was named "functional partial agonism." An interesting aspect of this pharmacological concept is that administration of an antagonist drug inherently establishes functional partial agonism together with the endogenous agonist at the target receptor.

1.4.3.3 Membrane Penetration: Including the Lipinski Rule of Five

In drug discovery projects, an issue of major importance is the design of drug molecules capable of penetrating different biological membranes effectively and that allow effective concentrations to build up at the therapeutic target. The structure and physiochemical properties of the drug molecule obviously are of decisive importance, and it is possible to establish the following empirical rules:

- Some small and rather water-soluble substances pass in and out of cells through water-lined transmembrane pores.
- Other polar agents are conducted into or out of cells by membrane-associated and energy-consuming proteins. Polar nutrients that the cell requires, such as glucose and many amino acids, fit into this category. More recently, drug resistance by cells has been shown to be mediated in many cases by analogous protein importers and exporters.
- The blood–brain barrier (BBB) normally is not easily permeable by neutral amino acids. However, such compounds with sufficiently small difference between the pK_a values will have a relatively low I/U ratio (the ratio between the ionized/zwitterionic form and the unionized form of the amino acid in solution). As an example, THIP (Figure 1.4) has pK_a values of 4.4 and 8.5 and a calculated I/U ratio of about 1000. Thus, 0.1% of THIP in solution is unionized, and this fraction apparently permits THIP to penetrate the BBB quite easily. Other neutral amino acids typically have I/U ratios around 500,000 and thus have much lower fractions of unionized molecules in solution, and such compounds normally do not penetrate into the brain after systemic administration.
- Molecules that are partially water soluble and partially lipid soluble can pass through cell membranes by passive diffusion and are driven in the direction of the lowest concentration.
- In cells lining the intestinal tract, it is possible for molecules with these characteristics to pass into the blood through the cell membrane alone.
- Finally, it is also possible for molecules with suitable water solubility, small size, and compact shape to pass into the blood between cells. This last route is generally not available for passage into the CNS, because the cells forming the BBB are organized much closer together and thus prevent such entry into the brain.

Whereas there are no guarantees and many exceptions, the majority of effective oral drugs obey the Lipinski rule of five:

- The substance should have a molecular weight of 500 or less.
- It should have fewer than five hydrogen-bond donors.
- It should have fewer than 10 hydrogen-bond acceptors.
- The substance should have a calculated log P (clog P) between approximately −1 and +5.

The Lipinski rule of five is thus an empirical rule, where the number five occurs several times. The rule is a helpful guide rather than a law of nature.

1.4.3.4 Structure-Based Drug Design

During the early 1980s, the possibility to rationally design drugs on the basis of structures of therapeutically relevant biomolecules was an unrealized dream for many medicinal chemists. The first projects were underway in the mid-1980s, and today, even though there are still many obstacles and