



Becoming a power user of Forge

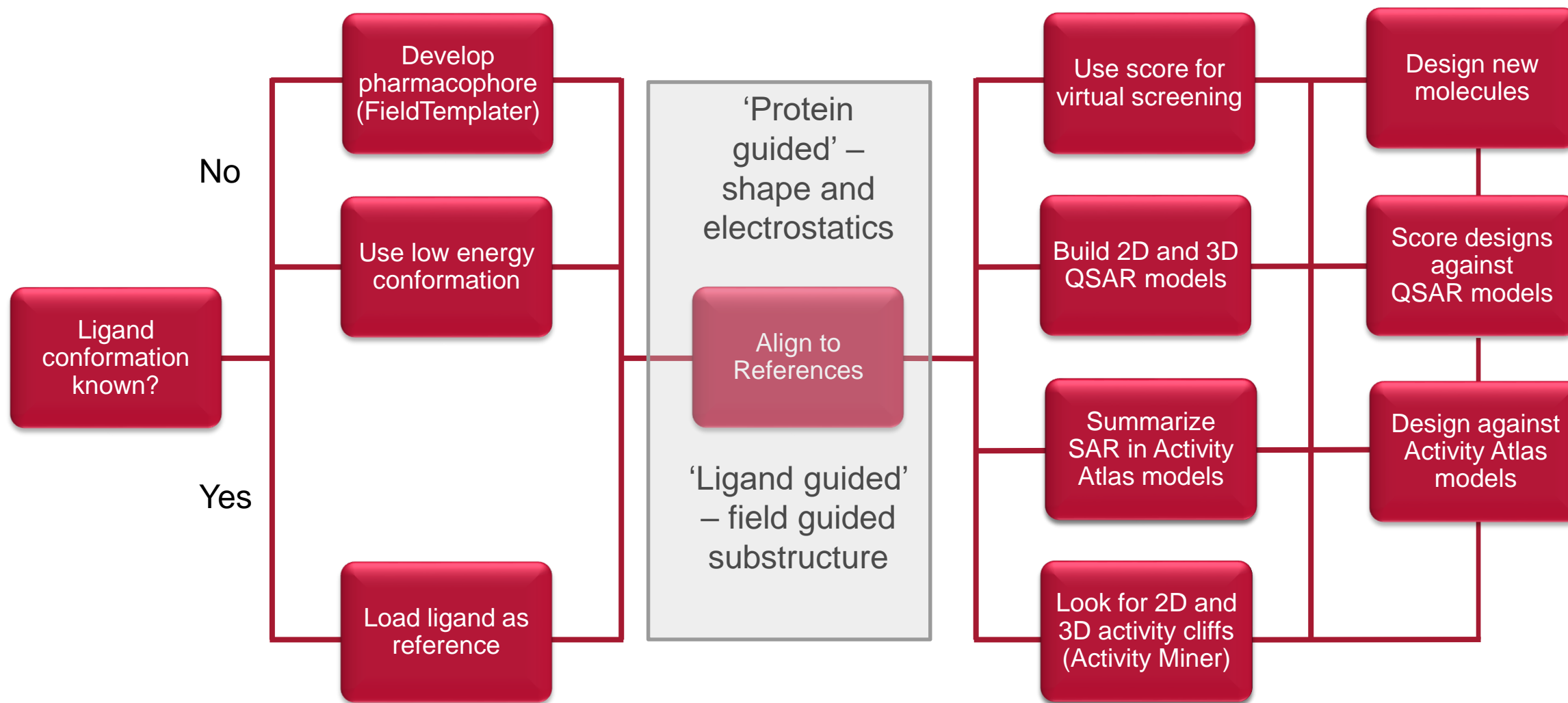
Cresset European User Group Meeting – Workshops

June 2016

Files for this workshop

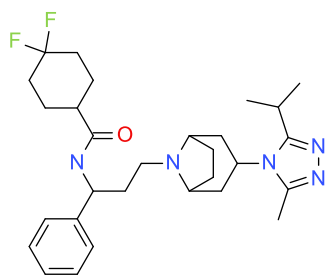
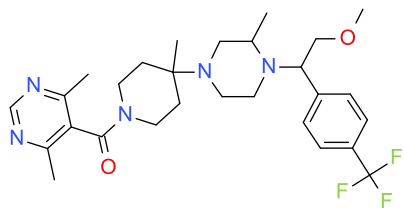
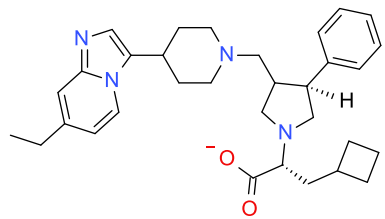
- > The files used in this workshop are available for download on request
- > Please send an email to enquiries@cresset-group.com stating the name of the workshop

