Bioorganic & Medicinal Chemistry Letters 22 (2012) 4640–4644

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel BACE1 inhibitors possessing a 5-nitroisophthalic scaffold at the P_2 position

Yoshio Hamada [a,b,*], Tomoya Nakanishi [b], Kenji Suzuki [b], Ryoji Yamaguchi [b], Takashi Hamada [b,d], Koushi Hidaka [a,b], Shoichi Ishiura [c], Yoshiaki Kiso [a,b,d,*]

[a] Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Minatojima, Chuo-ku, Kobe 650-8586, Japan
[b] Center for Frontier Research in Medicinal Science, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan
[c] Department of Life Sciences, Graduate School of Arts and Sciences, University of Tokyo, Meguro-ku, Tokyo 153-8902, Japan
[d] Laboratory of Peptide Science, Nagahama Institute of Bio-Science and Technology, Tamura-cho, Nagahama 526-0829, Japan

ARTICLE INFO

Article history:
Received 25 April 2012
Revised 23 May 2012
Accepted 24 May 2012
Available online 1 June 2012

Keywords:
Alzheimer's disease
β-Secretase
BACE1
BACE1 inhibitor

ABSTRACT

Recently, we reported substrate-based pentapeptidic BACE1 inhibitors possessing a hydroxymethylcarbonyl isostere as a substrate transition-state mimic. These inhibitors showed potent inhibitory activities in enzymatic and cell assays. We also designed and synthesized non-peptidic and small-sized inhibitors possessing a heterocyclic scaffold at the P_2 position. By studying the structure–activity relationship of these inhibitors, we found that the σ–π interaction of an inhibitor with the BACE1-Arg235 side chain played a key role in the inhibition mechanism. Hence, we optimized the inhibitors with a focus on their P_2 regions. In this Letter, a series of novel BACE1 inhibitors possessing a 5-nitroisophthalic scaffold at the P_2 position are described along with the results of the related structure–activity relationship study. These small-sized inhibitors are expected improved membrane permeability and bioavailability.

Amyloid β (Aβ) peptide is a main component of senile plaques in the brains of Alzheimer's disease (AD) patients. According to the amyloid hypothesis,[1] β-secretase [BACE1: β-site APP (amyloid precursor protein) cleaving enzyme 1] appears promising as a molecular target for therapeutic intervention in AD,[2–6] as BACE1 triggers Aβ peptide formation by cleaving APP at the Aβ domain N-terminus.[7–12] Potent peptidic BACE1 inhibitors[13–19] (IC_{50} ~1.2 nM) with a hydroxymethylcarbonyl (HMC) isostere as a substrate transition-state mimic have been reported.[20,21] Of these inhibitors, KMI-429 exhibited effective inhibition of BACE1 activity in cultured cells and significant reduction of Aβ production in vivo (via direct administration into the hippocampi of APP transgenic and wild-type mice).[14b] Some natural amino acids in these inhibitors seem to be required to improve both enzymatic stability in vivo and permeability across the blood–brain barrier. Recently, with the goal of developing a practical anti-AD drug, non-peptidic and small-sized BACE1 inhibitors possessing a 2,6-pyridinedicarboxylic or chelidonic scaffold at the P_2 position were designed based on the conformer structure of a virtual inhibitor docked on the enzyme (Fig. 1), so called 'in silico conformational structure-based design'.[20] As these non-peptidic inhibitors exhibited lower inhibitory activities than peptidic KMI-compounds, more potent forms were desired and, thus, inhibitors possessing a halogen atom on the P_2-pyridine ring were designed by focusing on their interaction with the guanidino π-orbital of BACE1-Arg235 (Fig. 2), and found to be more potent.[23] In this study, we designed and synthesized novel BACE1 inhibitors possessing a 5-nitroisophthalic scaffold at their P_2 position by focusing on the interaction with side

