The very toxic and convulsive alkaloid, strychnine, has been extensively studied pharmacologically. Using electrophysiological techniques and tritiated strychnine for binding studies, strychnine was shown to be an antagonist for the neuroreceptor mediating the inhibitory effect of glycine, through the $glycine_A$ receptor located primarily in the spinal cord.

Acetylcholine is a key transmitter in the central and the peripheral nervous system. Acetylcholine operates through multiple receptors, and the original demonstration of receptor heterogeneity was achieved using the naturally occurring compounds, nicotine and muscarine. Whereas the ionotropic class of acetylcholine receptors binds nicotine with high affinity and selectivity, muscarine specifically and potently activates the metabotropic class of these receptors. Using molecular biological techniques, a number of subtypes of both nicotinic and muscarinic acetylcholine receptors have been identified and characterized (Chapters 12 and 16).

The ryanodine receptor is named after the insecticidal naturally occurring compound, ryanodine. Extensive studies have disclosed that ryanodine interacts with high affinity and in a calcium-dependent manner with its receptor which functions as a calcium release channel. There are three genetically distinct isoforms of the ryanodine receptor which play a role in the skeletal muscle disorder, central core disease.

The sesquiterpene lactone, thapsigargin which is structurally unrelated to ryanodine, also interacts with an intracellular calcium mechanism. Thapsigargin has become the key pharmacological tool for the characterization of the sarco(endo)plasmic reticulum $Ca^{2+}$ ATPase (SERCA). Thapsigargin effectively inhibits this ATPase, causing a rise in the cytosolic calcium level which eventually leads to cell death. Although the SERCA pump is essential for all cell types, attempts to target thapsigargin toward prostate cancer cells have been made based on a prodrug approach (see Chapter 10).

### 1.4.2 Natural Products as Lead Structures

Although a number of biologically active natural products have been indispensable as tools for identification and characterization of pharmacological and potential therapeutic targets, these compounds normally do not satisfy the demands on drugs for therapeutic use (Chapter 7).

Thus, although morphine is used therapeutically, it is not an ideal drug and has, to some extent, been replaced by a number of analogs showing lower side effects and higher degrees of selectivity for subtypes of opiate receptors (Chapter 19). Prominent examples are the μ-selective opiate agonist fentanyl and the experimental tool U50,488 which selectively activates the κ-subtype of opiate receptors (Figure 1.4).

The main psychoactive constituent of *Cannabis sativa*, the highly lipophilic tetrahydrocannabinol (THC), has been a useful tool for the identification of the two cannabinoid receptors, CB1 and CB2 receptors, operated by endocannabinoids. Since different preparations of *C. sativa* have psychoactive effects, health authorities in most countries have been reluctant to accept THC and analogs as therapeutic agents for the treatment of pain and other disease-related conditions. This may change with time, as medicinal chemists have synthesized a number of cannabinoid receptor ligands, including the receptor agonist CP55,940 which is markedly less lipophilic than THC (Chapter 19).

The nicotine acetylcholine receptors (nAChRs) have become important targets for therapeutic approaches to treat pain, cognition disorders, depression, schizophrenia, and nicotine dependence. For several reasons, nicotine has limited utility as a therapeutic agent, and a wide variety of nAChR agonists have been synthesized and characterized (Chapter 16). (–)-Cytisine is a naturally occurring toxin acting as a partial nAChR agonist. Using (–)-cytisine as a lead structure, varenicline was developed as a partial nAChR agonist showing a balanced agonist/antagonist profile for smoking cessation. Muscimol is another example of a naturally occurring toxin which has been extensively used as a lead for the design of specific GABA receptor agonists and GABA uptake inhibitors (Chapter 15). Muscimol which is a 3-isoxazolol bioisostere (see Section 1.4.3.1) of GABA, is a