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STUDIES TOWARD IDENTIFYING THE PHARMACOPHORE OF L-755,807 FOR AMYLOID-β AGGREGATION INHIBITORY ACTIVITY

Kenichi Kobayashi,* Kosaku Tanaka III, Yusuke Honma, Momoko Suzuki, and Hiroshi Kogen*

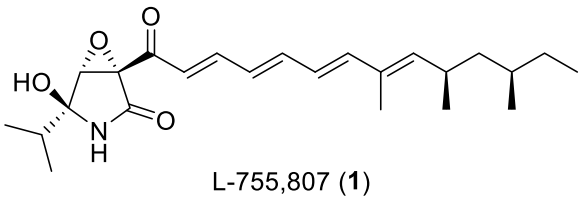
Graduate School of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

Abstract – To investigate the structure–activity relationship of L-755,807 for amyloid-β aggregation inhibitory activity, L-755,807 analogs were synthesized and biologically evaluated. The results suggest that a hydrophobic conjugated carbon chain with a terminal hydrophilic functional group is essential for the potent activity. These findings provide a starting point for identifying the pharmacophore of L-755,807.

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, and the World Health Organization has reported that AD accounts for 60-70% of the 50 million cases of dementia worldwide.[1] For pathogenesis of AD, the amyloid cascade hypothesis[2] and the more recent amyloid-β (Aβ) oligomer hypothesis[3-5] have been widely supported, in which aberrant aggregation and accumulation of Aβ protein are considered critical. In addition, Aβ protein is known to be released from amyloid precursor protein (APP) via the action of β- and γ-secretases.[6] Therefore, potential treatment strategies for AD include inhibition of Aβ aggregation and these two secretases. Drug discovery research targeting Aβ should be greatly accelerated in the future, because Biogen and Eisai very recently released the high-impact news that they will submit a new drug application for aducanumab for the treatment of AD.[7]

Our ongoing research project for dementia drug resource development[8] focuses on the discovery of inhibitors of these pathogenic mechanisms in AD, and we have reported that L-755,807 (**1**, Figure 1) has potent Aβ aggregation inhibitory activity. L-755,807 (**1**), isolated from the endophytic fungus *Microsphaeropsis* sp., was originally identified as a bradykinin B2 receptor antagonist with an IC_{50} of 71 μM.[9] Two decades after it was first isolated, our research group achieved the first total synthesis of L-755,807, and this synthesis resulted in revisions of the originally proposed structure of the natural product.[10,11] Additionally, biological evaluations of synthetic L-755,807 revealed its Aβ aggregation inhibitory activity with an IC_{50} of 21 μM. This activity is sufficiently potent to make L-755,807 a

promising seed compound for therapeutic agents against AD.[12,13]



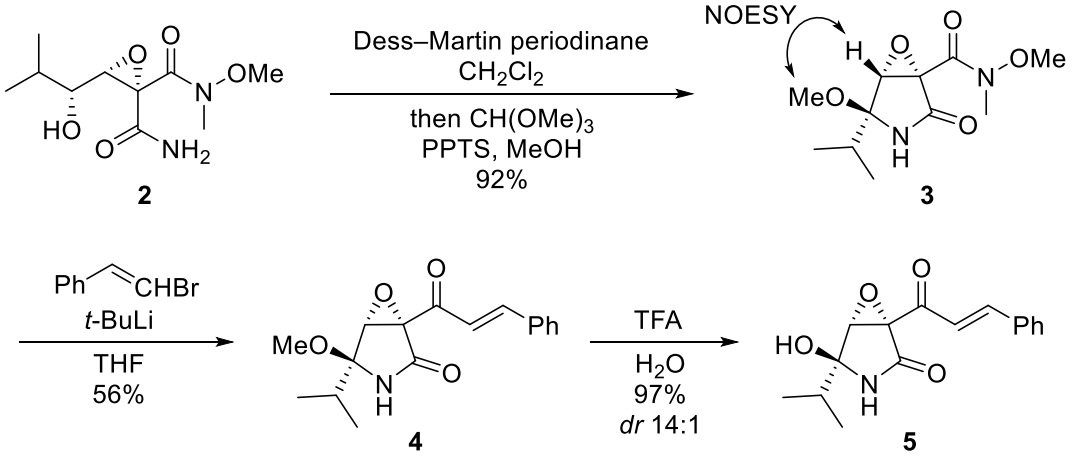
L-755,807 (**1**)

Figure 1. Structure of L-755,807 (**1**)

Toward identifying the pharmacophore of L-755,807, this paper reports the synthesis and structure–activity relationship (SAR) studies of L-755,807 analogs.

