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Synthesis and decreasing Aβ content evaluation of arctigenin-4-yl carbamate derivatives

Xingyu Xu [a,†], Cong Li [b,†], Min Lei [a,*], Zhiyuan Zhu [a], Jianming Yan [a], Xu Shen [a,b,*], Lihong Hu [a,*]

[a] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 201203, PR China
[b] School of Life Science, Shanghai University, 99 Shangda Road, Shanghai 200444, PR China

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ABSTRACT

A series of arctigenin-4-yl carbamate derivatives were synthesized and evaluated for potency in reducing β-amyloid (Aβ) content in HEK293-APPswe cells. Most of the arctigenin-4-yl aralkyl or aryl carbamate derivatives showed improved potency in reducing Aβ content. Among the synthesized compounds, arctigenin-4-yl (3-chlorophenyl)carbamate (**20**) exhibited the strongest potency with 78.7% Aβ content reduction at 20 μM. Furthermore, the effect of arctigenin-4-yl (4-chlorophenyl)carbamate (**19**) and arctigenin-4-yl (3-chlorophenyl)carbamate (**20**) on lowing Aβ content was better than arctigenin under the concentrations of 1, 10 and 20 μM.

Alzheimer's disease (AD), the most common type of dementia, is a progressively neurodegenerative disease characterized by emotional disturbance, cognitive decline and memory loss. AD is a serious global threat to public health, imposing enormous social and economic burdens on patients and their families. To date, there is no effective therapy for AD, and marketed drugs are limited in efficacy. In 2002, Hardy and Selkoe hypothesized that overproduction and aggregation of β-amyloid peptides (Aβ) was one of important causes leading to AD.[1] From then on, inhibiting production, promoting elimination, and decreasing aggregation of Aβ have been becoming an important strategy for anti-AD drugs development.[2]

In recent years, a number of natural products targeting Aβ were found and developed into clinical studies, such as scyllo-inositol,[3] curcumin,[4] and homotaurine.[5] Therefore, seeking and finding lead compounds of anti-AD from natural products has received considerable attention and emphasis in the world. Arctigenin (**1**, Fig. 1), a naturally occurring lignanolide of the dibenzylbutyrolactone type isolated from the seeds of *Arctium lappa L.*, has been reported to possess diverse pharmacological activities such as antitumor,[6] anti-inflammatory,[7] and antioxidant activities.[8] Furthermore, it was reported that arctigenin had neuroprotective activity.[9] In 2013, Zhang and his co-workers reported that arctigenin could prevent cell viability loss and reduce intracellular Aβ production in the SH-SY5Y cells.[10] Our group has long been engaged in the research of modification and bioactivity of arctigenin.[6b,11] We have previously reported[11a] that arctigenin could inhibited Aβ production by suppressing BACE1 expression and promote Aβ clearance by enhancing autophagy through AKT/mTOR signaling inhibition and AMPK/Raptor pathway activation. Furthermore, arctigenin also could ameliorate AD mouse memory impairment. All these results clearly indicated that arctigenin was a potential lead compound for anti-AD drug discovery.

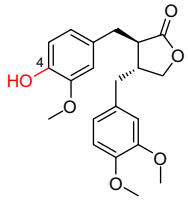

Figure 1. The structure of arctigenin (ATG).

Although several literature reported the anti-AD activity of arctigenin in vitro and vivo, the structure–activity relationships (SARs) of arctigenin derivatives was still not clear. Therefore, it is necessary to synthesis arctigenin analogues for further research of lowering Aβ content. As part of our current studies on the extraction, separation and modification of active natural products,

* Corresponding authors. Tel.: +86 21 2023 0223; fax: +86 21 2023 0233 (M.L.); tel./fax: +86 21 5080 6031 (X.S.), +86 21 2023 1965 (L.H.).
E-mail addresses: mlei@simm.ac.cn (M. Lei), xshen@simm.ac.cn (X. Shen), lhhu@simm.ac.cn (L. Hu).
† These authors contributed equally to this work.

