Volume 1 | Number 1 | Jan 2013 | Pages 1–100

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ARTICLE TYPE

Discovery of Dehydroabietylamine Derivatives as Multifunctional Agents for the Treatment of Alzheimer's Disease

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Dehydroabietylamine derivatives have been reported to eliminate the superoxide anion (O_2^-·) and 1,1-dipheny-2-picrylhydrazyl (DPPH·) radicals. Herein, several dehydroabietylamine derivatives showed potent anti-oxidative activity in SH-SY5Y cells and exhibited significant inhibition of Aβ42 self-mediated aggregation and the disaggregation of Aβ42 aging fibrils. In particular, compound 12N, 18N-

10 bis(caffeoyl)-14-nitrodehydroabietylamine (**3b)** showed the most potent inhibition activity against Aβ42 self-mediated aggregation with an IC_{50} value of 3.96±0.33 μM. Moreover, compound **3b** decreased the production of Aβ42 in swAPP HEK293 cells and showed neuroprotective activity against Aβ42-induced cytotoxicity. Furthermore, through reducing the production of Aβ42 species, compound **3b** alleviated Aβ42-induced paralysis in transgenic *Caenorhabditis elegans* strain CL4176. Considering its

15 multifunctional activity and lower cytotoxicity, **3b** is considered a potential multifunctional agent for the treatment of Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive impairment and memory loss[1,

20 2]. It has been reported that AD is caused and proceeded by many factors, such as oxidative stress, *β*-amyloid (Aβ) and τ-protein formation, neuronal toxicity, and acetylcholine breakdown[3]. The brains of AD patients feature characteristic Aβ plaques; therefore, great attention has been paid to this 39-43 residue polypeptide,

25 which is derived from the hydrolysis of amyloid precursor protein (APP)[4-6]. Serious neuronal toxicity may arise from the aggregation and deposition of Aβ species in the brain as oligomers or fibrils[7]. Consequently, reducing the production and aggregation of Aβ42 has been considered an important approach

30 for the treatment of AD. Several natural products have also been reported to reduce the production of Aβ42, such as curcumin (Cur)[8] and berberine[9]. Animal experiments have proven that polyphenols show neuroprotective effects on Aβ-induced toxicity as well[10-12]. In addition, oxidative damage also plays an important

35 role in this neurodegenerative disease[13, 14]. One of the earliest pathological features in AD pathogenesis is oxidative stress. Agents with anti-oxidative ability may also have potent anti-amyloid aggregation activity, as elucidated by the polyphenols[15]. Therefore, multifunctional compounds for the treatment of AD

40 are desirable[16]. Finding multi-targeted agents with anti-oxidant and Aβ42 inhibitory activity as well as the ability to reduce oxidative stress, Aβ42 self-mediated aggregation, and Aβ42-induced neurocytotoxicity might be an effective therapeutic strategy for AD[17-21].

45 Dehydroabietylamine, which contains a phenanthrene ring structure, is the main component of rosin amine and has been comprehensively studied for its wide range of biological effects. Dehydroabietylamine derivatives show anti-microbial, anti-viral, anti-inflammatory, and free radical scavenging activity[22-25]. In the

50 previous study, we synthesized and evaluated the anti-oxidant activity of the dehydroabietylamine derivatives *in vitro*[26]. Here, a series of dehydroabietylamine derivatives (Table 1) were evaluated for the treatment of AD, which included examining their anti-oxidative activity in SH-SY5Y cells, their inhibition of

55 Aβ42 aggregation, and their neuroprotective effect. Furthermore, the activity of 12N, 18N - bis (caffeoyl) - 14 - nitrodehydroabietylamine (**3b**) was sufficiently studied using Thioflavin T (ThT)[27], circular dichroism (CD) spectra[28, 29], transmission electron microscopy (TEM), and molecular

60 dynamics (MD) simulations. Moreover, swAPP HEK293 cells transfected with APP695[30] and *Caenorhabditis elegans* strain CL4176 were also used to evaluate their ability to inhibit the production of Aβ42 and alleviate the paralysis process of *C. elegans*[31].
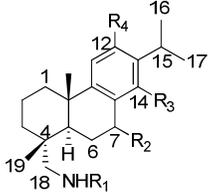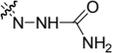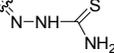
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Results and discussion

In the previous study, we have reported the design and synthesis of 22 dehydroabietylamine derivatives with their anti-oxidant

70 activities *in vitro* [26]. Herein, their anti-oxidant activities were evaluated by the levels of ROS generation in SH-SY5Y cell lines[32]. Most compounds didn't show cytotoxicities at the tested concentration of 10 μM. Curcumin (Cur) was used as a positive control. Compared with Cur, eight compounds (**1a, 1b, 1c, 2j, 3b,**

75 **3c, 3d**, and **3e**) significantly reduced the generation of ROS in SH-SY5Y cells (Table 1). These results indicated that eight compounds showed better anti-oxidant activity than Cur.

