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Structure-guided design and synthesis of P_1' position 1-phenylcycloalkylamine-derived pentapeptidic BACE1 inhibitors

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ABSTRACT

Previously, we reported potent pentapeptidic BACE1 inhibitors with the hydroxymethylcarbonyl isostere as a substrate transition-state mimic. To improve the in vitro potency, we further reported pentapeptidic inhibitors with carboxylic acid bioisosteres at the P_4 and P_1' positions. In the current study, we screened new P_1' position 1-phenylcycloalkylamine analogs to find non-acidic inhibitors that possess double-digit nanomolar range IC_{50} values. An extensive structure–activity relationship study was performed with various amine derivatives at the P_1' position. The most potent inhibitor of this pentapeptide series, KMI-1830, possessing 1-phenylcyclopentylamine at the P_1' position had an IC_{50} value of 11.6 nM against BACE1 in vitro enzymatic assay.

1. Introduction

Alzheimer's disease (AD)[1–3] is the most common chronic neurodegenerative disorder of the central nervous system. It is characterized by a progressive loss of memory, cognitive deficits, and psychiatric symptoms.[4,5] The pathology of AD is exemplified by the formation of insoluble extracellular amyloid plaques from amyloid fibril tangles, which are derived from the aggregation of amyloid peptides (Aβ) in the brain.[6,7] Aβ are found from 38 to 43 residues in length, with $Aβ_{40}$ being most numerous and $Aβ_{42}$ the most aggregative and pathogenic. Sequential cleavage of amyloid precursor protein (APP) by the enzyme, β-secretase (BACE1) at Met671-Asp672 (APP_{770} numbering) releases soluble sAPPβ in the pathogenic pathway. The remaining membrane-bound C99 fragment is further cleaved by the enzyme, γ-secretase, to generate amyloid Aβ and APP intracellular domain.[8,9] Of these two proteases, BACE1 catalyzes the initial proteolysis of APP, which is considered as a rate-limiting step in the cleavage cascade.[10] First identified in 1999, BACE1 belongs to the type-I class of aspartyl proteases.[11] BACE1 knockout mice with significantly reduced levels of β-amyloid was shown to maintain a relatively normal phenotype.[12] Moreover, deletion of the BACE1 gene in a Tg2576 mouse model was shown to reduce cognitive deficit.[13–15] Thus inhibition of BACE1 is considered a promising therapeutic target for the treatment and prevention of AD.[16] Although numerous BACE1 inhibitors have been reported, most of the peptide-based structures have relatively high molecular weights and possess unfavorable properties for traversing the blood–brain barrier (BBB).[17,18]

In our research on pentapeptidic BACE1 inhibitors, extensive structure–activity relationship (SAR) studies were used to derive the pentapeptidic inhibitor KMI-360 (**1**)[19] which has glutamic acid at the P_4 position and 3-aminophthalic acid at the P_1' position (Fig. 1). Acidic moieties at the prime and non-prime positions are thought to be unfavorable for crossing the BBB.[20,21] Indeed, more than 98% of drugs with high in vitro potency against their respective enzymes do not actually cross the BBB in vivo due to physicochemical features such as acidity, molecular mass and lipid solubility.[22] In order to reduce acidity of the peptide, we identified L-2,3-diaminopropionic acid (DAP) as a novel P_4 position linker which then led us to identify highly potent P_4 Dap(tetrazole) pentapeptidic BACE1 inhibitors, KMI-420 (**2a**) and KMI-429 (**2b**).[23] Further SAR studies yielded P_4 2,5-dihydroxybenzoyl (**3a**) and 5-fluoroorotyl (**3b**) inhibitors with a P_1' position 3-(1-*H*-tetrazol-5-yl)aniline moiety[24] possessing potent BACE1 inhibitory activity in vitro enzymatic assay. With 2,5-dihydroxybenzoyl and 5-fluoroorotyl at the P_4 position, we turned our attention to the P_1' position 3-(1-*H*-tetrazol-5-yl)aniline derivative of **3a**–**b**. Recently, we reported pentapeptidic inhibitors with 3-(1-*H*-tetrazol-5-yl)aniline bioisosteres at the P_1' position (**4a**–**c**).[25] Although the inhibitors of type **4a**–**c** showed excellent potency against BACE1 (IC_{50} =

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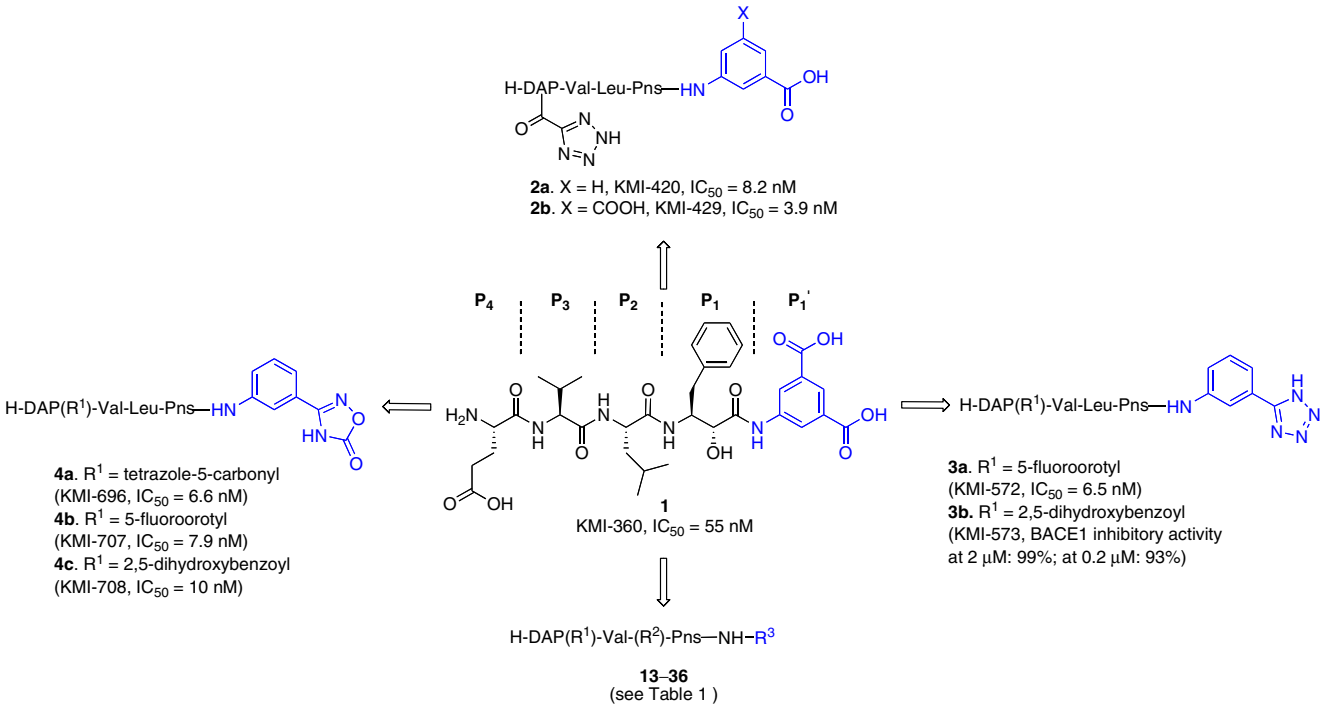
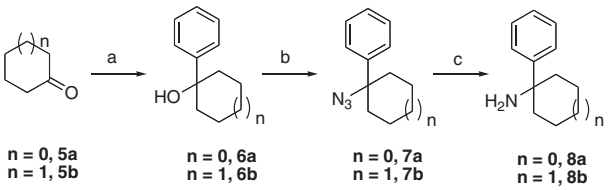


Figure 1. P_1' position modifications of our lead pentapeptidic BACE1 inhibitor **1**. (DAP: L-2,3-diaminopropionic acid; Pns [phenylnorstatine: (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid]).

7–10 nM), on comparison of P_1' residues of this inhibitors with inhibitors **2a** and **3a–b** displays similar ionizability.

