Synthesis of Altenusin Analogues as Tau Aggregation Inhibitors

Worldwide, around 50 million people have dementia, a figure set to increase to 152 million by 2050.[1] Alzheimer's disease (AD), the most common form of dementia, is characterized by the presence of amyloid plaques, in the brain, consisting of insoluble amyloid-β (Aβ) and tau protein-containing neurofibrillary tangles (NFTs).[1–3]

A critical pathological event in several neurodegenerative disorders is the aggregation of tau into intraneuronal filamentous inclusions. A large amount of research currently focuses on direct inhibition of tau aggregation with small molecules as one approach to slow the disease progression of AD.[4,5]

Accordingly, the Kassiou group have performed a methodical structure activity relationship (SAR) study to determine which features of *Altenusin,* a tau aggregation inhibitor *in vitro*[6]**,** contribute to its tau aggregation activity. Indole groups was suggested to be introduced according to an NMR-based fragment screen on the microtubule-binding domain of tau and some rudimentary electrostatic modelling studies. The lead compound from the library of "hybrid" molecules displayed similar activity to *Altenusin*. But the catechol group and ester group still worth doing a modification since they might contribute to low absorption and is a potential metabolic liability.[7] Thus, bioisosteric replacements of the lead compound has been done with the aim to overcome those such issues.

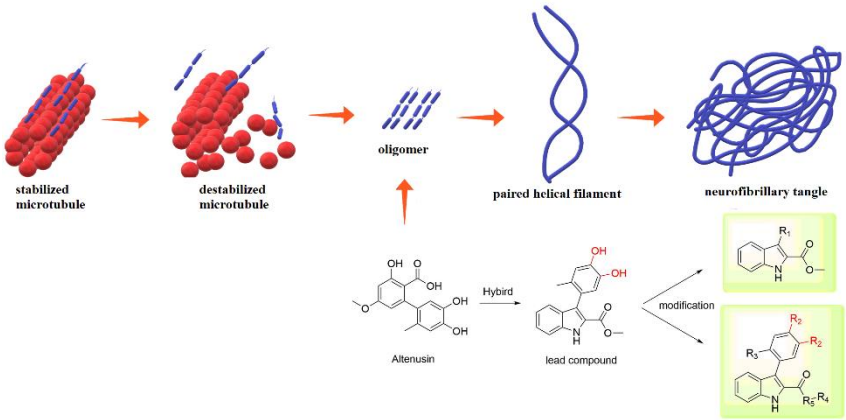

Figure 1: The pathway of tau aggregation. The tubulins are represented as red circles and tau protein as blue sticks.

References

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