MAPPING THE ALBUMIN AFFINITY OF CYTOTOXIC METAL CHELATES

Sheldon Sookai,[a] Matthew P. Akerman,[b] and Orde Q. Munro[a,c]

[a]School of Chemistry, University of the Witwatersrand, South Africa
[b]School of Chemistry, University of KwaZulu-Natal, South Africa
[c]School of Chemistry, University of Leeds, UK

Human serum albumin (HSA) efficiently transports drugs *in vivo*: most are organic, and their binding site(s) are known from X-ray crystallography. To better understand how metallodrug candidates are bound and transported by the protein, we have studied how a series of related d^8 metal chelates of bis(pyrrolide-imine) ligands interact with HSA (Fig. 1). The binding affinity and site specificity are shown to depend on (i) the identity of the d^8 metal ion in Ni^{II}, Pd^{II} and Pt^{II} chelates of the ligand [1], (ii) the substitution pattern and polarity of the chelating ligands in several Pt^{II} analogues [2], and (iii) the chirality of the chelating ligand in a pair of enantiopure Au^{III} derivatives [3]. Fluorescence quenching data for native and probe-bound HSA showed binding sites close to Trp-214 (subdomain IIA) are targeted. The Stern-Volmer constants, K_{SV}, typically range from 10^4 M^{-1} to 10^5 M^{-1} while the affinity constants, K_a, range from ~3.5×10^3 M^{-1} to ~1×10^6 M^{-1} at 37 °C, following the order Pd(PrPyrr) > Pt(PrPyrr) > Ni(PrPyrr) > H_2PrPyrr when the ligand is held constant. Ligand uptake is usually enthalpically driven, though some exceptions occur. Induced CD spectra for the protein-bound metal chelates can be simulated by hybrid QM:MM TD-DFT methods, proving that the metal complexes neither decompose nor demetallate after uptake by HSA [1–4].

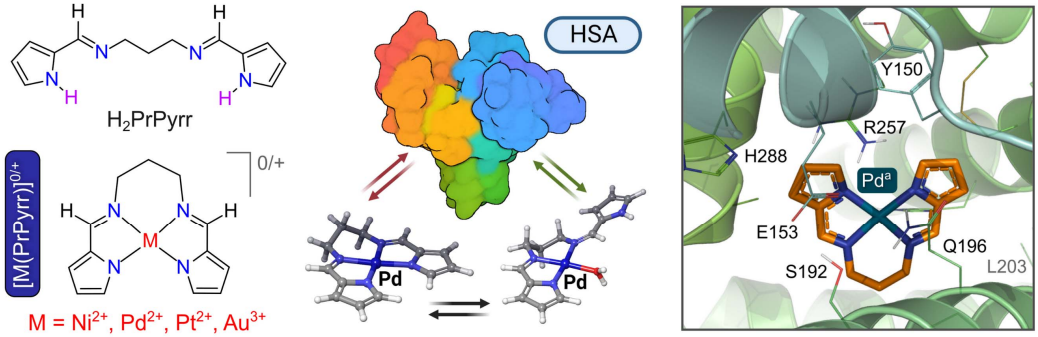

Fig. 1. Binding of bis(pyrrolide-imine) metal chelates by human serum albumin.

The broader picture emerging from this work is that transport and delivery of the metal chelates, including Au(III) derivatives that target human topoisomerase II [4], by HSA *in vivo* could be feasible for suitably redox-stabilized cytotoxic or bactericidal [5] complexes within this class of compounds.

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[1] S. Sookai and O. Q. Munro, *ChemistryEurope*, 2023, **1**, e202300012.

[2] S. Sookai and O. Q. Munro, *Dalton Trans.*, 2023, **52**, 14774–14789.

[3] S. Sookai, M. P. Akerman and O. Q. Munro, *Dalton Trans.*, 2024, **53**, 5089–5104.

[4] S. Sookai, M. Akerman, M. Færch, Y. Sayed and O. Q. Munro, *Eur. J. Med. Chem.*, 2025, **287**, 117330.

[5] R. Gupta, C. Rodrigues Felix, M. P. Akerman, K. J. Akerman, C. A. Slabber, W. Wang, J. Adams, L. N. Shaw, Y.-C. Tse-Dinh, O. Q. Munro, K. H. Rohde, *Antimicrob. Agents Chemother.* 2018, **62**, e01696-17.