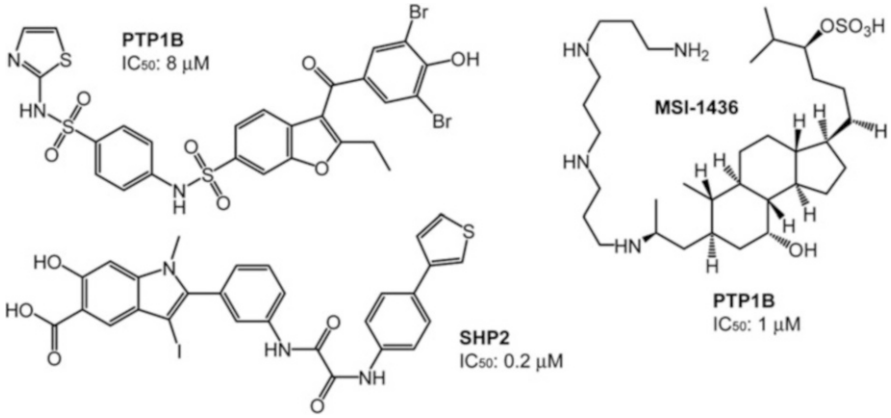

Fig. 3 Chemical structure of allosteric PTP1B inhibitors as well as the potent SHP2 inhibitor 11a-1 (Zeng et al. 2014)

MSI-1436 targets the C-terminal, non-catalytic domain of the long isoform of PTP1B. The PTP1B C-terminus is an intrinsically disordered region of the protein that allosterically regulates PTP1B catalytic activity by interaction with the catalytic domains. In breast cancer, MSI-1436 antagonized HER2 signalling and inhibited tumorigenesis and metastasis in xenografts (Krishnan et al. 2014).

Only few inhibitors have been reported for SHP2 so far. One of the most potent compounds targeting this PTP is NSC-87877 that is cell active and inhibits SHP1 and SHP2 with an IC50 value of 300 nM. Recently, a novel hydroxyindole carboxylic acid-based SHP2 inhibitor 11a-1, with an IC_{50} value of 200 nM and greater than fivefold selectivity against other PTPs, has been reported (Fig. 3) (Zeng et al. 2014).

3 Example 2: GTPases of the RAS Family

The small GTPases of the RAS family (*HRAS*, *NRAS* and *KRAS*) were the first mutated genes discovered in cancer and constitute today the most frequently mutated oncogenes. The high rate of RAS pathway activating mutations that have been detected in the most lethal cancer types has triggered a considerable research interest developing small molecules that interfere with RAS function. However, despite more than 3 decades of intensive efforts, no RAS inhibitor that targets this GTPase directly has reach clinical testing, suggesting poor druggability of these targets (Karnoub and Weinberg 2008; Cox et al. 2014).

GTPases are activated by GTP and inactivated by binding of GDP. This process is tightly controlled by a number of regulatory proteins such as the GTPase-activating proteins (GAPs) as well as GTP exchange factors (GEFs). Mutationally activated RAS usually show impaired GAP stimulation and the mutations stabilize