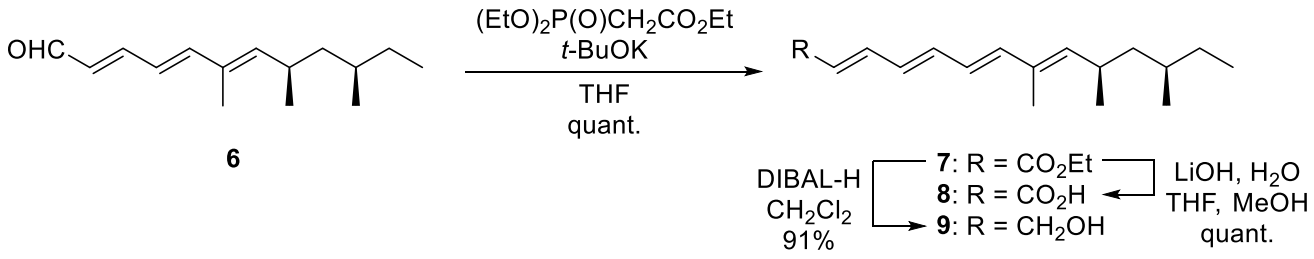
L-755,807 consists of an epoxy-γ-lactam ring and a conjugated tetraene side chain. Thus, we decided to prepare and biologically evaluate analogs with modification of each part of the molecule.

For the epoxy-γ-lactam analogs, aminal **4** and hemiaminal **5** were prepared as depicted in Scheme 1. The synthetic intermediate **2** for L-755,807[10-13] was oxidized with Dess–Martin periodinane to afford a hemiaminal via spontaneous cyclization, which was found to be difficult to extract after a standard aqueous workup because of its water solubility. Next, we carried out Dess–Martin oxidation and aminal formation via a one-pot operation and obtained the desired Weinreb amide **3** as a single diasteromer in 92% yield. The stereochemistry of the aminal portion in **3** was deduced from the observed NOESY correlation shown in Scheme 1. Nucleophilic addition of lithiated styrene prepared from β-bromostyrene (a 1:5 mixture of *cis*- and *trans*-isomers) and *t*-BuLi to Weinreb amide **3** afforded the desired *E*-configured enone **4** in 56% yield.[14] Aminal **4** was then hydrolyzed with 50% aqueous trifluoroacetic acid (TFA) to produce hemiaminal **5** in 97% yield as a 14:1 diastereomeric mixture.[15]



Scheme 1. Synthesis of epoxy-γ-lactam analogs **4** and **5**

We next turned our attention to the preparation of the side-chain analogs (Scheme 2). The known triene aldehyde **6**[10-13] was subjected to Horner–Wadsworth–Emmons reaction to give tetraene ester **7** in quantitative yield. From ester **7**, two analogs **8** and **9** were synthesized. Thus, ester **7** was hydrolyzed by treatment with aqueous LiOH in THF/MeOH to furnish tetraene acid **8** in quantitative yield, and reduction of **7** with DIBAL-H afforded tetraene alcohol **9** in 91% yield.



Scheme 2. Synthesis of the side-chain analogs **7**-**9**

Having synthesized two epoxy-δ-lactam analogs and three side-chain anologs of L-755,807 **4**, **5** and **7**-**9**, we next biologically evaluated their Aβ aggregation inhibitory activity[16,17] and obtained intriguing results (Table 1). The epoxy-γ-lactam analogs **4** and **5** without a long side-chain showed considerably reduced inhibitory activity compared with L-755,807, irrespective of the aminal or hemiaminal structure. Notably, ester **7** was found to be almost completely inactive, whereas carboxylic acid **8** had an IC_{50} value similar to that of L-755,807. To our surprise, tetraene alcohol **9** (IC_{50} = 7.1 μM) was about three times as potent as L-755,807.

