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Original article

Hybrids of oxoisoaporphine-tacrine congeners: Novel acetylcholinesterase and acetylcholinesterase-induced β-amyloid aggregation inhibitors

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ABSTRACT

A series of dual binding site acetylcholinesterase (AChE) inhibitors have been designed, synthesized, and tested for their ability to inhibit AChE, butyrylcholinesterase (BChE), AChE-induced and self-induced β-amyloid (Aβ) aggregation. The new hybrids consist of a unit of 1-azabenzanthrone and a tacrine or its congener, connected through an oligomethylene linker containing an amine group at variable position. These hybrids exhibit high AChE inhibitory activity with IC_{50} values in the nanomolar range in most cases. Moreover, five out of the 12 hybrids of this series, particularly those bearing a tetrahydroacridine moiety, exhibit a significant in vitro inhibitory activity toward the AChE-induced and self-induced Aβ aggregation, which makes them promising anti-Alzheimer drug candidates.

1. Introduction

Alzheimer's disease (AD) is the fourth leading cause of death in people over 65 years old in the world. As of 2008, there are an estimated 30 million people with dementia worldwide. By 2050, it is expected that the figure will have increased to over 100 million. Much of the increase will be contributed by the developing countries (data from Alzheimer's Disease International (ADI)). A century has passed since AD was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906. Alzheimer's disease treating remains a challenge for the pharmaceutical community. In spite of the multifactorial nature of AD, most treatment strategies have aimed at two main targets: the β-amyloid peptide [1,2] and the cholinergic neurotransmission [3].

β-Amyloid peptide is a main component of the senile plaques that constitute one of the neuropathological–histological features of AD [4]. Many factors can cause amyloid fibril formation. On the one hand, amyloid fibrils can be self-assembled *in vitro*. It has been postulated that the generic amyloid conformation, the cross-β structure, may be a universal, energetic minimum for aggregated proteins. Once formed, amyloid fibrils are extremely stable and difficult to solubilize [5]. Meanwhile, AChE can bind to the Aβ non-amyloidogenic form, inducing a conformational transition to the amyloidogenic conformation with subsequent amyloid fibril aggregation [6]. Structural analysis by X-ray crystallography [7] and competition assays with AChEIs [6] clearly identified enzyme peripheral anionic site (PAS) as a locus of protein interaction with Aβ. Therefore, dual-site inhibitors that interact simultaneously with both the catalytic site and the PAS appear to be a very promising therapeutic strategy, since they will not only stimulate the cholinergic system, but also inhibit the production or the aggregation of β-amyloid promoted by AChE [8]. Based on the dual-site theory, a number of studies have been performed. These include tacrine-melatonin hybrids (Fig. 1) [9], donepezil-tacrine hybrids(Fig. 1) [10,11], as well as tacrine-carbazole hybrids (Fig. 1) [12].

Tacrine (tetrahydroaminoacridine or THA), a reversible inhibitor of acetylcholinesterase active site, has been one of the mainly approved drugs for use in AD [13]. Although it lacks selectivity and its hepatotoxicity has reduced its therapeutic application [14], developing tacrine-analogues are still of interest in AD [12,15–17]. Crystal structures of the complexes of THA with AChE showed that tacrine can interact with AChE at the catalytic anionic subsite (CAS), principally through a stacking interaction with Trp84.

Oxoisoaporphine alkaloids [18] were isolated from the rhizome of *Menispermum dauricum* (Menispermaceae) which were widely present in the People's Republic of China. We recently reported that

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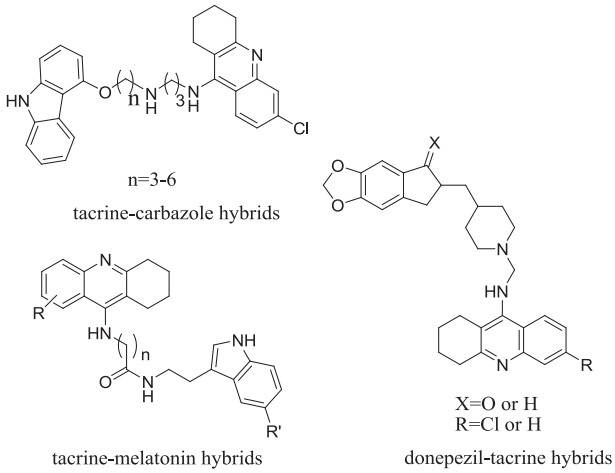


Fig. 1. Structures of some known dual-site inhibitors.

synthetic derivatives of oxoisoaporphine alkaloids exhibited high acetylcholinesterase inhibitory activity and high selectivity for AChE over BChE [19,20]. Molecular docking simulations on the oxoisoaporphine derivatives with AChE from *Torpedo californica* have demonstrated that 1-azabenzanthrone moiety of the ligands can interact with PAS of acetylcholinesterase, especially with Trp 279 of PAS [19]. It was thus predicted that hybrids of oxoisoaporphine-tacrine congeners in which the two pharmacophores were separated by a linker of a suitable length would have both greater inhibitory potency and selectivity than tacrine or oxoisoaporphine itself and should be involved in neurotrophic activity.

In this paper, we continue our research based on the dual-site theory. A series of hybrids of oxoisoaporphine-tacrine congeners designed to simultaneously interact with the active and peripheral binding sites of acetylcholinesterase have been synthesized. Their ability to inhibit AChE, BChE, AChE-induced and self-induced Aβ aggregation was tested. These compounds (Fig. 2) consist of a unit of tacrine or its congeners, which occupies the same position as tacrine at the AChE active site, and the 1-azabenzanthrone moiety whose position along the enzyme gorge and the peripheral site can be modulated by a suitable tether that connects tacrine and 1-azabenzanthrone.

2. Results and discussion

2.1. Chemistry

The bivalent ligand strategy involves the synthesis of drugs in which identical or different pharmacophores are linked via a suitable linker. As the pocket of AChE is deep, a few carbon chains as a linker were needed at the middle site between the gorge and the entrance of AChE. Total synthesis of hybrids of oxoisoaporphine-tacrine congeners was involved in two kinds of key intermediate compounds **6a**–**b** and **4a**–**i**.

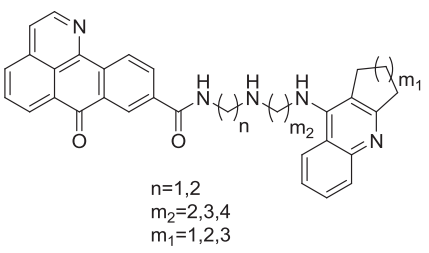
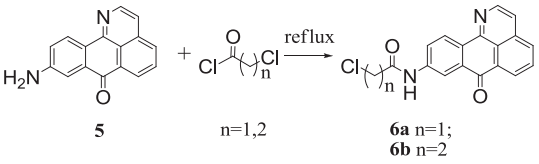


Fig. 2. Structures of synthesized hybrids of oxoisoaporphine-tacrine congeners.



Scheme 1. Synthesis of ω-haloalkanamides.

Preparation of the key intermediate compounds **6a**–**b** was shown in Scheme 1. Synthesis of 9-amino-1-azabenzanthrone **5** was carried out by a reported method [21,22]. The ω-haloalkanamides **6a**–**b** were prepared in essentially quantitative yield by acylation of **5** with the appropriate acid halide ($n = 1$–2).

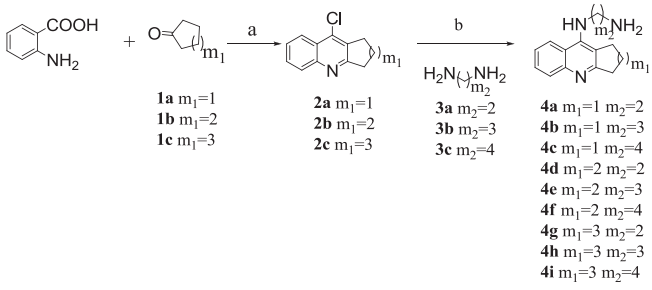
The related amines **4a**–**i** were chosen as the other critical intermediates for the synthesis of heterodimers. Their synthetical route is illustrated in Scheme 2. The $POCl_3$-mediated cyclodehydration reaction between o-aminobenzoic acid and cycloketones **1a**–**c** was adapted to the corresponding chlorides **2a**–**c** with moderate yields (54–94%). The amination of the chlorides **2a**–**c** was carried out in reaction with 5 equiv of α, ω-diamine **3a**–**c** in refluxing 1-pentanol [23] for 6–12 h, followed by removal of the solvent. The resulting mixture was diluted with dichloromethane and washed with large amount of water. Finally the organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give amines **4a**–**i** as pale-brown oily residue, which was used in the next step without further purification. However, for characterization purposes, the new amines **4a**–**i** were purified by column chromatography (CH_2Cl_2:CH_3OH = 100:3).

Finally, heterodimers **7a**–**l** were prepared by alkylation of **6a** and **6b** respectively, with amines **4a**–**i** in ethanol with moderate yields (Scheme 3).