Forge workflow

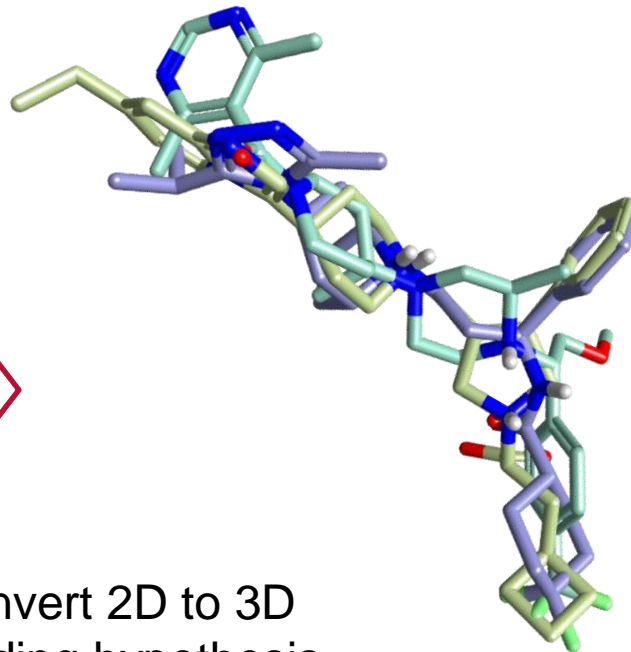


Core Forge experiments

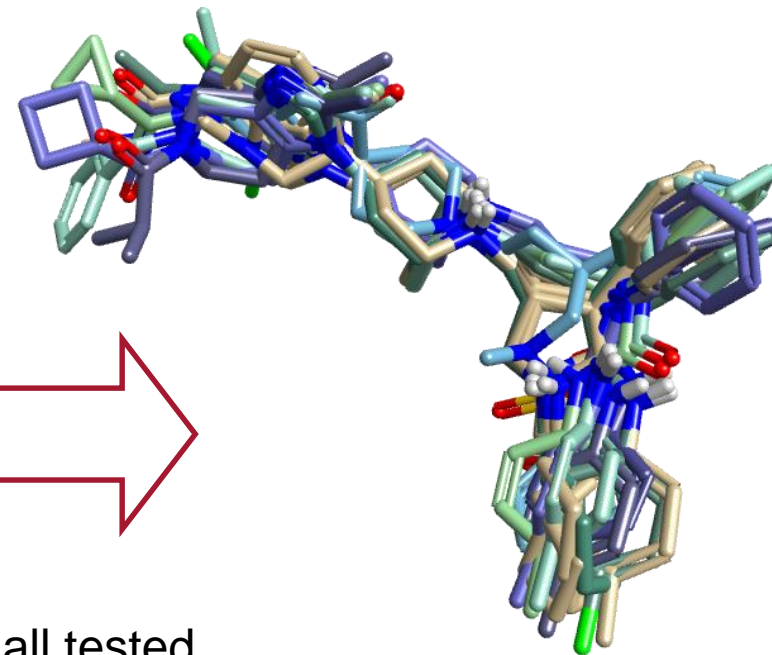
3 CCR5 actives



Convert 2D to 3D
binding hypothesis



Align all tested
compounds



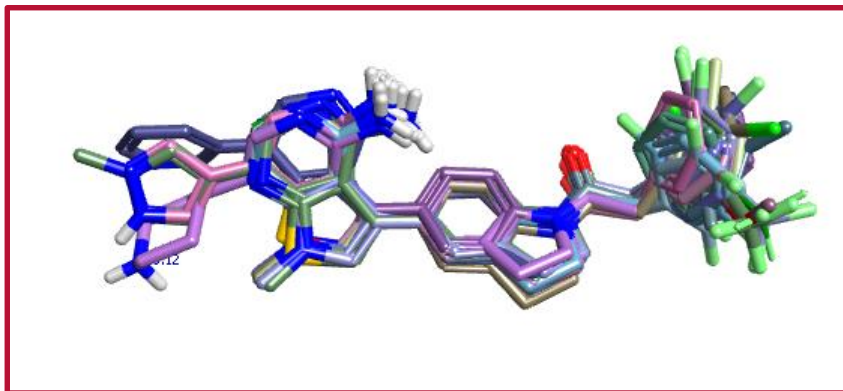
Understand structure-activity using Forge



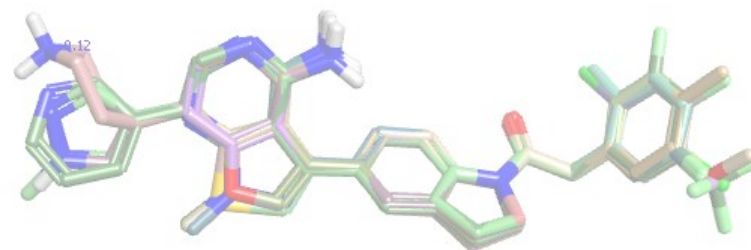
- > Uses ligand alignment as a basis for SAR interpretation
- > Ligands aligned to a reference or 'template' using
 - > Electrostatics and shape
 - > Shape only
 - > Substructure
- > Templates from XRAY or built-in FieldTemplater module
- > Aligned ligands from multiple chemotypes used for
 - > Virtual screening
 - > Relating activities from different series
 - > SAR transfer
- > Align ligands from single chemotype used for
 - > 3D activity cliff analysis
 - > Activity Atlas Models
 - > 3D QSAR
 - > Understanding design of new molecules

Which alignment. Normal or (Maximum Common) Substructure?

Normal



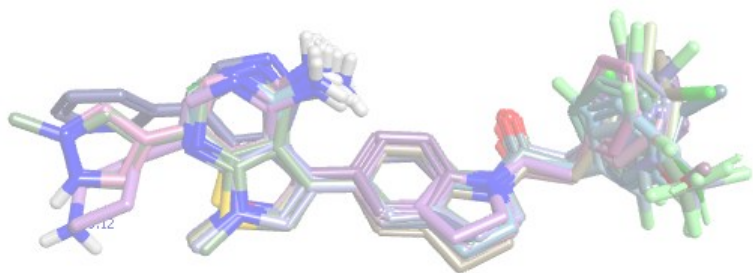
Substructure



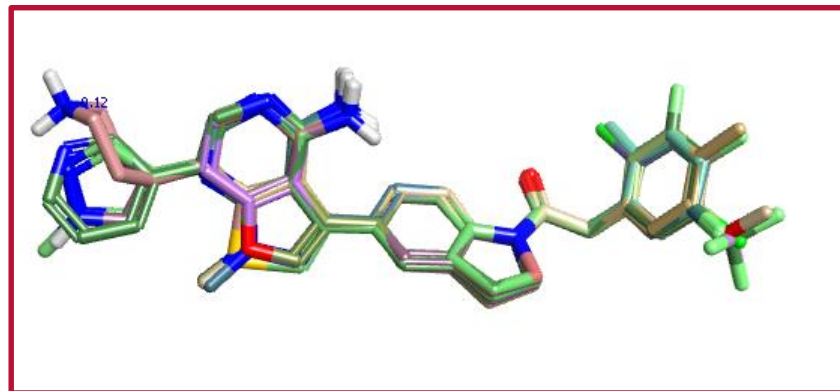
- > Normal: Field-based alignment
 - > Uses Cresset electrostatic, shape and hydrophobic field points to align
 - > Scored 50% field-based similarity with 50% shape similarity
 - > Independent of chemical structure
- > Better for datasets that have structurally diverse compounds

Which alignment. Normal or (Maximum Common) Substructure?

Normal

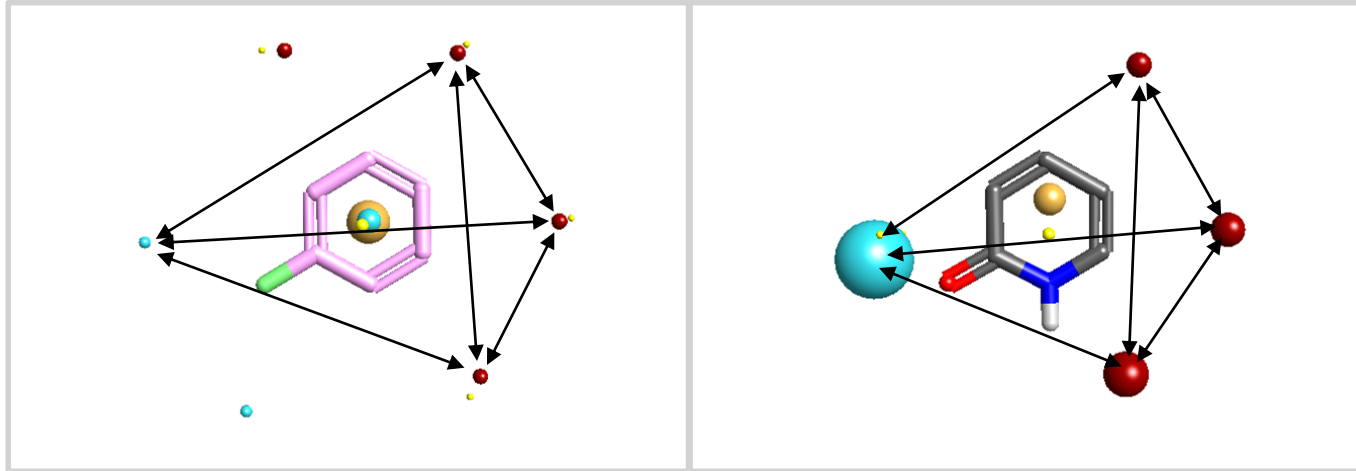


Substructure

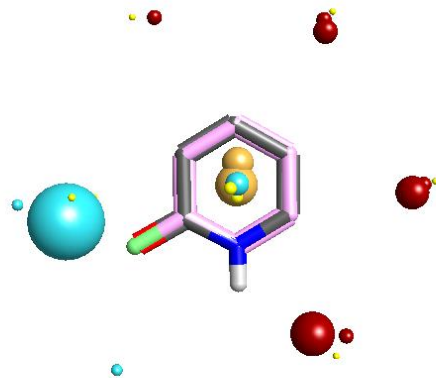


- > Maximum Common Substructure alignment
 - > Common structural features in database molecules are mapped onto conformation of corresponding features in reference molecule
 - > All other parts of the molecule are conformationally hunted
 - > Field/shape based scoring
- > Good for datasets with a common core or concentric series

