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Original article

# Design and synthesis of 5-cyclopropyl substituted cyclic acylguanidine compounds as BACE1 inhibitors

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ABSTRACT

By taking compound **1** as a lead, a series of 5-cyclopropyl substituted cyclic acylguanidine compounds were designed and synthesized as BACE1 inhibitors, compound **4d** exhibited 84-fold improved inhibition efficiency than lead compound **1**. The diphenyl fragment at the P3 position and the substituents at the second phenyl ring were essential for the compounds to achieve improved inhibition efficiency. This SAR studies provides new insights into the design and synthesis of more promising BACE1 inhibitors for the potential treatment of AD.



## 1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder. According to the amyloid cascade hypothesis [1], abnormal accumulation of amyloid peptides (A$\beta$) in the brain resulting in neuronal toxicity is the main cause of AD [2]. Although the amyloid cascade hypothesis remains polemic as it has not been fully validated [3], it still represents a widely supported theory, substantiated by genetic evidence from the various mutations of amyloid precursor protein (APP) [4]. BACE1 ($\beta$-secretase) is a rate-limiting enzyme that hydrolyzes $\beta$-amyloid precursor protein ($\beta$-APP) to produce amyloid peptides (A$\beta$) while most amino-acid mutations close to the cleavage site of APP result in faster proteolysis and increased rate of disease progression [5]. In currently, BACE1 is considered as an attractive therapeutic target for the treatment of AD [6]. To date, different structural classes BACE1 inhibitors have been designed and developed [7], but it is still a challenge to discover brain penetration BACE1 inhibitor with low molecule weight, potent activity and high selectivity. A cyclic acylguanidine compound, compound **1**, which was discovered each other independently by Schering-Plough [8], Wyeth [9] and Pfizer [10], is a weak BACE1 inhibitor ($IC_{50}$ = 7.1 $\mu$mol/L) [8] with brain penetration. This finding is a milestone to the development of BACE1 inhibitor based on the amyloid cascade hypothesis. Many excellent BACE1 inhibitors of this type that were effective *in vivo* have been discovered, some of which have entered clinical trial [11,12].

In our primary research, by taking compound **1** as a lead, we had design and synthesized a series of new cyclic acylguanidine compounds as BACE1 inhibitors and compound **2** exhibited sub-micromolar activity *in vitro* [13]. In this report, based on the SAR studies revealed in our previous paper [13], we then designed another type of compounds (**3** and **4**) (Fig. 1). The cyclopropyl fragment was introduced to make the molecule more flexible and lower the molecular weight. It is hoped that this could help the molecule to adjust its conformation to better fill the BACE1 active binding site to form the interactions essential for its biological activity.

## 2. Experimental

The synthetic route of target compounds **3** was shown in Scheme 1. To the mixture of cyclopropyl acetylene and 3-bromophenol in THF was added TBAF/$PdCl_2(PPh_3)_2$, the resulting mixture was heated to 80 °C for 8 h to get acetylene intermediate **6** (yield 92%). Then **6** was dissolved in a co-solvent of acetone and $H_2O$ to which $MgSO_4$/$Na_2CO_3$/$KMnO_4$ was added. After reacting at r.t. for 2 h, dione intermediate **7** was obtained in a yield of 63%. A mixture of **7**, 1-methylguanidine hydrochloride and $Na_2CO_3$ in

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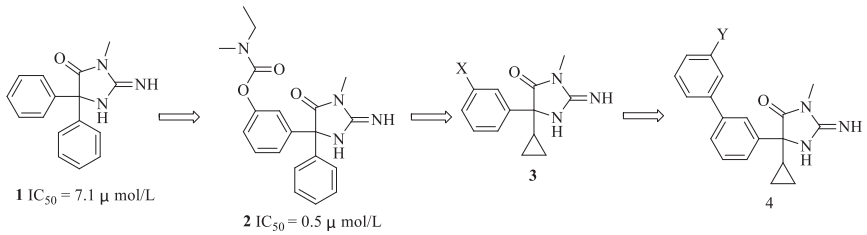
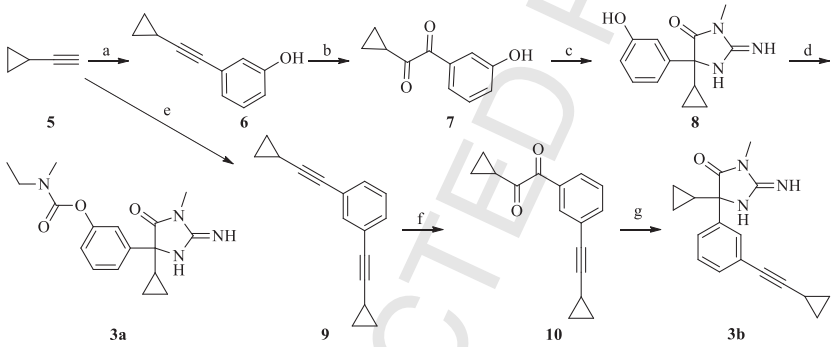


