Becoming a power user of Forge

Cresset European User Group Meeting – Workshops

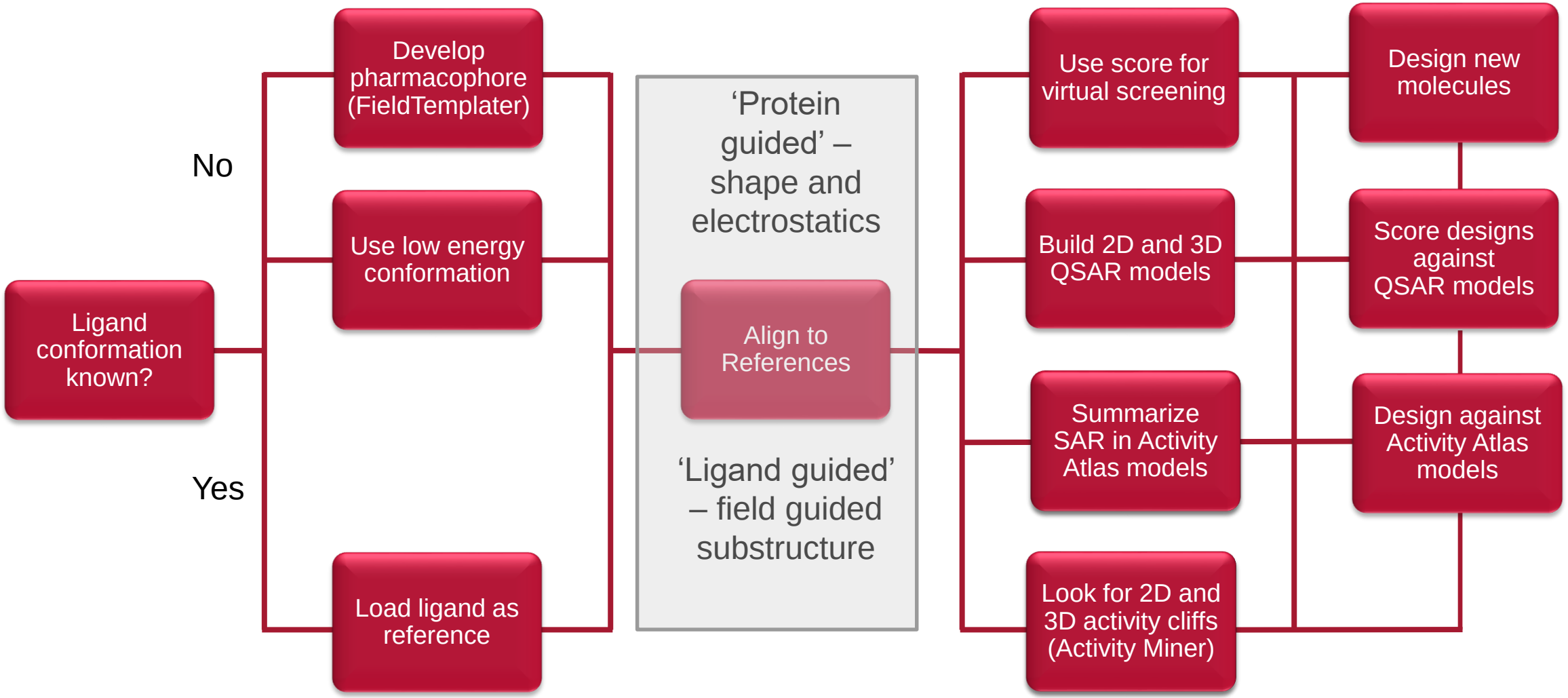
June 2016

Files for this workshop

> The files used in this workshop are available for download on request

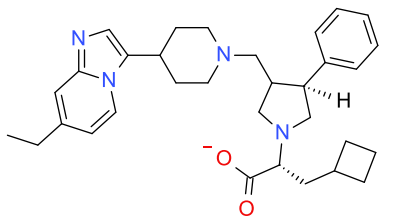
> Please send an email to enquiries@cresset-group.com stating the name of the workshop

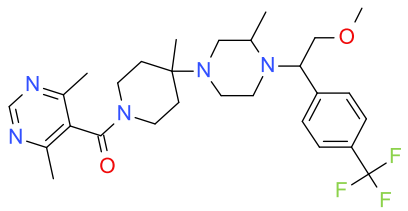
Forge workflow

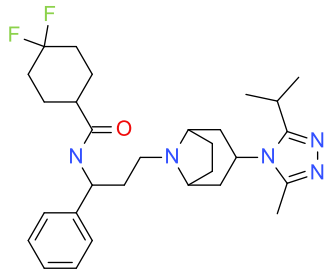


Core Forge experiments

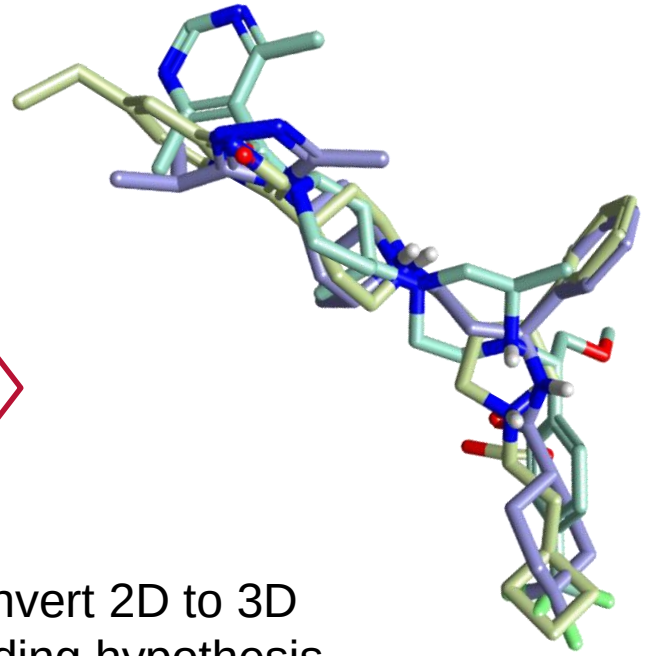
3 CCR5 actives



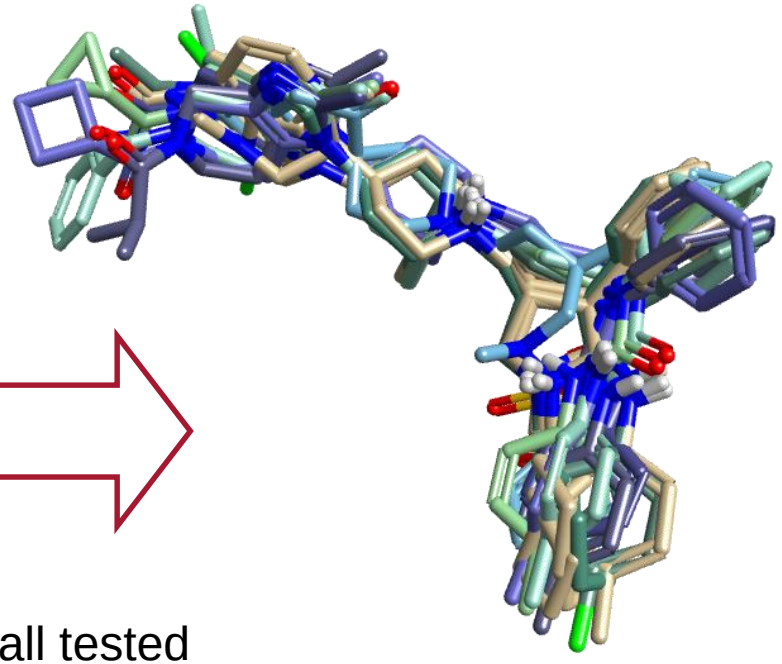




Convert 2D to 3D binding hypothesis



Align all tested compounds



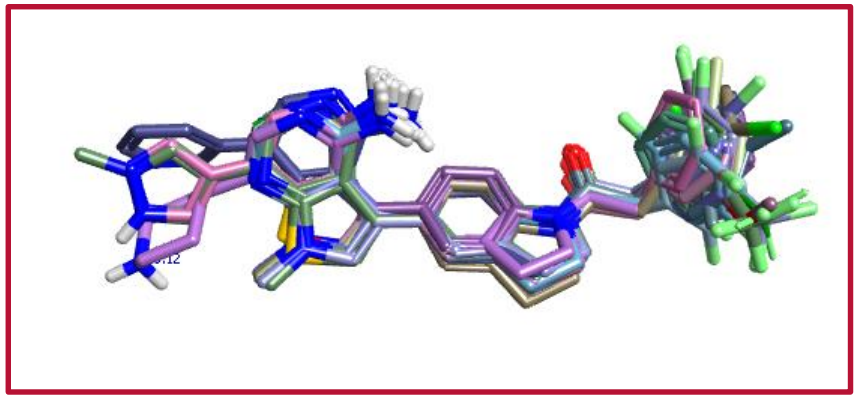
Understand structure-activity using Forge

