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Synthesis of 6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-Alkyl-1*H*-Indole-2-Carboxylic Acid and Inhibitory Activity on β-Amyloid Aggregation

Sun Mi Lee and Raok Jeon

College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea

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6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-alkyl-1*H*-indole-2-carboxylic acids were designed and synthesized as *β*-amyloid (A*β*) fibril assembly inhibitors. Their inhibitory activity on A*β* aggregation was evaluated by thioflavin T assay although their activities were insignificant.

Key words: Indole, Alzheimer's disease, β-Amyloid aggregation

INTRODUCTION

Alzheimer's disease (AD) is one of the most common disorders of the elderly. AD is a progressive, chronic, neurodegenerative disorder, characterized by loss of cognitive ability, severe behavioral abnormalities. Since this devastating illness affects a large number of older patients and their families and no effective treatment or cure currently exists, better diagnosis and treatment of AD are urgently needed. The characteristic feature of AD is the deposition of insoluble amyloid fibrils as senile plaques in the brains of patients. The amyloid fibrils are composed of *β*-amyloid peptides (A*β*) possessing 39-42 amino acids, which are produced by cleavage from a larger amyloid precursor protein APP (Hardy *et al.*, 1991; Yankner *et al.*, 1989; Selkoe, 1999). It is reported that A*β* itself is not toxic, but it reveals toxicity against neuronal cells once it is aggregated into macromolecular amyloid fibrils by peptide interaction (Serpell, 2000). Inhibition of A*β* aggregation is an important target for the design of therapeutic agents for the prevention and treatment of AD.

Small molecule inhibitors from various chemical classes have recently been reported to inhibit *β*-amyloid aggregation (LeVine, 2002). Recently, benzofuran derivative **1** as shown in Fig. 1 was reported the inhibitory activity on A*β* aggregation (Howlett *et al.*, 1999). To seek new leads for

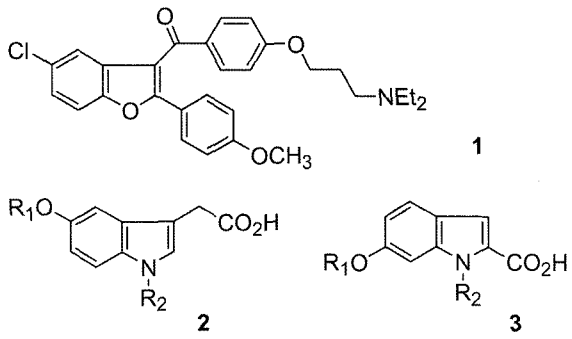


Fig. 1. The chemical structures of A*β* aggregation inhibitors

A*β* aggregation inhibitors, we employed the concept of bioisosterism to design indole derivatives and previously reported the synthesis of {5-[2-(benzoxazol-2-ylmethylamino) ethoxy]-1-methyl-1*H*-indol-3-yl}acetic acids (**2**) as A*β* aggregation inhibitors. We describe here synthesis of 6-alkoxy-1-alkyl-1*H*-indole-2-carboxylic acids (**3**) and their inhibitory activities on A*β* aggregation.

MATERIALS AND METHODS

Most of reagents and solvents were purchased from Aldrich chemicals and used without purification, with the following exceptions. Ethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Acetonitrile, methylene chloride, benzene, toluene, triethylamine, pyridine, dimethyl formamide, and diisopropylamine were distilled from calcium hydride under nitrogen. Flash column chromatography was performed using silica gel

Correspondence to: Raok Jeon, College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea
Tel: 82-2-710-9571, Fax: 82-2-715-9571
E-mail: rjeon@sookmyung.ac.kr

60 (230-400 mesh, Merck) with indicated solvents. Thin-layer chromatography (TLC) was performed using Kieselgel 60 F254 plates (Merck). IR spectra were recorded on a JASCO FT/IR 430 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian YH 400 spectrometer as solutions in $CDCl_3$, CH_3OH-d_4, or DMSO-d_6. Chemical shifts are expressed in parts per million (ppm, δ) downfield from an internal standard, tetramethylsilane.

