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Synthesis and evaluation of 1,2,3,4-tetrahydro-1-acridone analogues as potential dual inhibitors for amyloid-beta and tau aggregation

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ABSTRACT

Amyloid-β (Aβ) and tau protein are two crucial hallmarks in Alzheimer's disease (AD). Their aggregation forms are thought to be toxic to the neurons in the brain. A series of new 1,2,3,4-tetrahydro-1-acridone analogues were designed, synthesized, and evaluated as potential dual inhibitors for Aβ and tau aggregation. *In vitro* studies showed that compounds **25**–**30** (20 μM) with *N*-methylation of the quinolone ring effectively inhibited $Aβ_{1-42}$ aggregation by 84.7%–99.5% and tau aggregation by 71.2%–101.8%. Their structure-activity relationships are discussed. In particular, **30** could permeate the blood-brain barrier, bind to $Aβ_{1-42}$ and tau, inhibit $Aβ_{1-42}$ β-sheets formation, and prevent tau aggregation in living cells.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by cognitive decline and associated dementia for a period ranging from years to decades before death. However, memory can be retrieved at the early stage of AD.[1] Extracellular amyloid-β (Aβ) deposits and intracellular neurofibrillary tangles (NFT) composed of highly phosphorylated tau proteins are two major neuropathological lesions described in patients with AD. Both Aβ and tau aggregation could emerge far more years before cognitive decline, thus making them potential targets for AD treatment.

Aβ and tau have been studied independently and therapies based on Aβ cascade hypothesis and tau hyperphosphorylation have been examined in clinical trials; however, few breakthroughs were achieved. Recent studies determined that there are links between Aβ and tau. Some evidence suggests that Aβ formation can drive tau pathology, even though tau deposition in the brain might precede the formation of Aβ plaques.[2] Removal of extracellular and intraneuronal Aβ via immunization has been shown to reduce neural accumulation of tau.[3] On the other hand, crossing of APP transgenic mice with knockout mice lacking tau could prevent cognitive deficits associated with the presence of Aβ.[4] However, whether Aβ is necessary for tau neurotoxicity or whether the reverse is true remains a matter of debate.[5]

Due to the complex multifactorial nature of AD, molecules that modulate the activity of a single protein target are incapable of significantly altering the progression of the disease. In contrast, multifunctional agents with two or more correlative biological activities, which correspond with the multifactors of AD, have been widely designed for the treatment of AD.[6–8] Although some progress in this area has been made, the design of multifunctional drugs is still very difficult. Selecting a promising lead compound becomes the key point to explore potential multifunctional drugs.

Recently, some studies have suggested that the quinoline moiety is the pharmacophore of many anti-AD drugs, such as tacrine[9] and clioqunol.[10] Additionally, our previous research proved that **4a1**, which contains a quinoline moiety, is a potential multifunctional agent for AD treatment (Fig. 1A).[11]

In addition, many studies have suggested that α,β-unsaturated carbonyl compounds could act as covalent inhibitors in the aggregation pathway of tau, including oleocanthal,[12] cinnamaldehyde[13] and asperbenzaldehyde[14] (Fig. 1B).

Compounds containing highly conjugated π-electron networks with high polarizability such as methylene blue and crystal violet are both the most potent tau aggregation inhibitors reported (Fig. 1C),[15] and all share a centrosymmetric structure with extensive delocalization of their fixed cationic charge.

