Journal of Medicinal Chemistry

Article

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Conformational Restriction Approach to β-Secretase (BACE1) Inhibitors: Effect of a Cyclopropane Ring To Induce an Alternative Binding Mode

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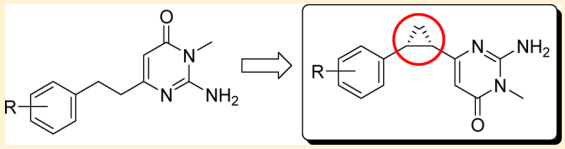
Supporting Information

ABSTRACT: Improvement of a drug's binding activity using the conformational restriction approach with sp^3 hybridized carbon is becoming a key strategy in drug discovery. We applied this approach to BACE1 inhibitors and designed four stereoisomeric cyclopropane compounds in which the ethylene linker of a known amidine-type inhibitor **2** was replaced with chiral cyclopropane rings. The synthesis and biologic evaluation of these compounds revealed that the *cis*-(1*S*,2*R*) isomer **6** exhibited the most potent BACE1 inhibitory activity among them. X-ray structure analysis of the complex of **6** and BACE1 revealed that its unique binding mode is due to the apparent CH−π interaction between the rigid cyclopropane ring and the Tyr71 side chain. A derivatization study using **6** as a lead molecule led to the development of highly potent inhibitors in which the structure−activity relationship as well as the binding mode of the compounds clearly differ from those of known amidine-type inhibitors.



INTRODUCTION

Alzheimer's disease (AD) is a progressive neurologic disorder of the brain, now considered to be the main form of dementia. AD causes a gradual and progressive loss of memory and cognitive ability, impaired orientation to surroundings, and impaired language ability, and it eventually leads to death. In the amyloid cascade hypothesis, overproduction of amyloid-beta (Aβ) is considered to trigger the onset of AD.[1] Aβ gradually accumulates in the brain, forming soluble oligomers and senile plaques. Neurofibrillary tangles caused by hyperphosphorylation of the τ protein are also observed and lead to neuronal death. Two key proteases, γ-secretase and β-secretase (BACE1), are considered to have an important role in Aβ production. BACE1 first cleaves amyloid precursor protein (APP) to generate soluble amyloid precursor protein β (sAPPβ) and C99 peptide, which remains bound to a membrane.[2] The γ-secretase cuts the C99 peptide to produce mature Aβ peptides of various lengths, including $Aβ_{42}$, which is thought to be the most pathogenic among the Aβs produced. Inhibition of BACE1 activity decreases the production of all forms of Aβ, and knockdown of BACE1 expression in mice stops the production of $Aβ_{40}$ and $Aβ_{42}$ in vivo, without any signs of significant dysfunction.[3] Therefore, BACE1 inhibitors are considered to be an attractive target for a causative treatment of AD.[4] Many pharmaceutical companies are now competing to develop these inhibitors, and clinical trials with some compounds have recently begun.[5]

The cyclic amidine unit is the main common component of many targeted BACE1 inhibitors. The first report of a cyclic amidine-type inhibitor using a fragment-based drug design technique was made by AstraZeneca/Astex reseachers in 2007 (Figure 1).[6] They used nuclear magnetic resonance screening to identify the first small fragment hit **1** containing an aminopyrimidone ring system. They then studied the structure/activity relationship (SAR) of the hit **1** using a fragment-growing approach based on the X-ray structure of the complex with BACE1, and they developed an effective inhibitor with submicromolar order inhibitory activity by extending the hydrophobic aryl substituent with an ethylene linker. They also reported the X-ray structures of some other amidine-based inhibitors complexed with BACE1, in which a common binding

Received: August 3, 2012
Published: September 21, 2012

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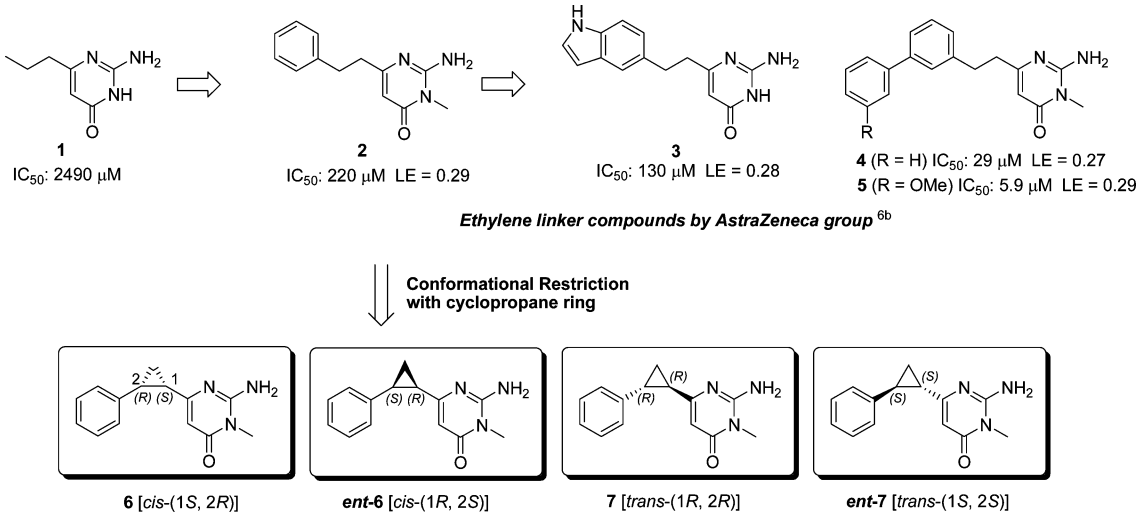


Figure 1. Basic concept of the compound design.

mode was disclosed.[6,7f,g] Two nitrogen atoms in the cyclic amidine ring make tight hydrogen bonds with the side chains of catalytic residues Asp32 and Asp228. The hydrophobic aryl part of the inhibitors is accommodated in the S1 and S3 pocket of the active sites, allowing for an effective hydrophobic interaction with BACE1. This binding mode is analogous in complexes of other amidine-type inhibitors.[7]

To convert the fragments into more effective lead compounds, saturated alkyl chains or sp^2 hybridized carbon-including linkers, such as carbon−carbon double bonds or amide bonds, are commonly utilized for fragment-growing.[8] Saturated alkyl chains are probably the most commonly utilized linkers because of their structural simplicity and facile synthesis, but their high degree of free rotation may impede their binding affinity. sp^2 linkers are also widely used for their availability as building blocks due to the recent development of coupling reactions. They are also advantageous as a facile method for introducing conformational fixation to molecules, due to their low degree of free rotation. On the other hand, the incorporation of sp^2 carbon-based components sometimes causes undesirable physical properties, *e.g.*, low solubility, probably due to intermolecular static interactions caused by the planar sp^2 carbon.[9] Further, identification of a structurally new drug candidate is often difficult because of the shortage of sp^2-carbon based chemical entities in a novel structure and its limited three-dimensional structural diversity. On the other hand, the use of rigid structures based on sp^3 carbons is now becoming a key topic in drug design in terms of improved selectivity.[10] This approach may enable the development of novel, structurally diverse compounds and potential binders with improved activity by compensating for the entropic loss generated by binding to the target compound.[11]

Cyclopropane is widely used in drug design and is incorporated in many drugs that are currently on the market. It is the smallest, rigid sp^3-carbon based ring system and has potential application in a conformational restriction approach, but the number of successful applications to date is small, probably due to the limited number of examples of its stereoselective and industrially feasible synthetic methods.[12] Our laboratory has been studying the synthesis of optically active cyclopropanes from commercially available chiral epichlorohydrin and their utilization in drug design. We successfully produced novel, selective NMDA antagonists,[13] histamine H_3 agonists,[14a,b] and histamine H_3/H_4 antagonists,[14c,d] whose conformation is effectively controlled by the characteristic stereochemical features of cyclopropane. Its low molecular weight and rigid framework may also be suitable for fragment-based drug design, especially in a fragment growing approach, as well as a component in a fragment compound library.

Therefore, here we investigated the feasibility of replacing the ethylene part of a known BACE1 inhibitor **2** with a cyclopropane ring, and we designed the conformationally restricted analogs **6** and **7** and their enantiomers ***ent*-6** and ***ent*-7** to improve their BACE1 inhibitory activity by placing the substituents at a position suitable for effective binding and by reducing the active entropic energy loss upon binding BACE1 due to the conformational restriction (Figure 1). Using the most active compound **6** among them as a lead, we obtained SAR results that were clearly different from those of the unrestricted inhibitors to identify potent BACE1 inhibitors based on the characteristic binding mode of the compounds due to the conformational restriction. In this report, we describe the results in detail.

RESULTS AND DISCUSSION

Docking Simulations of the Conformationally Restricted Analogs. First, the conformations of these four stereoisomers with the lowest energy were calculated in the MMFF94x force field[15] using the Molecular Operating Environment (MOE).[16] The structures obtained by the calculations were superimposed on the X-ray crystallographic structure of the ethylene linker compound **3** complexed with human BACE1 (PDB code no. 2VA5), as shown in Figure 2. In the BACE1 complex, compound **3** adopts a folded conformation that is not likely to be the most stable in its unbound state. While the two *cis* isomers **6** and ***ent*-6** assume conformations similar to that of compound **3**, the benzene rings of the *trans* isomers **7** and ***ent*-7** located at positions clearly different from that of the indole ring in **3**. On the basis of this observation, the inhibitory activities of the *trans* isomers were predicted to be weaker than those of the *cis* isomers. Comparison of the two *cis* isomers suggested that ***ent*-6** was superimposed on compound **3** more precisely than **6**.

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838−8858

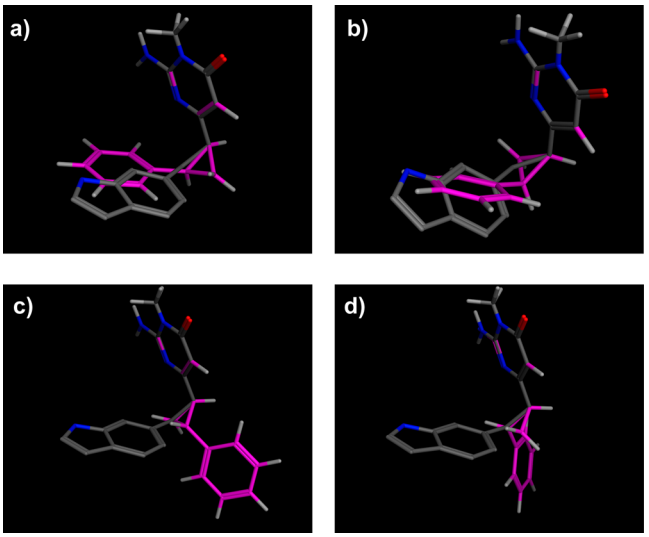


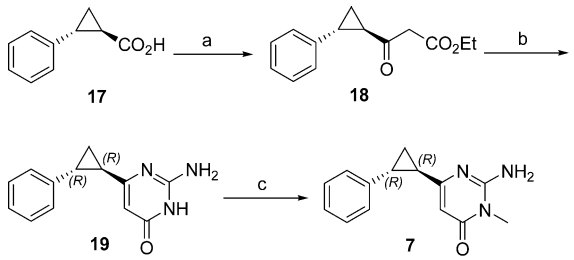
Figure 2. Superimpositions of the X-ray structure of compound **3** are in gray (PDB 2VA5) and the predicted conformations of each stereoisomer are in magenta: (a) **6** [*cis*-(1*S*,2*R*)]; (b) ***ent*-6** [*cis*-(1*R*,2*S*)]; (c) **7** [*trans*-(1*R*,2*R*)]; and (d) ***ent*-7** [*trans*-(1*S*,2*S*)].

We planned to synthesize compounds **6**, ***ent*-6**, **7**, and ***ent*-7**, to examine their BACE1 inhibitory activities to confirm the above predictions and to identify the most active stereoisomer.

Synthesis of Compounds. First generation synthesis of the *cis*-cyclopropane derivative **6** was performed based on our previous report of the stereoselective synthesis of phenylcyclopropane carboxylic acid **14** (Scheme 1).[17] Lactone **9a** was obtained by the condensation of optically pure (*S*)-(+)-epichlorohydrin **8** and phenylacetonitrile under basic conditions. Subsequent alkaline hydrolysis of the lactone followed by silylation gave the disilylated product on both the carboxyl and hydroxyl moieties, and then the silyl ester, which was selectively hydrolyzed under aqueous basic conditions to yield the carboxylic acid **10**. **10** was subjected to Barton decarboxylation, giving the *cis*-product selectively, which, without purification, was deprotected with TBAF to isolate the *cis* alcohol **12**. After oxidation of **12** into the carboxylic acid **14**, the *β*-ketoester **15** was successfully obtained from **14** using the Masamune conditions.[18] The minor *trans* isomer was completely removed by SiO_2 column chromatography at this stage. According to the aminopyrimidone synthesis method reported previously,[6b,c] **15** was treated with guanidine carbonate in the presence of MeONa. Epimerization at the 1-position of cyclopropane occurred concomitantly during cyclization to give a mixture of diastereomers **16** in a ratio of *cis*/*trans* = 1.3:1. Highly basic guanidine may have caused the isomerization via the enolization of the keto-cyclopropyl moiety in **15**. Selective methylation of **16** with MeI occurred at the lactam nitrogen, and finally the desired **6** was obtained after the reversed phase preparative HPLC purification, although the yield was poor. Its enantiomer, ***ent*-6**, was synthesized using the same reaction sequence starting from (*R*)-(−)-epichlorohydrin.

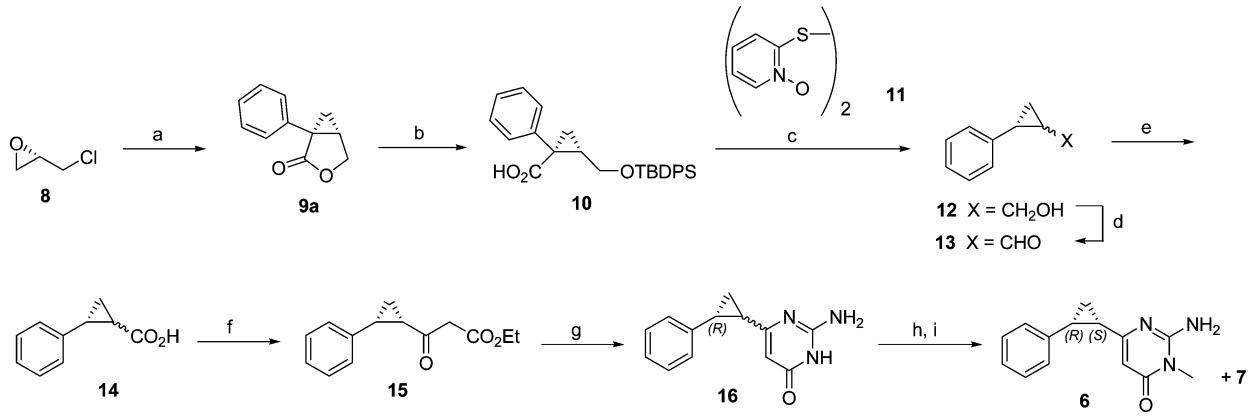
The *trans*-(1*R*,2*R*) isomer **7** and its enantiomer *trans*-(1*S*,2*S*) ***ent*-7** were prepared according to a procedure similar to those for the *cis*-isomers **6** and ***ent*-6**, from the known chiral phenylcyclopropane carboxylic acid **17** and ***ent*-17** (Scheme 2).[19] Neither epimerization nor a decrease in enantiomeric

Scheme 2. Synthesis of 7[a]



[a]Reagents and conditions: (a) (i) 1.5 equiv of CDI, MeCN, rt, 1 h, (ii) 2.1 equiv of potassium ethyl malonate, 2.5 equiv of $MgCl_2$, 3.2 eq Et_3N, MeCN, r.t., then 80 °C, 2 h, 82%; (b) 2 equiv of guanidine carbonate, 2 equiv of EtONa, EtOH, 80 °C, 5 h, 57%; (c) 1.1 equiv of MeI, 1.1 equiv of K_2CO_3, DMF, rt, 18 h, 67%.

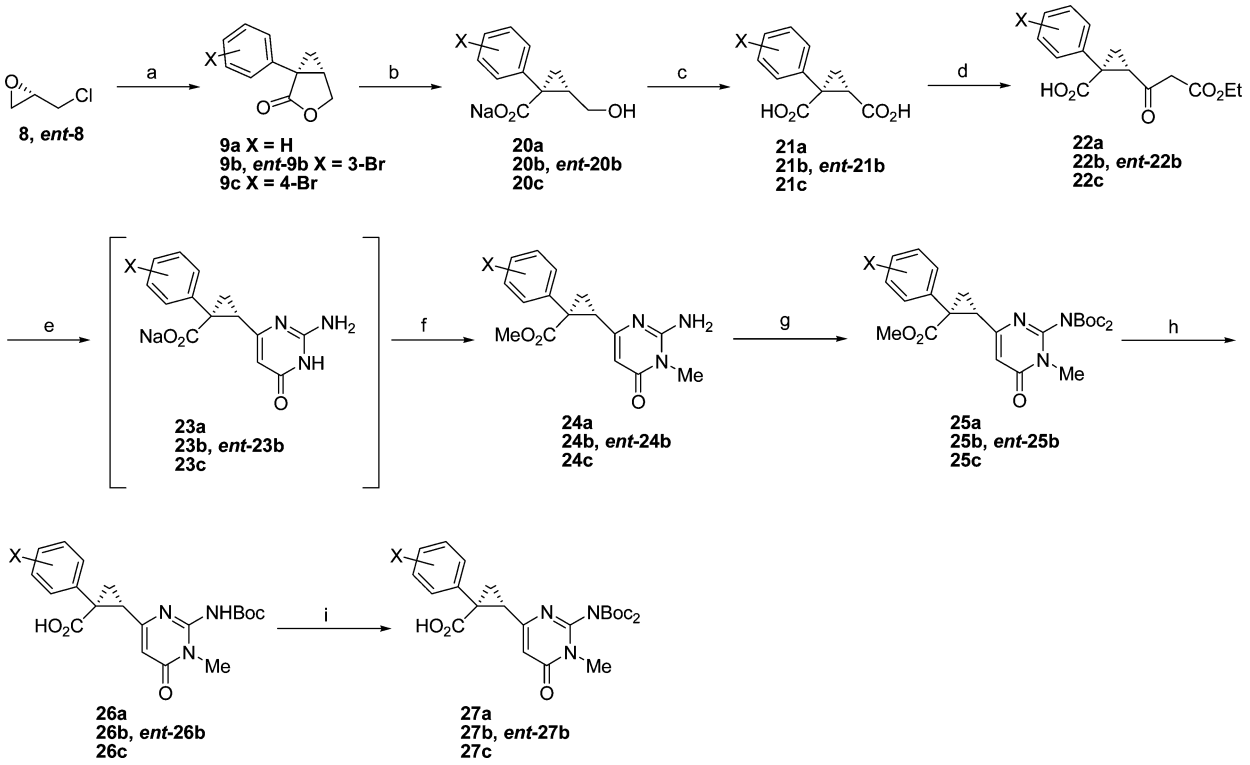
Scheme 1. First-Generation Synthesis of 6[a]