2-(Benzoxazol-2-ylmethylamino)ethanol (4)

A solution of 2-chlorobenzoxazole (2 g, 13.13 mmol), 2-methylaminoethanol (1.47 g, 19.54 mmol), and triethylamine (1.98 g, 19.54 mmol) in THF (10 mL) was stirred at 80°C for 2 h. The reaction mixture was diluted with ethyl acetate and washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrate under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/*n*-hexane, 1:1) to afford 2.44 g (97.4%) of the title compound **4** as a white solid : R_f= 0.125 (ethyl acetate/*n*-hexane, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 1H, *J* = 7.9 Hz), 7.14 (d, 1H, *J* = 7.9 Hz), 7.06 (t, 1H, *J* = 7.6 Hz), 6.92 (t, 1H, *J* = 7.6 Hz), 5.35 (s, 1H), 3.80 (t, 2H, *J* = 5.1 Hz), 3.54 (t, 2H, *J* = 5.1 Hz), 3.08 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.4, 148.2, 142.4, 123.5, 120.0, 115.1, 108.3, 59.2, 52.3, 36.1.

Methanesulfonic acid 2-(benzooxazol-2-ylmethylamino)ethyl ester (5)

To a solution of alcohol **4** (652 mg, 3.39 mmol) and TEA (0.94 mL, 6.74 mmol) in CH_2Cl_2 (2 mL) was added methanesulfonylchloride (0.31 mL, 4.07 mmol) at 0°C and was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate and washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrate under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/*n*-hexane, 1:1) to afford 654 mg, (71.4 %) for the title compound **5** as a yellow solid : R_f= 0.225 (ethyl acetate/*n*-hexane, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 1H, *J* = 7.6 Hz), 7.21 (d, 1H, *J* = 8.1 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 6.96 (t, 1H, *J* = 7.6 Hz), 4.42 (t, 2H, *J* = 4.9 Hz), 3.81 (t, 2H, *J* = 5.0 Hz), 3.22 (s, 3H), 2.91 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.9, 148.8, 142.9, 123.9, 120.6, 116.1, 108.7, 66.8, 49.7, 37.3, 37.0.

4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]benzaldehyde (6)

A mixture solution of sodium hydride (148 mg, 3.70 mmol), mesylate **5** (500 mg, 1.85 mmol) and anhydrous DMF (10 mL) was stirred at 0°C for 30 minutes. To a solution of 4-hydroxybenzaldehyde (271.1 mg, 2.22 mmol) in DMF (10 mL) was added the mixture solution at 0°C and was stirred at 0°C for 1 h. And then, the reaction temperature was increased to 80°C and was stirred of 6 h. To the reaction mixture was added the ice water and was diluted with ethyl acetate and washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrate under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/*n*-hexane, 1:2) to afford 285.7 mg (84.2%) for the title compound **6** as a white solid : R_f= 0.125 (ethyl acetate/*n*-hexane, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.66 (d, 2H, *J* = 8.8 Hz), 7.26 (d, 1H, *J* = 7.7 Hz), 7.14 (d, 1H, *J* = 7.7 Hz), 7.05 (td, 1H, *J* = 6.8, 1.0 Hz), 6.89 (td, 1H, *J* = 6.8, 1.0 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 4.17 (t, 2H, *J* = 5.2 Hz), 3.81 (t, 2H, *J* = 5.2 Hz), 3.20 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.3, 163.0, 161.9, 148.6, 143.0, 131.6, 129.8, 123.7, 120.1, 115.8, 114.3, 108.4, 66.0, 49.4, 36.9.

2-Azido-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy] phenyl}acrylic acid methyl ester (7)