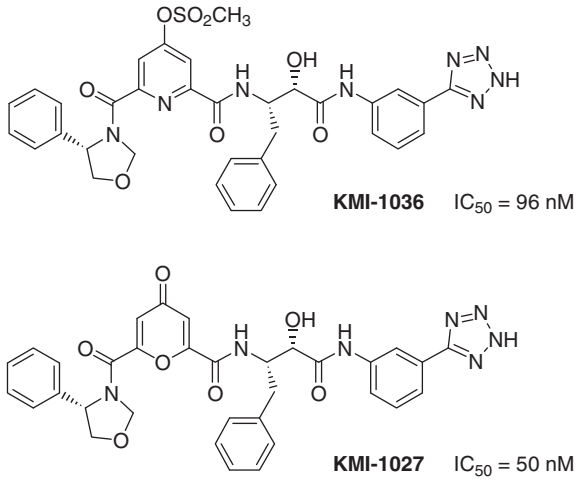


Figure 1. BACE1 inhibitors with a P_2 heterocyclic scaffold.

* Corresponding authors. Tel.: +81 749 64 8113; fax: +81 749 64 8140.
E-mail address: y_kiso@nagahama-i-bio.ac.jp (Y. Kiso).

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.05.089

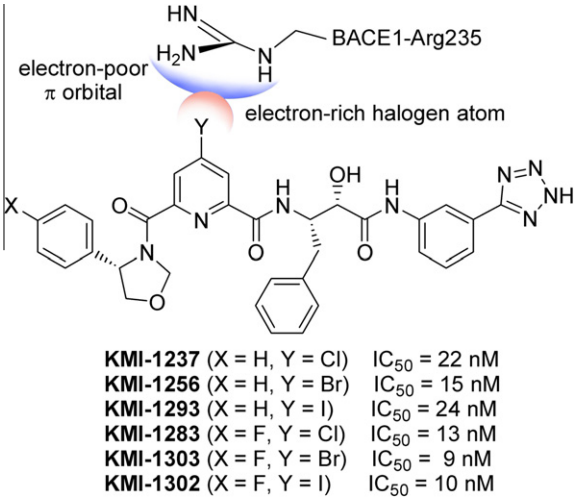
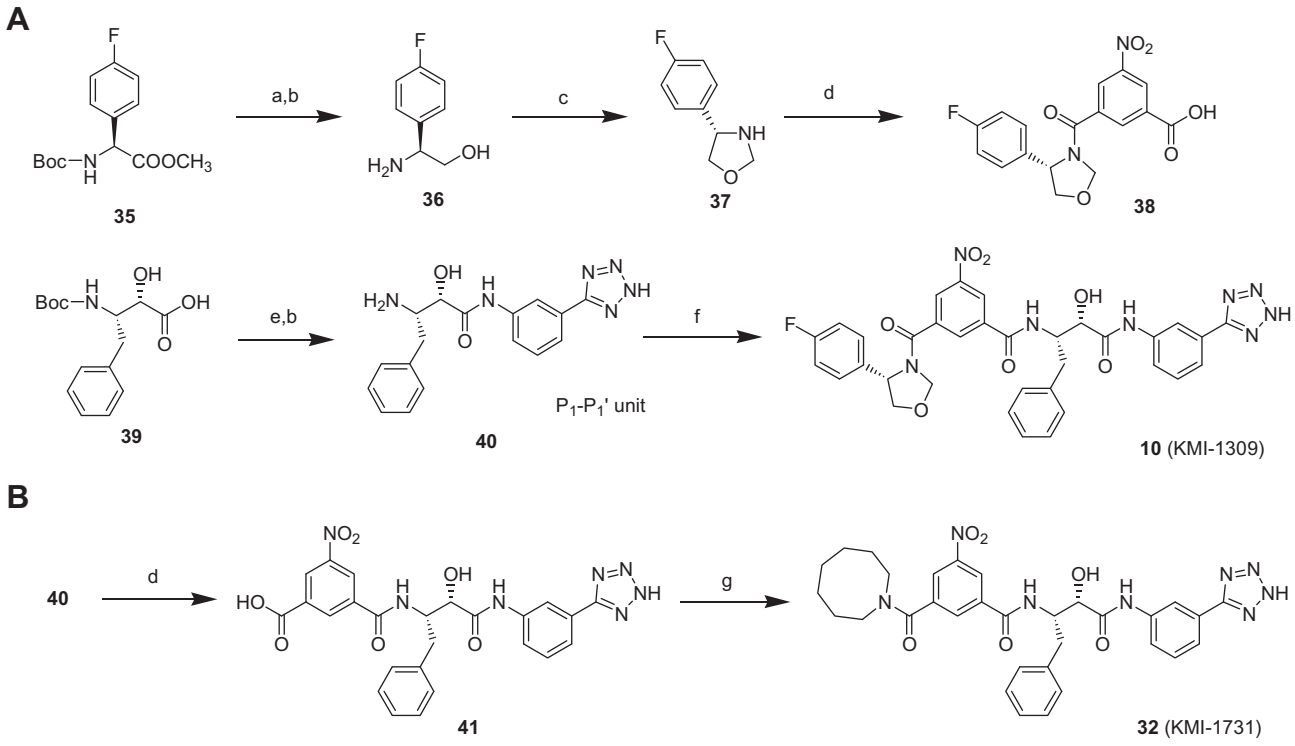