[a]Reagents and conditions: (a) (i) 1.1 equiv of $PhCH_2CN$, 2.5 equiv of $NaNH_2$, benzene, rt, 1 h, (ii) 10 M KOH aq, EtOH 20 h, reflux, 56%; (b) (i) 10 M KOH aq, EtOH, rt, 1 h, (ii) 4.5 equiv of TBDPS-Cl, 5 equiv of imidazole, DMF, rt, overnight, (iii) 10 M KOH aq, EtOH, 1 h, rt, 48%; (c) (i) 1.2 equiv of **11**, 1.5 equiv of *n*-Bu_3P, 3 equiv of $(TMS)_3SiH$, 0.2 equiv of AIBN, benzene, rt, 1 h, then 80 °C, 6.5 h, (ii) 1.5 equiv of TBAF, THF, 45%, *cis*/*trans* = 10.7: 1; (d) 0.1 equiv of TPAP, 3 equiv of NMO, MS4A, CH_2Cl_2, rt, 1 h, 75%, *cis*/*trans* = 10.6:1; (e) 1.5 equiv of $NaClO_2$, 1.5 equiv of H_2NSO_3H, MeOH/H_2O, 0 °C, 1 h, 90%, *cis*/*trans* = 7.6: 1; (f) (i) 1.5 equiv of CDI, MeCN, rt, 1 h, (ii) 2.1 equiv of potassium ethyl malonate, 2.5 equiv of $MgCl_2$, 3.2 equiv of Et_3N, MeCN, rt, then 80 °C, 2 h, 77%; (g) 2 equiv of guanidine carbonate, 2 equiv of EtONa, EtOH, 80 °C, 5 h, 80%, *cis*/*trans* = 1.3:1; (h) 1.3 equiv of MeI, 1.3 equiv of K_2CO_3, DMF, rt, 22 h, 47%; (i) preparative HPLC separation, **6** 23%, **7** 56%.

dx.doi.org/10.1021/jm3011405 | *J. Med. Chem.* 2012, 55, 8838−8858

Scheme 3. Improved Synthesis of *cis*-Cyclopropane Derivatives[a]



[a]Reagents and conditions: (a) (i) $ArCH_2CN$, $NaNH_2$, benzene or toluene, rt, (ii) 10 M KOH aq, EtOH, reflux, 58% (**9a**), 61% (**9b**), 63% (***ent*-9b**), 62% (**9c**); (b) (i) 10 M KOH aq, EtOH, H_2O, rt, (ii) 1 equiv of MeONa, Et_2O, 80% (**20a**), 87% (**20b**), 94% (***ent*-20b**), 95% (**20c**); (c) cat. $RuCl_3$, $NaIO_4$, MeCN, H_2O, rt, 75% (**21a**), 87% (**21b**), 80% (***ent*-21b**), 69% (**21c**); (d) (i) CDI, (ii) potassium ethyl malonate, $MgCl_2$, Et_3N, MeCN, rt, then 80 °C; (e) (i) EtONa, (ii) guanidine carbonate, EtOH, 90 °C, 14 h; (f) MeI, K_2CO_3, DMF, rt, 32% (**24a**), 34% (**24b**), 29% (***ent*-24b**), 33% (**24c**) for 3 steps; (g) Boc_2O, DMAP, CH_2Cl_2, rt, 85% (**25a**), 89% (**25b**), 82% (***ent*-25b**), 92% (**25c**); (h) 10 M KOH aq, EtOH, H_2O, 60 °C; (i) (i) *N*,*O*-bistrimethylsilylacetamide, (ii) Boc_2O, DMAP, CH_2Cl_2, rt, 78% (**27a**), 80% (**27b**), 78% (***ent*-27b**), 72% (**27c**) for 2 steps.

purity was observed during the synthesis of these *trans* isomers, indicating that intermediate ketoester **18** and ***ent*-18** were likely to be thermodynamically far more stable than the *cis*-oriented ketoester **15** under basic conditions.

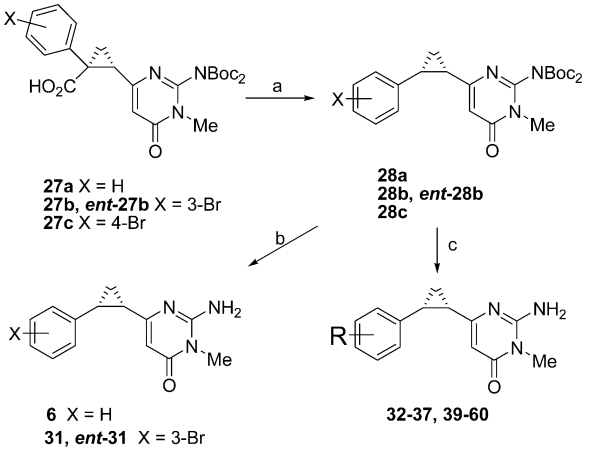
As described below, the *cis*-(1*S*,2*R*) isomer **6** was the most potent BACE1 inhibitor among the four conformationally restricted stereoisomers. The first generation synthetic route shown in Scheme 1 involved an undesired epimerization at the 1-position in the cyclopropane ring to the *trans*-isomer at the cyclization step, which was a big problem for scale-up synthesis and efficient exploration of the SAR, so we developed an alternative stereoelective synthetic route for the *cis*-cyclopropane derivatives (Scheme 3).

We planned to prepare various derivatives of the *cis*-(1*S*,2*R*) isomer **6** that have a substituent at the 3- or 4-position of the benzene ring using the Suzuki–Miyaura coupling reaction, and therefore, 3- or 4-bromo substituted derivatives of **6** were also required. Thus, the 3- or 4-bromo substituted lactones **9b**, ***ent*-9b**, and **9c** were prepared according to the procedure for the synthesis of **9a** described above, the enantiomeric excesses of which were confirmed to be around 95%. Compounds **9** were then hydrolyzed under aqueous basic conditions to convert them to a stable and fine crystalline carboxylic acid salt **20**, subsequent ruthenium tetroxide oxidation of which gave the bis-carboxylic acids **21** in good yields. Next, we introduced the *β*-ketoester moiety into **21**. *β*-Ketoesterification using Masamune conditions[18] proceeded selectively at the sterically less hindered carboxy group to yield the desired **22** as a sole product. Treatment of **22** with sodium ethoxide and subsequent heating with guanidine carbonate produced **23**; then methylation of **23** with MeI proceeded selectively at the carboxyl group and the lactam nitrogen in the aminopyrimidone ring to give **24** with ∼30% yield from **21**. After protection of the amino moiety of **24** with two Boc groups, alkaline hydrolyses of the resulting methyl ester **25** were carried out, where one of the two Boc groups was simultaneously removed to furnish **26**. In situ silylation of the carboxy group with *N*,*O*-bistrimethylsilylacetamide (BSA), and then a trial of Boc protection yielded **27**, the substrate for stereoselective Barton decarboxylation (Scheme 4).[17,20]

Optimization studies for the radical decarboxylative isomerization reaction were performed using ***ent*-27b** as a substrate (Table 1). First, according to the best conditions determined in our previous report,[17] ***ent*-27b** was heated with **11** (1.2 equiv), Bu_3P (3 equiv), and TMS_3SiH (3 equiv) in the presence of AIBN as a radical initiator to give ***ent*-28b** in 32% yield, whereas none of the *trans* isomer was produced. The thio-pyridine containing compound **29** was also isolated in 42% yield as a byproduct (entry 1).[21] We deduced that the side-reaction might proceed due to the low reactivity of $(TMS)_3SiH$. When 6 equiv of $(TMS)_3SiH$ was used to promote trapping of the radical intermediate by the reagent, the yield of ***ent*-28b** was slightly improved, but there was still significant production of **29** (entry 2 in Table 1). Thus, using a more reactive reductant, Bu_3SnH, the desired product ***ent*-28b** was successfully obtained in 57% yield (entry 3) without producing the *trans* isomer under the

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838–8858

Scheme 4. Barton Decarboxylation and Cross Coupling Reactions[a]



[a]Reagents and conditions: (a) **11** (1.2 equiv), *n*-Bu_3P (3 equiv), *n*-Bu_3SnH (3 equiv), AIBN (0.2 equiv), toluene, rt, then 80 °C, 53% (**28a**), 48% (**28b**), 52% (***ent*-28b**), 38% (**28c**); (b) TFA, CH_2Cl_2, rt, 75% (**6**), 81% (**31**), 80% (***ent*-31**); (c) R-B(OH)$_2$ or R-Bpin, K_2CO_3, $PdCl_2(PPh_3)_2$, dioxane, H_2O, 100 °C (Method A), 150 °C under microwave, 30 min (Method B).

same conditions. Although another radical initiator, 2,2′-azobisvaleronitrile, which initiates radical chain reactions at a lower temperature, was also tested, the reaction did not proceed (entry 4).

Using the conditions described for entry 3, Barton decarboxylation of other substrates was performed, and the desired *cis*-substituted cyclopropane compounds **28a−c** were obtained in 38−53% yield. Deprotection of **28a** gave the *cis*-(1*S*,2*R*) isomer **6**, whose enantiomeric excess was determined to be 94.8% by chiral column analysis (see Experimental Section). Compounds **28b** and ***ent*-28b** were also deprotected to give **31** and ***ent*-31**, respectively. Using **28b**, ***ent*-28b**, and **29c** as substrates for the Suzuki−Miyaura couplings, we obtained a variety of target compounds.

BACE1 Inhibitory Activities of Conformationally Restricted Analogs. The BACE1 inhibitory activities of the four isomers **6**, ***ent*-6**, **7**, and ***ent*-7** against human BACE1 are shown in Table 2. Among the four cyclopropane-based conformationally restricted analogs, the *cis*-(1*S*,2*R*) isomer **6** exhibited significant inhibitory activity [IC_{50} = 157 μM, ligand efficiency (LE) = 0.29], while the activity of its enantiomer ***ent*-6** was approximately four times weaker (IC_{50} = 619 μM, LE = 0.24). The two *trans* isomers did not show any inhibitory activity (>2000 μM). Although the IC_{50} value and LE of **6** were not definitely improved, it was equally active with the nonrestricted ethylene linker compound **2** (IC_{50} = 171 μM, LE = 0.30). Thus, the stereochemistry of the cyclopropane ring was closely related to the inhibitory activity of BACE1, and the *cis*-(1*S*,2*R*) isomer **6** was the most suitable for further design of compounds with improved activity.

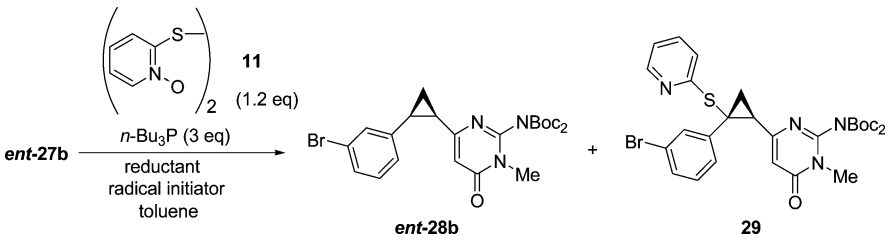
Table 2. BACE1 Inhibitory Activity of 2 and Its Conformationally Restricted Analogs

compd	BACE1 IC_{50} (μM)[b]	ligand efficiency (LE) (kcal/mol per heavy atom)
2[a]	171	0.30
6	157	0.29
***ent*-6**	619	0.24
7	>2000	
***ent*-7**	>2000	

[a]Compound **2** was prepared according to the reported procedures.[6b,c] [b]IC_{50} in ELISA. Values are means of at least two experiments.

X-ray Crystallographic Structure Analysis of 6 Complexed with BACE1. To clarify the bioactive conformation of **6** and to gain more detailed insight into the structure modification of **6**, we prepared the crystalline complex of human BACE1 and **6** and analyzed its X-ray crystallographic structure (Figure 3). As expected from the structures of other previously reported cyclic amidine-based inhibitors complexed with BACE1, the two nitrogen atoms of the amidine moiety formed hydrogen-bond contacts with the side chain of Asp32 and Asp228 of BACE1. The benzene ring of **6** was accommodated in the S1 pocket with favorable hydrophobic interactions. Superimposition of this structure on the previously reported structure of the ethylene linker compound **3**−BACE1 complex (PDB code no. 2VA5)[6b] (Figure 3) revealed some interesting differences. In the structure of **6**, the side chain of Tyr71 in the BACE1 enzyme flipped, which made space for the compound to be incorporated.[22] Furthermore, to our surprise, **6** was located at a position remarkably closer to the flap region of BACE1 compared with that of the ethylene linker compound **3**, making it possible for the cyclopropane ring to interact with

Table 1. Optimization of Barton Decarboxylation of *ent*-27b



entry	reductant (eq)	initiator	temp (°C)	yields (%) ent-28b	yields (%) 29
1	TMS_3SiH (3)	AIBN	80	32	42
2	TMS_3SiH (6)	AIBN	80	38	35
3	n-Bu_3SnH (3)	AIBN	80	57	10
4	n-Bu_3SnH (3)	AVN[a]	65	N.D.[b]	N.D.[b]

[a]2,2′-Azobisvaleronitrile. [b]Not detected.

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838−8858

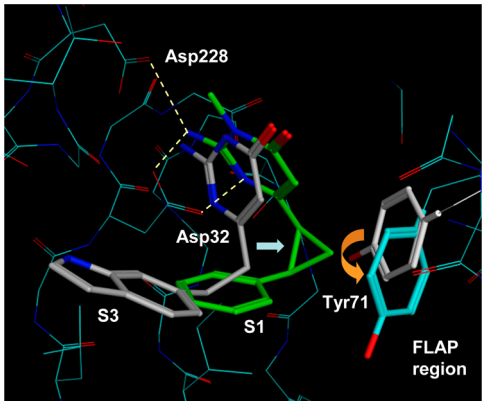


Figure 3. X-ray crystallographic structure of the BACE1 (in cyan) complexed with **6** (in green), superimposed with ligand **3** in PDB 2VA5 (**3** in gray and Tyr71 side chain in white). Key interactions between **6** and the side chains of Asp32 and Asp228 are depicted as yellow dashed lines.

the side chain moiety of Tyr71. The distance of the aromatic ring in Tyr71 and a carbon or hydrogen in the cyclopropane ring was around 3.4 Å or 2.7 Å, respectively (Figure 4),

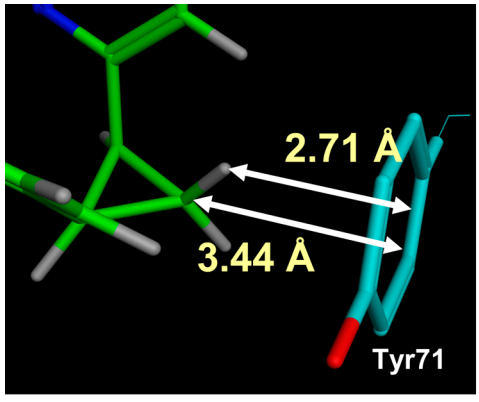


Figure 4. Distances between the π plane of Tyr71 and the cyclopropane carbon atom or hydrogen atom of compound **6** in the complex.

suggesting a CH−π interaction between those moieties.[23] A tight conformational restriction by the cyclopropane ring might have caused the unexpected induced-fit on the binding of **6** with BACE1, in which the effective CH−π interaction of the cyclopropane ring and the Tyr71 side chain was likely to stabilize the complex structure. The cyclopropane ring is more polarizable than the ethylene, which might result in effective dispersion interactions, leading to this interesting CH−π interaction mode.[24] Moreover, the sp^2-like hybrid orbital nature of cyclopropane might also make favorable contact with the Tyr71 side chain through electrostatic interactions.[25]

Thus, an alternative inhibitor-binding mode of BACE1 induced by the rigid cyclopropane ring was identified. We expected that the SAR, different from those reported for the derivatives of ethylene linker compounds **2**, might be determined in derivatization studies of **6** as a lead.

Compound Design Based on the Structure of 6 Complexed with BACE1. To explore more active compounds against BACE1, we performed docking studies using the **6** and BACE1 complex (Figure 3). Many potent BACE1 inhibitors reported to date bear a cyclic amidine moiety as the key component that interacts with the two catalytic Asp side chains, and they also contain a biaryl-based structure, which fits hydrophobic S1 and S3 pockets. In these biaryl cyclic amidine BACE1 inhibitors,[4] substituting the amidine moiety at the *meta* position on the aromatic ring usually leads to improved inhibitory activity by efficiently occupying the bent-shaped active site of BACE1.

We designed several compounds by taking these reported results and the structure of **6** complexed with BACE1 into account. First, we intended to introduce another benzene ring at the *meta* position of the benzene ring on **6**. A docking study was performed using the X-ray data of Figure 3; energy minimization of a newly designed ligand **32**, which bears a benzene ring at the *meta* position, was performed with MOE and then merged with the protein structure shown in Figure 3. An unfavorable steric crash between the binding site of BACE1 and the terminal benzene ring, however, was clearly observed (Figure 5), probably due to the position of this compound in

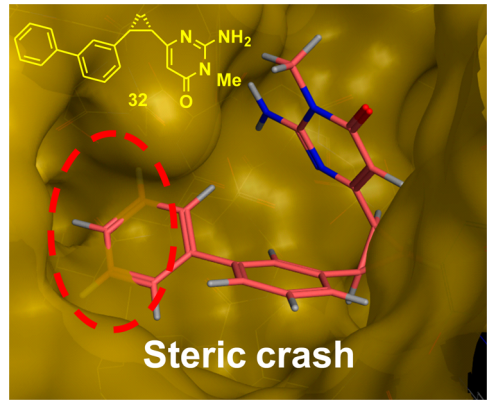


Figure 5. Docking study result for compound **32**, in which a phenyl substituent was introduced at the *meta* position of compound **6**.

the active site being more proximal to the flap region compared with that of the ethylene linker compound **3**. Thus, it was anticipated that the introduction of an additional aromatic ring into the *meta* position of the benzene ring in **6** might lead to weaker activity. We observed a new space around the *para* position of the benzene ring in **6**, however, which was not present in the complex structures of the known biaryl cyclic amidine BACE1 inhibitors (Figure 6). Therefore, we expected that introducing another substituent into this position might make it possible to develop a new type of potent inhibitor, and

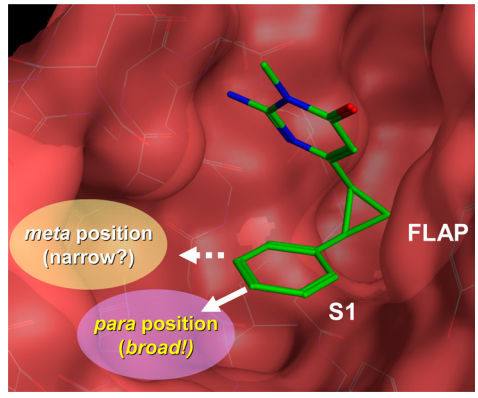
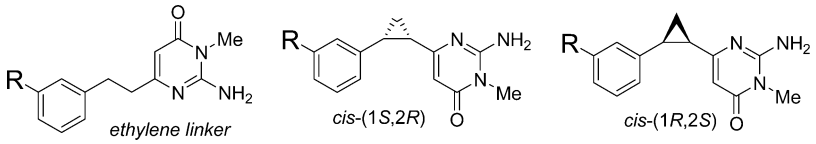


Figure 6. Possible substitutions at the *para* position of **6**.

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838−8858

Table 3. BACE1 Inhibitory Activity of the *meta*-Substituted Derivatives



R	Cpds.	BACE1 IC_{50} [a] (μM)	LE [b]	Cpds.	BACE1 IC_{50} [a] (μM)	LE [b]	Cpds.	BACE1 IC_{50} [a] (μM)	LE [b]
Br	**30**[c]	19.8	0.36	**31**	502	0.24	***ent*-31**	1114	0.21
Ph	**4**	6.5	0.31	**32**	614	0.18	***ent*-32**	1848	0.16
	**5**	4.2	0.29	**33**	4.6	0.28	***ent*-33**	103	0.21

[a] IC_{50} in ELISA. Values are means of at least two experiments. [b] Ligand efficiency. [c] Compound **30** was prepared according to the reported procedures.[6b,c]

we planned to synthesize the following two types of new compounds and examine their BACE1 inhibitory activity to verify our hypotheses: (a) *meta*-substituted biaryl derivatives to examine whether the SAR of our compounds differed from those of the previous biaryl cyclic amidine BACE1 inhibitors, and (b) *para*-substituted biaryl derivatives to improve the activity.

