

Synthesis and Biological Evaluation of 3-Amino-4-aryl-piperidine Derivatives as BACE 1 Inhibitors

Hee-Jong Lim,* Myung Hee Jung, Ihn Young Choi Lee, and Woo Kyu Park

Bio-Organic Science Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong-Gu, Daejeon 305-600, Korea. *E-mail: heejong@kRICT.re.kr
Received June 7, 2006

BACE 1 (β -secretase), a membrane bound aspartic protease, is a key enzyme in the process of amyloid precursor protein (APP) into $A\beta$ peptide which is considered to play a causative role in Alzheimer's Disease (AD). Here, we reported the synthesis and inhibitory activity of optically active 3-amino-4-aryl-piperidines.

Key Words : Alzheimer's disease (AD), BACE 1 (β -secretase), Non-peptidomimetic inhibitors, Piperidine derivatives

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and most common form of dementia affecting about 20 millions worldwide, which has clinical symptoms of memory loss, impairment of daily living activity, and ultimately leads to death.¹ AD is characterized pathologically by deposition of senile plaques and neurofibrillary tangles found in the brain of post-mortem AD patients.² Amyloid β peptide ($A\beta$), a major component of senile plaques, is derived from amyloid precursor protein (APP) by sequential endoproteolysis by β - and γ -secretase.³

Numerous evidences suggest that an excessive level of $A\beta$ as soluble oligomers and filamentous fibrils initiate neuronal loss and play a causative role in the disease process.⁴ Consequently, inhibition of $A\beta$ formation would prevent and suppress the development of AD. BACE 1 (β -secretase),⁵ a membrane bound aspartic protease, is a key enzyme responsible for APP processing into $A\beta$ peptide and thus considered a promising therapeutic target for the treatment of AD.⁶

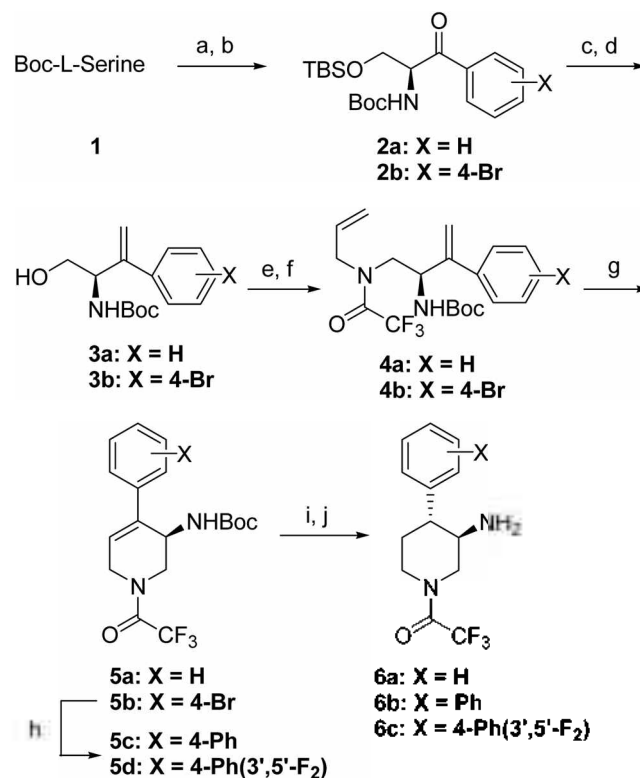
Although numerous peptidomimetic BACE 1 inhibitors, derived from statine, hydroxyethylene, hydroxyethylamine, hydroxymethylcarbonyl, and aminoethylamine as a transition state mimic core motif frequently found in other aspartic protease inhibitors, are highly active in enzymatic assay,⁷ they would not be potential drug leads due to their poor cell permeability and bioavailability. Recently, endeavors to develop nonpeptide cell permeable BACE 1 inhibitors have been extensively studied, and various scaffolds such as isophthalamide,⁸ diphenylurea,⁹ piperazine,¹⁰ and piperidine¹¹ were reported to possess BACE 1 inhibitory activity.

4-Aryl-3-alkoxypiperidines have been reported to bind to carboxyl group of aspartic residue in the active site of human renin in a similar binding mode to the binding of peptidomimetic inhibitors derived from statin and amino-statin and shown very potent activity against renin,¹² but they have not been fully studied in the development of BACE 1 inhibitors.¹¹ We anticipated new highly active non-peptidomimetic BACE 1 inhibitors could be developed by modification of piperidine scaffold with appropriate substi-

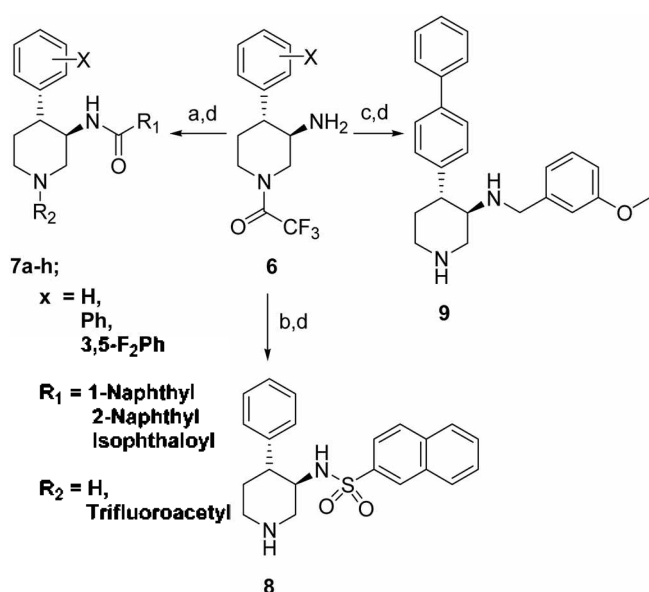
tuent. In this study, we present the synthesis and BACE 1 inhibitory activity of optically pure (3*R*)-amino-(4*R*)-aryl-piperidine derivatives.