ARTICLE TYPE

Table 1 The structures of 22 compounds and their activities at anti-oxidant and against Aβ aggregation

Comps	R$_1$	R$_2$	R$_3$	R$_4$	^{a}ROS	^{b}Aβ aggregation inhibition	^{c}β aging fibrils disaggregation
1	H	H	H	H	N/A	N/A	N/A
1a	(3,4,5-trihydroxybenzoyl)	H	H	H	50.84±3.25	74.63±1.28	48.98± 1.48
1b	(3,4,5-triacetoxybenzoyl)	H	H	H	41.75±4.98	55.26±1.35	37.63 ± 1.30
1c	(3,4,5-triacetoxy-HC=)	H	H	H	48.23±2.19	20.57±1.98	8.93 ± 3.24
1d	(3,4-dihydroxy-HC=)	H	H	H	26.06±2.54	24.53±2.31	10.72 ± 1.21
2	H	=O	H	H	N/A	N/A	N/A
2a	(C(=O)CH$_3$)	=N–NH–C(=O)NH$_2$	H	H	13.35±1.24	N/A	N/A
2b	(C(=O)CH$_3$)	=N–NH–C(=S)NH$_2$	H	H	N/A	N/A	N/A
2c	(C(=O)CH$_3$)	=N–N(H)–C(=O)CH$_3$	H	H	N/A	N/A	N/A
2d	(C(=O)CH$_3$)	=N–N(H)–C(=O)-pyridyl	H	H	N/A	N/A	N/A
2e	(C(=O)CH$_3$)	=N–N(H)–C(=O)-pyridyl	H	H	N/A	N/A	N/A
2f	(C(=O)CH$_3$)	=N–O–C(=O)-(4-Cl-phenyl)	H	H	10.4±3.27	N/A	N/A
2g	(C(=O)CF$_3$)	=NOH	H	H	34.14±1.09	N/A	N/A
2h	(C(=O)CF$_3$)	=O	H	H	19.77±2.45	N/A	N/A
2i	(C(=O)CF$_3$)	=N–N(H)–C(=O)-pyridyl	H	H	N/A	N/A	N/A
2j	(C(=O)CH$_3$)	=NOH	H	H	41.18±2.01	N/A	N/A
3	H	H	NO$_2$	NH$_2$	N/A	N/A	N/A
3a	(3,4-dihydroxybenzoyl)	H	NO$_2$	NH$_2$	31.24±2.18	26.07±2.15	14.25 ± 3.72

					ROS	ThT inhib.	Disaggr.
3b	(structure)	H	NO_2	(structure)	62.44±4.58	91.95±1.45	82.78 ± 1.37
3c	(structure)	H	(structure)	(structure)	53.85±5.13	93.3 ±2.39	82.46 ± 2.04
3d	(structure)	H	NO_2	(structure)	42.19±4.32	72.97±2.78	48.92 ± 3.03
3e	(structure)	H	NO_2	(structure)	48.4±4.35	77.87±2.46	51.99 ± 1.29
Cur	N/A	N/A	N/A	N/A	37.87±2.35	70.6 ±1.89	48.74 ± 1.34

[a] **ROS:** was measured using DCFH-DA in SH-SY5Y cells after incubation with or without 10 µM of the dehydroabietylamine derivatives or Cur (positive control). The results are described as the inhibition rate. The mean±the SD value is the expression of at least four independent measurements. b ThT fluorescence assay was used to detect aggregated Aβ42 by microplate reader at 450 nm and 490 nm. The inhibition rate of Aβ42 aggregation by dehydroabietylamine and its derivatives as well as Cur (Cur) at 50 µM compared with the negative control. c The disaggregation rate of Aβ42 preformed fibrils by the dehydroabietylamine derivatives and Cur at 50 µM by the ThT assays.
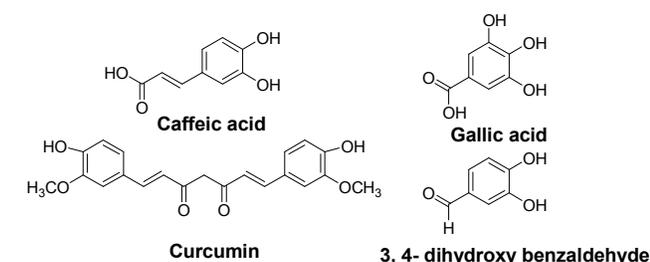