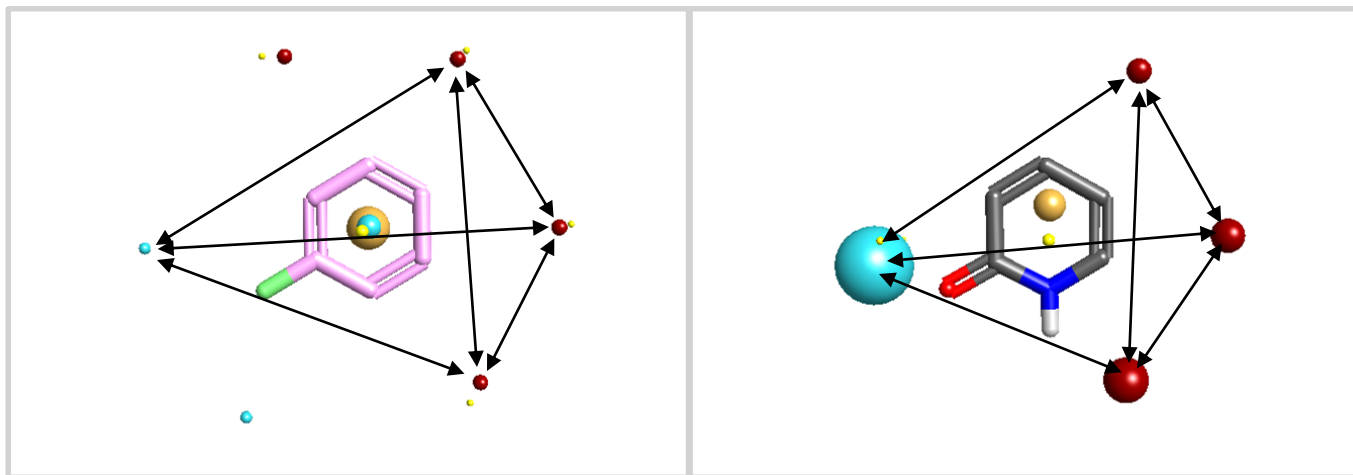
Field based alignment



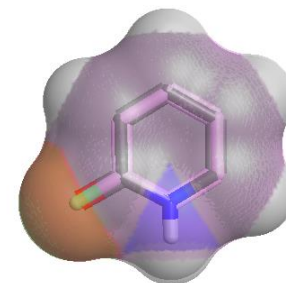
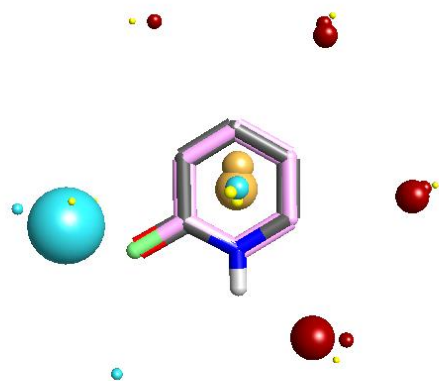
Fields
0.66



