ANTICANCER 8-HYDROXYQUINOLINE-AMINO ACID HYBRIDS AND THEIR HALF-SANDWICH Ru AND Rh COMPLEXES: SOLUTION CHEMISTRY AND INTERACTION WITH BIOMOLECULES

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Abstract

Development of novel chemotherapeutic agents aims to obtain more effective and selective compounds. Platinum(II)-containing chemotherapeutics have been widely used for decades in cancer therapy against solid tumors due to their effectiveness; although, their use is accompanied by drawbacks such the serious side-effects and resistance [1]. To overcome these problems, efforts have been made to find better alternatives such as the complexes of other platinum metals. 8-hydroxyquinolines and their metal complexes are widely investigated due to their anticancer properties [2,3]; however, they often have limited water solubility. In this work two novel water-soluble 8-hydroxyquinoline-D-amino acid hybrids, [(R)-1-((5-chloro-8-hydroxyquinolin-7-yl)methyl)pyrrolidine-2-carboxylic acid (8HQCl-D-Pro) and its homologue 8HQCl-D-hPro (Chart 1), and their $[Ru(\eta^6\text{-}p\text{-cymene})(H_2O)_3]^{2+}$ and $[Rh(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$ complexes were developed.

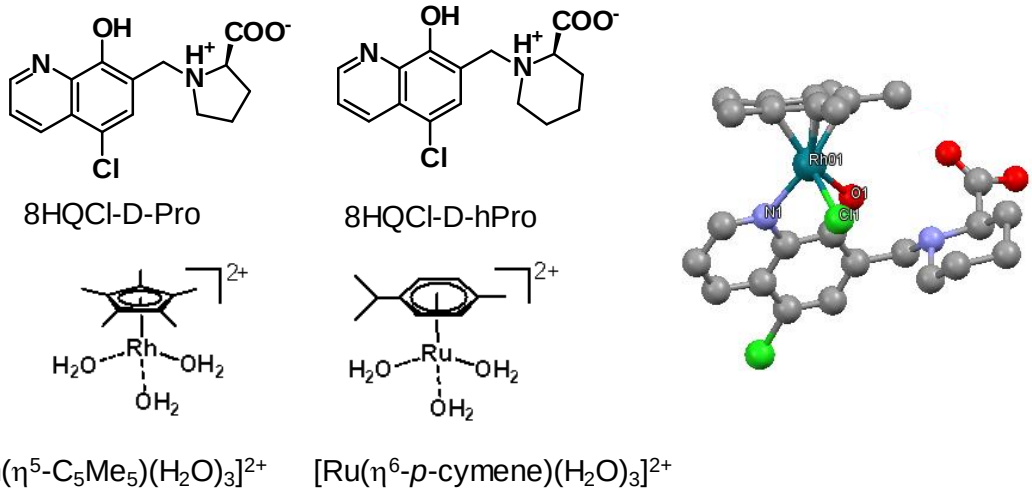

Chart 1. Chemical structure of the ligands and the organometallic triaqua cations and ORTEP view of the complex $[Rh(\eta^5\text{-}C_5Me_5)(8HQCl\text{-}D\text{-}hPro)Cl]$

An 8-hydroxyquinoline-L-proline hybrid and its half-sandwich complexes have already been investigated in our group [4]; herein, we aimed to investigate (i) the impact of changing the structure (proline *vs.* homoproline) and chirality (L *vs.* D) of the ligand on the anticancer activity, (ii) solution chemical properties, (iii) complex formation with $[Ru(\eta^6\text{-}p\text{-cymene})(H_2O)_3]^{2+}$ and $[Rh(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$ (Chart 1) as well as (iv) the interactions with biomolecules such as human serum albumin (HSA) and calf-thymus DNA (ct-DNA).

The coupling of 5-chloro-8-hydroxyquinoline with D-proline or D-homoproline was achieved via a modified Mannich reaction in methanol under reflux conditions. The ligands and the metal complexes were synthesized similarly as the analogous 8HQCl-L-Pro and its complexes in our previous work [4].

Proton dissociation processes of the ligands and complex formation equilibria were characterized using pH-potentiometry, UV-visible spectrophotometry and ^{1}H NMR spectroscopy in pure water in the absence of chloride ions. Based on the pK_a values determined for 8HQCl-D-Pro and 8HQCl-D-hPro, it was concluded that these ligands are neutral at physiological pH; however, due to their zwitter-ionic structure at the proline moiety they possess excellent water-solubility. The complex formation process was much slower with $[Ru(\eta^6\text{-}p\text{-cymene})(H_2O)_3]^{2+}$ in comparison to $[Rh(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$, and all the metal complexes were characterized by high solution stability in the whole pH range studied. The ligand coordinates via (N,O) donor atoms to the metal centers, which was confirmed by the X-ray crystallographic analysis of the complex $[Rh(\eta^5\text{-}C_5Me_5)(8HQCl\text{-}D\text{-}hPro)Cl]$ (Chart 1). The proton dissociation of the coordinated water and the non-coordinated proline-NH^+ of the bound ligand was characterized by such high pK_a values that their deprotonation does not take place at pH 7.4. The logK' values determined for the H_2O/Cl^- exchange process were significantly higher in case of the $Rh(\eta^5\text{-}C_5Me_5)$-complexes representing their stronger chloride ion affinity. Lipophilicity of the homoproline derivative 8HQCl-D-hPro was higher than 8HQCl-D-Pro, and the same trend was observed for the metal complexes as well. The higher chloride ion concentration of the medium increases the lipophilicity of the complexes due to the higher fraction of the neutral chlorido complex.

Interaction of the organometallic complexes of 8HQCl-D-Pro and 8HQCl-D-hPro with HSA and ct-DNA was investigated using of UV-visible spectrophotometry, spectrofluorometry, ^{1}H NMR spectroscopy and capillary zone electrophoresis (CZE), and results were compared to those of the analogous 8HQCl-L-Pro compounds. Formation of the complex-HSA adducts was much slower for $Ru(\eta^6\text{-}p\text{-cymene})$ complexes. No ligand release was found upon the protein binding. Our studies suggest the coordination nature of the binding, most likely a histidine nitrogen donor atom of the protein coordinates to the metal center. This suggestion was supported based on the results obtained with histidine-containing model oligopeptides. The complexes have similar and strong affinity towards HSA according to the fluorometric and CZE measurements. They also interact with ct-DNA however, significant differences were found between the complexes of the D-proline and the L-proline derivatives.

Cytotoxicity of the ligands as well as their complexes was measured *in vitro* against human cancer cells and normal cells. Both ligands showed significant cytotoxicity in Colo 205 and Colo 320 adenocarcinoma cells (IC_{50} = 12 – 17 μM). The $Rh(\eta^5\text{-}C_5Me_5)$-complexes display similar or a somewhat lower toxicity (IC_{50} = 19 – 34 μM) than the ligands; however they were more selective against the cancer cells. The $Ru(\eta^6\text{-}p\text{-cymene})$ complexes were ineffective against both cancer cell lines, possibly due to the loss of the arene ring.

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