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Synthesis and evaluation of curcumin derivatives toward an inhibitor of beta-site amyloid precursor protein cleaving enzyme 1

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ABSTRACT

To research a new non-peptidyl inhibitor of beta-site amyloid precursor protein cleaving enzyme 1, we focused on the curcumin framework, two phenolic groups combined with an sp_2 carbon spacer for low-molecular and high lipophilicity. The structure–activity relationship study of curcumin derivatives is described. Our results indicate that phenolic hydroxy groups and an alkenyl spacer are important structural factors for the inhibition of beta-site amyloid precursor protein cleaving enzyme 1 and, furthermore, non-competitive inhibition of enzyme activity is anticipated from an inhibitory kinetics experiment and docking simulation.

Alzheimer's disease (AD)[1] is caused by the aggregation of amyloid-beta (Aβ),[2] which is produced from amyloid precursor protein (APP), a transmembrane protein expressed in many tissues and organs, cleaved by the both β-secretase (β-site amyloid precursor protein cleaving enzyme 1, BACE1[3]) and γ-secretase in the brain. BACE1 has been recognized as a valuable target for the treatment of AD. Therefore, BACE1 inhibitors have potential to be developed as *anti*-dementia drugs. A variety of inhibitors against BACE1 have been reported in the literature in past decades, however it has not been permitted to give BACE1 inhibitors as AD therapeutic agents to date. Most peptidomimetic inhibitors with potent activity are promisingly based on the cleaving site of the APP sequence,[4–7] but these inhibitors tend to be *P*-glycoprotein substrates and have restricted brain penetration. Although non-peptidyl BACE1 inhibitors rationally designed from fragment-based screening techniques have also been reported by several groups,[8,9] the cytotoxicity of the candidate compounds is frequently a serious problem. In contrast, natural products are promising bioactive libraries from which *anti*-AD agents from microorganisms or food plants have been isolated,[10] although they tend to offer low inhibitory activity and/or an unknown mechanism of action for the target enzyme in exchange for oral bioavailability and brain penetration.

Curcumins[11] are components of turmeric, which is consumed as a curry spice and is especially used in traditional Indian medicine to treat biliary disorders, anorexia, coughs, etc. around South Asia. The main ingredient of curcumins is curcumin 1 (**1**) [1,7-bis(4-hydroxy-3-methoxyphenyl)heptane-1,6-diene-3,5-dione], so-called curcumin, and other compounds exist as curcumin 2 (**2**) [desmethoxycurcumin] and curcumin 3 (**3**) [bis-desmethoxycurcumin]. These curcumins form stable enols and are responsible for the yellow color. A variety of extensive investigations in past decades have indicated that curcumin 1 (**1**) is an antioxidant and *anti*-inflammatory and has promising *anti*-Alzheimer's disease activity.[12–14]

In the course of a research program on BACE1 inhibitors,[15] we focused on the curcumin[16,17] framework as non-peptidyl compounds with low-molecular weight and high lipophilicity. Two crucial structural features of curcumins have been associated with BACE1 inhibitors: phenolic rings and an alkenyl spacer to join the two rings.[18,19]

In the present study, the inhibitory activities of natural curcumins 1, 2 and 3 (**1**), (**2**) and (**3**) were evaluated against recombinant β-site amyloid precursor protein cleaving enzyme 1 (rBACE1)[15] and subsequently, the effects of phenolic hydroxy groups, double bonds and ketone groups were examined. Furthermore, a structure–activity

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relationship study of the aromatic substituents of curcumin derivatives and determination of the inhibition mechanism were attempted. Therefore, 37 curcumin derivatives were prepared from curcumin 1 (**1**) or benzaldehyde derivatives and subsequently screened for their effect on *anti*-BACE1 activity at a concentration of 1.3 or 0.67 mM. Then IC_{50} values of the selected inhibitors were determined and interactions between the inhibitors and rBACE1 was estimated (Fig. 1).

To investigate the importance of phenolic hydroxy groups, double bonds and keto carbonyl groups, we prepared a variety of curcumin derivatives from curcumin 1 (**1**). First of all, phenolic hydroxy groups of curcumin 1 (**1**) were protected using several protecting groups because of the insolubility of the curcumins in organic solvents. Although the selected protecting groups were TBS, MEM, MOM ethers, chemical yields of **4a**–**4f** remained moderate or low because of insolubility in reaction solvents. In addition, treatment of curcumin 1 (**1**) with methyl iodide and potassium carbonate in acetone afforded α,α-dimethyl-di-*O*-methylcurcumin (**4g**) in 47% yield. Attempts to deprotect phenolic methyl ether of **4g** under several conditions were unsuccessful to give complexed mixtures. A three step sequence with acetylation of phenolic hydroxyl groups/methylation of α,α-carbon on the spacer/deacetylation afforded **4h** in a trace amount (Table 1).