Structure–Activity Relationship of the *meta*-Substituted Biaryl Derivatives. We synthesized several *meta*-aryl substituted *cis*-(1*S*,2*R*) cyclopropane derivatives **31**–**33** and the corresponding ethylene linker compounds **30**, **4**, and **5**, and we compared their BACE1 inhibitory activity. We also prepared their enantiomers, ***ent*-31**–**33**, to reaffirm the suitable stereoconfiguration of the cyclopropane ring. The structures and activities of these compounds are shown in Table 3. When a bromo or a phenyl group was introduced into the meta-position of these three series of compounds, the IC_{50} values against BACE1 significantly decreased over 500 μM in the *cis*-(1*S*,2*R*)-type compounds (**31**, **32**) and over 1 mM in the *cis*-(1*R*,2*S*)-type compounds (***ent*-31**, **32**), while the corresponding ethylene linker-type compounds had remarkable inhibitory activity (**30**, **4**; IC_{50} = 19.8–6.5 μM). The declining activity of the cyclopropane derivatives was just as predicted from the docking study shown in Figure 5. To our surprise, however, substitution of the *m*-methoxyphenyl group on the *cis*-(1*S*,2*R*) cyclopropane compound dramatically improved the activity, with an IC_{50} value (**33**; 4.6 μM) comparable to that of the ethylene linker compound **5** (4.2 μM). The identical modification on the *cis*-(1*R*,2*S*) cyclopropane compound was also effective, but its IC_{50} value (***ent*-33**; 103 μM) was still ∼20 times weaker than those of **33** and **5**. As a result, compound **6** with the *cis*-(1*S*,2*R*)-cyclopropane structure was the most effective lead compared with its enantiomer ***ent*-6** having a (1*R*,2*S*) cyclopropane structure, in these *meta*-substituted biaryl derivatives.

X-ray Structure of 33 Complexed with BACE1. We then performed the X-ray structure analysis of the compound **33** and BACE1 complex to elucidate why only **33** among the *meta*-substituted cyclopropane derivatives exhibited strong inhibitory activity against BACE1. The aminopyrimidine moiety of **33** occupied a position almost identical to that of **6**, and its nitrogens interacted with the aspartic acid catalytic centers in the same manner (Figure 7a). The central benzene ring was placed in the S1 pocket, creating an effective hydrophobic interaction with the enzyme pocket. As predicted from the SAR study summarized in Table 3, the methoxy group on the terminal benzene ring played a key role in the interaction with BACE1. The methoxy oxygen formed a hydrogen bond with the water molecule, placed in the deeper position within the S3 pocket, which makes a hydrogen bond with the main chain of Ser229.[26] Interestingly, the side chain of Leu30 of the S1

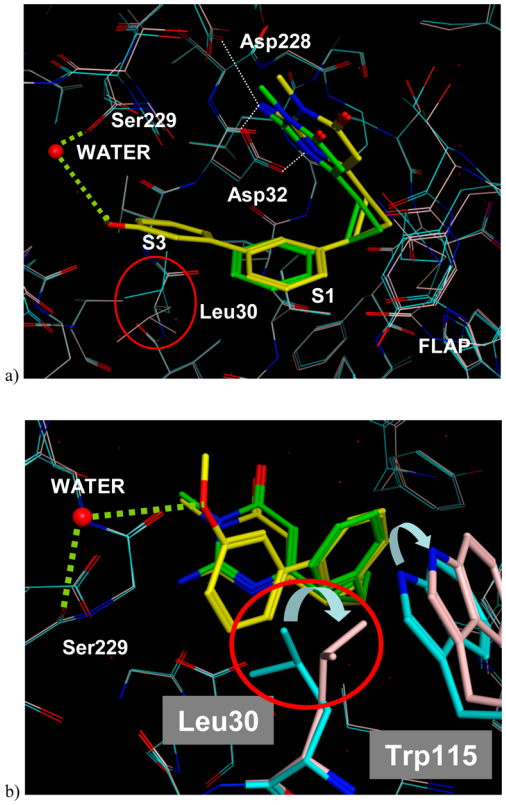


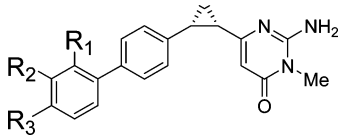
Figure 7. (a) X-ray crystallographic structure of **33** (in yellow) complexed with BACE1 (in beige), superimposed with BACE1 (in cyan) complexed with **6** (in green). The hydrogen binding network of the methoxy group of **33**, a water molecule, and the main chain of Ser229 is drawn in green dashed lines. (b) Seen from the bottom side of part a. Some residues were omitted for clarity.

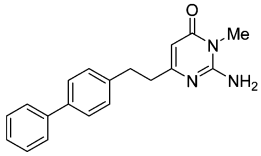
dx.doi.org/10.1021/jm3011405 | *J. Med. Chem.* 2012, 55, 8838–8858

pocket eventually rotated toward the indole ring of Trp115 to make a space accommodating the terminal aromatic ring (Figure 7b). Such an induced fit initiated by the interaction between the amidine-based BACE1 inhibitor and the Leu30 side chain is the first example, to our knowledge, among the many X-ray structures of the BACE1 and its inhibitor complex reported so far.[27] The hydrogen bond network mediated by the water molecule placed in the S3 pocket should be indispensable for the remarkable inhibitory activity of **33**. The unexpected binding mode of **33** to BACE1 would originate from the induced fit due to the rigid cyclopropane ring with the *cis*-(1*S*,2*R*) stereochemistry.

SAR of the *para*-Substituted Biaryl Derivatives. We examined the BACE1 inhibitory activities of the *para*-substituted biaryl derivatives **34**–**37** with the (1*S*,2*R*)-cyclopropane structure and the corresponding ethylene linker-type compound **38** (Table 4). As expected from the X-ray structural analysis of the parent compound **6**, substitution of a benzene ring in the *para* position of **6** successfully improved the activity; compound **34** had an IC_{50} value of 25.6 μM, which is about 5-fold more active than **6**, although the LE decreased slightly to 0.26. The corresponding ethylene linker compound **38** was completely inactive. These results suggest that the novel structural modification could be spread out by restricting the conformation of the ethylene chain using the (1*S*,2*R*)-cyclopropane structure.

Table 4. Primary SAR of the *para*-Substituted Biaryl Derivatives



Cpds.	R_1	R_2	R_3	BACE1 IC_{50}[a] (μM)	LE[b]
34	H	H	H	25.6	0.26
35	Me	H	H	39.4	0.24
36	H	Me	H	17.1	0.26
37	H	H	Me	119.0	0.22
38				> 200	-

[a]IC_{50} in homogeneous time-resolved fluorescence (HTRF) assay. Values are means of at least two experiments. [b]Ligand efficiency.

Compounds **35**–**37** methylated at the *ortho*-, *meta*-, or *para*-position on the terminal benzene ring of **34** were examined to investigate the feasibility of additional structural modification. Among those compounds, the *meta*-methylated **36** had improved activity with an IC_{50} of 17.1 μM, of which the LE (0.26) was equal to that of compound **34**. Thus, substitution at the *meta* position of the terminal benzene ring improved the inhibitory activity of these derivatives.

The X-ray structure of compound **36** complexed with BACE1 was then analyzed to obtain information for further structural modification (Figure 8). The biaryl moiety was in an almost planar conformation, and the terminal methyl group was directed toward the unoccupied S3 pocket. On the basis of this observation, we further examined the SAR using two strategies: (a) replacing the terminal benzene ring of **36** with a smaller heteroaromatic ring or a pyridine ring to more precisely fit the compound to the active site of BACE1 and to reduce the steric repulsion between the two benzene rings in **36** in the planar conformation; and (b) replacing the substituent at the *meta* position of the terminal benzene ring to effectively occupy the vacant space of the S3 pocket.

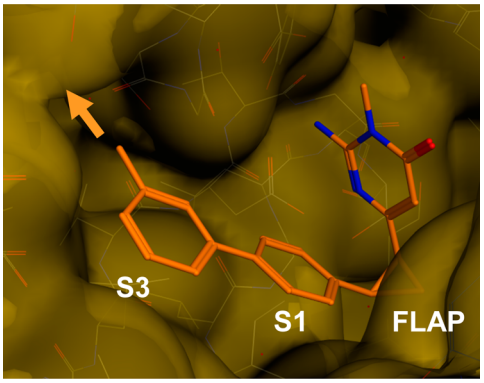


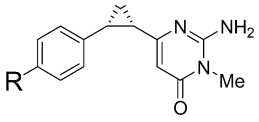
Figure 8. X-ray crystallographic structure of **36** (in orange) complexed with BACE1.

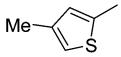
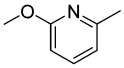
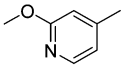
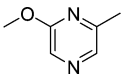
The SAR results based on strategy a are summarized in Table 5. Replacing the benzene ring with a sterically less-demanding 2-thienyl group (compound **39**) improved the activity (14.1 μM) and LE (0.29), but replacing the benzene ring with a 3-thienyl group or a 2-furanyl group was not effective. Further, introduction of a methyl group onto the thiophene ring of **39**, i.e., compounds **42** and **43**, was not effective, probably due to the different orientation of the methyl group from that in compound **36**. Replacement with a substituted pyridine ring was also carried out (compounds **44**, **45**), but this resulted in largely decreased activity. On the other hand, replacement with a pyrazine ring was fairly effective (compound **46**), with an IC_{50} value of 12.6 μM, but the LE was not significantly improved.

Replacing the terminal substituent based on strategy b was also investigated (Table 6). Various alkoxy chains were introduced in which the ethoxy-substituted compound **48** had excellent activity (IC_{50} = 10.2 μM). Introduction of shorter (**47**), longer (**49**), or branched (**50**, **51**) alkoxy chains led to dropped activity. Simple linear alkyl chains or alkylsulfanyl chains were fairly effective (**52**–**55**), with IC_{50} values of 10–20 μM. Ethylsulfanyl-substituted compound **55** exhibited the best activity among the *para*-substituted compounds synthesized (IC_{50} = 9.1 μM). The corresponding ethylene linker-type congener **61**, having the same ethylsulfanyl substituent as **55**, had no inhibitory activity against BACE1. Replacement with other substituents, such as $MeOCH_2$, $NCCH_2$, $HOCH_2CH_2$, AcHN, or H_2NOC, was less effective (compounds **56**–**60**). These data support the fact that the remaining space in the S3 pocket is a narrow "pipe"-like shape of approximately three single bonds in length with a hydrophobic nature.

dx.doi.org/10.1021/jm3011405 | *J. Med. Chem.* 2012, 55, 8838–8858

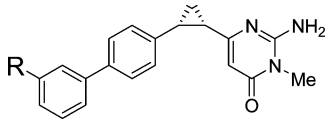
Table 5. SAR of the *para*-Substituted Biaryl Derivatives: Introduction of Heteroaromatics

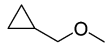
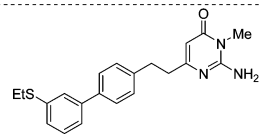


Cpds.	R	BACE1 IC_{50} [a] (μM)	LE [b]
34		25.6	0.26
39		14.1	0.29
40		46.5	0.26
41		59.0	0.25
42		165	0.22
43		50.7	0.25
44		53.3	0.23
45		116	0.21
46		12.6	0.26

[a]: IC_{50} in HTRF assay. Values are means of at least two experiments. [b]Ligand efficiency.

Table 6. SAR of the *para*-Substituted Biaryl Derivatives: Modification of the Terminal Substituent



Cpds.	R	BACE1 IC_{50} [a] (μM)	LE [b]
34	H	25.6	0.26
47	MeO	14.3	0.26
48	EtO	10.2	0.25
49	*n*-PrO	14.0	0.24
50	*i*-PrO	54.0	0.21
51		34.1	0.21
52	Et	23.2	0.24
53	*n*-Pr	11.0	0.25
54	MeS	14.9	0.25
55	EtS	9.1	0.26
56	$MeOCH_2$	24.3	0.24
57	$N{\equiv}CCH_2$	20.6	0.24
58	$HOCH_2CH_2$	24.5	0.23
59	AcHN	70.0	0.20
60		59.9	0.21
61		> 200	-

[a]IC_{50} in HTRF assay. Values are means of at least two experiments. [b]Ligand efficiency.

CONCLUSION

We designed and synthesized cyclopropane-based conformationally restricted analogs of the amidine-type BACE1 inhibitor **2**, and we identified the active *cis*-(1*S*,2*R*) isomer **6**. X-ray crystallographic structure analysis of **6** complexed with BACE1 revealed an unexpected binding mode that was clearly different from those of the known amidine-type inhibitors, which was induced by a CH−π interaction between the rigid cyclopropane ring and the Tyr71 side chain. On the basis of this unique binding mode, we performed a derivatization study using **6** as the lead compound to clarify the novel SAR, and we successfully developed potent BACE1 inhibitors. This study revealed a new feature of the conformational restriction approach: replacement of a flexible ethylene chain with a rigid cyclopropane ring triggered an induced fit of the target protein, leading to a unique space arrangement of the binding site and thus an alternative SAR, different from that for the conformationally unrestricted parent compound.

EXPERIMENTAL SECTION

General Experimental Methods for the Syntheses of Compounds. ^{1}H- and ^{13}C-NMR chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm). Coupling constants (*J*) were reported in hertz. Silica-gel chromatography was performed on a Yamazen Hi-Flash Column (Yamazen Corporation) using an automated flash chromatography system W-prep 2XY (Yamazen Corporation). Biotage Initiator was used for microwave irradiation reactions. The purity of the final products was ≥95% as determined by LCMS analysis. LC conditions are as follows: column, intakt Unison U-18 4.6 mm × 75 mm (3 μm); temperature, 50 °C; eluent, A H_2O (0.1% HCO_2H), B MeCN (0.1% HCO_2H); gradient condition, Eluent B 10%−95% 6 min, 95% 2 min; flow rate, 2 mL/min. For detailed data of each compounds, see Supporting Information.

*2-Amino-3-methyl-6-((1S,2R)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**6**).* To a solution of **16** (105 mg, 0.460 mmol) in DMF (3.1 mL) was added potassium carbonate (63.6 mg, 0.460 mmol) and iodomethane (28.7 μL, 0.460 mmol) under N_2 atmosphere, and the mixture was stirred for 25 h at room temperature. Then iodomethane (8.6 μL, 0.138 mmol) was added, and the mixture was stirred for another 15 h. Another portion of potassium carbonate (63.6 mg, 0.460 mmol) and iodomethane (28.7 μL, 0.460 mmol) were added, and the reaction mixture was stirred for 3 h and then partitioned between AcOEt and water. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (NH silica gel, $CHCl_3$/MeOH = 30:1) to obtain

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838−8858

the mixture of **6** and **7** (52.6 mg, 0.218 mmol, 47%) as a colorless foam.

The mixture of **6** and **7** (94.2 mg, 0.390 mmol) was dissolved in MeCN (6 mL) and water (2 mL), and separated by preparative reversed-phase HPLC (column: GL Science Inertsil-ODS-3, 10 mm × 250 mm; eluent: A 0.1% TFA in H_2O, B 0.1% TFA in MeCN; gradient condition: B 10%−60% 40 min; flow rate: 3 mL/min). All fractions were collected and concentrated to approximately half volume. After alkalinizing with 5% potassium carbonate in water, the product was extracted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified again via the same method to give **6** (21.2 mg, 0.0879 mmol, 23%) and **7** (52.7 mg, 0.218 mmol, 56%) as a colorless solid, respectively. **6**: mp 148−150 °C; $[\alpha]_D^{22}$ −34.1° (c = 0.511, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34−1.41 (1H, m), 1.57−1.65 (1H, m), 2.15−2.23 (1H, m), 2.52−2.62 (1H, m), 4.79 (2H, br s), 5.64 (1H, s), 7.07−7.20 (5H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.67, 25.14, 25.92, 27.45, 101.83, 126.05, 127.69, 129.30, 137.30, 153.68, 162.24, 164.29; HRMS (ESI) calcd for $C_{14}H_{16}N_3O$: 242.1288 [(M + H)$^+$], found 242.1288; Anal. Calcd for $C_{14}H_{15}N_3O{\cdot}0.2H_2O$: C, 68.66; H, 6.34; N, 17.16. Found: C, 68.83; H, 6.38; N, 16.91. Optical purity: 96.9% ee (column: Daicel CHIRALPAK AY-H; eluent: MeCN (0.1% diethylamine), 1.0 mL/min, 40 °C, 259 nm; retention time: 4.2 min).

*2-Amino-3-methyl-6-((1R,2S)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**ent-6**).* According to the procedure used to prepare **6**, a mixture of ***ent*-6** and ***ent*-7** (35.0 mg, 0.145 mmol, 42%) was obtained as a colorless powder from ***ent*-16** (77.8 mg, 0.342 mmol). Then a mixture of ***ent*-6** and ***ent*-7** (69.1 mg, 0.286 mmol) was purified to give ***ent*-6** (17.9 mg, 0.0742 mmol, 26%) and ***ent*-7** (35.7 mg, 0.148 mmol, 52%). ***ent*-6**: $[\alpha]_D^{22}$ +32.7° (c = 0.513, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{16}N_3O$: 242.1288 [(M + H)$^+$], found 242.1288. Optical purity: 93.0% ee (column: Daicel CHIRALPAK AY-H 4.6 mm × 250 mm, eluent: MeCN (0.1% diethylamine), 1.0 mL/min, 40 °C, 259 nm; retention time: 5.0 min).

*2-Amino-3-methyl-6-((1R,2R)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**7**).* To a solution of **19** (80.9 mg, 0.356 mmol) in DMF (2.4 mL) was added potassium carbonate (49.2 mg, 0.356 mmol) and iodomethane (22.2 μL, 0.356 mmol) under N_2 atmosphere, and the mixture was stirred for 18 h at room temperature. Then the reaction mixture was partitioned between AcOEt and water. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (NH silica gel, $CHCl_3$/MeOH = 30:1) to obtain **7** (57.8 mg, 0.240 mmol, 67%) as a colorless foam. mp 185−187 °C; $[\alpha]_D^{22}$ −399.2° (c = 0.512, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.29−1.35 (1H, m), 1.51−1.58 (1H, m), 1.92−1.98 (1H, m), 2.32−2.39 (1H, m), 3.21 (3H, s), 5.65 (1H, s), 7.05 (2H, br s), 7.11−7.19 (3H, m), 7.24−7.29 (2H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.16, 26.47, 27.55, 28.63, 100.08, 126.00, 126.05, 128.45, 141.65, 154.87, 162.26, 166.70; HRMS (ESI) calcd for $C_{14}H_{16}N_3O$: 242.1288 [(M + H)$^+$], found 242.1285; Anal. Calcd for $C_{14}H_{15}N_3O{\cdot}0.2H_2O$: C, 68.66; H, 6.34; N, 17.16. Found: C, 68.80; H, 6.45; N, 16.94. Optical purity: 95.3% ee (column: Daicel CHIRALPAK AY-H 4.6 mm × 250 mm; eluent: MeCN (0.1% diethylamine), 1.0 mL/min, 40 °C, 259 nm; retention time: 4.9 min).

*2-Amino-3-methyl-6-((1S,2S)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**ent-7**). **ent*-7* (78.8 mg, 0.327 mmol, 53%) was obtained as a colorless foam from ***ent*-19** (141 mg, 0.620 mmol) by the same procedure used to prepare **7**. $[\alpha]_D^{22}$ +435.9° (c = 0.515, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{16}N_3O$: 242.1288 [(M + H)$^+$], found 242.1288; Anal. Calcd for $C_{14}H_{15}N_3O{\cdot}0.1H_2O$: C, 69.17; H, 6.30; N, 17.29. Found: C, 69.23; H, 6.15; N, 17.31. Optical purity: 98.4% ee (column: Daicel CHIRALPAK AY-H 4.6 mm × 250 mm; eluent: MeCN (0.1% diethylamine), 1.0 mL/min, 40 °C, 259 nm; retention time: 6.7 min).