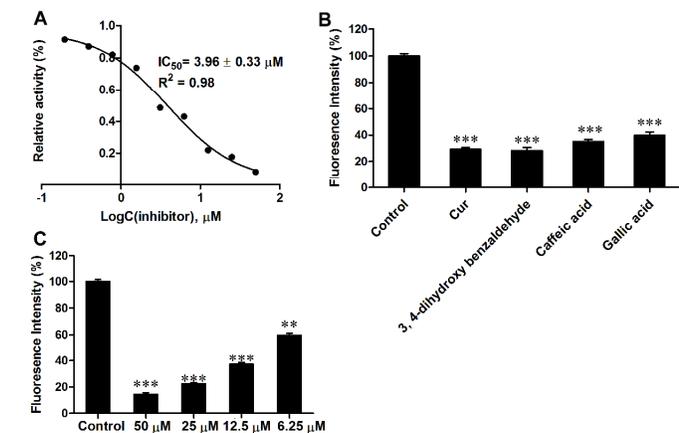**Fig.1** Structures of caffeic acid, gallic acid, 3,4-dihydroxybenzaldehyde, and curcumin (Cur).

Fig.2 Compound **3b**, caffeic acid, gallic acid, 3,4-dihydroxybenzaldehyde, and curcumin (Cur) inhibit Aβ42 aggregation and **3b** disaggregates preformed fibrils. (A) The IC_{50} of **3b** against Aβ42 aggregation; (B) The inhibition rate against Aβ42 aggregation by caffeic acid, gallic acid, 3,4-dihydroxybenzaldehyde, and Cur at 50 µM; (C) The effect of **3b** on the disaggregation of Aβ42 preformed fibrils at varying concentrations. Data represent the mean±the SEM from 5 independent experiments. ***$P<0.001$ and **$P<0.01$ compared to untreated control samples.

The Thioflavin T (ThT) fluorescence method was used to measure the inhibitory activities of compounds against Aβ42 self-mediated aggregation and the disaggregation of Aβ42 aging fibrils. Cur was used as the reference compound and the results are summarized in Table 1. According to the results, most compounds (**1a**, **1b**, **1c**, **1d**, **3a**, **3b**, **3c**, **3d**, and **3e**) showed moderate to potent inhibition activity (20.6% to 92.0%) compared with Cur (70.6%) at 50 µM. Moreover, six compounds **1a**, **1b**, **3b**, **3c**, **3d**, and **3e** also disaggregated the Aβ42 aging fibrils. Furthermore, the inhibitory activities of these compounds are similar to the trend of their anti-oxidant activities in SH-SY5Y cells. Noticeably, compound **3b** showed the most potent activity against Aβ42 aggregation with an IC_{50} value of 3.96±0.33 µM (Fig. 2A). As shown in Fig. 2C, compound **3b** also disaggregated the Aβ42 aging fibrils in a dose-dependent manner. In addition, the inhibitory activities of the substitute moieties (caffeic acid, gallic acid, and 3,4-dihydroxybenzaldehyde) at 50 µM were also evaluated (Fig. 2B). As shown in Table 1, the dehydroabietylamine scaffold (**1**) and the substituent moieties (caffeic acid, gallic acid, and 3,4-dihydroxybenzaldehyde) did not display good inhibitory activity. While the inhibition activity increased when the substituent was positioned at C-18, which indicated that this substituent is necessary for their inhibition activities. The dehydroabietylamine derivative with the caffeic acetyl substituent (**3b**) showed higher activity than the 3,4-dihydroxyl benzoyl substituted compound (**3a**). Furthermore, the compounds with two caffeic acetyls substituted at C-18 and C-12 exhibited better activity than one benzoyl substituted at C-18. However, three caffeic acetyl moieties substituted at C-12, C-14, and C-18 (**3c**) decreased the activity. These results indicated that the caffeic acid, gallic acid, and 3,4-dihydroxybenzaldehyde fragments can increase the inhibitory effect of dehydroabietylamine.

