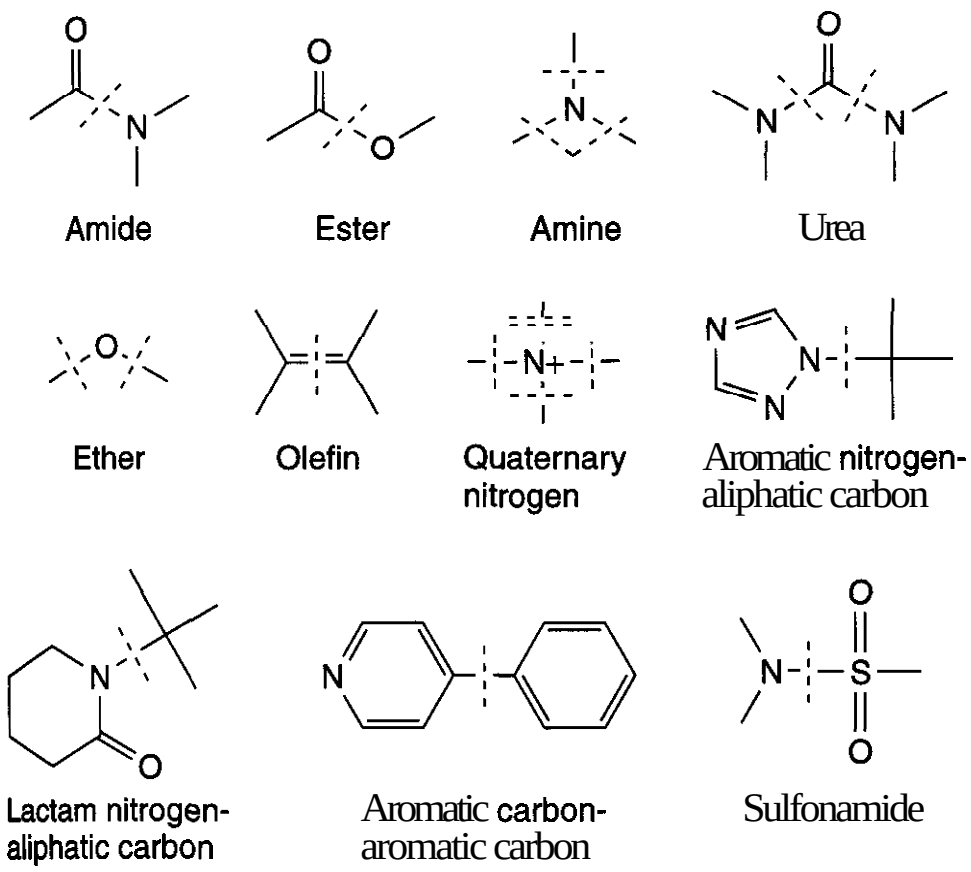


**Figure** 6.7. Retrosynthetic reactions in RECAP.

droxyl, methoxy, chloro, methylamine, primary amine, carboxylic acid, fluoro, and sulfone. Most molecules possess between one and five side-chains; more than 20% of the drugs stored in the CMC have two side chains per molecule.

For the analysis of virtual libraries according to the presence or absence of druglike frameworks, side-chains or structural motifs can be used for virtual screening. This idea has been extended in RECAP (retrosynthetic combinatorial analysis procedure), a technique that identifies common motifs in drugs based on fragmenting molecules around bonds formed by common reaction (46) (Fig. 6.7). Extrading rules from RECAP for virtual screening represents a possible way of addressing the questions of ease of synthesis of compounds. A similar approach to assess the occurrence of structural motifs in drug molecules was presented by Wang and Ramnarayan, who developed the concept of multilevel chemical compatibility (MLCC) between a drug database and a test molecule as a measure for druglikeness. In the MLCC method a compound is recognized as druglike if all of its topological motifs occur in other known drugs.

**2.1.4 Pharmacophore Point Filter.** The topological drug fragmentation approaches discussed above suggest that the occurrence of a relatively small number of frameworks (ring structures and linkers), an even smaller number of side chains, and a small number of polar groups characterize drugs very well. Although drugs and nondrugs are not completely distinguishable, it has been observed that drugs differ somewhat from nondrugs in their possession of hydrophobic moieties that are well functionalized. Non-, drugs often contain underfunctionalized hydrophobic groups (Fig. 6.8). Recent work to characterize the druglikeness of molecules focuses more on the presence of key functional groups in molecules.

A simple pharmacophore point filter has been introduced recently (47). It is based on the assumption that druglike molecules should contain at least two distinct pharmacophore groups (47). Four functional motifs have been identified that guarantee hydrogen-bonding capabilities that are essential for the specific interaction of a drug molecule with its biological target (Fig. 6.9). These motifs can be combined to functional groups that are also referred to here as *pharmacophore* points; they include: amine, amide, alcohol, ketone, sulfone, sulfonamide, carboxylic acid, carbamate, guanidine, amidine, urea, and ester. The following main rules apply to the pharmacophore point filter (PF1):