Regular Article

Synthesis and Biological Evaluation of Piperic Acid Amides as Free Radical Scavengers and α-Glucosidase Inhibitors

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A series of piperic acid amides (4–24, 29, 30) were synthesized and their 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and α-glucosidase inhibitory activities were evaluated. Among the synthesized compounds, the amides 11, 13 and 15, which contain *o*-methoxyphenol, catechol or 5-hydroxyindole moieties, showed potent DPPH free radical scavenging activity (11: EC_{50} 140 μM; 13: EC_{50} 28 μM; 15: EC_{50} 20 μM). The amides 10, 18 and 23 showed higher inhibitory activity of α-glucosidase (10: IC_{50} 21 μM; 18: IC_{50} 21 μM; 23: IC_{50} 12 μM). These data suggest that the hydrophobicity of the conjugated amines is an important determinant of α-glucosidase inhibitory activity. In addition, the amides 13 and 15 showed both potent DPPH free radical scavenging activity and α-glucosidase inhibitory activity (13: IC_{50} 46 μM; 15: IC_{50} 46 μM). This is the first report identifying the DPPH free radical scavenging and α-glucosidase inhibitory activities of piperic acid amides and suggests that these amides may serve as lead compounds for the development of novel α-glucosidase inhibitors with antioxidant activity.

Key words piperine; α-glucosidase inhibitor; antioxidant; structure–activity relationship

Hydroxycinnamic acid amides (phenylpropanoid amides) are found at low levels in a wide range of plants species. These amides are synthesized by the condensation of hydroxycinnamoyl-CoA thioesters with biogenic amines. As an example, the biosynthesis of tyramine and serotonin derivatives are catalyzed by the action of tyramine- and serotonin-*N*-hyroxycinnamoyltransferase, respectively.[1] Recent studies have reported the tyrosinase inhibitory effects of synthetic hydroxycinnamic acid amides, derived from coupling of caffeic acid and its derivatives with biogenic amines, such as tyramine, dopamine, and serotonin.[2–5] In addition, serotonin derivatives have a number of biological effects, such as α-glucosidase inhibition,[6] antioxidative activity,[7] and cyclooxygenase-2 (COX-2) inhibition.[8]

Piperine (1-piperoyl piperidine, 1-[(2*E*,4*E*)-5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine) is the major alkaloid present in the fruit of *Piper nigrum* L. The piperine structure consists of three important components, an aromatic ring moiety, a side chain with conjugated double bonds, and a basic piperidine moiety attached through an amide linkage to a side chain. Piperine can be synthesized from piperoyl-CoA, which is derived from a cinnamoyl-CoA precursor, and piperidine.[9,10] The reaction forming an acid-amide linkage is analogous to hydroxycinnamic acid amide biosynthesis.

The pungency of the piperine is generated by activating heat and acid-sensing transient receptor potential vanilloid receptors (TRPV1) on pain-sensing neurons, similar to capsaicin, a decylenic acid amide of vanillylamine.[11] Several beneficial biological and pharmacological properties of piperine and its derivatives have been reported, including antioxidant,[12] anti-inflammatory,[13] antitumor,[14,15] monoamine oxidase inhibitory[16] effects, and the enhancement of the bioavailability of some therapeutic drugs, possibly by inhibiting P-glycoprotein-mediated cellular efflux and cytochrome P450 (CYP) 3A4 activity.[17,18] Piperine also has been demonstrated to weakly inhibit α-glucosidase.[19] Recently, Singh *et al.* reported that piperine analogues, such as piperoyl-amino acid conjugates, exhibited greater biological activity than piperine.[20] This result suggests that structural changes in the amine moiety of piperine can increase its biological activity. However, studies of the biological activity of piperic acid amides have been limited to the aforementioned research areas.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from insufficiency of secretion or action of endogenous insulin. α-Glucosidase has been recognized as a therapeutic target for modulation of postprandial hyperglycemia. On the other hand, the accumulated evidence suggests that diabetic patients are under oxidative stress and that oxidative stress plays a major role in the pathogenesis of diabetes mellitus. Recently, several researchers have evaluated α-glucosidase inhibitors possessing free-radical scavenging activity.[21–27]

In order to further explore the biological activity of piperic acid amides, a series of piperine derivatives were synthesized. In this study, the effects of synthetic piperic acid amides (Fig. 1) on 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and α-glucosidase inhibitory activity were evaluated and the structure–activity relationships of the piperic acid amides were discussed.

Results and Discussion

Chemistry Several piperic acid amides (**4**–**24**) were synthesized by condensation of the acid chloride of piperic acid, derived from piperic acid (**2**) and oxalyl chloride, with selected amines, including the biogenic amines (Chart 1). Satisfactory yields were obtained in all cases. Piperic acid (**2**) was prepared by alkaline hydrolysis of piperine (**1**), by means of a previous procedure,[20] with modifications. Piperic acid amides (**29** and **30**) with aminoalkyl groups were synthesized by the condensation of the acid chloride (**3**) with the corresponding mono-Boc-diamines (**26** and **28**) followed by a deprotection step. Chemical structures of the piperic acid amides used in

