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Human serum albumin binding of certain antimalarials

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ABSTRACT

Interactions between eight in-house synthesized aminoquinolines, along with well-known chloroquine, and human serum albumin (HSA) have been studied by fluorescence spectroscopy. The synthesized aminoquinolines, despite being structurally diverse, were found to be very potent antimalarials. Fluorescence measurements indicate that three compounds having additional thiophene or benzothiophene substructure bind more strongly to HSA than other studied compounds. Competitive binding experiments indicate that these three compounds bind significantly stronger to warfarin compared to diazepam binding site. Fluorescence quenching at three temperatures (20, 25, and 37 °C) was analyzed using classical Stern-Volmer equation, and a static quenching mechanism was proposed. The enthalpy and entropy changes upon sulphur-containing compound–HSA interactions were calculated using Van't Hoff equation. Positive values of enthalpy and entropy changes indicate that non-specific, hydrophobic interactions are the main contributors to HSA–compound interaction. Molecular docking and calculated lipophilicity descriptors indicate the same, pointing out that the increased lipophilicity of sulphur-containing compounds might be a reason for their better binding to HSA. Obtained results might contribute to design of novel derivatives with improved pharmacokinetic properties and drug efficacy.

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1. Introduction

Human serum albumin (HSA) is single-chain, non-glycosylated polypeptide that contains 585 amino acids with molecular weight of 66,500 Da [1] (Fig. 1). The polypeptide chain forms a heart-shaped structure that is composed of three structurally similar α-helical domains (I, II and III) and each of them consists of two subdomains (A and B). HSA has a role in osmotic pressure and pH regulation, sequestering oxygen free radicals, inactivating various toxic lipophilic metabolites and transport of endogenous (fatty acids, hormones, bile acids, amino acids) and exogenous compounds (drug molecules and nutrients). It is shown that HSA (concentration in serum approximately 0.6 mM [1]) is a major binder of acidic drug molecules in plasma, unlike alpha-1-acid glycoprotein (AGP, concentration in serum approximately 20 μM [2]) which binds mainly basic drug molecules. Also, negatively charged compounds bind more strongly to HSA than positively charged ones [3].

Most drugs bind primarily to two specific binding sites on HSA. The site I (warfarin binding site) and site II (also called the indole-benzodiazepine site) are located in domains IIA and IIIA (Fig. 1), respectively [5]. Ligands that strongly bind to site I are dicarboxylic acids and/or bulky heterocyclic molecules with a negative charge localized in the middle of the molecule. Such ligands are warfarin, azapropazone, phenylbutazone, *etc.* Low stereoselectivity of this site toward small organic molecules might be ascribed to its flexibility. Ligands that bind to site II are generally aromatic carboxylic acids, with a negative charge located distant from the hydrophobic region of the molecule, like diazepam, diflunisal, and ibuprofen. Sudlow site II is smaller, but topologically similar to site I. Site II appears to be less flexible, since ligand binding often shows stereoselectivity, and is strongly affected by small structural modifications of the ligand. However, these structural features are not strict prerequisites for the site I and site II binding, since numerous ligands are known to bind to both drug binding sites, though with different affinities [6].

The nature and magnitude of HSA–drug interactions affect the pharmacological behavior and side effects of a drug. Strong binding between HSA and drug decreases the concentration of free drug in the blood, and thus decreases the pharmacological effect of a drug (only free drug in the tissues is able to bind to the target receptor). Weak binding leads to a short drug lifetime and its' poor tissue distribution. Connection

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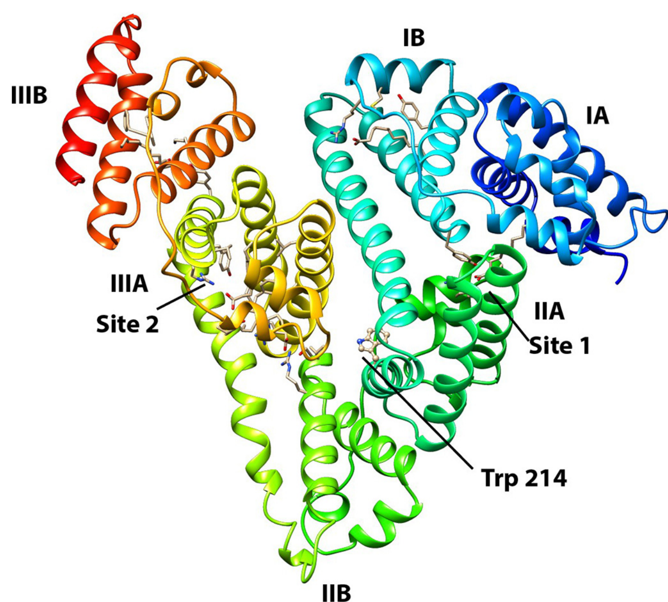

Fig. 1. Crystal structure of HSA (PDB ID 1BJ5) and the location of major binding sites. The image is made in Chimera [4].

between free drug concentration in plasma and free drug concentration in tissues can be used in designing the administration regimen dose and establishing the safety margins [7]. As drug binding to HSA and plasma proteins (PP) can be affected by some diseases, information about drug–PP binding might be useful in therapy [5]. Hence, HSA–drug interactions studies provide important information which can be used in pharmaceutical industry in pharmacokinetic (PK) and pharmacodynamic drug profiling.

