

Extended Abstract

Comparative Studies on the Human Serum Albumin Binding of the Investigational EGFR Inhibitor KP2187, Its Hypoxia-Activated Cobalt Complex, and a Series of Clinically Approved Inhibitors [†]

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Binding interactions between human serum albumin and four clinically approved epidermal growth factor receptor (EGFR) inhibitors, gefitinib, erlotinib, afatinib, and osimertinib, were compared to those of the experimental drug KP2187 and its hypoxia-activated kinetically inert cobalt(III) complex. Since hypoxia is a common feature in many solid tumors, it can be turned into an advantage for selective cancer therapy, as it occurs mainly in the tumor tissue compared to normal tissues. The [Co(III)(KP2187)(acac)₂]Cl complex was confirmed to be activated by reduction to the more labile Co(II) ion in the hypoxic environment of tumors, enabling the selective release of the EGFR inhibitor KP2187 [1]. The protein binding was studied by the combined use of steady-state and time resolved spectrofluorometric and molecular modelling methods. Proton dissociation processes, lipophilicity, and solvent-dependent fluorescence properties of the ligands were investigated as well [2]. The aim of our work was to study and compare the solution chemical properties and albumin binding of the selected compounds, which strongly influence their pharmacokinetic properties. Binding constants calculated on the basis of the various experimental data indicate a weak-to-moderate binding on albumin, with only osimertinib exhibiting a somewhat higher affinity towards this protein. However, our model calculations performed at physiological blood concentrations of albumin resulted in high (*ca.* 90%) bound fractions for the inhibitors, highlighting the importance of plasma protein binding.

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