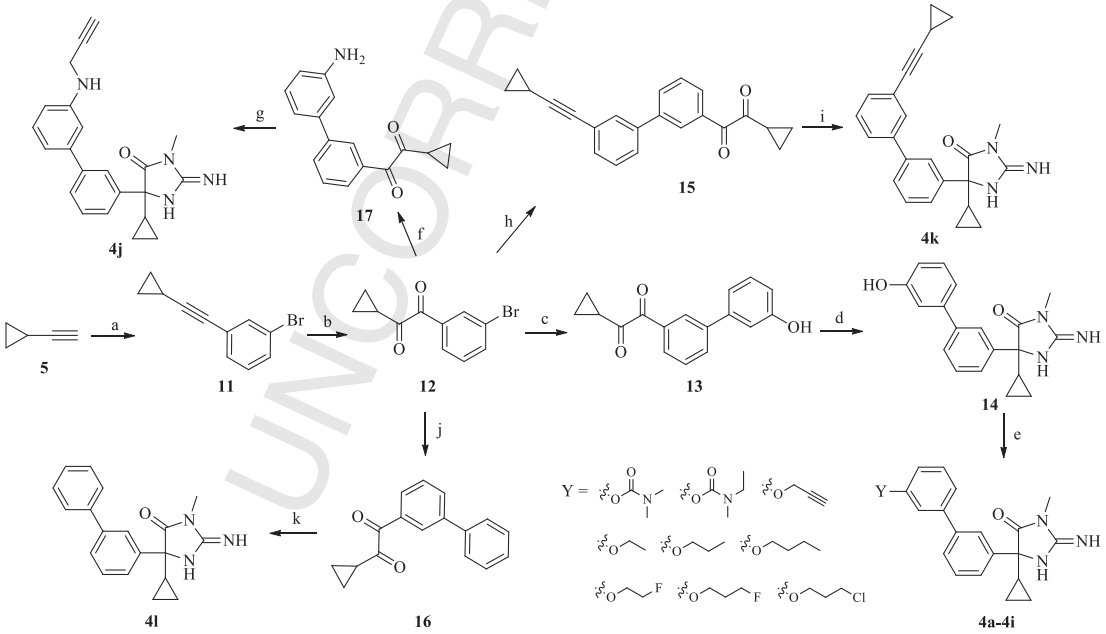

**Fig. 1.** Structures of lead and the designed compounds.

EtOH/$H_2O$ was refluxed for 2 h to give compound **8** (yield 42%). The phenol group then reacted with ethyl methyl-carbamic chloride to give one of the final product **3a** (yield 21%). The synthetic route of the other target compound **3b** also started from cyclopropyl acetylene (Scheme 1), which reacted with 1,3-dibromobenzene to give intermediate **9** (yield 70%). One of the acetylene fragments of **9** was then oxidized into dione intermediate **10** by $MgSO_4$/$Na_2CO_3$/$KMnO_4$ in acetone/$H_2O$ (yield 20%). Cyclization and re-arrangement of **10** with 1-methylguanidine hydrochloride at the presence of $Na_2CO_3$ gives final product **3b** (yield 24%).

The general synthetic route of compounds **4** (Scheme 2) also started from cyclopropyl acetylene, which reacted with 1,3-dibromobenzene at the presence of TBAF/$PdCl_2(PPh_3)_2$ in THF to get acetylene intermediate **11** (yield 72%). Oxidization of **11** with $MgSO_4$/$Na_2CO_3$/$KMnO_4$ gives dione intermediate **12** (yield 65%). $K_2CO_3$ and $PdCl_2$(dppf) were added to a solution of **12** and 3-hydroxyphenyl boronic acid in 1,4-dioxane at room temperature, then $H_2O$ was added until a clear solution was made, the resulting mixture was then heated to 90 °C for 12 h to afford **13** (yield 95%). The dione fragment then cyclized with 1-methylguanidine




**Scheme 1.** Synthetic route of the designed compounds **3a,3b.** Reagents and conditions: a) 3-bromophenol, TBAF, $PdCl_2(PPh_3)_2$, reflux; b) $KMnO_4$, $MgSO_4$, $Na_2CO_3$; c) 1-methylguanidine hydrochloride, $Na_2CO_3$, EtOH/$H_2O$; d) DIPEA/THF, reflux; e) 1,3-dibromobenzene, TBAF, $PdCl_2(PPh_3)_2$, reflux; f) $KMnO_4$, $MgSO_4$, $Na_2CO_3$; g) 1-methylguanidine hydrochloride, $Na_2CO_3$, EtOH/$H_2O$.




**Scheme 2.** Synthetic route of the designed compounds **4a–4l.** Reagents and conditions: a) TBAF, $PdCl_2(PPh_3)_2$, reflux; b) $KMnO_4$, $MgSO_4$, $Na_2CO_3$; c) 3-hydroxyphenyl boronic acid, $K_2CO_3$ and $PdCl_2$(dppf); d) 1-methylguanidine hydrochloride, $Na_2CO_3$, EtOH/$H_2O$; e) acetone/$K_2CO_3$; f) 3-aminobenzeneboronic acid, $K_2CO_3$ and $PdCl_2$(dppf); g) i: 1-methylguanidine hydrochloride, $Na_2CO_3$, EtOH/$H_2O$, ii: 3-bromopropyne, acetone/$K_2CO_3$; h) i: 3-bromobenzeneboronic acid, ii: TBAF, $PdCl_2(PPh_3)_2$, reflux; i) 1-methylguanidine hydrochloride, $Na_2CO_3$, EtOH/$H_2O$; j) phenylboronic acid, $K_2CO_3$ and $PdCl_2$(dppf); k) 1-methylguanidine hydrochloride, $Na_2CO_3$, EtOH/$H_2O$.



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