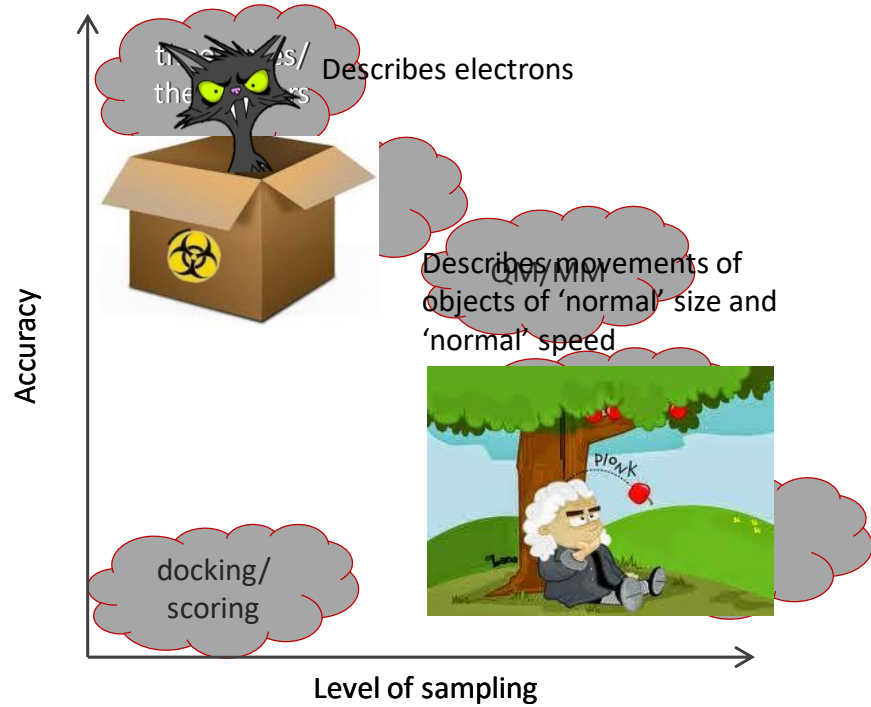




Predicting protein-ligand binding using quantum mechanics

Iva Lukac

UKQSAR, Sep 2019

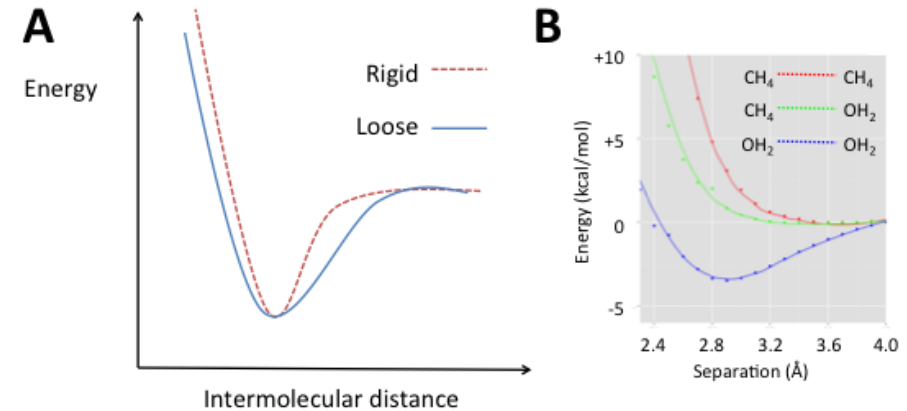


$$\Delta G_{binding}(aq) = \Delta E + \Delta H_{corr}(gas) - T\Delta S(gas) + \Delta\Delta G(solvent)$$

$clogP$

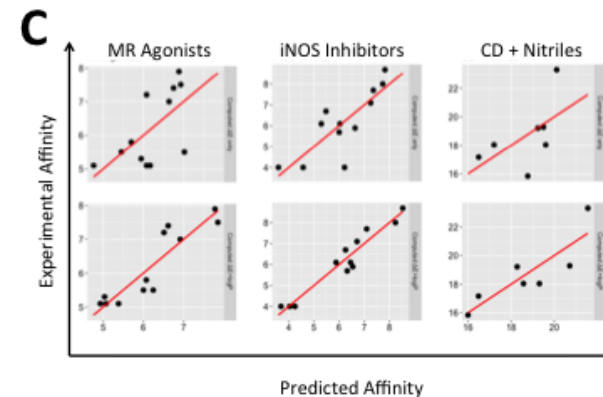
$$\Delta E = E_{complex} - E_{ligand} - E_{receptor}$$

$$Affinity = \alpha\Delta E + \beta\log P + \gamma$$

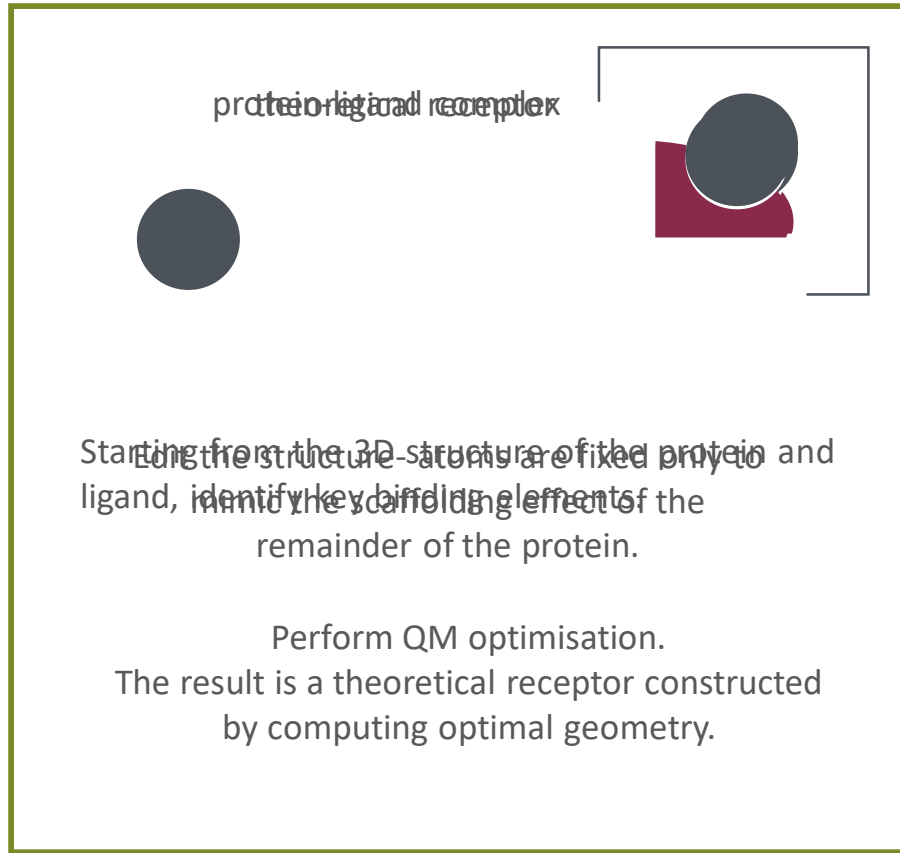


Xray structure checklist:

- ❖ 1) the protein structure is correct and known with high accuracy
- ❖ 2) the experimental conditions under which the crystal was obtained are relevant to the binding event
- ❖ 3) the ligand structure is accurate and that interactions between the binding partners are correct and well understood



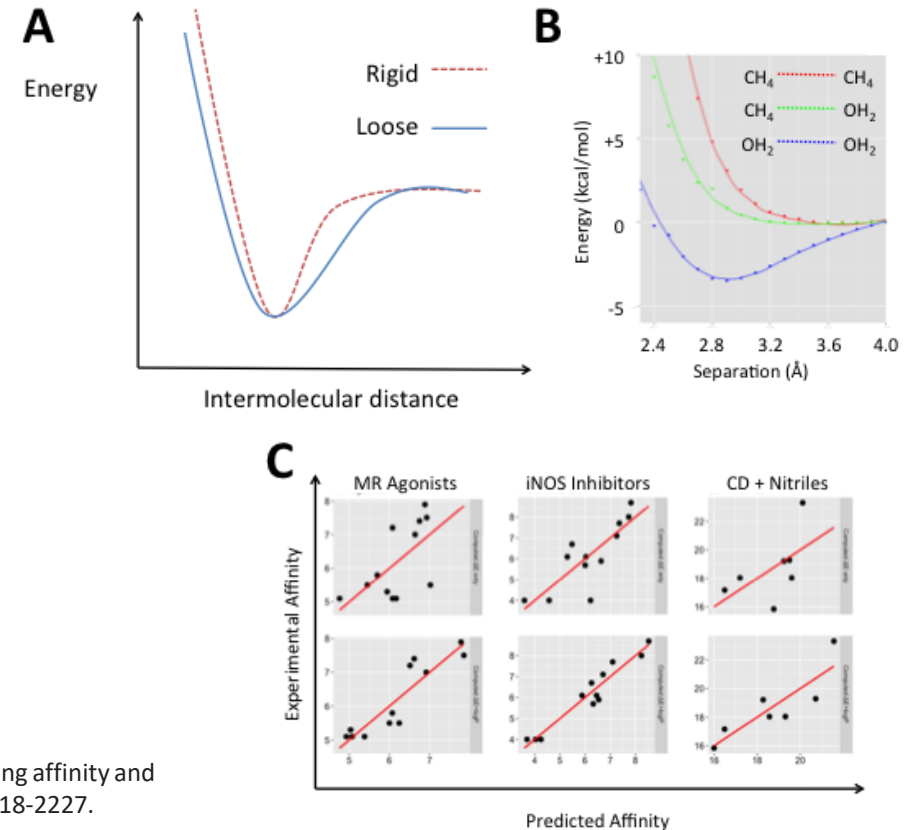
Development of the QM model



$$\Delta G_{binding}(aq) = \Delta E + \underbrace{\Delta H_{corr}(gas) - T\Delta S(gas) + \Delta\Delta G(solvent)}_{clogP}$$