Interaction between drugs and HSA can be studied by different instrumental techniques: Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (NMR), isothermal titration calorimetry (ITC), UV–Vis and fluorescence spectroscopy, circular dichroism spectroscopy (CD), high-performance liquid chromatography (HPLC), equilibrium dialysis *etc.* [3,8–21].

Fluorescence measurements are often used to study drug to protein binding because the variety of information on the binding mechanism, mode, constants, binding sites, intermolecular distances, *etc.*, can be easily obtained. HSA, as the majority of other proteins, has three fluorophores: tryptophan, tyrosine, and phenylalanine, but its' fluorescence almost exclusively originates from tryptophan 214 alone (Trp214, Fig. 1). Phenylalanine has a very low quantum yield and the fluorescence of tyrosine is almost entirely quenched if it is near to an amino group, a carboxyl group, or a tryptophan. As binding of a drug to HSA occurs, the microenvironment of Trp214 is changed, and the changes of HSA intrinsic fluorescence intensity are induced [22].

Although X-ray diffraction is used as the golden standard for determining protein and protein-ligand complexes structures, computational methods, like molecular docking, are nowadays often used for studying the protein-ligand interactions as well. In cases where structure of the protein is well known, like the structure of HSA is, the binding of various small molecules to the protein binding site can be successfully investigated using molecular modeling.

Chloroquine (CQ) is drug commonly used in the prevention and treatment of malaria and in the treatment of rheumatoid arthritis and influenza. CQ is one of the oldest, cheapest, and easily available synthetic agents used to cure malaria. No drugs have been found possessing the same pharmacological profiles as CQ. Thus, although CQ-resistance against different strains of malarial parasite strains worldwide was reported, many research groups are continuously working on the CQ core structure modification to get new efficient drug [23].

In the search for novel antimalarials with improved PK profile, we explored interactions of CQ and our eight derivatives of CQ (Fig. 2) with HSA using spectroscopic and molecular modeling techniques. The synthesized compounds, despite being structurally diverse, possess aminoquinoline moiety as pharmacophore and they have been found to be very potent nontoxic antimalarials *in vitro* and *in vivo* [24–27]. It is expected that obtained results will be valuable for the design of novel derivatives with improved PK properties and drug efficacy.

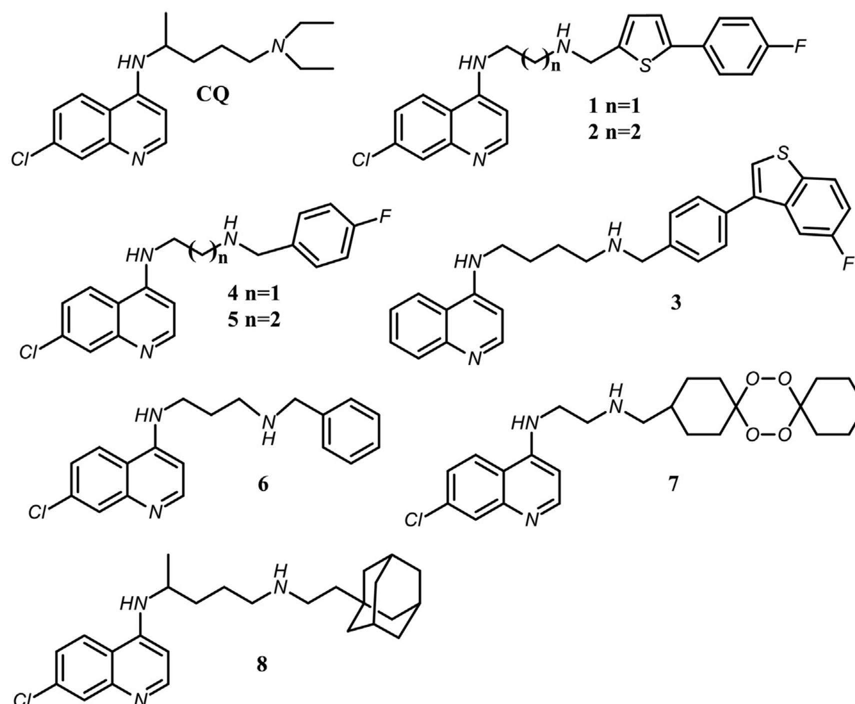

Fig. 2. Structures of chloroquine (CQ) and compounds **1**–**8**.

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