*(1R,5S)-1-(3-Bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (**9b**).* Sodium amide (10.5 g, 270 mmol) was suspended in benzene (60 mL), and *m*-bromophenylacetonitrile (23.29 g, 119 mmol) in benzene (30 mL) was added for 30 min, maintaining the temperature below 20 °C in an ice-bath. The reaction mixture was stirred at room temperature for 30 min. Then to the mixture was added (*S*)-(+)-epichlorohydrin (**8**) (10.0 g, 108 mmol) in benzene (30 mL) for 25 min, maintaining the temperature below 20 °C in an ice-bath, and the mixture was stirred for 30 min at room temperature. The solvent was evaporated, and to the residue was added EtOH (150 mL) and 10 M KOH solution (50 mL). The reaction mixture was stirred for 8 h under reflux, and the solvent was concentrated to approximately half amount. The residue was added to ice-cooled concentrated HCl (90 mL) and water (90 mL) with stirring. The mixture was extracted with AcOEt, and the organic layer was washed with saturated $NaHCO_3$, H_2O, and brine and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel chromatography (Hex/AcOEt = 2:1) to obtain **9b** (16.74 g, 66.1 mmol, 61%) as a light brown oil. $[\alpha]_D^{22}$ +58.3° (c = 1.015, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38−1.42 (1H, m), 1.62−1.67 (1H, m), 2.56−2.62 (1H, m), 4.31 (1H, d, J = 9.2 Hz), 4.47 (1H, dd, J = 9.2, 4.2 Hz), 7.23 (1H, t, J = 7.8 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.56 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.48, 25.20, 31.25, 67.99, 61.22, 122.61, 127.01, 130.15, 130.86, 131.23, 136.39, 175.29; HRMS (ESI) calcd for $C_{11}H_{10}BrO_2$: 252.9859 [(M + H)$^+$], found 252.9861; Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.57. Found: C, 51.93; H, 3.54; Br, 31.29; Optical purity: 96.4% ee (column: Daicel CHIRALCEL OJ-H 4.6 mm × 150 mm; eluent: hexane/2-propanol 98:2, 0.6 mL/min, 25 °C, 200 nm; retention time: 70.2 min).

*(1S,5R)-1-(3-Bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (**ent-9b**). **ent*-9b* (17.19 g, 67.9 mmol, 63%) was obtained as a brown oil from (*R*)-(−)-epichlorohydrin (10.0 g, 108 mmol) and *m*-bromophenylacetonitrile (23.29 g, 119 mmol) by the same procedure used to prepare **9b**. $[\alpha]_D^{22}$ −58.9° (c = 1.002, $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{10}BrO_2$: 252.9859 [(M + H)$^+$], found 252.9859; Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.57. Found: C, 52.06; H, 3.60; Br, 31.21; Optical purity: 94.7% ee (column: Daicel CHIRALCEL OJ-H 4.6 mm × 150 mm, eluent: hexane/2-propanol 98:2, 0.6 mL/min, 25 °C, 200 nm; retention time: 64.0 min).

*(1S,5R)-1-(4-Bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (**9c**).* **9c** (17.07 g, 67.4 mmol, 62%) was obtained as a pale brown solid from (*S*)-(+)-epichlorohydrin (10.0 g, 108 mmol) and *p*-bromophenylacetonitrile (23.29 g, 119 mmol) by the same procedure used to prepare **9b**. $[\alpha]_D^{22}$ +59.5° (c = 1.010, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.37−1.40 (1H, m), 1.59−1.62 (1H, m), 2.54−2.58 (1H, m), 4.29 (1H, d, J = 9.6 Hz), 4.46 (1H, dd, J = 9.6, 4.5 Hz), 7.31 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.46, 25.13, 31.21, 68.01, 61.22, 121.78, 129.91, 131.76, 133.19, 175.47; HRMS (ESI) calcd for $C_{11}H_{10}BrO_2$: 252.9859 [(M + H)$^+$], found 252.9863; Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.57. Found: C, 52.01; H, 3.55; Br, 31.21; Optical purity: 94.8% ee (column: Daicel CHIRALCEL OJ-H 4.6 mm × 150 mm; eluent: hexane/2-propanol 90:10, 0.6 mL/min, 25 °C, 200 nm; retention time: 38.3 min).

*(1R,2S)-2-((tert-Butyldiphenylsilyloxy)methyl)-1-phenylcyclopropanecarboxylic Acid (**10**).* To a solution of **9a**[13a] (7.34 g, 42.1 mmol) in EtOH (59 mL) was added a 10 M KOH solution (6.3 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was added to chilled AcOEt (50 mL), concentrated HCl (8 mL), and water (30 mL) with vigorous stirring, and the resulting mixture was extracted with AcOEt. The organic layer was washed with water and brine and dried with Na_2SO_4. DMF (59 mL) was added to the solution, Na_2SO_4 was filtered off, and the mother liquid was evaporated. Under argon atmosphere, imidazole (14.3 g, 211 mmol) and *tert*-butylchlorodiphenylsilane (32.9 mL, 126 mmol) were added to the solution at 0 °C, and the reaction mixture was stirred at rt for 30 min. Then *tert*-butylchlorodiphenylsilane (11.0 mL, 42.1 mmol) and DMF (15 mL) were added and stirred at rt for 30 min. Then another batch of *tert*-butylchlorodiphenylsilane (5.48 mL, 21.1 mmol) and DMF (15 mL) was added, and the reaction mixture was stirred at rt for 30 min. AcOEt and water were added, and the reaction mixture was extracted with AcOEt. The organic layer was washed with water and brine and dried with Na_2SO_4 and evaporated. The residue was dissolved in EtOH (80 mL), 10 M KOH solution (25 mL) was added, and the mixture was stirred for 1 h at rt. The solvent was evaporated to approximately half volume, and the residue was partitioned between

AcOEt and water. The water layer was acidified with HCl to pH = 1 and extracted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (hexane/AcOEt = 5:1) to give **10** (8.69 g, 20.2 mmol, 48%) as a pale brown oil. The spectrum data were identical with that reported previously.[17] Compound ***ent*-10** (7.49 g, 43.0 mmol, 56%) was obtained in the same manner from ***ent*-9a** (10.20 g, 58.6 mmol).

Compounds **11**−**14** and ***ent*-11**−**14** were prepared according to the reported procedure.[17]

*Ethyl 3-Oxo-3-((1S,2R)-2-phenylcyclopropyl)propanoate (**15**).* To a solution of **14** (201 mg, 1.24 mmol) in MeCN (2 mL) was added carbonyldiimidazole (221 mg, 1.36 mmol) under N_2 atmosphere at room temperature, and the mixture was stirred at the same temperature for 45 min to prepare the imidazolide solution of **14**. Using another independent reaction vessel, magnesium chloride (294 mg, 3.09 mmol), potassium ethyl malonate (442 mg, 2.60 mmol), and triethylamine (552 μL, 3.96 mmol) were suspended in MeCN (6 mL) under N_2 atmosphere, and the reaction mixture was stirred for 40 min. Then the prepared imidazolide solution of **14** was added, and the resulting suspension was stirred for 2 h at 80 °C. The insoluble solid was filtered off and washed with MeCN, and the mother liquid was concentrated. The residue was partitioned between AcOEt and 1 M HCl. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (hexane/AcOEt = 5:1) to give **15** (220 mg, 0.947 mmol, 77%) as a colorless oil: $[\alpha]_D^{22}$ −5.1° (*c* = 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (3H, t, *J* = 7.3 Hz), 1.39−1.43 (1H, m), 1.88−1.94 (1H, m), 2.55−2.61 (1H, m), 2.74−2.83 (1H, m), 3.31, 3.36 (2H, ABq, *J* = 15.1 Hz), 4.05−4.19 (2H, m), 7.17−7.30 (5H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.73, 14.05, 14.07, 29.69, 50.76, 61.22, 126.90, 127.99, 129.19, 135.38, 167.08, 197.93; HRMS (ESI) calcd for $C_{14}H_{17}O_3$: 233.1172 [(M + H)$^+$], found 233.1174.

*Ethyl 3-Oxo-3-((1R,2S)-2-phenylcyclopropyl)propanoate (**ent-15**).* ***ent*-15** (195 mg, 0.840 mmol, 56%) was obtained from ***ent*-14** (10.20 g, 58.6 mmol) as a colorless oil by the same procedure used to prepare **15**. $[\alpha]_D^{22}$ +4.3° (*c* = 0.51, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{17}O_3$: 233.1172 [(M + H)$^+$], found 233.1175.

*2-Amino-6-((1S,2R)-2-phenylcyclopropyl)pyrimidin-4(3H)-one and the 1R Trans Isomer (**16**).* To a solution of **15** (149 mg, 0.642 mmol) in EtOH (3.0 mL) was added guanidine carbonate (116 mg, 0.642 mmol), 20% sodium ethoxide solution in EtOH (503 μL, 1.284 mmol), and the mixture was stirred for 5 h at 80 °C under N_2 atmosphere. The reaction mixture was partitioned between AcOEt and water, and neutralized with diluted HCl to pH = 6. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (NH silica gel, $CHCl_3$/MeOH = 5:1) to give **16** (116 mg, 0.511 mmol, 80%) as a colorless foam: ^{1}H NMR (DMSO-d_6, 400 MHz): cis-isomer δ 1.23−1.29 (1H, m), 1.61−1.67 (1H, m), 2.11−2.19 (1H, m), 2.44−2.50 (1H, m), 5.20 (1H, s), 6.26 (2H, br s), 7.05−7.29 (5H, m), 10.4 (1H, br s). *cis*:*trans* ratio was 1.3:1 from ^{1}H NMR.

*2-Amino-6-((1R,2S)-2-phenylcyclopropyl)pyrimidin-4(3H)-one and the 1S Trans Isomer (**ent-16**).* ***ent*-16** (113 mg, 0.498 mmol, 79%) was obtained as a colorless foam from ***ent*-15** (147 mg, 0.632 mmol) by the same procedure used to prepare **16**. The *cis*:*trans* ratio was 1.5:1 from ^{1}H NMR.

*Ethyl 3-Oxo-3-((1R,2R)-2-phenylcyclopropyl)propanoate (**18**).* **18** (306 mg, 1.32 mmol, 82%) was obtained from **17**[19] (261 mg, 1.61 mmol) by the same procedure used to prepare **15**. $[\alpha]_D^{22}$ −422.4° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (3H, t, *J* = 7.3 Hz), 1.44−1.50 (1H, m), 1.74−1.79 (1H, m), 2.27−2.34 (1H, m), 2.56−2.64 (1H, m), 3.60 (2H, s), 4.18 (2H, q, *J* = 7.3 Hz), 7.09−7.13 (2H, m), 7.20−7.32 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.08, 19.50, 30.12, 32.35, 50.33, 61.41, 126.19, 126.74, 128.55, 139.80, 167.08, 200.86; HRMS (ESI) calcd for $C_{14}H_{17}O_3$: 233.1172 [(M + H)$^+$], found 233.1174.

*Ethyl 3-Oxo-3-((1S,2S)-2-phenylcyclopropyl)propanoate (**ent-18**).* ***ent*-18** (333 mg, 1.41 mmol, 81%) was obtained as a colorless oil from ***ent*-17**[19] (288 mg, 1.78 mmol) by the same procedure used to prepare **18**. $[\alpha]_D^{22}$ +424.0° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{17}O_3$: 233.1172 [(M + H)$^+$], found 233.1175.

*2-Amino-6-((1R,2R)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**19**).* **19** (105 mg, 0.462 mmol, 57%) was obtained as a colorless solid from **18** (189 mg, 0.814 mmol) by the same procedure used to prepare **16**. $[\alpha]_D^{25}$ −501.8° (*c* = 0.51, DMSO); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.28−1.34 (1H, m), 1.50−1.57 (1H, m), 1.93−1.99 (1H, m), 2.33−2.39 (1H, m), 5.56 (1H, s), 6.46 (2H, br s), 7.11−7.19 (2H, m), 7.24−7.29 (3H, m), 10.54 (1H, br s); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 17.79, 26.41, 29.70, 99.60, 126.65, 129.26, 142.61, 156.75, 163.19, 169.35; HRMS (ESI) calcd for $C_{13}H_{14}N_3O$: 228.1131 [(M + H)$^+$], found 228.1130.

*2-Amino-6-((1S, 2S)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**ent-19**).* ***ent*-19** (176 mg, 0.776 mmol, 78%) was obtained as a colorless solid from ***ent*-18** (232 mg, 0.995 mmol) by the same procedure used to prepare **19**. $[\alpha]_D^{25}$ +504.5° (*c* = 0.51, DMSO); HRMS (ESI) calcd for $C_{13}H_{14}N_3O$: 228.1131 [(M + H)$^+$], found 228.1129.

*Sodium (1R,2S)-2-(Hydroxymethyl)-1-phenylcyclopropanecarboxylate (**20a**).* To a suspension of **9a**[13a] (10.6 g, 61.0 mmol) in EtOH (53 mL) and water (9.2 mL) was added 10 N KOH solution (9.2 mL, 92 mmol), and the solution was stirred for 1 h at room temperature. The reaction mixture was poured into the chilled Et_2O (120 mL) and 2 M HCl (61 mL) with vigorous stirring. The mixture was extracted with Et_2O. The organic layer was washed with water and brine and dried with $MgSO_4$. $MgSO_4$ was filtered off, and to the mother liquid was added 28% sodium methoxide solution MeOH (12.5 mL). Precipitate was separated by filtration and washed with Et_2O to give **20a** (10.4 g, 48.6 mmol, 80%) as a pale brown solid. $[\alpha]_D^{23}$ +76.2° (*c* = 0.50, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 0.86−0.89 (1H, m), 1.62−1.67 (1H, m), 1.09−1.14 (1H, m), 1.22−1.28 (1H, m), 3.26−3.31 (1H, m), 3.79−3.84 (1H, m), 6.18 (1H, br s), 7.05−7.09 (1H, m), 7.16−7.20 (2H, m), 7.24−7.27 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 18.63, 28.88, 39.65, 64.50, 127.01, 128.96, 129.78, 145.15, 179.85; HRMS (ESI) calcd for $C_{11}H_{13}O_3$: 193.0859 [(M − Na + 2H)$^+$], found 193.0860.

*Sodium (1R,2S)-1-(3-Bromophenyl)-2-(hydroxymethyl)-cyclopropanecarboxylate (**20b**).* **20b** (16.26 g, 55.5 mmol, 87%) was obtained as a colorless solid from **9b** (16.13 g, 63.7 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{22}$ +64.0° (*c* = 0.50, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 0.90−0.93 (1H, m), 1.17−1.20 (1H, m), 1.23−1.30 (1H, m), 3.34−3.36 (1H, m), 3.77−3.82 (1H, m), 6.01 (1H, br s), 7.15 (1H, t, *J* = 7.8 Hz), 7.20 (1H, d, *J* = 7.8 Hz), 7.27 (1H, d, *J* = 7.8 Hz), 7.46 (1H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 16.85, 28.50, 37.43, 61.58, 120.58, 127.08, 127.68, 129.42, 131.57, 148.43, 174.18; HRMS (ESI) calcd for $C_{11}H_{12}BrO_3$: 270.9964 [(M − Na + 2H)$^+$], found 270.9967.

*Sodium (1S,2R)-1-(3-Bromophenyl)-2-(hydroxymethyl)-cyclopropanecarboxylate (**ent-20b**).* ***ent*-20b** (13.20 g, 45.0 mmol, 94%) was obtained as a colorless solid from ***ent*-9b** (12.15 g, 48.0 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{22}$ −65.6° (*c* = 0.50, MeOH); HRMS (ESI) calcd for $C_{11}H_{12}BrO_3$: 270.9964 [(M − Na + 2H)$^+$], found 270.9969.

*Sodium (1S,2R)-1-(4-Bromophenyl)-2-(hydroxymethyl)-cyclopropanecarboxylate (**20c**).* **20c** (18.40 g, 62.8 mmol, 95%) was obtained as a colorless solid from **9c** (16.69 g, 65.9 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{22}$ +64.0° (*c* = 0.50, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 0.86−0.90 (1H, m), 1.17−1.20 (1H, m), 1.21−1.27 (1H, m), 3.31−3.35 (1H, m), 3.77−3.81 (1H, m), 7.21 (2H, t, *J* = 8.7 Hz), 7.35 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 16.77, 28.41, 37.08, 61.56, 117.77, 130.00, 130.77, 145.08, 174.44; HRMS (ESI) calcd for $C_{11}H_{12}BrO_3$: 270.9964 [(M − Na + 2H)$^+$], found 270.9969.

*(1R,2S)-1-Phenylcyclopropane-1,2-dicarboxylic Acid (**21a**).* To a solution of **20a** (1.75 g, 8.17 mmol) in MeCN (17.5 mL) and water (8.8 mL) was added sodium periodate (3.50 g, 16.3 mmol) and ruthenium(III) chloride (51 mg, 0.245 mmol), and the mixture was stirred for 25 h at room temperature. The reaction mixture was poured into the chilled AcOEt (60 mL), 2 M HCl (20 mL), and water (60 mL) with vigorous stirring, and the resulting mixture was extracted

with AcOEt. Then the product was extracted with saturated $NaHCO_3$ two times. The water layer was acidified with HCl, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residual solid was washed with hexane to give **21a** (1.27 g, 6.16 mmol, 75%) as a pale gray solid. $[\alpha]_D^{22}$ +166.3° (c = 0.51, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.61−1.65 (1H, m), 2.19−2.23 (1H, m), 2.35−2.40 (1H, m), 7.30−7.36 (3H, m), 7.42−7.45 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.32, 29.61, 38.49, 128.34, 128.69, 129.75, 137.18, 176.78, 176.86; HRMS (ESI) calcd for $C_{11}H_{11}O_4$: 207.0652 [(M + H)$^+$], found 207.0654.

*(1R,2S)-1-(3-Bromophenyl)cyclopropane-1,2-dicarboxylic Acid (**21b**).* **21b** (16.20 g, 56.8 mmol, 87%) was obtained as a pale gray solid from **20b** (19.25 g, 65.7 mmol) by the same procedure used to prepare **21a**. $[\alpha]_D^{22}$ +155.0° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.62−1.65 (1H, m), 2.20−2.24 (1H, m), 2.35−2.39 (1H, m), 7.22 (1H, t, J = 7.8 Hz), 7.37 (1H, dt, J = 7.8, 1.8 Hz), 7.46 (1H, dt, J = 7.8, 1.8 Hz), 7.58 (1H, t, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.23, 29.73, 37.87, 122.49, 128.49, 130.19, 131.61, 132.89, 139.17, 176.47; HRMS (ESI) calcd for $C_{11}H_{10}BrO_4$: 284.9757 [(M + H)$^+$], found 284.9763.

*(1S,2R)-1-(3-Bromophenyl)cyclopropane-1,2-dicarboxylic Acid (**ent-21b**).* ***ent*-21b** (168.6 mg, 0.591 mmol, 80%) was obtained as a pale gray solid from ***ent*-20b** (218 mg, 0.743 mmol) by the same procedure used to prepare **21a**. $[\alpha]_D^{22}$ −143.2° (c = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{10}BrO_4$: 284.9757 [(M + H)$^+$], found 284.9760.

*(1R,2S)-1-(4-Bromophenyl)cyclopropane-1,2-dicarboxylic Acid (**21c**).* **21c** (13.43 g, 47.1 mmol, 69%) was obtained as a grayish brown solid from **20c** (20.13 g, 68.7 mmol) by the same procedure used to prepare **21a**. $[\alpha]_D^{22}$ +174.0° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59−1.63 (1H, m), 2.18−2.23 (1H, m), 2.32−2.36 (1H, m), 7.30 (2H, d, J = 8.6 Hz), 7.48 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.27, 29.69, 37.84, 122.59, 131.46, 131.85, 136.11, 176.43; HRMS (ESI) calcd for $C_{11}H_{10}BrO_4$: 284.9757 [(M + H)$^+$], found 284.9765.

*(1R,2S)-2-(3-Ethoxy-3-oxopropanoyl)-1-phenylcyclopropanecarboxylic Acid (**22a**).* The mixture of **22a** and ethyl malonate (2.33 g) was obtained as a light brown oil from **21a** (1.52 g, 7.37 mmol) by the same procedure used to prepare **15**, except for silica gel chromatography eluent ($CHCl_3$/MeOH = 30:1). It was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24−1.30 (1H, m), 1.31 (3H, t, J = 6.9 Hz), 1.58−1.61 (1H, m), 2.58−2.62 (1H, m), 2.98 (2H, br s), 4.23−4.28 (2H, m), 7.29−7.45 (5H, m).

