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Design and synthesis of curcumin derivatives as tau and amyloid β dual aggregation inhibitors

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia. In an AD patient's brain, senile plaques and neurofibrillary tangles, the abnormal aggregates of amyloid β (Aβ) peptide and tau protein, are observed as the two major hallmarks of this disease. To develop a new drug for treatment of AD, we have designed and synthesized a series of curcumin derivatives and evaluated their inhibitory activities against both tau and Aβ aggregation. In this study, we describe the development of the more potent aggregation inhibitor 3-[(1E)-2-(1H-indol-6-yl)ethenyl]-5-[(1E)-2-[2-methoxy-4-(2-pyridylmethoxy) phenyl] ethenyl]-1H-pyrazole (compound **4,** PE859). This compound has a better pharmacokinetic profile and pharmacological efficacy *in vivo* than curcumin, making it suitable as a drug for AD.

Alzheimer's disease (AD), a neurodegenerative disease, is the most common form of dementia. The number of worldwide patients with dementia today is estimated at 44 million, and more than half of them are AD.[1] The currently available drugs for AD are limited to symptomatic treatment such as the acetylcholinesterase inhibitors, Donepezil, rivastigmine, and galantamine, and the N-methyl-d-aspartate (NMDA) receptor antagonist memantine.[2] Therefore, new fundamental therapeutic approaches are required.

Pathologically, senile plaques (SP) composed of amyloid β (Aβ) peptide and neurofibrillary tangles (NFT) composed of tau protein are known as the two major hallmarks of AD.[3, 4] SP appear in the brain several years prior to the onset of AD.[5] Aβ is generated from an amyloid precursor protein (APP) through proteolytic cleavage by β-secretase and γ-secretase.[6] Aggregated Aβ, especially Aβ oligomers, show neurotoxicity.[7] Aβ further aggregates and eventually forms SP. Therefore, Aβ is widely believed to be fundamental in the onset or progression of AD. In fact, many of the following therapeutic studies on Aβ cascade are ongoing: the inhibition of Aβ production, promotion of Aβ clearance, and inhibition of Aβ aggregation;[8] however, recent clinical trials targeting Aβ have not yet been successfully developed. In contrast, tau is a microtubule-associated protein that plays a fundamental role in the stabilization of microtubules. In AD and tauopathies, hyperphosphorylated tau proteins dissociate from microtubules and aggregate into NFT. The NFT formation correlates with the progression of neuronal dysfunction, and the severity of AD is positively related to the number of NFTs.[9] Furthermore, oligomeric tau is more toxic than other forms, just like Aβ.[10]

We proposed that a dual inhibitor on both Aβ and tau cascades should be more effective in treating AD than existing inhibitors of Aβ or tau alone. Thus, we have designed and synthesized curcumin derivatives and performed screenings for more potent inhibitors on both Aβ and tau aggregation. The seed compound curcumin, 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is the main component in the rhizome of *Curcuma longa*, also known as turmeric. Although curcumin has a simple structure with two phenolic functional groups connected by a conjugated β-diketone system, it exhibits a variety of biological activities. For example, curcumin is an anti-inflammatory,[11]

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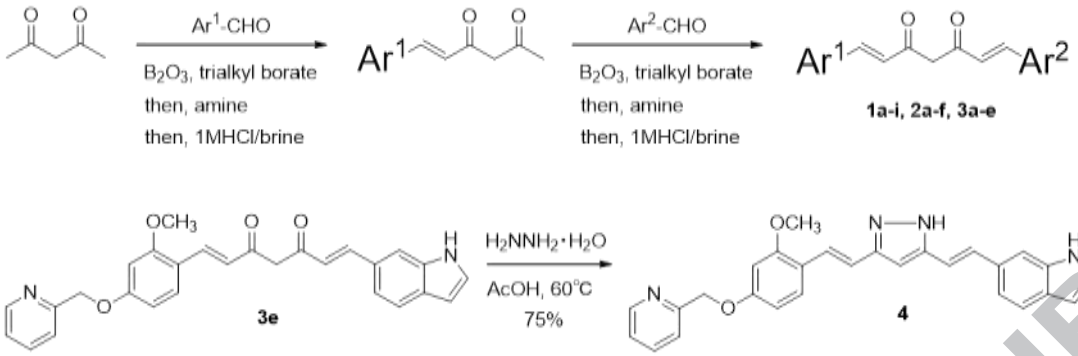


