Asian Journal of Chemistry Vol. 11, No. 4 (1999), 1543–1545

NOTE

Synthesis and Cytotoxic Activity of Some Novel *trans*-Palladium Complexes with Pyrazole Derivatives†

TALAL A.K. AL-ALLAF* and LUAY J. RASHAN‡
Department of Chemistry, College of Science;
Applied Science University, Amman-11931, Jordon

Novel palladium(II) complexes of the general formula *trans*-$[PdL_2Cl_2]$, where L is a pyrazole derivative, have been prepared and characterized physico-chemically and spectroscopically. It was shown that pyrazole derivatives coordinate with palladium in a monodentate fashion *via* the most reactive nitrogen site. The cytotoxic activity of these complexes was evaluated *in vitro* against four cell-lines using the MTT-assay, one fluid suspension (P388, leukaemia) and three solid human cell lines (Hep-2, larynx; RD, embryonal rhabdomyosarcoma and HeLa, cervical cells). One of these complexes, for example, demonstrated a potent cytotoxic activity against P388 and significant cytotoxicity against the other three-cell lines in comparison with the reference standards: cisplatin, carboplatin, oxaliplatin and 5-FU.

Pyrazole derivatives and their metal complexes represent an important target for most researchers due to their chemical and biological importance and hence these were covered by many review articles[1,2]. On the other hand, metal complexes of pyrazole-based ligands are known to play a significant role in many biological processes including antibacterial and antitumour activities[3–6]. As a group of researchers, we took part in the chemistry of pyrazole and its coordination complexes, as it is a rather popular ligand, and several articles were so far reported[7–9]. Recently, we reported the cytotoxic activity of some new class of platinum complexes of 3,5-dimethylpyrazole[10]. As a part of our interest we are presenting herein the synthesis of *trans*-$[PdL_2Cl_2]$ complexes, where L represents pyrazole-5-ones, pyrazoles, arylhydroxy pyrazoles and pyrano pyrazole (Fig. 1) Preliminary work was presented in part, at an international congress.

Pyrazole-5-ones, pyrazoles, arylhydroxy pyrazoles and pyrano pyrazoles were prepared as described in our article[8] and the *trans*-dichloro-bis(dimethylsulphoxide)palladium(II) complex; *trans*-$[Pd(DMSO)_2Cl_2]$ was prepared according to established method compiled in our recent article[11].

Preparation of complexes

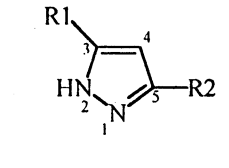
These were prepared according to the following equation:

$$trans\text{-}[Pd(DMSO)_2Cl_2] + 2L \rightarrow trans\text{-}[PdL_2Cl_2] + 2DMSO$$

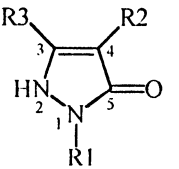
L = pyrazole derivative.

†Paper presented at 9th International Congress on Anticancer Treatment, 2–5 February 1999, Paris, France.

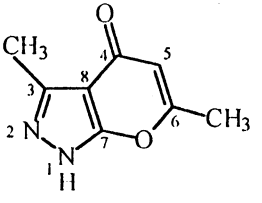
‡Department of Pharmacology, College of Pharmacy, Applied Science University, Amman-119 31, Jordan. Both authors are on leave from the University of Mosul, Iraq.

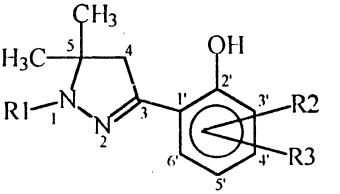


R1 = R2 = H or CH_3
R1 = CH_3, R2 = C_6H_5



R1 = H, R2 = R3 = CH_3
R1 = R3 = H, R2 = CH_3
R1 = C_6H_5, R2 = CH_3, R3 = H
R1 = R2 = CH_3, R3 = H





R1 = C_6H_5, R2 = 3'-OCH_3, R3 = 5'-OCH_3
R1 = H, R2 = 3'-CH_3, R3 = 4'-CH_3

Fig. 1. The pyrazole derivatives used in the coordination with palladium

The complex *trans*-$Pd(DMSO)_2Cl_2$] was suspended in chloroform or ethanol and two-molar equivalent of the pyrazole derivative was added to the suspension. The mixture was stirred vigorously under moderate heating for several hours and in the mean time, the suspension turned clear-coloured solution. Slow evaporation of some of the solvent leaves the crystalline product. The crystals were separated by filtration, washed several times with *n*-hexane and dried in vacuum at *ca.* 60°C for several hours. The yield an almost all complexes is quantitative.

