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Matched Molecular Pair and Activity Cliffs: the Next Dimension

Tim Cheeseright, Director Products

Agenda

- Background – activity cliffs and matched molecular pairs
- Activity cliffs in 3D
- Visualising activity cliffs
- Understanding the reason for an activity cliff
- Case study

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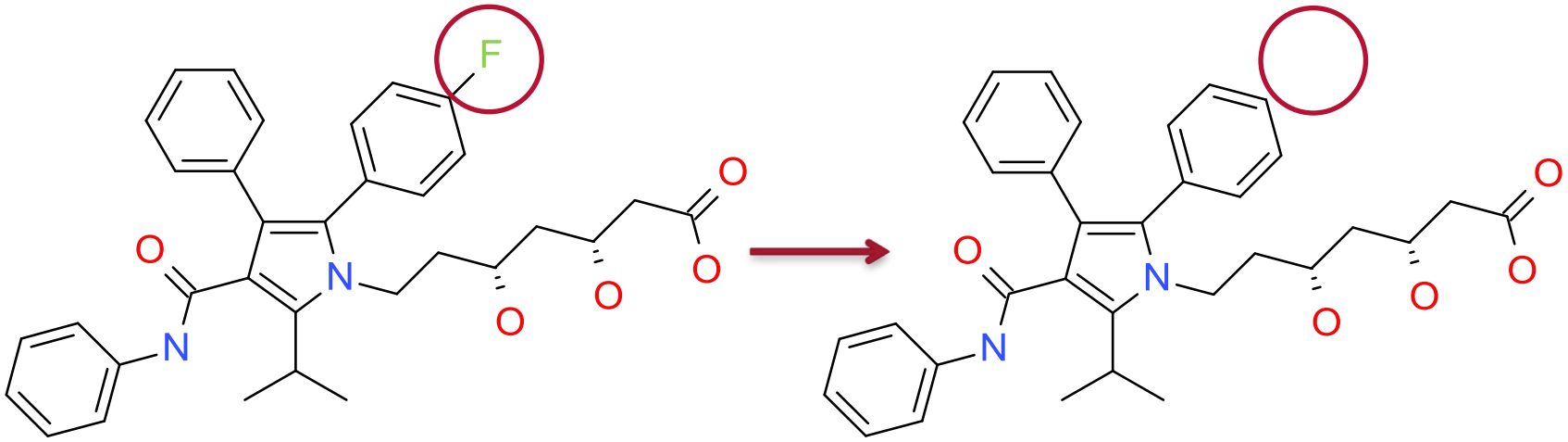
Drug Discovery's Similarity Hypothesis



> Similar molecules have similar activities

> Small changes lead to small changes

→ QSAR, virtual screening, Lead Optimization

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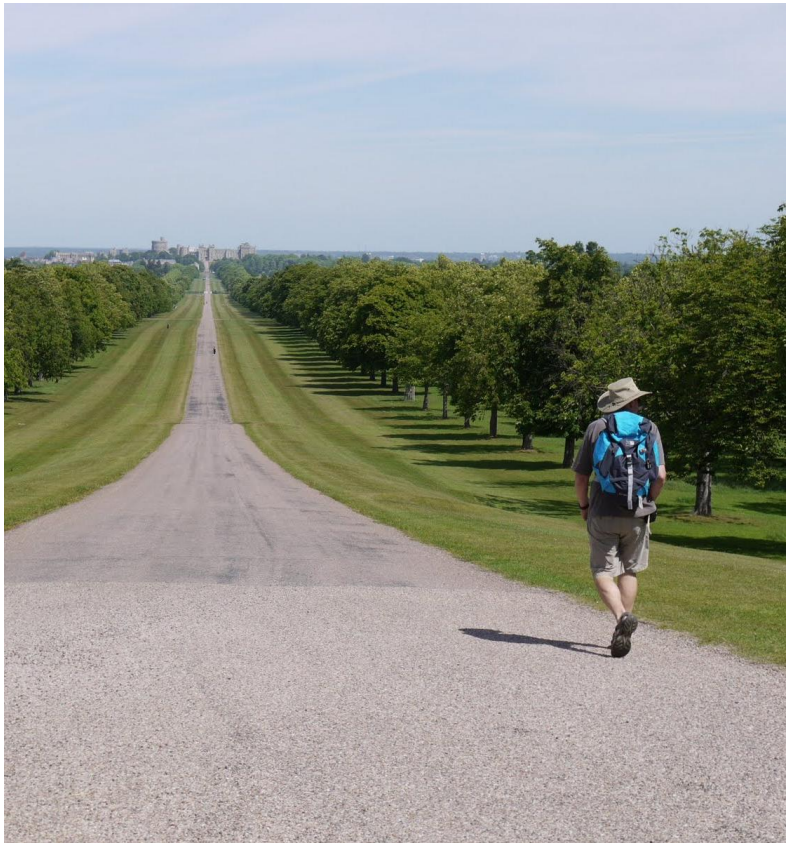
Activity Cliffs or Matched Molecular Pairs

What about the bits where the similarity hypothesis breaks down?

Something dramatic happens

Nothing happens



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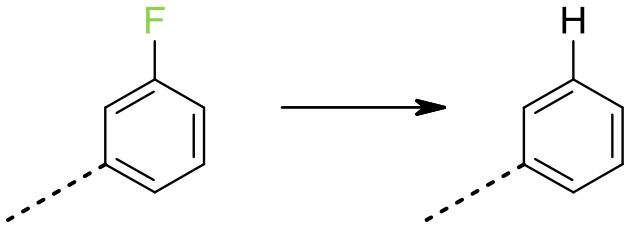
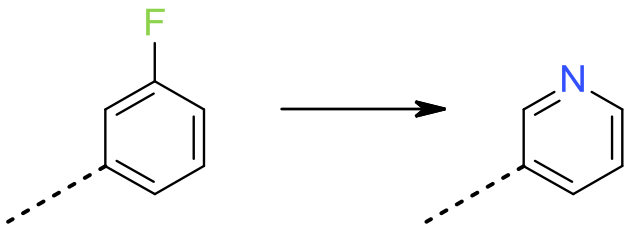
Activity Cliffs or Matched Molecular Pairs

What about the bits where the similarity hypothesis breaks down?



pIC50 8 pIC50 6



pIC50 8 pIC50 8

- Activity Cliff
  - Small change in structure
  - Large change in activity
  - → Critical region in structure activity relationship
  - → Understand activity, enable design of better molecules

- Matched Molecular Pair
  - Small change in structure
  - Small change in activity
  - “Bioisosteres”
  - → Critical region in property space
  - → Tune properties to match our global optimization problem

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Finding Activity Cliffs & MMPs

- Activity Cliffs and MMPs can be found using 2D similarity and substructure methods
- For each pair of molecules measure change in structure relative to change in activity

$$\kappa \approx \frac{\Delta\, Activity}{\Delta\, Structure}$$

- Large κ ➔ Activity cliff

- Small κ and small Δ Activity ➔ MMP

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Another Dimension in Activity Cliffs

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Activity Cliffs

- Many names:
  - Disparity (Merck 1990s)
  - SALI (Guha/Drie 2008)
  - Activity Landscapes
  - Activity Cliffs
- For each pair of molecules

$$\frac{Act_1 - Act_2}{Distance_{12}}$$

- Usually distance = 1 – similarity
  - Similarity in 2D

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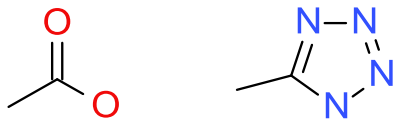
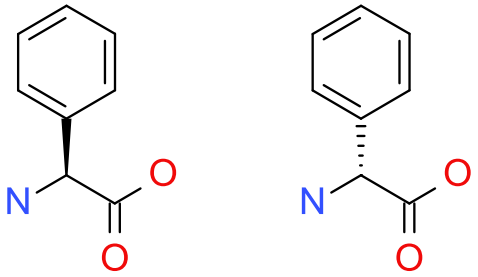
Where 2D similarity causes problems

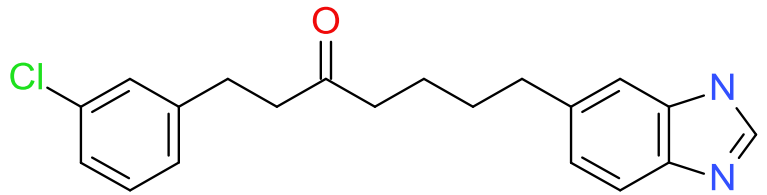
> Bioisosteres – low 2D similarity but biologically similar



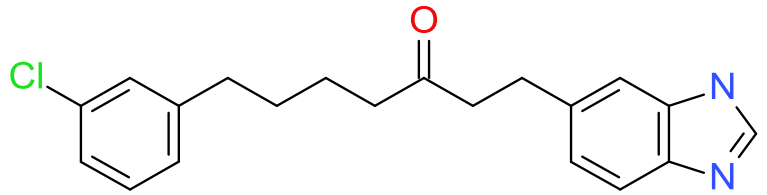
> Enantiomers and Chirality



> Locality issues



Fingerprint locality (ECFP4 sim=1.0)



