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Design, synthesis and biological evaluation of benzylisoquinoline derivatives as multifunctional agents against Alzheimer's disease

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ABSTRACT

A novel series of benzylisoquinoline derivatives were designed, synthesized, and evaluated as multifunctional agents against Alzheimer's disease (AD). The screening results showed that most of the compounds significantly inhibited cholinesterases (ChEs), human cholinesterases (h-ChEs) and self-induced β-amyloid (Aβ) aggregation. In particular, compound **9k** showed the strongest acetylcholinesterase (AChE) inhibitory activity, being 1000-fold and 3-fold more potent than its precursor benzylisoquinoline (**10**) and the positive control galanthamine, respectively. In addition, **9k** was a moderately potent inhibitor for h-ChEs. Compared with precursor benzylisoquinoline (36.0% at 20 μM), **9k** (78.4% at 20 μM) could further inhibit Aβ aggregation. Moreover, **9k** showed low cell toxicity in human SH-SY5Y neuroblastoma cells. Therefore, compound **9k** might be a promising lead compound for AD treatment.

Alzheimer's disease (AD), a progressive, neurodegeneration disease, is the most common cause of dementia among the elderly.[1,2] Data of 2010 reported that approximately 36 million people worldwide suffered from AD. By 2050, it is estimated that the figure is going to rise beyond 100 million. AD was first defined by the German psychiatrist and neuropathologist Alois Alzheimer in 1906. Over 100 years, the etiology of AD remains elusive. Several factors such as low levels of acetylcholine (ACh)[3,4] and amyloid β-peptide (Aβ) deposits[5] play significant roles in the pathophysiology of AD.[6]

Cholinergic hypothesis is one of the classical hypothesis of AD, based on which, the decline in cognitive and mental functions associated with AD is related to the weakened cortical cholinergic neurotransmission.[7] One rational way to enhance cholinergic neurotransmission is to break down the process of metabolism of ACh. ACh can be degraded by two types of cholinesterases (ChE), namely acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).[8] Compared with BuChE, AChE attracts more attention from the pharmaceutical academics since it accounts for nearly 80% ACh hydrolysis in normal brains.[9] The crystallographic structure of AChE indicates that it includes two separate ligand binding sites, a peripheral cationic site (PAS) at the entrance and a catalytic active site (CAS) at the bottom.[10–12] Inhibitors binding to either site can restrain the activity of AChE. Besides its catalytic function, AChE can further bind to Aβ and act as a promoter of Aβ fibril formation. PAS was associated with this action and several ligands that bind to this site have been shown to prevent Aβ aggregation.[13,14] Therefore, the design of dual-site inhibitors that interact simultaneously with both CAS and PAS appears to be a promising therapeutic strategy. Furthermore, in healthy brains, the ability of BuChE to hydrolyze ACh is inferior to that of AChE. While as AD progresses, the ability of BuChE significantly increases, and that of AChE diminishes in the hippocampus and temporal cortex.[14,15] Consequently, inhibition of both enzymes is beneficial to the treatment of AD.

Recent studies indicate another hypothesis, called amyloid hypothesis, may contribute to AD pathology. The amyloid hypothesis states that the accumulation and aggregation of Aβ is a pivotal factor to induce AD, as its accumulation in the brain may result in senile plaques, neurofibrillary tangles, neuronal cell death, and ultimately dementia.[16,17] Aβ is formed from a larger amyloid precursor protein (APP) via sequential proteolytic cleavage by β- and γ-secretases.[18] The cleavage of APP by β-secretase generates a soluble version of APP and a resultant membrane-bound C-terminal domain. Subsequent intramembrane proteolysis of the C-terminal domain by γ-secretase produces $A\beta_{40}$ and $A\beta_{42}$ peptides.[19] $A\beta_{42}$ is more prone to self-assembly into fibrils and is the major Aβ component in amyloid plaques.[20] Therefore, preventing this peptide from aggregation is a potential therapy for AD.