In the current study, we examined less ionizable P_1' moieties in our pentapeptidic BACE1 inhibitors. In the literature, substituted benzylamine derivatives have been used as P_1' residues in several hydroxyethylamine (HEA) type BACE1 inhibitors.[26–28] In our inhibitors, phenylnorstatine (Pns) served as an hydroxymethylcarbonyl transition-state mimic isostere. By using computer-assisted drug design, we initially calculated that a benzylamine structure could serve as an alternative for the P_1' residues found in inhibitors **1**, **2a–b**, **3a–b**, and **4a–c**.[19] However, because the P_1' benzylamine would most likely be easily degraded in vivo,[29] we examined more conformationally rigid P_1' benzylamine derivatives including alkyl and cycloalkyl amine moieties (**13–36**). Because we could not agree on the exact SAR for the P_2 and P_4 residues in our past studies,[24,25] modifications at these positions with P_2 leucine or L-cyclohexyl-alanine (Cha) and P_4 2,5-dihydroxybenzoic or 5-fluoroorotic acid were also examined.

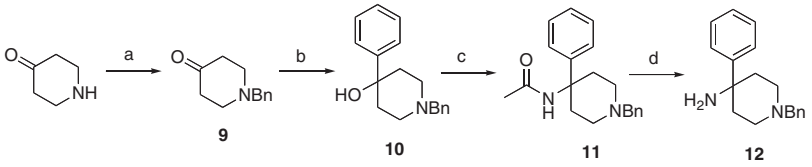


Scheme 1. Synthesis of 1-phenylcycloalkylamines: reagents and conditions: (a) PhMgI, 0 °C–rt, THF; (b) NaN_3, TFA, CH_2Cl_2; (c) LAH, Et_2O.

2. Chemistry

The P_1' position amines were prepared by using a three-step procedure starting from iodobenzene and its corresponding ketones as shown in Schemes 1 and 2. Commercially available cyclic ketones (**5a–b**) were reacted with phenylmagnesium iodide generated from iodobenzene and magnesium turnings in tetrahydrofuran (Grignard reagent) to give 1-phenylcyclopentanol (**6a**) and 1-phenylcyclohexanol (**6b**) in good yields. These alcohols were then converted to their respective azides (**7a** and **7b**) by using sodium azide and trifluoroacetic acid (TFA) followed by reduction with lithium aluminum hydride (LAH) to produce amines **8a** and **8b**.

A Ritter reaction[30,31] was used to prepare the 1-benzyl-4-phenylpiperidin-4-amine (**12**) that was needed for the synthesis of pentapeptides **33–36**. The tertiary alcohol required for the Ritter reaction was synthesized starting from 4-piperidone, as shown in Scheme 2. First, benzyl protection of the amine functionality of 4-piperidone was carried out with benzyl bromide by using



Scheme 2. Synthesis of 1-benzyl-4-phenylpiperidin-4-amine: reagents and conditions: (a) BnBr, K_2CO_3, CH_3CN; (b) PhMgI, 0 °C–rt, Et_2O; (c) MeCN, conc. H_2SO_4, 0 °C–rt; (d) 6 N HCl (aq), reflux.

K_2CO_3 in CH_3CN, followed by a Grignard reaction similar to that used for alcohol **6a–b**. The obtained alcohol **10** was converted into acetamide derivative **11** by using conc. H_2SO_4 and CH_3CN (Ritter reaction), which was further transformed into the required amine **12** under acidic hydrolysis conditions by using 6 N HCl (aq).[32] The α-methylbenzylamine and α,α-dimethylbenzylamine (cumylamine) were commercially available and used directly for the respective pentapeptide synthesis reactions.

All pentapeptides were synthesized in solution phase by using Boc chemistry as reported previously.[24] Peptide bonds were formed between an amine and the *N*-protected amino acid by using 1-ethyl-3(3-dimethylaminopropyl)carbodiimide·HCl (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) as coupling agents, with triethylamine (NEt_3) as a base in *N*,*N*-dimethylformamide (DMF). Pentapeptide synthesis was carried out starting from the P_1' position amines and Boc–Pns–OH followed by the respective amino acids couplings.

3. Results and discussion

The inhibition potency of pentapeptides against BACE1 is summarized in Table 1. The synthesized peptides were screened for BACE1 inhibition at 2 μM then 0.2 μM concentrations, and the IC_{50} values were determined only for the very potent (>75% of inhibition at 0.2 μM concentration) BACE1 inhibitors.

In the case of the P_1' residue, which is our main residue of interest we selected benzylamine, in agreement with a study that used a barely similar moiety,[33] the phenyl group that resides in the S_2' subsite. HEA types BACE1 inhibitors with benzylamine at the prime position suffer from low metabolic stability due to debenzylation by rat and human microsomes.[29] Therefore, we initially selected a commercially available benzylamine derivative, α-methylbenzylamine, for the P_1' position and synthesized pentapeptides by using leucine or Cha at the P_2 position with 2,5-dihydroxybenzoic acid or 5-fluoroorotic acid at the P_4 position. The pentapeptides with both *R* and *S* isomers were prepared (**13**–**20**) to examine the selectivity at the prime side position of the pentapeptides.

Compounds with *R* and *S* α-methylbenzylamine at the P_1' position (**13**–**20**) showed similar BACE1 inhibition potency at 0.2 μM concentration ranging from 79% to 83% for 5-fluoroorotyl (**13**, **14**, **17**, and **18**), and 44% to 54% for 2,5-dihydroxybenzoyl (**15**, **16**, **19**, and **20**). With respect to IC_{50} values, inhibitors with the *S* isomer (**17** and **18**) were approximately 1.5-fold more potent than those with the corresponding *R* isomer (**13** and **14**). We then inserted an additional methyl group at the benzylic position of α-methylbenzylamine, which is cumylamine, as a prime position analog and synthesized inhibitors (**21**–**24**). Inhibitors **21**–**24** (**21**: 83% and **22**: 78% inhibition at 0.2 μM concentration; **23**: 44% and **24**: 49% inhibition at 0.2 μM concentration) showed similar inhibition potency to that of compounds **13**–**20**, but the IC_{50} values of inhibitor **21** (IC_{50} = 27 nM) and **22** (IC_{50} = 32 nM) indicated a slight decrease in inhibition potency compared with that of inhibitors **17** (IC_{50} = 20 nM) and **18** (IC_{50} = 24 nM). To further improve the inhibition potency, we searched for new moieties at the prime position with increased acid stability.

Appending a cycloalkyl ring at the α-carbon of P_1' position benzylamine derivatives could play an important role in stability. Moreover, the new cyclic analogs do not possess any acidic functionality. With this in mind, we synthesized 1-phenylcyclopentylamine and produced the corresponding pentapeptides **25**–**28** (**25**: 86% and **26**: 84% inhibition at 0.2 μM concentration; **27** and **28**: 58% inhibition at 0.2 μM concentration). Surprisingly, the IC_{50} values of inhibitors **25** and **26** indicated that inhibitor **25** was a more potent inhibitor with an IC_{50} value of 12 nM. Then we turned our attention towards the more stable and hydrophobic six-member ring analog, 1-phenylcyclohexylamine, at the P_1' position, and synthesized pentapeptides **29**–**32**. Even after an increase in ring size from a five- to a six-member ring, there was no improvement in inhibition potency with respect to the P_2 and P_4 variants (**29** and **30**: 5-fluoroortyl, IC_{50} = 25 and 41 nM, respectively; **31** and **32**: 2,5-dihydroxybenzoyl, 43% and 46% inhibition, respectively, at 0.2 μM concentration).

