Structure-activity relationship study on the P4 structure of macrocyclic BACE1 inhibitors

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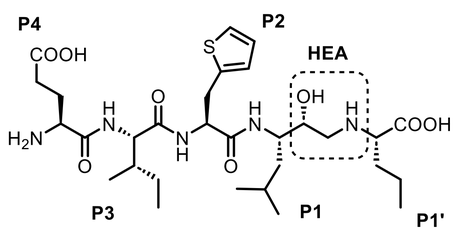
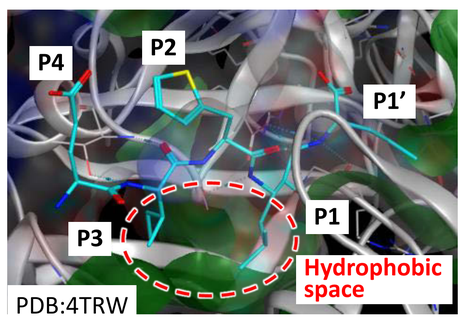
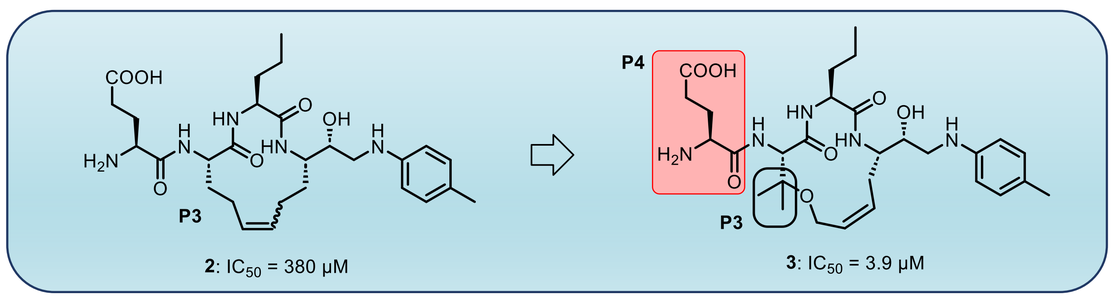
Introduction

β-Secretase (BACE1) is an aspartic protease involved in the production of amyloid β peptide (Aβ). Aβ accumulation in the brain is hypothesized to underlie the pathogenesis of Alzheimer's disease (AD), hence it is reasoned that inhibiting BACE1 will play a crucial role in the treatment of AD. Previously, we have synthesized and evaluated peptidic BACE1 inhibitors containing a hydroxyethylamine (HEA) type isostere[1,2] and discovered a macrocyclic inhibitor, inhibitor **3**, containing a hydrophobic bridge between the P1 and P3 side chains[3]. Despite displaying good activity, the membrane permeability of inhibitor **3** is constrained by high hydrophilicity, limiting its development as a drug. Therefore, we try to design macrocyclic derivatives of this inhibitor with lower hydrophilicity, to increase membrane permeability. In this study, the amino and carboxy groups of glutamic acid at the P4 position of inhibitor **3** significantly influence its hydrophilicity, hence some derivatives of inhibitor **3** with a less hydrophilic substituent at the P4 position were designed and synthesized, and their activities were evaluated.