Up to now, several AChE inhibitors have been launched for treating AD including tacrine, rivastigmine, donepezil, and

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galanthamine.[21] However, due to the complex nature of AD, those drugs that modulate such a single target can only improve the symptoms for most patients instead of reaching the etiology of AD.[22–26] Hence there is an urgent need for new, efficacious molecules decorated with additional pharmacological/biochemical properties other than ChE inhibition itself. Based on considerations above, in this study, we attempted to explore multifunctional agents not only inhibiting ChE but also decreasing Aβ aggregation.

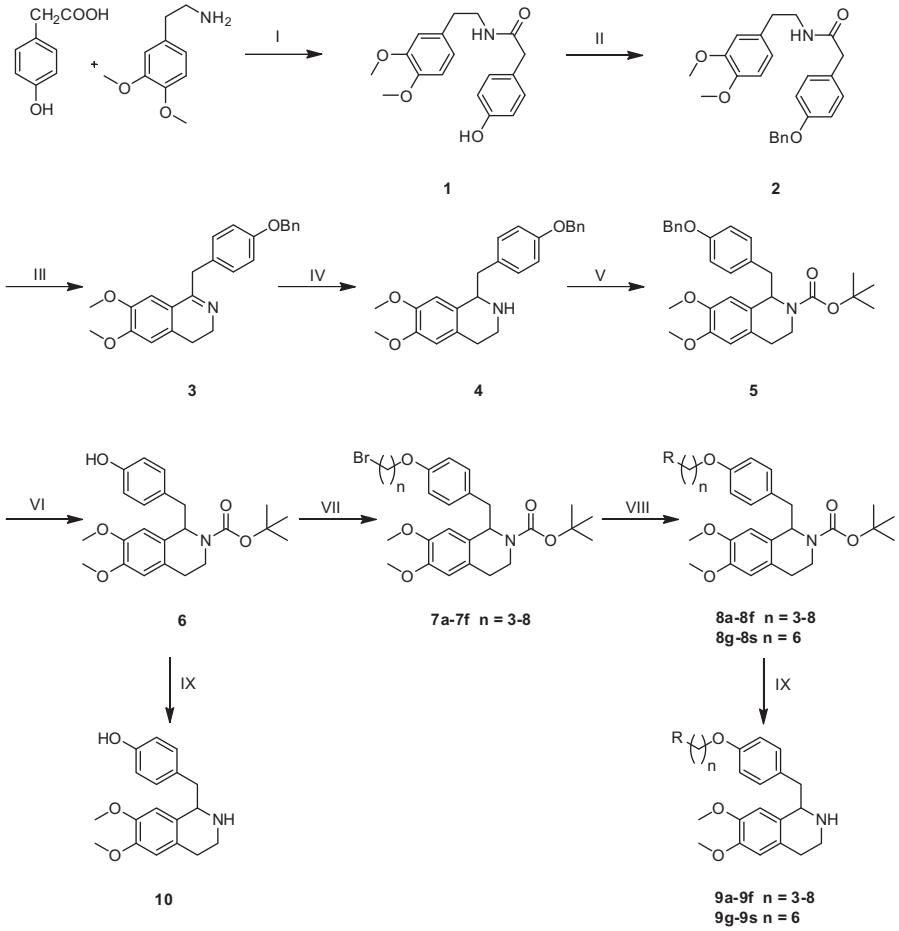
Isoquinoline alkaloids, a large family of natural products, have attracted increasingly widespread attention as they possess a wide range of pharmacological properties relevant to neurological disorders, especially for AD.[27–30] Many naturally occurring substances, such as berberine and chelerythrine, exhibited inhibiting potency of AChE and Aβ aggregation, which was exerted by interacting with PAS of AChE.[31] Subsequently, a number of chemically synthesized isoquinoline analogs were designed as AChE inhibitors.[32] Therefore, isoquinoline is a valuable scaffold for designing new effective compounds to treat AD.

