86. Compositions for treatment of neurological & OSD

(Oregon Health and Science University)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Small Molecule
Disease Area	Others
Indication	Neurological and Oxidative Stress Disorders
Current Stage	Lead Optimization
Target	mtPTP
MoA	Small molecules inhibit mtPTP
Brief Description	• The mitochondrial permeability transition pore (mtPTP) plays a key role in a wide variety of human diseases whose common pathology may be based in mitochondrial dysfunction; however, there are few small molecule inhibitors of mtPTP. The leading mtPTP inhibitor CsA also has limitations, including a likely indirectly mechanism of inhibition, an inability to cross the blood brain barrier, and immunosuppressive side effects. • The laboratories of Drs. Forte, Bernardi and Cohen have developed and optimized small molecule mtPTP inhibitors. The lead compounds demonstrate the following: ➢ Picomolar IC50s for inhibiting the opening of mtPTP ➢ Inhibition of mtPTP opening, independent of cyclophilin D, and synergism when combined with CsA. ➢ Inhibition of mitochondrial swelling in murine liver cells. ➢ Absence of mitochondrial toxicity as demonstrated by measurements of mitochondrial membrane potential, oxygen consumption rates and ATP synthesis. ➢ High stability in human serum over the course of several hours. ➢ Reduction in muscular dystrophy symptoms in zebrafish models. ➢ Cardioprotective effects in adult mouse ventricular myocytes, human iPSc-derived cardiomyocytes, and in ex vivo in perfused hearts.
Intellectual Property	US20220289690A1
Publication	• A novel class of cardioprotective small-molecule PTP inhibitors. Pharm Research, (2020) • Second-Generation Inhibitors of Mitochondrial Permeability Transition Pore with improved Plasma Stability. Chem MedChem. (2019) • Discovery, Synthesis, and Optimization of Diarylisoxazole-3-carboxamides as Potent Inhibitors of the Mitochondrial Permeability Transition Pore, Chem MedChem. (2015)
Inventors	Michael Cohen, Michael Forte, Justina SILEIKYTE, Aaron Nilsen, Jordan Devereaux, Paolo BERNARDI

Highlights

- This compounds enabled the construction of a series of picomolar mtPTP inhibitors that also potently increase the calcium retention capacity of the mitochondria.
- The therapeutic potential and in vivo efficacy of one of the most potent analogues, N-(3-chloro-2-methylphenyl)-5-(4-fluoro-3-hydroxyphenyl) isoxazole-3-carboxamide (60), was validated in a biologically relevant zebrafish model of collagen VI congenital muscular dystrophies.

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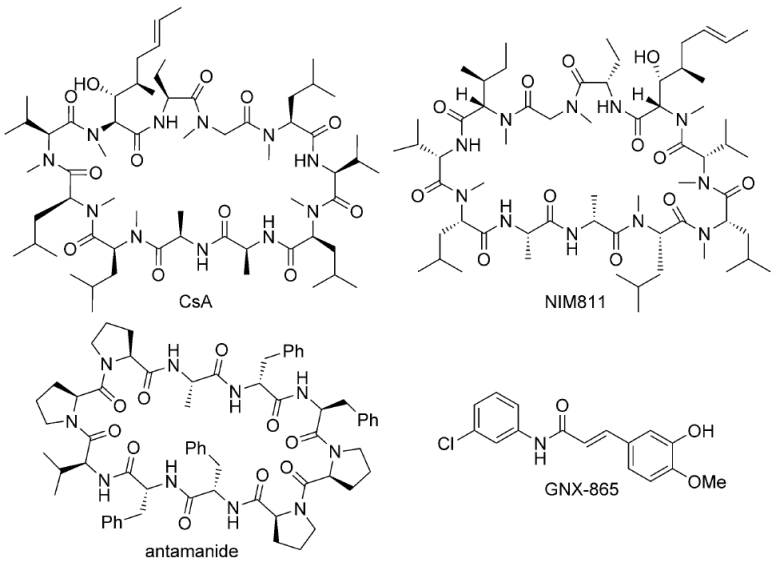
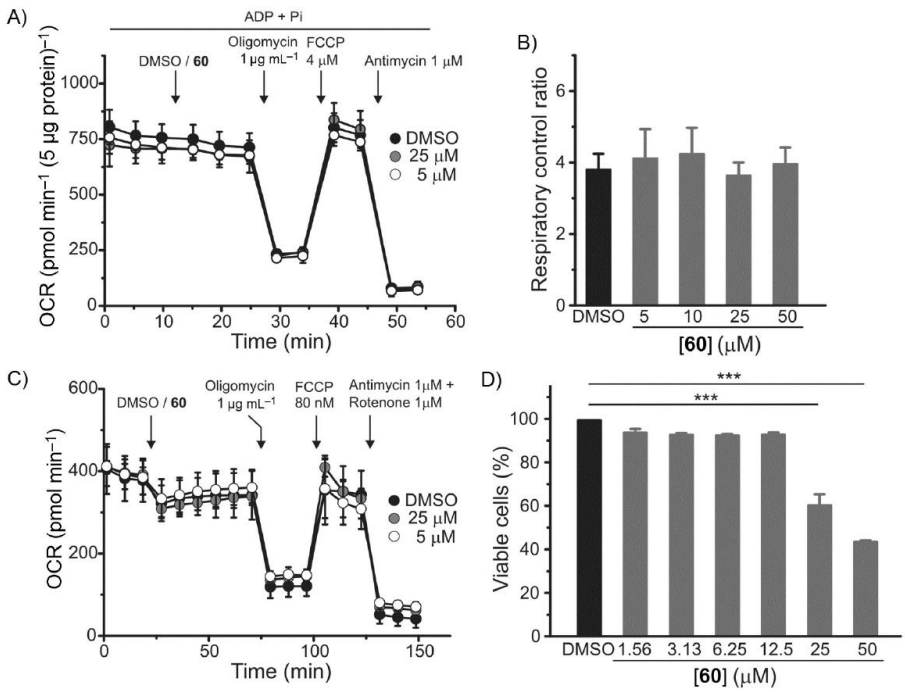
Key Data