Results and Discussion

Chemistry. 3-Amino-4-arylpiperidines **6**, key precursors for construction of various substituted piperidines, were prepared from N-Boc-(L)-serine by modification of known literature procedure as shown in Scheme 1.¹³



Scheme 1. Reagents; (a) TBS-Cl, Imidazole, DMF; (b) (i) CDI, THF, (ii) ArMgBr, CuI; (c) MePPh₃Br, *t*-BuOK, THF; (d) TBAF, THF; (e) Ms-Cl, TEA, CH₂Cl₂; (f) (i) Allylamine, (ii) Trifluoroacetic anhydride; (g) 2nd generation Grubbs Cat., CH₂Cl₂; (h) ArB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, aq.DME; (i) H₂, Pd-C, MeOH; (j) TFA, CH₂Cl₂.



Scheme 2. Reagents; (a) ArCOCl , pyridine; (b) 2-Naphthalene-sulfonyl chloride, pyridine; (c) 3-Methoxybenzylbromide, K_2CO_3 , DMF; (d) K_2CO_3 , MeOH.

Starting from Boc-L-serine, 2-aryl-3-amino-4-hydroxy-1-butene **3**, known precursors for 3-amino-4-aryl-piperidine ring **6**, were readily prepared in four steps via protection of hydroxyl group to TBS ether, addition of aryl anion to activated acid,¹⁴ Wittig olefination of ketone **2**, and deprotection of TBS ether. It is noteworthy that this procedure has an advantage over the reported method for the preparation of compound **3** in overall 8 steps.¹³ With an improved synthesis of alcohol **3** in hand, the remaining steps to (3R)-amino-(4R)-aryl-piperidine **6** were undertaken as known procedure: transformation of hydroxyl group to the corresponding mesylate, substitution with allylamine, and

followed by protection with trifluoroacetic anhydride to afford diene **4**. Ring closing metathesis of diene **4** with 2nd generation Grubbs catalyst gave 3-*t*-Boc-amino-4-aryl-1,2,3,6-tetrahydropyridine **5**. 4-Bromophenyl compound **5b** was converted to corresponding 4-biaryl compound **5c** and **5d** by a typical Suzuki coupling reaction with phenylboronic acid and 3,5-difluorophenylboronic acid, respectively. Finally, reduction of double bond and deprotection of Boc group gave desired 3-amino-4-aryl-piperidine **6**.

Reaction of 3-amino-4-arylpiperidines **6** with various acid chloride, sulfonyl chloride, and 3-methoxybenzyl bromide and then treatment with K_2CO_3 in MeOH to remove trifluoroacetyl group gave amide **7a-h**, sulfonamide **8**, and benzylamine **9**, respectively (Scheme 2).

Results and Discussion

The enzymatic inhibitory assay was carried out at the concentration of 100, 10, 2 μM of a compound by a fluorescence resonance energy transfer (FRET) assay, using a purified baculovirus-expressed BACE 1 and a specific substrate (Rh-EVNLDAEFK-Quencher). The assay data were summarized in Table 1.

Initially we prepared 4-phenyl piperidine derivatives with amide- (**7a-7d**), sulfonamide- (**8**) substituents on 3-amino group. These 4-phenyl piperidines showed very little activity. Next, we decided to introduce a bulky substituent at 4-position and prepared 4-biaryl substituted piperidines, which found in piperazine based BACE 1 inhibitors.^{10*} 4-Biaryl piperidines (**7e, 7f, and 7h**) showed high inhibitory activities with IC_{50} of 2.8-9.8 μM . In 4-biaryl piperidine series, 3-(2-naphtholamino) piperidine (**7f** and **7h**) showed *ca.* 4 fold higher activity than that of 4-phenyl-3-(4-biphenylcarbonyloxy)piperidine **10**, which was previously identified as BACE 1 inhibitor with IC_{50} of 11 μM .¹¹ Effect of substituent

Table 1. BACE 1 inhibitory activity of 3-amino-4-aryl-piperidines (**7-9**) and **10**

Compound	X	R ₁	R ₂	Enzyme Assay	
				% inhibition (at 100 μM)	IC_{50}
7a	H	4-Biphenyl	H	26%	–
7b	H	3-(Dipropylcarbonyl)phenyl	H	12%	–
7c	H	3-(Dipropylcarbonyl)phenyl	CF_3CO^-	17%	–
7d	H	3-(Diisopropylcarbonyl)phenyl	H	15%	–
7e	4-Ph	1-Naphthyl	H	50% ^a	9.83
7f	4-Ph	2-Naphthyl	H	77% ^a	2.81
7g	4-Ph	N,N-Dipropyl-isophthaloyl	H	39% ^a	–
7h	4-Ph(3,5-F ₂)	2-Naphthyl	H	77% ^a	2.87
8				44% ^a	–
9				8.0% ^a	–
					11.0

a. % inhibition at 10 μM

in 3-amino group on inhibitory activity was also studied. 2-Naphthoyl substituent (**7f** and **7h**) showed higher activity than 1-naphthoyl substituent (**7e**), and isophthaloyl (**7g**) and benzyl group (**9**) showed poor activities.

