

Discovery and Optimization of Novel Inhibitors of the Mitochondrial Permeability Transition Pore

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The mitochondrial permeability transition pore (mtPTP) is a Ca²⁺-requiring megachannel that permanently opens under pathological conditions and leads to deregulated release of Ca²⁺ and mitochondrial dysfunction. For the past couple of decades the mtPTP has been implicitly recognized as a therapeutic target for several deadly diseases such as Alzheimer's disease, muscular dystrophies, myocardial infarction, stroke, and diabetes. Herein we report the results of a high-throughput screening/chemical optimization approach that led to the discovery of two new chemotypes: (a) diarylisoxazole-3-carboxamides and (b) *N*-phenylbenzamides, which are first subnanomolar inhibitors of the mtPTP. The therapeutic potential and *in vivo* efficacy of the most potent analogues were validated in a biologically relevant zebrafish model of collagen VI congenital muscular dystrophies.

