COMPARISON OF DIFFERENT AROMATIC Pt(IV) COMPLEXES AS ANTITUMOR PRODRUGS

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Background

In the recent years octahedral Pt(IV) complexes have emerged as an alternative to the traditional square planar cisplatin-like Pt(II) compounds as anticancer drugs. They are generally considered antitumor prodrugs that can be reduced *in vivo* (in the hypoxic and acidic tumor milieu) to their active Pt(II) metabolites (Figure 1). Axial carboxylato ligands having long hydrocarbon chains or lipophilic aromatic rings are known to enormously improve the cell uptake, offering the best results in terms of *in vitro* potency of the resulting Pt(IV) compounds.

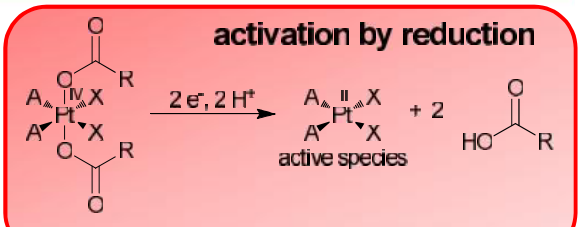

Figure 1: Proposed mechanism of activation of the Pt(IV) complexes *in vivo*

The aim of this work has been the synthesis, characterization and the evaluation of the antiproliferative activity of two small series of Pt(IV) complexes having the "$[Pt(Am)_2Cl_2]$" (Am = 2×NH_3 series **1**, or cyclohexane-1,2-diamine, dach, series **2**, Figure 1) moiety as equatorial arrangement and bearing axial aromatic carboxylato ligands with different length of the spacer.

Synthesis and crystal structure analysis of complex 1b

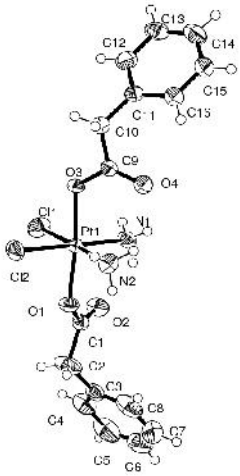

Figure 3. ORTEP plot of compound **1 b**.

The Pt(IV) coordination geometry is a distorted octahedron; in particular, the two carboxylate moieties have different orientations with respect to the equatorial coordination plane. The non-coordinated O4 is involved in tight hydrogen bonds with both the ammine groups bound to the Pt while the analogous O2 of the other phenylacetate group forms a single hydrogen bond with only one ammine nitrogen.

Synthetic pathway:

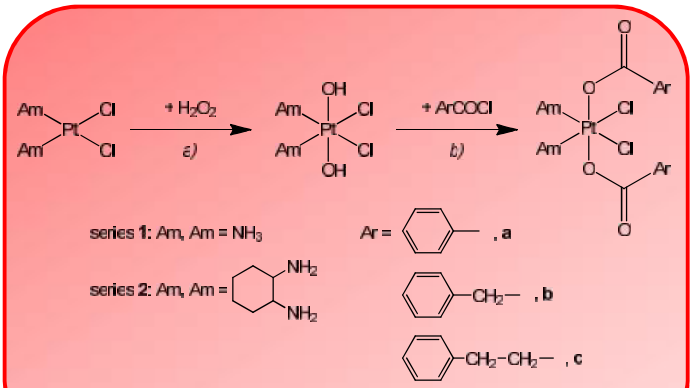

Figure 2. Synthetic route to prepare Pt(IV)-carboxylatos: *a)* H_2O_2 35%, water, RT, 24 h; *b)* acetone, reflux 4 h.

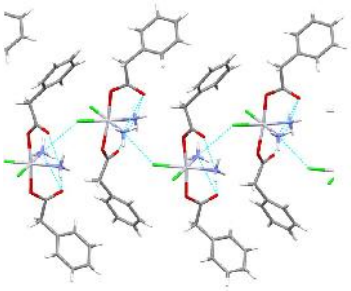

Figure 4. Intramolecular and intermolecular hydrogen bonds between adjacent molecules along the b direction.

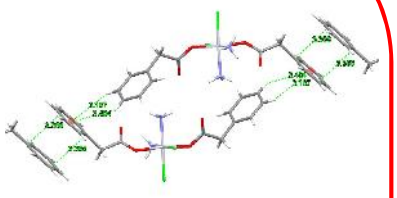

Figure 5. Phenyl-phenyl interactions in the packing of compound **1b.**

The other ammine nitrogen is involved in an additional hydrogen bond with a chlorine of an adjacent molecule producing a ribbon of molecules (the basic pattern of the crystal packing, (Figure 4).

Moreover, the phenyl rings of one molecule interact through face-to-edge interactions with a second molecule to form dimers. Further weak interconnections can be noticed between dimers through phenyl face-to-face interactions and the combination of these two π-π interactions provides a secondary pattern in the crystal packing (Figure 5).

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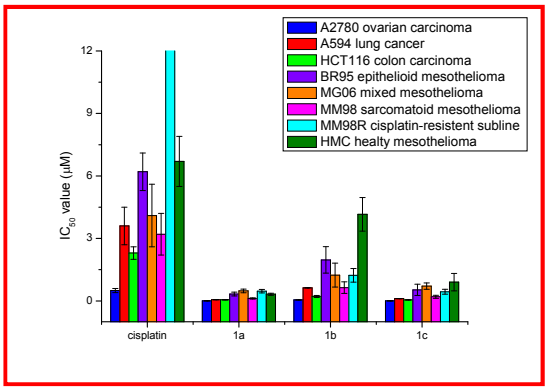

Figure 6: IC50 values for the serie of complexes **1** and the respective Pt(II)

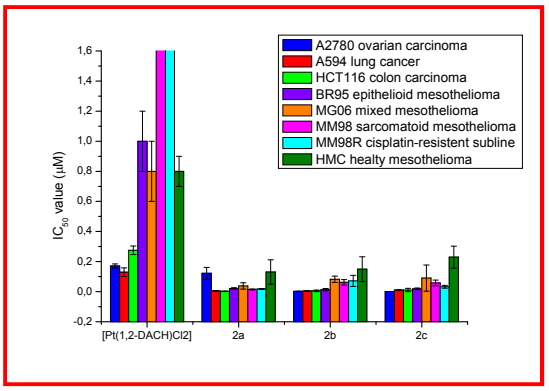

Figure 7: IC50 values for the serie of complexes **2** and the respective Pt(II)

All Pt(IV) complexes are more active than their respective Pt(II) counterparts on all the cell lines. It is worthy to observe that complexes **2** are slightly more cytotoxic than complexes **1**.

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