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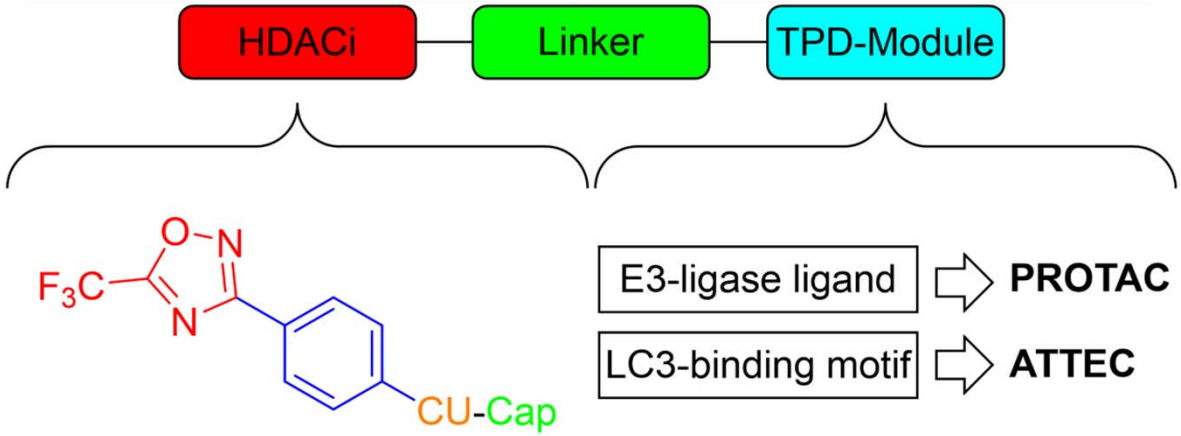
Synthesis and optimization of histone-deacetylase inhibitors (HDACi), dual target inhibitors and targeted protein degraders (TPD)



Dysregulation in the expression of class IIa histone deacetylases (HDACs), i.e. HDAC 4, 5, 7 and 9, has been linked to various forms of cancer, yet their specific role in this context is not fully understood. Therefore, the development of novel subclass- and isoenzyme-selective class IIa histone deacetylase inhibitors (HDACi) and targeted protein degraders (TPDs), for the elucidation of the involvement of HDAC enzymes in tumor genesis and maintenance is essential. FFK 24, a potent trifluoromethyl-oxadiazole(TFMO)-based class IIa HDACi, is the lead structure for this project. The first goal is the optimization of the inhibitors' physicochemical properties and selectivity profile towards the individual subclass enzymes by systematic structural variation. Based on the novel inhibitors, TPDs will be designed. The HDACi will be attached to either an E3-ligase ligand, forming a proteolysis targeting chimera (PROTAC) or to an LC3-binding motif, creating an autophagosome-tethering compound (ATTEC). These two approaches to targeted protein degradation of HDACs, in comparison to the HDAC inhibition should give insights into the biological role of class IIa HDACs. Additionally, novel isoform-selective inhibitors and TPDs might offer new, selective treatment approaches for certain malignant cancers. Furthermore, dual target inhibitors for HDACs and other (epigenetic) cancer targets will be designed.

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