In conclusion, we prepared 4-phenyl- and 4-biaryl-3-amidopiperidine derivatives which showed better BACE 1 activities than originally reported compound **10**. Further modification for improving activity and study of structure and activity relationship (SAR) are remained for future work.

Experimental Section

Melting points were determined on a capillary melting point apparatus and were uncorrected. ¹H NMR spectra were recorded with Varian Gemini 200 spectrometer. Reagents used were reagent grade and purified, if necessary. Solvents were dried by conventional methods. In enzymatic assay, fluorescence intensity was read at 545 nm excitation and 585 nm emission with FlexStation fluorometric imaging reader.

Enzymatic assay. The inhibitory activity was determined by a fluorescence resonance energy transfer (FRET) assay in 50 mM sodium acetate assay buffer at pH 4.5, using a purified baculovirus-expressed BACE 1 (1 U/mL in tris buffer) and a specific substrate (Rh-EVNLDAEFK-Quencher; 750 nM in assay buffer). This specific substrate based on the Swedish mutation of the amyloid precursor protein (APP) became highly fluorescent upon cleavage by BACE 1. For each compound, three different concentration (100, 10, and 2 μ M, respectively) were prepared by dissolving it in DMSO (up to 30% in total volume) and assay buffer.

After a solution of compound (10 μ L) and specific substrate (10 μ L) were gently mixed, BACE 1 (10 μ L) was introduced and incubated at room temperature for 1 h. BACE 1 stop solution (2.5 M sodium acetate buffer; 10 μ L) was added to the reaction mixture to stop the reaction. Fluorescence intensity was measured to determine inhibitory activity of a compound tested. Each inhibitory assay was carried out repeatedly for three times.

O-*tert*-Butyldimethylsilyl-N-boc-L-serine. To a solution of N-Boc-L-serine (10.06 g, 49.03 mmol) in DMF (100 mL) was added TBS-Cl (9.46 g, 62.76 mmol) and imidazole (10.01 g, 147.1 mmol) at 0 °C. After stirred for 10 h at rt, the reaction mixture was diluted with water (200 mL) and extracted with ether (2 \times 250 mL). The combined organic layer was washed with water (100 mL), dried (MgSO₄), and concentrated. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 4) to give 13.3 g (85%) of O-*tert*-butyldimethylsilyl-N-boc-L-serine as a colorless oil: ¹H NMR (CDCl₃): δ 0.06 (s, 6H), 0.88 (s, 9H), 1.46 (s, 9H), 3.84 (dd, *J* = 10.2, 3.8 Hz, 1H), 4.12 (m, 1H), 4.35 (m, 1H), 5.34 (d, *J* = 7.2 Hz, 1H), 8.40 (bs, 1H).

Phenyl ketone (2a). A solution of O-*tert*-butyldimethylsilyl-N-boc-L-serine (7.02 g, 22.0 mmol) and 1,1'-carbonyldiimidazole (3.57 g, 22.0 mmol) in dry THF (50 mL) was stirred for 1 h at rt, and then was added dropwise to a solution of phenylmagnesium bromide (3 M in hexane; 22

mL, 66 mmol) and CuI (0.38 mg, 1.98 mmol) in THF (50 mL) at -78 °C. After stirred at -78 °C for 1 h, the reaction mixture was quenched with 1 N HCl (50 mL) and extracted with EtOAc (3 \times 100 mL). The combined organic layer was washed with water (2 \times 100 mL), dried (MgSO₄), and concentrated. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 8) to give 6.58 g (78%) of **2a** as a colorless oil: ¹H NMR (CDCl₃): δ -0.13 (s, 3H), -0.11 (s, 3H), 0.76 (s, 9H), 1.46 (s, 9H), 3.86-4.99 (m, 2H), 5.25-5.31 (m, 1H), 5.68 (d, *J* = 7.6 Hz, 1H), 7.42-7.63 (m, 3H), 7.91-7.96 (m, 2H).

4-Bromophenyl ketone (2b). Compound **2b** was prepared with 4-bromophenyllithium¹⁵ as shown for **2a** in 85% yield as a white solid: mp 46-47 °C; ¹H NMR (CDCl₃): δ -0.12 (s, 3H), -0.101 (s, 3H), 0.76 (s, 9H), 1.46 (s, 9H), 3.86-4.99 (m, 2H), 5.25-5.31 (m, 1H), 5.64 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H).

