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# Design, synthesis and evaluation of vilazodone-tacrine hybrids as multitarget-directed ligands against depression with cognitive impairment

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ABSTRACT

Depression, a severe mental disease, is greatly difficult to treat and easy to induce other neuropsychiatric symptoms, the most frequent one is cognitive impairment. In this study, a series of novel vilazodone-tacrine hybrids were designed, synthesized and evaluated as multitarget agents against depression with cognitive impairment. Most compounds exhibited good multitarget activities and appropriate blood-brain barrier permeability. Specifically, compounds **1d** and **2a** exhibited excellent 5-$HT_{1A}$ agonist activities (**1d**, $EC_{50}$ = 0.36 ± 0.08 nM; **2a**, $EC_{50}$ = 0.58 ± 0.14 nM) and 5-HT reuptake inhibitory activities (**1d**, $IC_{50}$ = 20.42 ± 6.60 nM; **2a**, $IC_{50}$ = 22.10 ± 5.80 nM). In addition, they showed moderate ChE inhibitory activities (**1d**, AChE $IC_{50}$ = 1.72 ± 0.217 μM, BuChE $IC_{50}$ = 0.34 ± 0.03 μM; **2a**, AChE $IC_{50}$ = 2.36 ± 0.34 μM, BuChE $IC_{50}$ = 0.10 ± 0.01 μM). Good multitarget activities with goodt blood-brain barrier permeability of **1d** and **2a** make them good lead compounds for the further study of depression with cognitive impairment.



## 1. Introduction

Depression, a common, severe mental disorder, is the primary cause of disability, suicide, diminished productivity and dependent care, with approximate 350 million people affected worldwide.[1] It is also a chronic and recurrent affective disease with multifarious etiology and symptoms.[2–4] Depressed people always suffer from weak social skills, chronic stress, low emotion, decreased energy and cognitive impairment.[5] Currently, most antidepressants take effect by noradrenergic-serotonergic transmitter systems or inhibiting monoamine oxidase (MAO) to reduce the degradation of serotonin (5-HT) and norepinephrine (NE).[6] It has been proved that the co-morbidity with other neuro-affected diseases is a significant characteristic of depression.[7] Along with the in-depth research of depression, antidepressant drugs based on different strategies have been conducted.[8–11]

It is recognized that depression, especially late-onset depression, is associated with cognitive impairment, such as poor concentration, information processing and memory impairment, executive dysfunction.[12–15] Antidepressants exhibited deficiency in cognitive impairment despite of the successful depression remission. Also, depressive patients with concurrent cognitive impairment, in particular cognitive impairement, undergo a lower antidepressant therapy response and higher recurrence.[16,17] Besides, depressive patients with cognition decline are a high risk group of Alzheimer's disease (AD) and it also brings negative consequences in patients and heavy burden in caregivers.[18–21] Such impaired cognition and memory processes in depressive disorder may attribute to the dysfunction of the cholinergic system and it could be alleviated by acetylcholinesterase inhibitors (AChEIs).[22–25] AChEIs, reducing the hydrolysis of acetylcholine, are commonly accepted as first-line drugs in treatment of moderate cognitive impairment.[26–28] A study has indicated that donepezil, a cholinesterase inhibitor, improved cognition in depressed people and may delay conversion to a diagnosis of AD.[29] Therefore, therapeutic strategies which target at cholinesterase may improve cognitive

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function in depressive people and prevent depression from recurrencing by improving executive function.[28,30]

Above all, aiming at complexed pathological mechanisms of neuropsychiatric and neurodegenerative diseases, design of multi-target ligands is a promising research direction.[31] Several studies have been successful in developing multi-target ligands which acted on central nervous system (CNS), and multi-target ligands could exhibit multiple pharmacological activities in *vivo*.[32,33] It is therefore understandable that the attempts to develop a kind of drug candidate which can alleviate depressive symptoms and cognitive impairment simultaneously based on the multi-target design strategy have been in pressing need. Our group devoted to the research of drug repurposing and the secondary development of conventional drugs. Vilazodone, an antidepressant, was found possessing moderate acetylcholinesterase (AChE) inhibitory activity ($IC_{50}$ = 21.3 ± 3.0 μM) in a high throughput screening (HTS) test with an in-house old drug library. As reported, vilazodone is a selective serotonin reuptake inhibitor (SSRI) and 5-$HT_{1A}$ receptor agonist,[34] which can increase serotonin concentration of synaptic cleft. Serotonin, a significant neurotransmitter existing in the brain extensively, plays a pivotal role in normal brain function.[35,36] 5-$HT_{1A}$ receptor agonists play a significant role in the therapeutics of major depressive disorder (MDD).[37–39] Moreover, SSRI, could increase the amount of available synaptic 5-HT, also were a remarkable characteristic of antidepressants.[40–42]