Field based alignment and scoring



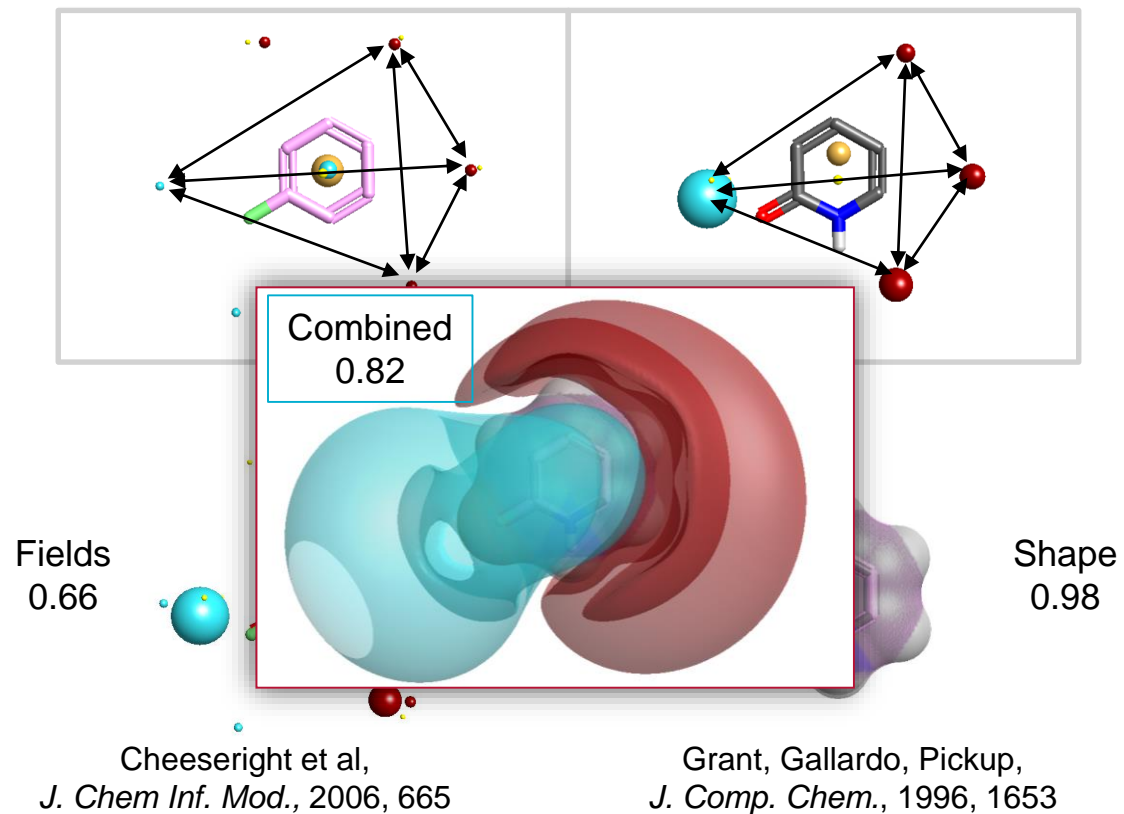
Fields
0.66



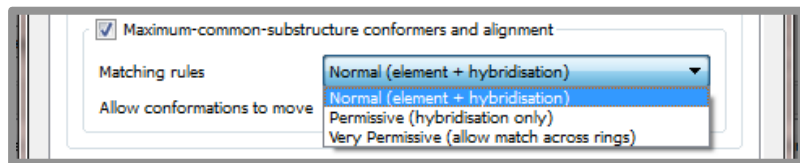
Shape
0.98

Cheeseright et al, *J. Chem Inf. Mod.*, 2006, 665

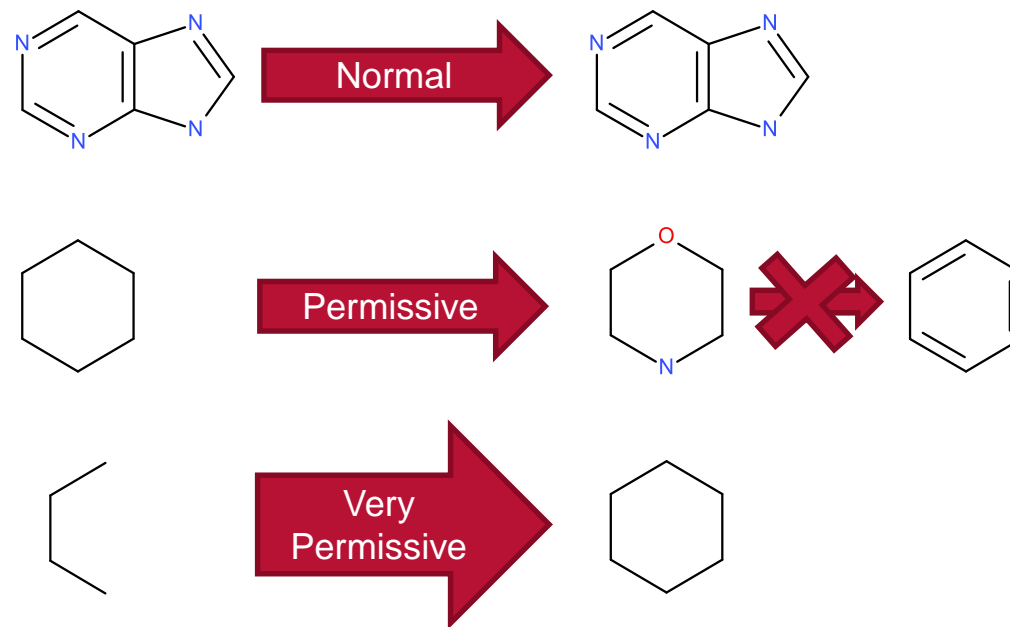
Alignment, scoring and comparisons



Maximum Common Substructure alignment

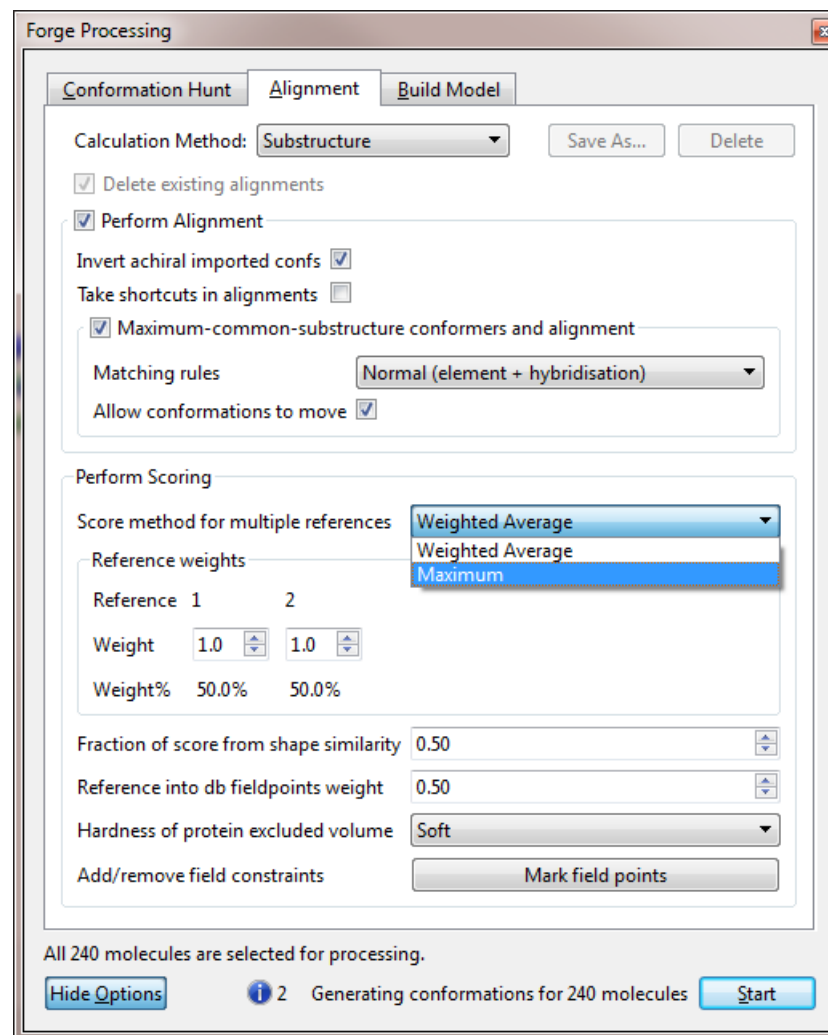


- > Common substructure matched to reference geometry
- > All other moieties are conformationally hunted
- > Generated conformations are scored against reference
- > Control of Maximum Common Substructure (MCS) is in Alignment options



Working with multiple reference structures

- > Use Normal with scoring set to Weighed Average to:
 - > Align heterogeneous data sets
 - > Best for virtual screening and ligand design
- > Use Maximum Common Substructure with scoring set to Maximum to:
 - > Align congeneric data sets
 - > Best for quantitative or qualitative SAR



Four typical alignment scenarios

- > Case 1: One chemical class, I don't have the X-ray structure of the reference compound
- > Case 2: One chemical class, I have the X-ray structure of one reference compound
- > Case 3: Several chemical classes, I don't have the X-ray structure of any reference compounds
- > Case 4: Several chemical classes, I have the X-ray structure of one (or more) reference compounds

Case 1

One chemical class, I don't have the X-ray structure of one reference compound

Case 1: One chemical class, I don't have the X-ray structure of the reference compound

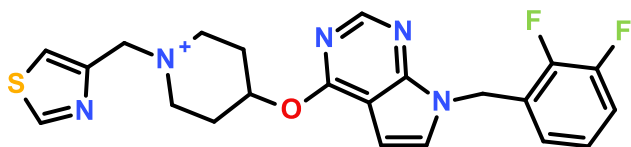
- 1 Select one of the most potent/less flexible compounds
- 2 Carry out an accurate conformation hunt on this compound
- 3 Choose a reasonable low energy conformation
- 4 Promote to reference
- 5 Use it to align the data set

Practical

Alignment and SAR of NaV1.7 sodium channels antagonists

Reference molecule

- > Published X-ray ligand/target structure information is not available for NaV1.7 sodium channels
- > The lowest energy conformation of one of the most active compounds in the dataset was promoted to reference structure
- > *ortho, meta* substitution will facilitate alignment of substituted phenyls in the data set



NaV1.7 pIC50 7.7

Choose the smallest, more rigid, more active compound (ligand efficiency)



Perform 'Very accurate but Slow' conformation analysis in Forge, no alignment



Turn conformations into alignments



Explore low energy conformations, choose one and promote to Reference role



Align the Training set to the new Reference:
Accurate but Slow conf hunt
Substructure alignment

