

Can 3D ligand based virtual screening compete with Docking? Application of Molecular fields to virtual screening with the DUD dataset.

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The use of virtual screening to find new hits and leads has become common place within the pharmaceutical industry. However, the majority of examples and methods in the literature are based around docking to a protein active site or use 2D ligand similarity methods. 3D ligand methods are rarely referenced. Moreover, there is a common perception that ligand based methods are inferior to docking, in that the search ligands do not necessarily encode all the information necessary to find new active molecules, particularly those with completely novel chemotypes. Herein we will present the application of 3D molecular fields¹ to virtual screening using the “directory of useful decoys”² as modified by Good for testing of chemotype retrieval rates.³

The FieldScreen virtual screening method uses the similarity of molecular electrostatic, steric and hydrophobic fields to rank molecules according to their similarity to a known active (Figure 1). If a protein structure is available, then it can be used as an excluded volume to further focus the search.

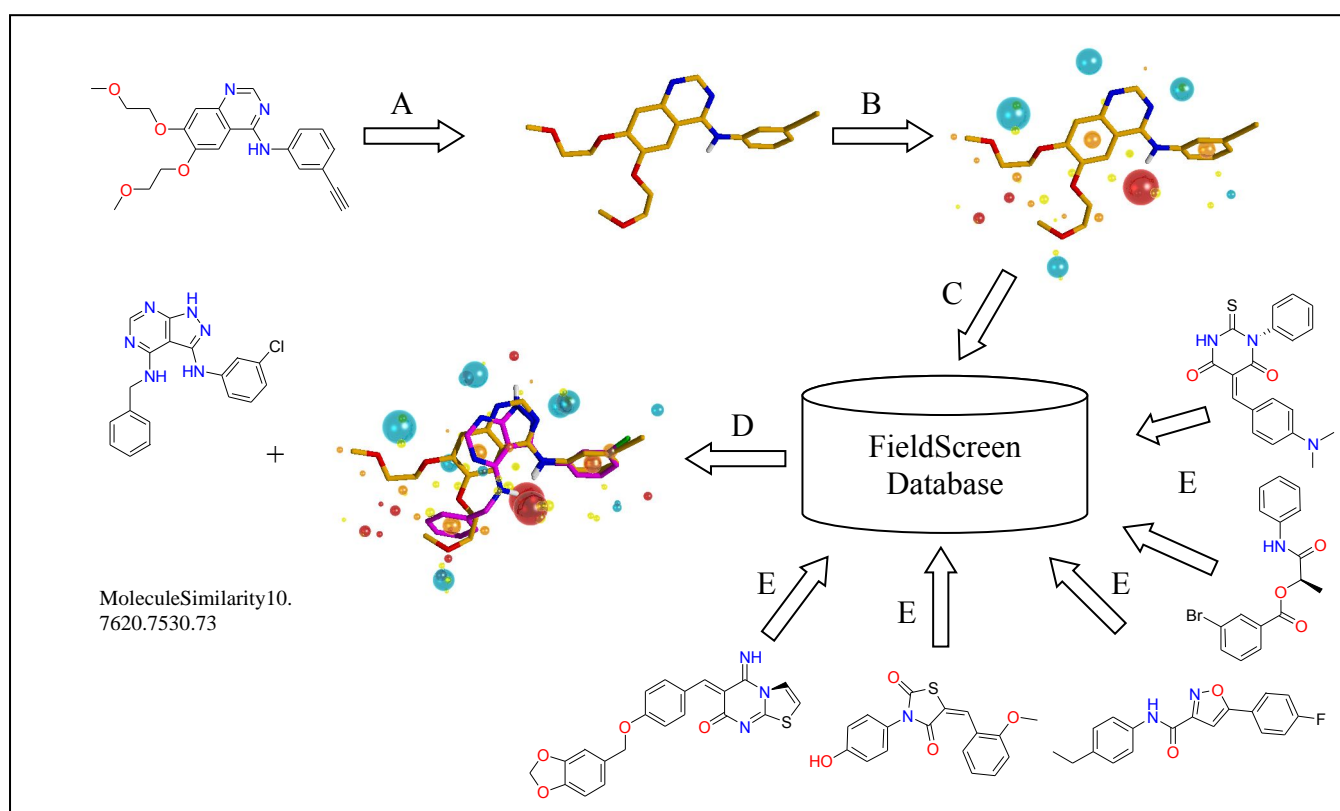


Figure 1. Schematic representation of the steps involved in searching the FieldScreen database.

