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)

Yang Shen[1,#], Mala L. Radhakrishnan[2], Bruce Tidor[1]*

[1] Department of Biological Engineering, Department of Electrical Engineering and Computer Science, and Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

[2] Department of Chemistry, Wellesley College, Wellesley, Massachusetts 02482

[#] Current Address: Toyota Technological Institute at Chicago, Chicago, Illinois 60637

* Email: tidor@mit.edu

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 ≤ 4) and promiscuous (coverage ≥ 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 ≤ 4) and promiscuous (coverage ≥ 9) inhibitors, respectively; cyan ones correspond to inhibitors of intermediate binding promiscuity.

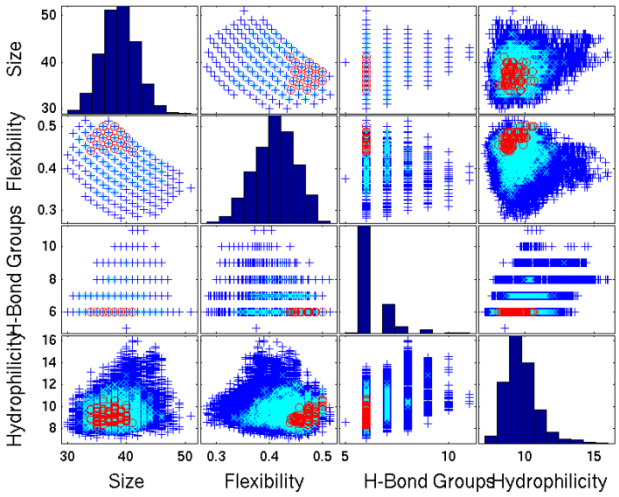

Figure S2. Distributions of physicochemical measures for designed inhibitors across coverage bins. Compared to **Figure 2**, an entropic component was introduced here into the binding energy calculation with an approximation of 0.4 kcal/mol per rotatable bond for designed inhibitors.

