in binding energy.[35] Therefore, the resulting ligand efficiency Δg tends to be maximal for small molecules (*e.g.* fragments) and then steadily decreases as more heavy atoms are added.

The concept of ligand efficiency and its importance as a useful parameter to assess and select leads for drug discovery has been discussed.[34] Simple calculations based on average molecular properties of drug-like compounds obeying the Lipinski 'rule of five'[28] defines the lowest acceptable limit for ligand efficiency of hits and drug leads around $1.2\,kJ\,mol^{-1}$ per NHA.[34] Analysis of several examples, in which lead compounds have been derived from the identification of starting fragments, has shown that in all cases both initial fragments and the leads derived from them had ligand efficiencies between 1.2 and 2.1.[20]

16.3 From Molecular Fragments to Drug Leads

The elaboration of fragment hits into lead compounds must improve the binding affinity from the mM range to nM. Throughout the process, the chemistry of fragment elaboration is guided by structural information on the binding mode of the fragment(s) and by inspection of additional potential interactions with the protein. Knowledge of binding thermodynamics can also help understanding the effect of particular structural modifications. Different strategies can be employed to elaborate small fragments into larger lead compounds: fragment growing, fragment linking, and fragment self-assembly.[18]

16.3.1 Fragment Growing

Fragments are used as starting points for extending or 'growing' an inhibitor in the binding pocket (illustrated schematically in Figure 16.2A). An initial fragment is steadily built up to explore favorable interactions with adjacent regions of the binding site. It has been found that the binding mode of a fragment is generally maintained during the optimization process.[33,36] Examples of this

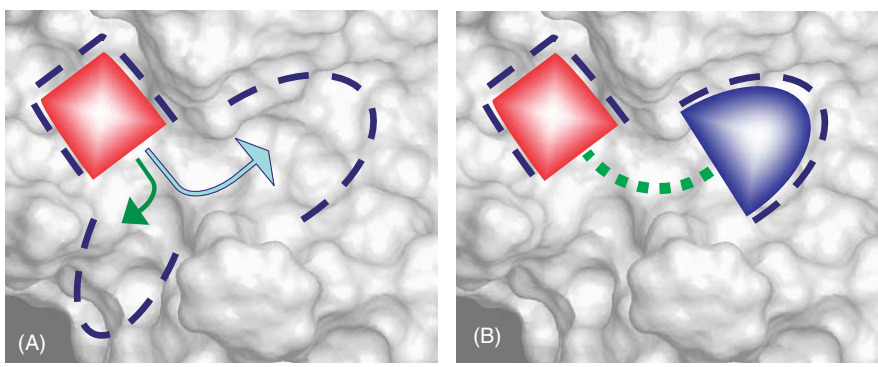

Figure 16.2 Schematic of the fragment growing (A) and linking (B) approaches.