Supplemental Material

For

Evaluation of Wilma-SIE Virtual Screening Method in CSAR 2013-2014 Blind Challenges

Hervé Hogues, Traian Sulea and Enrico O. Purisima*

Human Health Therapeutics, National Research Council Canada

6100 Royalmount Avenue, Montreal, Quebec H4P 2R2, Canada

*Corresponding author's email: Enrico.Purisima@nrc-cnrc.gc.ca

Figure S1. Stereo views depicting the conformational flexibility of the target included in docking via multiple crystal structures available. Docking region delimited by black box. Reference ligands shown as stick models with the C atoms in green. Regions of increased flexibility are indicated by red arrows. (A) Syk target – 5 structures. (B) TrmD target – 14 structures. (C) FXa target – 4 structures multiplied by 4 conformations of Q192 side chain (green arrow).

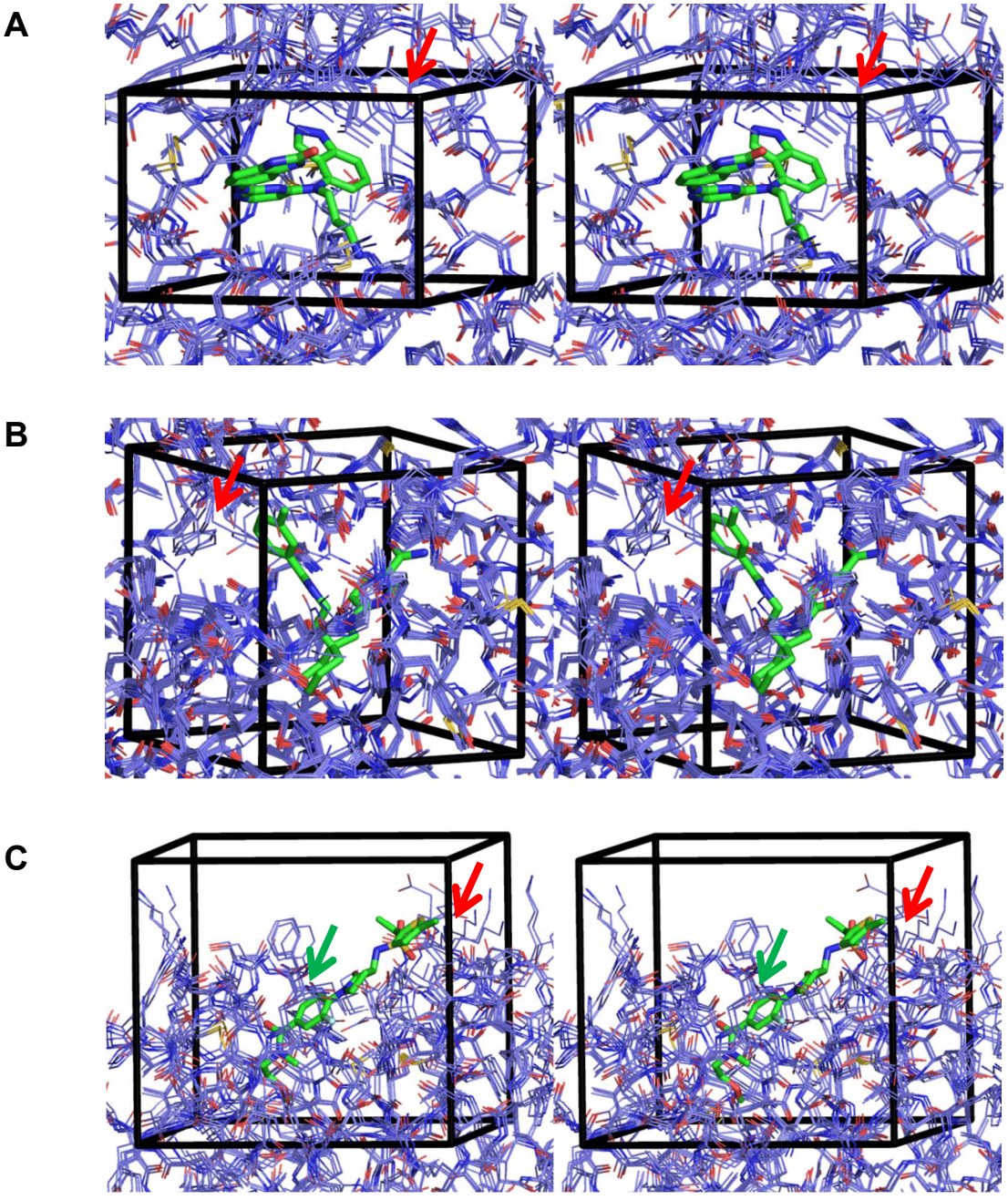
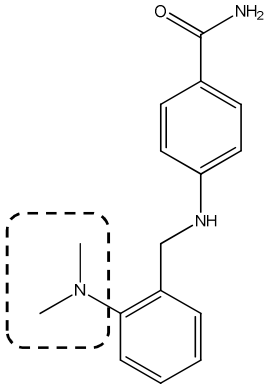
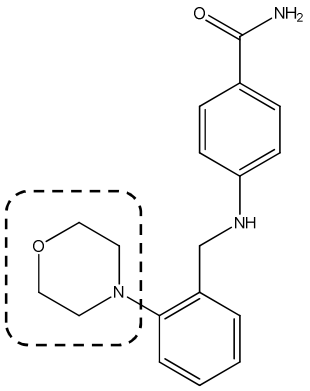