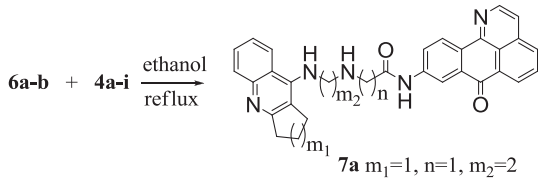
2.2. AChE and BuChE results and SAR discussion

To evaluate the biological profiles of these heterodimeric compounds for AD, AChE (*Electrophorus electricus*) and BChE (*equine serum*) inhibition was assayed in comparison with tacrine as reference compounds. The inhibitory potency against AChE and BChE was evaluated by the method of Ellman [24]. Table 1 summarizes the data comparing AChE and BChE inhibition as well as the selectivity for AChE or BChE inhibitory activities from IC_{50} values for the new synthesized heterodimers. Heterodimer **7f** exhibited an optimum AChE inhibitory activity, as noted in the fact that it is 31-fold more potent than tacrine. Moreover, compound **7f** possessed high AChE/BuChE selectivity ratios (32.4-fold).

According to the data shown in Table 1 and Fig 3, the synthesized heterodimers which consist of a unit of tacrine (**7e**–**h**)



Scheme 2. Synthesis of tacrine-analogues. Reagent and condition: (a) $POCl_3$, reflux 3h. (b) 4–5 equiv $NH_2(CH_2)_nNH_2$, 1-pentanol, reflux 6–12 h.



7a m_1=1, n=1, m_2=2
7b m_1=1, n=2, m_2=2
7c m_1=1, n=2, m_2=3
7d m_1=1, n=2, m_2=4
7e m_1=2, n=1, m_2=2
7f m_1=2, n=2, m_2=2
7g m_1=2, n=2, m_2=3
7h m_1=2, n=2, m_2=4
7i m_1=3, n=1, m_2=2
7j m_1=3, n=2, m_2=2
7k m_1=3, n=2, m_2=3
7l m_1=3, n=2, m_2=4

Scheme 3. Synthesis of hybrids of oxoisoaporphine-tacrine congeners.

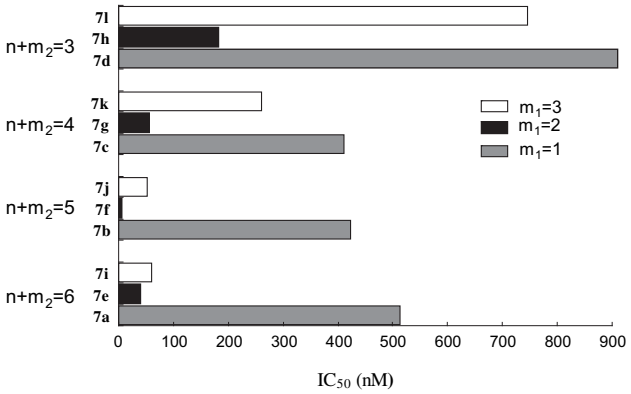


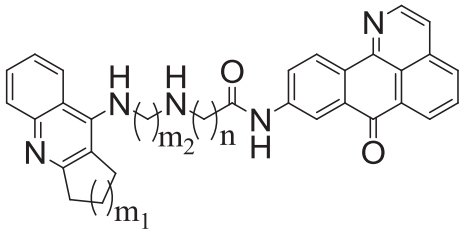
Fig. 3. Effects of structure of tacrine congeners on AChE.

showed higher inhibitory effect on AChE, compared with their congeners (**7a**–**d** and **7i**–**l**). In comparison with **7e**–**h** (3.4–182 nM for AChE), carbocyclic-shrinked congeners **7a**–**d** resulted in 5- to 124-fold (513–910 nM) less potency at AChE. By contrast, ring-expanded **7i**–**l** had moderate potency (61–745 nM) on AChE. This suggested that the binding pockets of AChE might accommodate a little more bulky moiety [25].

The effect on AChE inhibition of synthetic compounds with variation of chain length ($n + m_2 = 3$–6) are also shown in Table 1 and Fig 4. From the IC_{50} values of compounds **7a**–**l**, it appears that the proper tether length for the linker between the two anchoring groups, 9-aminoacridine and 9-amino-1-azabenzanthrone, seemed to be six (include secondary amine and carbonyl group) (compounds **7f** and **7j**).

Inspection of the BChE data for these dimeric congeners did not indicate clear trend in inhibition potency (Table 1 and Fig 5). Interestingly, cycloheptyl-fused congeners **7i**–**l** showed higher inhibitory effect on BChE (**7i**–**l** with BChE inhibitory activity at 21.1–211 nM) compared with the corresponding cyclopentyl and cyclohexyl nucleus (**7a**–**d** and **7e**–**h** with BChE inhibitory activity

Table 1
Inhibition of AChE and BChE activities, selectivity ratios, AChE-induced and self-induced Aβ aggregation by the synthesized compounds.



Compound	n	m_1	m_2	IC_{50}(nM) for AChE[a]	IC_{50}(nM) for BChE[b]	Selectivity for AChE[c]	Inhibition of Aβ aggregation (%)	
							Self-induced[e]	AChE-induced[f]
7a	1	1	2	513 ± 30	243 ± 12	0.5	52.2 ± 4.2	60.2 ± 1.7
7b	2	1	2	422 ± 25	1760 ± 110	4.2	63.9 ± 2.6	67.3 ± 1.8
7c	2	1	3	411 ± 25	399 ± 24	1.0	65.9 ± 3.1	73.3 ± 0.9
7d	2	1	4	910 ± 52	199 ± 10	0.2	85.8 ± 2.2	74.2 ± 1.2
7e	1	2	2	41.0 ± 2.3	433 ± 22	10.6	72.2 ± 1.4	82.6 ± 1.6
7f	2	2	2	3.4 ± 0.2	110 ± 7.3	32.4	79.8 ± 2.4	83.3 ± 1.2
7g	2	2	3	57.1 ± 3.4	199 ± 12	3.5	75.4 ± 2.8	89.6 ± 2.4
7h	2	2	4	182 ± 21	288 ± 17	1.6	76.6 ± 1.1	83.4 ± 1.9
7i	1	3	2	61.0 ± 2.5	211 ± 13	3.5	45.7 ± 1.7	53.6 ± 2.2
7j	2	3	2	51.7 ± 3.1	65 ± 4.0	1.3	35.5 ± 2.2	87.4 ± 0.8
7k	2	3	3	260 ± 16	21.1 ± 1.0	0.08	47.4 ± 1.5	78.6 ± 2.0
7l	2	3	4	745 ± 45	150 ± 21	0.2	41.2 ± 1.8	74.6 ± 2.5
5				>100,000	>100,000		nd	nd
Tacrine				104 ± 10	21 ± 1.3	0.2	nd	4.5 ± 0.7
Congo-red				nd[d]	nd		nd	97.0 ± 0.5
Curcumin				nd	nd		41.8 ± 1.7	34.5 ± 1.7

[a] IC_{50}: 50% inhibitory concentration (means ± SEM of three experiments) of AChE.
[b] IC_{50}: 50% inhibitory concentration (means ± SEM of three experiments) of BChE.
[c] Apparent selectivity for AChE is calculated as IC_{50}(BChE)/IC_{50}(AChE).
[d] Not determined.
[e] Inhibition of self-induced Aβ(1–42) aggregation (20 μM) produced by the tested compound at 10 μM concentration. Values are expressed as means ± SEM of three experiments.
[f] Co-aggregation inhibition of Aβ(1–40) and AChE 0.06 U was detected by ThT assay; The data (%) showed that the test compounds inhibited the co-aggregation at 100 μM. Values are expressed as means ± SEM of three experiments.

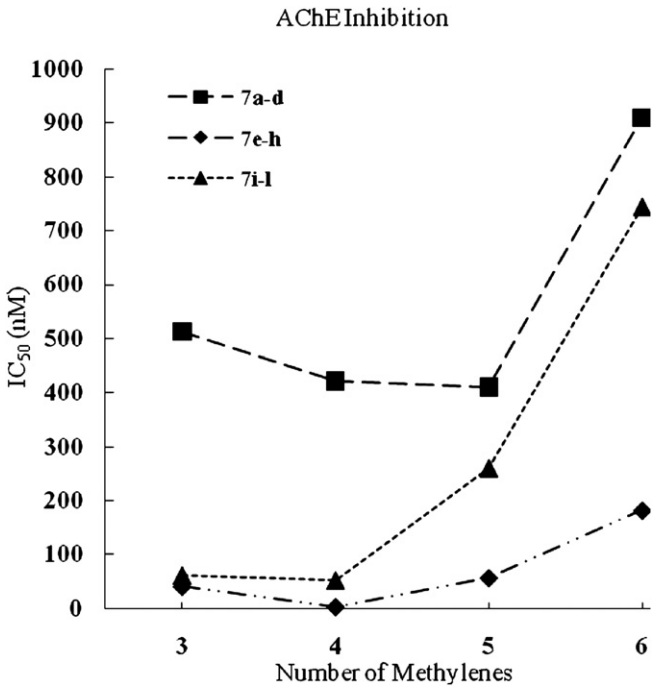


Fig. 4. Effects of tether length for the linker on AChE.

at 199–1760 and 110–433 nM, respectively). These results disclosed that BChE seems to be better able than AChE to accommodate steric bulk around the catalytic site [25,26].

