Synthesis and Characterisation of Novel Pt(IV) Complexes as Potential Anticancer Prodrugs

Dina Tolan,[1, 2] Diego Montagner,[1] Valentina Gandin,[3] Ahmed El-Nahas,[2] Andrea Erxleben[1]

[1] *School of Chemistry, National University of Ireland (NUIG), Galway, Ireland.*
[2] *Department of Chemistry, Faculty of Science, El-Menoufia University, Shebin El-Kom, Egypt.*
[3] *Departement of Pharmaceutical Science, University of Padua, Italy.*
d_tolan2005@yahoo.com

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Abstract

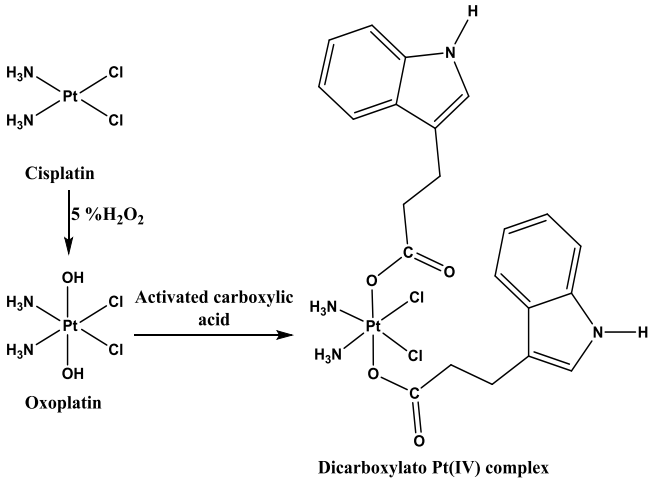
Pt(IV) prodrugs are an important class of molecules that might improve the pharmacological properties of the active Pt(II) compounds that are currently used as anticancer agents. This manuscript describes the synthesis, characterization, DFT studies and biological analyses of ten novel Pt(IV) complexes as cisplatin prodrugs with indole-3-acetic acid and indole-3-propionic acid as axial ligands.

Introduction

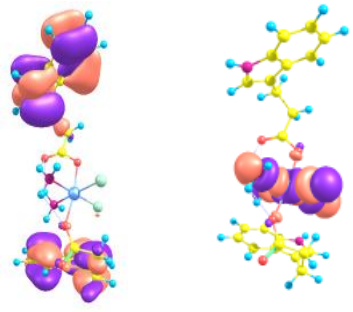
Platinum(II) complexes, cisplatin, carboplatin and oxaliplatin, are the most important anticancer drugs used in chemotherapy even if several drawbacks such as the high toxicity and poor stability restrict their usage [1]. Octahedral Pt(IV) complexes are promising candidates that can act as prodrugs for Pt(II) agents by intracellular reduction to the corresponding Pt(II) counterparts. Pt(IV) complexes are used to overcome Pt(II) drugs limitations by resisting premature aquation and binding to essential plasma proteins. Their axial ligands, that are detached during cellular activation by reduction, can be used to tune important pharmacological properties of the complexes. Furthermore, the axial coordination sites can serve as binding sites for other biologically active ligands [2]. These class of Pt(IV) complexes are of particular interest for the design of dual-threat pharmaceutical agents, which combine two biologically active components into a single molecule. The antioxidant properties of indole compounds have received considerable attention. Indole-3-acetic acid and indole-3-propionic acid plays a vital role in medicinal chemistry as anticancer and antioxidant agents [3].

Aim & Results

This project describes the synthesis, characterization and biological analyses of ten new Pt(IV) complexes as cisplatin prodrugs with indole-3-acetic acid and indole-3-propionic acid as biologically active axial ligands. The complexes were synthetized by the reaction of oxoplatin with the corresponding activated carboxylic acid of the ligands (**Scheme. 1** for indole propionic acid). The complexes have been characterized by elemental analysis, ESI-MS, FT-IR and ^{1}H, ^{13}C and ^{195}Pt NMR spectroscopy. The lipophilicity of the complexes was investigated using shake flask method. The reduction of the complexes was monitored via HPLC with the release of the axial ligands in the presence of ascorbic acid. Density functional theory (DFT) studies were undertaken to investigate the electronic structures of the complexes and to determine their adiabatic electron affinities (**Fig. 1**). Preliminary biological results show promising activity of the novel complexes toward several cancer cell lines and in particular Human Ovarian 2008.



Scheme 1: Synthesis of the Pt(IV) complexes.



HOMO **LUMO**

Figure 1: Frontier orbitals of dicarboxylato Pt(IV) complex with indole propionic acid ligand .

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