*(1R,2S)-1-(3-Bromophenyl)-2-(3-ethoxy-3-oxopropanoyl)-cyclopropanecarboxylic Acid (**22b**).* The mixture of **22b** and ethyl malonate (6.63 g) was obtained from **21b** (6.56 g, 23.0 mmol) by the same procedure used to prepare **22a**, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.18−1.30 (1H, m), 1.32 (3H, t, J = 7.3 Hz), 1.56−1.58 (1H, m), 2.59−2.63 (1H, m), 2.95 (2H, br s), 4.24−4.30 (2H, m), 7.23 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.45 (1H, d, J = 7.8 Hz), 7.57 (1H, s).

*(1S,2R)-1-(3-Bromophenyl)-2-(3-ethoxy-3-oxopropanoyl)-cyclopropanecarboxylic Acid (**ent-22b**).* The mixture of ***ent*-22b** and ethyl malonate (6.90 g) was obtained from ***ent*-21b** (5.51 g, 19.3 mmol) by the same procedure used to prepare **22a**, which was used in the next step without further purification.

*(1R,2S)-1-(4-Bromophenyl)-2-(3-ethoxy-3-oxopropanoyl)-cyclopropanecarboxylic Acid (**22c**).* The mixture of **22c** and ethyl malonate (10.15 g) was obtained from **21c** (7.51 g, 26.3 mmol) by the same procedure used to prepare **22a**, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.17−1.29 (1H, m), 1.31 (3H, t, J = 6.9 Hz), 1.53−1.56 (1H, m), 2.57−2.60 (1H, m), 2.93 (2H, br s), 4.23−4.29 (2H, m), 7.31 (2H, d, J = 8.7 Hz), 7.49 (2H, d, J = 8.7 Hz).

*(1R,2S)-Methyl 2-(2-Amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-phenylcyclopropanecarboxylate (**24a**).* To a solution of the mixture of **22a** and ethyl malonate (2.23 g) in EtOH (33 mL) was added 20% sodium ethoxide EtOH solution (2.76 mL, 7.05 mmol). After stirring for 10 min, guanidine carbonate (635 mg, 3.53 mmol) was added, and the suspension was stirred for 25 h at 95 °C. Then the reaction mixture was partitioned between AcOEt and water. The organic layer was washed water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography [$CHCl_3$/($CHCl_3$/MeOH/28% NH_3 = 32:6:0.5) = 3:1] to obtain **24a** (676 mg, 2.26 mmol, 32% from **21a**) as a colorless foam. $[\alpha]_D^{23}$ +178.0° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51−1.55 (1H, m), 2.19−2.23 (1H, m), 2.43−2.47 (1H, m), 3.36 (3H, s), 3.53 (3H, s), 5.24 (2H, s), 5.98 (1H, s), 7.27−7.36 (3H, m), 7.44−7.47 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.83, 27.49, 32.40, 38.34, 52.24, 102.30, 127.60, 128.51, 129.44, 139.39, 154.79, 162.43, 162.78, 171.16; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3$: 300.1343 [(M + H)$^+$], found 300.1346.

*(1R,2S)-Methyl 2-(2-amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(3-bromophenyl)cyclopropanecarboxylate (**24b**).* **24b** (2.94 g, 7.77 mmol, 34% from **21b**) was obtained as a colorless foam from the mixture of **22b** and ethyl malonate (6.63 g) by the same procedure used to prepare **24a**. $[\alpha]_D^{22}$ +165.4° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51−1.55 (1H, m), 2.19−2.22 (1H, m), 2.40−2.44 (1H, m), 3.39 (3H, s), 3.54 (3H, s), 5.16 (2H, s), 5.98 (1H, s), 7.21 (1H, t, J = 7.8 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.61 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.69, 27.59, 32.64, 37.80, 52.39, 102.52, 122.33, 128.29, 130.02, 130.85, 132.75, 141.63, 154.78, 162.28, 162.39, 170.58; HRMS (ESI) calcd for $C_{16}H_{17}BrN_3O_3$: 378.0448 [(M + H)$^+$], found 378.0453.

*(1S,2R)-Methyl 2-(2-amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(3-bromophenyl)cyclopropanecarboxylate (**ent-24b**).* ***ent*-24b** (2.08 g, 5.50 mmol, 29% from ***ent*-21b**) was obtained as a colorless foam from the mixture of ***ent*-22b** and ethyl malonate (6.80 g) by the same procedure used to prepare **24a**. $[\alpha]_D^{22}$ −164.6° (c = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}BrN_3O_3$: 378.0448 [(M + H)$^+$], found 378.0455.

*(1R,2S)-Methyl 2-(2-Amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(4-bromophenyl)cyclopropanecarboxylate (**24c**).* **24c** (3.22 g, 8.51 mmol, 33% from **21c**) was obtained as a colorless foam from the mixture of **20c** and ethyl malonate (10.02 g) by the same procedure used to prepare **24a**. $[\alpha]_D^{22}$ +198.0° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.49−1.52 (1H, m), 2.19−2.22 (1H, m), 2.36−2.40 (1H, m), 3.39 (3H, s), 3.53 (3H, s), 5.07 (2H, s), 5.97 (1H, s), 7.33 (2H, d, J = 8.1 Hz), 7.46 (2H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.69, 27.60, 32.62, 37.77, 52.34, 102.53, 121.71, 131.34, 131.60, 138.47, 154.68, 162.36, 162.48, 170.65; HRMS (ESI) calcd for $C_{16}H_{17}BrN_3O_3$: 378.0448 [(M + H)$^+$], found 378.0453.

*(1R,2S)-Methyl 2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-phenylcyclopropanecarboxylate (**25a**).* To a solution of **24a** (612 mg, 2.04 mmol) in CH_2Cl_2 (6.1 mL) was added *N*,*N*-dimethylaminopyridine (74.9 mg, 0.613 mmol) and di-*tert*-butyl carbonate (1.19 mL, 5.11 mmol) under N_2 atmosphere, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the residue was purified by silica gel chromatography (hexane/AcOEt = 1:1) to obtain **25a** (863 mg, 1.73 mmol, 85%) as a colorless foam. $[\alpha]_D^{22}$ +102.0° (c = 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.47 (9H, s), 1.49 (9H, s), 1.65−1.68 (1H, m), 2.16−2.19 (1H, m), 2.48−2.52 (1H, m), 3.43 (3H, s), 3.52 (3H, s), 6.43 (1H, s), 7.26−7.36 (3H, m), 7.44−7.47 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.11, 27.82, 27.85, 30.13, 32.28, 39.18, 52.27, 84.76, 85.13, 111.55, 127.70, 128.49, 129.50, 139.22, 148.51, 148.53, 148.55, 161.85, 162.62, 170.05; HRMS (ESI) calcd for $C_{26}H_{34}N_3O_7$: 500.2391 [(M + H)$^+$], found 500.2394.

*(1R,2S)-Methyl 2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(3-bromophenyl)-cyclopropanecarboxylate (**25b**).* **25b** (3.92 g, 6.78 mmol, 89%) was obtained as a colorless foam from **24b** (2.87 g, 7.59 mmol) by the same procedure used to prepare **25a**. $[\alpha]_D^{22}$ +105.4° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.47 (9H, s), 1.50 (9H, s), 1.63−1.67 (1H, m), 2.17−2.20 (1H, m), 2.47−2.50 (1H, m), 3.43 (3H, s), 3.53 (3H, s), 6.42 (1H, s), 7.21 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.60 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.03, 27.83, 27.86, 30.16, 32.40, 38.50, 52.40,

84.83, 85.18, 111.74, 111.76, 122.34, 128.33, 130.02, 130.91, 132.68, 141.39, 148.53, 148.54, 148.67, 161.28, 162.57, 169.54; HRMS (ESI) calcd for $C_{26}H_{34}BrN_3O_7$: 578.1496 [(M + H)$^+$], found 578.1501.

*(1S,2R)-Methyl 2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(3-bromophenyl)-cyclopropanecarboxylate (**ent-25b**).* ***ent*-25b** (1.32 g, 2.28 mmol, 82%) was obtained as a colorless foam from ***ent*-24b** (1.05 g, 2.78 mmol) by the same procedure used to prepare **25a**. $[\alpha]_D^{22}$ −101.0° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{26}H_{34}BrN_3O_7$: 578.1496 [(M + H)$^+$], found 578.1503.

*(1R,2S)-Methyl 2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(4-bromophenyl)-cyclopropanecarboxylate (**25c**).* **25c** (4.43 g, 7.66 mmol, 92%) was obtained as a colorless foam from **24c** (3.15 g, 8.33 mmol) by the same procedure used to prepare **25a**. $[\alpha]_D^{22}$ +118.8° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.47 (9H, s), 1.49 (9H, s), 1.61−1.65 (1H, m), 2.17−2.20 (1H, m), 2.40−2.48 (1H, m), 3.43 (3H, s), 3.52 (3H, s), 6.41 (1H, s), 7.33 (2H, d, *J* = 8.1 Hz), 7.46 (2H, d, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.00, 27.82, 27.85, 30.15, 32.49, 38.36, 52.36, 84.81, 85.16, 111.73, 121.80, 131.34, 131.62, 138.26, 148.52, 148.54, 148.64, 161.33, 162.57, 169.64; HRMS (ESI) calcd for $C_{26}H_{34}BrN_3O_7$: 578.1496 [(M + H)$^+$], found 578.1502.

*(1R,2S)-2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-phenylcyclopropanecarboxylic Acid (**27a**).* To a solution of **25a** (825 mg, 1.65 mmol) in EtOH (8.2 mL) was added water (0.8 mL) and 10 M KOH solution, and the mixture was stirred for 4 h at 60 °C. The reaction mixture was poured into the chilled AcOEt (20 mL), 2 M HCl (6 mL), and water (10 mL) with vigorous stirring, and the insoluble solid was filtered off. The mother liquor was extracted with AcOEt, and the organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was combined with the solid already obtained, and washed with hexane to give **26a** (595 mg) as a colorless solid.

To a suspension of **26a** (550 mg) was added *N*,*O*-bis(trimethylsilyl)acetamide (1.05 mL, 4.28 mmol) under N_2 atmosphere, and the mixture was stirred for 30 min at room temperature to give a clear solution. Then *N*,*N*-dimethylaminopyridine (34.8 mg, 0.285 mmol) and di-*tert*-butyl carbonate (0.497 mL, 2.14 mmol) were added, and the solution was stirred another 1 h at room temperature. The solvent was evaporated, and the residue was purified by silica gel chromatography ($CHCl_3$/MeOH = 20:1) to obtain **27a** (578 mg, 1.19 mmol, 78%) as a pale brown foam. $[\alpha]_D^{22}$ +120.2° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (9H, s), 1.53 (9H, s), 1.72−1.75 (1H, m), 2.21−2.24 (1H, m), 2.62−2.66 (1H, m), 3.42 (3H, s), 6.46 (1H, s), 7.28−7.36 (3H, m), 7.45−7.48 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.36, 27.78, 27.85, 30.19, 33.79, 38.80, 84.95, 85.15, 111.58, 127.85, 128.46, 130.00, 138.94, 148.35, 148.56, 148.56, 161.07, 162.90, 173.19; HRMS (ESI) calcd for $C_{25}H_{32}N_3O_7$: 486.2235 [(M + H)$^+$], found 486.2237.

*(1R,2S)-2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(3-bromophenyl)-cyclopropanecarboxylic Acid (**27b**).* **26b** (2.88 g) was obtained as a colorless solid from **25b** (3.85 g, 6.66 mmol) by the same procedure used to prepare **26a**. Then **27b** (2.99 g, 5.30 mmol, 80% from **25b**) was obtained as an orange brown foam from **26b** (2.85 g) by the same procedure used to prepare **27a**. $[\alpha]_D^{22}$ +107.3° (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.42 (9H, s), 1.48 (9H, s), 1.71−1.75 (1H, m), 2.22−2.25 (1H, m), 2.60−2.64 (1H, m), 3.42 (3H, s), 6.47 (1H, s), 7.21 (1H, t, *J* = 7.8 Hz), 7.40 (1H, d, *J* = 7.8 Hz), 7.43 (1H, d, *J* = 7.8 Hz), 7.60 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.40, 27.79, 27.86, 30.21, 33.47, 38.46, 85.20, 85.34, 111.62, 122.21, 128.75, 129.96, 130.89, 133.00, 141.38, 148.53, 148.58, 148.68, 161.06, 162.94, 172.80; HRMS (ESI) calcd for $C_{25}H_{31}BrN_3O_7$: 564.1340 [(M + H)$^+$], found 564.1345.

*(1S,2R)-2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(3-bromophenyl)-cyclopropanecarboxylic Acid (**ent-27b**).* ***ent*-26b** (897 mg) was obtained as a colorless solid from ***ent*-25b** (1.27 g, 2.20 mmol) by the same procedure used to prepare **26a**. Then ***ent*-27b** (790 mg, 1.40 mmol, 78% from ***ent*-25b**) was obtained as a yellow brown foam from ***ent*-26b** (729 mg) by the same procedure used to prepare **27a**. $[\alpha]_D^{22}$ −112.7° (*c* = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{25}H_{31}BrN_3O_7$: 564.1340 [(M + H)$^+$], found 564.1345.

*(1R,2S)-2-(2-(Bis(tert-butoxycarbonyl)amino)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-1-(4-bromophenyl)-cyclopropanecarboxylic Acid (**27c**).* **26c** (2.90 g) was obtained as a colorless solid from **25c** (3.89 g, 6.72 mmol) by the same procedure used to prepare **26a**. Then **27c** (2.71 g, 4.80 mmol, 72% from **25c**) was obtained as an orange brown foam from **26c** (2.88 g) by the same procedure used to prepare **27a**. $[\alpha]_D^{22}$ +122.0° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.44 (9H, s), 1.49 (9H, s), 1.71−1.74 (1H, m), 2.24−2.27 (1H, m), 2.60−2.64 (1H, m), 3.44 (3H, s), 6.48 (1H, s), 7.37 (2H, d, *J* = 8.7 Hz), 7.50 (2H, d, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.34, 27.78, 27.84, 30.22, 33.79, 38.17, 84.99, 85.22, 111.58, 121.93, 131.58, 131.74, 138.02, 148.36, 148.52, 148.61, 160.80, 162.94, 172.64; HRMS (ESI) calcd for $C_{25}H_{31}BrN_3O_7$: 564.1340 [(M + H)$^+$], found 564.1343.

*2-Bis(tert-butoxycarbonyl)amino-3-methyl-6-((1S,2R)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**28a**).* To a suspension of **27a** (74.0 mg, 0.152 mmol) and **11** (46.1 mg, 0.183 mmol) in toluene (11 mL) was added tri-*n*-butyltin hydride (0.122 mL, 0.457 mmol), azoisobutyronitrile (5.0 mg, 0.030 mmol), and tri-*n*-butylphosphine (0.114 mL, 0.457 mmol) under N_2 atmosphere and shading by wrapping the vessel with aluminum foil, and the mixture was stirred for 20 min at room temperature and then for 4.5 h at 80 °C. The solvent was evaporated, and the residue was purified by silica gel chromatography (hexane/AcOEt = 1:1) to obtain **28a** (35.5 mg, 0.084 mmol, 53%) as a colorless solid. $[\alpha]_D^{22}$ +4.0° (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (9H, s), 1.53 (9H, s), 1.72−1.75 (1H, m), 2.21−2.24 (1H, m), 2.62−2.66 (1H, m), 3.42 (3H, s), 6.46 (1H, s), 7.28−7.36 (3H, m), 7.45−7.48 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.03, 25.21, 27.02, 27.79, 27.81, 29.92, 84.54, 84.75, 110.09, 126.48, 128.03, 129.33, 136.27, 147.70, 148.15, 148.36, 162.51, 163.04; HRMS (ESI) calcd for $C_{24}H_{32}N_3O_5$: 442.2336 [(M + H)$^+$], found 442.2343.

*2-Bis(tert-butoxycarbonyl)amino-3-methyl-6-[(1S,2R)-2-(3-bromophenyl)cyclopropyl]pyrimidin-4(3H)-one (**28b**).* **28b** (442 mg, 0.850 mmol, 48%) was obtained as a colorless solid from **27b** (1.00 g, 1.77 mmol) by the same procedure used to prepare **28a**. $[\alpha]_D^{22}$ +1.6° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (9H, s), 1.40 (9H, s), 1.45−1.51 (1H, m), 1.60−1.65 (1H, m), 2.32−2.38 (1H, m), 2.60−2.66 (1H, m), 3.31 (3H, s), 6.06 (1H, s), 7.00−7.06 (2H, m), 7.23 (1H, d, *J* = 7.9 Hz), 7.36 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.04, 25.31, 26.41, 27.81, 27.81, 29.98, 84.61, 84.80, 110.52, 122.07, 127.59, 129.45, 129.62, 132.71, 138.85, 147.96, 148.20, 148.34, 162.46, 162.56; HRMS (ESI) calcd for $C_{24}H_{31}BrN_3O_5$: 520.1442 [(M + H)$^+$], found 520.1445.

*2-Bis(tert-butoxycarbonyl)amino-3-methyl-6-[(1R,2S)-2-(3-bromophenyl)cyclopropyl]pyrimidin-4(3H)-one (**ent-28b**).* ***ent*-28b** (122 mg, 0.235 mmol, 52%) was obtained as a pale gray solid from ***ent*-27b** (253 mg, 0.447 mmol) by the same procedure used to prepare **28a**. $[\alpha]_D^{22}$ −8.8° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{31}BrN_3O_5$: 520.1442 [(M + H)$^+$], found 520.1442.

*2-Bis(tert-butoxycarbonyl)amino-3-methyl-6-[(1S,2R)-2-(4-bromophenyl)cyclopropyl]pyrimidin-4(3H)-one (**28c**).* **28c** (355 mg, 0.681 mmol, 38%) was obtained as a colorless solid from **27c** (1.02 g, 1.80 mmol) by the same procedure used to prepare **28a**. $[\alpha]_D^{22}$ −17.8° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.37 (9H, m), 1.40 (9H, m), 1.44−1.49 (1H, m), 1.61−1.65 (1H, m), 2.33−2.38 (1H, m), 2.56−2.61 (1H, m), 3.31 (3H, s), 6.09 (1H, s), 7.01 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.80, 25.26, 26.18, 27.75, 27.79 29.97, 84.61, 84.88, 110.81, 120.32, 130.95, 131.07, 135.54, 147.93, 148.17, 148.31, 162.46, 162.59; HRMS (ESI) calcd for $C_{24}H_{31}BrN_3O_5$: 520.1442 [(M + H)$^+$], found 520.1450.

*2-Bis(tert-butoxycarbonyl)amino-6-((1S,2R)-2-(3-bromophenyl)-2-(pyridin-2-ylthio)cyclopropyl)-3-methylpyrimidin-4(3H)-one (**29**).* $[\alpha]_D^{22}$ +22.0° (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.39 (9H, s), 1.45 (9H, s), 1.89−1.93 (1H, m), 2.34−2.37 (1H, m), 2.88−2.91 (1H, m), 3.43 (3H, s), 6.24 (1H, s), 6.97 (1H, t, *J* = 7.8

Hz), 7.02 (1H, dd, J = 7.6, 4.8 Hz), 7.18 (1H, d, J = 7.8 Hz), 7.18 (1H, d, J = 7.8 Hz), 7.26 (1H, d, J = 7.6 Hz), 7.48 (1H, dt, J = 7.6, 0.9 Hz), 7.59 (1H, s), 8.50 (1H, dd, J = 4.8, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.23, 27.81, 27.90, 30.11, 33.37, 36.43, 84.71, 84.85, 111.98, 120.46, 121.80, 122.60, 128.74, 129.38, 130.34, 133.21, 136.29, 141.04, 148.24, 148.35, 148.52, 149.79, 158.42, 160.96, 162.47; HRMS (ESI) calcd for $C_{29}H_{33}BrN_4O_5SNa$: 651.1247 [(M + Na)$^+$], found 651.1260.

