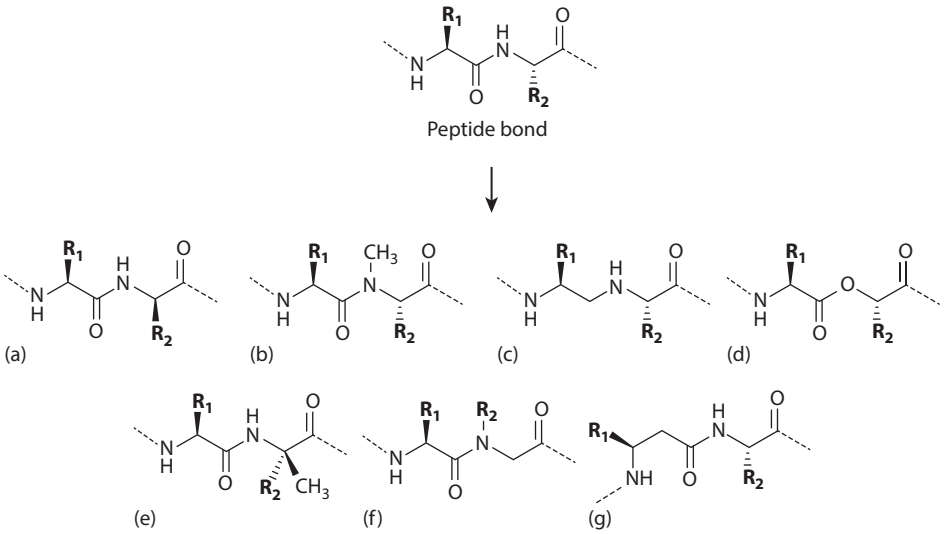

FIGURE 9.5 Examples of various structures that can be introduced in place for the labile peptide bond; D-amino acid (a), *N*-methyl-amino acid (b), reduced peptide bond (c), ester bond (d), Cα-methyl (e), *N*-substituted glycine (peptoid monomer) (f), and β-amino acid (g).

some cases very selective and potent compounds can be identified. Either way it often requires an empirical approach in which a larger set of peptides are synthesized and screened for receptor activity. Other consideration in the design phase is ease of synthesis of these analogs and again later on the cost-effectiveness in a larger scale production. As an example, the introduction of an ester bond requires the synthesis of building blocks that are not readily available. This naturally impedes the synthesis of a larger collection of peptides in a screening process. In contrast, the introduction of *N*-methyl amino acids (or D-amino acids) where a larger number of building blocks are commercially available or otherwise readily synthesized from relative inexpensive starting materials, makes it feasible to create large collections (arrays) of peptides by standard solid phase peptide synthesis (SPPS) that can be tested in various high-throughput receptor assays.

9.3.2 Methods for Structure–Activity Relationship

Getting usable information concerning the structure–function–activity relationship in a quantitative manner (Q-SAR) is an important part of the drug discovery process. Molecular modeling plays a pivotal role in this design process of biopharmaceuticals and is discussed in Chapter 4. While design of experiment (DoE) approaches are arguably gaining more and more attention in many disciplines, the way to intelligently reduce the number of analogs and still gain useful information about the SAR is a challenge, since residues in close proximity may influence each other's activity. In cases where there is no structural knowledge of the ligand–receptor interaction, a more empirical approach, e.g., the synthesis and screening of many analogs in a parallel or combinatorial fashion can prove highly advantageous.

9.3.2.1 Replacement and Analysis

For decades, simple truncation and replacement analysis in the peptide or protein have yielded very useful information about the receptor interaction. By replacing the residues with alanine (Ala-scan) which only displays a methyl group as the side chain, the significance of the individual side chains can be assessed since any peptide bond interaction is preserved (Figure 9.6). The key residues are often referred as hot spots in the ligand and are considered to be the most essential for