Although electrostatic interactions are generally restricted to polar molecules, there are also strong interactions between nonpolar molecules over small intermolecular distances. Dispersion or London/van der Waals forces are the universal attractive forces between atoms that hold nonpolar molecules together in the liquid phase. They are based on polarizability and these fluctuating dipoles or shifts in electron clouds of the atoms tend to induce opposite dipoles in adjacent molecules, resulting in a net overall attraction. The energy of this interaction decreases very rapidly in proportion to $1/r^6$, where r is the distance separating the two molecules. These van der Waals forces operate at a distance of about 0.4–0.6 nm and exert an attraction force of less than 0.5 kcal/mol. Yet, although individual van der Waals forces make a low energy contribution to an event, they become significant and additive when summed up over a large area with close surface contact of the atoms.

Hydrophobicity refers to the tendency of nonpolar compounds to transfer from an aqueous phase to an organic phase (49, 50). When a nonpolar molecule is placed in water, it gets solvated by a "sweater" of water molecules ordered in a somewhat icelike manner. This increased order in the water molecules surrounding the solute results in a loss of entropy. Association of hydrocarbon molecules leads to a "squeezing out" of the structured water molecules. The displaced water becomes bulk water, less ordered, resulting in a gain in entropy, which provides the driving force for what has been referred to as a hydrophobic bond. Although this is a generally accepted view of hydrophobicity, the hydration of apolar molecules and the noncovalent interactions between these molecules in water are still poorly understood and thus the source of continued examination (51–53).

Because noncovalent interactions are generally weak, cooperativity by several types of interactions is essential for overall activity. Enthalpy terms will be additive, but once the first interaction occurs, translational entropy is lost. This results in a reduced entropy loss in the second interaction. The net result is that eventually several weak interactions combine to produce a strong interaction. One can safely state that it is the involvement of myriad interactions that contribute to the overall selectivity of drug-receptor interactions.

2 TOOLS AND TECHNIQUES OF QSAR

2.1 Biological Parameters

In QSAR analysis, it is imperative that the biological data be both accurate and precise to develop a meaningful model. It must be realized that any resulting QSAR model that is developed is only as valid statistically as the data that led to its development. The equilibrium constants and rate constants that are used extensively in physical organic chemistry and medicinal chemistry are related to free energy values AG. Thus for use in QSAR, standard biological equilibrium constants such as K_i or K_m should be used in QSAR studies. Likewise only standard rate constants should be deemed appropriate for a QSAR analysis. Percentage activities (e.g., % inhibition of growth at certain concentrations) are not appropriate biological endpoints because of the nonlinear characteristic of dose-response relationships. These types of endpoints may be transformed to equieffective molar doses. Only equilibrium and rate constants pass muster in terms of the free-energy relationships or influence on QSAR studies. Biological data are usually expressed on a logarithmic scale because of the linear relationship between response and log dose in the midregion of the log dose-response curve. Inverse logarithms for activity ($\log 1/C$) are used so that higher values are obtained for more effective analogs. Various types of biological data have been used in QSAR analysis. A few common endpoints are outlined in Table 1.2.

Biological data should pertain to an aspect of biological/biochemical function that can be measured. The events could be occurring in enzymes, isolated or bound receptors, in cellular systems, or whole animals. Because there is considerable variation in biological responses, test samples should be run in duplicate or preferably triplicate, except in whole animal studies where assay conditions (e.g., plasma concentrations of a drug) preclude such measurements.