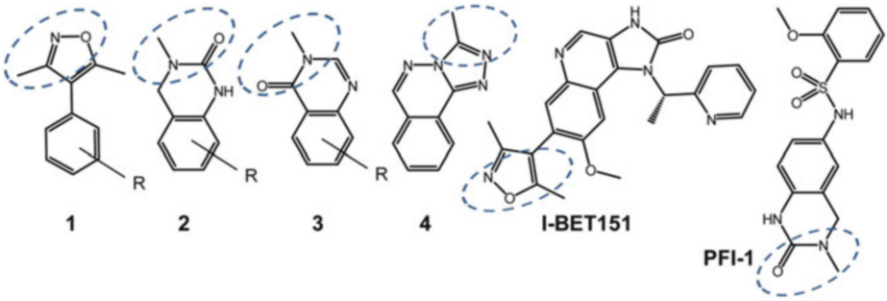

Fig. 6 Acetyl-lysine mimetic inhibitors of bromodomains. General scaffolds: (**a**) isoxazoles, (**b**) 3-methyl-dihydroquinazolin-2-one, (**c**) 3-methyl-quinazolin-4-one and (**d**) 3-methyl-triazolophthalazine. Developed high affinity inhibitors: I-BET151 and PFI-1. Acetyl-lysine mimetic moieties are highlighted by a *dashed circle*

most notably the highly potent panBET inhibitor I-BET151 (Dawson et al. 2011). Quinazolinone scaffolds (2-one or 4-one) have also been developed resulting in the panBET inhibitor PFI-1 (Picaud et al. 2013; Fish et al. 2012). Co-crystal structures confirmed the acetyl-lysine mimetic binding mode of the quinazolinone head group of PFI-1 which forms two hydrogen bonds with the conserved Asn140 in BRD4 (1) as well as a water-mediated hydrogen bond to the conserved tyrosine Tyr97 (Picaud et al. 2013).

BET bromodomain inhibition has recently been described as a frequent off-target activity of kinase inhibitors (Ciceri et al. 2014; Ember et al. 2014). A screen carried out on clinical kinase inhibitors revealed a number of inhibitors with potent BET activity suggesting that dual kinase/bromodomain inhibitors could be developed. The frequent hit rate in inhibitor screens and the large number of potent inhibitors that have been developed since the discovery of the triazolodiazepine-type inhibitors certify the excellent druggability of BET bromodomains (Fig. 6).

A number of potent bromodomain inhibitors have also been developed outside the now well-studied and well-explored BET family. Modification of the benzodiazepine scaffold led to the development of promiscuous bromodomain inhibitors (Bromosporines) that show broad spectrum activity targeting in particular BET family members, TAF1, CECR2, BRD7 and BRD9 and the BRPF family (Fig. 7). Selective inhibitors have been developed for bromodomains present in the histone acetyl transferases CREBBP/EP300 (I-CBP112 and CBP30) (Hay et al. 2014), BAZ2A/B (GSK2801 and BAZ2-ICR), BRPF1B (PFI-4) and panBRPF (OF1, NI-C-057), BRD7/9 (LP99) and panSMARCA/PB1(5) (PFI-3) (see http://www.thesgc.org/chemical-probes/epigenetics). The currently available probes represent a good coverage of chemical tool compounds for this family of epigenetic effector domains and demonstrate the feasibility targeting these interaction domains that have not been considered as druggable targets a few years ago. However, if any of the published inhibitors will be developed into an approved pharmaceutical remains to be shown. Clinical trials on BET inhibitors have been initiated recently.