Efficient Synthesis and Neuroprotective Effect of Substituted 1,3-Diphenyl-2-propen-1-ones

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An efficient synthesis involving a key aldol reaction and biological properties of 1,3-diphenyl-2-propen-1-ones **8**−**20** is described. The in vitro activity for 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging of **10** and **11** was 2 times higher than that for resveratrol. Compounds **9** and **11** were the strongest in suppression of in vitro nitric oxide (NO) generation and antiexcitotoxicity. Molecular modeling proposes an electron-donating group at the para position of acetophenones that leads to a dramatic increase in the suppression of NO production.

Introduction

1,3-Diarylpropenones (**1**, chalcones) constitute an important group of natural products and serve as precursors for the synthesis of different classes of various flavonoids, which are common substances in plants that have an array of biological activities.[1,2] In addition, yakuchinone analogues A and B (**2** and **3**) (Figure 1) have evoked much interest in recent years because of their significant biological activities in areas such as brain dysfunction,[3] cancer,[4,5] inflammation,[6] and cardiovascular disease.[7] Most of the phenolic natural products are potentially useful intermediates for many industrial products and agrochemical applications, including food sciences. The phenolic natural products are closely related to free radicals, which play a major role in the progression of many pathological disturbances.[8] Furthermore, free radical scavenging effects are a major cause in the deterioration of foods during processing and storage. In addition, free radicals are related to antioxidation in foods and biological systems.[9] Recently, antioxidants have been shown to play an important role in biological defense mechanisms.[10] In an ischemic condition, glutamate is released excessively and then activates the glutamate receptor. Overactivation of the glutamate receptors may induce elevation of intracellular Ca^{2+} levels, resulting in activation of Ca^{2+}-dependent proteases and kinases. Additionally, high intracellular Ca^{2+} may activate nitric oxide synthase, resulting in excessive production of nitric oxide (NO[a]) and cytotoxicity.[11] According to previous research, activated oxygen is considered a major factor in cytotoxicity. Therefore, a search for novel compounds with better neuroprotective effects and less neurotoxicity based on antioxidative effects has been undertaken.

In a preliminary communication,[12] the authors of this study reported the preparation of benzylideneacetophenone derivatives and an evaluation of their biological activities. In order to develop and design new compounds with increased potency and antioxidant and neuroprotective effects in terms of oxidative chalcone and its analogues, the substituted 1,3-diphenyl-2-propen-1-ones were synthesized and their biological activities determined. Here, the one-pot synthesis of substituted 1,3-diphenyl-2-propen-1-ones, which is an improvement made to previous routes,[13,14] is described and the free radical scavenging, anti-inflammatory, and antiexcitotoxic effects are established. Molecular modeling studies were consequently described to investigate the chemical structural characteristics required for the biological activities and schematized delocalized form of electron density. Molecular modeling can provide further information for exploring more specific targets of related 1,3-diarylpropenones as a logical starting point in studies of novel neurological disorders.

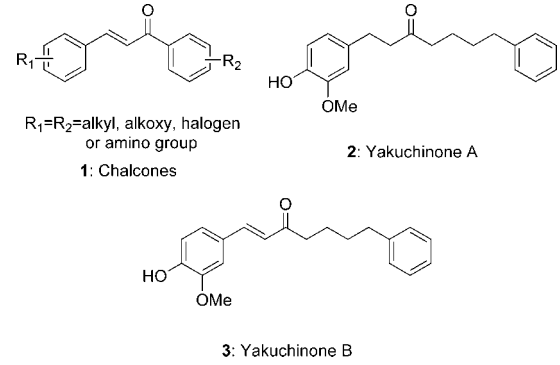

Figure 1. Structures of chalcones (**1**), yakuchinone A (**2**), and yakuchinone B (**3**).

