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Synthesis and evaluation of aminopyridine derivatives as potential BACE1 inhibitors

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ABSTRACT

To identify a new non-peptidyl BACE1 inhibitor, we focused on the aminopyridine structure, which binds to the active sites of BACE1. Synthesis of aminopyridine derivatives and evaluation of inhibitory activity against rBACE1 are described. The 2-aminopyridine moiety and/or 3-methoxybenzaldehyde could be converted to terminal acetylene derivatives by the Sonogashira method. Sonogashira or Glaser cross-coupling reactions with the corresponding derivatives followed by hydrogenation could derive the designed compounds. Although inhibitory activities of the synthetic compounds against rBACE1 were weak, the aminopyridine motif has potential as a BACE1 inhibitor.

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Alzheimer's disease (AD)[1–3] is caused by the aggregation of amyloid-beta (Aβ),[4–6] which is produced from amyloid precursor protein (APP) cleaved by proteases with β-secretase (β-site amyloid precursor protein cleaving enzyme 1, BACE1)[7,8] and γ-secretase in the brain. Since BACE1 has been recognized as a valuable target to inhibit production of Aβ, a variety of BACE1 inhibitors have been reported in past decades. However, BACE1 inhibitors have not been approved as AD therapeutic agents to date. Most peptidomimetic BACE1 inhibitors with potent activity are based on the promising cleaving site of the APP sequence,[9–13] but these inhibitors tend to be P-glycoprotein substrates, digested by proteases and have restricted brain penetration. Non-peptidyl natural products are promising bioactive libraries from which anti-AD agents from microorganisms or food plants have been isolated,[14] although they tend to offer low inhibitory activity and/or an unknown mechanism of action for the target enzyme despite oral bioavailability and brain penetration.

In contrast, aminopyridine derivatives are key components to inhibit the active site of aspartyl protease as established by the Murray group.[15,16] The aminopyridine motif was found by combination of fragment screening techniques and high throughput X-ray crystallography against BACE1 as a new approach.[15–18] These inhibitors are generated starting from small fragments and are novel non-peptidyl fragments which take advantage of bioavailability. The typical aminopyridine type BACE1 inhibitors by fragment screening are depicted in Figure 1. There are two types of inhibitors; aminopyridine connected with the biphenyl moiety (**1**) and a dipyridine derivative (**2**). 2-Aminopyridine binds to the active sites of BACE1 and the principle interactions are between the charged amino pyridine motif and the two catalytic aspartates (Asp32 and Asp228) of the enzyme. The region adjacent to this ligand is the S1 pocket, which is a highly hydrophobic area of the active site, and thus is attractive to target. Moreover, the S3 pocket is again rather hydrophobic in nature, and 3-methoxy biaryl or 3-pyridylphenyl groups make good contact with the target region (Fig. 1).

In the course of our research program to find a BACE1 inhibitor,[19,20] we focused on the aminopyridine structure and therefore needed to prepare a variety of aminopyridine derivatives. For the reason, we aimed to verify the advantage of the C4 or C5 spacer connected with the amino pyridine moiety and 3-methoxyphenyl groups for potent inhibitory activities. Additionally, connecting positions of aminopyridine were investigated. We herein describe a synthetic study of aminopyridine derivatives by Sonogashira[21] and/or Glaser[22–25] cross-coupling reactions as potential BACE1 inhibitors.

The synthetic plan for aminopyridine derivatives as the target molecules is depicted in Scheme 1. The 2-aminopyridine moiety (**A**) and/or 3-methoxybenzaldehyde (**B**) could be converted to terminal acetylene derivatives by the Sonogashira method. Subsequently, Sonogashira or Glaser coupling reactions with the

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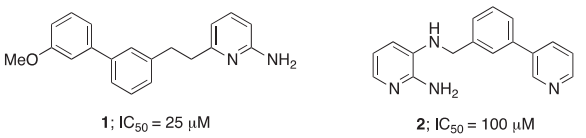
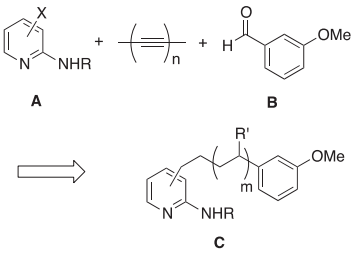
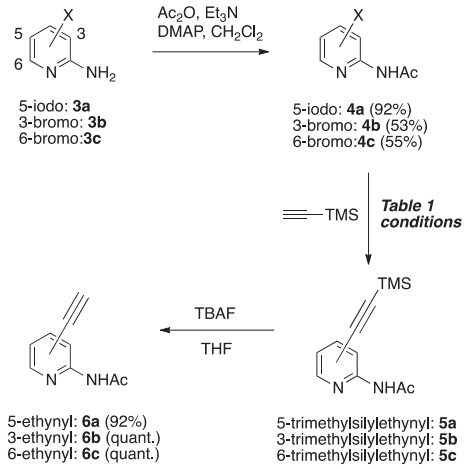


