Another target that raised a lot of attention is homodimerization of iNOS. Here, companies like Berlex Biosciences (Davey et al. 2007) and Adolor Corporation (Chu et al. 2009) reported discovery and optimization of disruptors of the iNOS/iNOS complex. **Compound 21b** from Berlex significantly ameliorated adjuvant-induced arthritis in a rat model and could be crystallized in complex with iNOS. **Compound 6** developed by Adolor is a potent inhibitor of iNOS dimerization in a cell-based iNOS assay (IC50 = 12 nM).

Human papillomavirus (HPV) is implicated in causing cervical cancer, the second most prevalent cancer in women worldwide. Here, the interaction of the viral proteins E1 and E2 as well as E6 with the host cell ubiquitin ligase E6AP has been targeted with small-molecule PPI inhibitors (D'Abramo and Archambault 2011). Researchers at Boehringer Ingelheim identified inhibitors of the herpes virus E1/E2 protein complex from a library of 140,000 compounds (Yoakim et al. 2003). Inhibitor 1 (**BILH434**) derived from this study displayed an IC50 of 0.18 μM and was crystallized in complex with E2 (Wang et al. 2004). Recently, a study was published identifying compounds from a library screen against the E6/E6AP interaction (Malecka et al. 2014). From the 30 validated hits (library size 88,000), seven inhibited p53 degradation in cell lines with HPV-integrated genomes, and two of these blocked p53 degradation and inhibited cell proliferation in cells specifically and stably transfected with E6. Progression through the cell cycle is among others regulated by the cyclin-dependent protein kinases (Cdks) with overactivation of these kinases being associated with the development of cancer (Murray 2004). Hence, inhibition of the stimulatory Cdk/cyclin interaction could be one strategy for anticancer therapy. At Merck Research Laboratories, a 5,000,000-compound library was screened to identify inhibitors of the Cdk2/cyclin A interaction (Deng et al. 2014). Quinoline-based **compound 2** bound to Cdk2 with a Kd of 0.3 μM and was crystallized in complex with Cdk2. The molecule binding to the kinase domain induced a conformational change mainly involving helix C that is incompatible with binding of cyclin A. At Wyeth Research, inhibitors of the ZipA/FtsZ complex were found by screening 250,000 compounds using a fluorescence polarization (FP) assay (Kenny et al. 2003). **Pyridopyrimidine 1 inhibitor** from this screen showed a K_I of 12 μM and could be co-crystallized with ZipA. This structure was used in a subsequent study for a scaffold hopping approach which produces new leads for further development (Rush et al. 2005). In a third, complementary approach at Wyeth, NMR fragment screening was employed to find novel inhibitors of the ZipA/FtsZ complex (Fig. 3) (Tsao et al. 2006).

Also, more and more academic groups involve themselves in the identification and development of PPI modulators as compound libraries and screening facilities become more available for noncommercial entities, too. For example, researchers at the FMP in Berlin, Germany, identified inhibitors of the clathrin terminal domain (CTD)/amphiphysin interaction named **pitstops 1** and **2** using an ELISA-based assay (von Kleist et al. 2011). The group of Wagner found inhibitors of the translation initiation factor eIF4E/eIF4G complex in a 16,000-compound library screened employing FP (Moerke et al. 2007). In addition to the use of disruptors of this complex as tool compounds to study processes such as cell growth, embryonic