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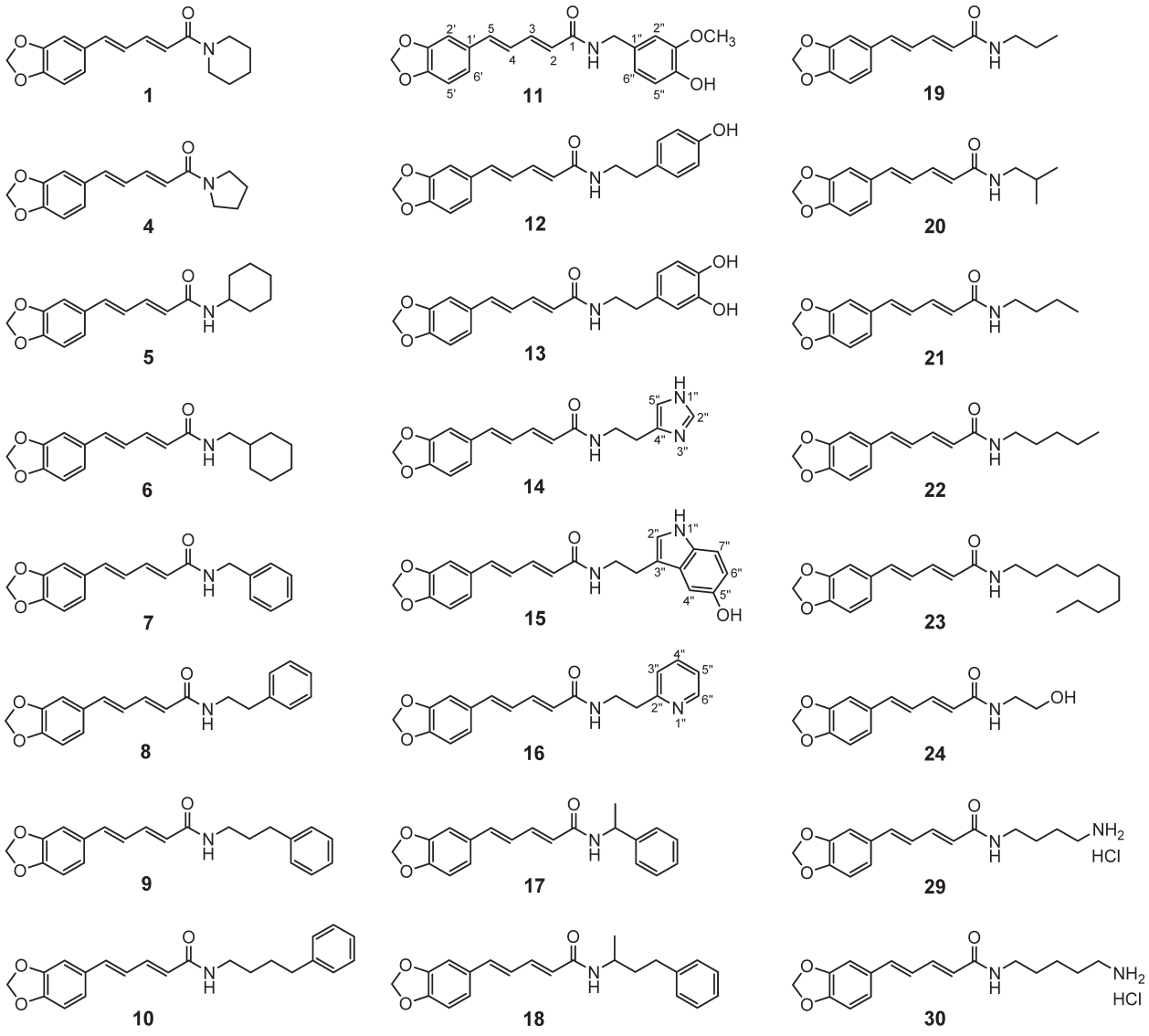
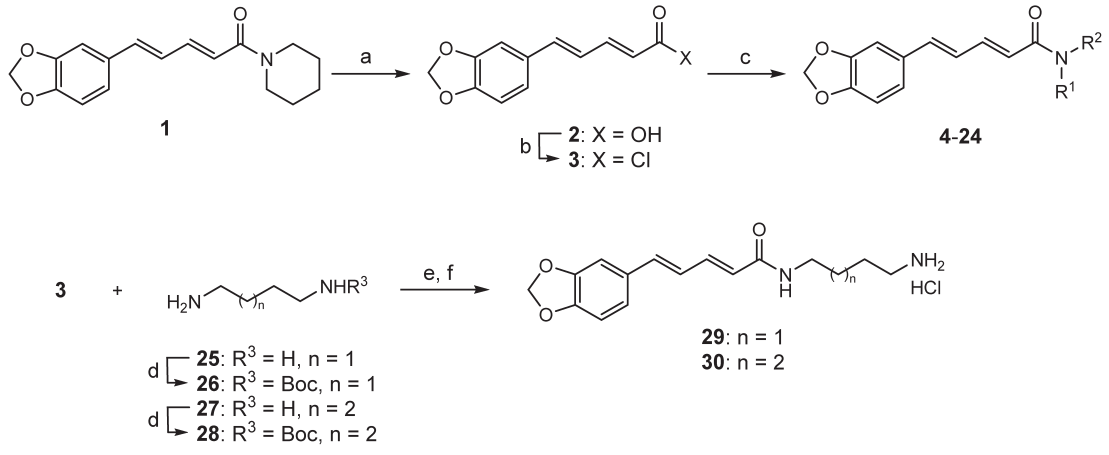


Fig. 1. Chemical Structures of the Piperic Acid Amides Used in This Study



Reagents and conditions: (a) KOH, EtOH, reflux; (b) $(COCl)_2$, CH_2Cl_2; (c) Amine (R^1R^2NH), Et_3N, CH_2Cl_2 or DMF; (d) $(Boc)_2O$, MeOH; (e) Et_3N, CH_2Cl_2; (f) TFA and then 2 M HCl–MeOH (1 : 1).

Chart 1. Protocol for the Synthesis of Piperic Acid Amides **4**–**24**, **29**, **30**

this study are shown in Fig. 1.

Biological Activity All synthesized compounds were evaluated for their DPPH free radical scavenging and α-glucosidase inhibitory activities. As shown in Table 1, three piperic acid amides, **11**, **13**, **15**, exhibited measurable DPPH free radical scavenging activity. In particular, amides **13** and **15** exhibited potent DPPH free radical scavenging activity, with EC_{50} values of 28 μM and 20 μM, respectively. Amide **11**, which contains an *o*-methoxyphenol moiety, also exhibited high activity (EC_{50}=140 μM). On the other hand, all other compounds tested did not exhibit DPPH free radical scavenging activity. It is well known that phenolic hydroxyl groups are important for DPPH free radical scavenging activity. Although **12** did not possess DPPH free radical scavenging activity, addition of a hydroxyl group at the *ortho* position of the phenolic hydroxyl group in **12**, to produce amide **13**, increased the DPPH free radical scavenging activity. This effect of *ortho* modification was consistent with a previous report.[28] The potent activity of **15** was also consistent with a previous report indicating that serotonin derivatives had a strong DPPH free radical scavenging activites.[6]

α-Glucosidase inhibitory activity of the piperic acid amides (Table 1) was determined, with 12 of the 24 tested piperic acid amides displaying various degrees of potency. Amide **23** was the most potent inhibitor (IC_{50}=12 μM). Increasing methylene chain lengths of the conjugated amines was associated with increased inhibitory activity: **5** and **6** (IC_{50}; **5**: >100 μM, **6**: 33 μM), **7** to **10** (IC_{50}; **7**: 41 μM, **8**: 30 μM, **9**: 29 μM, **10**: 21 μM), **17** and **18** (IC_{50}; **17**: 46 μM, **18**: 21 μM), and **19** to **23** (IC_{50}; **19**, **20**, **21**: >100 μM, **22**: 41 μM, **23**: 12 μM). This data suggests that the hydrophobicity of the conjugated amines is an important determinant of α-glucosidase inhibitory activity. It was also found that reducing hydrophobicity resulted in reduced α-glucosidase inhibition, such as the introduction of a hydroxyl group (**8** *vs.* **12**, **13**), introduction of hydroxyl and methoxy groups (**7** *vs.* **11**), introduction or substitution of amino group (**22** *vs.* **29**, **30**), and substitution of a phenyl group to pyridyl group (**8** *vs.* **16**).