$$\Delta E = E_{complex} - E_{ligand} - E_{receptor}$$

$$Affinity = \alpha\Delta E + \beta\log P + \gamma$$



Lactate Dehydrogenase A (LDHA) theoeceptor

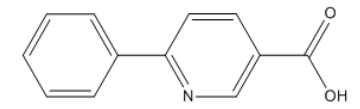
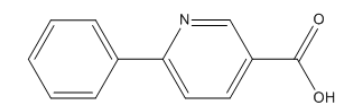
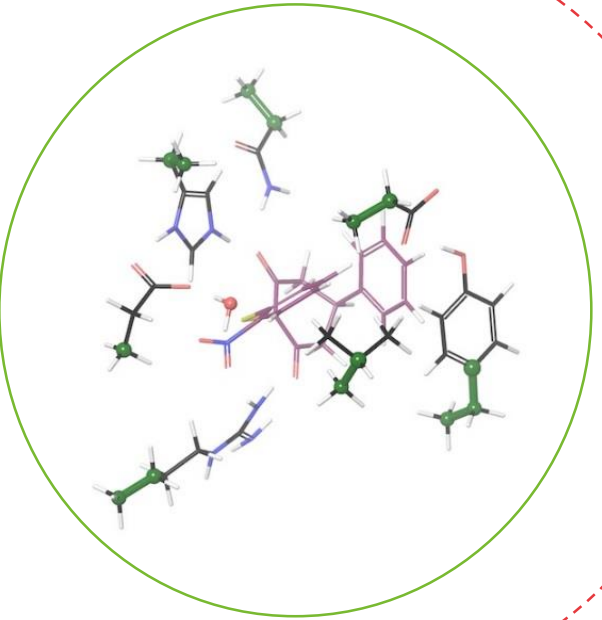
Interpretation
of heteroatom
positioning

Assessing
stereochemistry

Addressing
missing density

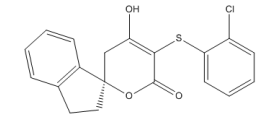
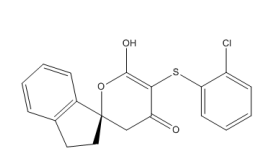
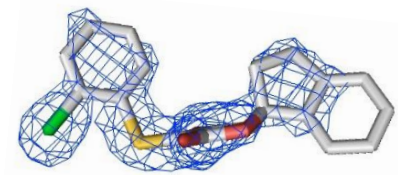
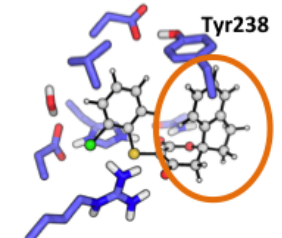
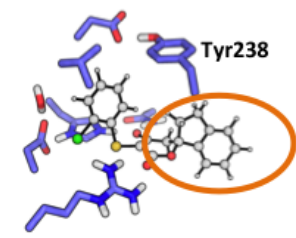
Binding mode
studies

Binding affinity
prediction



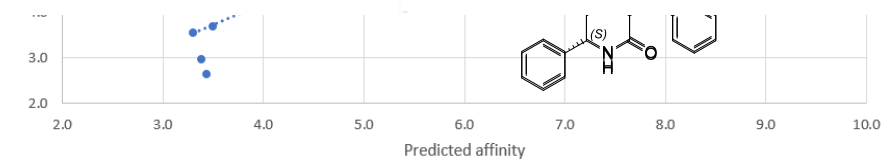
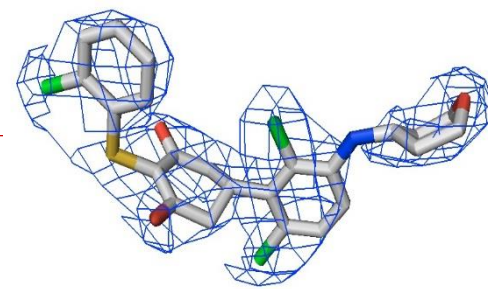
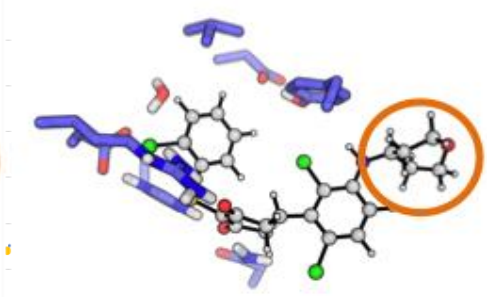
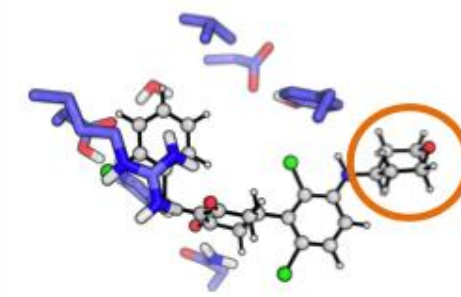
2 (Pseudo-equatorial)

2 (Pseudo-axial)



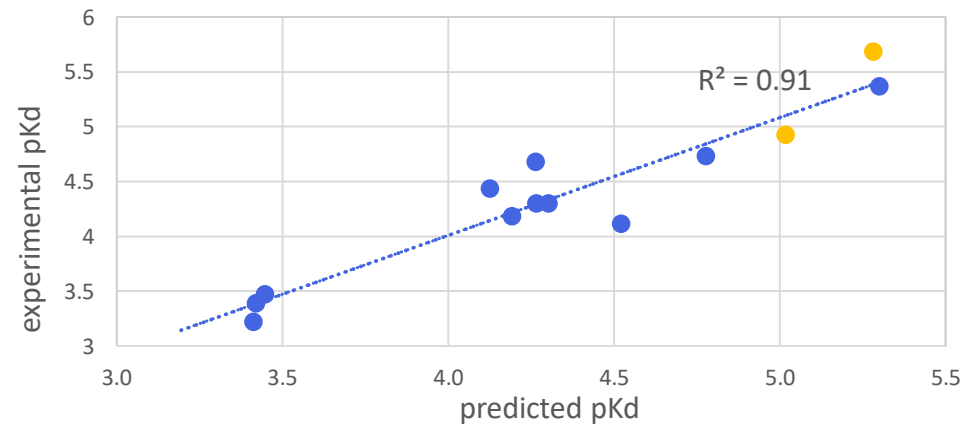
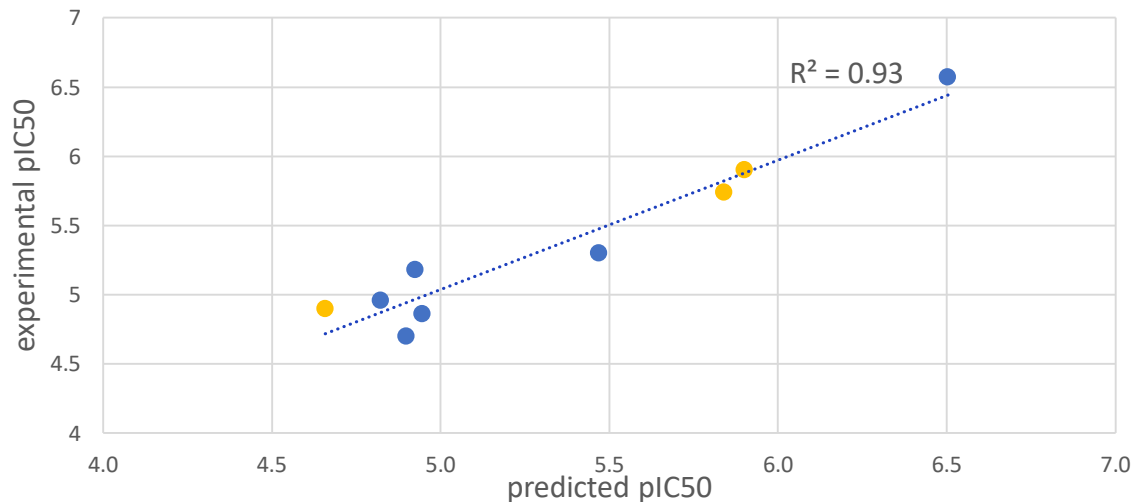
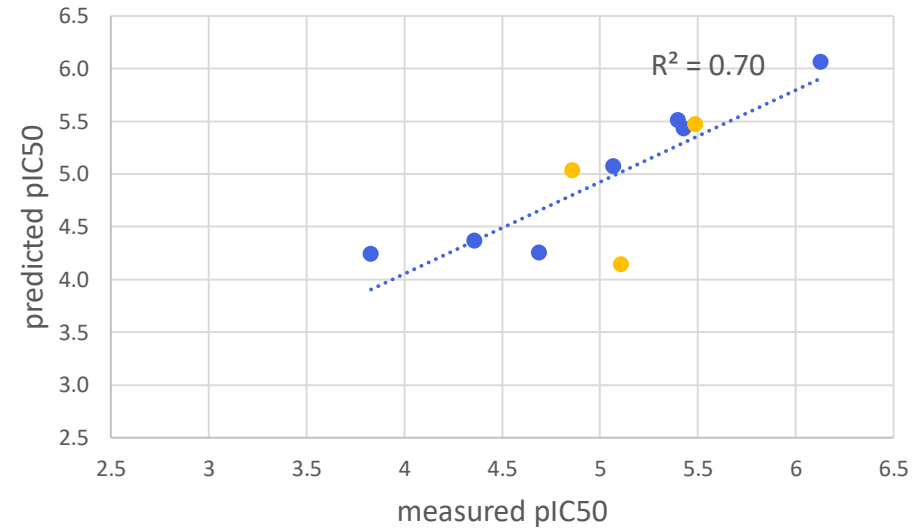
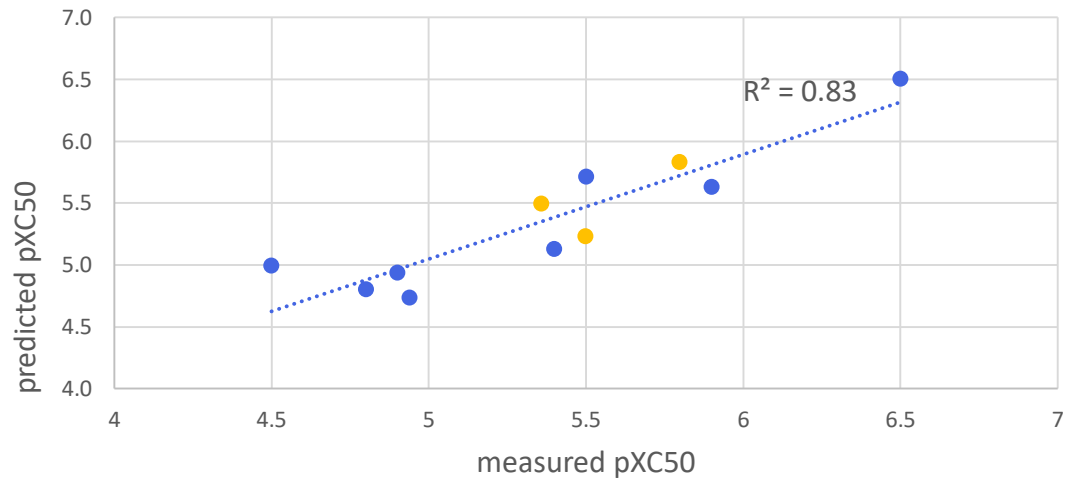
1 (Chair)

