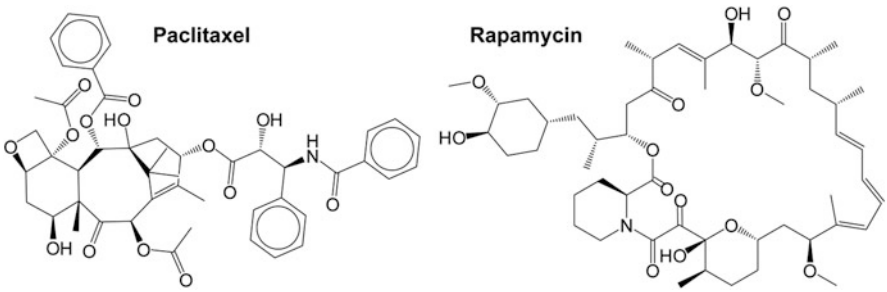

Fig. 1 Examples of approved bioactive 'non-Lipinski' drugs targeting protein interfaces

developing compounds with appropriate in vivo bioavailability, efficacy and safety profiles) or chemical tractability (likelihood developing a potent in vitro inhibitor) of target binding sites (Halgren 2009; Keller et al. 2006). The developed tools include methodologies estimating the 'maximum achievable affinity' (Cheng et al. 2007) or are based on experimental techniques that correlated with pocket properties, for instance, NMR screening hit rates (Hajduk et al. 2005).

A remarkable recent study examined potential drug binding pocket in the protein databank (PDB (http://www.rcsb.org/pdb/home/home.do)). The study identified 290,000 suitable binding pockets present in 42,000 crystal structures that were available during the time of analysis (Sheridan et al. 2010), suggesting that there is a large space of potential drug binding sites that has not been explored. Indeed, the currently accessed target space was recently compiled surveying 27,000 documents including patents. This study identified assay data for 1,736 human proteins that were targeted by 823,179 unique chemical structures (Southan et al. 2011). However, the top 278 most actively pursued targets were classical enzyme or membrane protein drug targets covering 90% of the identified compounds, suggesting that protein interaction inhibitors and nonclassical targets represent still a very small niche area. This is particularly evident analysing the current targets of approved drugs. In 2002 an analysis by Hopkins revealed 399 nonredundant protein targets. However, targets of drugs that are actually marketed constituted only 120 proteins (Hopkins and Groom 2002). Nearly half of the targets did fall into six different target families: G-protein-coupled receptors (GPCRs), serine/threonine and tyrosine protein kinases, zinc metallopeptidases, serine proteases, nuclear hormone receptors and phosphodiesterases. The rate of new target discovery is still slow (Overington et al. 2006). During the past decade, 19 new chemical entities and biologics have been approved on average each year. From this set, only four new drugs are developed against previously unexploited molecular targets (Rask-Andersen et al. 2011). In the following, I have selected a number of challenging target families with strong biological rationale for drug development.