After oral administration, one of many routes of administration, the drug must survive the acidic environment of the stomach. In the small intestine, the bulk of absorption takes place. Here, the pH is neutral to slightly acidic. In the gastrointestinal system metabolism can take place. The presence of digestive enzymes creates particular problems for polypeptide drugs which may call for other routes of administration, as the gut wall is rich in oxidative enzymes.

Unless the drug acts as a substrate for active energy-requiring uptake mechanisms which normally facilitate uptake of, for example, amino acids and glucose, it must be significantly unionized to penetrate cell membranes in order to enter the blood stream. Following absorption, the blood rapidly presents the drug to the liver, where Class I metabolic transformations (oxidation, hydrolysis, reduction, etc.) and in some cases phase II transformations (glucuronidation, sulfation, etc.) take place. The polar reaction products from these reactions are typically excreted in the urine or feces.

The rate of absorption of drugs, their degree of metabolic transformation, their distribution in the body, and their rate of excretion are collectively named pharmacokinetics. This is in effect the influence of the body on a drug as a function of time. The interaction of the drug with its targets, and the consequences of this interaction as a function of time are pharmacodynamics.

Both of these characteristics are alone governed by the drug's chemical structure. Thus, the medicinal chemist is expected to remedy any shortcomings by structural modification. In addition to ADME-Tox, a number of other characteristics must also be satisfactory, such as

- Freedom from mutagenesis
- Freedom from teratogenicity
- Chemical stability—shelf stability
- Synthetic or biological accessibility
- Acceptable cost
- Ability to patent
- Clinical efficacy
- Solubility
- Satisfactory taste (per oral administration)
- Ability to formulate satisfactorily for administration
- Freedom from idiosyncratic problems

A number of strategies are used by the medicinal chemists in order to optimize lead compounds in order to fulfill all these requirements related to optimization of desired activities and minimization of undesired effects:

- Variation of substituents—change of size, shape, and polarity
- Extension/contraction of structure—change chain size or ring size
- Ring closure/ring variation/ring fusion
- Simplification of structure
- Rigidification of structure

Examples of such modification are presented especially in Chapters 15 through 19, and generally these efforts aim toward optimizing the active conformation and physicochemical properties of the drugs with the essential and necessary pharmacophoric groups present. A very versatile principle for variation of molecules, functional groups, and substituents with focus on optimizing biological activity is the use of bioisosteres (see Section 1.4.3.1). Furthermore, stereochemical control of drug interactions with the chiral environment is essential as described in Section 1.4.3.2 and subsequent sections.

These challenges emphasize the key importance of scientists trained in interdisciplinary medicinal chemistry in drug discovery projects.