Mandeep Mann
2019/04/01

Molecular Forecaster Inc (MFI)-USP5 Zf-UBD

Objective: to assess self-docking of ligands in USP5 zinc finger ubiquitin binding domain (Zf-UBD) co-crystal structures using the Forecaster FITTED docking platform and to investigate the ranking success of FITTED rigid protein docking vs. MATCHUP flexible protein docking on a library of experimentally tested compounds

Method & Results:

MFI docking program was tested to reproduce the observed binding mode of ligands in the x-ray structure.

A. Self-Docking [rigid protein docking]

The following was completed for PDBs (6DXH, 6DXT, 6NFT):

1. Forecaster Interface Workflow: Docking small molecule(s) to protein(s)
   NB: do not include "MATCHUP and CONVERT boxes"

2. PREPARE: PDB prepared into corresponding mol2 format using PREPARE. PREPARE adds hydrogens, generates tautomer's and optimizes the H-bonds.
   - Source of protein structures: from working directory
   - Remove chains: no
   - Number of proteins: 1

   To define the active site and extract the ligand, the ligand was selected in a 3D viewer (Jmol):
   - Ligand Identifier: Load PDB structure
   - Use mouse to click on one atom of the ligand and then use toolbar: Forecaster/Select ligand residues. All ligand residues should now be selected. Forecaster/Write keywords. Exit 3D viewer.
   - Optimize: Yes
   - Iterations: 10
   - Side Chain conformation: Take from input file only
   - Water molecules: crystallographic
   - Macromolecule: Protein
   - Save and write keyword file (parameters-prepare.txt)

3. PROCESS: prepares protein mol2 files for docking with FITTED

   - Source of protein structure: from PREPARE box above
   - Number of proteins: 1
   - Macromolecule: protein
   - Number of ligands: 1
   - Ligand Cutoff: 7
   - Prepare for: docking to rigid protein
   - Save and write keyword file (parameters-process.txt)

4. SMART: prepares ligand files for docking with FITTED

- Source of ligand structures: from PREPARE box
- Charges: DGH
- Mode: Docking
- Save and write keyword file (parameters-smart.txt)

5. FITTED: docks small molecules to proteins
    - Source of protein structures: from boxes above
    - Number of proteins: 1
    - Macromolecule: Protein
    - Protein flexibility mode: Automatic
    - Water Molecules: Crystallographic
    - Covalent Docking: No
    - Run mode: Dock
    - Save and write keyword file (parameters-fitted.txt).

6. Run Workflow

Please find attached 1_selfdockXXXX.zip files for results of each self-docking simulation.

Table 1 and Figure 1 summarize the results of self-docking for USP5 Zf-UBD crystal structures. The observed binding modes in the x-ray structures were successful (less than 2 Å). Structure 6NFT had the best observed binding mode (i.e. lowest RMSD).

Table 1. Self-Docking Results

	6DXH	**6DXT**	**6NFT**
Score	-23.399	-19.122	-27.359
RMSD	0.55	0.60	0.40

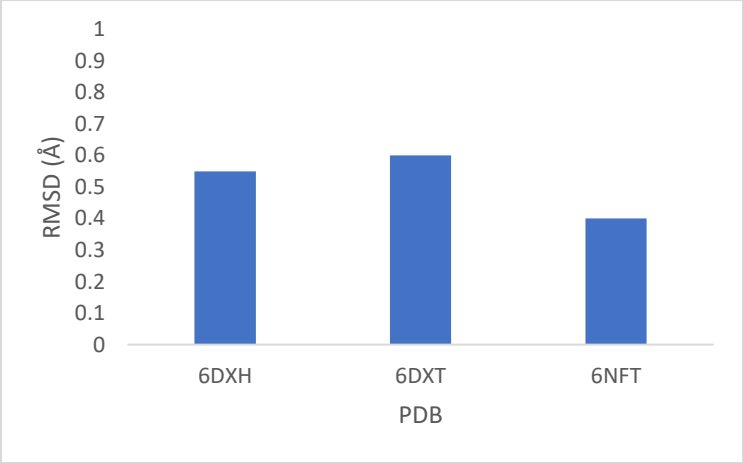


Figure 1. USP5 Zf-UBD self-docking root mean square deviation value (RMSD)

MFI's docking platform can dock ligands to a protein simulating the protein flexibility by providing a conformational ensemble of structures (i.e. multiple co-crystal structures).