2.3. Inhibition of Aβ aggregation with AChE or not

Besides assessing the ability to inhibit AChE, which is likely to be relevant on the brain of AD patients, we tested all the compounds (inhibitor:Aβ ratio 1:5) to assess the structural elements responsible for the *in vitro* inhibition of the self-assembly of Aβ(1–42), which is the most amyloidogenic Aβ fragment found in the AD plaques. To determine the amyloid-beta(1–42) aggregation inhibition of the new heterodimers (**7a**–**l**), thioflavin-T (ThT) assay was performed compared with Curcumin as reference compound [27–29]. Interestingly, all the synthesized compounds presented

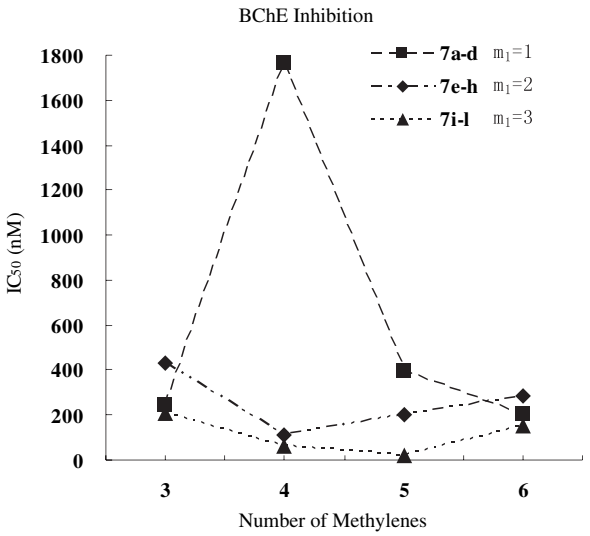


Fig. 5. Effects of tether length for the linker on BChE.

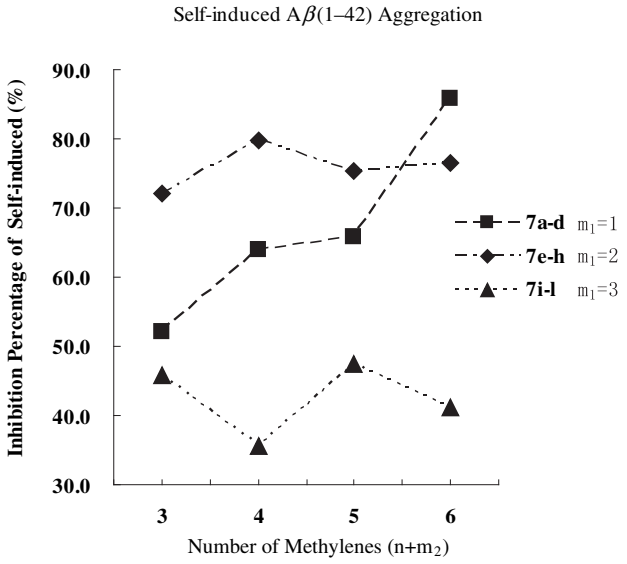


Fig. 6. Effects of tether length for the linker on self-induced Aβ (1–42) aggregation.

a good inhibitory potency on self-induced Aβ(1–42) aggregation. In the screening results (Table 1), the most effective compound is **7d**, followed by **7f**, **7h**, **7g** and **7e**, their inhibitory potency are 85.8%, 79.8%, 76.6%, 75.4% and 72.2%, respectively. The irregular inhibition percentage (Fig. 6) provided by **7a**–**d**; **7e**–**h** and **7i**–**l** with identical pharmacophore and different length of the spacer points to the conclusion that inhibitory potency on self-induced Aβ aggregation was not influenced by the chain length separating the pharmacophoric functions. Conversely, a major role seems to be played by the size of the tacrine congener, since the potency was decreased by expanding the ring **7i**–**l**. This suggested that bulky moiety may not favor the Aβ aggregation inhibition process.

In fact, AChE directly promotes *in vitro* the assembly of Aβ peptide into amyloid fibrils, forming stable AChE–Aβ complexes [6]. Structural analysis by X-ray crystallography [30] and competition assays with AChEIs clearly identified PAS of enzyme as a locus of protein interaction with Aβ [31]. We have already demonstrated

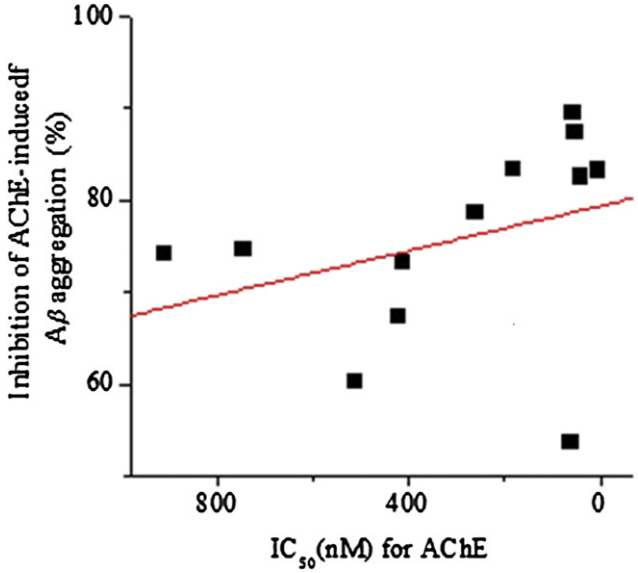


Fig. 7. Scatter plots representing in vitro inhibitory percent of AChE-induced Aβ aggregation versus IC_{50} value for AChE inhibition for a series of oxoisoaporphine derivatives (**7a**–**l**).

that 1-azabenzanthrone could interact with PAS of acetylcholinesterase, especially with Trp 279 of PAS [19]. To further explore the dual action of these compounds, AChE-induced Aβ(1–40) aggregation inhibitory activity was examined employing the same ThT-based fluorometric assay [32]. Table 1 summarizes the Aβ-antiaggregating activity of the novel hybrids and reference compounds. The twelve tested oxoisoaporphine-tacrine congeners exhibited, at a 100 μM concentration, a significant Aβ-antiaggregating effect with inhibition ranging from 53.6% to 89.6%, being 12- to 20-fold more potent than tacrine and 1.6- to 2.6-fold more potent than curcumin. Heterodimers which consist of a unit of tacrine **7e**–**h** are clearly more potent than other heterodimers **7a**–**d** and **7i**–**l**. The length of the linker has little effect on the Aβ-antiaggregating activity of the heterodimers, observing only a slightly increased effect in the hybrids bearing the four or five methylene units ($n + m_2 = 4$ or 5). For heterodimers which consist of a unit of tacrine, the proper tether length for the linker between the two pharmacophoric functions was seven (include secondary amine and carbonyl group) (compound **7g**). For cyclopentyl-fused and cycloheptyl-fused congeners, the proper tether length were eight and six respectively (compounds **7d** and **7j**).

Interestingly, nearly all the synthesized compounds presented higher inhibitory potency on AChE-induced Aβ (1–40) aggregation than on self-induced Aβ (1–42) aggregation. At the same time, there was a clear correlation between the AChE-induced Aβ aggregation inhibitory activity and AChE inhibitory potency. Fig. 7 shows a scatter plot of *in vitro* inhibitory percent of AChE-induced Aβ aggregation versus IC_{50} value for AChE inhibition. Utilization of a linear fitting procedure, a statistically significant fit was obtained, and it was clearly shown that the inhibitory effects for Aβ aggregation and acetylcholinesterase were positively correlated. These results appear to validate the dual-site theory that the compound which simultaneously binds both the catalytic site and PAS of AChE could strongly inhibit Aβ aggregation mediated by the enzyme.

2.4. Prediction of blood–brain barrier (BBB) permeability

In the central nervous system (CNS) drug development, it is important that the compounds are able to cross the blood–brain barrier (BBB). So BBB permeability properties of CNS drug candidates should be determined as early as possible in the drug discovery process. In order to assess the potential for synthetical hybrids to penetrate the BBB, a parallel artificial membrane permeation assay for BBB (PAMPA-BBB) was carried out. The PAMPA-BBB model applied in this study was based on the BBB model described by Di et al. [33]. This simple and rapid model was capable of identifying compounds as either BBB permeable (BBB+) or non-permeable (BBB−) with reasonable accuracy by modifying the lipid composition of the artificial membranes [9,34,35]. In this paper, a lipid extract of porcine brain was used. Assay validation was made comparing experimental permeabilities of 9 commercial drugs with reported values (Table 2).

Table 2
Permeability ($P_e \times 10^{-6}$ cm s^{-1}) in the PAMPA-BBB assay for nine commercial drugs, used in the experiment validation.

Compound	Bibliography[a]	Experiment[b]
Imipramine	13	11.5
Desipramine	12	10.1
Promazine	8.8	8.2
Chlorpromazine	6.5	8.7
Clonidine	5.3	6.3
Hydrocortisone	1.9	2.3
Enoxacin	0.9	0.5
Caffeine	1.3	1.4
Cimetidine	0	0.4

[a] Taken from Ref [33].
[b] Data are the mean of three independent experiments.

Table 3
Permeability ($P_e \times 10^{-6}$ cm s^{-1}) in the PAMPA-BBB assay for oxoisoaporphine-tacrine congener hybrids and their predictive penetration in the CNS.

