Developing Therapies for Prion Diseases

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Introduction

Prion Diseases

Prion diseases are transmissible neurodegenerative diseases. They are always fatal, and currently there exists no effective therapy in combating these diseases. As they can cross the species barrier, as seen with bovine spongiform encephalopathy, developing therapies for prion diseases will have both medicinal and veterinary impact.[1] The infectious prion protein (PrP^{Sc}) uses the native protein (PrP^{C}) as a template to spread the disease. Previous efforts to inhibit misfolding by thermodynamically stabilising PrP^{C} using small molecules have proved fruitless. Removal of this template by targeted degradation of PrP^{C} should halt the disease in its tracks, avoiding the toxic formation of plaques and amyloids found in the CNS.[2] Previous studies have shown that the absence of PrP^{C} does not cause detrimental effects in mice and humans.[3]

PROTACs and the UPS

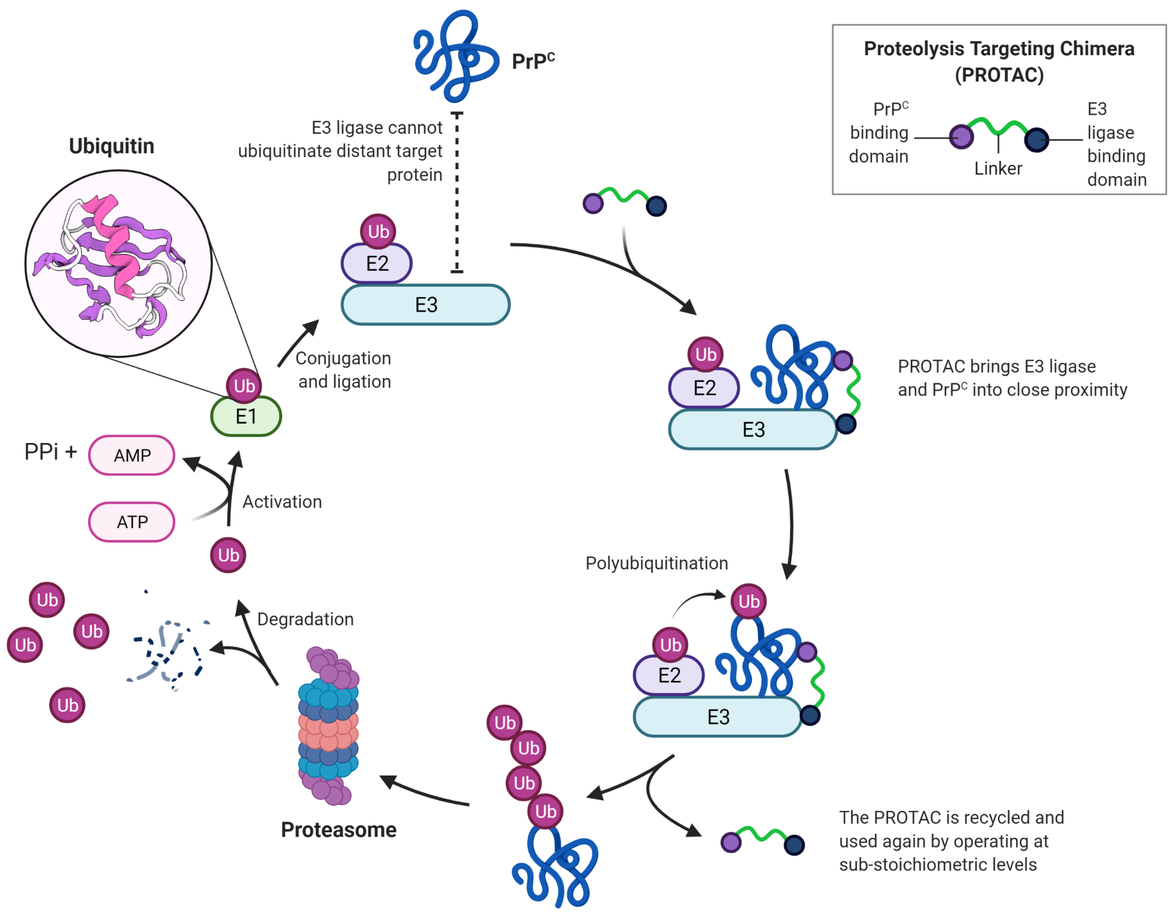

Figure 1 The role of a PrP^{C}-binding PROTAC molecule in the ubiquitin-proteasome system (UPS). Made using BioRender

Aims & Objectives

- Identify PrP^{C}-binding molecules as possible starting points for the synthesis of PROTACs by computational modelling in order to predict practical attachment points and vectors for linkers [4,5]
- Synthesise PROTACs with varying linker lengths, and E3 ligase-binding moieties — both VHL and CRBN E3 ligase binding moieties
- Show proof-of-principle that degradation of PrP^{C} by PROTACs is possible in cells and is safe

Materials & Methods

- Computationally modelled and predicted binding modes of a range of candidate small molecules that are known to bind to PrP^{C} by induced-fit docking (IFD) simulations
- PROTACs were designed based on these results
- Following several synthetic hurdles, a novel synthetic route was designed and implemented to allow rapid synthesis of the desired PROTAC molecules

Results

Computational

- Induced-Fit Docking (IFD) protocol applied to small molecules and human prion protein, PrP^{C}
- Practical attachment point determined for each small molecule
- Optimum vector for linker attachment identified

