A comparison of correlated ab initio methods and ONIOM methods for modeling protein-drug interactions: novel statin drugs.

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In previous work (*J. Phys. Chem. B*, **113**, 14810, 2009) it has been shown that the residue Tyr479 in the active site of 3-hydroxy-3-methyglutaryl-coenzyme A (HMG-CoA) reductase exerts a strong attraction on ligands. Statin drugs moderate blood cholesterol levels by acting as competitive inhibitors for this enzyme, blocking the biosynthesis of cholesterol early in the synthesis pathway. In this work a novel molecular fragment that binds strongly to Tyr479 has been developed using *ab initio* correlated methods and attached to known statin drugs to create novel drug candidates that interact more strongly with the enzyme than the original drugs. Interaction energies between small molecule ligands and the target enzyme active site are calculated with all-electron correlated methods and compared to ONIOM calculations which use the semi-empirical AM1 method for the low level of the active site. Different DFT methods are shown to model MP2 interaction energies well for different situations and ONIOM, while qualitatively similar to all-electron calculations, is shown to predict substantially different absolute protein-ligand interaction energies. Various molecular properties of known statin drugs were also correlated to the values of the *in vivo* potencies (the pIC50) of each drug in order to derive quantitative structure/activity trends. A possible correlation was found between the structural orientation of the LUMOs and the potency. The trends derived in the work are currently being used to predict the potency of novel statin drugs being developed in our research group.