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Benzoisothiazole-linked 2,5-dichlorotriazine derivative modulates alpha-synuclein, amylin, tau, and transthyretin aggregation

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Benzothiazole–triazine derivatives potently disrupt protein fibrils linked to Alzheimer's, Parkinson's, and diabetes.

Researchers at Purdue University have developed a portfolio of small molecules that can reduce protein misfolding associated with the development of various diseases. A plethora of known diseases are classified as protein misfolding diseases with subsequent fibril formation. These diseases include Alzheimer's disease, Parkinson's disease, Huntington's disease, Type 2 diabetes, Lewy body dementia, and spongiform encephalopathy. There are currently limited general strategies that have emerged for developing small molecules capable of inhibiting the formation of fibrils, or to disaggregate amyloid deposits. Further, there are no effective therapies for resolving or halting neurodegenerative diseases associated with protein disorders.

Researchers at Purdue University evaluated a set of 4-(2-benzothiazolyl) aniline (BTA) and its derivatives on their ability to modulate the folding of prone-to-aggregate proteins such as islet amyloid polypeptide (IAPP), amyloid-beta (A?1-40, A?1-42), transthyretin (TTR81-127, TTR101-125), ?-synuclein (?-syn), and tau isoform 2N4R (tau 2N4R). By utilizing various biophysical methods, researchers were able to study compounds and identify the compounds that held the most promise for treating protein misfolding disorders. This study provides an initial platform to generate more potent inhibitors of ?-syn, tau 2N4R, and TTR fibril formation in the future.

Technology Validation: Transmission electron microscopy was used to confirm anti-fibrillary activity. The photoreactive cross-linking assay identified the most promising compound in reducing oligomerization. The most promising compound reduced the inclusions based on the cell-based assay using M17D neuroblastoma cells that express inclusion-prone ?S-3K::YFP. A Thioflavin-T fluorescence assay was used to monitor fibril

formation after treatment with the BTA compounds and its derivatives. The most promising compound identified by this research abrogated the fibril, oligomer, and inclusion formation in a dose-dependent manner.

Advantages:

-Potent inhibition of fibril formation

Applications:

- Drug development

- Drug discovery

Related Publications:

5-Nitro-1,2-benzothiazol-3-amine and N-Ethyl-1-

[(ethylcarbamoyl)(5-nitro-1,2-benzothiazol-3-yl)amino]formamide

Modulate a-Synuclein and Tau Aggregation

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TRL: Pharmaceuticals

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Provisional-Gov. Funding, 2023-04-24, United States

NATL-Patent, 2024-02-02, Europe

PCT-Gov. Funding, 2024-02-02, WO

NATL-Patent, 2025-08-01, United States

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