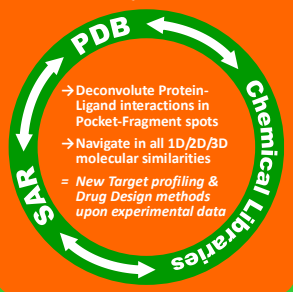
Fc-Rebuilder Software

a C2P component

Chemo Proteomic Platform
to crossmine all your molecular data



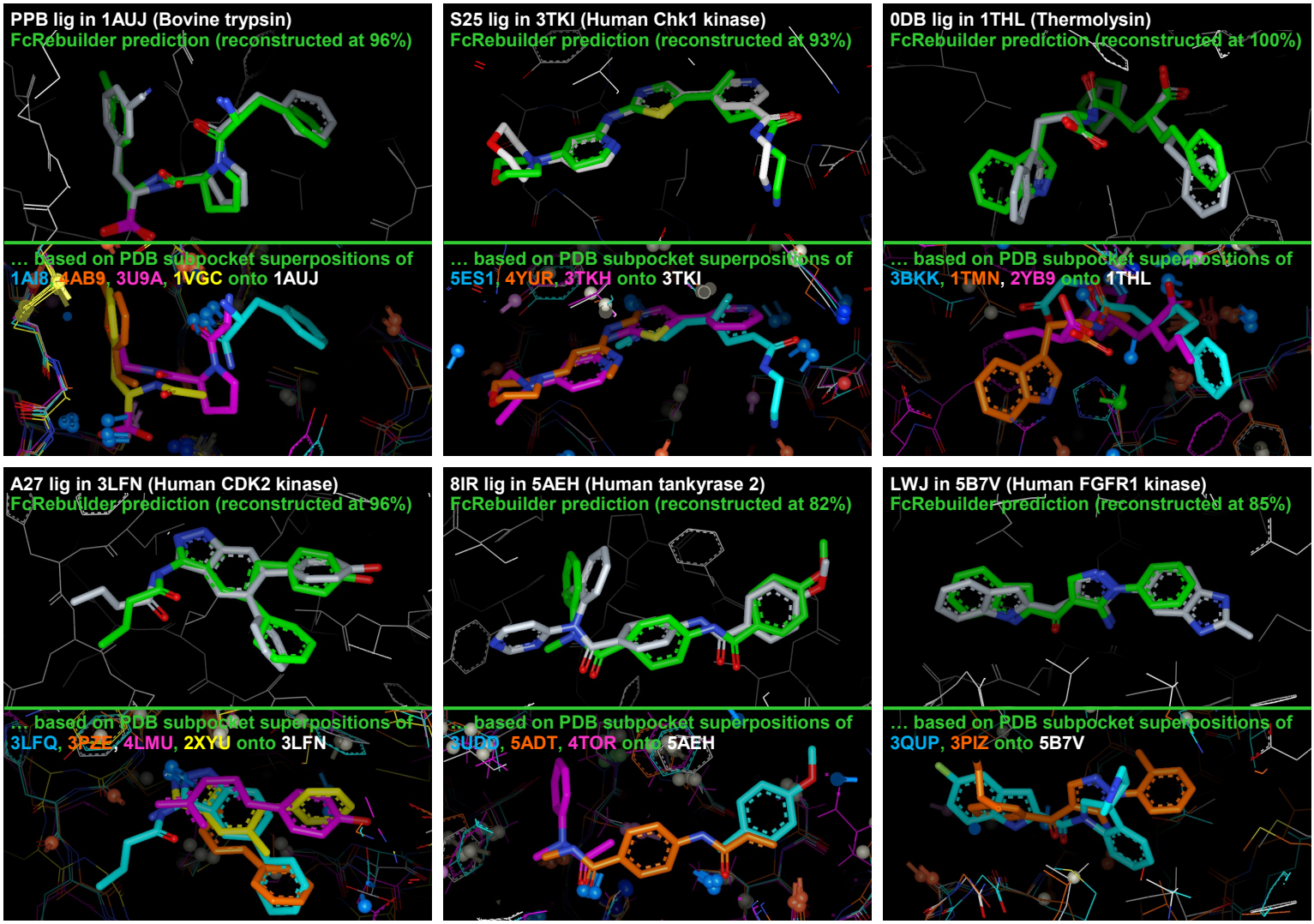
***FcRebuilder* a powerful Drug Design software to predict 3D bound conformation in binding site(s) by mining the PDB biostructural knowledge.** Protein Data Bank is now having more than 140,000 entries (June 2018), it's an attractive source of innovation when mined at subpockets level. From pool of aligned PDB subpocket-ligand structures, *FcRebuilder* is extracting substructures corresponding to the ligand to predict and then combining iteratively these fragments to rebuild as much of the 2D input ligand in a bound conformation. ***FcRebuilder* is bringing a new approach to dock molecules by taking advantage of existing biostructural knowledge.**

***FcLigand* requires in input one or multiple PDB files of protein targets and a SD file of 2D molecules to dock or partially rebuild.**

***FcRebuilder* main features are :** (1) **Connexion to MED-SuMo** software (from MEDIT SA) to drive the subpocket alignment of PDB knowledge onto your targeted binding site; MED-SuMo has now a long track record showing its robustness to align connected sets of 3D surface chemical features across the PDB, (2) **a Graphical Interface** to tune if required the various parameters such as RMSD cutoff to filter out too similar input ligand substructures or the geometrical hybridisation tolerances, (3) **optional connexion to FcBioiostere database** to enrich the pool of aligned ligand substructures by considering bioisosteric pairs onto the output pool of aligned subpocket-fragments, (4) **HeatMap mode** to screen your input list of 2D molecules onto multiple targets, (5) **optional display of all intermediate data** to explore or manually select some ligand substructures found in subpocket alignment step.