Figure 2. BACE1 inhibitors with a halogen atom on the P_2 aromatic ring.

chain of BACE1-Arg235. In addition, the results of their structure–activity relationship are discussed.

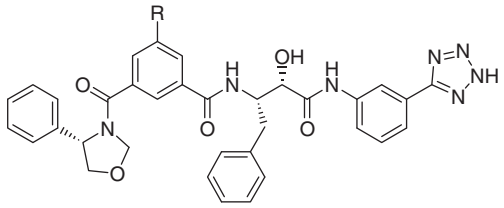
When the publicly-available X-ray crystal structures of BACE1-inhibitor complexes are compared, surprisingly, the guanidino-planes of Arg235-BACE1 show similar features in terms of flopping over the P_2 region of the inhibitors, and the nearest distances between the P_2 region and guanidino-plane show similar values of about 3 Å in the X-ray crystal structures of most BACE1-inhibitor complexes.[23] It was hypothesized here that the guanidino-plane of Arg235 pushes down on the P_2 region of the inhibitors, causing them to be affixed in the BACE1 active site, and that a slightly attractive force from a quantum effect, such as stacking or σ–π interactions, plays a significant role for packing down the inhibitors effectively in the active site of BACE1. Hence, an inhibitors, KMI-1303, was designed, which possessed a halogen atom on the P_2-pyridine scaffold, and proved to be quite potent (Fig. 2). The electron-rich halogen atom appeared able to interact with the electron-poor π-orbital of guanidino-plane by Coulomb's force. With the goal of identifying other forms of potent inhibitors by optimizing the inhibitor P_2 regions, we investigated the effect of other P_2 regions substituents which allowed to interact with the guanidino-plane of BACE1-Arg235. A 5-isophthalic scaffold was adopted as a P_2 residue for the synthesis of a series of BACE1 inhibitors.

BACE1 inhibitors **1–34** were synthesized with the plan to connect in tandem the blocks corresponding to the P_3–P_2 residues and P_1–P_1' residues (Scheme 1A) or to connect sequentially from the P_1' residues to P_3 residues (Scheme 1B). Amide bonds were produced by common solution-phase synthesis methods using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (EDC·HCl) in the presence of 1-hydroxybenzotriazole (HOBt) as a coupling agent. For examples, in the synthesis of inhibitors **10** and **32** (Scheme 1), P_3 amine **37** and 5-nitroisophthalic acid were coupled to produce the P_3–P_2 residue **38**, with the former compound, possessing an oxazolidine ring, prepared from the corresponding amino alcohol, itself previously prepared from L-amino acid derivatives. Other amines were commercially available. P_1–P_1' residue **40** was synthesized from Boc-Apns-OH **39** [Apns: (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid] and 5-(3-aminophenyl)tetrazole. Eventually, P_3–P_2 residue **38** and P_1–P_1' residue **40** were coupled to produce inhibitor **10**. Alternatively, some inhibitors, **32** for example, were synthesized from compound **40** by sequential connection with the P_2 residue and P_3 amine. BACE1 inhibitor **2** was synthesized from its methyl ester, by alkaline hydrolysis, which was prepared from monomethyl ester of benzene-1,3,5-tricarboxylic acid as a starting material. BACE1 inhibitor **4** was synthesized from compound **9** by catalytic hydrogenation using 5% Pd-C catalyst. All inhibitors were purified by preparative reversed phase-high performance liquid chromatography. BACE1 inhibitory activities of the synthesized inhibitors were determined



