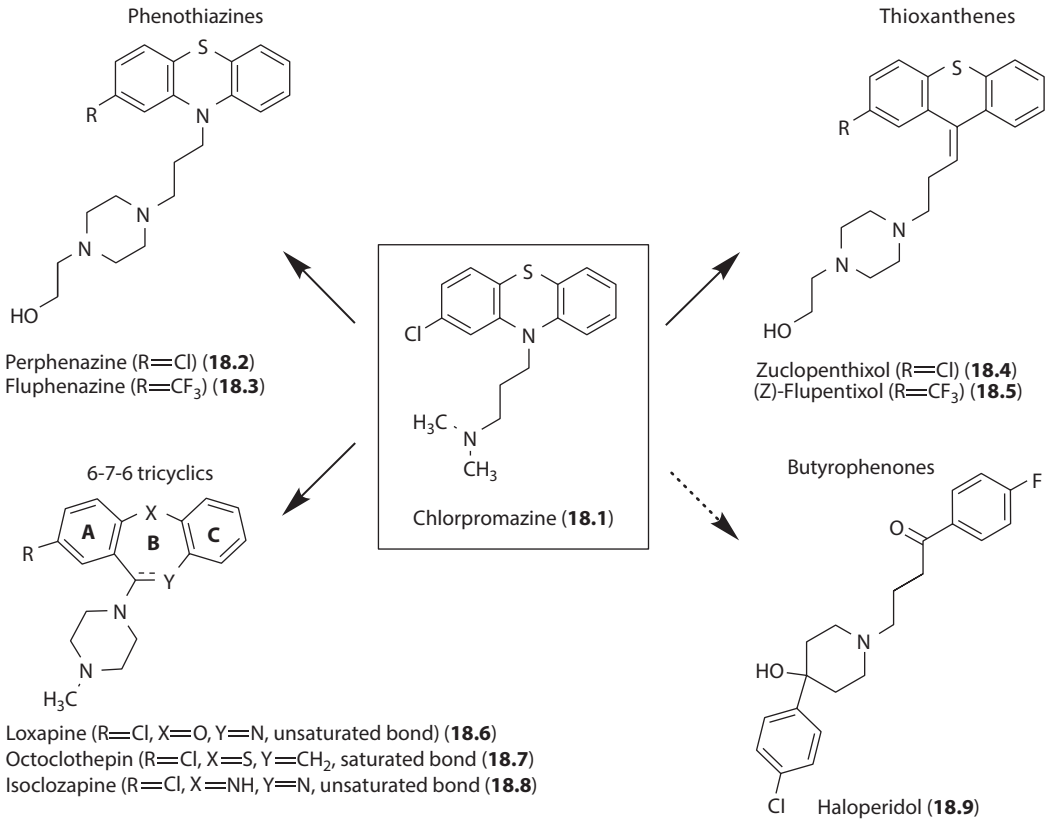

FIGURE 18.1 Classical antipsychotic drugs.

18.2.2 Classical Antipsychotic Drugs

Chlorpromazine was discovered in the beginning of the 1950s, and the structure of chlorpromazine with its phenothiazine backbone was an excellent lead for medicinal chemists. Thus, the modification of chlorpromazine without changing the phenothiazine backbone led to a number of drugs such as perphenazine (**18.2**) and fluphenazine (**18.3**) (Figure 18.1). Medicinal chemists also replaced the phenothiazine backbone with other tricyclic structures, and these modifications led to other classes of classical antipsychotic drugs such as the thioxanthenes and the 6–7–6 tricyclics.

Lundbeck in Denmark investigated in particular the thioxanthene backbone, and this work resulted in drugs such as zuclopenthixol (**18.4**) and (*Z*)-flupentixol (**18.5**) (Figure 18.1). The 6–7–6 tricyclic backbone has also led to a number of classical antipsychotic drugs such as loxapine (**18.6**), octoclothepin (**18.7**), and isoclozapine (**18.8**) (Figure 18.1). The R group found in all of these compounds is called the "neuroleptic substituent," and this substituent increases the D_2 receptor affinity/antagonism relative to unsubstituted molecules and is essential for potent neuroleptic effect.

In the late 1950s, researchers at Janssen discovered an entirely new class of classical antipsychotic drugs without a tricyclic structure, namely, the butyrophenones. Haloperidol (**18.9**, Figure 18.1) is the most prominent representative of this class of compounds, and today haloperidol is considered the archetypical classical antipsychotic drug.

The classical antipsychotic drugs were all discovered using in vivo animal models, as the current knowledge about receptor multiplicity and in vitro receptor-binding techniques were unknown at that time. However, many of the in vivo models which were used at that time as predictive for antipsychotic effect, are today considered more predictive of various side effects, e.g., EPS, and in