This chapter has focused upon synthetic molecules, but natural products are a rich source of leads. Natural products include all the compounds, even proteins, in the body that trigger biological responses. With regard to proteins, pharmaceutical companies are often in a position having knowledge of potent proteins that interact with a desired target. Proteins, unfortunately, are very problematic leads. They may have remarkable target binding and low $K_i$ values, but their other properties, especially bioavailability, are very poor. The human digestive system is after all designed to break down proteins. They are not absorbed intact.

A drug discovery group has two options when considering a peptide lead. Neither is easy. One option is to abandon the peptide lead and start the lead discovery process from scratch by screening large compound libraries against the desired target. Abandoning a potent lead is especially difficult because not all searches of compound libraries generate promising leads. The other option is to try to modify the peptide lead and improve its properties. This option requires peptidomimetics, which is the practice of discovering non-peptide structures with peptide-like activity.

The idea of improving a molecule's pharmacokinetic properties while retaining its favorable binding resembles a concept that we have already discussed – isosteres. Indeed, there are isosteres that have been developed specifically for use in peptidomimetics. These specific isosteres are mostly peptide bond isosteres and alter the amide linkage in a peptide backbone so that it is more stable toward digestive enzymes and able to be absorbed.

Structure 1 is a simple peptide segment. The amide linkage is highlighted. One peptide isostere (2) involves R-groups from the $\alpha$-carbon to the adjacent backbone nitrogen. This modification maintains the amide group, but the N-H is no longer present. Isostere 2 is called a peptoid. Another peptide isostere (3) is the retroinverso isostere. The position of the carbonyl and nitrogen are transposed, a change that inverts all the stereocenters along the peptide backbone. Other peptide isosteres are shown in structures 4 and 5. Both change the amide linkage. Through introduction of different peptide isosteres and other structural changes, the discovery team may be able to improve the pharmacokinetics of the lead while still retaining sufficient target binding for potency.