To a solution of sodium methoxide (28% w/w, 455.9 mg, 8.44 mmol) in methanol (1.5 mL) was slowly added dropwise the solution of compound **6** (626.5 mg, 2.11 mmol) and methyl azidoacetate (971.4 mg, 8.44 mmol) in methanol (2 mL) at -8°C. The reaction mixture was stirred below 5°C for 3 h. The heterogeneous mixture was poured over ice and was stirred manually. The suspension was filtered, washed with water, dried in the vacuum oven, and collected to provide the title compound **7** (white solid, 677.7 mg, 80.6%): R_f= 0.225 (ethyl acetate/*n*-hexane, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 8.6 Hz), 7.36 (d, 1H, *J* = 7.7 Hz), 7.25 (d, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 7.7 Hz), 7.01 (t, 1H, *J* = 7.6 Hz), 6.89 (s, 1H), 6.86 (d, 2H, *J* = 5.1 Hz), 4.29 (t, 2H, *J* = 4.9 Hz), 3.94 (t, 2H, *J* = 4.9 Hz), 3.87 (s, 3H), 3.20 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.1, 162.3, 159.2, 148.9, 143.3, 132.4, 126.3, 125.4, 123.9, 123.2, 120.4, 116.1, 114.3, 108.7, 66.1, 52.7, 49.9, 37.3.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1*H*-indole-2-carboxylic acid methyl ester (8)

To the boiling xylenes (10 mL) in three neck flask was slowly added dropwise the solution of compound **7** (661.3 mg, 1.68 mmol) in xylenes (12 mL) and was refluxed at 150 °C for 6 h. The xylenes were cooled and then removed under reduced pressure and the residue was crystallized from benzene to provide the title compound **8** (white solid, 458 mg, 74.6%): R_f= 0.375 (ethyl acetate/*n*-hexane, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.53 (d, 2H, *J* = 9.0 Hz), 7.36 (d, 1H, *J* = 7.6 Hz), 7.25 (d, 1H, *J* = 7.1 Hz), 7.15 (m, 2H), 7.00 (t, 1H, *J* = 7.6 Hz), 6.80 (s, 1H), 6.79 (s, 1H), 4.30 (t, 2H, *J* = 4.6 Hz), 3.97 (t, 2H, *J* = 4.6 Hz), 3.90 (s, 3H), 3.35 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.3, 157.6, 149.0, 143.4, 137.8, 126.3, 124.0, 123.5,

122.1, 120.4, 116.1, 112.4, 109.1, 108.7, 94.6, 66.5, 51.8, 50.1, 37.4.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-methyl-1*H*-indole-2-carboxylic acid methyl ester (9b)

A solution of Indole **8** (100 mg, 0.274 mmol), sodium hydride (19.72 mg, 0.822 mmol), and DMAP (16.74 mg, 0.138 mmol) in DMF (2 mL) was stirred at 0°C for 1 h and to the solution of the mixture was added iodomethane (0.052 mL, 0.822 mmol) at 0°C. And then, it was stirred at room temperature at 1 h. The reaction mixture was diluted with ethyl acetate and washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrate under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/*n*-hexane, 1:2) to afford 86.1 mg (82.9%) of the title compound **9b** as a white solid : R_f= 0.287 (ethyl acetate/*n*-hexane, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 1H, *J* = 8.79), 7.34 (d, 1H, *J* = 7.69), 7.23 (d, 1H, *J* = 7.88), 7.19 (s, 1H), 7.14 (t, 1H, *J* = 7.14), 7.00 (td, 1H, *J* = 7.23, 1.03), 6.77 (dd, 1H, *J* = 6.78, 2.02), 6.72 (s, 1H), 4.32 (t, 2H, *J* = 5.33), 3.96 (t, 2H, *J* = 5.13), 3.94 (s, 3H), 3.34 (s, 3H), 3.34 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.5, 162.4, 157.4, 149.0, 143.4, 140.5, 126.8, 123.9, 123.5, 120.4, 120.3, 116.0, 112.1, 110.6, 108.7, 93.0, 66.4, 51.4, 50.0, 37.3, 31.5.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-ethyl-1*H*-indole-2-carboxylic acid methyl ester (9c)

This compound was prepared using the same procedure as described for the preparation of **9b**. Indole compound **8** and iodoethane (0.064 mL, 0.822 mmol) were converted into the title compound **9c** (white solid, 32.5 mg, 30.3%): R_f= 0.325 (ethyl acetate/*n*-hexane, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1H, *J* = 8.61), 7.37 (d, 1H, *J* = 7.88), 7.26 (d, 1H, *J* = 7.87), 7.23 (d, 1H, *J* = 4.76), 7.17 (t, 1H, *J* = 7.42), 7.01 (t, 1H, *J* = 7.79), 6.80 (d, 1H, *J* = 9.0), 6.78 (s, 1H), 4.52 (t, 2H, *J* = 7.14), 4.36 (t, 3H, *J* = 5.22), 4.01 (t, 2H, *J* = 5.22), 3.88 (s, 2H), 3.38 (s, 3H), 1.34 (t, 3H, *J* = 7.05); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.4, 162.2, 157.5, 149.0, 143.4, 139.5, 126.4, 126.0, 124.0, 123.6, 120.4, 116.1, 112.1, 110.9, 108.7, 93.1, 66.6, 51.4, 50.1, 39.5, 37.4, 15.3.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-benzyl-1*H*-indole-2-carboxylic acid methyl ester (9d)

