Improving new molecule design using electrostatics

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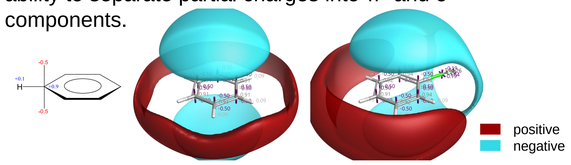
Introduction

Electrostatics are critical to ligand binding and yet largely overlooked in new molecule design due to the difficulty in calculation and visualization of meaningful potentials. We have previously shown how electrostatics can be used effectively for scaffold hopping, virtual screening, ligand alignment and SAR interpretation. In this poster we explore the application of ligand and protein electrostatics to the design of new molecules using our applications Torch[1] and Flare.[2]

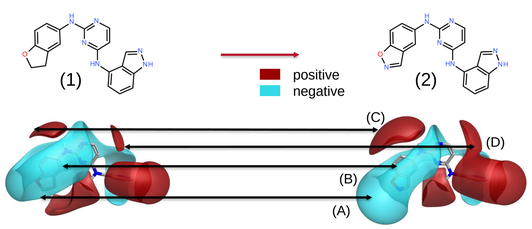
Calculating ligand electrostatics

Ligand electrostatics were generated using probe atoms surrounding a pre-defined ligand conformation. The energy of interaction of the probe with the ligand structure defines the potential at that point in space. In this poster we simply visualize the potentials as iso-surfaces. Cresset's XED force field[3] provides a detailed description of molecular electrostatics through the use of off-atom centre charges resulting in more detailed electrostatic representations.[4] Critical to the XED molecular mechanics approach is the ability to separate partial charges into π- and σ-components.



Electrostatics during design

Visual feedback on electrostatic changes during the design process is highly beneficial to the new molecule designer. However, changes are rarely simple. A change on one side of the molecule can often cause changes to a distal region, especially if the systems are electronically linked through π-systems. Consider a hypothetical example of changing a dihydrobenzofuran (1) into a benzoxazole (2) (modeled using PDB 2X9F):

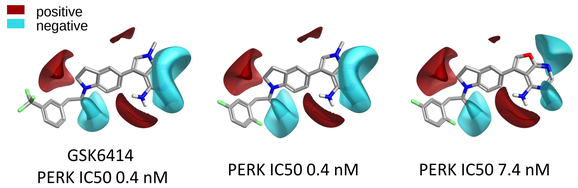


This simple change has multiple effects due to the change in electron withdrawing effect of the new heteroatom and the change in aromaticity: (A) the edge negative increases; (B) the shape and density of the negative of the aromatic face is significantly altered; (C) the size and depth of the positive associated with the aromatic edge increases; and (D) there is a small increase in the positive area associated with the aromatic hydrogens of the pyrimidine scaffold at the other end of the molecule.

Electrostatics to drive activity

Using a convenient view of the electrostatic properties of a ligand can significantly benefit the design process. This is particularly true for aromatic species where the changes that occur when swapping between scaffolds or shuffling heteroatoms around a ring can have large but often unpredictable effects on activity.

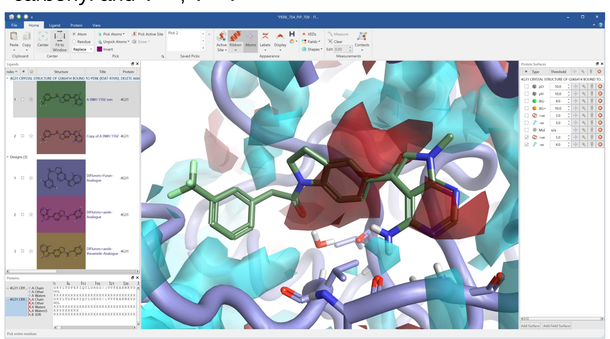
In a study of PERK inhibitors,[5] Axten *et al*. show that changes in electrostatics of the hinge binding heteroaryl group can be directly related to activity.



Heteroaryl groups such as furo[2,3-d]pyrimidin-4-amine (right), which are associated to a less negative electrostatic field with respect to pyrrolo[2,3-d]pyrimidin-4-amine (left and center), are also less potent on PERK.

Complement to protein

A similar approach to that used for ligand electrostatics was used to generate the PERK protein electrostatic environment in Flare, starting from PDB 4G31 and including the water molecule bridging the interaction between the carboxamide carbonyl and V^{952}, V^{651}.