Scheme 1. Reagents and conditions: (a) $LiBH_4$/THF-MeOH; (b) 4 N HCl/dioxane; (c) HCHO, water; (d) 5-nitroisophthalic acid, EDC·HCl, HOBt/DMF; (e) 5-(3-aminophenyl)tetrazole, EDC·HCl, HOBt/DMF; (f) **38**, EDC·HCl, HOBt/DMF; (g) azocane, EDC·HCl, HOBt/DMF.

Table 1
BACE1 inhibitors possessing a chelidonic scaffold at the P_3 position



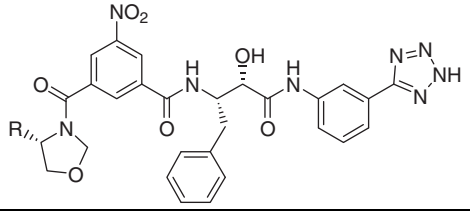
Compound (KMI-No.)	R	BACE1 inhibition %		IC_{50} (nM)
		at 2 μM	at 0.2 μM	
1 (KMI-1662)	–H	85	46	192
2 (KMI-1767)	–COOH	91	60	122
3 (KMI-1298)	$-OCOCH_3$	79	—	—
4 (KMI-1307)	$-NH_2$	49	—	—
5 (KMI-1280)	–Br	98	84	25
6 (KMI-1287)	–I	98	78	34
7 (KMI-1325)	$-CH_3$	95	65	67
8 (KMI-1277)	$-C(CH_3)_3$	63	—	—
9 (KMI-1214)	$-NO_2$	98	88	19

by an enzymatic assay using a recombinant human BACE1 and FRET (fluorescence resonance energy transfer) substrate as previously reported.[5,13–19,22,23]

First, BACE1 inhibitors **1**–**9** were synthesized possessing an isophthalic scaffold at the P_2 position and diverse groups on its aromatic ring (Table 1). Of these inhibitors, compound **9**, with a nitro group, exhibited the highest BACE1 inhibitory activity and compound **5**, **6**, and **7**, possessing a halogen atom or methyl group on the P_2 aromatic ring, also exhibited high BACE1 inhibitory activities, suggesting that a small-sized and hydrophobic substituent on the P_2 aromatic ring was preferential for BACE1 inhibition. Having previously reported the nature of a series of BACE1 inhibitors possessing a halogen atom on the P_2-heterocyclic scaffold, the focus here was on the nitro-group as a P_2-substituent, resulting in the design of inhibitors **10**–**34**. Inhibitors **10**–**24** possessed a 5-membered oxazolidine ring (Table 2) and, of these, compound **10** exhibited the highest BACE1 inhibitory activity, followed in activity by compounds **17**–**19** and **22**. The results also showed that compound **16**, with a small-sized group and compounds **13**, **15**, and **24**, with bulky oxazolidine ring substituents, showed low inhibitory activities, suggesting that size—being the length of as phenyl group—and planarity for an inhibitor P_2-substituent are important. In particular, a *p*-fluorophenyl group appeared to interact tightly with the BACE1 S_3 sub-pocket.