- 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

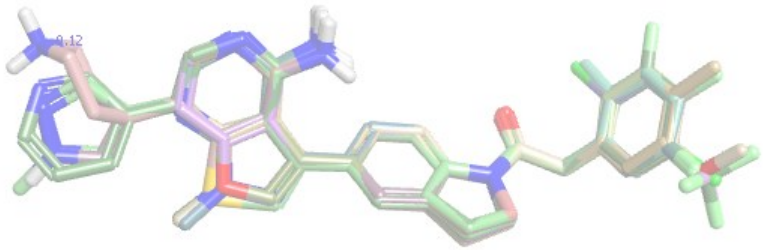
- Aligned ligands from multiple chemotypes used for
  - Virtual screening
  - Relating activities from different series
  - SAR transfer
- Align ligands from single chemotype used for
  - 3D activity cliff analysis
  - Activity Atlas Models
  - 3D QSAR
  - Understanding design of new molecules

Which alignment. Normal or (Maximum Common) Substructure?

Normal



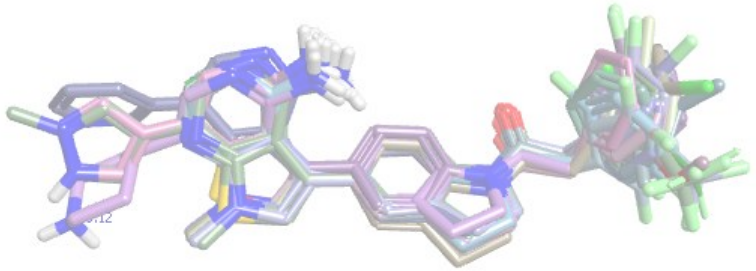
Substructure



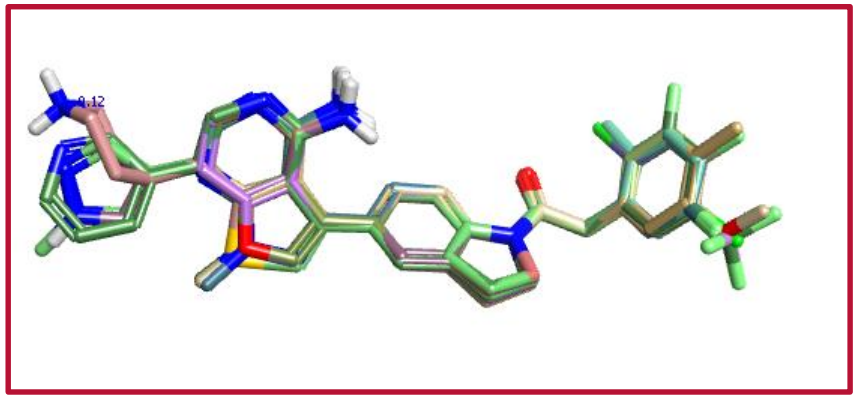
- Normal: Field-based alignment
  - Uses Cresset electrostatic, shape and hydrophobic field points to align
  - Scored 50% field-based similarity with 50% shape similarity
  - Independent of chemical structure
- Better for datasets that have structurally diverse compounds

Which alignment. Normal or (Maximum Common) Substructure?

Normal

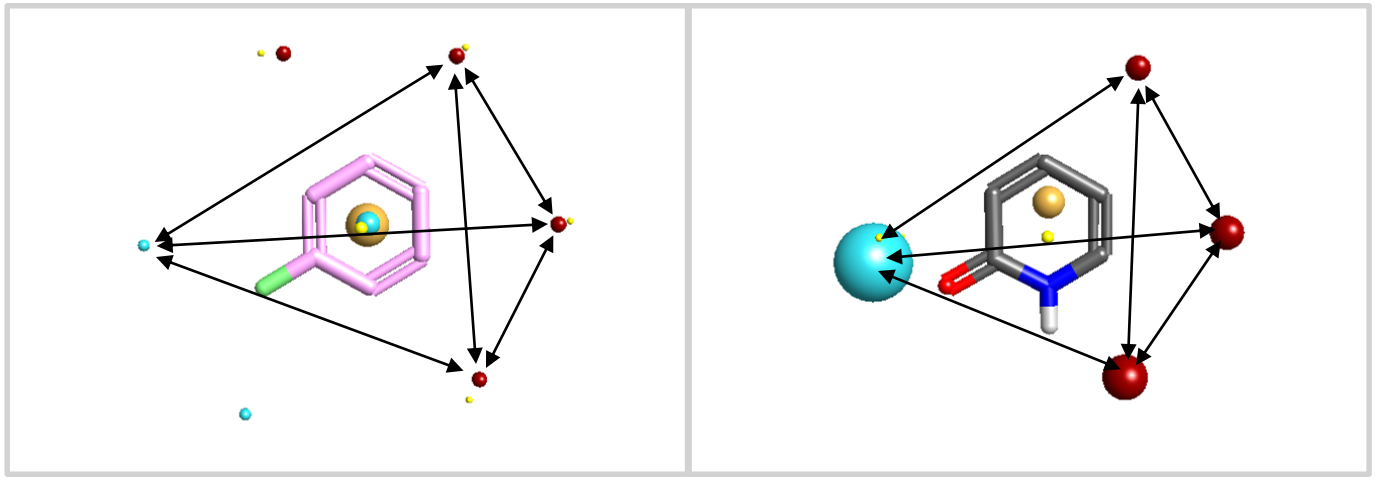


Substructure

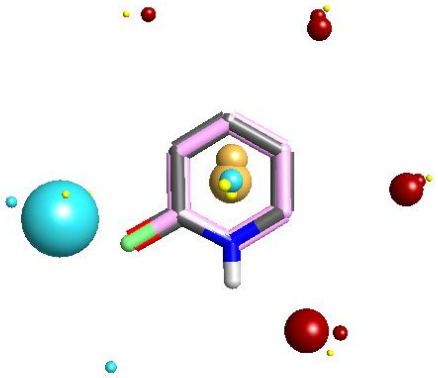


- Maximum Common Substructure alignment
  - Common structural features in database molecules are mapped onto conformation of corresponding features in reference molecule
  - All other parts of the molecule are conformationally hunted
  - Field/shape based scoring
- Good for datasets with a common core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

