative Programme (IRSIP) as a Graduate Research Trainee at Department of Chemistry, McGill University, Montreal, Quebec, Canada.

References

[1] J. Ruiz, M. a. D. Villa, N. Cutillas, G. López, C. n. d. Haro, D. Bautista, V. Moreno, L. Valencia, *Inorganic Chemistry* **2008**, *47*, 4490.

[2] K. J. Barnham, C. J. Bauer, M. I. Djuran, M. A. Mazid, T. Rau, P. J. Sadler, *Inorganic Chemistry* **1995**, *34*, 2826.

[3] A. C. Favero Caires, *Anti-Cancer Agents Med. Chem.* **2007**, *7*, 484.

[4] A. S. Abu-Surrah, M. Kettunen, *Curr. Med. Chem.* **2006**, *13*, 1337.

[5] A. S. Abu-Surrah, H. H. Al-Sa'doni, M. Y. Abdalla, *Cancer Ther.* **2008**, *6*, 1.

[6] P. Kalaivani, R. Prabhakaran, F. Dallemer, P. Poornima, E. Vaishnavi, E. Ramachandran, V. V. Padma, R. Renganathan, K. Natarajan, *Metallomics* **2012**, *4*, 101.

[7] E. J. Gao, L. Lei, M. C. Zhu, Y. Huang, G. Feng, X. N. Gao, M. Zhang, L. Wang, W. Z. Zhang, Y. G. Sun, *Inorg. Chem.* **2011**, *50*, 4732.

[8] A. S. Abu-Surrah, R. Al-Allaf, L. Rashan, M. Klinga, M. Leskela, *Eur. J. Med. Chem.* **2002**, *37*, 919.

[9] a)J. Ruiz, J. Lorenzo, C. Vicente, G. López, M. Monge, F. X. Avilés, D. Bautista, V. Moreno, A. Laguna, *Inorganic chemistry* **2008**, *47*, 6990; b)F. Linares, M. A. Galindo, S. Galli, M. A. Romero, J. A. Navarro, E. Barea, *Inorganic chemistry* **2009**, *48*, 7413; c)N. Cutillas, G. S. Yellol, C. de Haro, C. Vicente, V. Rodríguez, J. Ruiz, *Coordination Chemistry Reviews* **2013**, *257*, 2784.

[10] A. Divsalar, A. A. Saboury, H. Mansoori-Torshizi, F. Ahmad, *The journal of physical chemistry B* **2010**, *114*, 3639.

[11] a)G. García-Friaza, A. Fernández-Botello, J. M. Pérez, M. J. Prieto, V. Moreno, *Journal of inorganic biochemistry* **2006**, *100*, 1368; b)D. Kovala-Demertzi, M. A. Demertzis, E. Filiou, A. A. Pantazaki, P. N. Yadav, J. R. Miller, Y. Zheng, D. A. Kyriakidis, *Biometals* **2003**, *16*, 411.

[12] P. Genova, T. Varadinova, A. I. Matesanz, D. Marinova, P. Souza, *Toxicology and applied pharmacology* **2004**, *197*, 107.

[13] D. C. Onwudiwe, P. A. Ajibade, *Polyhedron* **2010**, *29*, 1431.

[14] a)D. C. Onwudiwe, P. A. Ajibade, *International journal of molecular sciences* **2012**, *13*, 9502; b)E. M. Nagy, S. Sitran, M. Montopoli, M. Favaro, L. Marchiò, L. Caparrotta, D. Fregona, *Journal of inorganic biochemistry* **2012**, *117*, 131.

[15] a)W. Lou, M. Chen, X. Wang, W. Liu, *The Journal of Physical Chemistry C* **2007**, *111*, 9658; b)W. Lou, M. Chen, X. Wang, Y. Zhang, W. Liu, *Chemistry Letters* **2006**, *35*, 850.

[16] M. Carreira, R. Calvo-Sanjuán, M. Sanaú, I. Marzo, M. Contel, *Organometallics* **2012**, *31*, 5772.

[17] G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem.* **2011**, *54*, 3.

