Synthesis of Functionalized Benzoxazoles and Their Binding Affinities to Aβ42 Fibrils

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Received June 29, 2008

Functionalized benzoxazole derivatives were designed and synthesized based on the structural features of PIB and FDDNP. which show excellent binding affinities to aggregated Aβ42 fibrils. All the synthesized compounds were evaluated by competitive binding assay against aggregated Aβ42 fibrils using [^{125}I]TZDM and displayed good *in vitro* binding affinities with K_i values (0.47-15.3 nM) from subnanomolar to nanomolar range. Among them, benzoxazoles **1f** and **1a** having malononitrile and ester moieties at C-6 exhibited superior binding affinities (K_i = 0.47 and 0.61 nM, respectively) to PIB (K_i = 0.77 nM).

Key Words : Alzheimer's disease, Aβ42 fibrils. Functionalized benzoxazoles. Binding affinity

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a slow and progressive decline in cognitive function and behavior.[1,2] The two characteristic neuropathological features in AD are senile plaques (SPs) composed of aggregates of amyloid β (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) in the brain.[3,4] The accumulation of Aβ and formation of plaques correlates with the severity of dementia. A regulated cascade of the proteolytic cleavage of β-amyloid precursor protein (β-APP) generates Aβ40 and Aβ42.[5,6] Of two most abundant forms of Aβ. Aβ42 as a toxic species of Aβ has been shown to aggregate into amyloid fibrils more readily than Aβ40.[7-9] Accordingly. extracellular deposits of amyloid fibrils formed by Aβ42 become the attractive targets for drug intervention.[10-12]

The Aβ fibrils binding agents may potentially be useful for early detection and monitoring the progression of AD. Currently. development of specific imaging agents available for direct mapping of Aβ aggregates in the living brain has been investigated. 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)-amino]-2-naphthyl}ethylidene)malononitrile ([^{18}F]FDDNP).[13,14] a neutral and highly lipophilic imaging agent. was developed for detection of both senile plaques and neurofibrillary tangles in the living brain of AD patients using positron emission tomography (PET). Recently. *N*-methyl-[^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]PIB)[15,16] as an *in vivo* PET β-sheet imaging agent exhibited high affinity for Aβ. good brain entry and clearance. For early diagnosis or monitoring of β-amyloid formation and aggregation in AD brain, a variety of radiolabeled compounds as imaging probes have been developed.[17-19] The development of ligands specifically binding to β-amyloid aggregates is very important for labeling agents as *in vivo* diagnostic tools.

Our continuous object has been to explore the novel ligands applicable to imaging probes with high binding
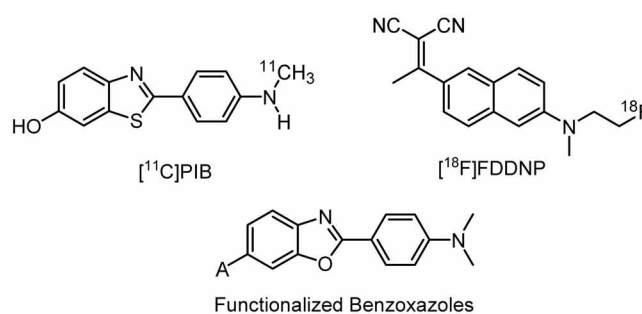

Figure 1. Structures of [^{11}C]PIB, [^{18}F]FDDNP, and functionalized benzoxazoles.

affinity to Aβ fibrils.[20,21] Based on the structural combination of PIB and FDDNP, functionalized benzoxazole derivatives capable of radioisotope labeling on terminal amine were designed as shown in Figure 1. We report here the synthesis and evaluation of a series of benzoxazole derivatives with high affinities for Aβ42 fibrils.

Results and Discussion

Chemistry. Benzoxazole-6-carboxylate **1a**, a key intermediate for further functionalization, was prepared by the sequence outlined in Scheme 1.

