Besides these three commonly used strategies, another FBDD strategy called in situ fragment assembly has rapidly gained recognition in recent years. The target is presented with various fragments which contain a bio-orthogonal functional group (i.e., a group that cannot directly react with the target) and then let the target "choose" which fragments fit best in its binding pocket. The bound fragments are then ligated in situ and the nonbinding fragments washed away (Fig. 19). While various reactions have been employed to ligate bound fragments (Mamidyala and Finn 2010), one of the most efficient and popular reactions is the copper-catalyzed azide-alkyne "click" reaction, which was employed by the group of Sharpless to assemble an acetylcholinesterase inhibitor with femtomolar inhibition concentrations (Lewis et al. 2002).

Analogous to Lipinski's "rule of five" for drug-like compounds (Lipinski et al. 1997), a "rule of three" was proposed for favorable fragment properties, which are MW $\leq$ 300 Da., number of hydrogen bond donors $\leq$3, number of hydrogen bond acceptors $\leq$3, and a ClogP value of $\leq$3 (Congreve et al. 2003). While there is still some debate on whether or not these rules hold up, they have proven to be valuable guidelines in the design of fragments (Jhoti et al. 2013).

As FBDD has been embraced by both industry and academics over the last two decades, the approach has started showing its merits in this decade. In 2011, the oncogenic agent Vemurafenib (**30**), a B-Raf kinase inhibitor which was discovered through FBDD (Fig. 20), was approved by the FDA, and multiple FBDD-based drugs are currently going through phase II/III clinical trials (Baker 2013).

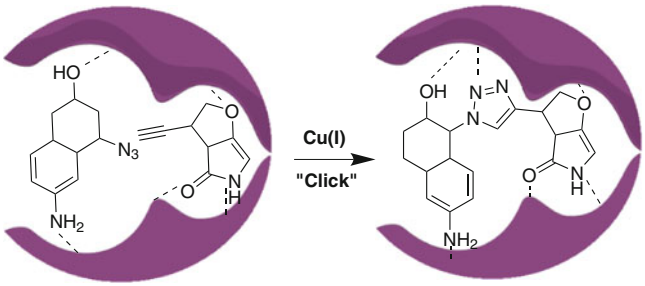


**Fig. 19** In situ fragment assembly via copper-mediated "click" chemistry

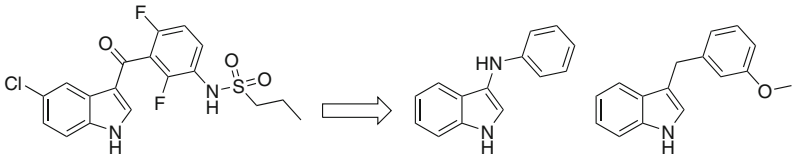


**Fig. 20** Structure of Vemurafenib (**30**), which was discovered by fragment merging of indoles **31** and **32**, followed by lead optimization (Tsai et al. 2011)