1 (Boat)

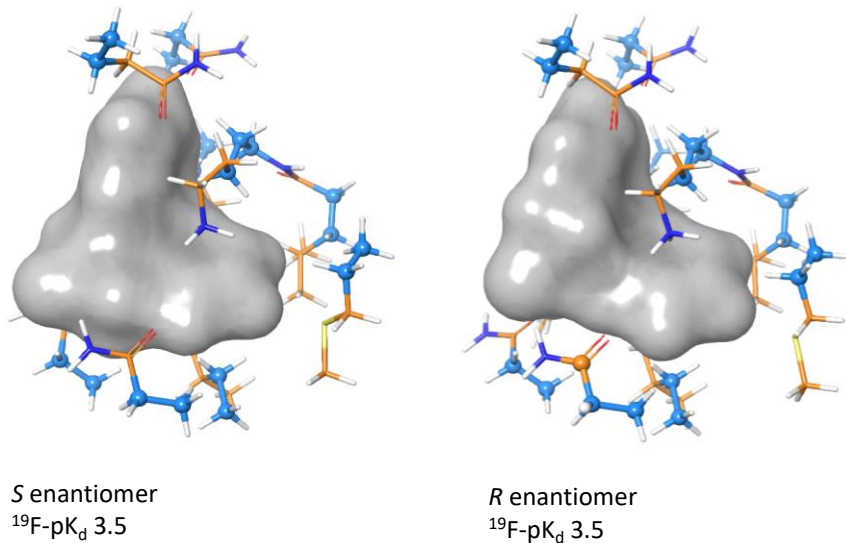


🌀 The approach has been successfully applied to several projects within the DDU

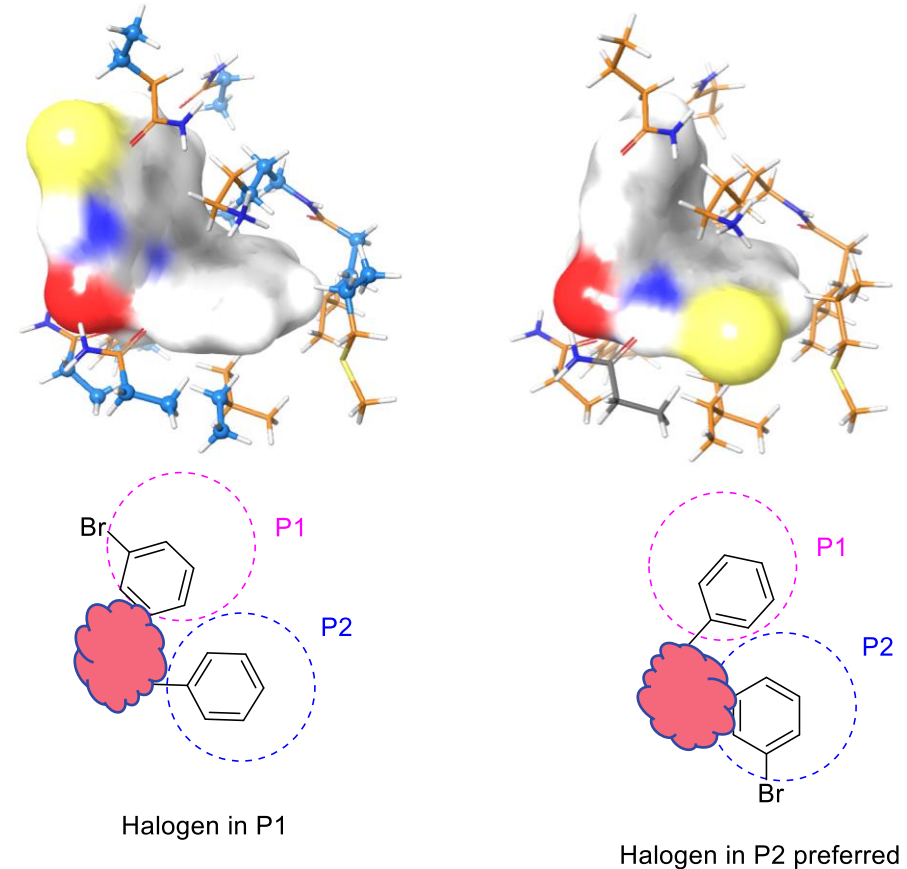
- Binding affinity prediction
 - Requirement: at least three compounds of known affinity are required - only relative affinity can be computed
 - A range of affinity assessment types (IC_{50} , K_i , K_D etc) can be used



- The approach has been successfully applied to several projects within the DDU
 - Binding affinity prediction
 - Requirement: at least three compounds of known affinity are required - only relative affinity can be computed
 - A range of affinity assessment types (IC_{50} , K_i , K_D etc) can be used
 - Binding mode studies
 - Tautomeric and protonation state preferences as well as stereoselectivity
 - Help resolve ambiguities in ligand refinement