Case 2

One chemical class, I have the X-ray structure of one reference compound

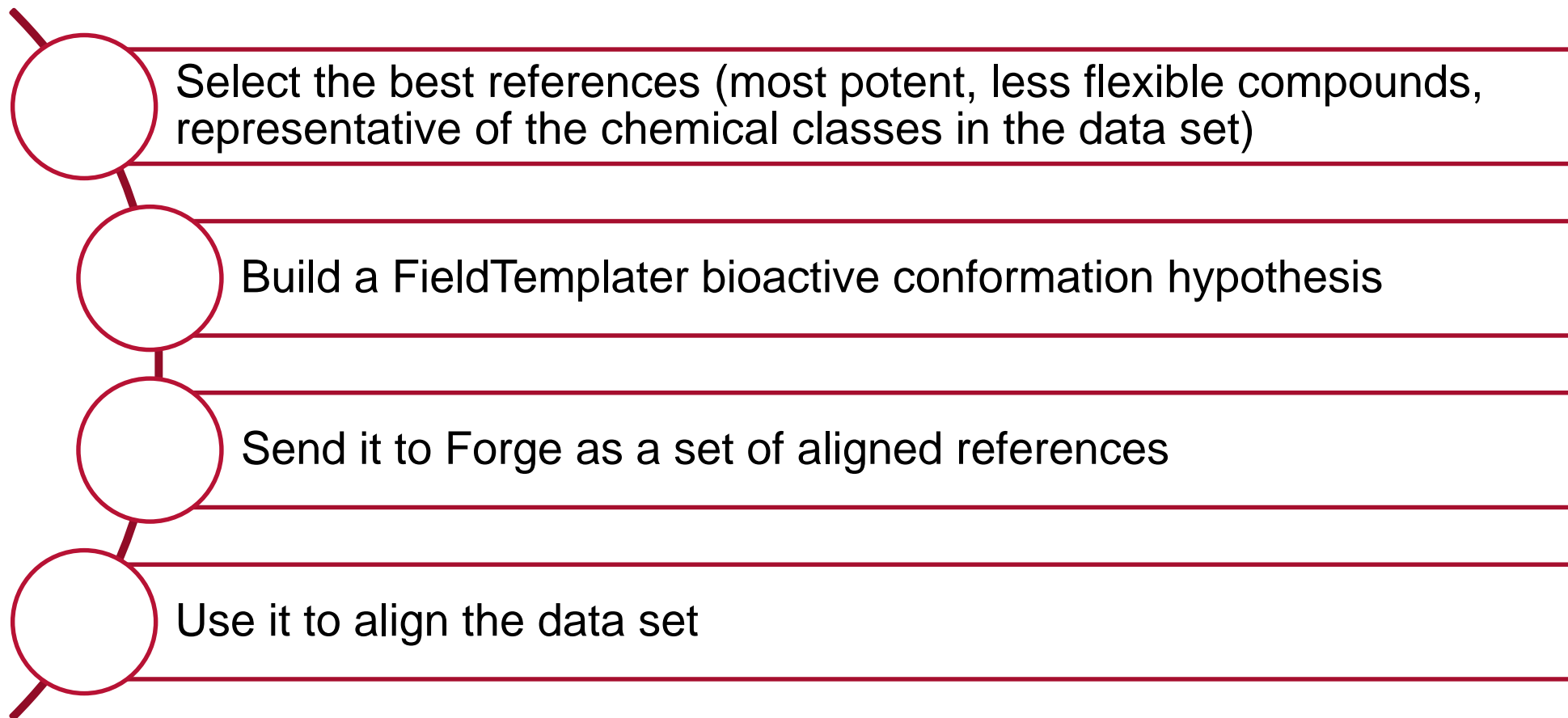
Case 2: One chemical class, I have the X-ray structure of one reference compound

- 1 Download the X-ray structure from the PDB into Forge
- 2 Check atoms/bonds/protonation
- 3 Gently minimize and compare with original reference
- 4 Use it to align all the other compounds in the data set

Case 3

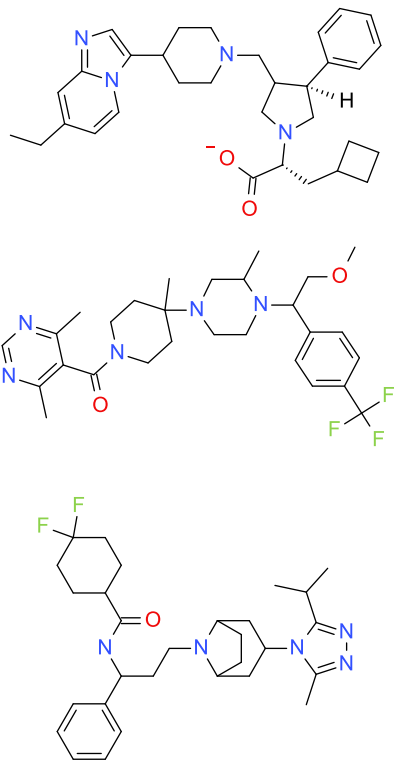
Several chemical classes, I don't have the X-ray structure of any reference compounds

Case 3: Several chemical classes, I don't have the X-ray structure of any reference compounds

