TABLE 18.3
Effect of Selective Serotonin Reuptake Inhibitors, Talopram, and Talsupram on the Inhibition of Reuptake of 5-Hydroxytryptamine, Norepinephrine, and Dopamine

	Uptake Inhibition IC_{50} (nM)			Ratio	
Compound	**5-HT**	**NE**	**DA**	**NE/5-HT**	**DA/5-HT**
Citalopram (**18.39**)	3.9	*6,100*	*40,000*	1,560	10,300
Escitalopram (*S*-**18.39**)	2.1	2,500	65,000	1,200	31,000
R-citalopram (*R*-**18.39**)	275	6,900	54,000	25	200
Indalpine (**18.44**)	2.1	2,100	1,200	1,000	570
Sertraline (**18.45**)	*0.19*	*160*	*48*	840	250
Paroxetine (**18.41**)	*0.29*	*81*	*5,100*	280	17,600
Fluvoxamine (**18.42**)	*3.8*	*620*	*42,000*	160	11,000
Zimelidine (**18.43**)	56	3,100	26,000	55	460
Fluoxetine (**18.40**)	*6.8*	*370*	*5,000*	54	740
Talopram (**18.28**)	1,400	2.5	44,000	0.0017	0.00006[a]
Talsupram (**18.29**)	770	0.79	9,300	0.0010	0.00008[a]

Source: Data in italics are from Hyttel, J., *Int. Clin. Psychopharmacol.*, 9(Suppl. 1), 19, 1994; Remaining data are from Lundbeck Screening Database, H. Lundbeck A/S, Valby.

[a] NE/DA.

induce an influenza-like symptom in 1%–2% of the patients which in rare cases (one of 10,000) resulted in the so-called Guillain–Barré syndrome. The drug was withdrawn in 1983 after 1½ years on the market. Indalpine (**18.44**) induced agranulocytosis in 1 of 20,000 patients and was withdrawn in 1984.

All the marketed SSRIs (except sertraline) were discovered in the first half of the 1970s (Figure 18.5), meaning that the companies lacked information regarding the structural classes their competitors were developing. Accordingly, this parallel development led to a rather diverse set of structural classes for the SSRIs. However, they were all selective 5-HT reuptake inhibitors (Table 18.3), although their selectivity ratios vary significantly, citalopram and escitalopram being the most SERT selective compounds. In general, the SSRIs have low affinity for DA, NE, and 5-HT receptors, although exceptions exist. With regard to interaction with cytochrome P450 enzymes, there are vital differences, e.g., paroxetine and fluoxetine have significant affinity for CYP2D6.

18.4 COMBINED RECEPTOR AND TRANSPORTER LIGANDS

18.4.1 Multimodal Antidepressant Drugs

The SSRI and SNRI antidepressant drugs made pharmacotherapy of depression safe and effective, but several medical needs remain to be addressed (see Section 18.3.1). Two recently approved multimodal antidepressants (vilazodone and vortioxetine) were designed to simultaneously modulate transporters and receptors (a multimodal drug is a compound interacting with ≥2 target classes, e.g., transporters and receptors) and thereby address some of those medical needs. Vortioxetine (Brintellix®) was approved for the treatment of MDD by the European Medicines Agency and the US Food and Drug Administration in 2013, whereas vilazodone (Viibryd®) is approved only in the United States. Vortioxetine was launched in the United States in January 2014 and subsequently in markets all over the world. The rationale behind the design of multimodal antidepressant drugs will be discussed, as will be the key steps in the development of vortioxetine.