CD spectroscopy was used to measure the transition structure of Aβ42, which includes α-helices, β-sheets, and random coils in the process of self-mediated aggregation and fibrillation. The β-sheet conformation was considered important in Aβ42 aggregation. The CD spectra of α-helices and β-sheets occur at approximately 217 and 195 nm, respectively. As shown in Fig. 3, after 48 h of incubation, 40 µM **3b** reduced the formation β-sheet structures and increased the formation of α-helices. Therefore, it was suggested that **3b** could inhibit the formation of β-sheets.
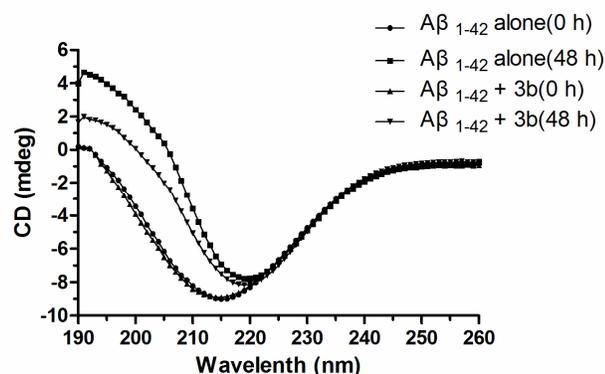
Fig. 3 CD spectra of the $A\beta_{42}$ secondary structure with and without **3b**. The CD spectra at 0 and 48 h were recorded using a wavelength range of 190-260 nm. The concentration of $A\beta_{42}$ in 20 mM PBS was 20 μM and **3b** was present at 40 μM.

To further study the ability of compound **3b** to inhibit $A\beta_{42}$ aggregation, TEM studies were performed (Fig. 4). Fresh $A\beta_{42}$ (25 μM) was incubated untreated or with 50 μM **3b** at 37 °C for 48 h. Many fibrils were observed (Fig. 4A) when the $A\beta_{42}$ peptide was incubated alone, while few fibrils were observed (Fig. 4B) when $A\beta_{42}$ was incubated with 50 μM **3b**. These results suggested that **3b** could significantly inhibit the formation of amyloid fibrils. In addition, after 25 μM aggregated $A\beta_{42}$ peptide was incubated in the absence or presence of 50 μM **3b** for another 48 h at 37 °C, amorphous aggregations were extensively observed (Fig. 4D) when no **3b** was present, but many short fibrils as balls were observed in the presence of **3b** (Fig. 4C). Therefore, based on the TEM and ThT assay results, we can conclude that compound **3b** effectively inhibits $A\beta_{42}$ fibril formation and disaggregates the $A\beta_{42}$ aging fibrils.
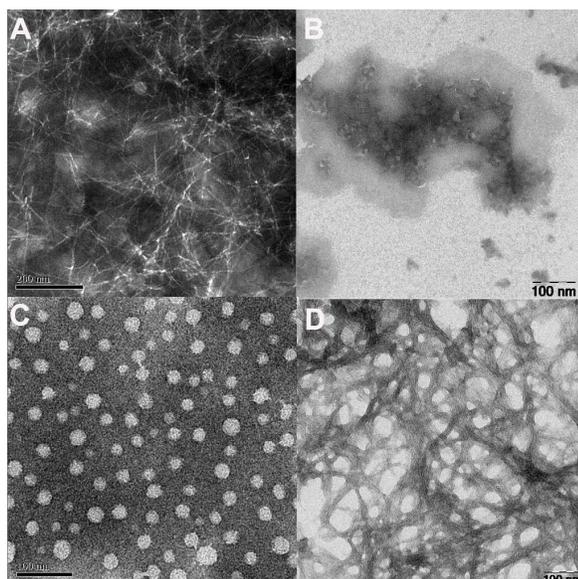

Fig.4 TEM image analysis of the aggregation of 25 μM $A\beta_{42}$ and the disaggregation of preformed fibrils in the absence or presence of 50 μM **3b**. $A\beta_{42}$ (25 μM) with (B) and without (A) 50 μM **3b**. The fibrils were incubated for 48 h at 37 °C, and then incubated with preformed $A\beta_{42}$ fibrils for another 48 h with 20 mM PBS (D) or 50 μM **3b** (C).