Table 1. DPPH Free Radical Scavenging and α-Glucosidase Inhibitory Activities of Piperic Acid Amides

Compound	DPPH radical scavenging activity EC_{50} (μM)	α-Glucosidase inhibition IC_{50} (μM)
1	>250	>100
4	>250	>100
5	>250	>100
6	>250	33
7	>250	41
8	>250	30
9	>250	29
10	>250	21
11	140	>100
12	>250	40
13	28	46
14	>250	>100
15	20	46
16	>250	>100
17	>250	46
18	>250	21
19	>250	>100
20	>250	>100
21	>250	>100
22	>250	41
23	>250	12
24	>250	>100
29	>250	>100
30	>250	>100
Ascorbic acid	12	—
Acarbose	—	900

Interestingly, the amides **13** and **15** showed potent activity toward both DPPH free radical scavenging and α-glucosidase inhibition. Accumulating evidence suggests that diabetic patients experience persistent oxidative stress and that oxidative stress plays a major role in the pathogenesis of diabetes mellitus.[29] Piperic acid amides, such as **13** and **15**, may serve as lead compounds for the development of novel α-glucosidase inhibitors with anti-oxidative activity.

Conclusion

A series of piperic acid amides (**4**–**24**, **29**, **30**) were synthesized and evaluated for their DPPH free radical scavenging and α-glucosidase inhibitory activities. As a result, the amides **11**, **13** and **15** showed potent DPPH free radical scavenging activity. The amides **10, 18** and **23** showed higher inhibitory activity of α-glucosidase. The data suggests that the hydrophobicity of the conjugated amines is an important determinant of α-glucosidase inhibitory activity. In addition, the amides **13** and **15** showed both potent DPPH free radical scavenging activity and α-glucosidase inhibitory activity. This is the first report to assess the DPPH free radical scavenging and α-glucosidase inhibitory activities of piperic acid amides. These results suggest that piperic acid amides, such as **13** and **15**, may serve as lead compounds for the development of novel α-glucosidase inhibitors having anti-oxidative activity.

Experimental

Chemistry All reagents and solvents were purchased from commercial sources. Analytical thin-layer chromatography was performed on silica-coated plates (silica gel 60 F-254, Merck) and visualized under UV light. Column chromatography was carried out using silica gel (Wakogel C-200, Wako Pure Chemical Industries, Ltd., Osaka, Japan). All melting points were determined using a Yanagimoto micro-hot stage and are uncorrected. IR spectra were recorded on a Shimadzu IRAffinity-1 spectrometer with KBr pellets. ^{1}H-NMR 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.

Procedure for Preparation of 5-(3,4-Methylenedioxyphenyl)-2*E*,4*E*-pentadienoic Acid (Piperic Acid, 2) A solution of piperine (5.14 g, 18.0 mmol), purchased from Wako Pure Chemical Industries, Ltd., in ethanol (220 mL) was refluxed for 22 h in the presence of KOH (45 g). After completion of hydrolysis, the solvent was evaporated under reduced pressure. The resulting reaction mixture was suspended in water (100 mL) and acidified with 4 N HCl to pH <1. The resultant pale brown precipitate was collected by filtration, washed with cold water and recrystallized from methanol

to give crystals of piperic acid (**2**, 3.2 g, 82%). Pale brown solid. mp 225–226°C (lit.[20] 212–215°C). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.31–7.24 (1H, m, H-3), 7.22 (1H, d, J=1.6 Hz, H-2′), 6.99 (1H, dd, J=8.0, 1.6 Hz, H-6′), 6.98–6.93 (2H, m, H-4 and H-5), 6.91 (1H, d, J=8.0 Hz, H-5′), 6.03 (2H, s, –OCH_2O–), 5.90 (1H, d, J=15.2 Hz, H-2). MS (electron ionization (EI)) m/z: 218 $[M]^+$.

General Procedure for Preparation of Piperic Acid Amides (4–24) Oxalyl chloride (1.27 g, 10 mmol) was added to a mixture of piperic acid (218 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for 3 h. The solvent and excess oxalyl chloride was then evaporated under reduced pressure. The crude acid chloride generated was dissolved in CH_2Cl_2 or *N*,*N*-dimethylformamide (DMF) (2 mL), and was added dropwise to a mixture of the appropriate amine or its hydrochloride salt (1.2 mmol) and Et_3N (808 mg, 8 mmol) in CH_2Cl_2 or DMF (5 mL) under ice-cooling. The reaction mixture was stirred for 5 h at room temperature. Ice-water was added to the mixture, which was subsequently extracted with $CHCl_3$. 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 ($CHCl_3$: MeOH : aq. NH_3=100 : 1 : 0.1) to give the corresponding piperic acid amides.

5-(3,4-Methylenedioxyphenyl)-1-(1-pyrrolidinyl)-2*E*,4*E*-pentadien-1-one (**4**) Yield 90%. Colorless solid. mp 147–148°C. IR (KBr) cm^{-1}: 1637, 1593, 1500, 1251. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.21 (1H, dd, J=14.7, 10.0 Hz, H-3), 7.20 (1H, d, J=1.7 Hz, H-2′), 6.98 (1H, dd, J=8.0, 1.7 Hz, H-6′), 6.98 (1H, dd, J=15.6, 10.0 Hz, H-4), 6.91 (1H, d, J=8.0 Hz, H-5′), 6.89 (1H, d, J=15.6 Hz, H-5), 6.42 (1H, d, J=14.7 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 3.52 (2H, t, J=6.7 Hz, CH_2), 3.36 (2H, t, J=6.7 Hz, CH_2), 1.94–1.86 (2H, m, CH_2), 1.82–1.74 (2H, m, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 163.6, 147.9, 147.8, 140.9, 138.1, 130.8, 125.5, 122.6, 122.3, 108.5, 105.5, 101.3, 45.9, 45.5, 25.7, 23.9. MS (EI) m/z: 271 $[M]^+$. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.57; H, 6.37; N, 5.11.

N-Cyclohexyl-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**5**) Yield 71%. Pale orange solid. mp 207–210°C. IR (KBr) cm^{-1}: 3308, 1644, 1608, 1540, 1255. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.90 (1H, d, J=7.9 Hz, NH), 7.25 (1H, d, J=1.6 Hz, H-2′), 7.13 (1H, dd, J=15.0, 9.8 Hz, H-3), 6.98 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.90 (1H, d, J=8.1 Hz, H-5′), 6.90 (1H, dd, J=15.4, 9.8 Hz, H-4), 6.83 (1H, d, J=15.4 Hz, H-5), 6.07 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 3.66–3.55 (1H, m, NCH), 1.80–1.52 (5H, m, CH_2), 1.37–1.05 (5H, m, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 164.1, 147.9, 147.6, 139.1, 137.6, 130.9, 125.3, 124.9, 122.6, 108.4, 105.6, 101.2, 47.5, 32.5, 25.3, 24.6. MS (EI) m/z: 299 $[M]^+$. *Anal.* Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.08; H, 7.09; N, 4.68.