Scheme 1

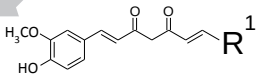
antioxidant,[12] anti-cancer,[13] anti-HIV integrase,[14] anti-angiogenic,[15] and antibacterial compound.[16] Additionally, curcumin has inhibitory effects on the pathology of AD, such as γ-secretase activity,[17] β-secretase upregulation,[18] Aβ aggregation,[19] and tau aggregation.[20] Although curcumin has such therapeutic activities, it is unsuitable for clinical use due to its poor solubility, stability, and bioavailability.[21] We developed the novel curcumin derivative PE859 (3-[(1E)-2-(1H-indol-6-yl)ethenyl]-5-[(1E)-2-[2-methoxy-4-(2-pyridylmethoxy) phenyl] ethenyl]-1H-pyrazole, compound **4**) as a potent inhibitor of both tau and Aβ aggregation with a good pharmacokinetic profile. Previously, we introduced the inhibitory effect of PE859 on tau aggregation.[22] In this study, we described the development of PE859 through the structure–activity relationships study of curcumin and its derivatives.

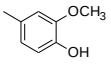
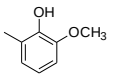
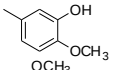
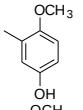
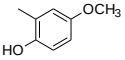
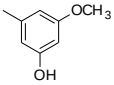
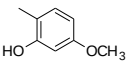
Inhibitory activity against tau and Aβ aggregation was determined using a thioflavin T (ThT) fluorescence assay.[23] ThT specifically binds to the β-sheet structure of the protein. It is reported that curcumin breaks the β-sheet structure of Aβ aggregates.[24] Several studies of curcumin analogues as Aβ and tau aggregation inhibitors are published[25,26] and these curcumin analogues are presumed to break the β-sheet structure of Aβ or tau aggregates, like curcumin. In our assay, curcumin had IC_{50} values of 5.4 μM for Aβ aggregation and 3.0 μM for tau aggregation (Table 1).

A series of asymmetric curcumin derivatives **1a–i** (Table 1), **2a–f** (Table 2), **3a–e** (Table 3) were synthesized in two steps as indicated in Scheme 1. Common starting material, acetylacetone was reacted with each aromatic aldehyde (Ar^1-CHO) in the presence of boron oxide, trialkyl borate (tributyl borate or triisopropyl borate) followed by the addition of amine (*n*-butylamine or piperidine), and then treated with 1M HCl/brine to obtain the corresponding mono-substituted intermediates.[27,28] This reaction sequence was repeated for the intermediates and each aromatic aldehyde (Ar^2-CHO) to obtain **1a–i**, **2a–f**, **3a–e** in low to moderate yields. Pyrazole **4** (PE859, table 4) was synthesized from **3e** and hydrazine monohydrate in acetic acid in 75% yield.[29,30]

First, we synthesized curcumin derivatives where the hydroxyl and methoxy substituents on one of the two aromatic rings were changed (**1a–i**, Table 1). The results indicated that the inhibitory activity on Aβ aggregation decreased when these substituents were located in *ortho* positions each other (curcumin, **1a**, **1b**, and **1c**) and that location of the hydroxyl substituent in *ortho* positions with a carbon chain linker decreased the inhibitory activities (**1d** vs. **1e** or, **1f**; **1g** vs. **1h**; **1i** vs. **1c**). Interestingly, all compounds had higher inhibitory activities than curcumin. Symmetric structures may decrease the inhibitory activities composed of asymmetric compounds. For example, the symmetric compound with the structure of **1f** (compound **1j;** data not shown) had lower activities than **1f,** which had IC_{50} values of 4.6 μM for Aβ aggregation and >10 μM for tau aggregation.

Table 1. Structure and inhibition data of curcumin and compounds **1a–i**.

