Regular Article

Synthesis of Amide and Ester Derivatives of Cinnamic Acid and Its Analogs: Evaluation of Their Free Radical Scavenging and Monoamine Oxidase and Cholinesterase Inhibitory Activities

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A series of cinnamic acid derivatives, amides (1–12) and esters (13–22), were synthesized, and structure–activity relationships for antioxidant activity, and monoamine oxidases (MAO) A and B, acetylcholinesterase, and butyrylcholinesterase (BChE) inhibitory activities were analyzed. Among the synthesized compounds, compounds 1–10, 12–18, and rosmarinic acid (23), which contained catechol, *o*-methoxyphenol or 5-hydroxyindole moieties, showed potent 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity. Compounds 9–11, 15, 17–22 showed potent and selective MAO-B inhibitory activity. Compound 20 was the most potent inhibitor of MAO-B. Compounds 18 and 21 showed moderate BChE inhibitory activity. In addition, compound 18 showed potent antioxidant activity and MAO-B inhibitory activity. In a comparison of the cinnamic acid amides and esters, the amides exhibited more potent DPPH free radical scavenging activity, while the esters showed stronger inhibitory activities against MAO-B and BChE. These results suggested that cinnamic acid derivatives such as compound 18, *p*-coumaric acid 3,4-dihydroxyphenethyl ester, and compound 20, *p*-coumaric acid phenethyl ester, may serve as lead compounds for the development of novel MAO-B inhibitors and candidate lead compounds for the prevention or treatment of Alzheimer's disease.

Key words cinnamic acid amide; cinnamic acid ester; monoamine oxidase; cholinesterase; antioxidant; Alzheimer's disease

Plant secondary metabolites are important sources of bioactive constituents that promote health. Natural products have long played a significant role in the development of new therapeutic leads. For example, phenolic compounds have been shown to prevent oxidative stress, a condition known to cause cell injury and death and to exacerbate the development of several age-related chronic pathologies like cancer, and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.[1–3)]

Alzheimer's disease is the most common fatal neurodegenerative disorder, and the number of affected people is expected to reach 106.8 million by 2050 with the worldwide increases in the aging population.[4)]

Although more than 100 years have passed since its discovery, effective treatments for Alzheimer's disease are lacking. Current therapeutic options, which include acetylcholinesterase and butyrylcholinesterase (AChE and BChE) inhibitors (donepezil, rivastigmine, and galantamine) and an *N*-methyl-D-aspartate (NMDA) receptor antagonist (memantine), have resulted in modest improvement in memory and cognitive function, but they do not prevent progressive neurodegeneration. The free radical and oxidative stress theory of aging also suggests that oxidative damage is an important factor in neuronal degeneration. Therefore, the successful protection of neuronal cells from oxidative damage could potentially prevent Alzheimer's disease.[5)]

In the treatment of Parkinson's disease, monoamine oxidase is regarded as a key target enzyme. Monoamine oxidases A and B (EC 1.4.3.4; MAO-A and MAO-B) are flavoenzymes, which play an important role in the oxidative degradation of neurotransmitters such as dopamine, serotonin and epinephrine. MAOs are found in the outer mitochondrial membrane of various mammalian cell types. MAO-A and MAO-B share approximately 70% sequence identity at the amino acid level, and were identified based on substrate selectivity and inhibitor sensitivity. MAO-A preferentially deaminates serotonin, norepinephrine, and epinephrine and is irreversibly inhibited by clorgyline, whereas MAO-B preferentially deaminates dopamine, β-phenethylamine, and benzylamine and is irreversibly inhibited by R-(−)-deprenyl. MAO inhibitors are important in the treatment of several neurodegenerative diseases. Selective MAO-A inhibitors are used as anti-depressant and anti-anxiety drugs, whereas selective MAO-B inhibitors are used in the treatment of Parkinson's disease. Because of their potential neuroprotective effects, MAO-B inhibitors may be useful for the treatment of Alzheimer's disease.[6–8)]

Several natural and synthetic cinnamic acid amides and their esters were found to possess various biological properties such as antioxidant,[9,10)] anti-inflammatory,[11)] anti-tumor,[12)] cytoprotective,[13,14)] protection of β-amyloid protein aggregation,[15)] tyrosinase inhibitory,[16,17)] α-glucosidase inhibitory,[18,19)] cholinesterase inhibitory,[20)] and MAO inhibitory[21–23)] activities. However, no systematically evaluated data are available on the antioxidant and MAO and ChE inhibitory activities of cinnamic acid derivatives.

In order to further explore the biological activities of this family of compounds, a series of cinnamic acid amide and ester derivatives were synthesized (Fig. 1), and the structure–activity relationships (SARs) of the cinnamic acid derivatives with respect to antioxidant capacity and MAO and ChE inhibitory activities were investigated.

Results and Discussion

Chemistry Cinnamic acid and its analogs such as caf-

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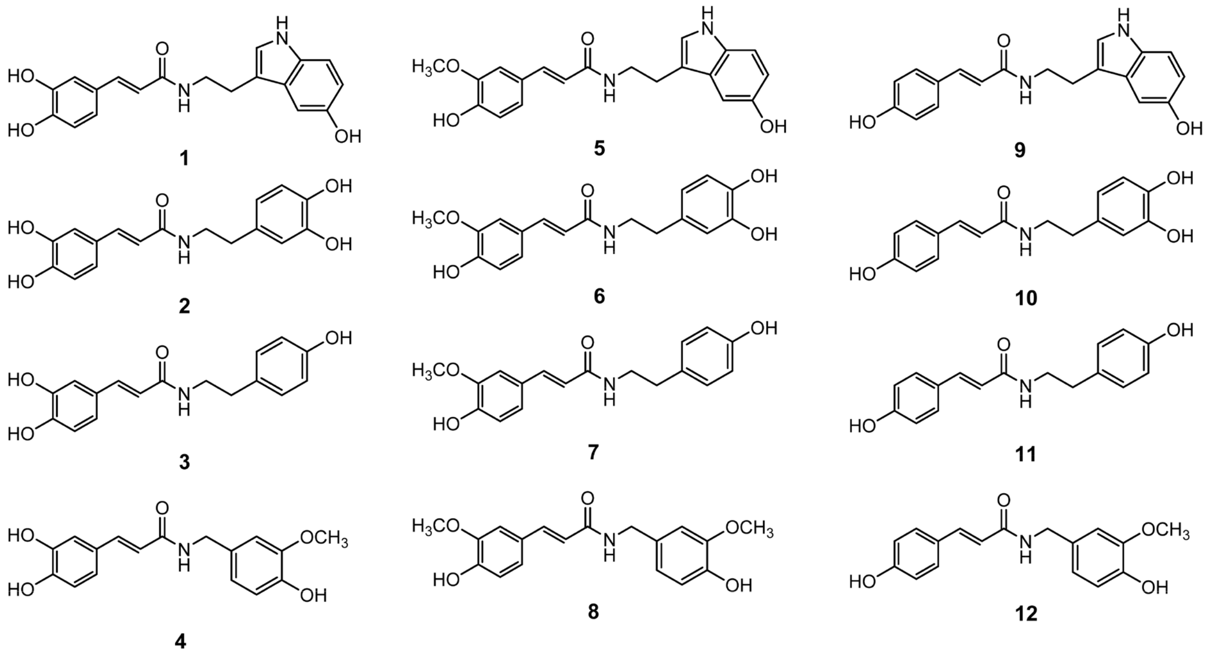
Amide derivatives



Ester derivatives

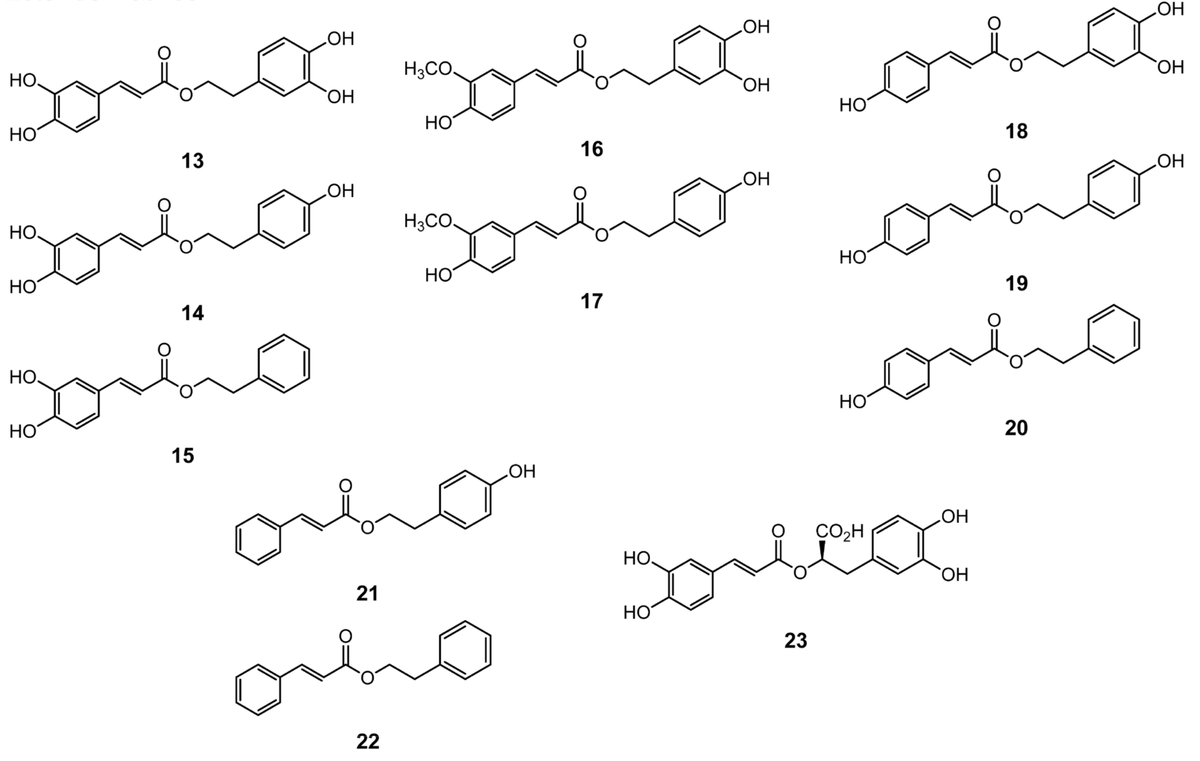


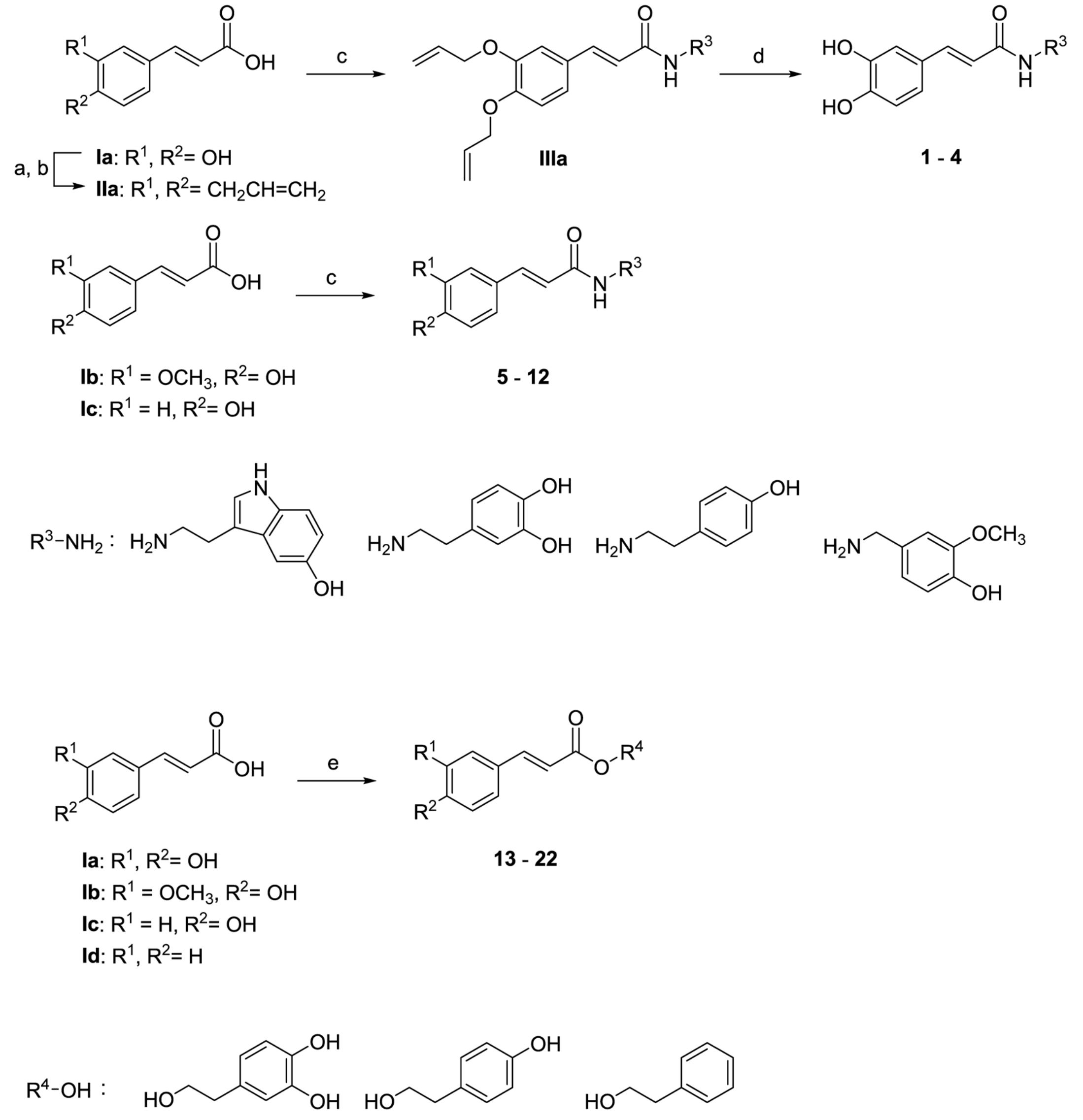
Fig. 1. Structures of Cinnamic Acid Derivatives

feic acid, ferulic acid and *p*-coumaric acid were reacted with biogenic amines (*i.e.*, serotonin, dopamine, tyramine, vanillylamine) to get amide compounds (**1**–**12**), and with alcohols (*i.e.*, 3,4-dihydroxyphenethylalcohol, 4-hydroxyphenethylalcohol, phenethylalcohol) to get ester compounds (**13**, **14**, **16**–**22**) (Chart 1). Their yields were satisfactory. Caffeic acid amides (**2**–**4**) were synthesized by condensation of the ally-protected caffeic acid with the corresponding amines followed by a deprotection step. Chemical structures of these compounds used in this study are shown in Fig. 1.

Biological Activity All the compounds synthesized were evaluated for their 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging, and MAO and ChE inhibitory activities. The results are summarized in Table 1.

DPPH Free Radical Scavenging Activity

Caffeic acid derivatives (**1**–**4**, **13**–**15**) containing catechol



Reagents and conditions: (a) allylbromide, K_2CO_3, acetone, reflux; (b) KOH, MeOH–H_2O; (c) R^3-NH_2, EDC, HOBt, Et_3N, CH_2Cl_2–DMF; (d) $Pd(PPh_3)_4$, morpholine, THF, 50°C; (e) R^4-OH, DIAD, TPP, THF.

Chart 1. Synthetic Protocol of Cinnamic Acid Derivatives

moiety showed a significant activity, followed by ferulic acid derivatives (**5**–**8**, **16**, **17**) containing *o*-methoxyphenol moiety. *p*-Coumaric acid derivatives (**9**, **10**) containing 5-hydroxyindole or catechol moiety, respectively, also showed a significant activity, but the other *p*-coumaric acid derivatives (**11**, **19**, **20**) except for compound **12** showed almost no activity similar to cinnamic acid derivatives (**21**, **22**). From the view of amines or alcohols, serotonin amide derivatives (**1**, **5**, **9**) showed significant activities, followed by dopamine amide derivatives (**2**, **6**, **10**), 3,4-dihydroxyphenethylalcohol ester derivatives (**13**, **16**, **18**), vanillylamine amide derivatives (**4**, **8**, **12**), tyramine amide derivatives (**3**, **7**), and 4-hydroxyphenethylalcohol ester derivatives (**14**, **17**). Of those, compounds **1** and **2** showed the most significant activity (EC_{50}=8.1 and 8.7 μM, respectively), which was about 3 fold more active than ascorbic acid used as a positive control. EC_{50} values of each corresponding pair of the amide derivatives (**2**, **3**, **6**, **7**, **10**) and the ester derivatives (**13**, **14**, **16**–**18**) were compared and showed a lower value for the amide derivative than the ester derivative without exception, being consistent with the previous report.[9] This would be probably due to a stabilization of resonance structure by amide bond.

MAO-A or MAO-B Inhibitory Activity

As can be seen in Table 1, all compounds had no inhibitory activity to MAO-A at 10 μM. However, compounds **9**–**11**, **15**, and **17**–**22** showed a widely different inhibitory activity to MAO-B. Of them compound **20** inhibited the enzyme most potently (IC_{50}=13 nM) and its inhibitory activity was about 17 fold more potent than that of pargylin used as a positive control. And compounds **15**, **19**, **21** and **22** showed a fairly potent activity with IC_{50} values of sub-micro molar, nearly equivalent to pargylin. Based on the low IC_{50} values of these compounds, the following SARs could be recognized. The ester derivatives of *p*-coumaric acid inhibited MAO-B more potently than those of caffeic acid (**20** *vs.* **15**), ferulic acid (**19** *vs.* **17**), and cinnamic acid (**19** *vs.* **21**, **20** *vs.* **22**). This indicated that the introduction of one hydroxyl group on cinnamic acid moiety was effective for their inhibitory activity, and a further addition of hydroxyl group on either cinnamic acid or phenetyalcohol moiety reduced the activity (**20** *vs.* **19**, **18**). From the

Table 1. DPPH Free Radical Scavenging, MAOs-A, -B, AChE, BChE Inhibitory Activities of Cinnamic Acid Derivatives

Compound	DPPH radical scavenging activity EC$_{50}$ (μM)	MAO-A inhibition IC$_{50}$ (μM)	MAO-B inhibition IC$_{50}$ (μM)	AChE inhibition IC$_{50}$ (μM)	BChE inhibition IC$_{50}$ (μM)
1	8.1	>10	>10	>10	>10
2	8.7	>10	>10	>10	>10
3	16	>10	>10	>10	>10
4	16	>10	>10	>10	>10
5	14	>10	>10	>10	>10
6	15	>10	>10	>10	>10
7	41	>10	>10	>10	>10
8	28	>10	>10	>10	>10
9	13	>10	1.2	>10	>10
10	16	>10	1.9	>10	>10
11	>250	>10	2.0	>10	>10
12	70	>10	>10	>10	>10
13	11	>10	>10	>10	>10
14	20	>10	>10	>10	>10
15	18	>10	0.10	>10	>10
16	18	>10	>10	>10	>10
17	87	>10	1.6	>10	>10
18	21	>10	1.3	>10	4.9
19	>250	>10	0.35	>10	>10
20	>250	>10	0.013	>10	>10
21	>250	>10	0.67	>10	6.8
22	>250	>10	0.65	>10	>10
23	20	>10	>10	>10	>10
Positive control	Ascorbic acid 23	Pargylin 4.6	Pargylin 0.22	Neostigmine 0.20	Neostigmine 7.1

view of ester or amide, the ester derivative (**18** or **19**) inhibited the enzyme more effectively than the corresponding amide derivative (**10** or **11**), respectively. Choi *et al.*[22] also reported that MAO-B inhibitory activities of the ester derivatives, (*E*)-3-(2-(trifluoromethyl)phenyl)-*N*-phenyl-2-propenester, (*E*)-3-(2-(trifluoromethyl)phenyl)-*N*-(4-methoxyphenyl)-2-propenester, (*E*)-3-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-2-propenester), were more potent than the corresponding amide derivatives, (*E*)-3-(2-(trifluoromethyl)phenyl)-*N*-phenyl-2-propenamide, (*E*)-3-(2-(trifluoromethyl)phenyl)-*N*-(4-methoxyphenyl)-2-propenamide, (*E*)-3-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-2-propenamide). Badavath *et al.*[21] recently reported feruloylphenetylamide as a selective MAO-B inhibitor, and found that *N*-phenethyl-3-(3-hydroxy-4-methoxyphenyl)acrylamide was the most potent MAO-B inhibitor. Also, their molecular docking study using *N*-phenethyl-3-(3-hydroxy-4-methoxyphenyl)-acrylamide and feruloylphenetylamide, demonstrated that the two compounds showed the same orientation at the MAO-B active site, however, the former inhibited MAO-B activity more potent than the latter. This suggested that the hydroxyl group on cinnamic acid moiety best fit at 3 position and the methoxy group at 4 position for the inhibition. From their results and ours, the synthesis of 3-hydroxy-4-methoxycinnamic acid phenethylester and its inhibitory activity to MAO-B should be tested in future. MAO-B inhibitor has been shown to be an important drug lead for several diseases.[8] Thus compound **20** may serve as such a drug lead.

AChE and BChE Inhibitory Activity

As can be seen in Table 1, no inhibitory activity to AChE was observed for all compounds at 10 μM. Kim and Lee reported AChE inhibitory activity of compound **11** using much higher concentration (IC$_{50}$=122 μM).[24] Only two compounds (**18**, **21**) inhibited BChE activity with similar IC$_{50}$ values to that of neostigmine used as a positive control. Compound **18** exhibited not only BChE inhibitory activity but also DPPH free radical scavenging or MAO-B inhibitory activity, suggesting the possibility of a multi-target-directed drug lead. Recent approaches in the development of drug leads for Alzheimer's disease have been multi-target-directed.[25,26]

This is the first report to identify *p*-coumaric acid phenethyl ester derivatives as potent and selective MAO-B inhibitors and multi-target-directed drug leads.

Conclusion

A series of cinnamic acid derivatives (**1**–**22**) were synthesized and their SARs were evaluated with respect to antioxidant activity, MAO-A, MAO-B, AChE, and BChE inhibitory activities. Among the synthesized compounds, compounds **1**–**10**, **12**–**18**, and **23**, which contained catechol, *o*-methoxyphenol or 5-hydroxyindole moieties, showed potent DPPH free radical scavenging activities. Compounds **9**–**11**, **15**, **17**–**22** showed potent and selective MAO-B inhibitory activities. Compound **20** was the most potent inhibitor for MAO-B (IC$_{50}$=13 nM). Compound **18** showed moderate BChE inhibitory activity and potent antioxidant and MAO-B inhibitory activities. In comparing cinnamic acid amides and esters, the amides had more potent DPPH free radical scavenging activities, while the esters showed stronger inhibitory activities against MAO-B and BChE. These results suggest that cinnamic acid derivatives, such as compound **18**, *p*-coumaric acid 3,4-dihydroxyphenethyl ester, and compound **20**, *p*-coumaric acid phenethyl ester, may be applicable as lead compounds for the development of novel MAO-B inhibitors and as candidate lead compounds for the prevention or treatment of Alzheimer's disease.

Experimental

Chemistry All reagents and solvents were purchased from commercial sources. Compounds **15** and **22** were purchased from Tokyo Chemical Industry Co., Tokyo, Japan. Compound **23** was purchased from Wako Pure Chemical Industries, Ltd., Tokyo, Japan. Analytical TLC was performed on silica-coated plates (silica gel 60 F-254; Merck Ltd., Tokyo, Japan) and visualized under UV light. Column chromatography was carried out using silica gel (Wakogel C-200; Wako Pure Chemical Industries, Ltd., Tokyo, Japan). All melting points were determined using a Yanagimoto micro-hot stage and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian 400-MR spectrometer using tetramethylsilane as the internal standard. MS spectra were measured using a JEOL JMS-700 spectrometer. Elemental analyses were carried out on a Yanaco CHN MT-6 elemental analyzer.

Preparation of Cinnamic Acid Amides (5–12) Cinnamic acid amides (**5**–**12**) were synthesized according to a modified previous procedure.[27] 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (2.1 mmol) and 1-hydroxybenzotriazole (HOBt) (2.1 mmol) were added to a solution of cinnamic acid derivatives (**Ib** or **Ic**, 2 mmol) in *N*,*N*-dimethylformamide (DMF) (2 mL) and CH_2Cl_2 (12 mL). The solution was stirred for 30 min at room temperature, and then the selected biogenic amines (2.0 mmol) and Et_3N (2.0 mmol) were added to the reaction mixture. The mixture was then stirred overnight at room temperature under argon atmosphere. The solvent was evaporated under reduced pressure and the residue was treated with water and extracted with ethyl acetate (AcOEt). The organic extract was washed successively with 10% citric acid solution, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 2) to give the title compound.

Preparation of Caffeoyl Amides (1–4) According to the general procedure for the preparation of cinnamic acid amides, 3,4-diallyloxy cinnamic acid (**IIa**)[28] and the biogenic amines (2.0 mmol) were treated with EDC (2.1 mmol), HOBt (2.1 mmol) and Et_3N (2.0 mmol), and then the residue was passed once through a short silica gel column (hexane : AcOEt = 1 : 2) and the solvent was evaporated. The obtained allyl protected compound (1.0 mmol) was dissolved in degassed anhydrated tetrahydrofuran (THF) (30 mL) and morpholine (20 mmol), and $Pd(PPh_3)_4$ (5 mol%) was added. The green mixture was stirred at 50°C (monitored by TLC) and concentrated under reduced pressure. The residue was treated with NH_4Cl solution and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 5) to give the title compound.

(2*E*)-3-(3,4-Dihydroxyphenyl)-*N*-[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]-2-propenamide (**1**)

Yield 42%. Pale gray solid. mp 105–108°C (hexane–AcOEt). ^{1}H-NMR (dimethylsulfoxide (DMSO)-d_6, 400 MHz) δ: 10.49 (1H, brs, H-1′), 9.21 (1H, brs, OH), 8.60 (1H, brs, OH), 8.61 (1H, brs, OH), 8.06 (1H, brt, *J*=5.6 Hz, NH), 7.24 (1H, d, *J*=15.7 Hz, H-β), 7.12 (1H, d, *J*=8.6 Hz, H-7′), 7.05 (1H, s, H-2′), 6.94 (1H, d, *J*=2.1 Hz, H-2), 6.84 (1H, d, *J*=2.3 Hz, H-4′), 6.83 (1H, dd, *J*=8.1, 2.1 Hz, H-6), 6.74 (1H, d, *J*=8.1 Hz, H-5), 6.59 (1H, dd, *J*=8.6, 2.3 Hz, H-6′), 6.33 (1H, d, *J*=15.7 Hz, H-α), 3.45–3.35 (2H, m, NCH_2), 2.77 (2H, t, *J*=7.5 Hz, CH_2). MS (electron ionization (EI)) *m/z* 338 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[16]

(2*E*)-3-(3,4-Dihydroxyphenyl)-*N*-[2-(3,4-dihydroxyphenyl)-ethyl]-2-propenamide (**2**)

Yield 70%. Ocher solid. mp 183–185°C (hexane–AcOEt) (lit. 180–182°C[29]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.05 (1H, brs, OH), 8.80 (1H, brs, OH), 8.02 (1H, brt, *J*=5.7 Hz, NH), 7.22 (1H, d, *J*=15.7 Hz, H-β), 6.93 (1H, d, *J*=2.0 Hz, H-2), 6.83 (1H, dd, *J*=8.1, 2.0 Hz, H-6), 6.73 (1H, d, *J*=8.1 Hz, H-5), 6.64 (1H, d, *J*=8.0 Hz, H-5′), 6.59 (1H, d, *J*=2.1 Hz, H-2′), 6.45 (1H, dd, *J*=8.0, 2.1 Hz, H-6′), 6.31 (1H, d, *J*=15.7 Hz, H-α), 3.35–3.25 (2H, m, NCH_2), 2.56 (1H, t, *J*=7.4 Hz, CH_2). MS (EI) *m/z* 315 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[9]

(2*E*)-3-(3,4-Dihydroxyphenyl)-*N*-[2-(4-hydroxyphenyl)-ethyl]-2-propenamide (**3**)

Yield 46%. Pale brown solid. mp 208–209°C (hexane–AcOEt) (lit. 206–208°C[9]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.02 (1H, brt, *J*=5.7 Hz, NH), 7.22 (1H, d, *J*=15.6 Hz, H-β), 7.01 (2H, d, *J*=8.4 Hz, H-2′ and H-6′), 6.93 (1H, d, *J*=2.0 Hz, H-2), 6.82 (1H, dd, *J*=8.1, 2.0 Hz, H-6), 6.73 (1H, d, *J*=8.1 Hz, H-5), 6.68 (2H, d, *J*=8.4 Hz, H-3′ and H-5′), 6.32 (1H, d, *J*=15.6 Hz, H-α), 3.36–3.26 (2H, m, NCH_2), 2.64 (1H, t, *J*=7.4 Hz, CH_2). MS (EI) *m/z* 299 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[9]

(2*E*)-3-(3,4-Dihydroxyphenyl)-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]-2-propenamide (**4**)

Yield 65%. Brown solid. mp 214–217°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.36 (1H, brt, *J*=5.6 Hz, NH), 7.27 (1H, d, *J*=15.7 Hz, H-β), 6.94 (1H, d, *J*=2.0 Hz, H-2), 6.86 (1H, d, *J*=1.8 Hz, H-2′), 6.84 (1H, dd, *J*=8.1, 2.0 Hz, H-6), 6.75–6.70 (2H, m, H-5 and H-5′), 6.68 (1H, dd, *J*=8.1, 1.8 Hz, H-6′), 6.38 (1H, d, *J*=15.7 Hz, H-α), 4.27 (2H, d, *J*=5.6 Hz, NCH_2), 3.74 (3H, s, OCH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 147.4, 147.3, 145.5, 145.4, 139.3, 130.2, 126.4, 120.5, 120.0, 118.4, 115.7, 115.2, 113.8, 111.9, 55.6, 42.2. HR-MS *m/z*: Calcd for $C_{17}H_{17}NO_5$ (M^+): 315.1107. Found: 315.1108.

(2*E*)-*N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-3-(4-hydroxy-3-methoxyphenyl)-2-propenamide (**5**)

Yield 57%. Pale violet solid. mp 117–120°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.49 (1H, d, *J*=2.4 Hz, H-1′), 9.41 (1H, brs, OH), 8.62 (1H, brs, OH), 8.06 (1H, brt, *J*=5.7 Hz, NH), 7.33 (1H, d, *J*=15.7 Hz, H-β), 7.13 (1H, d, *J*=8.6 Hz, H-7′), 7.12 (1H, d, *J*=1.9 Hz, H-2), 7.06 (1H, d, *J*=2.4 Hz, H-2′), 6.99 (1H, dd, *J*=8.1, 1.9 Hz, H-6), 6.85 (1H, d, *J*=2.3 Hz, H-4′), 6.79 (1H, d, *J*=8.1 Hz, H-5), 6.59 (1H, dd, *J*=8.6, 2.3 Hz, H-6′), 6.45 (1H, d, *J*=15.7 Hz, H-α), 3.80 (3H, s, OCH_3), 3.46–3.33 (2H, m, NCH_2), 2.78 (2H, t, *J*=7.5 Hz, CH_2). MS (EI) *m/z* 352 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[16]

(2*E*)-*N*-[2-(3,4-Dihydroxyphenyl)ethyl]-3-(4-hydroxy-3-methoxyphenyl)-2-propenamide (**6**)

Yield 56%. Pale yellow solid. mp 145–147°C (hexane–AcOEt) (lit. 144–146°C[29]). ^{1}H-NMR (DMSO-d_6, 400 MHz)

