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Discovery of the HCV NS3/4A Protease Inhibitor SCH503034. Key Steps in Structure-Based Optimization.

Andrew J. Prongay, Zhuyan Guo, John Pichardo, Nanhua Yao, Thierry Fischmann, Joseph Myers, Jr., Patricia C. Weber, Bruce Malcolm, Brian M. Beyer, Richard Ingram, Rumin Zhang, Ashok Arasappan, Frank Bennett, Stephane L. Bogen, Kevin Chen, Edwin Jao, Raymond G. Lovey, Srikanth Venkatraman, F. George Njoroge, Vincent Madison, Schering-Plough Research Inst., Kenilworth, NJ.

The structures of both native and S139A apo-HCV NS3/4A protease domain were solved to high resolution. Subsequently, structures were determined for a series of ketoamide inhibitors in complex with the protease. The changes in the inhibitor potency were correlated with changes in the buried surface area upon binding the inhibitor to the active site. The largest contributions to the binding energy arises from the hydrophobic interactions of the P1 and P2 groups as they bind to the S1 and S2 pockets. This correlation of the changes in potency with increased buried surface area contributed directly to the design of a potent tripeptide inhibitor of the HCV NS3/4a protease that is currently in clinical trials.