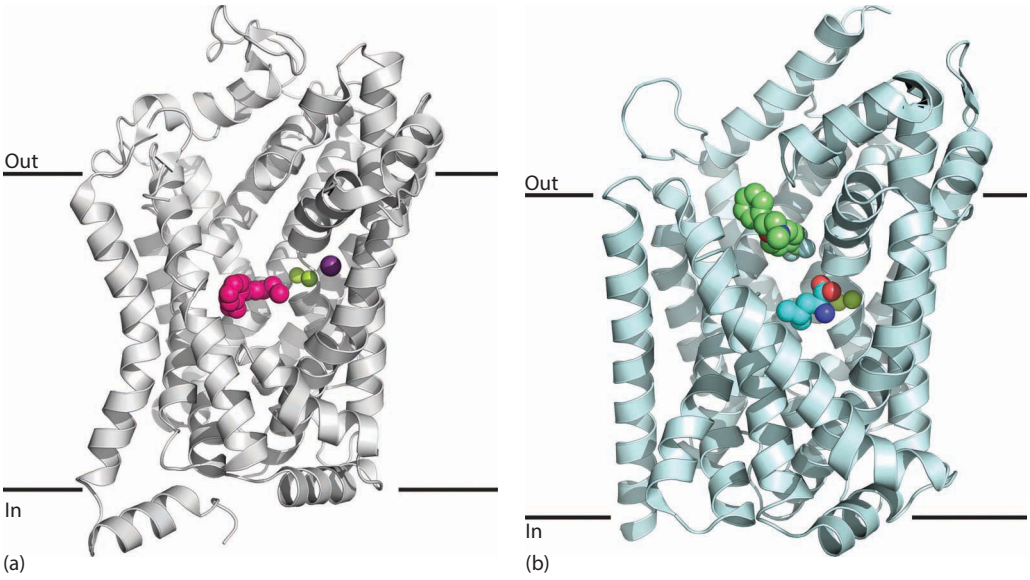

FIGURE 18.8 X-ray structures of (a) the DAT in complex with nortriptyline in the high-affinity primary binding site (PDB:4M48). The ligand, two Na^+ ions, and a Cl^- ion are shown as van der Waals spheres in magenta, yellow, and purple, respectively. The primary binding site is located at the core of the transporter which is locked in an outward open conformation with nortriptyline wedged between transmembrane helices 1, 3, 6, and 8, blocking the transporter from binding substrate and from isomerizing to an inward-facing conformation. (b) The LeuT in complex with substrate in the primary site and the selective serotonin reuptake inhibitor (*R*)-fluoxetine situated in an extracellular vestibule ~13 Å above the substrate binding pocket (PDB:3GWV). The substrate, the ligand, and two Na^+ ions are shown as van der Waals spheres in cyan, green, and yellow, respectively. The leucine transporter topology is shown in Chapter 14, Figure 2 (the DAT has the same topology). (Courtesy of Ana Negri Martinez, H. Lundbeck A/S, Copenhagen-Valby, Denmark.)

the substrate in the primary site and the SSRIs sertraline or fluoxetine situated in an extracellular vestibule ~13 Å above the substrate binding pocket has guided researchers to investigate whether the corresponding position in hSERT could be the allosteric site. Molecular modeling studies using a LeuT-based SERT homology model (induced fit docking to both the primary and allosteric sites in iteration with molecular dynamics simulations) were used to identify residues that could be involved in allosteric binding. The results of these studies have in turn guided steric hindrance mutagenesis studies of selected residues in hSERT that did indeed reduce allosteric binding of escitalopram and clomipramine. These studies support the hypothesis that the hSERT allosteric site is positioned in the extracellular vestibule and suggest that ligand binding to the allosteric site hinders both association and dissociation of antidepressants to and from the primary binding site (Figure 18.8).

18.6 CONCLUDING REMARKS

DA, 5-HT, and NE receptors and transporters have shown their relevance as drug targets over many years. The multimodal antidepressants vilazodone and vortioxetine further support the continued success of these targets, and cariprazine and brexpiprazole illustrate that this might continue. Recent years have led to an explosion in the understanding of the structure and function of these membrane-bound receptors and transporters which will enable a more rational design of new compounds. However, only the future can tell whether these new discoveries will result in novel and effective pharmacotherapies based on the DA and 5-HT systems.