*2-Amino-3-methyl-6-((1S,2R)-2-phenylcyclopropyl)pyrimidin-4(3H)-one (**6**) from **28a**.* To a solution of **28a** (31.2 mg, 0.0707 mmol) in CH_2Cl_2 (0.3 mL) was added trifluoroacetic acid (0.3 mL), and the mixture was stirred for 30 min at room temperature. The solvent was evaporated, and the residue was partitioned between AcOEt and 5% K_2CO_3 solution. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (AcOEt/MeOH = 20:1) to obtain **6** (12.8 mg, 0.0530 mmol, 75%) as a colorless solid. ^{1}H NMR and LCMS data were identical to those obtained by the previous procedure. Optical purity: 94.8% ee (column: Daicel CHIRALPAK AY-H 4.6 mm × 250 mm; eluent: MeCN (0.1% diethylamine), 1.0 mL/min, 40 °C, 259 nm; retention time: 4.2 min).

*2-Amino-6-((1S,2R)-2-(3-bromophenyl)cyclopropyl)-3-methylpyrimidin-4(3H)-one (**31**).* To a solution of **28b** (31.2 mg, 0.0707 mmol) in CH_2Cl_2 (0.3 mL) was added trifluoroacetic acid (0.3 mL), and the mixture was stirred for 30 min at room temperature. The solvent was evaporated, and the residue was partitioned between AcOEt and 5% K_2CO_3 solution. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (AcOEt/MeOH = 20:1) to obtain a free form of **31** (60.6 mg). To a solution of the free form of **31** (55.5 mg) in dioxane (1.1 mL) was added 4 M hydrogen chloride in dioxane (0.130 mL), and the resulting suspension was stirred for 1 h at room temperature. The precipitate was filtered off and washed with AcOEt to give **31** (51.4 mg, 0.144 mmol, 81%) as a colorless solid. mp 218−224 °C (dec); $[\alpha]_D^{20}$ −41.3° (c = 0.30, MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.41−1.48 (1H, m), 1.87−1.93 (1H, m), 2.28−2.34 (1H, m), 2.73−2.78 (1H, m), 3.15 (3H, s), 5.64 (1H, s), 7.15−7.23 (2H, m), 7.36 (1H, d, J = 8.4 Hz), 7.44 (1H, s), 8.47 (1H, br s); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.28, 22.73, 26.76, 28.76, 102.27, 123.32, 128.64, 131.12, 131.24, 133.06, 139.57, 152.99, 154.28, 160.36; HRMS (ESI) calcd for $C_{14}H_{15}BrN_3O$: 320.0393 [(M + H)$^+$], found 320.0388.

*2-Amino-6-((1S,2R)-2-(3-bromophenyl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**ent-31**). **ent**-31* (26.5 mg, 0.0743 mmol, 80%) was obtained as a colorless solid from ***ent*-28b** (48.3 mg, 0.0928 mmol) by the same procedure used to prepare **31**. $[\alpha]_D^{20}$ +46.0° (c = 0.30, MeOH); HRMS (ESI) calcd for $C_{14}H_{15}BrN_3O$: 320.0393 [(M + H)$^+$], found 320.0389.

Suzuki−Miyaura Coupling: Typical Procedures. *Method A (Conventional Heating): 2-Amino-6-[(1S,2R)-2-(biphenyl-3-yl)-cyclopropyl]-3-methylpyrimidin-4(3H)-one Hydrochloride (**32**).* To a solution of **28b** (100 mg, 0.193 mmol) in dioxane (1.1 mL) and water (0.5 mL) was added phenylboronic acid (35.2 mg, 0.289 mmol), potassium carbonate (80 mg, 0.578 mmol), and dichlorobis-(triphenylphosphine)palladium (6.8 mg, 0.00964 mmol), and the mixture was heated at 100 °C for 4.5 h. The reaction mixture was partitioned between AcOEt and water. The organic layer was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH = 50:1) to obtain the free form of **32**. This was dissolved in dioxane (0.7 mL), and 4 M hydrogen chloride in dioxane (0.089 mL, 0.356 mmol) was added. The precipitate was filtered and washed with AcOEt to give **32** (25.7 mg, 0.0726 mmol, 61%) as a colorless solid. mp 205−208 °C; $[\alpha]_D^{22}$ −64.0° (c = 0.30, MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.45−1.50 (1H, m), 1.94−2.02 (1H, m), 2.32−2.37 (1H, m), 2.77−2.85 (1H, m), 3.13 (3H, s), 5.69 (1H, s), 7.21 (1H, d, J = 7.5 Hz), 7.32 (1H, t, J = 7.5 Hz), 7.36 (1H, t, J = 7.5 Hz), 7.45 (3H, t, J = 7.3 Hz), 7.50 (1H, s), 7.63 (2H, d, J = 7.3 Hz), 8.46 (1H, br s); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.31, 22.89, 27.41, 28.69, 102.15, 126.75, 128.06, 128.47, 128.54, 128.92, 129.85, 129.92, 137.46, 142.10, 142.54, 154.24, 154.37, 160.72; HRMS (ESI) calcd for $C_{20}H_{20}N_3O$: 318.1601 [(M + H)$^+$], found 318.1602.

*2-Amino-6-((1R,2S)-2-(biphenyl-3-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**ent-32**). **ent**-32* (33.6 mg, 0.950 mmol, 76%) was obtained as a colorless solid from ***ent*-28b** (65.3 mg, 0.125 mmol) and phenylboronic acid (45.9 mg, 0.376 mmol) by the same procedure used to prepare **32** (**method A**). $[\alpha]_D^{22}$ +67.0° (c = 0.30, MeOH); HRMS (ESI) calcd for $C_{20}H_{20}N_3O$: 318.1601 [(M + H)$^+$], found 318.1601.

*2-Amino-6-((1S,2R)-2-(3′-methoxybiphenyl-3-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**33**).* **33** (35.3 mg, 0.920 mmol, 72%) was obtained as a colorless solid from **28b** (66.5 mg, 0.128 mmol) and 3-methoxyphenylboronic acid (29.1 mg, 0.192 mmol) by the same procedure used to prepare **32** (**method A**). mp 186−189 °C; $[\alpha]_D^{22}$ −56.0° (c = 0.30, MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.44−1.51 (1H, m), 1.97−2.03 (1H, m), 2.32−2.38 (1H, m), 2.78−2.85 (1H, m), 3.13 (3H, s), 3.83 (3H, s), 5.71 (1H, s), 6.93 (1H, d, J = 8.0 Hz), 7.15 (1H, s), 7.19 (1H, d, J = 8.0 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.31 (1H, t, J = 8.0 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.46 (1H, d, J = 8.0 Hz), 7.50 (1H, s); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.29, 26.62, 27.42, 28.72, 55.86, 102.30, 113.77, 113.92, 120.49, 126.91, 128.43, 129.04, 129.86, 130.94, 137.31, 142.49, 143.56, 153.26, 154.19, 160.36, 161.63; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$: 348.1707 [(M + H)$^+$], found 318.1705; Anal. Calcd for $C_{21}H_{21}N_3O_2$·HCl·0.3H_2O: C, 64.79; H, 5.85; N, 10.79. Found: C, 64.80; H, 5.83; N, 10.92.

*2-Amino-6-((1R,2S)-2-(3′-methoxybiphenyl-3-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**ent-33**). **ent**-33* (19.8 mg, 0.0516 mmol, 59%) was obtained as a colorless solid from ***ent*-28b** (45.4 mg, 0.0872 mmol) and 3-methoxyphenylboronic acid (19.9 mg, 0.131 mmol) by the same procedure used to prepare **32** (**method A**). $[\alpha]_D^{22}$ +52.0° (c = 0.30, MeOH); HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$: 348.1707 [(M + H)$^+$], found 348.1707; Anal. Calcd for $C_{21}H_{21}N_3O_2$·HCl·0.1H_2O: C, 65.40; H, 5.80; N, 10.90. Found: C, 65.29; H, 5.85; N, 10.97.

*2-Amino-6-((1S,2R)-2-(biphenyl-4-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one (**34**).* **34** (32.8 mg, 0.103 mmol, 98%) was obtained as a light brown solid from **28c** (54.8 mg, 0.105 mmol) and phenylboronic acid (19.3 mg, 0.158 mmol) by the same procedure used to prepare **32** (**method A**). mp 179−182 °C; $[\alpha]_D^{20}$ −66.7° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.38−1.43 (1H, m), 1.65−1.70 (1H, m), 2.19−2.24 (1H, m), 2.56−2.61 (1H, m), 3.26 (3H, s), 4.69 (2H, s), 5.72 (1H, s), 7.22 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.41 (1H, s), 7.42 (2H, d, J = 7.5 Hz), 7.55 (2H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.82, 25.42, 25.56, 27.47, 101.76, 126.32, 126.82, 127.08, 128.73, 129.58, 136.58, 138.66, 140.77, 153.89, 162.36, 164.22; HRMS (ESI) calcd for $C_{20}H_{19}N_3ONa$: 345.1420 [(M + Na)$^+$], found 345.1420.

*2-Amino-3-methyl-6-((1S,2R)-2-(2′-methylbiphenyl-4-yl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**35**).* **35** (20.2 mg, 0.0549 mmol, 50%) was obtained as a colorless solid from **28c** (57.3 mg, 0.110 mmol) and 2-methylphenylboronic acid (22.5 mg, 0.165 mmol) by the same procedure used to prepare **36** (**method B**). mp 165−168 °C; $[\alpha]_D^{20}$ −50.7° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 1.60−1.65 (1H, m), 1.78−1.82 (1H, m), 2.13 (3H, s), 2.32−2.37 (1H, m), 2.88−2.93 (1H, m), 3.27 (3H, s), 5.58 (1H, s), 7.09−7.24 (6H, m), 7.27 (2H, d, J = 8.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.56, 20.53, 22.47, 27.15, 28.70, 102.08, 126.87, 128.43, 129.84, 130.14, 130.47, 131.34, 135.40, 136.25, 142.16, 142.74, 153.81, 154.24, 160.43; HRMS (ESI) calcd for $C_{21}H_{22}N_3O$: 332.1757 [(M + H)$^+$], found 332.1758; Anal. Calcd for $C_{21}H_{21}N_3O$·HCl·0.3H_2O: C, 67.57; H, 6.10; N, 11.26; Cl, 9.50. Found: C, 67.43; H, 6.07; N, 11.41; Cl, 9.13.

*Method B (Microwave Heating): 2-Amino-3-methyl-6-((1S,2R)-2-(3′-methylbiphenyl-4-yl)cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**36**).* To a solution of **28c** (55.5 mg, 0.107 mmol) in dioxane (1.1 mL) and water (0.5 mL) was added 3-methylphenylboronic acid (21.8 mg, 0.160 mmol), potassium carbonate (44.2 mg, 0.320 mmol), and dichlorobis(triphenylphosphine)palladium (3.7 mg, 0.0053 mmol), and the mixture was heated at 150 °C under microwave irradiation for 30 min. The reaction mixture was partitioned between AcOEt and water. The organic layer was washed

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838−8858

with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (AcOEt/MeOH = 10:1) to obtain the free form of **36**. This was dissolved in dioxane (0.7 mL), and 4 M hydrogen chloride in dioxane (0.080 mL, 0.322 mmol) was added. After the evaporation of the solvent, the residue was solidified with AcOEt. The solid was filtered and washed with AcOEt to give **36** (29.2 mg, 0.0794 mmol, 74%) as a colorless solid. mp 173−178 °C; $[\alpha]_D^{20}$ −68.0° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 1.58−1.63 (1H, m), 1.77−1.81 (1H, m), 2.32−2.37 (1H, m), 2.37 (3H, s), 2.84−2.89 (1H, m), 3.26 (3H, s), 5.64 (1H, s), 7.13 (1H, d, J = 7.8 Hz), 7.27 (1H, t, J = 7.8 Hz), 7.28 (2H, d, J = 7.8 Hz), 7.33 (1H, d, J = 7.8 Hz), 7.37 (1H, s), 7.50 (2H, d, J = 7.8 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 21.58, 22.76, 27.14, 28.72, 102.12, 124.92, 127.82, 128.45, 129.11, 129,80, 130.42, 135.76, 139.61, 141.23, 141.70, 153.71, 154.28, 160.55; HRMS (ESI) calcd for $C_{21}H_{22}N_3O$: 332.1757 [(M + H)$^+$], found 332.1759; Anal. Calcd for $C_{21}H_{21}N_3O\cdot HCl\cdot 0.1H_2O$: C, 68.23; H, 6.05; N, 11.37; Cl, 9.59. Found: C, 68.07; H, 6.00; N, 11.56; Cl, 9.35.

*2-Amino-3-methyl-6-((1S,2R)-2-(4′-methylbiphenyl-4-yl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**37**).* **37** (26.7 mg, 0.0726 mmol, 67%) was obtained as a colorless solid from **28c** (56.5 mg, 0.109 mmol) and 4-methylphenylboronic acid (22.1 mg, 0.163 mmol) by the same procedure used to prepare **36** (**method B**). mp 223−228 °C (dec); $[\alpha]_D^{20}$ −78.0° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 1.58−1.63 (1H, m), 1.77−1.81 (1H, m), 2.31−2.35 (1H, m), 2.35 (3H, s), 2.84−2.89 (1H, m), 3.26 (3H, s), 5.64 (1H, s), 7.21 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.4 Hz); HRMS (ESI) calcd for $C_{21}H_{22}N_3O$: 332.1757 [(M + H)$^+$], found 332.1759; Anal. Calcd for $C_{21}H_{21}N_3O\cdot HCl\cdot 0.2H_2O$: C, 67.90; H, 6.08; N, 11.31; Cl, 9.54. Found: C, 67.80; H, 6.06; N, 11.41; Cl, 9.38.

*2-Amino-3-methyl-6-((1S,2R)-2-(4-(thiophen-2-yl)phenyl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**39**).* **39** (23.2 mg, 0.0645 mmol, 65%) was obtained as a colorless solid from **28c** (51.6 mg, 0.0992 mmol) and thiophen-2-ylboronic acid (19.0 mg, 0.149 mmol) by the same procedure used to prepare **36** (**method B**). mp 203−208 °C; $[\alpha]_D^{20}$ −74.3° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.58−1.63 (1H, m), 1.76−1.81 (1H, m), 2.31−2.36 (1H, m), 2.82−2.88 (1H, m), 3.26 (3H, s), 5.65 (1H, s), 7.06 (1H, dd, J = 5.1, 3.8 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.33−7.35 (2H, m), 7.53 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.39, 22.85, 27.07, 28.75, 102.24, 124.26, 125.91, 126.57, 129.19, 130.51, 134.61, 136.10, 144.90, 153.79, 154.33, 160.60; HRMS (ESI) calcd for $C_{18}H_{18}N_3OS$: 324.1165 [(M + H)$^+$], found 324.1167; Anal. Calcd for $C_{18}H_{17}N_3OS\cdot HCl\cdot 0.3H_2O$: C, 59.19; H, 5.13; N, 11.50. Found: C, 59.23; H, 5.17; N, 11.75.

*2-Amino-3-methyl-6-((1S,2R)-2-(4-(thiophen-3-yl)phenyl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**40**).* **40** (29.6 mg, 0.0823 mmol, 89%) was obtained as a colorless solid from **28c** (48.1 mg, 0.0924 mmol) and thiophen-3-ylboronic acid (17.7 mg, 0.139 mmol) by the same procedure used to prepare **36** (**method B**). mp 214−220 °C (dec); $[\alpha]_D^{20}$ −71.7° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.57−1.63 (1H, m), 1.76−1.81 (1H, m), 2.30−2.36 (1H, m), 2.82−2.88 (1H, m), 3.26 (3H, s), 5.64 (1H, s), 7.24 (2H, d, J = 8.4 Hz), 7.40 (1H, dd, J = 5.1, 1.3 Hz), 7.45 (1H, dd, J = 5.1, 2.9 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.57 (1H, dd, J = 2.9, 1.3 Hz); HRMS (ESI) calcd for $C_{18}H_{18}N_3OS$: 324.1165 [(M + H)$^+$], found 324.1166.

*2-Amino-6-((1S,2R)-2-(4-(furan-2-yl)phenyl)cyclopropyl)-3-methylpyrimidin-4(3H)-one (**41**).* **41** (26.0 mg, 0.0846 mmol, 90%) was obtained as a colorless solid from **28c** (48.7 mg, 0.0936 mmol) and furan-2-ylboronic acid (15.7 mg, 0.140 mmol) by the same procedure used to prepare **36** (**method B**). mp 160−162 °C; $[\alpha]_D^{20}$ −74.0° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35−1.41 (1H, m), 1.64−1.69 (1H, m), 2.17−2.23 (1H, m), 2.53−2.59 (1H, m), 3.25 (3H, s), 4.67 (2H, br s), 5.72 (1H, s), 6.42−6.45 (1H, m), 6.56 (1H, d, J = 3.2 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.42 (1H, s), 7.48 (2H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.65, 25.40, 25.63, 27.45, 101.87, 104.50, 111.62, 123.15, 128.67, 129.46, 136.67, 141.76, 153.82, 154.03, 162.25, 164.01; HRMS (ESI) calcd for $C_{18}H_{17}N_3O_2Na$: 330.1213 [(M + Na)$^+$], found 330.1215.

*2-Amino-3-methyl-6-((1S,2R)-2-(4-(5-methylthiophen-2-yl)-phenyl)cyclopropyl)pyrimidin-4(3H)-one (**42**).* **42** (24.8 mg, 0.0735 mmol, 82%) was obtained as a colorless solid from **28c** (46.9 mg, 0.0901 mmol) and 5-methylthiophene-2-ylboronic acid (19.2 mg, 0.135 mmol) by the same procedure used to prepare **36** (**method B**). mp 207−210 °C; $[\alpha]_D^{20}$ −72.3° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35−1.40 (1H, m), 1.62−1.67 (1H, m), 2.16−2.22 (1H, m), 2.48 (3H, s), 2.51−2.57 (1H, m), 3.25 (3H, s), 4.68 (2H, br s), 5.73 (1H, s), 6.68 (1H, dd, J = 3.5, 1.0 Hz), 7.03 (1H, d, J = 3.5 Hz), 7.12 (2H, d, J = 8.2 Hz), 7.35 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.70, 15.44, 25.44, 25.53, 27.45, 101.93, 122.43, 124.68, 126.13, 129.54, 132.36, 136.36, 139.10, 141.91, 153.82, 162.28, 164.08; HRMS (ESI) calcd for $C_{19}H_{19}N_3OSNa$: 360.1141 [(M + Na)$^+$], found 360.1141.

*2-Amino-3-methyl-6-((1S,2R)-2-(4-(4-methylthiophen-2-yl)-phenyl)cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**43**).* **43** (22.3 mg, 0.0596 mmol, 66%) was obtained as a colorless solid from **28c** (46.9 mg, 0.0901 mmol) and 4,4,5,5-tetramethyl-2-(4-methylthiophen-2-yl)-1,3,2-dioxaborolane (30.3 mg, 0.135 mmol) by the same procedure used to prepare **36** (**method B**). mp 193−196 °C; $[\alpha]_D^{20}$ −68.7° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.57−1.62 (1H, m), 1.75−1.80 (1H, m), 2.24 (3H, s), 2.30−2.36 (1H, m), 2.81−2.86 (1H, m), 3.26 (3H, s), 5.64 (1H, s), 6.91 (1H, s), 7.16 (1H, s), 7.21 (2H, d, J = 8.3 Hz), 7.49 (2H, d, J = 8.3 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.37, 15.80, 22.81, 27.11, 28.75, 102.21, 121.27, 126.33, 126.51, 130.48, 134.79, 135.91, 139.99, 144.59, 153.54, 154.30, 160.54; HRMS (ESI) calcd for $C_{18}H_{18}N_3OS$: 338.1322 [(M + H)$^+$], found 338.1324.