Next, inhibitors **25**–**34**, with no oxazolidine ring at the P_3 position were synthesized (Table 3). Inhibiters **26** and **27**, with a P_2-benzylamino type group, exhibited relatively high BACE1 inhibitory activities and, although compound **28** with a P_3-pyrrolidine ring, showed low inhibitory activity, inhibitor **29**, possessing a substituent on the P_3-pyrrolidine ring, showed superior inhibitory activity. This suggested that there was an empty space between the P_3-pyrrolidine ring and S_3 pocket of BACE1. Hence, inhibitors **30**–**34** were produced with cyclic amines at the P_3 position and, of these, compound **32** (KMI-1731), with an 8-memberd ring, showed the highest inhibitory activity. To understand these results, a docking simulation study was performed using MOE soft-

Table 2
BACE1 inhibitors possessing a 2,6-pyridinedicarboxylic scaffold at the P_3 position



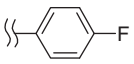
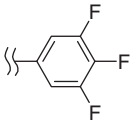
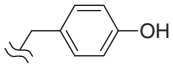
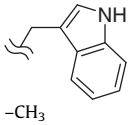
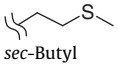
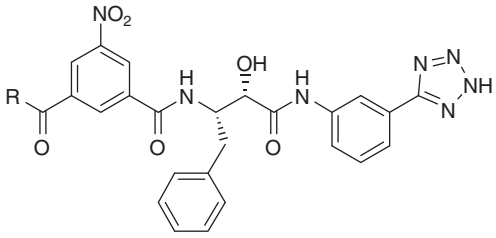
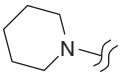
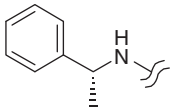
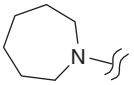
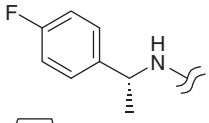
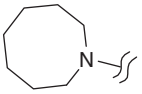
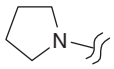
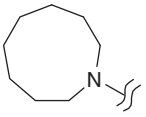
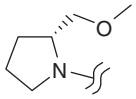
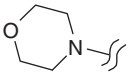
Compound (KMI-No.)	R	BACE1 inhibition %		IC_{50} (nM)
		at 2 μM	at 0.2 μM	
10 (KMI-1309)		99	91	13
11		81	41	—
12	Benzyl	89	45	—
13	Cyclohexylmethyl	50	—	—
14		80	—	—
15		57	—	—
16	$-CH_3$	33	—	
17	–Et	92	54	
18	–*n*-Pr	93	57	
19	–*n*-Bu	92	59	
20	Isopropyl	88	44	
21		86	45	
22	*sec*-Butyl	94	62	
23	Isobutyl	85	42	
24	*tert*-Butyl	71	—	

Table 3
BACE1 inhibitors possessing 2,6-pyridinedicarboxylic scaffold at the P_3 position



Compound (KMI-No.)	R	BACE1 inhibition %		Compound (KMI-No.)	R	BACE1 inhibition %	
		at 2 μM	at 0.2 μM			at 2 μM	at 0.2 μM
25-(KMI-1211)	–N(*n*-Pr)$_2$	79	–	**30** (KMI-1729)		49	–
26 (KMI-1212)		83	44	**31**-(KMI-1730)		60	–
27 (KMI-1213)		87	50	**32** (KMI-1731)		80	38
28 (KMI-1728)		24	–	**33** (KMI-1769)		28	–
29 (KMI-1219)		89	57	**34** (KMI-1732)		0	–

