Selectivity profiles in Activity Atlas

M Mackey, P Tosco, G Tedesco

Cresset, Cambridgeshire, UK mark@cresset-group.com https://cresset-group.com

Abstract

Recently we have developed a novel approach to activity cliff analysis that used the electrostatic and shape similarity of aligned ligands to detect and interpret the causes of activity cliffs. Activity cliff analysis is a powerful technique for locating the most important changes that have been made within a series, but looks at pairs of compounds in isolation rather than analysing the entire data set. We have extended the activity cliff approach to analyze multiple pairs of molecules simultaneously to derive a global view of the activity cliff data - a method called Activity Atlas[1] (Figure 1), incorporated into our ligand-focused workbench, Forge.[2]

A Bayesian approach was taken: each pair of molecules provides evidence as to whether the difference in electrostatic and steric potentials within the pair in a particular region of space contributes to a change in activity. More than one alignment is considered for a molecule, and a weight is assigned to each alignment based on its score compared to the best-scoring alignment. This allows cases where a molecule has a flexible substituent which is not fully constrained by the initial alignment to be handled correctly.

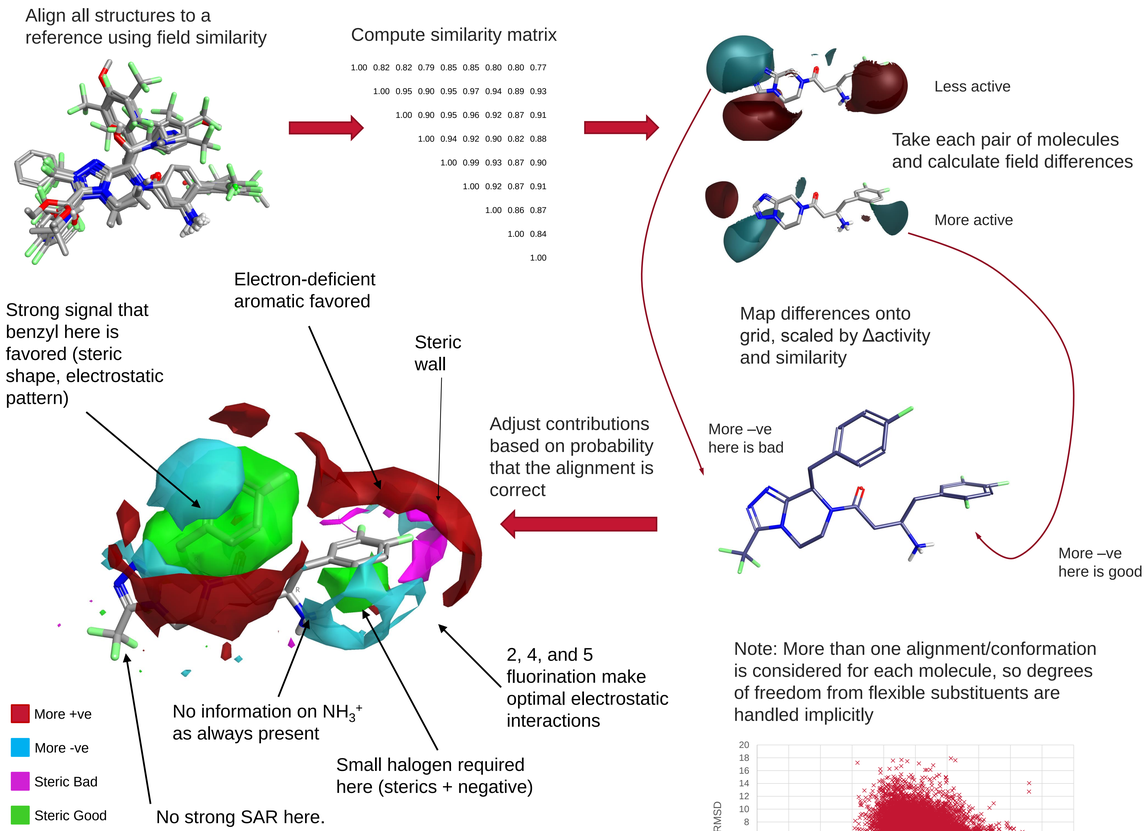

Figure 1: Activity Atlas technique.

Data set processing

A data set of 342 compounds originally published by Dimova and Bajorath[3] was downloaded from the supplementary material together with their adenosine A1, A2a and A3 receptor potency values. A subset of 102 tricyclic compounds was selected for the Activity Atlas analysis, and aligned to three representative structures (Figure 2).

Figure 2: Reference compounds for alignment.

The alignment was performed using Cresset's Maximum Common Substructure alignment method, in which the MCS of the compounds is pre-aligned prior to conformation exploration and scoring of the rest of the molecule. A few alignments were then manually adjusted to ensure that substituent positions were consistent.

