Inorganica Chimica Acta 479 (2018) 189–196

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Research paper

Pd(II)-based heteroleptic complexes with N-(acyl)-N′, N′-(disubstituted) thioureas and phosphine ligands: Synthesis, characterization and cytotoxic studies against lung squamous, breast adenocarcinoma and *Leishmania tropica*

Muhammad Riaz Khan [a], Sumera Zaib [d], Azim Khan [a], Amin Badshah [c], Muhammad Khawar Rauf [b,c,*], Imtiaz-ud-Din [c], Muhammad Nawaz Tahir [e], Muhammad Shahid [c], Jamshed Iqbal [d,*]

[a] Department of Chemistry, Gomal University, Dera Ismail Khan 29050, Pakistan
[b] Office of Research, Innovation and Commercialization, Quaid-i-Azam University, Islamabad 45320, Pakistan
[c] Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
[d] Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan
[e] Department of Physics, University of Sargodha, Sargodha, Pakistan

ARTICLE INFO

Article history:
Received 18 December 2017
Received in revised form 19 April 2018
Accepted 27 April 2018
Available online 30 April 2018

Keywords:
Heteroleptic palladium (II) complexes
Anticancer
N,N,N′-trisubstituted acyl thioureas
Phosphine ligands

ABSTRACT

A series of palladium (II) complexes (**1–8**) with N-(acyl)-N′,N′-(disubstituted) thioureas and phosphine ligands were synthesized and characterized by FT-IR, multinuclear (^{1}H, ^{13}C & ^{31}P) NMR spectroscopy and elemental analysis. The crystal structures of the Pd(II) complexes (**1**) & (**5**) of the type Pd^{II}(L-*O*,*S*)(Ĺ-*P*)Cl were determined by single crystal X-ray diffraction analysis. They adopted the square planar geometry, where the N-(acyl)-N′, N′-(disubstituted) thioureas showed bidentate coordination mode in a chelating fashion through O and S donor atoms, and phosphine ligands through P atom at palladium centre. *In vitro* cytotoxic profile of the synthesized palladium(II) complexes (**1–8**) was determined against lung squamous carcinoma and breast adenocarcinoma cell lines. These complexes were also tested for promastigote forms of *Leishmania tropica* to evaluate their antileishmanial activity. The complexes bearing 2,4-dichlorophenyl moiety among the screened complexes were the most active with IC_{50} values 1.72 ± 0.27, 2.12 ± 0.44, 1.57 ± 0.16 μM against the targets MDA-MB-231, H-157, *Leishmania tropica*, respectively.

1. Introduction

In the past few decades, palladium (II) complexes have been focused due to their structural diversity, reactivities and applications, particularly in the field of anti-proliferative activities and organo-catalysis. Many researchers are exploring palladium complexes containing pharmacophoric fragments in order to design new bioactive anticancer metallo-drugs for cheaper and safer therapies. On the basis of the structural resemblances like square-planar geometry and oxidation state, and thermodynamic disagreement with platinum(II) complexes, there is much potential in the study of palladium(II) complexes as potential anticancer drugs, especially with chelating ligands of pharmaceutical interests [1–6].

Many attempts have been made towards the development of effective and less toxic transition metal based metallo-drugs for various therapeutic applications. Earlier reports from our group and others includes Co(III), Ni(II), Cu(I), Cu(II), Co(II), Pt(II), Ru(II) and Pd(II) complexes have shown promising biological activities, especially, as anticancer agents [7–17].

Having this in mind we have been interested in developing new ligands, such as acyl thioureas, containing N, S and O atoms with the tendency to form transition metal complexes. It has been observed that these ligands are able to bind a variety of metal ions in different coordination modes like S, O/Sand N/S, forming stable complexes. In most of the complexes containing acyl thioureas, they act as neutral monodentate S-coordinated [7] and bidentate O, S-monoanionic ligands [8,9].

In the last thirteen years, we are engaged in investigating the synthesis, reactivity and biological properties of a variety of

* Corresponding authors at: Office of Research, Innovation and Commercialization, Quaid-i-Azam University, Islamabad 45320, Pakistan (M.K. Rauf).
E-mail addresses: mkrauf@qua.edu.pk (M.K. Rauf), drjamshed@ciit.net.pk (J. Iqbal).

https://doi.org/10.1016/j.ica.2018.04.060
0020-1693/

N,*N*-di- and trisubstituted thioureas [18,19]. Therefore, as a part of our ongoing research to develop new bioactive metallo-drug candidates, here we are going to report the synthesis and biological activities of heteroleptic Pd(II) complexes containing O,S-chelating acylthioureas and phosphine ligands.