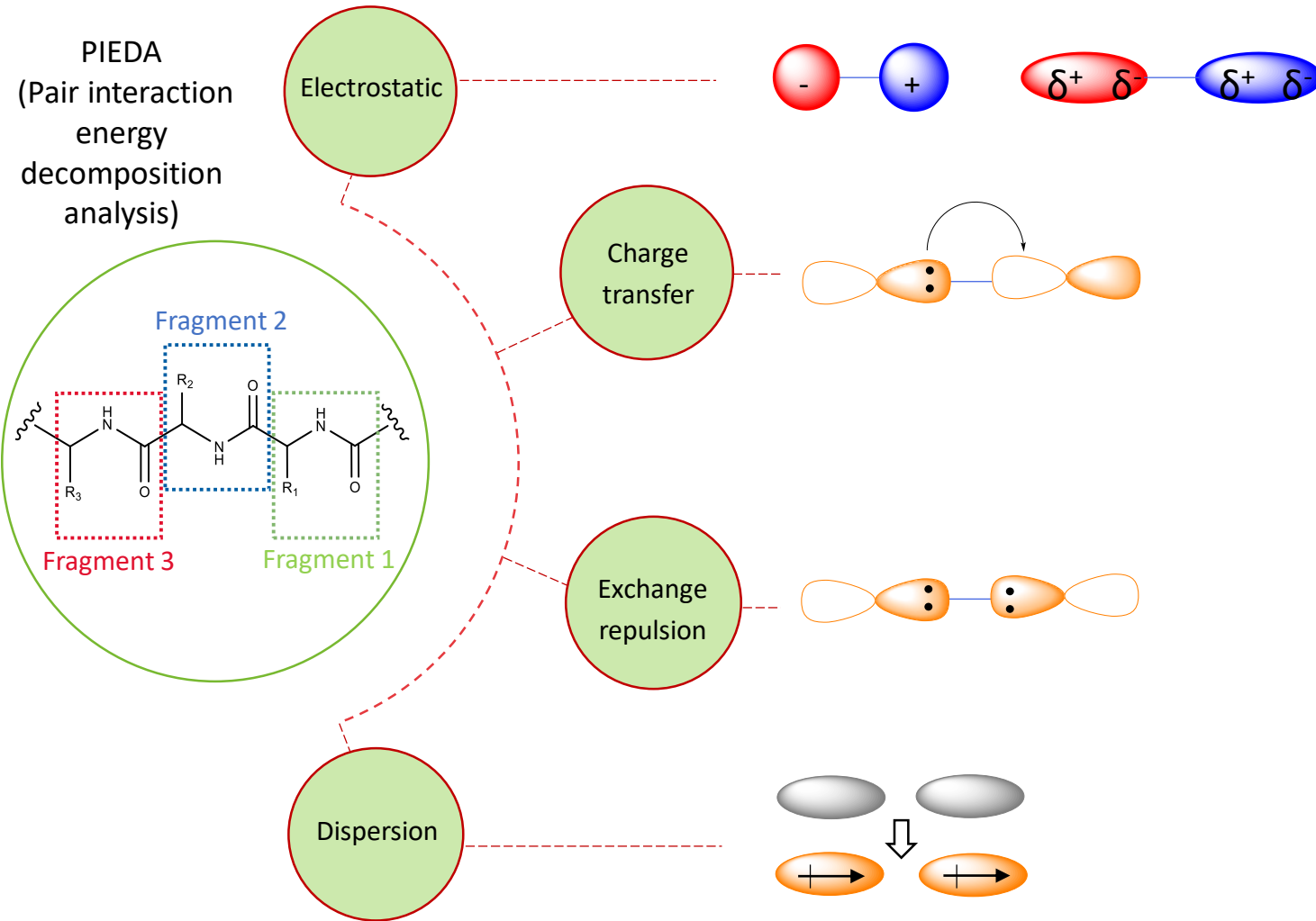


No stereochemical preference

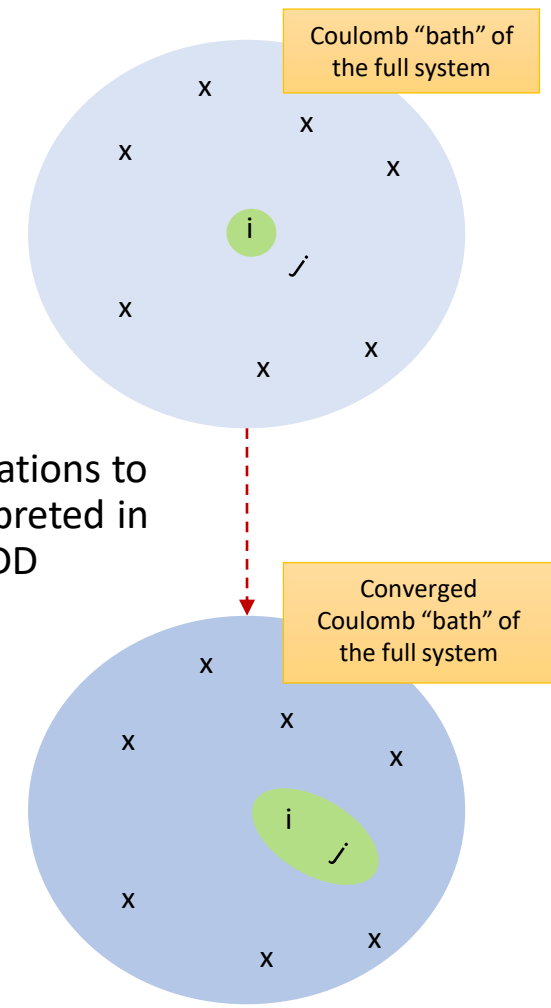


Binding mode studies

Fragment Molecular Orbital Method (FMO)



FMO enables QM calculations to be performed and interpreted in a way that can drive SBDD



*Applications of the fragment molecular orbital method to drug research. M. P. Mazanetz, E. Chudyk, D. G. Fedorov, Y. Alexeev, In Computer aided drug discovery. W. Zhang, Ed., Springer, New York, 2016, pp. 217-255.

*Exploring GPCR-ligand interactions with the fragment molecular orbital (FMO) Method. E. I. Chudyk, L. Sarrat, M. Aldeghi, D. G. Fedorov, M. J. Bodkin, T. James, M. Southey, R. Robinson, I. Morao, A. Heifetz, in Computational Methods for GPCR Drug Discovery. A. Heifetz (Ed.), Humana Press, New York, 2018, pp. 179-195.

*Characterising GPCR-ligand interactions using a fragment molecular orbital-based approach. A. Heifetz, T. James, M. Southey, I. Morao, M. Aldeghi, L. Sarrat, D. G. Fedorov, M. J. Bodkin, A. Townsend-Nicholson, Curr. Opin. Struct. Biol. 55 (2019) 85-92.

- Targeting crystallographically observed water molecules for displacement or specific interaction to improve ligand affinity has proven successful in drug discovery (increased potency, selectivity, better binding kinetics, etc.)
- Many programs exist to analyse water locations and their energetics






[Journal of Computer-Aided Molecular Design](#)

March 2019, Volume 33, [Issue 3](#), pp 307–330 | [Cite as](#)

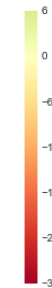
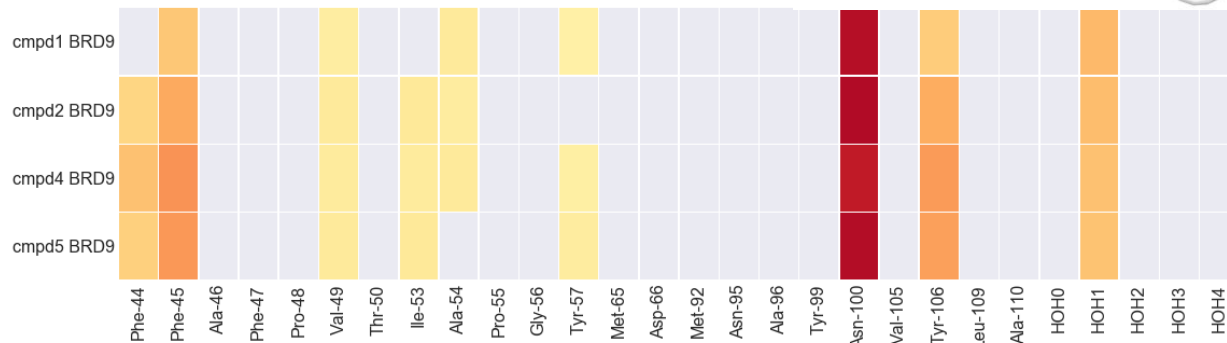
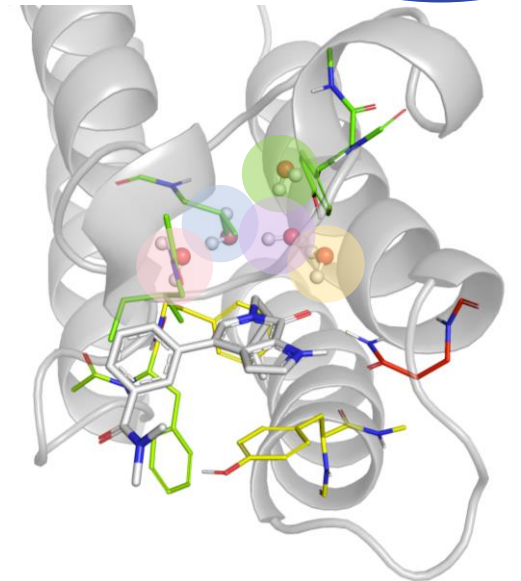
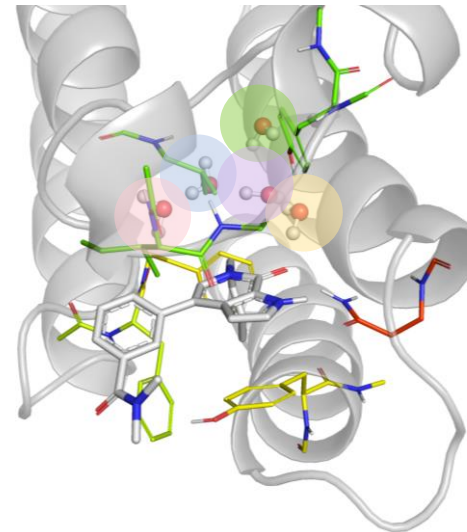
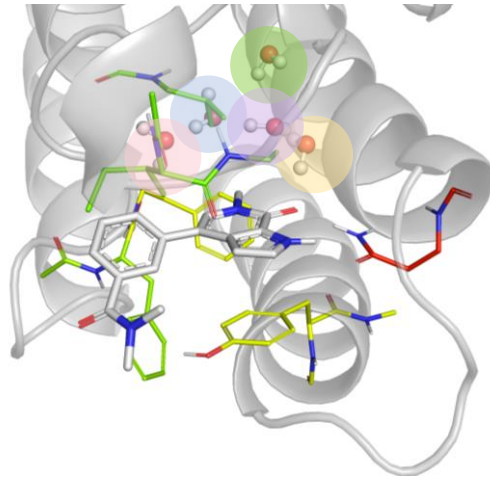
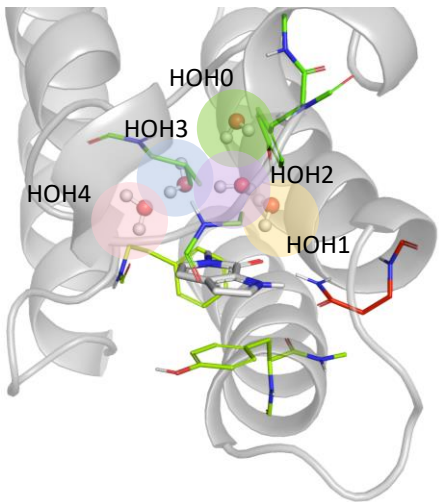
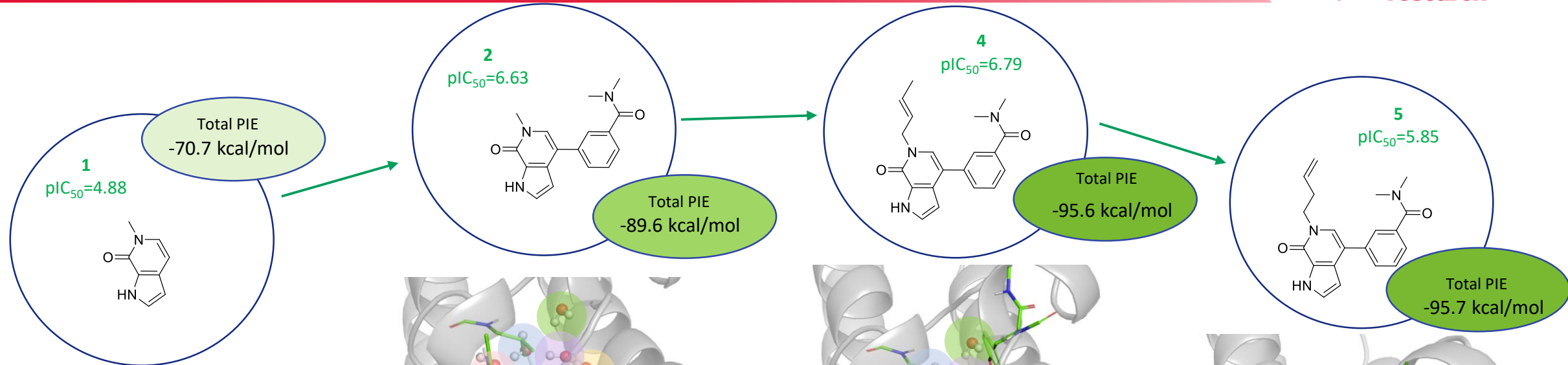
Water molecules in protein–ligand interfaces. Evaluation of software tools and SAR comparison

