Development of novel 2-acetylphenol-O-alkylhydroxyethylamine derivatives as multifunctional agents for Alzheimer’s disease treatment

Gaofeng Zhu1 · Xinfeng Li2 · Jing Yang3 · Ying He3 · Jing Mi3 · Lei Tang1 · Zhipei Sang1,3

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Abstract
Due to the complex pathogenesis of AD, the multitarget-directed ligands (MTDLs) strategy presented the best pharmacological option for AD treatment. Herein, a series of novel 2-acetylphenol-O-alkylhydroxyethylamine derivatives (5a–f and 6a–f) was rationally designed and synthesized. Of these derivatives, 5c was a good multifunctional agent (eeAChE IC50 = 7.9 μM, MAO-B IC50 = 9.9 μM, BACE1 IC50 = 8.3 μM) in vitro and displayed a mixed-type AChE inhibition, which could bind to the CAS and PAS of AChE. Compound 5c also exhibited good antioxidant activity (ORAC = 2.5 eq) and neuroprotective effects. Furthermore, compound 5c was a selective metal ions chelator. And it could cross blood–brain barrier in vitro and complied with drug-like properties rule of 5. Therefore, compound 5c was a promising multifunctional agent for the treatment of AD.

Graphical Abstract

These authors contributed equally: Gaofeng Zhu, Xinfeng Li

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Lei Tang
 tl1974@163.com

Zhipei Sang
 sangzhipei@126.com

1 State Key Laboratory of Functions and Applications of Medicinal Plants, Guizhou Provincial Engineering Technology Research Center for Chemical Drug R&D, School of Basic Medical Sciences, Guizhou Medical University, Guiyang 550004, China

2 Henan Key Laboratory of Unconventional Feed Resources Innovative Utilization, College of Veterinary Medicine, Henan University of Animal Husbandry and Economy, Zhengzhou 450046, China

3 College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang 473061, China

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Introduction

Alzheimer’s disease (AD), the utmost common form of dementia, is one of the most complex neurodegenerative disorders, characterized by progressive cognitive decline and behavioral disorders throughout the disease course [1]. Current data exhibits that more than 50 million dementia patients worldwide, and the figure will increase to 152 million by 2050 [2]. The disease course is divided into four stages with a progressive pattern of cognitive decline: preclinical stage, mild cognitive impairment stage, moderate stage, and severe stage [3]. Up to now, no treatments stop or reverse its progression, through some may temporarily improve symptoms. Furthermore, the failures of the current phase III trials of bapineuzumab and solanezumab the offer lessons for the development of Aβ immunotherapies. Anti-amyloid therapies should be given in the early stage of the disease as a preventative measure [4].

Although the cause of AD is poorly understood, scientists accept that low levels of acetylcholine (ACh), accumulation of beta amyloid (Aβ), hyperphosphorylated tau protein and loss of neurons serve as crucial role in the progression of AD, and propose several hypotheses, such as cholinergic hypothesis, amyloid cascade hypothesis, metals hypothesis, tau hypothesis, oxidative stress hypothesis, and so on [5].

The cholinergic hypothesis states that ACh is responsible for the learning and memory. In the brain of AD patients, the ACh levels significantly reduces in the hippocampus and the neocortex regions, which directly contributes to cognitive decline. Investigations show that the high levels of acetylcholinesterase (AChE) facilitate the hydrolysis of ACh leading to memory disorder in the early stages of AD [6]. In progressed AD, level of AChE in brain reduces to 55–67% of normal values while butyrylcholinesterase (BuChE), an enzyme closely related to AChE, increases to 120% of normal levels, demonstrating that BuChE takes over the hydrolysis of ACh in the late stage of AD [7]. So, selective inhibiting AChE still be the promising strategy for the early stages of AD.

The amyloid hypothesis states that accumulation of Aβ is the triggering event in the pathogenesis of AD and it further facilitates the form of tau-related neurofibrillary tangles (NFTs), neuroinflammation, neuronal degeneration, and death [8, 9]. Studies show that the β-site amyloid precursor protein cleaving enzyme 1 (BACE1) initiates the production of Aβ and is a prime target for AD [10]. Several BACE1 inhibitors, such as verubecestat, elenbecestat, lanabecestat and atabecestat have been evaluated in different clinical stages [11] http://integrity.thomson-pharma.com. Thus, inhibition of BACE-1 would be a potent therapeutic strategy for the early stage of AD by reducing the production of Aβ.

Metal ion hypothesis states that the dyshomeostasis of metal ions, especially Cu²⁺, Zn²⁺, Fe²⁺, accelerates the formation of metal-induced Aβ aggregates and causes NFTs formation and produces reactive oxygen species in the brain [12–14]. Thus, modulation of metal ions in the brain could be useful for treating AD.

In addition, monoamine oxidase-B (MAO-B), one of the flavoproteins present in the outer mitochondrial membranes of neuronal cells, significantly increases up to threefold in the parietal and frontal cortex of AD patients [15]. Selective inhibition of MAO-B could improve AD symptoms. Rasagiline, a selective MAO-B inhibitor, is in Phase II clinical trial with mild to moderate AD https://www.alzforum.org/therapeutics/rasagiline. Therefore, selective MAO-B inhibitors provide a potential way to treat AD.