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Gaining Understanding of Activity Cliffs

- 2D Activity cliffs highly valuable
- But no explanation for why the cliff is present
- Without an explanation we cannot use the cliff to design new compounds with confidence

- True understanding can only come from 3D metrics
  - Shape
  - Electrostatics

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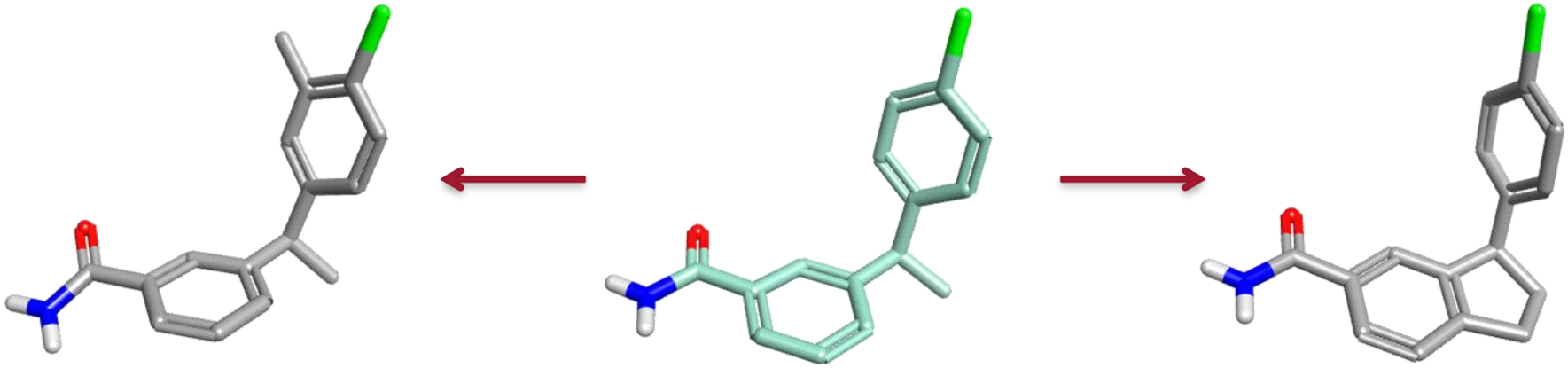
Using 3D molecular similarity

> 2D metrics are easy: 1:1 map to topology

> 3D is defined for **conformers**, not for **molecules**



0.94 0.92

In this conformation both changes are equivalent

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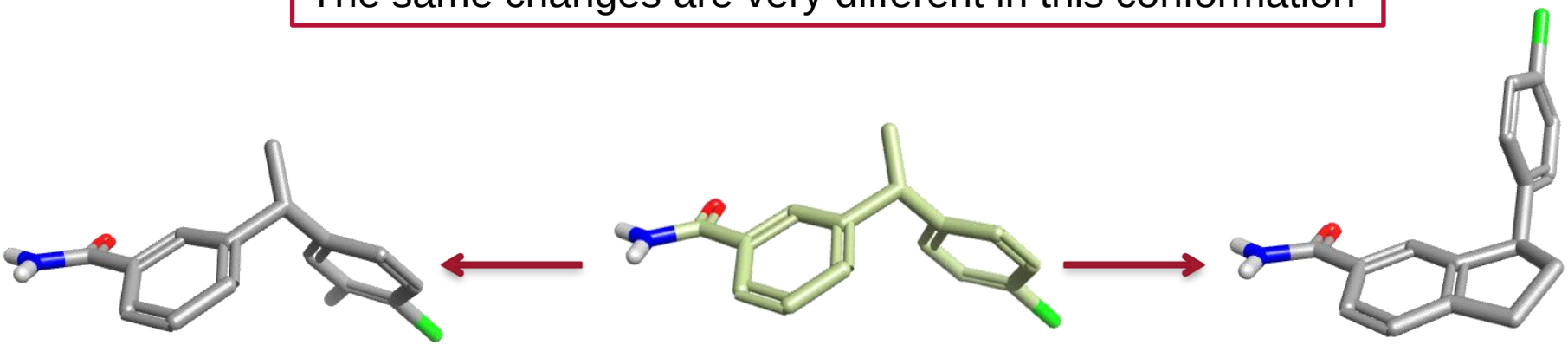
Using 3D molecular similarity

> 2D metrics are easy: 1:1 map to topology

> 3D is defined for **conformers**, not for **molecules**

The same changes are very different in this conformation



0.96

0.66

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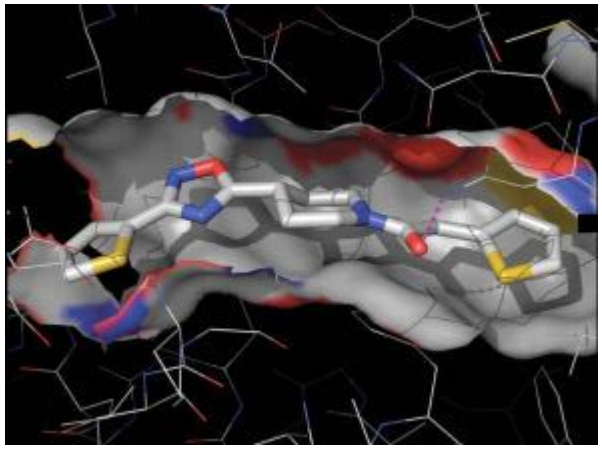
Context is everything

- Don’t need/want **generic** 3D similarity
  - Have activity context – bound to the protein



- Align all molecules to known bioactive reference conformer
- Provides a conformation context to each molecule

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3D disparity

1. Generate conformers
2. Align to reference(s)
3. Calculate similarity matrix on aligned conformations

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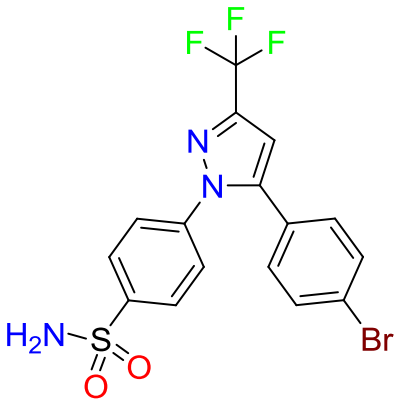
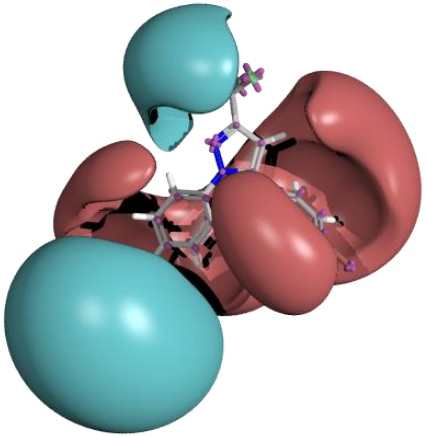
3D Similarity using Shape and Electrostatics

> Condensed representation of electrostatic, hydrophobic and shape properties ("protein's view")

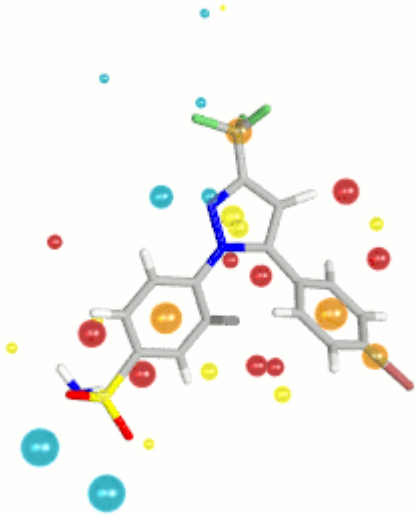
→ Molecular Field Extrema ("field points")



2D



3D Molecular Electrostatic Potential (MEP)



Field Points

= Positive
= Negative
= Shape
= Hydrophobic

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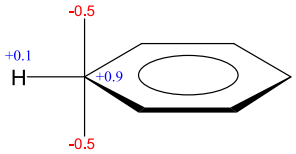
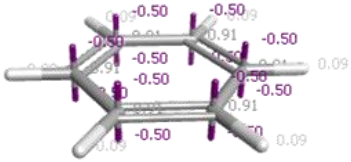
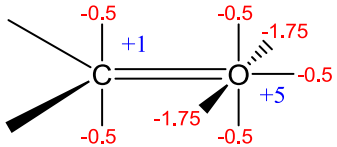
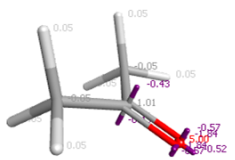
Electrostatics from Molecular Mechanics

- XED force field – eXtended Electron Distribution
  - Multipoles via additional monopoles

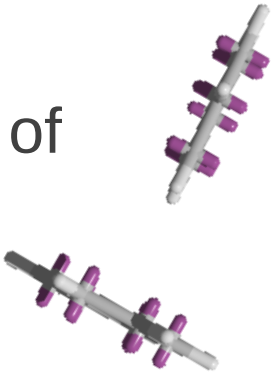








  - Huckel
    - separation of π and σ charges
      - π charges added to “xed” atoms
      - σ charges added to nuclei
      - Excellent modelling of substituent effects
    - find bond orders and assign hybridization
      - Analogue N(sp3) atoms – pyramidal to planar
  - Full MM Force Field with excellent coverage of organic chemistry and proteins
    - Minimization, Conformations etc.



