HIGHLIGHTS

COMPUTATIONAL CHEMISTRY

Panning for gold

Virtual screening of large compound libraries for lead discovery can be an attractive and complementary alternative to high-throughput screening when enough structural information about the target, or compounds that bind to the target, is available. Accurate predictive assessment of compound binding affinity is crucial to such strategies, but is expensive in computational time, and so rational methods to reduce the number of compounds that are assessed for target binding without sacrificing potentially useful leads are of great interest. Using carbonic anhydrase as an example target, Klebe and colleagues now describe a new protocol in which successive 'filters' are used to reduce the number of compounds to be assessed fully for binding from ~90,000 to ~100, which led to the identification of several novel nanomolar-affinity leads.

Carbonic anhydrase — a target for the treatment of glaucoma — was chosen for the study, as the crystal structure has been solved to high resolution and several protein–ligand complexes have been determined, from which it can be seen that the binding site is constant. As a first step, a library of more than 90,000 compounds from commercially available databases was filtered for the presence of zinc-binding anchor groups, which are known to be important for binding in the active site of carbonic anhydrase. This reduced the library to ~5,900 entries, which were assessed for the level of match with a set of pharmacophores — arrangements of steric and electronic features of the ligand thought to be necessary for high-affinity binding — on the basis of analysis of the characteristics of the binding pocket of carbonic anhydrase. Of the 5,900 compounds, ~3,300 satisfied the pharmacophore criteria, and these were then ranked by comparison with known ligands, thus exploiting available information on protein–ligand interactions more fully. Finally, the 100 best-ranked compounds were docked into the protein-binding pocket and ranked by predicted binding affinity.

At this stage, 13 hits for biological testing were selected by visual inspection, of which three were subnanomolar, one was nanomolar and seven were micromolar inhibitors. The predicted binding mode of two of the inhibitors was confirmed by crystal-structure analysis. Excitingly, the subnanomolar leads all comprise scaffolds that are not covered by existing patents — a generally accepted criteria for potential leads — highlighting the potential of such computational screening strategies.

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References and links

ORIGINAL RESEARCH PAPER Grüneberg, S. *et al*. Successful virtual screening for novel inhibitors of human carbonic anhydrase: strategy and experimental confirmation. *J. Med. Chem.* **45**, 3588–3602 (2002)