1.4 DISCOVERY OF DRUG CANDIDATES

Prehistoric drug discovery started with higher plant and animal substances, and this continues today to be a fruitful source of biologically active molecules frequently belonging to unanticipated structural types. Adding to the long list of classical plant products that are still used in modern medicine, one can list many substances of more recent origin, including antibiotics such as penicillins, cephalosporins, tetracyclines, aminoglycosides, various glycopeptides, and many others (Chapter 23). Anticancer agents of natural origin comprise taxol, camptothecin, vinca alkaloids, doxorubicin, and bleomycin (Chapter 21). Among immunosuppressant agents, cyclosporine and tacrolimus deserve special mention.

Other sources of lead structures and drug candidates include endogenous compounds and other compounds with known activity at the target(s) in question, as well as screening programs. The role of natural products in target identification and as lead structures is further described in the following sections, whereas examples of use of other sources are described in different chapters throughout the textbook.

1.4.1 Natural Products: Role in Target Identification

Many naturally occurring compounds have potent and/or selective activity on different biological targets and are of potential therapeutic value. Most often these activities are toxic effects, since these compounds are either animal venoms (e.g., snake poison, spider, or wasp toxins) which can paralyze or kill prey or plant toxins preventing animals to eat the plants. However, toxicity is generally a matter of dose, and in some instances a toxin can be used as a drug in the appropriate dose.

Various biologically active natural products have played a key role in the identification and characterization of receptors, and such receptors are often named after these compounds (Chapter 12). Morphine is a classical example of a natural product used for receptor characterization. Radiolabeled morphine was shown to bind with high affinity to receptors in the nervous system, and these receptors are known as opiate receptors. More than three decades ago, the physiological relevance of these receptors was documented by the findings that endogenous peptides, notably enkephalins and endorphins, served as receptor ligands (agonists). Analogs of morphine have been useful tools for the demonstration of heterogeneity of opiate receptors (Chapter 19) (Figure 1.3).

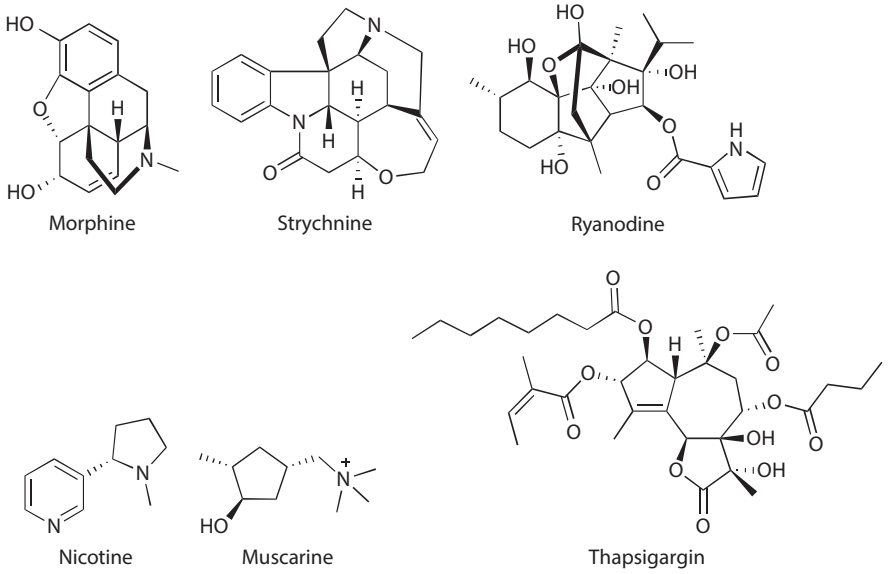

FIGURE 1.3 Chemical structures of morphine, strychnine, ryanodine, nicotine, muscarine, and thapsigargin.