groups, and including simple molar refractivity, polar surface area, and Moriguchi

- Molconnz-EduSoft LC—provides MOLCONNZ molecular connectivity and electrotopological state descriptors of Kier and Hall (115)

4.2 Physicochemical Descriptors

As a complement to topological descriptors, physicochemical descriptors often have a strong relationship to mechanism, and are widely used in lead optimization and QSAR. The classic triad—steric, electronic, and lipophilic descriptors—are considered the foundation of QSAR, and adequate coverage of the space of these factors is still a major goal in drug discovery. The most common physicochemical descriptor is Log*P*, the 1-octanol/water partition coefficient. Because it is so important, a number of programs and vendors provide Log*P* calculations based on a variety of methods. Many of these programs also compute other physicochemical properties, such as p*K*a and solubility.

- BioByte, Inc.—developers of CLOGP, premier Log*P*, and molar refractivity calculator (116)
- a Syracuse Research Corporation—provide KOWWIN and 11 other structure-based property calculations (117)
- CompuDrug Ltd.—the PALLAS System—including programs for for pK_a, log*P*, log*D* predictions, metabolism and toxicity, and high pressure liquid chromatography (HPLC) development (118)
- a ACDLabs—physicochemical laboratory program calculates p*K*a, Log*P*, log*D*, aqueous solubility, boiling point and vapor pressure, Hammett electronic constants, and a variety of liquid properties (119)
- XLOGP—The Peking University Log*P* calculator—a similar version for proteins is available as PLOGP (120)
- EduSoft LC—provider of Hint!-Lo@—to accompany the HINT! Hydropathic interaction modeling program (121)
- SciVision—provider of software for chemical property calculation, and to estimate QSAR, toxicology, oncology, and other biological properties (122)
- Sirius-Analytical—provider of instruments for Log*P* and p*K*a determination, and the Absolv program to predict physicochemical properties (123)

Most of the commercial molecular modeling systems also provide some property calculations, which range from simply calculating the polar surface area of a structure to a full range of topological and physicochemical descriptors. These may be based on fragment additivity, like most of the programs mentioned above, or they may involve correlations with quantum mechanical or even molecular dynamics-based calculations.

4.3 Absorption, Distribution, Metabolism, and Excretion Properties

Perhaps the most critical aspect of drug development—the behavior of the drug in *vivo*—is also one of the least predictable. Each year, many drug candidates reach the very expensive stage of clinical trials, only to be discontinued because of problems with absorption, distribution, metabolism, or excretion (ADME). Toxicity is often added to this acronym (ADMET), because we increasingly find critical differences in the way children respond versus adults, males versus females, etc. Among the hopes that accompany the deciphering of the human genome, is that drug selection can someday be tailored to an individual's genotype, to lessen the possibility of untoward drug response. For the present, drug designers are focusing increased attention on the prediction of ADME properties, pharmacokinetics, and in vivo behavior. Compared with topological and physicochemical predictions, ADME calculations are still rather crude and approximate. They are usually based on correlations with other properties. And, if the method for obtaining the correlation is a neural network, the predictions may be superior to simpler regression-based approaches, but the interpretability of the model is missing. Some of the programs that are used to predict ADME descriptors include the following: