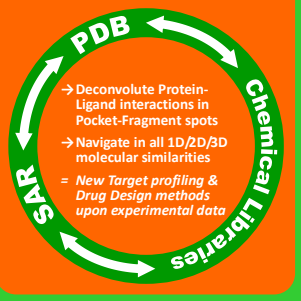
FC-Bioisostere

a C2P component

Chemo Proteomic Platform
to crossmine all your molecular data



FC-Bioisostere* software from *Felix Concordia SARL opens access to 3D bioisosteric replacement onto your molecule of interest to find chemical groups having similar 3D biological interactions. While maintaining target potencies, it helps Chemists to optimize additional properties in pharmacokinetics and metabolic response, and/or to escape from existing patents by selecting alternative equivalent chemical groups.

***FC-Bioisostere* is a 2 step application:** First, users can automatically build a database of 3D bioisosteric fragment pairs from :

-1a- an input set of pre-aligned ligands (3D SD files) where pairs of 3D overlapping fragments are detected and stored ; or

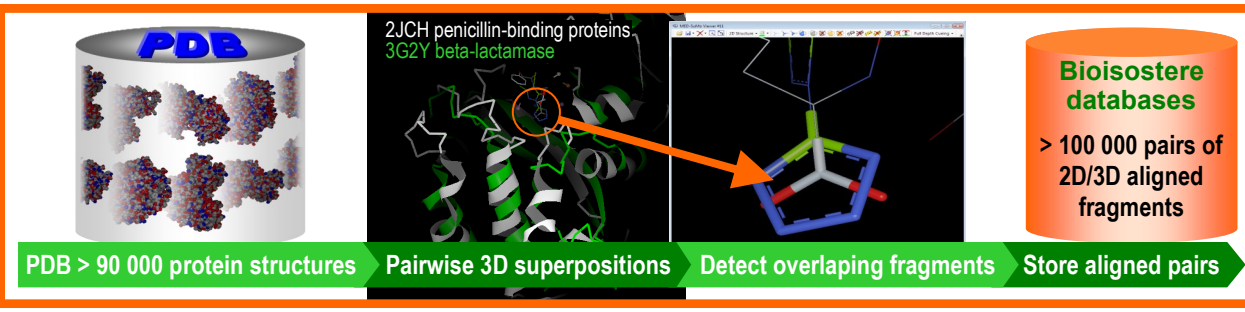
-1b- by driving *MED-SuMo MEDIT SA* software to extract from the *PDB* files (*Protein Data Bank*, ~90000 protein) and/or your in-house bio-structural data all local protein-ligand similar superpositions (defined by charges, Hbond, hydrophobic, aromatic, ... interactions); or

-1c- alternatively we provide pre-computed databases of bioisostere pairs built upon the whole *PDB* prepared by *Felix Concordia* experts.

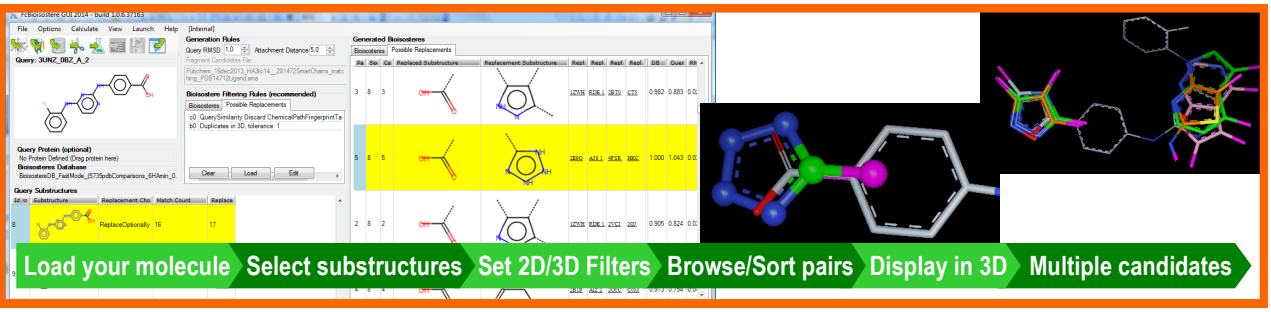
Second, the input molecule of interest is deconvoluted in fragments (6 methods). Once fragments to be replaced are selected, all fitting replacement pairs of fragment are retrieved from the database. Different methods to merge/fuse those fragments into the input molecule are provided to generate full bioisosteres. 1D/2D/3D chemical and protein scoring filters help to sort/focus on the best bioisostere candidates.