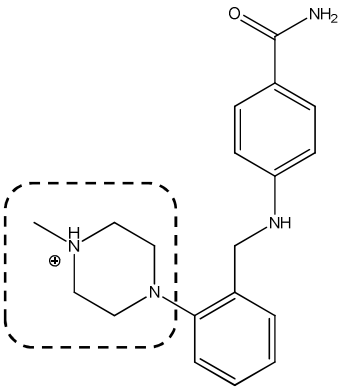
Figure S2. 2D-structures of the cross-docking outliers for the TrmD target (see Figure 3 in the main paper). These compounds are closely related, and ligands with ID numbers 455, 470 and 471 form a tight chemical cluster. All four outliers present a bulky substituent (highlighted) that may generate steric hindrance for cross-docking into rigid protein structures, which may explain their mis-docking.



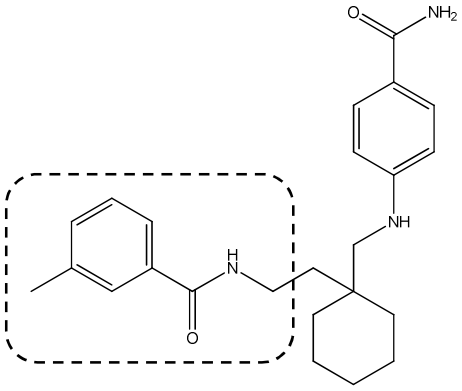
ID 455



ID 470

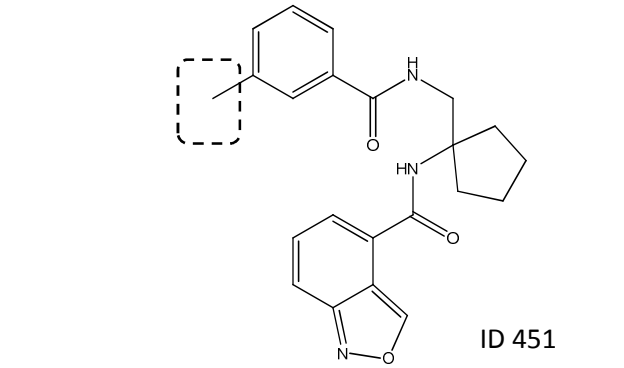


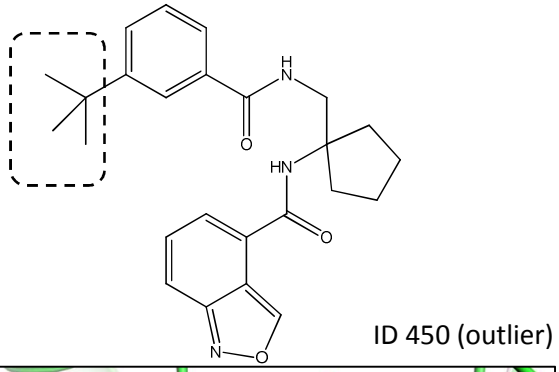
ID 471

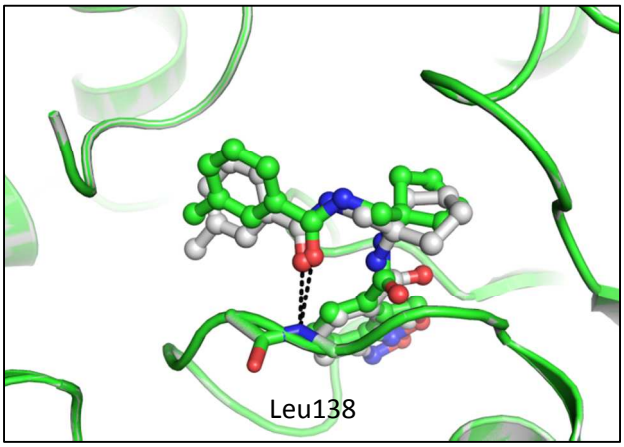


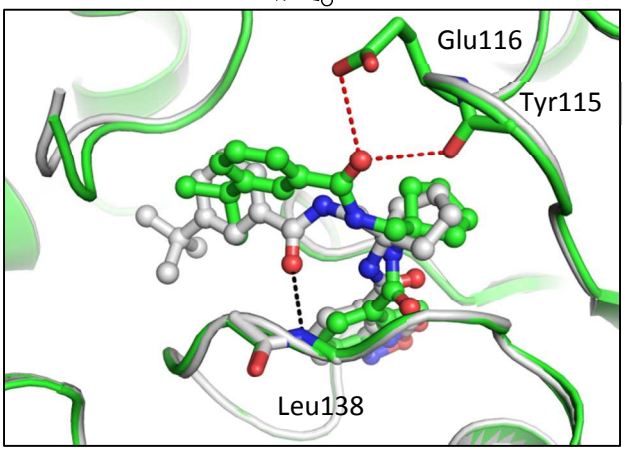
ID 461

Figure S3. Structural basis for the outliers of affinity prediction on the TrmD target. See also the scatter plot of predicted vs actual binding data in Figure 4B in the main paper. Outliers with ID 450 and 449 have a bulky t-butyl substituent (highlighted) replacing the smaller methyl substituent (highlighted) of the close analog ID 451, which are more accurately predicted. Docking was also more precise in the latter case, whereas the bulky t-butyl substituent introduced steric hindrance and could not be accommodated without distortion of the outliers, hence less accurate cross-docking. This distortion abolished a hydrogen bond (black dotted lines) and introduced electrostatic repulsions (red dotted lines). Crystallographic structures – white rendering of C-atoms, docked structures – green rendering of C-atoms. Ligands shown as ball-and-stick models.