The multitarget-directed ligand strategy (MTDLs) has been employed to tackle the multifactorial nature of AD and the encouraging results have convinced researchers that MTDLs display the best pharmacological option for AD treatment [16–18]. Several MTDLs candidate drugs, such as ALZT-OP1, leuco methylthioninium, masitinib mesylate, blarcamesine hydrochloride, and troriluzole hydrochloride have reached testing stage in clinical phase II/III trials (Fig. 1) http://integrity.thomson-pharma.com.

2-Acetylphenol skeleton is a potent reversible MAO inhibitor, especially, 2-acetyl-5-alkoxyphenol analog DDDT-15 (Fig. 1) is a potent selective MAO-B inhibitor [19]. Based on this, our previous work has developed a series of 2-acetylphenol-O-alkylamine derivatives as multifunctional agents for the treatment of AD, and the lead compound BMCL-14 displayed selective MAO-B inhibitory activity, metal ions chelation properties and AChE inhibitory potency [20, 21]. Furthermore, hydroxyethylamine, an essential functional group in BACE1 inhibitors, is able to interact through hydrogen bonds and ion pairs with the Asp dyad of BACE enzyme [22]. Thus, a series of novel 2-acetylphenol-O-alkylhydroxyethylamine derivatives were designed by introducing hydroxyethylamine fragment into 2-acetylphenol skeleton using MTDLs strategy (Fig. 2). And then the target derivatives were evaluated by inhibition of ChEs (AChE and BuChE) and MAOs (MAO-A and MAO-B), metal chelation and BACE1 inhibitory activity. They were found to show
potentially applicable biological activities, including inhibition of AChE/BuChE and MAO-A/MAO-B, antioxidant properties, neuroprotective effects, and metal chelation.

Results and discussion

Chemistry

Total 14 2-acetylphenol-\(\text{O-} \)alkylhydroxyethylamine derivatives were rationally designed and synthesized as presented in Scheme 1. The yield of target derivatives were above 78%. Briefly, the key intermediates 3a and 3b were obtained by the starting material 2′,4′-dihydroxyacetophenone 1 with excessive amounts of (R)-(-)-epichlorohydrin 2a or (S)-(+)-epichlorohydrin 2b in the presence of \(\text{K}_2\text{CO}_3\) in anhydrous CH\(_3\)CN under reflux. Similarly, target compounds 6a-f were obtained by the reaction of 3b with NR\(^1\)R\(^2\) 4a-f. The synthetic route for accessing target compounds was outlined in Scheme 1, and the property, yields of the target compounds were shown in Table 1. All the target compounds were new, and the target compounds were purified by chromatography, and their structures were confirmed by \(\text{^1H} \) NMR, \(\text{^13C} \) NMR, and ESI-MS.

Biological activity

AChE and BuChE inhibition studies

The inhibitory potency of 2-acetylphenol-\(\text{O-} \)alkylhydroxyethylamine derivatives against AChE (\text{ratAChE}, from rat cortex homogenate; \text{eeAChE}, from electric eel) and BuChE (\text{ratBuChE}, from rat serum; \text{eqBuChE}, from equine serum) were measured by Ellman’s method [23, 24]. FDA-approved AChE inhibitors donepezil was used as a reference compound. The results were summarized in Table 2. The activity of these derivatives were expressed as IC\(_{50}\). Firstly, the target
Compounds were evaluated by ratAChE and ratBuChE. The compounds showed moderate to good ratAChE inhibitory activity and moderate ratBuChE inhibitory activity. In particular, compound 5c showed good ratAChE inhibitory potency with IC50 value of 10.7 μM. Generally, the compounds with R configuration displayed slightly better ratAChE inhibitory activity than the compounds with S configuration. Moreover, the secondary amine fragment also affected ratAChE inhibitory activity. Under the condition with the same configuration, the potency to inhibit ratAChE were in the order: 1-isopropylpiperazine (5c) > N-benzylethanamine (5e) > 4-benzylpiperidine (5a) > diethylamine (5f) > 1-benzylpiperazine (5b) > piperidine (5d). Further, we re-evaluated the target compounds using eeAChE and eqBuChE and explored the structure-activity-relationship. All the target compounds showed moderate to good AChE inhibitory activity and weak BuChE inhibitory potency. Particularly, compound 5c presented the best eeAChE inhibitory activity with IC50 value of 7.9 μM and moderate eqBuChE inhibitory activity (IC50 = 31.7 μM). In addition, the R/S configuration and secondary amine fragment significantly affected the AChE inhibitory activity. The target derivatives (5a–5f) with R configuration showed better eeAChE inhibitory potency than the derivatives (6a–6f) with S configuration. Under both the condition of R configuration and S configuration, the secondary amine fragment of side chain also affected eeAChE inhibitory activity. Compound 5a with 4-benzylpiperidine exhibited good eeAChE inhibitory activity with IC50 value of 9.7 μM. Replacing 4-benzylpiperidine of 5a with 1-benzylpiperazine to obtain compound 5b, the eeAChE inhibitory activity was 11.2 μM. And then replacing 1-benzylpiperazine of 5b with 1-isopropylpiperazine to get compound 5c, the eeAChE inhibitory activity was 7.9 μM. While, when 4-benzylpiperidine of 5a was replaced by piperidine, N-benzylethanamine and diethylamine to get compounds 5d, 5e and 5f, respectively, all of them showed weak inhibitory activity. Taken together, compound 5c exhibited the best eeAChE inhibitory potency with IC50 value of 7.9 μM.

