

# 2-(4-aminophenyl)benzothiazole derivatives modulate transthyretin aggregation

*Vivek Grandhe, Kendall B. E. Moore, A Prasanth Saraswati, Jessica S. Fortin*

Department of Basic Medical Sciences, College of Veterinary Medicine, Purdue University, 625 Harrison Street, West Lafayette, Indiana, USA;

**Introduction:** Transthyretin (TTR), a protein produced in the liver, plays a key role in thyroxine and retinol transportation. TTR is prone to generate amyloid deposits and has been causally implicated in two fatal, hereditary conditions: familial amyloid polyneuropathy (FAP) and familial amyloid cardiomyopathy (FAC). To provide a diverse portfolio of therapeutic small molecules, we prepared a set of TTR-interacting compounds: 4-(2-benzothiazolyl)aniline (BTA) and its derivatives containing urea (**1**), thiourea (**2**), and sulfonamide (**3**), and triazole (**4**) linker to prevent the formation of transthyretin oligomers and fibrils. This study aims to define the activity of BTA and its derivatives on TTR aggregation by utilizing biophysical methods and relevant TTR fragment peptides.

**Methods:** Thioflavin-T (ThT) fluorescence assay was used to monitor fibril formation with synthetic TTR truncated peptides, TTR<sub>81-127</sub> and TTR<sub>101-125</sub>, and other neuropeptides treated with BTA and its derivatives. At the end of a time-course study, fibrils were detected and measured by transmission electron microscopy (TEM). Oligomer formation was monitored with photoreactive cross-linking assay.

**Results:** As confirmed by TEM, BTA and its derivatives were able to abrogate fibril formation *via* the ThT fluorescence assay. Moreover, BTA inhibited the aggregation of other prone-to-aggregate proteins, such as alpha-synuclein and islet amyloid polypeptides. By photoreactive cross-linking assay, BTA and compound **2** failed to prevent the formation of TTR fragment oligomers. Among twelve newly prepared compounds, two BTA derivatives abrogated the aggregation of alpha-synuclein and other neuropeptides. Compound **15** demonstrated an anti-fibrillary effect on TTR<sub>101-125</sub> truncated peptide.

**Conclusions:** This study provides an initial platform to generate more potent inhibitors of prone-to-aggregate neuropeptides including TTR fragment peptides.

**Acknowledgement:** This research was supported by the National Institutes of Health (NIA NIH R21AG070447-01A1 and 1K08AG071985-01A1), Pharmaceutical Research, Manufacturers of America Foundation (730313), and American Society of Investigative Pathology (ASIP) Summer Research Opportunity in Pathology Program (SORP).