Table 1. Aβ aggregation inhibitory activity of the synthetic compounds

Compound	Aβ aggregation inhibitory activity (IC_{50})
1 (L-755,807)	21 μM
4	601 μM
5	448 μM
7	>1000 μM
8	30 μM
9	7.1 μM
Myricetin[a]	4.1 μM

[a]Myricetin was used as a positive control.

These results suggest that a planar long carbon chain bearing a terminal hydrophilic functional group such as carboxyl, hydroxy, or hemiaminal group is crucial for potent inhibitory activity. A literature search

revealed structures moderately similar to our active synthetic compounds in some recent related works,[18-24] indicating that these structural features can serve as a helpful guide for designing other molecules based on L-755,807 for anti-Alzheimer's drug discovery.

In conclusion, we synthesized and biologically evaluated two epoxy-γ-lactam analogs and three side-chain analogs of L-755,807 and discovered that the combination of a planar carbon chain and a hydrophilic functional group is highly important for potent inhibitory activity against Aβ aggregation. These preliminary results provide a starting point for developing novel anti-Alzheimer's drugs based on the Aβ aggregation inhibitory activity of L-755,807. Further SAR studies are currently under way in our laboratory to identify the pharmacophore of L-755,807, and the results will be disclosed in due course.

EXPERIMENTAL

General: ^{1}H NMR spectra were recorded on a JEOL JNM-AL300 (300 MHz) or JEOL JNM-ECS400 (400 MHz) instrument. Chemical shifts are expressed in ppm relative to tetramethylsilane (δ = 0) as an internal standard ($CDCl_3$ solution). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sep, septet; m, multiplet; br, broad peak. ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 (100 MHz) or JEOL JNM-ECA500 (125 MHz) instrument. The chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. Infrared (IR) spectra were measured on a JASCO VALOR-III spectrometer and are reported in wavenumbers (cm^{-1}). Both low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained using a JEOL JMS 700 instrument (EI or FAB mode) with a direct inlet system. Optical rotations were measured with a JASCO P-2200 polarimeter using a cell with an optical path length of 100 mm. Column chromatography was performed on silica gel (40–100 mesh). Analytical thin-layer chromatography was performed using 0.25 mm silica gel 60 F plates.

(1*S*,4*S*,5*R*)-*N*,4-Dimethoxy-*N*-methyl-2-oxo-4-(propan-2-yl)-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxamide (3)

To a stirred solution of **2** (31.5 mg, 0.128 mmol)[10-13] in CH_2Cl_2 (2.5 mL) was added Dess–Martin periodinane (84.8 mg, 0.200 mmol) at room temperature, and the mixture was stirred for 1 h. After addition of MeOH (2.5 mL), CH_2Cl_2 was removed by heat at 75 °C with stirring. Then, $CH(OMe)_3$ (0.24 mL, 2.2 mmol) and pyridinium *p*-toluenesulfonate (32.7 mg, 0.130 mmol) were added, and the resultant mixture was refluxed for 16 h. The reaction was quenched by addition of Et_3N (0.08 mL, 0.6 mmol), and the mixture was concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 1:2) to afford **3** (30.5 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, d, *J* = 7.0 Hz), 1.09 (3H, d, *J* = 7.0 Hz), 2.11 (1H, dsep, *J* = 2.6, 7.0 Hz), 3.28 (3H, s), 3.34 (3H,

s), 3.78 (3H, s), 3.99 (1H, d, *J* = 2.6 Hz), 5.61 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 17.3, 32.3, 33.2, 50.1, 59.9, 61.3, 62.0, 90.6, 160.7, 168.6; IR ($CHCl_3$) 3267, 2972, 2943, 1720, 1672, 1460, 1427, 1389, 1097, 1065, 942 cm^{-1}; $[\alpha]_D^{24}$ –41.1 (*c* 0.61, $CHCl_3$); HRMS (FAB+) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{19}N_2O_5$ 259.1294; Found 259.1293.