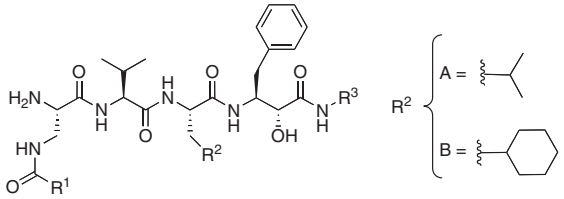
For a thorough analysis, we also performed computer-assisted docking experiments and chemical property calculations to correlate structural properties with inhibition potency by using the Chemical Computing Group's Molecular Operating Environment 2010.10. The models were designed primarily from the X-ray diffraction crystallography data of the classical peptidic inhibitor OM99-2 (PDB ID: 1FKN), and secondarily, from the non-peptidic inhibitor Z75 (PDB ID: 3LPJ), which possess similar non-prime and P_1' moieties that of our pentapeptides (Fig. S1 of Supplementary data). At the P_4 side-chain, in agreement with a recent study of a series of BACE1 inhibitors,[24] the models indicate that 5-fluoroorotic acid is favored over 2,5-dihydroxybenzoic acid by the protease because of stronger hydrogen bond potentials. At the P_2 position, although no appreciable potency difference was seen, leucine was slightly favored over Cha, which is also in agreement with the inhibition profiles of related inhibitors.[25] Also our computer models suggests that there is ample hydrophobic space and flexibility at the S_2 subsite to accommodate either residue, despite a slight obstruction by Arg^{235} (Fig. S2 of Supplementary data).

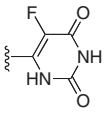
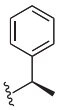
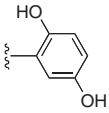
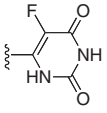
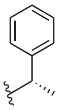
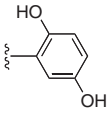
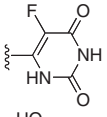
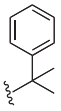
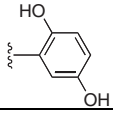
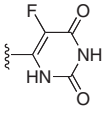
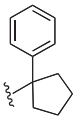
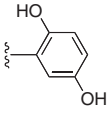
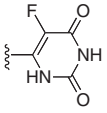
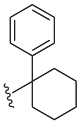
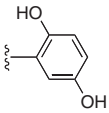
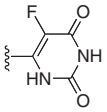
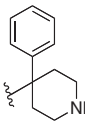
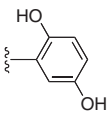
Coinciding with the inhibition profiles of compounds **13**–**32**, our models propose that the S_1' subsite is sufficiently flexible and large to accommodate several hydrophobic bulky moieties up to a six-member ring system (Fig. 2). The amino group of the piperidinyl moiety can form a direct hydrogen bond interaction with the side-chain of Thr^{72} as shown in Figure 2A for the 1-benzyl-4-phenylpiperidin-4-amine at the P_1' position, which could offer an advantage over inhibitors **13**–**32**. Based on this observation, we synthesized pentapeptides (**33**–**36**) with variations at the P_2 and P_4 positions. However, the inhibition potency profiles of these inhibitors (**33**: 59% and **34**: 64% inhibition at 0.2 μM concentration; **35**: 59% and **36**: 57% inhibition at 2 μM concentration) were relatively low compared with those of compounds **13**–**32** (5-fluoroorotyl, 77–86% inhibition at 0.2 μM concentration; 2,5-dihydroxybenzoyl, 86–90% inhibition at 2 μM concentration). This is likely due to an obstruction of the inhibitors large benzyl group by Thr^{329} (Fig. 2B) relative to the exactly fitting cyclopentyl ring of most potent pentapeptide KMI-1830 (**25**) (Fig. 2C). Hence, piperidinyl analogs with smaller moieties on the nitrogen atom may be a more appropriate size.

4. Conclusions

In conclusion, by using a structure-based approach, we designed and synthesized novel pentapeptidic BACE1 inhibitors modified at the P_1' position. A structure–activity relationship study revealed that the S_4 subsite of BACE1 favors 5-fluoroorotyl over 2,5-dihydroxybenzoyl in the P_4 side-chain, and that the S_2 subsite can accommodate either leucine or Cha, although leucine may be slightly preferred. Through comparative analysis, we found the following general potency order from most to least for the P_1' moiety: cyclopentyl, *S*-methyl, cyclohexyl, α,α-dimethyl, *R*-methyl, and *N*-benzylpiperidinyl group at the α-carbon of benzylamide derivative with leucine at the P_2 position of pentapeptide. This study identified a stable, hydrophobic, and non-ionizable BACE1 inhibitor possessing a 1-phenylclopentylamine moiety at the P_1' position, KMI-1830 (**25**, IC_{50} = 12 nM), with a five-fold improvement in potency over lead compound **1** (IC_{50} = 55 nM).

Table 1
BACE1 inhibitory activity of synthesized pentapeptides (**13**–**36**) with modification at the P_1' position



Compound (KMI No.)	R^1	R^2	R^3	BACE1 inhibition (%)		IC_{50}[a] (nM)
				at 2 μM	at 0.2 μM	
13 (KMI-1825)		A		98	81	34.8 ± 1.0
14 (KMI-1827)		B		98	79	39.6 ± 2.5
15 (KMI-1826)		A		87	44	—
16 (KMI-1828)		B		88	51	—
17 (KMI-1834)		A		99	83	20.4 ± 0.7
18 (KMI-1836)		B		98	80	24.2 ± 1.1
19 (KMI-1835)		A		88	47	—
20 (KMI-1837)		B		89	54	—
21 (KMI-1779)		A		98	83	27.0 ± 1.5
22 (KMI-1781)		B		98	78	31.9 ± 1.3
23 (KMI-1780)		A		88	44	—
24 (KMI-1782)		B		89	49	—
25 (KMI-1830)		A		99	86	11.6 ± 0.6
26 (KMI-1832)		B		98	84	29.0 ± 0.9
27 (KMI-1831)		A		90	58	—
28 (KMI-1833)		B		89	58	—
29 (KMI-1720)		A		98	85	24.8 ± 0.6
30 (KMI-1838)		B		97	77	40.6 ± 0.2
31 (KMI-1771)		A		86	43	—
32 (KMI-1839)		B		87	46	—
33 (KMI-1876)		A		93	59	—
34 (KMI-1829)		B		95	64	—
35 (KMI-1877)		A		59	—	—
36 (KMI-1875)		B		57	—	—

[a] Errors expressed as standard error of the mean, $n = 3$. For less potent inhibitors, percent inhibition at a tested compound concentration is described.

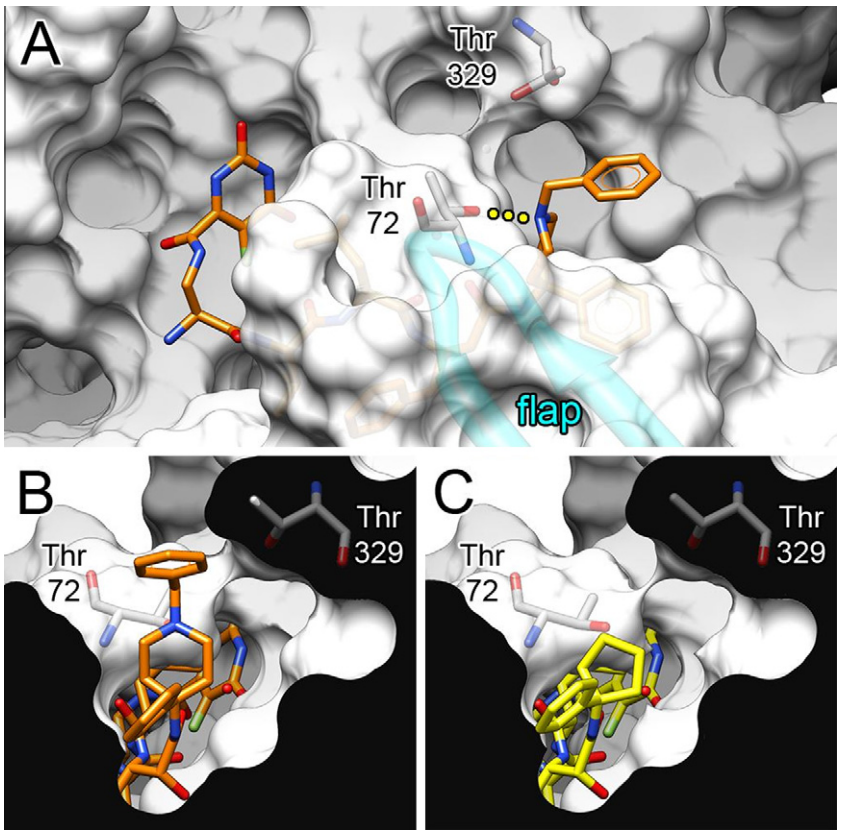


Figure 2. A hydrogen bond might form with the flap's Thr^{72} in KMI-1876 (**33**, A) while BACE1's Thr^{329} obstructs the inhibitor's benzyl group (B). The more potent inhibitor KMI-1830 (**25**) has less steric strain than inhibitor **33** in the S_1' subsite in the model (C).