Esterification of carboxylic group of **2** with thionyl chloride in ethanol followed by ring closure of resulting ester **3** with 4-dimethylaminobenzoyl chloride in the presence of boric acid provided the compound **1a**.[22,23] The ethyl ester of **1a** was reduced using lithium aluminum chloride in THF to give the hydroxyl compound **4**. and then oxidized with pyridinium dichromate to afford the aldehyde **5**. Weinreb amide coupling of **1a** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine.[24] and subsequent alkylation with methylmagnesium iodide were carried out in usual manner to give the ketone **6**.[25] Carboxylic
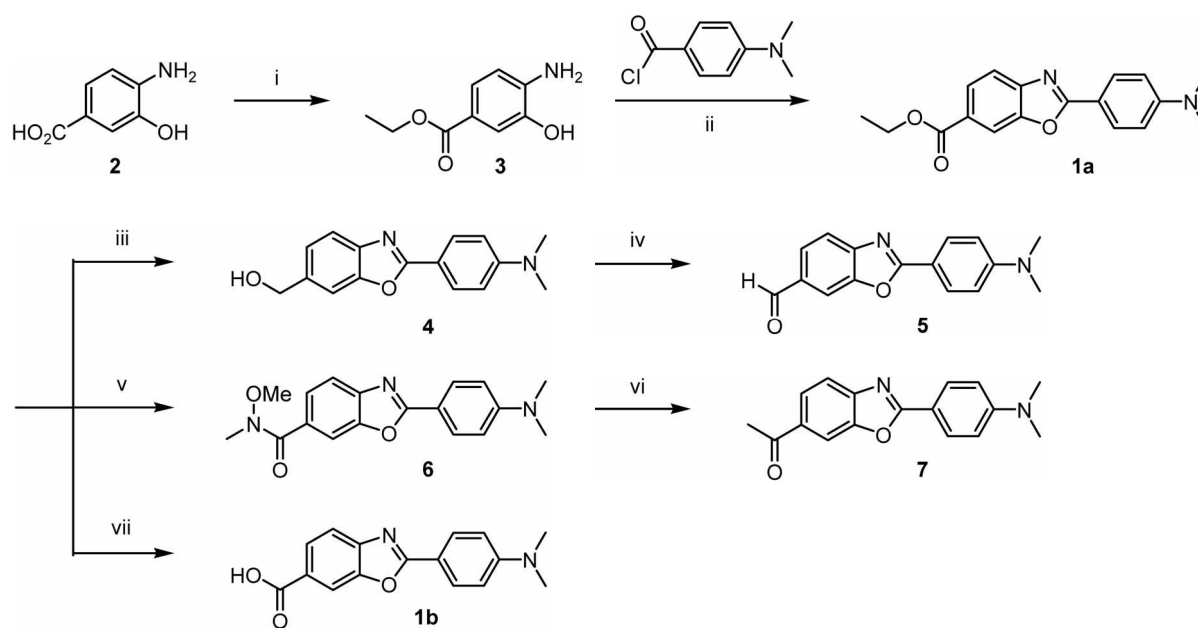
Scheme 1. Reagent and reaction conditions: (i) SOCl₂, EtOH, reflux, 2 h, 83%; (ii) boric acid, *o*-xylene, reflux, 18 h, 63%; (iii) LiAlH₄, THF, −78 °C to rt, 2 h, 85%; (iv) pyridinium dichromate, CH₂Cl₂, rt, 18 h, 53%; (v) MeONHMe·HCl, Et₃N, CH₂Cl₂, rt, 5 h, 87%; (vi) MeMgI, Et₂O, 0 °C to rt, 3 h, 37%; (vii) KOH, EtOH-H₂O, reflux, 1 h, 34%.
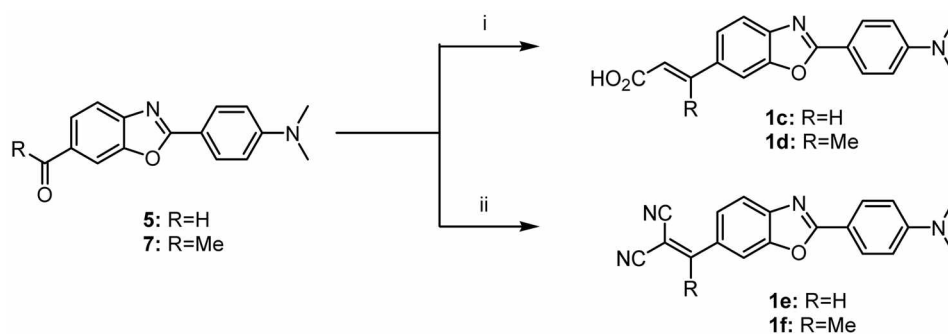
Scheme 2. Reagent and reaction conditions: (i) malonic acid, pyridine, piperidine, reflux, 2-4 h, 32% (for **1c**), 52% (for **1d**); (ii) malononitrile, PPh₃, pyridine, reflux, 6-18 h, 58% (for **1e**), 37% (for **1f**).

acid **1b** was obtained by the hydrolysis of ester **1a** with potassium hydroxide.[26]

Compounds **5** and **7** were served as intermediates for the synthesis of benzoxazoles **1c-f** bearing olefin moieties (Scheme 2).