(R)-*tert*-Butyl 1-hydroxy-3-phenylbut-3-en-2-ylcarbamate (3a). To a stirred suspension of methyltriphenylphosphonium bromide (4.5 g, 12.6 mmol) in dry THF (30 mL) was added *n*-BuLi (1.6 M in hexane; 8.4 mL, 13.4 mmol) at 0 °C. The reaction mixture was warmed to rt, stirred for 1 h, and then cooled to -78 °C. A solution of ketone **2a** (1.5 g, 3.95 mmol) in THF (10 mL) was added dropwise to above solution, and the resulting mixture was slowly warmed to rt. After stirred for 1 h, the reaction mixture was poured into cold 1 N HCl (100 mL) and extracted with ether (50 mL). The organic layer was washed with water (100 mL), dried (MgSO₄), and concentrated. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 20) to give 0.93 g (62%) of the desired compound: ¹H NMR (CDCl₃): δ -0.06 (s, 3H), -0.04 (s, 3H), 0.86 (s, 9H), 1.46 (s, 9H), 3.50 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.68 (dd, *J* = 10.2, 4.0 Hz, 1H), 4.67-4.73 (m, 1H), 5.10-5.12 (m, 1H), 5.22 (s, 1H), 5.30 (s, 1H), 7.28-7.40 (m, 5H).

Tetra-*n*-butylammonium fluoride (1 M in THF; 1.71 mL, 1.71 mmol) was added to a solution of silyl ether (0.59 g, 1.56 mmol) in CH₂Cl₂ (10 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was washed with water (10 mL), dried (MgSO₄), and concentrated. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 20) to give 0.383 g (92%) of **3a**: ¹H NMR (CDCl₃): δ 1.47 (s, 9H), 2.00 (bs, 1H), 3.60-3.76 (m, 2H), 4.75 (m, 1H), 5.15 (m, 2H), 5.25 (s, 1H), 5.39 (s, 1H), 7.31-7.38 (m, 5H).

(R)-*tert*-Butyl 3-(4-bromophenyl)-1-hydroxybut-3-en-2-ylcarbamate (3b). Compound **3b** was prepared from **2b** as shown for **3a**. White solid: mp 158-160 °C; ¹H NMR (CDCl₃): δ 1.47 (s, 9H), 1.68 (bs, 1H), 3.54-3.74 (m, 2H), 4.70 (m, 1H), 5.15 (m, 2H), 5.28 (s, 1H), 5.39 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H).

(R)-*tert*-Butyl 1-(*N*-allyl-2,2,2-trifluoroacetamido)-3-phenylbut-3-en-2-ylcarbamate 4a. To a solution of alcohol **3a** (1.15 g, 4.37 mmol) and triethylamine (1.3 mL, 9.32 mmol) in CH₂Cl₂ (20 mL) was added dropwise MsCl (0.41 mL, 5.3 mmol) at 0 °C. The reaction mixture was warmed to

rt, stirred for 1 h, and washed with cold 1 N HCl (20 mL). The organic layer was dried (MgSO₄) and concentrated to give corresponding mesylate. Without purification, mesylate was dissolved in allylamine (15 mL) and heated to reflux overnight under N₂ atmosphere. The reaction mixture was concentrated and dissolved in CH₂Cl₂ (20 mL) and treated sequentially with triethylamine (1.3 mL, 9.32 mmol) and trifluoroacetic anhydride (0.93 mL, 6.58 mmol) at 0 °C and slowly warmed to rt. After stirred for 2 h, the reaction mixture was washed with cold 1 N HCl (20 mL) and water (20 mL). The organic layer was dried (MgSO₄), and concentrated. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 6) to give 1.59 g (91%) of **4a** as a colorless oil: ¹H NMR (CDCl₃): δ 1.43 (s, 9H), 3.16 (dd, *J* = 13.8, 3.4 Hz, 1H), 3.77-4.02 (m, 3H), 4.99-5.25 (m, 4H), 5.30 (s, 1H), 5.38 (s, 1H), 5.58-5.66 (m, 1H), 7.29-7.44 (m, 5H).

(R)-tert-Butyl 1-(N-allyl-2,2,2-trifluoroacetamido)-3-(4-bromophenyl)but-3-en-2-ylcarbamate 4b. Compound **4b** was prepared from **3b** as shown for **4a**. White solid: mp 137-139 °C; ¹H NMR (CDCl₃): δ 1.43 (s, 9H), 3.16 (dd, *J* = 13.8, 3.4 Hz, 1H), 3.77-4.02 (m, 3H), 4.90-5.38 (m, 4H), 5.32 (s, 1H), 5.38 (s, 1H), 5.58-5.66 (m, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H).

(R)-tert-Butyl 4-phenyl-1-(2,2,2-trifluoroacetyl)-1,2,3,6-tetrahydropyridin-3-ylcarbamate 5a. To a solution of diene **4a** (0.83 g, 2.09 mmol) was added 2nd generation Grubbs catalyst (89 mg, 0.104 mmol) and heated to reflux overnight under argon atmosphere. The reaction mixture was concentrated and purified by flash column chromatography (EtOAc : Hex = 1 : 4) to give 0.68 g (87%) of **5a** as a colorless oil: ¹H NMR (CDCl₃): δ 1.41 (m, 9H), 3.45 (dd, *J* = 14.0, 2.2 Hz, 1H), 3.80-3.91 (m, 1H), 4.32-4.39 (m, 1H), 4.59-4.63 (m, 1H), 4.78-4.88 (m, 3H), 6.25-6.28 (m, 1H), 7.26-7.41 (m, 5H).

