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Design, synthesis, and evaluation of multitarget-directed ligands against Alzheimer's disease based on the fusion of donepezil and curcumin

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ABSTRACT

By fusing donepezil and curcumin, a novel series of compounds were obtained as multitarget-directed ligands against Alzheimer's disease. Among them, compound **11b** displayed potent acetylcholinesterase (AChE) inhibition (IC_{50} = 187 nM) and the highest BuChE/AChE selectivity (66.3). Compound **11b** also inhibited 45.3% $A\beta_{1-42}$ self-aggregation at 20 μM and displayed remarkable antioxidant effects. The metal-chelating property of compound **11b** was elucidated by determining the 1:1 stoichiometry for the **11b**–Cu(II) complex. The excellent blood–brain barrier permeability of **11b** also indicated the potential for the compound to penetrate the central nervous system.

1. Introduction

Alzheimer's disease (AD), a complex, progressive neuro-degenerative disorder, is characterized by cognitive decline, memory loss, and regression of acquired skills leading to language dysfunction, visuospatial deficits, loss of insight, and frequent disturbances in emotion with interpersonal and social communication.[1] Since the first case of AD was identified by Alois Alzheimer in 1901,[2] approximately 44 million people worldwide have suffered from it over the past one hundred years. The disease poses a significant threat to older individuals and places serious spiritual and economic burdens on their families. Although the aetiology of AD remains not fully understood, two main clinical hallmarks of AD in the upper cortical layer of patients' brains have been recorded: senile plaques (SPs)[3] and neurofibrillary tangles (NFTs).[4,5] Several pathogenesis associated with these hallmarks include amyloid beta (Aβ) peptide deposition, tau protein hyperphosphorylation, oxidative stress, biometal dyshomeostasis, and low levels of acetylcholine (ACh), which have been observed in the development of AD. During the past few decades, a considerable number of therapies, including anti-cholinesterases, antioxidants, anti-inflammatories, anti-amyloid aggregation agents, metal chelates, and anti-apoptotic approaches have been explored in the search for strategies to treat AD.[6,5] However, there are still no effective treatments to prevent or even to reverse the effects of AD. The primary therapeutic options currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD are drugs directly targeting acetylcholinesterase (AchE), namely, AchE inhibitors (AChEIs) such as tacrine, donepezil, rivastigmine, and galantamine.[7,8] Among these drugs, donepezil is the most widely used pharmacological agent in clinical treatment.[9]

Natural products and their derivatives provide a diverse source of bioactive lead compounds for drug development.[10,11] Curcumin, extracted from the rhizome of Curcuma longa, possesses various biological and pharmacological activities. Gregory M. Cole and co-workers have reported that curcumin inhibited amyloid oligomer formation and reduced amyloid fibrils and plaques *in vivo*.[12] Numerous studies have also validated that curcumin exhibited Aβ-binding activity, induced degradation of deposited plaques and exerted cytoprotective effects by reducing Aβ-induced neurotoxicity.

Considering the multifactorial pathogenetic nature of AD, our group and other researchers has been committed to developing new multitarget-directed ligands (MTLDs) to fight back against this disease. Herein, we fused the pharmacophores of donepezil and curcumin to obtain a series of derivatives that were expected to be AChE inhibitor, metal chelator, antioxidant, and inhibitor of Aβ aggregation (Fig. 1). Furthermore, optimized compound **11b** was also chosen to be evaluated for its blood–brain barrier (PAMPA-BBB) permeability.

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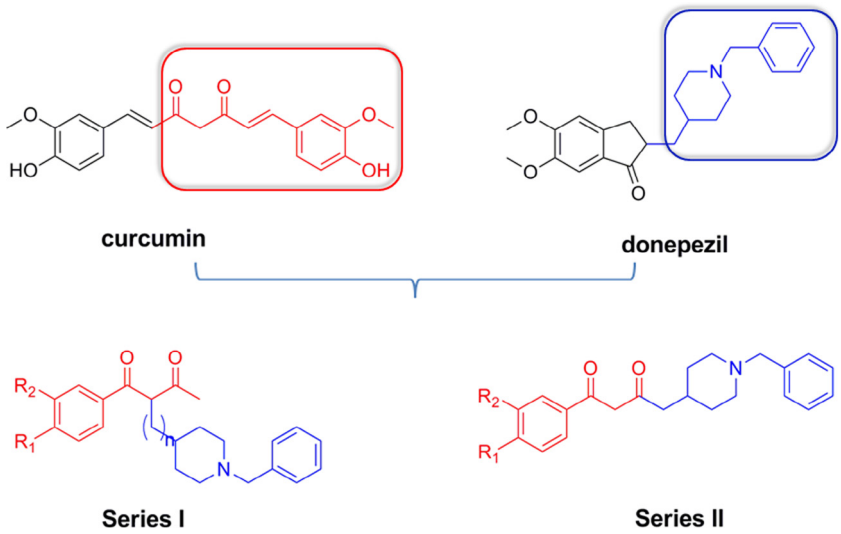


Fig. 1. Multitarget-directed design strategy of fusing the pharmacophore moieties of donepezil and curcumin.