**Kinetic studies of AChE inhibition**

According to the above results, compound 5c was the best AChE inhibitor and was chosen to carry out a kinetic study using eeAChE [23]. As shown in Fig. 3, the reciprocal Lineweaver–Burk plots displayed that both increasing slopes (decreased Vmax) and intercepts (higher Km) at increasing concentration of 5c, revealing a mixed-type inhibition. Compound 5c was able to bind to both catalytic active site (CAS) and peripheral anionic site (PAS) of AChE or was able to bind to both free and acylated-AChE [24].

**Antioxidant activity**

The antioxidant potency of all the target compounds were assessed by oxygen radical absorbance capacity fluorescein (ORAC-FL) method using Trolox as a reference compound [25]. As indicated in Table 3, all the target compounds showed good antioxidant activity and ORAC values ranging from 1.9 eq to 2.6 eq. According to the screening data, the R/S configuration did not obviously influence the antioxidant potency. It was noted that the compounds (5b, 2.5 eq; 6b, 2.6 eq) with 1-benzylpiperazine fragment and compounds (5c, 2.5 eq; 6c, 2.4 eq) with 1-isopropylpiperazine fragment displayed better antioxidant activity than other compounds.

**Monoamine oxidase inhibition studies**

The inhibitory potency of target 2-acetylphenol-O-alkylhydroxyethylamine derivatives against human MAO-A and MAO-B was assessed by a fluorimetric method with rasagiline as a positive compound [26]. The results were summarized in Table 3. Most of the target compounds showed good MAO-B inhibitory activity and weak MAO-A inhibitory potency, indicating most of the synthesized compounds were selective MAO-B inhibitors. The data also displayed that the compounds (6a–6f) with S configuration...
### Table 1 The structure, property, and yields of the target compounds 5a–f, 6a–f

| Compound | Structure | Property        | Yield (%) |
|----------|-----------|-----------------|-----------|
| 5a       | ![5a structure](image) | Light yellow oil | 80.7%     |
| 5b       | ![5b structure](image) | Light yellow oil | 86.1%     |
| 5c       | ![5c structure](image) | Light yellow oil | 89.3%     |
| 5d       | ![5d structure](image) | Light yellow oil | 83.7%     |
| 5e       | ![5e structure](image) | Light yellow oil | 88.6%     |
| 5f       | ![5f structure](image) | Light yellow oil | 84.6%     |
| 6a       | ![6a structure](image) | Light yellow oil | 84.7%     |
| 6b       | ![6b structure](image) | Light yellow oil | 78.4%     |
| 6c       | ![6c structure](image) | Light yellow oil | 86.2%     |
| 6d       | ![6d structure](image) | Light yellow oil | 85.8%     |
| 6e       | ![6e structure](image) | Light yellow oil | 88.1%     |
| 6f       | ![6f structure](image) | Light yellow oil | 88.9%     |
showed slightly better MAO-B inhibition than the compounds (5a~5f) with R configuration. In addition, the secondary amine also affected the MAO-B inhibitory activity. Among the target compounds, compound 5e presented the best MAO-B inhibitory activity with IC50 value of 8.9 μM and the representative compound 5c displayed good MAO-B inhibitory potency with IC50 value of 9.9 μM.

**BACE1 inhibition assay**

According to the results from AChE/BuChE inhibition and MAO-A/MAO-B inhibition, the compounds 5a, 5b, 5c, and...
The metal ions (Cu$^{2+}$, Zn$^{2+}$, Fe$^{2+}$, and Al$^{3+}$) chelation ability of compound 5c was tested using UV–visual spectrometry [25, 26]. As presented in Fig. 4A, the characteristic absorption peak of 5c displayed a red shift from 314 to 360 nm after adding CuCl$_2$. Whereas, the electronic spectra of compound 5c presented no obvious change after treating with AlCl$_3$, FeSO$_4$, and ZnCl$_2$, respectively. The results revealed that compound 5c was a selective Cu$^{2+}$ chelator.

The molar ratio method was employed to assess the stoichiometry of the 5c-Cu$^{2+}$ complex. The UV spectra was treated by numerical subtraction of CuCl$_2$ and 5c at different concentrations at 360 nm. As exhibited in Fig. 4B, the two linearly straight lines intersected at a mole fraction of 1.96, revealing a 1:2 stoichiometry for the 5c-Cu$^{2+}$ complex. The o-hydroxyacetophenone structure of 5c may bind to Cu$^{2+}$ [27], and the hydroxyethylamine structure of 5c may also bind to Cu$^{2+}$ [28].