[18] a)A. Kastl, A. Wilbuer, A. L. Merkel, L. Feng, P. Di Fazio, M. Ocker, E. Meggers, *Chem. Commun.* **2012**, *48*, 1863; b)P. K. Lee, W. H. T. Law, L. Hua-Wei, K. W. Kenneth, *Inorg. Chem.* **2011**, *50*, 8570.

[19] S. D. Shyder, Y. Fu, A. Habtemariam, S. H. van Rijt, P. A. Cooper, P. M. Loadman, P. J. Sadler, *Med. Chem. Commun.* **2011**, *2*, 666.

[20] P. Sathyadevi, P. Krishnamoorthy, R. R. Butorac, A. H. Cowley, N. Dharmaraj, *Metallomics* **2012**, *4*, 498.

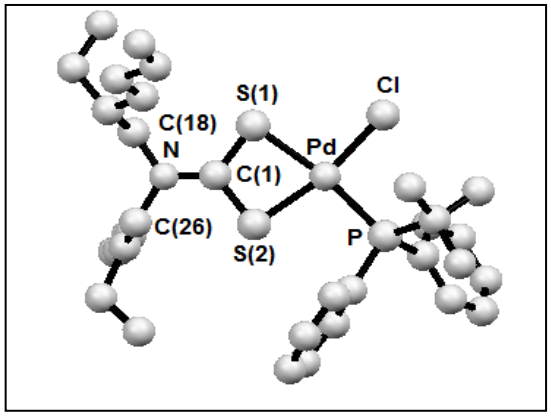
[21] W. H. Ang, A. Casini, G. Sava, P. J. Dyson, *J. Organomet. Chem.* **2011**, *696*, 989.

[22] S. J. Berners-Price, E. Alessio, *Bioinorganic Medicinal Chemistry*, **2011**.
[23] U. Olzewski, J. Clafeey, M. Hogan, M. Tacke, R. Zeillinger, P. Bednarski, G. Hamilton, *Invest. New Drugs* **2011**, *29*, 607.
[24] D. Nieto, A. M. González-Vadillo, S. Bruna, C. J. Pastor, C. Ríos-Luci, L. G. León, J. M. Padrón, C. Navarro-Ranninger, I. Cuadrado, *Dalton Trans.* **2012**, *41*, 432.
[25] E. Gao, M. Zhu, L. Liu, Y. Huang, L. Wang, C. Shi, W. Zhang, Y. Sun, *Inorganic chemistry* **2010**, *49*, 3261.
[26] M. Sirajuddin, S. Ali, M. N. Tahir, *Inorganica chimica acta* **2016**, *439*, 145.
[27] X. Area, Stoe, Cie, Darmstadt, **2006**.
[28] a)L. Boyanova, G. Gergova, R. Nikolov, S. Derejian, E. Lazarova, N. Katsarov, I. Mitov, Z. Krastev, *Journal of medical microbiology* **2005**, *54*, 481; b)J. Parekh, D. Jadeja, S. Chanda, *Turkish Journal of Biology* **2006**, *29*, 203.
[29] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, M. R. Boyd, *J. Natl. Cancer Inst.* **1990**, *82*, 1107.
[30] a)H.-B. Song, Z.-Z. Zhang, T. C. Mak, *Polyhedron* **2002**, *21*, 1043; b)F. Shaheen, A. Badshah, M. Gielen, G. Croce, U. Florke, D. de Vos, S. Ali, *Journal of Organometallic Chemistry* **2010**, *695*, 315.
[31] a)A. Garoufis, S. Hadjikakou, N. Hadjiliadis, *Coordination Chemistry Reviews* **2009**, *253*, 1384; b)E. Gao, C. Liu, M. Zhu, H. Lin, Q. Wu, L. Liu, *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)* **2009**, *9*, 356.
[32] V. Alverdi, L. Giovagnini, C. Marzano, R. Seraglia, F. Bettio, S. Sitran, R. Graziani, D. Fregona, *Journal of inorganic biochemistry* **2004**, *98*, 1117.
[33] J. J. Criado, J. A. Lopez-Arias, B. Macias, L. R. Fernandez-Lago, J. M. Salas, *Inorganica chimica acta* **1992**, *193*, 229.
[34] N. Manav, A. Mishra, N. Kaushik, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2004**, *60*, 3087.
[35] a)C. Paparizos, J. Fackler Jr, *Inorganic chemistry* **1980**, *19*, 2886; b)D. F. Brayton, K. Tanabe, M. Khiterer, K. Kolahi, J. Ziller, J. Greaves, P. J. Farmer, *Inorganic chemistry* **2006**, *45*, 6064.
[36] L. Giovagnini, L. Ronconi, D. Aldinucci, D. Lorenzon, S. Sitran, D. Fregona, *Journal of medicinal chemistry* **2005**, *48*, 1588.
[37] a)A. Yenesew, S. Derese, J. O. Midiwo, H. A. Oketch-Rabah, J. Lisgarten, R. Palmer, M. Heydenreich, M. G. Peter, H. Akala, J. Wangui, *Phytochemistry* **2003**, *64*, 773; b)Z.-f. Dai, B.-x. Peng, X.-a. Chen, *Dyes and pigments* **1999**, *40*, 219; c)Y.-X. Jin, A.-G. Zhong, C.-H. Ge, F.-Y. Pan, J.-G. Yang, Y. Wu, M. Xie, H.-W. Feng, *Journal of Molecular Structure* **2012**, *1010*, 190; d)N. Q. Shixaliyev, A. M. Maharramov, A. V. Gurbanov, V. G. Nenajdenko, V. M. Muzalevskiy, K. T. Mahmudov, M. N. Kopylovich, *Catalysis Today* **2013**, *217*, 76.