N-(Cyclohexylmethyl)-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**6**) Yield 83%. Pale yellow solid. mp 164–166°C. IR (KBr) cm^{-1}: 3328, 1644, 1606, 1540, 1503, 1259. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.00 (1H, br t, J=5.9 Hz, NH), 7.25 (1H, d, J=1.6 Hz, H-2′), 7.13 (1H, dd, J=15.0, 10.0 Hz, H-3), 6.98 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.90 (1H, d, J=8.1 Hz, H-5′), 6.90 (1H, dd, J=15.5, 10.0 Hz, H-4), 6.83 (1H, d, J=15.5 Hz, H-5), 6.10 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 2.96 (2H, t, J=5.9 Hz, NCH_2), 1.70–1.56 (5H, m, CH_2), 1.46–1.34 (1H, m, CH_2), 1.24–1.06 (3H, m, CH_2), 0.94–0.81 (2H, m, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 147.9, 147.7, 139.1, 137.7, 130.9, 125.3, 124.7, 122.6, 108.4, 105.6, 101.2, 44.9, 37.5, 30.5, 26.0, 25.4. MS (EI) m/z: 313 $[M]^+$. *Anal.* Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.57; H, 7.37; N, 4.48.

5-(3,4-Methylenedioxyphenyl)-*N*-(phenylmethyl)-2*E*,4*E*-pentadienamide (**7**) Yield 79%. Pale yellow solid. mp 184–187°C. IR (KBr) cm^{-1}: 3283, 1642, 1608, 1546, 1501, 1255. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.56 (1H, brt, J=5.9 Hz, NH), 7.35–7.30 (2H, m, Ph), 7.29–7.22 (4H, m, H-2′, Ph), 7.20 (1H, dd, J=15.5, 10.4 Hz, H-4), 6.99 (1H, dd, J=8.0, 1.7 Hz, H-6′), 6.94 (1H, dd, J=15.5, 10.4 Hz, H-4), 6.90 (1H, d, J=8.0 Hz, H-5′), 6.87 (1H, d, J=15.5 Hz, H-5), 6.15 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 4.36 (2H, d, J=5.9 Hz, NCH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 147.9, 147.7, 139.7, 139.5, 138.0, 130.8, 128.3, 127.3, 126.8, 125.2, 124.2, 122.7, 108.4, 105.6, 101.2, 42.2. MS (EI) m/z: 307 $[M]^+$. *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.57; N, 4.56. Found: C, 74.00; H, 5.51; N, 4.31.

5-(3,4-Methylenedioxyphenyl)-*N*-(2-phenylethyl)-2*E*,4*E*-pentadienamide (**8**) Yield 72%. Pale yellow solid. mp 168–171°C. IR (KBr) cm^{-1}: 3285, 1641, 1615, 1603, 1540, 1502, 1261. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.15 (1H, brt, J=5.6 Hz, NH), 7.32–7.27 (2H, m, Ph), 7.26 (1H, d, J=1.6 Hz, H-2′), 7.24–7.17 (3H, m, Ph), 7.14 (1H, dd, J=15.0, 10.1 Hz, H-3), 6.99 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.92 (1H, dd, J=15.5, 10.1 Hz, H-4), 6.91 (1H, d, J=8.1 Hz, H-5′), 6.85 (1H, d, J=15.5 Hz, H-5), 6.07 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 3.39–3.34 (2H, m, NCH_2), 2.75 (2H, t, J=7.4 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 147.9, 147.7, 139.5, 139.3, 137.9, 130.9, 128.6, 128.3, 126.1, 125.3, 124.5, 122.7, 108.5, 105.6, 101.3, 40.3, 35.2. MS (EI) m/z: 321 $[M]^+$. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.55; H, 5.90; N, 4.37.

5-(3,4-Methylenedioxyphenyl)-*N*-(3-phenylpropyl)-2*E*,4*E*-pentadienamide (**9**) Yield 78%. Pale yellow solid. mp 161–164°C. IR (KBr) cm^{-1}: 3287, 1643, 1615, 1607, 1555, 1502, 1252. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.09 (1H, br t, J=5.6 Hz, NH), 7.32–7.25 (2H, m, Ph), 7.27–7.25 (1H, m, H-2′), 7.23–7.15 (3H, m, Ph), 7.14 (1H, dd, J=15.0, 10.2 Hz, H-3), 6.99 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.92 (1H, dd, J=15.5, 10.2 Hz, H-4), 6.91 (1H, d, J=8.1 Hz, H-5′), 6.85 (1H, d, J=15.5 Hz, H-5), 6.09 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 3.12 (2H, td, J=7.1, 5.6 Hz, NCH_2), 2.59 (2H, t, J=7.7 Hz, CH_2), 1.73 (2H, tt, J=7.7, 7.1 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 147.9, 147.7, 141.7, 139.2, 137.8, 130.9, 128.3, 125.7, 125.3, 124.6, 122.6, 108.4, 107.9, 105.6, 101.3, 38.3, 32.6, 31.0. MS (EI) m/z: 335 $[M]^+$. *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.11; H, 6.15; N, 4.27.

5-(3,4-Methylenedioxyphenyl)-*N*-(4-phenylbutyl)-2*E*,4*E*-pentadienamide (**10**) Yield 85%. Pale orange solid. mp 155–157°C. IR (KBr) cm^{-1}: 3296, 1641, 1604, 1539, 1501, 1261. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.01 (1H, brt, J=5.7 Hz, NH), 7.28–7.22 (3H, m, H-2′, Ph), 7.19–7.12 (3H, m, Ph), 7.11 (1H, dd, J=15.0, 10.0 Hz, H-3), 6.97 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.88 (1H, dd J=15.5, 10.0 Hz, H-4), 6.87 (1H, d, J=8.1 Hz, H-5′), 6.82 (1H, d, J=15.5 Hz, H-5), 6.04 (1H, d, J=15.0 Hz, H-2), 6.02 (2H, s, –OCH_2O–), 3.14 (2H, td, J=6.5, 5.7 Hz, NCH_2), 2.56 (2H, t, J=7.5 Hz, CH_2), 1.60–1.51

(2H, m, CH_2), 1.47–1.38 (2H, m, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.0, 147.9, 147.6, 142.1, 139.1, 137.7, 130.9, 128.3, 128.2, 125.6, 125.2, 124.6, 122.6, 108.4, 105.6, 101.2, 38.4, 34.8, 28.8, 28.5. MS (EI) *m/z*: 349 $[M]^+$. *Anal*. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.48; H, 6.66; N, 4.05.