Structures of prominent mtPTP inhibitors



Effect of compound 60 on oxygen consumption rate (OCR) and HeLa cell proliferation



Source: https://pubmed.ncbi.nlm.nih.gov/26286375/

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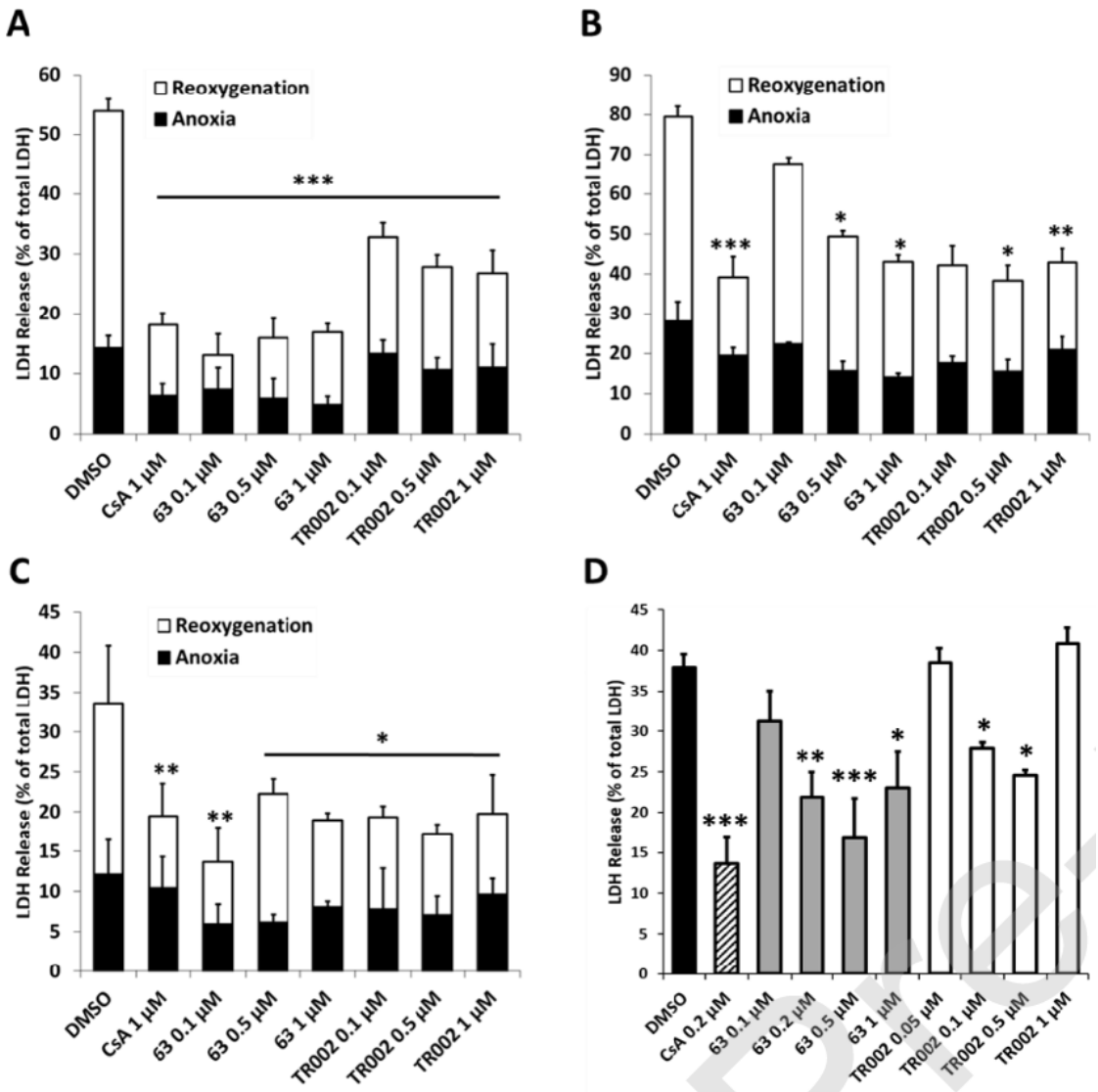
Key Data

Effects of compounds 63 and TR002 on cardiomyocytes viability



Cell death measured by LDH release from **A)** isolated NRVMs, **B)** isolated AMVMs and **C)** hiPSc-CMs treated for 30 minutes with different concentrations of either 63 or TR002 or with 1 µM CsA. *p < 0.05, **p < 0.01, *** p< 0.001 vs DMSO Reoxygenation. **D)** Cell death measured by LDH release in *ex vivo* hearts perfused in a Langendorff model of I/R, with or without 63, TR002 or CsA. *p < 0.05, **p < 0.01, ***p < 0.001 vs DMSO. For *in vitro* experiments (**A, B, C**), approximately 3/4 wells were analyzed per condition in each experiment and all the experiments were performed at least three times using three different animal preparations or cell differentiations. For *ex vivo* experiments (**D**), n = 5 to 13. Data are expressed as mean ± SEM