1: IC_{50} = 72 μM



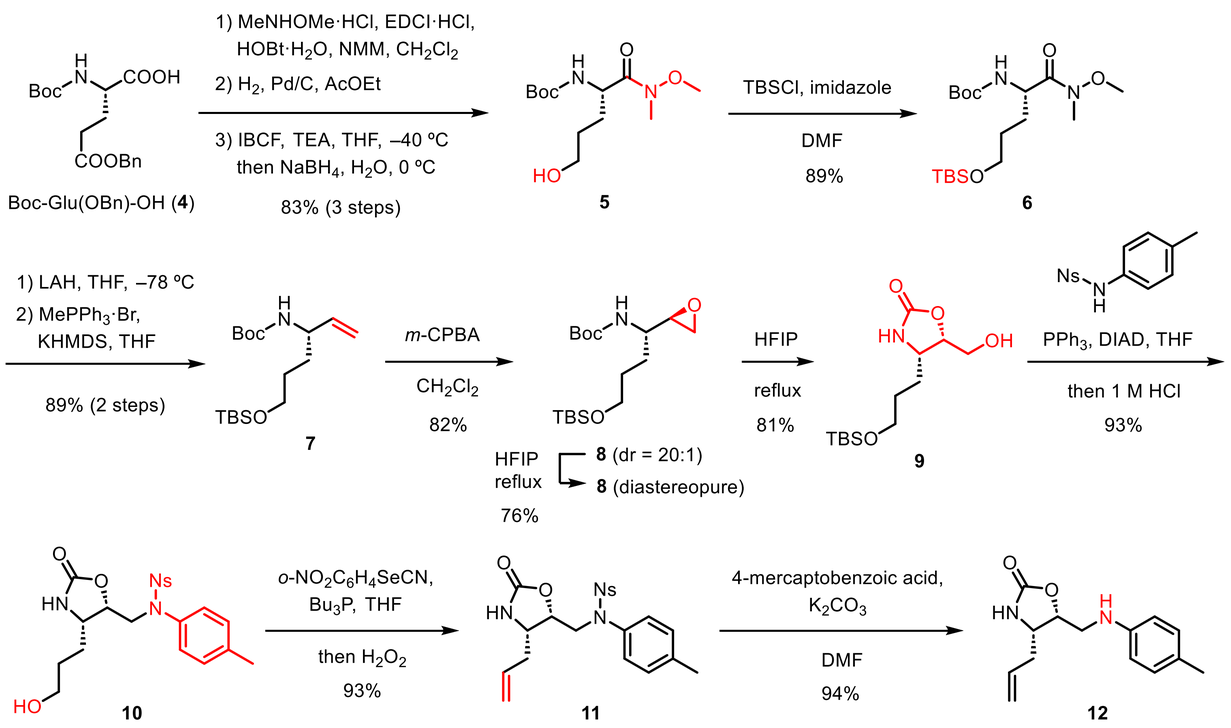


2: IC_{50} = 380 μM

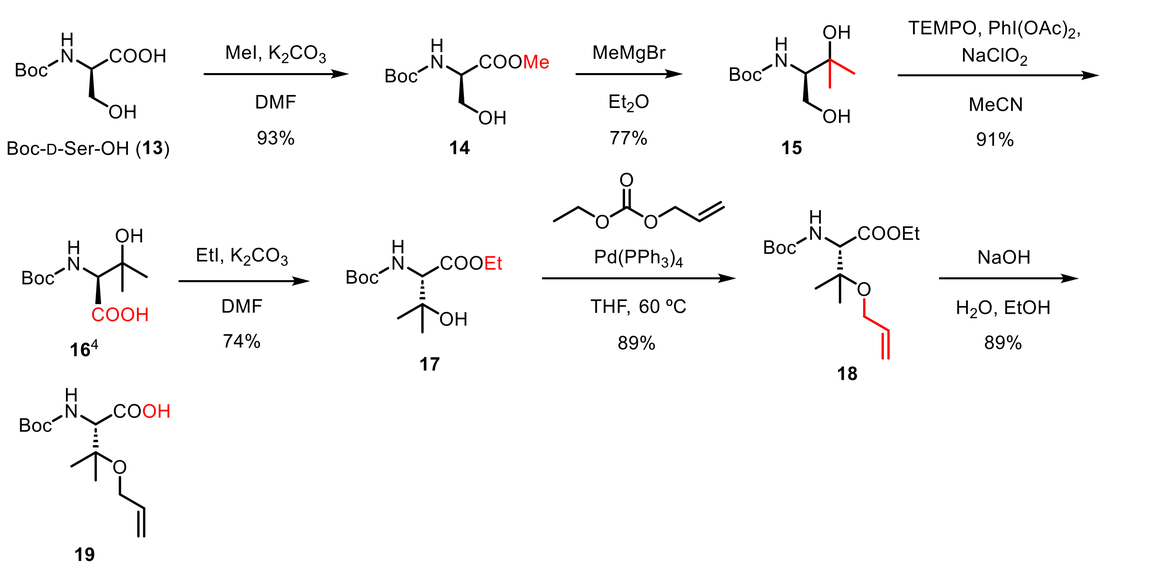
3: IC_{50} = 3.9 μM

Results and Discussion

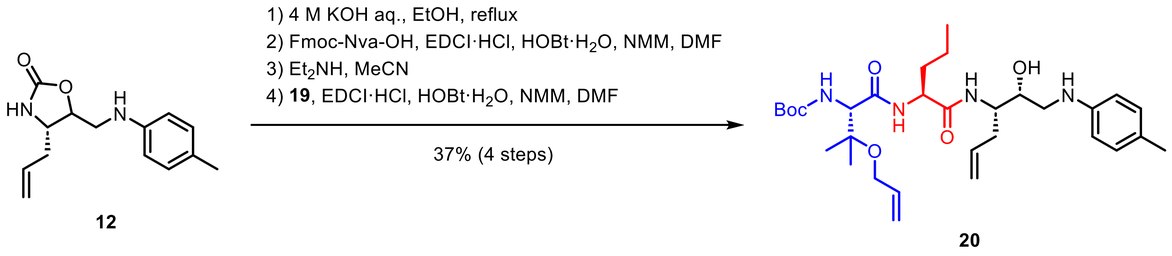
■ Synthesis of P1 fragment precursor 12



■ Synthesis of P3 fragment 19

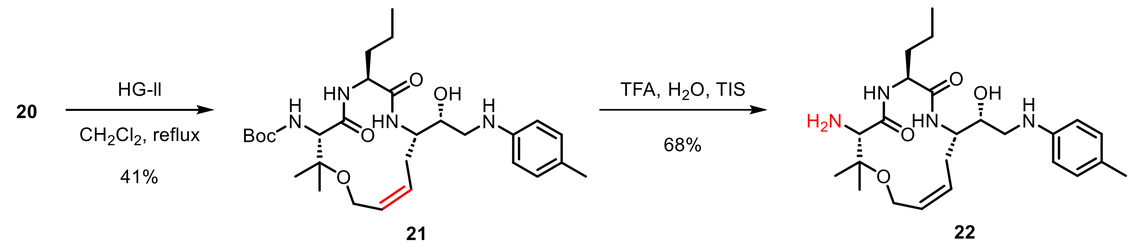


■ Synthesis of macrocyclic precursor 20

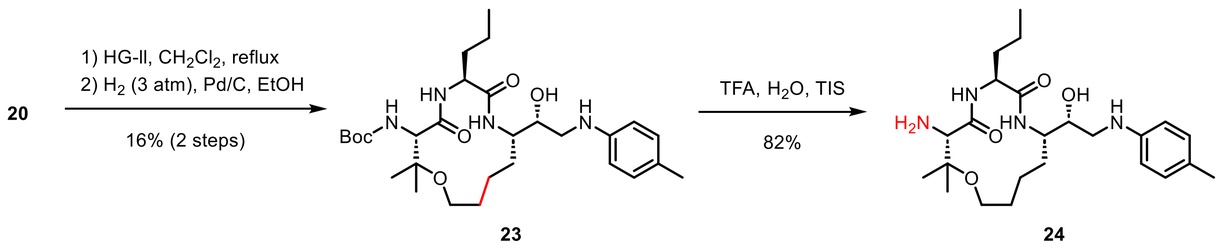


■ Synthesis of macrocyclic P4 derivatives

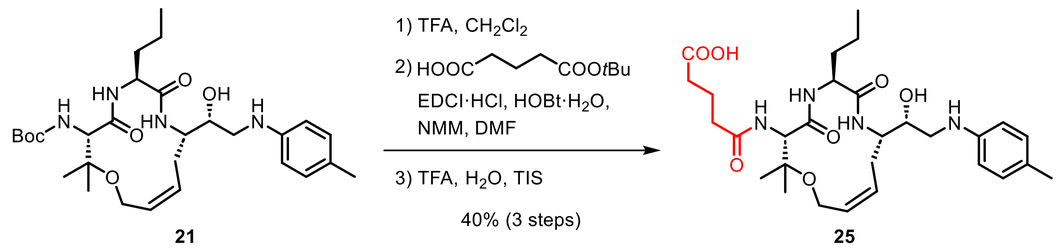
➢ Removal of the glutamic acid



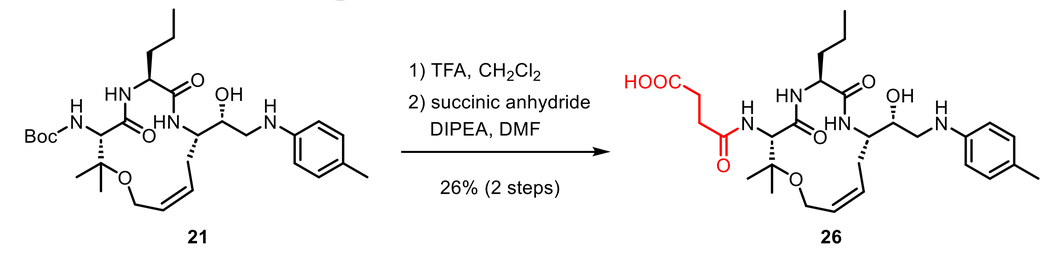
➢ Removal of the glutamic acid and reduction of the alkene