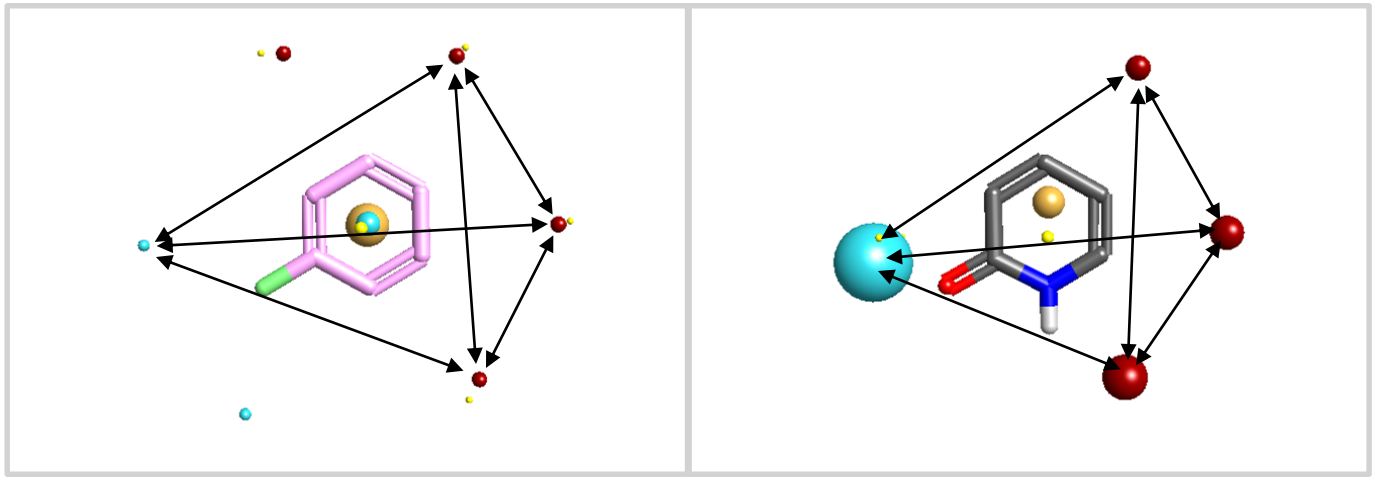
Field based alignment



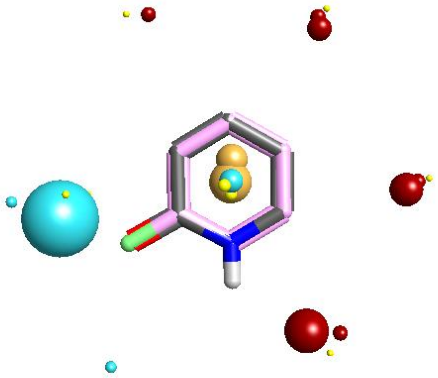
Fields
0.66

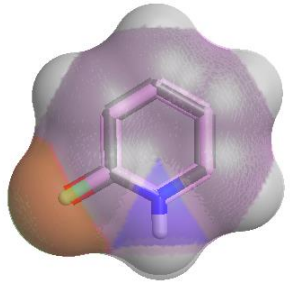


Field based alignment and scoring



Fields
0.66

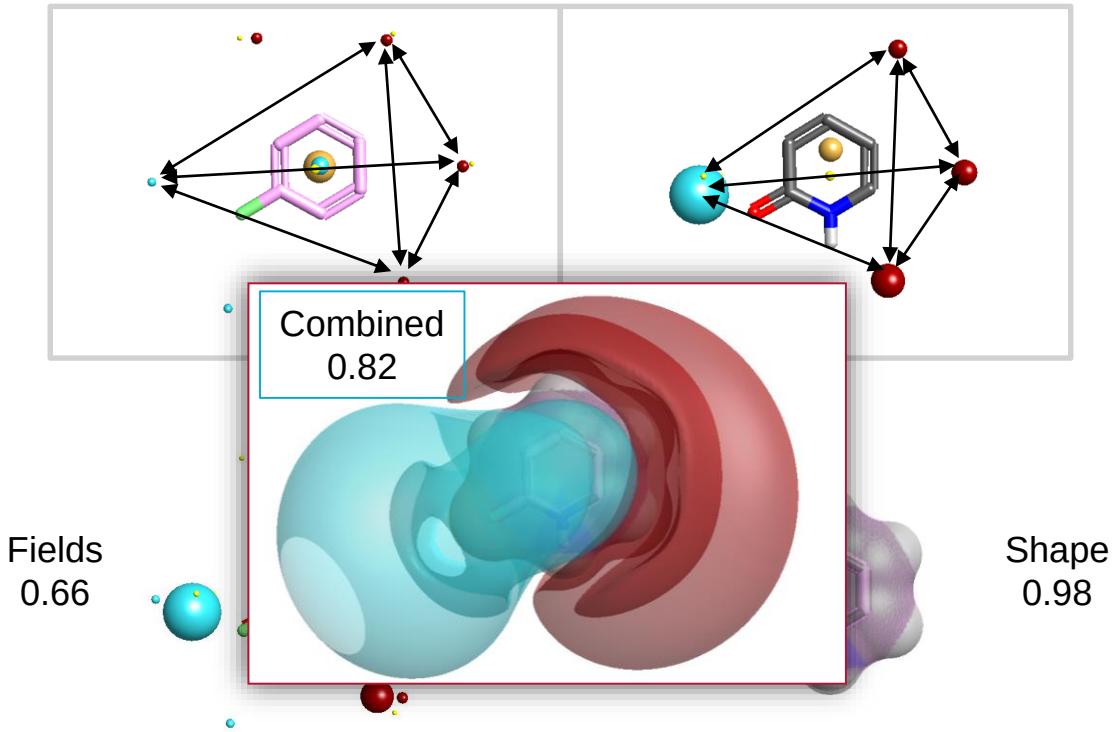




Shape
0.98

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

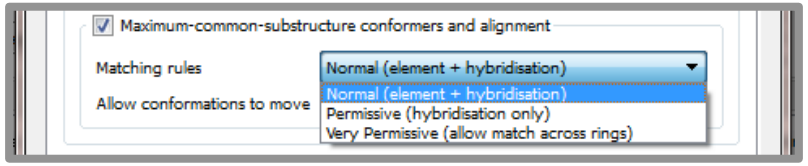
Alignment, scoring and comparisons



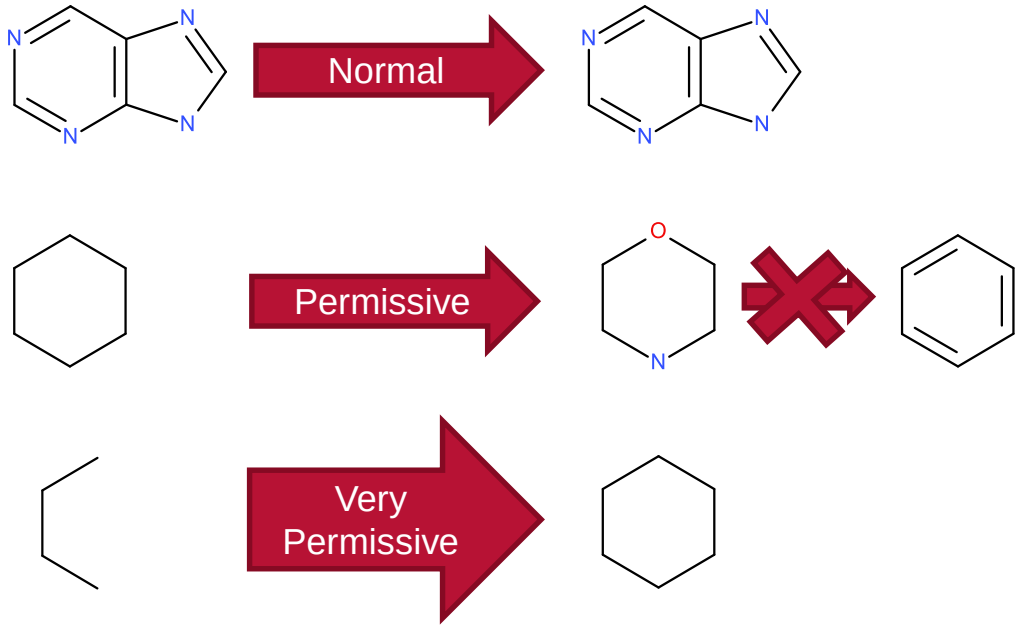
Cheeseright et al,
J. Chem Inf. Mod., 2006, 665