Compound	$P_e \times 10^{-6}$ cm s^{-1} [a]	Prediction
7a	4.6 ± 0.2	CNS +
7b	1.9 ± 0.1	CNS −
7c	4.9 ± 0.2	CNS +
7d	2.4 ± 0.2	CNS −
7e	4.8 ± 0.1	CNS +
7f	2.6 ± 0.2	CNS +/−
7g	3.3 ± 0.2	CNS +/−
7h	2.1 ± 0.1	CNS -
7i	4.0 ± 0.2	CNS +/−
7j	7.9 ± 0.1	CNS +
7k	8.9 ± 0.4	CNS +
7l	1.1 ± 0.1	CNS −

[a] Data are the mean ($n = 3$) ± SD.

A plot of experimental data versus bibliographic values gave a good linear correlation, $P_e(\text{exp.}) = 0.87P_e(\text{bibl.}) + 0.71$ ($R^2 = 0.93$). From this equation and taking into account the limit established by Di et al. [33] for blood–brain barrier permeation, we classified compounds as follows:

(a) 'CNS +' (high BBB permeation predicted); P_e (10^{-6} cm s^{-1}) > 4.2
(b) 'CNS −' (low BBB permeation predicted); P_e (10^{-6} cm s^{-1}) < 2.5
(c) 'CNS +/−' (BBB permeation uncertain); P_e (10^{-6} cm s^{-1}) from 4.2 to 2.5

Finally, new synthetical hybrids were tested in the PAMPA-BBB assay, and the results were presented in Table 3. Among them, five of the hybrids (**7a**, **7c**, **7e** and **7j**–**k**) could be able to cross the blood–brain barrier (CNS +) and four of them (**7b**, **7d**, **7h** and **7l**) were classified as 'CNS −' (low brain penetration).

3. Conclusions

The present study reports the synthesis and biological evaluation of a series of new hybrids of oxoisoaporphine-tacrine congener. Regarding AChE inhibition, synthesized compounds show less inhibitory potency than that of 9-aminoalkanamido-1-azabenzanthrones derivatives [20] which we previously reported. Five hybrids (**7e**–**g** and **7i**–**j**) exhibited IC_{50} values in the nanomolar range and being clearly more potent than tacrine. The most potent AChE inhibitor is **7f**. Besides assessing the ability to inhibit AChE and BChE, which is likely to be relevant in the brain of AD patients [36], all the compounds were tested for their ability to block the self-induced Aβ(1–42) aggregation and the AChE-induced Aβ (1–40) aggregation. All the tested hybrids exhibited a significant Aβ antiaggregating activity, being more potent than tacrine and curcumin. Overall, these results suggest that the novel oxoisoaporphine-tacrine congener hybrids herein reported may have a potential disease-modifying role in the treatment of AD.

4. Experimental

4.1. Synthesis

Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator.Detection was done by UV (254 nm) followed by charring with 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry

organic solutions during work-ups and the removal of solvents which was carried out under vacuum with a rotary evaporator. Melting points (mp) were determined using an WRR melting point instrument without correction. ^{1}H NMR spectra were recorded with a Varian Mercury-Plus 300 and Bruker Avance AV500 NMR Spectrometer with tetramethylsilane (TMS) as an internal standard. Elemental analysis was carried out on a PE2400II Elemental Analyzer. Mass spectra analysis was performed on a BRUKER HCT mass spectrometer and recorded on an electrospray ionization mass spectrometer as the value *m*/*z*.

4.1.1. 9-Chloro-2,3-dihydro-1H-cyclopenta[b]quinoline (**2a**)

General cyclization procedure: to a mixture of o-aminobenzoic acid 3 g (22 mmol) and cyclopentanone **1a** 1.68 g (20 mmol) was carefully added 15 mL of $POCl_3$ at ice bath. The mixture was heated under reflux for 4 h, then cooled at room temperature, and concentrated to give a slurry. The residue was diluted with EtOAc, neutralized with aqueous K_2CO_3, and washed with brine. The organic layer was dried over anhydrous K_2CO_3 and concentrated in vacuo to furnish a pale-brown solid. Column chromatography of the solid, eluting with 4% EtOAc in petroleum ether, gave compound **2a** (3.1 g, 76%); mp 87–88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 2.22–2.28 (m, 2H), 3.17 (t, 2H, J = 7.5 Hz), 3.23 (t, 2H, J = 7.7 Hz), 7.56 (dd, 1H, J_1 = 7.8 Hz, J_2 = 8.3 Hz), 7.66 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.8 Hz), 8.02 (d, 1H, J = 8.3 Hz), 8.16 (d, 1H, J = 8.3 Hz); ESI-MS *m*/*z*: 204 $[M+H]^+$.

4.1.2. 9-Chloro-1,2,3,4-tetrahydroacridine (**2b**)

O-Aminobenzoic acid 3 g (22 mmol) was treated with cyclohexanone **1b** 2.0 g (20 mmol) according to the general cyclization procedure to give **2b** (2.7 g, 62%) as pale solid; mp 69–70 °C (literature mp 66–68 °C)[37]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.95–1.98 (m, 4H), 3.02 (t, 2H, J = 6.0 Hz), 3.13 (t, 2H, J = 6.1 Hz), 7.54 (dd, 1H, J_1 = 7.3 Hz, J_2 = 8.3 Hz), 7.67 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.3 Hz), 7.98 (d, 1H, J = 8.3 Hz), 8.16 (d, 1H, J = 8.3 Hz); ESI-MS *m*/*z*: 218 $[M+H]^+$.

4.1.3. 11-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline (**2c**)

O-Aminobenzoic acid 3 g (22 mmol) was treated with cycloheptanone **1c** 2.2 g (20 mmol) according to the general cyclization procedure to give **2c** (2.4 g, 52%) as pale solid; mp 88–89 °C (literature mp 87–89 °C)[25]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.75–1.76 (m, 2H), 1.81–1.82 (m, 2H), 1.89–1.90 (m, 2H), 3.21–3.26 (m, 4H), 7.56 (dd, 1H, J_1 = 7.3 Hz, J_2 = 8.3 Hz), 7.67 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.3 Hz), 7.99 (d, 1H, J = 8.3 Hz), 8.17 (d, 1H, J = 8.3 Hz); ESI-MS *m*/*z*: 232 $[M+H]^+$.

4.1.4. N′-(2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)ethane-1,2-diamine (**4a**)

General procedure: a mixture of **2a** (5.0 g, 24.6 mmol), phenol (4.5 g), and NaI (0.1 g) was stirred at 90 °C for 2 h and then **3a** (5.9 g, 98.4 mmol) was added. The internal temperature was raised to 120 °C and maintained there while the mixture was stirred for 4 h. The mixture was cooled to room temperature and was poured onto 100 ml. of water. Then the mixture was diluted with $CHCl_3$ and made basic with 10% NaOH solution. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. After concentration, the resulting residue was purified on silica gel chromatography ($CHCl_3$:MeOH = 100:3) to give **4a** (4.0 g, 72%) as amber glass foam. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.56 (s, 2H, NH_2), 2.10–2.16 (m, 2H), 3.00 (t, 2H, J = 5.5 Hz), 3.05 (t, 2H, J = 7.7 Hz), 3.20 (t, 2H, J = 7.2 Hz), 3.62–3.63 (m, 2H), 5.47 (s, 1H, NH), 7.36 (dd, 1H, J_1 = 7.4 Hz, J_2 = 7.6 Hz), 7.55 (dd, 1H, J_1 = 7.6 Hz, J_2 = 7.4 Hz), 7.82 (d, 1H, J = 8.4 Hz), 7.91 (d, 1H, J = 8.4 Hz); ESI-MS *m*/*z*: 228 $[M+H]^+$.

4.1.5. N′-(2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)propane-1,3-diamine (**4b**)

2a (5.0 g, 24.6 mmol) and phenol was treated with **3b** (7.3 g, 98.4 mmol) according to the general amination procedure to give diamine **4b** (3.8 g, 64%) as amber glass foam. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.78–1.83 (m, 2H), 2.08–2.14 (m, 2H), 2.97 (t, 2H, J = 6.1 Hz), 3.03 (t, 2H, J = 7.8 Hz), 3.25 (t, 2H, J = 7.3 Hz), 3.78 (t, 2H, J = 6.3 Hz), 6.20(m, 1H, NH), 7.33 (dd, 1H, J_1 = 7.4 Hz, J_2 = 7.8 Hz), 7.53 (dd, 1H, J_1 = 8.1 Hz, J_2 = 7.2 Hz), 7.82 (d, 1H, J = 8.3 Hz), 7.88 (d, 1H, J = 8.2 Hz); ESI-MS *m*/*z*: 242 $[M+H]^+$.

4.1.6. N′-(2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)butane-1,4-diamine (**4c**)

2a (5.0 g, 24.6 mmol) and phenol was treated with **3c** (8.7 g, 98.4 mmol) according to the general amination procedure to give diamine **4c** (2.9 g, 47%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.61–1.66 (m, 2H), 1.70–1.76 (m, 2H), 2.08–2.14 (m, 2H), 2.82(t, 2H, J = 6.8 Hz), 3.06 (t, 2H, J = 7.8 Hz), 3.19(t, 2H, J = 7.2 Hz), 3.65 (t, 2H, J = 6.8 Hz), 7.36(dd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz), 7.35 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz), 7.76 (d, 1H, J = 8.4 Hz), 7.894 (d, 1H, J = 8.3 Hz); ESI-MS *m*/*z*: 256 $[M+H]^+$.

