Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2380–2386

# Design and synthesis of potent β-secretase (BACE1) inhibitors with $P_1'$ carboxylic acid bioisosteres

Tooru Kimura,[a] Yoshio Hamada,[a] Monika Stochaj,[a] Hayato Ikari,[a] Ayaka Nagamine,[a] Hamdy Abdel-Rahman,[a] Naoto Igawa,[a] Koushi Hidaka,[a] Jeffrey-Tri Nguyen,[a] Kazuki Saito,[b] Yoshio Hayashi[a] and Yoshiaki Kiso[a,*]

[a]*Department of Medicinal Chemistry, Center for Frontier Research in Medicinal Science and 21st Century COE Program, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan*
[b]*Laboratory of Proteomic Sciences, 21st Century COE Program, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan*

Received 28 December 2005; revised 25 January 2006; accepted 27 January 2006
Available online 14 February 2006

**Abstract**—Recently, we reported potent and small-sized β-secretase (BACE1) inhibitors KMI-420 and KMI-429 in which we replaced the Glu residue at the $P_4$ position of KMI-260 and KMI-360, respectively, with a 1*H*-tetrazole-5-carbonyl DAP (L-α,β-diaminopropionic acid) residue. At the $P_1'$ position, these compounds contain one or two carboxylic acid groups, which are unfavorable for crossing the blood–brain barrier. Herein, we report BACE1 inhibitors with $P_1'$ carboxylic acid bioisosteres in order to develop practical anti-Alzheimer's disease drugs. Among them, tetrazole ring-containing compounds, KMI-570 ($IC_{50}$ = 4.8 nM) and KMI-684 ($IC_{50}$ = 1.2 nM), exhibited significantly potent BACE1 inhibitory activities.
© 2006 Elsevier Ltd. All rights reserved.

Proteolytic processing of amyloid precursor protein (APP)[1,2] leads to the formation of amyloid β peptide (Aβ), which is the main component of senile plaques found in the brains of Alzheimer's disease (AD) patients.[3] According to the amyloid hypothesis,[4] BACE1 (β-site APP cleaving enzyme, β-secretase) is considered as a molecular target for therapeutic intervention in AD,[5–8] because BACE1 triggers Aβ formation by cleaving at the N-terminus of the Aβ domain.[9–12] Recently, we reported potent and small-sized BACE1 inhibitors, KMI-420 (**3**) and KMI-429 (**4**),[13] that contained phenylnorstatine [Pns: (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid] as a substrate transition-state mimic.[14,15] From KMI-260 (**1**) and KMI-360 (**2**),[16] KMI-420 and KMI-429 were designed with a tetrazole ring as a carboxylic acid bioisostere[17] at the $P_4$ position (Fig. 1). According to structure–activity relationship (SAR) studies of KMI-compounds, we found that the acidic moieties at the $P_4$ and $P_1'$ positions were important for improving BACE1 inhibitory activity. However, acidic moieties, such as carboxylic groups, often possess low membrane permeability across the blood–brain barrier. Herein, we replaced one or two carboxylic acid groups at the $P_1'$ position of KMI-compounds with some carboxylic acid bioisosteres in order to develop practical anti-AD drugs. Naka and co-workers reported some bioisosteres of a tetrazole ring and their applications in angiotensin II receptor antagonists.[18] Using tetrazole rings or acidic heterocycles as carboxylic acid bioisosteres at the $P_1'$ position of KMI-420 and KMI-429, we designed and synthesized novel potent BACE1 inhibitors, KMI-570 (**24**) and KMI-684 (**25**), that do not possess carboxylic acid.

The synthesis of aniline derivatives **6**, **8**–**10**, **12**, and **13**, which correspond to residues at the $P_1'$ position of KMI-compounds, is shown in Scheme 1. 3,5-Bis(1*H*-tetrazol-5-yl)-aniline **6a** was synthesized from nitrile **5a** by cyclization using sodium azide and subsequent reduction using tin in hydrochloric acid. Aniline derivatives **8**–**10** were synthesized from amidoxime **7**, which was prepared by addition of hydroxylamine to the corresponding nitrile **5b**, according to Naka's method.[18] Compounds **12** and **13** were synthesized from benzoate **11** by cyclization using carbon disulfide[19] and methyl