Knoevenagel condensation of compounds **5** and **7** with malonic acid in pyridine-piperidine gave the corresponding title compounds **1c** and **1d**. Compounds **1e** and **1f** were prepared by the treatment with malononitrile and triphenyl-phospine in pyridine.[27]

Biological Evaluation. Table 1 shows the *in vitro* binding affinities (*K*ᵢ values) of benzoxazole derivatives **1a-f** against aggregated Aβ42 fibrils together with that of PIB as a reference compound.

All the synthesized compounds were evaluated by competitive binding assays against Aβ42 fibrils using [¹²⁵I]TZDM, and showed good binding affinities (*K*ᵢ = 0.47-1.63 nM) except **1c**. Especially, benzoxazoles **1f** and **1a** having malononitrile and ester moieties at C-6 exhibited superior

Table 1. *K*ᵢ values of **1a-f** against [¹²⁵I]TZDM for binding affinities to Aβ42 aggregates

Compds	K_i (nM)^a	Compds	K_i (nM)^a
1a	0.61	**1e**	0.80
1b	1.63	**1f**	0.47
1c	15.3	**PIB**	0.77
1d	1.18		

$^a K_i$ was calculated by the Cheng-Prusoff equation ($K_i = IC_{50}/(1 - [L]/K_d)$)[23] using *Graphpad Prism* software.

binding affinities (*K*ᵢ = 0.47 and 0.61 nM, respectively) to PIB (*K*ᵢ = 0.77 nM). In case of olefinic moiety onto benzoxazole nucleus, malononitrile compounds **1e, f** (*K*ᵢ = 0.80, 0.47 nM) possessed better affinities than but-2-enoic acid compounds **1c, d** (*K*ᵢ = 15.3, 1.18 nM). As for the additional methyl group of olefin, compounds **1d, f** having methyl group were more higher affinties than the corresponding compounds **1c, e** having no methyl group.

In conclusion, functionalized benzoxazole derivatives based on the structural features of PIB and FDDNP showed excellent binding affinities to aggregated Aβ42 fibrils. These compounds could be considered as ligands for molecular imaging agents to monitor Aβ42 fibrils in AD brain due to their high binding affinity.

Experimental

Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR system spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 Ultrashield spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as an internal standard. GC-Mass spectra were determined on a Agilent Technology 6890N network GC system. Column chromatography was carried out using silica gel (230-400 mesh). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade.

Ethyl 4-amino-3-hydroxy benzoate (3). To a stirred solution of 4-amino-3-hydroxybenzoic acid **2** (25.0 g, 0.163 mol) in EtOH (100 mL) was slowly added thionyl chloride (29.1 mL, 0.245 mol) at 0 °C. After being stirred at reflux for 2 h, the reaction mixture was cooled to room temperature and neutralized with 1 N NaOH. The mixture was extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* to give **3** (24.5 g, 83%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 1.8, 8.1 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.18 (bs, 2H), 1.36 (t, J = 7.1 Hz, 3H).

Ethyl 2-(4-dimethylaminophenyl)benzo[d]oxazole-6-carboxylate (1a). To a stirred solution of **3** (5.0 g, 27.6 mmol) in *o*-xylene (60 mL) were added 4-dimethylaminobenzoyl chloride (5.6 g, 30.4 mmol) and boric acid (6.3 g, 101.2 mmol), and the reaction mixture was refluxed for 18 h. When the reaction was completed, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from THF and diethyl ether to give **1a** (5.4 g, 83%): mp 180.0-181.5 °C; IR (KBr): 2924, 1712, 1607, 1503, 1283, 1192 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21 (d, J = 1.2 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H), 8.06 (dd, J = 1.2, 8.3 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 8.9 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 3.09 (s, 6H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.75, 166.45, 152.77, 150.25, 146.75, 129.53, 126.16, 126.10, 118.38, 113.37, 111.61, 111.54, 61.10, 40.10, 14.40; MS *m/z* 310 (M$^-$).

