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Abstract

The Z mutant of α1-antitrypsin (Glu342Lys) causes a domain swap and the formation of intrahepatic polymers that aggregate as inclusions and predispose the homozygote to cirrhosis. We have identified an allosteric cavity that is distinct from the interface involved in polymerization for rational structure-based drug design to block polymer formation. Virtual ligand screening was performed on 1.2 million small molecules and 6 compounds were identified that reduced polymer formation in vitro. Modeling the effects of ligand binding on the cavity and re-screening the library identified an additional 10 compounds that completely blocked polymerization. The best antagonists were effective at ratios of compound to Z α1-antitrypsin of 2.5:1 and reduced the intracellular accumulation of Z α1-antitrypsin by 70% in a cell model of disease. Identifying small molecules provides a novel therapy for the treatment of liver disease associated with the Z allele of α1-antitrypsin.