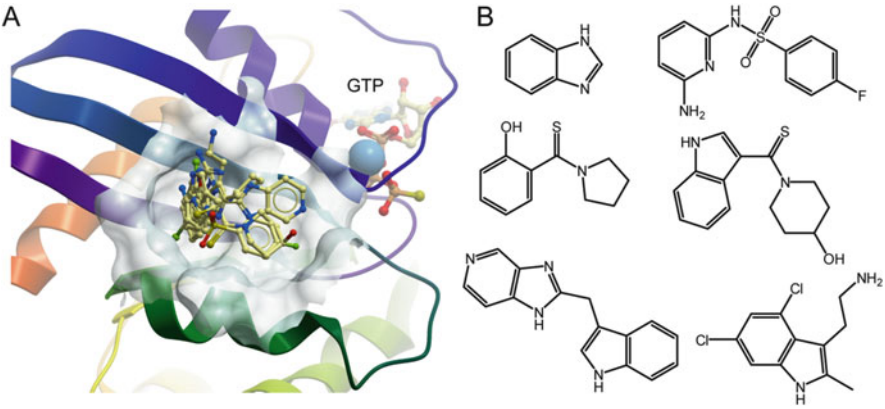


**Fig. 4** Fragment binding site identified in RAS. Shown is a superimposition of several fragments co-crystallized with RAS (**a**) as well as the chemical structures of the co-crystallized compounds (**b**). The GTP/Mg binding site is indicated as well

the persistently GTP-bound active RAS state (Bos et al. 2007). The extremely high affinity of GTPases for GTP precluded unfortunately the development of GTP competitive ligands. Other targeting strategies have been therefore attempted. Among the most advanced strategies targeting RAS regulators has been the development of farnesyltransferase inhibitors. This enzyme transfers a C15 farnesyl isoprenoid lipid to its carboxy-terminal CAAX motif in RAS resulting in targeting of RAS to the plasma membrane. Several highly potent inhibitors have been developed that showed remarkable efficacy in mouse models, and several inhibitors such as lonafarnib and tipifarnib advanced to phase III clinical trials. Unfortunately, however the developed inhibitors failed to demonstrate efficacy in RAS-driven tumours, a finding that was later rationalized by the compensating action of other lipidation enzymes in particular prenyltransferases (Whyte et al. 1997).

Direct targeting strategies for RAS have been hampered by the absence of druggable binding pockets (Buhrman et al. 2011). However, a number of weakly binding fragments have been identified (Wang et al. 2012) (Fig. 4). Structural analysis revealed that all crystallized fragments bind to a pocket adjacent to the switch I/II regions. Indeed, the identified fragments inhibited SOS-mediated nucleotide exchange and prevented RAS activation by blocking the formation of intermediates of the exchange reaction (Maurer et al. 2012; Sun et al. 2012).

Other inhibitors have been developed based on the nonsteroidal, anti-inflammatory drug sulindac sulphide. Compounds of this class have been reported inhibiting the formation of the RAS–RAF complex and have been shown to inhibit proliferation of RAS-transformed cells. However, this compound class may have other off-target effects that may contribute to the observed phenotypes (Karaguni et al. 2002).

An interesting approach has been reported recently by Shokat and colleagues who recently reported small molecules that covalently and selectively bind to the