Mandeep Mann
2019/04/01

B. Flexible protein docking

1. MATCHUP: superposes protein structures or makes protein sequences similar
    - Number of protein structures: 3 [PDB: 6DXH, 6DXT, 6NFT]
    - Ligand Identifier from pdb #1: Load pdb structure, select and write keyword for ligand residue. Repeat for each structure.
    - Mode: Make similar
    - Save and write keyword file (parameters-match-up.txt)

2. PREPARE:
    - Source of protein structures: from MATCH-UP box above
    - Remove chains: No
    - Number of protein structures: 3
    - Optimize: Yes
    - Iterations: 5
    - Side chain conformation: take from input file only
    - Water molecules: crystallographic
    - Macromolecule: Protein
    - Save and write keyword file (parameters-prepare.txt)

3. PROCESS
    - Source of protein structures: from PREPARE box above
    - Number of proteins: 3
    - Macromolecule: Protein
    - Number of ligands: 3
    - Ligand cutoff: 7
    - Prepare for: docking to flexible protein
4. SMART:
    - Source of ligand structures: from PREPARE box
    - Charges: DGH
    - Mode: Docking
    - Save and write keyword file (parameters-smart.txt)
5. FITTED:
    - Source of protein structures: from boxes above
    - Number of proteins: 3
    - Macromolecule: Protein
    - Protein flexibility mode: Automatic
    - Water Molecules: Crystallographic
    - Covalent Docking: No
    - Evaluate RMSD: Yes
    - Run Mode: Dock
    - Save and write keyword file (parameters-fitted.txt)

Please find attached 2_Flexdock_Matchup.zip file for docking simulation results.

All ligands had RMSDs less than 2 Å using flexible docking; however, flexible docking RMSDs are greater than self-docking RMSDs for DAT201 (PDB: 6DXH) and DAT180 (PDB: 6DXT). Structure 6NFT had the best observed binding, with a RMSD of 0.19, similar to the self-docking results. Table 2 summarizes the flexible docking results and Figure 2 compares the rigid self-docking and MATCHUP flexible docking RMSDs.

Table 2. Flexible Docking of USP5 Zf-UBD Structures with MATCHUP

	6DXH (DAT201)	**6DXT (DAT180)**	**6NFT (DAT194)**
Score	-24.053	-16.723	-26.778
RMSD	1.72	1.92	0.19

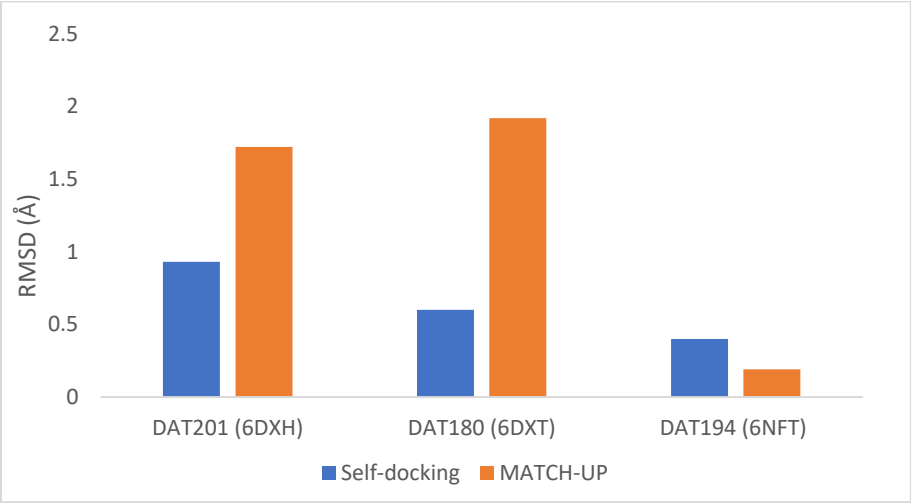


Figure 2. Self-docking (rigid) vs. flexible docking (MATCHUP)

C. Cross-Docking

1. MATCHUP
    - Number of protein structures: 3 [PDB: 6DXH, 6DXT, 6NFT]
    - Ligand Identifier from pdb #1: Load pdb structure, select and write keyword for ligand residue. Repeat for each structure.
    - Mode: Superpose
    - Save and write keyword file (parameters-match-up.txt)
2. PREPARE
    - Source of protein structures: from MATCH-UP box above
    - Remove chains: No
    - Number of protein structures: 3
    - Optimize: Yes
    - Iterations: 5
    - Side chain conformation: take from input file only
    - Water molecules: crystallographic
    - Macromolecule: Protein

- Save and write keyword file (parameters-prepare.txt)

3. PROCESS
    - Source of protein structures: from PREPARE box above
    - Number of proteins: 3
    - Macromolecule: Protein
    - Number of ligands: 3
    - Ligand cutoff: 7
    - Prepare for: cross-docking
4. SMART
    - Source of ligand structures: from PREPARE box
    - Charges: DGH
    - Mode: Docking
    - Save and write keyword file (parameters-smart.txt)
5. FITTED
    - Source of protein structures: from boxes above
    - Number of proteins: 3
    - Macromolecule: Protein
    - Protein flexibility mode: Automatic
    - Water Molecules: Crystallographic
    - Covalent Docking: No
    - Evaluate RMSD: Yes
    - Run Mode: Cross-docking
    - Save and write keyword file (parameters-fitted.txt)

Please find attached 3_crossdock.zip for crossdocking results.

