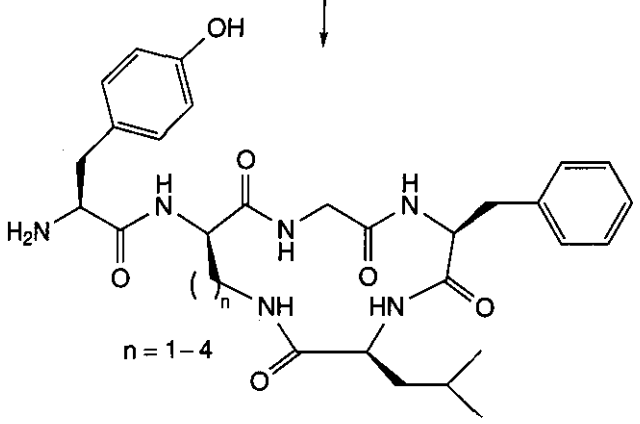
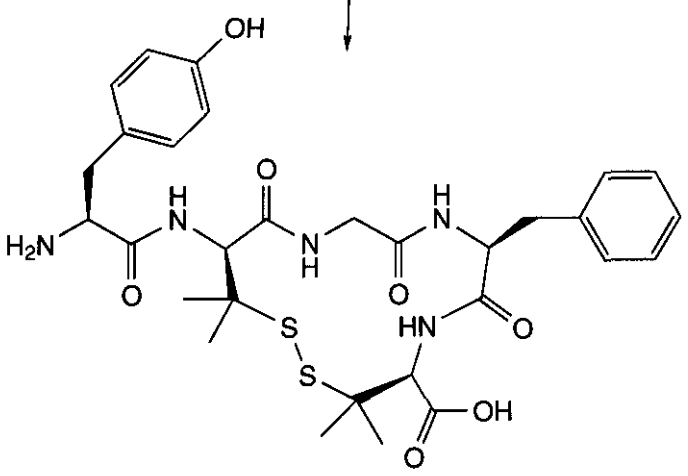
H_2N-Tyr-Gly-Gly-Phe-Leu-OH
Leu-enkephalin
(**4a**)



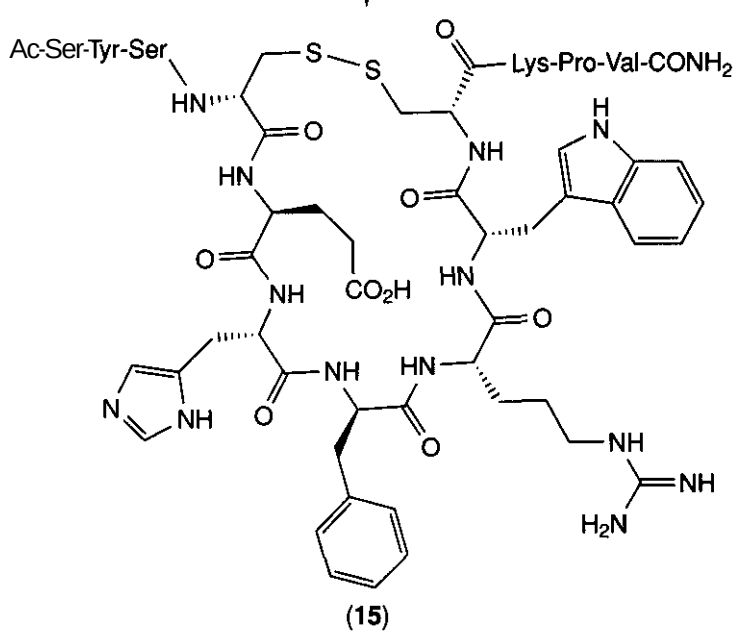
(**12**)

H_2N-Tyr-Gly-Gly-Phe-Met-OH
Met-enkephalin
(**4b**)



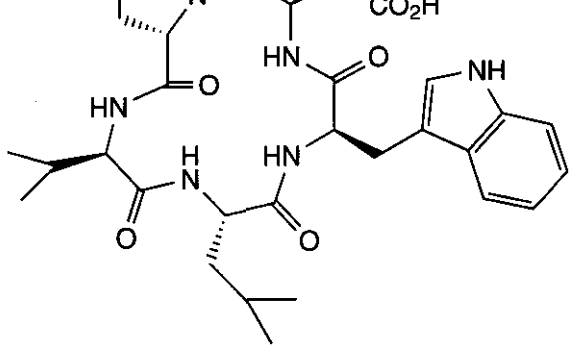
(**13**)

Ac-HN-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-$CONH_2$
α-Melanotropin
(**14**)



(**15**)

H_2N-Cys-Ser-Cys-Ser-Ser-Leu-Met
HO-Trp-Ile-Ile-Asp-Leu-His-Cys-Phe-Tyr-Val-Cys-Glu-Lys-Asp
Endothelin
(**16**)



(**17**)

Figure 15.6. Cyclic hormone peptide analogs.

15.6). Peptide chemists routinely apply conformational restriction in their attempts to determine possible bioactive conformations.

Flexible peptides can be conformationally restricted by a variety of methods other than macrocyclization of the peptide. For example, Marshall et al. introduced a-methyl amino acid substituents into peptides as a way to decrease the conformational space available to the resulting peptide (42); these types of approaches led to his "Active Analog" approach for determining bioactive conformations of flexible molecules (43). Some other traditional modifications of the peptide substrate are the replacement of the amino acids of the P_1-P_1' cleavage site by D-amino acids or the employment of *a-C* or a-N alkylated amino acids and cyclic or β-amino acids (Fig. 15.7).

Mimicking the secondary structure of peptides has become one of the most important tools for rational drug design (44–47). These methods induce the synthetic analog to adopt a set of target conformations, which are designed to mimic the bioactive conformation predicted in the native substrate from biophysical techniques. Molecular surrogates