Selective CDK12 inhibitors to treat Myotonic Dystrophy Type 1 (DM1)

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Myotonic dystrophy type 1 (DM1) is a common genetic muscular dystrophy disorder with no current cure or treatment. Cyclin-dependant kinase 12 (CDK12) is a protein that has been implicated in the pathogenesis of DM1 (**Figure *1***).[1] Inhibiting CDK12 is challenging as its protein structure is very similar to other cyclin-dependent kinases which are crucial for RNA transcription. In this presentation I will show our covalent approach to inhibit CDK12 selectively and our synthetic routes.

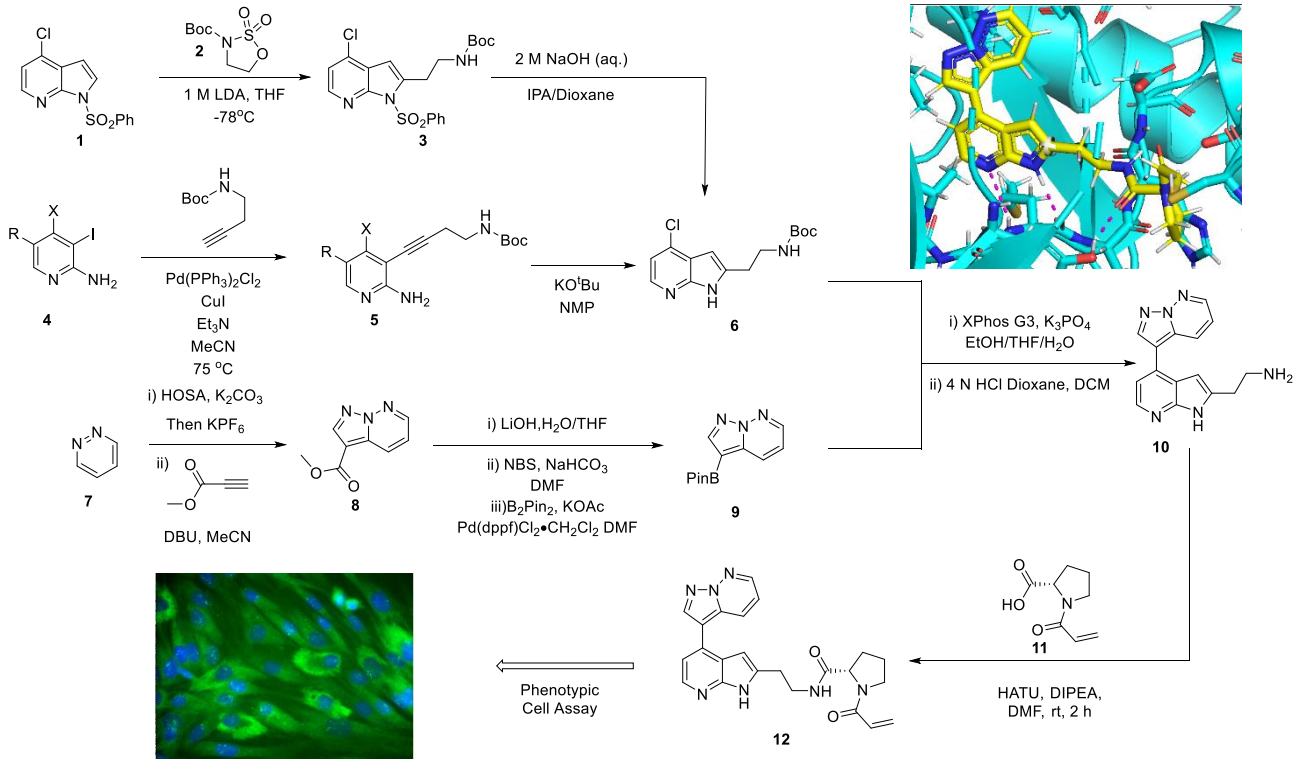

Figure 1. Shows the route to an example compound along with its X-ray cocrystal structure in CDK12 and an image of phenotypic cell assay.[1] R=H or a desirable EWG, X= Cl or Br

One key highlight of our synthetic chemistry was the development of a new route to the key hinge binding core **6**. The new route allows to access a diverse range of cores in a convenient and convergent way and has several advantages over the previous route including avoiding an anhydrous cryogenic step which had poor reproducibility.

1 A. Ketley, *et al.*, *Sci. Transl. Med.*, **2020**, *12*, 1–12.