δ: 9.42 (1H, brs, OH), 8.72 (2H, brs, OH), 7.97 (1H, brt, J=5.7 Hz, NH), 7.30 (1H, d, J=15.7 Hz, H-β), 7.11 (1H, d, J=1.9 Hz, H-2), 6.98 (1H, dd, J=8.2, 1.9 Hz, H-6), 6.78 (1H, d, J=8.2 Hz, H-5), 6.64 (1H, d, J=7.9 Hz, H-5′), 6.59 (1H, d, J=2.1 Hz, H-2′), 6.46 (1H, dd, J=7.9, 2.1 Hz, H-5′), 6.43 (1H, d, J=15.7 Hz, H-α), 3.80 (3H, s, OCH_3), 3.35–3.26 (2H, m, NCH_2), 2.57 (1H, t, J=7.4 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.4, 148.4, 148.0, 145.3, 143.7, 139.0, 130.4, 126.6, 121.7, 119.4, 119.2, 116.1, 115.8, 115.7, 110.9, 55.7, 40.8, 34.9. HR-MS m/z: Calcd for $C_{18}H_{19}NO_5$ (M^+): 329.1263. Found: 329.1254. The ^{1}H-NMR spectrum was similar to that a previous report.[11)]

(2E)-3-(4-Hydroxy-3-methoxyphenyl)-N-[2-(4-hydroxyphenyl)ethyl]-2-propenamide (**7**)

Yield 58%. White solid. mp 143–145°C (hexane–AcOEt) (lit. 144–145°C[29)]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.38 (1H, brs, OH), 9.24 (1H, brs, OH), 7.98 (1H, brt, J=5.6 Hz, NH), 7.31 (1H, d, J=15.7 Hz, H-β), 7.11 (1H, d, J=2.0 Hz, H-2), 7.02 (2H, d, J=8.4 Hz, H-2′ and H-6′), 6.98 (1H, dd, J=8.1, 2.0 Hz, H-6), 6.78 (1H, d, J=8.1 Hz, H-5), 6.68 (2H, d, J=8.4 Hz, H-3′ and H-5′), 6.43 (1H, d, J=15.6 Hz, H-α), 3.80 (3H, s, OCH_3), 3.35–3.26 (2H, m, NCH_2), 2.64 (1H, t, J=7.4 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.3, 155.6, 148.2, 147.8, 138.8, 129.5, 129.5, 126.4, 121.5, 119.0, 115.6, 115.1, 110.7, 55.5, 40.7, 34.4. MS (EI) m/z 313 $[M]^+$. *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.78; H, 5.96; N, 4.48. The ^{1}H-NMR spectrum was similar to that a previous report.[10)]

(2E)-3-(4-Hydroxy-3-methoxyphenyl)-N-[(4-hydroxy-3-methoxyphenyl)methyl]-2-propenamide (**8**)

Yield 44%. Pale brown solid. mp 142–144°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.44 (1H, brs, OH), 8.85 (1H, brs, OH), 8.32 (1H, brt, J=5.7 Hz, NH), 7.35 (1H, d, J=15.7 Hz, H-β), 7.12 (1H, d, J=1.9 Hz, H-2), 6.99 (1H, dd, J=8.1, 1.9 Hz, H-6), 6.86 (1H, d, J=1.8 Hz, H-2′), 6.78 (1H, d, J=8.1 Hz, H-5), 6.72 (1H, d, J=8.0 Hz, H-5′), 6.68 (1H, dd, J=8.0, 1.8 Hz, H-6′), 6.50 (1H, d, J=15.7 Hz, H-α), 4.27 (2H, d, J=5.7 Hz, NCH_2), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 148.3, 147.8, 147.5, 145.5, 139.2, 130.2, 126.4, 121.5, 120.0, 118.9, 115.7, 115.2, 111.9, 110.8, 55.6, 55.5, 42.2. HR-MS m/z: Calcd for $C_{18}H_{19}NO_5$ (M^+): 329.1263. Found: 329.1247. *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.78; N, 4.26. Found: C, 65.43; H, 5.72; N, 4.23.

(2E)-N-[2-(5-Hydroxy-1H-indol-3-yl)ethyl]-3-(4-hydroxyphenyl)-2-propenamide (**9**)

Yield 82%. Pale gray solid. mp 200–203°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.47 (1H, d, J=2.4 Hz, H-1′), 8.60 (2H, brs, OH), 8.06 (1H, brt, J=5.6 Hz, NH), 7.37 (2H, d, J=8.6 Hz, H-2 and H-6), 7.31 (1H, d, J=15.7 Hz, H-β), 7.10 (1H, d, J=8.6 Hz, H-7′), 7.03 (1H, d, J=2.4 Hz, H-2′), 6.83 (1H, d, J=2.3 Hz, H-4′), 6.77 (2H, d, J=8.6 Hz, H-3 and H-5), 6.57 (1H, dd, J=8.6, 2.3 Hz, H-6′), 6.39 (1H, d, J=15.7 Hz, H-α), 3.43–3.32 (2H, m, NCH_2), 2.75 (2H, t, J=7.5 Hz, CH_2). MS (EI) m/z 322 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[16)]

(2E)-N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-(4-hydroxyphenyl)-2-propenamide (**10**)

Yield 72%. Pale yellow solid. mp 200–202°C (hexane–AcOEt) (lit. 204–206°C[29)]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.82 (1H, brs, OH), 8.72 (2H, brs, OH), 8.00 (1H, brt, J=5.7 Hz, NH), 7.38 (2H, d, J=8.6 Hz, H-2 and H-6), 7.30 (1H, d, J=15.7 Hz, H-β), 6.78 (2H, d, J=8.6 Hz, H-3 and H-5), 6.64 (1H, d, J=8.0 Hz, H-5′), 6.59 (1H, d, J=2.0 Hz, H-2′), 6.45 (1H, dd, J=8.0, 2.0 Hz, H-5′), 6.39 (1H, d, J=15.7 Hz, H-α), 3.29 (2H, m, NCH_2), 2.57 (1H, t, J=7.4 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 158.7, 145.0, 143.5, 138.5, 130.2, 129.1, 125.9, 119.2, 118.7, 115.9, 115.7, 115.4, 40.7, 34.7. HR-MS m/z: Calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1158, Found: 299.1174. The ^{1}H-NMR spectrum was similar to that a previous report.[11)]

(2E)-3-(4-Hydroxyphenyl)-N-[2-(4-hydroxyphenyl)ethyl]-2-propenamide (**11**)

Yield 63%. White solid. mp 245–248°C (hexane–AcOEt) (lit. 247–248°C[30)]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.84 (1H, brs, OH), 9.18 (1H, brs, OH), 8.01 (1H, brt, J=5.6 Hz, NH), 7.38 (2H, d, J=8.6 Hz, H-2 and H-6), 7.31 (1H, d, J=15.7 Hz, H-β), 7.01 (2H, d, J=8.5 Hz, H-2′ and H-6′), 6.78 (2H, d, J=8.6 Hz, H-3 and H-5), 6.67 (2H, d, J=8.5 Hz, H-3′ and H-5′), 6.39 (1H, d, J=15.6 Hz, H-α), 3.35–3.27 (2H, m, NCH_2), 2.63 (1H, t, J=7.4 Hz, CH_2). MS (EI) m/z 283 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[26)]