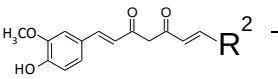


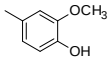
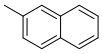
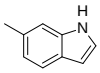
	R^1	Aggregation Inhibition IC_{50} (μM)	
		Aβ	Tau
Curcumin		5.4 ± 0.3	3.0 ± 0.4
1a		5.4 ± 0.3	0.69 ± 0.04
1b		1.9 ± 0.3	0.71 ± 0.04
1c		2.1 ± 0.2	0.52 ± 0.11
1d		1.6 ± 0.2	0.91 ± 0.09
1e		1.3 ± 0.2	0.60 ± 0.05
1f		0.92 ± 0.4	0.58 ± 0.04
1g		1.8 ± 0.4	0.92 ± 0.03
1h		1.1 ± 0.3	0.32 ± 0.02
1i		0.93 ± 0.05	1.4 ± 0.3

Next, we synthesized derivatives where the aromatic ring was replaced with other cyclic structures (**2a–f**, Table 2). These results suggest that a bicyclic structure (**2a–c**) may increase

inhibitory activities, especially in tau aggregation, relative to the monocyclic structures (**2d**–**f**).

Table 2. Structure and inhibition data of compounds **2a**–**2f**.

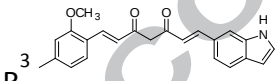


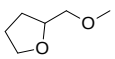
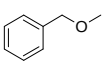
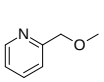
	R^2	Aggregation Inhibition IC50 (μM) Aβ	Tau
Curcumin		5.4 ± 0.3	3.0 ± 0.4
2a		3.7 ± 1.4	1.2 ± 0.2
2b		0.59 ± 0.07	0.42 ± 0.12
2c		0.42 ± 0.10	0.44 ± 0.03
2d		2.2 ± 0.3	1.4 ± 0.1
2e		> 10	> 10
2f		0.76 ± 0.14	2.0 ± 0.01

The results reported in Tables 1 and 2 were combined to synthesize derivative **3a** (Table 3). The moieties used in **1f** and **2c** were selected because these compounds had higher inhibitory activities than curcumin. As a result, compound **3a** had IC_{50} values of 0.52 μM for Aβ aggregation and 0.23 μM for tau aggregation.

Previous reports have demonstrated that curcumin is subject to conjugation of glucuronide or sulfate with hydroxyl substituents on aromatic rings in the body.[31] To protect compounds from being metabolized, various residues were introduced to the phenolic hydroxyl group of **3a** (**3b**–**3e**, Table 3). In these compounds, only **3e** had the same level of inhibitory activities as **3a**.

Table 3. Structure and inhibition data of compounds **3a**–**3e**.

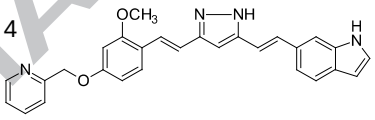


	R^3	Aggregation Inhibition IC_{50} (μM) Aβ	Tau
3a	HO−	0.52 ± 0.04	0.23 ± 0.06
3b	H_3CO−	0.61 ± 0.52	0.70 ± 0.05
3c		2.5 ± 0.2	0.42 ± 0.01
3d		5.4 ± 0.2	0.61 ± 0.04
3e		0.47 ± 0.02	0.33 ± 0.09

The pharmacokinetic profiles of curcumin and **3e** (Fig. 1) were compared. Each compound was orally administered to rats at 50 mg/kg and concentrations in plasma were measured for up to 3 h (Fig. 1a). The C_{max} of **3e** was found to be 1/20 lower than that of curcumin (5.7 ± 3.3 ng/mL at 30 min and 125 ± 65 ng/mL at 15 min). Additionally, the concentration of **3e** in the brain was 1/13 of the concentration of curcumin (Fig. 1b). These results suggest that further structural change on **3e** is required for a better pharmacokinetic profile.