Results and Discussion

Chemistry. A series of benzalacetophenone derivatives **8**−**20** were prepared from inexpensive vanillin (**4**, 4-hydroxy-3-mehoxybenzaldehyde), isovanillin (**5**, 3-hydroxy-4-methoxybenzaldehyde), and *o*-vanillin (**6**, 2-hydroxy-3-methoxybenzaldehyde). Thus, treatment of various vanillins with commercially available several acetophenones (**7a**, acetophenone, **7b**, 3,4-mehtylenedioxyacetophenone, **7c**, 3,4,5-trifluoroacetophenone, and **7d**, 3-fluoro-4-methoxyacetophenone) in the presence of 2 equiv of lithium hydroxide (LiOH) as the most effective coupling base in MeOH produced high yields of 1,3-diphenyl-2-propen-1-ones (Scheme 1). The effectiveness of LiOH could

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[a] Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; NO, nitric oxide; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; LPS, lipopolyssarcharide; WST, water soluble tetrazolium salts; NMDA, *N*-methyl-D-aspartate.

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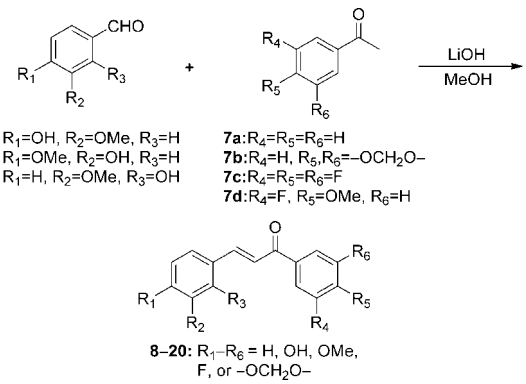
Scheme 1. Aldol Condensation Reaction



be explained in part by a lithium chelating effect. This aldol condensation via a one-step reaction produced eight new substituted 1,3-diphenyl-2-propen-1-ones (**9**−**11**, **13**−**15**, and **18**, **19**) and five known derivatives (**8**,[4] **12**,[15] **16**,[15] **17**,[5] and **20**[16]) as listed in Table 1.

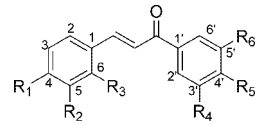
Biology Evaluation. (A) Radical Scavenging Activity. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) is one of the few stable and commercially available organic nitrogen radicals. DPPH radicals are considered a representative method for the preliminary screening of compounds capable of scavenging activated oxygen species, since they are more stable and easier to handle than oxygen free radicals. The radical scavenging activity of the 1,3-diphenyl-2-propen-1-ones **8**−**20** was evaluated by the established text method.[17] All the compounds exhibited free radical scavenging ability as shown in Table 2 at 10, 50, and 100 μM compared with standard (control) material. Although prepared compounds showed less DPPH radical scavenging activity than resveratrol, the 1,3-diphenyl-2-propen-1-ones **10** and **11** showed 2-fold higher scavenging activity than resveratrol under lower (10−50 μM) concentrations. However, **12**, **14**, **15**, and **18**−**20** exhibited less activity than the standard material. Compound **10** exhibited the strongest radical scavenging activity among the analogues. The vanillin analogues (**8**−**11**) showed a greater rate of DPPH radical scavenging activity than *o*-vanillin analogues (**12**−**15**) or isovanillin analogues (**16**−**19**). This increase in activity may be attributed to the electronic distribution due to the generation of free radicals in the aromatic conjugation system.

(B) Inhibition of NO Generation. The in vitro suppression of NO production of **8**−**20** were evaluated in lipopolyssarcharide (LPS) treated microglia cells, and the results are summarized in Figure 2. All compounds showed a strong suppression of NO generation on microglia cells with **11** being the strongest at 10−20 μM. In addition, vanillin moieties **8**−**11** showed a greater activity of NO generation than isovanillin moieties **12**−**15** or *o*-vanillin moieties **16**−**19**. This result indicated that the hydroxyl group at the para position of the benzene ring is enhanced to delocalize the electron density based on a resonance effect. Compounds with a hydroxyl group at the para position of the benzene ring generally showed increased suppression of NO production, while compounds with a hydroxyl group at the ortho or meta position exhibited relatively weaker activity of NO generation.