The cross-docking results are summarized in Table 3. Structure 6NFT had the best overall average RMSD.

Table 3. Cross-docking: RMSDs of ligand pose with best energy complex from 3 poses

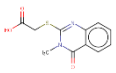
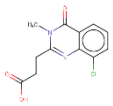
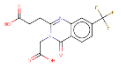
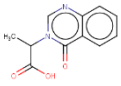
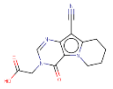
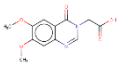
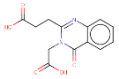
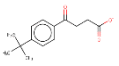
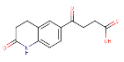
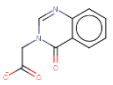
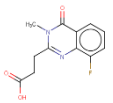
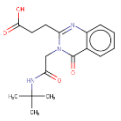
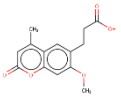
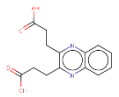
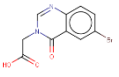
	6DXH	**6DXT**	**6NFT**
6DXH (DAT201)	0.93	1.83	1.18
6DXT (DAT180)	2.16	1.43	0.96
6NFT (DAT194)	1.36	1.18	0.39
Average RMSD	1.48	1.48	0.84

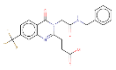
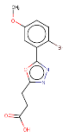
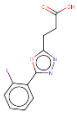
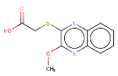
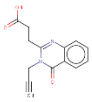
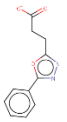
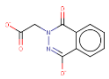
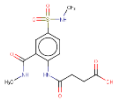
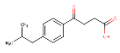
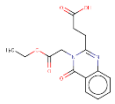
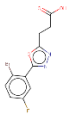
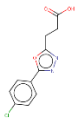
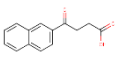
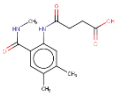
D. Pseudo Virtual Screen using Experimentally tested compounds

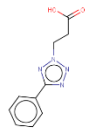
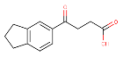
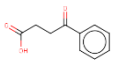
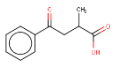
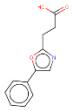
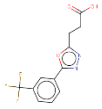
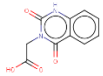
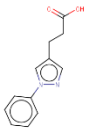
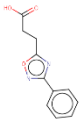
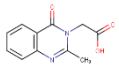
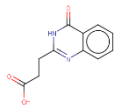
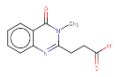
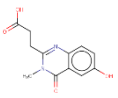
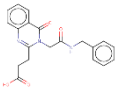
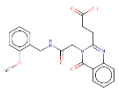
48 compounds that have been previously experimentally tested were used in a pseudo virtual screen to determine the best predictive ranking method. PDBs 6DXH, 6DXT, 6NFT were each used for virtual screening with rigid protein docking and a virtual screen using flexible docking with MATCHUP was also performed, with and without solvation GBSA on. Docking scores were compared and ROC curves were generated. The docking results with solvation GBSA turned off are summarized in Table 4 and Figure 3. The docking results when solvation GBSA is turned on is summarized in Table 5 and Figure 4. Please see attached ROC.xlsx for analysis of results.

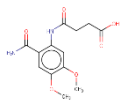
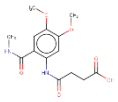
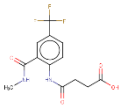
Mandeep Mann
2019/04/01

Table 4. Virtual Screen of USP5 Zf-UBD compounds (Solvation: Off)

