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Discovery of 4-aminoindole Carboxamide Derivatives to Curtail Tau Isoform 2N4R Oligomer and Fibril Formation

4-aminoindole carboxamides inhibit tau and alpha-synuclein aggregation with low toxicity for neurodegenerative therapy.

Alzheimer's and Parkinson's are neurodegenerative diseases with symptoms that encompass cognitive decline, movement disorders, functional incapacitation, and often premature death. These diseases arise from the protein fibrillization processes where the tau protein and alpha-synuclein aggregates form neurofibrillary tangles (NFTs) and Lewy bodies. Current treatment methods for these diseases focus mainly on the alleviation of symptoms rather than treating underlying causes.

Purdue researchers have developed a pharmaceutical strategy that involves aminoindole carboxamide-based compounds for the treatment of Alzheimer's and Parkinson's. These compounds can modify the tau protein and alpha-synuclein without altering their fundamental structure. Furthermore, they have shown efficacy at therapeutic doses. This strategy allows researchers to combine the developed compounds with pharmaceutical carriers, which can be pharmaceutical additives like lactose, mannitol, and microcrystalline cellulose for the administration of the carrier via various pathways. Researchers have also further developed multiple formulations for oral intake, spanning from tablets to syrups, optionally augmented with sugar or gastric/enteric coatings for enhanced adaptability. This strategy shows promise as a next step treatment therapy for Alzheimer's and Parkinson's and exhibits potential adaptability for other analogous neurodegenerative diseases.

Technology Validation:

- Anti-fibrillary activity using tau isoform 2N4R in ThT fluorescence assay was confirmed

- Structural analogs were tested at various concentrations in the presence of tau 2N4R

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Category
Pharmaceuticals/Drug Discovery & Development
Pharmaceuticals/Pharmaceutical Packaging & Delivery Systems

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- Alpha-syn and tau oligomer formation with aminoindole carboxamides by photo-inducing cross uncoupled protein (PICUP) assay was tested

- Various amide compounds at different concentrations tested demonstrated protein oligomerization inhibition

- Alpha-syn and tau oligomer formation by transmission electron microscopy was examined.

- Direct changes in alpha-syn and tau isoform 2N4R fibril morphology were observed, showing a significant inhibition of fibril formation in tau isoform 2N4R

Advantages:

- Strategy effectively targets and reduces fibrillization in specific proteins like tau isoform 2N4R and alpha-syn

- Minimal toxicity in neuroblastoma cells was shown for developed compounds

- Strategy can evaluate both fibrillary and oligomer formation, lending itself for applications in various stages of protein aggregation

Applications:

- Neurodegenerative Disease Therapeutics for Parkinson's Disease and Alzheimer's Disease

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TRL: Pharmaceuticals

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