4.1.7. N′-(1,2,3,4-Tetrahydroacridin-9-yl)ethane-1,2-diamine (**4d**)

2b (5.3 g, 24.6 mmol) and phenol was treated with **3a** (5.9 g, 98.4 mmol) according to the general amination procedure to give diamine **4d** (3.7 g, 62%) as straw yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.91–1.95(m, 4H), 2.77 (m, 2H), 2.95 (t, 2H, J = 5.7 Hz), 3.06 (m, 2H), 3.50 (t, 2H, J = 5.6 Hz), 7.34 (dd, 1H, J_1 = 7.4 Hz, J_2 = 7.8 Hz), 7.54 (dd, 1H, J_1 = 7.3 Hz, J_2 = 8.0 Hz), 7.90 (d, 1H, J = 8.0 Hz), 8.00 (d, 1H, J = 8.4 Hz); ESI-MS *m*/*z*: 242 $[M+H]^+$.

4.1.8. N′-(1,2,3,4-Tetrahydroacridin-9-yl)propane-1,3-diamine (**4e**)

2b (5.3 g, 24.6 mmol) and phenol was treated with **3b** (7.3 g, 98.4 mmol) according to the general amination procedure to give diamine **4e** (3.6 g, 57%) as grew oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.77–1.82 (m, 2H), 1.89–1.91 (m, 4H), 2.71 (t, 2H, J = 6.0 Hz), 2.88 (t, 2H, J = 6.5), 3.05 (t, 2H, J = 6.0 Hz), 3.59(t, 2H, J = 6.6 Hz), 7.33 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz), 7.53(dd, 1H, J_1 = 8.1 Hz, J_2 = 7.1 Hz), 7.89 (d, 1H, J = 8.4 Hz), 7.98 (d, 1H, J = 8.4 Hz); ESI-MS *m*/*z*: 256 $[M+H]^+$.

4.1.9. N′-(1,2,3,4-Tetrahydroacridin-9-yl)butane-1,4-diamine (**4f**)

2b (5.3 g, 24.6 mmol) and phenol was treated with **3c** (8.7 g, 98.4 mmol) according to the general amination procedure to give diamine **4f** (2.6 g, 39%) as grew oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.53–1.58 (m, 4H), 1.69–1.75 (m, 2H), 1.91–1.93 (m, 4H), 2.72–2.76 (m, 4H), 3.03–3.06 (m, 2H), 3.51(t, 2H, J = 7.2 Hz), 7.34 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.1 Hz), 7.55(dd, 1H, J_1 = 8.2 Hz, J_2 = 7.0 Hz), 7.91 (d, 1H, J = 8.4 Hz), 7.96 (d, 1H, J = 8.5 Hz); ESI-MS *m*/*z*: 270 $[M+H]^+$.

4.1.10. N′-(7,8,9,10-Tetrahydro-6H-cyclohepta[b]quinolin-11-yl) ethane-1,2-diamine (**4g**)

2c (4.1 g, 17.6 mmol) and phenol was treated with **3a** (5.3 g, 88.2 mmol) according to the general amination procedure to give diamine **4g** (2.9 g, 65%) as oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.72–1.74 (m, 2H), 1.77–1.80 (m, 2H), 1.86–1.88 (m, 2H), 2.93–2.98 (m, 4H), 3.17 (t, 2H, J = 5.5 Hz), 3.30 (t, 2H, J = 5.6 Hz), 7.42 (dd, 1H, J_1 = 7.5 Hz, J_2 = 7.8 Hz), 7.57 (dd, 1H, J_1 = 7.2 Hz, J_2 = 7.9 Hz), 7.95 (d, 1H, J = 8.3 Hz), 8.03 (d, 1H, J = 8.4 Hz); ESI-MS *m*/*z*: 256 $[M+H]^+$.

4.1.11. N′-(7,8,9,10-Tetrahydro-6H-cyclohepta[b]quinolin-11-yl) propane-1,3-diamine (**4h**)

2c (4.1 g, 17.6 mmol) and phenol was treated with **3b** (6.6 g, 88.2 mmol) according to the general amination procedure to give

diamine **4h** (2.8 g, 60%) as oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.72–1.74 (m, 2H), 1.77–1.81 (m, 4H), 1.86–1.88 (m, 2H), 2.89–2.94 (m, 4H), 3.17 (t, 2H, $J = 5.4$ Hz), 3.37 (t, 2H, $J = 6.6$ Hz), 7.40 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 8.0$ Hz), 7.56 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 7.9$ Hz), 7.93–7.95 (m, 2H); ESI-MS *m/z*: 270 $[M + H]^+$.

4.1.12. *N′-(7,8,9,10-Tetrahydro-6H-cyclohepta[b]quinolin-11-yl) butane-1,4-diamine (**4i**)*

2c (4.1 g, 17.6 mmol) and phenol was treated with **3c** (7.8 g, 88.2 mmol) according to the general amination procedure to give diamine **4i** (1.7 g, 35%) as oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.53–1.59 (m, 2H), 1.69–1.75 (m, 4H), 1.80–1.81 (m, 2H), 1.88–1.90 (m, 2H), 2.75 (t, 2H, $J = 6.9$ Hz), 2.92–2.95 (m, 2H), 3.17–3.19 (m, 2H), 3.30 (m, 2H, $J = 7.2$ Hz), 7.42 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 8.2$ Hz), 7.58 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 8.2$ Hz), 7.90 (d, 1H, $J = 8.4$ Hz), 7.95 (d, 1H, $J = 8.5$ Hz); ESI-MS *m/z*: 284 $[M + H]^+$.

4.1.13. *9-(2-Chloroacetamido)-1-azabenzanthrone (**6a**)*

General acylation procedure: a suspension of 9-amino-1-azabenzanthrone (**5**) (1.0 g, 4 mmol) in chloroacetyl chloride (15 mL) was heated at reflux for 4 h. After cooling to 0–5 °C, the mixture was filtered and the crude solid washed with ether. Recrystallization from EtOH-DMF (4:1 v/v) afforded chloroamide **6a** (1.1 g, 85%) as yellow/brown solid; mp 262–264 °C. ^{1}H NMR (DMSO, 300 MHz): δ_H 4.35 (s, 2H), 7.98 (d, 1H, $J = 5.6$ Hz), 8.01–8.09 (m, 2H), 8.41 (d, 1H, $J = 8.2$ Hz), 8.51 (d, 1H, $J = 2.2$ Hz), 8.54 (d, 1H, $J = 7.2$ Hz), 8.73–8.78 (m, 2H), 10.76(s, 1H -CONH); ESI-MS *m/z*: 323 $[M + H]^+$.

4.1.14. *9-(3-Chloropropionamido)-1-azabenzanthrone (**6b**)*

9-Amino-1-azabenzanthrone (**5**) (1.0 g, 4 mmol) was treated with 3-chloropropanoyl chloride according to the general acylation procedure to give chloroamide **6b** (1.0 g, 74%) as orange/yellow solid; mp ~242 °C(darkened). ^{1}H NMR (DMSO, 300 MHz): δ_H 2.92 (t, 2H, $J = 6.2$ Hz), 3.93 (t, 2H, $J = 6.2$ Hz), 7.98 (d, 1H, $J = 5.6$ Hz), 8.01–8.11 (m, 2H), 8.42 (d, 1H, $J = 8.2$ Hz), 8.54–8.56 (m, 2H), 8.73–8.78 (m, 2H), 10.55(s, 1H -CONH); ESI-MS *m/z*: 337 $[M + H]+$.

4.1.15. *2-((2-((2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)amino) ethyl)amino)-N-(7-oxo-7H-dibenzo[de,h]quinolin-9-yl)acetamide (**7a**)*

General procedure: to a stirred refluxing suspension of 9-(2-chloroacetamido)-1-azabenzanthrone **6a** (0.5 g, 1.5 mmol) and NaI (0.15 g) in EtOH (40 mL) was added dropwise **4a** (1.7 g, 7.5 mmol) in EtOH (10 mL). The mixture was stirred at reflux for 6 h, cooled to 0 °C, filtered, and was washed with ether and water. The crude solid was purified by column chromatography with chloroform/methanol (100:2) elution to afford a yellow solid **7a** (0.42 g, 55%). ^{1}H NMR (DMSO, 500 MHz): δ_H 2.04–2.08 (m, 2H), 2.92–2.97 (m, 4H) , 3.26 (t, 2H, $J = 7.2$ Hz), 3.50 (s, 2H), 3.79 (t, 2H, $J = 6.2$ Hz), 7.51 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 8.2$ Hz), 7.67–7,68 (m, 2H), 8.01–8.08 (m, 3H), 8.35 (d, 1H, $J = 8.5$ Hz), 8.44 (d, 1H, $J = 8.2$ Hz), 8.56–8.57(m, 2H), 8.73 (d, 1H, $J = 8.6$ Hz), 8.80 (d, 1H, $J = 5.6$ Hz), 10.39 (s, 1H). ^{13}C NMR (DMSO, 500 MHz): δ 181.9, 170.6, 163.5, 149.7, 147.3, 143.8, 141.6, 140.6, 134.5, 133.9, 132.2, 131.0, 130.7, 130.2, 129.5, 128.0, 125.7, 124.5, 124.3, 123.0, 122.2, 121.3, 120.5, 117.4, 116.2, 111.9, 52.2, 49.0, 44.00, 32.3, 30.7, 22.2. ESI-MS *m/z*: 514 $[M + H]^+$. Anal. calcd for $C_{32}H_{27}N_5O_2$: C, 74.83; H, 5.30; N, 13.64. Found: C, 74.56; H, 5.61; N, 13.43.

