Glide XP fragment docking and structure-based pharmacophores

SHERMAN W (a). and FRIESNER R. (b)

Schrödinger, 120 West 45th Street, 29th Floor, New York, NY 10036; US

Department of Chemistry, Columbia University, 3000 Broadway, Mail Code 3110, New York, NY 1002; US

In recent years, fragment-based drug design has become increasingly popular. Common computational approaches include building fragments up sequentially, or linking disparate fragments. However, the former approach can restrict the exploration of chemical space and may produce ligands that are not sufficiently drug-like, whereas the latter approach may result in difficulties when linking together the individual fragments.

Here, we describe a third approach that avoids these problems with the use of fragment-derived pharmacophore hypotheses. In our computational workflow a pharmacophore hypothesis is created using fragments docked and ranked by Glide XP, and virtual databases are screened against this hypothesis using Phase [1]. In an initial validation study on P38 Map Kinase, known active compounds were successfully retrieved and good enrichment factors were obtained.

References

[1] Dixon, S. L.; Smondyrev, A. M.; Knoll, E. H.; Rao, S. N.; Shaw, D. E.; Friesner, R. A., "PHASE: A New Engine for Pharmacophore Perception, 3D QSAR Model Development, and 3D Database Screening. 1. Methodology and Preliminary Results," *J. Comput. Aided Mol. Des., 20*, 647-671, (2006).