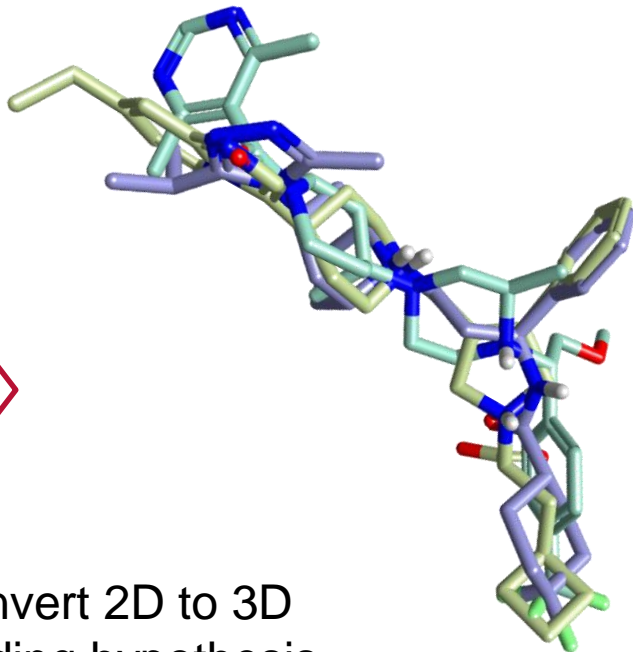


CCR5: Finding a pharmacophore

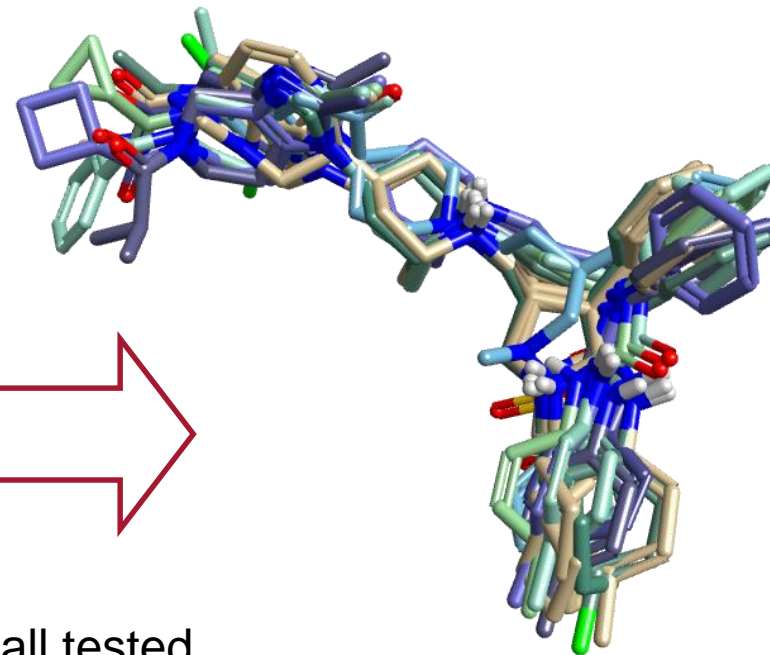
3 CCR5 actives



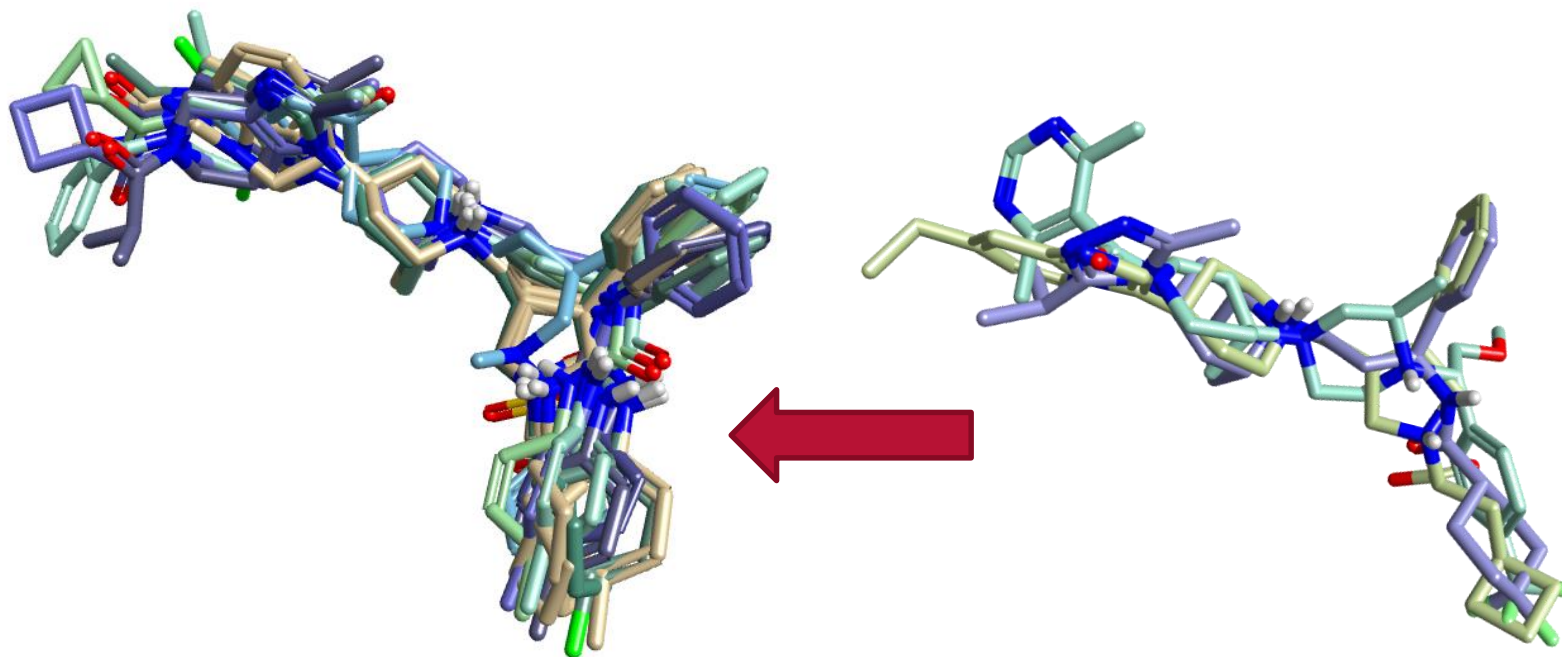
Convert 2D to 3D
binding hypothesis



Align all tested
compounds



Template gives alignment of larger dataset



- > Compare other molecules to our template using Fields
- > - Actives, inactives, ideas, libraries, HTS results
- > Understand SAR through activity cliffs
- > Build QSAR models
- > Design new molecules using the Fields

FieldTemplater process

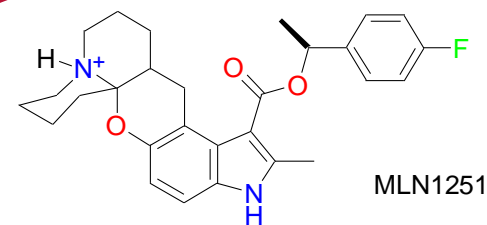
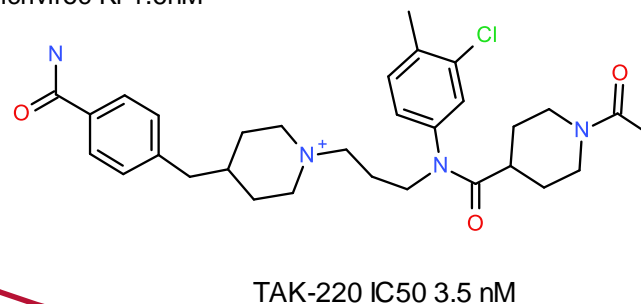
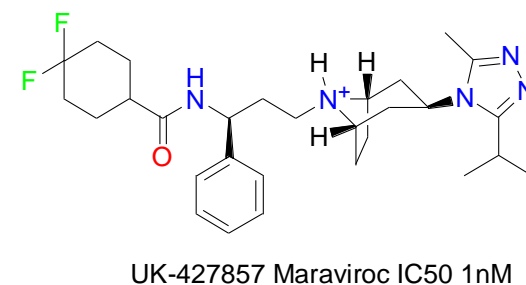
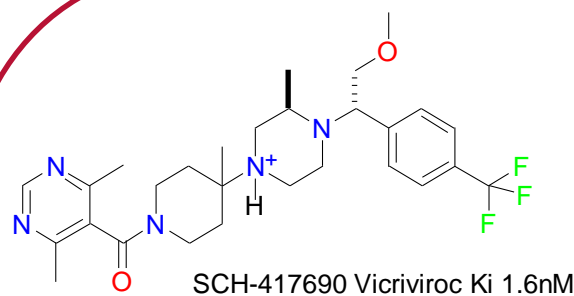
- > Choose molecules to template
- > Load (paste) into Forge
- > Transfer to FieldTemplater module
 - > Run menu
 - > Right click menu
 - > Drag and drop
- > Process
- > Visually inspect results
- > Return results to Forge

Things to note

- > FieldTemplater relates actives only
- > It tries to generate more than a 'pharmacophore' – a bio-active conformation hypotheses
- > Alignment of inactives to a template gives additional information
- > FieldTemplater compares molecules in pairs
- > The pairwise data is used to find templates
- > **The defaults work – but the best results come from changing parameters**