(C) Neuroprotective Activity. Inhibition of Glutamate-Induced Neurotoxicity. The neuroprotective effect of 1,3-diphenyl-2-propen-1-ones **8**−**20** on the inhibition of glutamate-induced neurotoxicity in cultured cortical neurons was examined (Figure 3). Most of the 1,3-diphenyl-2-propen-1-ones **8**−**20** showed good antiexcitotoxicity at 10 μM. Compound **15** exhibited the strongest activity among these analogues. The increase of efficacy of vanillin moieties **8**−**11** is presumably due to the para position, which increased the electron density of the hydroxyl group and lowered the oxygen−hydrogen bonding energy. In addition, the moieties (**11**, **15**, and **19**) of the attached 3-fluoro-4-methoxyacetophenone group were found to exhibit a significant improvement in activity compared to other attached acetophenones (acetophenone, 3,4-mehtylenedioxyacetophenone, 3,4,5-trifluoroacetophenone).

Molecular Modeling. The main object for molecular modeling was the determination of the effect of aromatic substitution in the ortho and para positions of diphenylpropenones to the free radical scavenging effect, LPS-induced NO generation, and the neuroprotective effect. In the first part of the present study, the synthesized compounds were divided into three vanillin moieties and the structural characteristics of the three groups were investigated. The results of the molecular modeling study for 1,3-diphenyl-2-propen-1-ones **8**−**20** are shown in Table 3. In the structure of acetophenones, the presence of the methoxy group (**11**, **15**, and **19**) shows that their cell viability is as good as that of other substituted groups and they indicate low dipole moment values in our result. The neurotoxicity is probably affected by the dipole moment, which can be a relevant parameter for evaluating the interaction efficiency of ligand with a receptor. In addition, the dipole moment indicates the strength and orientation behavior of a molecule in an electrostatic field in a CoMFA map.[18] The electrostatic nature of the molecule may lead to large variations of the biological activity. Particularly, in the vanillin moieties **8**−**11**, compounds **9** and **11** have a small dipole moment while they have a high value in lowest unoccupied molecular orbital (LUMO) energy compared with **8** and **10**. Compounds **9** and **11** showed increased suppression of NO production. At the para substituent of the acetophenones, the electron-donating group (−OMe > −H > −F) was shown to lead to a dramatic increase in the suppression of NO generation. In addition, the weaker is the electron-donating ability, the lower is the highest unoccupied molecular orbital (HOMO) energy and the higher is the HOMO energy, implying that the para substituent is a good electron donor. Molecules with high HOMO can donate electrons with ease and are hence relatively reactive compared to molecules with low HOMO. Thus, HOMO measures the nucleophilicity of a molecule. This fact reveals a close relation to the electron density based on the resonance and inductive effect, which is represented in Figure 4. Further insight can be derived from some features of **8**−**11** by analyzing the frontier orbitals. In Figure 4, the HOMO distribution of the compounds with 4′-H, 4′,5′-OCH_2O−, 4′-F, and 4′-OCH_3 substituents is shown. The values of the activity of these compounds are given to explain their correlation with some features of the nucleophilic and electrophilic frontier electron density distributions. As seen Figure 4, **9** and **11** are much delocalized over entire structures in a π molecular orbital and involve the electron-donating ability over the conjugated framework. In the case of **9** and **11**, the methylenedioxy group of **9** and the methoxy group of **11** caused the potent biological activities. A high radical scavenging effect for 1,3-diphenyl-2-propen-1-ones can be expected because the LUMO energy generated at the para-positioned electron-donating group could be kinetically lowered through interaction with other external radicals. These electronic descriptors (HOMO and LUMO) may play an important role in the interaction of substituted 1,3-diphenyl-2-propen-1-ones with the active sites. The relationship of the ligand−receptor interactions could be explained by the

Table 1. Substituted 1,3-Diphenyl-2-propen-1-ones **8**−**20** Prepared via Aldol Condensation Reaction