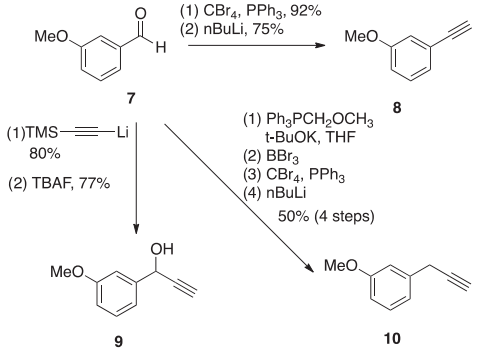
Figure 1. BACE1 inhibitors (**1**) and (**2**) with an aminopyridine moiety.



Scheme 1. Synthetic plan for aminopyridine derivatives.



Scheme 2. Preparation of amino ethynylpyridines.



Scheme 3. Preparation of phenylacetylene derivatives (**8**), (**9**) and (**10**).

corresponding derivatives followed by hydrogenation could obtain the designed compounds (**C**) (Scheme 1).

Preparation of 2-aminopyridylacetylene fragments to apply to cross-coupling reactions were attempted using commercially available 5-iodo-, 3-bromo- and 6-bromo-2-aminopyridines (**3a–c**). After the acetylation of the amino group of **3a–c** with Ac_2O/Et_3N/catalytic DMAP in CH_2Cl_2, Sonogashira coupling was performed. The results of the reaction are summarized in Table 1. At first, we used the reaction conditions of the Murray group[15] to give 5-ethynylpyridine (**5a**) at a moderate yield (entry 1). After switching of the base from Et_3N to DIPEA, the reaction proceeded smoothly to give **5a** in 92% yield (entry 2). Although preparation of 2-acetylamino-3-ethynylpyridine (**5b**) was attempted under the conditions in entry 2, the reaction failed to recover **4b** with the complexed mixture (entry 3). We therefore examined the $Pd^{(II)}Cl_2(PPh_3)_2$ catalyst in the presence of 10 mol % CuI and DIPEA at room temperature to give **5b** in 53% yield (entry 4). As for 2-acetylamino-6-bromo-pyridine (**4c**), additional optimization of the reaction conditions was needed to obtain 2-acetylamino-6-ethynylpyridine (**5c**) because the above-mentioned conditions did not progress to the desired reaction (entries 5 and 6). Fortunately, we found that treatment of a Pd(II) catalyst with 50 mol % KI[26] under reflux conditions gave **5c**. Under the conditions using 10 mol % $Pd^{(II)}Cl_2(PPh_3)_2$/30 mol % CuI/50 mol % KI in THF at reflux, **4c** was converted to **5c** in 43% yield (entry 9). **4c** is unfavorable for Pd catalyst insertion due to the m-orientation in the amino group of 2-aminopyridine and therefore the reaction was slow and yielded moderate results. Moreover, TBAF-mediated deprotection of silyl compounds (**5a–c**) gave **6a–c** at good yields (Scheme 2) (Table 1).

3-Methoxyphenyl fragments (**8**), (**9**) and (**10**) were prepared from commercially available 3-methoxybenzaldehyde (**7**). Corey–Fuchs reaction[27,28] was employed for **7** to give **8** in 69% yield (over 2 steps) and the alkynylation of **7** with lithium acetylide followed by the deprotection of the silyl group afforded **9** in 62% yield (over 2 steps). Additionally, the 2 step sequences with methylene Wittig and Corey–Fuchs reactions were conducted to give **10** at an adequate yield (Scheme 3).

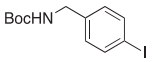
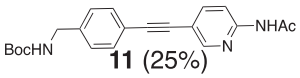
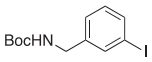
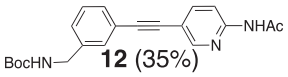
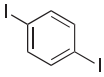
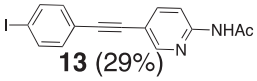
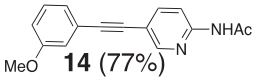
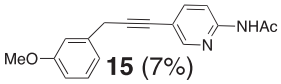
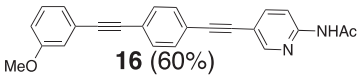
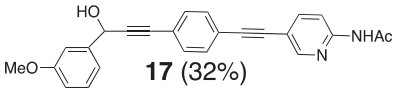
For the structure–activity relationship study of the biaryl derivatives connected with C2 or C3 spacers, Sonogashira coupling of the terminal alkyne with a pyridine fragment and aryl halide

Table 1
Palladium-catalyzed Sonogashira coupling of 2-aminopyridyl halide with trimethylsilylacetylene[a]

Entry	Substrate	Catalyst (mol %)	Additive (mol %)	Base (equiv)	Solvent	Temp	Time (h)	Product[b] (yield)
1	**4a**	$Pd(PPh_3)_4$ (3.5)	CuI (20)	Et_3N (2.0)	THF	rt	24	**5a** (69%)
2	**4a**	$Pd(PPh_3)_4$ (3.5)	CuI (20)	DIPEA (2.0)	THF	rt	24	**5a** (92%)
3	**4b**	$Pd(PPh_3)_4$ (5.0)	CuI (10)	DIPEA (3.0)	THF	rt	24	NI[c]
4	**4b**	$PdCl_2(PPh_3)_2$ (5.0)	CuI (10)	DIPEA (3.0)	THF	rt	24	**5b** (53%)
5	**4c**	$Pd(PPh_3)_4$ (5.0)	CuI (10)	DIPEA (3.0)	THF	rt	24	NR[d]
6	**4c**	$PdCl_2(PPh_3)_2$ (5.0)	CuI (10)	DIPEA (3.0)	THF	rt	96	NR[d]
7	**4c**	$Pd(dba)_2$ (5.0)	CuI (30) KI (50)	DIPEA (2.0)	Dioxane	Reflux	96	**5c** (21%)
8	**4c**	$PdCl_2$(dppf) (10)	CuI (50) KI (50)	DIPEA (2.0)	THF	Reflux	96	**5c** (12%)
9	**4c**	$PdCl_2(PPh_3)_2$ (10)	CuI (30) KI (50)	DIPEA (3.0)	THF	Reflux	96	**5c** (43%)

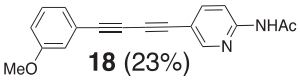
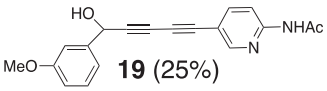
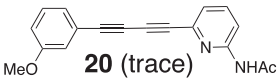
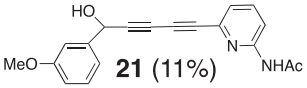
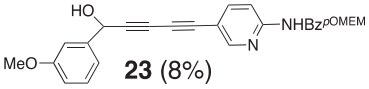
[a] Reactions of aminopyridines (**4a–c**) with trimethylsilylacetylene (6 equiv) were carried out with the conditions.
[b] Isolation yield.
[c] Not isolated.
[d] No reaction.

Table 2
Biaryl derivatives connected with C2 or C3 spacers and triacyl derivatives[a]

Entry	Pyridine	Benzene	Catalyst (mol %)	Product[b] (yield)
1	**6a**		$Pd(PPh_3)_4$ (3.5), CuI (50)	 **11** (25%)
2	**6a**		$Pd(PPh_3)_4$ (10), CuI (50)	 **12** (35%)
3	**6a**		$Pd(PPh_3)_4$ (3.5), CuI (20)	 **13** (29%)
4	**8**	**4a**	$Pd(PPh_3)_4$ (3.5), CuI (20)	 **14** (77%)
5	**10**	**4a**	$Pd(PPh_3)_4$ (3.5), CuI (20)	 **15** (7%)
6	**8**	**13**	$Pd(PPh_3)_4$ (3.5), CuI (20)	 **16** (60%)
7	**9**	**13**	$Pd(PPh_3)_4$ (3.5), CuI (100)	 **17** (32%)