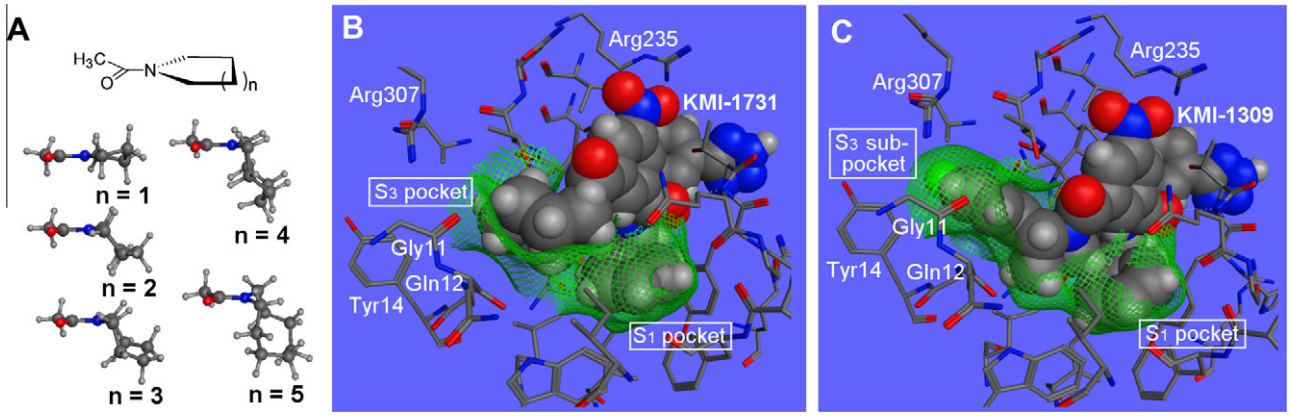


Figure 3. (A) Configurations of some cyclic amides. (B) Inhibitor **32** (KMI-1731) docked in BACE1. (C) Inhibitor **10** (KMI-1309) docked in BACE1 (PDB ID: 2B8L). Space-filing models and green lines indicate inhibitors and BACE1 hydrophobic pockets, respectively, and stick models indicate BACE1 amino acid residues around each inhibitor.

ware (Chemical Computing Group Inc., Canada, Figure 3). The configurations of cyclic acetyl amides from 5- to 9-membered rings after energy minimization under the MMFF94x force field are shown in Figure 3A. The molecular sizes of these cyclic acetyl amides appeared to be similar in the direction of the amide bonds regardless of their ring-sizes, because the larger rings present more greatly curved configurations. When inhibitor **32**, with an 8-membered ring, was docked in BACE1, this ring appeared to interact tightly with the S_3 pocket of BACE1 due to its very bent structure (Fig. 3B). However, compound **33**, with a 9-membered ring, showed surprisingly low inhibitory activity. In general, an odd-membered, medium-sized ring has higher strain energy and no symmetric properties, resulting in a bulky configuration (Figure 3A). Consequently, compound **33** might not have been able to bind to the S_3 pocket of BACE1. On the other hand, compound **34,** with a P_3-morpholine ring, exhibited no inhibitory activity, suggesting that a hydrophilic moiety, such as an oxygen atom, could not interact with the hydrophobic S_3 pocket of BACE1. For comparison, BACE1 docked inhibitor **10** is shown in Figure 3C. Inhibitor **32**'s P_3 moiety could have interacted with the S_3 pocket of BACE1, while inhibitor **10**'s P_3-benzene ring appeared able to interact effectively with the S_3 sub-pocket lying behind the S_3 pocket.

As described above, inhibitors with a nitro group on the P_2-isophthalic scaffold exhibited the highest inhibitory activities among the present inhibitors possessing an isophthalic scaffold. To better understand this finding, a docking simulation performed using MOE software. As inhibitor **5**–**7** exhibited potent BACE1 inhibitory activities, a halogen and methyl groups were speculated

