Molecular Mechanisms and Design Principles for Promiscuous Inhibitors to Avoid Drug Resistance: Lessons Learned from HIV-1 Protease Inhibition

(Short Title: Promiscuous Inhibitors to Avoid Resistance)

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**Supplementary Material** 

**Keywords**: binding specificity; molecular mechanisms; drug resistance; drug design principles; drug cocktails

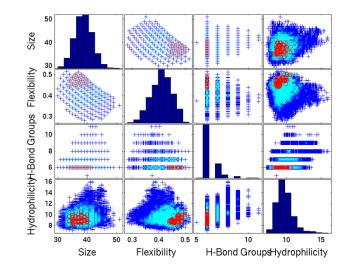
Figure S1. Pairwise distributions of physicochemical measures for inhibitors. Blue and red symbols correspond to selective (coverage  $\leq 4$ ) and promiscuous (coverage  $\geq 9$ ) inhibitors, respectively; cyan ones correspond to inhibitors of intermediate binding promiscuity.

**Figure S2.** Distributions of physicochemical measures for designed inhibitors across coverage bins. Compared to **Figure 4**, an entropic component was introduced here into the binding energy calculation with an approximation of 0.4 kcal/mol per rotatable bond for designed inhibitors.

**Figure S3**. Comparison of physicochemical properties of selective and promiscuous inhibitor sets. Compared to **Figure 5**, entropic loss of inhibitors was introduced as 0.4 kcal/mol per rotatable bond.

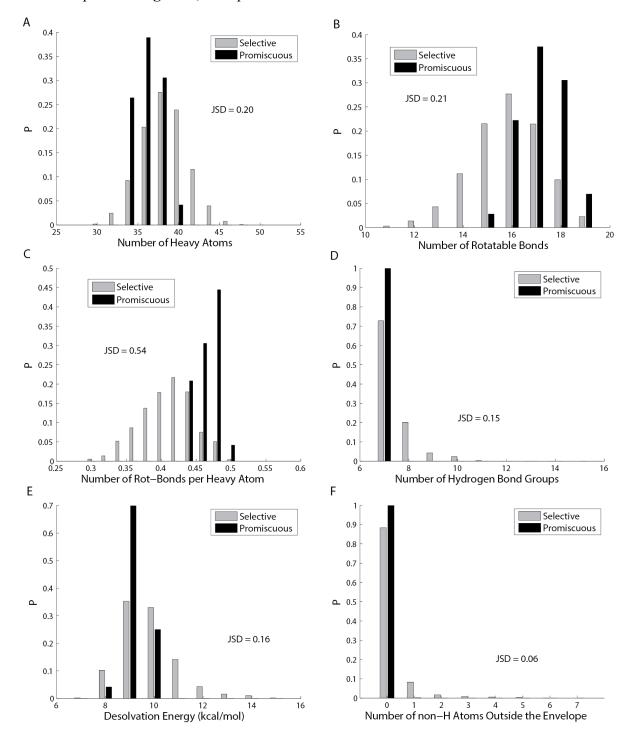
**Figure S4**. Distributions of normalized flexibility score for designed inhibitors across coverage bins when increasing parameters for entropic loss of inhibitors were used: (A) 0.4 (as in Figure S2A) ; (B) 1.0; (C) 1.5; and (D) 2.0 kcal/mol per rotatable bond.

**Figure S1.** Pairwise distributions of physicochemical measures for inhibitors. Blue and red symbols correspond to selective (coverage  $\leq 4$ ) and promiscuous (coverage  $\geq 9$ ) inhibitors, respectively; cyan ones correspond to inhibitors of intermediate binding promiscuity.



В А 50 19 48 18 Number of Rotatable Bonds Number of Heavy Atoms by Atoms 1E-1 1E– 1 17 16 40 1E-2 15 1E– 2 38 14 36 13 1E-3 1E– 3 12 32 1 30 1E-4 1E- 4 2 6 8 10 12 2 4 8 10 12 6 Coverage Coverage С D 0.5 Number of Rot-Bonds per Heavy Atom 12 Number of Hydrogen Bond Groups 0.48 11 0.46 1E-1 1E-1 0.44 10 0.42 0.4 1E-2 1E-2 0.3 8 0.3 6 1E-3 1E-3 0.3 4 0.3 2 0.3 1E-4 1E-4 6 Coverage 6 Coverage 10 12 10 12 2 4 8 2 4 8 Ε F 15 Number of Atoms Outside the Envelope Desolvation Energy (kcal/mol) 1E-1 1E-1 13 12 1E-2 1E-2 10 1E-3 1E-3 1E-4 1E-4 10 12 2 6 Coverage 10 12 6 Coverage 2 8 4 8 4

**Figure S2.** Distributions of physicochemical measures for designed inhibitors across coverage bins. Compared to **Figure 2**, an entropic component was introduced here into the binding energy calculation with an approximation of 0.4 kcal/mol per rotatable bond for designed inhibitors.



**Figure S3.** Comparison of physicochemical properties of selective and promiscuous inhibitor sets. Compared to **Figure 3**, entropic loss of inhibitors was introduced.

**Figure S4**. Distributions of normalized flexibility score for designed inhibitors across coverage bins when increasing parameters for entropic loss of inhibitors were used: (A) 0.4 (as in Figure S2A); (B) 1.0; (C) 1.5; and (D) 2.0 kcal/mol per rotatable bond.

