rationale for targeting remain intractable. In the following chapter I will summarize progress made in developing inhibitors for challenging drug binding sites and emerging target families.

Keywords
Druggability · Epigenetic reader domains · Protein interaction inhibitors · Phosphatases · RAS · Structure based design

1 The Concept of Druggability and Properties of Drug-Like Molecules

Lipinski et al. noted in 1997 a number of shared physicochemical properties of drug candidates successfully entering phase II clinical trials (Lipinski et al. 2001). These parameters defined in this study are now known as the 'rule of 5' (Ro5). Based on the initially defined Ro5 criteria, a pharmacological small molecule is more likely to be active when administered orally if it has no more than one violation of the following criteria: It should not have a) more than 5H-bond donors, b) a molecular weight larger than 500, c) a cLogP (calculated octanol/water partition coefficient) larger than 5 and d) no more than 10 hydrogen bond acceptors. In a subsequent study, the molecular weight constraint has been questioned, and this parameter is nowadays often replaced with the related polar surface area criteria, which should ideally less than 140 $Å^2$.

In addition, the number of rotatable bonds (less than 10) has been identified as an important predictor for compounds that are orally active (Veber et al. 2002). During lead development the molecular weight and lipophilicity are usually increased by medicinal chemists in order to increase potency and target specificity. As a consequence, stricter requirements are usually applied to lead compounds (rule of three, Ro3) which are defined by an octanol/water partition coefficient log *P* not greater than 3, by a molecular mass less than 300 Da and by the presence of not more than three hydrogen bond donors and not more than three hydrogen bond acceptors as well as not more than three rotatable bonds (Congreve et al. 2003). There are however many exceptions to these rules, in particular for drugs that act at protein interfaces such as taxanes that target tubulin or rapamycin, targeting the interaction of the kinase mTOR/FRAP with FKPB12 (FK506 binding protein). These very successful approved drugs largely exceed the molecular weight/polar surface area constraint as well as the recommended number of hydrogen bond donor/acceptors that would be expected to result in a bioactive drug. However, both rapamycin and paclitaxel are natural products and may have been adapted through a natural selection process to function in vivo despite their poor drug-like properties (Fig. 1).

The physicochemical constraints of drug-like molecules naturally constrain the type of binding sites that can be targeted. Thus, large and shallow surfaces are not likely to interact with drug-like small molecules with sufficient potency and highly polar surfaces will result in interacting ligands with poor cellular activity. Several prediction tools have been developed to assess the druggability (likelihood of