

Going on SARfari in the protein kinase data jungle

J. Günther¹

¹ *Bayer Schering Pharma, Berlin, Germany*

Focusing drug discovery on protein families can enable quite a number of synergies between individual projects, provided that appropriate tools are in place to analyse all relevant data in the context of the target family. In particular, interpretation of SAR data in view of the similarities and differences between the individual targets can guide the way to obtaining the right compounds with the desired selectivity profiles. At BSP, we developed an integrated chemogenomics workbench focused on protein kinases, called Kinase SARfari. It incorporates and links kinase sequence, structure, compounds and screening data. Both in-house data and data from the literature, as found in Biofocus DPI's StARLITE database, are included.

Apart from giving a general overview on the data organisation in the database and highlighting some of the applications, the talk will introduce a novel methodology for picking nearest neighbours to a given target in the family. Identification of the targets with which cross-reactivities are most likely to be expected allows for the early set-up of relevant counter-screens. Moreover, drug-like ligands known to hit a close neighbour provide interesting starting points for a new lead-optimisation program. Accordingly, the approach we chose focuses on similarities in the recognition of small molecule inhibitor structures rather than on phylogenetic relationships between targets. To this end, we exploited the wealth of 3D data that is available for protein kinase targets, while making sure the method is applicable to any set of kinases, independent of whether their 3D structures have been determined or not. The physicochemical distance measure we developed to describe the binding site similarity of two protein kinases has been shown to correlate with the average difference in IC50 values obtained for these targets in our in-house kinase selectivity panel.

1. Chan, E.; StARLITE – A Chemogenomics Knowledge Base. *Abstract book of 7th International Conference on Chemical Structures*; Noordwijkerhout, 2005.