The amino acid sequences are YGGFM and YGGFL and termed [Met]-and [Leu]-enkephalin, respectively. Since then, many other peptide opioids of varying lengths have been identified. They are all cleavage products of longer peptides and can be divided into four families based on their precursors. Three of these families all start with the [Met]- and [Leu]-enkephalin. The endogenous opioid peptides have varying affinities for the opioid receptor subtypes; however, none of them are specific for a single subtype, although the neuropeptide nociceptin is the endogenous ligand specific for ORL_1. The precursors are often made up of repeating copies of the opioid peptide products.

High-affinity opioid receptor peptides (dermorphins and deltorphins) have been isolated from frog skins and are quite unusual in having D-amino acids in the sequence. Also, milk-derived casomorphins, hemorphins from hemoglobin and cytochrophins (fragments of cytochrome B), have low affinity for the opioid receptors.

Besides the endogenous peptides, it has been shown that morphine is present in various tissues and body fluids and SH-SY5Y human neuroblastoma cells are capable of producing morphine. The biosynthetic route is similar to that found in *Papaver somniferum*.

19.1.3 NONENDOGENOUS OPIOID RECEPTOR LIGANDS

The synthetic efforts in the opioid field over the last century have mainly been stimulated by the search for a safer alternative to morphine that maintained the analgesic effects but was devoid of respiratory depression and abuse potential. Different medicinal chemistry approaches have been followed in the development of opioid receptor ligands:

- Chemical modification of morphine and related structures (opiates)
- Simplification of the morphine structure
- Dimerization (bivalent ligands)
- Peptides and peptidomimetics

Early development was focused on the first two approaches. Examples of opiates that display similar affinity to all subtypes are shown in the upper part of Figure 19.3. Introduction of bulky substituents to the morphine structure generally yields antagonists, and naloxone and naltrexone are unselective antagonists. *N*-allyl analog nalorphine is an example of a mixed agonist–antagonist. It was originally characterized as an antagonist but later shown to have antagonist activity at MOR but agonist activity at KOR. Nalorphine was one of the first compounds to be extensively tested in the clinic in combination with morphine to find an ideal agonist–antagonist ratio for maximizing analgesics properties and minimizing adverse effects. Buprenorphine is a potent analgesic and partial agonist at the MOR and antagonist at DOR and KOR. Diprenorphine is reported as an unselective antagonist.

An increasing number of subtype-selective ligands has been reported, and a few examples are shown in the lower part of Figure 19.3. Compounds that are μ-selective include morphine that is an agonist and the irreversible antagonist β-FNA. SIOM and NTI are examples of δ-selective antagonists, and gNTI represents a κ-selective antagonist. Interestingly, gNTI was recently shown to have higher affinity toward HEK-293 cells expressing KOR together with DOR or MOR compared to cells expressing only KOR, and the agonist effect of gNTI at the heterodimers KOR/DOR and KOR/MOR could be blocked by antagonists selective against DOR and MOR, respectively. This underlines the importance of heterodimerization and the fact that gNTI is analgesic when injected into the spinal cord but not when injected into the brain could arise from different heteromeric populations.

The development of selective opiates has followed the "message-address" concept. This states that the amino and the aromatic group in the morphine determine the activity (the "message") of the opiates, whereas the lipophilic region around the allylic alcohol confers selectivity (the "address"). This is demonstrated by the conversion of NTI from a δ-selective antagonist into the κ-selective