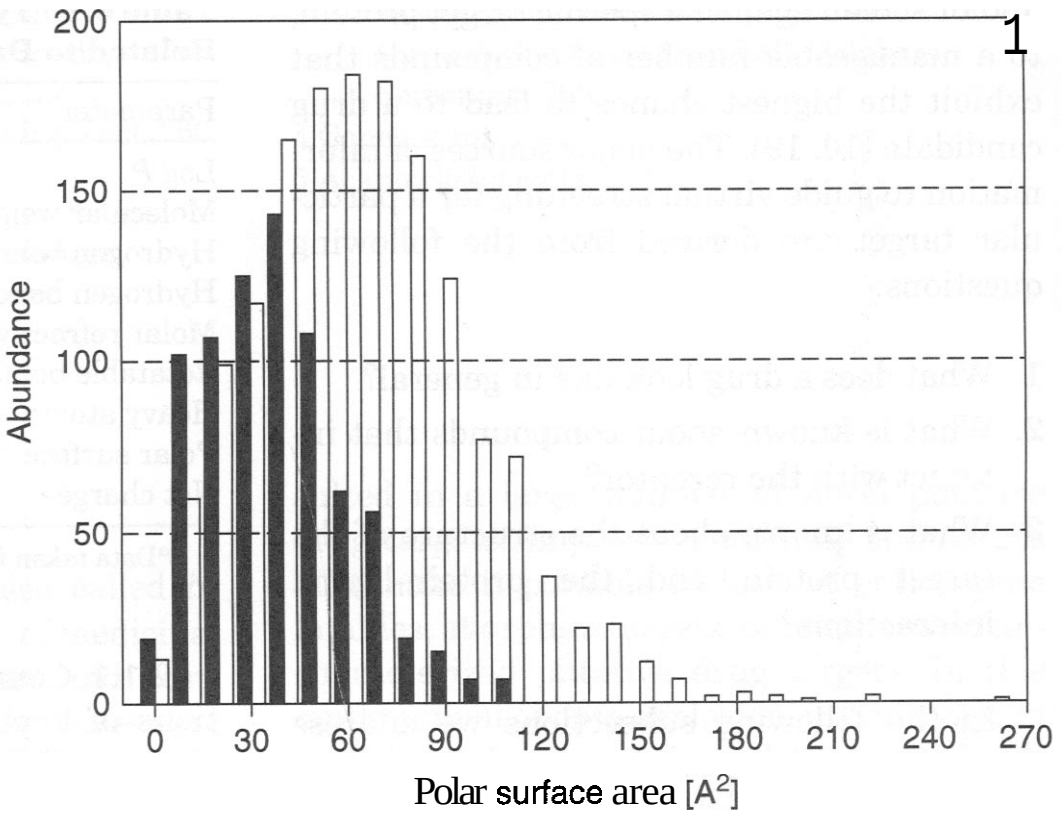

Figure 6.1. Distribution of polar surface area for 776 orally administered CNS drugs (black bars) and for 1590 orally administered non-CNS drugs (white bars) that have reached clinical phase II efficacy studies (35).

< 120 Å²), especially if the compound lies outside the optimal region for several descriptors (e.g., MW > 500 and Clog P > 5).

Simple descriptors as described above are quickly calculated and counted. Therefore, after typically removing compounds with atoms other than C, N, O, S, H, P, Si, Cl, Br, F, and I, counting schemes present the first filter in virtual screening approaches.

2.1.2 Functional Croup Filters. Reactive, toxic, or otherwise unsuitable compounds, such as natural product derivatives, are removed using specific substructure filters. Figure 6.2 shows a subset of substructures that lead to the dismissal of compounds in virtual screening. Typical reactive functional groups include, for example, reactive alkyl halides, peroxides, and carbazides. Unsuitable leads may include crown ethers, disulfides, and aliphatic methylene chains seven or more long. Unsuitable natural products may include quinones, polyenes, or cycloheximide derivatives. A list of such fragments coded in Daylight SMARTS is given, for example, by Hann and coworkers (36). It should be noted, however, that natural product derivatives are not always unsuitable leads.

Screening out compounds that contain certain atom groups associated with toxicity provides a practical and fast way to reduce large databases; however, it is only a crude approximation for eliminating potentially toxic compounds. Better descriptions of toxicity may be provided by structure-based methods to assess toxicity of compounds. They draw primarily from mutagenicity, carcinogenicity, and acute toxicity databases assembled, for instance, by the National Toxicology Program (37) and the Toxic Effect of Chemical Substances database, RTECS (38). CASETox (39), TOPKAT (40), and DEREK (41) are commercial software

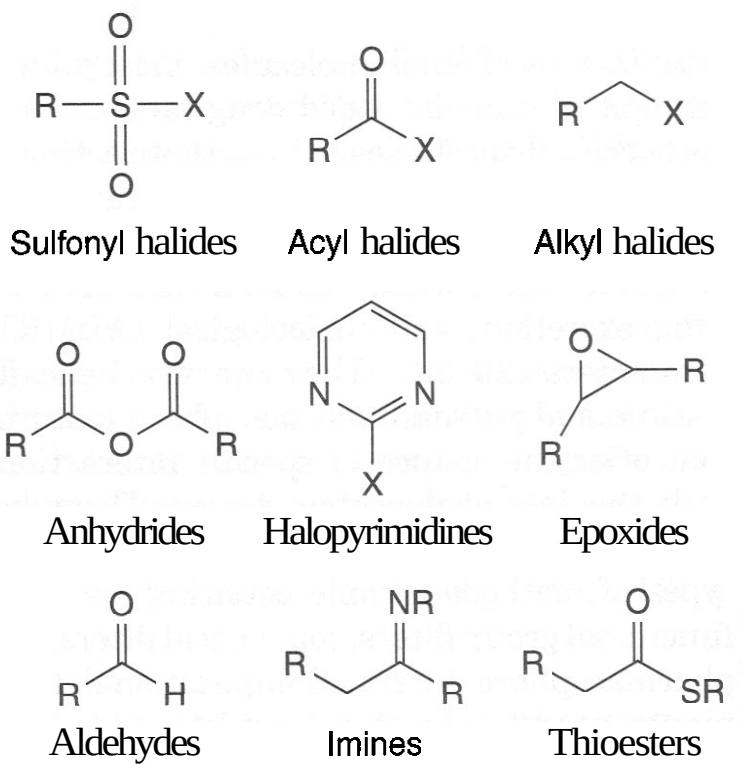

Figure 6.2. Selection of reactive functional groups that should be removed from a virtual screen (examples taken from Ref. 212).