A versatile method for the oxidative chlorination of Pt(II) antitumour drugs

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Introduction

The platinum(II) complexes are the most important drugs in anticancer chemotherapy. In recent years more attention has been paid to Pt(IV) complexes as anticancer pro-drugs [1]. These complexes can be reduced *in vivo*, through a two electron reduction, in the hypoxic, reducing environment of the tumour tissue so that the octahedral Pt(IV) complexes are transformed into the active square-planar Pt(II) metabolites by loss of the axial ligands. Pt(IV) complexes exhibit greater chemical inertness than their Pt(II) counterparts and undergo fewer side reactions with biomolecules. The choice of the ligands is essential to modulate their lipophilicity (and related cellular uptake) and their redox properties. The axial ligands may also be biologically active molecules themselves or also only chemical linker from the Pt core to the active molecule [2]. Therefore, it is useful to have two different axial ligands: the former can be used for the coupling with drug delivery vectors, while the latter may be used to modulate the reduction potential (e.g. chloride can facilitate the reduction respect to an alkoxide ligand).

It's important for a potential antitumor drug targeted molecule, show different kind of functional group that can be used for the coupling to the active vector.

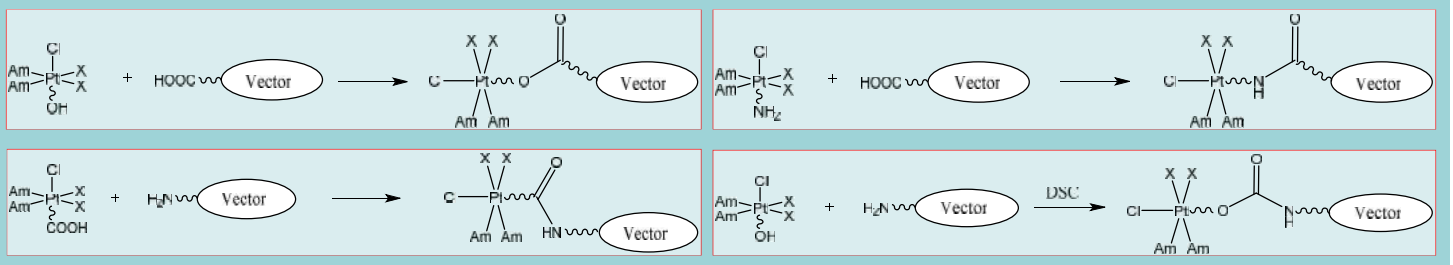

Fig X : General coupling reaction of a Pt(IV) complex to an appropiate vector

Synthesis

Pt(IV) complexes are usually prepared by oxidation of the corresponding Pt(II) counterparts, typically using hydrogen peroxide or chlorine. A different way to oxidize the Pt(II) compounds is represented by the use of N-chlorosuccinimide [3]. The reaction between Pt(II) complexes and this reagent in different coordinating solvents was set up to get the final asymmetric complex $[PtA_2ClX_2(Solv)]$. The solvent is crucial for the product that we want to obtain.

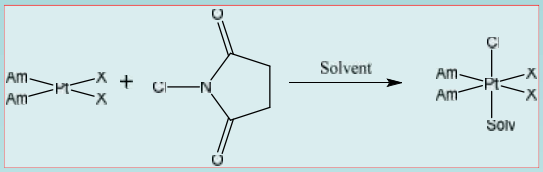

Fig X : General oxidation reaction for this Pt(II) complexes

The reaction between (DACH)(CBDC)platinum(II) and N-chlorosuccinimide in the corresponding solvent was set up to get the final asymmetric complex reported in figure in high yield and purity. The synthesis of complex **4** is performed in acetone (a non coordinating solvents) but the presence of traces of water (humidity) produces in any case complex **2** that act as an intermediate that reacts through nucleophilic attack to the succinic anhydride to give the final asymmetric Pt(IV) complex.

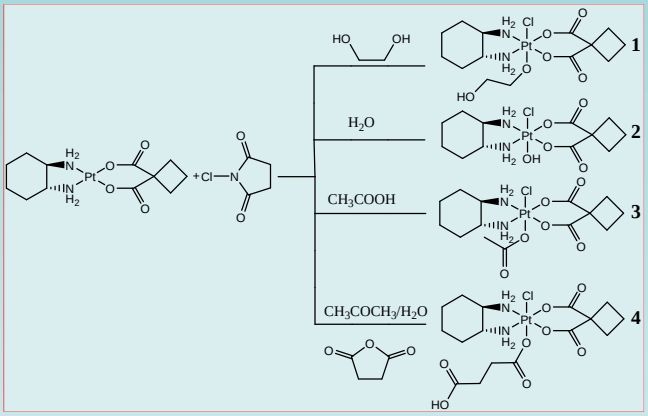

Fig X: Complexes synthesized by oxidation with N-chlorosuccinimmide

Characterization

All of these complexes have been characterized by HPLC-MS and NMR spectroscopy to confirm the formation of Pt(IV) complexes with solvent moiety as axial ligands.

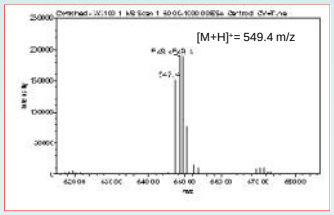

Fig : Mass spectra of compound 1 (MW = 547.9 uma)

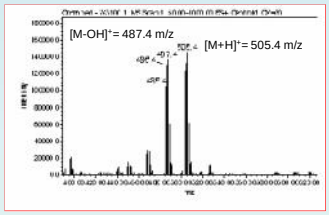

Fig : Mass spectra of compound 2 (MW = 503.9 uma)

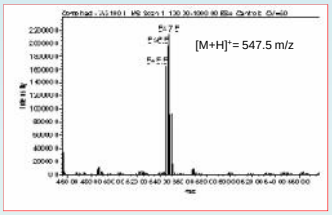

Fig : Mass spectra of compound 3 (MW = 545.9 uma)

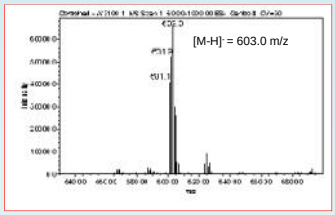

Fig : Mass spectra of compound 1 (MW = 603.9 uma)

Perspectives

In this work we have reported the synthesis of four new asymmetric platinum IV complexes with a chlorine and a solvent molecule as axial ligands, except the complex **3**, other complex present functional groups that can be used for the linking to a wide variety of vectors (e.g . nanomaterial or active species). The future of this work is the efficient coupling of this prodrug to an opportune species suitable in the context of the drug delivery strategy.

References

[1] Hall, M.D.; Hambley, T.W. Coord. Chem. Rev. 2002, 232, 49-67.

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