# Is this compound worth making?

Mark Mackey, Paolo Tosco, Giovanna Tedesco, Tim Cheeseright, Susana Tomásio

Cresset, New Cambridge House, Bassingbourn Road, Litlington, Cambridgeshire, SG8 0SS, UK
paolo@cresset-group.com www.cresset-group.com

cresset
smarter chemistry | smarter decisions

## Background

In deciding if a compound is worth making medicinal chemists need to consider a number of factors including:

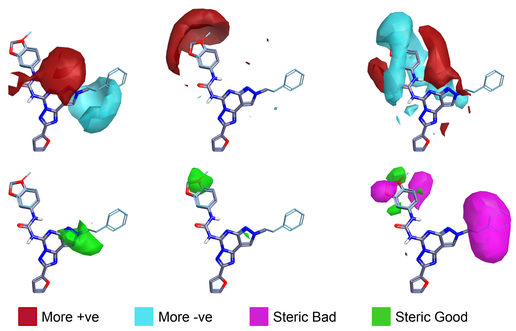
- does it fit with the known SAR?
- does it explore new interactions or regions of space?
- does it have good physico-chemical properties?

Summarizing the SAR content of large compound series in a single informative picture is challenging. Traditional 3D-QSAR techniques have been used for this purpose, but are known to perform poorly where the structure-activity landscape is not smooth. 3D Activity cliff analysis has the potential to explore such rugged SAR landscapes: pairs of compounds with a high similarity and a large difference in activity carry important information relating to the factors required for activity. However, looking at pairs of compounds in isolation makes it hard to pinpoint the changes which consistently lead to increase potency across a series.

Similarly, summarizing the regions and interactions that have been explored in a single picture is not trivial, especially if the electrostatic character of compounds is to be considered (e.g., replacement of electron rich with electron poor rings).

Here we present Activity Atlas, a new technique to analyse a series of compounds and derive a global view of the structure-activity relationship data.

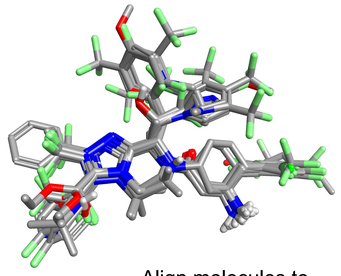
## Application to selectivity




Application to a set of adenosine receptor antagonists with activities against $A_1$, $A_{2a}$ and $A_3$ receptors[3] demonstrates the utility of the technique in locating critical regions for selectivity. Examination of the steric and electrostatic maps for the three subtypes clearly shows which regions should be targeted in order to enhance subtype selectivity.
In the example above, the right hand side of the molecules can be used to discriminate between $A_3$ and the other two subtypes, while $A_1$ and $A_{2a}$ can be separated by increasing steric bulk and positive charge around the top of the molecules.

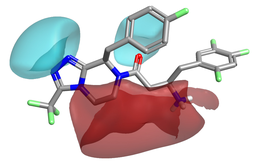
smarter chemistry | smarter decisions

## Methodology



Align molecules to one or more references using a combination of shape and fields[1]

Calculate individual fields

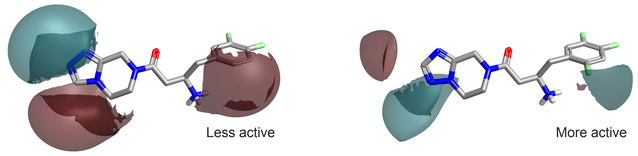


Map fields on a 3D grid

Compute 3D similarity matrix across all alignments

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1.00 | 0.82 | 0.99 | 0.96 | 0.90 | 0.95 | 0.96 | 0.95 | 0.90 | 0.93 |
| | 1.00 | 0.82 | 0.82 | 0.79 | 0.85 | 0.85 | 0.80 | 0.80 | 0.77 |
| | | 1.00 | 0.95 | 0.90 | 0.95 | 0.97 | 0.94 | 0.89 | 0.93 |
| | | | 1.00 | 0.90 | 0.95 | 0.96 | 0.92 | 0.87 | 0.91 |
| | | | | 1.00 | 0.94 | 0.92 | 0.90 | 0.82 | 0.88 |
| | | | | | 1.00 | 0.99 | 0.93 | 0.87 | 0.90 |
| | | | | | | 1.00 | 0.92 | 0.87 | 0.91 |
| | | | | | | | 1.00 | 0.86 | 0.87 |
| | | | | | | | | 1.00 | 0.84 |
| | | | | | | | | | 1.00 |

