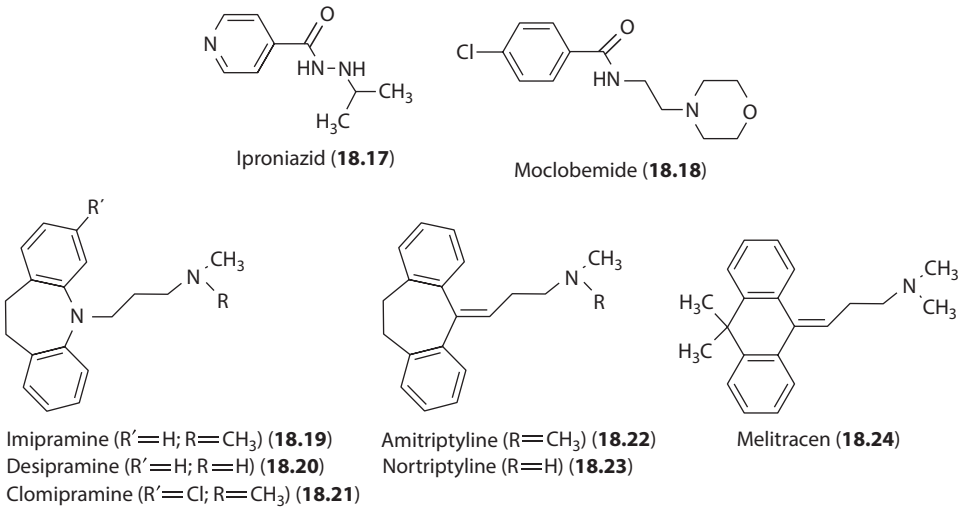

FIGURE 18.3 Antidepressant drugs from MAO inhibitor and tricyclic classes.

18.3.3 Selective Serotonin Reuptake Inhibitors

Nortriptyline (**18.23**) is a relative selective NE reuptake inhibitor, while the corresponding dimethyl derivative, amitriptyline (**18.22**) (Figure 18.3), is a mixed 5-HT/NE reuptake inhibitor with concomitant high affinity for postsynaptic receptors as well. The same is true for the corresponding pair desipramine (**18.20**)/imipramine (**18.19**). Swiss psychiatrist Paul Kielholz coupled these observations to the clinical profiles of these drugs, and Swedish scientist Arvid Carlsson noticed that the tertiary amine drugs, which were mixed 5-HT and NE reuptake inhibitors, were "mood elevating," while the secondary amines, being primarily NE reuptake inhibitors, increased more "drive" in the depressed patients. As the foremost quality of an antidepressant drug should be mood elevation (elevation of drive before mood could induce a suicidal event), Carlsson advocated for the development of selective 5-HT reuptake inhibitors. Consequently, a number of pharmaceutical companies initiated drug discovery programs aiming at design of such drugs in the early 1970s.

18.3.4 Discovery of Citalopram

In the mid-1960s, chemists at Lundbeck were looking for more potent derivatives of the TCAs amitriptyline, nortriptyline, and melitracen (**18.24**) which the company had developed and marketed previously. The trifluoromethyl group had in other in-house projects proved to increase potency in thioxanthene derivatives with antipsychotic activity (see Figure 18.1), and it was therefore decided to attempt to synthesize the 2-CF_3 derivative of melitracen (**18.26**, Figure 18.4). The precursor molecule **18.25** was readily synthesized, but attempts to ring-close it in a manner corresponding to the existing melitracen method, using concentrated sulfuric acid, failed. However, another product was formed which through meticulous structural elucidation proved to be the bicyclic phthalane (or dihydroisobenzofuran) derivative **18.27**. Fortunately, this compound was examined in models for antidepressant activity and was very surprisingly found to be a selective NET inhibitor. Some analogs were synthesized, among them two compounds that later got the International Nonproprietary Names talopram (**18.28**) and talsupram (**18.29**). These compounds are still among the most selective NE reuptake inhibitors (SNIs) ever synthesized (Figure 18.4 and Table 18.2).

Both talopram and talsupram were investigated for antidepressant effect in clinical trials but were stopped in phase II for various reasons, among which was an activating profile in accordance with their potent NE reuptake inhibition. A project was, therefore, started in the beginning of 1971 with the aim of discovering an SSRI from the talopram structure.