4.1.16. *3-((2-((2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)amino) ethyl)amino)-N-(7-oxo-7H-dibenzo[de,h]quinolin-9-yl) propanamide (**7b**)*

Following the general procedure described for **7a**, reaction of **6b** and **4a** in EtOH, yielded compound **7b** (59%) as yellow solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.83–1.89 (m, 2H), 2.66(t, 2H, $J = 7.8$ Hz), 2.74 (t, 2H, $J = 6.2$ Hz), 2.93 (t, 2H, $J = 5.9$ Hz), 3.04 (t, 2H, $J = 7.3$ Hz), 3.10 (t, 2H, $J = 6.1$ Hz), 3.62 (t, 2H, $J = 5.9$ Hz), 6.95 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 7.9$ Hz), 7.28–7.33 (m, 2H, $J = 8.5$ Hz), 7.58 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 8.0$ Hz), 7.73 (d, 1H, $J = 8.5$ Hz), 7.90–7.91 (m, 2H), 8.03(dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 7.6$ Hz), 8.36 (d, 1H, $J = 8.1$ Hz), 8.46 (d, 1H, $J = 7.1$ Hz), 8.67(d, 1H, $J = 5.6$ Hz), 9.03(d, 1H, $J = 8.4$ Hz), 14.38 (s, 1H). ^{13}C NMR (DMSO, 500 MHz): δ 181.4, 170.8, 165.3, 149.6, 147.0, 143.8, 140.5, 139.8, 134.3, 134.2, 132.3, 131.1, 130.8, 130.5, 129.5, 128.4, 125.6, 124.8, 124.7, 123.2, 121.5, 120.9, 120.7, 119.0, 117.5, 111.7, 48.5, 44.6, 43.1, 38.7, 33.0, 30.2, 22.06. ESI-MS *m/z*: 528 $[M + H]^+$. Anal. calcd for $C_{33}H_{29}N_5O_2 \cdot H_2O$: C, 72.64; H, 5.73; N, 12.84. Found: C, 72.41; H, 5.87; N, 12.72.

4.1.17. *3-((3-((2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)amino) propyl)amino)-N-(7-oxo-7H-dibenzo[de,h]quinolin-9-yl) propanamide (**7c**)*

Following the general procedure described for **7a**, reaction of **6b** and **4b** in EtOH, yielded compound **7c** (51%) as yellow/orange solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.91–1.97 (m, 4H), 2.86(t, 2H, $J = 7.5$ Hz), 2.98 (t, 2H, $J = 6.0$ Hz), 3.06–3.08 (m, 4H), 3.13 (t, 2H, $J = 7.1$ Hz), 3.68 (t, 2H, $J = 6.5$ Hz), 7.25 (dd, 1H, $J_1 = 7.8$, Hz $J_2 = 7.6$ Hz), 7.57–7.66 (m, 4H), 8.03 (d, 1H, $J = 7.7$ Hz), 8.09–8.13 (m, 2H), 8.47 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 8.2$ Hz), 8.59 (dd, 1H, $J_1 = 7.3$ Hz, $J_2 = 7.7$ Hz),8.86 (d, 1H, $J = 5.6$ Hz), 8.99 (d, 1H, $J = 8.2$ Hz) , 12.66 (s, 1H). ^{13}C NMR (DMSO, 500 MHz): δ 181.3, 169.2, 162.5, 150.1, 146.8, 144.1, 140.7, 139.4, 135.2, 134.4, 132.3, 131.3, 130.9, 130.7, 129.6, 128.1, 125.2, 124.8, 124.7, 122.3, 121.8, 121.3, 121.0, 119.4, 117.0, 111.8, 45.0, 43.4, 41.8, 35.0, 31.8, 30.4, 27.3, 21.9. ESI-MS m/z: 542 $[M + H]^+$. Anal. calcd for $C_{34}H_{31}N_5O_2 \cdot H_2O$: C, 72.97; H, 5.94; N, 12.51. Found: C, 73.31; H, 6.16; N, 12.69.

4.1.18. *3-((4-((2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)amino) butyl)amino)-N-(7-oxo-7H-dibenzo[de,h]quinolin-9-yl) propanamide (**7d**)*

Following the general procedure described for **7a**, reaction of **6b** and **4c** in EtOH, yielded compound **7d** (37%) as yellow/orange solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.70 (brs, 4H), 2.12(t, 2H, $J = 7.4$ Hz), 2.84 (t, 2H, $J = 6.5$ Hz), 3.00–3.05 (m, 4H), 3.24–3.26 (m, 4H), 3.67 (brs, 2H), 7.54 (dd, 1H, $J_1 = 7.4$ Hz $J_2 = 7.8$ Hz), 7.70 (d, 1H, $J = 8.0$ Hz), 7.75 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 7.9$ Hz), 8.01 (d, 1H, $J = 5.6$ Hz), 8.03–8.08 (m, 2H), 8.33 (d, 1H, $J = 8.5$ Hz), 8.44 (d, 1H, J = 8.2 Hz), 8.56 (d, 1H, $J = 7.2$ Hz), 8.61 (d, 1H, $J = 1.9$ Hz), 8.76–8.79 (m, 2H). ^{13}C NMR (DMSO, 500 MHz): δ 181.3, 169.4, 163.1, 150.4, 147.5, 143.4, 140.9, 140.1, 134.8, 134.6, 131.9, 131.2, 130.9, 130.3, 129.8, 128.0, 125.5, 125.0, 124.6, 123.3, 121.9, 121.1, 120.4, 118.8, 117.3, 111.4, 44.8, 42.9, 38.3, 34.9, 31.7, 30.5, 24.0, 23.2, 21.9. ESI-MS m/z: 556 $[M + H]^+$. Anal. calcd for $C_{35}H_{33}N_5O_2$: C, 75.65; H, 5.99; N, 12.60. Found: C, 75.47; H, 6.21; N, 12.41.

4.1.19. *N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-2-((2-((1,2,3,4-tetrahydroacridin-9-yl)amino)ethyl)amino)acetamide (**7e**)*

Following the general procedure described for **7a**, reaction of **6a** and **4d** in EtOH, yielded compound **7e** (37%) as yellow solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.81 (brs, 4H), 2.70(brs, 2H), 2.88 (brs, 2H), 3.02 (t, 2H, $J = 5.8$ Hz), 3.51 (s, 2H), 3.97 (t, 2H, $J = 5.6$ Hz), 7.54 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 8.0$ Hz), 7.70 (d, 1H, J = 8.3 Hz), 7.79 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 7.9$ Hz), 8.01–8.03 (m, 2H), 8.07 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 7.5$ Hz), 8.41 (d, 1H, $J = 8.5$ Hz), 8.44 (d, 1H, $J = 8.3$ Hz), 8.52(d, 1H, $J = 2.2$ Hz) , 8.58 (d, 1H, $J = 6.8$ Hz), 8.73 (d, 1H, $J = 8.6$ Hz), 8.80(d, 1H, $J = 5.6$ Hz). ^{13}C NMR (DMSO, 500 MHz): δ 181.8, 170.2, 154.8, 150.8, 147.2, 143.7, 140.6, 138.5, 134.5, 133.9, 132.1, 131.8, 131.0, 130.6, 129.4, 127.9, 125.6, 124.7, 124.5, 124.2, 121.2, 120.4, 119.7, 116.1, 115.7, 111.4, 51.8, 48.0, 46.5, 28.2, 23.4, 21.2, 20.2. ESI-MS *m/z*: 528

$[M+H]^+$. Anal. calcd for $C_{33}H_{29}N_5O_2\cdot 2H_2O$: C, 70.32; H, 5.90; N, 12.43. Found: C, 70.22; H, 5.68; N, 12.32.