Although isoquinoline scaffolds exhibited these obvious advantages in AD drug design, few studies focused on designing multifunctional isoquinoline hybrids. In this paper, isoquinoline hybrids were designed by combining benzylisoquinoline and a series of different terminal amine groups as multifunctional agents for AD treatment. Benzylisoquinoline could interact with the PAS of AChE via aromatic stacking interactions, and the terminal amine groups, protonated at physiological pH, could occupy the CAS via cation–π interaction. Considered the distance between CAS and PAS sites, to better connect benzylisoquinoline and terminal amine groups, different lengths of carbon spacers were tried. Unbranched carbon spacer was able to embed in the narrow midgorge,[14] and the length of carbon spacer was changed to obtain optional conformation that could make the designed compounds interact with both CAS and PAS of AChE.

In this study, the synthesis of a series of benzylisoquinoline hybrids and their biological evaluation including inhibitory activities of AChE, BuChE and anti-Aβ aggregation were described. The structure–activity relationship (SAR) was discussed based on the pharmacological activities. Moreover, kinetic analysis and molecular modeling were also performed to further investigate the mechanism of interaction with AChE.

The synthetic strategy of target compounds was shown in Scheme 1. The synthetic route started with the condensation of 2-(3,4-dimethoxyphenyl) ethylamine with (*p*-hydroxyphenyl) acetic acid, which provided the amide **1** in 80.5% yield.[33] The classical Bischler–Napieralski cyclization reaction and reduction reaction was then used to obtain compound **4** from amide **2** after the hydroxyl group had been conveniently protected.[34] After protecting the compound **4** with $(Boc)_2O$, the *O*-benzyl protecting group of product **5** was removed. The alkylation of **6** with different α,ω-dibromoalkanes in butanone provided **7a–f** in 65–70% yields.[35] The compounds **8a–s** were obtained by the reaction of **7** with commercially available secondary amines. Finally, after removing the Boc group, the target products **9a–s**/**10** were obtained.

Taking into account the cost, firstly animal enzymes were used to determine biological activities of target compounds. The inhibitory activities of target compounds **9a–s** against AChE (from



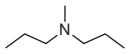
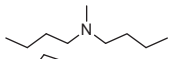
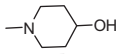
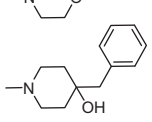
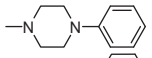
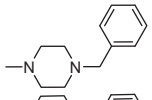
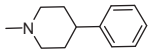
Scheme 1. Reagents and conditions: (I) EDCI, Et_3N, DCM, rt, overnight; (II) BrBn, K_2CO_3, EtOH, reflux, 12 h; (III) $POCl_3$, toluene, reflux, 4 h; (IV) $NaBH_4$, MeOH, 0 °C–rt, 6 h; (V) $(Boc)_2O$, DCM, rt, 2 h; (VI) Pd/C, H_2, MeOH, rt, 48 h; (VII) 1, *n*-dibromoalkane, K_2CO_3, butanone, reflux, 6 h; (VIII) NHR, $NaHCO_3$, DMF, 60 °C, 24 h (R- were showed in Table 1); (IX) 2 M HCl, ether, rt, 3 h.

electric eel) and BuChE (from equine serum) were measured according to the spectrophotometric method of Ellman et al. using galanthamine as the reference compound.[36,37] All IC_{50} values of test compounds for AChE and BuChE inhibition were summarized in Table 1. Most of benzylisoquinoline derivatives were moderately potent inhibitors for both ChEs with IC_{50} values ranging from micromolar to sub-micromolar. Among these compounds, **9k** revealed the most potent inhibition for AChE (IC_{50} = 0.95 μM). By contrast, **9m** gave the most potent inhibition of BuChE (IC_{50} = 2.34 μM). Most of compounds showed slightly higher inhibitory activity for AChE than for BuChE, indicating that these compounds were selective inhibitors for AChE. Moreover, the inhibitory activities for both ChEs of all target compounds (IC_{50} = 0.95–53.50 μM for AChE; IC_{50} = 2.34–15.29 μM for BuChE) were much more potent than that of their precursor compound benzylisoquinoline (**10**) (IC_{50} >100 μM for AChE; IC_{50} = 39.7 μM for BuChE), demonstrating the introduction of amino group side chains could significantly increase the inhibitory activities of derivatives. It was eventually confirmed that our molecular design is reasonable.

