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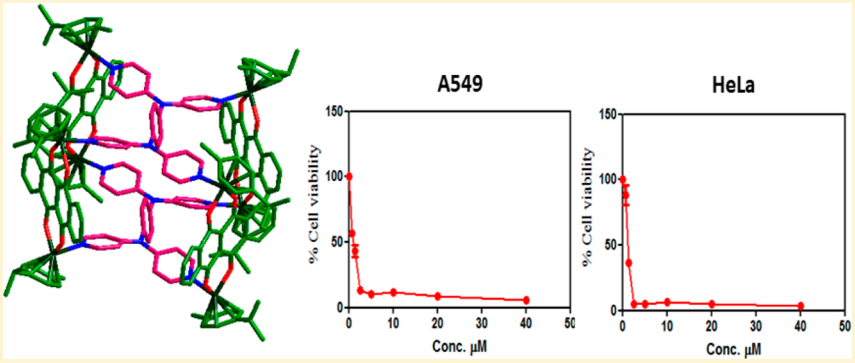
Self-Assembly of Discrete Ru^{II}_8 Molecular Cages and Their in Vitro Anticancer Activity

Aderonke Ajibola Adeyemo,[‡,#] Abhijith Shettar,[†,#] Imtiyaz Ahmad Bhat,[‡] Paturu Kondaiah,[*,†] and Partha Sarathi Mukherjee[*,‡]

[‡]Department of Inorganic and Physical Chemistry and [†]Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore 560012, India

Supporting Information



ABSTRACT: Four new octanuclear Ru(II) cages (**OC-1**−**OC-4**) were synthesized from dinuclear *p*-cymene ruthenium(II) acceptors $[Ru_2(\mu-\eta^4\text{-}C_2O_4)(CH_3OH)_2(\eta^6\text{-}p\text{-cymene})_2](O_3SCF_3)_2$ ($\mathbf{A_1}$), $[Ru_2(\mu-\eta^4\text{-}C_6H_2O_4)(CH_3OH)_2(\eta^6\text{-}p\text{-cymene})_2](O_3SCF_3)_2$ ($\mathbf{A_2}$), $[Ru_2(dhnq)(H_2O)_2(\eta^6\text{-}p\text{-cymene})_2](O_3SCF_3)_2$ ($\mathbf{A_3}$), and $[Ru_2(dhtq)(H_2O)_2(\eta^6\text{-}p\text{-cymene})_2](O_3SCF_3)_2$ ($\mathbf{A_4}$) separately with a tetradentate pyridyl ligand ($\mathbf{L_1}$) in methanol using coordination-driven self-assembly [$\mathbf{L_1}$= *N,N,N′,N′*-tetra(pyridin-4-yl)benzene-1,4-diamine]. The octanuclear cages are fully characterized by various spectroscopic techniques including single-crystal X-ray diffraction analysis of **OC-4**. The self-assembled cages show strong in vitro anticancer activity against human lung adenocarcinoma A549 and human cervical cancer HeLa cell lines as observed from the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Of all the octanuclear cages, **OC-3** exhibits remarkable anticancer activity against both cancer cell lines and is more active than that reported for cisplatin. The excellent anticancer activity of **OC-3** and **OC-4** highlights the importance of the synergistic effects of the spacer component of the dinuclear *p*-cymene Ru(II) acceptor clips.

INTRODUCTION

Ruthenium chemistry is a rising field in the search for proficient metallodrugs using diverse synthetic methods to symbiotically develop drugs that are not toxic to normal cells and selective for cancer cells.[1] Of these synthetic methods, metal−ligand self-assembly stands out as an advanced field of research that has generated large number of intricate structural motifs in a single step from predesigned molecular building units in a facile manner.[2] Our group and others have extensively studied and reported varieties of *p*-cymene ruthenium(II)-based metallacycles and metallacages with diverse shapes, functionalities, and properties using this approach.[3] The ambidexterity of the confined space generated in these cage architectures has found applications in encapsulation of compounds, recognition and trapping of guest molecules, protection and stabilization of an otherwise unstable molecule, and as microreactor for specific reactions among others.[4] Organometallic anticancer compounds have generated increasing interest since the discovery of the DNA binding property of cisplatin, but the high toxicity and multifactorial resistance of platinum-based anticancer drugs in clinical applications propelled scientists to design and develop better alternatives.[5] Mononuclear and dinuclear ruthenium complexes represent a new class of promising metal-based drugs with low toxicity (fewer side effects) and high activity (broader spectrum) in tumors possessing the potential to overcome platinum resistance.[6] Two ruthenium-based anticancer drug candidates: NAMI-A ([ImH]trans-$[Ru^{III}Cl_4(DMSO)Im]$; Im = imidazole, DMSO = dimethyl sulfoxide) and KP1019 ([HInd][trans-$Ru^{III}Cl_4$ $(Ind)_2$]; Ind = indazole) have successfully passed phase I clinical trials;[7] however, the need to improve both activity and selectivity is still of utmost importance. Neutral or cationic arene ruthenium complexes provide both hydrophilic and hydrophobic interactions with biomolecules by stabilizing the oxidation states of these complexes due to the robustness of the ruthenium *p*-

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