Trifunctional High-Throughput Screen Identifies Promising Scaffold To Inhibit Grp94 and Treat Myocilin-Associated Glaucoma

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Gain-of-function mutations within the olfactomedin (OLF) domain of myocilin result in its toxic intracellular accumulation and hasten the onset of open-angle glaucoma. The absence of myocilin does not cause disease; therefore, strategies aimed at eliminating myocilin could lead to a successful glaucoma treatment. The endoplasmic reticulum Hsp90 paralog Grp94 accelerates OLF aggregation. Knockdown or pharmacological inhibition of Grp94 in cells facilitates clearance of mutant myocilin via a non-proteasomal pathway.

Here, we expanded our support for targeting Grp94 over cytosolic paralogs Hsp90? and Hsp90?. We then developed

Comparison of the co-crystal structure of compound 2 and another non-selective hit in complex with the N-terminal domain of Grp94 reveals a docking mode tailored to Grp94 and explains its selectivity. A new lead compound has been identified, supporting a targeted chemical biology assay approach to develop a protein degradation-based therapy for myocilin-associated glaucoma by selectively inhibiting Grp94.

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