### Docking studies on AChE and MAO-B

According to the ChEs/MAOs/BACE1 inhibition assay, compound 5c was a balanced and high effective multifunctional agent, such as AChE inhibition (IC$_{50}$ = 7.9 μM), MAO-B inhibition (IC$_{50}$ = 9.9 μM) and BACE1 inhibition (IC$_{50}$ = 8.3 μM). So, compound 5c was selected to perform molecular docking using TcAChE (code ID: 1EVE) and hMAO-B (code ID: 2V60) to explore the possible binding mode and to explain the reasons for multiple potencies. As shown in Fig. 5, the docking results displayed that compound 5c occupied the entire enzymatic CAS, the mid-gorge sites and the PAS and could simultaneously bind to both the CAS and PAS. In the TcAChE-5c complex, the hydroxyl and carbonyl group at the 2-acetylphenol skeleton formed a intramolecular hydrogen bond. The hydroxyl group of 2-acetylphenol interacted with residue Tyr130 via two intermolecular hydrogen bond interactions. The carbonyl group of 2-acetylphenol fragment interacted with key active residue Gly117 and Tyr130 via one intermolecular hydrogen bond, respectively. The benzene ring of 2-acetylphenol fragment also interacted with key active residue Trp84 via two π-π interactions. In addition, the hydroxyl group of the hydroxyethylamine group could interact with residue Gln69 via one intermolecular hydrogen bond interaction. Furthermore, compound 5c could also interact with Trp84, Asp72, Tyr334, and Tyr70 through hydrophobic interaction. In addition, the known AChE inhibitor donepezil was also re-docked with TcAChE, the characteristic interaction were also observed in Fig. 5D, such as the benzene ring of 4-benzylpiperidine also interacted with key active residue Trp84 via two π-π interactions, and the benzene ring of indanone interacted with key active residue Phe331 via one π-π interaction.

In 5c-hMAO-B complex (Fig. 6A), the hydroxyl and carbonyl group at the 2-acetylphenol skeleton formed a intramolecular hydrogen bond. The hydroxyl group of 2-acetylphenol interacted with residues Glu84 and Thr314 via intermolecular hydrogen bond interaction, respectively. The carbonyl group of 2-acetylphenol fragment interacted with residues Cys312 and Thr314 via intermolecular hydrogen bond interaction, respectively. The oxygen atom of O-alkyl fragment interacted with residue Tyr326 via one intermolecular hydrogen bond interaction. Moreover, the N atom of the 1-isopropylpiperazine fragment interacted with residue Thr201 via one intermolecular hydrogen bond interaction. Furthermore, some hydrophobic interactions were presented between compound 5c and important active residues Phe99, Gly101, Pro102, Ile199, Leu88, Ser200, Thr202, Glu84, Cys312, Pro104, Thr314, Thr201, and Tyr326. Furthermore, in order to compared with the known selective MAO-B inhibitor 7-(3-chlorobenzyloxy)-4-carboxaldehyde-coumarin, the other docking was performed. The results were displayed in Fig. 6B, the carbonyl group of

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**Fig. 4** A The UV spectrum of compound 5c in methanol was investigated using CuCl$_2$, FeSO$_4$, ZnCl$_2$ and AlCl$_3$; B The molar ratio method was used to evaluate the stoichiometry of complex-Cu$^{2+}$ with ascending amounts of CuCl$_2$ (ranging from 3.75 to 112.5 μM).
coumarin fragment interacted with key residues Cys312 and Glu84 via one intermolecular hydrogen bond interaction, respectively. The O atom of coumarin interacted with residue Thr314 via one intermolecular hydrogen bond interaction. The benzene ring interacted with important amino acid Ser200 via sigma-π interaction.

Neuroprotective effects against H2O2-induced PC12 cell injury

Compound 5c was selected to assess the neuroprotective effect against H2O2-induced PC12 cell injury using Vitamin E (VE) as a positive control [26]. According to the data in Fig. 7A, compound 5c did not show obvious cytotoxicity until the concentration increased up to 50 μM. As displayed in Fig. 7B, when PC12 cells were treated with 100 μM H2O2, the cell viability significantly declined to 48.9% (p < 0.01) vs normal group. When adding 100 μM VE, the cell viability increased to 67.3% (p < 0.01). Moreover, when the PC12 cells were treated with 10 and 50 μM compound 5c, respectively, the cell viability was 63.1% (p < 0.05) and 75.8% (p < 0.01), respectively. The high dose (50 μM) of 5c presented better neuroprotective effect than VE, revealing that compound 5c exhibited potent neuroprotective effect against H2O2-induced PC12 cell injury.

In vitro blood–brain barrier permeation assay

The ability of 5c to cross blood–brain barrier was assessed by the parallel artificial membrane permeation assay of the blood–brain barrier [29, 30]. Compound BMCL-14 acted as a positive compound. 11 standard drugs were used as the references in our previous work. The following ranges of permeability (Pe, 10^{-6} cm/s) had been established in our previous work: Pe > 3.44 for compounds with predicted high BBB permeation, Pe ≤ 1.61 for compounds with predicted low BBB permeation, 3.44 ≥ Pe > 1.61 for compounds with uncertain BBB permeation. As shown in Table 4, compared with BMCL-14, compound 5c presented 5.78 × 10^{-6} cm/s permeability, revealing that compound 5c could cross the BBB via passive diffusion.