*2-Amino-6-((1S,2R)-2-(4-(6-methoxypyridin-2-yl)phenyl)-cyclopropyl)-3-methylpyrimidin-4(3H)-one (**44**).* **44** (9.2 mg, 0.026 mmol, 30%) was obtained as a colorless solid from **28c** (46.3 mg, 0.0890 mmol) and 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62.8 mg, 0.267 mmol) by the same procedure used to prepare **36** (**method B**). mp 188−190 °C; $[\alpha]_D^{20}$ −61.0° (c = 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38−1.44 (1H, m), 1.67−1.71 (1H, m), 2.20−2.26 (1H, m), 2.56−2.62 (1H, m), 3.25 (3H, s), 4.01 (3H, s), 4.65 (2H, br s), 5.75 (1H, s), 6.64 (1H, dd, J = 8.2, 0.6 Hz), 7.25 (2H, d, J = 8.3 Hz), 7.29 (1H, dd, J = 7.4, 0.6 Hz), 7.59 (1H, dd, J = 8.3, 7.4 Hz), 7.88 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.72, 25.63, 25.70, 27.46, 53.20, 102.04, 108.89, 112.47, 125.95, 129.34, 136.65, 138.39, 139.14, 153.79, 154.42, 162.28, 163.69, 163.96; HRMS (ESI) calcd for $C_{20}H_{20}N_4O_2Na$: 371.1479 [(M + Na)$^+$], found 371.1482.

*2-Amino-6-((1S,2R)-2-(4-(2-methoxypyridin-4-yl)phenyl)-cyclopropyl)-3-methylpyrimidin-4(3H)-one (**45**).* **45** (23.5 mg, 0.0675 mmol, 78%) was obtained as a light brown solid from **28c** (45.1 mg, 0.0867 mmol) and 2-methoxypyridin-4-ylboronic acid (19.9 mg, 0.130 mmol) by the same procedure used to prepare **36** (**method B**). mp 224−226 °C; $[\alpha]_D^{20}$ −57.3° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39−1.44 (1H, m), 1.67−1.71 (1H, m), 2.20−2.26 (1H, m), 2.56−2.62 (1H, m), 3.27 (3H, s), 3.97 (3H, s), 4.64 (2H, br s), 5.72 (1H, s), 6.91 (1H, dd, J = 1.7, 0.8 Hz), 7.07 (1H, dd, J = 5.4, 1.7 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.44 (2H, d, J = 8.2 Hz), 8.17 (1H, dd, J = 5.4, 0.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.74, 25.44, 25.64, 27.48, 53.51, 102.02, 108.01, 115.10, 126.17, 129.90, 135.65, 138.65, 147.16, 150.87, 153.73, 162.24, 163.99, 164.92; HRMS (ESI) calcd for $C_{20}H_{21}N_4O_2$: 349.1659 [(M + H)$^+$], found 349.1662.

*2-Amino-6-((1S,2R)-2-(4-(6-methoxypyrazin-2-yl)phenyl)-cyclopropyl)-3-methylpyrimidin-4(3H)-one (**46**).* **46** (20.3 mg, 0.0581 mmol, 67%) was obtained as a light yellow powder from **28c** (45.1 mg, 0.0867 mmol) and 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine (30.7 mg, 0.130 mmol) by the same procedure used to prepare **36** (**method B**). mp 192−195 °C; $[\alpha]_D^{20}$ −64.0° (c = 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40−1.46 (1H, m), 1.67−1.73 (1H, m), 2.22−2.28 (1H, m), 2.57−2.62 (1H, m), 3.26 (3H, s), 4.10 (3H, s), 4.73 (2H, br s), 5.72 (1H, s), 7.27 (2H, d, J = 8.1 Hz), 7.87 (2H, d, J = 8.1 Hz), 8.11 (1H, s), 8.54 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.74, 25.65, 25.72, 27.49, 53.38, 101.96, 126.07,

127.70, 132.80, 133.23, 133.84, 139.42, 148.72, 153.80, 159.77, 162.26, 163.89; HRMS (ESI) calcd for $C_{19}H_{19}N_5O_2Na$: 372.1431 [(M + Na)$^+$], found 372.1430.

*2-Amino-6-((1S,2R)-2-(3′-methoxybiphenyl-4-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**47**).* **47** (21.0 mg, 0.0547 mmol, 51%) was obtained as a colorless solid from **28c** (55.4 mg, 0.106 mmol) and 3-methoxyphenylboronic acid (24.3 mg, 0.160 mmol) by the same procedure used to prepare **36** (**method B**). mp 151−154 °C; $[\alpha]_D^{20}$ −67.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.58−1.64 (1H, m), 1.77−1.82 (1H, m), 2.31−2.37 (1H, m), 2.37 (3H, s), 2.84−2.90 (1H, m), 3.26 (3H, s), 3.82 (3H, s), 5.65 (1H, s), 6.88 (1H, dd, *J* = 7.8, 2.5 Hz), 7.08 (1H, dd, *J* = 2.5, 1.7 Hz), 7.08 (1H, dd, *J* = 7.8, 1.7 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 7.51 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 22.75, 27.13, 28.74, 55.76, 102.17, 113.54, 113.76, 120.23, 127.88, 130.43, 130.93, 136.03, 140.96, 143.18, 153.53, 154.25, 160.50, 161.62; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$: 348.1707 [(M + H)$^+$], found 348.1709; Anal. Calcd for $C_{21}H_{21}N_3O_2$·HCl·0.3H_2O: C, 64.79; H, 5.85; N, 10.79; Cl, 9.11. Found: C, 64.70; H, 5.87; N, 10.81; Cl, 9.10.

*2-Amino-6-((1S,2R)-2-(3′-ethoxybiphenyl-4-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**48**).* **48** (22.5 mg, 0.0565 mmol, 63%) was obtained as a colorless solid from **28c** (46.6 mg, 0.0895 mmol) and 3-ethoxyphenylboronic acid (22.3 mg, 0.134 mmol) by the same procedure used to prepare **36** (**method B**). mp 153−155 °C; $[\alpha]_D^{20}$ −63.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.39 (3H, t, *J* = 7.1 Hz), 1.58−1.64 (1H, m), 1.77−1.82 (1H, m), 2.31−2.37 (1H, m), 2.84−2.90 (1H, m), 3.26 (3H, s), 4.07 (2H, q, *J* = 7.1 Hz), 5.65 (1H, s), 6.87 (1H, ddd, *J* = 8.1, 2.0, 0.8 Hz), 7.07 (1H, dd, *J* = 2.0, 1.4 Hz), 7.11 (1H, ddd, *J* = 8.1, 1.4, 0.8 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 7.30 (1H, t, *J* = 8.1 Hz), 7.51 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 15.23, 22.74, 27.12, 28.74, 64.55, 102.19, 114.13, 114.36, 120.15, 127.87, 130.41, 130.91, 135.99, 141.01, 143.15, 153.48, 154.25, 160.48, 160.90; HRMS (ESI) calcd for $C_{22}H_{24}N_3O_2$: 362.1863 [(M + H)$^+$], found 364.1863. Anal. Calcd for $C_{22}H_{23}N_3O_2$·HCl·0.4H_2O: C, 65.23; H, 6.17; N, 10.37; Cl, 8.75. Found: C, 65.31; H, 6.22; N, 10.60; Cl, 8.50.

*2-Amino-3-methyl-6-((1S,2R)-2-(3′-propoxybiphenyl-4-yl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**49**).* **49** (15.7 mg, 0.0381 mmol, 38%) was obtained as a colorless solid from **28c** (51.7 mg, 0.0993 mmol) and 3-propoxyphenylboronic acid (26.8 mg, 0.149 mmol) by the same procedure used to prepare **36** (**method B**). mp 161−164 °C; $[\alpha]_D^{20}$ −74.0° (*c* = 0.10, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.05 (3H, t, *J* = 7.4 Hz), 1.60−1.64 (1H, m), 1.76−1.84 (3H, m), 2.31−2.37 (1H, m), 2.84−2.90 (1H, m), 3.26 (3H, s), 3.95 (2H, t, *J* = 6.4 Hz), 5.65 (1H, s), 6.87 (1H, ddd, *J* = 8.0, 2.6, 1.0 Hz), 7.07 (1H, dd, *J* = 2.6, 1.6 Hz), 7.11 (1H, ddd, *J* = 8.0, 1.6, 1.0 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.30 (1H, t, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 10.91, 22.72, 23.75, 27.12, 28.75, 70.63, 102.19, 114.13, 114.38, 120.13, 127.87, 130.42, 130.91, 135.98, 141.03, 143.15, 153.46, 154.23, 160.49, 161.09; HRMS (ESI) calcd for $C_{23}H_{26}N_3O_2$: 376.2020 [(M + H)$^+$], found 376.2020.

*2-Amino-6-((1S,2R)-2-(3′-isopropoxybiphenyl-4-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**50**).* **50** (26.4 mg, 0.0641 mmol, 75%) was obtained as a colorless solid from **28c** (44.6 mg, 0.0857 mmol) and 3-isopropoxyphenylboronic acid (23.1 mg, 0.129 mmol) by the same procedure used to prepare **36** (**method B**). mp 168−171 °C; $[\alpha]_D^{20}$ −60.0° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.32 (6H, d, *J* = 6.1 Hz), 1.58−1.64 (1H, m), 1.77−1.82 (1H, m), 2.31−2.37 (1H, m), 2.84−2.90 (1H, m), 3.26 (3H, s), 4.64 (1H, septet, *J* = 6.1 Hz), 5.65 (1H, s), 6.86 (1H, ddd, *J* = 7.9, 2.5, 0.8 Hz), 7.05 (1H, dd, *J* = 2.5, 1.7 Hz), 7.10 (1H, ddd, *J* = 7.9, 1.7, 0.8 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 7.29 (1H, t, *J* = 7.9 Hz), 7.50 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 22.41, 22.73, 27.12, 28.74, 71.05, 102.19, 115.67, 115.77, 120.18, 127.85, 130.42, 130.94, 135.97, 141.01, 143.22, 153.45, 154.25, 159.75, 160.48; HRMS (ESI) calcd for $C_{23}H_{26}N_3O_2$: 376.2020 [(M + H)$^+$], found 376.2023; Anal. Calcd for $C_{23}H_{25}N_3O_2$·HCl·0.4H_2O: C, 65.91; H, 6.44; N, 10.03; Cl 8.46. Found: C, 66.02; H, 6.39; N, 10.19; Cl 8.42.

*2-Amino-6-((1S,2R)-2-(3′-(cyclopropylmethoxy)biphenyl-4-yl)-cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**51**).* **51** (16.8 mg, 0.0396 mmol, 46%) was obtained as a colorless solid from **28c** (44.6 mg, 0.0857 mmol) and 3-cyclopropylmethoxyphenylboronic acid (24.7 mg, 0.129 mmol) by the same procedure used to prepare **36** (**method B**). mp 152−155 °C; $[\alpha]_D^{20}$ −55.3° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.33−0.37 (2H, m), 0.59−0.64 (2H, m), 1.21−1.30 (1H, m), 1.60−1.64 (1H, m), 1.77−1.82 (1H, m), 2.31−2.37 (1H, m), 2.84−2.90 (1H, m), 3.26 (3H, s), 5.65 (1H, s), 6.86 (1H, ddd, *J* = 8.0, 2.4, 1.0 Hz), 7.07 (1H, dd, *J* = 2.4, 1.7 Hz), 7.12 (1H, ddd, *J* = 8.0, 1.7, 1.0 Hz), 7.28 (2H, d, *J* = 8.8 Hz), 7.29 (1H, t, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 3.56, 10.43, 11.28, 22.77, 27.12, 28.73, 73.84, 102.19, 114.26, 114.50, 120.20, 127.87, 130.41, 130.91, 136.00, 141.00, 143.16, 153.60, 154.27, 160.51, 161.00; HRMS (ESI) calcd for $C_{24}H_{26}N_3O_2$: 388.2020 [(M + H)$^+$], found 388.2021.

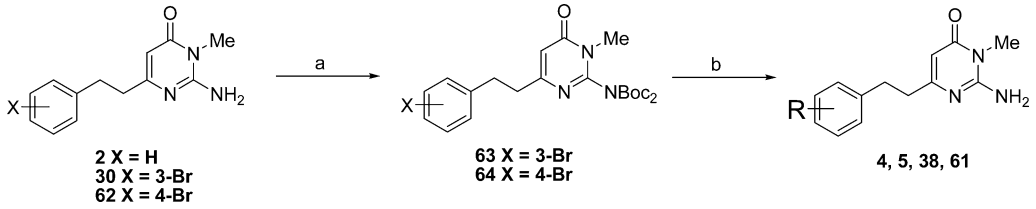
*2-Amino-6-((1S,2R)-2-(3′-ethylbiphenyl-4-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**52**).* **52** (24.2 mg, 0.0634 mmol, 73%) was obtained as a colorless solid from **28c** (45.0 mg, 0.0865 mmol) and 3-ethylphenylboronic acid (19.5 mg, 0.130 mmol) by the same procedure used to prepare **36** (**method B**). mp 175−178 °C; $[\alpha]_D^{20}$ −62.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.25 (3H, t, *J* = 7.6 Hz), 1.61−1.66 (1H, m), 1.77−1.82 (1H, m), 2.32−2.37 (1H, m), 2.68 (2H, q, *J* = 7.6 Hz), 2.85−2.91 (1H, m), 3.26 (3H, s), 5.65 (1H, s), 7.16 (1H, d, *J* = 7.6 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.30 (1H, t, *J* = 7.6 Hz), 7.36 (1H, d, *J* = 7.6 Hz), 7.38 (1H, s), 7.51 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 16.32, 22.70, 27.15, 28.73, 29.97, 102.18, 125.21, 127.35, 127.86, 127.98, 129.91, 130.41, 135.71, 141.35, 141.77, 146.15, 153.46, 154.25, 160.47; HRMS (ESI) calcd for $C_{22}H_{24}N_3O$: 346.1914 [(M + H)$^+$], found 346.1914.

*2-Amino-3-methyl-6-((1S,2R)-2-(3′-propylbiphenyl-4-yl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**53**).* **53** (26.5 mg, 0.0669 mmol, 76%) was obtained as a colorless solid from **28c** (45.7 mg, 0.0878 mmol) and 4,4,5,5-tetramethyl-2-(3-propylphenyl)-1,3,2-dioxaborolane (32.4 mg, 0.132 mmol) by the same procedure used to prepare **36** (**method B**). mp 177−182 °C; $[\alpha]_D^{20}$ −66.3° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.95 (3H, t, *J* = 7.6 Hz), 1.59−1.64 (1H, m), 1.67 (3H, sextet, *J* = 7.6 Hz), 1.77−1.82 (1H, m), 2.32−2.37 (1H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.85−2.91 (1H, m), 3.26 (3H, s), 5.65 (1H, s), 7.14 (1H, d, *J* = 7.6 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.30 (1H, t, *J* = 7.6 Hz), 7.36 (1H, d, *J* = 7.6 Hz), 7.37 (1H, s), 7.51 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.43, 14.13, 22.70, 25.86, 27.14, 28.73, 39.14, 102.20, 125.25, 127.86, 127.97, 128.63, 129.81, 130.41, 141.34, 141.68, 144.46, 153.42, 154.25, 160.46; HRMS (ESI) calcd for $C_{23}H_{26}N_3O$: 360.2070 [(M + H)$^+$], found 360.2073; Anal. Calcd for $C_{23}H_{25}N_3O$·HCl·0.3H_2O: C, 68.83; H, 6.68; N, 10.47; Cl 8.83. Found: C, 68.91; H, 6.58; N, 10.76; Cl 8.62.

*2-Amino-3-methyl-6-((1S,2R)-2-(3′-(methylthio)biphenyl-4-yl)-cyclopropyl)pyrimidin-4(3H)-one Hydrochloride (**54**).* **54** (20.5 mg, 0.0513 mmol, 57%) was obtained as a colorless solid from **28c** (46.6 mg, 0.0895 mmol) and 3-(methylthio)phenylboronic acid (22.6 mg, 0.134 mmol) by the same procedure used to prepare **36** (**method B**). mp 154−159 °C; $[\alpha]_D^{20}$ −67.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.59−1.64 (1H, m), 1.77−1.82 (1H, m), 2.32−2.38 (1H, m), 2.50 (3H, s), 2.84−2.90 (1H, m), 3.26 (3H, s), 5.65 (1H, s), 7.22 (1H, ddd, *J* = 6.0, 2.6, 2.0 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 7.32−7.34 (2H, m), 7.42 (1H, dd, *J* = 2.6, 1.3 Hz), 7.51 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.43, 15.74, 22.80, 27.12, 28.75, 102.13, 124.60, 125.78, 126.41, 127.87, 130.40, 130.52, 136.23, 140.58, 140.80, 142.41, 153.66, 154.27, 160.56; HRMS (ESI) calcd for $C_{21}H_{22}N_3OS$: 364.1478 [(M + H)$^+$], found 364.1480.

*2-Amino-6-((1S,2R)-2-(3′-(ethylthio)biphenyl-4-yl)cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**55**).* **55** (28.3 mg, 0.0684 mmol, 76%) was obtained as a colorless solid from **28c** (47.0 mg, 0.0903 mmol) and 3-(ethylthio)phenylboronic acid (24.7 mg, 0.135 mmol) by the same procedure used to prepare **36** (**method B**). mp 141−144 °C; $[\alpha]_D^{20}$ −62.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.30 (3H, t, *J* = 7.3 Hz), 1.59−1.65 (1H, m), 1.77−1.82

Scheme 5. Synthesis of Reference Compounds with Ethylene Linker (4, 5, 38, and 61)[a]



[a](a) 2.5 equiv of Boc_2O, 0.3 equiv of DMAP, CH_2Cl_2, rt, 72% (**63**), 92% (**64**); (b) R-$B(OH)_2$, K_2CO_3, $PdCl_2(PPh_3)_2$, dioxane, H_2O, 100 °C (Method A), 150 °C under microwave, 30 min (Method B).

(1H, m), 2.32−2.38 (1H, m), 2.85−2.91 (1H, m), 2.98 (2H, q, *J* = 7.3 Hz), 3.26 (3H, s), 5.65 (1H, s), 7.28 (1H, dt, *J* = 7.6, 1.7 Hz), 7.30 (2H, d, *J* = 8.1 Hz), 7.34 (1H, t, *J* = 7.6 Hz), 7.37 (1H, dt, *J* = 7.6, 1.7 Hz), 7.49 (1H, t, *J* = 1.7 Hz), 7.51 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.45, 14.81, 22.76, 27.11, 28.27, 28.75, 102.20, 125.38, 127.88, 128.21, 128.81, 130.44, 130.52, 136.24, 138.85, 140.53, 142.48, 153.43, 154.26, 160.48; HRMS (ESI) calcd for $C_{22}H_{24}N_3OS$: 378.1635 [(M + H)$^+$], found 378.1638; Anal. Calcd for $C_{22}H_{23}N_3OS{\cdot}HCl{\cdot}0.2H_2O$: C, 63.28; H, 5.89; N, 10.06; S, 7.68; Cl, 8.49. Found: C, 63.49; H, 5.89; N, 10.12; S, 7.39; Cl, 8.37.

*2-Amino-6-((1S,2R)-2-(3′-(methoxymethyl)biphenyl-4-yl)-cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**56**).* **56** (27.1 mg, 0.0681 mmol, 77%) was obtained as a colorless solid from **28c** (46.2 mg, 0.0888 mmol) and 3-(methoxymethyl)phenylboronic acid (22.1 mg, 0.133 mmol) by the same procedure used to prepare **36** (**method B**). mp 183−185 °C; $[\alpha]_D^{20}$ −65.0° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.59−1.65 (1H, m), 1.78−1.83 (1H, m), 2.32−2.38 (1H, m), 2.85−2.91 (1H, m), 3.26 (3H, s), 3.40 (3H, s), 4.50 (2H, s), 5.65 (1H, s), 7.28−7.31 (3H, m), 7.39 (1H, t, *J* = 7.8 Hz), 7.50 (1H, ddd, *J* = 7.8, 1.7, 1.3 Hz), 7.52−7.55 (3H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 22.71, 27.13, 28.73, 58.43, 75.62, 102.19, 127.19, 127.25, 127.87, 127.94, 129.99, 130.49, 135.99, 140.17, 140.90, 141.88, 153.40, 154.24, 160.44; HRMS (ESI) calcd for $C_{22}H_{24}N_3O_2$: 362.1863 [(M + H)$^+$], found 362.1866.