FC-Bioisostere* is a component of the *C2P Chemo-Proteomic Platform to cross-mine altogether biostructural, structure-activities and chemical libraries data. *C2P* includes : (a) *MED-SuMo* to detect/superpose 3D protein surface interactions, (b) *MEDP-Fragmentor* to deconvolute protein-ligand structure in pocket-fragment interactions, (c) *MEDP-SiteClassifier* to navigate in all intra-famillly/inter-family similarities between binding sites across the full PDB, (d) *FcLigand* to explore 1D/2D/3D ligand/fragment similarities, (e) *FcHybridise* to combine in 3D fragments, (f) *FcCutlass* to filter/score according to 1D/2D/3D ligand and protein-ligand properties.

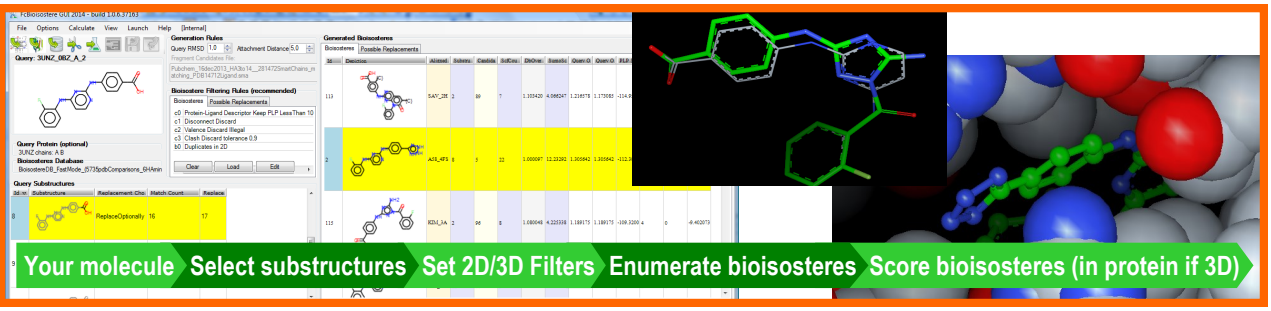
Bioisostere database



Exploring possible replacements



Scoring bioisostere candidates



Chemo-Proteomic software approach using all biostructural data
to provide an innovative environment for bioisosteric replacement
from interaction-surface similarities measured between 3D Protein-Ligands

Case study with *FcBioisostere* software

Context: The alkenyldiarylmethanes (ADAMs) are a class of potent and highly specific HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs). Unfortunately, most of the ADAMs are too unstable toward hydrolysis in blood plasma to be considered as potential therapeutic candidates. A series of alkenyldiarylmethanes (ADAMs) with a benzo[d]isoxazole ring in place of the metabolically unstable methyl ester moiety and an adjacent methoxyl group were synthesized by [1]Deng *et al.* The authors demonstrated that the benzo[d]isoxazole ring is an effective bioisosteric replacement of the metabolically labile methyl ester moiety in ADAMs.

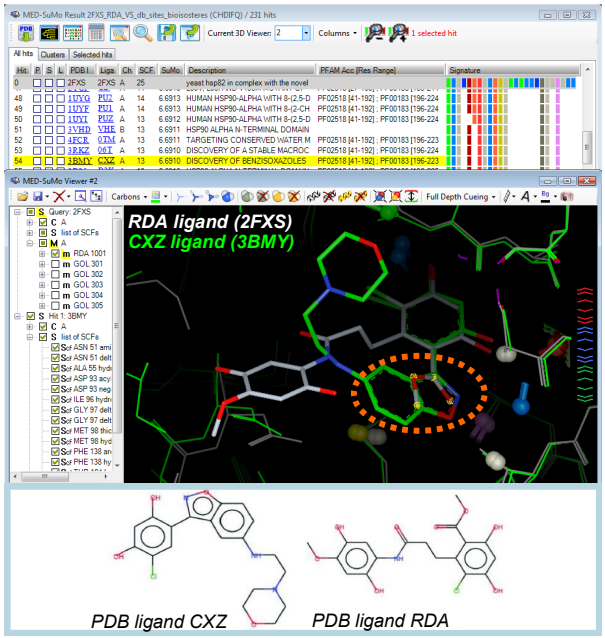


Fig.: *MED-SuMo* showing the superposition of pockets RDA in HSP82 protein (2FXS in white) and CXZ of HSP90 protein (3BMY in green) ; Surface Chemical Features used for 3D superposition are shown (balls and ball&sticks) ; the dash line highlights the overlap between methyl ester and benzo[d]isoxazole groups.