2. Experimental

2.1. Materials and measurements

All the chemicals were purchased from commercial sources (Daeyang Chemicals, South Korea & Sigma-Aldrich Chemicals) and were used as obtained. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer (4000–400 cm^{-1}). The ^{1}H and ^{13}C NMR were recorded on a Bruker 300 MHz internally referenced to TMS. Distilled $CDCl_3$ was used as solvent, unless mentioned otherwise. Elemental analyses (C, H, N, S) were carried out on a LECO, CHNS-932 elemental analyzer. The melting point was determined by the capillary tube method using an electro thermal melting point apparatus (MPD Mitamura Riken Kogyo) and is reported as recorded.

2.2. Synthesis of Pd(II) complexes (**1–8**)

A solution of *N,N,N'*-trisubstitutedacyl thiourea (0.564 mmol) and phosphine ligand (0.564 mmol) in a minimal amount of methanol, was added drop wise to a solution of K_2PdCl_4 (0.564 mmol) in 40 mL of methanol at 50–60 °C. The resulting mixture was stirred for 3–4 h and the precipitated complexes (**1–8**) (Scheme 1) were filtered, and washed with methanol. Single crystal X-ray diffraction measurement quality crystals were obtained by slow evaporation of chloroform/methanol (3:1) solution of the complexes. The ^{1}H and ^{13}C NMR, FT-IR, the elemental analyses, melting point data for the complexes (**1–8**) are as follows:

2.2.1. (1) *(Triphenylphosphine-κP)(1-(3-fluorobenzoyl)-3-(N-methylphenyl) thioureido-κ²(O, S)palladium(II) chloride*

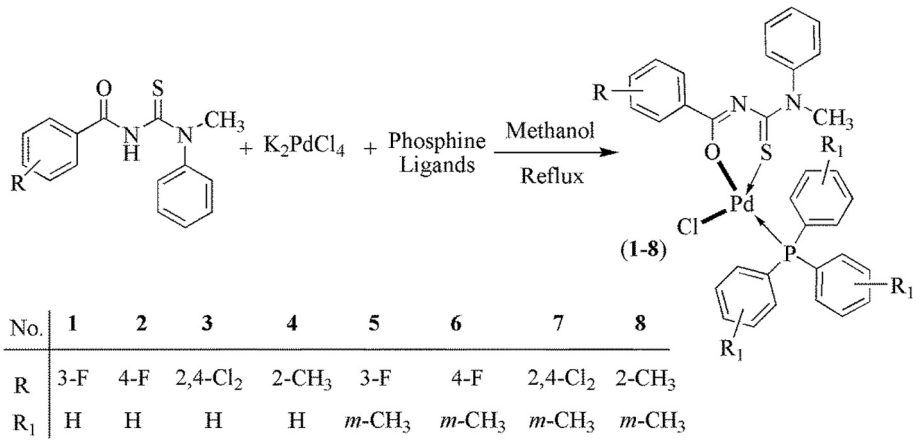
Quantities used were 0.184 g (0.564 mmol) K_2PdCl_4, 0.163 g (0.564 mmol) 1-(3-fluorobenzoyl)-3-(*N*-methylphenyl)thiourea, 0.148 g (0.564 mmol) triphenylphosphine in methanol. Yield ≥ 80%; Orange solid; m.p. 200–201 °C. FTIR (cm^{-1}) 3067(w), 3004 (w), 1636(m), 1508(s), 1419(s), 1369(m), 1315(w), 1293(w), 1249 (w), 1193(w), 1165(w), 1093(w), 1067(w), 1026(m), 999(w), 947 (s), 913(s), 860(s), 780(s), 690(s), 618(w); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3H, N-CH_3), 7.07–8.18 (m, 24H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.2 (C), 116.7 & 117.0 (d,1C, ^{13}C-^{19}F, ^{2}J = 22.50 Hz), 118.7 & 119.0(d, 1C, ^{13}C-^{19}F, ^{2}J = 21.5 Hz), 126.1 (C), 127.0 (C), 128.02 & 128.16 (d, 6C, ^{13}C-^{31}P, ^{2}J = 10.50 Hz), 128.2 (C), 129.3 (C), 129.6 (C), 129.9 (C), 130.5 (C), 131.2& 134.8 (d,^{13}C-^{19}F, ^{1}J = 270 Hz), 134.8 (C), 134.98 & 135.14 (d, 6C, ^{13}C-^{31}P, ^{3}J = 12.0 Hz), 135.2 (C), 171.9 (1C, C = O), 173.9 (1C, C = S); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 34.5; Anal. Calc. for $C_{33}H_{27}ClFN_2OPPdS$ (Mol. mass: 691.49) C, 57.32; H, 3.94; N, 4.05; S, 4.64. Found: C, 57.19; H, 3.87; N, 4.08; S, 4.59.