This compound was prepared using the same procedure as described for the preparation of **9b**. Indole compound **8** and benzyl bromide (0.098 mL, 0.821 mmol) were converted into the title compound **9d** (white solid, 66.8 mg, 53.6%): R_f= 0.25 (ethyl acetate/*n*-hexane, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (td, 1H, *J* = 5.86, 2.93), 7.34 (m, 3H), 7.31 (m, 1H), 7.23~7.12 (m, 5H), 6.99 (m, 3H), 6.79 (dt, *J* = 3.67, 2.56), 6.69 (s, 1H), 5.72 (s, 2H), 4.21 (t, 2H, *J* = 5.13), 3.89 (t, 2H, *J* = 5.13), 3.80 (s, 3H), 3.29 (s, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.6, 161.8, 157.9, 149.4, 143.7, 140.8, 138.3, 136.3, 128.8, 127.3, 126.4, 124.2, 120.6, 116.3, 112.7, 112.1, 111.7, 109.0, 93.9, 66.6, 51.7, 50.2, 48.0, 37.6.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1*H*-indole-2-carboxylic acid (10a)

To a solution of compound **8** (64.7 mg, 0.177 mmol) in ethanol (3 mL) was added 1 M sodium hydroxide (1 mL) and was stirred at room temperature for 12 h. The reaction solution was concentration, added water, and acidified with 10% hydrochloric acid. The precipitate was filtered, stirred in chloroform for 5 minutes, cooled under -5°C, and refiltered to provide the title compound **10a** (white solid, 30.8 mg, 49.7%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.55 (s, 1H), 7.49 (d, 1H, *J*=8.79), 7.37 (d, 1H, *J* = 7.87), 7.28 (d, 1H, *J* = 7.69), 7.13 (t, 1H, *J* = 7.60), 6.99 (m, 2H), 6.88 (s, 1H), 6.68 (dd, 1H, *J* = 2.02, 6.78), 4.26 (t, 2H, *J* = 5.31), 3.92 (t, 3H, *J* = 5.31), 3.25 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 162.3, 156.6, 148.6, 143.3, 138.2, 127.5, 123.9, 122.9, 121.5, 120.2, 115.6, 111.7, 108.9, 107.8, 95.0, 65.4, 49.2, 36.3.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-methyl-1*H*-indole-2-carboxylic acid (10b)

This compound was prepared using the same procedure as described for the preparation of **10a**. Compound **9b** (86.1 mg, 0.227 mmol) was converted into the title compound **10b** (white solid, 68.5 mg, 82.4%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.47 (d, 1H, *J* = 8.55), 7.33 (d, 1H, *J* = 7.81), 7.24 (d, 1H, *J* = 7.81), 7.10 (t, 1H, *J* = 7.69), 7.03 (s, 1H), 6.95 (t, 1H, *J* = 7.81), 6.70 (t, 2H, *J* = 8.55), 4.32 (t, 2H, *J* = 5.37), 3.92 (s, 2H), 3.90 (s, 3H), 3.22 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.4, 161.7, 156.4, 148.0, 142.8, 139.8, 126.9, 123.4, 122.6, 119.6, 119.2, 115.0, 111.5, 109.4, 108.3, 93.2, 64.9, 48.6, 35.9, 31.0.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-ethyl-1*H*-indole-2-carboxylic acid (10c)

