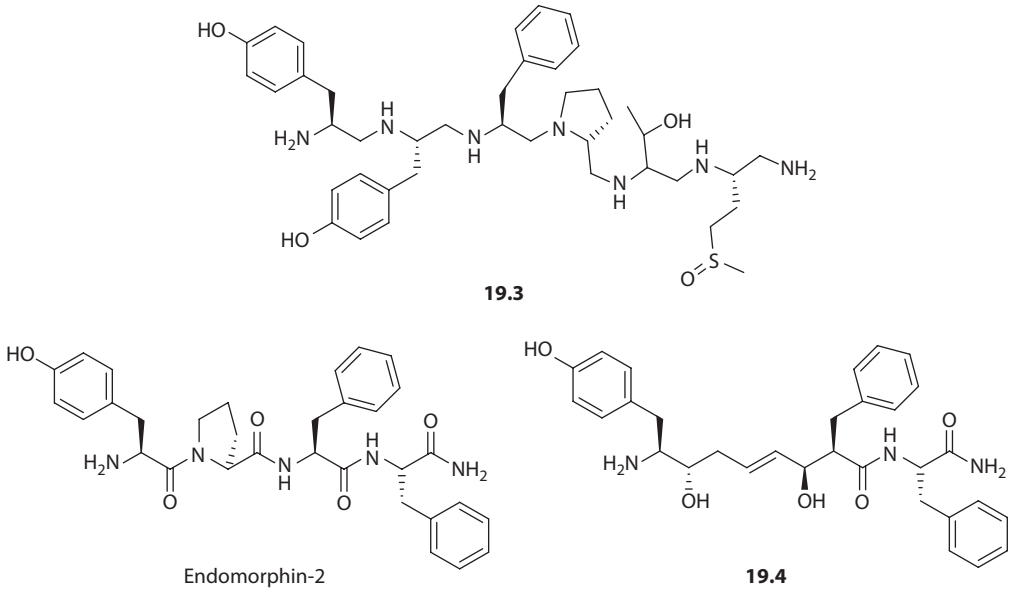

FIGURE 19.7 Examples of peptidomimetic opioid receptor ligands.

There is today substantial evidence that GPCRs exist as dimers. The concept of making bivalent ligands has been shown in many other areas to be able to modulate other pharmacological properties of a ligand such as degradation, uptake, etc. The concept has also been used to target heterodimeric receptor populations. For example, a series of heterobivalent ligands **19.2** (**A**, n = 2–7) were made by linking analogs of naltrexone and NTI, where tolerance and dependence was significantly reduced with increasing linker length, while agonist potency was increased. It is hypothesized that δ–κ heterodimers are targeted specifically with longer linkers. Also, ligands that selectively target δ–κ heterodimers that are localized in the spinal cord have been developed. More recently, heterobivalent ligands **19.2** have been developed linking an opioid ligand with ligands for other GPCRs such as the cannabinoid receptor or the metabotropic glutamate receptor (mGluR5). Thus, an analog of the opioid ligand naltrexone was covalently linked to a Rimonabant analog (**B**, cannabinoid receptor CB_1 inverse agonist) and M-MPEP (**C**, mGluR5 antagonist), respectively. These compounds also displayed reduced tolerance along with potent analgesic and antinociceptive properties. Furthermore, these compounds provide further evidence for the existence of such heteromeric receptor complexes.

The last approach that will be mentioned here is the use of peptides and peptidomimetics. New agonists and antagonists at opioid receptors have been obtained by making large combinatorial libraries of D- and L-amino acids and screening these compounds against MOR, KOR, and DOR. The sequences span from tetra- to deca-peptides. In this way, potent and selective peptides have been obtained that differ from the endogenous peptides. Furthermore, the modification of the peptide backbone has yielded potent peptidomimetics. The modifications include minor modifications such as backbone amide alkylation. But examples of more extensive modifications are the use of a polyamine backbone as in compound **19.3** or compound **19.4** which is a peptidomimetic analog of endomorphin-2, a potent agonist at MOR with high selectivity for MOR over DOR and KOR (Figure 19.7).

19.1.4 Therapeutic Applications and Prospects

Although development of opiates has been spurred primarily by the search for efficient analgesics with few side effects, other clinical applications of opioid receptor agonists and antagonists are known. Agonists are primarily applied as analgesic, anesthetic, antitussive, and in the treatment