(1*R*,4*S*,5*R*)-1-Cinnamoyl-4-isopropyl-4-methoxy-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (4)

To a stirred solution of β-bromostyrene (121 mg, 0.661 mmol) in THF (3.3 mL) was added dropwise *t*-BuLi (1.65 M solution in *n*-pentane, 0.66 mL, 1.1 mmol) at –78 °C. After stirring for 15 min, **3** (28.2 mg, 0.109 mmol) in THF (1.8 mL) was slowly added, and the resultant mixture was stirred for 15 min. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with Et_2O. The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 3:1) to afford **4** (18.5 mg, 56%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.8 Hz), 1.12 (3H, d, *J* = 6.8 Hz), 2.12 (1H, sep, *J* = 6.8 Hz), 3.28 (3H, s), 4.03 (1H, d, *J* = 2.8 Hz), 6.27 (1H, br s), 7.09 (1H, d, *J* = 16.0 Hz), 7.37-7.49 (3H, m), 7.57-7.65 (2H, m), 7.88 (1H, d, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 17.4, 33.3, 49.8, 61.3, 63.0, 90.3, 119.9, 129.02 (2C), 129.05 (2C), 131.5, 134.0, 146.6, 168.8, 188.3; IR ($CHCl_3$) 3236, 2969, 1727, 1606, 1401, 1335, 1072, 983, 761 cm^{-1}; $[\alpha]_D^{25}$ –67.0 (*c* 1.2, $CHCl_3$); HRMS (FAB+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_4$ 302.1392; Found 302.1395.

(1*R*,4*S*,5*R*)-1-Cinnamoyl-4-hydroxy-4-isopropyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (5)

Aminal **4** (7.7 mg, 0.026 mmol) was dissolved in 50% aqueous TFA (0.42 mL), and the resultant mixture was stirred at room temperature for 45 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 2:1) to afford **5** (7.1 mg, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, d, *J* = 6.9 Hz), 1.21 (3H, d, *J* = 6.9 Hz), 2.11 (1H, sep, *J* = 6.9 Hz), 4.43 (1H, d, *J* = 2.4 Hz), 4.78 (1H, br s), 6.87 (1H, d, *J* = 15.9 Hz), 7.20-7.41 (5H, m), 7.52 (1H, d, *J* = 15.9 Hz), 8.54 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 17.8, 33.5, 60.7, 65.6, 87.5, 118.6, 129.0, 131.2 (4C), 133.9, 146.1, 169.7, 189.9; IR ($CHCl_3$) 3461, 3235, 2968, 1732, 1606, 1403, 1336, 1029, 763 cm^{-1}; $[\alpha]_D^{25}$ –130.5 (*c* 0.47, $CHCl_3$); HRMS (FAB+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_4$ 288.1236; Found 288.1244.

Ethyl (2*E*,4*E*,6*E*,8*E*,10*R*,12*R*)-8,10,12-trimethyltetradeca-2,4,6,8-tetraenoate (7)

To a stirred solution of triethyl phosphonoacetate (55 mg, 0.25 mmol) in THF (1 mL) was added *t*-BuOK

(1.0 M solution in THF, 0.18 mL, 0.18 mmol) at 0 °C. After stirring for 30 min, a solution of aldehyde **6** (27 mg, 0.12 mmol)[10-13] in THF (0.5 mL) was added dropwise. After stirring for 1.5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 20:1) to afford **7** (36 mg, quant.) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 6.0 Hz), 0.84 (3H, t, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 1.04-1.18 (2H, m), 1.20-1.34 (3H, m), 1.29 (3H, t, *J* = 7.2 Hz), 1.79 (3H, s,), 2.55-2.68 (1H, m), 4.20 (2H, q, *J* = 7.2 Hz), 5.37 (1H, d, *J* = 9.6 Hz), 5.84 (1H, d, *J* = 14.8 Hz), 6.22 (1H, dd, *J* = 10.8, 14.8 Hz), 6.31 (1H, dd, *J* = 11.2, 14.8 Hz), 6.42 (1H, d, *J* = 15.2 Hz), 6.60 (1H, dd, *J* = 10.8, 14.8 Hz), 7.33 (1H, dd, *J* = 11.2, 15.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 12.4, 14.3, 19.1, 21.4, 30.1, 30.6, 32.3, 44.8, 60.2, 119.7, 125.4, 128.6, 132.3, 141.7, 142.7, 143.7, 144.8, 167.3; IR ($CHCl_3$) 2959, 1711, 1624, 1596, 1257, 1131, 1002 cm^{-1}; $[\alpha]_D^{29}$ –52.0 (*c* 0.91, $CHCl_3$); HRMS (EI+) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{30}O_2$ 290.2246; Found 290.2247.