To explore the binding mode of **3b** and $A\beta_{42}$, molecular docking and molecular dynamics (MD) studies were performed. The crystal structure of $A\beta_{42}$ used in the docking study was obtained from the Protein Data Bank (1IYT). As shown in Fig. 5A, **3b** is bound to the C-terminus of $A\beta_{42}$ and forms a hydrogen bond with Ala30. After 90 ns MD simulations in water, the representation conformation of **3b** and $A\beta_{42}$ was calculated based on clustering analysis and is described in Fig. 5B. MD results indicated that **3b** interacts primarily through hydrophobic interactions with $A\beta_{42}$, and forms two hydrogen bonds with Ala30 and Gly9. The RMSD evolution curves (Fig. 5C) indicated that the complex of $A\beta_{42}$ and **3b** became stable after 19 ns. The time evolution of the secondary structures changes of $A\beta_{42}$ in the complex of $A\beta_{42}$ and **3b** was calculated and showed in Fig. 5D. Fig. 5D showed that most residues (2-15, 32-35) adopted α-helical structure; residues 15-23 formed α-helix or 3-helix; residues 35-42 mainly adopted coil and bend structure at the C-terminus of $A\beta_{42}$, while residues 23-32 mainly formed turn structure (occasionally, bend and 3-helix). β-sheet structure is not observed during the whole 90 ns simulation in water. These results indicated **3b** can stabilize α-helices and further inhibit the conversion of many secondary structures into β-sheets. MD results are consistent with our CD experimental results. Therefore, it can be concluded that **3b** inhibits $A\beta_{42}$ aggregation by stabilizing the α-helix structure.
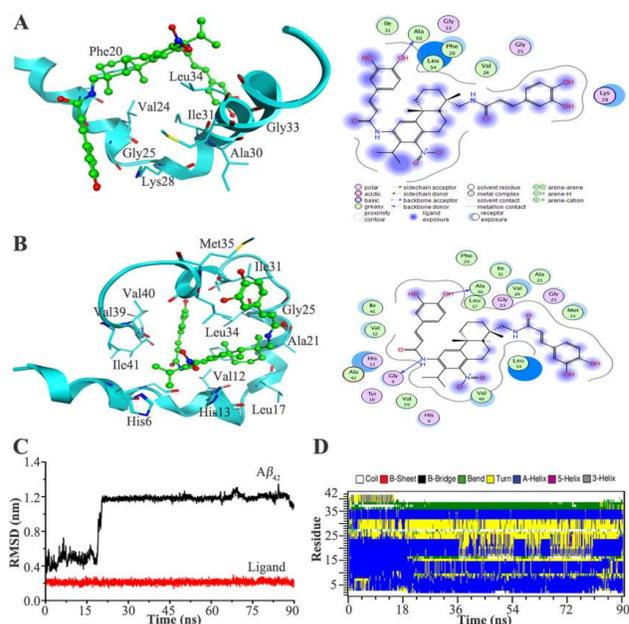

Fig. 5 The binding mode of **3b** and $A\beta_{42}$. (A) **3b** was docked into the C-terminus of the α-helical conformation of $A\beta_{42}$. (B) The binding mode of **3b** and $A\beta_{42}$ was calculated from simulations. Hydrogen bonds are represented by blue lines. (C) The black line represents the RMSD of the $A\beta$ helix for $A\beta_{42}$ (black) and the red line represents the **3b**-$A\beta_{42}$ complex compared to their previous conformational changes over time. (D) The time evolution of the secondary structures of $A\beta_{42}$ in the presence of **3b**.

To further evaluate the cell viability and the neuroprotective effect of the dehydroabietylamine derivatives, MTT assay was used on the human neuroblastoma cell line SH-SY5Y. The compounds that inhibited $A\beta_{42}$ aggregation (**1a**, **1b**, **1c**, **1d**, **3b**, **3c**, **3d**, and **3e**) were chosen to evaluate their cell viability. As indicated in Fig. 6A, except for **3e**, compounds **1a**, **1b**, **1c**, **1d**, **3b**, **3c**, and **3d** at 10 μM did not affect cell viability. Especially,

compound **3b** did not show significant effect on cell viability in the concentration range of 1-50 µM (Fig. 6C). Moreover, the IC_{50} value of **3b** for the inhibition of $A\beta_{42}$ aggregation was below 10 µM, which showed promise for future applications. The activity of **3b** on $A\beta_{42}$-induced cytotoxicity was also measured. As shown in Fig. 6B, after incubation at 37 °C for 48 h, 20 µM $A\beta_{42}$ oligomers caused a significant decrease in the cell viability rate to

