Rapid identification and understanding of selectivity cliffs

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Abstract

During lead optimization, many compounds are synthesized, with wealth of potency, selectivity and ADMET information.

Locating **Activity Cliffs** can help extract critical chemical transformations. **Activity Cliffs - pairs of compounds where relatively small structural changes results in a large change in activity.**

Activity Cliff interpretation can be challenging: a small structural change can result in a large change in potency due to different reasons: steric clash with protein, loss/gain of H bond donors/acceptors, forcing alternate conformation of the ligand etc.

This work presents a technique for locating activity cliffs in the context of the target active site. **Using this method critical SAR regions are clearly and rapidly identified. Furthermore the reason for the activity differences between pairs of compounds is readily discernable, leading to a true understanding of the SAR landscape.**

PI3Kα *vs.* PI3Kβ inhibition

PI3K enzymes are lipid kinases responsible for intercellular signal transduction by phosphorylating membrane-bound 4,5-phosphatidylinositolbisphosphate to 3,4,5-phosphatidylinositoltriphosphate. This conversion triggers activation of Akt and mTOR pathways, whose disruption has been associated with cancer.[1]

There are four forms of class I PI3K enzymes (α, β, δ, γ) involved in signaling cascades. The α form is implicated in cancer; the β form is potentially involved in insulin signaling. Small molecules that selectively inhibit PI3Kα are of interest as potential treatments for some cancers.[2]

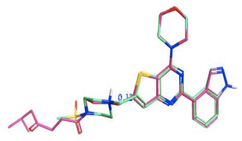
In this case study, we present how we are able to quickly examine and identify the **'Structure Selectivity Relationship'** of PI3Kα and PI3Kβ by exploring multivariate activity cliffs. In this retrospective analysis, we present the key SAR features that drive selective inhibition to the PI3Kα isoform, while decreased activity towards the β isoform.

GDC-0941 reference

Celgene's CNX-1351 in binding mode (PDB:3ZIM).[3]

GDC-0941[1,2] (green) aligned to CNX-1351 (pink).

Shown conformation of GDC-0941 used as reference for series alignment.



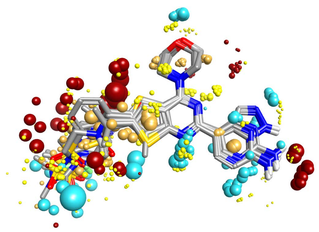
♦ Alignment within Cresset's Torch[4], 50% fields / 50% shape

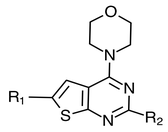
Alignment of analogues

Analogues[1,2] were aligned to GDC-0941 (reference conformation)

Alignment scores ranged from 0.7-0.9.

3ZIM used as protein excluded volume.





♦ Alignment within Cresset's Torch[4], 50% fields / 50% shape

Cresset's Activity Miner

Cresset's Activity Miner takes a set of aligned molecules and compares them in a pairwise fashion based on 'disparity'.

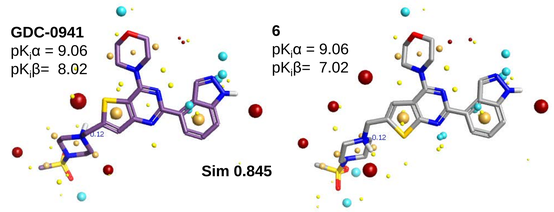
$$\textbf{Disparity} \propto \frac{\Delta\textbf{Activity}}{(1 - \textbf{Similarity})}$$

Thus, molecules that have high disparity show a large change in activity corresponding to small changes in structure (or structural features).

The notion of disparity enables the rapid identification of Activity Cliffs, which are areas of the SAR landscape that carry the most information in terms of what features drive potency.

Activity Miner to rapidly identify and explore activity cliffs

Disparity Matrix shows a colour-coded overview of the disparity-activity relationships between pairs of molecules. Navigate to find example 6:

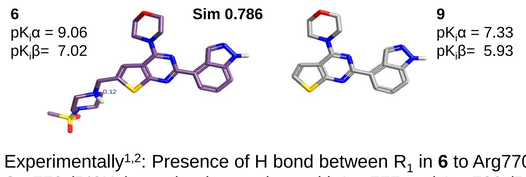


Switching position of sulphur results in improved α selectivity.

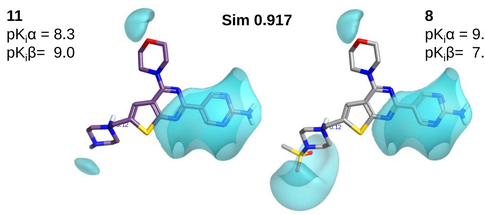
Experimentally[1,2]: The thieno-pyrimidine (**6**) results in more distant H-bond contacts between it's sulphonamide oxygens and the ASP780, Lys777 residue pair of the β form.

SAR analysis with Activity View

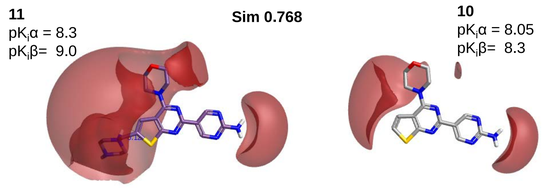
Molecular pairs showing selectivity SAR



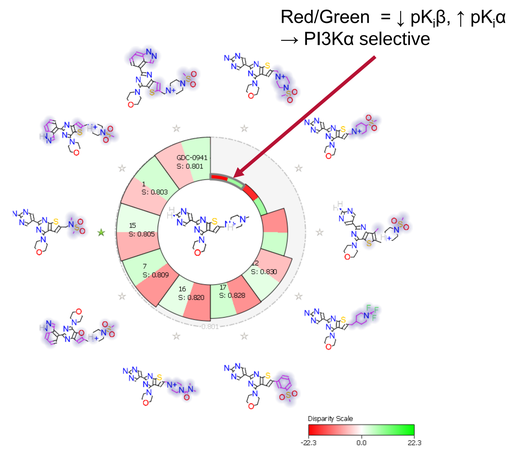
Experimentally[1,2]: Presence of H bond between R_1 in **6** to Arg770 and Ser773 (PI3Kα); weaker interactions with Lys777 and Asp780 (PI3Kβ).



Increased negativity around R_1 terminus results in decreased potency against PI3Kβ, thus enhanced selectivity towards PI3Kα.



Increased positivity around R_1 terminus results in decreased selectivity to PI3Kα via enhanced potency to PI3Kβ.



Activity View allows us to focus on one molecule (center), and examine the next most similar compounds with respect to disparity and activity.

We interactively examine similar neighbours where $pK_i\alpha$ increases and $pK_i\beta$ decreases. (PI3Kα selective).

Summary

A **20 minute experiment** using Cresset's **Activity Miner** allowed navigation and understanding of the PI3Kα selectivity SAR landscape and explanation of the rapidly identified activity cliffs.

The rationale for the SAR elucidated from within Activity Miner was consistent with the published results[1,2].

References

1. *J. Med. Chem.*, **2013**, *56*, 4597-4610.
2. *J. Med. Chem.*, **2011**, *54*, 7815-7833.
3. *J. Med. Chem.*, **2013**, *56*, 712-721.
4. *J. Chem. Inf. Model*, **2006**, *46*, 665-676.