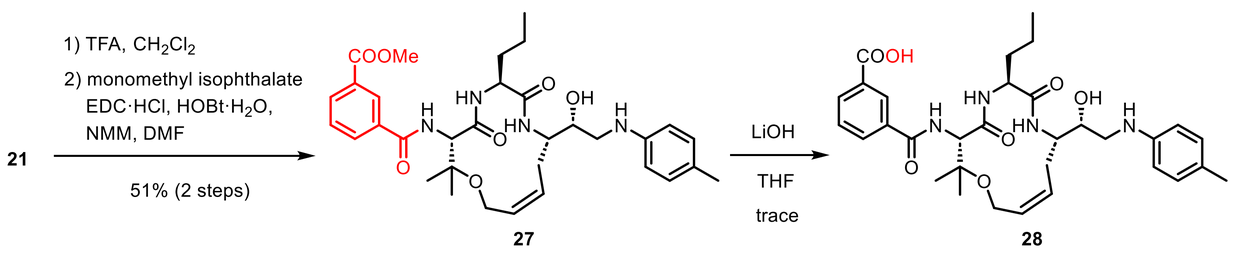
➢ Conversion of the glutamic acid to glutaric acid



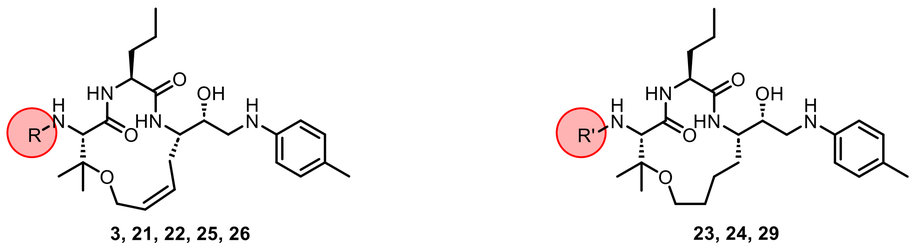
➢ Conversion of the glutamic acid to succinic acid



➢ Conversion of the glutamic acid to isophthalic acid (Not completed)



■ Evaluation of BACE1 inhibitory activity



Comp.	R	IC_{50} (μM)	Comp.	R'	IC_{50} (μM)
3	H-Glu-	3.9	**29**[3]	H-Glu-	6.1
21	Boc-	124	**23**	Boc-	185
22	H-	177	**24**	H-	315
25	$HOOCCH_2CH_2CH_2CO$-	3.3			
26	$HOOCCH_2CH_2CO$-	14			

Summary

Synthesis and evaluation of macrocyclic P4 derivatives were conducted. Our study showed an alkene-containing macrocycle was a suitable ring structure for inhibitory activity compared to a reduced macrocycle (**21** and **22** vs. **23** and **24**, respectively), which was consistent with our previous work (**3** vs. **29**).

We also showed that the removal of the glutamic acid at the P4 position reduced inhibitory activity. However, the glutamate amino group has little effect on activity, while the positioning of the carboxy group is important. Optimization of the arrangement of the carboxy group is underway.

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4. Meng, Z.; Fürstner, A. *et al. J. Org. Chem.* **2018**, *83*, 6977-6994.