Grant, Gallardo, Pickup,
J. Comp. Chem., 1996, 1653

Maximum Common Substructure alignment

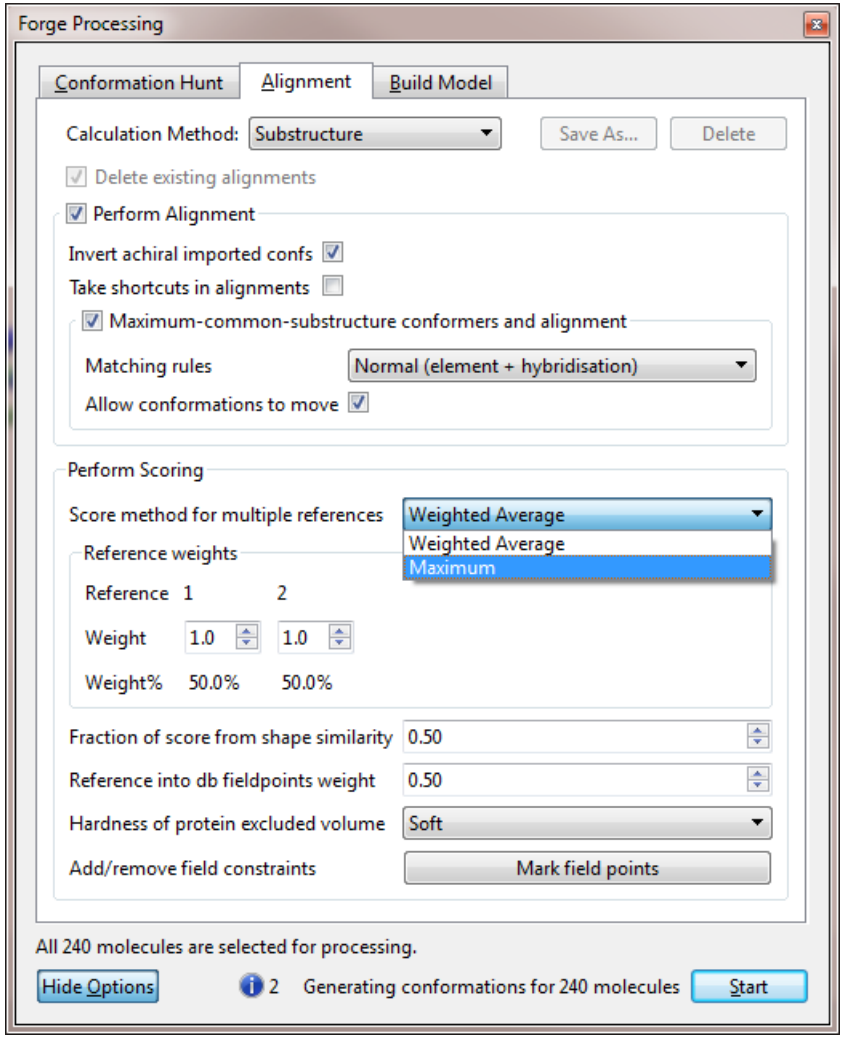


- Common substructure matched to reference geometry
- All other moieties are conformationally hunted
- Generated conformations are scored against reference
- Control of Maximum Common Substructure (MCS) is in Alignment options