This compound was prepared using the same procedure as described for the preparation of **10a**. Compound **9c** (32.5 mg, 0.083 mmol) was converted into the title compound **10c** (white solid, 25 mg, 79.5%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 1H, *J* = 8.61), 7.34 (d, 1H, *J* = 8.06), 7.24 (d, 1H, *J* = 7.69), 7.10 (t, 1H, *J* = 7.60), 7.04 (s, 2H), 6.95 (t, 1H, *J* = 7.7), 6.67 (d, 1H, *J* = 7.69), 4.32 (q, 2H, *J* = 7.14, 6.78), 4.30 (t, 2H, *J* = 5.48), 3.90 (t, 2H, *J* = 5.22), 3.22 (s, 3H), 1.17 (t, 3H, *J* = 6.87); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.8, 155.7, 148,1, 142,8, 138.1, 123.4, 122.1, 122.1, 119.7, 119.6, 115.1, 110.7, 108.3, 107.9, 93.2, 65.0, 48.7, 40.3, 35.9, 15.1.

6-[2-(Benzoxazol-2-ylmethylamino)ethoxy]-1-benzyl-1*H*-indole-2-carboxylic acid (1d)

This compound was prepared using the same procedure as described for the preparation of **10a**. Compound **9d** (50.9 mg, 0.112 mmol) was converted into the title compound **10d** (white solid, 33.9 mg, 68.6%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 8.61), 7.43 (d, 1H, *J* = 7.87), 7.32 (d, 1H, *J* = 7.69), 7.24~7.16 (m, 5H), 7.07 (m, 2H), 6.99 (d, 2H, *J* = 7.88), 6.76 (d, 1H, *J* = 7.33), 5.81 (s, 2H), 4.28 (t, 2H, *J* = 5.13), 3.93 (t, 2H, *J* = 5.22), 3.26 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.2, 160.8, 156.5, 147.3, 139.6, 138.2, 127.9, 126.6, 126.4, 125.8, 123.9, 122.8, 120.5, 119.5, 114.4, 111.6, 110.5, 108.8, 93.8, 64.9, 48.9, 46.3, 36.2.

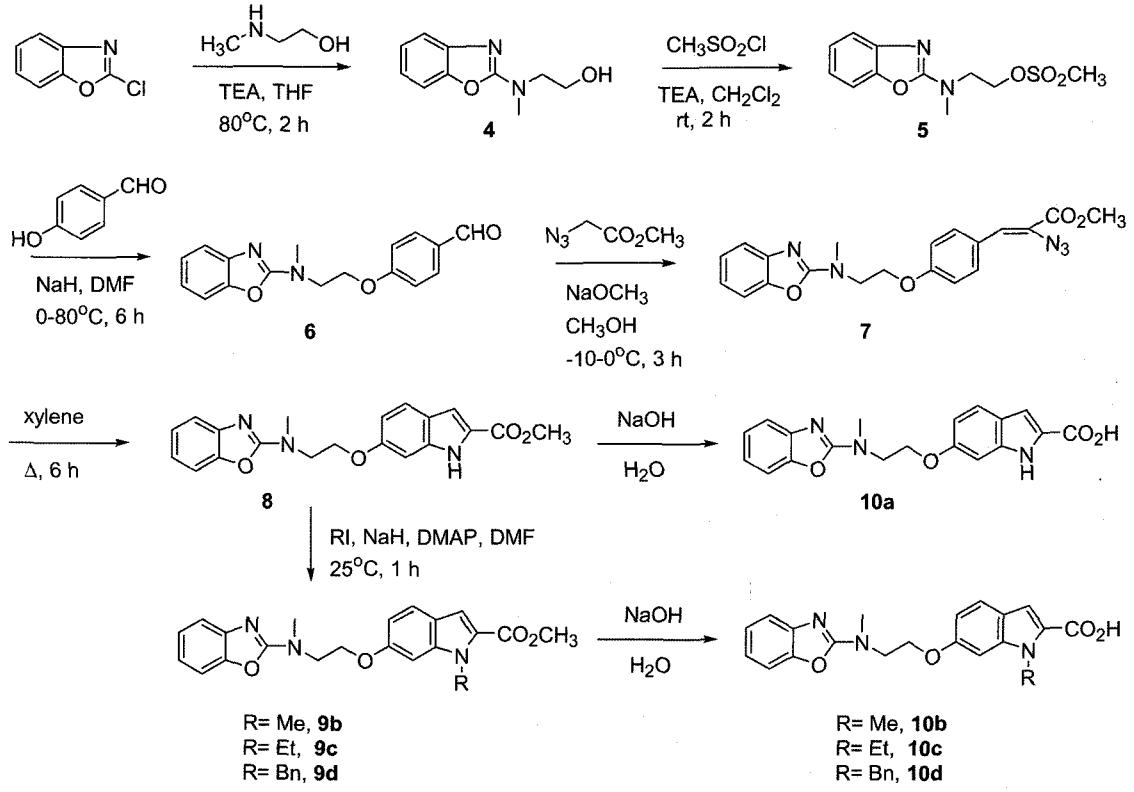
β-Amyloid (Aβ) aggregation inhibition assay (Thioflavine T assay)