N-[(4-Hydroxy-3-methoxyphenyl)methyl]-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**11**) Yield 56%. Yellow solid. mp 170–172°C. IR (KBr) cm^{-1}: 3341, 1641, 1582, 1515, 1502, 1255. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.86 (1H, s, OH), 8.43 (1H, br t, *J*=5.8 Hz, NH), 7.27 (1H, d, *J*=1.6 Hz, H-2′), 7.19 (1H, dd, *J*=15.0, 10.0 Hz, H-3), 6.99 (1H, dd, *J*=8.1, 1.6 Hz, H-6′), 6.93 (1H, dd, *J*=15.5, 10.0 Hz, H-4), 6.91 (1H, d, *J*=8.1 Hz, H-5′), 6.86 (1H, d, *J*=15.5 Hz, H-5), 6.84 (1H, d, *J*=1.9 Hz, H-2″), 6.71 (1H, d, *J*=8.0 Hz, H-5″), 6.67 (1H, dd, *J*=8.0, 1.9 Hz, H-6″), 6.13 (1H, d, *J*=15.0 Hz, H-2), 6.04 (2H, s, $-OCH_2O-$), 4.25 (2H, d, *J*=5.8 Hz, NCH_2), 3.74 (3H, s, OCH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.0, 147.9, 147.7, 147.5, 145.5, 139.5, 137.9, 130.8, 130.2, 125.2, 124.4, 122.7, 119.9, 115.2, 111.9, 108.4, 105.6, 101.2, 55.6, 42.1. MS (EI) *m/z*: 353 $[M]^+$. *Anal*. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.70; H, 5.36; N, 3.93.

N-[2-(4-Hydroxyphenyl)ethyl]-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**12**) Yield 69%. Pale orange solid. mp 193–194°C. IR (KBr) cm^{-1}: 3281, 1641, 1614, 1602, 1546, 1501, 1240. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.18 (1H, br s, OH), 8.09 (1H, br t, *J*=5.6 Hz, NH), 7.24 (1H, d, *J*=1.6 Hz, H-2′), 7.12 (1H, dd, *J*=15.0, 10.1 Hz, H-3), 6.98 (2H, d, *J*=8.4 Hz, H-2″ and H-6″), 6.98–6.95 (1H, m, H-6′), 6.89 (1H, dd, *J*=15.5, 10.1 Hz, H-4), 6.88 (1H, d, *J*=8.0 Hz, H-5′), 6.82 (1H, d, *J*=15.5 Hz, H-5), 6.66 (2H, d, *J*=8.4 Hz, H-3″ and H-5″), 6.05 (1H, d, *J*=15.0 Hz, H-2), 6.02 (2H, s, $-OCH_2O-$), 3.31–3.23 (2H, m, NCH_2), 2.61 (2H, t, *J*=7.4 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 155.6, 147.9, 147.7, 139.2, 137.8, 130.9, 129.5, 129.4, 125.3, 124.6, 122.6, 115.1, 108.4, 105.6, 101.2, 40.7, 34.4. MS (EI) *m/z*: 337 $[M]^+$. *Anal*. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.95; H, 5.69; N, 4.16.

N-[2-(3,4-Dihydroxyphenyl)ethyl]-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**13**) Yield 64%. Pale orange solid. mp 169–170°C. IR (KBr) cm^{-1}: 3332, 3276, 1645, 1587, 1503, 1255. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.70 (2H, br s, OH), 8.08 (1H, br t, *J*=5.4 Hz, NH), 7.24 (1H, d, *J*=1.6 Hz, H-2′), 7.12 (1H, dd, *J*=14.9, 10.1 Hz, H-3), 6.97 (1H, dd, *J*=8.1, 1.6 Hz, H-6′), 6.90 (1H, dd, *J*=15.5, 10.1 Hz, H-4), 6.89 (1H, d, *J*=8.1 Hz, H-5′), 6.82 (1H, d, *J*=15.5 Hz, H-5), 6.61 (1H, d, *J*=8.0 Hz, H-5″), 6.56 (1H, d, *J*=2.0 Hz, H-2″), 6.42 (1H, dd, *J*=8.0, 2.0 Hz, H-6″), 6.04 (1H, d, *J*=14.9 Hz, H-2), 6.02 (2H, s, $-OCH_2O-$), 3.28–3.20 (2H, m, NCH_2), 2.53 (2H, t, *J*=7.5 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.0, 147.9, 147.7, 145.0, 143.5, 139.2, 137.7, 130.9, 130.2, 125.3, 124.6, 122.6, 119.2, 115.9, 115.5, 108.4, 105.6, 101.2, 40.7, 34.7. MS (EI) *m/z*: 353 $[M]^+$. *Anal*. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.70; H, 5.37; N, 3.96.

N-[2-(1*H*-Imidazol-4-yl)ethyl]-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**14**) Yield 76%. Pale orange solid. mp 193–194°C. IR (KBr) cm^{-1}: 3287, 3267, 1641, 1602, 1539, 1503, 1260. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.11 (1H, br t, *J*=5.6 Hz, NH), 7.50 (1H, d, *J*=1.1 Hz, H-2″), 7.23 (1H, d, *J*=1.6 Hz, H-2′), 7.13 (1H, dd, *J*=15.0, 10.0 Hz, H-3), 6.97 (1H, dd, *J*=8.0, 1.6 Hz, H-6′), 6.90 (1H, dd, *J*=15.5, 10.0 Hz, H-4), 6.88 (1H, d, *J*=8.0 Hz, H-5′), 6.83 (1H, d, *J*=15.5 Hz, H-5), 6.77 (1H, br s, H-5″), 6.05 (1H, d, *J*=15.0 Hz, H-2), 6.02 (2H, s, $-OCH_2O-$), 3.37–3.28 (2H, m, NCH_2), 2.64 (2H, t, *J*=7.4 Hz, CH_2). ^{13}C-NMR (CD_3OD, 100 MHz) δ: 169.0, 149.8, 149.7, 142.2, 140.3, 136.1, 136.0, 132.4, 125.9, 124.1, 123.8, 109.4, 106.7, 102.73, 102.70, 40.6, 27.9. MS (EI) *m/z*: 311 $[M]^+$. *Anal*. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.31; H, 5.41; N, 13.46.