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



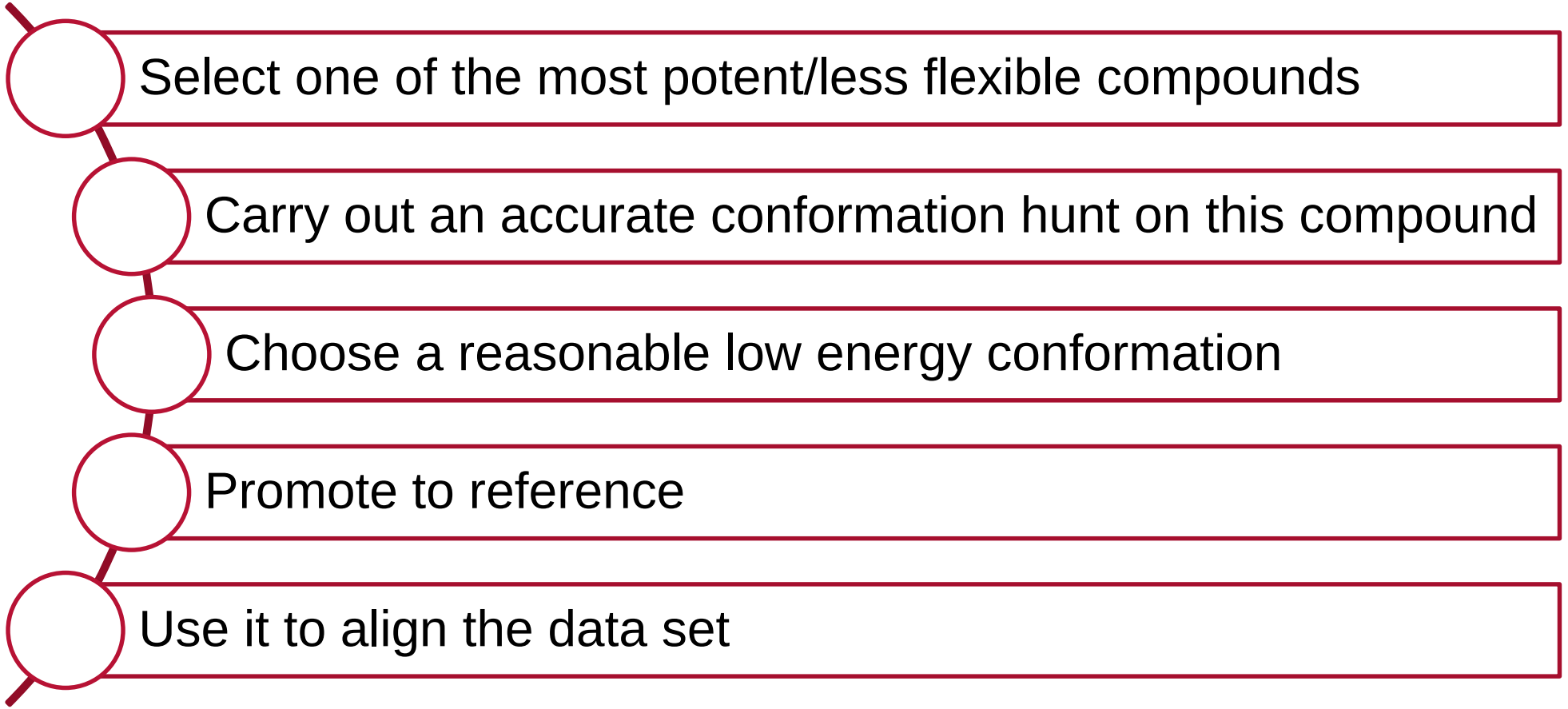
Four typical alignment scenarios

- 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

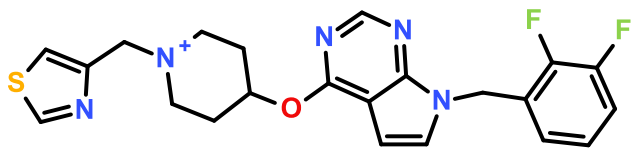


Practical

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

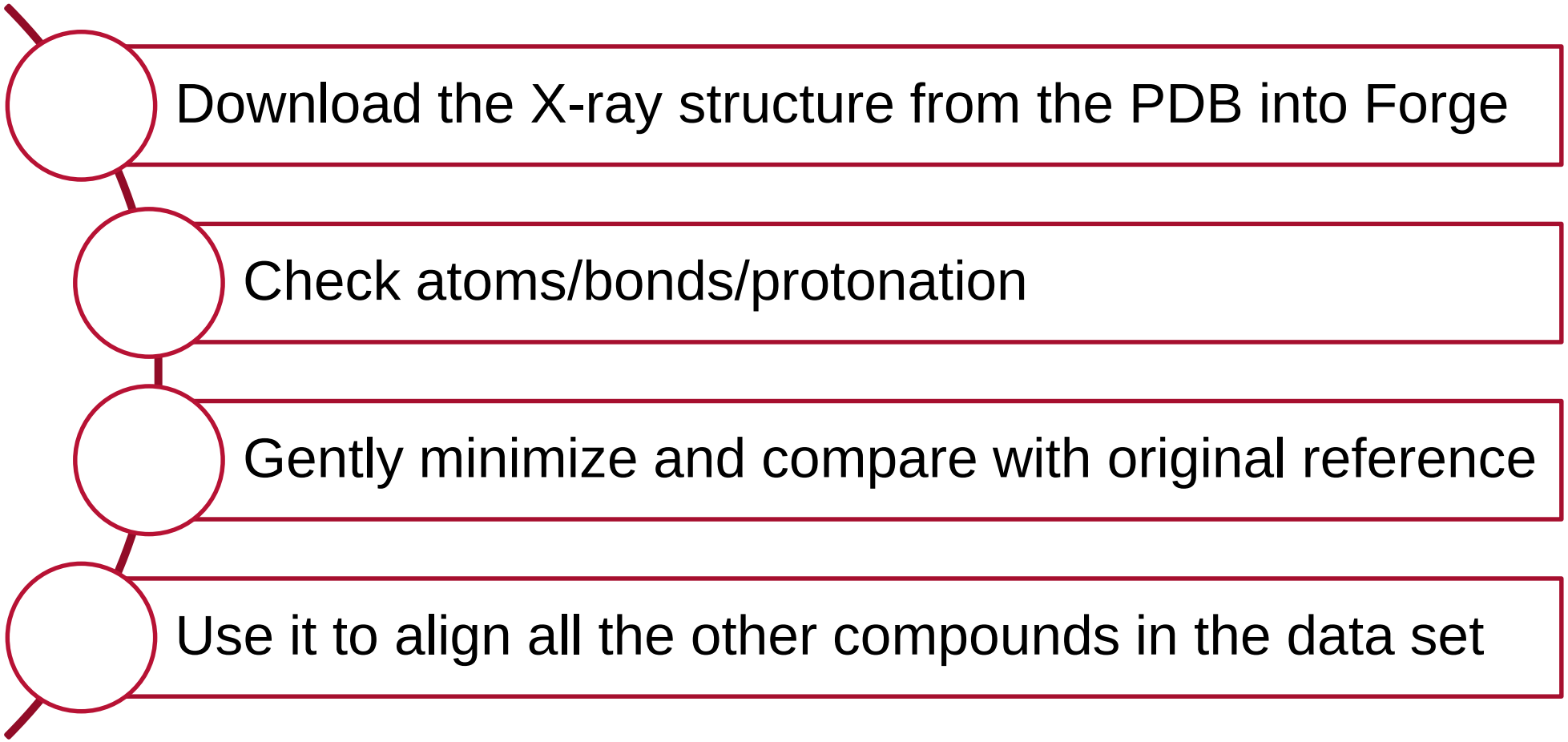
↓

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

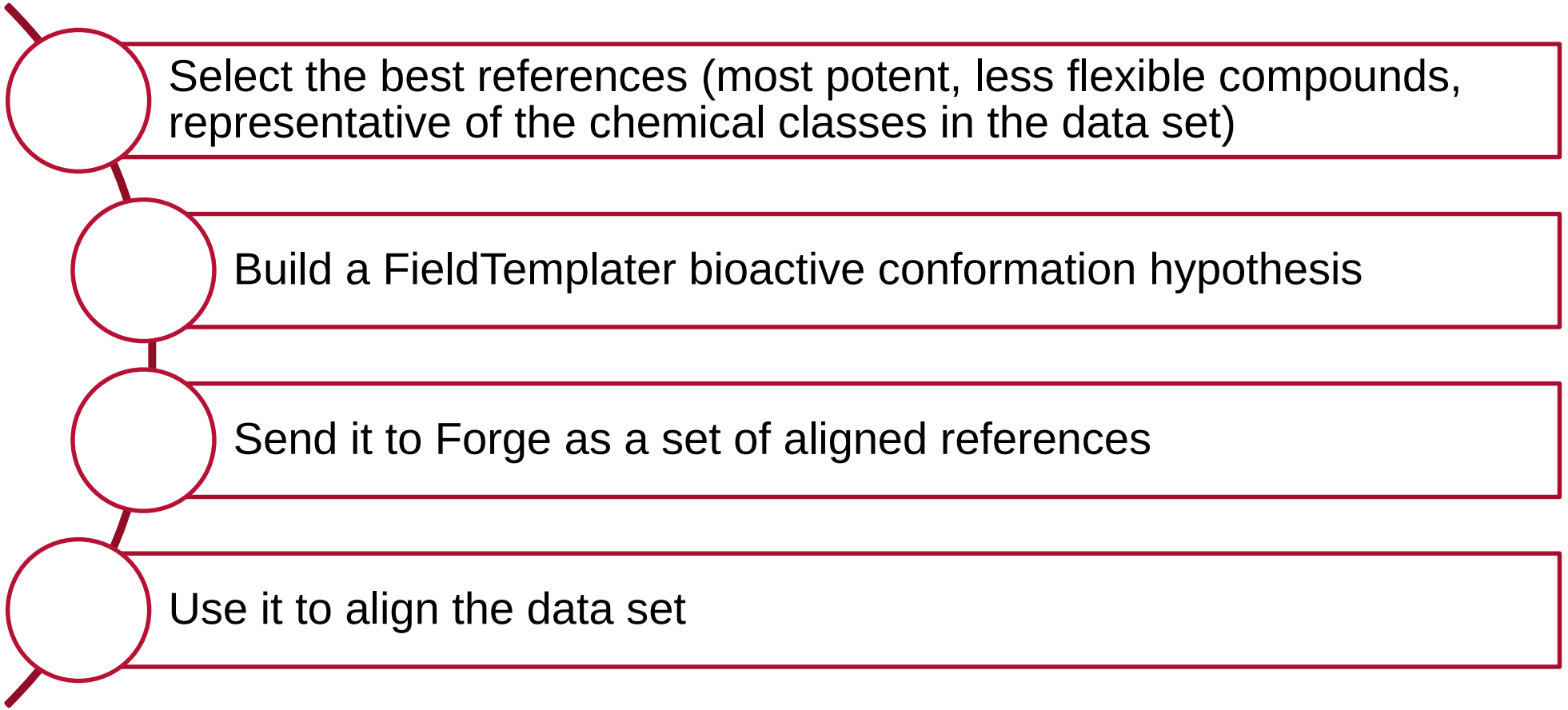
Case 2: One chemical class, I have the X-ray structure of one reference compound



Case 3

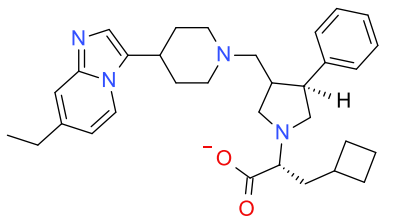
Several chemical classes, I don’t have the X-ray structure of any reference compounds

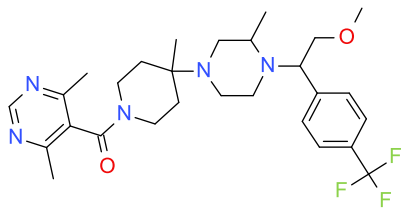
Case 3: Several chemical classes, I don’t have the X-ray structure of any reference compounds