The previous reports suggested that the length of the alkyl chain between aromatic moiety and terminal amino group could affect the ability to interact with both sites of AChE and thereby influence the AChE inhibitory potency.[38] Hence, to determine the optimal length in present study, compounds **9a–f** with linker varied from three to eight carbons were synthesized. The results showed that **9d** was the most potent inhibitor for AChE, which pointed out that the optimal length for present compounds was six carbons.

The optimal length of the linker was confirmed as a chain of six carbons, then different terminal amine groups were introduced to further explore SAR. Compounds (**9j–m**) with a cyclic amine group in their side chains were stronger inhibitors than those with alkyl amine groups (**9g–i**). For instance, compounds **9l** and **9m** had lower IC_{50} values than compounds **9g** and **9h** for both AChE and BuChE. Interestingly, it was found that the AChE inhibitory activities of six-membered N-containing heterocyclic compounds **9k** and **9l** were higher than five-membered N-containing heterocyclic compounds **9j** and **9m**, respectively, which indicated that increased lipophilicity could lead to a rise in AChE inhibitory potency.[39,40] Introduction

Table 1
Inhibition of ChEs activity, selectivity index and inhibition of self-induced $A\beta_{42}$ aggregation

Compound	R	*n*	Formula	IC_{50} (μM)		Selectivity index[c]	$A\beta_{42}$ aggregation inhibition[d](%)
				AChE[a]	BuChE[b]		
9a		3	$C_{25}H_{36}N_2O_3$	13.23 ± 0.34	20.81 ± 0.22	1.57	41.1 ± 2.1
9b		4	$C_{26}H_{38}N_2O_3$	7.58 ± 0.41	15.29 ± 0.61	2.02	47.3 ± 1.4
9c		5	$C_{27}H_{40}N_2O_3$	7.02 ± 0.25	10.28 ± 0.52	1.46	34.3 ± 1.2
9d		6	$C_{28}H_{42}N_2O_3$	2.28 ± 0.14	4.95 ± 0.39	2.17	56.4 ± 9.1
9e		7	$C_{29}H_{44}N_2O_3$	4.67 ± 0.53	9.13 ± 0.81	1.96	43.9 ± 4.7
9f		8	$C_{30}H_{46}N_2O_3$	6.33 ± 0.20	20.06 ± 0.65	3.17	39.6 ± 1.1
9g		6	$C_{26}H_{38}N_2O_3$	3.14 ± 0.13	8.65 ± 0.13	2.75	55.3 ± 3.6
9h		6	$C_{30}H_{46}N_2O_3$	3.01 ± 0.04	4.32 ± 0.27	1.44	51.2 ± 7.0
9i		6	$C_{32}H_{50}N_2O_3$	3.43 ± 0.27	3.46 ± 0.51	1.01	51.4 ± 2.7
9j		6	$C_{29}H_{42}N_2O_3$	1.34 ± 0.11	3.35 ± 0.04	2.50	72.3 ± 1.2
9k		6	$C_{30}H_{44}N_2O_3$	0.95 ± 0.02	3.13 ± 0.16	3.29	78.4 ± 0.6
9l		6	$C_{29}H_{42}N_2O_3$	1.14 ± 0.09	2.51 ± 0.37	1.96	76.4 ± 2.8
9m		6	$C_{28}H_{40}N_2O_3$	1.28 ± 0.13	2.34 ± 0.28	2.05	69.0 ± 1.3
9n		6	$C_{29}H_{42}N_2O_4$	13.27 ± 0.21	14.16 ± 1.38	1.07	62.1 ± 0.78
9o		6	$C_{28}H_{40}N_2O_4$	28.64 ± 0.34	13.01 ± 0.45	0.45	57.4 ± 1.29
9p		6	$C_{36}H_{48}N_2O_4$	41.75 ± 0.20	12.83 ± 1.26	0.31	62.7 ± 3.35
9q		6	$C_{34}H_{45}N_3O_3$	17.09 ± 0.44	8.78 ± 0.92	0.51	65.8 ± 5.82
9r		6	$C_{35}H_{47}N_3O_3$	53.50 ± 1.23	10.53 ± 0.05	0.20	61.4 ± 0.03
9s		6	$C_{35}H_{46}N_2O_3$	6.69 ± 0.03	7.99 ± 0.47	1.19	61.2 ± 1.76
Benzylisoquinoline (**10**)			$C_{18}H_{21}NO_3$	>100	39.7 ± 0.54		36.0 ± 5.7
Galanthamine				2.67 ± 0.15	12.7 ± 0.20	2.76	
Resveratrol							61.5 ± 2.10

