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

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The mitochondrial permeability transition pore (mtPTP) is a Ca\textsuperscript{2+}-requiring megachannel that permanently opens under pathological conditions and leads to deregulated release of Ca\textsuperscript{2+} 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) diarylisoazole-3-carboxamides and (b) \textit{N}-phenylbenzamides, which are first subnanomolar inhibitors of the mtPTP. The therapeutic potential and \textit{in vivo} efficacy of the most potent analogues were validated in a biologically relevant zebrafish model of collagen VI congenital muscular dystrophies.

![Chemical structures and SAR optimization]

\begin{itemize}
  \item \textbf{isoxazole hit}
  \item \textbf{SAR optimization}
  \item \textbf{mtPTP inhibitors}
  \item \textbf{SAR optimization}
  \item \textbf{subnanomolar probe}
  \item \textbf{submicromolar probe}
\end{itemize}