5. Experimental section

5.1. Materials

Reagents and solvents were purchased from Wako Pure Chemical Ind. Ltd (Osaka, Japan), Nacalai Tesque (Kyoto, Japan), Aldrich Chemical Co. Inc. (Milwaukee, WI, USA), and Tokyo Kasei Kogyo Co. Ltd (Tokyo, Japan) and used without further purification. The column chromatography was performed on Merck 107734 silica gel 60 (70–230 mesh). Preparative HPLC was carried out on a C18 reverse phase column (250 × 20 mm I.D.; YMC-Pack-ODS-AM) with a binary solvent system: a linear gradient of CH_3CN in 0.1% aqueous TFA with a flow rate of 5.0 mL/min and detection at 230 nm. NMR spectra's were recorded on a JEOL AL300 (300 MHz) and EX 270 (270 MHz) spectrometer for ^1H with TMS as an internal standard and at 75 MHz for ^{13}C NMR. Mass spectra (electrospray ionization, MeOH as the mobile phase) were analyzed with SHIMADZU LCMS-2010 spectrometer. MALDI-TOF MS was performed on a Voyager-DE RP spectrometer (Per Septive Biosystems Inc.). Analytical HPLC was performed using a C18 reverse phase column (4.6 × 150 mm; YMC-Pack-ODS AM-302) with a binary solvent system: linear gradient of CH_3CN 0–100% in 0.1% aqueous TFA in 40 min at a flow rate of 0.9 mL/min, detected at 230 nm. The purity of the desired compounds was >99% pure.

5.2. Synthesis of 1-phenylcyclopentylamine (8a) and 1-phenylcyclohexylamine (8b)

5.2.1. 1-Phenylcyclopentanol (6a)

Magnesium turnings (217 mg, 8.93 mmol) in dry THF (5 mL) was placed in ice cold water and iodobenzene (0.73 mL, 6.55 mmol) in dry THF (2 mL) was added dropwise over 10 min. The mixture was stirred at room temperature for 30 min, followed by refluxed for 30 min. The solution was cooled in ice bath and cyclopentanone **5a** (0.53 mL, 5.95 mmol) in dry THF (1 mL) was added dropwise over 5 min. The ice bath was removed and the mixture was allowed to warm to ambient temperature over 3 h. The reaction mixture was decanted into aqueous saturated NH_4Cl solution and combined with an ether wash of the residual magnesium turnings. The organic phase was washed twice more with the saturated solution of aqueous NH_4Cl solution, dried over anhydrous Na_2SO_4, filtered and concentrated to give the corresponding alcohol. The resulting crude product was purified by column chromatography (hexane/EtOAc = 8:2) to afford compound **6a** (646 mg, 67%) as colorless oil. TLC: R_f = 0.53 (hexane/EtOAc = 8:2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.57 (bs, 1H, OH), 1.83–1.85 (m, 2H, CH_2), 1.90–2.09 (m, 6H, $(CH_2)_3$), 7.21–7.37 (m, 3H, ArH), 7.47–7.51 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.85, 41.88, 83.50, 125.07, 126.80, 128.19, 147.11.

5.2.2. 1-Phenylcyclohexanol (6b)

Compound **6b** was synthesized from cyclohexanone **5b** and iodobenzene in 61% yield as a white solid by following the same procedure used for the synthesis of **6a**. TLC: R_f = 0.49 (hexane/EtOAc = 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.13–1.98 (m, 11H, $(CH_2)_5$, OH), 7.19–7.78 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.97, 25.66, 38.72, 73.06, 124.52, 126.56, 128.10, 149.37.

5.2.3. 1-(1-Azidocyclopentyl)benzene (7a)

To 1-phenylcyclopentanol **6a** (500 mg, 3.09 mmol) in CH_2Cl_2 (6 mL) under nitrogen was added sodium azide (441 mg, 6.79 mmol). The stirred suspension was cooled to −5 °C and a solution of TFA (1.94 mL, 25.3 mmol) in CH_2Cl_2 (4 mL) was added

dropwise over 15 min. The resulting suspension was stirred at 0 °C for an additional 1 h. Distilled water (10 mL) was added dropwise to the cold, vigorously stirred mixture, followed by dropwise addition of a mixture of distilled water (5 mL) and 28% aqueous NH_4OH solution (5 mL). After 30 min the mixture was poured into a separating funnel containing hexane and EtOAc (20 mL of 1:1 mixture), and water (10 mL). The organic phase was washed with an additional portion of water, followed successively by 1 N KH_2PO_4 (aq), water, and finally brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. After workup, the resulting crude product was purified by column chromatography (in hexane) to afford azido compound **7a** (409.8 mg, 71%) as colorless oil. TLC: R_f = 0.57 (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.82–2.01 (m, 6H, $(CH_2)_3$), 2.21–2.27 (m, 2H, CH_2), 7.26–7.44 (m, 5H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.17, 37.58, 50.82, 126.13, 127.67, 128.51, 146.31.

5.2.4. 1-(1-Azidocyclohexyl)benzene (7b)

Compound **7b** was synthesized from 1-phenylcyclohexanol **6b** in 69% of yield as colorless liquid by following the similar procedure used for synthesis of **7a**. TLC: R_f = 0.82 (hexane/EtOAc = 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.42–1.99 (m, 10H, $(CH_2)_5$), 7.12–7.78 (m, 5H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.37, 25.18, 35.87, 50.82, 66.56, 125.40, 127.10, 127.20, 127.47, 128.58, 128.70, 141.18, 144.29.

5.2.5. 1-Phenylcyclopentylamine (8a)

A solution of 1-phenylcyclopentylazide **7a** (132 mg, 1.42 mmol) in diethyl ether (Et_2O) (1 mL) was added dropwise to a suspension of lithium aluminum hydride (54 mg, 1.42 mmol) in Et_2O (4 mL). The mixture was stirred at room temperature under nitrogen for 3 h, whereupon the reaction was quenched with 1 N NaOH (aq). The reaction mixture was then partitioned between Et_2O (5 mL) and 1 N HCl (aq) (5 mL). The aqueous layer was collected and basified with 28% NH_4OH (aq) and extracted with $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude product **8a** (70.5 mg, 62%) was used directly for next step without further purification. TLC: R_f = 0.19 (hexane/EtOAc = 1:1); ESI-MS m/z 162.10 for $[M+H]^+$.

5.2.6. 1-Phenylcyclohexylamine (8b)

Compound **8b** was synthesized from 1-(1-azidocyclohexyl)benzene **7b** by similar procedure used for synthesis of compound **8a**. Yield: (98.5 mg, 67%); TLC: R_f = 0.21 (hexane/EtOAc = 1:1); ESI-MS m/z 198.1 for $[M+Na]^+$.

5.3. Synthesis of 1-benzyl-4-phenylpiperidin-4-amine (12)

5.3.1. 1-Benzylpiperidin-4-one (9)

To a solution of 4-piperidone (307 mg, 1.99 mmol) in CH_3CN (5 mL), was added K_2CO_3 (690 mg, 4.99 mmol), followed by dropwise addition of benzylbromide (0.28 mL, 2.40 mmol) at room temperature. This was refluxed at 85 °C for 16 h. The reaction mixture was cooled and filtered to isolate the product. The remaining solid was re-suspended in CH_3CN and filtered again. The filtrates were combined and evaporated in vacuo to give yellowish oily product, which was further purified by column chromatography (EtOAc/hexane = 3:7) to give compound **9** (294 mg, 78%) as colorless oil. TLC: R_f = 0.15 (hexane/EtOAc = 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.45 (t, J = 6.3 Hz, 4H, $(CH_2)_2$), 2.75 (t, J = 6.0 Hz, 4H, $(CH_2)_2$), 3.62 (s, 2H, Ar–CH_2), 7.25–7.35 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.30, 52.91, 61.97, 127.31, 128.37, 128.88, 138.14, 209.17; ESI-MS m/z 190 for $[M+H]^+$.