(2E)-N-[(4-Hydroxy-3-methoxyphenyl)methyl]-3-(4-hydroxyphenyl)-2-propenamide (**12**)

Yield 75%. White solid. mp 173–175°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.84 (1H, brs, OH), 8.86 (1H, brs, OH), 8.34 (1H, brt, J=5.8 Hz, NH), 7.38 (2H, d, J=8.6 Hz, H-2 and H-6), 7.35 (1H, d, J=15.7 Hz, H-β), 6.86 (1H, d, J=1.8 Hz, H-2′), 6.78 (2H, d, J=8.6 Hz, H-3 and H-5), 6.72 (1H, d, J=8.0 Hz, H-5′), 6.68 (1H, dd, J=8.0, 1.8 Hz, H-6′), 6.46 (1H, d, J=15.7 Hz, H-α), 4.27 (2H, d, J=5.8 Hz, NCH_2), 3.74 (3H, s, OCH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 158.8, 147.4, 145.5, 138.9, 130.2, 129.2, 125.9, 119.9, 118.6, 115.7, 115.2, 111.9, 55.6, 42.1. HR-MS m/z: Calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1158. Found: 299.1166. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.23; H, 5.69; N, 4.68. Found: C, 67.98; H, 5.73; N, 4.69.

Preparation of Cinnamic Acid Esters (13–22) Cinnamic acid esters (**13**–**22**) were synthesized according to a modified previous procedure.[31)] To a mixture of cinnamic acid derivatives (**Ia**–**d**, 3.0 mmol) and the appropriate alcohol (2.0 mmol) in dry tetrahydrofuran (6 mL) were added triphenylphosphine (3.0 mmol) and diisopropyl azodicarboxylate (DIAD) (3.0 mmol). The reaction mixture was stirred for 48 h at room temperature and the whole mixture was extracted with AcOEt and saturated $NaHCO_3$ solution, and the organic extract was washed with brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was then purified by silica gel column chromatography (hexane : AcOEt=2 : 1) to give the title compound.

(2E)-3-(3,4-Dihydroxyphenyl)-2-propenoic Acid 2-(3,4-dihydroxyphenyl)ethyl Ester (**13**)

Yield 73%. Pale yellow solid. mp 137–139°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.90 (4H, brs, OH), 7.44 (1H, d, J=15.9 Hz, H-β), 7.02 (1H, d, J=2.0 Hz, H-2), 6.98 (1H, dd, J=8.2, 2.0 Hz, H-6), 6.74 (1H, d, J=8.2 Hz, H-5), 6.64 (1H, d, J=8.0 Hz, H-5′), 6.63 (1H, d, J=2.1 Hz, H-2′), 6.48 (1H, dd, J=8.0, 2.1 Hz, H-6′), 6.20 (1H, d, J=15.9 Hz, H-α) 4.20 (2H, t, J=7.0 Hz, OCH_2), 2.74 (2H, t, J=7.0 Hz, CH_2). MS (FAB) m/z 316 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[32)]

(2*E*)-3-(3,4-Dihydroxyphenyl)-2-propenoic Acid 2-(4-Hydroxyphenyl)ethyl Ester (**14**)

Yield 33%. Pale brown solid. mp 186–189°C (hexane–AcOEt) (lit. 184–186°C[33]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.25 (1H, brs, OH), 7.46 (1H, d, J=15.9 Hz, H-β), 7.07 (2H, d, J=8.4 Hz, H-2′ and H-6′), 7.05 (1H, d, J=2.1 Hz, H-2), 7.00 (1H, dd, J=8.2, 2.1 Hz, H-6), 6.76 (1H, d, J=8.1 Hz, H-5), 6.69 (2H, d, J=8.4 Hz, H-3′ and H-5′), 6.24 (1H, d, J=15.9 Hz, H-α), 4.24 (2H, t, J=7.0 Hz, OCH_2), 2.83 (2H, t, J=7.0 Hz, CH_2). MS (EI) *m/z* 300 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[33]

(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic Acid 2-(3,4-Dihydroxyphenyl)ethyl Ester (**16**)

Yield 70%. White solid. mp 135–137°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.56 (1H, brs, OH), 8.75 (2H, brs, OH), 7.50 (1H, d, J=15.9 Hz, H-β), 7.30 (1H, d, J=2.0 Hz, H-2), 7.09 (1H, dd, J=8.1, 1.9 Hz, H-6), 6.77 (1H, d, J=8.1 Hz, H-5), 6.64 (1H, d, J=8.0 Hz, H-5′), 6.64 (1H, d, J=2.0 Hz, H-2′), 6.49 (1H, dd, J=8.0, 2.0 Hz, H-6′), 6.42 (1H, d, J=15.9 Hz, H-α), 4.22 (2H, t, J=7.0 Hz, OCH_2), 3.80 (3H, s, OCH_3), 2.75 (2H, t, J=7.0 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 166.6, 149.4, 147.9, 145.1, 145.0, 143.7, 128.6, 125.5, 123.2, 119.5, 116.2, 115.5, 115.4, 114.4, 111.1, 64.7, 55.7, 33.9. HR-MS *m/z*: Calcd for $C_{18}H_{19}O_6$ (M^+): 331.1182. Found: 331.1190. The ^{1}H-NMR spectrum was similar to that a previous report.[34]

(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic Acid 2-(4-Hydroxyphenyl)ethyl Ester (**17**)

Yield 14%. Pale yellow semisolid. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.28 (1H, brs, OH), 7.50 (1H, d, J=15.7 Hz, H-β), 7.30 (1H, d, J=2.0 Hz, H-2), 7.10 (1H, dd, J=8.0, 2.0 Hz, H-6), 7.06 (2H, d, J=8.3 Hz, H-2′ and H-6′), 6.78 (1H, d, J=8.0 Hz, H-5), 6.68 (2H, d, J=8.3 Hz, H-3′ and H-5′), 6.44 (1H, d, J=15.7 Hz, H-α), 4.25 (2H, t, J=7.0 Hz, OCH_2), 3.80 (3H, s, OCH_3), 2.82 (2H, t, J=7.0 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 166.6, 155.8, 149.3, 147.9, 145.1, 129.8, 128.0, 125.5, 123.2, 115.4, 115.2, 114.4, 111.1, 64.7, 55.7, 33.7. HR-MS *m/z*: Calcd for $C_{18}H_{18}O_5$ (M^+): 314.1154. Found: 314.1155. The ^{1}H-NMR spectrum was similar to that a previous report.[34]

(2*E*)-3-(4-Hydroxyphenyl)-2-propenoic Acid 2-(3,4-Dihydroxyphenyl)ethyl Ester (**18**)