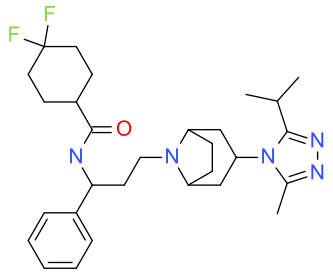


CCR5: Finding a pharmacophore

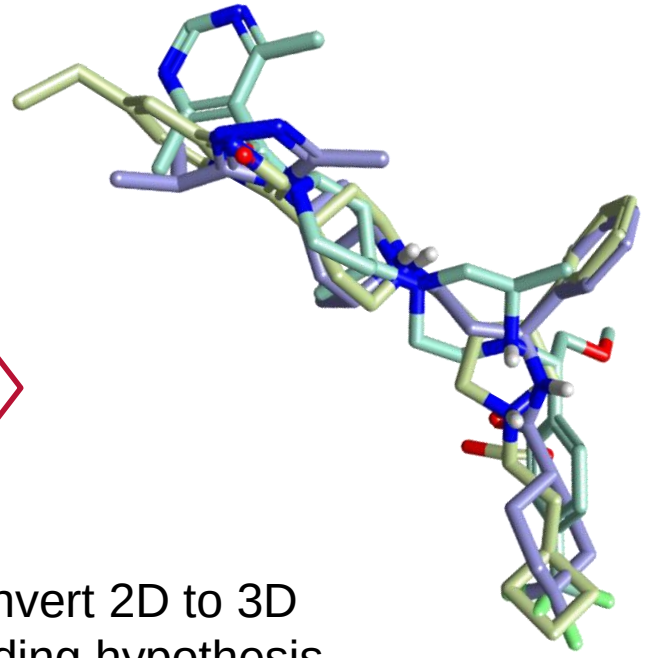
3 CCR5 actives



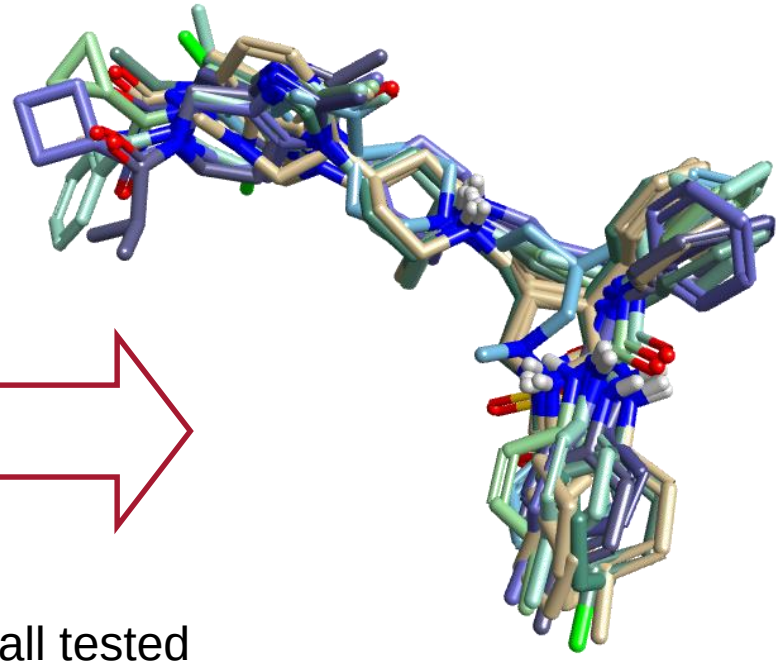




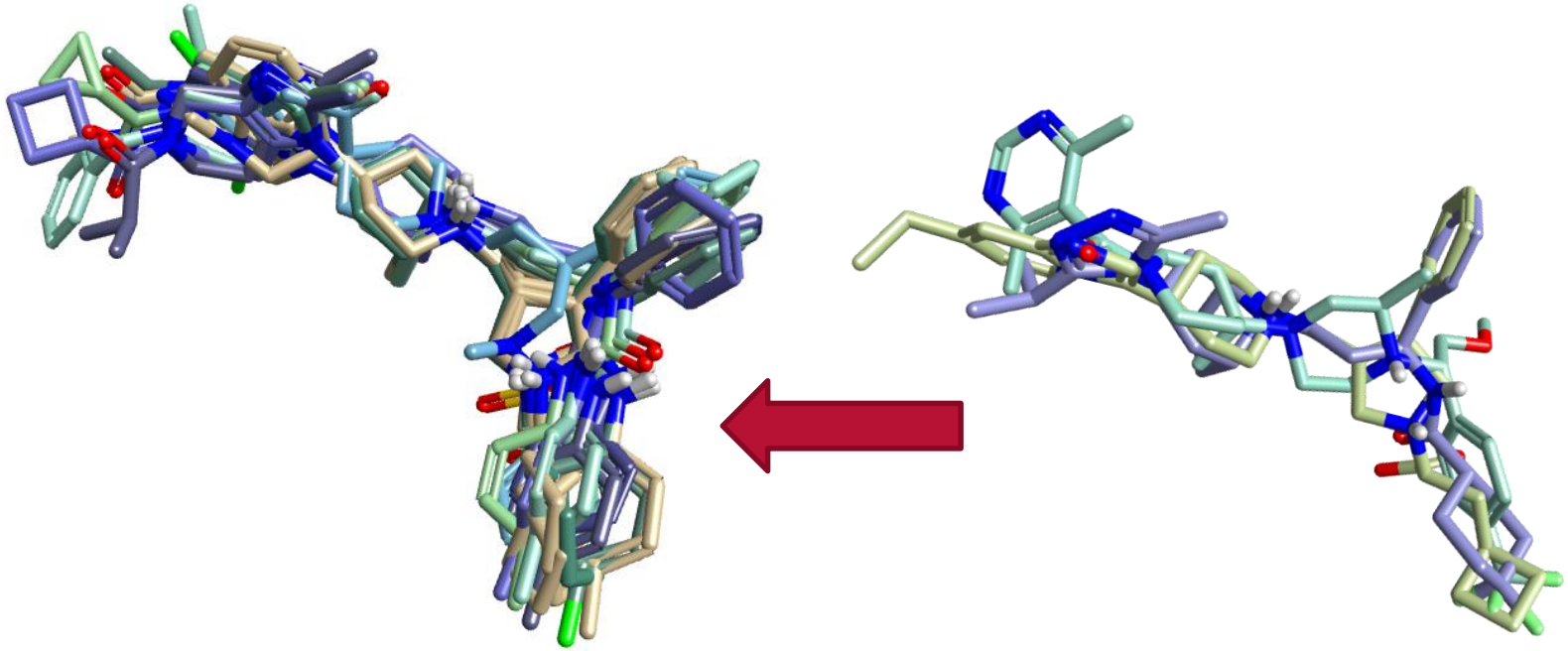
Convert 2D to 3D binding hypothesis



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

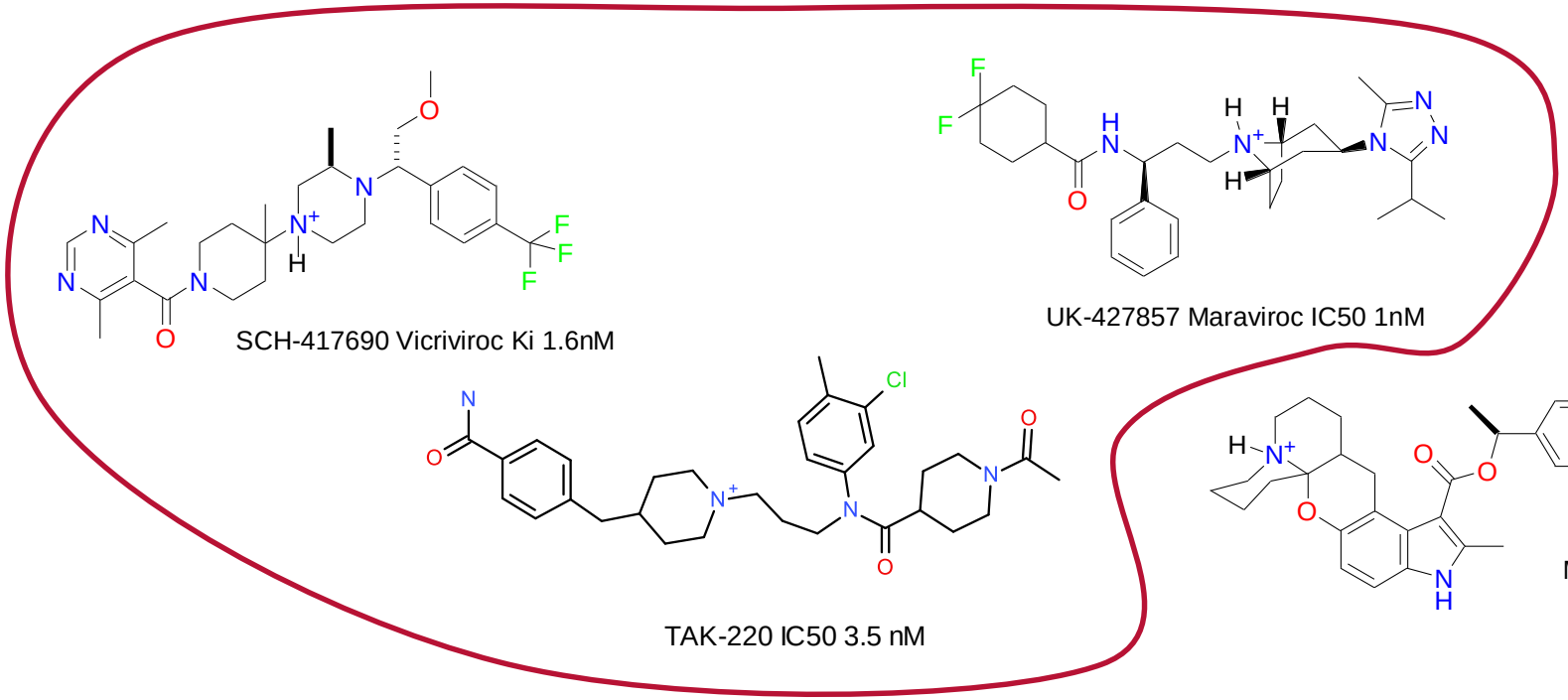
- Choose molecules to template
- Load (paste) into Forge
- Transfer to FieldTemplater module
  - Run menu
  - Right click menu
  - Drag and drop
- Process
- Visually inspect results
- Return results to Forge