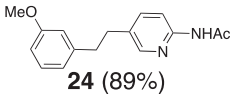
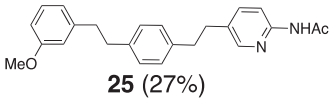
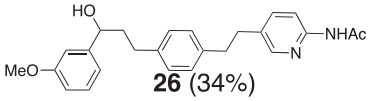
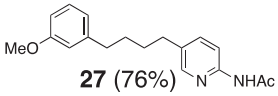
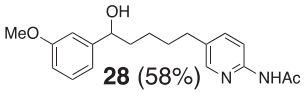
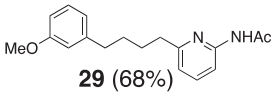
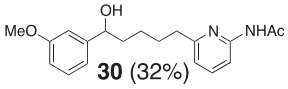
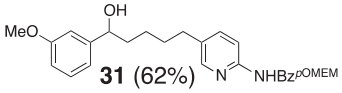
[a] Coupling reactions of pyridyl compounds (1 equiv) and phenyl halides (1 equiv) were performed with a palladium catalyst, CuI, Et_3N (2 equiv) in THF for 10 h at room temperature.
[b] Isolation yield.

Table 3
Glaser cross-coupling of pyridyl alkyne and phenyl alkyne[a]

Entry	Pyridine	Benzene	Catalyst (mol %)	Product[b] (yield)
1	**6a**	**8**	CuI (50)	 **18** (23%)
2	**6a**	**9**	CuI (50)	 **19** (25%)
3	**6b**	**9**	CuI (100)	NR
4	**6b**	**9**	CuI (50), $Pd_2(dba)_3$ (3)	NR
5	**6b**	**9**	CuI (50), $PdCl_2(PPh_3)_4$ (3)	NR
6	**6c**	**8**	CuI (100)	 **20** (trace)
7	**6c**	**8**	CuI(50), $Pd_2(dba)_3$ (3)	**20** (15%)
8	**6c**	**9**	CuI (60)	 **21** (11%)
9	**22**	**8**	CuI (60)	NR
10	**22**	**9**	CuI (70)	 **23** (8%)

[a] Coupling reactions of pyridyl compounds (1 equiv) and phenyl compounds (1 equiv) were performed with catalyst(s) and base in THF for 10 h at room temperature.
[b] Isolation yield.

Table 4
Hydrogenation to afford alkyl aminopyridine derivatives

Entry	Substrate	Condition	Product (yield)
1	**14**	A	 **24** (89%)
2	**16**	B	 **25** (27%)
3	**17**	B	 **26** (34%)
4	**18**	A	 **27** (76%)
5	**19**	A	 **28** (58%)
6	**20**	B	 **29** (68%)
7	**21**	C	 **30** (32%)
8	**23**	C	 **31** (62%)

Condition A: H_2/Pd-C/MeOH; B: H_2/Pd-C/$CHCl_3$; C: H_2/Lindlar cat./MeOH.

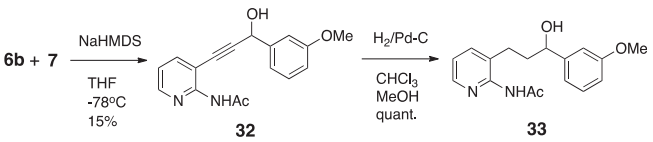
with a $Pd^{(0)}$ catalyst and CuI were employed as depicted in Table 2. All reactions used the $Pd^{(0)}(PPh_3)_4$ catalyst, CuI and 2 equiv of Et_3N in THF at room temperature. Coupling of 5-ethynyl-2-aminopyridine (**6a**) and iodobenzene derivatives gave biaryl derivatives (**11**), (**12**) and (**13**) in 25%, 35% and 29% yields, respectively, (entries 1–3). On the other hand, the combination of aryl acetylene (**8**) and iodopyridine (**4a**) gave **14** in 77% yield (entry 4). Unfortunately, propargyl derivative (**10**) rarely afforded the desired compound (**15**) (entry 5). When a biaryl compound (**13**) with aryl acetylene (**8**) or (**9**) were employed, the yields of the respective triaryl products (**16**) and (**17**) were 60% and 32% (entries 6 and 7). The Sonogashira cross-coupling reactions as mentioned above resulted the lower yields. Because the solubility of substrates, especially pyridine type compounds, was excessively low. The reactions hardly proceed to give desired products and additionally work-up and purification by chromatography were in trouble (Table 2).

