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Synthesis of (3*S*,4*S*)-4-aminopyrrolidine-3-ol derivatives and biological evaluation for their BACE1 inhibitory activities

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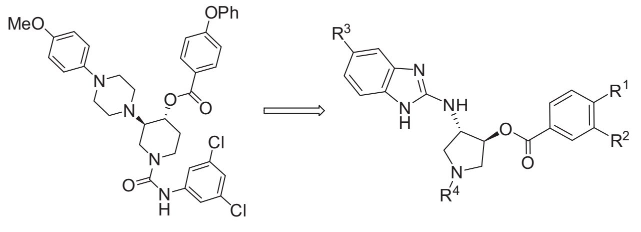
ABSTRACT

Synthesis, SAR study and BACE1 inhibitory activity of (3*S*,4*S*)-4-aminopyrrolidine-3-ol derivatives (**2**) were described. The compound **7c** exhibited more inhibition activity than **11a** (IC_{50}: 0.05 μM vs 0.12 μM, respectively), but the latter was more effective in cell-based assay (IC_{50}: 1.7 μM vs 40% inhibition by **7c** @ 10 μM) due to the relatively higher cell permeability. Most of the compounds showed high selectivity over BACE2 and cathepsin D. This work will provide useful information for further structural modifications to develop potent BACE1 inhibitors in cell.

Alzheimer's disease (AD), characterized by clinical symptoms of progressive decline in memory and cognitive function, is the most common form of dementia affecting over 44 million wordwide.[1] Patients in late stages often show severe personality changes and various neuropsychiatric symptoms impairing daily life and ultimately leading to death. Although the role of amyloid β (Aβ) peptides on pathogenicity is still unclear, evidence suggests that abnormal accumulation of amyloid β (Aβ) peptides as soluble oligomers or extracellular plaques in AD brain is the major characteristic of Alzheimer's disease. Aβ peptides are produced from proteolytic cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase. Inhibition of either enzyme has been considered as the potential molecular target for developing the disease modifying drugs. But inhibition of BACE1 is considered a more attractive target for the treatment of AD since BACE1 is the first enzyme for APP processing into Aβ and BACE1 knockout mice do not have clear phenotype and were unable to generate Aβ.[2,3]

The reported peptidomimetic BACE1 inhibitors including hydroxyethylene, hydroxyethylamine, hydroxymethylcarbonyl, and aminoethylamine had poor metabolic stability and thus lacked ideal pharmacokinetic properties.[4–7] Over the past decade, extensive research has been focused to develop non-peptidic BACE1 inhibitors including, isophthalamide,[8] diphenylurea,[9] piperazine,[10] piperidine,[11] acylguanidine and cyclic amidines.[12]



1 (IC_{50} : 0.6 μM)

2

Earlier we have reported the 3-amino-4-aryl-piperidines and 4-arylpiperazinylpiperidines (**1**) as the non-peptide BACE1 inhibitors with modest inhibition.[13] In an effort to improve potency against BACE1, computational docking of **1** using Autodock Vina (version—1.1.2) was further investigated.[14] In the lowest energy binding mode, the central piperidine ring was placed in the region between S1 and S1′ pocket where the catalytic aspartic acid residues are present. The aryl ester and aryl urea groups occupied the S3 and S2′ pockets respectively. The arylpiperazine moiety was close to the S2 pocket which is composed of side chains of Arg235 and Thr71 (Fig. 1).

Though inhibitor **1** had access to the active sites of BACE1, it appeared lacking proper orientation and angle for the optimal interactions. The docking studies of structural analogs by replacing the piperidine with pyrrolidine ring led to compound **7c** with better interaction potential with BACE1. Herein we report the synthesis and biological evaluation of the (3*S*,4*S*)-4-aminopyrro-

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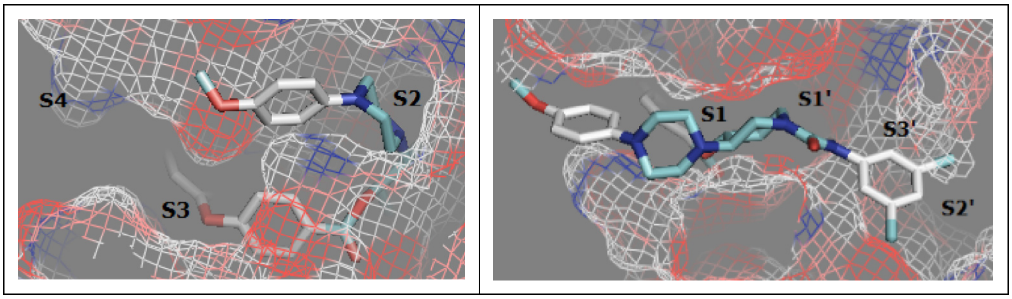


Figure 1. Orientation of **1** (2 different views) in the ligand binding site of BACE1.

lidine-3-ol derivatives (**2**) as highly selective non-peptide BACE1 inhibitors.

The synthetic route for the preparation of (3*S*,4*S*)-4-((1*H*-benzo[*d*]-imidazol-2-yl)amino)pyrrolidine-3-yl benzoate derivatives (**7–8**) was shown in Scheme 1. Asymmetric ring opening of epoxide (**3**) in the presence of Jacobsen's chiral (salen) chromium(III) complex proceeded to give chiral (3*S*,4*S*)-azido-alcohols (**4**).[15] Coupling of **4** with various benzoic acids to afford azido esters followed by reduction of azido group afforded amino benzoates (**5**).