Calculate field differences for each pair of alignments

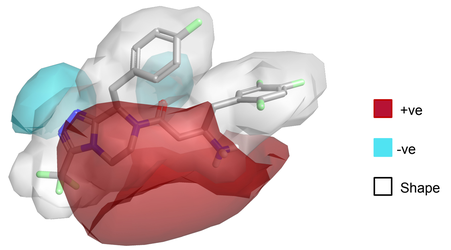



Map field differences on a 3D grid, weighted by Δactivity and similarity to get a global view at the activity cliff landscape

Find what active molecules have in common

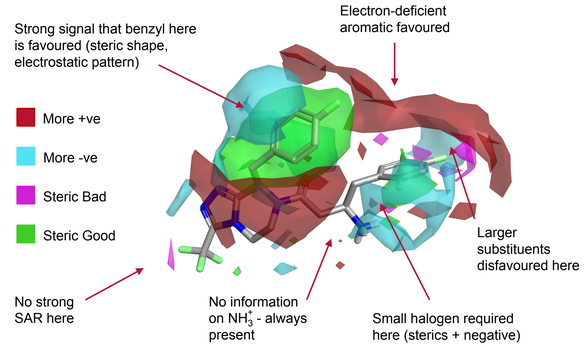
Find which regions have been fully explored

## Average of actives summary

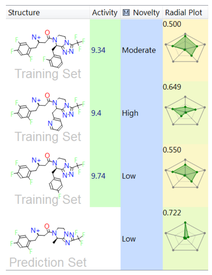


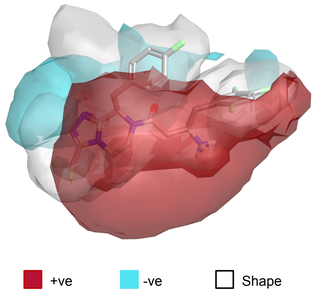

This picture summarizes electrostatic and shape properties which consistently lead to potent ligands across the series.

## Activity cliff summary




## Regions explored summary



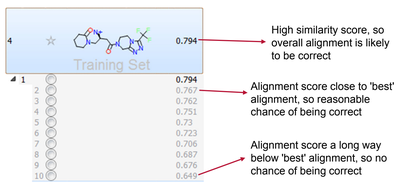




The Regions explored summary gives a comprehensive 3D picture of the regions explored in electrostatic and shape space. A novelty score is assigned to each compound, enabling to predict whether newly designed candidates are likely to contribute additional SAR knowledge, and are thus worth making.

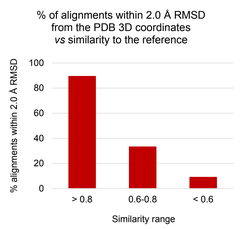
## Accounting for uncertainties in the alignment

Activity Atlas takes into account multiple alignments, weighted by their probability to be correct:

1) Based on the distance from the top result

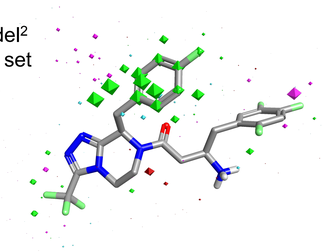



2) Based on the absolute similarity value (CCDC-AZ dataset)




Analysing multiple alignments per molecule enables the technique to account for uncertainties in the orientation of flexible side chains not represented in the reference(s).

A traditional 3D-QSAR model[2] was built on the same data set ($q^2$ = 0.7). While 3D-QSAR seems better at extracting information where SAR is continuous, Activity Atlas gives more definition in regions where SAR requirements are critical.



## Conclusion

The Activity Atlas technique is a powerful way of summarizing SAR data in 3D. By combining information across multiple pairs, it enables a global view of the critical points in the activity landscape. The Average of actives summary captures in one picture the 3D requirements for potency, while the Regions explored summary enables prioritizing compounds which add crucial SAR information over trivial analogues.

## References

1. *J. Chem. Inf. Model.* **2006**, 46, 665-676
2. http://www.cresset-group.com/forge
3. *J. Chem. Inf. Model.* **2011**, *51*, 258-266

cresset
smarter chemistry | smarter decisions