Journal of Physical Chemistry B 2016 vol.120 N37, pages 9903-9912

Volume of Hsp90 Protein-Ligand Binding Determined by Fluorescent Pressure Shift Assay, Densitometry, and NMR

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Abstract

© 2016 American Chemical Society.Human heat shock protein 90 (Hsp90) is a key player in the homeostasis of the proteome and plays a role in numerous diseases, such as cancer. For the design of Hsp90 ATPase activity inhibitors, it is important to understand the relationship between an inhibitor structure and its inhibition potential. The volume of inhibitor binding is one of the most important such parameters that are rarely being studied. Here, the volumes of binding of several ligands to recombinant Hsp90 were obtained by three independent experimental techniques: fluorescent pressure shift assay, vibrating tube densitometry, and high-pressure NMR. Within the error range, all techniques provided similar volumetric parameters for the investigated protein-ligand systems. Protein-ligand binding volumes were negative, suggesting that the protein-ligand complex, together with its hydration shell, occupies less volume than the separate constituents with their hydration shells. Binding volumes of tightly binding, subnanomolar ligands were significantly more negative than those of weakly binding, millimolar ligands. The volumes of binding could be useful for designing inhibitors with desired recognition properties and further development as drugs.

http://dx.doi.org/10.1021/acs.jpcb.6b06863