Field similarity searching with FieldScreen is found to significantly outperform DOCK on almost all of the targets tested, both in terms of raw enrichment rates and in terms of enrichments of novel chemotypes. To allow fair comparison with the “fully automated” nature of the DOCK results², the FieldScreen searches were run where possible using the native ligands from the proteins used in the DOCK study with no optimisation or manual tweaking. The inclusion of protein information into the ligand-based screening protocol as an “excluded volume” is shown to further enhance enrichment rates (Figure 2). Moreover, FieldScreen preferentially retrieves small actives, which are more likely to be useful as leads (Figure 3).

We conclude that field similarity searching should be included either as a replacement for or in

conjunction with docking in all 3D virtual screening situations.

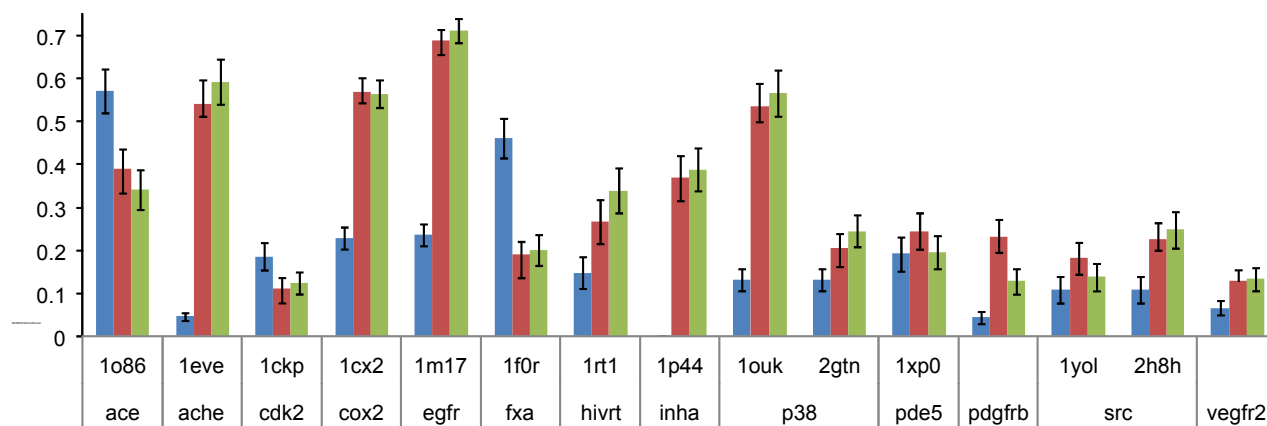


Figure 2. BEDROC enrichments for DOCK (Blue), FieldScreen (Red) and FieldScreen including excluded volume data (Green) for each target.

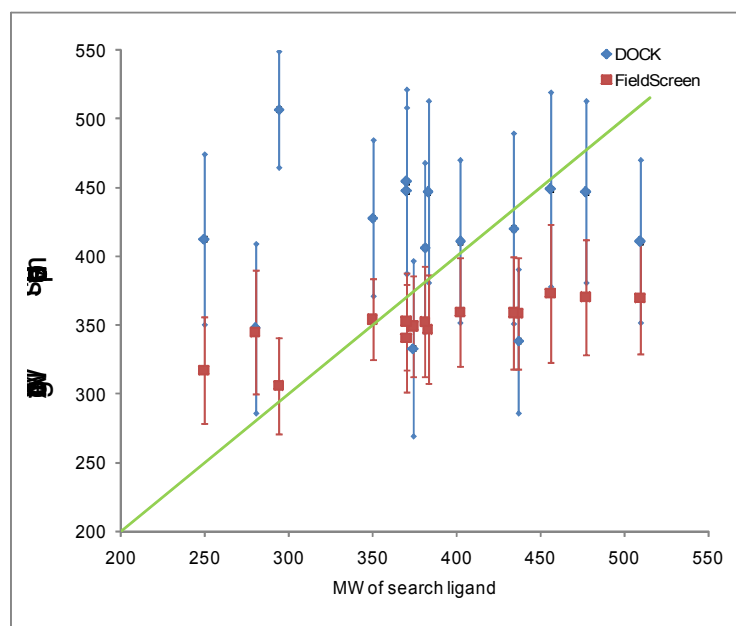


Figure 3 Average Molecular weight (MW) of the top scoring 500 compounds in the DUD all decoys dataset plotted against the MW of the search query. Error bars are 1 standard deviation.

1. T. Cheeseright, M. Mackey, S. Rose, A. Vinter; *J. Chem. Inf. Model.* **2006**; 46, 665-676
2. N. Huang, B. Shoichet, J.J. Irwin; *J. Med. Chem.* **2006**, 49, 6789-6801
3. A. C. Good, T. I. Oprea, *J. Comput. Aided Mol. Des.*, in press, DOI 10.1007/s10822-007-9167-2