FieldTemplater hints and tips

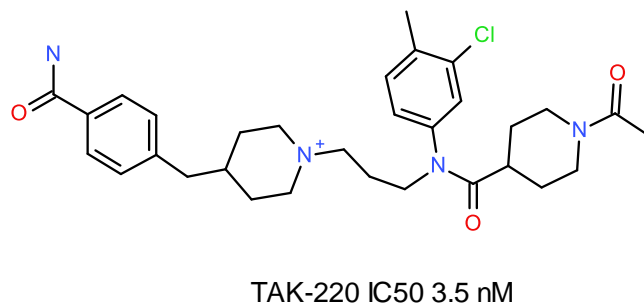
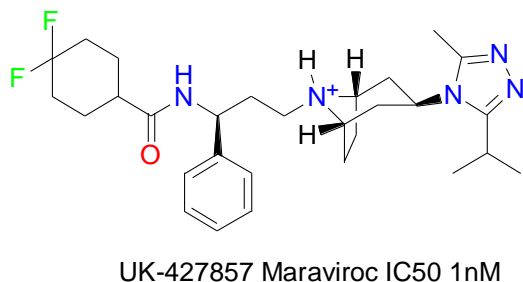
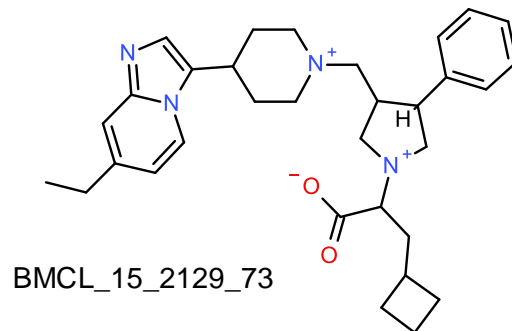
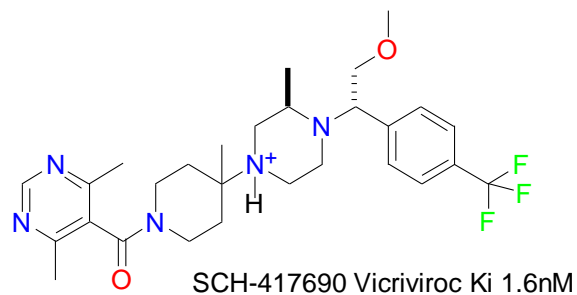
- > Enter 3-5 active, efficient ligands; choose:
 - > Similar size with same binding site
 - > Prefer more active, more efficient compounds with fewer rotatable bonds



Practical

Alignment of CCR5 inhibitors using a FieldTemplater hypothesis

CCR5 inhibitors: Building the FieldTemplater hypothesis



Open the CCR5_start file in Forge

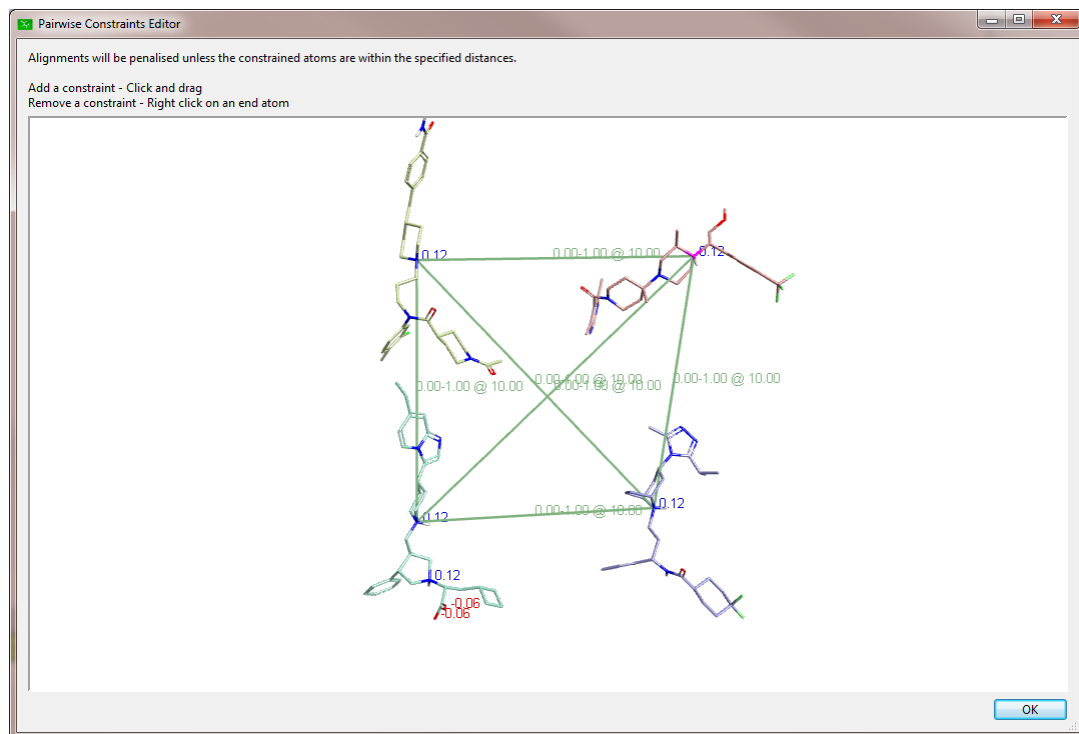
Select molecules in 'Molecules to be Templated' role and send to FieldTemplater

Define constraints on basic N and set-up the FieldTemplater processing

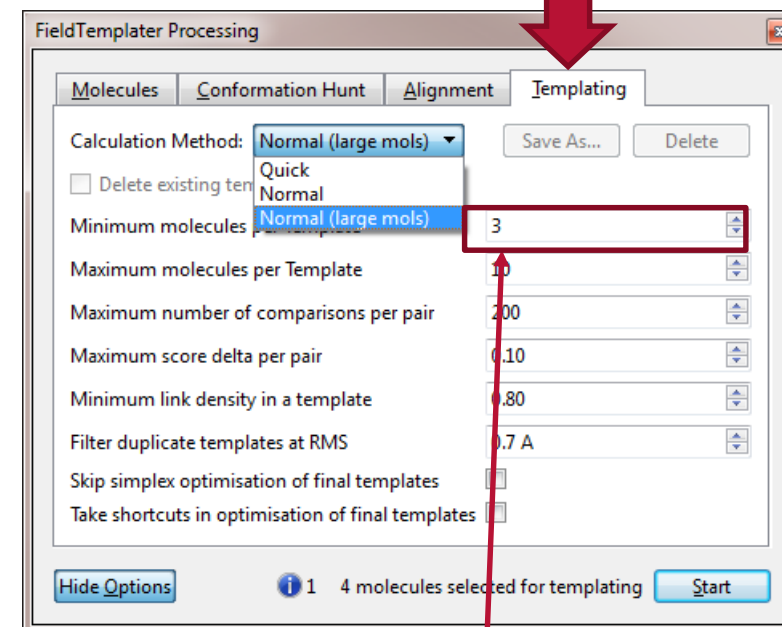
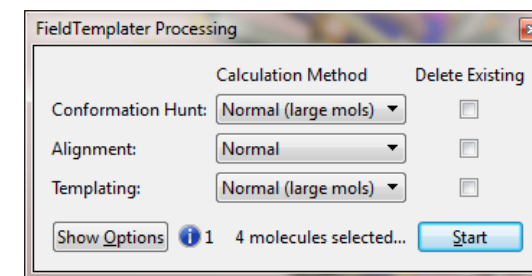
Build the FT hypothesis

