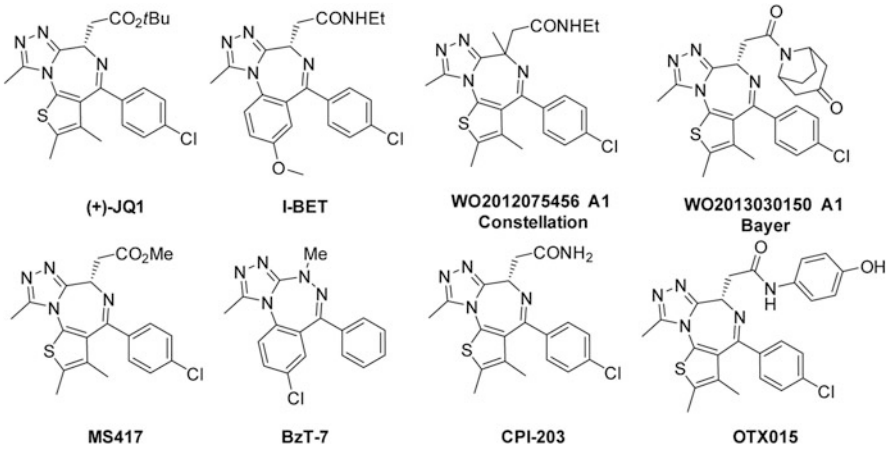

Fig. 5 Examples of benzodiazepine- and thienodiazepine-type BET inhibitors

The first bromodomain inhibitors appeared in the patent literature and were developed targeting the BET family (Miyoshi et al. 2009; Adachi et al. 2006). These inhibitors belong to the thieno-triazolo-1,4-diazepines which showed strong growth inhibitory activity on a panel of cancer cell lines. The disclosure of thieno-triazolo-1,4-diazepines as BET inhibitors led to the development of the thieno-triazolo-1,4-diazepines JQ1 (Filippakopoulos et al. 2010) (Fig. 5). In parallel, GSK discovered the benzo-triazolo-1,4-diazepine class of BET inhibitors (I-BET) using a combination of phenotypic screens and chemoproteomics (Chung et al. 2011; Nicodeme et al. 2010). Selectivity screening showed that benzo- and thienodiazepines are highly selective for BET bromodomains. Interestingly, the introduction of a stereo centre at the diazepine ring yielded a highly potent (S) enantiomer, (+)-JQ1, whereas the (R) enantiomer, (−)-JQ1, is inactive and may be used as a negative control compound. Crystal structures with BET bromodomains showed that the methyl-triazol ring served as an acetyl-lysine mimetic moiety and formed the canonical hydrogen bond with the conserved asparagine (N140 in BRD4(1)) or analogue residues in other BET family members (Filippakopoulos et al. 2010; Matzuk et al. 2012). The strong anti-proliferative effects of JQ1 and I-BET in cancer and the anti-inflammatory properties of these agents prompted the development of a number of similar benzodiazepine and thienodiazepine molecules which all include either modification on the ester/amid linkage (Zhang et al. 2012) or substitutions in the diazepine ring, which led for instance to benzotriazepines (Bzt-7) in which the asymmetric carbon was replaced by a nitrogen (Filippakopoulos and Knapp 2014; Filippakopoulos et al. 2012; Knapp and Weinmann 2013).

Novel acetyl-lysine competitive ligands have been developed based on fragment hits. In particular based on the 4-phenyl 3,5-dimethyl isoxazole fragment, a number of isoxaxoles have been developed as potent BET inhibitors (Hewings et al. 2011),