### Supplementary Text S1. Preparation of fragment set for docking.

The fragment subset contained about 534,000 molecules and was prepared from the ZINC library[[1](#_ENREF_1),[2](#_ENREF_2)] by filtering for compounds with molecular weight between 30 and 250 Da. Each molecule was prepared for docking using the program OMEGA[[3](#_ENREF_3)]. Partial atomic charges and transfer free energies were calculated using AMSOL[[4](#_ENREF_4),[5](#_ENREF_5)] and van der Waals parameters were derived from an all-atom AMBER potential[[6](#_ENREF_6)]. For the first round of docking the target pH of the database was set to 4.5 (pH of the assay conditions) with a tolerance of +/- 1 pH unit (Epik software package, Schrödinger Inc). For the second round of docking, after it became apparent that many molecules included in the initial docking were not present in their charged form at sufficient concentration in the assay conditions, the target pH was set to 6 +/- 0.75 to ensure the ligands were correctly charged, both in the assay and in the crystallographic conditions. Fifteen compounds were selected among the top 500 molecules, purchased and tested experimentally. To evaluate the accuracy of the docking, the predicted poses were overlaid onto the crystallographic conformations, using protein backbone and ligand atoms. R.m.s.d. values were calculated by using ligand atoms only.

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