2-(4-Dimethylaminophenyl)benzo[d]oxazol-6-yl)methanol (4). To a solution of **1a** (450 mg, 1.45 mmol) in THF (20 mL) was added lithium aluminum hydride (165 mg, 4.35 mmol), and the reaction mixture was stirred at −73 °C for 20 min. After being stirred at room temperature for 2 h, the reaction mixture was treated with NH$_4$Cl. The mixture was extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* to give **4** (346 mg, 85%): ^{1}H

NMR (400 MHz, CDCl$_3$) δ 8.08 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 0.7 Hz, 1H), 7.28 (dd, J = 0.7, 8.0 Hz, 1H), 6.75 (d, J = 9.0 Hz, 2H), 4.79 (d, J = 5.0 Hz, 2H), 3.06 (s, 6H), 1.87 (t, J = 5.0 Hz, 1H).

2-(4-Dimethylaminophenyl)benzo[d]oxazole-6-carbaldehyde (5). To a solution of **4** (544 mg, 2.0 mmol) in CH$_2$Cl$_2$ (30 mL) was added pyridinium dichromate (903 mg, 2.4 mmol), and the reaction mixture was stirred at room temperature for 18 h. When the reaction was completed, the reaction mixture was treated with NH$_4$Cl. The mixture was extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* to give **4** (346 mg, 85%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 0.7 Hz, 1H), 7.28 (dd, J = 0.7, 8.0 Hz, 1H), 6.75 (d, J = 9.0 Hz, 2H), 4.79 (d, J = 5.0 Hz, 2H), 3.06 (s, 6H), 1.87 (t, J = 5.0 Hz, 1H).

2-4-(Dimethylaminophenyl-*N*-methoxy-*N*-methylbenzo[d]oxazole-6-carboxamide (6). To a solution of **5** (300 mg, 3.0 mmol) in CH$_2$Cl$_2$ (15 mL) were added *N*,*O*-dimethylhydroxylamine hydrochloride (264 mg, 2.7 mmol) and Et$_3$N (0.8 mL, 6.0 mmol), and the reaction mixture was stirred at room temperature for 5 h. When the reaction was completed, the reaction mixture was treated with 10% NaHCO$_3$. The mixture was extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 3:1) to give **6** (255 mg, 87%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.29 (s, 1H), 8.14 (d, J = 9.1 Hz, 2H), 7.82-7.73 (m, 3H), 6.79 (d, J = 9.1 Hz, 2H), 3.39 (s, 3H), 3.13 (s, 3H), 2.99-2.94 (m, 6H).

1-(2-(4-Dimethylaminophenyl)benzo[d]oxazol-6-yl)ethanone (7). To a solution of **6** (83 mg, 0.25 mmol) in diethyl ether (2 mL) was added methylmagnesium iodide (10 mL, 0.28 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. When the reaction was completed, the reaction mixture was treated with 10% NaHCO$_3$. The mixture was extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 3:1) to give **7** (26 mg, 37%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.29 (s, 1H), 8.14 (d, J = 9.1 Hz, 2H), 7.82-7.73 (m, 2H), 6.79 (d, J = 9.1 Hz, 2H), 3.13 (s, 6H), 2.59 (s, 3H).

2-(4-Dimethylamino)phenylbenzo[d]oxazole-6-carboxylic acid (1b). To a solution of **1a** (62 mg, 0.20 mmol) in EtOH (5 mL) was added potassium hydroxide (34 mg, 0.33 mmol) at 0 °C, and the reaction mixture was refluxed for 1 h. When the reaction was completed, the reaction mixture was cooled to 0 °C and acidified with 6 M hydrochloric acid. The resulting precipitate was collected by filtration to give **1b** (19 mg, 34%): ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.05 (bs, 1H), 8.16 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 3.05 (s, 6H).