Cpd #	Compound Name	Compound SMILES	Compound Structure	Experimental K_D (μM)	ACTIVE*	Score [6DXH]	Score [6DXT]	Score [6NFT]	Score [MATCHUP]
1	UBXML130	CN1C(=Nc2ccccc2C1=O)SCC(O)=O		13	1	-18.819	-17.886	-21.246	-14.001
2	UBXML112	CN1C(CCC(O)=O)=Nc2c(cccc2[Cl])C1=O		47	1	-18.872	-15.213	-22.07	-22.161
3	UBXML78	C(CC(O)=O)C1=Nc2cc(ccc2C(N1CC(O)=O)=O)C(F)(F)F		59	1	-24.506	-21.445	-22.668	-19.148
4	AE-641/11456811	CC(C(=O)O)n2cnc1ccccc1c2=O		61	1	-18.380	-18.114	-24.392	-23.2749
5	DAT80b	C1CCn2c(C1)c(C#N)c1c2C(N(CC(O)=O)C=N1)=O		94	1	-19.602	-18.008	-27.125	-26.6133
6	DAT76b	COc1cc2C(N(CC(O)=O)C=Nc2cc1OC)=O		109	1	-20.572	-16.440	-26.259	-25.15
7	UBXML70	C(CC(O)=O)C1=Nc2ccccc2C(N1CC(O)=O)=O		136	1	-27.552	-23.939	-30.459	-25.609
8	DAT201	CC(C)(C)c1ccc(cc1)C(CCC([O-])=O)=O		173	1	-24.409	-19.657	-25.271	-23.825
9	EN300-137714	C1=C(C=C2C(=C1)NC(CC2)=O)C(CCC(=O)O)=O		192	1	-25.711	-18.494	-24.649	-19.7098
10	DAT194	C(C([O-])=O)N1C=Nc2ccccc2C1=O		215	2	-19.760	-17.408	-26.784	-25.3132
11	UBXML111	CN1C(CCC(O)=O)=Nc2c(cccc2F)C1=O		231	2	-17.928	-14.993	-20.006	-21.845
12	UBXML93	CC(C)(C)NC(CN1C(CCC(O)=O)=Nc2ccccc2C1=O)=O		238	2	-20.664	-17.343	-20.737	-15.924
13	DAT198	Cc1cc(=O)oc2c1cc(c(c2)OC)CCC(=O)O		251	2	-17.090	-19.460	-19.884	-19.71
14	UBXML131	C(Cc1c(CCC(O)=O)nc2ccccc2n1)C(O)=O		252	2	-28.630	-24.128	-26.107	-25.692
15	DAT53b	C(C(O)=O)N1C=Nc2ccc(cc2C1=O)[Br]		253	2	-18.988	-15.021	-25.575	-24.3447

16	UBXML113	C(CC(O)=O)C1=Nc2cc(ccc2C(N1CC(NCc1ccccc1)=O)=O)C(F)(F)F		265	2	-20.728	-14.355	-20.148	-15.703
17	Z1259155895	COc1ccc(Br)c(c1)-c1nnc(CCC(O)=O)o1		271	2	-20.263	-18.592	-25.718	-22.378
18	Z1270387185	OC(=O)CCc1nnc(o1)-c1ccccc1I		277	2	-21.823	-19.400	-24.203	-20.012
19	UBT160a	COc1c(nc2ccccc2n1)SCC(O)=O		296	2	-19.165	-16.423	-22.441	-14.282
20	UBXML94	C#CCN1C(CCC(O)=O)=Nc2ccccc2C1=O		347	2	-19.788	-16.725	-20.357	-19.92
21	DAT180	C(Cc1nnc(c2ccccc2)o1)C([O-])=O		365	2	-22.868	-19.705	-25.325	-20.285
22	DAT19b	C(C([O-])=O)N1C(c2ccccc2C(=N1)[O-])=O		377	2	-20.579	-19.347	-25.668	-22.706
23	UBXML88	CNC(c1cc(ccc1NC(CCC(O)=O)=O)S(NC)(=O)=O)=O		378	2	-20.229	-20.403	-29.69	-21.965
24	EN300-39820	C1=CC(=CC=C1C(CCC(=O)O)=O)CC(C)C		393	2	-24.046	-19.855	-25.268	-25.105
25	UBXML95	CCOC(CN1C(CCC(O)=O)=Nc2ccccc2C1=O)=O		398	2	-16.965	-19.191	-21.026	-20.119
26	Z992717354	OC(=O)CCc1nnc(o1)-c1cc(F)ccc1Br		426	2	-22.150	-18.778	-23.772	-19.019
27	Z1270443867	OC(=O)CCc1nnc(o1)-c1ccc(Cl)cc1		445	2	-20.847	-17.568	-23.292	-17.202
28	EN300-14900	C1=C(C=C2C(=C1)C=CC=C2)C(CCC(=O)O)=O		485	2	-18.781	-19.458	-24.935	-23.567
29	EN300-23733	C1(=CC=CC2=C1N=CN(C2=O)CC(=O)O)C		492	2	-19.336	-17.510	-27.353	-23.3645
30	UBXML89	Cc1cc(C(NC)=O)c(cc1C)NC(CCC(O)=O)=O		518	2	-22.007	-20.274	-24.537	-11.979

