model consisting of a linear ascending part and a parabolic part (190). See Equations 1.73 and 1.74.

$$\text{Log } 1/C = a \cdot \log P + \text{c} \quad (\text{if } \log \text{P} < \log P_{\text{x}}) \tag{1.73}$$

$$\text{Log } 1/C = -a(\log P)^2 + \text{b} \cdot \log \text{P} + \text{c} \quad (\text{if } \log \text{P} > \log P_{\text{x}}) \tag{1.74}$$

The binding of drugs to proteins is linearly dependent on hydrophobicity up to a limited value, log P_{x}, after which steric hindrance causes the linear dependency to alter to a nonlinear one. The major limitation of this approach involves the inclusion of highly hydrophobic congeners that tend to cause systematic deviations between experimental and predicted values.

Another cutoff model, which deals with nonlinearity in biological systems, is one defined by McFarland (191). It attempts to elucidate the dependency of drug transport on hydrophobicity in multicompartment models. McFarland addressed the probability of drug molecules traversing several aqueous lipid barriers from the first aqueous compartment to a distant, final aqueous compartment. The probability $P_{0,n}$ of a drug molecule to access the final compartment n of a biological system was used to define the drug concentration in this compartment.

$$\text{Log } C_{\text{R}} = a \cdot \log P - 2a \cdot \log(P + 1) + \text{constant} \tag{1.75}$$

The ascending and descending slopes are equal (=1) and linear. However, a major drawback of this model is that it forces the activity curves to maximize at log P = 0. These studies were extended by Kubinyi, who developed the elegant and powerful bilinear model, which is superior to the parabolic model and is extensively used in QSAR studies (192).

$$\text{Log } 1/C = a \cdot \log P - b \cdot \log(\beta \cdot P + 1) + \text{constant} \tag{1.76}$$

where β is the ratio of the volumes of the organic phase and the aqueous phase. An important feature of this model lies in the symmetry of the curves. For aqueous phases of this model system, symmetrical curves with linear ascending and descending sides (like a teepee) and a limited parabolic section around the hydrophobicity optimum are generated. Unsymmetrical curves arise for the lipid phases. It is highly compatible with the linear model and allows for quick comparisons of the ascending slopes. It can also be used with other parameters such as MR and σ, where it appears to pinpoint a change in mechanism similar to the breaks in linearity of the Hammett equation. The following example of the bilinear model reveals the symmetrical nature of the curve.

4.2.2 Induction of Ataxia in Rats by ROH

$$\begin{aligned}\text{Log } 1/C = {} & 0.77(\pm 0.10)\log P \\ & - 1.53(\pm 0.12)\log(\beta \cdot P + 1) \\ & + 1.68(\pm 0.12) \\ & n = 35, \quad r^2 = 0.887, \\ & s = 0.165, \quad \log P_{\text{O}} = 2.0\end{aligned} \tag{1.77}$$

The bilinear model has been used to model biological interactions in isolated receptor systems and in adsorption, metabolism, elimination, and toxicity studies, although it has a few limitations. These include the need for at least 15 data points (because of the presence of the additional disposable parameter β and data points beyond optimum Log P. If the range in values for the dependent variable is limited, unreasonable slopes are obtained.

4.3 Free-Wilson Approach

The Free-Wilson approach is truly a structure-activity-based methodology because it incorporates the contributions made by various structural fragments to the overall biological activity (22, 193, 194). It is represented by Equation 1.78.

$$\text{BA}_i = \sum_j a_j \text{X}_{ij} + \mu \tag{1.78}$$

Indicator variables are used to denote the presence or absence of a particular structure feature.