*Keywords*: Alzheimer's disease; BACE1 inhibitor; β-Secretase; Bioisostere.
* Corresponding author. Tel.: +81 75 595 4635; fax: +81 75 591 9900; e-mail: kiso@mb.kyoto-phu.ac.jp

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.01.108

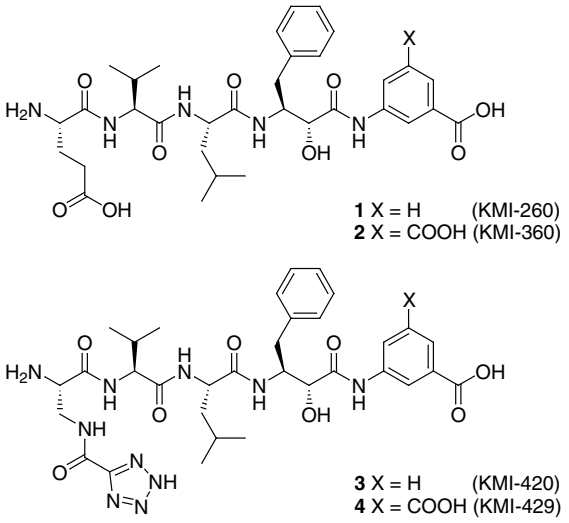
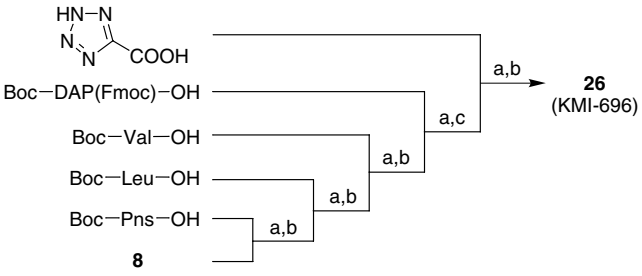
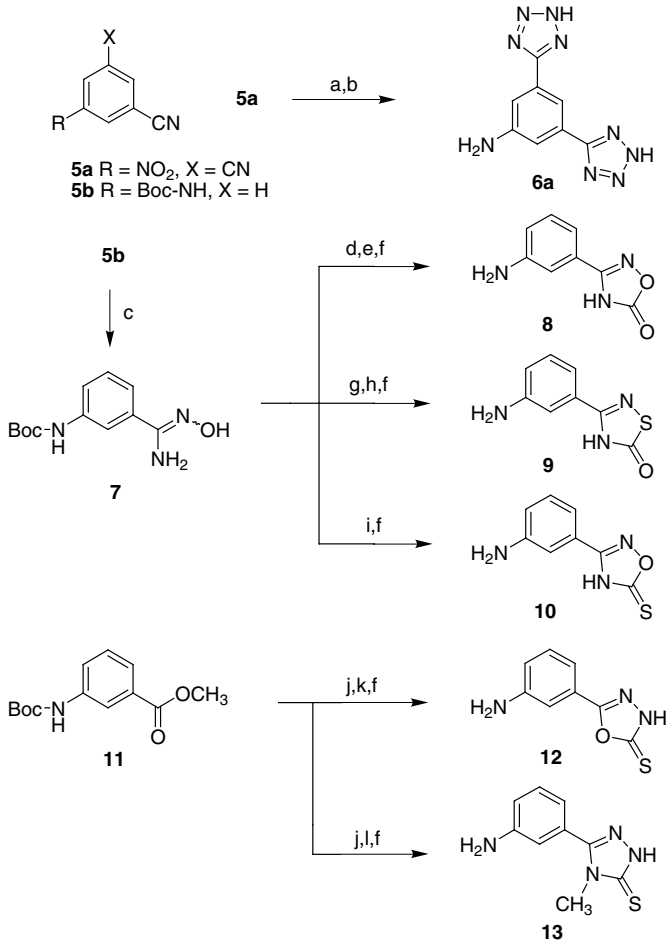



**Figure 1.** Structure of BACE1 inhibitors containing 3-aminobenzoic acid derivatives at the $P_1'$ position.

isothiocyanate,[20] respectively, and subsequent deprotection. BACE1 inhibitors **18**–**22**, **26**, and **27** were synthesized by traditional solution-phase peptide methods (Scheme 2) from aniline derivatives **8**–**10**, **12**, and **13**, respectively. Peptidic bonds were formed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (EDC·HCl) in the presence of 1-hydroxybenzotriazole (HOBt) as coupling reagents. Protection groups Boc and Fmoc (9-fluorenylmethoxycarbonyl) were removed using 4 M HCl in dioxane and 20% diethylamine in DMF, respectively. The final Boc deprotection was performed with 4 M HCl in dioxane and anisole. Subsequent purification by preparative RP-HPLC afforded the desired inhibitors **18**–**22**, **26**, and **27**.



