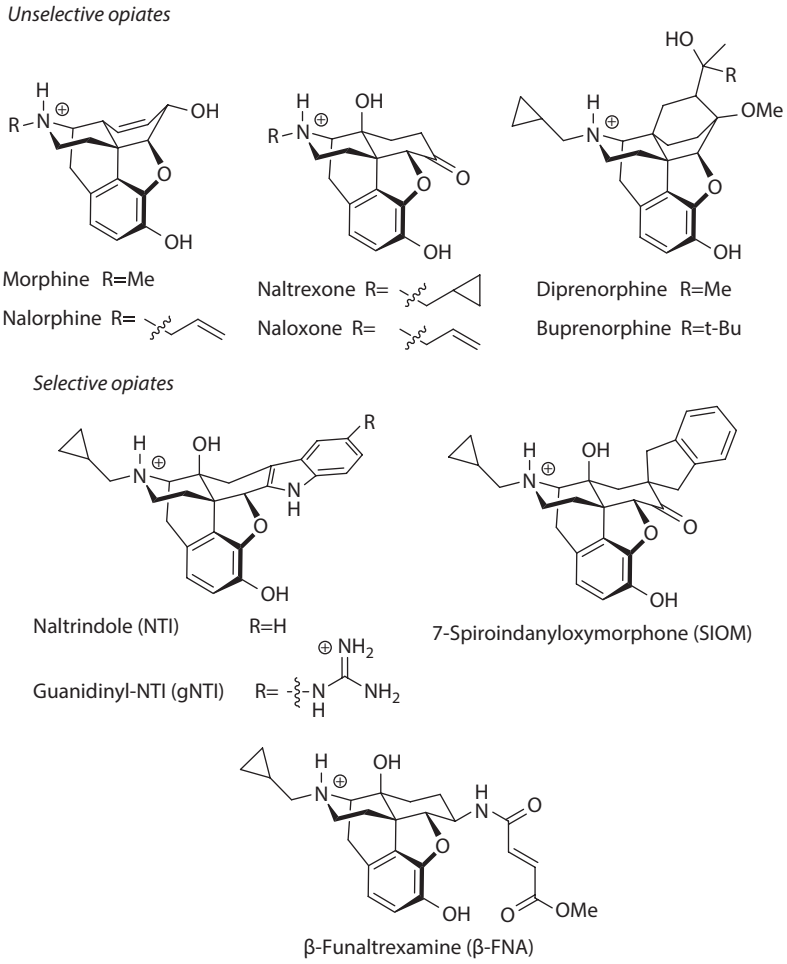

FIGURE 19.3 Chemical structures of classical unselective opiates (except morphine which is μ-selective) based on the morphine scaffold and chemical structures of selective opiates. Morphine and β-FNA are μ-selective agonist and irreversible antagonist, respectively. SIOM and NTI are examples of δ-selective antagonists, whereas the introduction of charged guanidinium group converts NTI into the κ-selective antagonist gNTI.

antagonist gNTI by the introduction of charged guanidinium group. Already in the 1960s, a 3D pharmacophore model was conceived stating the importance of the spatial placement of the amine, the aromatic group, and the lipophilic region for ligand affinity. The successive breakdown of the morphine structure has led to a number of simpler nonopiate structures obeying this early and simple 3D pharmacophore model. This breakdown is shown schematically in Figure 19.4 defining structural classes of opioid receptor ligands developed over the last century.

Examples of these classes are μ-selective agonist fentanyl (piperidine), ethyl-ketocyclazine (benzomorphane), methadone (phenylpropylamine), and meperidine (piperidine) (Figure 19.5). However, other structural classes have appeared, such as δ-selective agonist SNC-80 and κ-selective agonist U50,488, and, more recently, several new scaffolds come from screening compound libraries on the cloned opioid receptors including heteromeric combinations.

Dimerization of ligands is a popular strategy in medicinal chemistry to alter the pharmacological properties of a monomeric ligand. This strategy was advanced in the early 1980s by Portoghese and coworkers using opiates. Initially, the idea was to develop such bivalent ligands