ABSTRACT

Bromodomains (BRDs) are epigenetic readers able to selectively recognize the acetylated lysine residues on histone and non-histone proteins. Through their activity, bromodomain-containing proteins (BRDs) are involved in a wide range of cellular events, such as chromatin remodeling and transcriptional activation. One of the most studied and druggable family of bromodomain-containing proteins is the Bromo and Extra Terminal domain (BET) family, whose members (BRD2, BRD3, BRD4, and BRDT) contain two highly homologous bromodomains: BD1 and BD2. Despite several ligands have been discovered, there is still need to identify novel classes of compounds with high potency, selectivity and in vivo activity.

This Ph. D. project is focused on the design, synthesis, biochemical and biophysical evaluation of new chemical probes for BET proteins. To this purpose, three different medicinal approaches were applied to obtain different classes of compounds. Exploiting the bisubstrate approach, bivalent ligands were designed and synthesized. Biochemical and biophysical assays allowed the identification of compound **3** (EML896), a promising bivalent compound able to bind both BD1 and BD2 bromodomain of BET proteins. Applying a frozen analogue approach, the diazobenzene core of reported diazobenzene-ligands was rigidized, yielding a benzimidazole scaffold. A small library of benzimidazole-based ligands has been designed and synthesized and compound **15** (EML765) was identified as promising BD1 selective ligand. Finally, at the University of Dundee, the attention was focused on compounds able to induce protein degradation. Specifically, proteolysis targeting chimera compounds (PROTACs) containing BD1 and BD2 selective warhead were designed, synthesized and biological evaluated.