FcRebuilder* is a new component of the *C2P* initiative *(Chemo-Proteomic Platform) to cross-mine altogether biostructural database,s structure-activities data and chemical libraries. *C2P* now includes : (a) *FcLigand* to explore 1D/2D/3D ligand/fragment similarities, (b) *FcBioisostere* for lead optimization, (c) *MED-SuMo* to superpose 3D protein interaction surfaces, (d) *MEDP-SiteClassifier* to navigate in all PDB binding site similarities. (e) *FcCutlass* to filter/score with various 1D/2D/3D (protein)-ligand properties, (f) *C2P-Miner* to navigate into binding sites, subpockets, ligands, and fragments based similarities altogether.

Example for 6 PDB ligands: prediction of bound conformation by mining biostructural subpockets in FcRebuilder

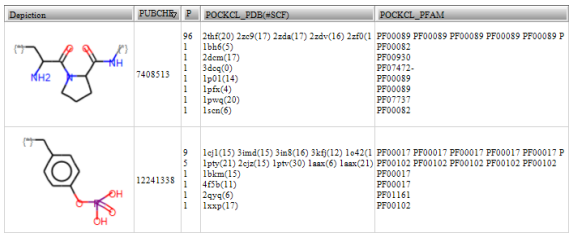


Don't miss PDB biostructural valuable knowledge to predict bound conformations in your drug design process

Conserved Subpocket-ligandSubstructure patterns in PDB biostructural data

Protocol: In a C2P-API C# script, a large set of small Pubchem molecules were crossmined onto a full PDB binding site pairwise comparison to extract for each Pubchem molecules all clusters belonging to similar binding mode within the PDB.

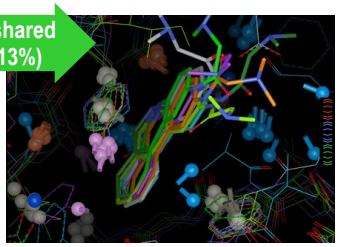
Results: Full results are available on *www.felixc.eu* in *download* section. Here we review 4 fragments with their conserved binding modes across the PDB (columns are respectively Pubchem CID, subpocket clusters with their size, PDB IDs and Pfam IDs per cluster). **These Fragment-to-Subpocket redundancies are valuable information to try to reconstruct bound ligand conformation.**



Depiction	PUBCHEM	P.	POCKCL_PDB(#SCF)	POCKCL_PFAM
	7408513	96	2thf(20) 2zc9(17) 2zda(17) 2zdv(16) 2zf0(1	PF00089 PF00089 PF00089 PF00089 PF00089 P
		1	1bh6(5)	PF00082
		1	2dcm(17)	PF00930
		1	3dcq(0)	PF07472-
		1	1p01(14)	PF00089
		1	1pfx(4)	PF00089
		1	1pwq(20)	PF07737
		1	1scn(6)	PF00082
	12241338	9	1cj1(15) 3imd(15) 3in8(16) 3kfj(12) 1e42(1	PF00017 PF00017 PF00017 PF00017 PF00017 P
		5	1pty(21) 2cjz(15) 1ptv(30) 1aax(6) 1aax(21)	PF00102 PF00102 PF00102 PF00102 PF00102
		1	1bkm(15)	PF00017
		1	4f5b(11)	PF00017
		1	2qyq(6)	PF01161
		1	1xxp(17)	PF00102

Depiction	PUBCHEM			
	1853	9	2q6m(14) 3gsy(19) 4bjb(16) 3ce0(19) 1zm9	PF09009 PF00644 PF00644 PF02877 PF09009 P
		1	4fz7(5)	PF03496
	77417	7	2e4p(14) 4nju(12) 2e4l(15) 3spk(21) 1d4y(1	PF00077- PF00077- PF00077- PF00077- PF0007
		2	2wap(12) 3lj6(11)	PF01425 PF01425
		1	4g16(5)	PF12605
		1	4jtu(8)	PF00998
		1	3zg4(6)	PF00067

The 9 phenanthridone-based PDB ligands shared a similar subpocket (lowest Seq identity is 13%)

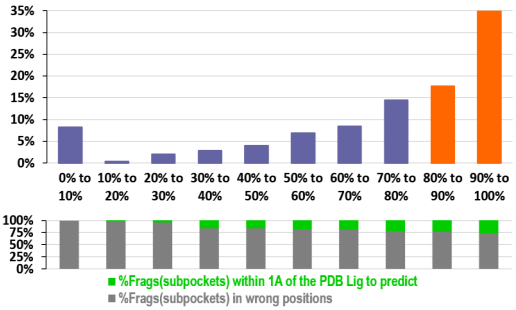


PDB biostructural data to predict 2241 ligand bound conformations?