*4.1.20. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-3-((2-((1,2,3,4-tetrahydroacridin-9-yl)amino)ethyl)amino)propanamide (**7f**)*

Following the general procedure described for **7a**, reaction of **6b** and **4d** in EtOH, yielded compound **7f** (55%) as yellow solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.68 (brs, 4H), 2.52–2.53 (m, 2H), 2.62(t, 2H, $J=5.2$ Hz), 2.73 (brs, 2H), 3.01–3.06 (m, 4H), 3.83–3.84 (m, 2H), 7.44 (dd, 1H, $J_1=7.8$ Hz, $J_2=7.7$ Hz), 7.51 (d, 1H, $J=8.5$ Hz), 7.64 (dd, 1H, $J_1=7.7$ Hz, $J_2=7.6$ Hz), 7.96–7.99 (m, 2H), 8.04 (dd, 1H, $J_1=7.6$ Hz, $J_2=7.9$ Hz), 8.24(d, 1H, $J=8.5$ Hz), 8.41 (d, 1H, $J=8.2$ Hz), 8.47 (brs, 1H), 8.52 (d, 1H, $J=7.2$ Hz), 8.62 (d, 1H, $J=8.5$ Hz), 8.76 (d, 1H, $J=5.6$ Hz). ^{13}C NMR (DMSO, 500 MHz): δ 181.9, 170.2, 154.3, 150.6, 147.3, 143.8, 141.0, 138.3, 134.6, 134.0, 132.1, 131.7, 130.8, 130.4, 129.5, 128.0, 125.8, 124.8, 124.5, 124.1, 121.3, 120.6, 119.9, 116.0, 115.5, 111.5, 47.4, 45.3, 43.7, 35.7, 29.1, 23.4, 21.5, 20.7. ESI-MS *m/z*: 542 $[M+H]^+$. Anal. calcd for $C_{34}H_{31}N_5O_2\cdot 2H_2O$: C, 70.69; H, 6.11; N, 12.12. Found: C, 70.78; H, 5.82; N, 12.45.

*4.1.21. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-3-((3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)amino)propanamide (**7g**)*

Following the general procedure described for **7a**, reaction of **6b** and **4e** in EtOH, yielded compound **7g** (46%) as yellow solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.80 (brs, 4H), 1.86–1.88 (m, 2H), 2.60 (brs, 2H), 2.69 (t, 2H, $J=5.2$ Hz), 2.80 (brs, 2H), 2.95 (t, 2H, $J=5.9$ Hz), 3.08–3.09 (m, 2H), 3.75 (brs, 2H), 7.34 (dd, 1H, $J_1=7.2$ Hz, $J_2=7.6$ Hz), 7.40 (brs, 1H), 7.47 (dd, 1H, $J_1=7.2$ Hz, $J_2=7.7$ Hz), 8.01–8.02 (m, 2H), 8.07 (dd, 1H, $J_1=7.6$ Hz, $J_2=7.7$ Hz), 8.15(d, 1H, $J=8.5$ Hz), 8.45 (d, 1H, $J=8.1$ Hz), 8.49 (brs, 1H), 8.53 (d, 1H, $J=7.2$ Hz), 8.60 (d, 1H, $J=7.7$ Hz), 8.79 (d, 1H, $J=5.5$ Hz), 10.56 (s, 1H). ^{13}C NMR (DMSO, 500 MHz): δ 181.7, 169.8, 153.0, 152.5, 147.1, 143.7, 141.4, 140.8, 134.5, 133.9, 131.9, 130.7, 130.6, 129.9, 129.4, 127.9, 125.6, 124.1, 123.9, 123.7, 122.7, 121.2, 120.4, 117.2, 115.8, 113.2, 46.7, 46.0, 44.0, 34.3, 30.1, 27.8, 24.0, 21.7, 21.0. ESI-MS m/z: 556 $[M+H]^+$. Anal. calcd for $C_{35}H_{33}N_5O_2$: C, 75.65; H, 5.99; N, 12.60. Found: C, 75.42; H, 6.21; N, 12.51.

*4.1.22. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-3-((4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)amino)propanamide (**7h**)*

Following the general procedure described for **7a**, reaction of **6b** and **4f** in EtOH, yielded compound **7h** (41%) as yellow/orange solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.67–1.70 (m, 2H), 1.76–1.80 (m, 6H), 2.62 (brs, 2H), 2.83 (t, 2H, $J=6.5$ Hz), 2.91 (brs, 2H), 2.99 (t, 2H, $J=7.5$ Hz), 3.24 (t, 2H, $J=6.5$ Hz), 3.84 (t, 2H, $J=6.5$ Hz), 7,54 (dd, 1H, $J_1=7.5$ Hz $J_2=7.8$ Hz), 7.72 (d, 1H, $J=8.4$ Hz), 7.81 (dd, 1H, $J_1=7.5$ Hz, $J_2=7.8$ Hz), 7.99–8.01 (m, 2H), 8.05 (dd, 1H, $J_1=7.8$ Hz, $J_2=7.6$ Hz), 8.32(d, 1H, $J=8.7$ Hz), 8.43 (d, 1H, $J=8.2$ Hz), 8.55 (d, 1H, $J=7.1$ Hz), 8.59 (d, 1H, $J=1.9$ Hz), 8.74 (d, 1H, $J=8.7$ Hz), 8.78 (d, 1H, $J=5.5$ Hz). ^{13}C NMR (DMSO, 500 MHz): δ 182.5, 169.1, 155.7, 151.0, 147.5, 144.3, 140.9, 138.2, 135.0, 134.6, 132.9, 132.6, 131.7, 131.3, 130.2, 128.3, 126.3, 125.4, 125.1, 124.9, 121.7, 121.2, 119.4, 116.7, 115.7, 111.7, 46.7, 42.6, 32.3, 30.8, 28.2, 27.1, 24.0, 22.8, 21.6, 20.4. ESI-MS m/z: 570 $[M+H]^+$. Anal. calcd for $C_{36}H_{35}N_5O_2$: C, 75.90; H, 6.19; N, 12.29. Found: C, 75.62; H, 5.93; N, 12.47.

*4.1.23. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-2-((2-((7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)ethyl)amino)acetamide (**7i**)*

Following the general procedure described for **7a**, reaction of **6a** and **4g** in EtOH, yielded compound **7i** (56%) as yellow solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.66 (brs, 4H), 1.79–1.80 (m, 2H), 2.81 (t, 2H, $J=6.0$ Hz), 2.94–2.95 (m, 2H), 3.04–3.06 (m, 2H), 3.32–3.33 (m, 2H), 3.42 (s, 2H), 5.43 (t, 1H, $J=5.1$ Hz), 7.40 (dd, 1H, $J_1=7.5$ Hz, $J_2=7.4$ Hz), 7.54 (dd, 1H, $J_1=7.7$ Hz, $J_2=7.2$ Hz), 7.76 (d, 1H, $J=8.3$ Hz), 7.99 (d, 1H, $J=5.6$ Hz), 8.05 (dd, 1H, $J_1=7.7$ Hz, $J_2=7.8$ Hz), 8.11 (dd, 1H, $J_1=8.6$ Hz, $J_2=1.8$ Hz), 8.19 (d, 1H, $J=8.3$ Hz), 8.42(d, 1H, $J=8.2$ Hz), 8.56 (d, 1H, $J=7.3$ Hz), 8.61 (d, 1H, $J=1.8$ Hz), 8.75(d, 1H, $J=8.7$ Hz), 8.78(d, 1H, $J=5.6$ Hz), 10.35(s, 1H). ^{13}C NMR (DMSO, 500 MHz): δ 182.0, 170.8, 164.5, 149.6, 147.4, 146.1, 143.8, 141.2, 134.5, 133.9, 132.2, 130.8, 130.6, 129.4, 128.3, 128.1, 127.6, 125.7, 124.3, 123.9, 122.9, 122.4, 121.7, 121.3, 120.4, 116.1, 49.1, 48.9, 44.7, 37.0, 31.1, 27.8, 26.8, 26.4. ESI-MS *m/z*: 542 $[M+H]^+$. Anal. calcd for $C_{34}H_{31}N_5O_2\cdot H_2O$: C, 72.97; H, 5.94; N, 12.51. Found: C, 73.14; H, 6.12; N, 12.42.

*4.1.24. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-3-((2-((7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)ethyl)amino)propanamide (**7j**)*

Following the general procedure described for **7a**, reaction of **6b** and **4g** in EtOH, yielded compound **7j** (48%) as yellow solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.62 (brs, 4H), 1.75 (brs, 2H), 2.61 (t, 2H, $J=6.4$ Hz), 2.82 (t, 2H, $J=6.0$ Hz), 2.88–2.89 (m, 2H), 2.93 (t, 2H, $J=6.5$ Hz), 3.01–3.03 (m, 2H), 3.35 (t, 2H, $J=6.0$ Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.55 (dd, 1H, $J_1=7.8$ Hz, $J_2=7.5$ Hz), 7.77 (d, 1H, $J=8.3$ Hz), 7.94 (d, 1H, J = 5.6 Hz), 7.98 (dd, 1H, $J_1=8.7$ Hz, $J_2=1.9$ Hz), 8.02(t, 1H, $J=7.7$ Hz), 8.11 (d, 1H, $J=8.3$ Hz), 8.36 (d, 1H, $J=8.2$ Hz), 8.50–8.53 (m, 2H), 8.63 (d, 1H, $J=8.6$ Hz) , 8.72 (d, 1H, $J=5.6$ Hz). ^{13}C NMR (DMSO, 500 MHz): δ 181.8, 170.4, 164.4, 149.7, 147.6, 146.8, 143.4, 141.0, 134.6, 133.9, 132.1, 131.6, 130.8, 129.5, 128.8, 128.3, 127.2, 125.9, 124.1, 123.8, 123.2, 122.7, 121.8, 121.5, 119.8, 116.4, 47.8, 46.1, 43.2, 38.2, 34.5, 30.8, 27.9, 26.8, 26.3. ESI-MS *m/z*: 556 $[M+H]^+$. Anal. calcd for $C_{35}H_{33}N_5O_2$: C, 75.65; H, 5.99; N, 12.60. Found: C, 75.46; H, 6.24; N, 12.75.

