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## Structural Mechanism for Statin Inhibition of HMG-CoA Reductase

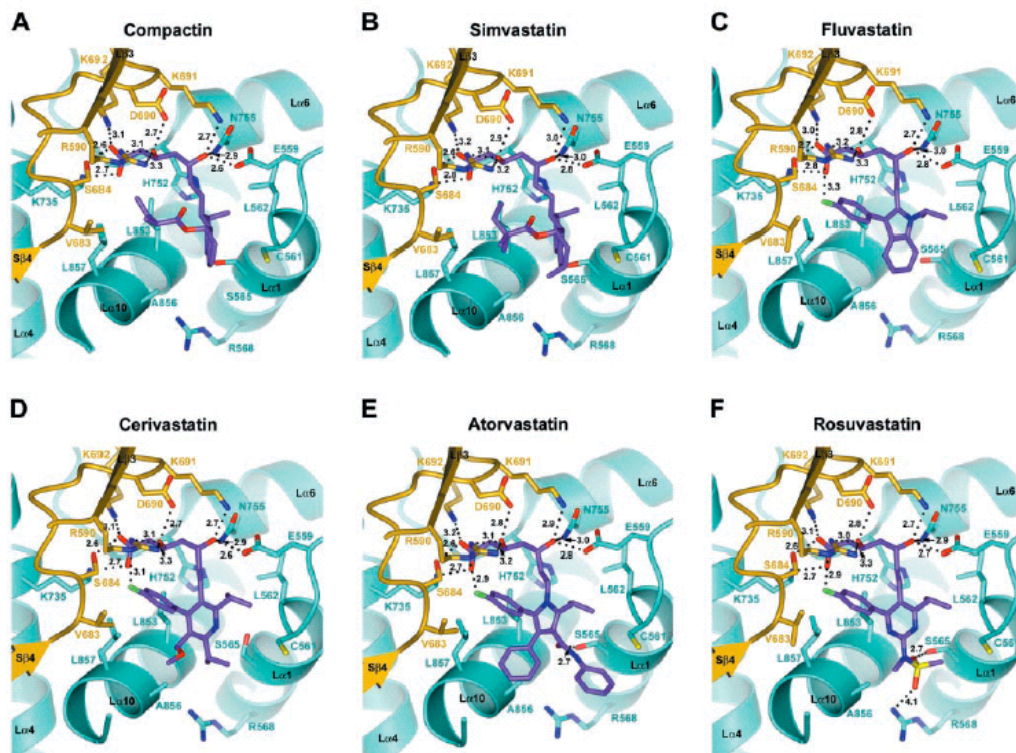
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### Abstract

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase (HMGR) catalyzes the committed step in cholesterol biosynthesis. Statins are HMGR inhibitors with inhibition constant values in the nanomolar range that effectively lower serum cholesterol levels and are widely prescribed in the treatment of hypercholesterolemia. We have determined structures of the catalytic portion of human HMGR complexed with six different statins. The statins occupy a portion of the binding site of HMG-CoA, thus blocking access of this substrate to the active site. Near the carboxyl terminus of HMGR, several catalytically relevant residues are disordered in the enzyme-statin complexes. If these residues were not flexible, they would sterically hinder statin binding.

### Introduction

Elevated cholesterol levels are a primary risk factor for coronary artery disease. This disease is a major problem in developed countries and currently affects 13 to 14 million adults in the United States alone. Dietary changes and drug therapy reduce serum cholesterol levels and dramatically decrease the risk of stroke and overall mortality. Inhibitors of HMGR, commonly referred to as statins, are effective and safe drugs that are widely prescribed in cholesterol-lowering therapy. In addition to lowering cholesterol, statins appear to have a number of additional effects, such as the nitric oxide-mediated promotion of new blood vessel growth, stimulation of bone formation, protection against oxidative modification of low-density lipoprotein, as well as anti-inflammatory effects and a reduction in C-reactive protein levels. All statins curtail cholesterol biosynthesis by inhibiting the committed step in the biosynthesis of isoprenoids and sterols. This step is the four-electron reductive acylation of HMG-CoA to CoA and mevalonate catalyzed by HMGR.



**Fig. 4.** Mode of binding of compactin (**A**), simvastatin (**B**), fluvastatin (**C**), cerivastatin (**D**), atorvastatin (**E**), and rosuvastatin (**F**) to human HMGR. Interactions between the HMG moieties of the statins and the protein are mostly ionic or polar. They are similar for all inhibitors and are indicated by the dotted lines. Numbers next to the lines indicate distances in Å. The rigid hydrophobic groups of the statins are situated in a shallow groove between helices La1 and La10. Additional interactions between Arg590 and the fluorophenyl group are present in the type 2 statins (C, D, E, F). Atorvastatin and rosuvastatin form a hydrogen bond between Ser565 and a carbonyl oxygen atom (atorvastatin) (E) or a sulfone oxygen atom (rosuvastatin) (F).

How is the specificity and tight binding of statin inhibitors achieved? The HMG-moieties of the statins occupy the enzyme active site of HMGR. The orientation and bonding interactions of the HMG moieties of the inhibitors clearly resemble those of the substrate complex. Several polar interactions are formed between the HMG-moieties and residues that are located in the cistop (Ser684, Asp690, Lys691, Lys692)... The large number of hydrogen bonds and ion pairs results in charge and shape complementarity between the protein and the HMG-like moiety of the statins. Identical bonding interactions are observed between the protein and HMG and presumably also with the reaction product mevalonate.