SUPPORTING INFORMATION

Novel P2 *tris*-tetrahydrofuran group in antiviral compound 1 (GRL-0519) fills the S2 binding pocket of selected mutants of HIV-1 protease

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Figure S1: Alternate Conformations for Flap Residues

F_o-F_c omit map (contoured at 3.0 σ) for the flap residues Gly48'- Gly52' in complex PR_{I54M}– inhibitor **1** and residues Gly48 - Gly52 in complexes of inhibitor **1** with PR_{R8Q}, PR_{D30N}**,** PR_{I50V} and PR_{V82A}. Carbon atoms are colored cyan and magenta for the major and minor conformation, respectively.

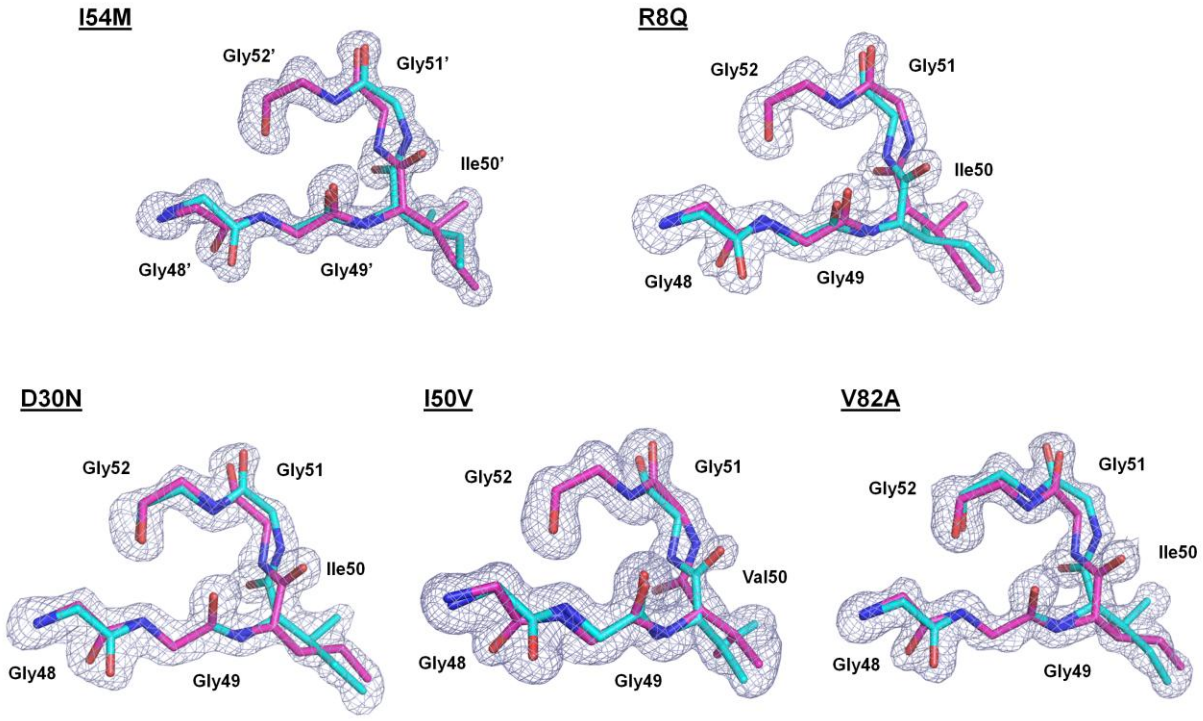

Table S1. Hydrogen Bond Interactions between Protease and Inhibitor 1

PR atom	Inhibitor atom	Distance (Å)					
Hydrogen Bonds		PR_{WT}	PR_{R8Q}	PR_{D30N}	PR_{I50V}	PR_{I54M}	PR_{V82A}
Asp25 OD1	O18	2.7	2.6	2.6	2.7	2.6	2.6
Asp25 OD2	O18	2.4	2.6	2.4	3.2	2.5	2.6
Asp25' OD1	O18	2.9	2.7	2.8	2.7	2.8	2.7
Asp25' OD2	O18	3.3	3.0	3.2	2.6	3.3	3.1
Gly27' O	N20	3.2	3.3	3.2	3.2	3.2	3.3
Asp30' OD2/Asn30' ND2	O26	3.4		3.1			
Asp30' NH/Asn30' NH	O26	3.4	3.3	3.4	3.2	3.4	3.3
Asp29' NH	O26	3.4	3.3	3.4	3.3	3.3	3.2
Asp29' NH	O28	3.0	3.0	2.9	2.8	3.0	2.9
Asp29' OD2	O28	3.5	3.5	3.5	3.5	3.5	3.4
Asp29' OD2	O41	3.5	3.5	3.4	3.4	3.5	3.5
H_2O (D)	O41	3.2	3.4	3.2	3.3	3.3	3.3
Asp29' OD1	H_2O (D)	3.0	2.9	2.9	2.9	2.9	2.9
Gly27' O	H_2O (D)	2.8	2.8	2.9	2.8	2.8	2.8
H_2O (A)	O10	2.6	2.4	2.4	2.6	2.6	2.4
H_2O (A)	O22	2.9	3.2	3.1	3.0	3.0	3.1
Ile50'/Val50' NH	H_2O (A)	2.9	2.8	2.9	3.0	2.8	3.1
Ile50/Val50 NH	H_2O (A)	3.0	3.1	3.1	2.9	2.9	3.3
Asp30 OD2/Asn30 ND2	O39	2.5	3.3	-	2.9	2.4	3.4
Asp30 NH/Asn30 NH	O39	3.3	3.2	3.2	3.1	3.1	3.2

Distances are listed for the major conformation of inhibitor and PR residues. Interatomic distances of 3.4-3.5Å indicate weak hydrogen bonds.