*4.1.25. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-3-((3-((7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)propyl)amino)propanamide (**7k**)*

Following the general procedure described for **7a**, reaction of **6b** and **4h** in EtOH, yielded compound **7k** (48%) as yellow/orange solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.61 (brs, 4H), 1.75–1.76 (m, 2H), 1.84–1.87 (m, 2H), 2.69 (t, 2H, $J=6.3$ Hz), 2.84–2.86 (m, 4H), 2.94–2.96 (m, 2H), 3.06 (t, 2H, $J=6.3$ Hz), 3.38 (t, 2H, $J=6.5$ Hz), 7.43 (dd, 1H, $J_1=7.2$ Hz, $J_2=8.0$ Hz), 7.54 (dd, 1H, $J_1=7.7$ Hz, $J_2=7.2$ Hz), 7.65(d, 1H, J = 8.2 Hz), 7.81(dd, 1H, $J_1=8.5$ Hz, $J_2=2.1$ Hz), 7.90(d, 1H, J = 5.6 Hz), 7.97 (dd, 1H, $J_1=7.8$ Hz, $J_2=7.7$ Hz), 8.07(d, 1H, $J=8.4$ Hz), 8.31(d, 1H, $J=8.2$ Hz), 8.38(d, 1H, $J=2.1$ Hz), 8.43(d, 1H, $J=7.2$ Hz), 8.46(d, 1H, $J=8.6$ Hz), 8.66 (d, 1H, $J=5.6$ Hz). ^{13}C NMR (DMSO, 500 MHz): δ 181.9, 169.6, 164.0, 149.9, 147.3, 145.3, 143.8, 140.9, 134.5, 133.9, 132.2, 130.9, 130.6, 129.4, 128.0, 127.9, 127.6, 125.7, 124.2, 124.1, 122.9, 122.7, 121.5, 121.2, 120.5, 116.1, 47.4, 45.9, 43.7, 38.7, 34.3, 31.1, 28.3, 27.7, 26.8, 26.3. ESI-MS *m/z*: 570 $[M+H]^+$. Anal. calcd for $C_{36}H_{35}N_5O_2\cdot 2H_2O$: C, 71.38; H, 6.49; N, 11.56. Found: C, 71.62; H, 6.62; N, 11.34.

*4.1.26. N-(7-Oxo-7H-dibenzo[de,h]quinolin-9-yl)-3-((4-((7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)butyl)amino)propanamide (**7l**)*

Following the general procedure described for **7a**, reaction of **6b** and **4i** in EtOH, yielded compound **7l** (32%) as yellow/orange solid. ^{1}H NMR (DMSO, 500 MHz): δ_H 1.68–1.69(m, 4H), 1.75–1.77 (m, 4H), 1.86 (brs, 2H), 2.86 (t, 2H, $J=6.5$ Hz), 2.93–2.95 (m, 2H), 3.01 (t, 2H, $J=7.5$ Hz), 3.10–3.13 (m, 2H), 3.18 (brs, 2H), 3.27 (t, 2H, $J=6.6$ Hz), 7.58 (dd, 1H, $J_1=7.8$ Hz, $J_2=6.5$ Hz), 7.79–7.83 (m, 2H), 8.04–8.11 (m, 3H), 8.35 (d, 1H, $J=8.5$ Hz), 8.47(d, 1H, $J=8.2$ Hz) , 8.59(d, 1H, $J=7.2$ Hz), 8.64 (d, 1H, $J=2.0$ Hz), 8.78–8.82 (m, 2H). ^{13}C NMR (DMSO, 500 MHz): δ 181.3, 170.3, 164.2, 149.7, 147.1, 146.7, 143.2, 140.5, 134.0, 133.4, 131.8, 131.6, 130.1, 129.1, 128.5, 128.1, 127.5, 125.5, 124.8, 124.0, 123.1, 122.6, 121.8, 120.9, 119.9, 116.0, 48.8, 47.8, 47.4,

37.7, 33.9, 30.2, 27.7, 26.9, 26.1, 25.8, 24.8. ESI-MS *m/z*: 584 $[M+H]^+$. Anal. calcd for $C_{37}H_{37}N_5O_2 \cdot 2H_2O$: C, 71.71; H, 6.67; N, 11.30. Found: C, 71.93; H, 6.91; N, 11.32.

4.2. In vitro inhibition studies on AChE and BuChE

All the assays were under 0.1 M KH_2PO_4/K_2HPO_4 buffer, pH 8.0, using a Shimadzu 2450 Spectrophotometer. AChE from *Electrophorus electricus* (Sigma) were prepared to give 2.0 units/ml in 2 ml aliquots. The assay medium contained phosphate buffer, pH 8.0 (1 mL), 50 mL of 0.01 M DTNB, 10 mL of enzyme, and 50 mL of 0.01 M substrate (acetylthiocholine chloride). The substrate was added to the assay medium containing enzyme, buffer, and DTNB with inhibitor after 15 min of incubation time. The activity was determined by measuring the increase in absorbance at 412 nm for 1 min interval at 37 °C. Calculations were performed according to the method of the equation in Ellman et al. [24].

In vitro BChE (from *equine serum*, Sigma) assay uses the similar method described above.

4.3. Determination of the inhibitory effect on the self-mediated Aβ(1–42) aggregation

The thioflavin-T fluorescence method was used [27,29,38], and Aβ(1–42) peptide (Anaspec Inc) was dissolved in phosphate buffer (pH 7.4, 0.01 M) to give a 40 μM solution. Compounds were firstly prepared in DMSO at a concentration of 10 mM. The final concentration of Aβ (1–42) and inhibitors were 20 μM and 10 μM, respectively. After incubating at 37 °C for 48 h, thioflavin-T (5 μM in 50 mM glycine-NaOH buffer, pH 8.0) was added. Fluorescence was measured at 450 nm (λ ex) and 485 nm (λ em). Each inhibitor was examined in triplicate. The fluorescence intensities were recorded, and the percentage of inhibition on aggregation was calculated with the following equation: $(1 - IFi/IFc) \times 100\%$. IFi and IFc were the fluorescence intensities obtained in the presence and absence of inhibitors, respectively, after subtracting the fluorescence of corresponding blanks.

4.4. Inhibition of AChE-induced Aβ(1–40)peptide aggregation assay

For co-incubation experiments [4,32], of Aβ(1–40) peptide (GL Biochem Ltd) and AChE from *Electrophorus electricus*, the mixtures of Aβ(1–40)peptide and AChE in presence or absence of the test inhibitors were incubated for 8 h at 37 °C. The final concentrations of *Aβ* (dissolved in DMSO and diluted 0.215 M sodium phosphate buffer, pH 8.0) and AChE (dissolved in 0.1 M sodium phosphate buffer, pH 8.0) are 23 μM and 0.06 U, respectively. To analyze co-aggregation inhibition, the ThT fluorescence method was used and the fluorescence was measured at 446 nm (λ excitation) and 490 nm (λ emission). After co-incubation, to the mixture solutions of 20 μL was added 1.5 μM ThT 180 μL. Each assay was run in triplicate and each reaction was repeated at least three independent times.

4.5. PAMPA-BBB procedure

Brain penetration of new compounds was evaluated using a parallel artificial membrane permeation assay (PAMPA), in a similar manner as described by Di et al. [33]. Commercial drugs were purchased from Sigma and Aladdin (china). The porcine brain lipid (PBL) was obtained from Avanti Polar Lipids. The donor microplate was a 96-well filter plate (PVDF membrane, pore size 0.45 μm) and the acceptor microplate was an indented 96-well plate, both from Millipore. The 96-well UV plate (COSTAR®) was from Corning Incorporated. The acceptor 96-well microplate was filled with 300 μL of Phosphate Buffered Saline (PBS):ethanol (9:1) and the filter membrane was coated with 4 μL of porcine brain lipid (PBL) in dodecane (20 mg mL^{-1}). Test compounds were dissolved in DMSO at 5 mg mL^{-1}. Then the compound solution was diluted 200-fold in PBS : ethanol (9:1) (final concentration 25 μg mL^{-1}) to make secondary stock solution. 300 μL of the secondary stock solution were added to the donor wells. The acceptor filter plate was carefully put on the donor plate to form a 'sandwich', which was left undisturbed for 10 h at 25 oC. The concentration of drug in the acceptor, the donor, and the reference wells was determined using the UV plate reader (Tecan Infinite® M1000). P_e can be calculated from the following equation as reported by Faller et al. [39] and Sugano et al. [40].

$$P_e = -\left(\frac{V_d \times V_a}{(V_d + V_a)A \times t}\right) \times \ln\left(1 - \frac{[drug]_{acceptor}}{[drug]_{equilibrium}}\right)$$

where V_d is the volume of donor well; V_a, volume in acceptor well; *A*, filter area; *t*, permeation time; $[drug]_{acceptor}$, the absorbance of compound found in the acceptor well; $[drug]_{equilibrium}$, the theoretical equilibrium absorbance. All compounds were tested in triplicate at pH 7.4 and the results were given as the mean ± standard deviation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.08.002.

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