Summarizing and Understanding SAR and Activity Cliffs in GPCRs

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Introduction

Activity Atlas™[1] is a probabilistic method of analyzing the structure-activity relationships of a set of aligned compounds as a function of their electrostatic, hydrophobic and shape properties. Activity Atlas is particularly useful to condense large data tables into a single picture, summarizing structure-activity data into highly visual 3D maps that inform the design and optimization of new compounds.

The method uses a Bayesian approach to take a global view of the data in a qualitative manner. Each pair of aligned molecules in the data set 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.

Results are displayed using Forge™[2] visualization capabilities to gain a better understanding of the features which underlie the SAR of your set of compounds (Figure 1).

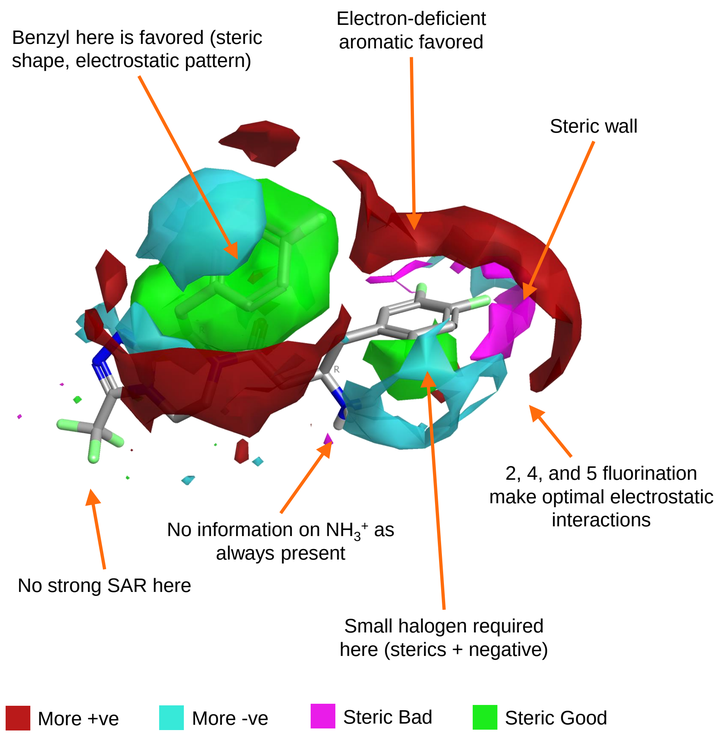

Figure 1: An Activity Atlas 3D map in Forge.

SAR analysis of Orexin 2 receptor ligands

A data set of 377 compounds spanning an OX_2R pK_i range from 5 to 8.5 was downloaded from BindingDB.[3] These records cover patent information published by Janssen[4] in 2014. The most potent compound was aligned by field-based alignment to the published X-ray crystal structure of Suvorexant (PDB: 4S0V, Figure 2) and then used as a reference compound for aligning the other compounds.

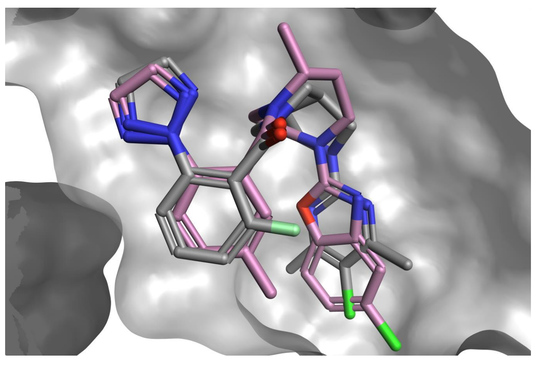

Figure 2: Reference compound for alignment (grey) superimposed to the crystal structure of Suvorexant (pink) bound to OX_2R (PDB: 4S0V).

This second alignment was performed using Cresset's Maximum Common Substructure (MCS) 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 manually adjusted to ensure that substituent positions were consistent.

An Activity Atlas model (Figure 3) was then built for the OX_2R activity.