The central diketone of curcumin is unstable in an aqueous solution; the modification of this moiety improves the aqueous stability.[32] Additionally, the C–C bond of a β-diketone moiety is enzymatically cleaved *in vivo*.[33] Other studies on curcumin derivatives indicate that the modification of the central diketone moiety improves its pharmacokinetic profile[34] and brain permeability.[35] Thus, we substituted the diketone in **3e** with a pyrazole (**4**, Table 4). Compound **4** had IC_{50} values of 1.2 μM for Aβ aggregation and 0.66 μM for tau aggregation.

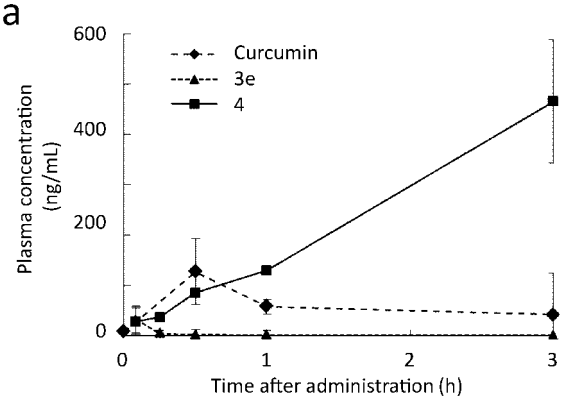
Table 4. Structure and inhibition data of compound 4 (PE859).

	Structure	Aggregation Inhibition IC_{50} (μM) Aβ	Tau
4		1.2 ± 0.2	0.66 ± 0.13

The plasma concentration of **4,** after oral administration to rats at 50 mg/kg, was 466 ± 123 ng/mL after 3 h, and the concentration was still increasing (Fig. 1a). Previously, we reported pharmacokinetics of compound **4** in mice,[22] and the T_{max} of **4** occurred at 6 h in that study. After 3 h of administration, brains were collected and concentrations of these compounds were measured (Fig. 1b). The concentration of **4** in the brain was ~300 times higher than that of **3e** and 20 times higher than that of curcumin. To compare the metabolic stability of **3e** and **4** in the body, they were intravenously administered at 5 mg/kg and the concentrations in plasma were measured up to 3 h (Fig. 1c). The concentration of **4** maintained a higher level than that of **3e**. These results suggest that this modification drastically improved its pharmacokinetic profile *in vivo* and that **4** has a better pharmacokinetic profile than curcumin.

The efficacy of **4**, *in vivo*, was next confirmed (Fig. 2). In the *in vivo* study, we compared the efficacy of **4** to those of curcumin and methylene blue (MB). MB is one of the best-known tau aggregation inhibitors and phase 2 clinical trials of MB in AD have been completed.[36] Additionally, MB inhibits Aβ aggregation *in vitro*.[37] In our ThT fluorescence assay, MB had IC_{50} values of 1.4 μM for tau aggregation and 0.50 μM for Aβ aggregation. We administered these compounds orally to JNPL3 human tau P301L transgenic mice. In JNPL3 mice, tau proteins abnormally aggregate and accumulate as sarkosyl-insoluble tau in the brain.[38] After a four-week administration, **4** significantly reduced the amount of sarkosyl-insoluble tau in the brain at doses of 20 and 40 mg/kg/day. In contrast, MB and curcumin showed no effect on the amount of sarkosyl-insoluble tau, even at 40 mg/kg/day. These results suggest that **4** has a more potent effect than curcumin and MB.

a



b

Compound	Brain concentration (ng/g-tissue)
3e	1.0 ± 1.5
4	276 ± 158
Curcumin	13 ± 11

c

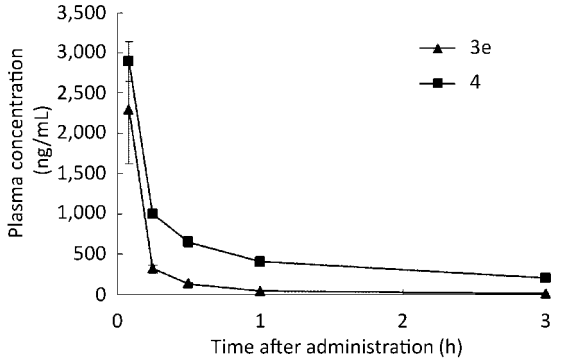


Figure 1. Pharmacokinetic profile of curcumin, **3e**, and **4**. (a) The concentration of compounds **3a**, **4**, and curcumin in plasma after oral administration to SD rats at 50 mg/kg. (b) The concentration of the compounds in the brain at 3 h after oral administration. (c) The concentration of **3e** and **4** in plasma after intravenous administration to SD rats at 5 mg/kg. Mean ± SD, n = 3.