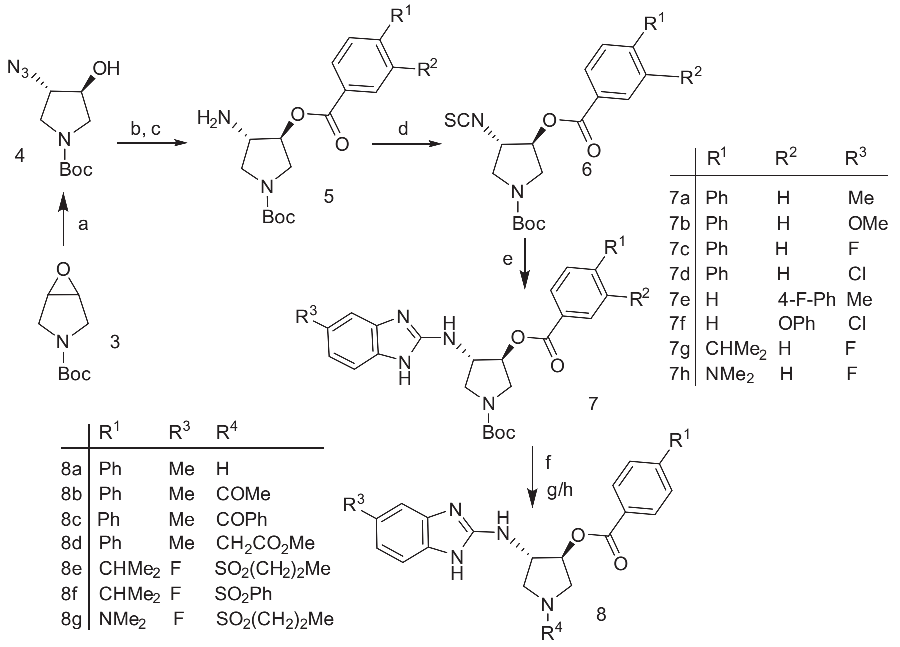
Isothiocyanates (**6**), prepared from **5** by treatment with di-2-pyridyl thionocarbonate, were then coupled with 1,2-diaminobenzenes and subsequently cyclized to yield benzimidazole derivatives (**7**). Finally, Boc-deprotection of **7** followed by acylation or sulfonation or alkylation afforded the desired compounds **8**.

Employing the same procedure as described above, benzyl ether linked pyrrolidine derivatives (**11**) were prepared from azido benzyl ether (**9**) derived from benzylation of alcohol **4** (Scheme 2).

Compounds **7**, **8** and **11** were tested for the inhibition of BACE1 in vitro FRET and the results are shown in Table 1. As predicted by docking experiments, Boc protected (3*S*,4*S*)-4-((benzimidazol-2-yl)-amino)-3-aroylpyrrolidine derivatives (**7**) were substantially more potent than compound **1**. Compounds **7a-7g** bearing phenyl, phenoxy and alkyl group at 3- or 4-position of benzoate ring exhibited similar inhibitory activities, but **7h** with relatively polar dimethylamino substituent showed drastic loss in the potency. Among the compounds tested, **7c** and **7g**, bearing 5-fluorobenzimidazole group were found to be more potent (IC_{50}: 0.05 and 0.07 μM, respectively).

Compared to Boc pyrrolidine derivatives (**7a**–**h**), analogs having central pyrrolidine ring either unsubstituted (**8a**) or having alkyl, acyl and sulfonyl groups (**8b**–**8g**) showed significantly diminished potency. For further exploration of the structure–activity-relationships, we replaced the ester functionality of compound **7c** with benzyl ethers. While 4-phenylbenzyl ether (**11a**) showed only slightly decreased activity, the corresponding *iso*-propyl derivative (**11b**) resulted significantly decreased inhibition (IC_{50}: 0.73 μM). Similarly, it was observed that either Boc-deprotection or introduction of alkyl, acyl or sulfonyl groups on the pyrrolidine ring nitrogen resulted in drastic loss of activity (**11c**–**g**).

The higher potency of compound **7c** could be explained from a docking study. Overall, the docking of compound **7c** in BACE1 active site revealed that the benzimidazole substituent projected to S1′ pocket composed of catalytic Asp 228, the biphenyl group placed to the open space close to S4 pocket, and nonpolar tertiary



	R¹	R²	R³
7a	Ph	H	Me
7b	Ph	H	OMe
7c	Ph	H	F
7d	Ph	H	Cl
7e	H	4-F-Ph	Me
7f	H	OPh	Cl
7g	$CHMe_2$	H	F
7h	NMe_2	H	F

	R¹	R³	R⁴
8a	Ph	Me	H
8b	Ph	Me	COMe
8c	Ph	Me	COPh
8d	Ph	Me	CH_2CO_2Me
8e	$CHMe_2$	F	$SO_2(CH_2)_2Me$
8f	$CHMe_2$	F	SO_2Ph
8g	NMe_2	F	$SO_2(CH_2)_2Me$

Scheme 1. Reagents and conditions: (a) (1*S*,2*S*)-(−)-[1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)]chromium(III)chloride, azidotrimethylsilane, ether, rt, 24 h; (b) corresponding benzoic acid, EDC, DMAP, dry DMF, rt, 12 h; (c) H_2, Pd-C, EtOH, rt, 12 h; (d) di-2-pyridyl thionocarbonate, dry CH_2Cl_2, rt, 5 h; (e) corresponding diamino benzene, HgO, dry THF, 60 °C, 12 h; (f) TFA/CH_2Cl_2/H_2O, 0 °C to rt, 2 h; (g) respective sulfonyl chloride, DIPEA, CH_2Cl_2, rt, 2 h; (h) acetic anhydride or benzoyl chloride or methyl 2-bromo acetate, TEA, dry CH_2Cl_2, Rt, 2 h.