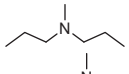
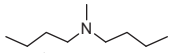
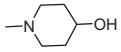
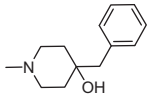
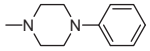
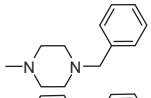
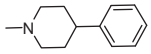
[a] Inhibitor concentration (mean ± SEM of three experiments) required for 50% inactivation of AChE.
[b] Inhibitor concentration (mean ± SEM of three experiments) required for 50% inactivation of BuChE.
[c] Selectivity index = IC_{50} (BuChE)/IC_{50} (AChE).
[d] Inhibition of self-induced $A\beta_{42}$ aggregation, the thioflavin-T fluorescence method was used, the mean ± SD of at least three independent experiments and the measurements were carried out in the presence of 20 μM compounds.

of a methyl group to 2-positon of cyclic amine group (pyrrolidinyl and piperidinyl) led to an increase in AChE inhibition but a decrease in BuChE inhibition. For example, AChE inhibitory activity of compound **9k** was higher than that of **9l**, but its BuChE inhibitory activity was lower than **9l**. Moreover, introducing additional oxygen atom or hydroxyl to terminal cyclic amino group afforded compounds **9n** and **9o**, which led a sharp decrease in both AChE and BuChE inhibition. This phenomenon can be explained by a previous report.[38] Electron-withdrawing effects of oxygen atom could reduce the electronic density of the terminal amine and further impact its protonation, which finally diminished the cation–π interaction between the terminal nitrogen and the CAS of AChE. Finally, four compounds (**9p**–**s**) with phenyl or benzyl groups at 4-positon of heterocycle (piperazinyl and piperidinyl) were also synthesized. Unfortunately, with exception of **9s** showing IC_{50} value in one-digit micromolar, all of them showed weak inhibitory activity to both AChE and BuChE, which might be caused by the steric hindrance of phenyl group.

In next step, the 6-carbon chain lead compounds (**9d**, **9g**–**s**) and **10** were then evaluated as inhibitors of human ChEs (h-ChEs). The IC_{50} values of test compounds for human AChE (h-AChE) and BuChE (h-BuChE) inhibition were summarized in Table 2. All tested derivatives showed an IC_{50} against h-ChEs in the low micromolar range and they were slightly less potent efficient for inhibition of the human enzyme than that of animal enzyme. Although the best h-AChE inhibitor was **9l** (IC_{50} = 2.14 μM) rather than **9k** (IC_{50} = 2.20 μM), their inhibitory activities were about the same. This phenomenon could be due to the differences between h-AChE and electric eel AChE.[14] By contrast, **9m** revealed the most potent inhibition for both BuChEs (IC_{50} = 2.27 μM for h-BuChE; IC_{50} = 2.34 μM for horse serum BuChE). Moreover, the inhibitory activities for both h-ChEs of all target compounds (IC_{50} = 2.14 to 39.63 μM for h-AChE; IC_{50} = 2.27 to 23.73 μM for h-BuChE) were much more potent than that of their precursor benzylisoquinoline (**10**) (IC_{50} >100 μM for h-AChE; IC_{50} = 46.77 μM for h-BuChE), once again demonstrating the introduction of amino group side chains is reasonable.