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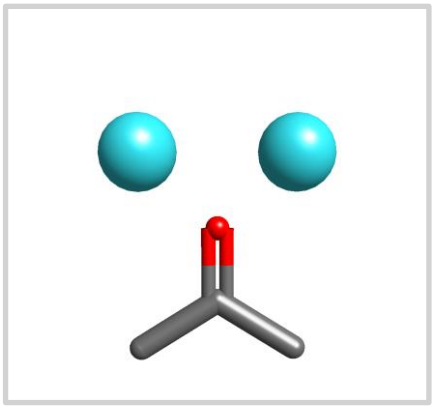
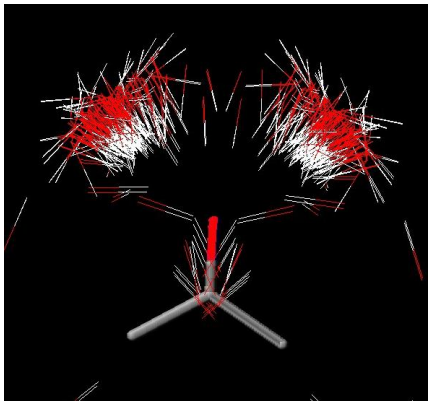
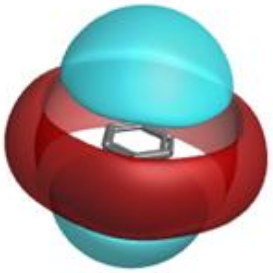
Detailed Electrostatics from XED

> eXtended Electron Distribution gives detailed electrostatic interaction patterns

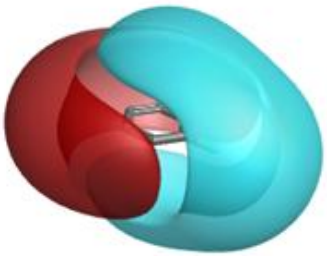




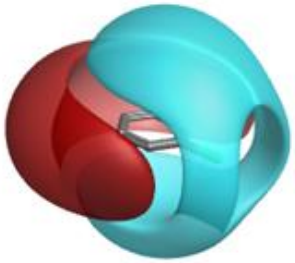
Interaction of Acetone and Any-OH from small molecule crystal structures



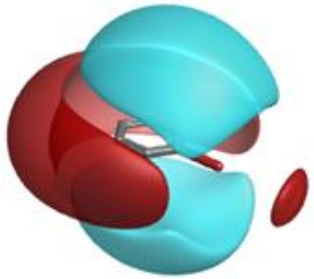
benzene



flurobenzene



chlorobenzene



bromobenzene

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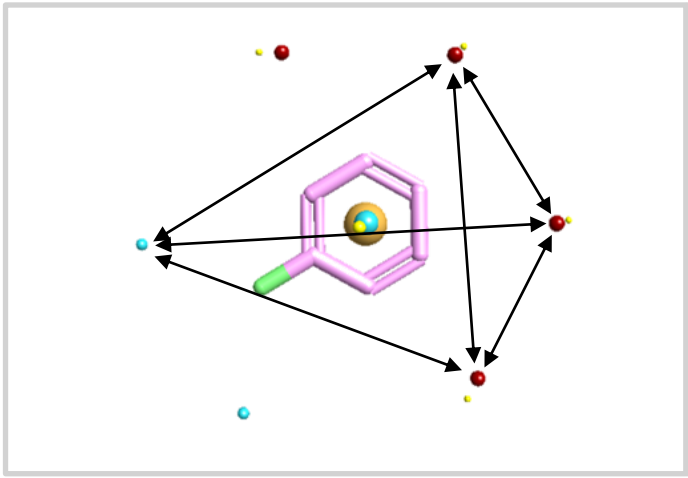
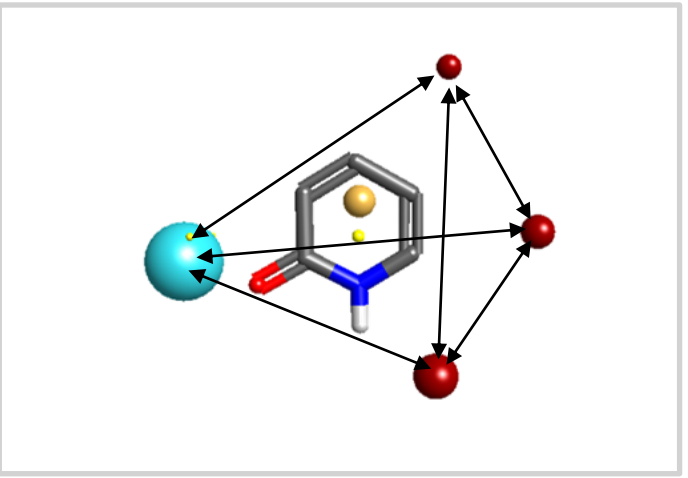
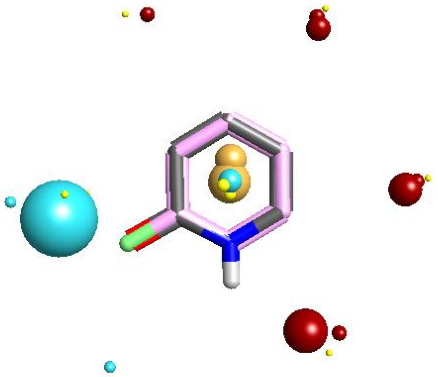
Alignment, Scoring and Comparisons

Clique based alignment







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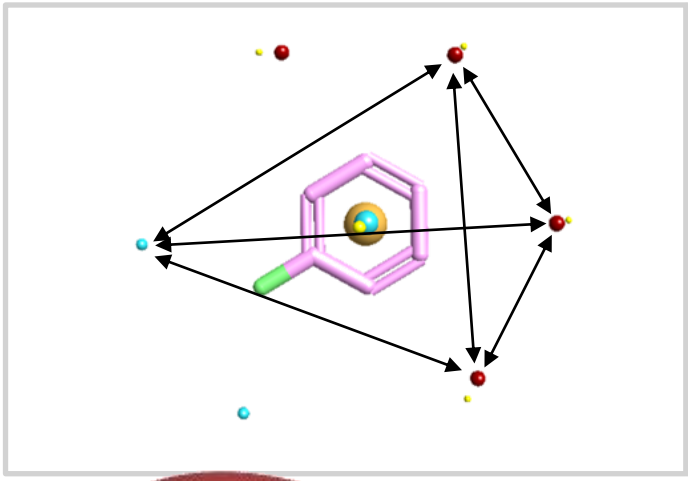
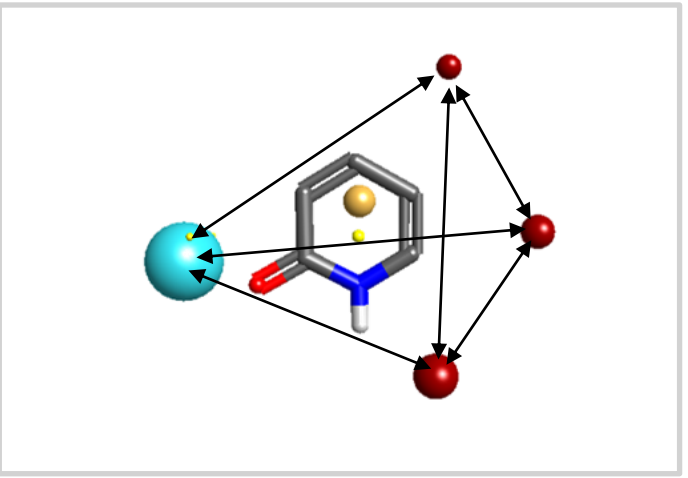
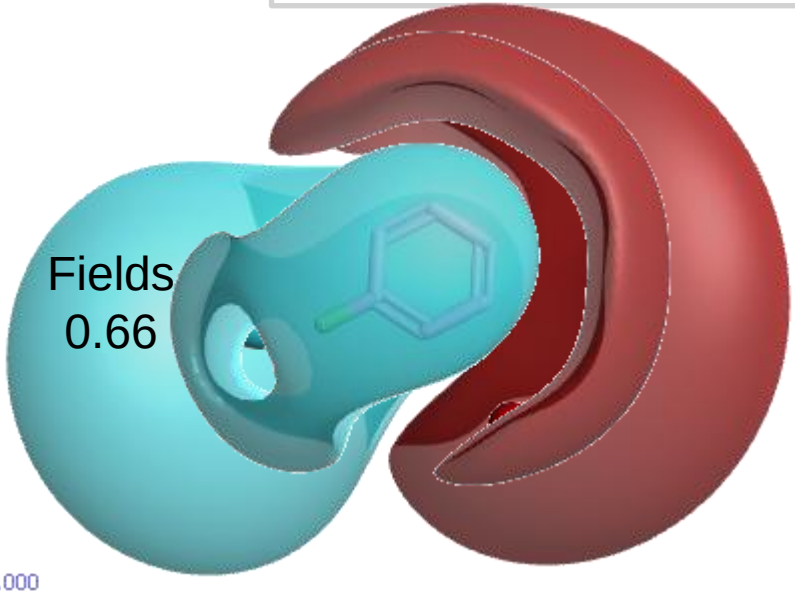
Alignment, Scoring and Comparisons