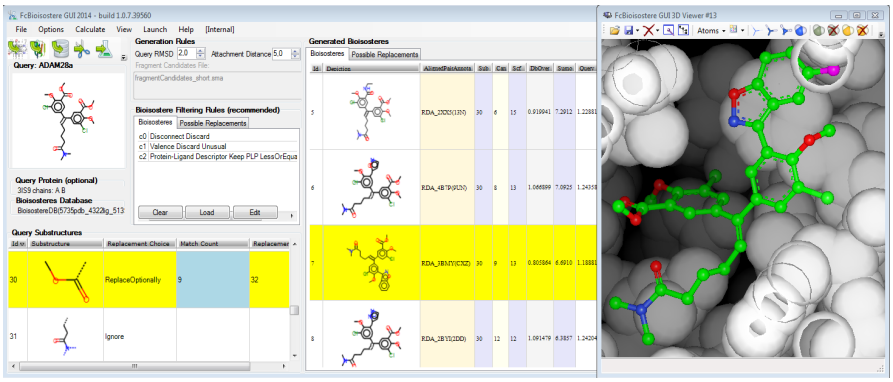


Fig.: *Fc-Bioisostere* on ADAM28a ; Query & QuerySubstructures on the left ; PossibleReplacements and Bioisosteres on the middle ; 3D display with 3IS9 on the right

FC-Bioisostere protocol[2] to explore bioisostere candidates on ADAM:

1) Database: we build a database of bioisosteric pairs by driving *MED-SuMo MEDIT* software from *FC-Bioisostere*: a whole set of 5139 protein-ligand binding site queries (Res<2,5A ; 350<MW<550 ; PDB_occurencies<11 ; Sept2013) are performed toward all PDB (SuMoScore>6 ; MaxHit=100). From those ligand superpositions, a Database of 376096 pairs of bioisosteric fragments is generated (Fragmentor mode to deconvolute PDB ligand in fragments with a list of 281472 Pubchem fragment having 3 to 13 atoms ; FragmentCandidate>5Heavy/dummy Atom ; 2D filter per binding site ; [2]SealScore_to_detect_overlaping_fragment>0,7).

2) Query: we load a 3D model of ADAM28a[3] (BindingDB_2786) as the starting point for bioisostere enumeration. This Query is deconvoluted in 49 QuerySubstructures according to 2D matches to Database, only methyl ester is selected.

3) Possible replacement: 2D searching this methyl ester in Database retrieves 28 possible replacements (RMSD_to_QuerySubstructure<2A), including the methyl-ester/benzo[d]isoxazole bioisoster (as detected by *MED-SuMo*, see Fig. on the left)

3bis) Bioisostere enumeration: 18 molecules are generated including the benzo[d]isoxazole bioisostere (see Fig. above) by using TwoWayAttachment algorithm for bioisostere recombination (filter on disconnected molecule and bad valences)

[1]Deng BL, Zhao Y, Hartman TL, Watson K, Buckheit RW Jr, Pannecouque C, De Clercq E, Cushman M, Eur. J. Med. Chem. 2009 Mar, 44 (3), 1210–4
[2]Moriaud F, Adcock SA, Vorotyntsev A, Doppelt-Azeroual O, Richard SB and Delfaud F, ACS Symposium series1076, Chapter book 5, p71-88

Summary

- **Access to unique bioisosteric rules observed by mining similar protein-fragment interactions in biostructural data (Protein Data Bank) with *MED-SuMo MEDIT*'s technology**
- **Drive *MED-SuMo-server* software over the whole PDB in few clicks (requires a separate license for *MED-SuMo-server*)**
- **Generate various bioisostere databases to focus on best PDB material to get faster performance, or to orient around a specific protein or ligand family**
- **Can be used in stand-alone mode on a simple MS-Windows computer by using pre-calculated bioisosteres databases (sell by *Felix Concordia SARL*)**
- **2D/3D chemical spreadsheet and viewer**
- **Multiple fragmentation algorithms to deconvolute ligands and input molecule in fragments/substructures**
- **Powerful filters (1) to manage in 2D/3D duplicates, (2) to control the chemical diversity, (3) orient the process in direction to chemical supplier library**
- **Review pair of bioisosteric fragment on your input molecule**
- **Protein binding score to sort bioisosteric candidates (in case you have a protein target structure)**
- **Export possible replacements and bioisosteres SD files format**
- **MS-Windows based intuitive graphical interface**

To test the software or get pricing, please contact:

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Felix Concordia

HT-Molecular Data Mining