31	AL-291/37197008	O=C(O)CCn2nnc(c1ccccc1)n2		529	2	-22.218	-19.414	-24.336	-19.637
32	EN300-11365	C1=CC2=C(C=C1C(CCC(=O)O)=O)CCC2		540	2	-23.511	-19.864	-25.341	-24.294
33	AC90725014276	O=C(O)CCC(=O)c1ccccc1		677	2	-23.244	-19.768	-25.037	-23.801
34	AE56203842058	CC(CC(=O)c1ccccc1)C(=O)O		695	2	-19.345	-20.435	-19.552	-19.889
35	AG-219/09579029	O=C(O)CCc2ncc(c1ccccc1)o2		912	2	-22.510	-18.725	-23.299	-20.745
36	Z221603948	OC(=O)CCc1nnc(o1)-c1cccc(c1)C(F)(F)F		923	2	-21.780	-18.662	-22.766	-18.706
37	Z355423170	OC(=O)Cn1c(=O)[nH]c2ccccc2c1=O		1000	2	-20.541	-18.220	-26.866	-21.850
38	Z126932466	OC(=O)CCc1cnn(c1)-c1ccccc1		1000	2	-19.774	-16.768	-21.764	-21.989
39	Z57674484	OC(=O)CCc1nc(no1)-c1ccccc1		1000	2	-20.892	-20.308	-24.967	-24.434
40	EN300-197134	C1=CC=CC2=C1C(N(C(=N2)C)CC(=O)O)=O		1000	2	-21.285	-16.503	-22.906	-22.6192
41	UBXML57	C(CC(O)=O)C1NC(c2ccccc2N=1)=O		1000	2	-22.524	-18.955	-23.352	-20.5970
42	DAT108c	[H]c1c([H])c([H])c2c(C(N(C(C([H])([H])C([H])([H])C([O-])=O)=N2)C([H])([H])[H])=O)c1[H]		1000	2	-20.083	-16.282	-21.445	-20.2673
43	UBXML133	CN1C(CCC(O)=O)=Nc2ccc(cc2C1=O)O		1000	2	-18.487	-18.599	-21.492	-18.519
44	UBXML83b	C(CC(O)=O)C1=Nc2ccccc2C(N1CC(NCc1ccccc1)=O)=O		1000	2	-21.432	-13.464	-21.741	-13.910
45	UBXML100	COc1ccccc1CNC(CN1C(CCC(O)=O)=Nc2		1000	2	-20.185	-14.669	-19.804	-12.842

46	UBXML86	ccccc2C1=O)=O COc1cc(C(N)=O)c(cc1OC)NC(CCC(O)=O)=O		1000	2	-21.662	-27.776	-23.777	-23.777
47	UBXML87	CNC(c1cc(c(cc1NC(CCC(O)=O)=O)OC)OC)=O		1000	2	-18.954	-24.728	-18.385	-18.385
48	UBXML90	CNC(c1cc(ccc1NC(CCC(O)=O)=O)C(F)(F)F)=O		1000	2	-17.014	-23.590	-21.609	-21.609

***1= active (K_D<200 µM); 2=inactive (K_D>200 µM)**

	6DXH	6DXT	6NFT	MATCHUP
AUC	0.56	0.48	0.65	0.65

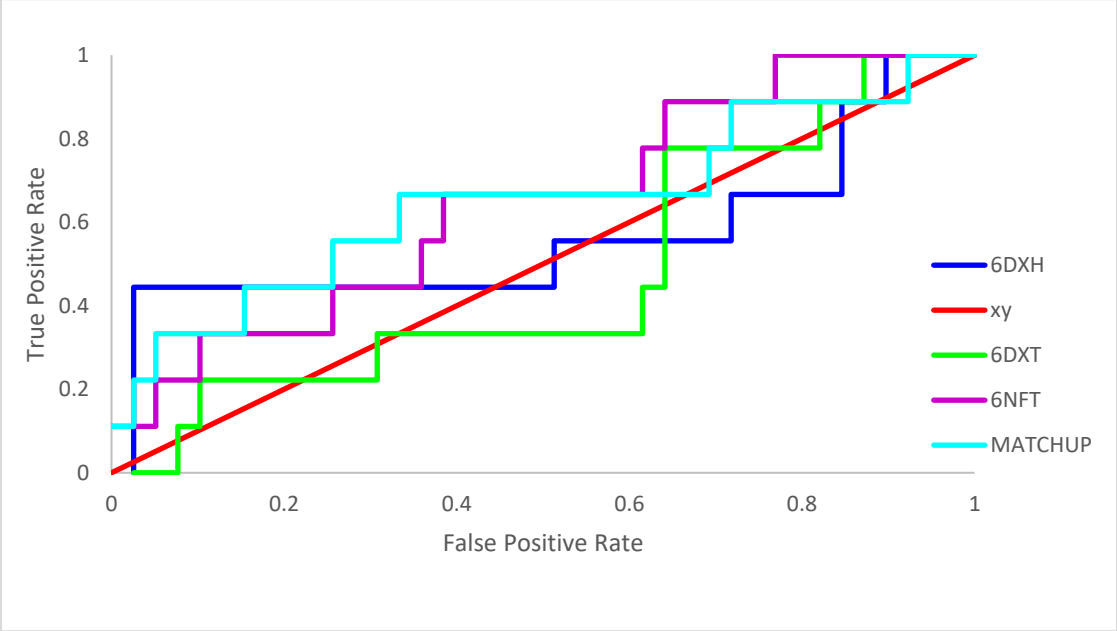
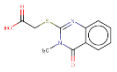
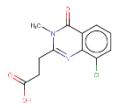
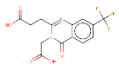
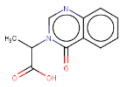
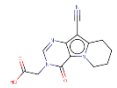
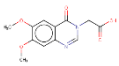
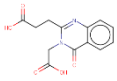
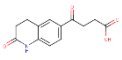
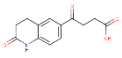
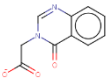
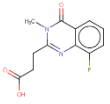
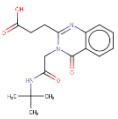
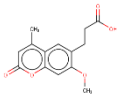
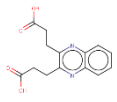
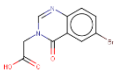
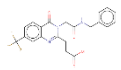
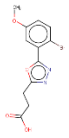
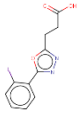
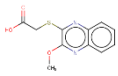
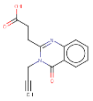
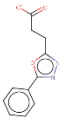
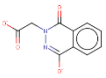
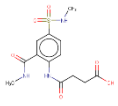
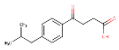
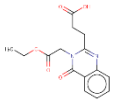
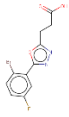
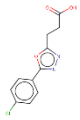
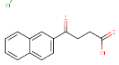