Clique based alignment







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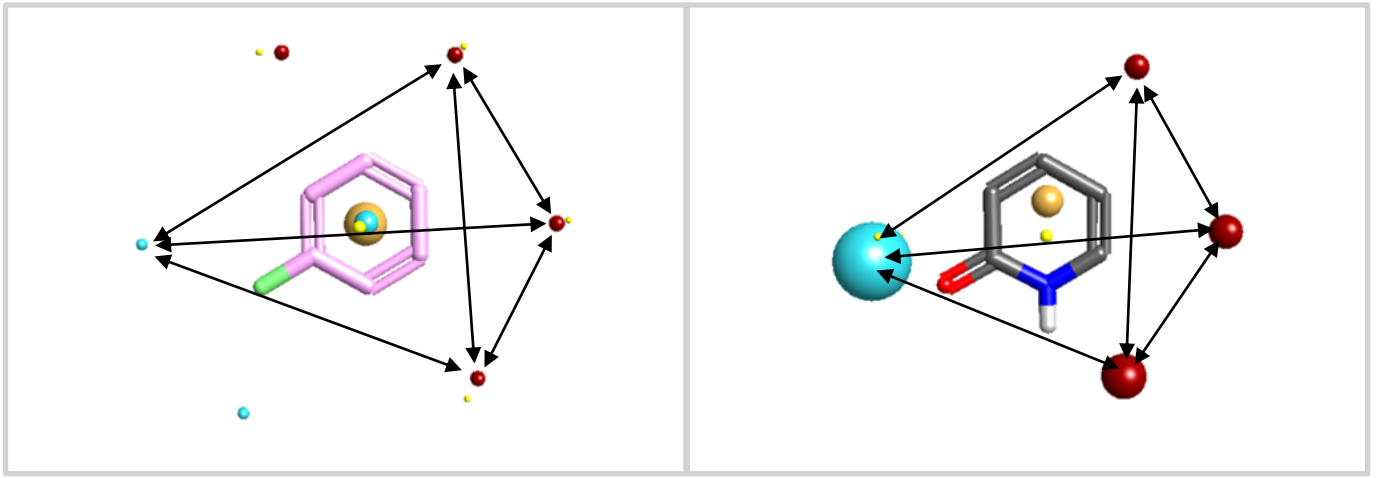
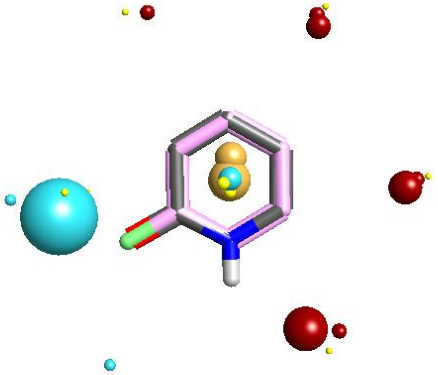
Alignment, Scoring and Comparisons

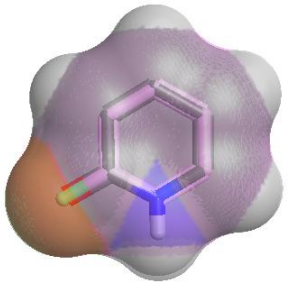
Clique based alignment



Fields
0.66



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



Shape
0.98

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

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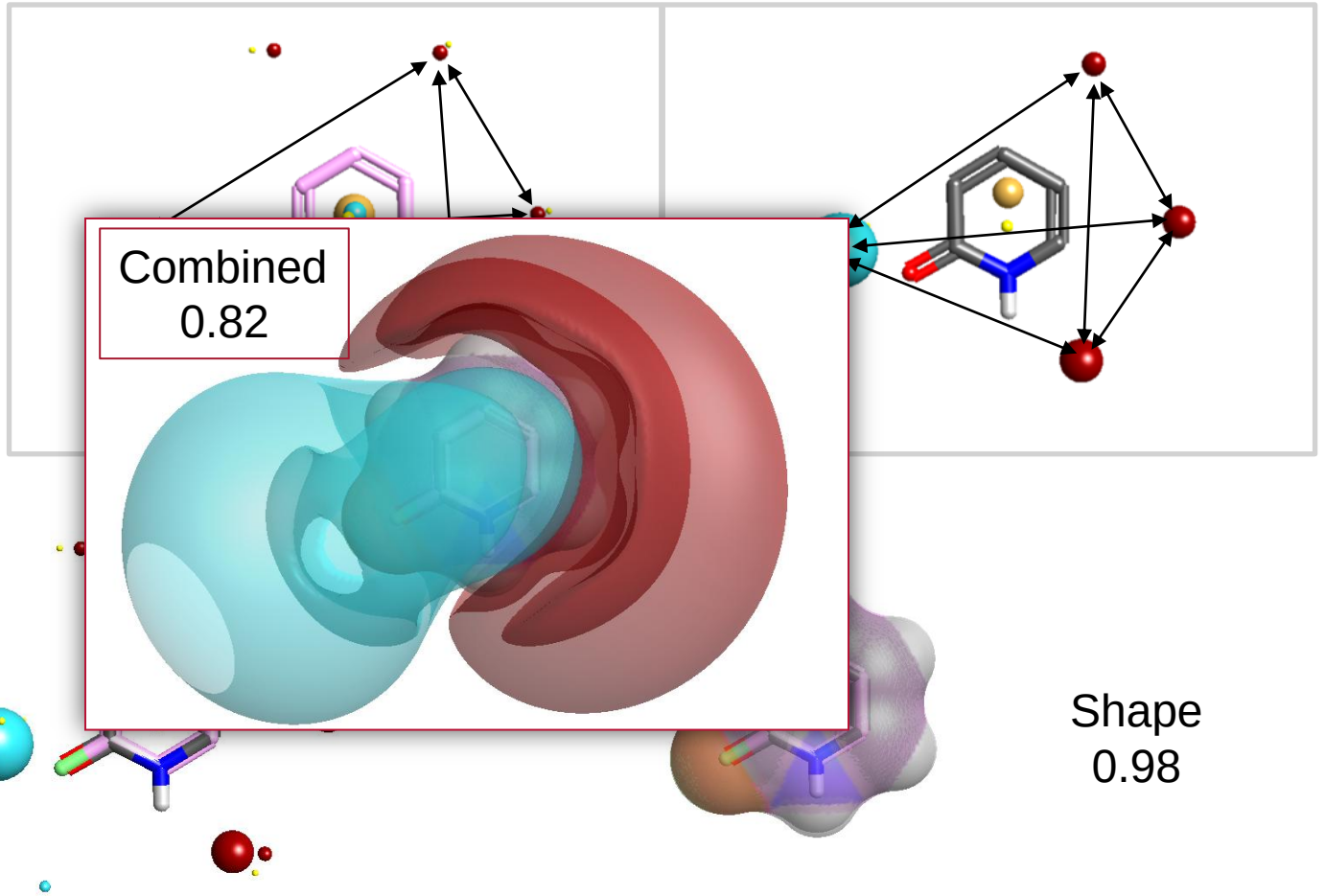
Alignment, Scoring and Comparisons

Clique based alignment



Fields
0.66

Shape
0.98

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

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

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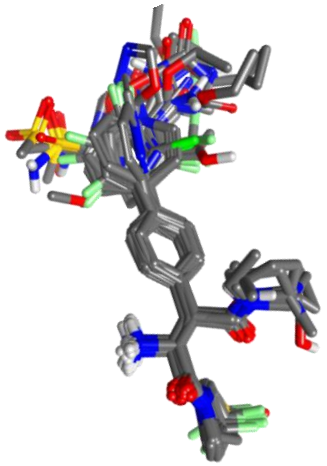
3D disparity

1. Generate conformers
2. Align to reference(s)
3. Calculate similarity matrix on aligned conformations
   > Allow small movements
4. Calculate disparity matrix from similarity numbers
   > Similarity cutoff of 0.95 (Distance cutoff of 0.05)
5. Visualise
   > Difficult – 100 molecules gives 4950 pairs!



