Natural Product Research
Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Xi-xin He, Xiao-hong Yang, Rui-ying Ou, Ying Ouyang, Sheng-nan Wang, Zi-wei Chen, Shi-jun Wen & Rong-biao Pi (2016): Synthesis and evaluation of multifunctional ferulic and caffeic acid dimers for Alzheimer's disease, Natural Product Research, DOI: 10.1080/14786419.2016.1219862

To link to this article: http://dx.doi.org/10.1080/14786419.2016.1219862

NATURAL PRODUCT RESEARCH, 2016
http://dx.doi.org/10.1080/14786419.2016.1219862

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SHORT COMMUNICATION

Synthesis and evaluation of multifunctional ferulic and caffeic acid dimers for Alzheimer's disease

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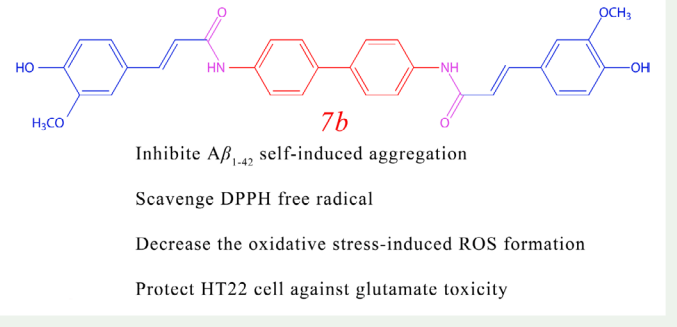
ABSTRACT

In this study, a series of novel ferulic and caffeic acid dimers was designed and synthesised, and their multifunctional properties against Alzheimer's disease (AD) were evaluated. Results showed that our multifunctional strategy was great supported by enhancing the inhibition of $A\beta_{1-42}$ self-induced aggregation. Moreover, **7b** also had potent protective effects against glutamate-induced cell death without significant cell toxicity in mouse hippocampal neuronal HT22 cells and **10c** effectively scavenged diphenylpicrylhydrazyl free radicals. Collectively, these data strongly encourage further optimisation of **7b** as a new hit to develop multifunctional agents for the treatment of AD.



ARTICLE HISTORY
Received 26 January 2016
Accepted 6 July 2016

KEYWORDS
Ferulic acid; caffeic acid; multifunctional neuroprotective agents; amyloid protein; aggregation; free radicals

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative brain disorder resulting in loss of memory and cognitive functions, often accompanied by behavioural disturbances like aggression and depression with the typical pathological hallmarks, loss of cholinergic neurons, neurofibrillary tangles and beta-amyloid (Aβ) deposition and affects about 6% of the population over the age of 65 (Querfurth & LaFerla 2010;

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Supplemental data for this article can be accessed at http://dx.doi.org/10.1080/14786419.2016.1219862.

Huang & Mucke 2012). At present, effective therapeutics are urgently needed because there is no efficacious disease-modified treatment available.

In AD patients, amyloid protein β (Aβ) deposition impairs mitochondria, which results in the elevated level of reactive oxygen species (ROS) and ultimately leads to oxidative damage (D'Autreaux & Toledano 2007; Gu et al. 2013; Luque-Contreras et al. 2014). Therefore, a drug that can simultaneously decrease the ROS generation and the Aβ aggregation, in principle, may effectively block the progression of AD. For inhibiting Aβ aggregation, chemical features are the presence of two aromatic end groups, which are substituted by one or more polar groups and combined with an appropriate linker with a reduced flexibility in order to confer a good interaction with Aβ (Reinke & Gestwicki 2007). In addition, our previous study suggested that cinnamic acid might be a good pharmacophore to develop agents against Aβ aggregation with ROS scavengiability (Chao et al. 2012). Based on above, this paper described the synthesis and the pharmacological evaluation of **3a**–**3d**, **5a**–**5b** (Sánchez, Guillén-Villar et al. 2014; Sánchez, Martínez-Mora et al. 2014), **5c**–**5d**, **7a**–**7d** and **10a**–**10d**, which combined two cinnamic acids, caffeic acid (CA) and ferulic acid (FA), into an entity, and were designed to simultaneously enhance the inhibition of Aβ self-induced aggregation and preserve the ability to prevent oxidative damage.

2. Results and discussion

In vitro, **3c**, **7b**, **10a** and **10c** had a significant inhibition of $A\beta_{1-42}$ self-induced aggregation by using a single-dose thioflavin T (Th–T) assay, while **3a**, **3c**, **7a** and **10a** significantly scavenged diphenylpicrylhydrazyl (DPPH) free radicals than CA (Table 1). HT22 cell line is an excellent model for the study of glutamate oxidative toxicity due to lacking ionotropic glutamate receptors, which excludes glutamate receptor-mediated excitotoxicity. Our results showed that **3a**, **7b**, **10a** and **10d** could protect HT22 cells against glutamate-induced oxidative damage at 10 μM, while **3a**, **3d**, **5b**, **7a**, **7b**, **10a** and **10c** showed cell toxicity at 30 μM. But it seems hard to reach an agreement on scavenging DPPH free radicals and protecting

Table 1. The preliminary evaluation of test compounds *in vitro*.