(R)-tert-Butyl 4-(4-bromophenyl)-1-(2,2,2-trifluoroacetyl)-1,2,3,6-tetrahydropyridin-3-ylcarbamate 5b. Compound **5b** was prepared from **4b** as shown for **5a**. White solid: mp 123-125 °C; ¹H NMR (CDCl₃): δ 1.41 (m, 9H), 3.45 (dd, *J* = 13.8, 2.0 Hz, 1H), 3.78-3.89 (m, 1H), 4.29-4.36 (m, 1H), 4.57-4.86 (m, 3H), 6.25-6.28 (m, 1H), 7.28 (d, *J* = 9.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H).

(R)-tert-Butyl 4-(biphenyl-4-yl)-1-(2,2,2-trifluoroacetyl)-1,2,3,6-tetrahydropyridin-3-ylcarbamate 5c. To a solution of **5b** (1.0 g, 2.22 mmol), phenylboronic acid (0.3 g, 2.46 mmol), and CsF (0.67 g, 4.41 mmol) in DME (10 mL) was added tetrakis (triphenylphosphine) palladium (77 mg, 66 μmol). The reaction mixture was heated to reflux overnight under argon atmosphere. After cooled to rt, the reaction mixture was diluted with EtOAc (30 mL), washed with water (50 mL), dried (MgSO₄), and concentrated. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 6) to give 0.84 g (84%) of **5c** as a colorless oil: ¹H NMR (CDCl₃): δ 1.42 (s, 9H), 3.46 (dd, *J* = 13.8, 2.0 Hz, 1H), 3.82-3.92 (m, 1H), 4.33-4.41 (m, 1H), 4.64-4.90 (m, 3H), 6.31-6.34 (m, 1H), 7.32-7.63 (m, 9H).

(R)-tert-Butyl 4-(3',5'-difluorobiphenyl-4-yl)-1-(2,2,2-

trifluoroacetyl)-1,2,3,6-tetrahydropyridin-3-ylcarbamate 5d. Compound **5d** was prepared from **5b** with 3,5-difluorophenylboronic acid as shown for **5c**. ¹H NMR (CDCl₃): δ 1.41 (s, 9H), 3.43-3.54 (m, 1H), 3.80-3.89 (m, 1H), 4.30-4.39 (m, 1H), 4.57-4.94 (m, 3H), 6.29-6.30 (m, 1H), 6.67-6.76 (m, 1H), 6.99-7.09 (m, 2H), 7.34-7.57 (m, 7H), 7.71-7.92 (m, 4H), 8.21 (s, 1H).

1-((3R,4R)-3-Amino-4-phenylpiperidin-1-yl)-2,2,2-trifluoroethanone 6a. A solution of tetrahydropyridine **5a** (0.67 g, 1.82 mmol) and 5% Pd-C (97 mg, 0.91 mmol) in MeOH (20 mL) was stirred under hydrogen balloon for 4 h. The reaction mixture was filtered over celite pad and concentrated *in vacuo*. The remaining residue was purified by flash column chromatography (EtOAc : Hex = 1 : 8) to give 3-*tert*-butoxycarbonyl-amino-piperidine. To a solution of 3-*tert*-butoxycarbonyl-amino-4-phenyl-piperidine in CH₂Cl₂ (10 mL) was added TFA (3 mL) at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 1 h. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc (20 mL), washed with sat'd NaHCO₃ (20 mL), and water (20 mL). The organic layer was dried (MgSO₄), concentrated, and purified by flash column chromatography (EtOAc : Hex = 1 : 1) to give 0.59 g (87%) of **6a**: ¹H NMR (CDCl₃): δ 1.09 (bs, 2H), 1.71-1.78 (m, 1H), 2.20-2.38 (m, 1H), 2.80-3.51 (m, 4H), 3.95-4.28 (m, 1H), 4.59-4.85 (m, 1H), 7.19-7.40 (m, 5H).

1-((3R,4R)-3-Amino-4-(biphenyl-4-yl)piperidin-1-yl)-2,2,2-trifluoroethanone 6b. Compound **6b** was prepared from **5c** as shown for **6a**. ¹H NMR (CDCl₃): δ 1.16-1.26 (m, 1H), 1.86-2.02 (m, 1H), 2.55-2.92 (m, 1H), 3.07-3.32 (m, 3H), 3.74 (s, 1H), 4.18-4.25 (m, 1H), 4.86-4.94 (m, 1H), 7.32-7.62 (m, 9H).

1-((3R,4R)-3-Amino-4-(3',5'-difluorobiphenyl-4-yl)piperidin-1-yl)-2,2,2-trifluoroethanone 6c. Compound **6c** was prepared from **5d** as shown for **6a**. ¹H NMR (CDCl₃): δ 1.19-1.26 (m, 2H), 1.81-1.95 (m, 1H), 2.64-2.88 (m, 1H), 3.08-3.42 (m, 3H), 3.77 (s, 1H), 4.02-4.27 (m, 1H), 4.85-4.92 (m, 1H), 6.73-6.81 (m, 1H), 7.02-7.05 (m, 2H), 7.35-7.39 (m, 2H), 7.52-7.56 (m, 2H).