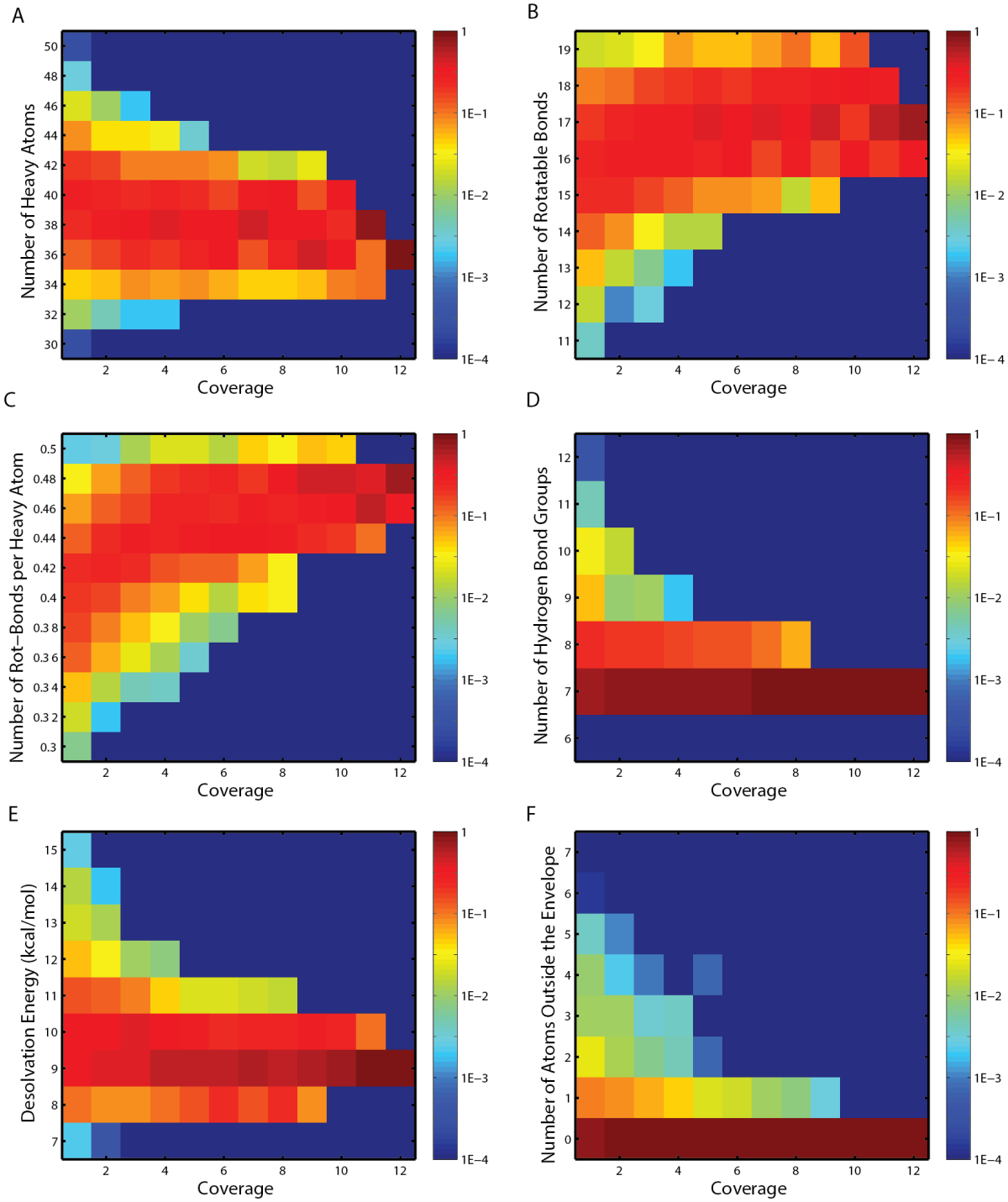

Figure S3. Comparison of physicochemical properties of selective and promiscuous inhibitor sets. Compared to **Figure 3**, entropic loss of inhibitors was introduced.

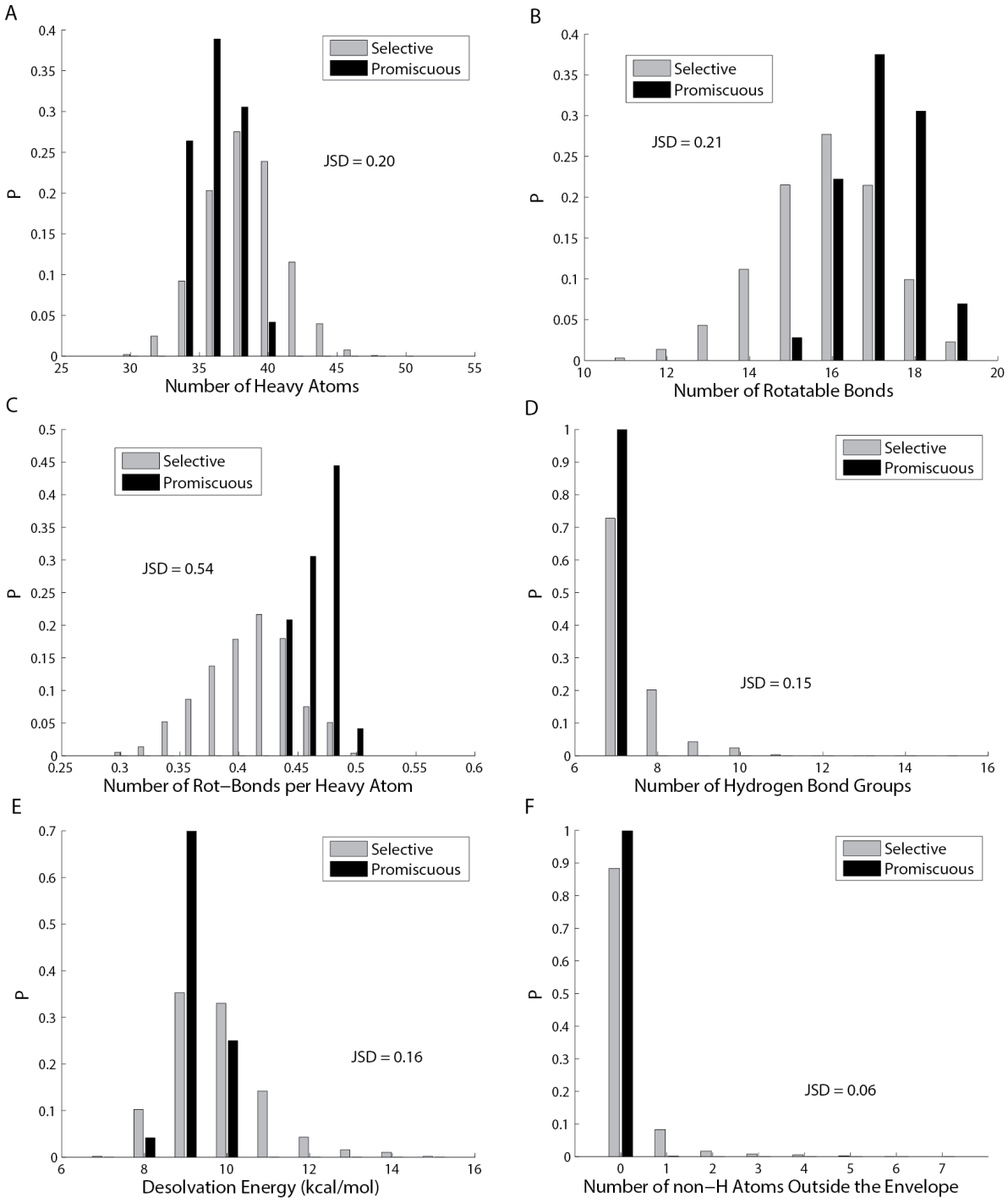

Figure S4. Distributions of normalized flexibility score for designed inhibitors across coverage bins when increasing parameters for entropic loss of inhibitors were used: (A) 0.4 (as in Figure S2A) ; (B) 1.0; (C) 1.5; and (D) 2.0 kcal/mol per rotatable bond.