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

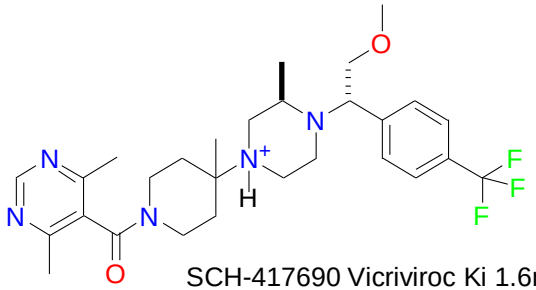
- Enter 3-5 active, efficient ligands; choose:
  - Similar size with same binding site
  - Prefer more active, more efficient compounds with fewer rotatable bonds



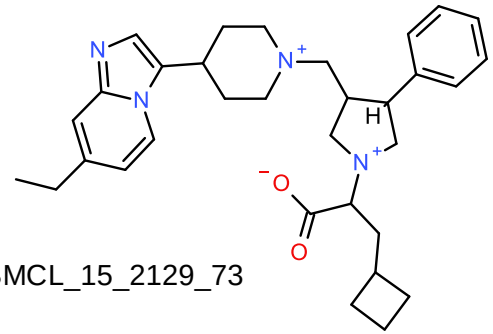
Practical

Alignment of CCR5 inhibitors using a FieldTemplater hypothesis

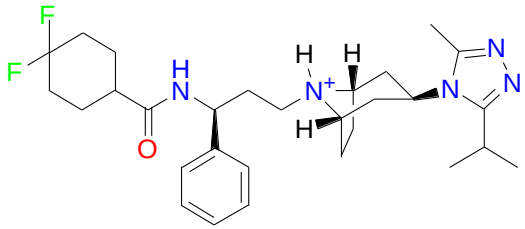
CCR5 inhibitors: Building the FieldTemplater hypothesis



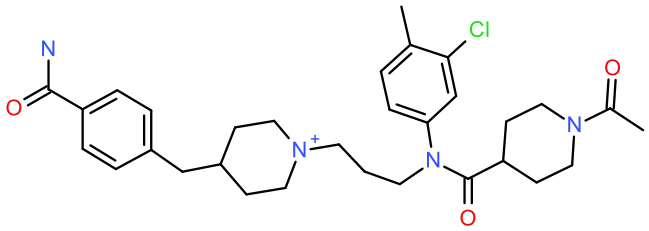
SCH-417690 Vicriviroc Ki 1.6nM



BMCL_15_2129_73



UK-427857 Maraviroc IC50 1nM



TAK-220 IC50 3.5 nM

Open the CCR5_start file in Forge

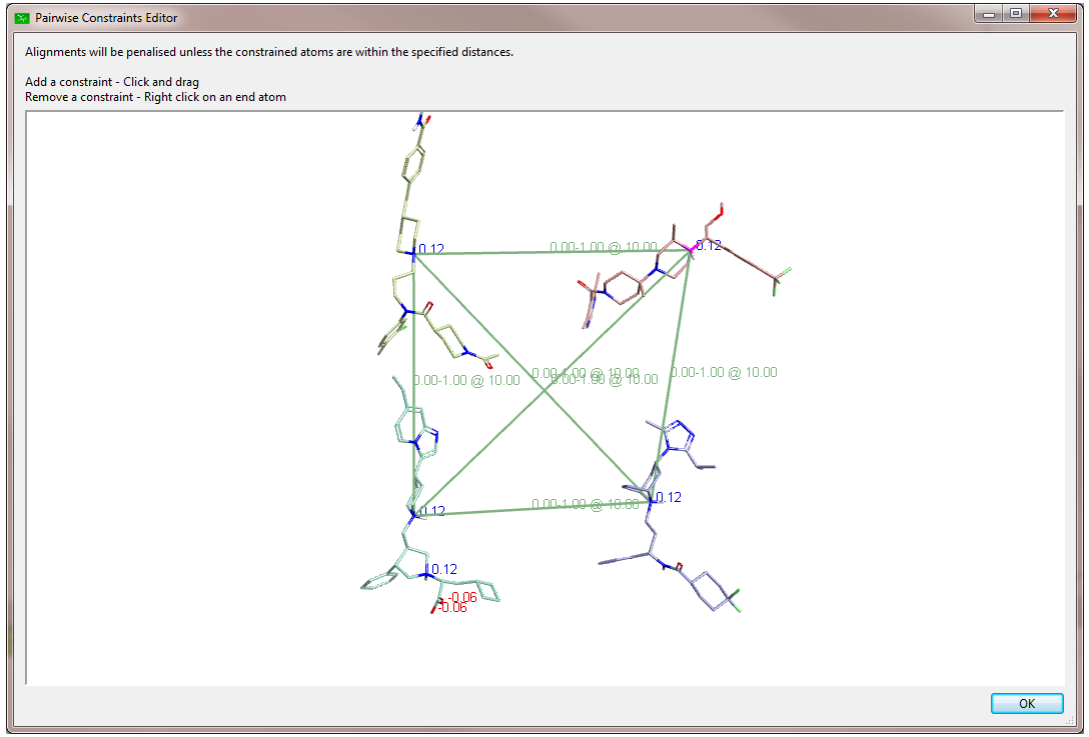
Select molecules in ‘Molecules to be Templated’ role and send to FieldTemplater