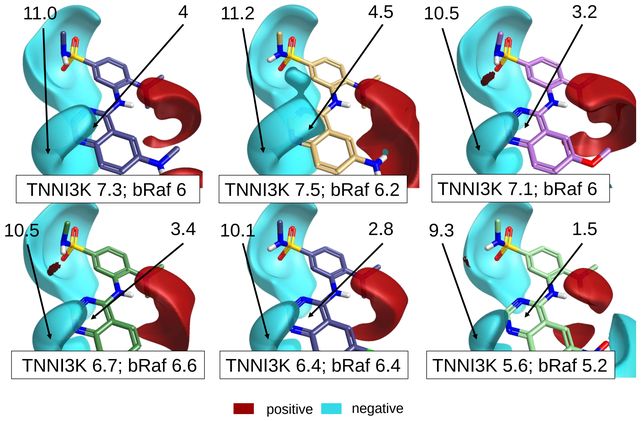


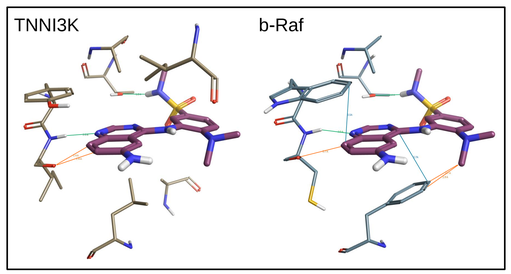
The protein interaction potentials for PERK nicely complement those of GSK6414. The electron-rich pyrrolo[2,3-d]pyrimidine heteroaryl system and the carboxamide carbonyl sit in the middle of an area of positive interaction potential in the PERK active site. At the same time, the areas of positive electrostatic potential from the ligand corresponding to the 4-amine group and the CH_2 bridge sit in an area of negative interaction potential in the protein.

The protein interaction potential of the PERK active site also explains the SAR for these compounds, as the furo[2,3-d]pyrimidin-4-amine heteroaryl is associated with a negative electrostatic potential which clashes with an area of negative potential in the PERK active site.

Electrostatics to drive selectivity

Electrostatic changes can be used to drive selectivity as well as activity. In an excellent study of TNNI3K inhibitors, Lawhorn *et al.*[6] showed how the H-bonding strength of a range of substituted benzopyrimidines could be directly related to activity. Interestingly, they contrasted this using activity against the related b-Raf where aromatic residues changed the relationship to include a π-stacking component, showing how this could be exploited to gain selectivity.





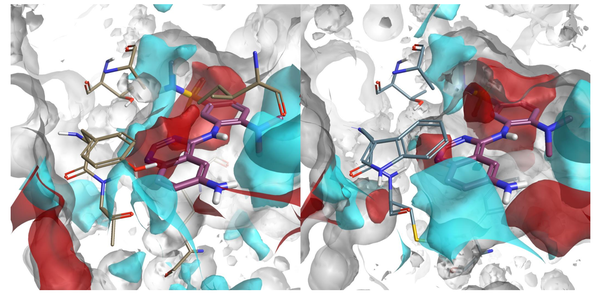
(Top): 6 Inhibitors of TNNI3K taken from Lawhorn *et al*. showing negative electrostatic strength at edge and face of benzopyrimidine together with activity data against TNNI3K and b-Raf.

(Bottom): One inhibitor in active site of TNNI3K (PDB 4YFF) and b-RAF (PDB 4YHT). All compounds were modeled by in-place editing of crystal ligand from 4YFF.

Complement to protein

The protein interaction potentials for TNNI3K and b-Raf nicely explain the selectivity trend.

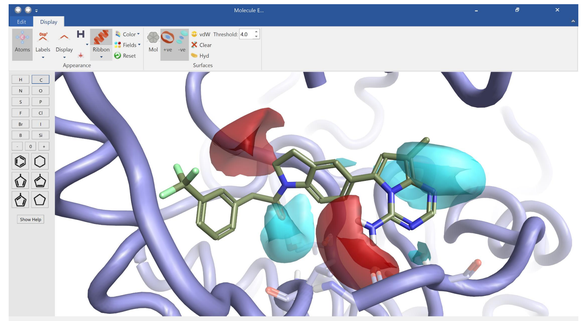
In TNNI3K, the negative electrostatic region at the edge and face of benzopyrimidine sits nicely in a region of positive electrostatics. Electron-donating substituents which enrich the benzopyrimidine ring accordingly favor TNNI3K activity.



On the contrary, in b-RAF the benzopyrimidine sits in a region which is mainly negative, due to the aromatic residues which line this active site. This makes the effect of electron-donating substituents detrimental for b-RAF activity, and accordingly favorable for TNNI3K and b-Raf selectivity.

Electrostatics on the fly

The Molecule Editor in Flare enables you to quickly make changes to your ligand in the context of the protein, immediately visualizing their impact on the ligand fields. Below we can see the effect of changing the hinge binding group to a pyrrolo-triazine.



Conclusion

Protein interaction potentials and ligand fields are a powerful way of understanding the electrostatics of ligand-protein interactions. The knowledge gained is invaluable for informing ligand design, with the aim to optimize activity and selectivity of new compounds. Flare is a new Cresset application which makes protein and ligand electrostatics available as a desktop application with a user friendly and highly interactive GUI.

References

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