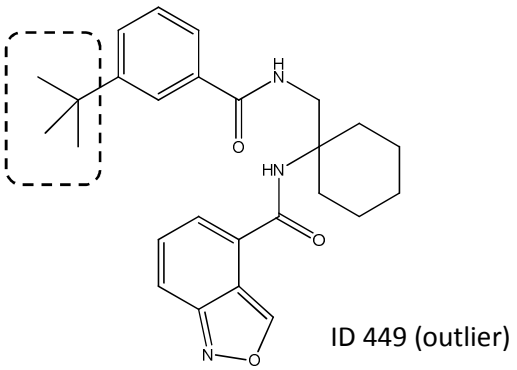


Figure S4. Electrostatic repulsion (highlighted by a red circle) in the protonated form of the 2-amino-1.3-pyrimidine moiety of the Syk core inhibitory scaffold. Ligand shown as ball-and-stick model with C atoms in green. A H-bond (black dotted line) is established by the neutral form of this moiety with the main-chain amide NH group of the Syk residue Ala451, as shown crystallographically.

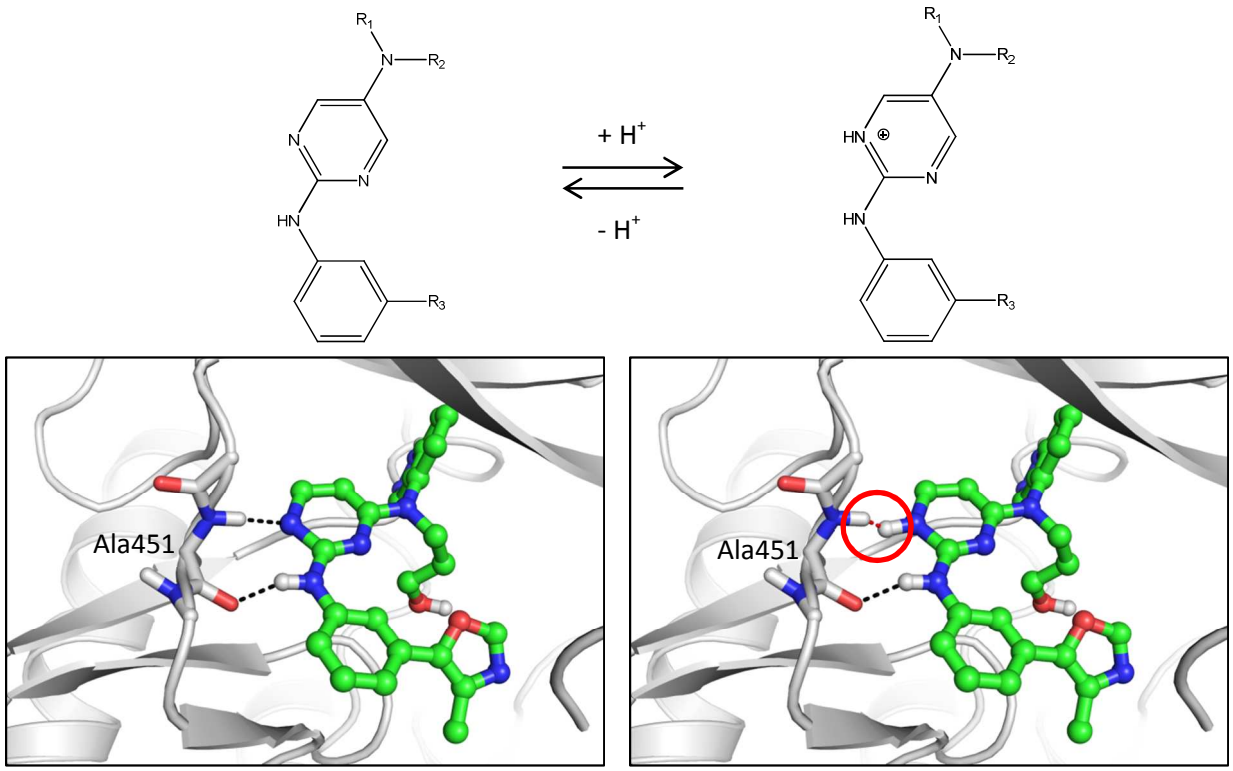


Figure S5. Affinity predictions after cross-docking using the Wilma-SIE+FiSH approach. Scatter plots to be compared with those in Figure 4 from the main paper. (A) DIGbp-ligand affinities. (B) TrmD-ligand affinities. (C) Syk-ligand affinities, original prospective prediction. (D) Syk-ligand affinities, retrospective data after correcting protonation state of 2-amino-1.3-pyrimidine analogs (indicated by red circles).