Chemicals	Inhibition of $A\beta_{1-42}$ aggregation[a]	DPPH radicals scavenging capacity (%)[a]
CA	30.9	58.91
FA	n.t.[c]	27.3
CR[b]	94.7	n.t.
Curcumin	n.t.	18.56
3a	59.6	92.60
3b	67.2	26.00
3c	81.7	88.12
3d	70.3	17.33
5a	48.1	80
5b	69.3	19.86
7a	41.0	85.26
7b	83.7	21.52
10a	88.8	74.78
10b	n.a.[d]	21.62
10c	90.0	71.45
10d	7.8	9.44

[a]The measurements were carried out in the presence of 10 μM compounds.
[b]CR means congo red.
[c]n.t. means no test.
[d]n.a. means not active.

against oxidative damage in HT22, particularly in **3d**, **5b** and **7b**. Sodium ferulate protected cultured cortical neurons against glutamate toxicity due to activations of the PI3K/Akt/p70S6K pathway and the MEK/ERK1/2 pathway (Jin et al. 2007), while FA did not have a good capacity in scavenging DPPH free radicals, only 27.3% (Kikuzaki et al. 2002). This indicated that the ability to scavenge DPPH free radicals *in vitro* may not be closely related with the protection against glutamate-induced oxidative damage *in vivo*.

Further study showed that **7b** did not have a high solubility at the concentration of 100 μM, but had an excellent neuroprotective capacity at 10 μM. The release of lactate dehydrogenase demonstrated that **7b** may inhibit the proliferation but not induce cell toxicity at 30 μM. Measurement of intracellular ROS accumulation indicated that **7b** instead of **7a** could decrease the level of oxidative stress-induced ROS accumulation. Additionally, it has been reported that **10a** showed a pharmacological properties in both anti-neuroinflammatory (Lu et al. 2013) and anti-perglycemic effect (Weng et al. 2010).

3. Conclusion

In summary, our multi-target strategy is to combine two cinnamic acids, CA and FA, through three different rigid groups with a limited flexibility in order to confer a good interaction with amyloid-β. Our findings contribute to further optimise FA, such as **7b** as a new hit to develop multifunctional agents for the treatment of AD.

Disclosure statement

The authors declare that there is no conflict of interest.

Funding

This work was supported by Guangdong Provincial International Cooperation Project of Science & Technology [grant number 2012B050300015], [grant number 2013B051000038]; National Natural Science Foundation of China [grant number 31371070].

References

Chao X, He X, Yang Y, Zhou X, Jin M, Liu S, Cheng Z, Liu P, Wang Y, Yu J, et al. 2012. Design, synthesis and pharmacological evaluation of novel tacrine-caffeic acid hybrids as multi-targeted compounds against Alzheimer's disease. Bioorg Med Chem Lett. 22:6498–6502.

D'Autreaux B, Toledano MB. 2007. ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis. Nat Rev Mol Cell Biol. 8:813–824.

Gu Q, Li Y, Chen Y, Yao P, Ou T. 2013. Sciadopitysin: active component from *Taxus chinensis* for anti-Alzheimer's disease. Nat Prod Res. 27:2157–2160.

Huang Y, Mucke L. 2012. Alzheimer mechanisms and therapeutic strategies. Cell. 148:1204–1222.

Jin Y, Yan EZ, Fan Y, Guo XL, Zhao YJ, Zong ZH, Liu Z. 2007. Neuroprotection by sodium ferulate against glutamate-induced apoptosis is mediated by ERK and PI3 kinase pathways. Acta Pharmacol Sin. 28:1881–1890.

Kikuzaki H, Hisamoto M, Hirose K, Akiyama K, Taniguchi H. 2002. Antioxidant properties of ferulic acid and its related compounds. J Agric Food Chem. 50:2161–2168.

Lu DY, Huang BR, Yeh WL, Lin HY, Huang SS, Liu YS, Kuo YH. 2013. Anti-neuroinflammatory effect of a novel caffeamide derivative, KS370G, in microglial cells. Mol Neurobiol. 48:863–874.

Luque-Contreras D, Carvajal K, Toral-Rios D, Franco-Bocanegra D, Campos-Pena V. 2014. Oxidative stress and metabolic syndrome: cause or consequence of Alzheimer's disease? Oxid Med Cell Longevity. 2014:1–11.

Querfurth HW, LaFerla FM. 2010. Alzheimer's disease. N Engl J Med. 362:329–344.

Reinke AA, Gestwicki JE. 2007. Structure-activity relationships of amyloid beta-aggregation inhibitors based on curcumin: influence of linker length and flexibility. Chem Biol Drug Des. 70:206–215.

Sánchez A, Guillén-Villar RC, Sánchez R, Vargas R, Garza J, Matus MH, Salas-Reyes M, Domínguez Z. 2014. Electrochemical oxidation of symmetrical amides of ferulic acid in aprotic medium. Electrochim Acta. 133:546–554.

Sánchez A, Martínez-Mora O, Martínez-Benavidez E, Hernández J, Domínguez Z, Salas-Reyes M. 2014. Electrochemical behaviour of new dimeric esters and amides derived from caffeic acid in dimethylsulfoxide. Org Biomol Chem. 12:5981–5989.

Weng YC, Chiu HL, Lin YC, Chi TC, Kuo YH, Su MJ. 2010. Antihyperglycemic effect of a caffeamide derivative, KS370G, in normal and diabetic mice. J Agric Food Chem. 58:10033–10038.