Yield 73%. White solid. mp 188–190°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.00 (1H, brs, OH), 8.73 (2H, brs, OH), 7.54 (2H, d, J=8.6 Hz, H-2 and H-6), 7.52 (1H, d, J=15.8 Hz, H-β), 6.77 (2H, d, J=8.6 Hz, H-3 and H-5), 6.63 (1H, d, J=8.0 Hz, H-5′), 6.63 (1H, d, J=2.0 Hz, H-2′), 6.48 (1H, dd, J=8.0, 2.0 Hz, H-6′), 6.35 (1H, d, J=15.8 Hz, H-α), 4.21 (2H, t, J=7.0 Hz, OCH_2), 2.74 (2H, t, J=7.0 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 166.6, 159.9, 145.1, 144.8, 143.8, 130.4, 128.7, 125.1, 119.5, 116.2, 115.8, 115.5, 114.1, 64.7, 33.9. MS (FAB) *m/z* 300 $[M]^+$. *Anal.* Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.94; H, 5.42. The ^{1}H-NMR spectrum was similar to that a previous report.[34]

(2*E*)-3-(4-Hydroxyphenyl)-2-propenoic Acid 2-(4-Hydroxyphenyl)ethyl Ester (**19**)

Yield 40%. White solid. mp 228–231°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.28 (H, brs, OH), 7.54 (2H, d, J=8.3 Hz, H-2 and H-6), 7.52 (1H, d, J=16.0 Hz, H-β), 7.05 (2H, d, J=8.3 Hz, H-2′ and H-6′), 6.77 (2H, d, J=8.3 Hz, H-3 and H-5), 6.67 (2H, d, J=8.3 Hz, H-3′ and H-5′), 6.35 (1H, d, J=16.0 Hz, H-α), 4.23 (2H, t, J=7.1 Hz, OCH_2), 2.81 (2H, t, J=7.1 Hz, CH_2). MS (EI) *m/z* 284 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[34]

(2*E*)-3-(4-Hydroxyphenyl)-2-propenoic Acid 2-Phenylethyl Ester (**20**)

Yield 40%. White solid. mp 86–88°C (hexane–AcOEt) (lit. 90–92°C[14]). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.01 (1H, brs, OH), 7.55 (2H, d, J=8.6 Hz, H-2 and H-6), 7.54 (1H, d, J=16.0 Hz, H-β), 7.34–7.20 (5H, m, H-2′, H-3′, H-4′, H-5′ and H-6′), 6.79 (2H, d, J=8.6 Hz, H-3 and H-5), 6.37 (1H, d, J=16.0 Hz, H-α), 4.33 (2H, t, J=6.9 Hz, OCH_2), 2.96 (2H, t, J=6.9 Hz, CH_2). MS (EI) *m/z* 268 $[M]^+$. The ^{1}H-NMR spectrum was similar to that a previous report.[14]

(2*E*)-3-Phenyl-2-propenoic Acid 2-(4-Hydroxyphenyl)ethyl Ester (**21**)

Yield 76%. White solid. mp 138–140°C (hexane–AcOEt). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.73–7.66 (2H, m, Ph), 7.62 (1H, d, J=16.0 Hz, H-β), 7.43–7.38 (3H, m, Ph), 7.06 (2H, d, J=8.3 Hz, H-2′ and H-6′), 6.68 (2H, d, J=8.3 Hz, H-3′ and H-5′), 6.60 (1H, d, J=16.0 Hz, H-α), 4.27 (2H, t, J=7.0 Hz, OCH_2), 2.82 (2H, t, J=7.0 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 166.2, 155.9, 144.6, 1340, 130.5, 129.8, 128.9, 128.4, 127.9, 118.0, 115.2, 65.0, 33.6. HR-MS *m/z*: Calcd for $C_{17}H_{16}O_3$ (M^+): 268.1099. Found: 268.1096. *Anal.* Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.84; H, 5.82.

Biological Assays Recombinant human monoamine oxidase A (MAO-A), MAO-B, acetylcholinesterase, horse serum butyrylcholinesterase, pargyline and kynuramine were purchased from Sigma-Aldrich Japan Co., Tokyo, Japan. DPPH free radical, neostigmine and 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) were purchased from Tokyo Chemical Industry Co., Tokyo, Japan.

DPPH Free Radical Scavenging Assay DPPH free radical scavenging activity was measured according to the method of Nile *et al.*[35] with minor modifications. Briefly, 180 μL of 100 μM DPPH free radical solution in MeOH was mixed with 20 μL of various concentrations of the sample solution in MeOH. The absorbance of the mixture was measured at 517 nm using a microplate reader (Molecular Devices SPECTRA MAX M2). The sample solution was replaced with MeOH as a control. Ascorbic acid was used as a positive control.

MAO Inhibitory Assay MAO inhibitory activity was assayed using the method of Novaroli *et al.*[36] with minor modifications. Briefly, 140 μL of 0.1 M potassium phosphate buffer (pH 7.4), 8 μL of 0.75 mM kynuramine, and 2 μL of DMSO inhibitor solution (final DMSO concentration of 1% v/v) were preincubated at 37°C for 10 min. Diluted human recombinant enzyme (50 μL) was then added to obtain a final protein concentration of 0.0075 mg/mL (MAO-A) or 0.015 mg/mL (MAO-B) in the assay mixture. Further incubation was carried out at 37°C and the reaction was stopped after 20 min by the addition of 75 μL of 2 M NaOH. The fluorescence at *Ex* 310 nm/*Em* 400 nm, due to the production of 4-quinolinol by MAO, was measured with a micro-plate reader (Molecular Devices SPECTRA MAX M2). The sample solution was replaced with DMSO as a control. Pargyline was used as a positive control.

AChE and BChE Inhibitory Assays AChE and BChE inhibitory activity were assayed using the method of Oboh *et al.*[37] Briefly, 2 μL of cinnamic acid derivatives dissolved in DMSO, 6 μL of 0.06 mg/mL acetylthiocholine or 0.12 mg/mL butyrylthiocholine dissolved in 0.1 M phosphate buffer (pH 8.0), 180 μL of the buffer, 6 μL of 0.3 mM DTNB dissolved in the buffer, 6 μL of 0.15 U/mL AChE or 0.075 U/mL BChE dissolved in the buffer were added and mixed in a 96-well plate. The enzyme activity was determined as the change in absorbance at 412 nm every 5 min during 30 min with a micro-plate reader (Molecular Devices SPECTRA MAX M2). The sample solution was replaced with DMSO as a control. Neostigmine was used as a positive control.

Conflict of Interest The authors declare no conflict of interest.

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