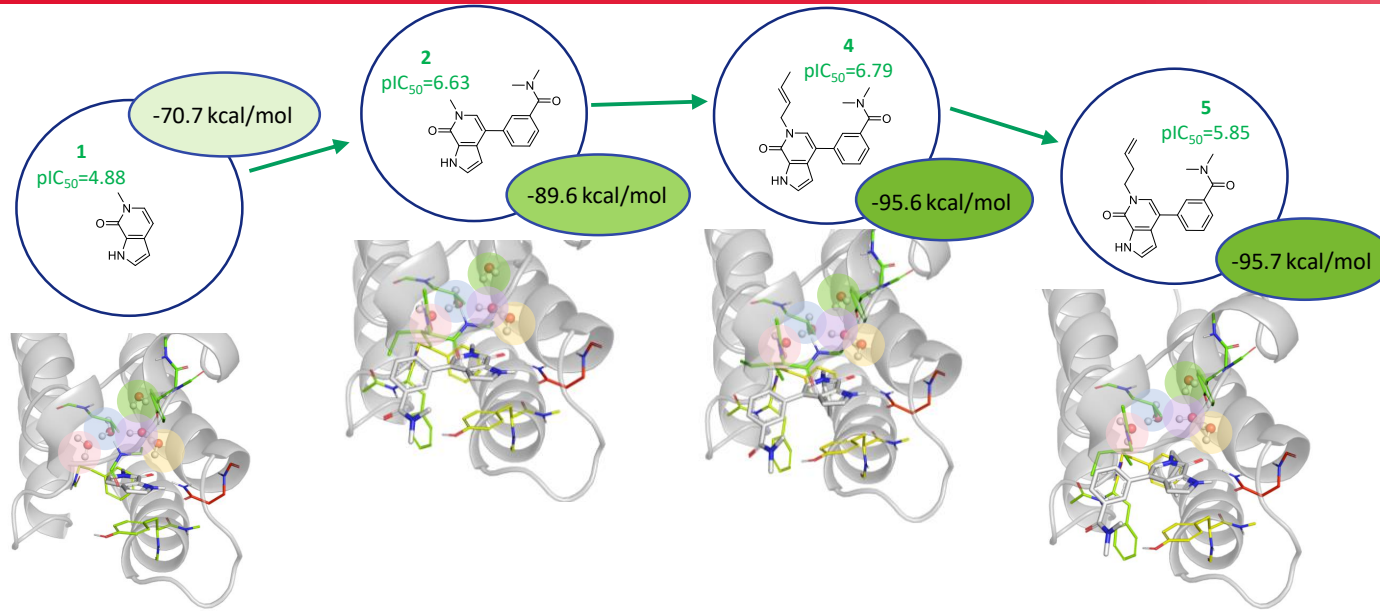
Authors

[Authors and affiliations](#)

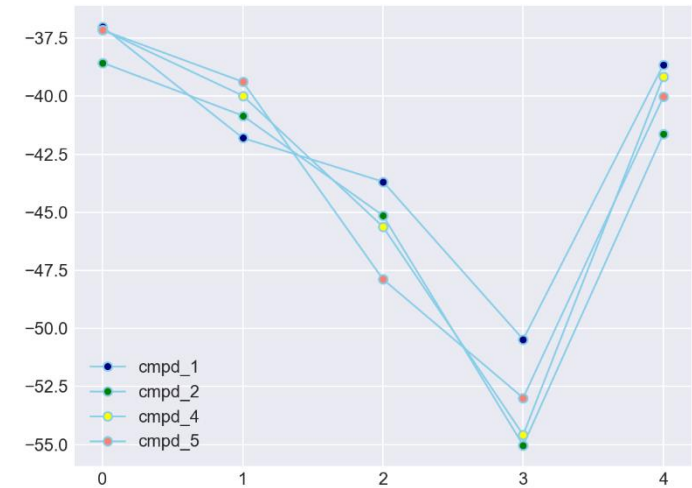
Eva Nittingger , Paul Gibbons , Charles Eigenbrot , Doug R. Davies, Brigitte Maurer, Christine L. Yu, James R. Kiefer, Andreas Kuglstatter, Jeremy Murray, Daniel F. Ortwine, Yong Tang, Vickie Tsui

- Evaluating solvent energetic contribution is the most challenging aspect:
 - Overall, the placement of water molecules was fairly accurate, with all programs predicting 60–90% of water oxygens within 1 Å of their observed locations.*
 - A major problem for all tools was a consistent prediction of energetic contributions of water molecules. The tools seldom agreed with each other and also the consistency within each tool was very low*
- Poor correlation of the predicted water energies with the experimentally observed SAR
- The quality of the prediction is indirectly read out as a relative affinity of a new ligand that displaces water molecule, and/or perturbs the existing water network
- Can FMO help with the interpretation?

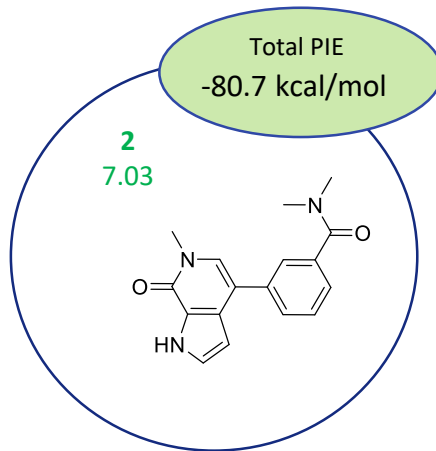
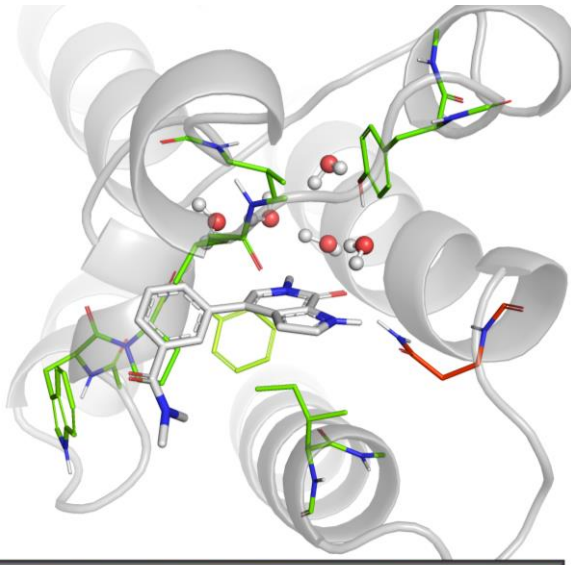




