Introduction to designing new molecules in Forge

Cresset India Symposium 2016
Cresset application philosophy

> Find new ways to discover or view compounds and data that provide results which would otherwise be missed

> Deliver this new science in easy-to-use interfaces with minimal learning curves
   > GUIs, command lines, KNIME nodes, Pipeline Pilot components ….

> Ligand based applications
   > Forge, Spark, Blaze, Torch
Detailed electrostatics from XED

> eXtended Electron Distribution gives detailed electrostatic interaction patterns

Separation of π- and σ- charges enables modeling of substituent effects

XED adds p-orbitals to get detailed representation of atoms

= Positive
= Negative
Electrostatic and shape similarity

Score

Virtual screening scaffold hopping

Fields 0.66

Combined 0.82

Bioactive conformation hypothesis

SAR interpretation molecule design

Pose

Shape 0.98
Grant, Gallardo, Pickup, *J. Comp. Chem.*, 1996, 1653
Comparing structurally disparate molecules

Bioisosteres

Bioisosteric groups

PDB:2ogz

PDB:3g0g
Understanding and using SAR to improve molecule design and intellectual property
Understand structure-activity using Forge

> Uses ligand alignment as a basis for SAR interpretation
> Ligands aligned to a reference or ‘template’ using
  > Electrostatics and shape
  > Shape only
  > Substructure

> Align single chemotype
  > Decipher complex SAR
  > Understanding design of new molecules

> Aligned many chemotypes
  > Virtual screening (small scale)
  > Relating activities from different series
  > SAR transfer
  > Bioactive conformation hypothesis
Forge design workflow

Yes

Load ligand as reference

No

Use low energy conformation

Develop pharmacophore (FieldTemplater)

‘Protein guided’ – electrostatics and shape

Align to references

‘Ligand guided’ – field guided substructure

Build 2D and 3D QSAR models

Use score for virtual screening

Score designs against QSAR models

Design new molecules

Summarize SAR in Activity Atlas models

Look for 2D and 3D activity cliffs (Activity Miner)

Design against Activity Atlas models

Ligand conformation known?

Ligand conformation known?

Use low energy conformation

Load ligand as reference
Launch Forge

Click **New Project**
Choose a project template

Click **Align Molecules**
Bring in reference molecule from protein

Click **Protein**
Bring in the protein

Click **Browse**

Choose **1oit.pdb**

Then click **OK**
Protonation state

Choose **Let Forge choose the protonation state**

Click **Open**

Then click **Next**
Split PDB into protein and ligand

- Sort the table on Structure to show the ligand
- Click on the ligand structure
- Click **Use as Reference**
- Click **Delete Waters**
- Click **Import as Protein**
Protein loaded

Click **Next**
Load molecules to align

Click **Browse**

Choose `cdk_test_IC50.sdf`

Click **Open**

Choose *Let Forge choose the protonation state*

Click **Finish**
Align molecules

Choose **Normal** for both Conformation Hunt and Alignment

Click **Start**
Forge GUI
Choose your windows and layout

> Structures
  > Tiles (Choose what data)
  > Spreadsheet (Molecules)

> Project Notes
  > Good for keeping track of what you’ve done

> Filters
  > Finding the interesting molecules in a larger dataset

> Storyboard
  > Capture a scene for posterity
  > Create a Story
  > An interesting molecule

> Radial Plot
  > Summary for individual and multiple molecules
  > Also present in Molecules and Tiles windows

> Radial Plot Properties
  > Set up the radial plot
  > Use to set a project profile for scoring

> QSAR Model
  > Controls the view of the QSAR model
  > Only useful with QSAR models
Simplified Forge GUI

- Project notes
- Filters window
- Storyboard window
- Molecule Table
- Reference
- Training Set
Molecules table

- Calculated columns
- Molecule Roles
- Colored by Radial Plot profile
- Click here to open Expanded View
- Favorite
- Score for best alignment or best preferred alignment
Choosing what is shown in the 3D View

- Show/Hide all reference molecules
- Show/Hide all molecules marked as favorites
- Show reference molecule separately
- Show/Hide Model features
- Show/Hide all molecules marked as protein molecules
- Show/Hide selected molecules
- Show molecules in a grid display rather than overlaid
Separate vs Grid
Choosing how structures are displayed in the 3D View

- Reset display
- Show/Hide hydrogens
- Show/Hide Field points
- Change molecule color
- Label atoms or structure

- Show/Hide structure
- Show/Hide XED atoms
- Show field points as:
  - Spheres
  - Tetrahedra
  - Cubes
  - ...

- Show/Hide hydrogens
- Show/Hide XED atoms
- Show/Hide Field points
- Change molecule color
- Label atoms or structure

- Show/Hide structure as:
  - Lines
  - Thin sticks
  - Sticks
  - ...

- Remove all surfaces
- Show/Hide positive Field
- Show/Hide shape Field
- Change Field contour level
- Show/Hide solvent surface
- Show/Hide negative Field
- Show/Hide hydrophobic Field
The Chooser

Selected Molecule:

and

Selected Molecule:

-ve

All References

and

Selected Molecule:

-ve

All Ligands

and

Selected Molecule:

-ve
Alignments and scores
Design a new molecule based on the 1PXO ligand

1pxo ligand is a fragment that can be ‘grown’ to approximate the field points associated with the phenyl sulphonamide in the reference.
Edit a copy of the 1PXO ligand

Right-click on the 1pxo ligand and choose Edit a Copy.
Molecule Editor

Right-hand button bar has buttons for showing/hiding reference molecule, protein, and 3DQSAR model information.

Sim score shown in lower left-hand corner.

Change the title – 1pxo+Ph – or make any notes.
Grow the molecule using the Molecule Editor

Phenyl has been added to the terminal amine, and the bond rotated to get a similar conformation to the reference.

Sim score has increased.

Press Process to conformation hunt and align the new molecule.
Alignment results
Find the new molecule and create a new Role

> Find your new molecule
> Right click on it
> Select ‘Set Role → New Role’

![New Role Dialog]

Role Name ➔ ‘Designs’
Description ➔ ‘Molecules that have been designed but not made yet’

> Examine Tile or Molecules window – find the new role and new molecule
Visualize in the protein active site
Coloring in the Molecules Table
Radial Plot and multi-parameter optimization

> Radial plot allows for simultaneous viewing of numerical parameters

> Customizable

> By default, the smaller the area encased in green, the better the properties
Expansion tasks

- **Tagging**
  - Tag 2 results with 'Like'
  - Tag 3 results with 'Good'
- **Filter to find the 5 tagged results**

- **Create a radial plot profile**
  - MW 300-400
  - SlogP 2-4
  - BIF 65-80
- **Order results by Radial Plot score**

- **Create an image of 2 results in PowerPoint**
- **Export 2 results to a drawing program**
- **Send 1 result to Forge for editing**

- **Use Filters to**
  - Find all results with MW < 396
  - Find all results with TPSA between 60 and 90
Torch features

> Combine multiple numerical properties into a single score
> Create a project profile for physico-chemical (or other) properties
> Add properties from external server
> Color by fit to profile
  > 2D
  > 3D
> Interactive scatter plots and histograms
> Storyboard to record important 3D views
> Split datasets into roles
> Tag molecules across roles
> Record experiments in Project notes

> Design in 3D
  > Reject designs that make no sense in 3D
> No protein required – wholly ligand based approach
> Protein can be used data used in visualization
> Electrostatic focus reveals more detail than available from 2D design
> Enables hypothesis led design
Questions welcomed

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