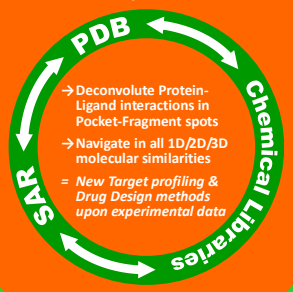
Fc-Ligand Software

a C2P component

Chemo Proteomic Platform
to crossmine all your molecular data



***FcLigand*, a powerful cheminformatic software for Lead Generation and Lead Optimisation has been designed to take advantage of biostructural and chemical library information**. Protein Data Bank is now having more than 89000 entries with protein(s) -ligand(s) complexes (June 2016), it's an attractive source of innovation when mined with a software such as *MED-SuMo* from MEDIT to 3D compare and superpose protein/ligands in binding sites or sub-pockets. From such pool of ligand/fragment alignment, *FcLigand* provides a rich environment to deconvolute ligands in smaller entities, or to 3D combine fragments and ligands in larger molecules with a chemical diversity few times higher than the PDB. ***FcLigand* is essential for FBDD (Fragment-Based Drug Design).**

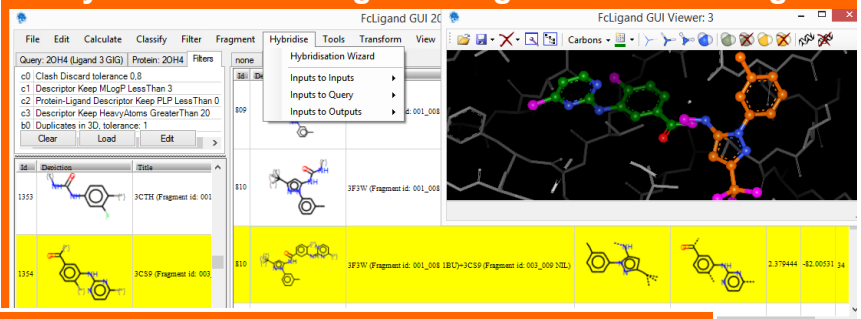
***FcLigand* can manage 3 sorts of input material :** (a) pool of molecules aligned in a 3D protein binding site, (b) aligned molecules without 3D target, or (c) set of 2D molecules.

***FcLigand* provides into a chemical spreadsheet many methods for:** (1) **3D-Hybridisation** to combine in 3D pre-aligned molecules by detecting overlapping bonds, fusing rings or bonding non-overlapping pair of molecules, (2) **Fragmentation/Deconvolution** based on graph or chemistry rules to list fragments and scaffolds, (3) **1D/2D/3D Filters** to refine/select the set of chemical compound based on advanced filtering rules including list of unwanted chemistry, (4) **2D sub/super/MCS-structures searches**, (5) **clustering and classification** on various fingerprints

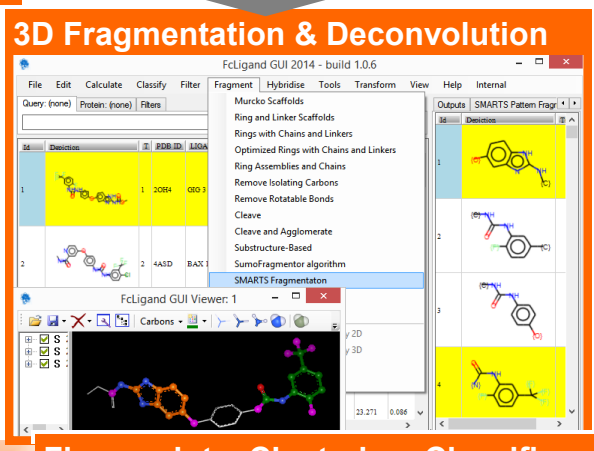
FcLigand* is a component of the *C2P* initiative *(Chemo-Proteomic Platform) to cross-mine altogether biostructural database, structure-activities data and chemical libraries. *C2P* includes : (a) *FcBioisostere* for bioisosteric replacement, *MED-SuMo* to superpose 3D protein interaction surfaces, (c) *MEDP-SiteClassifier* to navigate in all PDB binding site similarities.(d) *FcCutlass* to filter/score with various 1D/2D/3D (protein)-ligand properties, (e) *FcHitsBinding* to 3D-rebuild an input 2D molecule from a pool of aligned molecules.