5.3.2. 1-Benzyl-4-phenylpiperidin-4-ol (10)

Compound **10** was synthesized from 1-benzylpiperidin-4-one **9** using phenylmagnesium iodide in 73% (205 mg) yield as a white solid following the procedure used for the synthesis of **6a**–**b**. TLC: R_f = 0.30 (hexane/EtOAc = 6:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.73 (dd, J = 2.6 Hz, 2H), 2.18 (td, J = 12.8 Hz, 2H), 2.50 (td, J = 12.3 Hz, 2H), 2.79 (d, J = 10.7 Hz, 2H), 3.59 (s, 2H), 7.22–7.38 (m, 8H), 7.51 (dd, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 38.35, 49.44, 63.24, 71.30, 124.53, 126.92, 126.99, 128.20, 128.29, 129.20, 138.41, 148.41; ESI-MS m/z 268.1 for $[M+H]^+$.

5.3.3. *N*-(1-Benzyl-4-phenylpiperidin-4-yl)acetamide (11)

To a suspension of 1-benzyl-4-phenylpiperidin-4-ol **10** (105 mg, 0.39 mmol) in CH_3CN (1 mL) at 0 °C was added conc. H_2SO_4 (0.13 mL, 2.46 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred over 19 h, poured onto ice and basified with 20% solution of NaOH (aq). The mixture was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give acetamide **11** (86 mg, 71%) as colorless solid. TLC: R_f = 0.25 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.08–2.17 (m, 2H), 2.24–2.36 (m, 4H), 2.75–2.79 (m, 2H), 3.54 (s, 2H), 5.61 (br s, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.31, 35.60, 49.58, 56.48, 63.14, 125.06, 126.69, 127.10, 128.23, 128.29, 129.09, 138.18, 145.69, 169.09; ESI-MS m/z 309.1 for $[M+H]^+$ and 331.1 for $[M+Na]^+$.

5.3.4. 1-Benzyl-4-phenylpiperidin-4-amine (12)

The *N*-(1-benzyl-4-phenylpiperidin-4-yl)acetamide **11** (86 mg, 0.28 mmol) was taken in 6 N HCl (aq) and refluxed for 10 h. Reaction mixture was cooled, ice cold water was added followed by alkalinization with 3 N NaOH (aq) and then extraction with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude compound **12** (34.91 mg, 47%) was used directly for next step without further purification. TLC: R_f = 0.27 (EtOAc); ESI-MS m/z 267.1 for $[M+H]^+$.

5.4. Experimental data for pentapeptides (13–36)

5.4.1. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylethylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide

*Compound **13**:* The title compound was prepared from (*R*)-(+)-α-methylbenzylamine in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 39%; ^{1}H NMR [270 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.81–0.99 (m, 12H), 1.46 (d, J = 7 Hz, 3H), 1.51–1.70 (m, 3H), 2.19–2.31 (m, 1H), 2.77–2.94 (m, 2H), 3.66–3.72 (m, 1H), 3.90 (d, J = 2.6 Hz, 1H), 3.94–4.04 (m, 1H), 4.22–4.44 (m, 4H), 4.96 (q, J = 7.5 Hz, 1H), 7.13–7.22 (m, 4H), 7.28–7.31 (m, 3H), 7.53 (d, J = 9 Hz, 1H), 7.60–7.70 (m, 2H); TOF-MS (m/z): 776.1 for $[M+Na]^+$.

*Compound **17**:* The title compound was prepared from (*S*)-(−)-α-methylbenzylamine in a manner similar to that described for compound **13**. Yield: 27%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.81–0.94 (m, 12H), 1.42 (d, J = 6.9 Hz, 3H), 1.48–1.59 (m, 3H), 2.18–2.24 (m, 1H), 2.70 (dd, J = 6.9 Hz, 1H), 2.85 (dd, J = 7.8 Hz, 1H), 3.72–3.80 (m, 1H), 3.93 (d, J = 2.4 Hz, 1H), 3.97–4.04 (m, 1H), 4.22–4.37 (m, 4H), 4.95 (q, J = 7.2 Hz, 1H), 7.12–7.21 (m, 4H), 7.28–7.30 (m, 3H), 7.46 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 6.6 Hz, 1H); TOF-MS (m/z): 753.8 for $[M+H]^+$.

5.4.2. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylethylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide

*Compound **14**:* The title compound was prepared from (*R*)-(+)-α-methylbenzylamine in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 48%; ^{1}H NMR [270 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.79–0.96 (m, 6 + 1H), 1.03–1.25 (m, 5H), 1.37–1.45 (m, 3 + 1H), 1.52–1.73 (m, 6H), 2.16–2.30 (m, 1H), 2.71 (dd, *J* = 8.1 Hz, 1H), 2.86–2.94 (m, 1H), 3.79–3.85 (m, 1H), 3.99–4.10 (m, 2H), 4.22–4.31 (m, 2H), 4.34–4.43 (m, 2H), 4.97 (q, *J* = 5.1 Hz, 1H), 7.13–7.22 (m, 4H), 7.24–7.31 (m, 3H), 7.46 (d, *J* = 5.7 Hz, 1H), 7.53–7.60 (m, 1H), 7.65–7.70 (m, 1H); TOF-MS (*m*/*z*): 816.3 for $[M+Na]^+$.

*Compound **18**:* The title compound was prepared from (*S*)-(−)-α-methylbenzylamine in a manner similar to that described for compound **14**. Yield: 51%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.78–0.94 (m, 6 + 1H), 1.06–1.25 (m, 5H), 1.38–1.44 (m, 3 + 1H), 1.52–1.74 (m, 6H), 2.20–2.32 (m, 1H), 2.67–2.76 (m, 1H), 2.85–2.94 (m, 1H), 3.77–3.85 (m, 1H), 3.97–4.00 (m, 1H), 4.11–4.20 (m, 1H), 4.25–4.34 (m, 2H), 4.36–4.44 (m, 2H), 4.98 (q, *J* = 4.5 Hz, 1H), 7.17–7.23 (m, 4H), 7.26–7.29 (m, 3H), 7.43 (d, *J* = 5 Hz, 1H), 7.60–7.67 (m, 2H); TOF-MS (*m*/*z*): 815.9 for $[M+Na]^+$.

5.4.3. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylethylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide

*Compound **15**:* The title compound was prepared from (*R*)-(+)-α-methylbenzylamine in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 61%; ^{1}H NMR [270 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.76 (d, *J* = 5.9 Hz, 3H), 0.78 (d, *J* = 5.9 Hz, 3H), 0.88 (d, *J* = 6.2 Hz, 6H), 1.23–1.36 (m, 3H + 3H), 2.0–2.07 (m, 1H), 2.62 (dd, *J* = 6.5 Hz, 1H), 2.77 (dd, *J* = 5.1 Hz, 1H), 3.64–3.72 (m, 3H), 3.84 (d, *J* = 1.9 Hz, 1H), 4.13–4.32 (m, 3H), 4.86 (q, *J* = 6.7 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 2.7 Hz, 1H), 7.14–7.30 (m, 10H), 7.54 (d, *J* = 8.3 Hz, 1H); TOF-MS (*m*/*z*): 755.9 for $[M+Na]^+$.

*Compound **19**:* The title compound was prepared from (*S*)-(−)-α-methylbenzylamine in a manner similar to that described for compound **15**. Yield: 53%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.77 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 5.1 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H), 1.44 (d, *J* = 5.4 Hz, 3H), 1.47–1.57 (m, 3H), 2.10–2.21 (m, 1H), 2.58 (dd, *J* = 9 Hz, 1H), 3.00 (dd, *J* = 8.4 Hz, 1H), 3.82–3.85 (m, 1H), 3.91–3.95 (m, 1H), 4.03 (d, *J* = 2.4 Hz, 1H), 4.15 (t, *J* = 6.3 Hz, 1H), 4.29–4.33 (m, 2H), 4.43–4.50 (m, 1H), 4.99 (q, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.94 (dd, *J* = 3.3 Hz, 1H), 7.13–7.17 (m, 5H), 7.26–7.28 (m, 2H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.65 (dd, *J* = 8.1 Hz, 2H); TOF-MS (*m*/*z*): 756.2 for $[M+Na]^+$.