$$\frac{Act_1 - Act_2}{Distance_{12}}$$

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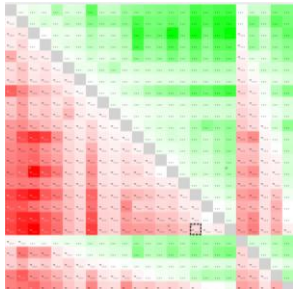
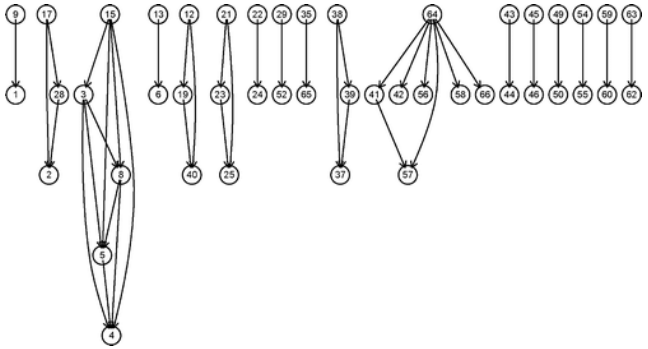
Visualisation

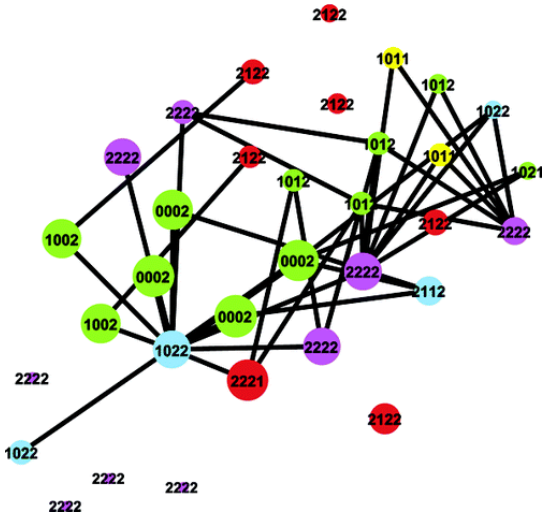
- Existing ways to visualise
  - Matrix views



  - Graph view (Guha/van Drie 2008)



  - Activity landscapes (Bajorath)



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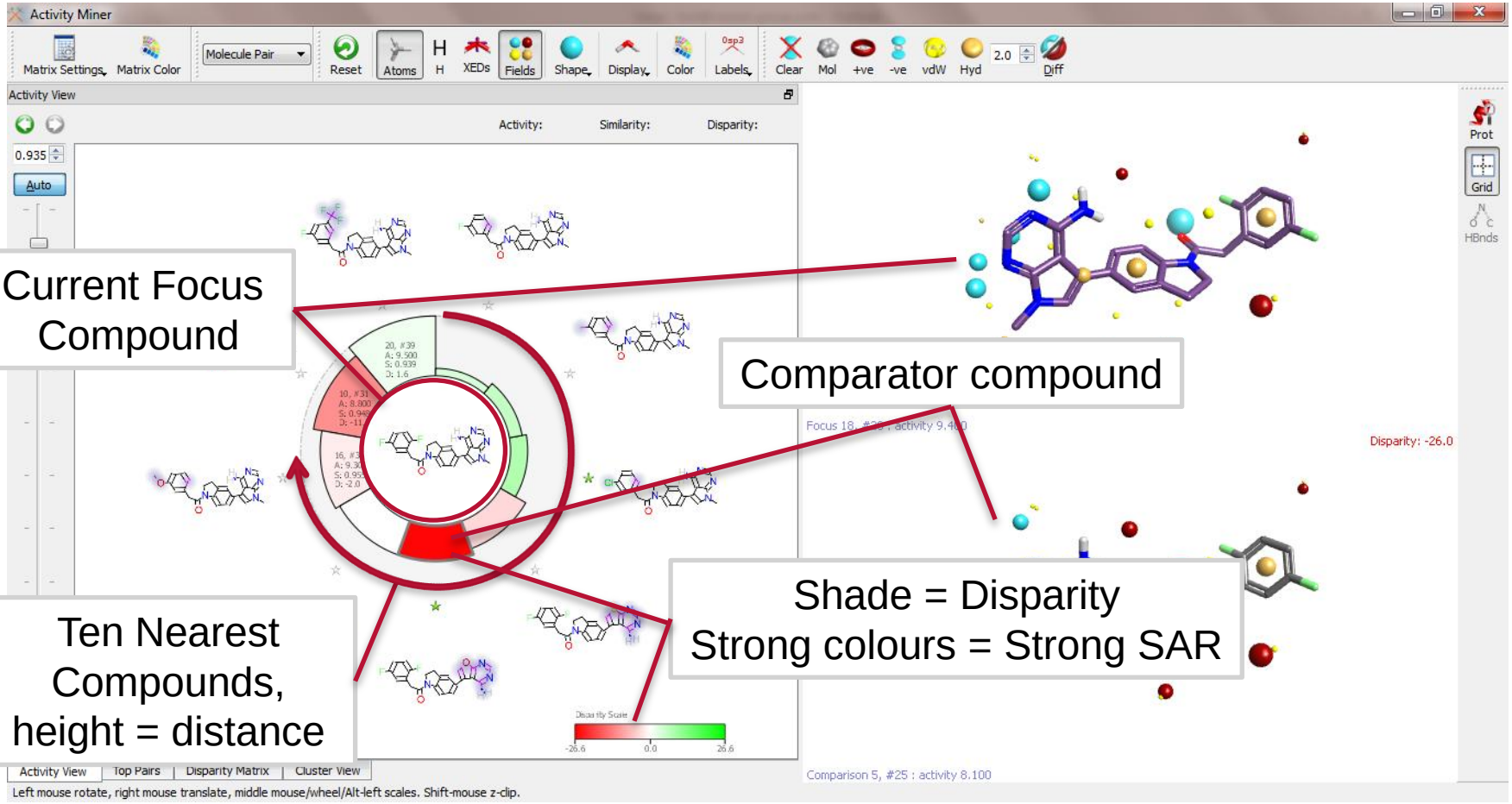
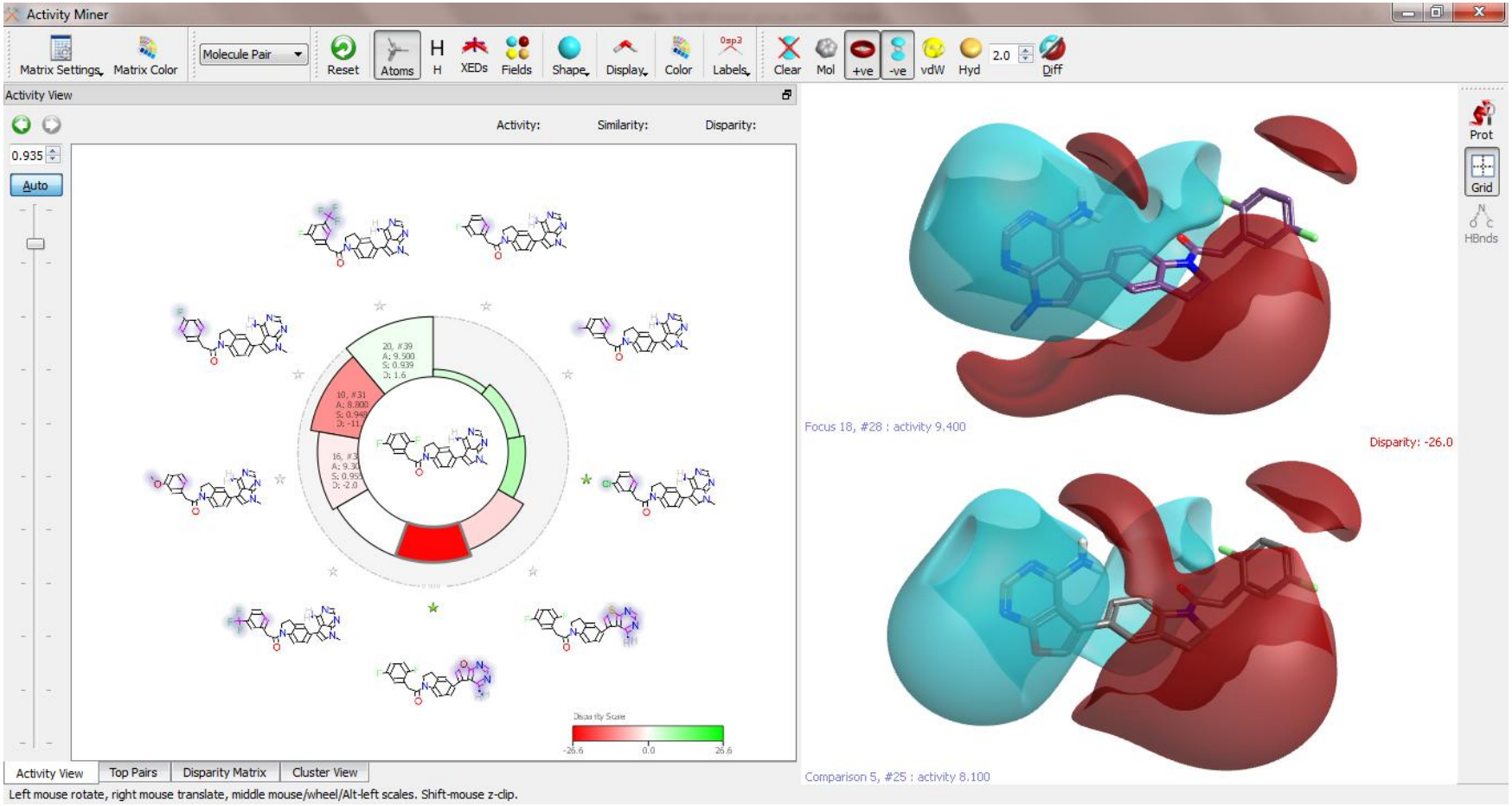
Activity View



