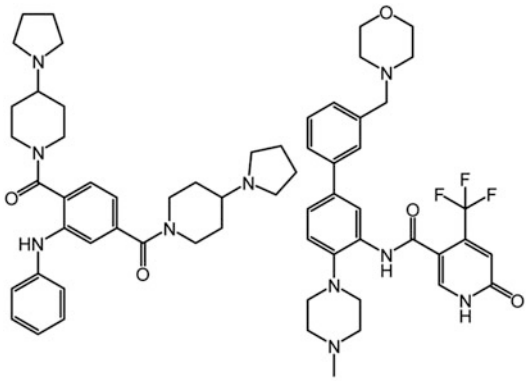

Fig. 8 Chemical probes targeting methyl-lysine reader domains

A recent druggability analysis of the methyl-lysine/arginine family of reader domains suggested that there are many additional opportunities for the development of selective and potent inhibitors. Improved druggability of these domains may be achieved targeting adjacent pockets. For instance, the methyl-lysine binding site present in CBX is largely extended by a channel that harbours flanking peptide sequences. The ankyrin repeat protein GLP is another example for extended binding sites that lead to improved druggability scores. A mono- or dimethyl containing sequence is anchored into a central cavity containing a typical aromatic cage. The duggability of this pocket is poor ($D_{score} = 0.64$; PDB code, 3B95); however, considering two adjacent pockets less than 7 Å apart improved the druggability score to $D_{score} = 0.98$ (Herold et al. 2011a). Methyl-lysine reader domains are often mutated in cancer and genetic diseases suggesting that targeting these domains may be beneficial for a number of disease applications.

Recent reports strongly suggest that many protein–protein interactions that are mediated by localized interactions are highly druggable and that potent and bioactive inhibitors can be identified. Some of the developed inhibitors are now also tested in phase I/II clinical trials, and it is likely that many more protein–protein interaction inhibitors will be identified and developed in the near future. The development of bioactive inhibitors that target larger interfaces remains however very challenging, and this area would require additional intensive research efforts before potent bioactive inhibitors will be identified and tested clinically.

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