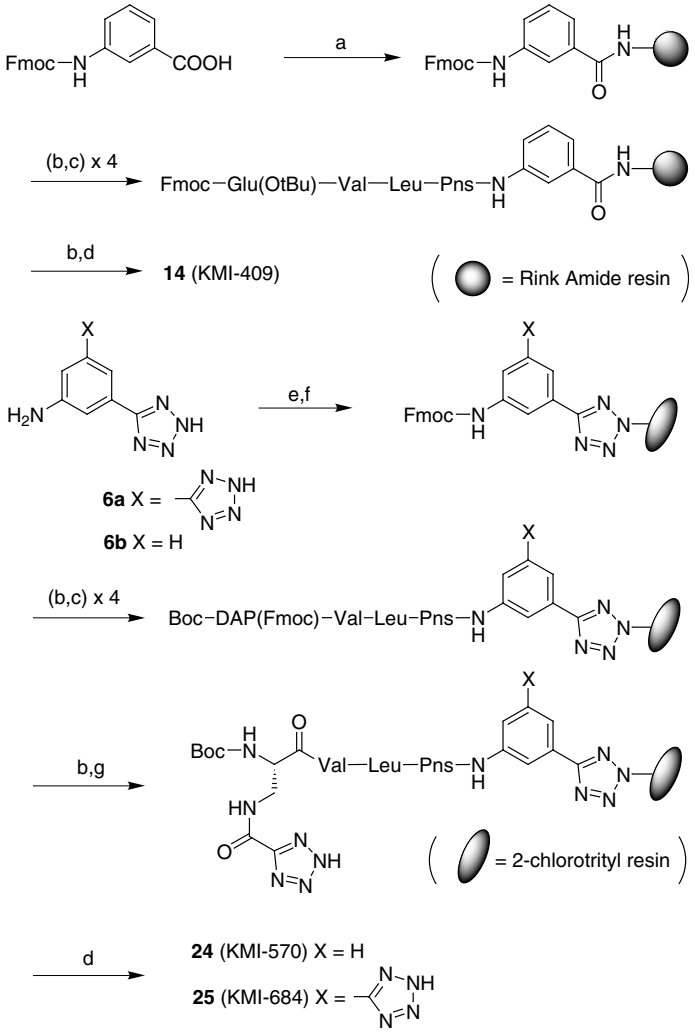

**Scheme 2.** Reagents: (a) EDC·HCl, HOBt, DMF; (b) anisole, 4 M HCl/dioxane; (c) 20% $Et_2NH$/DMF.



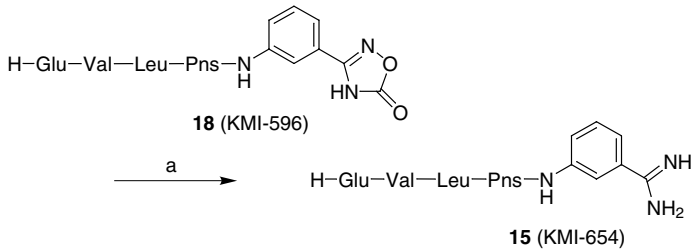

**Scheme 1.** Reagents and conditions: (a) $NaN_3$, *n*-BuOH-AcOH, reflux; (b) Sn, concd HCl; (c) $NH_2OH$·HCl, $Et_3N$, DMSO, 75 °C; (d) pyridine, 2-ethylhexyl chloroformate, THF, 0 °C; (e) xylene, reflux; (f) anisole, 4 M HCl/dioxane; (g) TCDI, THF; (h) $BF_3$·$OEt_2$, THF; (i) TCDI, DBU, MeCN; (j) $NH_2NH_2$·$H_2O$, EtOH, reflux; (k) $CS_2$, KOH, EtOH; (l) MeNCS, THF.

