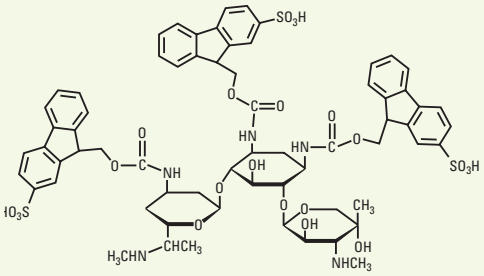
Piggybacking for extended drug life

One of the key problems faced when using therapeutic drugs is controlling the effective dose over time. The surge and purge nature of many therapeutics—where large quantities of effective compound flow into the bloodstream and then are relatively quickly flushed out through the kidneys—is often neither the most effective nor the safest way to provide medication.

Over the years, several methods have been derived to increase the effective lifespan of drugs to avoid this problem. Generally, these rely on modifying the structure of the active compound or providing some sort of stable carrier or time-release system.

Researchers at the Weizmann Institute of Science (Rehovot, Israel) recently reported on adapting a technique used successfully to prolong the life of peptide and protein drugs in animal model systems to increase the activity of common small-molecule drugs that are generally short-lived in the circulatory system (*J. Med. Chem.* **2002,** *45* (19), 4264–4270).



Proposed structure of FMS-gentamicin C_1. (*J. Med. Chem.* **2002,** *45* (19), 4264–4270.)

This method relies on covalently linking 2-sulfo-9-fluorenylmethoxycarbonyl (FMS) to the compounds of interest. For proteins, the added FMS inhibits proteolysis, but this is not the source of the extended drug life for nonpeptide small molecules. For these molecules, FMS serves to promote reversible binding of the conjugate to circulating serum albumin. This binding has been found to protect the compounds from excretion through the kidneys.

Specifically, the team probed the effects on a derivative of the non-orally available antibiotic gentamicin, used for the treatment of many serious Gram-negative infections, denoted gentamicin C_1. Although FMS-derivatized gentamicin C_1 shows only 1% of the clinical activity of the nonderivatized drug, this was beneficially offset by the fact that under physiological conditions, the FMS was gradually hydrolyzed, thereby eliminating the albumin binding and restoring the drug activity over time. High doses could be injected all at once without toxic side effects.

Although this method significantly prolonged the active life of injected gentamicin C_1, it is far from practical use. Matching the retention/activation profile of a technique such as this to an optimal therapeutic pattern requires extensive pharmacological studies, which have yet to be carried out. Currently, the research is more focused on proof of concept than on particular therapeutic ends.

—MARK S. LESNEY

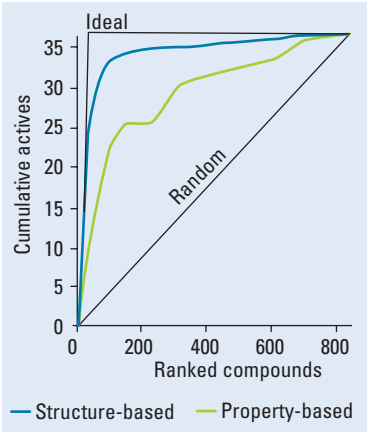
Virtual library screening

In screening a library of compounds for activity against a given protein target, information about the molecular properties of ligands that are known to interact with target family members can provide useful clues. For example, if all of the known ligands carry a substituted benzene ring near a hydroxyl group, there is reason to believe that the best potential ligands will carry similar groups in similar positions. But scanning a library of thousands of compounds with dozens of molecular descriptors requires computational assistance. At the recent IBC Drug Discovery Technology 2002 conference in Boston, Andrey Skorenko and his colleagues at Chemical Diversity Labs, Inc. (San Diego, *www.chemdiv.com*) described their approach to this problem, developing a target-specific library against κ-opioid receptors, members of the family of G-protein coupled receptors (GPCRs).

The researchers divided known GPCR-active compounds into a test set (841 compounds) and a training set (2523 compounds). They then performed two comparative evaluations of the compounds. In a structure-based study, they sorted the test compounds on the basis of their similarity to an internal reference set of 110 κ-opioid receptor ligands. Then, in a property-based approach, an artificial neural network (ANN) was used to divide the full complement of compounds on the basis of 15 molecular descriptors, including hydrogen-bonding potential, bond types, interatomic distances, lipophilicity, and cell permeability. The compounds were then scored by their ability to bind κ-opioid receptors.

When the ranked results of the two methods are compared to ideal (i.e., the top 37 ligands are ranked 1–37) and random (i.e., the top 37 ligands are dispersed throughout the list) situations, the structure-based method approximates the ideal conditions better than the property-based method (see figure). However, the top-ranked property-based compounds showed greater substructural diversity than those of the structure-based method, suggesting that screening using ANNs is preferred when the goal is to identify novel ligand chemotypes. Using the property-based approach, the researchers identified a library of potential GPCR ligands that can subsequently undergo biological screening, increasing the likelihood of finding novel lead structures.

—RANDALL C. WILLIS



Ranking active compounds. A structure-based approach to library screening of compounds that bind to κ-opioid receptors correlates more with the ideal ranking of such compounds than a property-based approach. (Adapted from Skorenko, A. V.; et al. Property-based approach for target-specific library design. Presented at IBC Drug Discovery Technology 2002, Boston, August 2002.)

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