Glaser cross-coupling of pyridyl alkyne and phenyl alkyne are depicted in Table 3. Glaser coupling is a prominent carbon–carbon bond formation between terminal alkynes to give 1,3-diynes. In most cases, copper and palladium salts are used as a mild catalytic system for the homo-coupling of terminal alkynes. We employed the reaction condition to give hetero-coupling products for BACE1 inhibitors. Biaryl derivatives connected with C4 or C5 spacers could be briefly obtained by the method. Using a heterocycle terminal alkyne as a substrate has scarcely been reported in the literature probably due to the interaction between copper and nitrogen of the heterocyclic ligand. Although treatment of pyridyl alkyne and phenyl alkyne under a variety of conditions predictably afforded three products, a hetero-coupling product and two homo-coupling products, it was an important tool to give the desired product quickly. Because the aminopyridine derivatives have high polarity and insolubility in organic solvents, another synthetic methods with multi step reactions were often disadvantageous. In the initial experiments, treatment of **6a** and **8** or **9** with 50 mol % of CuI gave **18** or **19** with the homo-coupling products (entries 1 and 2). Cross-coupling reactions of **6b** under a variety of conditions were attempted; however, the reaction did not proceed to give the desired product probably because of steric hindrance with the acetylamino group and terminal acetylene of **6b**. In this case, the homo-coupling diyne product derived from **9** was preferentially obtained at high yields (entries 3–5). Although the coupling of **6c** and **8** with CuI as a sole reagent hardly proceeded to give the desired hetero-coupling product, the reaction conditions in the presence of a $Pd_2(dba)_3$ catalyst afforded diyne (**20**) in 15% yield (entries 6 and 7). Using **9** as a coupling partner, **21** was obtained (11%). Moreover, **22**[29] with **9** using CuI coupled to give diyne (**23**) in 8% yield (entry 10). Thus, the designed compounds (**18**)–(**23**) were given using 5-alkenyl- and 6-alkenyl-2-aminopyridine (**6a**) and (**6c**) at low yields (Table 3).

Subsequently, hydrogenation of the 1,3-diynes with H_2/Pd–C gave the corresponding alkanes (**24**)–(**31**) at moderate yields. It is noted that the solubility of the aminopyridine derivatives in organic solvents is an important factor to consume the substrate. In addition, treatment of **21** or **23** in the hydrogenation condition leads decomposed products. To attempt several conditions, a Lindlar catalyst gave reasonable results (entries 7 and 8); purification of crude final compounds was a laborious task because of its high polarity and insolubility. Therefore, the chemical yields frequently decreased (Table 4).

As shown in Table 3, a Glaser cross-coupling reaction of 3-alkynyl-2-aminopyridine (**6b**) with a variety of conditions was attempted. However, the reactions did not proceed to give the desired products because of steric hindrance with the acetylamino group and terminal acetylene of **6b**. For this reason, alkylation of **6b** using a strong base was selected to afford the corresponding diaryl derivative. Treatment of **6b** and **7** with NaHMDS in THF gave **32** in 15% yield and subsequently hydrogenation with Pd–C in 20% MeOH/$CHCl_3$ solution was done to yield **33** quantitatively (Scheme 4).

tPSA, *C* log *P* and inhibition value of compounds are summarized in Table 5. The inhibition of rBACE1 activity was determined by the previous procedure using a synthetic dodecapeptide with the BACE1 cleavage sequence of the Swedish type as a substrate. The inhibition potency of aminopyridine derivatives was screened for rBACE1 inhibition at a 2.0 mM concentration. The fragment molecules were investigated as potential BACE1 inhibitors in the study and therefore these compounds showed relatively lower potent inhibitory effects. For this reason, a high concentration of inhibitors was needed for the assay. Biaryl derivatives connected with C2 or C3 spacers and triaryl type compounds showed no



Scheme 4. Synthesis of **33**.

Table 5
rBACE1 inhibitory activity of aminopyridine derivatives (**27**)–(**33**)

Compd	tPSA[a]	*C* log *P*[a]	Inhibition[b] (%)	Compd	tPSA[a]	*C* log *P*[a]	Inhibition[b] (%)
27	50.69	3.915	20	**30**	70.92	2.687	56
28	70.92	2.687	20	**31**	41.82	2.840	19
29	50.69	3.915	21	**33**	70.92	0.759	18

[a] tPSA and *C* log *P* were calculated by Chem 3D Ultra 12.0 (PerkinElmer).
[b] Inhibitory activity was measured with 2.0 mM.