Transfer the chosen FT hypothesis to Forge into Reference role

Set-up of FieldTemplater processing

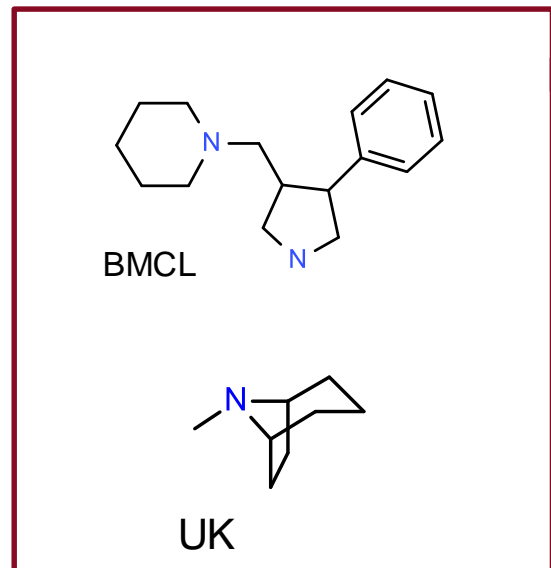
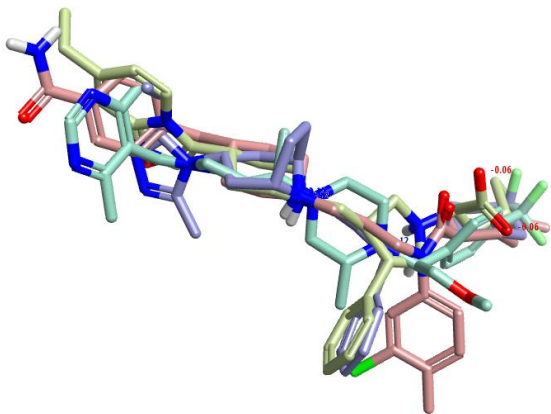


> When you are happy with the set-up, press Start



Change this value to 4

CCR5 inhibitors: aligning the BCML and UK series



Filter by substructure to identify the BCML and UK series

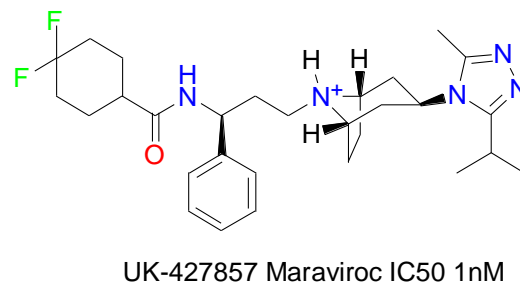
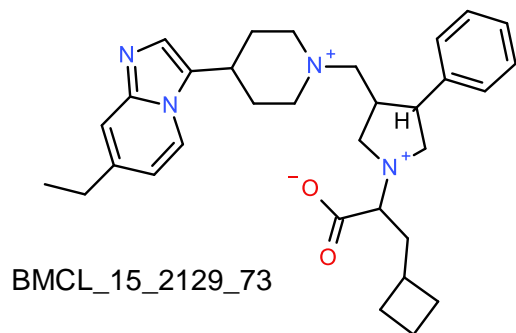
Tag the BCML compounds with a 'BCML' tag and the UK compounds with a 'UK' tag

Remove compounds without BCML/UK tag

Remove TAK and SCH References

Align the Training set to the Reference:

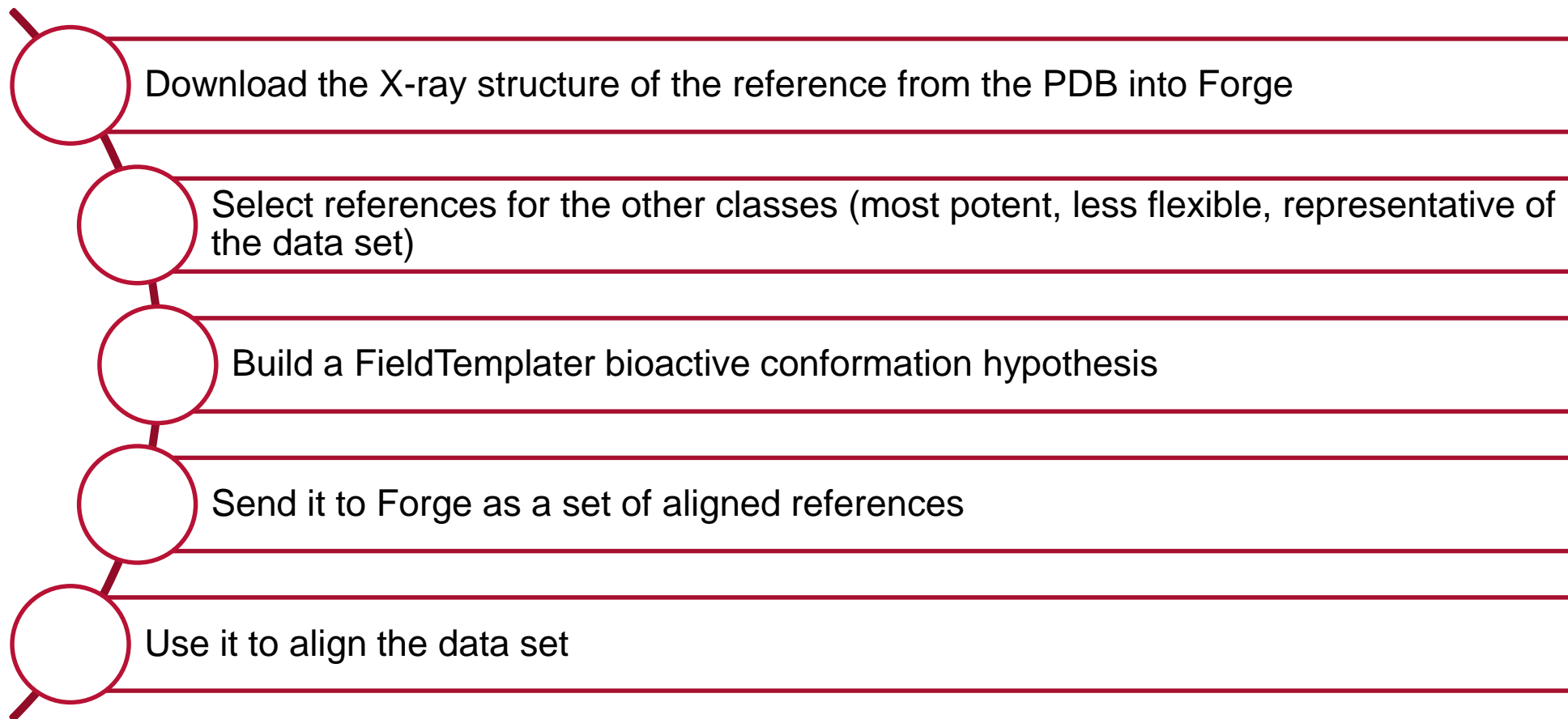
- 'Accurate but slow' conf hunt
- Substructure alignment using 'Very permissive' matching rules
- 'Maximum' scoring method



Case 4

Several chemical classes, I have the X-ray structure of one (or more) reference compounds

Case 4: Several chemical classes, I have the X-ray structure of one (or more) reference compounds





smarter chemistry | smarter decisions

Questions welcomed

support@cresset-group.com

Example files available from

enquiries@cresset-group.com

Contact us for our tailored training courses

