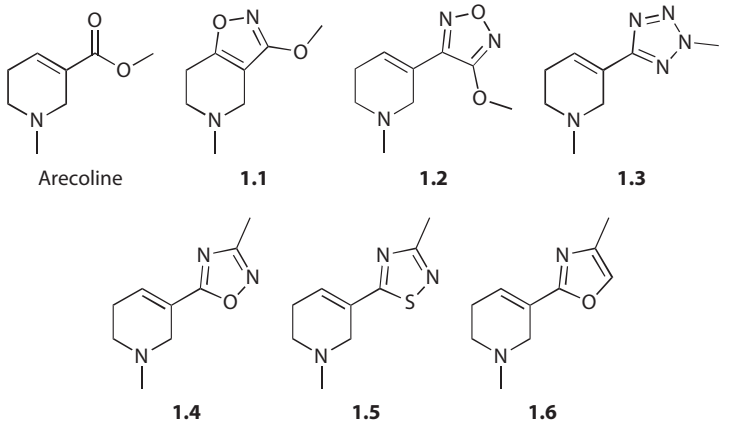

FIGURE 1.5 Chemical structures of arecoline and analogs.

is often considered to be qualitative and intuitive, and there are numerous and a constantly growing number of such bioisosteres used effectively in drug design projects (see, e.g., Chapters 15 and 16).

The conversion of the muscarinic acetylcholine receptor agonist arecoline, containing a hydrolysable ester group, into different hydrolysis-resistant heterocyclic bioisosteres is illustrated in Figure 1.5. The annulated (**1.1**) and nonannulated (**1.2** and **1.3**) bicyclic bioisosteres are potent muscarinic agonists. Similarly, compounds **1.4** and **1.5** interact potently with muscarinic receptors as agonists, whereas **1.6**, in which the 1,2,4-oxadiazole ester bioisosteric group of **1.4** is replaced by an oxazole group, shows reduced muscarinic agonist effects. Thus, the electronic effects associated with these heterocyclic rings appear to be essential for muscarinic activity.

It must be emphasized that a bioisosteric replacement strategy which has been successful for a particular group of pharmacologically active compounds, may not necessarily be effectively used in other groups of compounds active at other pharmacological targets.

1.4.3.2 Stereochemistry

Receptors, enzymes, and other pharmacological targets which by nature are protein constructs, are highly chiral. Other targets like DNA and other macromolecules in the human body are all build up of chiral building blocks. Thus, it is not surprising that chirality in the drug structures generally plays an important role in pharmacological responses. In racemic drug candidates, the desired pharmacological effect typically resides in one enantiomer, whereas the other stereoisomer(s) are pharmacologically inactive or possess different pharmacological effects. Thus, chiral drugs should preferentially be resolved into stereochemically pure isomers prior to pharmacological examination. Since many, especially of older date, synthetically prepared chiral biologically active compounds have been described pharmacologically as racemates, much of the older pharmacological literature should be read and interpreted with great care. At best the nonactive stereoisomer in a racemate is inactive and can be looked upon as chemical waste. However, with the introduction of an "inactive enantiomer" by therapeutic application of a racemic drug, one always runs the risk of introducing undesired and unknown activities and side effects. The most significant example of undesired effects of a racemic drug is the tragic case of thalidomide (Figure 1.6a). Racemic thalidomide was developed in the 1950s and was used as a mild sleeping agent and to treat morning sickness in pregnant women. Unfortunately, the drug was teratogenic and gave serious fetal abnormalities. Later it was discovered that the (*S*)-enantiomer possessed the teratogenic effect and the (*R*)-enantiomer possessed the desired activity. However, the studies also revealed that the enantiomers of thalidomide racemize under physiological conditions; thus the use of pure (*R*)-form was not a solution. This caused major changes for the legislative requirements for the introduction of chiral