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Abstract

Title

Preparation and characterization of different metal complexes of amino hydroxy-9,10-anthraquinones: Computational, spectroscopic, electrochemical and biophysical studies

Submitted by
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Anthracylines and their analogues, that includes metal-complexes exhibit extra-ordinary role as chemotherapeutic agents in the treatment of various forms of human cancers. The presence of a planar anthraquinone ring with a sugar residue was identified to play a significant role in healing ovarian, bladder, Hodgkin's and non-Hodgkin's lymphomas,Wilmi's tumour and neuroblastoma. Although anticancer features and drug functioning mechanism of such anthracyclines and their derivatives including those of metal complexes are well investigated, some ambiguity exists owing to high price and severe cardio-toxic features with an unexpected multi-drug resistance (MDR) that restrict frequent use by oncologists. To overcome such limitations, various attempts have been made by several research groups to arrive at suitable alternatives of anthracyclines, particularly those that have low cardiotoxicity and other side effects either through structural modification or synthesis of metal-anthracyclines complexes.

In the present study, sodium 3-amino-2-hydroxy-9,10-anthraquinone-1-sulphonate (AQSH) was initially prepared and characterized. Its Cu^{II} and Ni^{II} complexes and a Co^{III} complex of 1-amino-4-hydroxy-9,10-anthraquinone were prepared. These were characterized by elemental analysis, UV-Vis spectroscopy, fluorescence spectroscopy, FTIR spectroscopy, mass spectrometry, PXRD and theoretical studies, with the help of which their binding to metal ions were identified and compared with that reported for standard anthracyclines.

Cu^{II} forms 1:2 and Ni^{II} forms 1:1 metal-ligand complexes with 3-amino-2-hydroxy-9,10-anthraquinone-1-sulphonate while Co^{III} forms a ternary (1:3) complex with 1-amino-4-hydroxy-9,10-anthraquinone.

In the current study, different methods were employed to obtain single crystals of metal complexes taking different compositions of solvents. However, all efforts to obtain an appropriate single crystal failed; the planarity of the anthraquinone unit in these complexes could possibly be a hindrance in procuring single crystals. For this reason, an effort was made to characterize the 1:3 Co^{III} complex of 1-amino-4-hydroxy-9,10-anthraquinone theoretically using density functional theory (DFT) based on experimental evidence obtained like elemental analysis, IR spectroscopy, mass spectrometry, powder X-ray diffraction, molecular spectroscopy

and electrochemistry. DFT helped to generate energy optimized structures. Various essential parameters of the complex were obtained from such theoretical studies.

Electrochemical studies on the chosen analogues and their metal complexes in aqueous and organic solvents having different polarity were performed using cyclic voltammetry. Several electrochemical parameters were evaluated to find out the actual mechanism of electrochemical reduction. These were then compared with those of the different standard drugs. This is crucial for determining the biochemical and biophysical action of chosen molecules. Electrochemical behavior indicates that experimental compounds mimic action of standard anthracycline drugs. To see whether such molecules permeate biological membranes, studies on interaction with surfactant micelles were performed. Mode of interaction whether it is hydrophilic or hydrophobic,were evaluated. The study suggests that chosen analogues and their corresponding metal complexes might easily penetrate cell membranes in an encapsulated form without any form of degradation. Partition coefficients, binding constants and other thermodynamic parameters were evaluated that confirmed that such drug-micelle interactions were thermodynamically favorable with adequate negative value of the Gibb's free energy, under the experimental conditions.

Finally, the chosen amino-anthraquinone ligands and their prepared complexes were tested on different human cancer cell lines to see whether they initiate apoptosis. IC_{50} of different compounds chosen for experiments were estimated by employing a cell viability assay. Apoptosis was characterized by cellular morphological changes observed during the process of cell death which was analyzed by the dual staining method of acridine orange (AO) and ethidium bromide (EB). Results of this study show that chosen molecules may be considered as less costly alternatives of anthracyclines that are already in use.

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