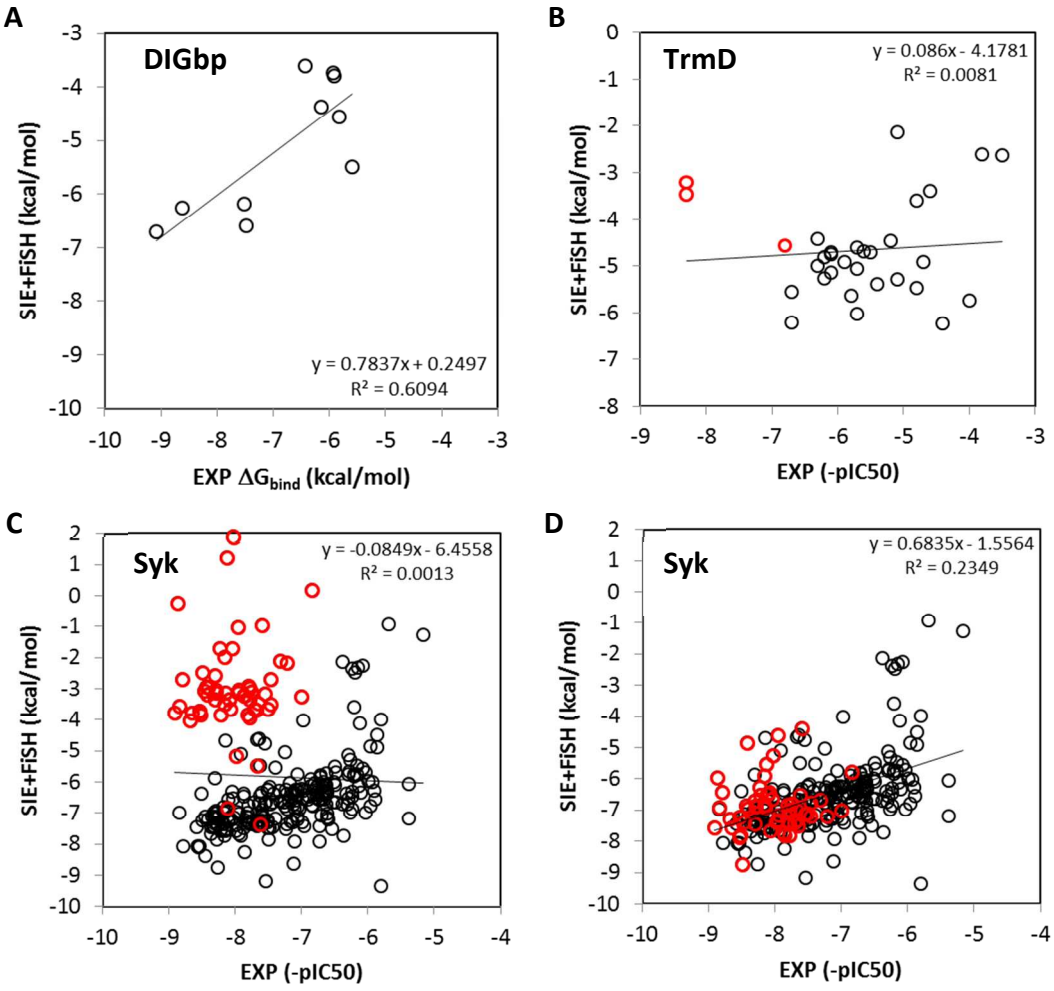


Figure S6. Affinity predictions after cross-docking for the FXa target with the SIE and SIE+FiSH scoring functions. (A) Set 1 (N=45). (B) Set 2 (N=67). (C) Set 3 (N=51).