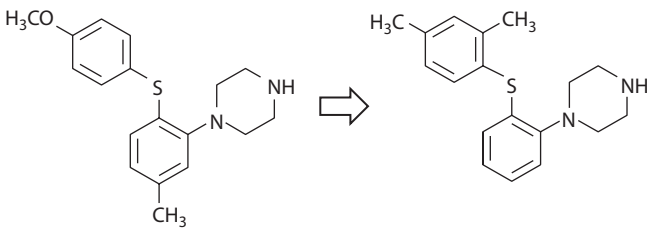
18.4.2 Discovery of Vortioxetine

In the early 1990s, preclinical and clinical research indicated that the combination of a SERT inhibitor with an antagonist of somatodendritic 5-HT_{1A} autoreceptors resulted in a significantly larger increase in extracellular 5-HT levels in rat brain than seen for SSRIs alone. In addition, chronic dosing studies indicated that the maximum increase in 5-HT could be achieved faster for the drug combination than with the SSRI alone. Since the combination also led to a more rapid antidepressant effect and improved response rates in a clinical study, a search for single drugs modulating this combination of targets was initiated by many pharmaceutical companies. However, it turned out to be difficult to find such compounds, especially because it was not easy to define and obtain the right level of functional activity at the 5-HT_{1A} receptor. Vilazodone is the only approved antidepressant drug that so far has come out of this specific effort.

At Lundbeck, the effort toward a combined 5-HT_{1A} receptor antagonist and SERT inhibitor led to an increased understanding of which 5-HT receptors, apart from the 5-HT_{1A} receptor, might also augment the SSRI-induced increase in extracellular 5-HT. One such project was started in 2001 with the aim of finding a combined 5-HT_{2C} receptor antagonist and SERT inhibitor. A focused screen using the Lundbeck monoamine compound library led to the identification of the lead compound **18.46** (Table 18.4) which displayed the desired in vitro pharmacodynamic profile. Compound **18.46** was tested in a rat model that was established to determine the change in 5-HT levels in the brain after acute treatment (i.e., "acute microdialysis model"). Compound **18.46** significantly increased the extracellular 5-HT levels beyond that seen with an SSRI. However, compound **18.46** turned out to have an unsatisfactory in vitro DMPK profile due to its poor metabolic stability in human microsomes and potent inhibition of the cytochrome P450 isozyme CYP2D6.

Compound **18.47** (Table 18.4), later known as vortioxetine, was discovered during the lead optimization program and was initially characterized as having combined SERT inhibition and 5-HT_{2C} receptor activity (Table 18.4). As vortioxetine displayed a suitable in vitro DMPK profile, it was tested in the acute rat microdialysis model, where it increased the extracellular 5-HT level beyond

TABLE 18.4
From Lead Compound to Vortioxetine



Assay	18.46	Vortioxetine (18.47)
SERT (IC_{50}, nM)	7.9	5.3/5.4[a]
5-HT_{2C} (K_i, nM)	13	180[b]
5-HT_{1A} (K_i, nM)	4000	39/15[a]
5-HT_{3A} (K_i, nM)	190	23/3.7[a]
Cl_{int} (L/min)[c]	2.8	0.5
CYP2D6 (IC_{50}, nM)	0.1	9.8

Source: Data are from Bang-Andersen, B. et al., *J. Med. Chem.*, 54, 3206, 2011.

[a] Data from different assays.

[b] Published value which is higher than that initially measured.

[c] Liver blood flow 1.4 L/min.