5.4.4. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylethylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide

*Compound **16**:* The title compound was prepared from (*R*)-(+)-α-methylbenzylamine in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 35%; ^{1}H NMR [270 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.72–0.95 (m, 8H), 1.06–1.25 (m, 5H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.54–1.66 (m, 6H), 2.12–2.20 (m, 1H), 2.74 (dd, *J* = 8.1 Hz, 1H), 2.95–3.03 (m, 1H), 3.71–3.81 (m, 1H), 3.89–4.05 (m, 2H), 4.16 (t, *J* = 6.1 Hz, 1H), 4.29–4.38 (m, 2H), 4.44–4.47 (m, 1H), 4.98 (q, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.93 (dd, *J* = 2.2 Hz, 1H), 7.15–7.20 (m, 5H), 7.27–7.32 (m, 5H), 7.49 (d, *J* = 7.3 Hz, 1H); TOF-MS (*m*/*z*): 795.7 for $[M+Na]^+$.

*Compound **20**:* The title compound **20** was prepared from (*S*)-(−)-α-methylbenzylamine in a manner similar to that described for compound **16**. Yield: 43%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.71–0.96 (m, 8H), 1.06–1.25 (m, 5H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.48–1.68 (m, 6H), 2.12–2.23 (m, 1H), 2.74 (dd, *J* = 7.2 Hz, 1H), 2.97 (dd, *J* = 8.1 Hz, 1H), 3.83–3.91 (m, 1H), 3.96–4.06 (m, 2H), 4.15 (t, *J* = 6.6 Hz, 1H), 4.27–4.36 (m, 2H), 4.48 (q, *J* = 7.8 Hz, 1H), 4.99 (q, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 9 Hz, 1H), 6.93 (dd, *J* = 1.8 Hz, 1H), 7.12–7.22 (m, 5H), 7.25–7.32 (m, 4H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H); TOF-MS (*m*/*z*): 796.1 for $[M+Na]^+$.

5.4.5. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(2-phenylpropan-2-ylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (21)

Compound **21** was prepared from cumylamine in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 65%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.84–0.95 (m, 12H), 1.06–1.13 (m, 1H), 1.37–1.48 (m, 2H), 1.65 (s, 6H), 2.19–2.29 (m, 1H), 2.74 (dd, *J* = 6.5 Hz, 1H), 2.89 (dd, *J* = 6.5 Hz, 1H), 3.86 (d, *J* = 4.2 Hz, 2H), 4.01–4.10 (m, 1H), 4.26–4.44 (m, 4H), 7.16–7.35 (m, 8H), 7.46 (d, *J* = 10.2 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H); TOF-MS (*m*/*z*): 789.6 for $[M+Na]^+$.

5.4.6. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(2-phenylpropan-2-ylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (22)

Compound **22** was prepared from cumylamine in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 67%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.79–0.94 (m, 6 + 2H), 1.06–1.45 (m, 5H), 1.47–1.75 (m, 6 + 6H), 2.19–2.30 (m, 1H), 2.72–2.79 (m, 1H), 2.87–2.94 (m, 1H), 3.80–3.89 (m, 2H), 4.05–4.14 (m, 1H), 4.26–4.38 (m, 3H), 4.41–4.49 (m, 1H), 7.11–7.41 (m, 11H); TOF-MS (*m*/*z*): 830.1 for $[M+Na]^+$.

5.4.7. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(2-phenylpropan-2-ylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (23)

Compound **23** was prepared from cumylamine in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 57%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.79 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6 Hz, 3H), 0.92–0.97 (m, 6H), 1.35–1.42 (m, 1H), 1.53–1.60 (m, 2H), 1.66 (s, 6H), 2.19–2.29 (m, 1H), 2.71 (dd, *J* = 6.9 Hz, 1H), 2.96 (dd, *J* = 8.1 Hz, 1H), 3.90–3.94 (m, 2H), 4.05–4.13 (m, 1H), 4.20–4.31 (m, 3H), 4.45 (q, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 9 Hz, 1H), 6.90 (dd, *J* = 3.3 Hz, 1H), 7.13–7.19 (m, 7H), 7.25–7.30 (m, 2H), 7.34–7.37 (m, 2H); TOF-MS (*m*/*z*): 770.1 for $[M+Na]^+$.

5.4.8. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(2-phenylpropan-2-ylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (24)

Compound **24** was prepared from cumylamine in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 49%; ^{1}H NMR

[300 MHz, $CDCl_3$ + CD_3OD (9:1)] δ 0.67–0.83 (m, 2H), 0.88–0.90 (m, 6H), 1.01–1.22 (m, 4H), 1.43–1.48 (m, 2H), 1.51–1.63 (m, 5 + 6H), 1.99–2.11 (m, 1H), 2.72 (dd, J = 8.4 Hz, 1H), 3.05 (dd, J = 7.5 Hz, 1H), 3.49 (dd, J = 4.8 Hz, 1H), 3.83 (dd, J = 3.9 Hz, 1H), 3.92–3.95 (m, 2H), 4.11–4.19 (m, 2H), 4.28–4.33 (m, 1H), 6.79 (d, J = 9.3 Hz, 1H), 6.90 (dd, J = 3 Hz, 1H), 7.12–7.19 (m, 5H), 7.21–7.29 (m, 6H); TOF-MS (m/z): 809.8 for $[M+Na]^+$.

5.4.9. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclopentylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (25)

Compound **25** was prepared from amine **8a** in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 35%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.84–0.94 (m, 12H), 1.36–1.44 (m, 1H), 1.55–1.63 (m, 2H), 1.71–1.83 (m, 4H), 1.97–2.03 (m, 2H), 2.21–2.39 (m, 3H), 2.71 (dd, J = 7.2 Hz, 1H), 2.82 (dd, J = 8.1 Hz, 1H), 3.73–3.83 (m, 2H), 3.98–4.07 (m, 1H), 4.23–4.42 (m, 4H), 7.11–7.16 (m, 2H), 7.21–7.26 (m, 6H), 7.34 (d, J = 6.9 Hz, 2H); TOF-MS (m/z): 815.74 for $[M+Na]^+$.

5.4.10. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclopentylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (26)

Compound **26** was prepared from amine **8a** in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 57%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.79–0.94 (m, 6+2H), 1.07–1.18 (m, 3H), 1.25–1.48 (m, 2H), 1.50–1.80 (m, 10H), 1.95–2.09 (m, 2H), 2.22–2.40 (m, 2 + 1H), 2.71 (dd, J = 7.5 Hz, 1H), 2.87 (dd, J = 6.3 Hz, 1H), 3.77–3.87 (m, 2H), 4.04–4.14 (m, 1H), 4.26–4.33 (m, 3H), 4.38–4.46 (m, 1H), 7.11–7.27 (m, 7H), 7.34 (d, J = 4.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H); TOF-MS (m/z): 856.1 for $[M+Na]^+$.

5.4.11. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclopentylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (27)

Compound **27** was prepared from amine **8a** in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 46%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.74 (d, J = 6.6 Hz, 3H), 0.85–0.92 (m, 9H), 1.39–1.53 (m, 4H), 1.75–1.83 (m, 4H), 2.04–2.12 (m, 3H), 2.23–2.29 (m, 2H), 2.67 (dd, J = 9 Hz, 1H), 3.57 (dd, J = 6 Hz, 1H), 3.91–4.00 (m, 3H), 4.04–4.29 (m, 3H), 6.81 (d, J = 9 Hz, 1H), 6.91 (dd, J = 3 Hz, 1H), 7.16–7.34 (m, 11H); TOF-MS (m/z): 796.4 for $[M+Na]^+$.

