JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2020.1775126

Ruthenium complexes with *mono*- or *bis*-heterocyclic chelates: DNA/BSA binding, antioxidant and anticancer studies

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Communicated by Ramaswamy H. Sarma

ABSTRACT

Deoxyribonucleic acid (DNA) and bovine serum albumin (BSA) binding interactions for a series of ruthenium heterocyclic complexes were monitored using ultraviolet-visible (UV-Vis) spectrophotometry, fluorescence emission spectroscopy and agarose gel electrophoresis. Investigations of the DNA interactions for the metal complexes revealed that they are groove-binders with intrinsic binding constants in the order of $10^4 - 10^7\ M^{-1}$. Electronic spectrophotometric DNA titrations of the *bis*-heterocyclic metal complexes illustrated hypochromism of their intraligand electronic transitions and the presence of diffuse isosbestic points which are synonymous with homogeneous binding modes. Metal complexes with the *mono*-heterocyclic chelates also showed alterations in their intraligand transitions and changes in their metal-based electronic transitions which are suggestive of metal coordination to the CT-DNA structure. Using agarose gel electrophoresis assessments, Hoechst DNA binding competition studies corroborate that the metal complexes are DNA groove-binders. Optimal uptake of these metal complexes by BSA was observed based on their optimal apparent association and Stern-Volmer constants (K_{app} and $K_{SV} > 10^4\ M^{-1}$). Radical scavenging studies revealed that the metal complexes have high activities towards the neutralization of NO and DPPH radicals. Data attained from the BSA electronic spectrophotometric titrations for the majority of the metal complexes illustrated distinct hyperchromism accompanied with blue shifts which indicates unwinding of the protein strands. Predominately, the metal complexes showed moderate cytotoxicity against both triple-negative breast cancer and cervical cancer cell lines that was greater than that of 5-fluorouracil.

ARTICLE HISTORY
Received 18 February 2020
Accepted 19 May 2020

KEYWORDS
Ruthenium heterocyclic complexes; DNA/BSA binding; antioxidant activities; cytotoxicity

1. Introduction

Ruthenium-based anticancer drugs have demonstrated cytotoxicity against a wide variety of cancer cells accompanied with minimal side effects to healthy cells (Lazarević et al., 2017; Thota et al., 2018; Zhang & Sadler, 2017). It is hypothesized that the biocompatibility of these potential metallopharmaceuticals culminates from the similar chemistry of ruthenium and the essential metal, iron, as these elements are group congeners (Merlino, 2016). In addition, ruthenium can induce cancer cell apoptosis through utilization of its high coordination affinities to nucleotides (Pages et al., 2015). Alteration of the co-ligands within the coordination sphere of ruthenium have been shown to lead to intriguing structure-activity relationships and diverse mechanisms of action (Zeng et al., 2017). In fact, the leading candidates of ruthenium chemotherapeutic agents, *e.g. trans*-[$RuCl_4$(DMSO)(Im)](ImH) (ImH = protonated imidazole) (NAMI-A), are prodrugs which are activated upon hydrolysis (Dwyer et al., 2018). Furthermore, conjugated aromatic chelating ligands of metal complexes are able to promote DNA interaction through intercalation or groove-binding as the possible mechanism of anticancer activity (Levina et al., 2009).

Current research focuses on designing target-specific ruthenium anticancer drugs and involves encompassing biologically relevant moieties (BAMs) in ligand scaffolds where the meticulously selected BAMs may facilitate defined biodistribution patterns (Caruso et al., 2016). This design approach is exemplified by arene metal complexes with flavone or chromone analogs, where a correlation between the lipophilicity and the *in vitro* screening of melanoma cell lines was found (Pastuszko et al., 2016). In addition, a fascinating bifunctional metal complex, (ethacrynic acid-*g6*-benzylamide)(1,3,5-triaza-7-phosphaadamantane)dichloride (ethaRAPTA) induced death of MCF-7 breast cancer cells, which is regarded as a significant advancement considering that these cells are resistant to cisplatin (Chatterjee et al., 2011). The dual functionality of this metal complex stems from the inherent cytotoxicity of the RAPTA constituent and ethacrynic acid-*g6*-benzylamide moiety's glutathione *S*-transferase inhibiting capability which combats drug resistance.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/07391102.2020.1775126.