In order to meet our goal in developing novel drug candidate which can alleviate depressive symptoms and cognitive impairment simultaneously, we attempt to enhance the AChE inhibitory potency of vilazodone while keeping its effect on 5-HT system by two molecular design strategies. Firstly, traditional medicinal chemistry structural modification strategy was employed to modify the chemical structure of vilazodone. We had obtained several vilazodone derivatives in previous work, but their AChE inhibitory activities were not significantly ehnhanced. Alternatively, pharmacophore grafting is also considered as an efficient method to enhance AChE inhibitory potency. Hence, grafting an AChE inhibitory pharmacophore of known AChE inhibitors (AChEIs) into vilazodone was employed in the current study. In view of the simple structure and structure-modifying accessibility, tacrine was selected as the grafting pharmacophore of AChEI.

According to structure-activity relationships (SARs) of vilazodone, the benzofuran-2-carboxamide fragment is an appropriate site for structural modification and can tolerate a diversity of substituents.[43,44] Therefore, benzofuran-2-carboxamide fragment of vilazodone can be substituted by tacrine derivatives. In previous work of our group, Li et al.[45] have designed and synthesized the first class of vilazodone-tacrine hybrids targeting at ChE, 5-$HT_{1A}$ and 5-HT transport. In his design strategy, piperazine ring of vilazodone was linked to amino of tacrine. Although his design improved ChE inhibitory activity of vilazodone, the antidepressive activity was decreased severely. In order to enhance ChE inhibitory activity while the 5-$HT_{1A}$ agonist and 5-HT reuptake inhibitory activities are remained, a novel design strategy was conducted: piperazine ring of vilazodone was linked to benzene ring of tacrine (Fig. 1). We aim at developing a series multifunctional compounds with optimal antidepressive activity and adjuvant cognition promotion.

Based on the strategy mentioned above, a series of novel vilazodone-tacrine hybrids were designed, synthesized and evaluated in this article. Their AChE, BuChE, 5-HT reuptake inhibitory activities and 5-$HT_{1A}$ agonist activity were evaluated in vitro. Besides, the parallel artificial membrane permeability assay (PAMPA) was performed to provide preliminary predictions of the blood-brain barrier (BBB) penetration, expecting to provide evidence for optimized selection.

## 2. Results and discussion

### 2.1. Chemistry

The synthesis of the target compounds was accomplished according to the route shown in Schemes 1–3. In Scheme 1 and 2, intermediate **6a** (commercial available) and **6b** reacted with tacrine derivatives respectively in the presence of $Et_3N$ to obtain **1a**–**h**. In tacrine derivatives, piperazine connected to 9-amino-1,2,3,4-tetrahydroacridine in four different points, was depicted in **7a**–**d**.

In Scheme 3, derivatives were synthesized from indole intermediate and different tacrine derivatives respectively. The synthesis of key intermediates **6b**–**k** and **7a**–**g** were described in Supporting information. The detailed structures of compounds were illustrated in Table 1, and the synthesis of intermediates were showed in Supporting information.

### 2.2. 5-HT agonist activity

In order to evaluate the antidepressant-like activity of newly designed and synthesized vilazodone-tacrine hybrids, 5-$HT_{1A}$ agonism assay was conducted by using Human Embryonic Kidney 293

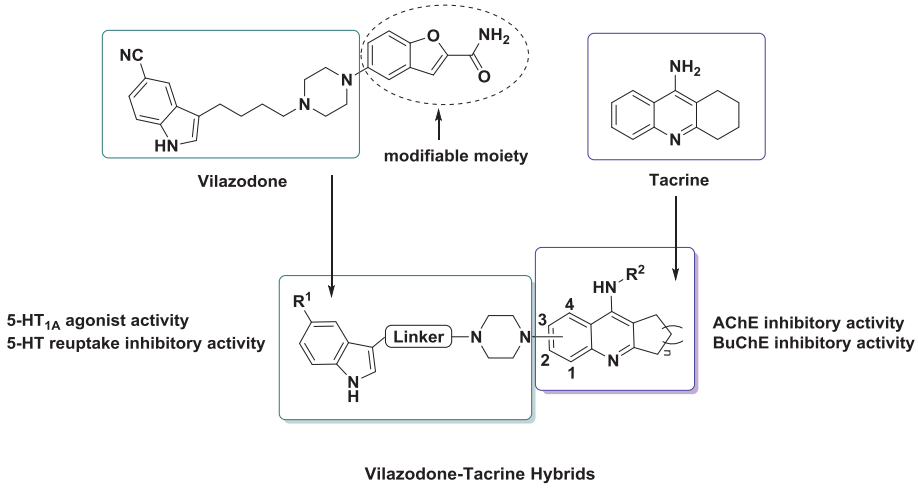


**Fig. 1.** Design strategy of novel vilazodone-tacrine hybrids.