G12C mutant form of KRAS, a frequent mutation often found in non-small-cell lung cancer. The developed compounds blocked SOS1-mediated nucleotide exchange and decreased the binding of RAS to both BRAF and CRAF in G12C-mutated cell lines (Ostrem et al. 2013).

4 Example 3: Protein–Protein Interactions

Targeting protein has gained popularity after a number of highly potent inhibitors have been developed. The targeted interactions are however typically characterized by a well-defined binding site. For instance, interaction inhibitors that disrupt the binding of MDM2 (murine double minute 2) and MDMX to the tumour suppressor p53 have now entered clinical testing in cancer (Vassilev 2007; Brown et al. 2009). MDM2 binds the p53 tumour suppressor protein with high affinity and negatively modulates its transcriptional activity and stability. Overexpression of MDM2 is frequently found in tumours leading to impairment of p53 function. Thus, it has been hypothesized that inhibition of MDM2–p53 interaction can stabilize p53 and may offer a pharmacological strategy restoring p53 function in MDM2 overexpressing tumours.

Recent structural studies showed that a new class of dual MDM2/MDMX inhibitors block the binding of MDM2 and MDMX to p53 by stabilizing MDM2/MDMX homo- and heterodimerization occluding the p53 binding pocket (Graves et al. 2012).

A number of protein–protein interaction domains that selectively recognize sequences containing post-translational modifications have recently emerged as interesting targets for the development of inhibitors. The targeted interaction modules comprise in particular members of the so-called epigenetic reader domain family which include acetyl-lysine-dependent bromodomains (Muller et al. 2011; Filippakopoulos and Knapp 2014) as well as readers of methyl-lysine or methyl-arginine containing sequences such as PHD zinc finger domains and the Royal family of reader domains, which is composed of Tudor, MBT, PWWP and chromodomains (Herold et al. 2011a; James et al. 2013a). Several members of this family of protein interaction modules have good predicted druggability, and several inhibitors have been developed in particular for acetyl-lysine-dependent bromodomains (Vidler et al. 2012; Santiago et al. 2011). A shared feature of epigenetic reader domains that makes these protein interaction modules attractive targets is the observation that the interaction with their specific recognition sites is usually weak and localized to a binding pocket of suitable size for inhibitor development. Typically K_{Ds} of reader domain interactions are in the low μM regions suggesting that protein interactions mediated by these domains can be easily inhibited by low molecular weight inhibitors. In addition, lysine acetylation neutralizes the charge of the lysine side chain resulting in aromatic and hydrophobic binding sites. Indeed, fragment-based screening approaches identified several diverse chemotypes suggesting excellent druggability of bromodomains (Vidler et al. 2013).