IMPACT 8 ON MEDICINE

Molecular recognition and drug design

The binding of a ligand, or *guest*, to a biopolymer, or *host*, is governed by molecular interactions. To devise efficient therapies, it is important to know how to characterize and optimize molecular interactions between the host and the guest. Examples of biological *host–guest complexes* include enzyme–substrate complexes, antigen–antibody complexes, and drug–receptor complexes. In all these cases, a site on the guest contains functional groups that can interact with complementary functional groups of the host. For example, for tight binding to occur a hydrogen-bond donor group of the guest must be positioned near a hydrogen-bond acceptor group of the host. Typically, many specific intermolecular contacts must be made in a biological host–guest complex and, as a result, a guest binds only hosts that are chemically similar. The strict rules governing molecular recognition of a guest by a host control every biological process, from metabolism to immunological response, and provide important clues for the design of effective drugs for the treatment of disease.

Interactions between nonpolar groups can be important in the binding of a guest to a host. For example, many enzyme active sites have hydrophobic pockets that bind nonpolar groups of a substrate. In addition to dispersion, repulsive, and hydrophobic interactions, **π-stacking interactions** are also possible in which the planar π systems of aromatic macrocycles lie one on top of the other, in a nearly parallel orientation. Such interactions are responsible for the stacking of hydrogen-bonded base pairs in DNA (Fig. 1). Some drugs with planar π systems (the molecule shown with a space-filling model in Fig. 1) are effective because they penetrate between base pairs through π as a result of interactions, causing the helix to unwind slightly and thereby altering the function of the DNA molecule.

Coulombic interactions can be important in the interior of a biopolymer host, where the relative permittivity can be much lower than that of the aqueous exterior. For example, at physiological pH, amino acid side chains containing carboxylic acid or amine groups are negatively and positively charged, respectively, and can attract each other. Dipole–dipole interactions are also possible because many of the building blocks of biopolymers are polar, including the peptide link, —CONH—. However, hydrogen bonding interactions are by far the most prevalent in biological host–guest complexes. Many effective drugs bind tightly and inhibit the action of enzymes that are associated with the progress of a disease. In many cases, a successful inhibitor will be able to form the same hydrogen bonds with the binding site that the normal substrate of the enzyme can form, except that the drug is chemically inert towards the enzyme.

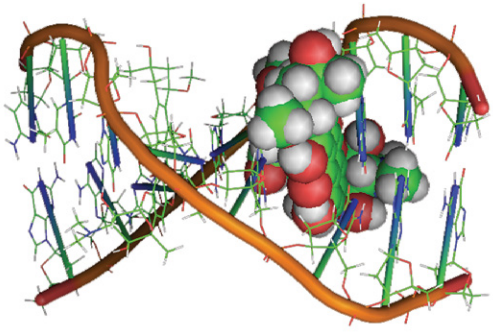

Fig. 1 Some drugs with planar π systems intercalate between base pairs of DNA.

There are two main strategies for the discovery of a drug. In *structure-based design*, new drugs are developed on the basis of the known structure of the receptor site of a known target. However, in many cases a number of so-called *lead compounds* are known to have some biological activity but little information is available about the target. To design a molecule with improved pharmacological efficacy, **quantitative structure–activity relationships** (QSAR) are often established by correlating data on activity of lead compounds with molecular properties, also called *molecular descriptors*, which can be determined either experimentally or computationally for a large number of lead compounds. Descriptors include molar mass, molecular dimensions and volume, and relative solubility in water and nonpolar solvents are available from routine experimental procedures, bond orders, and HOMO and LUMO energies.

The traditional QSAR technique has been refined into **3D QSAR**, which is based on the premise that common structural features among lead compounds are indicative of molecular properties that enhance binding of the drug to the receptor. Important features included in the analysis are molecular size and shape, location of functional groups, and electrostatic potential plots. Figure 2 shows results of a 3D QSAR study of the binding of steroids, molecules with the carbon skeleton shown, to human corticosteroid-binding globulin (CBG).

The QSAR and 3D QSAR methods, though powerful, have limited power: the predictions are only as good as the data used in the correlations are both reliable and abundant. However, the techniques have been used successfully to identify compounds that deserve further synthetic elaboration, such as addition or removal of functional groups, and testing.

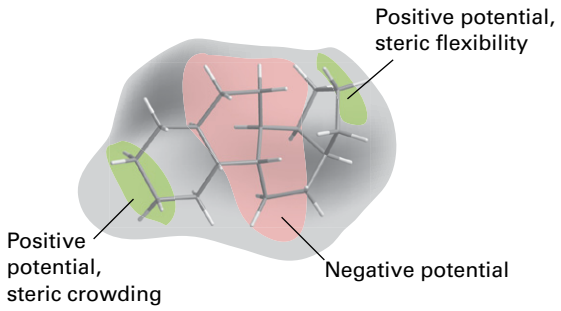

Fig. 2 A 3D QSAR analysis of the binding of steroids, molecules with the carbon skeleton shown, to human corticosteroid-binding globulin (CBG). The ellipses indicate areas in the protein's binding site with positive or negative electrostatic potentials and with little or much steric crowding. It follows from the calculations that addition of large substituents near the left-hand side of the molecule (as it is drawn on the page) leads to poor affinity of the drug to the binding site. Also, substituents that lead to the accumulation of negative electrostatic potential at either end of the drug are likely to show enhanced affinity for the binding site. [Adapted from P. Krogsgaard-Larsen, T. Liljefors, and U. Madsen (ed.), *Textbook of drug design and discovery*, Taylor & Francis, London (2002).]