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Aminostyrylbenzofuran derivatives as potent inhibitors for Aβ fibril formation

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ABSTRACT

The synthesis of a novel series of aminostyrylbenzofuran derivatives **1a–w** and their inhibitory activities for Aβ fibril formation were described. All the synthesized compounds were evaluated by thioflavin T (ThT) assay and displayed potent inhibitory activities for Aβ fibril formation. Among them, compounds **1i** and **1q** exhibited excellent inhibitory activities (IC_{50} = 0.07 and 0.08 μM, respectively) than those of Curcumin (IC_{50} = 0.80 μM) and IMSB (IC_{50} = 8.00 μM) as reference compounds. Both compounds were selected as promising candidates for further biological evaluation.

Alzheimer's disease (AD) is a neurodegenerative disorder of the brain that is characterized by dementia, cognitive impairment, and memory loss.[1,2] A major hallmark of AD is the formation and accumulation of fibrillar β-amyloid (Aβ) peptides in the brain.[3–6] Of the two most abundant forms of Aβ, Aβ42 are aggregated into oligomers, protofibrils, and fibrils more readily than relatively soluble Aβ40.[7,8]

Preventing of Aβ fibril formation in the brain are currently being targeted as potential therapies for AD.[9–11] Various promising approaches to develop ligands exhibiting specific high binding affinity to Aβ fibrils have been proposed. Hence, several series of inhibitors such as *E,E*-1-iodo-2,5-bis-(3-hydroxycarbonyl-4-methoxy)-styrylbenzene (IMSB),[12,13] (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Curcumin),[14,15] 4-*N*-methylamino-4′-hydroxystilbene (SB-13),[16] and benzofuran analogues[17–19] were designed, and these compounds were found to interfere with the fibrillization of Aβ as determined by thioflavin T (ThT) assay.

In this paper, the structural modification by the introduction of styryl conjugated system of IMSB and Curcumin into benzofuran nucleus was designed as shown in Figure 1.

We report here the synthesis and evaluation of a novel series of aminostyrylbenzofuran derivatives **1a–w** with potent inhibitory activities for Aβ fibril formation.

Aminostyrylbenzofurans **1a–o,v,w** with varying R^1, R^2, R^3, and R^4 groups were prepared by the sequence of reactions shown in Scheme 1. Ethyl 2-benzofuran carboxylates **4** were obtained by first Casiraghi formylation[20] of phenol derivatives **2** with paraformaldehyde and magnesium chloride, and subsequent Perkin-typed intramolecular Aldol condensation[21] of **3** (**3a,b,d,f,g,i,k**: com. avail.). Reduction of ester group of **4** with aluminum chloride followed by bromination with phosphorus tribromide gave the bromomethylbenzofurans **6**, which were reacted with triethylphosphite by Arbuzov reaction[22] to give the corresponding compounds **7**, respectively. Subsequent Horner–Emmons olefin-

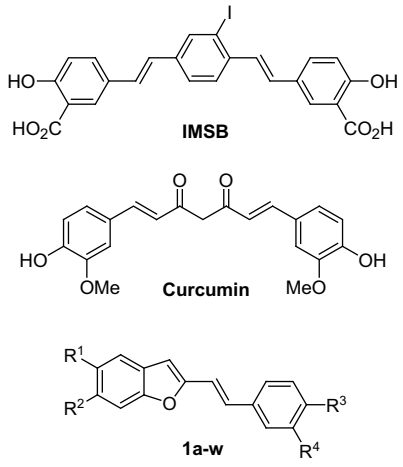

Figure 1. Structures of IMSB, Curcumin, and aminostyrylbenzofuran derivatives.