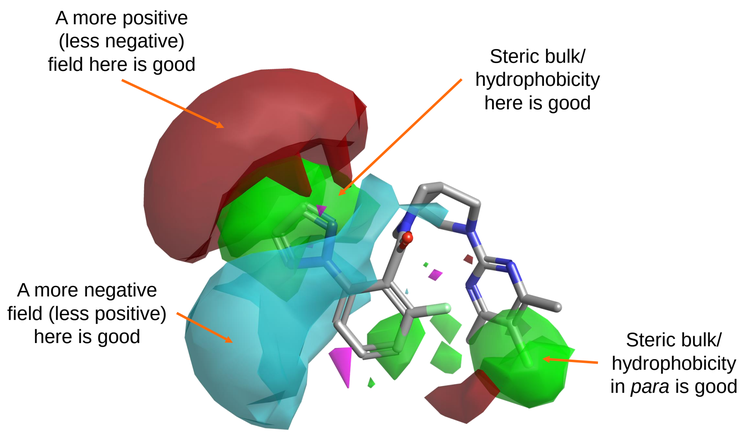

Figure 3: Activity Atlas model for OX_2R activity.

On the left, OX_2R activity is increased by having an *ortho* substituent on the phenyl ring associated with a stronger positive (red) field at the top edge, as well as by substitution patterns in the *meta* and *ortho* positions generating a stronger negative (cyan) field above and below the plane of the molecule.

This is in agreement with the electrostatic potential of the active site of OX_2R calculated with Flare,[5] using Cresset's XED force field.[6] In Figure 4, the more electron-rich portion of the triazole ring of Suvorexant sits near an area of positive electrostatic potential. Accordingly, the choice of an appropriate heterocycle and substituents (such as small halogens) for the decoration of the left phenyl ring, which help creating the right pattern of positive and negative electrostatic fields around the molecule, can be an effective way to modulate OX_2R activity.

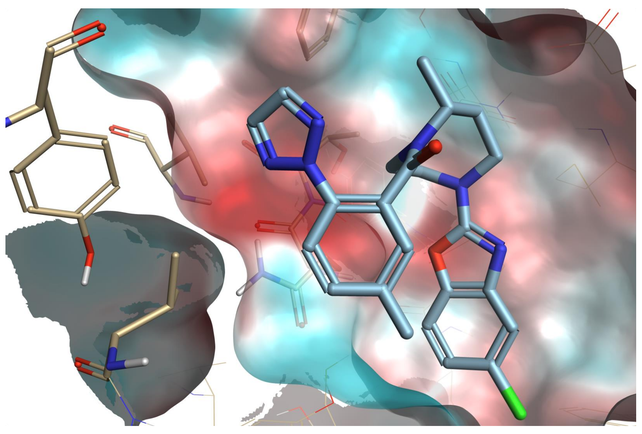

Figure 4: Electrostatic potential map of the active site of PDB: 4S0V.

Selectivity of Adenosine A1, A2a and A3 antagonists

A data set of 342 compounds originally published by Dimova and Bajorath[7] 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 the three representative structures shown In Figure 5.

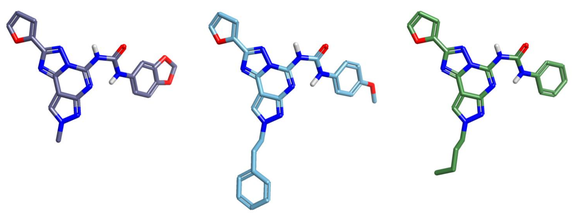

Figure 5: Reference compounds for alignment.

The alignment was performed using Cresset's MCS alignment method. A few alignments were then manually adjusted to ensure that substituent positions were consistent.

Activity Atlas models were built for the desired selectivity values (A2a-A1, and A2a-A3).

The A2a/A1 model (Figure 6) clearly shows that too large a substituent on the left of the system reduces selectivity over A1 (even if it improves A2a activity – data not shown), as well as emphasising that increasing the size of the furan is a bad idea.

