2-YIA-48 YIA

Identification of a chemical chaperone for preventing protein aggregation and proteotoxicity under endoplasmic reticulum stress

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Endoplasmic reticulum (ER) is responsible for protein biosynthesis and folding, but accumulation of unfolded proteins leads to disturbance of ER proteostatis and subsequent clinical pathologies including diabetes, neurodegenerative disease and cancer. Chemical chaperones are chemical compounds that help protein folding and suppress aggregation, and receiving increased attention as potential therapeutic approaches for ER stress-related diseases. In this study, we established a novel ER stress reporter cell line and identified compound X as a chemical chaperone from the 217,765-compound chemical library. Compound X directly binds to secreted or membrane proteins and inhibits protein aggregation during tunicamycin induced ER stress. Furthermore, compound X significantly prevented cell death caused by chemically induced ER stress and by an aggression-prone mutant prion protein. These results show the therapeutic potential of compound X as a chemical chaperone that can ameliorate ER stress-related diseases.