Design, synthesis and characterization of novel potential TAU-degraders

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Tauopathies, including Alzheimer's disease, are a class of heterogeneous neurodegenerative disorders characterised by progressive cognitive decline, personality changes and memory impairment in patients. This concerning class of pathologies is distinguished by the aggregation and increased phosphorylation of the microtubule-associated protein tau, making this protein as a prime target for drug development.

As abnormal forms of tau have been shown to trigger a plethora of pathomechanisms, targeting a single downstream mechanism has been demonstrated to have limited therapeutic effect. Polypharmacological drugs may provide a solution to this problem by simultaneously modulating tau aggregation, tau phosphorylation, and potential additional tau functions that may be impaired due to disease. Indeed, the employment of polypharmacological approaches has demonstrated significant advantages over single-target drugs, particularly in the treatment of complex diseases[1]. In a recent work published on Nature communication, the small molecule PHOX15 was identified as putative polypharmacological drug that interact with tau and modulate tau kinases GSK3β and Cdk5. They found that PHOX15 inhibits tau aggregation, restores tau's physiological microtubule interaction, and reduces tau phosphorylation at disease-relevant sites[2].

In light of all these considerations, the aim of this research project is to explore the potential of PHOX15 in the field of Targeted Protein Degradation (TPD)[3,4]. This group of innovative approaches enables the selective degradation of a protein of interest by exploiting the ubiquitin-proteasome system. In order to investigate the proposed idea, a computational study, incorporating molecular docking and molecular dynamics simulations (MDs), was conducted to identify a portion of PHOX15 suitable for the construction of the degraders. Subsequently, a small library of potential tau candidate degraders was designed, screened and evaluated through computational calculations. The most promising candidates are currently under development: the design, synthesis and characterization will be presented and discussed.

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