MP2 and DFT studies of potential non-competitive inhibition of HMG-CoA-reductase: complementing statin drugs

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Statin drugs moderate blood cholesterol levels by acting as competitive inhibitors for 3-hydroxy-3-methyglutaryl-coenzyme-A (HMG-CoA) reductase, blocking the biosynthesis of cholesterol early in the synthesis pathway In previous work (*J. Phys. Chem. B*, **113**, 14810, 2009) it has been shown that the residue Tyr479 in the active site of HMG-CoA reductase exerts a strong attraction on ligands. Other work in our group has shown that small molecules can be designed that span and bind strongly to the entire active site, including Tyr479 (*Computational and Theoretical Chemistry*, **967**, 171, 2011). In this work, we investigate the binding of small molecule inhibitors to an allosteric site in HMG-CoA reductase that also contains Tyr479. We believe that binding to this allosteric site may disrupt the shape of the primary active site, further disrupting the synthesis of cholesterol. Interaction energies between the small molecule ligands and the target enzyme active site are calculated with all-electron correlated methods such as MP2 and DFT. Initial results show strong interactions for ligands in this site.