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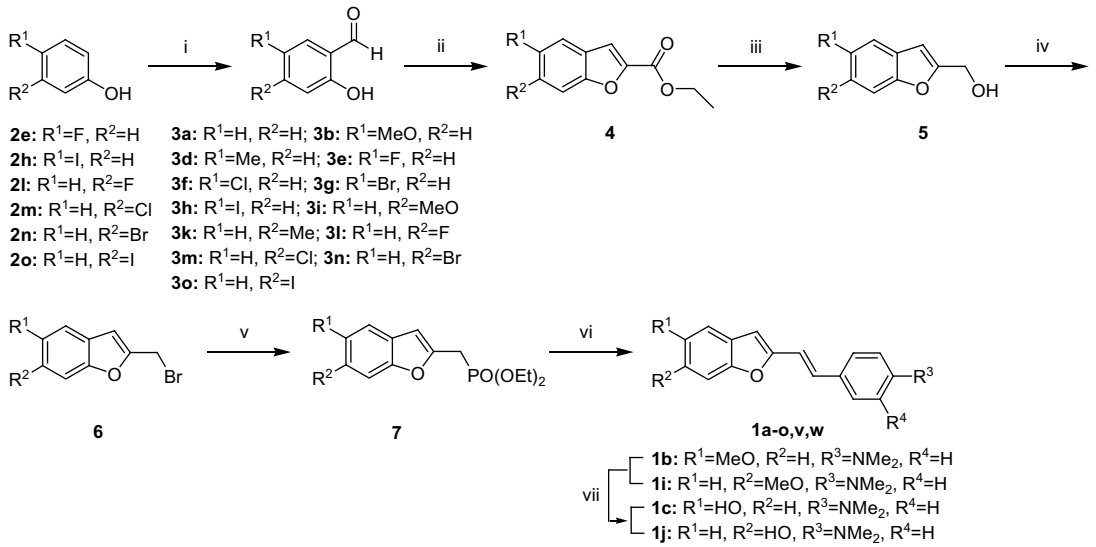
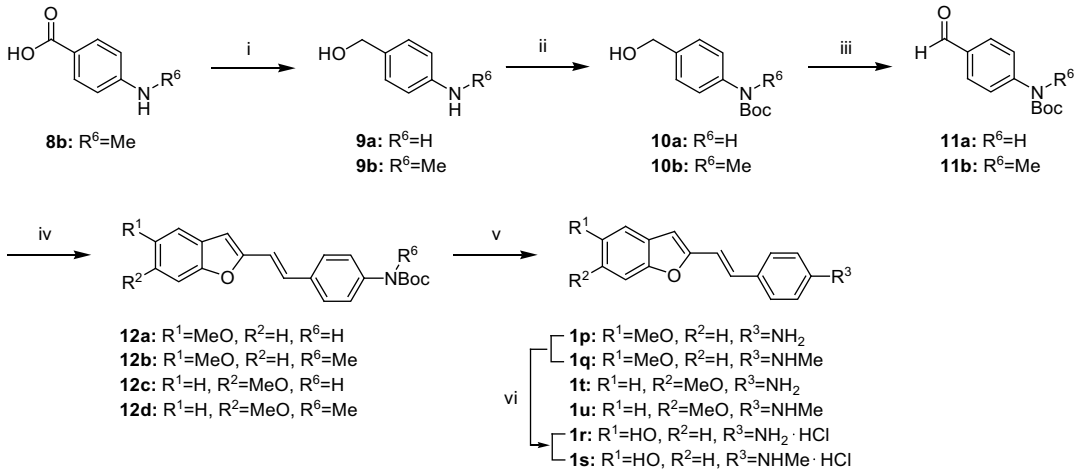


Scheme 1. Reagents and conditions: (i) paraformaldehyde, $MgCl_2$, Et_3N, CH_3CN, molecular sieve, reflux, 18 h, 34–58% (for **3e**,**h**,**l**–**o**); (ii) ethyl bromoacetate, K_2CO_3, DMF, molecular sieve, reflux, 1.5 h, 61–77%; (iii) $LiAlH_4$, THF, 0 °C, 20 min, 90–92%; (iv) PBr_3, DMF, 0 °C, 1 h; (v) $PO(OEt)_3$, reflux, 4 h, 74–95% (for two steps from **5**); (vi) NaHMDS, benzaldehyde, 0 °C to rt, 1 h, 36–80%; (vii) BBr_3, CH_2Cl_2, −78 °C to rt, 3 h, 50%.



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C, 24 h, 65% (for **9b**); (ii) $(Boc)_2O$, dioxane+H_2O, rt, 6 h, 98% (for **10a**), 85% (for **10b**); (iii) MnO_2, CH_2Cl_2, rt, 12 h, 81% (for **11a**), 84% (for **11b**); (iv) **7**, 1 M NaHMDS, 0 °C to rt, 2 h, 47–57%; (v) TFA, CH_2Cl_2, 0 °C to rt, 24 h, 97–99%; (vi) BBr_3, CH_2Cl_2, −78 °C to rt, 3 h, 98%.

ation[23] for only trans configuration of **7** with the appropriate benzaldehydes was achieved to give the title compounds **1**. Hydroxyl compounds **1c** and **1j** were obtained from methoxy compounds **1b** and **1i** by demethylation using boron tribromide, respectively.[24]

The synthesis of terminal primary and secondary aminostyrylbenzofurans **1p–u** were outlined in Scheme 2. Reduction of carboxylic acid group of **8b** with lithium aluminum hydride[25] followed by Boc-protection[26] of **9** (**9a:** com. avail.) led to the compounds **10**, which were oxidized with magnesium dioxide to yield the aldehydes **11**. Compounds **11** were coupled with **7** by Horner–Emmons olefination in the presence of sodium hexamethyldisilazane to give compounds **12**. Deprotection of **12** provided the title compounds **1**, and compounds **1p** and **1q** were demethylated using boron tribromide to yield the compounds **1r** and **1s**, respectively.

