mode prediction for compounds like vortioxetine. The model can then be used for structure-based design purposes, including virtual screening to identify novel 5-HT_1 receptor ligands. With known GPCR protein structures, rational approaches become possible not only to identify and optimize the potency of new ligands, but to also control selectivity and kinetics (residence time). Drugability analyses of GPCR ligand binding sites have shown the importance of lipophilic hotspots in ligand binding, and knowing where these are located enables the design of ligands with drug-like physicochemical properties. Lipophilicity is a key property of most CNS drugs, and through structure-based design it can be used effectively for both potency and selectivity, avoiding less-productive presence that easily leads to drug candidates with too high a logP.

18.5.2 Modeling of Transporter-Ligand Binding at the Primary Site of BATs

Structure-based design approaches were not applicable when the first antidepressant drugs were developed because no protein structures sufficiently similar in sequence and function to human neurotransmitter transporters were available at the time. Thus, less powerful ligand-based methods like pharmacophore modeling were applied. In 2005, the crystal structure of a prokaryote (*Aquifex aeolicus*) LeuT with leucine bound within the protein core was published (see Chapter 14). The LeuT is a homolog of the BATs and belongs to the same transporter family. The overall sequence identity between LeuT and SERT is ~20% which is in the low end for "safe homology modeling," and, in particular, for ligand design. This structure was, nevertheless, a significant improvement over previous templates that do not belong to the same transporter family as the BATs. Publication of the structure initiated a cascade of homology modeling studies proposing 3D structural models for

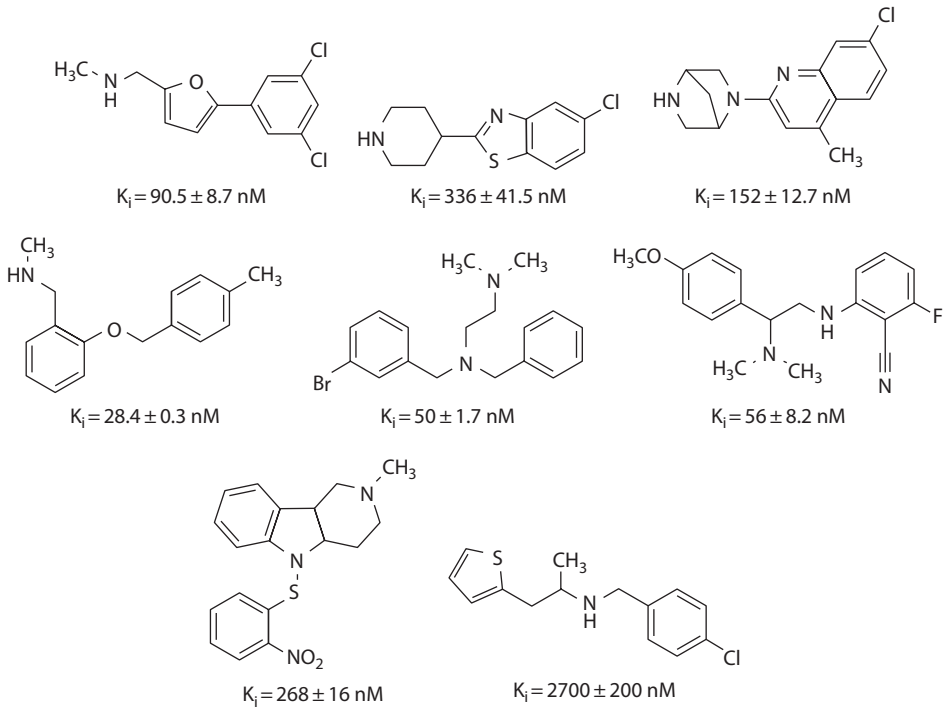

FIGURE 18.6 Structures and binding affinities of novel SERT compounds found by virtual screening. The compounds have no or little structural resemblance to known SERT binders. LeuT-based SERT homology models were used in the virtual screening cascade, demonstrating the power of virtual screening as a method to identify new chemical matter. Binding affinities were measured by inhibition of specific [^{3}H]-citalopram binding to SERT. (Data and structures are from Gabrielsen, M. et al., *J. Chem. Inf. Model*, 54, 933, 2014.)