***FcLigand* Input = pool of 3D aligned ligands/fragments (eg. exported from binding site superposition by *MED-SuMo*) or set of 2D ligands/fragments**

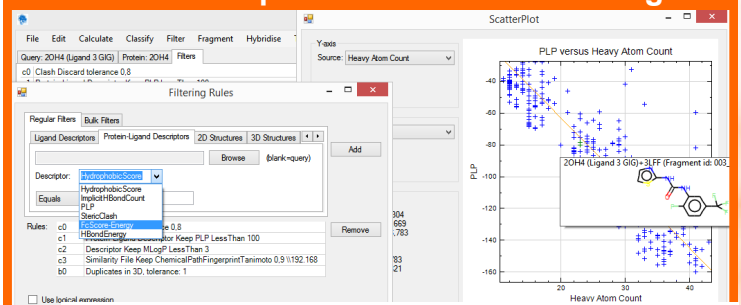
3D Hybridisation of fragments/ligands and Filtering



3D Fragmentation & Deconvolution

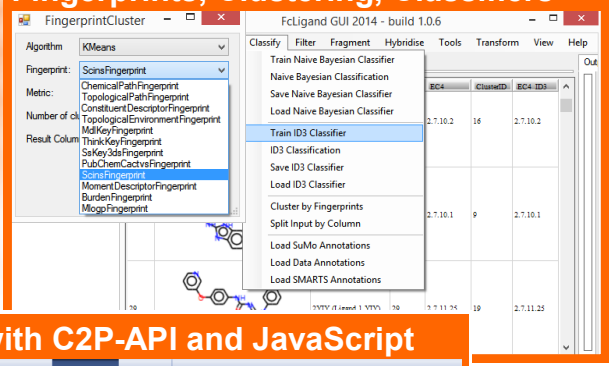


1D/2D/3D Descriptor calculation & Filtering

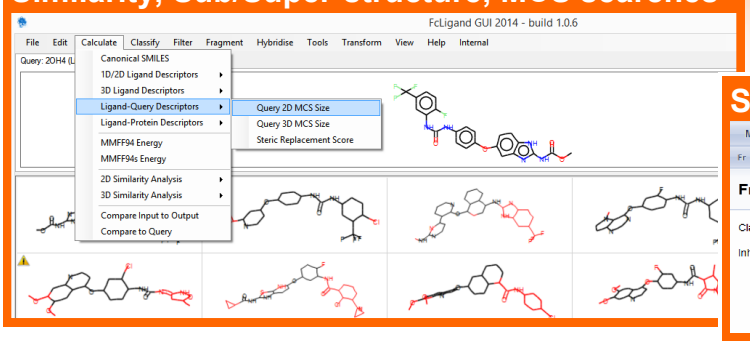


FcLigand 2D/3D Chemical Spreadsheet

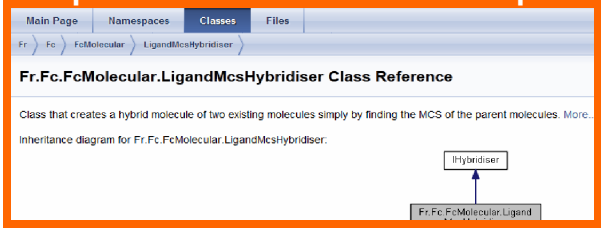
Fingerprints, Clustering, Classifiers



Similarity, Sub/Super-structure, MCS searches



Script with C2P-API and JavaScript



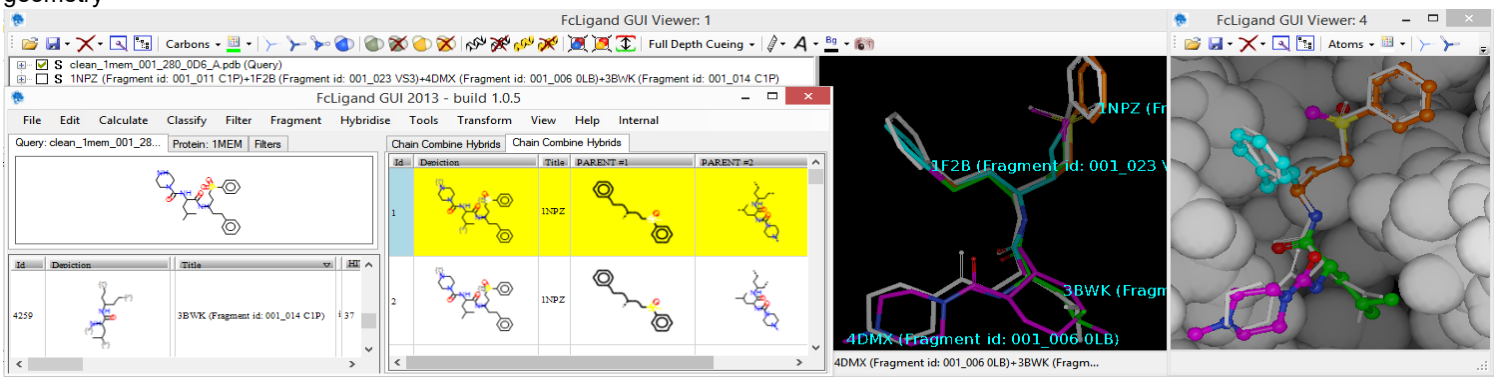
Hybridise or Deconvolute pool of 3D ligands/fragments
innovative solution for Ligand Design and Lead Optimisation

