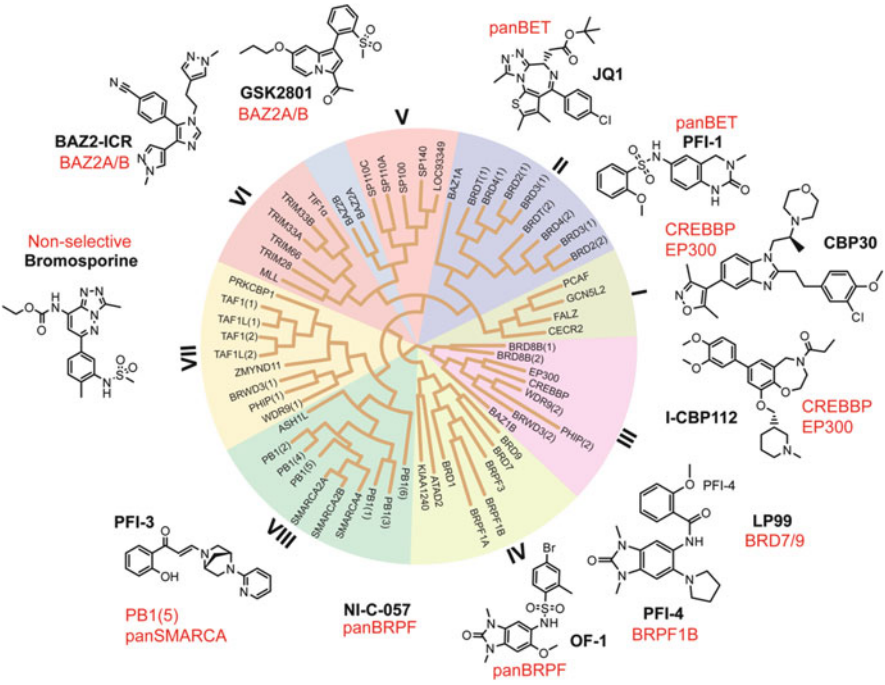

Fig. 7 Bromodomain chemical probes. Shown is a phylogenetic tree (*centre*) and the currently available chemical probes developed by the SGC (http://www.thesgc.org/chemical-probes/epigenetics). Targets that are inhibited are shown in *red*. The structure of the BRD9/7 inhibitor LP99 and the panBRPF inhibitors is currently undisclosed

Methyl-lysine/arginine reader domains have also recently been targeted but the diversity of this large protein interaction module family and the binding site properties of most methyl-lysine/arginine readers render chemical probe/inhibitor development more challenging. One of the first methyl-lysine epigenetic reader domains that have been targeted was L3MBTL3, a member of the malignant brain tumour (MBT) family of chromatin-interacting transcriptional repressors. Optimization of weaker starting points (Herold et al. 2011b) led to the discovery of UNC1215 as a potent and selective chemical probe for L3MBTL3 (James et al. 2013b). This chemical probe binds with a K_D (dissociation constant) of 120 nM and has excellent selectivity for the targeted reader domain. Biophysical analysis revealed that UNC1215 has a methyl-lysine competitive binding mode, effectively displacing dimethyllysine-containing peptides from the L3MBTL3 binding site.

Recently, another potent methyl-lysine reader domain has been reported. OICR-9429 is a selective chemical probe for WDR5, a protein that is present in several chromatin regulatory complexes including the MLL1 (mixed lineage leukaemia 1) complex. OICR-9429 binds to WDR5 with K_D values of 24 nM (Biacore) and 52 nM (ITC) and was found to be more than 100 selective over other chromatin 'reader' domains, methyltransferases and other non-epigenetic targets (Fig. 8).