Targeted Degradation of Pathogenic Protein Aggregates

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Introduction

The tau protein is of great interest in drug discovery as various forms of the protein act as hallmarks for several sporadic and familial neurodegenerative diseases, often referred to as tauopathies. The most well-known tauopathy is Alzheimer's disease but other tauopathies include frontotemporal dementia, progressive supranuclear palsy, chronic traumatic encephalopathy, Pick's disease and corticobasal syndrome[1]. These diseases are progressive, difficult to diagnose early and there are currently no disease-modifying therapies for the treatment of tauopathies[2].

Numerous methods have been explored to target these diseases including small inhibitor-based drugs but with very little success[3,4]. Proteolysis targeting chimera (PROTACs) have emerged as a new class of degraders, showing great promise for degrading disease causing proteins such as tau. These compounds utilise the UPS system to degrade pathogenic protein targets[5,6] . The development of a brain penetrant PROTAC compound with the ability to degrade disease related forms of tau would be an enormous breakthrough in modern medicine.

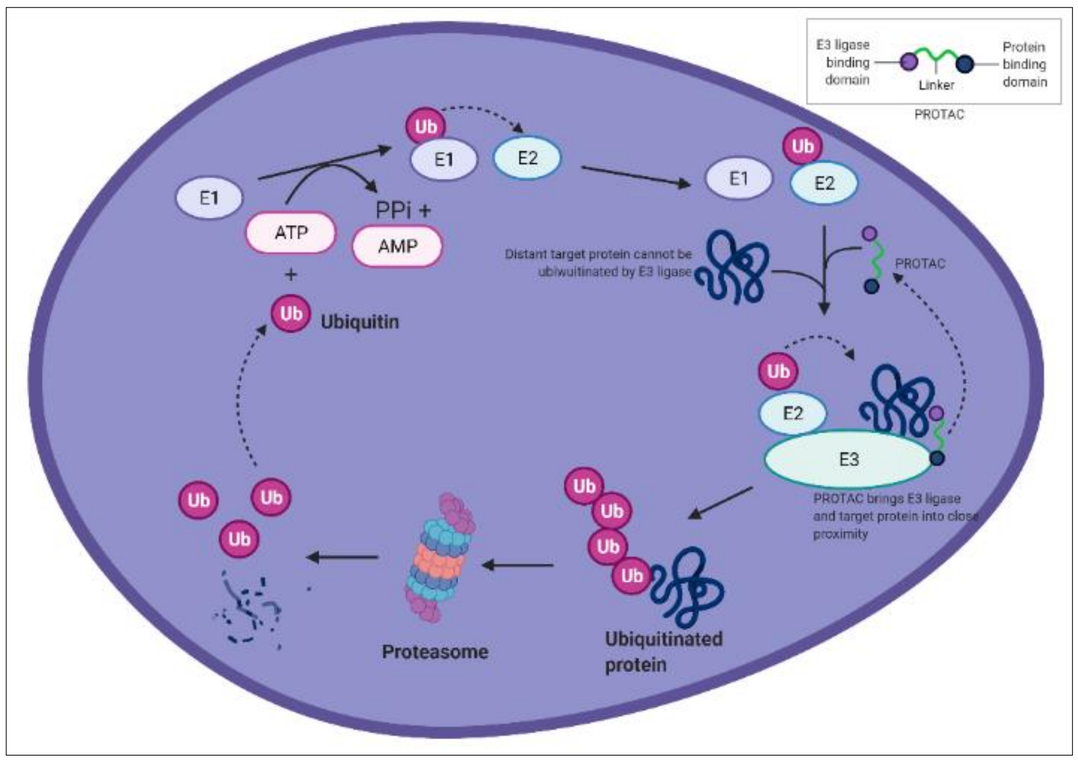

***Figure 1**: PROTAC mediated ubiquitination and degradation via the UPS system. This image was created using ©BioRender - biorender.com*