Lead Generation on Cathepsin-K

Input : A pool of 2127 PDB 3D-aligned fragments by MED-SuMo (superposition of protein chemical features) onto human cathepsin-K 1MEM binding site where 1MEM ligands/fragments were removed

Protocol: 2 hybridisation rounds with ChainCombine mode combining pair of fragments having an overlapping bond of similar geometry

Results: OD6(1MEM) vinyl sulfone inhibitor in grey is rebuilt in a similar conformation to PDB coordinates, from 4 input 3D fragments:
- frag6 0LB (4DMX, cathepsin-K) **in magenta**
- frag23 VS3 (1F2B, cruzain protein, 44% id seq to cathepsin-K) **in cyan**
- frag14 C1P (3BWK, falcipain-3 protein, 51% id seq to cathepsin-K) **in green**
- frag11 C1P (1NPZ, cathepsin-S, 60% id seq to cathepsin-K) **in orange**



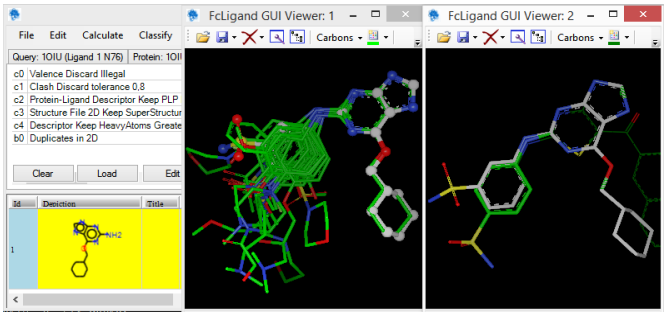
Lead Optimisation on a CDK2 inhibitor

Input: ATP competitive CDK2 inhibitor 3-{[6-(cyclohexylmethoxy)-9H-purin-2-yl]amino}benzenesulfonamide, pdb code 1OIU-N76, IC50=210nM

Tentative: try to optimize the benzenesulfonamide group

Protocol: from 323 aligned PDB human CDK2, corresponding ligands are 3D hybridised with ChainCombined mode (combining pair of fragments having an overlapping bond of similar geometry) on N76 input molecule. Filters upon hybridisation include 2D superstructure match to the N76 scaffold, PLP protein-ligand score cutoff, 2D duplicate check.

Results: 33 analogs were generated ; hybrid combining ligands N76 (1OIU) in white with **20Z(3RMF) in green IC50=82µM** (right view) where sulfonamide moved to para position and matchs to ligand 4SP(2IW9) with



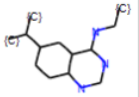
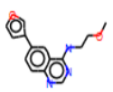
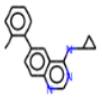
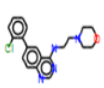
Ligand deconvolution on CLK4 inhibitors to characterize frequent functions

Input: 1352 substances have been tested in a CDC-like Kinase 4 inhibition assay (AID1771: 356 active and 747 inactive).

Tentative: highlights fragments having specific modes of binding.

Protocol: in the C2P initiative, 2D pubchem-like fragments of 3D PDB ligands are classified according to pocket similarity defined by 3D interaction surfaces (HBond donor/acceptor, charges, hydrophobic groups, …) and by Pfam codes of the initially bound protein. Fragments are exported in a SD file with cluster annotations and stored for ligand deconvolution. In FcLigand, a javascript protocol using substructure search command as available in C2P API was set up to build and display the relations between the input set of 3D/2D ligands and 2D pubchem-like PDB fragments.

Results: the represented fragment (CID:84759) is included in 118 active and 2 inactive ligands (4 active ligands are displayed hereunder). In the PDB, it is a substructure of 10 ligands that bind to proteins of the kinase family (PF00069).

Depiction	LIG2D_COUNT	FRAG2D_ACTIVITY	PUBCHEMCID	PFAM_LIST	LIG2D(3)	LIG2D(	ACTIVI	LIG2D(4)	LIG2D(	ACTIVI	LIG2D(5)	LIG2D(	ACTIVI	LIG2D(6)	LIG2D(	ACTIVI
	120	0.98	84759	10_PF00069 3_PF07714 1_PF00587 1_PF00141 1_PF00452		3234019	Active		3235346	Active		3232871	Active		3235337	Active

Key feature summary

- **3D hybridisation methods on aligned molecules**
- **Powerful filters to (1) drive in direction of chemical libraries, (2) manage duplicates in 1D/2D/3D, (3) control the chemical diversity, (4) apply 1D/2D/3D molecular descriptor profiles, (5) select best intermolecular binding scores.**
- **Multiple fragmentation rules to deconvolute input molecules in fragments/substructures**
- **Various 1D/2D/3D molecular descriptors including logBBB, polar surface area, solubilities, and unwanted chemical lists**
- **Build predictive models by training a classifier**
- **Run Javascript with any methods from C2P API**
- **Optimised for multicore processors**
- **MS-Windows based 2D/3D chemical spreadsheet supporting smile, sdf, mol2, pdb file formats**

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