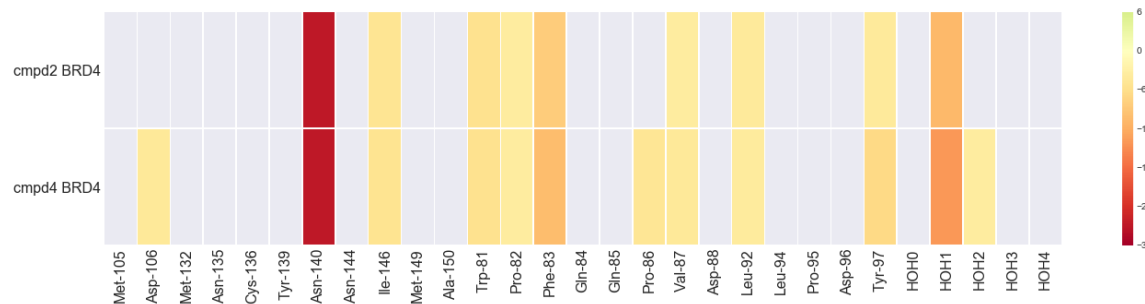
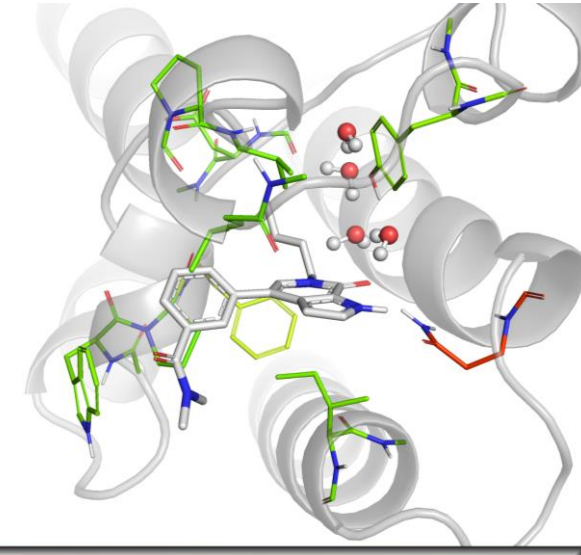
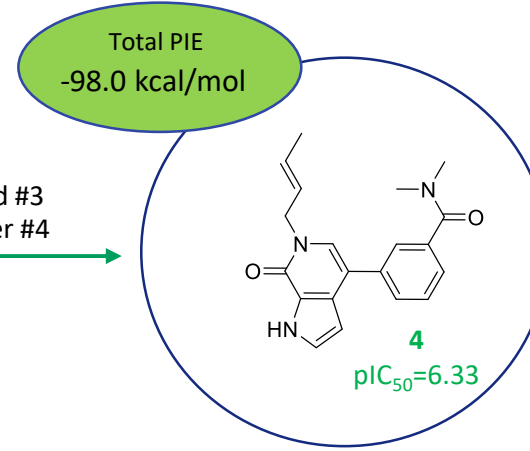
	HOH0	HOH1	HOH2	HOH3	HOH4
cmpd1 BRD9	-37.0	-41.8	-43.7	-50.5	-38.6
cmpd2 BRD9	-38.6	-40.8	-45.1	-55.0	-41.6
cmpd4 BRD9	-37.1	-40.0	-45.6	-54.6	-39.2
cmpd5 BRD9	-37.2	-39.4	-47.9	-53.0	-40.0



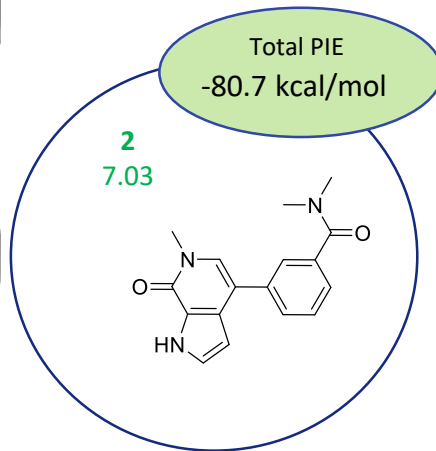
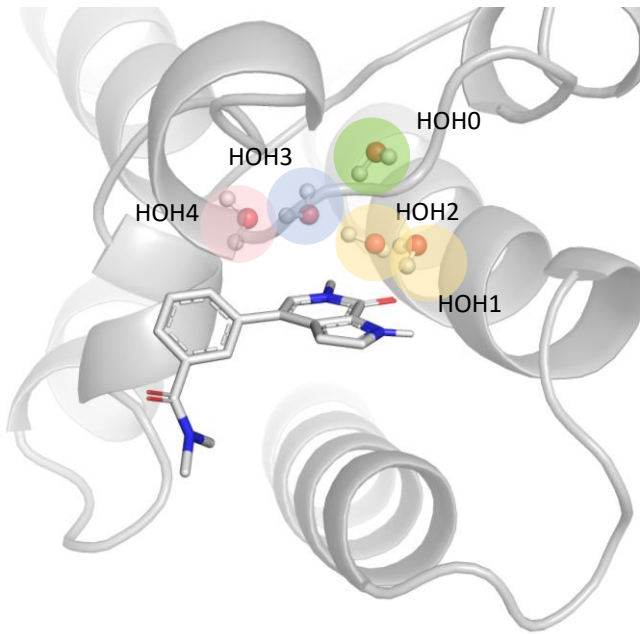
- Expansion of the ligand leaves the water network unperturbed
- Hydrophobic tails of **4** and **5** lead to a slight shift of Phe45, Tyr106 and Ile113
- PIE correlates with the SAR going from **1** to **2** to **4**
- 4** and **5** energetically equivalent (\neq #rot bonds, entropic penalty?)
- The energies of water molecules should remain fairly similar for all BRD9 structures
 - The energies are within ~ 5 kcal/mol



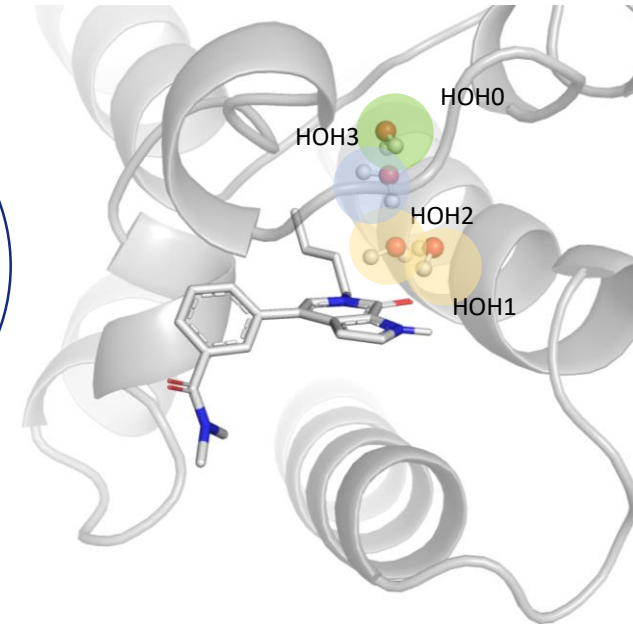
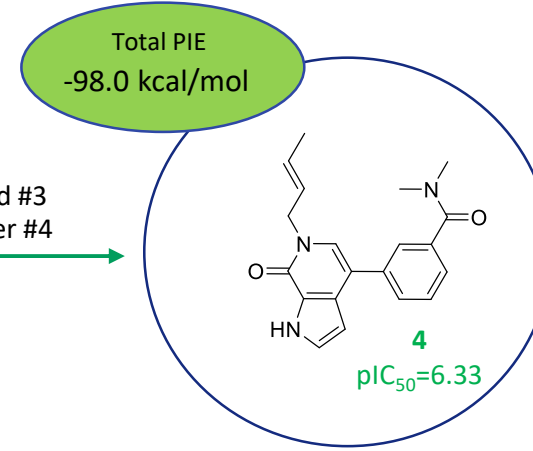
Shift of waters #0 and #3
Displacement of water #4



- ❖ Ligand extends into the water network, displacing water molecules and causing perturbations
- ❖ PIE does not explain the observed SAR
- ❖ Energetic contribution from perturbed water network