5.4.12. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclopentylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (28)

Compound **28** was prepared from amine **8a** in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 59%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.91 (d, J = 6.6 Hz, 6H), 1.07–1.26 (m, 6H), 1.43–1.50 (m, 2H), 1.54–1.63 (m, 5H), 1.75–1.82 (m, 4H), 2.05–2.12 (m, 2H), 2.19–2.29 (m, 2H), 2.67 (dd, J = 5.4 Hz, 1H), 3.06 (dd, J = 6.3 Hz, 2H), 3.56 (dd, J = 4.8 Hz, 1H), 3.89–3.99 (m, 2H), 4.16–4.22 (m, 2H), 4.27–4.32 (m, 2H), 6.81 (d, J = 8.7 Hz, 1H), 6.92 (dd, J = 3 Hz, 1H), 7.14–7.33 (m, 11H); TOF-MS (m/z): 836.4 for $[M+Na]^+$.

5.4.13. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclohexylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (29)

Compound **29** was prepared from amine **8b** in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 69%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.83–0.93 (m, 12H), 1.25–1.44 (m, 3H), 1.51–1.80 (m, 8H), 2.2–2.38 (m, 3H), 2.71 (dd, J = 6.9 Hz, 1H), 2.89 (dd, J = 7.5 Hz, 1H), 3.72–3.78 (m, 1H), 3.87 (d, J = 2.1 Hz, 1H), 3.97–4.06 (m, 1H), 4.23–4.42 (m, 4H), 7.12–7.16 (m, 2H), 7.21–7.35 (m, 6H), 7.45 (d, J = 8.7 Hz, 1H); TOF-MS (m/z): 829.4 for $[M+Na]^+$.

5.4.14. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclohexylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (30)

Compound **30** was prepared from amine **8b** in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 50%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.72–1.02 (m, 6 + 3H), 1.04–1.32 (m, 6H), 1.38–1.85 (m, 14H), 2.18–2.40 (m, 3H), 2.70 (dd, J = 7.6 Hz, 1H), 2.90 (dd, J = 4.6 Hz, 1H), 3.72–3.85 (m, 1H), 3.89 (s, 1H), 3.97–4.12 (m, 1H), 4.19–4.5 (m, 2H), 7.15–7.45 (m, 10H); TOF-MS (m/z): 870.4 for $[M+Na]^+$.

5.4.15. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclohexylamino)butan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (31)

Compound **31** was prepared from amine **8b** in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 54%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.76 (d, J = 5.1 Hz, 3H), 0.86–0.92 (m, 9H), 2.28 (d, J = 11.7 Hz, 1H), 1.48–1.55 (m, 6H), 1.64–1.86 (m, 6H), 2.06–2.12 (m, 1H), 2.20 (d, J = 13.2 Hz, 1H), 2.36 (d, J = 13.5 Hz, 1H), 2.67–2.74 (m, 1H), 3.11–3.18 (m, 1H), 3.39–3.40 (m, 1H), 3.77–3.83 (m, 1H), 3.99 (d, J = 3.3 Hz, 1H), 4.13–4.19 (m, 1H), 4.29–4.34 (m, 1H), 6.82 (d, J = 9 Hz, 1H), 6.93 (dd, J = 2.7 Hz, 1H), 7.15–7.34 (m, 11H); TOF-MS (m/z): 809.4 for $[M+Na]^+$.

5.4.16. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-3-cyclohexyl-1-((2*S*,3*R*)-3-hydroxy-4-oxo-1-phenyl-4-(1-phenylcyclohexylamino)butan-2-ylamino)-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (32)

Compound **32** was prepared from amine **8b** in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 41%; ^1H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.73–0.93 (m, 6H), 1.05–1.25 (m, 6H), 1.40–1.83 (m, 17H), 2.12–2.18 (m, 1H), 2.26 (d, J = 13.5 Hz, 1H), 2.37 (d, J = 11.7 Hz, 1H), 2.66–2.73 (m, 1H), 3.03–3.10 (m, 1H), 3.69–3.74 (m, 1H), 3.98 (d, J = 2.7 Hz, 1H), 4.14 (t, J = 12.6 Hz, 1H), 4.22–4.37 (m, 2H), 6.78 (d, J = 9 Hz, 1H), 6.91 (dd, J = 2.4 Hz, 1H), 7.11–7.49 (m, 10H), 7.64 (d, J = 7.2 Hz, 1H); TOF-MS (m/z): 849.8 for $[M+Na]^+$.

5.4.17. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-4-(1-benzyl-4-phenylpiperidin-4-ylamino)-3-hydroxy-4-oxo-1-phenylbutan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (33)

Compound **33** was prepared from amine **12** in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and

finally 5-fluoroorotic acid. Yield: 44%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.79 (d, J = 5.7 Hz, 3H), 0.86 (d, J = 5.6 Hz, 3H), 0.91–0.96 (m, 8H), 1.19–1.39 (m, 4H), 1.45–1.51 (m, 2H), 2.02–2.09 (m, 2H), 2.64–2.89 (m, 4H), 3.57–3.75 (m, 3H), 3.87–3.90 (m, 1H), 4.13–4.44 (m, 5H), 7.10–7.29 (m, 10H), 7.31–7.38 (m, 5H); TOF-MS (m/z): 898.4 for $[M+H]^+$.

5.4.18. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-4-(1-benzyl-4-phenylpiperidin-4-ylamino)-3-hydroxy-4-oxo-1-phenylbutan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-5-fluoro-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (34)

Compound **34** was prepared from amine **12** in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 5-fluoroorotic acid. Yield: 74%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.71–0.92 (m, 2H), 0.98 (d, J = 7.3 Hz, 6H), 1.06–1.43 (m, 8H), 1.51–1.66 (m, 8H), 2.13–2.37 (m, 3H), 2.75–2.88 (m, 2H), 3.22 (d, J = 11.7 Hz, 2H), 3.34–3.38 (m, 1H), 3.97–4.13 (m, 2 + 2H), 4.32–4.43 (m, 2H), 4.51–4.61 (m, 1H), 7.13–7.31 (m, 10H), 7.39–7.41 (m, 3H), 7.59–7.62 (m, 2H); TOF-MS (m/z): 939.4 for $[M+H]^+$.

5.4.19. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-4-(1-benzyl-4-phenylpiperidin-4-ylamino)-3-hydroxy-4-oxo-1-phenylbutan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (35)

Compound **35** was prepared from amine **12** in following order: Boc–Pns–OH, Boc–Leu–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 35%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.79 (d, J = 6 Hz, 3H), 0.87 (d, J = 6 Hz, 3H), 0.95–0.98 (m, 6H), 1.25–1.33 (m, 1H), 1.41–1.50 (m, 2H), 2.09–2.15 (m, 1H), 2.21–2.28 (m, 2H), 2.79–2.91 (m, 4H), 3.12–3.35 (m, 4H), 4.02–4.03 (m, 2H), 4.09 (s, 2H), 4.31–4.36 (m, 2H), 4.41–4.50 (m, 2H), 4.62–4.64 (m, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.96 (dd, J = 2.4 Hz, 1H), 7.12–7.34 (m, 14H), 7.55–7.61 (m, 2H); TOF-MS (m/z): 878.7 for $[M+H]^+$.

5.4.20. *N*-((*S*)-2-Amino-3-((*S*)-1-((*S*)-1-((2*S*,3*R*)-4-(1-benzyl-4-phenylpiperidin-4-ylamino)-3-hydroxy-4-oxo-1-phenylbutan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)-3-oxopropyl)-2,5-dihydroxybenzamide (36)

Compound **36** was prepared from amine **12** in following order: Boc–Pns–OH, Boc–Cha–OH, Boc–Val–OH, Boc–DAP(Fmoc)–OH, and finally 2,5-dihydroxybenzoic acid. Yield: 67%; ^{1}H NMR [300 MHz, $CDCl_3$ + DMSO (9:1)] δ 0.74–0.97 (m, 9H), 1.04–1.15 (m, 5H), 1.26–1.44 (m, 3H), 1.48–1.64 (m, 6H), 2.02–2.16 (m, 2H), 2.2–2.3 (m, 1H), 2.65 (d, J = 12 Hz, 1H), 2.77–2.93 (m, 3H), 3.29–3.42 (m, 3H), 3.63–3.77 (m, 1H), 3.92 (d, J = 6.6 Hz, 1H), 4.10 (bs, 1H), 4.18 (d, J = 5.7 Hz, 1H), 4.30–4.38 (m, 1H), 4.47–4.52 (m, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.95 (dd, J = 2.7 Hz, 1H), 7.15–7.51 (m, 16H); TOF-MS (m/z): 918.7 for $[M+H]^+$.