Theoretical evaluation of ADME properties

The Molinspiration property program was employed to evaluate the drug-like properties of 5c, the items including log P, MW, topological polar surface area (TPSA), the number of hydrogen-bond acceptors, and the number of hydrogen-bond donors [31]. According to the screening data in Tables 5, 5c complied with the Lipinski’s rule of 5, which might be a promising candidate compound.
Fig. 6  A compound 5c (green stick) interacting with residues in the binding site of huMAO-B (code ID: 2V60). B 7-(3-chlorobenzyloxy)-4-carboxaldehyde-coumarin (green stick) interacting with residues in the binding site of huMAO-B (code ID: 2V60)
Conclusion

In conclusion, AD is a complex neurodegenerative disorder with poorly understood pathogenesis. The MTDLs strategy has been considered as the best pharmacological option for AD treatment. Thus, a series of novel 2-acetylphenol-O-alkylhydroxyethylamine derivatives was rationally designed based on the MTDLs strategy. The synthesized derivatives were assessed by biological activity evaluation in vitro including AChE/BuChE inhibition, antioxidant, MAO-A/MAO-B inhibition, BACE1 inhibition and neuroprotective effects. The results revealed that compound 5c was a good AChE inhibitor (IC50 = 7.9 μM) and showed a mixed-type AChE inhibition. Compound 5c also was a good antioxidant agent (ORAC = 2.5 eq) and selective metal ions chelator, as well as a promising neuroprotectant. Furthermore, compound 5c was a significant selective MAO-B inhibitor (IC50 = 9.9 μM) and BACE1 inhibitor (IC50 = 8.3 μM). Compared with compound BMCL-14 in our previous work, the AChE inhibitory activity of 5c significantly decreased and the MAO-B inhibitory potency slightly increased, might be the length of linker and secondary amine served as important roles on AChE inhibition. In addition, the antioxidant activity of compound 5c significantly improved compared with BMAL-14. Further, compound 5c presented good BBB permeability and complyed with drug-like properties rule of 5. Therefore, compound 5c was a promising multifunctional agent for the treatment of AD. The in-depth study and structural modification are in progress.

Experimental

Chemistry

General information

All reagents were obtained from commercial sources and utilized without further purification unless otherwise noted. 1H and 13C NMR spectra were recorded on a Varian INOVA spectrometer and referenced to Tetramethylsilane (TMS), using CDCl3 or DMSO-d6 as solvents at 400 and 100 MHz, respectively. Chemical shifts (δ) are given in ppm. Splitting patterns are indicated as follow: s, single; d, doublet; dd, double-doublet; t, triplet; m, multi-plet. HPLC analysis was carried out on a Waters e2695 plus system with the use of a Ultimate CQ-C18 column (4.6 × 250 mm, 5 μm) at a flow ratio of 1 mL/min. Mobile phase: A: 0.1%TFA in H2O, B: 0.1% TFA in CH3CN.

General procedure for the preparation of intermediate compounds 3a and 3b

The starting material 2’,4’-dihydroxyacetophenone 1 (3 mmol) was purchased from Sigma-Aldrich and was used without any pretreatment. Compound 1 was reacted with excessive amounts of (R)-(−)-epichlorohydrin or (S)-(−)-epichlorohydrin (3.6 mmol), respectively, in the presence of K2CO3 (1.2 mmol) in anhydrous CH3CN (15 mL) under reflux followed by thin layer chromatography. Upon completion, the solvent was concentrated by vacuum and K2CO3 was removed by filtration. The crude products were purified by silica gel chromatography using petroleum ether/acetone (50:1) as eluent to obtain the intermediates 3a and 3b with 79.5% and 75.8% yield, respectively.

Table 4 Permeability Pe (×10−6 cm/s) of compound 5c and its predictive penetration in the CNS

| Compound  | Pe (×10−6 cm/s) | Prediction |
|-----------|----------------|------------|
| BMCL-14   | 15.79 ± 0.67   | CNS +      |
| 5c         | 5.78 ± 0.37    | CNS +      |

Compounds BMCL-14 and 5c was dissolved in DMSO at 5 mg/mL and diluted with PBS/EtOH (70:30). The final concentration of compounds was 100 μg/mL.

Values are expressed as the mean ± SD of three independent experiments.

Fig. 7 A The cell viability on PC12 cells, **p<0.01, *p<0.05 vs control. B The cell viability (%) of compound 5c on H2O2-induced PC12 cell injury using MTT assay. Three independent experiments were carried out in triplicate. Data were expressed as mean ± SD and percentage of control value. #p<0.01 vs control; **p<0.01, *p<0.05 vs H2O2 group

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General procedure for the preparation of 2-acetylphenol-O-alkylhydroxyethylamine derivatives 5a–f. The crude intermediate 3a (1 mmol) was dissolved in anhydrous CH2CN (10 mL). K2CO3 and respective secondary amine (4a–4f) (1.5 mmol) was added to the mixture. The reaction mixture was stirred and refluxed. Upon completion, CH2CN was concentrated under reduced pressure. The residue was extracted with water (40 mL) and dichloromethane (20 mL × 3). The organic phases were washed with saturated NaCl aqueous, dried over Na2SO4, filtered and evaporated to dryness under reduced pressure. The crude products were purified by silica gel chromatography using petroleum ether/ethyl acetate (20:1) as eluent to give the target compounds 5a–f, and the final step yielded range from 80.7% to 89.3% due to the different nucleophilicity of secondary amine (4a–4f). The target derivatives 6a–6f were also obtained through intermediate 3b as acting the starting material and the final step yielded range from 78.4 to 88.95%.