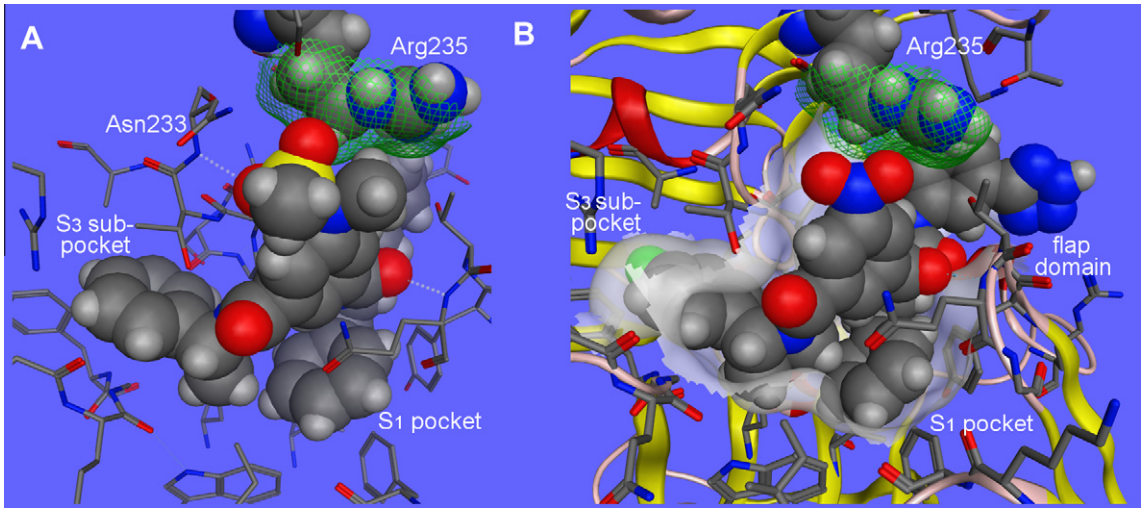


Figure 4. Interaction between BACE1-Arg235 and inhibitors docked in BACE1 (PDB ID: 2B8L). (A) Merck's compound. (B) Compound **10** (KMI-1309). Inhibitors and Arg235 were depicted by space-filling models. Stick models indicate BACE1 amino acid residues around each inhibitor.

to be fixed on the P_2-isophthalic ring by direct covalent bonding and effectively bound to the guanidino-plane of BACE1-Arg235 by σ–π interactions. The X-ray crystal structure of Merck's inhibitor bound in BACE1 (PDB ID: 2B8L) is shown in Figure 4A. Because the sulfonyl-oxygen atom of P_2-*N*-methyl-*N*-methanesulfonyl group of Merck's inhibitor appears to interact with the α-amino group of BACE1-Asn233 by hydrogen bonding, the *N*-methyl group is fixed on the P_2-isophthalic ring and might bind effectively to the BACE1-Arg235 by CH–π interactions. Considering the nitro group on the P_2-isophthalic ring of inhibitor **10** (Fig. 4B), the rotation of a nitro group on an aromatic ring is restricted by resonance effects and is thus fixed on its ring. For this reason, the oxygen atom of the nitro group is speculated here to be fixed on the P_2-isophthalic ring and can thus effectively bind to BACE1-Arg235 by O–π interactions.

In conclusion, we synthesized a series of BACE1 inhibitors possessing an isophthalic scaffold at the P_2 position, and found some potent BACE1 inhibitors with a nitro group on the P_2 ring. Notably, inhibitor **10** (KMI-1309) was shown to have potent BACE1 inhibitory activity (IC_{50} = 13 nM). These small-sized and non-peptidic inhibitors are expected to provide improvement of clinical inhibitor bioavailability and membrane permeability across the blood–brain barrier.

Acknowledgments

This study was supported in part by the Grants-in-Aid for Scientific Research (A) and (C) from MEXT (Ministry of Education, Culture, Sports, Science and Technology), Japan. (KAKENHI No.21249007 and No.23590137, respectively) We thank T. Hamada and Dr. J.-T. Nguyen for performing the in vitro enzyme assays and his help in preparing the manuscript, respectively.

