Chiral platinum(II) and palladium(II) phenanthridine-phosphine complexes: DNA interaction and cytotoxic activity

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The selectivity and specificity of chiral molecules in nature make them of great interest for understanding the behavior of bioactive molecules, by providing information about the chiral discrimination[1]. We present the synthesis and characterization of twelve chiral platinum(II) and palladium(II) complexes with phenanthridine and phosphine ligands with the general formula $[MCl(P)_2(PHD)]PF_6$, (where M = Pt or Pd, $(P)_2$ = triphenylphosphine (PPh_3) (**1,7**), 1,1-bis(diphenylphosphino)methane (dppm) (**2,8**), 1,2-bis(diphenylphosphino)ethane (dppe) (**3,9**), 1,3-bis(diphenylphosphino)propane (dppp) (**4,10**), 1,4-bis(diphenylphosphino)butane (dppb) (**5,11**), 1,1'-bis(diphenylphosphino)ferrocene (dppf) (**6,12**). These complexes displayed an axial chirality, generated by the rotation of the Metal-N bond (atropisomerism), evidenced in the X-ray structures (Figure 1), behavior reported for other phenanthridine complex[2]. The interactions of the phenanthridine-phosphine complexes with DNA were studied by circular dichroism, viscosity measurements and electrophoresis in gel. These experiments showed that all complexes interact strongly with the DNA. Additional assays were performed in order to investigate the cytotoxicity of the compounds against five tumor cells lines: B16-F10 (murine melanoma), HepG2 (human liver), HL-60 (human promyelocytic leukemia), K562 (human erythroleukemic), A549 (human lung) and non-tumor cells PBMC (peripheral blood mononuclear). The results displayed that the complexes *cis*-$[PtCl(PPh_3)_2(PHD)]PF_6$ (**1**) (IC_{50} HL-60 7.74 μM) and $[PdCl(dppm)(PHD)]PF_6$ (**8**) (IC_{50} A549 1.62 μM), showed the best antiproliferative activity and selectivity, showing that they are promising as anticancer drugs.

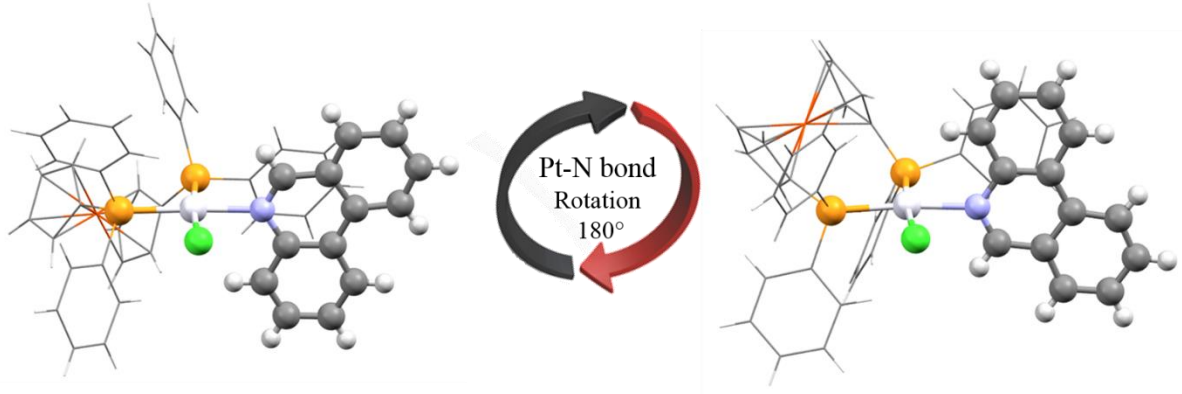

Figure 1. Crystal structure of $[PtCl(dppf)(PHD)]PF_6$ emphasizing the orientation of the phenanthridine ligand.

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2. Johnstone, T. C.; Lippard, S. J.; *J. Am. Chem. Soc.* **2014**, *136, 2126.*

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