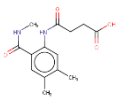
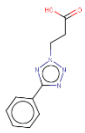
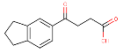
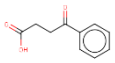
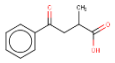
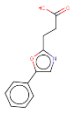
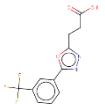
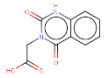
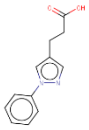
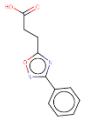
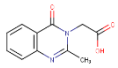
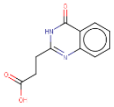
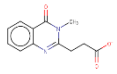
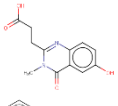
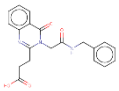
Figure 3. ROC of virtual screen of USP5 Zf-UBD compounds with solvation off

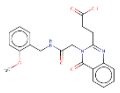
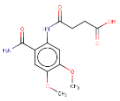
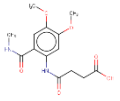
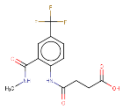
Mandeep Mann
2019/04/01

Table 5. Virtual Screen of USP5 Zf-UBD compounds (Solvation: On)

Cpd #	Compound Name	Compound SMILES	Compound Structure	Experimental K_D (μM)	ACTIVE*	Score [6DXH]	Score [6DXT]	Score [6NFT]	Score [MATCHUP]
1	UBXML130	CN1C(=Nc2ccccc2C1=O)SCC(O)=O		13	1	-18.5270	-17.8861	-20.9020	-13.8656
2	UBXML112	CN1C(CCC(O)=O)=Nc2c(cccc2[Cl])C1=O		47	1	-18.3828	-15.1565	-21.8691	-21.9186
3	UBXML78	C(CC(O)=O)C1=Nc2cc(ccc2C(N1CC(O)=O)=O)C(F)(F)F		59	1	-24.2373	-21.3418	-22.3048	-19.0681
4	AE-641/11456811	CC(C(=O)O)n2cnc1ccccc1c2=O		61	1	-18.3799	-18.1137	-23.6325	-22.5946
5	DAT80b	C1CCn2c(C1)c(C#N)c1c2C(N(CC(O)=O)C=N1)=O		94	1	-19.5764	-17.9595	-27.1251	-26.2217
6	DAT76b	COc1cc2C(N(CC(O)=O)C=Nc2cc1OC)=O		109	1	-20.5715	-16.4397	-26.2587	-25.1500
7	UBXML70	C(CC(O)=O)C1=Nc2ccccc2C(N1CC(O)=O)=O		136	1	-27.1405	-23.9394	-27.8951	-25.4605
8	DAT201	CC(C)(C)c1ccc(cc1)C(CCC([O-])=O)=O		173	1	-24.3298	-19.6569	-25.1059	-23.7331
9	EN300-137714	C1=C(C=C2C(=C1)NC(CC2)=O)C(CCC(=O)O)=O		192	1	-25.7112	-17.8089	-24.5128	-23.9895
10	DAT194	C(C([O-])=O)N1C=Nc2ccccc2C1=O		215	2	-19.7432	-17.4046	-26.7836	-25.3132
11	UBXML111	CN1C(CCC(O)=O)=Nc2c(cccc2F)C1=O		231	2	-17.1750	-14.9862	-19.4548	-21.6281
12	UBXML93	CC(C)(C)NC(CN1C(CCC(O)=O)=Nc2ccccc2C1=O)=O		238	2	-19.8684	-17.3000	-17.9121	-15.7543
13	DAT198	Cc1cc(=O)oc2c1cc(c(c2)OC)CCC(=O)O		251	2	-16.1847	-19.4601	-19.7237	-18.5822
14	UBXML131	C(Cc1c(CCC(O)=O)nc2ccccc2n1)C(O)=O		252	2	-28.6136	-24.1282	-25.6310	-24.7452

