

W0050

Atomic Resolution Structures of Potent Non-peptidic Inhibitor with High-level Resistant HIV-1 Protease Mutants. Andrey Y. Kovalevsky,^{1a} Yunfeng Tie,^{1b} Fengling Liu,^{1a} Peter I. Boross,² Yuan-Fang Wang,^{1a} Laquasha Gaddis,^{1a} Arun K. Ghosh,³ Irene T. Weber^{1a,b}, ^{1a}Dept. of Biology and ^{1b}Chemistry, Georgia State Univ., Atlanta, GA 30303, ayk@gsu.edu, ²Dept. of Biochemistry and Molecular Biology, Faculty of Medicine, University of Debrecen, Debrecen Hungary, ³Dept. of Chemistry, Univ. of Illinois at Chicago, Chicago IL 60607.

It is important to find new antiviral drugs due to the appearance of highly drug-resistant strains of HIV-1. The structures of HIV-1 protease (PR) in complex with UIC94017 (TMC114) at nearly atomic resolution are described. TMC114 is an extremely potent inhibitor with excellent antiviral properties. It is designed to form many favorable intermolecular contacts with PR in order to withstand the effects of mutation and tightly bind in the active site of mutants. High resolution structures are a prerequisite for the understanding of the molecular basis of PR inhibition, and can provide a pathway towards the future drug design. The complexes prepared include wild-type PR and commonly isolated high-level resistant mutants V82A, I84V, L90M, D30N, M46L with the inhibitor. The structural changes observed in the mutants are compared with those seen in complexes with clinical inhibitors. (Research supported by NIH grants GM62920, GM53386 and OTKA F35191).