The *trans*-palladium complexes of pyrazole derivatives have been identified by their physical properties, *i.e.*, ^1H, ^{13}C NMR and IR spectral data, and by thier CHN elemental composition. The data obtained confirm the suggested formula *trans*-[$Pd(pyrazole)_2Cl_2$]. Pyrazole derivatives were found to coordinate with palladium *via* the most reactive nitrogen site of the ligand to give Pd(II) complexes of square planar structures[11], as shown below:

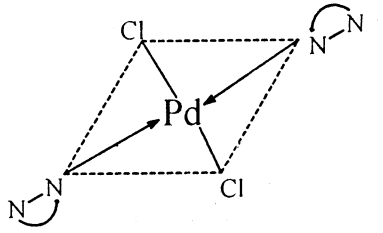


Fig. 2

where N–N *is a pyrazole derivative* (Fig. 2.)

Evaluation of Cytotoxicity

The cytotoxic evaluation of the complexes *in vitro* was carried out against four tumour cell lines using the MTT-assay as described in our previous articles.[9–12]

The palladium-pyrazole complexes were purified by the successive crystallizations from proper solvents before used for their cytotoxic activity. One of the cell lines used is a fluid suspension animal-cell line (lymphocytic leukeamia, P388), whereas, the other three cell lines are human solid cell lines (the larynx, Hep-2; the embryonal rhabdomyosarcoma, RD and the cervix, HeLa cell lines).

The *in vitro* cytotoxic results of these complexes were obtained with mixed success, but one of these complexes demonstrated a potent cytotoxicity, against the cell lines used, compared with that of the reference standards used in this study, as shown in the following Table:

Compound	IC_{50} ($\mu g\ mL^{-1}$)			
	HeLa	Hep-2	RD	P388
trans-[Pd(Pyrazole)$_2$Cl$_2$]	1.5	5.0	2.0	0.12
Cisplatin	1.8	3.0	6.0	0.14
Carboplatin	6.0	>10	>10	>10
Oxaliplatin	9.0	8.0	>10	>10
5-FU	NT*	NT*	NT*	0.12

*NT : Not tested

It is obvious from the Table that the cytotoxicity of the palladium complex against P388 cell-line ($IC_{50} = 0.12\ \mu g\ mL^{-1}$) is almost similar to those of cisplatin ($IC_{50} = 0.14\ \mu g\ mL^{-1}$) and 5-FU ($IC_{50} = 0.12\ \mu g\ mL^{-1}$). In addition, a significant cytotoxicity was also demonstrated against HeLa, RD and Hep-2 cell lines (IC_{50} = 1.5, 2.0 and 5.0 $\mu g\ mL^{-1}$, respectively) when compared with the IC_{50} of cisplatin against the same cell-lines (IC_{50} = 1.8, 6.0 and 3.0 $\mu g\ mL^{-1}$, respectively). On the other hand, it appears that this Pd complex possesses at least one order of magnitude better activity than those of carboplatin and oxaliplatin against the four cell lines used. However, further *in vivo* tests are required to confirm these results.

REFERENCES

1. S. Trofimenko, *Chem. Rev.*, 943 (1993).
2. A.P. Sadimenko and S.S. Basson, *Coord. Chem. Rev.*, **147**, 247 (1996).
3. M.J. Clear, *J. Clin. Hematol. Oncol.*, **7**, 1 (1977).
4. K.R. Harrap, *Platinum Met. Rev.*, **28**, 14 (1984).
5. Tanabe Seiyaku Co. Ltd., Platinum Complexes for Cancer Treatment, *Eur. Appl.*, **115**, 929; *Platimum Met. Rev.*, **29**, 48 (1985).
6. M.S. Stianker, B.R. Rao, G.P.V.C. Mouli and Y.D. Reddy, *J. Indian Chem. Soc.*, **59**, 1104 (1982).
7. T.A.K. Al-Allaf, M.T. Ayoub and R.I. Al-Bayati, *Inorg. Chim. Acta*, **147**, 185 (1988).
8. T.A.K. Al-Allaf and R.I. Al-Bayati, *Asian J. Chem.*, **7**, 465 (1995).
9. T.A.K. Al-Allaf, R.I. Al-Bayati and A.S. Al-Botany, *Asian J. Chem.*, **8**, 489 (1996); *ibid.*, **10**, 297 (1998).
10. T.A.K. Al-Allaf, L.J. Rashan, R.F. Khuzaie and W.F. Halaseh, *Asian J. Chem.*, **9**, 239 (1997).
11. T.A.K. Al-Allaf and L.J. Rashan, *Eur. J. Med. Chem.*, **33**, 817 (1998).
12. ———, *Asian J. Chem.*, **10**, 342 (1998).

(*Received*: 28 May 1999; *Accepted*: 3 August 1999) AJC-1835