50.02±4.98% of the control (P < 0.001), while the co-incubation of 20 µM $A\beta_{42}$ with varying concentrations of **3b** (5, 10, 25, and 50 µM) increased the cell viability rate from 53.5% to 74.04%. Therefore, **3b** could reduce the $A\beta_{42}$-induced cytotoxicity in the SH-SY5Y cell line, which indicated that **3b** could be considered a neuroprotective agent for the treatment of AD.
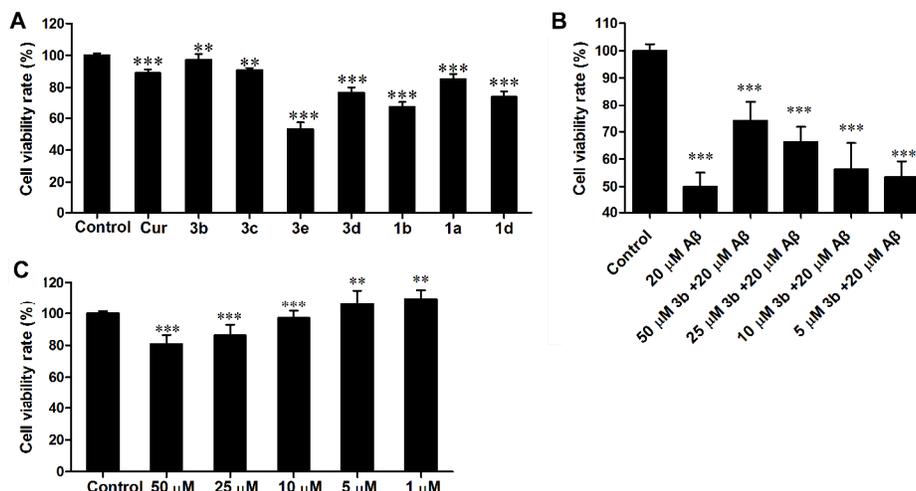

Fig. 6 Cell viability in the absence or presence of dehydroabietylamine derivatives, and the neuroprotective effect of **3b** at various concentrations on $A\beta_{42}$-induced cytotoxicity (20 µM). (A) Dehydroabietylamine derivatives (10 µM) were added to SH-SY5Y cells for 48 h and then the cell viability was determined. (B) Pre-incubated mixtures of $A\beta_{42}$ (20 µM) left untreated or treated with various concentrations of **3b** for 48 h. The cell viability was measured using the MTT method and the data are represented as the mean±the SD of four independent experiments. The significant neuroprotective activity of **3b** was observed in a dose-dependent manner at all tested concentrations (***P＜0.001, **P＜0.01). (C) **3b** (50, 25, 10, 5, and 1µM) was added to SH-SY5Y cells for 48 h. The compound-free (untreated) cells were considered the negative control.
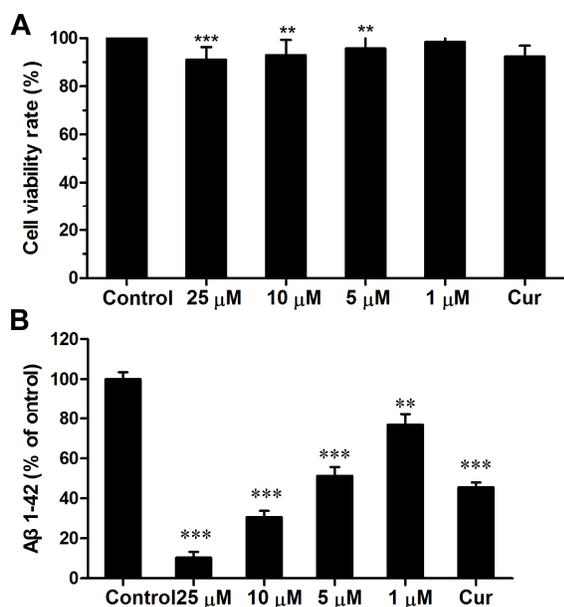

Fig. 7 Inhibition of the production of $A\beta_{42}$ in HEK293 cells by **3b** as measured by ELISA assay. (A) The effect of **3b** (25, 10, 5, and 1µM) on the cytotoxicity of HEK293 cells incubated at 37 °C for 48 h, where Cur (10 µM) was used as the positive control. ***P＜0.001, **P＜0.01, and P ＞0.05 compared with untreated cells (n=5). (B) The effect of varied concentrations of **3b** (25, 10, 5, and 1µM) on the production of $A\beta_{42}$ after incubation for 48 h. ***P＜0.001 and **P＜0.01 compared with the vehicle-treated group (n=5).

