



FIGURE 3.36

Analogues of the GnRH hormone.

severely limits their formulation.⁷⁸ The following are the main modifications that have been explored (Figures 3.37 and 3.38):

1. Replacement of the first three amino acids by D-amino acids with unnatural side chains. The most widely employed replacements are *N*-acetyl-D-(β -naphthyl)alanine for the first residue, D-(4-chloro)phenylalanine for the second, and D-(2-pyridyl)alanine or D-Trp for the third residue.
2. Modification of the sixth amino acid, which normally bears chains with amide, urea, or guanidine substituents. The purpose of this substitution is to increase the hydrogen bond-formation capabilities of the molecules and improve their solubilities.