General procedure for the synthesis of amide 7a-7h. To a solution of 3-aminopiperidine **6** and triethylamine in CH₂Cl₂ (10 mL) was added acid chloride at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The reaction mixture was washed with 1 N HCl (10 mL), aq. NaHCO₃ (10 mL), and water (10 mL). The organic layer was dried (MgSO₄), concentrated, and purified by flash column chromatography (EtOAc : Hex = 1 : 1) to yield the desired amide.

The corresponding N-trifluoroacetyl piperidine was treated with K₂CO₃ in MeOH (3 mL) at rt for 1-4 h. The reaction mixture concentrated and purified by flash column chromatography (EtOAc : Hex = 1 : 1) to give desired free piperidine **7**.

N-((3R,4R)-4-Phenylpiperidin-3-yl)biphenyl-4-carboxamide 7a. ¹H NMR (CDCl₃): δ 1.80-1.95 (m, 1H), 2.0-2.15 (m, 1H), 2.78-2.88 (m, 1H), 3.00-3.10 (m, 2H), 3.20-3.25 (m, 2H), 4.57-4.62 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 7.20-

7.72 (m, 14H).

***N*¹-((3*R*,4*R*)-4-Phenylpiperidin-3-yl)-*N*³,*N*³-dipropylisophthalamide 7b.** ¹H NMR (CDCl₃): δ 0.75 (bt, 3H), 0.98 (bt, 3H), 1.40-1.45 (m, 2H), 1.62-1.65 (m, 2H), 1.81-1.87 (m, 1H), 2.09-2.16-2.28 (m, 2H), 2.83 (m, 1H), 2.97-3.42 (m, 9H), 4.62-4.65 (m, 1H), 7.15-7.44 (m, 9H).

***N*¹-((3*R*,4*R*)-4-Phenyl-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)-*N*³,*N*³-dipropylisophthalamide 7c.** ¹H NMR (CDCl₃): δ 0.75 (bt, 3H), 0.98 (bt, 3H), 1.40-1.80 (m, 5H), 2.04-2.15 (m, 2H), 3.14-3.45 (m, 7H), 4.39-4.40 (m, 2H), 6.44 (bs, 1H), 7.15-7.44 (m, 9H).

***N*¹,*N*¹-Diisopropyl-*N*³-((3*R*,4*R*)-4-phenyl-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)isophthalamide 7d.** ¹H NMR (CDCl₃): δ 0.75 (bt, 3H), 0.98 (bt, 3H), 1.40-1.45 (m, 2H), 1.62-1.65 (m, 2H), 1.81-1.87 (m, 1H), 2.09-2.16-2.28 (m, 2H), 2.83 (m, 1H), 2.97-3.42 (m, 9H), 4.62-4.65 (m, 1H), 7.15-7.44 (m, 9H).

***N*-((3*R*,4*R*)-4-(Biphenyl-4-yl)piperidin-3-yl)-1-naphthamide 7e.** ¹H NMR (CDCl₃): δ 1.80-1.97 (m, 2H), 2.65 (s, 2H), 2.79 (dt, *J* = 11.4, 2.8 Hz, 1H), 3.04-3.33 (m, 3H), 4.85 (d, *J* = 6.8 Hz, 1H), 6.90-6.95 (m, 1H), 7.21-7.24 (m, 1H), 7.39-7.62 (m, 12H), 7.74-7.84 (m, 2H).

***N*-((3*R*,4*R*)-4-(Biphenyl-4-yl)piperidin-3-yl)-2-naphthamide 7f.** ¹H NMR (CDCl₃): δ 1.86 (-1.92 (m, 1H), 2.06-2.21 (m, 1H), 2.35 (s, 2H), 2.85 (dt, *J* = 11.6, 2.6 Hz, 1H), 3.01-3.14 (m, 2H), 3.25-3.30 (m, 2H), 4.71 (d, *J* = 6.4 Hz, 1H), 7.13-7.90 (m, 15H), 8.16 (s, 1H).

***N*¹-((3*R*,4*R*)-4-(Biphenyl-4-yl)piperidin-3-yl)-*N*³,*N*³-dipropylisophthalamide 7g.** ¹H NMR (CDCl₃): δ 0.66 (bt, 3H), 0.96 (bt, 3H), 1.43-1.47 (m, 2H), 1.64-1.67 (m, 2H), 1.83-1.89 (m, 1H), 2.09-2.16-2.28 (m, 2H), 2.83 (dt, *J* = 11.8, 2.8 Hz, 1H), 2.99-3.44 (m, 9H), 4.62-4.65 (m, 1H), 7.03-7.07 (m, 1H), 7.26-7.68 (m, 12H).

***N*¹-((3*R*,4*R*)-4-(3',5'-Difluorobiphenyl-4-yl)piperidin-3-yl)-2-naphthamide 7h.** ¹H NMR (CDCl₃): δ 1.85-1.91 (m, 1H), 2.10-2.31 (m, 1H), 2.81-2.93 (m, 1H), 3.05-3.12 (m, 2H), 3.23-3.50 (m, 2H), 4.74 (d, *J* = 9.4 Hz, 1H), 6.66-6.76 (m, 1H), 6.98-7.08 (m, 2H), 7.34-7.57 (m, 7H).

