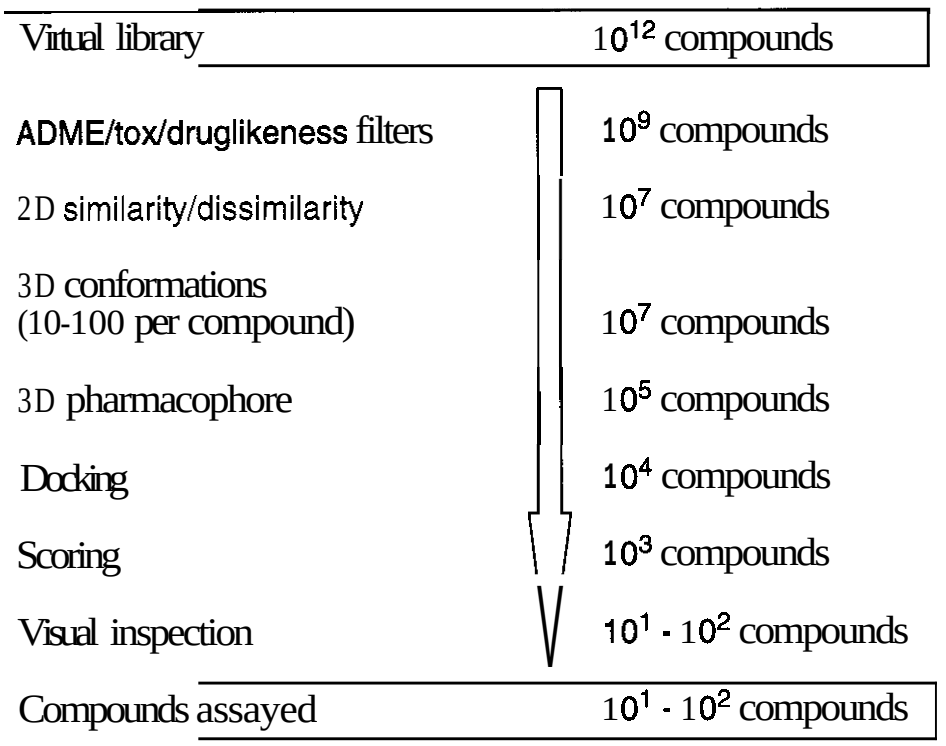

Figure 6.21. Virtual screening filter cascade.

marking hydrogen-bond donors/acceptors, and so forth, are sometimes internally included in the docking software (e.g., in FlexX) and sometimes done separately (e.g., DOCK).

Because of the large number of molecules, manual steps in the preparation of ligand databases obviously have to be avoided. Starting typically from 2D structures, bond types have to be checked, protonation states must be determined, charges must be assigned, and solvent molecules removed. 3D coordinates can be generated using a program such as CONCORD or CORINA (74) (see Section 2.3.2). Next, site points for hydrogen-bonding interactions have to be assigned and rotational barriers must be calculated. These tasks are sometimes included in the docking program (e.g., FlexX).

The docking calculation is typically done for one ligand at a time. Depending on optimization and sampling parameters as well as on the flexibility of the compound, typically between a few seconds and a few minutes of CPU time are needed to dock a ligand. Because the individual docking events are independent of each other, they can run on parallel hardware. Task schedulers that distribute ligand docking on available CPUs are used in many docking programs.

Postprocessing steps of hits may include refinement of placement using MD techniques, specific pharmacophore-based filters that penalize certain features, such as unformed hydrogen bonds or other constraints that were not met in the primary scoring function. Because of the limitations of scoring functions, a postscoring protocol can be used to reach consensus about hits (discussed above). The recognition of known active ligands mixed within the database can be used to find an appropriate threshold for separating the top-ranking compounds from the rest of the database.

2.5 Filter Cascade

Virtual screening is the process of reducing a given database as quickly and efficiently as possible to a small number of putative lead compounds for a given drug discovery project. The techniques described above form a cascade of different filter functions that are ordered by their speed. Fast ADMET filters are followed by 2D and 3D pharmacophore filters and finally by docking and scoring methods. Figure 6.21 shows a scheme of a possible virtual screening filter cascade.

3 APPLICATIONS

3.1 Identification of Novel DAT Inhibitors through 3D Pharmacophore-Based Database Search

The dopamine transporter (DAT) is a 12-transmembrane helix protein that plays a critical role in terminating dopamine neurotrans-