15	DAT53b	C(C(O)=O)N1C=Nc2ccc(cc2C1=O)[Br]		253	2	-18.9586	-15.0211	-25.5748	-24.3191
16	UBXML113	C(CC(O)=O)C1=Nc2cc(ccc2CN1CC(NCc1ccccc1)=O)=O)C(F)(F)F		265	2	-20.3487	-13.8286	-19.5488	-15.5407
17	Z1259155895	COc1ccc(Br)c(c1)-c1nnc(CCC(O)=O)o1		271	2	-20.0099	-18.5756	-24.9950	-22.0043
18	Z1270387185	OC(=O)CCc1nnc(o1)-c1ccccc1I		277	2	-21.7609	-19.3245	-23.8635	-19.8378
19	UBT160a	COc1c(nc2ccccc2n1)SCC(O)=O		296	2	-19.0924	-16.1558	-22.0615	-14.2822
20	UBXML94	C#CCN1C(CCC(O)=O)=Nc2ccccc2C1=O		347	2	-19.7125	-16.6827	-19.4424	-19.8730
21	DAT180	C(Cc1nnc(c2ccccc2)o1)C([O-])=O		365	2	-22.8444	-19.7046	-25.2439	-20.0177
22	DAT19b	C(C([O-])=O)N1C(c2ccccc2C(=N1)[O-])=O		377	2	-20.4983	-19.2819	-25.6681	-22.7060
23	UBXML88	CNC(c1cc(ccc1NC(CCC(O)=O)=O)S(NC)(=O)=O)=O		378	2	-19.8674	-17.5556	-29.5118	-21.9185
24	EN300-39820	C1=CC(=CC=C1C(CCC(=O)O)=O)CC(C)C		393	2	-24.0459	-19.8091	-25.1597	-25.0090
25	UBXML95	CCOC(CN1C(CCC(O)=O)=Nc2ccccc2C1=O)=O		398	2	-16.7954	-18.7858	-20.5075	-18.4455
26	Z992717354	OC(=O)CCc1nnc(o1)-c1cc(F)ccc1Br		426	2	-20.9755	-18.7780	-23.4364	-19.0193
27	Z1270443867	OC(=O)CCc1nnc(o1)-c1ccc(Cl)cc1		445	2	-20.7851	-17.5681	-23.2152	-16.9328
28	EN300-14900	C1=C(C=C2C(=C1)C=CC=C2)C(CCC(=O)O)=O		485	2	-18.6452	-19.4402	-24.9353	-23.5092
29	EN300-23733	C1(=CC=CC2=C1N=CN(C2=O)CC(=O)O)C		492	2	-19.2852	-17.5101	-27.3136	-23.3645

30	UBXML89	Cc1cc(C(NC)=O)c(cc1C)NC(CCC(O)=O)=O		518	2	-21.2015	-20.2331	-23.7156	-11.7365
31	AL-291/37197008	O=C(O)CCn2nnc(c1ccccc1)n2		529	2	-22.2040	-19.4138	-24.0060	-19.5208
32	EN300-11365	C1=CC2=C(C=C1C(CCC(=O)O)=O)CCC2		540	2	-23.4838	-19.8643	-25.2156	-24.3186
33	AC907250014276	O=C(O)CCC(=O)c1ccccc1		677	2	-23.2040	-19.7683	-24.9607	-23.7700
34	AE5620384 2058	CC(CC(=O)c1ccccc1)C(=O)O		695	2	-18.8134	-20.4350	-19.3828	-19.8266
35	AG-219/09579029	O=C(O)CCc2ncc(c1ccccc1)o2		912	2	-22.4733	-18.7250	-23.2043	-20.7209
36	Z221603948	OC(=O)CCc1nnc(o1)-c1cccc(c1)C(F)(F)F		923	2	-21.7077	-18.6617	-22.6751	-16.0031
37	Z355423170	OC(=O)Cn1c(=O)[nH]c2ccccc2c1=O		1000	2	-20.5411	-17.3790	-26.1855	-21.8500
38	Z126932466	OC(=O)CCc1cnn(c1)-c1ccccc1		1000	2	-19.5175	-16.7683	-21.7642	-21.6033
39	Z57674484	OC(=O)CCc1nc(no1)-c1ccccc1		1000	2	-20.8923	-20.3080	-24.7987	-24.2566
40	EN300-197134	C1=CC=CC2=C1C(N(C(=N2)C)CC(=O)O)=O		1000	2	-21.2851	-16.4618	-22.7814	-22.6192
41	UBXML57	C(CC(O)=O)C1NC(c2ccccc2N=1)=O		1000	2	-22.5245	-17.9843	-23.3523	-20.5643
42	DAT108c	[H]c1c([H])c([H])c2c(C(N(C(C([H])([H])C([H])([H])C([O-])=O)=N2)C([H])([H])[H])=O)c1[H]		1000	2	-20.0580	-16.2822	-21.4309	-19.4598
43	UBXML133	CN1C(CCC(O)=O)=Nc2ccc(cc2C1=O)O		1000	2	-18.2985	-17.9607	-21.4240	-18.5189
44	UBXML83b	C(CC(O)=O)C1=Nc2ccccc2C(N1CC(NCc1ccccc1)=O)=O		1000	2	-20.4590	-13.4638	-19.7603	-13.9007