Protocol: for 2241 ligands co-crystallized in unique PDB structure, we ran this sequence:

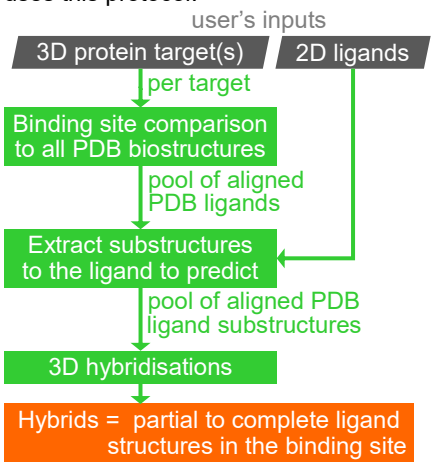
1. MED-SuMo software superposed onto each binding site of reference all similar PDB subpockets defined by small Puchem molecules (alignment driven by interaction features)
2. these aligned Subpocket-Fragment complexes were exported to FcLigand software to extract all 3D MCSs (Maximum Common Substructure within 1A of the ligand to predict)
3. a Javascript FcLigand macro checked which atoms of the reference ligand were 3D predicted by at least one MCS moiety and summarized in a pourcent of recoverable atoms.

Results: The lower plot represents in green the ratio of true positive positions in the each 2241 pools of aligned MCSs. The upper plot represents the distribution of 2241 ligands in respect to the pourcent of recoverable atoms (x axis). **In 52% of the case, more than 80% of the ligand bound conformation could be predicted by PDB data.**

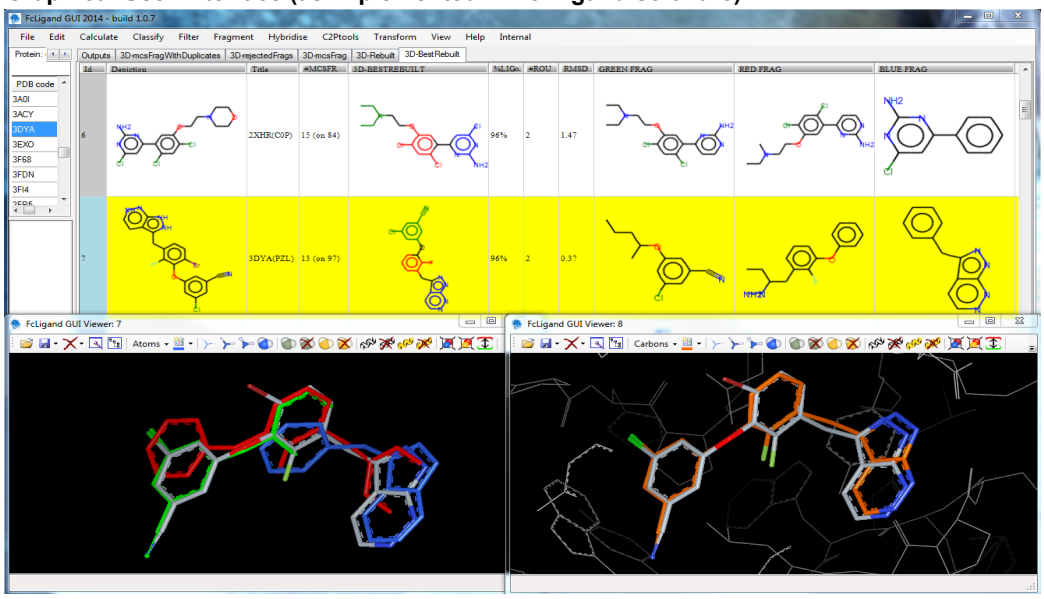


Fc-Rebuilder

Heuristic: Fc-Rebuilder is rebuilding as much as possible from existing PDB ligand substructures the bound conformations of the ligand to predict. It's a complementary technology to virtual screening tools. Fc-Rebuilder uses this protocol:



Graphical User Interface (as implemented in Fc-Ligand software):



Key feature summary

- **Take advantage of experimental PDB biostructural knowledge to predict 3D binding modes of input 2D ligands**
- **Include a remote connexion to *MED-SuMo* server to align PDB subpockets onto your binding site(s) of interest**
- **Heat-Map mode to manage rebuilding on multiple targets**
- **Optional connexion to *FcBioisostere* database to enrich rebuilding performances with PDB-based bioisosteric pairs**
- **Fast and optimised for multicore processors**
- **Smart user interface in MS-Windows *FcLigand* GUI to further explore results (filters, clustering, scores, …)**

To test the software or get pricing, please contact : info@felixc.eu or Tel +33 (0)6 7513 0847

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HT-Molecular Data Mining