Structures of SARS Coronavirus Main Protease Bound by an Aza-peptide Epoxide

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Soon after the global outbreak of severe acute respiratory syndrome (SARS) in the spring of 2003, a novel coronavirus (CoV) was identified to be the etiological agent of this highly infectious and fatal disease. The main protease (M^{pro}) of this virus is essential for viral replication, and therefore is one of the major targets for the development of anti-SARS agents. We have determined the crystal structures of SARS-CoV M^{pro} unbound in the space group C2, and bound by an aza-peptide epoxide in the space groups C2 and $P2_12_12_1$. These structures show that the peptide binds, like a true substrate, to the substrate-binding and active site of the enzyme, without inducing any significant change in the structure of the enzyme. A covalent bond forms between the S_γ atom of the catalytic residue Cys-145 of the enzyme and one of the epoxide carbon atoms of the peptide, thereby blocking the active site of the enzyme. With an appropriate sequence, the peptide also has its side chains nicely fitted into in the specificity pockets of the enzyme. These results form the structural basis for our suggestion that the aza-peptide epoxide is a potential inhibitor of SARS-CoV M^{pro} worthy of further evaluation as in the development of leads for anti-SARS agents.

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