The structure of drug compounds is intimately tied to their physiological effects and their clinical safety. But how do medical researchers determine how quantitative structure–activity relationships (QSARs) or, more recently, structure–property relationships (QSPRs) play out? This is done through ADMET studies—research on the absorption, distribution, metabolism, excretion, and toxicity of compounds with drug potential. Although in vitro research using a variety of cell types is critical to this process, increasingly, efforts are dedicated to developing in silico methods for calculating the probable behavior of compounds before biological testing. Modeling the behavior of such compounds can thus be an important first step in the development of new drugs—allowing early evaluation of candidates based on criteria developed from good old-fashioned chemical know-how.

In fact, according to Christopher Lipinski of Pfizer (www.pfizer.com), who developed the “rule of 5”—the most famous “rule” for determining whether a compound is druglike: “the quality of the starting point in a chemistry optimization process is a good index of the final quality of the clinical candidate. . . A good starting point is likely to lead to a good drug. Conversely, it is very difficult (but not impossible) to convert a poor starting point into a quality drug clinical candidate” (1).

A is for Absorption

One of the most important characteristics researchers monitor to determine the druglike qualities of a prospective compound is its ability to be absorbed through the gut lining. The Caco-2 cell culture system—derived from a human colorectal carcinoma—is most often used for in vitro analysis of intestinal absorption of drugs.

Drug behavior is measured by following the disappearance of the compound in the reservoir above the Caco-2 cell layer and its passage through the permeable membrane on which it is grown, to determine the appearance of the compound and/or its breakdown product on the other side. Sophisticated combinations of HPLC and HPLC-MS analysis have been devised for accurate and sensitive analysis of these compounds. But for all the utility of such in vitro systems, the current ideal is to develop computer methods to eliminate candidates as rapidly as possible after creation of an actual or virtual library.

Computational models to evaluate absorption overwhelmingly rely on this parameter, at least to begin their analysis. Lipinski’s rule of 5 is the first and most often used criterion. It is based on 4 observations, all of which have multiples of 5 in their formulation. According to these criteria, a compound is likely to be absorbed in a druglike manner and correctly permeate the body if

- there are more than 5 H-bond donors,
- the molecular weight is over 500,
- the CLog P is over 5 (or MLOGP is over 4.15), and
- the sum of nitrogens and oxygens is more than 10 (1).

These criteria are critical to controlling both solubility in aqueous solutions and the simultaneous ability to interact with lipid membranes. Thus, a compound must not be too big, too lipophilic, too insoluble, or too highly charged. A major limitation of this
rule in developing drug-modeling protocols is that it is not applicable to compounds that are actively transported, which is often the case in drugs derived from or modeled after natural products such as antibiotics.

Drug companies use the rule of 5 in their choice of screening as well as in their molecular modeling efforts. According to Lipinski, “Pfizer uses the rule of 5 in a variety of ways. For example, it is used as an on-line alert at compound registration. It is used as a filter for high-throughput screening (HTS) libraries. We do not screen libraries (collections) of compounds with significant noncompliance to the rule of 5. We use the rule of 5 as a filter for purchased compounds. We use it as a criterion for focused library synthesis, and we use it as a guideline for quality clinical candidates” (1).

Many argue that the rule of 5 has limited the potential search field of new chemical entities too greatly. For example, Fabio Zuccotto of Inpharmatica, Ltd. (www.inpharmatica.com) recently reported on the use of a pharmacophore approach to analyze compounds for being druglike (2). This approach went beyond Lipinski’s rule and followed (coincidentally) five parameters: hydrogen-bond acceptors and donors, negatively and positively charged ionizable centers, and hydrophobic sites (Figure 1). According to Zuccotto, the use of ionizable centers was an especially valuable criterion. For the average drug compound studied, the average sum of ionizable centers was 0.7–0.9; for nondrugs examined, it was 0.32. Significantly, “the values obtained for compounds in the commercially available HTS collections were even more distant from the druglike space: 0.25 for HTS1 and 0.22 for HTS2” (2).

D is for Distribution

Drugs absorbed through the intestines travel through tissues and the bloodstream to their sites of action. Distribution of a drug can be disrupted by nonspecific binding of the compound to plasma proteins such as albumin or blood cell components. Additionally, a drug is ineffective if it cannot move to its appropriate site of action. Drugs that target the central nervous system, for example, need to cross the blood–brain barrier (BBB).

Cambrex (www.cambrex.com) has developed the Clonetics Bovine Brain Microvascular Cell System, which uses cryogenically preserved primary microvascular cells from bovine brain tissue to create a monolayer with the appropriate structural integrity and transport characteristics of the BBB. This allows in vitro cell-based testing (similar to that used for the Caco-2 assay) of compounds for their ability to cross this critical physiological boundary.

But here too, attempts are being made to develop appropriate models. Researchers at Peking University have reported on using molecular descriptors of 115 test organic compounds to model blood–brain partitioning. They developed the QSPR model using the n-octanol/water partition coefficient, a calculated high-charged polar surface area value, and an “excessive molecular weight larger than 360,” which could predict BBB partitioning behavior of sample compounds (3).

