UMEÅ UNIVERSITET

Synthesis of Ring-fused Peptidomimetics

Interacting with Amyloid Fibrils

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Glasburen, KBC. Audiens kan vara med via Zoom eller i Stora Fokusrummet, KBC.
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Avhandlingen kommer att försvaras på engelska.

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Abstract
Parkinson's and Alzheimer's disease are the two most common neurological disorders in humans. Both conditions involve progressive death of neurons in the central nervous system, decline in bodily functions and eventually (and invariably), death. So far, no cure exists and the available treatments can only ease symptoms. Despite substantial investments in research, the biomolecular processes are still far from fully understood. However, both diseases are associated with formation of fibrillar protein aggregates called amyloid deposits. Whereas Alzheimer's disease involves aggregation of the Tau and Amyloid β proteins, α-Synuclein fibrilization plays a key role in Parkinson's disease. Although they are chemically distinct, the deposits consist of protein fibres with similar morphology and fold. Small molecules, such as the thiazoline fused 2-pyridones herein presented, can interfere with the formation of amyloid fibres, or bind to them. Besides having potential for diagnostication and treatment, such small molecules constitute valuable tool compounds in future research, to unravel the mechanisms of amyloid formation and pathology. The first step towards successful treatment, diagnostication and prevention of Alzheimer's and Parkinson's disease is understanding the causes and underlying mechanisms better. This thesis narrates the synthesis and development of novel chemical structures: multi ring fused peptidomimetics with the ability to bind mature amyloid fibrils, consisting of α-Synuclein or Amyloid β.

The first project (articles I, III and VI) describes method development for the extension of bicyclic thiazolino 2-pyrdiones by fusion with aromatic nitrogen heterocycles, which enables the desired amyloid binding properties. Derivatisations of the newly generated central scaffold, and variation of the multiple attached substituents, were subsequently performed in efforts to improve binding strength and solubility, and gain selectivity towards certain fibrils. One of the most promising amyloid fibril binders was evaluated in a human cell line and in mice, and found to be protective against accelerator induced neurotoxicity. One pyrimidine fused compound moreover indicated potent inhibition of Amyloid β aggregation. The second project (articles II, IV and V) focuses on development of methods to modify the thiazoline ring. Ring opening induced by electrophiles generates *N*-alkenyl 2-pyridones but decreases amyloid binding potency. Introduction of a cyclobutane moiety fused with the thiazoline ring is better tolerated, and adds a terminal alkene moiety that can be exploited in future chemical modifications. Expansion of the five membered thiazoline ring to a six membered dihydrothiazine ring, equipped with a nitrophenyl substituent, provides compounds with enhanced fibril binding capacity, which further inhibits Amyloid β fibril formation *in vitro*. Taken together, the synthetic methodologies allow construction and late stage modification of complex fused heterocycles, with several points of variation. Thus, the developed methods may be of future value in our laboratories and elsewhere.

Keywords
organic chemistry, synthesis, peptidomimetics, thiazoline fused 2-pyridones, Alzheimer's disease, Parkinson's disease, Amyloid, Amyloid β, α-Synuclein, method development

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