3.2 Fragment-Based Drug Discovery (FDBB)

FDBB is a technique where highly water-soluble fragments (molecules <300 Da) are screened for interaction with the target, after which structural information of how the fragments bind to the target guide the subsequent fragment optimization and development towards a drug lead.

FBDD arose from the idea to first identify smaller fragments that bind to the target and to develop these fragments into drug leads (Jencks 1981). The smaller size of the fragments allows for a more efficient interaction with binding pockets within the target, even though the binding affinities of the fragments are much lower (typically 0.1–10 mM as opposed to μM/nM affinities screened for in HTS). Furthermore, the amount of candidate molecules of this size is smaller, allowing for a larger structural diversity to be explored with a smaller library size.

The various approaches to lead development through FBDD are illustrated by a hypothetical example in Fig. 18. Once various binding fragments are identified and their binding interactions are understood through analytical methods such as NMR spectroscopy, MS, or X-ray crystallography, these fragments can either be recombined through merging or fusion to fully take advantage of each fragment's binding interactions. Alternatively the fragments can be expanded in an attempt to fill up the binding pocket (Scott et al. 2012).

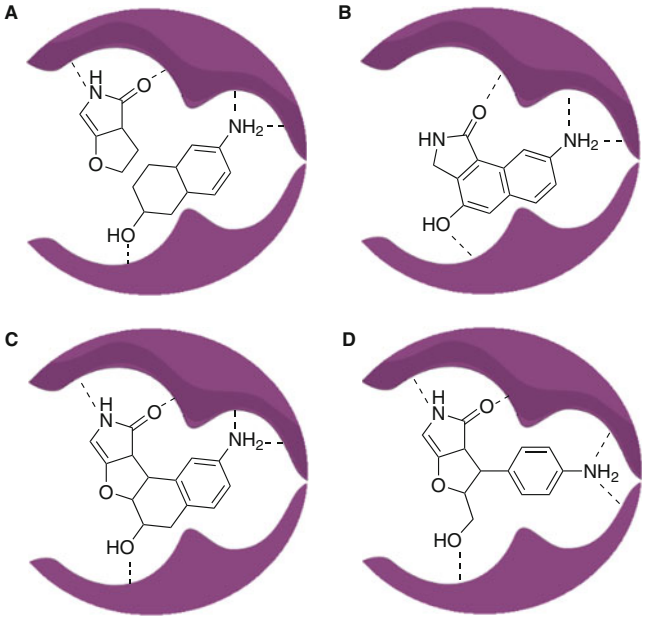

Fig. 18 The principle of fragment-based drug discovery. Various small hydrophilic fragments are screened for receptor interactions (**a**). Binding fragments attached to different sites of the binding pockets are either merged (**b**), linked (**c**), or one of the fragments could be optimized/grown (**d**) in an attempt to fill up the binding pocket (Scott et al. 2012)