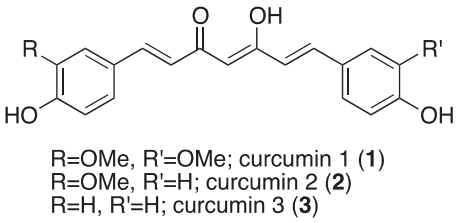


Figure 1. Structure of curcumins.

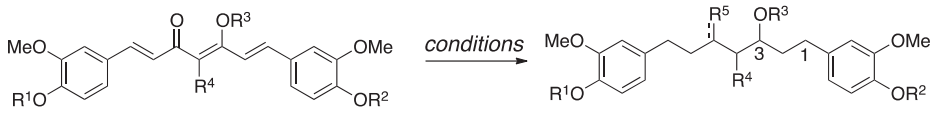
As depicted in Table 2, curcumin derivatives (**5a**)–(**9b**) were prepared by hydrogenolysis of double bonds and reduction of ketones. As the above-mentioned results, using the reductive reactions of curcumin derivatives it was difficult to afford one or more products in satisfied yield. Although reactions at 0 °C or −20 °C were attempted, insolubility of the substrates prevented use of the reactants. In contrast, conjugated alkenyl groups of the curcumin framework often gave the over-reduced products. In entry 1, hydrogenation of curcumin 1 (**1**) with Pd/C in MeOH/AcOEt at H_2 atmosphere afforded the expected compound (**5a**) and ketone-reduced compounds (**5b**) and (**5c**) in 69%, 10% and 8% yields, respectively. On the other hand, treatment of **4c** with $NaBH_4$ in MeOH/AcOEt gave **9a** in 30% yield with the recovered material (**4c**) in ca. 50% yield (entry 5). Stereochemistry of hydroxyl groups of these products was not still determined in this case (Table 2).

Table 1
Protected curcumin derivatives (**4a**)–(**4h**)

Entry	Conditions	Product	R^1	R^2	R^3	R^4	Yield (%)
1	TBSCl, imidazole, DMF	**4a**	TBS	H	H	H	45
		4b	TBS	TBS	H	H	33
2	MEMCl, iPr_2NEt, CH_2Cl_2	**4c**	MEM	MEM	H	H	49
		4d	MEM	H	H	H	32
		4e	MEM	MEM	MEM	H	5
3	MOMCl, iPr_2NEt, CH_2Cl_2	**4f**	MOM	MOM	H	H	30
4	MeI, K_2CO_3, acetone	**4g**[a]	Me	Me	H	Me_2	47
5	(a) Ac_2O, py.; (b) MeI, K_2CO_3; (c) 1M NaOH	**4h**[a]	H	H	H	Me_2	1

[a] **4g** and **4h** were isolated with keto form.

Table 2
Protected curcumin derivatives (**5a**)–(**9b**)



Entry	Substrate	Conditions	Product	R^1	R^2	R^3	R^4	R^5		Yield (%)
1	**1**	H_2/Pd-C	**5a**	H	H	H	H	O	Δ^3	69
		MeOH/AcOEt	**5b**	H	H	H	H	O		10
			5c	H	H	H	H	OH, H		8
2	**4b**	H_2/Pd-C	**6a**	TBS	TBS	H	H	O	Δ^3	23
		MeOH/AcOEt								
3	**4c**	H_2/Pd-C	**7a**	MEM	MEM	H	H	O	Δ^3	45
		MeOH/AcOEt	**7b**	MEM	MEM	H	H	O		25
4	**4g**	H_2/Pd-C	**8a**[a]	Me	Me	—	Me_2	O		28
		MeOH/AcOEt	**8b**	Me	Me	H	Me_2	O		7
			8c	Me	Me	H	Me_2	OH, H		3
5	**4c**	$NaBH_4$	**9a**	MEM	MEM	H	H	OH, H	$\Delta^{1,3}$	30
		MeOH/AcOEt	**9b**	MEM	MEM	H	H	O	Δ^3	3

[a] Chemical structure of **8a** was shown diketone derivative.