(R)-1-(2-hydroxy-4-(oxirane-2-ylmethoxy)phenyl)ethan-1-one (3a). White solid, 79.5% yield. 1H NMR (400 MHz, CDCl3) δ 12.73 (s, 1H, OH), 7.65 (d, J = 8.8 Hz, 1H, Ar–H), 6.49 (d, J = 6.4 Hz, 1H, Ar–H), 4.30 (d, J = 9.2 Hz, 1H, 1/2 OCH2), 3.96 (d, J = 6.0 Hz, 1H, 1/2 OCH2), 3.38–3.37 (m, 1H, OCH), 2.94 (t, J = 4.4 Hz, 1H, 1/2 OCH2), 2.78–2.77 (m, 1H, 1/2 OCH2), 2.57 (s, 3H, COCH3).

(S)-1-(2-hydroxy-4-(oxirane-2-ylmethoxy)phenyl)ethan-1-one (3b). White solid, 75.8% yield. 1H NMR (400 MHz, CDCl3) δ 12.73 (s, 1H, OH), 7.65 (d, J = 9.2 Hz, 1H, Ar–H), 6.49 (d, J = 6.4 Hz, 1H, Ar–H), 4.64 (d, J = 2.8 Hz, 1H, Ar–H), 4.30 (d, J = 8.4 Hz, 1H, 1/2 OCH2), 3.95 (d, J = 6.0 Hz, 1H, 1/2 OCH2), 3.39–3.36 (m, 1H, OCH), 2.94 (t, J = 4.8 Hz, 1H, 1/2 OCH2), 2.77 (d, J = 2.8 Hz, 1H, 1/2 OCH2), 2.57 (s, 3H, COCH3).

Table 5 Theoretical prediction of the ADME properties of compound 5c

| Comp. | Log P | MW | TPSA (Å²) | n-ON | n-OHNH | aviolations | mrotb | Volume (Å³) |
|-------|-------|----|-----------|------|--------|-------------|-------|-------------|
| 5c    | 1.76  | 336.4 | 73.24 | 6    | 2      | 0           | 7     | 326.92      |

(R)-1-(4-(3-(4-benzylpiperazin-1-yl)-2-hydroxypropoxy)2-hydroxyphenyl)ethan-1-one (5b). Light yellow oil, 86.1% yield, 97.6% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.67 (s, 1H, ph-OH), 7.55 (d, J = 8.8 Hz, 1H, Ar–H), 7.26 (d, J = 4.0 Hz, 4H, 4 × Ar–H), 7.22–7.21 (m, 1H, Ar–H), 6.41 (d, J = 8.8 Hz, 1H, Ar–H), 6.37 (s, 1H, Ar–H), 4.05 (d, J = 8.8 Hz, 1H, OCH), 3.94 (t, J = 5.2 Hz, 2H, OCH2), 3.49–3.47 (m, 2H, NCH2), 2.67–2.65 (m, 2H, NCH2), 2.51–2.49 (m, 1H, 4 × NCH2, COCH3). 13C NMR (100 MHz, CDCl3) δ 202.6, 165.1, 165.1, 137.6, 132.3, 129.2 (2 C), 128.2 (2 C), 127.2, 114.0, 107.8, 101.5, 70.6, 65.3, 62.8, 60.2, 52.9 (4C), 26.2. HR-ESI-MS: Calcd. for C22H23NO4 [M + H]+: 337.1583, found: 337.1515.

(R)-1-(2-hydroxy-4-(2-hydroxy-3-(4-isopropylpiperazin-1-yl)propoxy)phenyl)ethan-1-one (5c). Light yellow oil, 89.3% yield, 98.1% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.64 (s, 1H, ph-OH), 7.55 (d, J = 8.8 Hz, 1H, Ar–H), 6.40 (d, J = 8.8 Hz, 1H, Ar–H), 6.35 (s, 1H, Ar–H), 4.05 (d, J = 8.8 Hz, 1H, OCH), 3.95–3.93 (m, 2H, OCH2), 2.67–2.65 (m, 3H, NCH2, NCH3), 2.49–2.47 (m, 11H, 4 × NCH2, COCH3), 1.02 (d, J = 6.4 Hz, 6H, 2 × CH3). 13C NMR (100 MHz, CDCl3) δ 202.5, 165.1, 165.0, 132.2, 113.9, 107.7, 101.4, 70.6, 65.3, 60.2, 54.5, 53.2, 48.5 (3C), 26.1, 18.4, 18.3. HR-ESI-MS: Calcd. for C19H23N2O4 [M + H]+: 337.2072, found: 337.2083.

