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Synthesis and Antitumor Effect of Two New Pd(II) Complexes on a Newly Established Non-Small Cell Lung Cancer (NSCLC) Cell Line

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Objectives: Non-small lung cancer is the leading cause of cancer-related mortality in the worldwide. For a deeper understanding of tumor biology, cell lines are widely used for in vitro and in vivo analyses of carcinogenesis, as well as in the development of new therapies. The aims of this study are 1- To establish a primary NSCLC cell line and 2- To assess antitumor activities of two novel palladium complexes comparing to cisplatin on a newly established primary cell line.

Methods: 1- Establishment of primary cell line: The lung tumor specimens derived from a pathologist approved squamous cell carsinoma of 61-year-old male patient. Small fragments of the tumor tissue (1 mm^3) washed twice in PBS and re-suspended in cell culture medium (RPMI-1640 supplemented with 10% fetal bovine serum (FBS) and 1%, 200 IU/ml penicillin-streptomycin) then plated in flasks. The cells were cultured under standard conditions at 37°C with 5% CO2. Cell-culture medium was replaced every 3-5 days, the cells were cultivated for 20 passages to eliminate fibroblasts.
2- Synthesis of novel Pd(II) complexes: The reaction of ligand (1.0 mmol) 1-(2-(bis(3,5-dimethylphenyl)phosphinyl) phenyl)-N-phenylmethanimine and 1-(2-(bis(3,5-dimethylphenyl) phosphinyl)phenyl)-N-2,6-diisopropylphenylmethanimine with dichloro(1,5-cyclooctadiene)palladium(II) (1.0 mmol) [Pd(COD)Cl2] in CH2Cl2 (50 mL) at room temperature gave K7 and K8, respectively. The novel Pd(II) complexes (K7 and K8) fully characterized using spectroscopic and analytical methods, including 31P, 1H, 13C, 19F NMR, FTIR and high resolution mass spectroscopy (HRMS).
3- Cell viability tests: The cytotoxic activities of the complexes were evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, after incubation with different concentrations (0 to 100 μM) of the compounds for 7SA and A549 cell lines. IC50 values were analyzed using Prism V6 program.
4- Apoptosis assays: After incubation with compounds, cells were stained with Annexin V and Propidium Iodide (PI) and analyzed via flow cytometry.

Results: K7 K8 and Cisplatin were dissolved in DMSO at 10mM concentrations. IC50 values of compounds K7, K8 and cisplatin are determined as 13μM, 48 μM and 14 μM respectively for 48h incubation with 7SA cells. Flow cytometry results showed a significantly shift in Annexin V: FITC positive population in the 7SA of K7 (13μM), K8 (47μM) and cisplatin (14μM)-treated cells compared to that of the control groups. Experiments were also repeated with A549 cells.

Conclusion: According to the findings of this study, the novel Pd complexes has potential as anticancer agents and patient derived cell lines can be used for further studies.

Keywords: Palladium complexes, primary cells, NSCLC, cytotoxicity, antitumor