Thioflavine T (ThT) Assay used the synthesized peptide $A\beta_{1-42}$ (BACHEM). The solution of $A\beta_{1-42}$ in DMSO was diluted with PBS in Fluorescence black plate. The synthesized compounds (10 μM) were reacted in the diluted $A\beta_{1-42}$ solution (25 μM), in compare of the diluted $A\beta_{1-42}$ solution (25 μM) without the prepared compounds. The solution of 5 μM thioflavine (150 mL) in 50 mM glycine buffer was added each $A\beta_{1-42}$ solution and shaked for 10 seconds. ThT fluorescence intensity measurements were performed by exciting samples at 450 nm and measuring emission intensities at 480 nm using a microplate reader (SAFIRE).

RESULTS AND DISCUSSION

The synthesis of the target compounds **10a-d** is outlined in Scheme 1. The aromatic substitution of 2-chlorobenzoxazole with methyl aminoethanol, followed by mesylation of the resulting alcohol **4**, provided mesylate **5**. *O*-alkylation of hydroxybenzaldehyde with mesylate **5** gave aldehyde **6** and condensation of **6** with methyl azidoacetate led to azidoacrylate **7**. Indole **8** was obtained after heating in xylene for 6 h. The *N*-alkylation of indole and hydrolysis gave the target compounds **10a-d**.

The Aβ aggregation inhibitory activities of the synthetic compounds were measured using a thioflavin-T (ThT) fluorescence binding assay. As shown in Fig. 2, all of the compounds tested showed slight inhibition of Aβ aggregation. The inhibitory activity of compound **10a-c** on Aβ aggregation were below 15%. Although benzyl substituted indole **10d** showed 27% of inhibition, it involved almost 18% of standard deviation. We further examined the effect of **10d** in reducing Aβ cytotoxicity in the cells, which were pre-treated with β-amyloid peptides. The cell viability using MTT assay with **10d** was also evaluated



Scheme 1. Synthesis of 6-[2-(benzoxazol-2-ylmethylamino)ethoxy]-1-alkyl-1*H*-indole-2-carboxylic acids

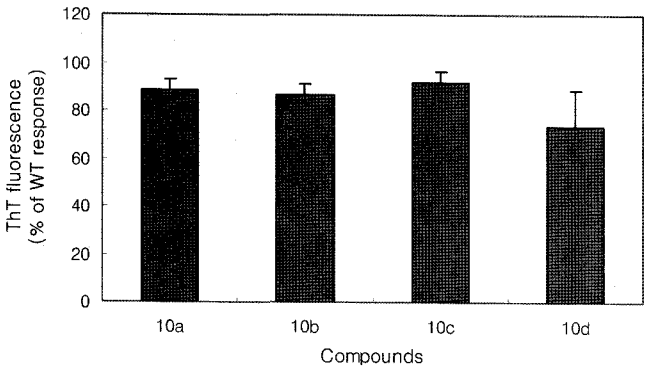


Fig. 2. Effects of the compounds **10** on Aβ aggregation as determined with the thioflavin T assay. The Aβ_{1-42} peptide (25 μM) was incubated with the compounds (10 μm) or vehicle control at room temperature for 1 h. The Fig. shows the means±S.D. (n=3). Data were compared with the wild type (WT) response of Aβ_{1-42} alone.

and the result showed no cytotoxicity of the compound. These results suggested that further study and structural modification of indole derivatives may bring a promising lead for therapeutic drugs for AD.

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