It may not be obvious to use an SNI as template structure for an SSRI. However, in the first series synthesized, two compounds (**18.31** and **18.32**, Table 18.2) without the dimethylation of the phthalane ring showed a tendency for increased 5-HT reuptake, and in accordance with the structure–activity relationship (SAR) studies mentioned earlier for tricyclics, the *N*,*N*-dimethyl derivative **18.32** was the more potent compound. Therefore, compound **18.32** became a template structure for further structural investigation.

In this phase of the project, neuronal test models for measuring reuptake were not available, so 5-HT reuptake inhibition was measured as inhibition of tritiated 5-HT into rabbit blood platelets, while inhibition of NE reuptake was measured ex vivo as inhibition of tritiated NE into the heart of the mouse (Table 18.2). Although these models were not directly comparable, they were acceptable for the discovery of selective compounds.

The introduction of a chloro substituent into the template structure further increased 5-HT reuptake and decreased NE reuptake inhibition (**18.32** versus **18.34**), in accordance with observations by Carlsson that halogen substituents in both zimelidine (**18.43**, Figure 18.5) (see the following) and in imipramine derivatives (clomipramine, **18.21**, Figure 18.3) increased 5-HT reuptake. Indeed, the dichloro derivative **18.35** proved to be a selective 5-HT reuptake inhibitor. So the goal of obtaining an SSRI from an SNI was achieved very fast (in 1971), when less than 50 compounds had been synthesized.

The SAR were further explored, and it was established that high activity was generally found in 5,4′-disubstituted compounds where both substituents were halogen or other electron-withdrawing groups. Cyano-substituted compounds were obtained by the reaction of the bromo precursors

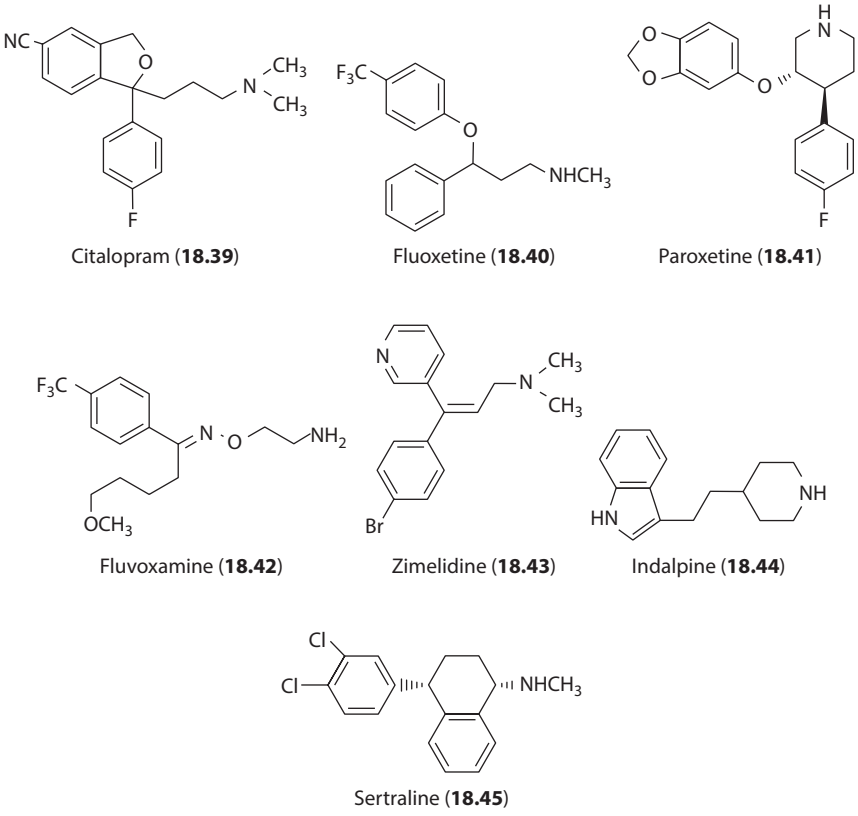

FIGURE 18.5 Selective serotonin reuptake inhibitors.