E is for Excretion

Drug compounds are excreted primarily through feces (in bile after processing through the liver) and urine. To determine kidney excretion, Mandin-Darby canine kidney (MDCK) cells are frequently used as a cellular model for studying drug transport in distal renal epithelia. These cells behave similarly to Caco-2 cells, forming a layer with tight junctions when cultured on semipermeable membranes. Thus, the same type of cell assay is used. In silico models rely on predicting such behavior.

Along with metabolism, excretion is critically important in determining the effective dose of even “safe” drugs. For example, older patients with decreased liver and kidney function require
A Selection of Companies Supplying ADMET Software

<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelrys</td>
<td><a href="http://www.accelrys.com">www.accelrys.com</a></td>
</tr>
<tr>
<td>Advanced Chemistry Development</td>
<td><a href="http://www.acdlabs.com">www.acdlabs.com</a></td>
</tr>
<tr>
<td>Arqule</td>
<td><a href="http://www.arqule.com">www.arqule.com</a></td>
</tr>
<tr>
<td>BioRad</td>
<td><a href="http://www.biorad.com">www.biorad.com</a></td>
</tr>
<tr>
<td>Bioreason</td>
<td><a href="http://www.bioreason.com">www.bioreason.com</a></td>
</tr>
<tr>
<td>Chemical Computing Group</td>
<td><a href="http://www.chemcomp.com">www.chemcomp.com</a></td>
</tr>
<tr>
<td>Daylight</td>
<td><a href="http://www.daylight.com">www.daylight.com</a></td>
</tr>
<tr>
<td>IDBS</td>
<td><a href="http://www.id-bs.com">www.id-bs.com</a></td>
</tr>
<tr>
<td>Incyte</td>
<td><a href="http://www.incyte.com">www.incyte.com</a></td>
</tr>
<tr>
<td>LeadScope</td>
<td><a href="http://www.leadscope.com">www.leadscope.com</a></td>
</tr>
<tr>
<td>Lhasa</td>
<td><a href="http://www.chem.leeds.ac.uk/uk">www.chem.leeds.ac.uk/uk</a></td>
</tr>
<tr>
<td>Lion Bioscience</td>
<td><a href="http://www.lionbioscience.com">www.lionbioscience.com</a></td>
</tr>
<tr>
<td>MDL Information Systems</td>
<td><a href="http://www.mdll.com">www.mdll.com</a></td>
</tr>
<tr>
<td>pION</td>
<td><a href="http://www.pion-inc.com">www.pion-inc.com</a></td>
</tr>
<tr>
<td>Schrödinger</td>
<td><a href="http://www.schrodinger.com">www.schrodinger.com</a></td>
</tr>
<tr>
<td>Sirius Analytical Instruments</td>
<td><a href="http://www.sirius-analytical.com">www.sirius-analytical.com</a></td>
</tr>
<tr>
<td>Spotfire</td>
<td><a href="http://www.spotfire.com">www.spotfire.com</a></td>
</tr>
<tr>
<td>Tripos</td>
<td><a href="http://www.tripos.com">www.tripos.com</a></td>
</tr>
</tbody>
</table>

**References**

5. Bioreason www.bioreason.com
6. Advanced Chemistry Development www.acdlabs.com
7. Arqule www.arqule.com
11. Daylight www.daylight.com
12. IDBS www.id-bs.com
13. Incyte www.incyte.com
15. Lhasa www.chem.leeds.ac.uk/uk
16. Lion Bioscience www.lionbioscience.com
17. MDL Information Systems www.mdll.com
18. pION www.pion-inc.com
19. Schrödinger www.schrodinger.com
20. Sirius Analytical Instruments www.sirius-analytical.com
21. Spotfire www.spotfire.com
22. Tripos www.tripos.com

**KEY TERMS:** biotech, data handling, pharmaceutical, synthesis

much smaller drug doses than healthy, middle-aged adults to achieve the same effect. For drugs with potentially toxic effects, the rate differences in metabolism and excretion are even more critical.

**T is for Toxicity**

Adverse drug reactions are the fifth-leading cause of death in the United States (6), and toxicity is one of the top three reasons for the failure in the development of new drugs, along with lack of efficacy and poor biopharmaceutical properties (generally, absorption). Hepatotoxicity and nephrotoxicity are two of the most important problems. Thus, in vitro toxicity studies test compounds for their effects on liver and kidney cells and their enzymes. Ultimately, toxicity testing is carried out on human patients in clinical trials. Here too, in silico modeling efforts abound in an attempt to streamline the process.

According to Han van de Waterbeemd and Eric Gifford of Pfizer, there are two primary strategies for modeling toxicity: the expert system approach that codifies “knowledge from human experts and the scientific literature” and the structural descrip-

**S is for Modeling**

In many ways, modeling ADMET features is as much about the money as the drugs. A growing list of software suppliers sell packages to help researchers and managers in evaluating their libraries—real and in silico (see box, “A Selection of Companies”). Companies such as Bio-Rad with its Know-it-All system, Accel-

But although money is one of the most frequently assumed rationales for computational models, perhaps rather than their use as predictive devices it may be their utility as information-generation tools, revealing hitherto unexplored research areas for medicinal chemists to investigate, that may prove their greatest value in the immediate future. For, as one critic put it, referring to the 60 and 70% rates raved about by some model-

**References**