45	UBXML100	COc1ccccc1CNC(CN1C(CCC(O)=O)=Nc2ccccc2C1=O)=O		1000	2	-18.4347	-14.6691	-19.8040	-12.8422
46	UBXML86	COc1cc(C(N)=O)c(cc1OC)NC(CCC(O)=O)=O		1000	2	-21.6039	-21.3917	-26.8699	-17.5854
47	UBXML87	CNC(c1cc(c(cc1NC(CCC(O)=O)=O)OC)OC)=O		1000	2	-17.6234	-18.2061	-24.0475	-18.1929
48	UBXML90	CNC(c1cc(ccc1NC(CCC(O)=O)=O)C(F)(F)F)=O		1000	2	-18.4972	-16.8936	-23.5542	-21.5583

***1= active (K_D<200 µM); 2=inactive (K_D>200 µM)**

	6DXH	6DXT	6NFT	MATCHUP
AUC	0.58	0.53	0.61	0.72

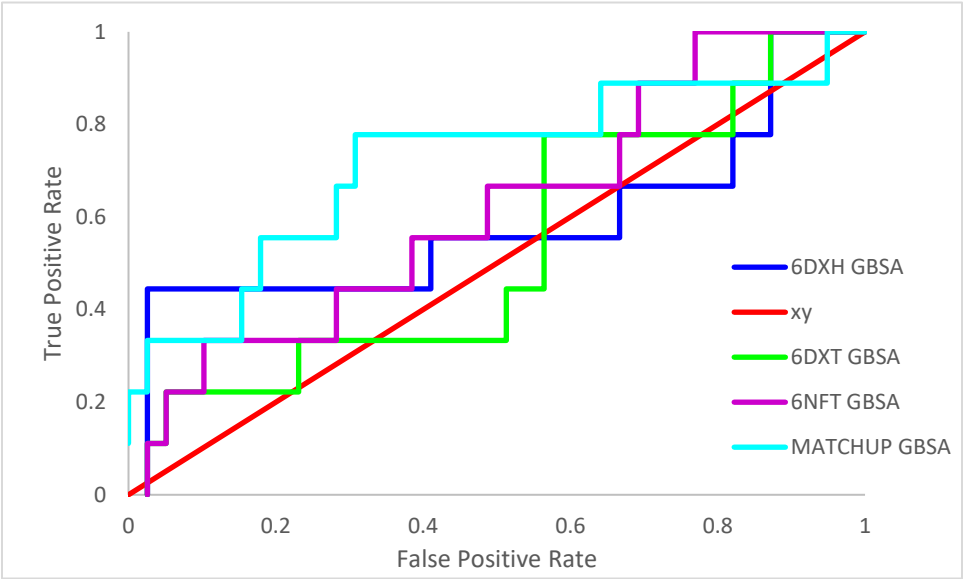


Figure 3. ROC of virtual screen of USP5 Zf-UBD compounds with solvation on

Conclusions & Future Directions:

Self-docking and flexible docking were validated using the MFI FITTED docking platform, as all docking RMSDs were less than 2 Å suggesting successful binding poses in the USP5 Zf-UBD pocket. Structure 6NFT had the best overall average RMSD for cross-docking with the FITTED platform. For virtual screening, flexible docking with MATCHUP results in the best predictive ranking of a library of 48 USP5 Zf-UBD compounds, with solvation GBSA on. Next, MFI's flexible protein docking with MATCHUP will be used to screen larger commercial libraries in the search for different ligand scaffolds against USP5 Zf-UBD.

Mandeep Mann
2019/04/01

References

Corbeil C.R., Englebienne P., Moitessier N. Docking ligands into flexible and solvated macromolecules. 1. Development and validation of FITTED 1.0 *J. Chem. Inf. Model.* (2007), 47, 2, 435-449

Corbeil C.R., Moitessier N. Docking ligands into flexible and solvated macromolecules. 3. Impact of input ligand conformation, protein flexibility, and water molecules on the accuracy of docking programs *J. Chem. Inf. Model.* (2009), 49, 4, 997-1009

Moitessier N., Pottel J., Therrien E., Englebienne P., Liu Z., Tomberg A., Corbeil C.R. Medicinal Chemistry Projects Requiring Imaginative Structure-Based Drug Design Methods *Acc. Chem. Res.* (2016), 49 (9), 1646-1657