With respect to the right-hand-side of the molecule, *para* substitution is clearly preferred to *meta.*

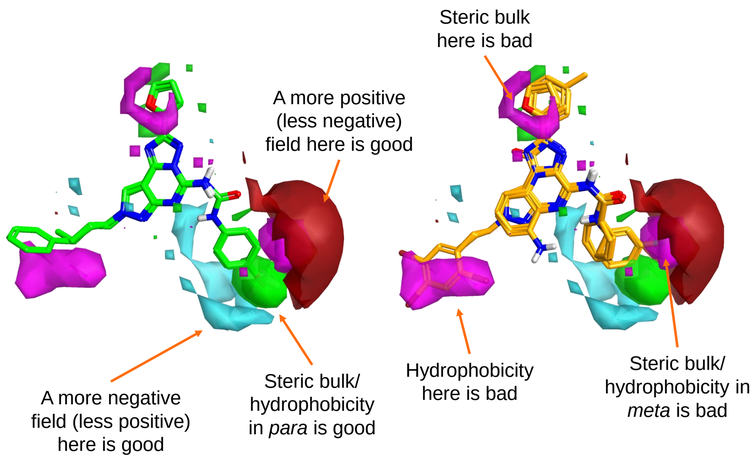

Figure 6: Adenosine A2a selectivity over A1.

Selectivity over A3 can 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* (Figure 7).

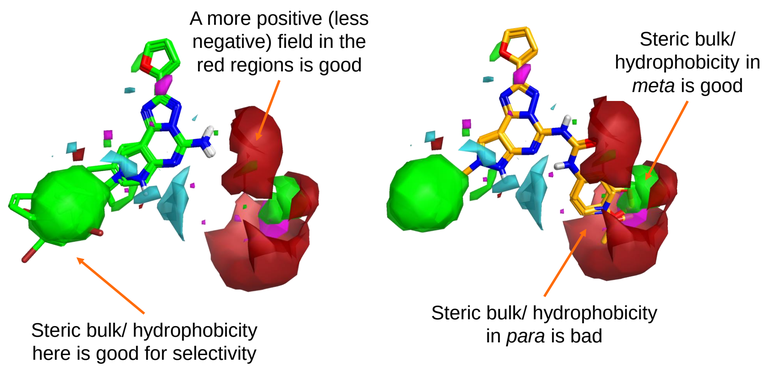

Figure 7: Adenosine A2a selectivity over A3.

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.

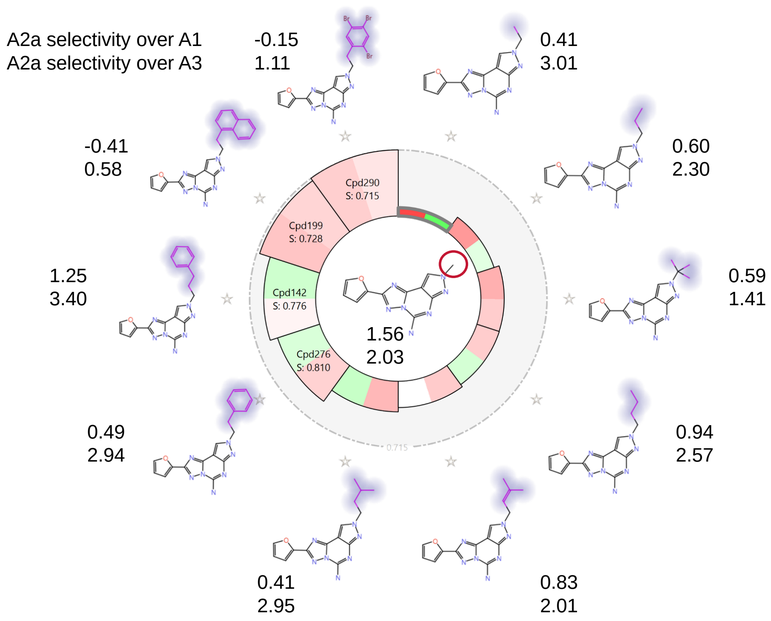

Figure 8: Activity View[6] map for 'A2a selectivity over A1' and 'A2a selectivity over A3', showing the SAR on the left.

Conclusion

Activity Atlas is a method for summarizing the SAR for a series into a visual 3D model that can be used to inform new molecule design. Particularly useful for those project teams where there is not enough SAR for a traditional 3D-QSAR approach, Activity Atlas can be successfully applied to the qualitative analysis of large SAR tables and to understand the selectivity landscape for your project.

References

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