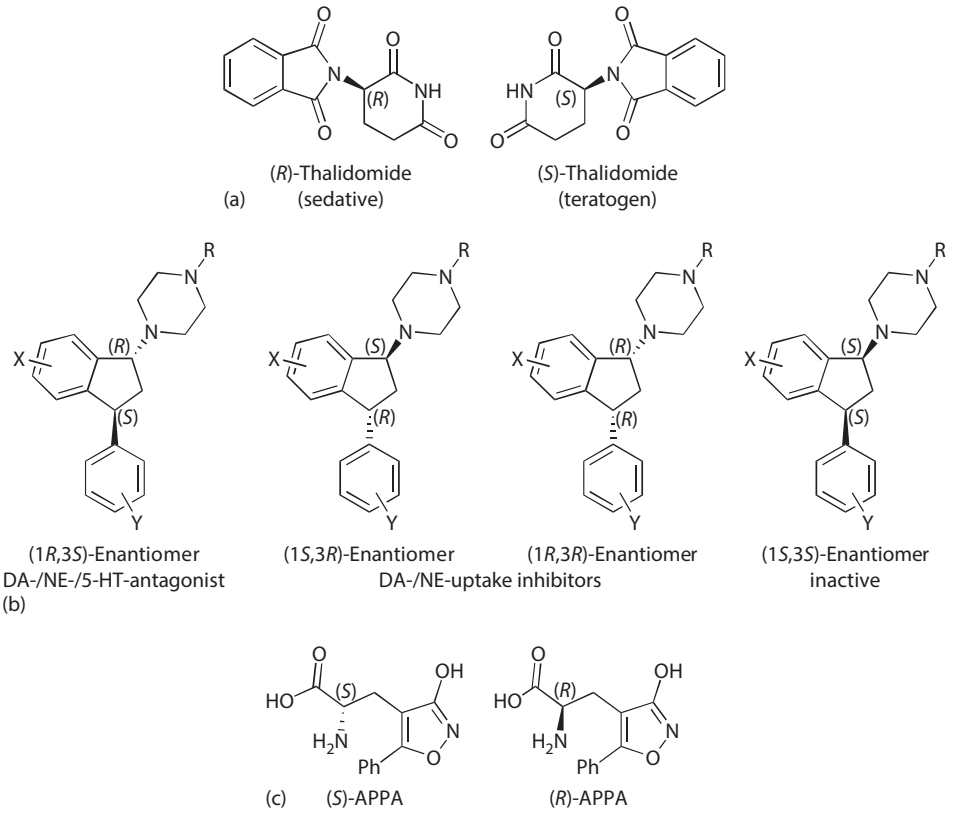

FIGURE 1.6 Chemical structures of (a) (*R*)- and (*S*)-thalidomide, (b) the four stereoisomers of 1-piperazino-3-phenylindans, and (c) the two enantiomers of the phenyl analog of AMPA (APPA).

drugs subsequently and mandatory test for teratogenic activity. Thalidomide was off the market for many years, but has been introduced again for treatment of leprosy and other diagnoses, but under very strict guidelines.

Figure 1.6 exemplifies the importance of stereochemistry in studies of the relationship between structure and pharmacological activity (SAR studies). Figure 1.6b shows four stereoisomers which are two pairs of enantiomers of two diastereomeric compounds. These 1-piperazino-3-phenylindans were synthesized, resolved, structurally analyzed, and pharmacologically characterized as part of a comprehensive drug research program in the field of central biogenic amine neurotransmission. Whereas one of these stereoisomers turned out to be inactive, two of them were inhibitors of dopamine (DA) and norepinephrine (NE) uptake, and one isomer showed antagonist effects at DA, NE, and serotonin (5-HT) receptors. It is evident that a pharmacological characterization of a synthetic mixture of these compounds would be meaningless.

The 3-isoxazolol amino acid, APPA (Figure 1.6c), is an analog of the standard agonist, AMPA, for the AMPA subtype of excitatory glutamate receptors (Chapter 15). APPA was tested pharmacologically as the racemate which showed the characteristics of a partial agonist at AMPA receptors. Subsequent pharmacological characterization of the pure enantiomers quite surprisingly disclosed that (*S*)-APPA is a full AMPA receptor agonist, whereas (*R*)-APPA turned out to be an AMPA antagonist. This observation prompted intensive pharmacological studies, and as a result it was demonstrated that administration of a fixed ratio of an agonist and a competitive antagonist always provides a partial agonist response at an efficacy level dependent on the administered ratio of compounds and their relative potencies as agonist and antagonist, respectively. This phenomenon