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; BBB, blood-brain barrier; CAs, cinnamic acid derivatives; CD, circular dichroism; DAPI, 4′,6-diamidino-2-phenylindole; DMED, Dulbecco's modified Eagle's medium; DMSO, dimethylsulfoxide; HRMS, high resolution mass spectra; LMTM, leucomethylene blue; NFT, intracellular neurofibrillary tangles; PBL, porcine brain lipid; SPR, surface plasmon resonance; TEM, transmission electron microscope; ThS, Thioflavin S; ThT, Thioflavin T

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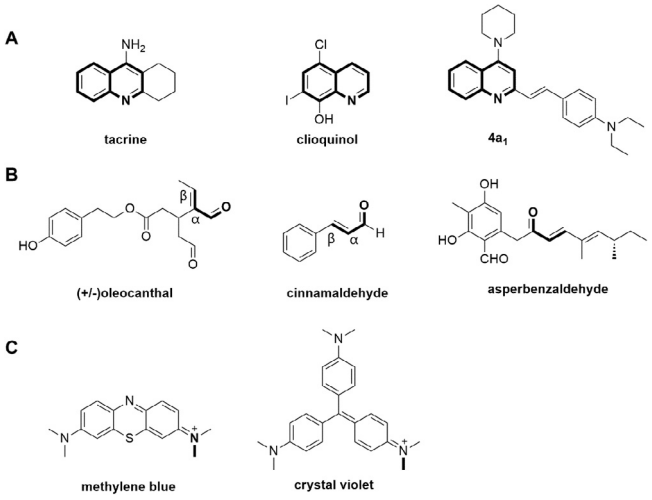
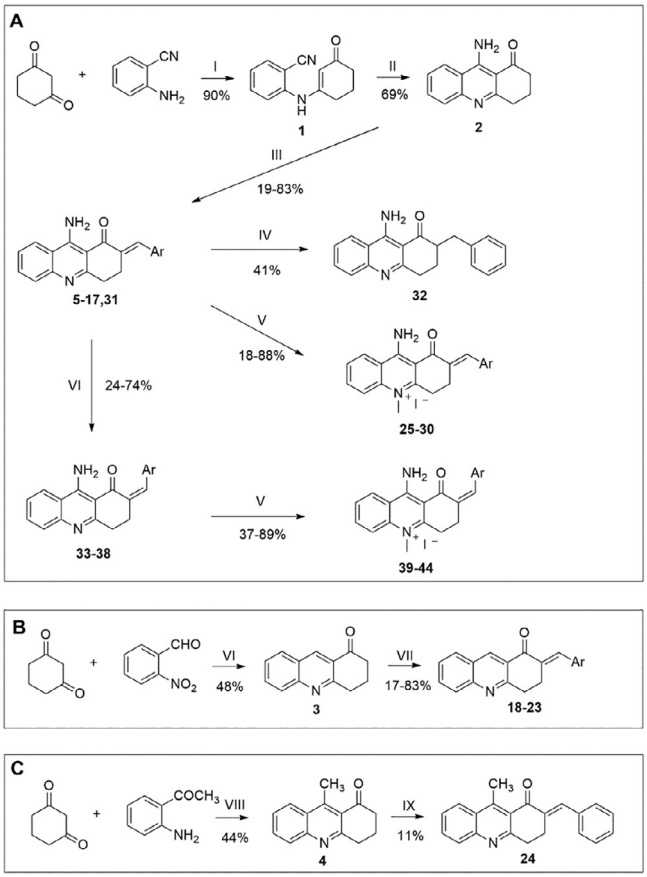


Fig. 1. (A) Chemical structures of tacrine, clioquinol, and **4a1**. (B) Chemical structures of oleocanthal, cinnamaldehyde, and asperbenzaldehyde. (C) Chemical structures of methylene blue and crystal violet.

In the present study, we fused the structure of tacrine and cinnamaldehyde in a single molecular entity to obtain compound **5** to make the quinoline group and α,β-unsaturated ketone group work in a synergistic manner (Fig. 2). It has been reported that the polar substitutions on the aromatic rings of the compounds are essential for their binding with Aβ.[16] Therefore, we introduced a series of aromatic rings with different substituents to the D ring to obtain compounds **6–17**. The amino substituent at the 9-position of the B ring was also modified to obtain compounds **18–24**. In addition, a cationic charge was introduced at the *N*-position of the quinolone ring to obtain compounds **25–30**. To study the impact of the chain between the C ring and D ring, compounds **31–44** were also designed. With the above considerations, a series of new 1,2,3,4-tetrahydro-1-acridone analogues were synthesized, and their inhibitory activities against Aβ and tau aggregation were evaluated.