General procedure for the synthesis of (*E*)-benzo[d]oxazolylethenoic acids 1c, d. To a solution of the appropriate carbonyl compound (1.0 mmol) in pyridine (15 mL)

were added malonic acid (3.0 mmol) in piperidine (5 mL). and the reaction mixture was refluxed for 2-4 h. When the reaction was completed, the reaction mixture was cooled to 0 °C. The resulting precipitate was collected by filtration to give the title compound. **1c:** yield 32%: ^{1}H NMR (400 MHz. DMSO-d$_6$) δ 7.99 (s. 1H). 7.91 (d. $J = 7.1$ Hz, 2H), 7.62-7.47 (m. 2H), 7.49 (d. $J = 15.8$ Hz. 1H), 6.67 (d. $J = 7.1$ Hz, 2H), 6.52 (d. $J = 15.8$ Hz, 1H), 2.74 (s, 6H). **1d:** yield 52%: ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.22 (s, 1H), 7.98 (d. $J = 9.0$ Hz. 2H), 7.96 (s, 1H), 7.93 (d. $J = 6.9$ Hz. 1H), 7.71 (d. $J = 6.9$ Hz. 1H), 6.83 (d. $J = 9.0$ Hz. 2H), 3.01 (s. 6H), 2.60 (s. 3H).

General procedure for the synthesis of benzo[d]oxazolylmalononitriles 1e, f. To a solution of the appropriate carbonyl compound (1.0 mmol) in pyridine (15 mL) were added malononitrile (1.5 mmol) and triphenylphosphine (20% mol), and the reaction mixture was refluxed for 6-18 h. When the reaction was completed, the reaction mixture was cooled to 0 °C. The resulting precipitate was collected by filtration to give the title compound. **1e:** yield 58%: ^{1}H NMR (400 MHz. CDCl$_3$) δ 8.29 (s. 1H). 8.14 (d. $J = 9.1$ Hz, 2H). 7.83 (s. 1H). 7.75-7.43 (m. 2H). 6.79 (d. $J = 9.1$ Hz. 2H). 3.13 (s. 6H). **1f:** yield 37%: mp 197.0-198.0 °C: IR (KBr): 2922. 2225. 1615. 1513. 1435. 1191 cm^{-1}; ^{1}H NMR (400 MHz. DMSO-d$_6$) δ 8.09 (s. 1H). 8.01 (d. $J = 6.7$ Hz, 2H). 7.79 (d. $J = 6.1$ Hz. 1H). 7.68 (d. $J = 6.1$ Hz, 1H), 6.85 (d. $J = 6.7$ Hz. 2H). 3.03 (s. 6H). 2.68 (s. 3H); ^{13}C NMR (100 MHz. DMSO-d$_6$) δ 176.73, 166.51, 153.35. 150.14. 145.94. 131.95. 129.69. 125.37. 119.26. 114.23. 113.99. 112.22. 110.73, 83.19, 24.98: MS m/z 328 (M$^-$).

In vitro **competitive binding assay against Aβ42 fibrils.** We estimated K_d value (0.13 nM) of [^{125}I]TZDM for Aβ42 aggregates. For inhibition studies. the reaction mixture contained 50 μL of Aβ42 aggregates (11.5 nM in the final conc.), 50 μL of inhibitors ($10^{-6} \sim 10^{-12}$ M in DMSO), 50 μL of [^{125}I]TZDM (in 40% EtOH, 0.05 nM in the final conc.) and 10% EtOH in a final volume of 1 mL. Nonspecific binding was defined by adding 2 μL Th-T for [^{125}I]TZDM binding. The mixture was incubated at room temperature for 3 h and the bound and the free radioactivity were separated by a vacuum filtration through Whatman GF/B filters using a Brandel M-24R cell harvester followed by 2·3 mL washes of 10% EtOH at room temperature. Filters containing the bound radioligand were counted in a gamma-counter (Cobra-II). The result of inhibition assays was subjected to nonlinear regression analysis using software Graphpad Prism by K_i values was calculated.