In order to test the effect of **3b** on the production of $A\beta_{42}$ in the cell level, swAPP HEK293 cell lines were used. First, the cell viability of swAPP HEK293 cells treated with **3b** was measured using the MTT method. As shown in Fig. 7A, the cell viability did not decline significantly when treated with **3b** at 25, 10, 5, and 1 µM. Moreover, compared with the control group, the cell viability rate was above 90% at 25 µM **3b**. A sandwich ELISA assay was used to detect extracellular $A\beta_{42}$ levels in the conditioned media from HEK293 cells. As shown in Fig. 7B, after 48 h of incubation, 25 µM **3b** remarkably reduced the extracellular $A\beta_{42}$ levels of the control (100±3.45%) to 10.4 ±2.89% (n=4; P < 0.001). Cur was used as a reference, which reduced the extracellular $A\beta_{42}$ levels of the control from 100± 3.45 % to 45.6±2.38 % (n=4, P < 0.001) at 10 µM. According to these results, **3b** may be regarded as a potential agent for the treatment of AD by reducing the production of $A\beta_{42}$.

To determine whether **3b** could reduce Aβ-induced toxicity *in vivo*, a transgenic *C. elegans* model was used that highly expresses the Aβ peptide, which can lead to paralysis. After synchronization for 12 h, the transgenic worms were placed on OP50 food containing 0.1% DMSO or **3b** (10, 50, 200, and 500 µM) at 15 °C for 12 h. The worms were then transferred to 26 °C to induce Aβ expression for an additional 36 h. Huperzine A (Hup A, 500 µM) was used as a positive control. The worms were regarded as paralyzed when they were touched with a platinum loop and didn't move. Fig. 8A showed the time course of the paralysis rate of *C. elegans* CL4176 worms fed with vehicle (0.1% DMSO; filled circles), Hup A (500 µM; filled circles) and **3b** (10, 50, 200, and 500 µM; filled circles) after the 36 h

induction of Aβ expression. A delay of paralysis by **3b** at 10 and 50 μM was observed in comparison with the control group. Moreover, 50 μM **3b** was better than 500 μM Hup A in delaying Aβ-induced paralysis. Fig. 8C is a set of histograms representing
5 the average life expectancy of untreated CL4176 worms or worms treated with **3b**. According to these data, the average life expectancy of CL4176 worms was 46.9±0.54 h (n=4; P<0.001) when they were cultured with OP50 alone; however, **3b** extended the average life expectancy of CL4176 to 48.2±0.55 h (n=4;
10 P<0.001) at 10 μM and 50.5±0.55 h (n=4; P<0.001) at 50 μM (n=4; P<0.001). Moreover, **3b** had more activity than 500 μM Huperzine A, which could extend the average life expectancy of CL4176 to 48.3±0.12 h (n=4; P<0.001). However, 200 and 500

μM **3b** did not extend the average life expectancy of CL4176; in
15 fact, it reduced it to 45.8±0.58 h (n=4; P<0.01) and 44.7±0.34 h (n=4; P<0.001), respectively. This suggested that high concentrations of **3b** may be toxic for the CL4176 worms and speeded up Aβ-induced paralysis.