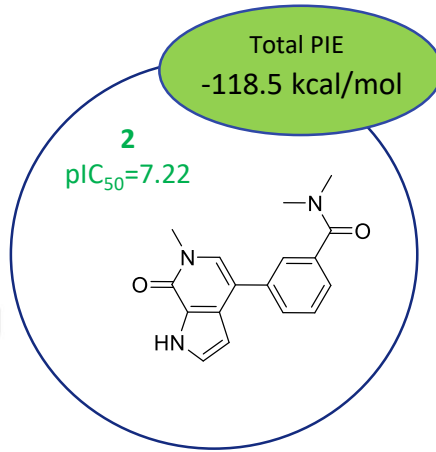
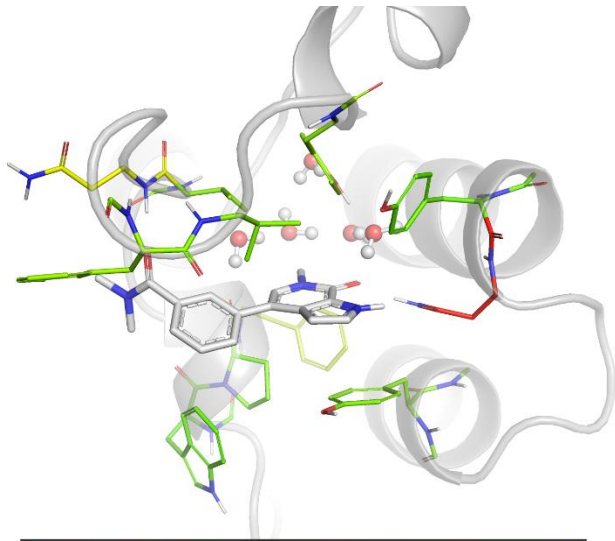


Shift of waters #0 and #3
Displacement of water #4

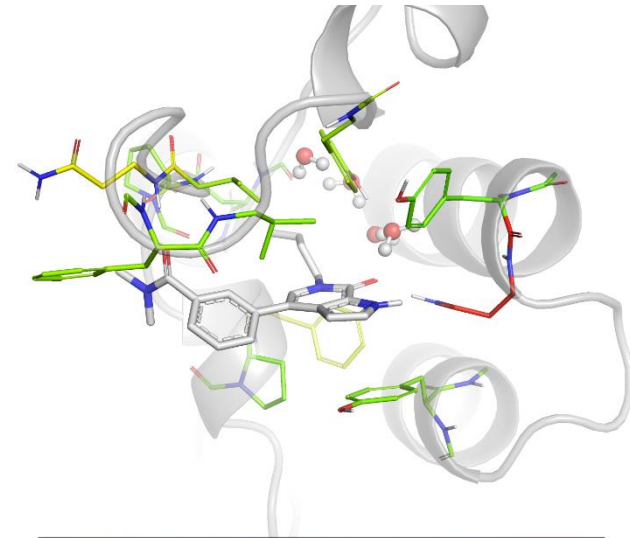
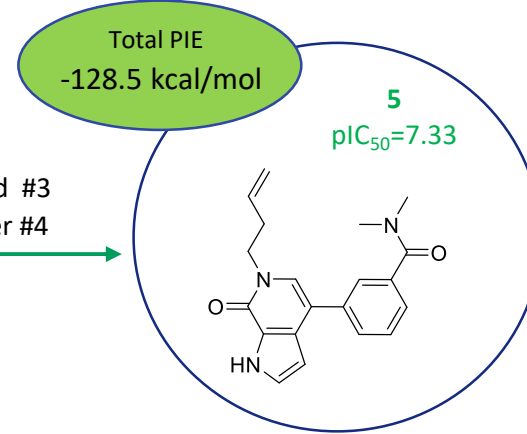


- Overall energy change of the perturbed water network is unfavourable
- Average 'happiness' of the water network gives better interpretation of the observed SAR

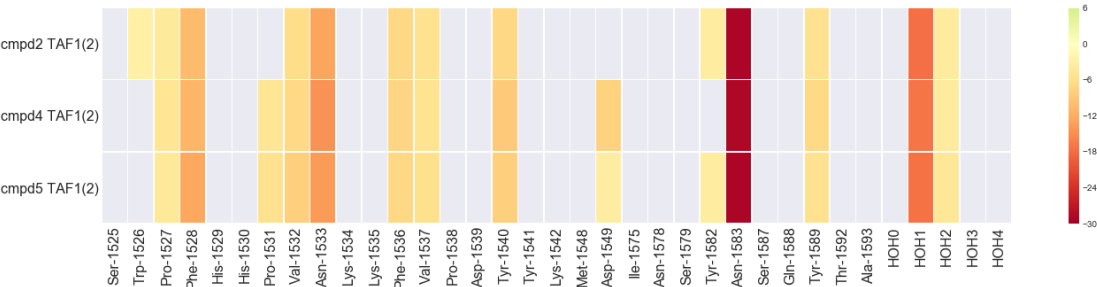
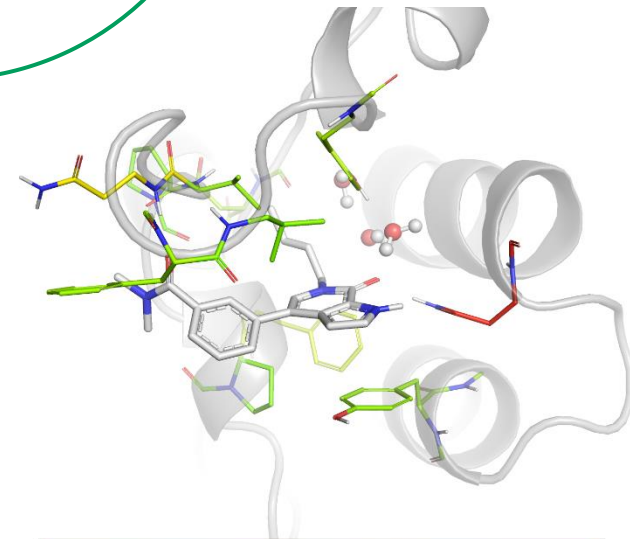
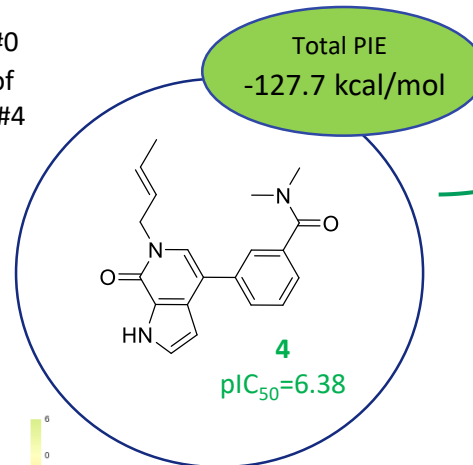
TAF1(2)