Table 1 shows the in vitro inhibitory activities (IC_{50} values) of aminostyrylbenzofurans **1a–w** for Aβ42 fibril formation together with those of Curcumin and IMSB as reference compounds. All the synthesized compounds were evaluated by thioflavin T (ThT) assay.[27]

Shown in Table 1, 9 compounds displayed better inhibitory activities (IC_{50} = 0.07–0.53 μM) than those of Curcumin (IC_{50} = 0.80 μM) and IMSB (IC_{50} = 8.00 μM) as reference compounds. In particular, compounds **1i** (R^1 = H, R^2 = MeO, R^3 = NMe_2) and **1q** (R^1 = MeO, R^2 = H, R^3 = NMe_2) exhibited 10-fold superior inhibitory activities (IC_{50} = 0.07 and 0.08 μM, respectively) to Curcumin. In general, compounds **1c–h** having R^1 substituents possessed slightly potent activities as compared to compounds **1j–o** with R^2 substituents, except **1b**. Electronic effect according to electron-donating or -withdrawing of substituents at benzofuran nucleus did not make any significant difference of inhibitory activity. R^3 and R^4 substituents at aminobenzene ring also did not show a meaningful trend.

In conclusion, aminostyrylbenzofuran derivatives showed excellent inhibitory activities for Aβ42 fibril formation. Especially, **1i** and **1q** exhibited 10-fold better inhibitory activities than Curcu-

Table 1
Biological activity of aminostyrylbenzofurans **1a–w** for the inhibition of Aβ42 fibril formation

Compound	R_1	R_2	R_3	R_4	IC_{50}[a] (μM)
1a	H	H	NMe_2	H	2.30
1b	MeO	H	NMe_2	H	0.81
1c	HO	H	NMe_2	H	0.16
1d[28]	Me	H	NMe_2	H	0.13
1e	F	H	NMe_2	H	1.98
1f	Cl	H	NMe_2	H	0.20
1g	Br	H	NMe_2	H	0.47
1h	I	H	NMe_2	H	0.17
1i[28]	H	MeO	NMe_2	H	0.07
1j	H	HO	NMe_2	H	3.62
1k	H	Me	NMe_2	H	3.44
1l	H	F	NMe_2	H	2.19
1m	H	Cl	NMe_2	H	3.21
1n	H	Br	NMe_2	H	1.34
1o	H	I	NMe_2	H	2.80
1p	MeO	H	NH_2	H	0.82
1q[28]	MeO	H	NHMe	H	0.08
1r	HO	H	NH_2·HCl	H	2.95
1s	HO	H	NHMe·HCl	H	2.16
1t	H	MeO	NH_2	H	5.44
1u	H	MeO	NHMe	H	0.80
1v	MeO	H	NMe_2	MeO	0.16
1w	H	MeO	NMe_2	MeO	0.53
Curcumin					0.80
IMSB					8.00

[a] ThT assay. IC_{50} was calculated from non-linear regression by *Graphpad Prism* software.

min. Above results demonstrate that the introduction of styryl conjugated system into benzoxazole nucleus led to the potent inhibitors, and these informations will helpful for designing AD treatments.

Acknowledgments

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28. Selected data.
1d: Mp: 188.0–189.0 °C; IR (KBr): 3437, 1600, 1518, 1359, 1184, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, 2H, J = 8.8 Hz), 7.32 (d, 1H, J = 8.3 Hz), 7.28 (s, 1H), 7.23 (d, 1H, J = 16.1 Hz), 7.04 (d, 1H, J = 8.3 Hz), 6.79 (d, 1H, J = 16.1 Hz), 6.72 (d, 2H, J = 8.8 Hz), 6.50 (s, 1H), 3.00 (s, 6H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 153.1, 150.4, 132.4, 130.4, 129.6, 127.9, 125.1, 124.9, 120.3, 112.3, 112.2, 110.1, 103.0, 40.4, 21.3; MS *m/z* 277 (M+).
1i: Mp: 194.5–195.5 °C; IR (KBr): 3437, 1602, 1489, 1356, 1146, 1107, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, 2H, J = 8.8 Hz), 7.33 (d, 1H, J = 9.0 Hz), 7.23 (d, 1H, J = 16.1 Hz), 6.97 (d, 1H, J = 2.5 Hz), 6.84 (dd, 1H, J = 2.6, 8.8 Hz), 6.79 (d, 1H, J = 16.1 Hz), 6.72 (d, 2H, J = 8.8 Hz), 6.52 (s, 1H), 3.85 (s, 3H), 3.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 155.9, 150.4, 149.7, 130.5, 130.0, 127.9, 124.8, 112.3, 112.1, 111.0, 103.4, 103.1, 55.9, 40.4; MS *m/z* 293 (M+).
1q: Mp: 174.0–175.0 °C; IR (KBr): 3409, 1602, 1519, 1201, 1183, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, 2H, J = 8.6 Hz), 7.33 (d, 1H, J = 8.9 Hz), 7.2 (d, 1H, J = 16.1 Hz), 6.97 (d, 1H, J = 2.5 Hz), 6.83 (dd, 1H, J = 2.6, 8.8 Hz), 6.77 (d, 1H, J = 16.1 Hz), 6.61 (d, 2H, J = 8.5 Hz), 6.51 (s, 1H), 3.85 (s, 3H), 2.88 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 155.8, 149.7, 149.3, 130.5, 130.0, 128.0, 125.8, 112.4, 112.4, 111.0, 103.4, 103.0, 55.9, 30.5; MS *m/z* 279 (M+).