N-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**15**) Yield 70%. Yellow solid. mp 114–117°C. IR (KBr) cm^{-1}: 3360, 3290, 1661, 1641, 1590, 1500, 1246. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.49 (1H, br s, H-1″), 8.61 (1H, br s, OH), 8.16 (1H, br t, *J*=5.7 Hz, NH), 7.26 (1H, d, *J*=1.6 Hz, H-2′), 7.16 (1H, dd, *J*=15.0, 10.1 Hz, H-3), 7.12 (1H, d, *J*=8.5 Hz, H-7″), 7.04 (1H, d, *J*=2.3 Hz, H-2″), 6.99 (1H, dd, *J*=8.1, 1.6 Hz, H-6′), 6.92 (1H, dd, *J*=15.5, 10.1 Hz, H-4), 6.91 (1H, d, *J*=8.1 Hz, H-5′), 6.85 (1H, d, *J*=15.5 Hz, H-5), 6.84 (1H, d, *J*=2.3 Hz, H-4″), 6.59 (1H, dd, *J*=8.5, 2.3 Hz, H-6″), 6.09 (1H, d, *J*=15.0 Hz, H-2), 6.04 (2H, s, $-OCH_2O-$), 3.44–3.33 (2H, m, NCH_2), 2.76 (2H, t, *J*=7.4 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 150.2, 147.9, 147.7, 139.2, 137.7, 130.9, 130.8, 127.9, 125.3, 124.7, 123.1, 122.6, 111.6, 111.3, 110.8, 108.4, 105.6, 102.2, 101.2, 25.4. MS (EI) *m/z*: 376 $[M]^+$. *Anal*. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.17; H, 5.60; N, 7.40.

5-(3,4-Methylenedioxyphenyl)-*N*-[2-(2-pyridinyl)ethyl]-2*E*,4*E*-pentadienamide (**16**) Yield 66%. Colorless solid. mp 144–145°C. IR (KBr) cm^{-1}: 3299, 1643, 1607, 1540, 1499, 1256. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.49–8.46 (1H, m, H-6″), 8.13 (1H, brt, *J*=5.6 Hz, NH), 7.68 (1H, td, *J*=7.6, 1.9 Hz, H-4″), 7.25–7.18 (2H, m, H-3″ and H-5″), 7.23 (1H, d, *J*=1.7 Hz, H-2′), 7.12 (1H, dd, *J*=15.0, 9.9 Hz, H-3), 6.97 (1H, dd, *J*=8.1, 1.7 Hz, H-6′), 6.89 (1H, dd, *J*=15.4, 9.9 Hz, H-4), 6.88 (1H, d, *J*=8.1 Hz, H-5′), 6.83 (1H, d, *J*=15.4 Hz, H-5), 6.03 (1H, d, *J*=15.0 Hz, H-2), 6.02 (2H, s, $-OCH_2O-$), 3.52–3.44 (2H, m, NCH_2), 2.88 (2H, t, *J*=7.3 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 159.1, 149.0, 147.9, 147.7, 139.2, 137.8, 136.4, 130.8, 125.2, 124.5, 123.1, 122.6, 121.5, 108.4, 105.6, 101.2, 38.6, 37.4. MS (EI) *m/z*: 322 $[M]^+$. *Anal*. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.71; H, 5.57; N, 8.69.

(±)-5-(3,4-Methylenedioxyphenyl)-*N*-(1-phenylethyl)-2*E*,4*E*-pentadienamide (**17**) Yield 83%. Pale orange solid. mp 163–165°C. IR (KBr) cm^{-1}: 3282, 1643, 1603, 1539, 1502, 1244. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 8.47 (1H, brd, *J*=8.1 Hz, NH), 7.34–7.29 (4H, m, Ph), 7.26 (1H, d, *J*=1.6 Hz, H-2′), 7.25–7.19 (1H, m, Ph), 7.15 (1H, dd, *J*=15.0, 10.2 Hz, H-3), 6.99 (1H, dd, *J*=8.2, 1.6 Hz, H-6′), 6.93 (1H, dd, *J*=15.5, 10.2 Hz, H-4), 6.90 (1H, d, *J*=8.2 Hz, H-5′), 6.85 (1H, d, *J*=15.5 Hz, H-5), 6.15 (1H, d, *J*=15.0 Hz, H-2), 6.04 (2H, s, $-OCH_2O-$), 5.01 (1H, dq, *J*=8.1, 7.0 Hz, NCH), 1.38 (3H, d, *J*=7.0 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 164.3, 147.9, 147.7, 144.7, 139.6, 137.9, 130.8, 128.2, 126.6, 126.0, 125.2, 124.5, 122.7, 108.4, 105.6, 101.2, 47.8, 22.5. MS (EI) *m/z*: 321 $[M]^+$. *Anal*. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.73; H, 5.96; N, 4.37.

(±)-*N*-(1-Methyl-3-phenylpropyl)-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**18**) Yield 60%. Pale yellow solid. mp 183–185°C. IR (KBr) cm^{-1}: 3271, 1645, 1616, 1540, 1502, 1252. ^{1}H-NMR (DMSO-d_4, 400 MHz) δ: 7.95

(1H, d, J=8.2 Hz, NH), 7.29–7.24 (2H, m, Ph), 7.26 (1H, d, J=1.7 Hz, H-2′), 7.21–7.14 (3H, m, Ph), 7.15 (1H, dd, J=15.0, 10.3 Hz, H-3), 6.99 (1H, dd, J=8.1, 1.7 Hz, H-6′), 6.92 (1H, dd, J=15.5, 10.3 Hz, H-4), 6.91 (1H, d, J=8.1 Hz, H-5′), 6.85 (1H, d, J=15.5 Hz, H-5), 6.10 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 3.92–3.80 (1H, m, NCH), 2.62–2.51 (2H, m, CH_2), 1.77–1.62 (2H, m, CH_2), 1.09 (3H, d, J=6.6 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 164.5, 147.9, 147.8, 141.9, 139.1, 137.7, 130.9, 128.3, 128.2, 125.7, 125.3, 124.9, 122.6, 108.4, 105.6, 101.2, 44.0, 38.0, 31.9, 20.8. MS (EI) m/z: 349 $[M]^+$. *Anal*. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.44; H, 6.64; N, 4.04.

5-(3,4-Methylenedioxyphenyl)-*N*-propyl-2*E*,4*E*-pentadienamide (**19**) Yield 92%. Pale orange solid. mp 167–168°C. IR (KBr) cm^{-1}: 3277, 1642, 1616, 1546, 1502, 1262. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.02 (1H, br t, J=5.7 Hz, NH), 7.25 (1H, d, J=1.6 Hz, H-2′), 7.14 (1H, dd, J=15.0, 10.2 Hz, H-3), 6.98 (1H, dd, J=8.0, 1.6 Hz, H-6′), 6.91 (1H, dd, J=15.5, 10.2 Hz, H-4), 6.90 (1H, d, J=8.0 Hz, H-5′), 6.84 (1H, d, J=15.5 Hz, H-5), 6.08 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 3.09 (2H, td, J=6.7, 5.7 Hz, NCH_2), 1.49–1.39 (2H, m, CH_2), 0.86 (3H, t, J=7.4 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 147.9, 147.6, 139.1, 137.7, 130.9, 125.3, 124.7, 122.6, 108.4, 105.6, 101.2, 40.4, 22.4, 11.5. MS (EI) m/z: 259 $[M]^+$. *Anal*. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.19; H, 6.61; N, 5.38.