(R)-1-(2-hydroxy-4-(2-hydroxy-3-(4-piperidin-1-yl)propoxy)phenyl)ethan-1-one (5d). Light yellow oil, 83.7% yield, 98.1% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.65 (s, 1H, ph-OH), 7.56 (d, J = 8.8 Hz, 1H, Ar–H), 6.41 (d, J = 8.8 Hz, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 4.07 (dd, J = 8.8, 4.4 Hz, 1H, OCH), 3.94 (d, J = 4.4 Hz, 2H, OCH2), 2.59 (d, J = 4.4 Hz, 2H, NCH2), 2.48–2.46 (m, 5H, NCH2, COCH3), 2.40–2.38 (m, 2H, NCH2), 1.58–1.56 (m, 4H, 2 × CH2), 1.42–1.40 (m, 2H, CH2). 13C NMR (100 MHz, CDCl3) δ 202.6, 165.2, 165.0, 132.3, 114.0, 107.8, 101.5, 70.7, 65.1, 61.0 (2C), 54.7, 26.1, 25.8 (2C), 24.0. HR-ESI-MS: Calcd. for C19H23N2O4 [M + H]+: 337.1661, found: 324.1700.

(R)-1-(4-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-2-hydroxyphenyl)ethan-1-one (5e). Light yellow oil, 88.6% yield, 98.3% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.73 (s, 1H, OH), 7.59 (d, J = 8.8 Hz, 1H, Ar–H), 7.32–7.31 (m, 4H, 4 × Ar–H), 7.28–7.27 (m, 1H, Ar–H), 6.43 (d, J = 8.8 Hz, 1H, Ar–H), 6.38 (s, 1H, Ar–H), 4.05–4.03 (m, 1H, OCH), 3.97–3.95 (m, 2H, OCH2), 3.78 (d, J = 13.6 Hz, 1H, 1/2NCH2), 3.57 (d, J = 13.6 Hz, 1H, 1/2NCH2), 2.64–2.63 (m, 4H, 2 × NCH2), 2.51 (s, 3H, COCH3), 1.09 (t, J = 7.2 Hz, 3H, CH3). 13C NMR
(100 MHz, CDCl3) δ 202.6, 165.3, 165.1, 138.3, 132.4, 129.1 (2C), 128.5 (2C), 127.4, 114.0, 107.8, 101.6, 70.6, 66.0, 58.3, 55.7, 47.9, 26.2, 11.7. HR-ESI-MS: Calcd. for C20H25NO4 [M + H]+: 344.1817, found: 344.1862.

(R)-1-(4-(3-(diethylamino)-2-hydroxypropoxy)-2-hydroxyphenyl)ethan-1-one (5f). Light yellow oil, 84.6% yield, 97.6% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.73 (s, 1H, OH), 7.56 (d, J = 8.8 Hz, 1H, Ar–H), 6.40 (t, J = 10.0 Hz, 1H, Ar–H), 6.33 (d, J = 15.2 Hz, 1H, Ar–H), 4.04 (d, J = 22.8 Hz, 1H, OCH), 3.95 (d, J = 4.8 Hz, 2H, OCH2), 2.68–2.66 (m, 6H, 3 × NCH2), 2.49 (s, 3H, COCH3), 1.05 (t, J = 7.2 Hz, 6H, 2 × CH3). 13C NMR (100 MHz, CDCl3) δ 202.6, 165.1, 164.9, 132.3, 114.0, 107.7, 101.5, 70.5, 65.6, 55.6, 47.3 (2C), 26.1, 11.3 (2C). HR-ESI-MS: Calcd. for C15H23NO4 [M + H]+: 282.1661, found: 282.1698.

(S)-1-(4-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-2-hydroxyphenyl)ethan-1-one (6a). Light yellow oil, 84.7% yield, 98.2% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.74 (s, 1H, ph-OH), 7.64 (d, J = 8.8 Hz, 1H, Ar–H), 7.30 (t, J = 7.2 Hz, 2H, 2 × Ar–H), 7.22 (d, J = 7.2 Hz, 1H, Ar–H), 7.16 (d, J = 7.2 Hz, 2H, 2 × Ar–H), 6.50 (d, J = 8.8 Hz, 1H, Ar–H), 6.44 (s, 1H, Ar–H), 4.0–4.07 (m, 1H, OCH), 4.01 (d, J = 5.6 Hz, 2H, OCH2), 3.00 (d, J = 11.2 Hz, 1H, 1/2NCH2), 2.83 (d, J = 11.2 Hz, 1H, 1/2NCH2), 2.58–2.55 (m, 5H, NCH2, COCH3), 2.50–2.48 (m, 2H, NCH2), 2.29 (d, J = 11.6 Hz, 1H, 1/2 phCH2), 1.98 (d, J = 11.2 Hz, 1H, 1/2 phCH2), 1.69–1.67 (m, 2H, CH2), 1.33–1.31 (m, 3H, CH, CH2). 13C NMR (100 MHz, CDCl3) δ 202.7, 165.3, 165.2, 140.5, 132.4, 129.2 (2C), 128.3 (2C), 126.0, 114.1, 108.0, 101.6, 70.7, 65.2, 60.5, 55.6, 52.7, 43.1, 37.8, 32.3, 32.0, 26.3. HR-ESI-MS: Calcd. for C23H29NO4 [M + H]+: 384.2130, found: 384.2172.