***N*-((3*R*,4*R*)-4-Phenylpiperidin-3-yl)naphthalene-2-sulfonamide 8.** To a solution of aminopiperidine **6a** (40 mg, 0.15 mmol) and triethylamine (61 μL, 0.43 mmol) was added in CH₂Cl₂ (10 mL) was 2-naphthalenesulfonyl chloride (40 mg, 0.18 mmol). The reaction mixture was stirred for 4 h at rt, diluted with EtOAc, and washed with 1 N HCl (10 mL), sat'd NaHCO₃ (10 mL), and water (10 mL). The organic layer was dried (MgSO₄), concentrated, and purified by flash column chromatography (EtOAc : Hex = 1 : 3) to give sulfonamide.

The corresponding sulfonamide was treated with K₂CO₃ in MeOH (3 mL) at rt for 4 h. The reaction mixture was concentrated and purified by flash column chromatography (EtOAc : Hex = 2 : 1) to give 38 mg (69%) of desired sulfonamide **8**. ¹H NMR (CDCl₃): δ 1.6-2.1 (m, 3H), 2.60-2.90 (m, 3H), 3.18-3.24 (m, 2H), 3.55 (s, 1H), 6.85-6.93 (m, 5H), 7.25-7.35 (m, 2H), 7.56-7.61 (m, 2H), 8.03 (s, 1H).

(3*R*,4*R*)-4-(Biphenyl-4-yl)-*N*-(3-methoxybenzyl)piperidin-3-amino 9. To a solution of aminopiperidine **6b** (40 mg, 0.115 mmol) and K₂CO₃ (18 mg, 0.13 mmol) was added 3-

methoxybenzyl bromide (18 μL, 0.13 mmol). The reaction mixture was stirred overnight at rt, diluted EtOAc, and washed with 1 N HCl (10 mL) and water (10 mL). The organic layer was dried (MgSO₄), concentrated, and purified by flash column chromatography (EtOAc : Hex = 1 : 1) to give corresponding benzylamine.

The benzylamine was treated with K₂CO₃ in MeOH (3 mL) at rt for 4 h. The reaction mixture concentrated and purified by flash column chromatography (EtOAc : Hex = 3 : 1) to give 35 mg (83%) of desired benzylamine derivatives **9**. ¹H NMR (CDCl₃): δ 1.75-1.80 (m, 1H), 2.02-2.04 (m, 1H), 2.64-2.98 (m, 4H), 3.20 (m, 2H), 3.72 (s, 3H), 4.10-4.17 (m, 1H), 4.89 (s, 2H), 5.79 (d, *J* = 9.4 Hz, 1H), 6.79 (m, 2H), 7.12-7.16 (m, 1H), 7.25-7.58 (m, 10H).