To detect whether **3b** can reduce the expression of Aβ species
20 in *C. elegans* strain CL4176, western blot assays were used to measure the levels of Aβ species in CL4176. As shown in Fig. 8B and 8D, **3b** (10 and 50 μM) reduced the expression of Aβ species in the control from 1.00±0.03 (n=4) to 0.71±0.05 (n=4; P<0.001) and 0.45±0.07 (n=4; P<0.001), respectively. These results
25 suggested that **3b** can reduce the expression of Aβ species and delay Aβ-induced toxicity in *C. elegans* strain CL4176.
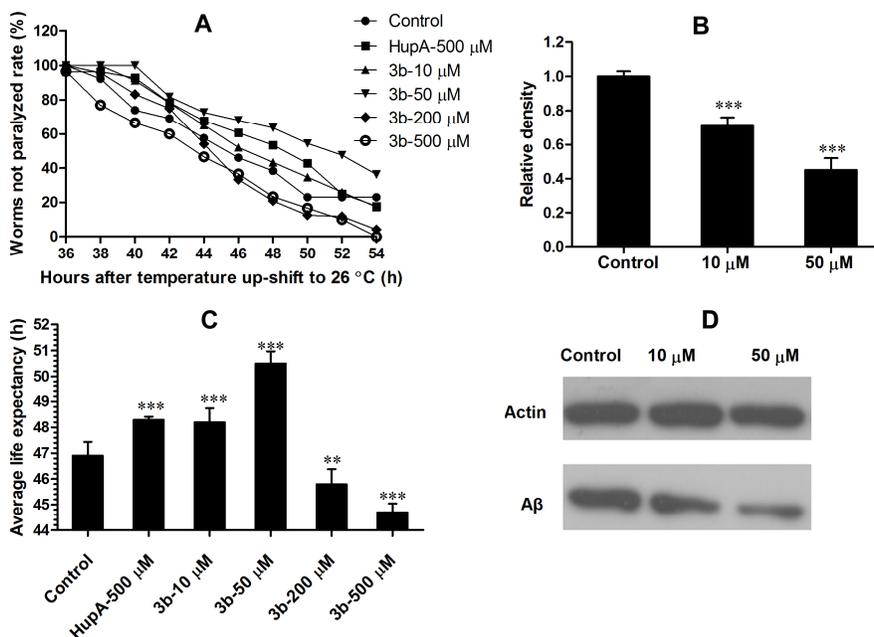

Fig. 8 Effect of **3b** on Aβ-induced paralysis in *Caenorhabditis elegans* CL4176. (A) Time course of the paralysis assays in CL4176 worms fed with or without different concentrations of **3b**. Huperzine A (500 μM) was used as a positive control. (B) A representative western blot of the expression of the
30 Aβ species in transgenic *C. elegans* CL4176 worms fed vehicle or **3b** (10 and 50 μM). The worms were maintained and scored at 26 °C. When the non-paralyzed worms constituted 50% of all worms, they were collected, loaded on gel lane (80 μg) and immunoblotted with the 6E10 antibody. (C) The average life expectancy of CL4176 worms fed vehicle or **3b**. Vehicle (control), Huperzine A (Hup A, 500 μM), or **3b** (10, 50, 200 and 500 μM) was added into the 35×10 mm culture plates, maintained at 16 °C for 48 h and then shifted to 26 °C to induce the expression of Aβ. The paralysis was recorded at 2 h intervals. The results are expressed as the percentage of non-paralyzed worms from at least four independent assays of 50 worms per experiment. (D)
35 The quantification of immunoreactive Aβ species by Western blot. The results are expressed as the relative density of the previously indicated band from four independent experiments. ***P<0.001 compared with the vehicle-treated group (n=4).

Conclusions

In summary, eight dehydroabietylamine derivatives (**1a**, **1b**, **1c**,
40 **2j**, **3b**, **3c**, **3d**, and **3e**) showed anti-oxidant activity in the SH-SY5Y cell line, and six (**1a**, **1b**, **3b**, **3c**, **3d**, and **3e**) of these simultaneously displayed a potent inhibitory effect on Aβ$_{42}$ aggregation and the disaggregation of Aβ$_{42}$ aging fibrils. In particular, **3b** exhibited the most potent activity compared to the
45 control of Cur. SAR analysis suggested that the introduction of two aromatic structure linkers at the C-18 and C-2 position of dehydroabietylamine is crucial for the inhibition of Aβ$_{42}$ aggregation. The CD and MD assays indicated that **3b** reduced the formation of β-sheets and stabilized α-helices. The TEM experiment further showed that **3b** not only inhibited Aβ$_{42}$

50 aggregation and fibril formation but also disaggregated the aging fibrils. Moreover, **3b** showed low cell toxicity in SH-SY5Y and swAPP HEK293 cells, and exhibited a protective effect on the Aβ$_{42}$-induced neurotoxicity. Besides that, compound **3b** also reduced the secretion of extracellular Aβ$_{42}$ in the swAPP
55 HEK293 cells. Furthermore, **3b** delayed Aβ$_{42}$-induced paralysis in *C. elegans* strain CL4176 and reduced the expression of Aβ$_{42}$ species in CL4176. Therefore, **3b** exhibited multifunctional activity for the treatment of AD. These evidence provided important information to support the structure optimization of **3b**
60 and to develop dehydroabietylamine derivatives as multifunctional agents for AD treatment.

Acknowledgments

Notes and references

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Electronic Supplementary Information (ESI) available: [details of experimental procedures, materials and methods]. See DOI: 10.1039/b000000x/

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