(2*E*,4*E*,6*E*,8*E*,10*R*,12*R*)-8,10,12-Trimethyltetradeca-2,4,6,8-tetraenoic acid (8)

To a stirred solution of ester **7** (12 mg, 0.040 mmol) in a mixed solvent (THF/MeOH/H_2O 4:1:1, 1.8 mL) was added $LiOH·H_2O$ (20 mg, 0.48 mmol) at room temperature. After stirring for 15 h, the reaction mixture was diluted with Et_2O. The reaction was then quenched by addition of 1 M aqueous HCl, and the mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 1:1) to afford **8** (11 mg, quant.) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, *J* = 6.0 Hz), 0.84 (3H, t, *J* = 7.2 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 1.06-1.18 (2H, m), 1.21-1.34 (3H, m), 1.80 (3H, d, *J* = 0.8 Hz), 2.56-2.68 (1H, m), 5.40 (1H, d, *J* = 10.0 Hz), 5.84 (1H, d, *J* = 15.2 Hz), 6.23 (1H, dd, *J* = 11.2, 15.2 Hz), 6.34 (1H, dd, *J* = 11.2, 14.8 Hz), 6.45 (1H, d, *J* = 14.8 Hz), 6.65 (1H, dd, *J* = 11.2, 15.2 Hz), 7.42 (1H, dd, *J* = 11.2, 14.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 12.4, 19.1, 21.4, 30.1, 30.7, 32.3, 44.7, 118.5, 125.3, 128.4, 132.3, 142.9, 143.5, 144.2, 147.2, 172.3; IR ($CHCl_3$) 2960, 2924, 1683, 1593, 1418, 1270, 1143, 1003 cm^{-1}; $[\alpha]_D^{24}$ –26.3 (*c* 0.65, $CHCl_3$); HRMS (FAB+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{26}O_2$ 262.1933; Found 262.1931.

(2*E*,4*E*,6*E*,8*E*,10*R*,12*R*)-8,10,12-Trimethyltetradeca-2,4,6,8-tetraen-1-ol (9)

To a stirred solution of ester **7** (17 mg, 0.059 mmol) in CH_2Cl_2 (3 mL) was added dropwise DIBAL-H (1.0 M solution in *n*-hexane, 0.18 mL, 0.18 mmol) at –78 °C. After stirring for 2 h, the reaction mixture was quenched by addition of MeOH and saturated aqueous Rochelle salt, and vigorously stirred for 1 h. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over

Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 4:1) to afford alcohol **9** (13 mg, 91%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 6.0 Hz), 0.84 (3H, t, *J* = 7.6 Hz), 0.94 (3H, d, *J* = 6.4 Hz), 1.01-1.17 (2H, m), 1.20-1.33 (3H, m), 1.78 (3H, s), 2.53-2.65 (1H, m), 4.20 (2H, t, *J* = 6.0 Hz), 5.27 (1H, d, *J* = 9.6 Hz), 5.82 (1H, td, *J* = 6.0, 15.2 Hz), 6.13-6.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 12.5, 19.1, 21.5, 30.1, 30.5, 32.3, 44.9, 63.6, 126.0, 130.5, 131.0, 132.1, 132.3, 134.2, 138.9, 141.3; IR ($CHCl_3$) 3409, 2960, 1461, 1379, 991 cm^{-1}; $[\alpha]_D^{24}$ –15.5 (*c* 0.95, $CHCl_3$).

Biological assay against Aβ aggregation

The aggregation of Aβ was evaluated using the thioflavin-T (Th-T) method developed by Naiki and co-workers, with slight modification.[16,17] Briefly, $A\beta_{40}$ (Peptide Institute, Osaka, Japan) was dissolved to a concentration of 250 μM in 0.02% NH_4OH. The sample solution (10 μL) was diluted with 80 μL of 50 mM sodium phosphate containing 100 mM NaCl at pH 7.4, followed by addition of the peptide solution (10 μL). All procedures were performed on ice. The mixture (containing 25 μM of $A\beta_{40}$ and the test sample in phosphate buffer solution) was incubated at 37 °C for 24 h and then diluted with 300 μL of 5 μM Th-T (Wako Pure Chemical Industries, Ltd., Osaka, Japan) in 50 mM Gly–NaOH buffer (pH 8.5). The solution was transferred to black-bottomed 96-well plates (100 μL per well) and then gently vortexed for 30 min. The fluorescence intensity was measured at excitation and emission wavelengths of 440 nm and 485 nm, respectively, using a Synergy HTX Multi-Mode Reader (BioTek, Winooski, VT). The aggregation of $A\beta_{40}$ was calculated by comparing the fluorescence intensity of each sample to that of a control (25 μM $A\beta_{40}$ in DMSO containing no test sample).