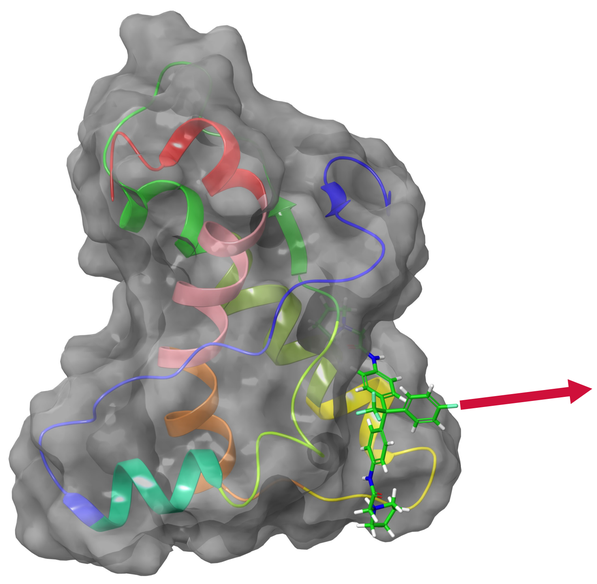

Figure 2 Computational modelling of PrP^{C}-binding small molecule using IFD on Schrödinger software v12.6. PDB: 1AG2

Chemistry

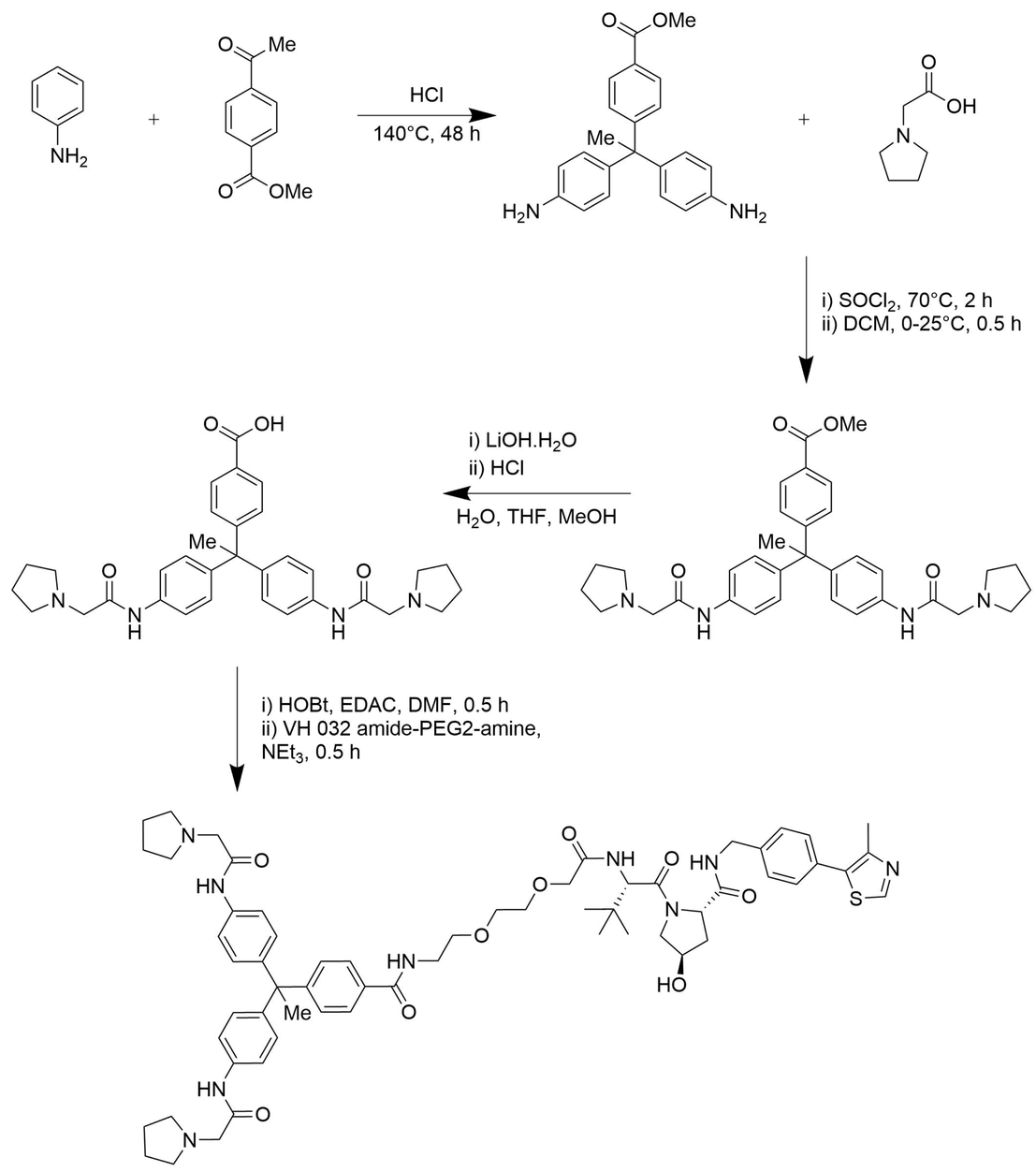

Figure 3 Reaction scheme of the general synthetic route used to rapidly produce a series of PROTACs

Conclusions and Outlook

Despite challenging chemistry, the recent successful synthesis of the first PROTAC molecule represents a major milestone in the project. This synthetic route will allow rapid synthesis of several analogues.

Biochemical, biological, and biophysical assays will be used to test the ability of the PROTACs to degrade the PrP^{C} protein, which would serve as an exciting starting point for developing future therapies for prion diseases.

References

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