ABSTRACT

Excessive mitochondrial fission contributes to a variety of pathologies, including cardiovascular diseases (CVDs), neurodegenerative disorders and cancer. Dynamin-related protein 1 (Drp1), a mitochondrial GTPase, plays a crucial role in mitochondrial homeostasis and was demonstrated to interact with Fission protein 1 (Fis1), leading to excessive mitochondrial fission, and mitochondrial impairment. Therefore, inhibition of the Drp1/Fis1 protein-protein interaction (PPI) is important for both basic research and drug discovery. Previously, we developed P110, a linear peptide that inhibits excessive mitochondrial fission and specifically targets the Drp1/Fis1 PPI. This peptide demonstrated various therapeutic potentials in a variety of disease models. Herein, based on a rational design approach and structure-activity relationship (SAR) studies, we present the development of CVP-350, a macrocyclic Drp1/Fis1 PPI inhibitor, with 'drug-like' properties. CVP-350 demonstrated: (1) Effective and specific inhibition of the Drp1/Fis1 interaction, underscoring their potential bioactivity *in vitro*. (2) Preservation of mitochondrial integrity and function under multiple cellular stressors *in vitro,* suggesting promising effects on mitigating mitochondrial-related cellular dysfunction. (3) Reduction of myocardial damage by 50-70% in a rodent infraction model, without causing any observable toxicity. Overall, our findings indicate that CVP-350 can serve as a promising lead for the treatment of diseases related to mitochondrial dysfunction.

Keywords: Dynamin-related protein 1 (Drp1), Fission protein 1 (Fis1), Protein-protein interactions (PPIs), Peptide, Macrocyclic, Structural activity relationship (SAR), Peptidomimetic, Mitochondria, Cardiovascular Diseases (CVDs).