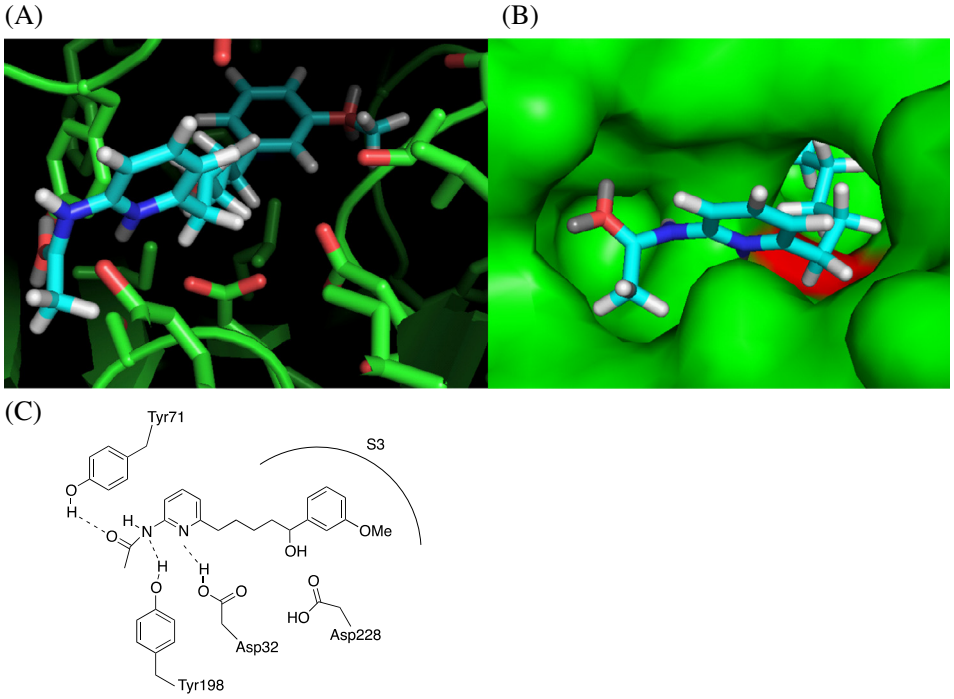


Figure 2. Docking simulation of inhibitor (**30**) bound to BACE1 (PDB code 1FKN) using GOLD from CCDC. Molecular graphics image using PyMOL from Schrödinger; oxygen (red), nitrogen (blue) and carbon (skyblue) of **30**; oxygen (red) of BACE1. (A) Cartoon mode with the side chains of BACE1. (B) Surface mode; Asp32 and Asp228 (red). (C) Model of interaction.

inhibitory activities. Alkenyl compounds (**18**)–(**23**), synthetic intermediates, were also inactive (data not shown). On the other hand, biaryl derivatives connected with C4 or C5 spacers (**24**)–(**31**) showed relatively weak inhibitory effects on rBACE1 activity. This suggested that biaryl derivatives connected with C4 or C5 spacers are effective and consequently the aminopyridine motif reported by the Murray group has potential as a BACE1 inhibitor although a structure–activity relationship study needs to show an increase in inhibitory activity. In addition, 6-alkyl-2-aminopyridine (**30**) exhibited greater inhibitory activity in comparison with 5-alkyl-2-aminopyridines (**27**) and (**28**). Surprisingly, aminopyridine derivatives, which had an acetyl group removed, tended to show similar activities to the corresponding compounds (data not shown). There was no correlation between the inhibition value, tPSA and *C* log *P* in this case (Table 5).

The binding mode of **30** to BACE1 (PDB code 1FKN[30]) was predicted by docking simulations using GOLD from CCDC.[31–33] A hydrophobic space at the S3 pocket fitted with the phenyl group of **30**. Two polar nitrogen of amino pyridine of **30** were involved in hydrogen bonding interactions with one catalytic aspartate (Asp32) and phenolic hydrogen (Tyr198). This suggested that the binding mechanism of **30** with BACE1 in silico was slightly different to those of the Murray group (Fig. 2).

In conclusion, we found that the aminopyridine derivative 6-position-connected with an alkyl spacer showed good potential as a BACE1 inhibitor. It seems worthwhile to design and study small molecules derived from fragment screening and further studies will be developed to investigate potent active inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10.007.

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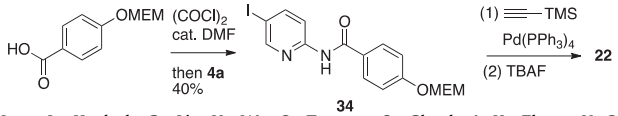

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