To further explore the interaction mode for AChE, molecular docking study was performed with the most active compound **9k** by software package MOE 2008.10. The X-ray crystallographic structure of AChE complex with bis(7)-tacrine (PDB code: 2CKM) was obtained from the Protein Data Bank. As shown in Figure 1, compound **9k** could perfectly fit into the gorge of AChE and simultaneously interact with both CAS and PAS of AChE, manifesting multiple binding modes with AChE. The aromatic ring of benzylisoquinoline moiety binding to the PAS site interacts with the indole ring of Trp279 via the π–π stacking. Moreover, the charged nitrogen of benzylisoquinoline group bound to the PAS was via a cation–π interaction with Tyr70 and Trp279. At the bottom of the gorge, the charged nitrogen of 2-methylpiperidine was also able

Table 2
Inhibition of human ChEs activity and selectivity index[a]

Compound	R	*n*	Formula	IC_{50} (μM)		Selectivity index[d]
				h-AChE[b]	h-BuChE[c]	
9d		6	$C_{28}H_{42}N_2O_3$	4.99 ± 0.23	16.70 ± 2.71	3.35
9g		6	$C_{26}H_{38}N_2O_3$	7.13 ± 0.31	3.43 ± 0.45	0.48
9h		6	$C_{30}H_{46}N_2O_3$	3.46 ± 0.16	11.17 ± 1.39	3.23
9i		6	$C_{32}H_{50}N_2O_3$	3.85 ± 0.07	6.02 ± 1.77	1.56
9j		6	$C_{29}H_{42}N_2O_3$	4.50 ± 0.44	6.42 ± 2.03	1.43
9k		6	$C_{30}H_{44}N_2O_3$	2.20 ± 0.12	5.83 ± 1.43	1.49
9l		6	$C_{29}H_{42}N_2O_3$	2.14 ± 0.03	3.25 ± 0.64	1.69
9m		6	$C_{28}H_{40}N_2O_3$	2.98 ± 0.20	2.27 ± 0.40	0.76
9n		6	$C_{29}H_{42}N_2O_4$	9.59 ± 0.27	23.73 ± 3.15	2.47
9o		6	$C_{28}H_{40}N_2O_4$	35.48 ± 0.08	10.59 ± 2.73	0.29
9p		6	$C_{36}H_{48}N_2O_4$	39.63 ± 0.39	15.90 ± 1.88	0.40
9q		6	$C_{34}H_{45}N_3O_3$	16.33 ± 1.93	12.90 ± 0.91	0.23
9r		6	$C_{35}H_{47}N_3O_3$	5.59 ± 2.11	21.71 ± 2.27	3.88
9s		6	$C_{35}H_{46}N_2O_3$	9.33 ± 0.57	9.29 ± 1.20	0.46
Benzylisoquinoline (**10**)			$C_{18}H_{21}NO_3$	>100	46.77 ± 0.36	

[a] AChE from human erythrocytes and BuChE from human serum were used.
[b] Inhibitor concentration (mean ± SEM of three experiments) required for 50% inactivation of AChE.
[c] Inhibitor concentration (mean ± SEM of three experiments) required for 50% inactivation of BuChE.
[d] Selectivity index = IC_{50} (BuChE)/IC_{50} (AChE).