References

- Iqbal, K.; Sisodia, S. S.; Winblad, B. *Alzheimer's Disease: Advances in Etiology, Pathogenesis and Therapeutics*; John Wiley & Son: England, 2001.
- (a) Selkoe, D. J. *Nature* **1999**, *399*, A23. (b) Roggo, A. *Curr. Top. Med. Chem.* **2002**, *2*, 359. (c) Vassar, R. *Science* **1999**, *286*, 375.
- (a) Sinha, S.; Lieberburg, I. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11049. (b) Citron, M.; Diehl, T. S.; Gordon, G.; Biere, A. L.; Seubert, P.; Selkoe, D. J. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 13170.
- (a) Hardy, J.; Selkoe, D. J. *Science* **2002**, *297*, 353. (b) Hsiao, K.; Chapman, P.; Nilsen, S.; Eckman, C.; Harigaya, Y.; Younkin, S.; Yang, F.; Cole, G. *Science* **1996**, *274*, 99.
- (a) Lin, X.; Koelsch, G.; Wu, S.; Downs, D.; Dashti, A.; Tang, J. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 1456. (b) Hussain, I.; Powell, D.; Howlett, D. R.; Tew, D. G.; Meek, T. D.; Chapman, C.; Gloger, I. S.; Murphy, K. E.; Southan, C. D.; Ryan, D. M.; Smith, T. S.; Simmons, D. L.; Walsh, F. S.; Dingwall, C.; Christie, G. *Mol. Cell Neurosci.* **1999**, *14*, 419. (c) Yan, R.; Bienkowski, M. J.; Shuck, M. E.; Miao, H.; Tory, M. C.; Pauley, A. M.; Brashier, J. R.; Stratman, N. C.; Mathews, W. R.; Buhl, A. E.; Carter, D. B.; Tomasselli, A. G.; Parodi, L. A.; Heinrichson, R. L.; Gurney, M. E. *Nature* **1999**, *402*, 533. (d) Sinha, S.; Anderson, J. P.; Barbour, R.; Basi, G. S.; Caccavello, R.; Davis, D.; Doan, M.; Dovey, H. F.; Frigon, N.; Hong, J.; Jacobson-Croak, K.; Jewett, N.; Keim, P.; Knops, J.; Lieberburg, I.; Power, M.; Tan, H.; Tatsuno, G.; Tung, J.; Schenk, D.; Seubert, P.; Suomensaar, S. M.; Wang, S.; Walker, D.; John, V. *Nature* **1999**, *402*, 537. (e) Vassar, R.; Bennett, B. D.; Babu-Kahn, S.; Kahn, S.; Mendiaz, E. A.; Denis, P.; Teplow, D. B.; Ross, S.; Amarante, P.; Loeloff, R.; Luo, Y.; Fisher, S.; Fuller, J.; Edenson, S.; Lile, J.; Jarosinski, M. A.; Biere, A. L.; Curran, E.; Burgess, T.; Louis, J. C.; Collins, F.; Treanor, J.; Rogers, G.; Citron, M. *Science* **1999**, *286*, 735.
- (a) Wolf, M. S. *Nature Rev. Drug Discovery* **2002**, *1*, 859. (b) Citron, M. *Nature Rev. Neurosci.* **2004**, *5*, 677. (c) Gosh, A. K.; Hong, L.; Tang, J. *Curr. Med. Chem.* **2002**, *9*, 1135. (d) Walter, J.; Haass, C. *Drug Develop. Res.* **2002**, *56*, 201. (e) Vassar, R. *Acta Drug Del. Rev.* **2002**, *54*, 1589.
- (a) Gosh, A. K.; Shin, D. W.; Downs, D.; Koelsch, G.; Lin, X.; Ermolieff, J.; Tnag, J. *J. Am. Chem. Soc.* **2000**, *122*, 3522. (b) John, V.; Beck, J. P.; Bienkowski, M. J.; Sinha, S.; Heinrichson, R. L. *J. Med. Chem.* **2002**, *46*, 4625. (c) Hom, R. K.; Gailunas, A. F.; Mamo, S.; Fang, L. Y.; Tung, J. S.; Walker, D. E.; Davis, D.; Thorsett, E. D.; Jewett, N. E.; Moon, J. B.; John, V. *J. Med. Chem.* **2004**, *47*, 158. (d) Chen, S.; Lamar, J.; Guo, D.; Kohn, T.; Yang, H.; McGee, J.; Timm, D.; Erickson, J.; Yip, Y.; May, P.; McCarthy, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 245. (e) Hanessian, S.; Yun, H.; Hou, Y.; Yang, G.; Bayraktarian, M.; Therrien, E.; Moitessier, N.; Roggo, S.; Veenstra, S. *et al. J. Med.*

- Chem.* **2005**, *48*, 5175. (f) Yang, W.; Lu, W.; Lu, Y.; Zhong, M.; Sun, J.; Thomas, A. E.; Wilkinson, J. M.; Fucini, R. V.; Lam, M.; Randal, M.; Shi, X.-P.; Jacobs, J. W.; McDowell, R. S.; Gordon, E. M.; Ballinger, M. D. *J. Med. Chem.* **2006**, *49*, 839.
8. Stachel, S. J.; Coburn, C. A.; Steele, T. G.; Jones, K. G.; Loutzenhiser, E. F.; Gregro, A. R.; Rajapakse, H. A.; Lai, M. T.; Crouthamel, M.-C.; Xu, M.; Tugusheva, K.; Lineberger, J. E.; Pietrak, B. L.; Espeseth, A. S.; Shi, X.-P.; Chen-Dodson, E.; Holloway, M. K.; Munshi, S.; Simon, A. J.; Kuo, L.; Vacca, J. P. *J. Med. Chem.* **2004**, *47*, 6447.
9. Huang, D.; Luthi, U.; Kolb, P.; Edler, K.; Cecchini, M.; Audetat, S.; Barberis, A.; Caffisch, A. *J. Med. Chem.* **2005**, *48*, 5108.
10. (a) Park, H.; Lee, S. *J. Am. Chem. Soc.* **2003**, *125*, 16416. (b) Bhisetti, G. R.; Saunders, J. O.; Murcko, M. A.; Lepre, C. A.; Britt, S. D.; Come, J. H.; Deninger, D. D.; Wang, T. *PCT Int. Appl. WO 02/088101*, 2002. (c) Garino, C.; Pietrancosta, N.; Laras, Y.; Moret, V.; Rolland, A.; Quelever, G.; Kraus, J.-L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1995.
11. John, V.; Moon, J. B.; Pulley, S. R.; Rich, D. H.; Brown, D. L.; Jagodzinski, B.; Jacobs, J. S. *PCT Int. Appl. WO 03/043987*, 2003.
12. (a) Bursarvich, M. G.; West, C. W.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2317. (b) Oefner, C.; Binggeli, A.; Breu, V.; Bur, D.; Clozel, J. P.; D'arcy, A.; Dorn, A.; Fischli, W.; Gruninger, F.; Guller, R.; Hirth, G.; Marki, H.; Mathews, S.; Miller, M.; Ridley, R. G.; Stadler, H.; Viera, E.; Wilhelm, M.; Winkler, F.; Wostl, W. *Chem. Biol.* **1999**, *6*, 127.
13. Hu, X. E.; Kim, N. K.; Ledoussal, B. *Org. Lett.* **2002**, *4*, 4499.
14. Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **1998**, 1013.
15. Rogers, H. R.; Houk, J. *J. Am. Chem. Soc.* **1982**, *104*, 522.
-