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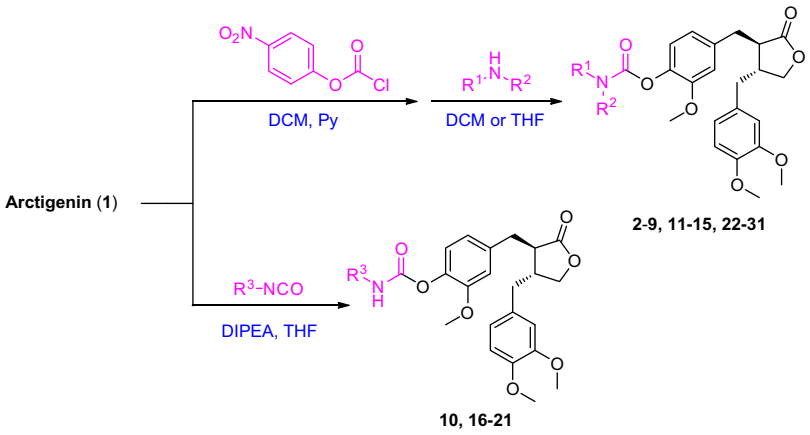
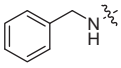


Scheme 1. The synthesis of arctigenin-4-yl carbamate derivatives.

Table 1
Lowering Aβ content activity of arctigenin-4-yl carbamate derivatives **1**–**11** in 20 μM

Compd	R^1 R^2 or R^3 H	Time (h)	Yield[a] (%)	Lowering Aβ content (%)
1	–	–	–	44.6
2		0.25	69	29.8
3		0.25	67	36.3
4		0.25	77	20.3
5		0.25	49	21.4
6		0.25	30	35.4
7		0.25	79	28.5
8		0.25	75	11.9
9		0.25	67	26.2
10		12	42	43.5
11		0.25	70	41.3

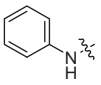
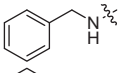
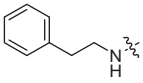
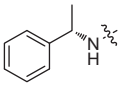
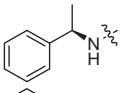
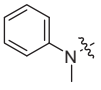
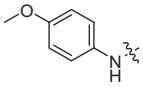
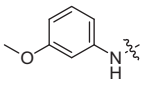
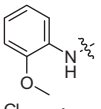
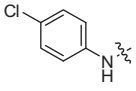
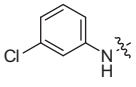
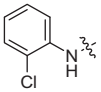
[a] Isolated yields.

we herein report a series of arctigenin derivatives for their lowering Aβ content activity.

In a previous study, we found that the etherification and esterification of hydroxyl on C-4 of arctigenin would lead to the activity of lowering Aβ content disappeared. Conversely, arctigenin-4-yl carbamate derivatives could maintain and improve the activities than that of arctigenin. In order to find new compounds with better bioactivity, a series of arctigenin-4-yl carbamate derivatives were synthesized, and evaluated for their lowering Aβ content activities.

As shown in Scheme 1, in order to synthesize of arctigenin-4-yl carbamate derivatives, we developed two methods which including: (a) arctigenin reacted with 4-nitrophenyl chloroformate in the presence of pyridine as base in DCM at rt to obtain the

Table 2
Lowering content activity of arctigenin-4-yl carbamate derivatives **1**, **10**–**21** in 20 μM

Compd	R^1 R^2 or R^3 H	Time (h)	Yield[a] (%)	Lowering Aβ content (%)
1	–	–	–	44.6
10		12	42	43.5
11		0.25	70	41.3
12		0.25	59	49.0
13		0.25	51	70.8
14		0.25	37	45.0
15		48	47	30.0
16		12	39	52.9
17		12	32	52.8
18		48	27	61.7
19		12	39	66.9
20		12	42	78.7
21		48	30	58.3

[a] Isolated yields.