2.2.2. (2) *(Triphenylphosphine-κP)(1-(4-fluorobenzoyl)-3-(N-methylphenyl) thioureido-κ²(O, S)palladium(II) chloride*

Quantities used were 0.184 g (0.564 mmol) K_2PdCl_4, 0.163 g (0.564 mmol) 1-(4-fluorobenzoyl)-3-(*N*-methylphenyl)thiourea, 0.148 g (0.564 mmol) triphenylphosphine in methanol. Yield ≥ 80%; Orange solid; m.p. 202–204 °C. FTIR (cm^{-1}) 3141(w), 3000 (w), 1633(m), 1506(s), 1419(s), 1370(w), 1316(m), 1291(m), 1248(m), 1190(w), 1162(w), 1093(m), 1062(w), 1024(w), 998(w), 948(s), 913(s), 860(s), 781(s), 690(s), 615(w); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H, N-CH_3), 6.86–8.40 (m, 24H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.2 (1C), 114.7 & 115.0 (2C, d,^{13}C-^{19}F, ^{2}J = 21.8 Hz), 127.1 (1C), 127.6 (C), 128.05 & 128.20 (d, 6C, ^{13}C-^{31}P, ^{2}J = 11.25 Hz), 128.3(C), 129.5 (2C), 131.2 (6C), 132.7 &132.9 (2C, d,^{13}C-^{19}F, ^{3}J = 9.8 Hz), 134.8–134.9 (m, 4C)145.6 (1C), 155.7 (1C), 170.4 (1C, C = O), 173.9 (1C, C = S); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 34.5; Anal. Calc. for $C_{33}H_{27}ClFN_2OPPdS$ (Mol. mass: 691.46) C, 57.32; H, 3.94; N, 4.05; S, 4.64. Found: C, 57.15; H, 3.87; N, 4.06; S, 4.60.

2.2.3. (3) *(Triphenylphosphine-κP)(1-(2,4-dichlorobenzoyl)-3-(N-methylphenyl)thioureido-κ²(O, S)palladium(II) chloride*

Quantities used were 0.184 g (0.564 mmol) K_2PdCl_4, 0.192 g (0.564 mmol) 1-(2,4-dichlorobenzoyl)-3-(*N*-methylphenyl)thiourea, 0.148 g (0.564 mmol) triphenylphosphine in methanol. Yield ≥ 80%; Orange solid; m.p. 220–221 °C. FTIR (cm^{-1}) 3068(w), 2962 (w), 1638(m), 1594(m), 1509(s), 1420(s), 1370(w), 1315(w), 1292 (w), 1247(w), 1193(w), 1164(w), 1093(w), 1068(w), 1023(w), 993(w), 948(s), 913(s), 861(s), 781(s), 690(s), 619(w); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (s, 3H, N-CH_3), 7.04–8.00 (m, 23H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.6 (C), 126.7 (C), 126.9 (C), 127.5 (C), 128.04 & 128.19 (d, 6C, ^{13}C-^{31}P, ^{2}J = 11.3 Hz), 129.6 (3C), 130.4 (2C), 131.2 (3C), 133.3 (2C), 134.0 (C),134.3(C), 134.77 & 134.91 (d, 6C, ^{13}C-^{31}P, ^{3}J = 10.5 Hz), 135.4(C), 136.2 (C), 145.2 (C), 171.4 (1C, C═O), 174.0 (1C, C═S); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 34.5; Anal. Calc. for $C_{33}H_{26}Cl_3N_2OPPdS$ (Mol. mass: 742.39) C, 53.39; H, 3.53; N, 3.77; S, 4.32. Found: C, 53.19; H, 3.46; N, 3.76; S, 4.27.



No.	1	2	3	4	5	6	7	8
R	3-F	4-F	2,4-Cl_2	2-CH_3	3-F	4-F	2,4-Cl_2	2-CH_3
R_1	H	H	H	H	*m*-CH_3	*m*-CH_3	*m*-CH_3	*m*-CH_3

Scheme 1.