Targeting Protein Aggregation with Steroid-Quinoline Hybrids and Chromeno[3,4-*b*]xanthones

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Inhibiting and/or reversing protein aggregation is a vital tool to fight protein-misfolding disorders such as Alzheimer's, Parkinson's, and cardiovascular diseases. The most recognizable type of protein aggregation is perhaps the amyloid-β, associated to Alzheimer's disease. Different types of small-molecule compounds have been developed in attempting to stop the Aβ1-42 aggregation, which ultimately leads to the formation of senile plaques. It seems that hitting protein aggregation alone is not enough to provide disease-modifying effects. Therefore, the drug discovery paradigm for conformational disorders is shifting for multi-target compounds, designed to hit protein aggregation in combination with other targets. Following this quest, we develop two types of multi-functional compounds - Steroid–Quinoline Hybrids and Chromeno[3,4-b]xanthones (Fig. 1 and 2).

The Steroid-Quinoline Hybrids were designed as hydrophobic structures, based on the framework combination approach. This set of non-toxic compounds proved their efficacy inhibiting the Aβ 1-42 self-aggregation in vitro by delaying the growth phase and/or reducing the number of fibrils in the steady state (Fig. 1). Their efficacy was further demonstrated against pre-aggregated Aβ1-42 peptides in cellular assays in neuroblastoma cells, as they reverted both the number and the average area of fibrils back to basal levels (Fig. 1). The anti-aggregation effect of these hybrids was further demonstrated in a cellular model of general protein aggregation expressing a protein aggregation fluorescent sensor (Fig. 1).

Chromeno[3,4-b]xanthones were designed, synthesized, and evaluated as first-in-class acetylcholinesterase (AChE) and Aβ aggregation dual-inhibitors (Fig. 2). The core structure of chromeno[3,4-b]xanthones emerged as AChE lead with IC50 of 2.1 μM, whether the methoxy-substituted derivative stood up as AChE and Aβ aggregation dual-inhibitor with IC50 of 3.9 μM and 70% inhibition, respectively (Fig. 2).

FIGURE 1
Steroid-quinoline hybrids with wide and marked disaggregation capacities. Micrographs of cells incubated with Aβ1–42 alone (left) or in combination with compound 4c (center) or 6c (right).

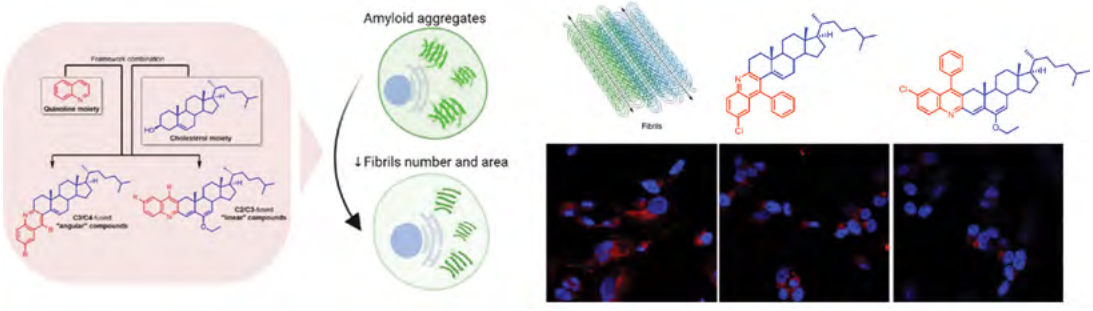

FIGURE 2
Chromeno[3,4-b]xanthones as first-in-class AChE and Aβ-aggregation dual-inhibitors. In vitro inhibition of Aβ-self aggregation (left); Aβ1-42 and AChE dual-target lead compounds (center); AChE binding mode of chromeno[3,4-b]xanthones (right).