

Title: Performance of docking strategies in the enrichment of fragment-like inhibitors of indoleamine 2,3-dioxygenase

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Abstract #238 **Topic category: Drug screening**

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Background: Virtual screening of compound libraries by molecular docking can help narrow down a large list of compounds to a more manageable size for testing. Fitness functions within molecular docking programme's software calculate how a compound fits the target site of the protein and assigns a numerical value quantifying how well it fits. Different molecules can be compared and ranked based on these values. As fitness functions calculate 'fitness' based on different parameters and perform differently depending on the properties of the target site, the success of a virtual screen can depend on the choice of the fitness function and the conformation of the target protein used for docking. We evaluated Goldscore, Astex Statistical Potential (ASP), Chemscore, ChemPLP fitness functions within the GOLD molecular docking suite to find the combination of fitness functions that performs the best for enrichment of inhibitors of the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO1).

Methods: IDO1 inhibitory compounds were identified from a fragment library by sequential screening using differential scanning fluorimetry followed by enzyme inhibition assays. This same library was docked into three conformations of the IDO1 active site and rescored with combinations of the four fitness functions in the GOLD suite. The performance of the different scoring function combinations was evaluated by comparison to the empirical screen.

Results: For binding mode calculations, all fitness functions in GOLD, except ASP, reproduced the known binding mode of 4-phenylimidazole to within 1.0Å RMSD. A larger active site conformation was important in reproducing known binding of the inhibitor Amg-1. With respect to early enrichment of inhibitors, the Chemscore fitness function performed the best when used to rank compounds. The top 5% of Chemscore-ranked libraries contained >25% of the inhibitors in the library. Only 5-15% of the inhibitors were found in the top 5% of Goldscore-ranked libraries. We also noted that different fitness functions selected different types of compounds. Chemscore ranked inhibitory naphthalene compounds highly, but failed to rank inhibitory benzoxazole and some benzothiazole compounds favourably. In contrast Goldscore ranks inhibitory naphthalene compounds inconsistently, but performs well with benzoxazole and benzothiazole inhibitors. Although apparently worse than Chemscore overall in this study, Goldscore is valuable as it is able to capture inhibitory compounds missed by Chemscore. The active site conformation had little effect on enrichment of fragments.

Conclusions: A small pilot screen, such as the one presented here, can be useful for deciding on the docking parameters before embarking on more extensive screens.