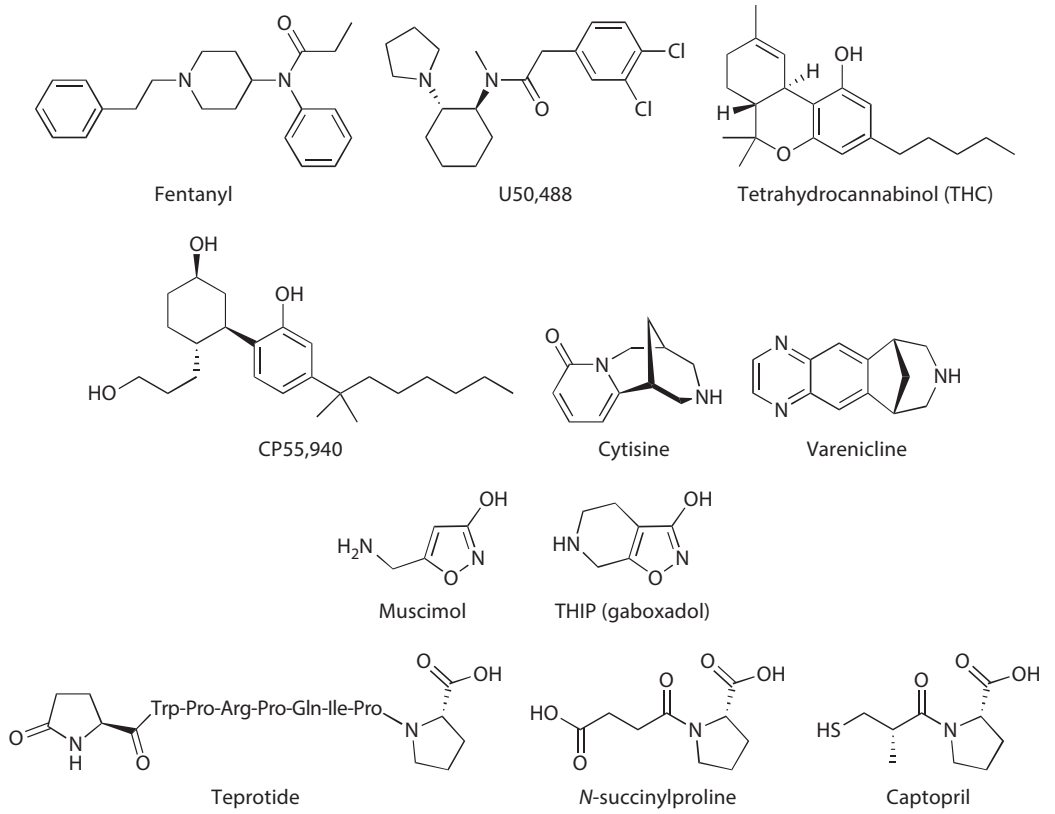

FIGURE 1.4 Chemical structures of fentanyl, U50,488, tetrahydrocannabinol (THC), CP55,940, cytisine, varenicline, muscimol, THIP (gaboxadol), teprotide, *N*-succinylproline, and captopril.

constituent of the mushroom *Amanita muscaria*. Muscimol is toxic, it is metabolically unstable, and it interacts with the different GABA synaptic mechanisms and with a broad range of $GABA_A$ receptor subtypes. The cyclic analog of muscimol, THIP (gaboxadol), is highly selective for the therapeutically interesting extrasynaptic $GABA_A$ receptors. Gaboxadol is a clinically active nonopioid analgesic and a nonbenzodiazepine hypnotic which at present is in clinical trials (see also Chapter 15).

The angiotensin-converting enzyme (ACE) is a zinc carboxypeptidase centrally involved in the regulation of blood pressure and is an important target for therapeutic intervention. Peptide toxins from the Brazilian pit viper, *Bothrops jararaca*, and the synthetic peptide analog, teprotide, are inhibitors of ACE (Figure 1.4), but are not suitable for therapeutic use. Systematic molecular dissection of teprotide led to the nonpeptide ACE inhibitor, *N*-succinylproline which was converted into the structurally related and much more potent analog, captopril, that is now marketed as an effective antihypertensive drug.

1.4.3 Basic Principles in Lead Development and Optimization

Potency, efficacy, and selectivity are essential but certainly not the only parameters to fulfill for a pharmacologically active compound to become a therapeutic drug. A large number of additional requirements have to be met, and the most important ones have been summarized in the acronym, ADME or ADME-Tox (ADME and toxicity). Obviously, the drug must reach the site of action in a timely manner and in sufficient concentration to produce the desired therapeutic effect.