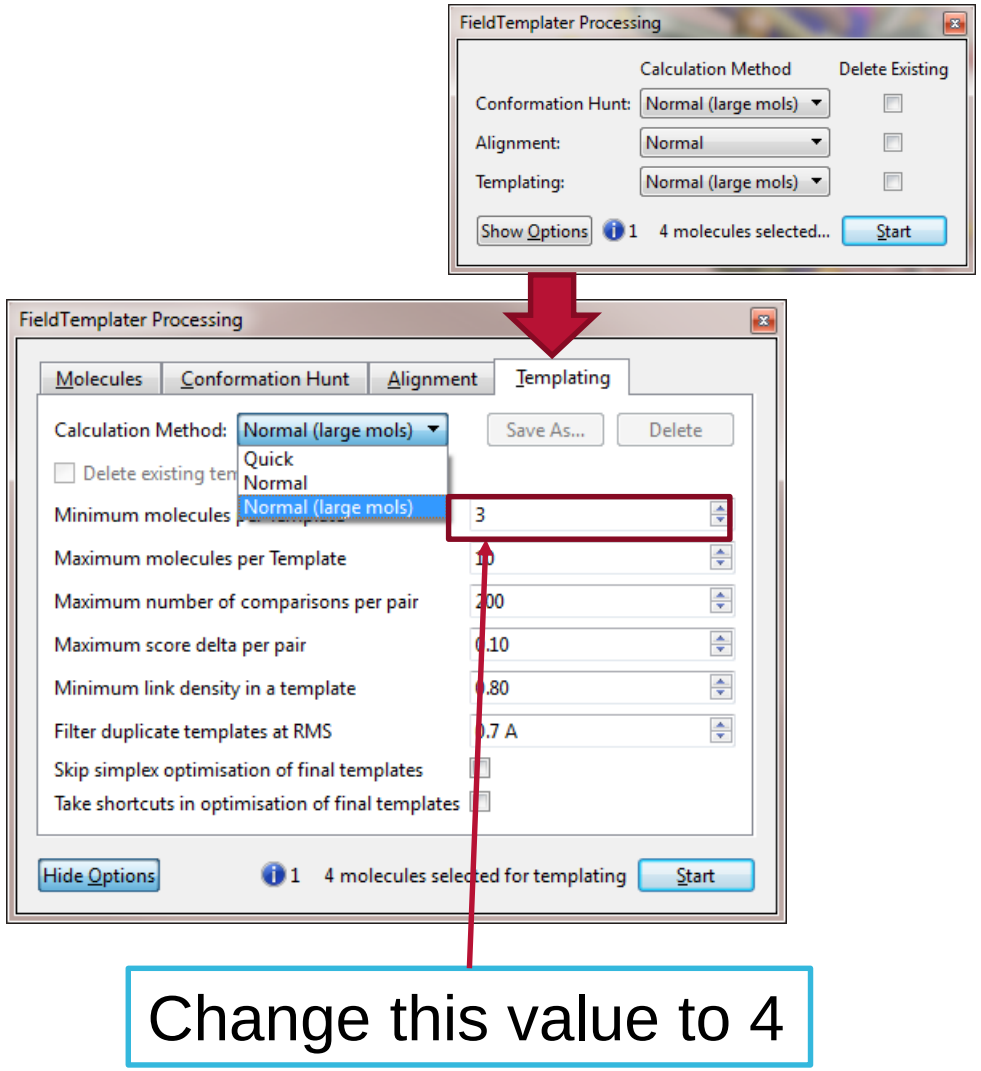
Define constraints on basic N and set-up the FieldTemplater processing

Build the FT hypothesis

Transfer the chosen FT hypothesis to Forge into Reference role

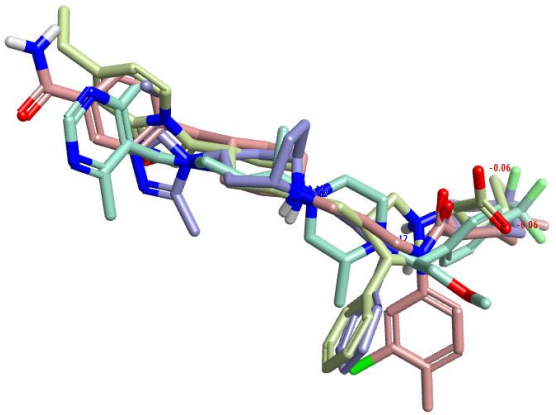
Set-up of FieldTemplater processing

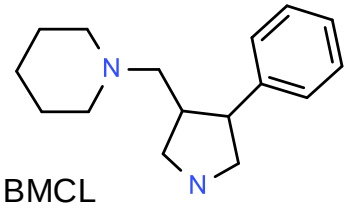




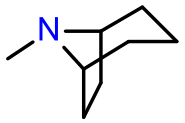
> When you are happy with the set-up, press Start

CCR5 inhibitors: aligning the BCML and UK series

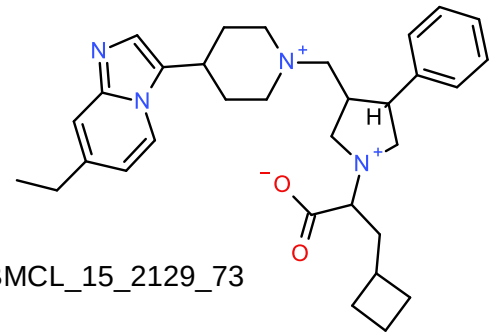




BMCL



UK



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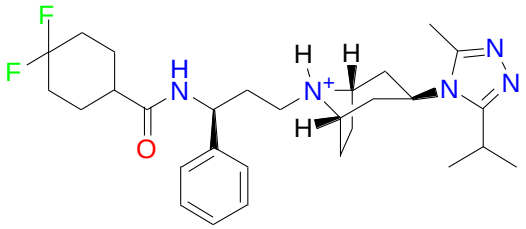


UK-427857 Maraviroc IC50 1nM

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:

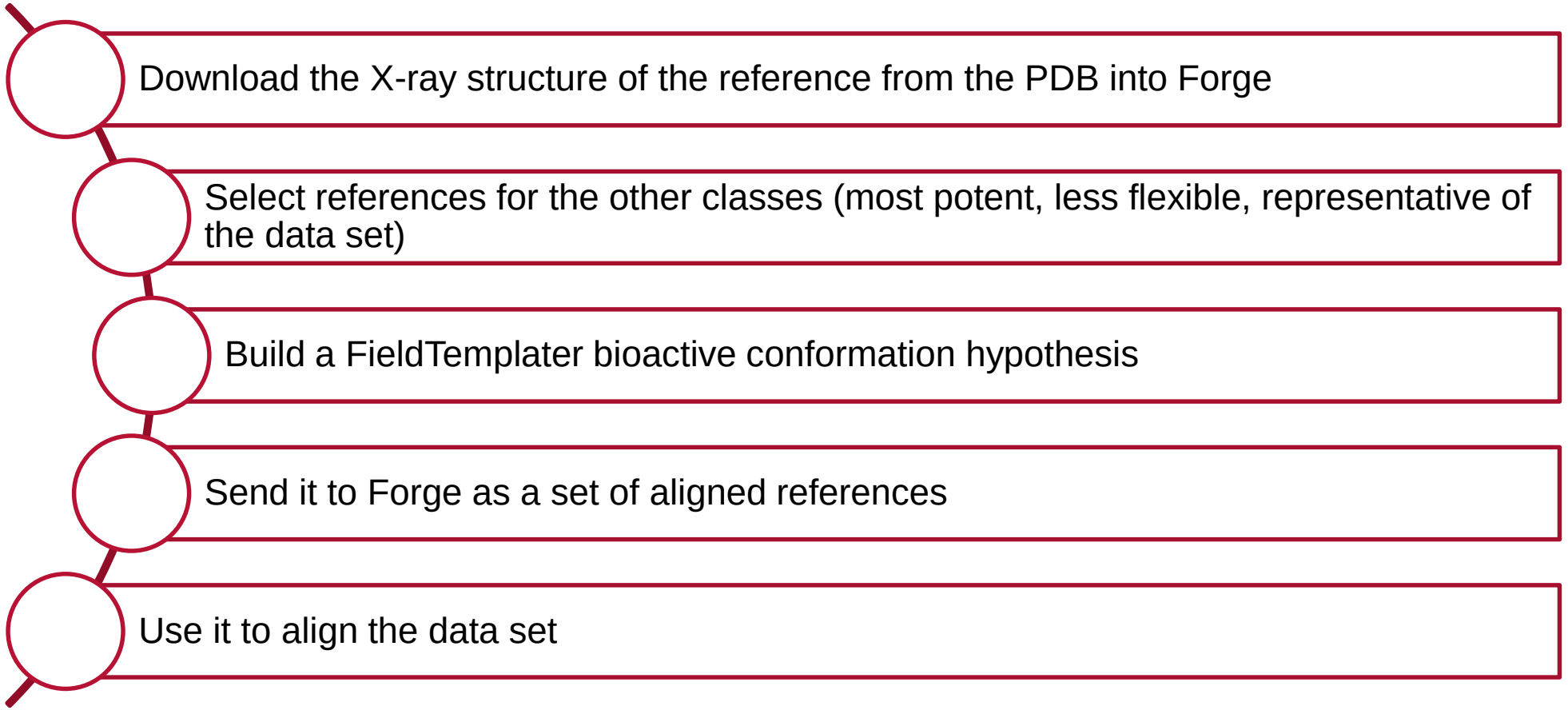
- ‘Accurate but slow’ conf hunt
- Substructure alignment using ‘Very permissive’ matching rules
- ‘Maximum’ scoring method

cresset

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



cresset

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

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