BACE1 inhibitors **14**, **16**, **17**, and **23**–**25** were synthesized by Fmoc-based solid-phase peptide synthesis methods using previously reported procedures.[13a] As an example, the synthesis of inhibitors **14**, **24** and **25** is outlined in Scheme 3. Namely, *N*-Fmoc-3-aminobenzoic acid was attached to the deprotected Rink amide resin using diisopropylcarbodiimide (DIPCDI) in DMF. N-Fmoc-protected compounds, which were obtained from tetrazole derivatives (**6a** and **6b**) by treatment with Fmoc-OSu [*N*-(9-fluorenylmethyloxycarbonyl)succinimide] in THF–water, were attached to 2-chlorotrityl chloride resin using diisopropylethylamine (DIPEA) in dichloromethane (DCM). The Fmoc group was removed with 20% piperidine in DMF and peptide bonds were formed using DIPCDI in the presence of HOBt as coupling reagents. After elongation of the peptide chain, cleavage from the resin was achieved using trifluoroacetic acid (TFA) in the presence of *m*-cresol and thioanisole. The crude peptide was purified by preparative RP-HPLC. BACE1 inhibitor **15** was synthesized from compound **18** by catalytic hydrogenation (Scheme 4) and purified by preparative RP-HPLC.

To evaluate carboxylic acid bioisosteres on BACE1 inhibition, we selected inhibitor **1** (KMI-260), containing a Glu residue at the $P_4$ position, as the reference compound and replaced its carboxylic acid functional group at the $P_1'$ position with different moieties. The inhibitory activity against BACE1 for the compounds **14**–**22** is summarized in Table 1. In inhibitors **14** and **15**, the carboxamide and amidine functional groups, similar in size to that of a carboxylic acid, induced low BACE1 inhibitory activities, suggesting that the acidic property of the $P_1'$ side chain is essential for improving BACE1 inhibitory activity. On the other hand, inhibitors **16**–**21**, which contained one or two tetrazole rings, or acidic heterocycles (5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, and 2-thioxo-1,3,4-oxadiazole)[18,19] at $P_1'$ position, respectively, showed significantly higher BACE1 inhibitory activities than their lead compound **1**. This finding supported the fact that acidic heterocycles[18] act as bioisosteres of carboxylic acid, as well as tetrazole ring. However inhibitor **22**, which contained *N*-methyl heterocycle (4-methyl-3-thioxo-1,2,4-triazole)[20] at $P_1'$ position, possessed low BACE1 inhibitory activity,

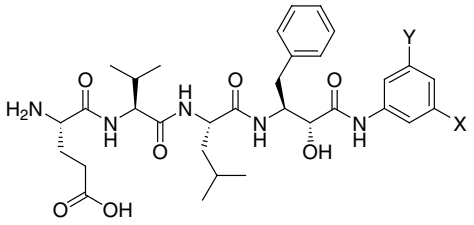


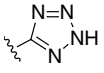
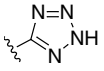
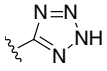
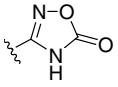
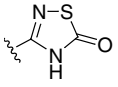
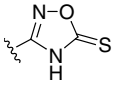
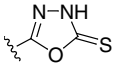
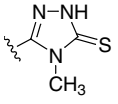

**Scheme 3.** Reagents and conditions: (a) deprotected Rink amide resin, DIPCDI, DMF; (b) 20% piperidine/DMF; (c) Fmoc-AA-OH, DIPCDI, HOBt, DMF; (d) TFA, *m*-cresol, thioanisole; (e) Fmoc-OSu, $K_2CO_3$, THF-$H_2O$ (1:1); (f) 2-chlorotrityl chloride resin, DIPEA, DCM; (g) 1*H*-tetrazole-5-carboxylic acid, DIPCDI, HOBt, DMF.




**Scheme 4.** Reagents: (a) $H_2$, Pd/C, MeOH.

**Table 1.** BACE1 inhibitory activity of $P_4$ glutamic compounds

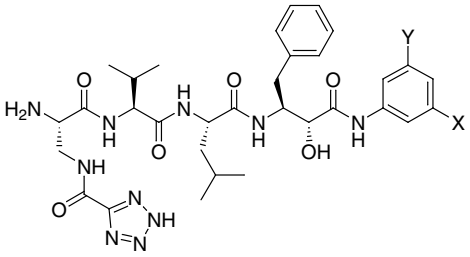


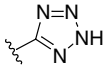
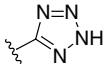
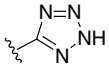
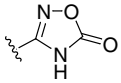
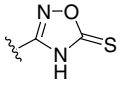