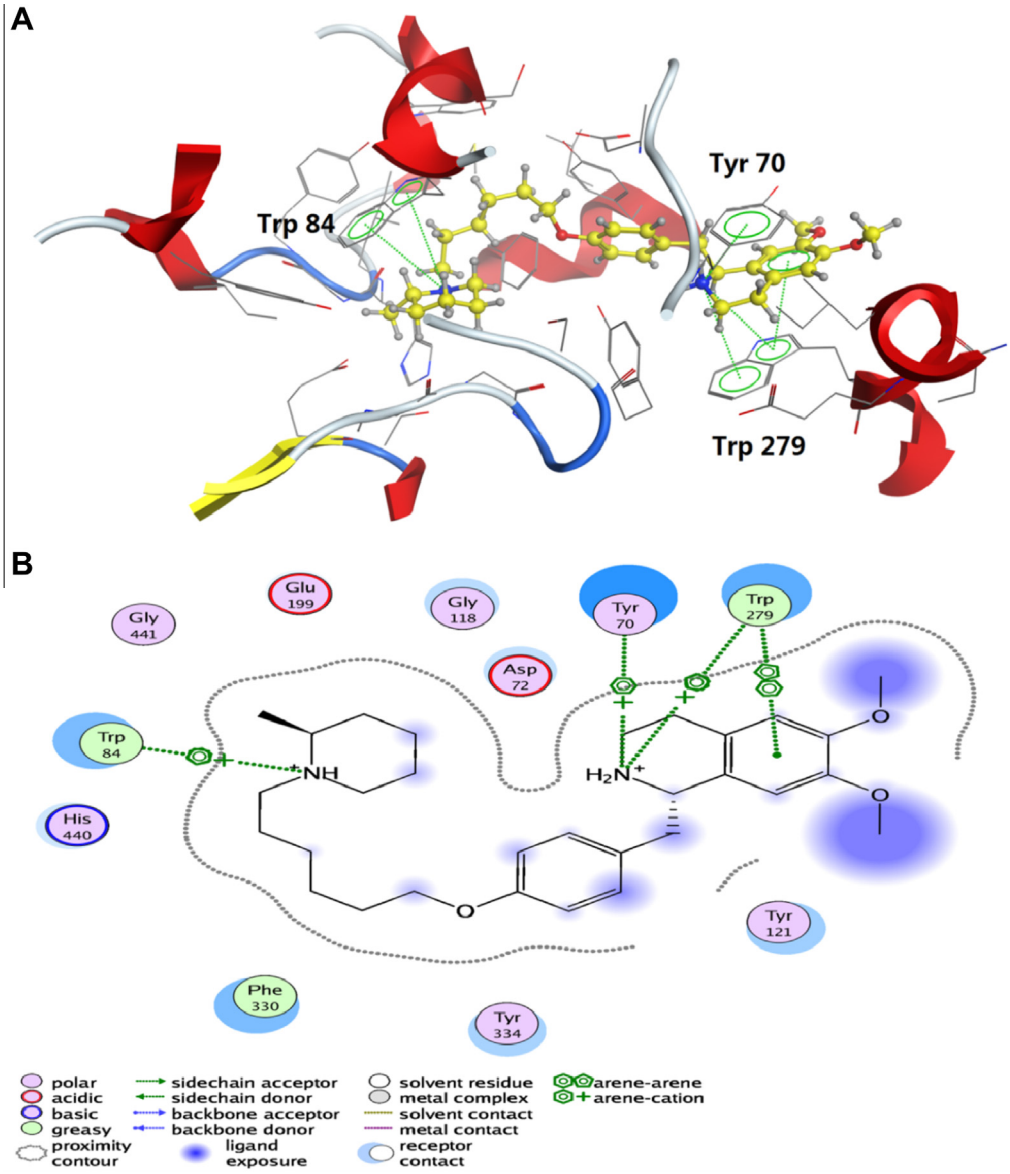


Figure 1. Molecular modeling of compound **9k** with AChE (A and B) generated with MOE.

to bind to the CAS via a cation–π interaction with Trp84. All these results clearly indicated that compound **9k** could simultaneously bind to CAS and PAS of AChE.

Kinetic study of compound **9k** was further examined to investigate the AChE inhibitory mechanism. The Lineweavere–Burk plots (Fig. 2) showed both increasing slopes and increasing intercepts on the *y*-axis at increasing inhibitor concentration. This pattern indicated a mixed-type inhibition and therefore revealed that compound **9k** bound to the both sites of AChE, which were consistent with our design.