In conclusion, compound **4** is the best candidate for an AD drug, as determined by this study. This compound is a more potent both tau and Aβ dual aggregation inhibitor than curcumin *in vitro*. Furthermore, this compound has a better pharmacokinetic profile and potent pharmacological effect than curcumin *in vivo*.

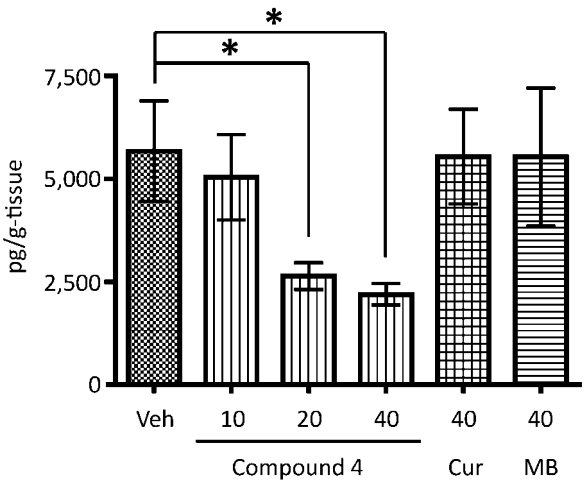


Figure 2. Inhibitory activities on tau aggregation by **4**, curcumin (Cur), and methylene blue (MB) *in vivo*. Each compound was orally administered to JNPL3 human tau P301L transgenic mice for four weeks, and sarkosyl-insoluble tau in the brain was measured. Mean ± standard error, n = 15–16. *P < 0.05 vs. Vehicle (Veh).

Acknowledgments

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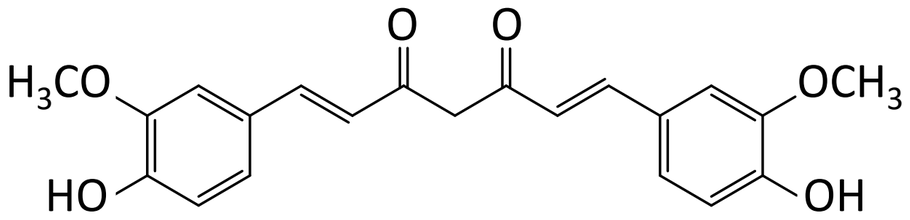
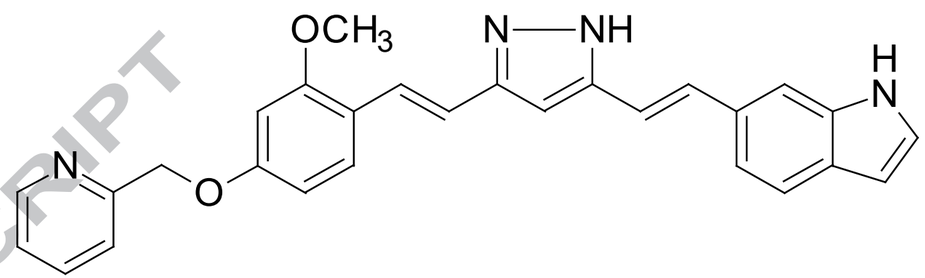
Supplementary data

Supplementary data (synthetic procedures for curcumin derivatives reported in this letter and procedures for ThT fluorescence assay, pharmacokinetic study and *in vivo* study) is available via the Internet at http://

Curcumin



Compound 4



Aβ aggregation IC_{50}	5.4 µM	1.2 µM
Tau aggregation IC_{50}	3.0 µM	0.66 µM
Brain concentration (50 mg/kg p.o., at 3h)	13 ng/g-tissue	276 ng/g-tissue