| Compound (KMI No.) | X | Y | BACE1 inhibition (%) | | $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| | | | at 2 μM | at 0.2 μM | |
| **14** (KMI-409) | $CONH_2$ | H | 62.1 | — | — |
| **15** (KMI-654) |  | H | 29.2 | — | — |
| **16** (KMI-569) |  | H | 92.2 | 73.7 | — |
| **17** (KMI-597) |  |  | 99.7 | 94.0 | 6.4 |
| **18** (KMI-596) |  | H | 94.4 | 66.3 | — |
| **19** (KMI-683) |  | H | 91.9 | 63.2 | — |
| **20** (KMI-879) |  | H | 94.5 | 68.4 | — |
| **21** (KMI-666) |  | H | 92.0 | 72.3 | — |
| **22** (KMI-686) |  | H | 74.2 | — | — |
| **1** (KMI-260) | COOH | H | 83.7 | 44.4 | — |
| **2** (KMI-360) | COOH | COOH | 98.3 | 84.3 | 55 |

suggesting that the *N*-methyl group might prevent hydrogen bond formation to the $S_1'$ site of BACE1.

Previously, we reported that replacing the carboxylic acid at the $P_4$ position with a tetrazole ring enhanced inhibitory activity against BACE1.[13] In the current report, we wanted to observe if such enhancements would be preserved for non-carboxylic acid $P_1'$ residues. Consequently, we synthesized compounds possessing a $P_4$ tetrazole ring while replacing $P_1'$ carboxylic acid in **3** (KMI-420) and **4** (KMI-429) with a carboxamide, one or two tetrazole rings, 5-oxo-1,2,4-oxadiazole or 5-thioxo-1,2,4-oxadiazole. As shown in Table 2, BACE1 inhibitors possessing a $P_4$ tetrazole ring **23**–**27**

**Table 2.** BACE1 inhibitory activity of $P_4$ tetrazole compounds



| Compound (KMI No.) | X | Y | BACE1 inhibition (%) | | $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| | | | at 2 μM | at 0.2 μM | |
| **23** (KMI-419) | $CONH_2$ | H | 97.3 | 78.1 | — |
| **24** (KMI-570) |  | H | 100 | 98.1 | 4.8 |
| **25** (KMI-684) |  |  | 100 | 100 | 1.2 |
| **26** (KMI-696) |  | H | 100 | 94.2 | 6.6 |
| **27** (KMI-808) |  | H | 99.8 | 97.2 | 6.4 |
| **3** (KMI-420) | COOH | H | 99.1 | 87.1 | 8.2 |
| **4** (KMI-429) | COOH | COOH | 100 | 98.1 | 3.9 |

demonstrated vastly greater inhibitory activities in comparison with inhibitors possessing at $P_4$ carboxylic acid **14**–**21**. In particular compounds containing tetrazole rings at $P_1'$ position, **24** ($IC_{50}$ = 4.8 nM) and **25** ($IC_{50}$ = 1.2 nM) exhibited highest BACE1 inhibitory activities.

Computer-assisted simulated docking experiments were carried out in a BACE1 enzyme (PDB ID: 1FKN),[21] in order to correlate affinity with activity. In all compounds listed in Tables 1 and 2, the most energy-favored conformations assumed similar poses with excellent hydrogen bond interactions between the inhibitor's Pns anchor and BACE1's Asp32 and Asp228. Moreover, the inhibitor is firmly secured throughout its backbone by strong hydrogen bond interactions coming from Gly11, Thr232, Gly230, Gln73, and Thr72, which coincided with the previously reported modeling study of KMI-429 (**4**).[13a] As an example, the results for KMI-684 (**25**) is shown in Figure 2A. Previously, we predicted that the tetrazole carbonyl group at the $P_4$ position of KMI-429 (**4**) formed hydrogen bonds to both Arg235 and Arg307 residues to explain its enhanced BACE1 inhibitory activity upon replacing the $P_4$ carboxylic acid with a tetrazole ring.[13] However, docking simulation to BACE1 enzyme (PDB ID: 1FKN) showed that the tetrazole carbonyl group at $P_4$ position formed hydrogen bonds to Arg307, Gly264, and Asn233 as shown in Figure 2A. The inhibitor which was used to co-crystallize this BACE1 enzyme contained a hydrophilic side chain group at the $P_2$ position (Asn). However, our compounds contained a hydrophobic amino acid (Leu) at the same position. Hence, we repeated the docking simulation study using another structure of the BACE1 enzyme (PDB ID: 1W51) in which the ligand had a hydrophobic group (benzene ring) at the $P_2$ position. For the case of the 1FKN BACE1 enzyme, Arg235 formed hydrogen bonds with Gln326 and the co-crystallized ligand's $P_2$ Asn side chain. On the other hand, for the case of the 1W51 BACE1 enzyme, Arg235 assumed a different orientation to repel the co-crystallized inhibitor's $P_2$ benzene ring and had hydrogen bond interaction with Asn233. As shown in Figure 2B, docking simulation study to BACE1 enzyme (PDB ID: 1W51) gave a similar result to our previous report.[13a] These findings suggested that the docking simulation which absolutized crystal structures by X-ray diffraction method might have given irrelevant output, because enzymes often changed their three-dimensional structure depending on the nature of the ligands.