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Supplementary data

Supplementary data (general experimental procedures, MALDI-TOF mass and HPLC profiles of compounds **13**–**36**, the docking study, and assay protocol) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.07.002.

References and notes

1. Nguyen, J.; Yamani, A.; Kiso, Y. *Curr. Pharm. Des.* **2006**, *12*, 4295.
2. Zimmermann, M.; Gardoni, F.; Di Luca, M. *Drugs Aging* **2005**, *22*, 27.
3. Citron, M. *Nat. Rev. Neurosci.* **2004**, *5*, 677.
4. Roberson, E. D.; Mucke, L. *Science* **2006**, *314*, 781.
5. Goedert, M.; Spillantini, M. G. *Science* **2006**, *314*, 777.
6. Selkoe, D. J. *Physiol. Rev.* **2001**, *81*, 741.
7. Sinha, S.; Lieberburg, I. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11049.
8. Vassar, R. *J. Mol. Neurosci.* **2004**, *23*, 105.
9. Cole, S. L.; Vassar, R. *Mol. Neurodegeneration* **2007**, *2*, 22.
10. Lundkvist, J.; Naslund, J. *Curr. Opin. Pharmacol.* **2007**, *7*, 112.
11. Johnstone, J. A.; Liu, W. W.; Todd, S. A.; Coulson, D. T. R.; Murphy, S.; Irvine, G. B.; Passmore, A. P. *Biochem. Soc. Trans.* **2005**, *33*, 1096.
12. Willem, M.; Garratt, A. N.; Novak, B.; Citron, M.; Kaufmann, S.; Rittger, A.; DeStrooper, B.; Saftig, P.; Birchmeier, C.; Haass, C. *Science* **2006**, *314*, 664.
13. Nishitomi, K.; Sakaguchi, G.; Horikoshi, Y.; Gray, A. J.; Maeda, M.; Hirata-Fukae, C.; Becker, A. G.; Hosono, M.; Sakaguchi, I.; Minami, S. S.; Nakajima, Y.; Li, H.-F.; Takeyama, C.; Kihara, T.; Ota, A.; Wong, P. C.; Aisen, P. S.; Kato, A.; Kinoshita, N.; Matsuoka, Y. *Neurochemistry* **2006**, *99*, 1555.
14. Roberds, S. L.; Anderson, J.; Basi, G.; Bienkowski, M. J.; Branstetter, D. G.; Chen, K. S.; Freedman, S.; Frigon, N. L.; Games, D.; Hu, K.; Johnson-Wood, K.; Kappenman, K. E.; Kawabe, T.; Kola, I.; Kuehn, R.; Lee, M.; Liu, W.; Motter, R.; Nichols, N. F.; Power, M.; Robertson, D. W.; Schenk, D.; Schoor, M.; Shopp, G. M.; Shuck, M. E.; Sihna, S.; Svensson, K. A.; Tatsuno, G.; Tintrup, H.; Wijsman, J.; Wright, S.; McConlogue, L. *Hum. Mol. Genet.* **2001**, *10*, 1317.
15. Luo, Y.; Bolon, B.; Damore, M. A.; Fitzpatrick, D.; Liu, H.; Zhang, J.; Yan, Q.; Vassar, R.; Citron, M. *Neurobiol. Dis.* **2003**, *14*, 81.
16. Ohno, M.; Sametsky, E. A.; Younkin, L. H.; Oakley, H.; Younkin, S. G.; Citron, M.; Vassar, R.; Disterhoft, J. F. *Neuron* **2004**, *41*, 27.
17. John, V.; Beck, J. P.; Bienkowski, M. J.; Sinha, S.; Heinrikson, R. L. *J. Med. Chem.* **2003**, *46*, 4625.
18. McConlogue, L.; Buttini, M.; Anderson, J. P.; Brigham, E. F.; Chen, K. S.; Freedman, S. B.; Games, D.; Johnson-Wood, K.; Lee, M.; Zeller, M.; Liu, W.; Motter, R.; Sinha, S. *J. Biol. Chem.* **2007**, *282*, 26326.
19. Kimura, T.; Shuto, D.; Kasai, S.; Liu, P.; Hidaka, K.; Hamada, T.; Hayashi, Y.; Hattori, C.; Asai, M.; Kitazume, S.; Saido, T. C.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1527.
20. Shuto, D.; Kasai, S.; Kimura, T.; Liu, P.; Hidaka, K.; Hamada, T.; Shibakawa, S.; Hayashi, Y.; Hattori, C.; Szabo, B.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4273.
21. Ghosh, A. K.; Shin, D.; Downs, D.; Koelsch, G.; Lin, X.; Ermolieff, J.; Tang, J. *J. Am. Chem. Soc.* **2000**, *122*, 3522.
22. Pardridge, W. M. *Mol. Interv.* **2003**, *3*, 90.
23. Kimura, T.; Shuto, D.; Hamada, Y.; Igawa, N.; Kasai, S.; Liu, P.; Hidaka, K.; Hamada, T.; Hayashi, Y.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 211.
24. Hamada, Y.; Igawa, N.; Ikari, H.; Ziora, Z.; Nguyen, J.-T.; Yamani, A.; Hidaka, K.; Kimura, T.; Saito, K.; Hayashi, Y.; Ebina, M.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2006**, *43*, 4354.
25. Tagad, H. D.; Hamada, Y.; Nguyen, J.-T.; Hamada, T.; Abdel-Rahman, H.; Yamani, A.; Nagamine, A.; Ikari, H.; Igawa, N.; Hidaka, K.; Sohma, Y.; Kimura, T.; Kiso, Y. *Bioorg. Med. Chem.* **2010**, *18*, 3175.
26. Sealy, J. M.; Truong, A. P.; Tso, L.; Probst, G. D.; Aquino, J.; Hom, R. K.; Jagodzinska, B. M.; Dressen, D.; Wone, D. W. G.; Brogley, L.; John, V.; Tung, J. S.; Pleiss, M. A.; Tucker, J. A.; Konradi, A. W.; Dappen, M. S.; Toth, G.; Pan, H.; Ruslim, L.; Miller, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6386.
27. Lerchner, A.; Machauer, R.; Betschart, C.; Veenstra, S.; Rueeger, H.; McCarthy, C.; Tintelnot-Blomley, M.; Jaton, A. L.; Rabe, S.; Desrayaud, S.; Enz, A.; Staufenbiel, M.; Paganetti, P.; Rondeau, J. M.; Neumann, U. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 603.
28. Hanessian, S.; Shao, Z.; Betschart, C.; Rondeau, J. M.; Neumann, U.; Tintelnot-Blomley, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1924.
29. Kortum, S. W.; Benson, T. E.; Bienkowski, M. J.; Emmons, T. L.; Prince, D. B.; Paddock, D. J.; Tomasselli, A. G.; Moon, J. B.; LaBordea, A.; TenBrink, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3378.
30. Theerthagirl, P.; Lalitha, A.; Arunachalam, P. N. *Tetrahedron Lett.* **2010**, *51*, 2813. and references therein.
31. Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.
32. Nitta, A.; Fujii, H.; Sakami, S.; Nishimura, Y.; Ohyama, T.; Satoh, M.; Nakaki, J.; Satoh, S.; Inada, C.; Kozono, H.; Kumagai, H.; Shimamura, M.; Fukazawa, T.; Kawai, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5435.
33. Cumming, J.; Babu, S.; Huang, Y.; Carrol, C.; Chen, X.; Favreau, L.; Greenlee, W.; Guo, T.; Kennedy, M.; Kuvelkar, R.; Le, T.; Li, G.; McHugh, N.; Orth, P.; Ozgur, L.; Parker, E.; Saionz, K.; Stamford, A.; Strickland, C.; Tadesse, D.; Voigt, J.; Zhang, L.; Zhang, Q. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2837.