References

1. Kung. H. F.: Lee. C.-W.: Zhuang. Z.-P.: Kung. M.-P.: Hou. C.: Plössl. K. *J. Am. Chem. Soc.* **2001**. *123*. 12740.
2. Förstl. H.: Kurz. A. *Eur. Arch. Psychiatry Clin. Neurosci.* **1999**. *249*. 288.
3. Hardy, J.: Selkoe, D. J. *Science* **2002**. *297*. 353.
4. Meyer-luemen, M. *Nat. Neurosci.* **2003**, *6*. 1.
5. Tanzi. R. E.: Bertram. L. *Neuron* **2001**. *32*. 184.
6. Scorer. C. A. *Drug. Discov. Today* **2001**. *6*. 1207.
7. Jarrett. J. T.: Berger. E. P.: Lansbury. P. T. *Biochemistry* **1993**. *32*. 4693.
8. Hammarstrom, P.: Wiseman. R. L.: Powers. E. T.: Kelly, J. W. *Science* **2003**. *299*, 713.
9. Cai. X. D.: Golde. T. E.: Younkin. S. G. *Science* **1993**. *259*, 514.
10. Vickers. J. C.: Dickson. T. C.: Adlard. P. A.: Sounders. H. L.: King. C. E.: McCormack. G. *Prog. Neurobiol.* **2000**. *60*. 139.
11. Thorsett, E. D.: Latimer, L. H. *Curr. Opin. Chem. Biol.* **2000**, *4*, 377.
12. Wolfe, M. S.: Citron, M.: Diehl, T. S.: Xia, W.: Donkor. I. O.: Selkoe, D. J. *J. Med. Chem.* **1998**. *41*. 6.
13. Agdeppa. E. D.: Kepe. V.: Liy. J.: Flores-Torres. S.: Satyamurthy. N.: Petric. A.: Cole. G. M.: Small. G. W.: Huang. S. C.: Barrio. J. R. *J. Neurosci.* **2001**. *21*. RC189.
14. Shoghi-Jadid. K.: Small. G. W.: Agdeppa. E. D.: Kepe, V.: Ercoli. L. M.: Siddarth, P.: Read. S.: Satyamurthy. N.: Petric, A.: Huang. S. C.: Barrio. J. R. *Am. J. Geriatr. Psychiatry* **2002**. *10*. 24.
15. Mathis. C. A.: Wang. Y.: Holt. D. P.: Huang. G.-f.: Debnath. M. L.: Klunk. W. E. *J. Med. Chem.* **2003**. *46*. 2740.
16. Klunk. W. E.: Engler. H.: Nordberg. A.: Wang. Y.: Blomqvist. G.: Holt. D. P.: Bergstrom, M.: Savitcheva, I.: Huan. G.-f.: Estrada, S.: Ausen. B.: Debnath, M. L.: Barletta. J.: Price. J. C.: Sndell. J.: Lopresti, B. J.: Wall. A.: Koivisto. P.: Antoni. G.: Mathis, C. A.: Langstrom. B. *Ann. Neurol.* **2004**. *55*. 306.
17. Mathis. C. A.: Mahmood. K.: Debnath. M. L.: Klunk. W. E. *J. Labelled Compd. Radiopharm.* **1997**. *40*. 94.
18. Ono. M.: Haratake. M.: Nakayama. M.: Kaneko, Y.: Kawabata. K.: Mori, H.: Kung. M.-P.: Kung. H. F. *Nucl. Med. Biol.* **2005**, *32*. 329.
19. Zeng. F.: Southerland. J. A.: Voll. R. J.: Williams. L.: Ciliax. B. J.: Levey. A. I.: Goodman. M. J. *Bioorg. Med. Chem. Lett.* **2006**. *16*. 3015.
20. Byeon, S. R.: Jin. Y. J.: Lim. S. J.: Lee, J. H.: Yoo. K. H.: Shin. K. J.: Oh, S. J.: Kim. D. J. *Bioorg. Med. Chem. Lett.* **2007**. *17*. 4022.
21. Lee. J. H.: Byeon, S. R.: Lim. S. J.: Oh, S. J.: Moon. D. H.: Yoo. K. H.: Chung. B. Y.: Kim. D. J. *Bioorg. Med. Chem. Lett.* **2008**. *18*. 1534.
22. Kumar. D.: Jacob. M. R.: Reynolds. M. B.: Kerwin. S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3997.
23. Hodson, S. J.: Bishop. M. J.: Speake. J. D.: Navas. F., III: Garrison, D. T.: Bigham. E. C.: Saussy. D. L., Jr.: Liacos. J. A.: Irving. P. E.: Gobel. M. J.: Sherman. B. W. *J. Med. Chem.* **2002**. *45*. 2229.
24. Shimizu. T.: Osako. K.: Nakata. T.-i. *Tetrahedron Lett.* **1997**. *38*. 2685.
25. Nahm. S.: Weinreb. S. M. *Tetrahedron Lett.* **1981**, *22*. 3815.
26. Nasu. T.: Tagawa, T.: Imafuku. K. *J. Heterocycl. Chem.* **1998**. *35*. 389.
27. Yadav. J. S.: Reddy. B. V. S.: Bask. A. K.: Visali. B.: Narsaiah. A. V.: Nagaiah. K. *Eur. J. Org. Chem.* **2004**. *35*. 546.