Docking simulation using two structures of BACE1 enzyme (PDB ID: 1FKN and 1W51) gave similar results at the $P_1'$ position. Alpha sphere pharmacophore predictions suggest that an anionic group or hydrogen-bond acceptor at the $P_1'$ carboxylic acid's coordinates in the $S_1'$ pocket would improve inhibitor–site interactions. Carboxylic acids are excellent hydrogen-bond acceptors; carboxamides have partial hydrogen-bond-accepting and -donating properties; while amidines are mainly

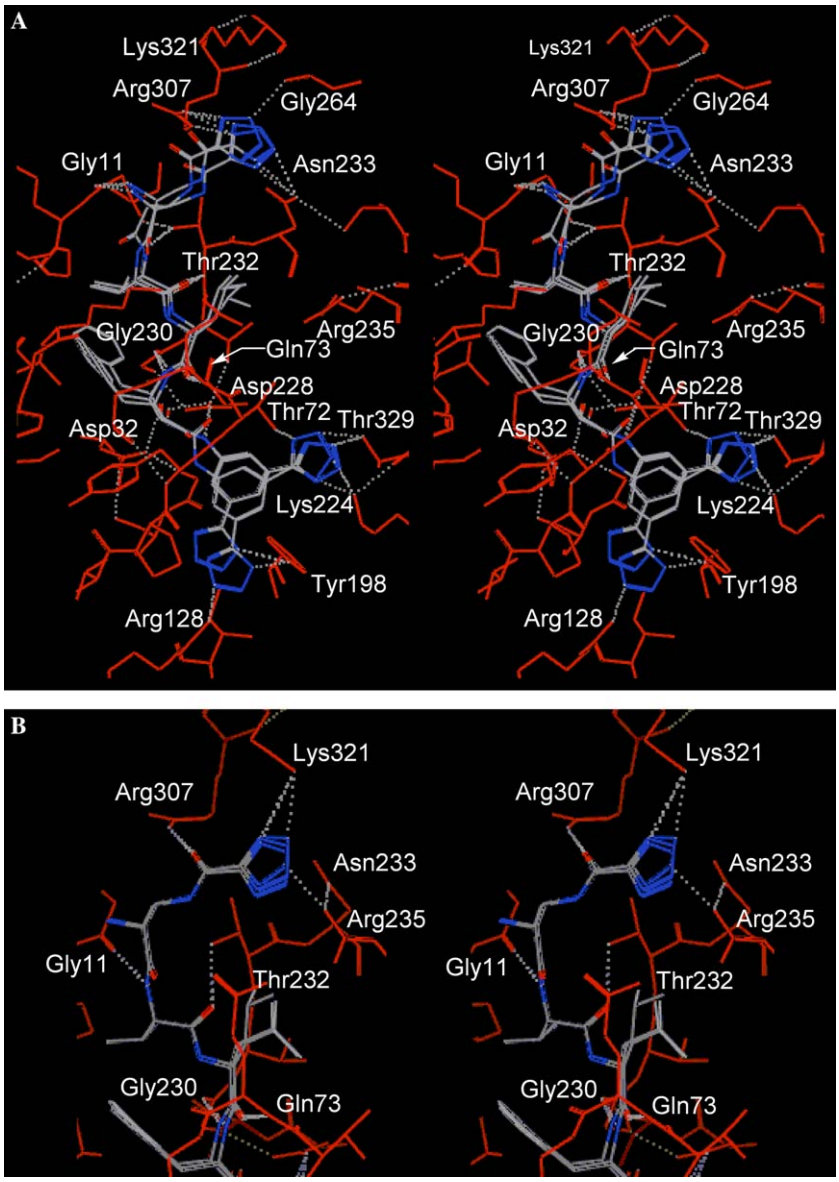



**Figure 2.** 3D Views of docked inhibitor KMI-684. (A) Docking simulation of **25** (KMI-684, white line) in BACE1 enzyme (PDB ID: 1FKN, red lines). (B) Docking simulation of **25** (KMI-684, white line) in BACE1 enzyme (PDB ID: 1W51, red lines). In both A and B, three stable conformers of inhibitor **25** were superimposed. White dashed lines depict hydrogen bond interactions. Two docking simulations using 1FKN and 1W51 gave similar results at the lower omitted part in B.

hydrogen-bond donors. As a result, the observed inhibitory potency trend can be correlated with the hydrogen-bond-accepting ability of the functional group. The nature of tetrazole rings and other acidic heterocycles, which are slightly larger than a carboxylic acid and possessed a delocalized negative charge around the rings,[22] is thought to favor the binding to hydrogen-bond donors. Moreover, the partially hydrophobic regions above and below these heterocycles may interact favorably with the partially hydrophobic inner walls of the $S_1'$ pocket, which consists of Tyr71, Pro70, Tyr198, Ile126, Ser35 (α- and β-carbons), Thr329, Ile226, and Val332.

BACE1 inhibitors bearing tetrazole ring and acidic heterocycle bioisosteres were synthesized and some inhibitors demonstrated more potent enzyme inhibitory activity than their carboxylic acid counterparts and may also be more efficient in crossing the blood–brain barrier. 5-Oxo-1,2,4-oxadiazole and its sulfur-substituted derivatives have been reported to be converted metabolically to their corresponding amidoximes, which released NO by cytochrome 450 isoenzymes.[23] The use of these acidic heterocycles in drug development might become an issue in point of the formation of NO, although this problem had not exposed in the case of the antihypertensive agents, angiotensin II receptor antagonists,[18] that served a common bioactivity to blood pressure.