References and notes

1. (a) Hong, L.; Koelsch, G.; Lin, X.; Wu, S.; Terzyan, S.; Ghosh, A. K.; Zhang, X. C.; Tang, J. *Science* **2000**, *290*, 150; (b) Sipe, J. D. *Annu. Rev. Biochem.* **1992**, *61*, 947; (c) Selkoe, D. J. *Ann. N.Y. Acad. Sci.* **2000**, *924*, 17; (d) Steiner, H.; Capell, A.; Leimer, U.; Haass, C. *Eur. Arch. Psychiatric Clin. Neurosci.* **1999**, *249*, 266; (e) Selkoe, D. J. *Ann. Med.* **1989**, *21*, 73.
2. (a) Ghosh, A. K.; Shin, D.; Downs, D.; Koelsch, G.; Lin, X.; Ermolieff, J.; Tang, J. *J. Am. Chem. Soc.* **2000**, *122*, 3522; (b) Ghosh, A. K.; Bilcer, G.; Harwood, C.; Kawahara, R.; Shin, D.; Hussain, K. A.; Hong, L.; Loy, J. A.; Nguyen, C.; Koelsch, G.; Ermolieff, J.; Tang, J. *J. Med. Chem.* **2001**, *44*, 2865.
3. Tung, J. S.; Davis, D. L.; Anderson, J. P.; Walker, D. E.; Mamo, S.; Jewett, N.; Hom, R. K.; Sinha, S.; Thorsett, E. D.; John, V. *J. Med. Chem.* **2002**, *45*, 259.
4. Tamamura, H.; Kato, T.; Otaka, A.; Fujii, N. *Org. Biomol. Chem.* **2003**, *1*, 2468.
5. 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.
6. (a) Hamada, Y.; Kiso, Y. *Expert Opin. Drug Discov.* **2009**, *4*, 391; (b) Ziora, Z.; Kimura, T.; Kiso, Y. *Drugs Future* **2006**, *31*, 53; (c) Nguyen, J.-T.; Yamani, A.; Kiso, Y. *Curr. Pharm. Design* **2006**, *12*, 4309.
7. Vassar, R.; Bennett, B. D.; Babu-Khan, 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.
8. 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.; Heinrikson, R. L.; Gurney, M. E. *Nature* **1999**, *402*, 533.
9. 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.; Suomensaari, S. M.; Wang, S.; Walker, D.; Zhao, J.; McConlogue, L.; John, V. *Nature* **1999**, *402*, 537.
10. 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.
11. Selkoe, D. J. *Nature* **1999**, *399*, A23.
12. Sinha, S.; Lieberburg, I. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11049.
13. 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.
14. (a) 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; (b) Asai, M.; Hattori, C.; Iwata, N.; Saido, T. C.; Sasagawa, N.; Szabó, B.; Hashimoto, Y.; Maruyama, K.; Tanuma, S.; Kiso, Y.; Ishiura, S. *J. Neurochem.* **2006**, *96*, 533.
15. Kimura, T.; Hamada, Y.; Stochaj, M.; Ikari, H.; Nagamine, A.; Abdel-Rahman, H.; Igawa, N.; Hidaka, K.; Nguyen, J-T.; Saito, K.; Hayashi, Y.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2380.
16. 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**, *16*, 4354.
17. Hamada, Y.; Abdel-Rahman, H.; Yamani, A.; Nguyen, J.-T.; Stochaj, M.; Hidaka, K.; Kimura, T.; Hayashi, Y.; Saito, K.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1649.
18. Hamada, Y.; Tagad, H. D.; Nishimura, Y.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1130.
19. Hamada, Y.; Ishiura, S.; Kiso, Y. *Bioorg. ACS Med. Chem. Lett.* **2012**, *3*, 193.
20. Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Takahashi, O.; Kisanuki, S.; Nagano, Y.; Shintani, M.; Hayashi, H.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 2465.
21. Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Kisanuki, S.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 3088.
22. Hamada, Y.; Ohta, H.; Miyamoto, N.; Yamaguchi, R.; Yamani, A.; Hidaka, K.; Kimura, T.; Saito, K.; Hayashi, Y.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1654.
23. Hamada, Y.; Ohta, H.; Miyamoto, N.; Sarma, D.; Hamada, T.; Nakanishi, T.; Yamasaki, M.; Yamani, A.; Hidaka, K.; Ishiura, S.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2435.