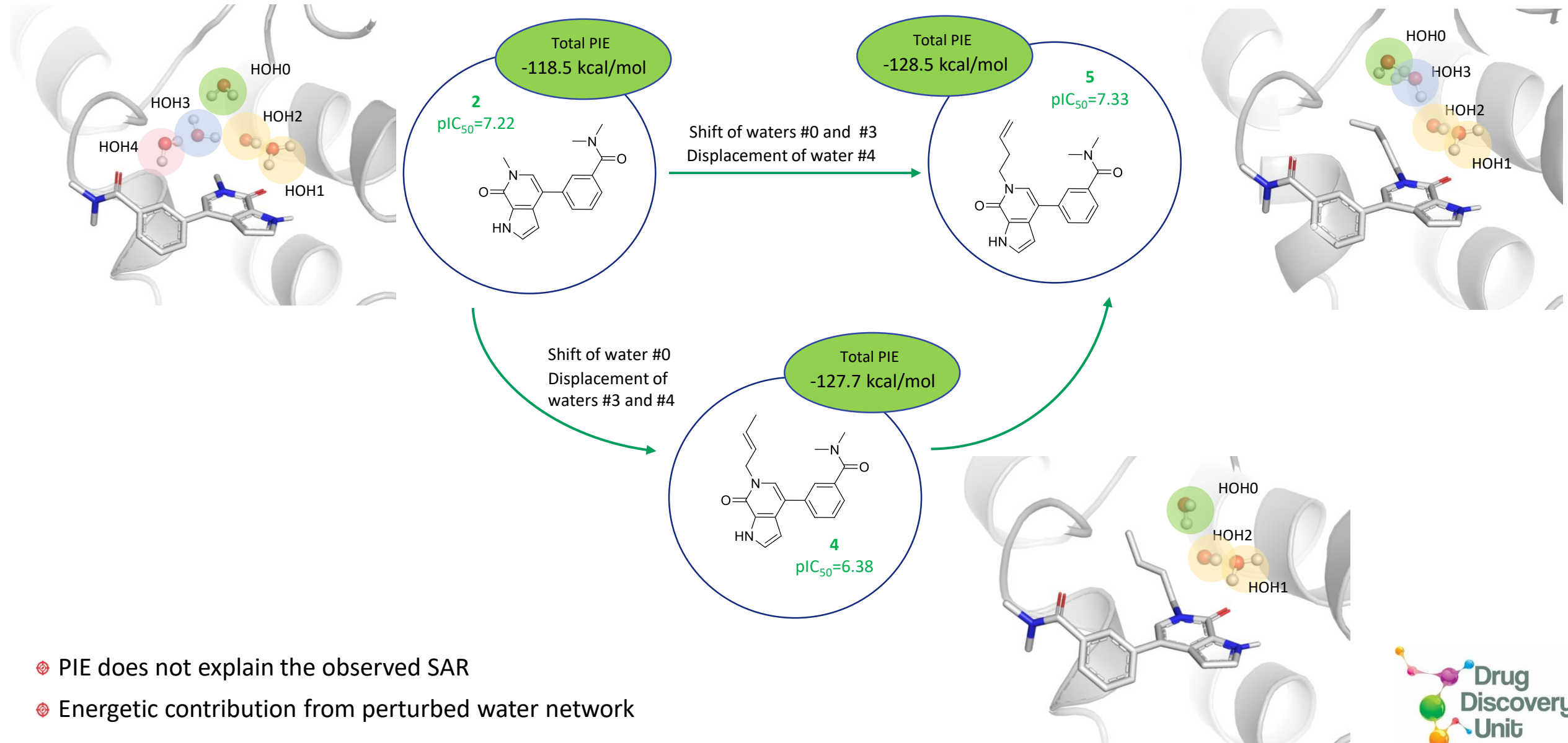


Shift of waters #0 and #3
Displacement of water #4



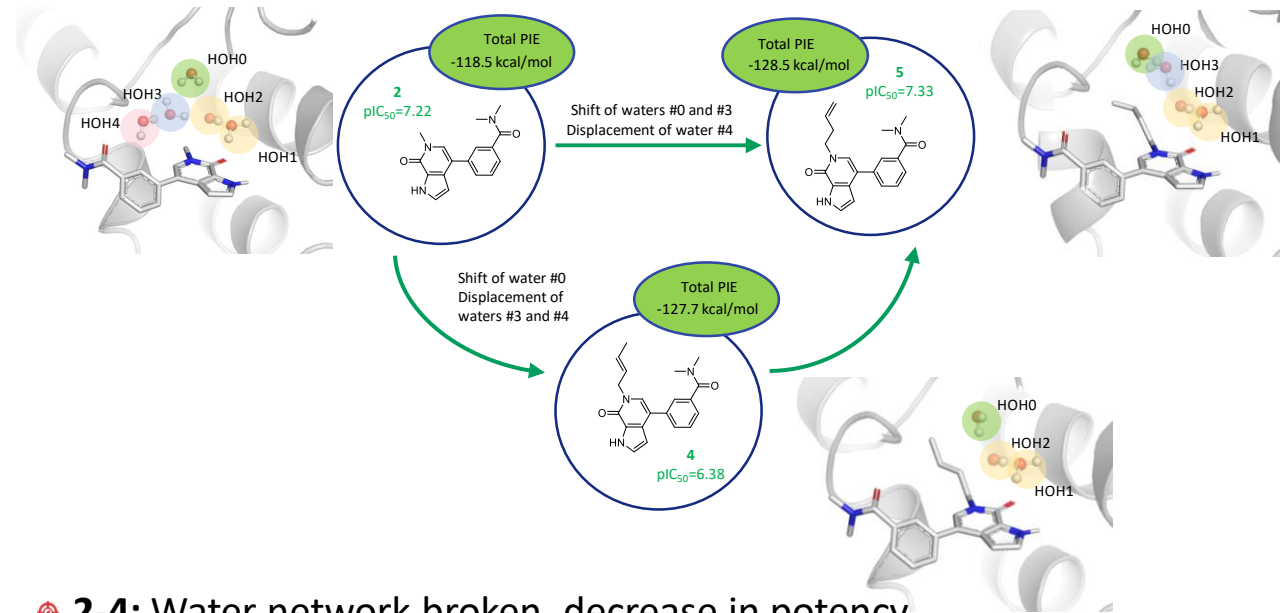
Shift of water #0
Displacement of waters #3 and #4





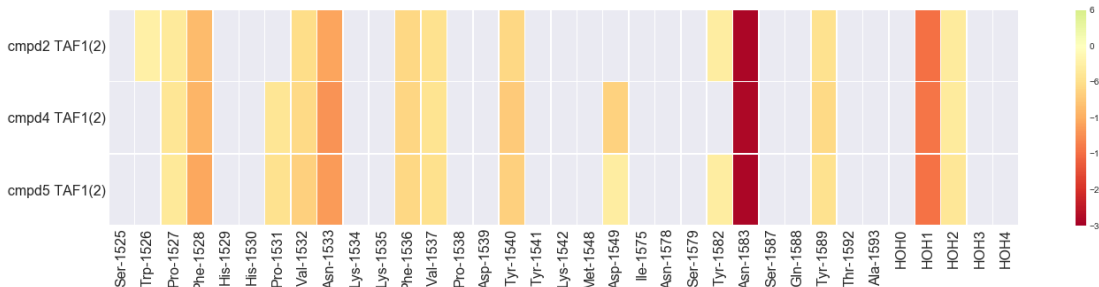
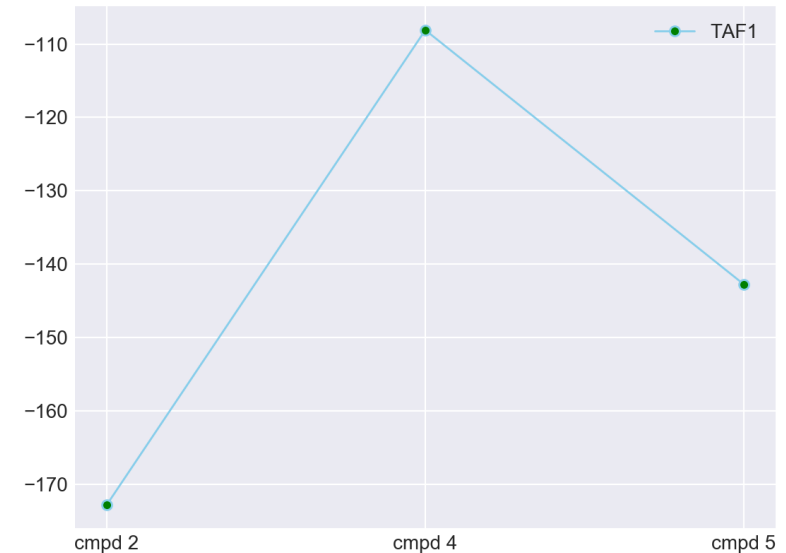
- ❖ PIE does not explain the observed SAR
- ❖ Energetic contribution from perturbed water network

TAF1(2)



- 2-4: Water network broken, decrease in potency
- 2-5: Re-establishing the water network
 - HOH2 and HOH3 still 'happy'
 - HOH0 less 'happy'
- 4-5: Alters the conformation of the ligand, disrupts the network, increase in potency

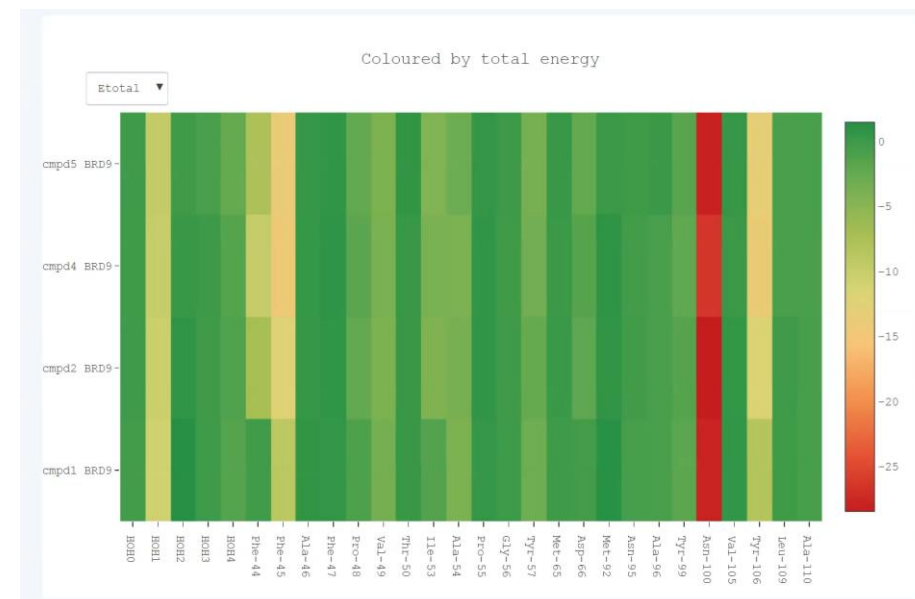
	HOH0	HOH1	HOH2	HOH3	HOH4
cmpd2 TAF1(2)	-36.2	-45.2	-34.6	-38.2	-18.5
cmpd4 TAF1(2)	-32.5	-44.2	-31.4		
cmpd5 TAF1(2)	-23.1	-44.4	-36.3	-39.0	



- ❖ Correctly quantifying and describing interactions between protein and the ligand computationally requires a physically accurate description of the molecules
- ❖ Binding affinity prediction
 - The combination of computed QM binding energies with measured or predicted logP values can provide usefully accurate predictions of protein-ligand binding energies
- ❖ Rationalising SAR
 - Going beyond 'visual inspection' and identifying nonintuitive interactions
- ❖ Binding mode studies
 - Predicting the correct binding pose
 - Tautomeric and protonation state preferences as well as stereochemistry
 - Help resolve ambiguities in ligand refinement
- ❖ Assessing water energetics

Current work:

- ❖ How to deal with the systems where there is a movement in the protein backbone?
- ❖ Throughput is getting better, but slowly
 - Scripts that enable quicker setup and analysis of the results
 - How different settings affect accuracy
 - Focus on group efficiency
- ❖ How to best communicate the results to the project?



Acknowledgments

Fabio Zuccotto

Juan Bueren-Calabuig

Michael Kiczun

Judith Hobrath

Carmine Morgillo

Riccardo Guareschi

David Robinson

Alain-Pierre Petit

Andrew Leach

Steve St-Gallay

Richard Ward

DDU Management

Paul Wyatt

Kevin Read

Ian Gilbert

David Gray

Julie Brady