In addition, the inhibition of self-induced $A\beta_{42}$ aggregation of these compounds was evaluated by a thioflavin-T based fluorometric assay.[41,42] Resveratrol (RES), a known active natural product for the inhibition of $A\beta_{42}$ self-aggregation, was used as reference compound and the results were showed in Table 1. From the results, it could be seen that most compounds exhibited moderate-to-good potencies (34.3–78.4% at 20 μM) compared to that of RES (61.5% at 20 μM) and benzylisoquinoline (36.0% at 20 μM). The result indicated that **9k** (78.4% at 20 μM) was the most potent inhibitor of $A\beta_{42}$ aggregation among the target compounds. From the inhibition values of compounds **9a**–**f**, it seemed that the linker length indeed played a role in determining the inhibition of $A\beta_{42}$ self-aggregation. The compound **9d** with six-carbon length showed better anti-$A\beta_{42}$ aggregation activity than the others with shorter or longer carbon spacers. Moreover, it could be found that compounds **9j**–**s** with closed-loop groups exhibited better inhibitory potency than compounds **9a**–**i** with open-loop ones. Unlike the trend of AChE inhibition, our data showed that the inhibition of $A\beta_{42}$ aggregation was slightly influenced by the introduction of electron-withdrawing groups or bulky groups. For example, the anti-$A\beta_{42}$ aggregation activities of **9n**–**s** were slightly weaker than that of **9j**–**m**. Consequently, these results implied that benzylisoquinoline was indeed a potent inhibitor of $A\beta_{42}$ aggregation.

On basis of the screening results above, the most potent compound **9k** was selected to further examine the potential toxicity effect on the human neuroblastoma cell line SH-SY5Y.[43,44] After exposing the cells to **9k** for 24 h, the cell viability was evaluated by the 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay. The result indicated that **9k** did not show significant effect on cell viability at 0.1–10 μM (0.1 μM: 96.8 ± 10.7%; 0.5 μM:

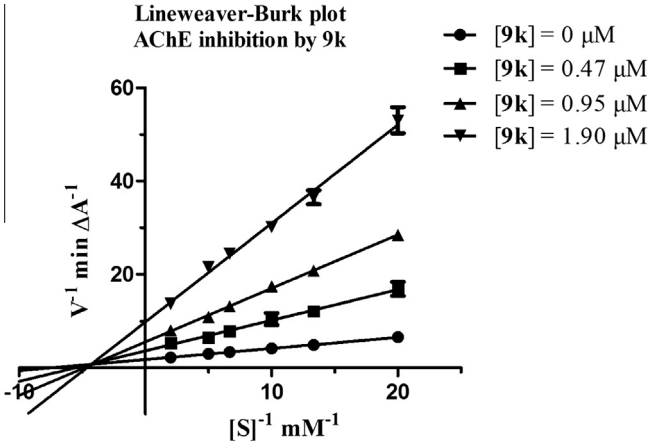


Figure 2. Lineweaver–Burk plots resulting from subvelocity curve of AChE activity with different substrate concentrations (0.05–0.50 mM) in the absence and presence of 0.47, 0.95, 1.90 μM **9k**.

98.8 ± 13.1%; 1 μM: 96.8 ± 8.1%; 2 μM: 96.1 ± 11.6%; 5 μM: 94.5 ± 7.3%; 10 μM: 91.1 ± 16.3%). This suggested that **9k** was non-toxic to SH-SY5Y cells and might be a suitable multifunctional agent for treating AD.

In conclusion, a variety of novel benzylisoquinoline derivatives were designed, synthesized and evaluated with the aim to prepare multifunctional compounds for treating AD. It was observed that most of the compounds could effectively inhibit ChEs, h-ChEs and $A\beta_{42}$ aggregation in vitro, especially compound **9k** exhibited the best AChE and h-AChE inhibitory activity, good inhibition of $A\beta_{42}$ aggregation activity and low cytotoxic activity. Furthermore, molecular modeling and inhibitory kinetic analysis revealed that **9k** bound simultaneously to both CAS and PAS of AChE. Overall, the new hybrids with multifunctional effects, especially **9k**, were determined as potential anti-AD candidate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.03.058.

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