5-(3,4-Methylenedioxyphenyl)-*N*-(2-methylpropyl)-2*E*,4*E*-pentadienamide (**20**) Yield 86%. Pale yellow solid. mp 168–170°C. IR (KBr) cm^{-1}: 3290, 1645, 1616, 1551, 1505, 1255. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.02 (1H, brt, J=5.9 Hz, NH), 7.25 (1H, d, J=1.6 Hz, H-2′), 7.14 (1H, dd, J=15.0, 10.0 Hz, H-3), 6.98 (1H, dd, J=8.0, 1.6 Hz, H-6′), 6.91 (1H, dd, J=15.5, 10.0 Hz, H-4), 6.90 (1H, d, J=8.0 Hz, H-5′), 6.84 (1H, d, J=15.5 Hz, H-5), 6.12 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, –OCH_2O–), 2.96 (2H, dd, J=6.9, 5.8 Hz, NCH_2), 1.76–1.65 (1H, m, CH), 0.85 (6H, d, J=6.7 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 147.9, 147.7, 139.1, 137.7, 130.9, 125.3, 124.7, 122.6, 108.4, 105.6, 101.2, 46.2, 28.1, 20.2. MS (EI) m/z: 273 $[M]^+$. *Anal*. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.01; H, 7.02; N, 5.13.

N-Butyl-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**21**) Yield 88%. Pale orange solid. mp 151–153°C. IR (KBr) cm^{-1}: 3292, 1642, 1614, 1604, 1539, 1501, 1261. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.00 (1H, brt, J=5.7 Hz, NH), 7.25 (1H, d, J=1.6 Hz, H-2′), 7.13 (1H, dd, J=15.0, 10.2 Hz, H-3), 6.98 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.91 (1H, dd, J=15.5, 10.2 Hz, H-4), 6.90 (1H, d, J=8.1 Hz, H-5′), 6.84 (1H, d, J=15.5 Hz, H-5), 6.07 (1H, d, J=15.0 Hz, H-2), 6.03 (2H, s, –OCH_2O–), 3.12 (2H, td, J=7.0, 5.7 Hz, NCH_2), 1.45–1.37 (2H, m, CH_2), 1.34–1.24 (2H, m, CH_2), 0.88 (3H, t, J=7.3 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.5, 148.4, 148.1, 139.5, 138.1, 131.3, 125.7, 125.1, 123.0, 108.9, 106.0, 106.0, 101.7, 38.7, 31.7, 20.1, 14.1. MS (EI) m/z: 273 $[M]^+$. *Anal*. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.11; H, 7.03; N, 5.13.

5-(3,4-Methylenedioxyphenyl)-*N*-pentyl-2*E*,4*E*-pentadienamide (**22**) Yield 70%. Pale yellow solid. mp 148–149°C. IR (KBr) cm^{-1}: 3289, 1642, 1614, 1605, 1540, 1501, 1261. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.99 (1H, brt, J=5.7 Hz, NH), 7.23 (1H, d, J=1.6 Hz, H-2′), 7.11 (1H, dd, J=15.0, 10.0 Hz, H-3), 6.96 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.89 (1H, dd, J=15.5, 10.0 Hz, H-4), 6.88 (1H, d, J=8.1 Hz, H-5′), 6.82 (1H, d, J=15.5 Hz, H-5), 6.05 (1H, d, J=15.0 Hz, H-2), 6.02 (2H, s, –OCH_2O–), 3.10 (2H, td, J=7.1, 5.7 Hz, NCH_2), 1.45–1.36 (2H, m, CH_2), 1.31–1.20 (4H, m, CH_2), 0.85 (3H, d, J=6.8 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 147.9, 147.7, 139.1, 137.7, 130.9, 125.3, 124.7, 122.6, 108.4, 105.6, 101.3, 38.6, 28.9, 28.7, 21.9, 13.9. MS (EI) m/z: 287 $[M]^+$. *Anal*. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.85; H, 7.39; N, 4.91.

N-Decanoyl-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**23**) Yield 88%. Pale yellow solid. mp 140–142°C. IR (KBr) cm^{-1}: 3308, 1644, 1614, 1606, 1534, 1501, 1262. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.00 (1H, brt, J=5.6 Hz, NH), 7.24 (1H, d, J=1.6 Hz, H-2′), 7.13 (1H, dd, J=15.0, 10.2 Hz, H-3), 6.98 (1H, dd, J=8.0, 1.6 Hz, H-6′), 6.91 (1H, dd, J=15.5, 10.2 Hz, H-4), 6.90 (1H, d, J=8.0 Hz, H-5′), 6.83 (1H, d, J=15.5 Hz, H-5), 6.07 (1H, d, J=15.0 Hz, H-2), 6.03 (2H, s, –OCH_2O–), 3.11 (2H, td, J=6.9, 5.6 Hz, NCH_2), 1.46–1.37 (2H, m, CH_2), 1.28–1.21 (14 H, m, CH_2), 0.85 (3H, t, J=6.9 Hz, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.5, 148.3, 148.1, 139.5, 138.1, 131.3, 125.7, 125.1, 123.0, 108.9, 106.0, 101.7, 39.1, 31.8, 29.6, 29.5, 29.4, 29.21, 29.15, 26.9, 22.6, 14.4. MS (EI) m/z: 357 $[M]^+$. *Anal*. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.80; H, 8.72; N, 3.96.

N-(2-Hydroxyethyl)-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide (**24**) Yield 64%. Pale orange solid. mp 167°C. IR (KBr) cm^{-1}: 3290, 1647, 1598, 1559, 1502, 1259. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.07 (1H, brt, J=5.7 Hz, NH), 7.24 (1H, d, J=1.6 Hz, H-2′), 7.12 (1H, dd, J=15.1, 10.1 Hz, H-3), 6.97 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.89 (1H, dd, J=15.5, 10.1 Hz, H-4), 6.88 (1H, d, J=8.1 Hz, H-5′), 6.83 (1H, d, J=15.5 Hz, H-5), 6.09 (1H, d, J=15.1 Hz, H-2), 6.02 (2H, s, –OCH_2O–), 4.72 (1H, br t, J=5.8 Hz, OH), 3.44–3.36 (2H, m, CH_2), 3.18 (2H, q, J=5.8 Hz, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.3, 147.9, 147.7, 139.2, 137.8, 130.8, 125.2, 124.6, 122.6, 108.4, 105.6, 101.2, 59.9, 41.6. MS (EI) m/z: 261 $[M]^+$. *Anal*. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.16; H, 5.77; N, 5.32.