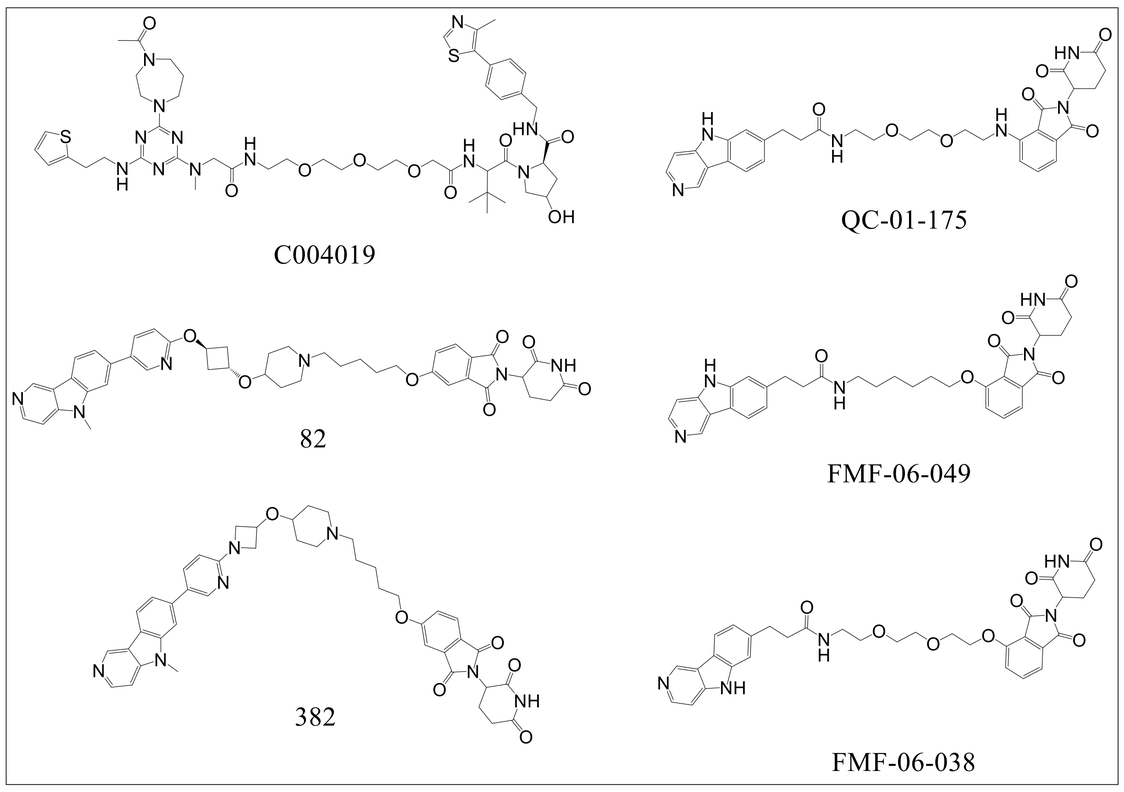

***Figure 2**: Small molecule PROTAC compounds targeting tau from literature* [7, 8, 9, 10, 11]

Aims & Objectives

Synthetic / Organic

Synthesise PROTACs using various tau binders from literature, varying linker lengths and CRBN E3 ligase-binding moieties

Tau binding moiety — Linker — E3 ligase binding moiety

Biological

Test Chemical Stability	Test Microsomal Stability	Test Permeability	Test Efficacy

Materials & Methods

- Synthesis of the various PROTAC compounds
- Testing the chemical stability of the compounds in conditioner buffer
- Testing the compounds with a MDCK permeability assay
- Use of an in vitro model from AD patient-derived cells with high abundance of tau aggregates to test the efficacy of the compounds

Current and Future work

Current work is ongoing for the synthesis of a range of PROTAC compounds, with various tau binders and linkers. The synthesis analysis of these compounds stability, permeability and ability to degrade various forms of tau will provide useful SAR information that could allow the improvement of of current lead compounds pharmokinetic properties and efficacies. All of this work can aid the development of brain penetrant PROTACs with potential use as therapies for tauopathies

References

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