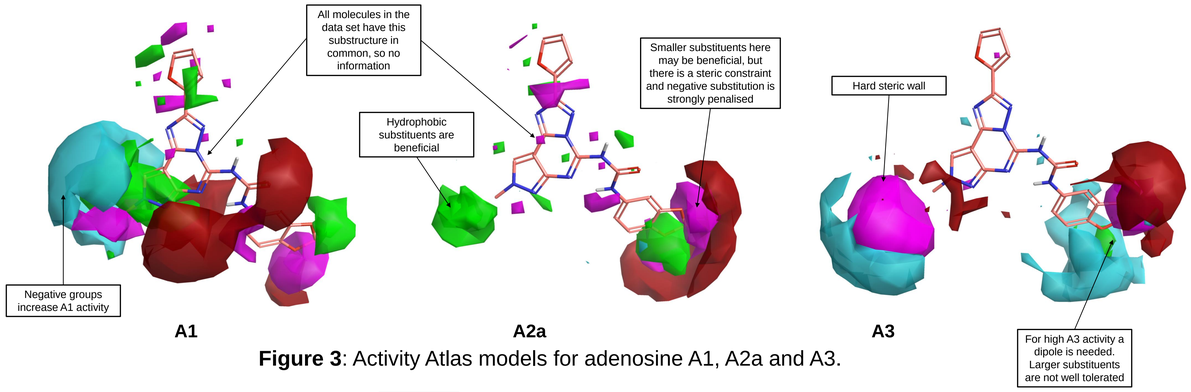

Figure 3: Activity Atlas models for adenosine A1, A2a and A3.

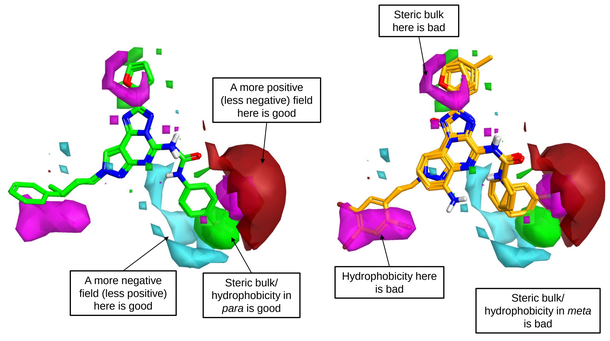

Figure 4: Adenosine A2a selectivity over A1.

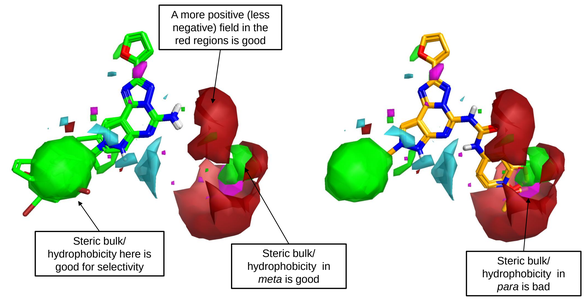

Figure 5: Adenosine A2a selectivity over A3.

Selectivity models

Activity Atlas models were built for each activity value (A1, A2a, and A3; Figure 3), as well as for the desired selectivity values (A2a-A1, A2a-A3; Figure 4-5).

The individual activity models suggest that A2A activity can be enhanced on the left-hand-side of the molecule, and that this should give selectivity over A3. How to gain selectivity over A2 in this region is much less clear. The right side of the molecule has a complicated set of requirements for increasing activity for all three subtypes, and it is hard to get a clear picture of how best to gain selectivity here.

The selectivity models instantly provide more detail. As well as emphasising that increasing the size of the furan is a bad idea (which was not evident in the individual models), the A2a/A1 model clearly shows that while a substituent on the left-hand-side of the system improves A2a activity, making it too large reduces selectivity over A1. With respect to the right-hand-side of the molecule, *para* substitution is clearly preferred to *meta.* Selectivity over A3 can clearly be gained by substitution on the left-hand side primarily, while the right hand side shows the opposite signal from A1, *meta* being preferable to *para*. Overall, the best chance of selectivity comes from providing only a small hydrophobic substituent on the left-hand side, while neglecting the right-hand-side or using a *para* substituent to reduce A1 liability.

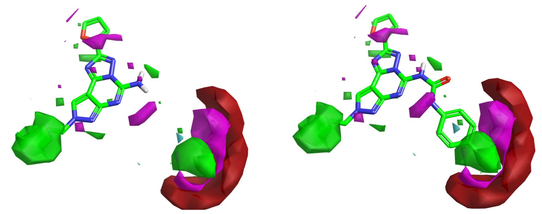

Figure 6: Highly selective A2a compounds.

Conclusion

Activity Atlas is a powerful method to gain understanding of the SAR at the level of steric and electrostatic requirements. Applying the method to activity deltas rather than to absolute activities provides additional insight into the often conflicting requirements of selectivity across multiple subtypes.

References

1. https://cresset-group.com/activity-atlas
2. https:// cresset-group.com/forge
3. *J. Chem. Inf. Model.* **2011**, *51*, 258-266