Synthesis of *tert*-Butyl 4-Aminobutylcarbamate (26) A solution of di-*tert*-butyl dicarbonate (22 g, 100 mmol) in MeOH (20 mL) was added over 30 min to a stirred solution of 1,4-diaminobutane (**25**, 1.8 g, 20 mmol) in MeOH (160 mL) under ice-cooling. After stirring for 4 h at room temperature, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH: aq. NH_3=10 : 1 : 0.1) to give the title compound (**26**) in 83% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.68 (1H, br s, NH), 3.11 (2H, q, J=6.7 Hz, NCH_2), 2.69 (2H, t, J=6.7 Hz, NCH_2), 1.55–1.40 (4H, m, CH_2), 1.42 (9H, s, CH_3). MS (EI) m/z: 188 $[M]^+$. The ^{1}H-NMR spectrum was similar to that of a previous report.[30]

Synthesis of *tert*-Butyl 4-Aminopentylcarbamate (28) According to the procedure for the preparation of compound (**26**), 1,5-diaminopentane (**27**, 5.1 g, 50 mmol) was treated with di-*tert*-butyl dicarbonate (5.5 g, 25 mmol) in MeOH (200 mL) to give the title compound (**28**) in 72% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.56 (1H, br s, NH), 3.10 (2H, q, J=6.8 Hz, NCH_2), 2.67 (2H, t, J=6.7 Hz, NCH_2), 1.55–1.25 (6H, m, CH_2), 1.42 (9H, s, CH_3). MS (EI) m/z: 202 $[M]^+$. The ^{1}H-NMR spectrum was similar to that of a previous report.[30]

General Procedure for Preparation of Piperic Acid

Amides with an Aminoalkyl Group (29, 30) A solution of the crude acid chloride, generated from piperic acid (436 mg, 2 mmol) and oxalyl chloride, in CH_2Cl_2 (4 mL) was added dropwise to a solution of the mono-Boc-protected diamine (2.4 mmol) and Et_3N (1.6 g, 16 mmol) in CH_2Cl_2 (10 mL) under ice-cooling. The reaction mixture was stirred for 5 h at room temperature. Ice-water was added to the mixture, which was subsequently extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was passed once through a short silica gel column ($CHCl_3$: MeOH : aq. NH_3=50 : 1 : 0.1) and the solvent was evaporated. The residue was treated with trifluoroacetic acid (TFA) followed by 2 M HCl–MeOH (1 : 1) to give the corresponding crude piperic acid amide hydrochloride salt. The obtained crude compound was then recrystallized from aqueous MeOH.

N-(4-Aminobutyl)-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide Hydrochloride (**29**) Yield 74% (for 2 steps). Pale orange solid. mp 243–248°C. IR (KBr) cm^{-1}: 3286, 3013, 2934, 1641, 1604, 1540, 1500, 1261. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.16 (1H, br t, J=5.8 Hz, NH), 7.83 (2H, br s, NH_2), 7.26 (1H, d, J=1.6 Hz, H-2′), 7.15 (1H, dd, J=15.0, 10.2 Hz, H-3), 6.99 (1H, dd, J=8.0, 1.6 Hz, H-6′), 6.92 (1H, dd, J=15.5, 10.2 Hz, H-4), 6.91 (1H, d, J=8.0 Hz, H-5′), 6.85 (1H, d, J=15.5 Hz, H-5), 6.09 (1H, d, J=15.0 Hz, H-2), 6.04 (2H, s, $-OCH_2O-$), 3.19–3.11 (2H, m, NCH_2), 2.78 (2H, t, J=7.0 Hz, NCH_2), 1.60–1.43 (4H, m, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.2, 147.9, 147.7, 139.3, 137.8, 130.8, 125.2, 124.5, 122.6, 108.4, 105.6, 101.3, 38.5, 37.9, 26.2, 24.5. HR-MS *m*/*z*: Calcd for $C_{16}H_{20}N_2O_3$ (M^+): 288.1474; Found: 288.1490.

N-(4-Aminopentyl)-5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienamide Hydrochloride (**30**) Yield 72% (for 2 steps). Pale brown solid. mp 218–222°C. IR (KBr) cm^{-1}: 3023, 2934, 1646, 1497, 1261. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.12 (1H, br s, NH), 7.91 (2H, br s, NH_2), 7.26 (1H, d, J=1.6 Hz, H-2′), 7.14 (1H, dd, J=15.0, 10.1 Hz, H-3), 6.99 (1H, dd, J=8.1, 1.6 Hz, H-6′), 6.92 (1H, dd, J=15.5, 10.1 Hz, H-4), 6.91 (1H, d, J=8.1 Hz, H-5′), 6.84 (1H, d, J=15.5 Hz, H-5), 6.09 (1H, d, J=15.0 Hz, H-2), 6.05 (2H, s, $-OCH_2O-$), 3.17–3.09 (2H, m, NCH_2), 2.81–2.70 (2H, m, NCH_2), 1.61–1.51 (2H, m, CH_2), 1.49–1.40 (2H, m, CH_2), 1.37–1.28 (2H, m, CH_2). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 165.1, 147.9, 147.7, 139.1, 137.7, 130.8, 125.2, 124.7, 122.6, 108.4, 105.6, 101.2, 38.6, 38.3, 28.5, 26.6, 23.3. HR-MS *m*/*z*: Calcd for $C_{17}H_{22}N_2O_3$ (M^+): 302.1630; Found: 302.1620.

Biological Assay α-Glucosidase from *Saccharomyces cerevisiae* and 4-nitrophenyl α-D-glucopyranoside (PNP-G) were purchased from Sigma Chemical Co., St. Louis, MO, U.S.A. DPPH radical was purchased from Tokyo Chemical Industry Co., Tokyo, Japan.

DPPH Radical Scavenging Assay DPPH radical scavenging activity was measured according to the method of Nile *et al.*[31] with minor modifications. Briefly, 180 μL of 100 μM DPPH 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 micro-plate reader (Molecular Devices SPECTRA MAX 190). The sample solution was replaced by MeOH as a control. Ascorbic acid was used as a positive control.

α-Glucosidase Inhibitory Assay α-Glucosidase inhibitory activity was assayed using the method of Takahashi and Miyazawa[6] with minor modifications. Briefly, 210 μL of 50 mM phosphate buffer (pH 6.8) containing 100 mM NaCl, 30 μL of 0.25 U/mL α-glucosidase dissolved in the buffer, 30 μL of 7 mM PNP-G as a substrate dissolved in the buffer, and 30 μL of various concentrations of samples dissolved in dimethyl sulfoxide (DMSO) were mixed and the increment in absorption at 405 nm, due to the hydrolysis of PNP-G by α-glucosidase, was monitored continuously with a micro-plate reader (Molecular Devices SPECTRA MAX 190). The sample solution was replaced by DMSO as a control. Acarbose was used as a positive control.

Conflict of Interest The authors declare no conflict of interest.

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