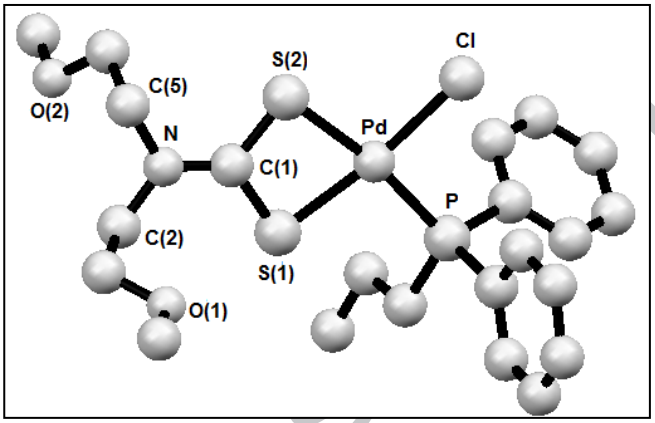
Synopsis

Mixed ligand Pd(II) complexes have been synthesized in good yields. All the complexes were characterized by analytical and spectroscopic techniques. The prepared compounds have shown moderate antitumor and antibacterial activity.

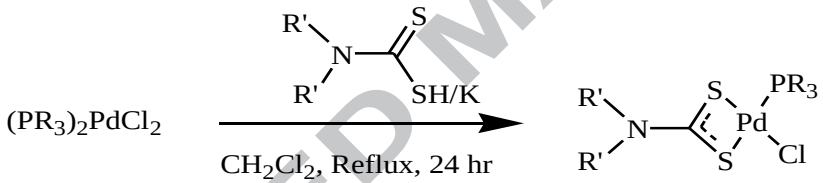
Graphical Abstract



Complex 1



Complex 2



PR_3 = $PPh_2C(CH_3)_3$ (1), PPh_2-n-propyl (2), PPh_3 (3,4,5,10), PPh_2-p-tolyl (6,7,8), PPh_2(benzyl) (9)

R' = 2-ethylhexyl (1,8,9,10), 2-methoxyethyl (2), n-decyl (3,6), n-hexyl (4,7), 2-methylbutyl (5)

Scheme: Synthesis of heteroleptic palladium(II) complexes

Highlights

- ✓ Ten heteroleptic palladium(II) complexes have been synthesized in good yields
- ✓ The single crystal XRD analyses of the two prepared complexes have exhibited pseudo square-planar geometry around the central metal atom
- ✓ The C=N absorption peak is observed in the range of 1510-1526 cm^{-1}, which is intermediate between a single bond C-N (1250-1350 cm^{-1}) and a double bond C=N (1640-1690 cm^{-1})
- ✓ The synthesized metallodrugs have shown moderate anticancer and antibacterial activity