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REFERENCES AND NOTES

1. World Health Organization. “Dementia”: <https://www.who.int/news-room/fact-sheets/detail/dementia>, cited 19 September, 2019.
2. J. Hardy and D. J. Selkoe, *Science*, 2002, **297**, 353.
3. C. Haass and D. J. Selkoe, *Nat. Rev. Mol. Cell Biol.*, 2007, **8**, 101.

4. K. Ono and M. Yamada, *J. Neurochem.*, 2011, **117**, 19.
5. K. L. Viola and W. L. Klein, *Acta Neuropathol.*, 2015, **129**, 183.
6. B. De Strooper, R. Vassar, and T. Golde, *Nat. Rev. Neurol.*, 2010, **6**, 99.
7. Eisai Co., Ltd. "Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based on New Analysis of Larger Dataset from Phase 3 Studies": <https://www.eisai.com/news/2019/news201979.html>, cited 22 October, 2019.
8. Dementia Drug Resource Development Center Project (DRC), MEXT, Japan (S1511016).
9. Y.-K. T. Lam, O. D. Hensens, R. Ransom, R. A. Giacobbe, J. Polishook, and D. Zink, *Tetrahedron*, 1996, **52**, 1481.
10. K. Tanaka III, K. Kobayashi, and H. Kogen, *Org. Lett.*, 2016, **18**, 1920.
11. K. Tanaka III, K. Kobayashi, K. Takatori, and H. Kogen, *Tetrahedron*, 2017, **73**, 2062.
12. K. Tanaka III, Y. Honma, C. Yamaguchi, L. Aoki, M. Saito, M. Suzuki, K. Arahata, K. Kinoshita, K. Koyama, K. Kobayashi, and H. Kogen, *Tetrahedron*, 2019, **75** 1075.
13. K. Tanaka III, K. Kobayashi, and H. Kogen, *J. Synth. Org. Chem. Jpn.*, 2019, **77**, 673.
14. H. Neumann and D. Seebach, *Tetrahedron Lett.*, 1976, **52**, 4839.
15. The stereostructure of the hemiaminal moiety in compound **5** was deduced by comparison of ^{1}H NMR spectra of **5** and L-755,807. The methine proton in the lactam ring of **5** had a chemical shift similar to that of L-755,807.
16. H. Naiki and F. Gejyo, *Methods Enzymol.*, 1999, **309**, 305.
17. M. Hirohata, K. Ono, H. Naiki, and M. Yamada, *Neuropharmacology*, 2005, **49**, 1088.
18. S. Brahmachari, A. Paul, D. Segal, and E. Gazit, *Future Med. Chem.*, 2017, **9**, 797.
19. T. Puksasook, S. Kimura, S. Tadtong, J. Jiaranaikulwanitch, J. Pratuangdejkul, W. Kitphati, K. Suwanborirux, N. Saito, and V. Nukoolkarn, *J. Nat. Med.*, 2017, **71**, 665.
20. F. Abedinifar, S. M. F. Farnia, M. Mahdavi, H. Nadri, A. Moradi, J. B. Ghasemi, T. T. Küçükkılınç, L. Firoozpour, and A. Foroumadi, *Bioorg. Chem.*, 2018, **80**, 180.
21. R. Xu, G. Xiao, Y. Li, H. Liu, Q. Song, X. Zhang, Z. Yang, Y. Zheng, Z. Tan, and Y. Deng, *Bioorg. Med. Chem.*, 2018, **26**, 1885.
22. S. D. Sukumaran, F. L. Faraj, V. S. Lee, R. Othman, and M. J. C. Buckle, *RSC Adv.*, 2018, **8**, 7818.
23. N. Sirimangkalakittia, L. D. Juliawaty, E. H. Hakim, I. Waliana, N. Saito, K. Koyama, and K. Kinoshita, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1994.
24. L. Cong, X. Dong, Y. Wang, Y. Deng, B. Li, and R. Dai, *Eur. J. Med. Chem.*, 2019, **166**, 11.