Fields Electrostatic Environment



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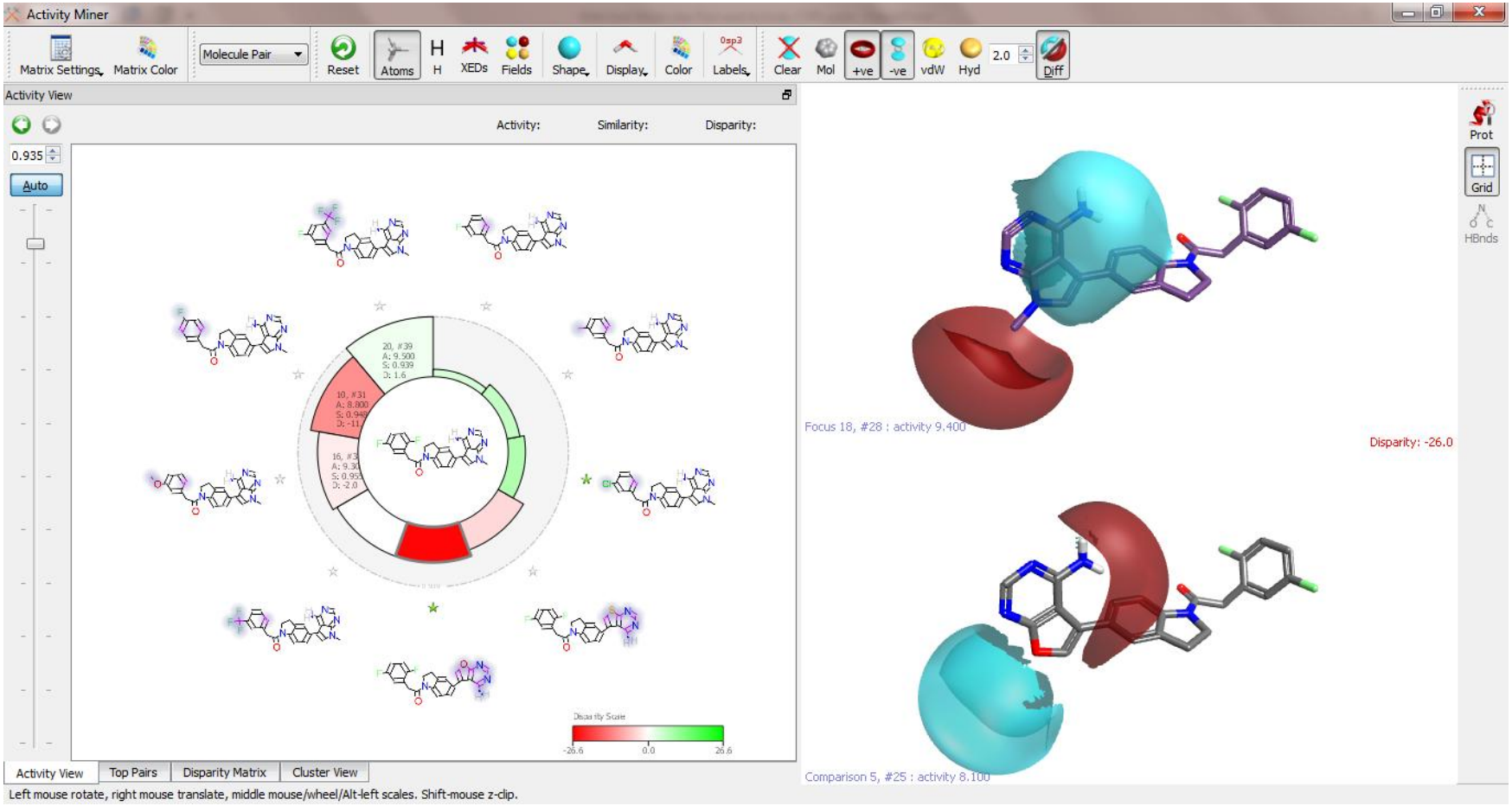
Field Differences Inform Decisions

Difference plot – Regions where each molecule has stronger electrostatics



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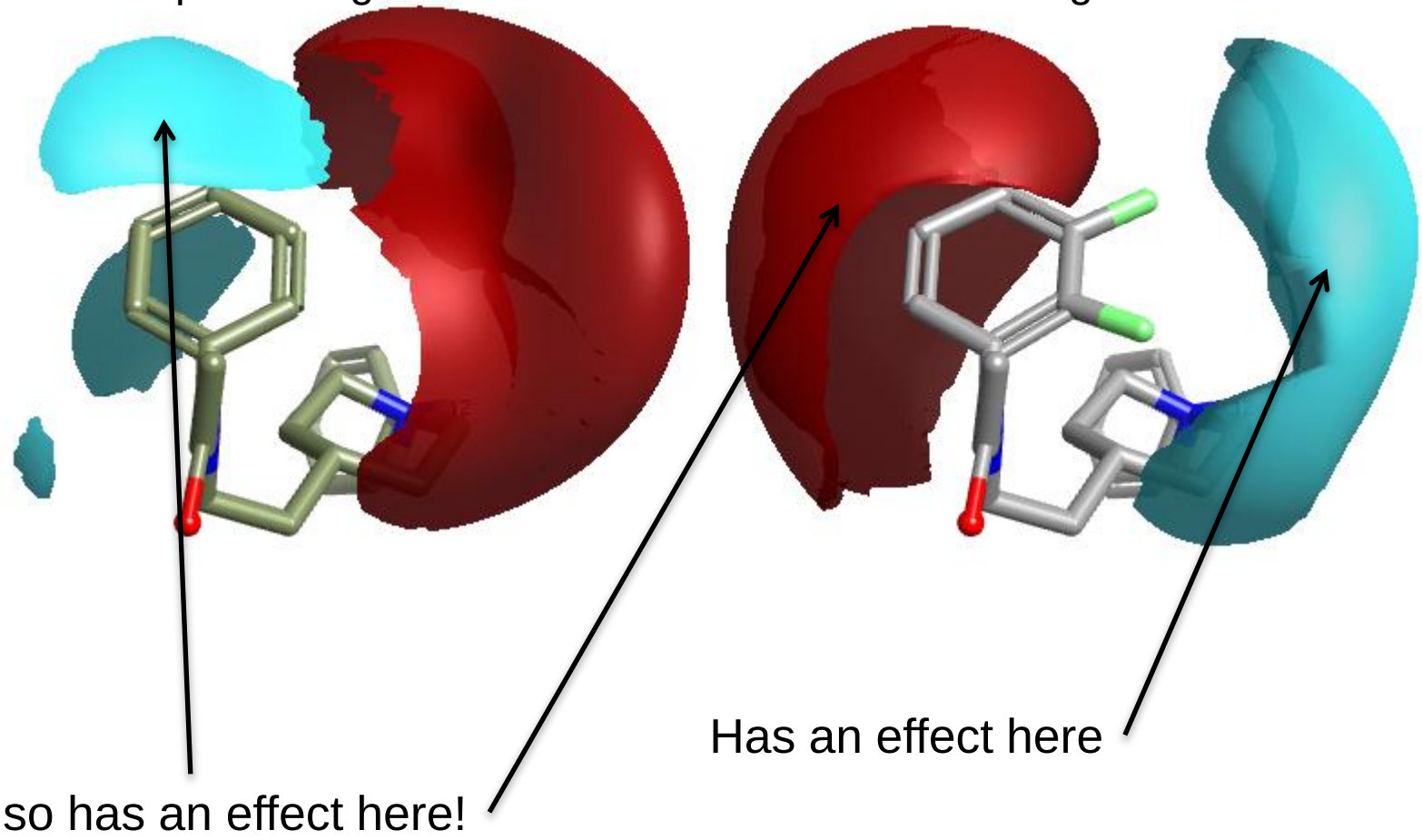
Detailed Electrostatics decode SAR

