$$\text{Log } 1/C = a \cdot \log P - b \cdot \log(\beta \cdot P + 1) + k \quad (1.4)$$

Besides the Hansch approach, other methodologies were also developed to tackle structure-activity questions. The Free-Wilson approach addresses structure-activity studies in a congeneric series as described in Equation 1.5 (22).

$$\text{BA} = \sum a_i x_i + u \quad (1.5)$$

BA is the biological activity, $u$ is the average contribution of the parent molecule, and $a_i$ is the contribution of each structural feature; $x_i$ denotes the presence $X_i = 1$ or absence $X_i = 0$ of a particular structural fragment. Limitations in this approach led to the more sophisticated Fujita-Ban equation that used the logarithm of activity, which brought the activity parameter in line with other free energy-related terms (23).

$$\text{Log } BA = \sum G_i X_i + u \quad (1.6)$$

In Equation 1.6, u is defined as the calculated biological activity value of the unsubstituted parent compound of a particular series. $G_i$ represents the biological activity contribution of the substituents, whereas $X_i$ is ascribed with a value of one when the substituent is present or zero when it is absent. Variations on this activity-based approach have been extended by Klopman et al. (24) and Enslein et al. (25). Topological methods have also been used to address the relationships between molecular structure and physical/biological activity. The minimum topological difference (MTD) method of Simon and the extensive studies on molecular connectivity by Kier and Hall have contributed to the development of quantitative structure property/activity relationships (26, 27). Connectivity indices based on hydrogen-suppressed molecular structures are rich in information on branching, 3-atom fragments, the degree of substitution, proximity of substituents and length, and heteroatom of substituted rings. A method in its embryonic state of development uses both graph bond distances and Euclidean distances among atoms to calculate E-state values for each atom in a molecule that is sensitive to conformational structure. Recently, these electrotopological indices that encode significant structured information on the topological state of atoms and fragments as well as their valence electron content have been applied to biological and toxicity data (28). Other recent developments in QSAR include approaches such as HQSAR, Inverse QSAR, and Binary QSAR (29–32). Improved statistical tools such as partial least square (PLS) can handle situations where the number of variables overwhelms the number of molecules in a data set, which may have collinear X-variables (33).

## 1.2 Development of Receptor Theory

The central theme of molecular pharmacology, and the underlying basis of SAR studies, has focused on the elucidation of the structure and function of drug receptors. It is an endeavor that proceeds with unparalleled vigor, fueled by the developments in genomics. It is generally accepted that endogenous and exogenous chemicals interact with a binding site on a specific macromolecular receptor. This interaction, which is determined by intermolecular forces, may or may not elicit a pharmacological response depending on its eventual site of action.

The idea that drugs interacted with specific receptors began with Langley, who studied the mutually antagonistic action of the alkaloids, pilocorpine and atropine. He realized that both these chemicals interacted with some receptive substance in the nerve endings of the gland cells (34). Paul Ehrlich defined the receptor as the "binding group of the protoplasmic molecule to which a foreign newly introduced group binds" (35). In 1905 Langley's studies on the effects of curare on muscular contraction led to the first delineation of critical characteristics of a receptor: recognition capacity for certain ligands and an amplification component that results in a pharmacological response (36).

Receptors are mostly integral proteins embedded in the phospholipid bilayer of cell membranes. Rigorous treatment with detergents is needed to dissociate the proteins from the membrane, which often results in loss of