2. Results and discussion

2.1. Chemistry

The synthetic routes for the donepezil-curcumin derivatives are outlined in Schemes 1–4. To summarize, this series of compounds were obtained by aldol condensation using the corresponding important intermediates listed in Schemes 1 and 2.

Using commercially available material **1**, the Wittig reaction in the presence of inorganic base (K_2CO_3) gave **2**, which was then subjected to a hydrogenation reduction with Pd/C to give intermediate **3**. After the reduction of ester **3** by $LiAlH_4$ produced primary alcohol **4**, a subsequent Swern oxidation yielded aldehyde **5** (Scheme 1).

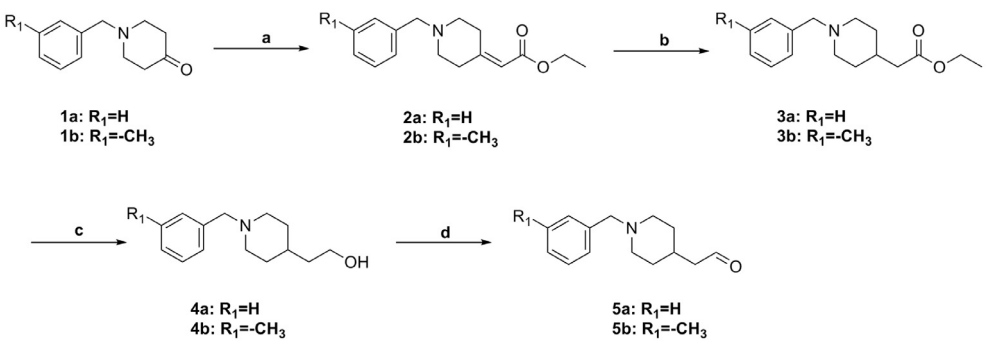
Starting from commercially available starting material **6**, the MOM-protected compounds **7a**–**7b** and the commercially available compounds **7c**–**7e** were reacted with ethyl acetate respectively to obtain important intermediates **8a**–**8b** via the Claisen condensation (Scheme 2).[13]

Target compounds **10a**–**10l** shown in Scheme 3 were obtained in two steps. The first was an aldol condensation using a ketone (**5a**–**5b**, **9**) and the corresponding β-diketonate derivatives (**8a**–**8e**) in the presence of a catalytic amount of L-proline to produce α,β-unsaturated compounds, and the second was a hydrogenation reduction reaction using 10% Pd/C as the catalyst (Scheme 3).

Target compounds **11a**, **11c**, **11e**, and **11f** were obtained via a Claisen condensation using the same conditions described in Scheme 2. Compounds **11b** and **11d** were obtained by the deprotection of the MOM-group from **11a** and **11c**, respectively (Scheme 4).

2.2. In vitro inhibition studies of AChE and BuChE

According to the cholinergic hypothesis, acetylcholine (ACh) levels selectively decline, while butyrylcholinesterase (BuChE) levels are unchanged or even increase in the central nervous system (CNS) of AD patients.[14,15] Therefore, agents that are expected to enhance ACh level by inhibiting AchE activity and keeping a balance of AChE and BuChE were designed. The AChE (*Electrophorus electricus*, eeAChE) and BuChE (equine serum) inhibitory effects of the hybrids were evaluated by the spectroscopic method described by Ellman et al.[16] Tacrine, donepezil, and galantamine were chosen as reference compounds (Table 1). From the results for the compounds in Series I, some structure and activity relationships (SARs) could be obtained. When the carbon chain length between the diketone group and benzyl piperidine group is 2 (n = 2), the inhibitory activity increased significantly. When n = 1 (compounds **10a**, **10b**, **10c**), the compound with the methoxy group located at *para*-position (compound **10c)** displayed the best AchE inhibition. While comparing the results for compounds **10d** and **10e**, it was demonstrated that replacing the R_3 group with a methyl group was advantageous to the activity. Moreover, when the 4-methoxy group was replaced by hydroxy group, it was unfavourable for the inhibitory activity (compound **10d** *vs* **10j**,



Scheme 1. Reagents and conditions: (a) $(EtO)_2POCH_2CO_2Et$, K_2CO_3, THF; (b) Pd/C, H_2, MeOH; (c) $LiAlH_4$, THF; (d) Swern oxidation.