Difference plot – Regions where each molecule has stronger electrostatics



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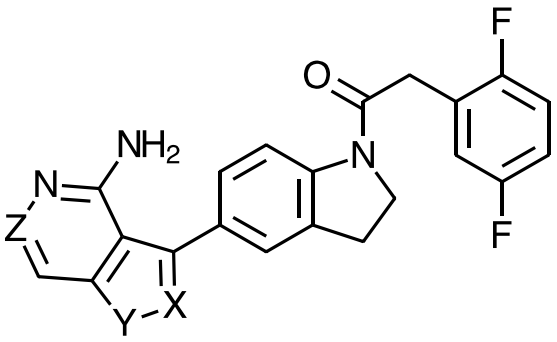
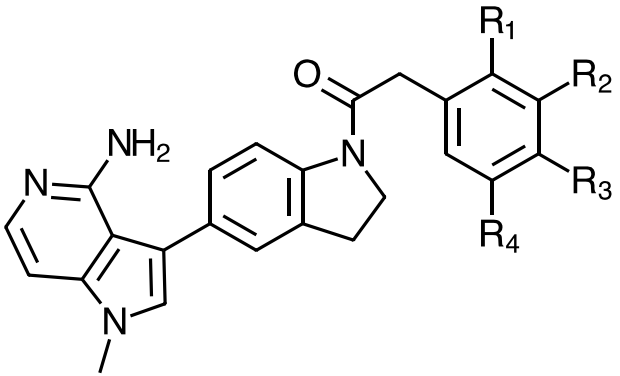
Example: PERK Kinase Inhibitors

- When PERK is inhibited in cancer cells, the viability of those cells in nutrient or oxygen deprived conditions is reduced, which can lead to apoptosis and inhibition of tumor
- Two related series:





J. Med. Chem., **2012**, *55*, 7193.

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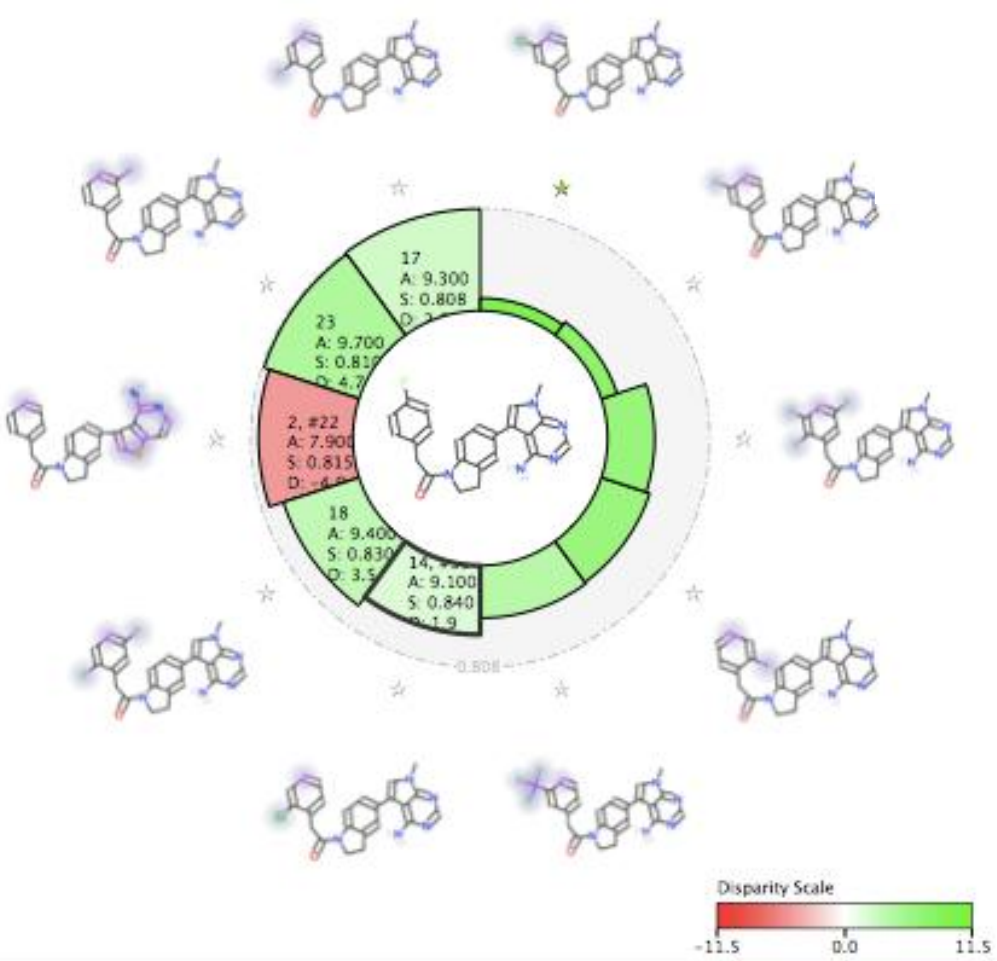
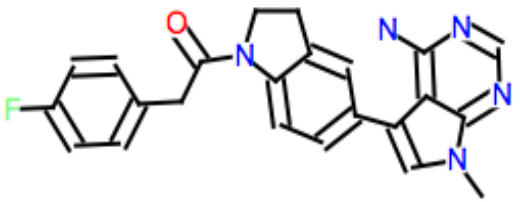
Activity View: Focus on Molecule #31





pIC50 = 8.8

- Short slices = high Similarity
- Darker colour = higher Disparity
- Green = Improved Activity
- Areas of structural changes are “haloed”

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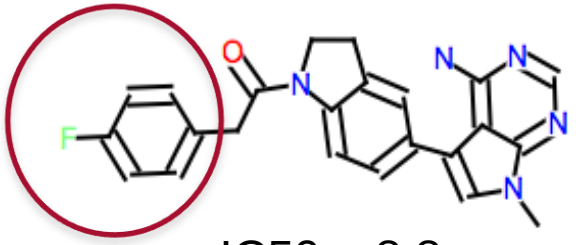
Investigating Molecule #31 (Activity View)

> Substituent position on the terminal ring

	pIC50	Similarity	Substituent
25	9.8	0.897	*meta*-Cl
21	9.6	0.893	*meta*-F
24	9.7	0.862	*meta*-F *meta*-F *ortho*-F
22	9.7	0.859	*ortho*-CH_3
19	9.4	0.857	*meta*-CF_3
35	9.1	0.840	*ortho*-Cl
18	9.4	0.830	2-F(*ortho*), 5-F(*meta*)
23	9.7	0.810	*meta*-Cl



pIC50 = 8.8

> Small structural changes (high Sim) resulting in pIC50 improvement.

> Removal of *para* substituent and replacement with *meta* and/or *ortho* groups improves activity.

> Consistent with observations reported by GSK. (*J. Med. Chem.*, **2012**, *55*, 7193)

3D Sim = 50% Fields, 50% Shape

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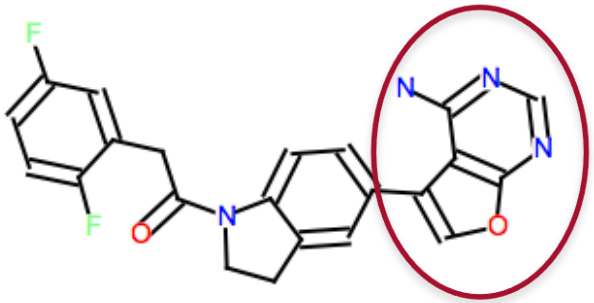
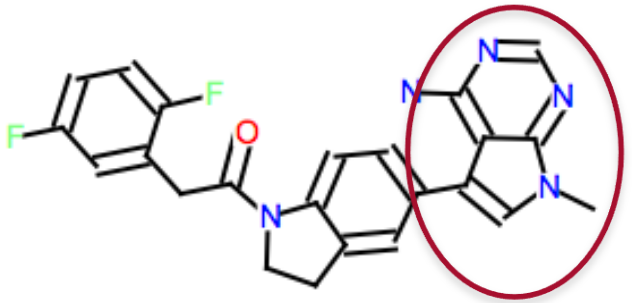
Activity View: Focus on Molecule #25



#25, pIC50 = 8.1



#18, pIC50 = 9.4

> Furanopyrimidine core replaced by a N-methyl pyrrolopyrimidine gives >1 log unit improvement.

