In deciding if a compound is worth making medicinal chemists need to consider a number of factors including:
- does it fit within 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 increased 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.

Methodology

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

Activity Atlas uses 3D activity mapping to explore SAR in a single picture. Each field is weighted by the similarity of the molecule to the reference and a 3D similarity matrix is calculated across all alignments. This matrix is then used to calculate the differences for each pair of alignments. 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.

Application to selectivity

Application to a set of adenosine receptor antagonists with activities against A1, A2a and A3 receptors 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 A1 and the other two subtypes, while A2a and A3 can be separated by increasing steric bulk and positive charge around the top of the molecules.

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 captures the 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 increased potency across a series.

Similarity range

1) Based on the distance from the top result
2) Based on the absolute similarity value (CCDC-AZ dataset)