(S)-1-(4-(3-(benzyl(ethyl)amino)-2-hydroxypropoxy)-2-hydroxyphenyl)ethan-1-one (6b). Light yellow oil, 88.9% yield, 98.1% HPLC purity. 1H NMR (400 MHz, CDCl3) δ 12.68 (s, 1H, ph-OH), 7.59 (d, J = 8.8 Hz, 1H, Ar–H), 6.44 (d, J = 8.8 Hz, 1H, Ar–H), 6.39–6.37 (m, 1H, Ar–H), 4.02–4.00 (m, 1H, OCH), 3.96 (d, J = 5.2 Hz, 2H, OCH2), 2.62–2.60 (m, 6H, 3 × NCH2), 2.51 (s, 3H, COCH3), 1.04 (t, J = 7.2 Hz, 6H, 2 × CH3). HR-ESI-MS: Calcd. for C15H23NO4 [M + H]+: 282.1661, found: 282.1687.

Biological activity

Inhibition experiments of AChE and BuChE

AChE and BuChE inhibitory potency of the target compounds were tested by slightly modified Ellman assay [23]. Briefly, for AChE inhibition assays, a reaction mixture (100 µL) included substrate ATC (1 mmol/L), phosphate-buffered solution (0.1 M KH2PO4/K2HPO4, pH = 8.0, 40 µL), diverse concentrations (DMSO < 1%) of test compounds (20 µL) and 10 µL enzyme (eeAChE 0.45 U/mL) was incubated at 37 °C for 15 min. After that 5,5'-dithiobis-2-nitrobenzoic acid (DTNB, 0.2%, 30 µL) was added to the mixture. Using a Varioskan Flash Multimode Reader at 412 nm to determine the activities. The inhibition percent was calculated by the following expression: (1 – A1/A0) × 100, in which A1 and A0 are the absorbance obtained for AChE in the presence and absence of inhibitors after subtracting the
background. All samples were performed in triplicate. The procedure of BuChE assay was similar as described above using BTC and BuChE instead of ATC and AChE.

**Antioxidant activity assay**

The antioxidant activity was assessed by the ORAC-FL assay. The detailed procedure referenced our previous work [25, 26].

**Recombinant human MAO-A and MAO-B inhibition studies [29]**

Recombinant human MAO-A and MAO-B, purchased from Sigma-Aldrich, were pre aliquoted and stored at −80 °C. The test compounds were dissolved in DMSO (2.5 mM) and diluted with potassium phosphate buffer (100 mM, pH 7.40, containing KCl 20.2 mM) to a final volume of 500 μL composed of different concentrations of test compounds (0–100 μM) and kynuramine (45 μM for MAO-A and 30 μM for MAO-B). The reactions were triggered via the addition of the enzyme (7.5 μg/mL) and then incubated for 30 min at 37 °C. After that 400 μL NaOH (2 N) and 1000 μL water were added to terminate the reactions and finally the mixtures were centrifuged at 16,000 g for 10 min. The reactions were quantified on a Varioskan Flash Multimode Reader (PerkinElmer) based on the fluorescence of the supernatant with excitation and emission wavelengths at 310 and 400 nm, respectively. IC50 values were calculated using GraphRad Prism 5. IC50 values were determined in triplicate and expressed as mean ± SD.

**Metal chelation studies**

The UV absorption of the target compound, alone or in the presence of CuCl2, ZnCl2, FeSO4, and AlCl3, was recorded with Shimadzu UV-2450 spectrophotometer with wavelength ranging from 200 to 600 nm after incubating for 30 min at room temperature [25]. The final concentrations of tested compound and metals were 37.5 μM, and the final volume of reaction mixture was 1 mL. The spectra of the metal alone and the compound alone numerically subtracted from the spectra of the mixture to give the difference UV–vis spectra due to complex formation. The procedure referenced our previous work.

**BACE-1 inhibition studies**

BACE-1 in vitro inhibition assay was tested as described in the assay procedure by utilizing the β-secretase Inhibitor Screening Assay Kit [30]. Reaction mixture comprised of test compound (2.5 μL) or Donepezil (control), BACE-1 enzyme (15 μL) and the substrate was incubated for 1 h at 25 °C. The fluorescence signal was recorded at an excitation wavelength of 340 nm and an emission wavelength 490 nm by microplate reader (EnSpire Multimode; PerkinElmer). The inhibition percentage was calculated by the equation: Percent inhibition (%) = 100 – [AFi/AF0] × 100%, where AFi and AF0 mean the fluorescence intensities obtained for BACE-1 in the presence and absence of an inhibitor, respectively.

**Neuroprotective effect**

The neuroprotective effects were evaluated with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The detailed procedure referenced our previous work [25, 26].

**In vitro blood–brain barrier permeation assay**

The parallel artificial membrane permeation assay was used to evaluate the blood–brain barrier penetration of compounds [31, 32]. The donor microplate (PVDF membrane, pore size 0.45 mm) and acceptor microplate were both from Millipore. The 96-well UV plate (COSTAR) was from Corning Incorporated. According to the detailed procedure in our previous work, we concluded that compounds with Pe values above 3.44 × 10−6 cm/s could cross the blood–brain barrier [33, 34].

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**Conflict of interest** The authors declare no competing interests.

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