> Examine shape and electrostatics to understand

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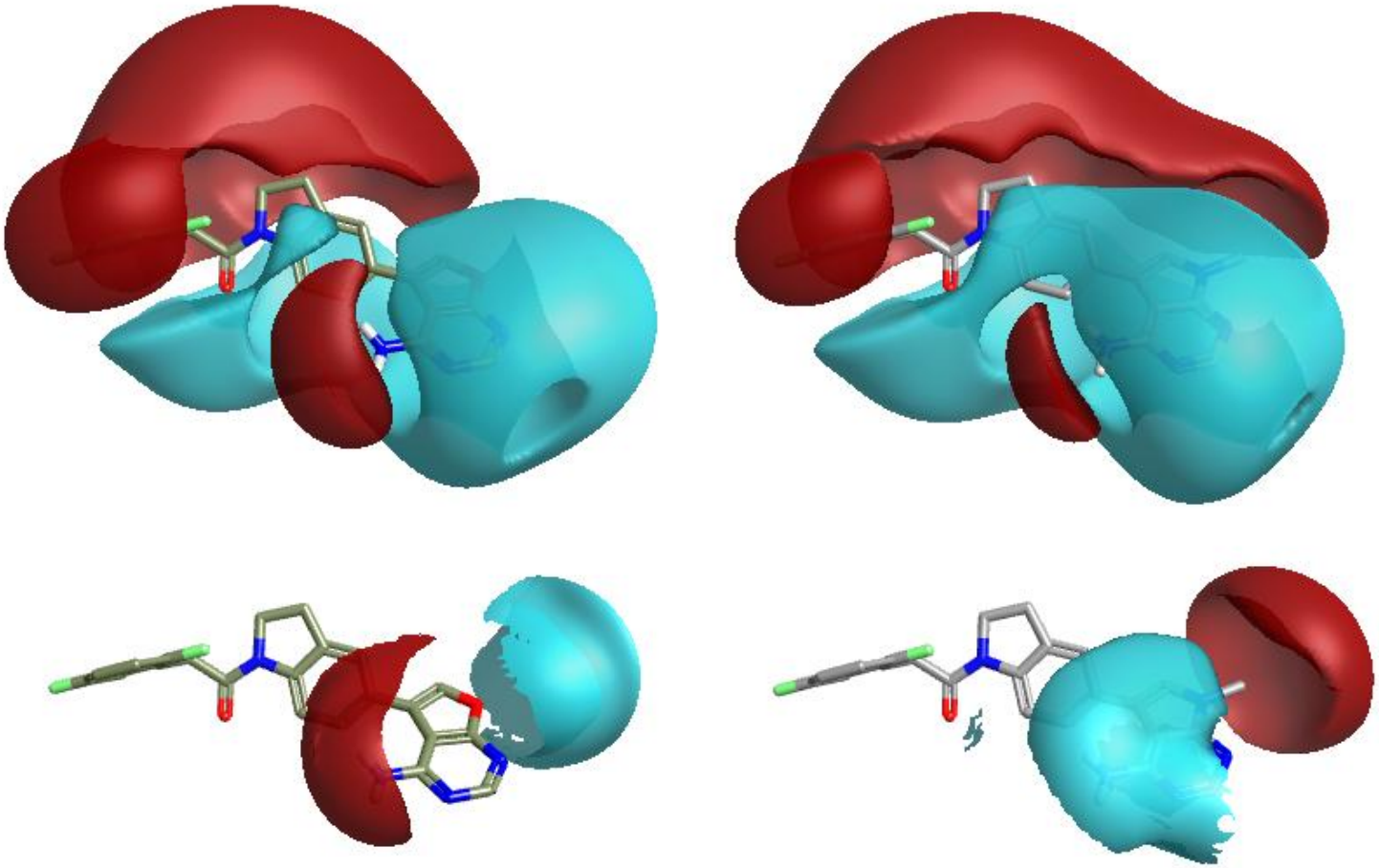
#25 (pIC50=8.1) *vs.* #18 (pIC50=9.4)



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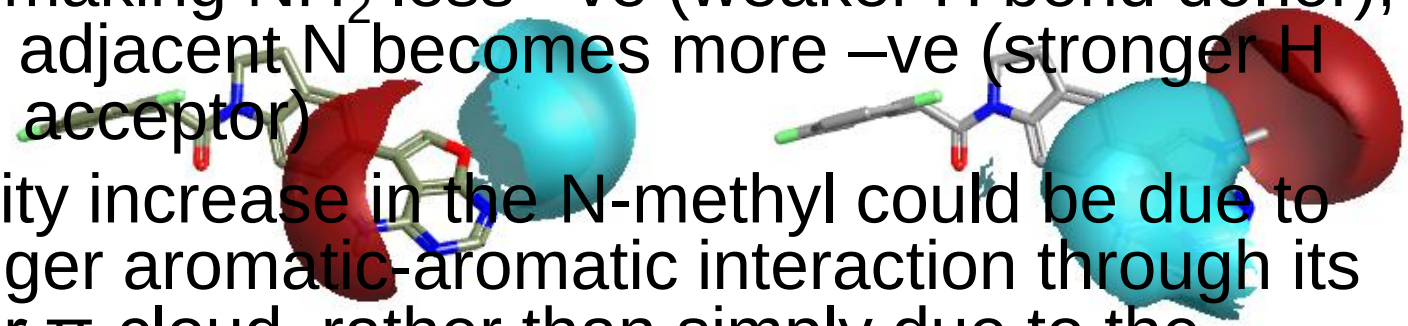
#25 (pIC50=8.1) *vs.* #18 (pIC50=9.4)

- N-methyl substitution changes dipole across the ring, making NH_2 less +ve (weaker H bond donor), BUT, adjacent N becomes more –ve (stronger H bond acceptor)
- Activity increase in the N-methyl could be due to stronger aromatic-aromatic interaction through its larger π-cloud, rather than simply due to the substituent itself.



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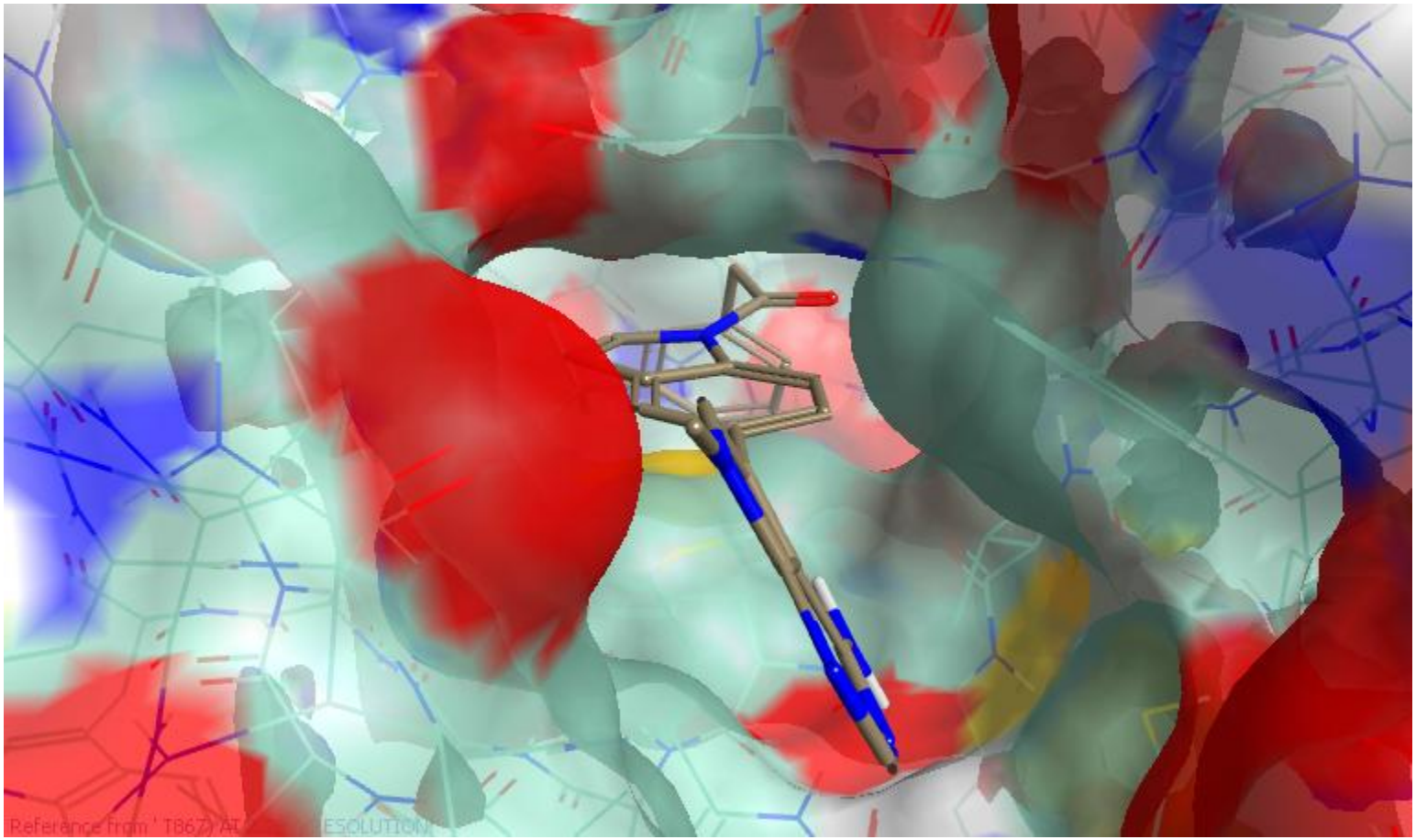
Pi-stacking probably part of the activity increase



4G31

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Conclusions

- Disparity/Activity Cliff analysis in 3D is a powerful tool
  - Discovery of Strong SAR
  - Why Activity Changes
- Needs reliable 3D alignment and scoring
- Data sets can be complicated, so clear visualisations are necessary

- Extensions to MMP analysis under investigation

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Acknowledgements

- Dr Andy Vinter
  - Founder Cresset
- Dr Mark Mackey
  - Chief Scientific Officer
- Mr Nigel Palmer
  - Developer

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3D Activity Cliffs

> 3D Activity Cliffs available in Activity Miner module for Forge and Torch

3D Design tool, SAR interpretation

SAR interpretation & Activity Cliffs, 3D Design, 3D QSAR, Pharmacophore modeling

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Thank you!

Questions Welcomed



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