*2-(4′-((1R,2S)-2-(2-Amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)cyclopropyl)biphenyl-3-yl)acetonitrile Hydrochloride (**57**).* **57** (25.7 mg, 0.0654 mmol, 73%) was obtained as a colorless solid from **28c** (46.7 mg, 0.0897 mmol) and 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile (32.7 mg, 0.135 mmol) by the same procedure used to prepare **36** (**method B**). mp 184−186 °C; $[\alpha]_D^{20}$ −59.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.59−1.65 (1H, m), 1.78−1.83 (1H, m), 2.33−2.39 (1H, m), 2.85−2.91 (1H, m), 3.26 (3H, s), 3.95 (2H, s), 5.65 (1H, s), 7.30−7.35 (3H, m), 7.44 (1H, t, *J* = 7.7 Hz), 7.53−7.58 (4H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.44, 22.74, 23.56, 27.10, 28.74, 102.21, 127.33, 127.51, 127.91, 128.07, 130.57, 130.69, 133.08, 136.38, 140.34, 142.66, 153.42, 154.27, 160.47; HRMS (ESI) calcd for $C_{22}H_{21}N_4O$: 357.1710 [(M + H)$^+$], found 357.1713.

*2-Amino-6-((1S,2R)-2-(3′-(2-hydroxyethyl)biphenyl-4-yl)-cyclopropyl)-3-methylpyrimidin-4(3H)-one Hydrochloride (**58**).* **58** (30.7 mg, 0.0771 mmol, 77%) was obtained as a colorless solid from **28c** (52.4 mg, 0.101 mmol) and 3-(2-hydroxyethyl)phenylboronic acid (25.1 mg, 0.151 mmol) by the same procedure used to prepare **36** (**method B**). mp 166−168 °C; $[\alpha]_D^{20}$ −65.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.59−1.64 (1H, m), 1.77−1.82 (1H, m), 2.32−2.37 (1H, m), 2.84−2.91 (1H, m), 2.86 (2H, t, *J* = 7.0 Hz), 3.26 (3H, s), 3.78 (2H, t, *J* = 7.0 Hz), 5.65 (1H, s), 7.19 (1H, d, *J* = 7.6 Hz), 7.29 (2H, d, *J* = 8.2 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 7.40 (1H, d, *J* = 7.6 Hz), 7.43 (1H, s), 7.52 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 22.74, 27.14, 28.72, 40.29, 64.21, 102.17, 125.71, 127.87, 128.57, 129.13, 129.92, 130.43, 135.80, 141.11, 141.20, 141.79, 153.53, 154.26, 160.48; HRMS (ESI) calcd for $C_{22}H_{23}N_3O_2Na$: 384.1681 [(M + Na)$^+$], found 384.1683; Anal. Calcd for $C_{22}H_{23}N_3O_2{\cdot}HCl{\cdot}0.5H_2O$: C, 64.94; H, 6.19; N, 10.33; Cl 8.71. Found: C, 64.98; H, 6.09; N, 10.43; Cl 8.48.

*N-(4′-((1R,2S)-2-(2-Amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)cyclopropyl)biphenyl-3-yl)acetamide Hydrochloride (**59**).* **59** (33.1 mg, 0.0806 mmol, 76%) was obtained as a light brown solid from **28c** (55.2 mg, 0.106 mmol) and 3-acetoamidophenylboronic acid (28.5 mg, 0.159 mmol) by the same procedure used to prepare **36** (**method B**). mp 163−166 °C; $[\alpha]_D^{20}$ −58.0° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.59−1.65 (1H, m), 1.78−1.83 (1H, m), 2.14 (3H, s), 2.33−2.38 (1H, m), 2.85−2.91 (1H, m), 3.26 (3H, s), 5.66 (1H, s), 7.30 (2H, d, *J* = 8.1 Hz), 7.30 (1H, d, *J* = 7.9 Hz), 7.35 (1H, t, *J* = 7.9 Hz), 7.41 (1H, d, *J* = 7.9 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.87 (1H, s); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.38, 22.64, 23.93, 27.11, 28.78, 102.27, 119.55, 120.10, 123.56, 130.34, 130.46, 136.07, 140.45, 140.80, 142.38, 153.02, 154.16, 160.32, 171.86; HRMS (ESI) calcd for $C_{22}H_{23}N_4O_2$: 375.1816 [(M + H)$^+$], found 375.1816.

*4′-((1R,2S)-2-(2-Amino-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)cyclopropyl)biphenyl-3-carboxamide Hydrochloride (**60**).* **60** (29.0 mg, 0.0731 mmol, 68%) was obtained as a colorless solid from **28c** (55.8 mg, 0.107 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (39.7 mg, 0.161 mmol) by the same procedure used to prepare **36** (**method B**). mp 165−169 °C; $[\alpha]_D^{20}$ −61.7° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.60−1.66 (1H, m), 1.79−1.84 (1H, m), 2.34−2.40 (1H, m), 2.87−2.93 (1H, m), 3.26 (3H, s), 5.66 (1H, s), 7.33 (2H, d, *J* = 8.2 Hz), 7.51 (1H, t, *J* = 7.8 Hz), 7.60 (2H, d, *J* = 8.2 Hz), 7.77 (1H, ddd, *J* = 7.8, 1.7, 1.1 Hz), 7.82 (1H, ddd, *J* = 7.8, 1.7, 1.1 Hz), 8.09 (1H, t, *J* = 1.7 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.42, 22.65, 27.11, 28.77, 102.25, 127.13, 127.54, 127.96, 130.20, 130.61, 131.21, 135.55, 136.44, 140.12, 142.10, 153.01, 154.17, 160.32, 172.31; HRMS (ESI) calcd for $C_{21}H_{20}N_4O_2Na$: 383.1479 [(M + Na)$^+$], found 383.1481.

Synthesis of Reference Compounds (Scheme 5). Starting materials **2**, **30**, and **62** were prepared according to the literature or patent.[6b,c]

*2-Amino-6-(2-(biphenyl-3-yl)ethyl)-3-methylpyrimidin-4(3H)-one (**4**).*[6b,c] **4** (33.9 mg, 0.111 mmol, quant) was obtained as a colorless solid from **63** (53.6 mg, 0.105 mmol) and phenylboronic acid (19.3 mg, 0.158 mmol) by the same procedure used to prepare **32** (**method A**). Spectrum data were found to be identical to those in the literature.

*2-Amino-6-(2-(3′-methoxybiphenyl-3-yl)ethyl)-3-methylpyrimidin-4(3H)-one (**5**).*[6b,c] **5** (36.9 mg, 0.110 mmol, 100%) was obtained as a colorless solid from **63** (56.0 mg, 0.110 mmol) and 3-methoxyphenylboronic acid (25.1 mg, 0.165 mmol) by the same procedure used to prepare **32** (**method A**). Spectrum data were found to be identical to those in the literature.

*2-Amino-6-(2-(biphenyl-4-yl)ethyl)-3-methylpyrimidin-4(3H)-one (**38**).*[6c] **38** (19.2 mg, 0.0629 mmol, 56%) was obtained as colorless solid from **64** (57.0 mg, 0.112 mmol) and phenylboronic acid (20.5 mg, 0.168 mmol) by the same procedure used to prepare **36** (**method B**). mp 213−216 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.70 (2H, dd, *J* = 9.2, 7.0 Hz), 2.97 (2H, dd, *J* = 9.2, 7.0 Hz), 3.41 (3H, s), 5.05 (2H, br s), 5.84 (1H, s), 7.28 (2H, d, *J* = 8.2 Hz), 7.30−7.34 (1H, m), 7.40−7.44 (2H, m), 7.51 (2H, d, *J* = 8.2 Hz), 7.55−7.59 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.59, 33.72, 38.93, 101.87, 126.99, 127.10, 127.17, 128.35, 128.74, 128.78, 139.97, 140.22, 140.95, 154.81, 162.68, 166.55; HRMS (ESI) calcd for $C_{19}H_{20}N_3O$: 306.1601 [(M + H)$^+$], found 306.1606.

*2-Amino-6-(2-(3′-(ethylthio)biphenyl-4-yl)ethyl)-3-methylpyrimidin-4(3H)-one (**61**).* **61** (32.4 mg, 0.0886 mmol, 95%) was obtained as colorless solid from **64** (47.7 mg, 0.0938 mmol) and 3-(methylthio)-phenylboronic acid (25.6 mg, 0.141 mmol) by the same procedure

dx.doi.org/10.1021/jm3011405 | J. Med. Chem. 2012, 55, 8838−8858

used to prepare **36** (**method B**). mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (3H, t, J = 7.3 Hz), 2.68−2.72 (2H, m), 2.95−3.00 (2H, m), 2.99 (2H, d, J = 7.3 Hz), 3.41 (3H, s), 5.11 (2H, br s), 5.83 (1H, s), 7.27 (2H, d, J = 8.3 Hz), 7.28 (1H, dt, J = 7.5, 1.7 Hz), 7.34 (1H, t, J = 7.5 Hz), 7.37 (1H, dt, J = 7.5, 1.7 Hz), 7.49 (2H, d, J = 8.3 Hz), 7.50 (1H, t, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.42, 27.61, 27.69, 33.68, 38.80, 101.76, 124.57, 127.17, 127.53, 127.58, 128.81, 129.17, 137.14, 138.55, 140.47, 141.63, 154.88, 162.68, 166.37; HRMS (ESI) calcd for $C_{21}H_{24}N_3OS$: 366.1635 [(M + H)$^+$], found 366.1640; Anal. Calcd for $C_{21}H_{23}N_3OS\cdot 0.2H_2O$: C, 68.34; H, 6.39; N, 11.38; S, 8.69. Found: C, 68.59; H, 6.21; N, 11.61; S, 8.31.

*2-Bis(tert-butoxycarbonyl)amino-6-(3-bromophenethyl)-3-methylpyrimidin-4(3H)-one (**63**).* **63** (275 mg, 0.541 mmol, 72%) was obtained as a colorless solid from **30** (233 mg, 0.756 mmol) by the same procedure used to prepare **25a**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.46 (9H, s), 2.80 (2H, dd, J = 9.0, 6.6 Hz), 2.93 (2H, dd, J = 9.0, 6.6 Hz), 3.42 (3H, s), 6.21 (1H, s), 7.10 (1H, d, J = 7.6 Hz), 7.14 (1H, t, J = 7.6 Hz), 7.33 (1H, d, J = 7.6 Hz), 7.35 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.90, 30.08, 33.48, 38.17, 84.96, 111.40, 122.57, 127.00, 129.44, 130.05, 131.42, 142.80, 148.46, 149.02, 162.85, 164.58; HRMS (ESI) calcd for $C_{23}H_{31}BrN_3O_5$: 508.1442 [(M + H)$^+$], found 508.1443.

*2-Bis(tert-butoxycarbonyl)amino-6-(4-bromophenethyl)-3-methylpyrimidin-4(3H)-one (**64**).* **64** (261 mg, 0.514 mmol, 92%) was obtained as a colorless solid from **62** (172 mg, 0.558 mmol) by the same procedure used to prepare **25a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (9H, s), 2.79 (2H, dd, J = 8.6, 7.4 Hz), 2.92 (2H, dd, J = 8.6, 7.4 Hz), 3.42 (3H, s), 6.20 (1H, s), 7.05 (2H, d, J = 8.4 Hz), 7.38 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.89, 30.77, 33.26, 38.26, 84.95, 111.46, 120.06, 130.14, 131.56, 139.40, 148.48, 148.98, 162.83, 164.63; HRMS (ESI) calcd for $C_{23}H_{31}BrN_3O_5$: 508.1442 [(M + H)$^+$], found 508.1453.

Protein Expression and Purification. A cDNA fragment encoding human BACE1 (hBACE1) residues 43−454 was cloned into pET28a and expressed in E. coli BL21(DE3) cells. The hBACE1 protein was expressed as insoluble inclusion bodies and was refolded by a modified method using iFOLD protein Refolding System 3 (Novagen). The refolded protein was applied on a Q-Sepharose FF column. The fractions with BACE catalytic activity were collected and applied to a His Trap HP column followed by a HiLoad Q Sepharose HP column and Superdex 200 column for further purification. After thrombin digestion, a HisTrap Benzamine FF column was used for removal of thrombin. The flow through fraction was loaded onto a His trap column, and the purified hBACE1 protein was >98% purity on SDS-PAGE. The buffer was exchanged into 20 mM Tris-HCl (pH 8.0), 150 mM NaCl, 2 mM DTT.

ELISA (High-Sensitive Enzyme Assay). In vitro high-sensitive BACE1 activity assays were performed using substrate peptides from the American Peptide Company, Inc. (Sunnyvale, CA) and human BACE1 prepared as above. The substrate peptide sequence was SEVNLDAEFRHDSGYEK-biotin. Peptides and inhibitors were dissolved in dimethyl sulfoxide (DMSO), and dissolved peptides were stored at −20 °C. The substrate peptide was captured on a streptavidin 96-well-format plate (Nunc) at 25 nM (100 μL scale reaction). The reaction buffer was 50 mM sodium acetate, pH 4.5, containing 0.25 mg/mL bovine serum albumin (BSA). The reactions were started by adding 70 μL of reaction buffer, 10 μL of inhibitor solution or DMSO, and 20 μL of BACE1 (final 0.45 nM) in each well. After 3 h of incubation at 25 °C, reaction mixtures except cleaved and uncleaved substrates were washed out with TBST (Tris-buffered saline containing 0.1% of Tween-20). The cleaved product on plates was detected with horseradish peroxidase (HRP)-conjugated 82E1, which is a monoclonal antibody specific for the N-terminal end generated by BACE1 cleavage (82E1; IBL Co., Ltd., Gunma, Japan), like the general ELISA assay. The quantifications of HRP activity were carried out by a colorimetric method using TMB substrate (Thermo Scientific, Inc.).

Homogeneous Time-Resolved Fluorescence (HTRF) Assay. 0.5 μL of the test compounds (dissolved in dimethyl sulfoxide) was incubated with 48.5 μL of the fluorescence-quenching peptide substrate solution (Biotin-XSEVNLDAEFRHDSGC-Eu: X = ε-amino-*n*-capronic acid, Eu = europium cryptate) and 1 μL of recombinant human BACE1 protein (R & D systems) for 3 h at 30 °C in the 96 well half area plate (black color plate, Costar). The substrate peptide was synthesized by reacting with Biotin-XSEVNL-DAEFREDSGC (Peptide Institute) and cryptate TBPCOOH mono SMP (CIS bio international). The final concentrations of the substrate peptide and recombinant human BACE1 protein were 18 nM and 7.4 nM, respectively. The enzymatic reaction was performed in sodium acetate buffer (50 mM sodium acetate (pH 5.0), 0.008% Triton X-100). After the reaction, a 50 μL of 8.0 μg/mL Streptavidin-XL665 (CIS bio international) dissolved in phosphate buffer (160 mM K_2HPO_4−H_2PO_4 (pH 7.0), 0.008% TritonX-100, 0.8 M KF) was added to each well and incubated for l h at 30 °C. Then, the fluorescence intensity (excitation wavelength 320 nm, emission wavelength 620 and 665 nm) in each well was measured using a Wallac 1420 multilabel counter (Perkin-Elmer life sciences). The enzymatic activity was calculated by each fluorescence intensity ratio ([ratio of fluorescence at 665 nm to that at 620 nm] × 10,000).

Crystallography. Crystallization of apo human BACE1 was performed by the sitting-drop vapor diffusion method at 20 °C. ∼3 mg/mL of human BACE1 prepared as above was mixed with an equal volume of mother liquor containing 120 mM sodium citrate pH 6.5, 200 mM ammonium iodide, and 28−30% w/v polyethylene glycol 5000 monomethyl ether (PEG 5000 MME). In order to prepare **6**-bound crystals, apo crystals were soaked in a 50 mM solution of **6**, 10% (v/v) dimethyl sulfoxide (DMSO), 90 mM sodium citrate pH 6.6, 180 mM ammonium iodide, and 25.2% (w/v) PEG 5000 MME for 20 min. For **33**, apo crystals were soaked in 10 mM **33**, 10% (v/v) DMSO, 90 mM sodium citrate pH 6.6, 180 mM ammonium iodide, and 25.2% (w/v) PEG 5000 MME for 20 min. For **36**, apo crystals were soaked in 10 mM **36**, 10% (v/v) DMSO, 90 mM sodium citrate pH 5.0, and 25.2% (w/v) PEG 5000 MME for 15 min. Inhibitor soaked crystals were transferred into cryoprotectant (0.1 M sodium citrate pH 6.6, 0.2 M ammonium iodide, 28% w/v PEG 5000 MME, 20% v/v glycerol or 0.1 M sodium citrate pH 5.0, 28% w/v PEG5000 MME, 20% v/v glycerol) for a few seconds and were flash-frozen prior to data collection.

Diffraction data were collected at 100 K using a MicroMax-007 HF X-ray generator (Rigaku). Data reduction was performed with HKL2000,[28] iMosflm,[29] and SCALA.[30] Structures were solved by molecular replacement using apo BACE1 structure (PDB ID: 1W50) as a search model. Model rebuilding and structure refinement were performed with COOT[31] and Refmac5,[30] respectively. The structure factors and coordinates of **6**, **33**, and **36** are available in accession numbers 3VV6, 3VV7, and 3VV8, respectively.

Molecular Modeling. Figure 1: Conformations of compounds **6**, ***ent*-6**, **7**, and ***ent*-7** were energy-minimized on Molecular Operating Environment (MOE), 2011.10,[15] with default settings using the MMFF94x force field[16] and three minimization algorithms (steepest descent method, conjugate gradient method, truncated Newton method) until the root-mean-square gradient falls less than 0.05. The resulting structures were superimposed with that of **3** in PDB code 2VA5 on an aminopyrimidone ring.

Figure 5: The crystal structure of a complex between BACE1 and **6** (PDB code: 3VV6) was used for a molecular modeling with MOE. A molecular structure of compound **32** was constructed by editing the molecule of **6** extracted from the complex. Energy-minimization of **32** was performed under the constraint of fixing the positions of atoms in aminopyrimidone, the cyclopropane ring, and the middle benzene ring with default settings as was done in Figure 1. Then, the ligand **6** complexed with the BACE1 protein was replaced with the energy-minimized structure of **32**.

All calculations were performed on Panasonic CF-V8.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

LCMS (ESI-LRMS) data and plausible reaction mechanism for the production of ***ent*-28** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes
3VV6, 3VV7, 3VV8.

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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Mr. Rikio Ikenishi (Shionogi Techno Advance Research Co., Ltd.) for elemental analysis, Ms. Izumi Fujisaka (Shionogi Techno Advance Research Co., Ltd.) for measuring the optical rotation, Ms. Naomi Umesako (Shionogi & Co., Ltd.), and the members of the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University for the high-resolution mass spectroscopy analysis. This investigation was supported by a Grant-in-Aid for Scientific Research (21390028) from the Japan Society for the Promotion of Science.

ABBREVIATIONS USED

AVN, 2,2′-azobisvaleronitrile; BSA, *N*,*O*-bistrimethylsilylacetamide; Bpin, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl; CDI, carbonyl diimidazole; HRP, horseradish peroxidase; HTRF, homogeneous time-resolved fluorescence; LRMS, low-resolution mass spectrometry; MMFF94x, Merck molecular force field 94x; MME, monomethyl ether; MOE, Molecular Operating Environment; MS4A, molecular sieves 4A; TBDPS, *tert*-butyldiphenylsilyl; TBST, tris-buffered saline containing 0.1% of Tween-20; TPAP, tetrapropylammonium perruthenate; sAPPβ, soluble amyloid precursor protein β

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