In conclusion, novel series of BACE1 inhibitors were designed and synthesized using bioisosteres of carboxylic acid at the $P_1'$ position. In particular, compounds **24** (KMI-570) and **25** (KMI-684), which contained

tetrazole rings, demonstrated significantly more potent BACE1 inhibitory activities. These modifications are expected to enhance blood–brain barrier permeability, which is one of the greatest challenges to overcome during the development of drug against AD.

## Acknowledgments

This study was supported in part by the Frontier Research Program and the 21st Century COE Program of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, Japan Society for the Promotion of Science's Post-Doctoral Fellowship for Foreign Researchers, and grants from MEXT.

## References and notes

1. Selkoe, D. J. *Nature* **1999**, *399*, A23.
2. Sinha, S.; Lieberburg, I. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11049.
3. Selkoe, D. J. *Neuron* **1991**, *6*, 487.
4. (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.
5. (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.
6. 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.
7. Tamamura, H.; Kato, T.; Otaka, A.; Fujii, N. *Org. Biomol. Chem.* **2003**, *1*, 2468.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. (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.
14. 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.
15. Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Kisanuki, S.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 3088.
16. 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.
17. (a) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563; (b) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151; (c) Butler, R. N. *Adv. Heterocyl. Chem.* **1977**, *21*, 323; (d) Lipinski, C. A. *Annu. Rep. Med. Chem.* **1986**, *21*, 283.
18. (a) Kohara, Y.; Imamiya, E.; Kubo, K.; Wada, T.; Inada, Y.; Naka, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1903; (b) Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228.
19. Young, R. W.; Wood, K. H. *J. Am. Chem. Soc.* **1955**, *77*, 400.
20. Godefroi, E. F.; Wittle, E. L. *J. Org. Chem.* **1956**, *21*, 1163.
21. Computer-assisted simulated docking experiments were carried out under an MMFF94X force field in a BACE1 enzyme (PDB ID: 1FKN and 1W51) using Chemical Computing Group's Molecular Operating Environment (moe2005) with Ryoka Systems Inc.'s ASEDock 2005 module.
22. Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
23. Rehse, K.; Brehme, F. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 375.