2. Chemistry

The synthetic pathway for 1,2,3,4-tetrahydro-1-acridone analogues is shown in Scheme 1. The treatment of 1,3-cyclohexanedione with different substrates (for example, anthranilonitrile, 2-nitrobenzaldehyde or 2-aminoacetophenone) yielded the intermediates **1**, **2**,[17] **3**,[18] or **4**.[19] The target compounds **5–24** and **31** were obtained by the aldol reaction of intermediates **2**, **3**, and **4** with different aromatic aldehydes in the presence of sodium hydroxide. Compound **32** was obtained by the catalytic hydrogenation of compound **5** in the presence



Scheme 1. (A) Synthetic route of compounds **5–17** and **25–44**. Reagents and reaction conditions: (i) toluene, 120 °C, 3 h; (ii) copper (I) chloride, potassium carbonate, THF, reflux, 4 h; (iii) aromatic aldehyde, NaOH, ethanol, r.t. ~ 80 °C, 3 ~ 24 h; (iv) Pd/C, ethanol, H_2, r.t., 96 h; (v) CH_3I, acetone, 80 °C, 48 h; (vi) λ = 365 nm, DMSO, r.t., 24 h. (B) Synthetic route of compounds **18–23**. Reagents and reaction conditions: (i) methanol, acetic acid, H_2O, iron, 100 °C, 1 h; (ii) aromatic aldehyde, NaOH, ethanol, r.t. ~ 50 °C, 10 ~ 60 min. (C) Synthetic route of compound **24**. Reagents and reaction conditions: (i) H_2O, 70 °C, overnight; (ii) aromatic aldehyde, NaOH, ethanol, reflux, 48 h.

of Pd/C. Compounds **33–38** were obtained by the exposure of compounds **5**, **7**, **9**, **11**, **16** or **17** under UV light for 24 h in dimethylsulfoxide (DMSO). Compounds **5**, **7**, **9**, **11**, **16** or **17** and **33–38**, via interaction with iodomethane under sealed conditions at 80 °C for 48 h, yielded the target compounds **25–30** and **39–44**. The structures of the target compounds were validated by using ^{1}H NMR, ^{13}C NMR and HRMS. The *E*/*Z* isomers can be identified by using NOESY spectra. As

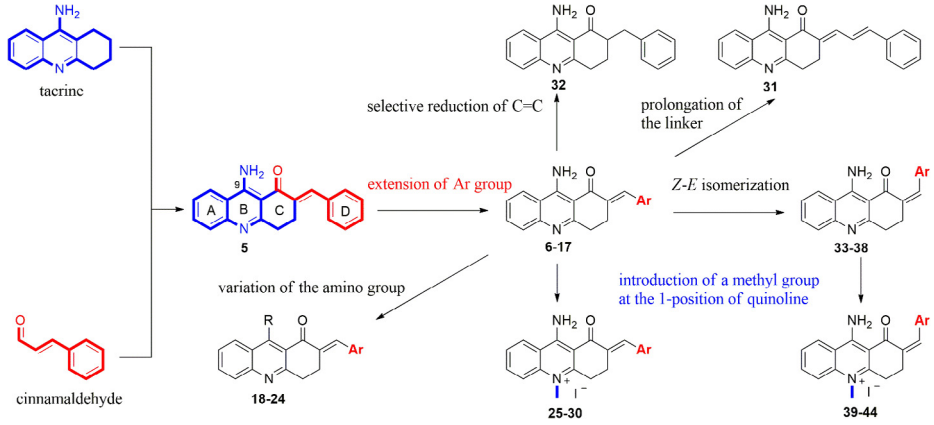


Fig. 2. Design of the new compounds derived from tacrine and cinnamaldehyde.