integrity and activity. Pure proteins such as enzymes also act as drug receptors. Their relative ease of isolation and amplification have made enzymes desirable targets in structure-based ligand design and QSAR studies. Nucleic acids comprise an important category of drug receptors. Nucleic acid receptors (aptamers), which interact with a diverse number of small organic molecules, have been isolated by *in vitro* selection techniques and studied (37). Recent binary complexes provide insight into the molecular recognition process in these biopolymers and also establish the importance of the architecture of tertiary motifs in nucleic acid folding (38). Groove-binding ligands such as lexitropsins hold promise as potential drugs and are thus suitable subjects for focused QSAR studies (39).

Over the last 20 years, extensive QSAR studies on ligand-receptor interactions have been carried out with most of them focusing on enzymes. Two recent developments have augmented QSAR studies and established an attractive approach to the elucidation of the mechanistic underpinnings of ligand-receptor interactions: the advent of molecular graphics and the ready availability of X-ray crystallography coordinates of various binary and ternary complexes of enzymes with diverse ligands and cofactors. Early studies with serine and thiol proteases (chymotrypsin, trypsin, and papain), alcohol dehydrogenase, and numerous dihydrofolate reductases (DHFR) not only established molecular modeling as a powerful tool, but also helped clarify the extent of the role of hydrophobicity in enzyme-ligand interactions (40–44). Empirical evidence indicated that the coefficients with the hydrophobic term could be related to the degree of desolvation of the ligand by critical amino acid residues in the binding site of an enzyme. Total desolvation, as characterized by binding in a deep crevice/pocket, resulted in coefficients of approximately 1.0 (0.9–1.1) (44). An extension of this agreement between the mathematical expression and structure as determined by X-ray crystallography led to the expectation that the binding of a set of substituents on the surface of an enzyme would yield a coefficient of about 0.5 (0.4–0.6) in the regression equation, indicative of partial desolvation.

Probing of various enzymes by different ligands also aided in dispelling the notion of Fischer's rigid lock-and-key concept, in which the ligand (key) fits precisely into a receptor (lock). Thus, a "negative" impression of the substrate was considered to exist on the enzyme surface (geometric complementarity). Unfortunately, this rigid model fails to account for the effects of allosteric ligands, and this encouraged the evolution of the induced-fit model. Thus, "deformable" lock-and-key models have gained acceptance on the basis of structural studies, especially NMR (45).

It is now possible to isolate membrane-bound receptors, although it is still a challenge to delineate their chemistry, given that separation from the membrane usually ensures loss of reactivity. Nevertheless, great advances have been made in this arena, and the three-dimensional structures of some membrane-bound proteins have recently been elucidated. To gain an appreciation for mechanisms of ligand-receptor interactions, it is necessary to consider the intermolecular forces at play. Considering the low concentration of drugs and receptors in the human body, the law of mass action cannot account for the ability of a minute amount of a drug to elicit a pronounced pharmacological effect. The driving force for such an interaction may be attributed to the low energy state of the drug-receptor complex: $K_D = [Drug][Receptor]/[Drug\text{-}ReceptorComplex]$. Thus, the biological activity of a drug is determined by its affinity for the receptor, which is measured by its K_D, the dissociation constant at equilibrium. A smaller K_D implies a large concentration of the drug-receptor complex and thus a greater affinity of the drug for the receptor. The latter property is promoted and stabilized by mostly noncovalent interactions sometimes augmented by a few covalent bonds. The spontaneous formation of a bond between atoms results in a decrease in free energy; that is, AG is negative. The change in free energy AG is related to the equilibrium constant K_{eq}.

$$\Delta G^\circ = -RT \ln K_{eq} \qquad (1.7)$$

Thus, small changes in ΔG° can have a profound effect on equilibrium constants.