8–**20**

entry	R_1	R_2	R_3	R_4	R_5	R_6	formula	product	yield(%)[a]
1	OH	OMe	H	H	H	H	$C_{16}H_{14}O_3$	**8**	90
2	OH	OMe	H	H	$-OCH_2O-$		$C_{17}H_{14}O_5$	**9**	75
3	OH	OMe	H	F	F	F	$C_{16}H_{11}F_3O_3$	**10**	78
4	OH	OMe	H	F	OMe	H	$C_{17}H_{15}FO_4$	**11**	82
5	OMe	OH	H	H	H	H	$C_{16}H_{14}O_3$	**12**	87
6	OMe	OH	H	H	$-OCH_2O-$		$C_{17}H_{14}O_5$	**13**	70
7	OMe	OH	H	F	F	F	$C_{16}H_{11}F_3O_3$	**14**	75
8	OMe	OH	H	F	OMe	H	$C_{17}H_{15}FO_4$	**15**	80
9	H	OMe	OH	H	H	H	$C_{16}H_{14}O_3$	**16**	89
10	H	OMe	OH	H	$-OCH_2O-$		$C_{17}H_{14}O_5$	**17**	68
11	H	OMe	OH	F	F	F	$C_{16}H_{11}F_3O_3$	**18**	77
12	H	OMe	OH	F	OMe	H	$C_{17}H_{15}FO_4$	**19**	81
13	OMe	OMe	H	H	$-OCH_2O-$		$C_{18}H_{16}O_5$	**20**	89

[a] Isolated yield including recovered starting material.

Table 2. Rate of DPPH Radical Scavenging of 1,3-Diphenyl-2-propen-1-ones **8**−**20**

	DPPH radical scavenging activity (%)			
compd	10 μM	50 μM	100 μM	200 μM
8	7.53	11.80	14.43	22.63
9	7.90	12.02	14.14	25.11
10	22.85	23.53	32.05	37.96
11	17.80	18.90	28.35	37.45
12	1.26	1.46	2.05	5.38
13	8.75	9.14	9.63	10.98
14	1.99	2.71	3.25	5.29
15	1.55	1.68	2.73	5.02
16	5.40	6.09	7.94	10.96
17	13.93	14.87	18.60	22.25
18	3.08	3.28	5.50	6.81
19	1.74	1.14	2.42	2.87
20	3.27	1.95	1.75	1.56
4-hydroxy-3-methoxycinnamaldehyde[a]	2.37	0.28	0.43	10.56
Trolox[b]	12.10	30.24	62.44	78.25
resveratrol[c]	9.45	8.44	28.39	33.79

[a] A control material.[12] [b] A standard material. [c] A standard material.

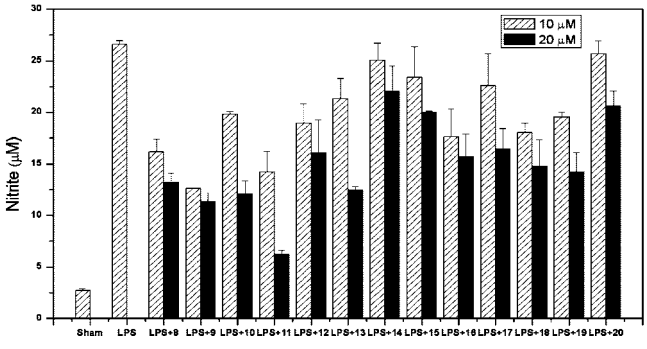


Figure 2. Suppression of NO production in LPS-treated microglia. The cells were treated with 1 μg/mL LPS only or LPS plus a different concentration (10 or 20 μM) of **8**−**20** at 37 °C for 24 h. At the end of incubation, 50 μL of the medium was removed to measure nitrite production. All values represent the mean ± SE of three independent experiments performed in triplicate.

observation that the regions of the molecules that contain a greater HOMO contribution tend to be electron-donor to the active site and that the regions that contain a greater LUMO contribution tend to be electron-acceptor. On the basis of these results and future in vivo evaluation of neuroprotective effects,

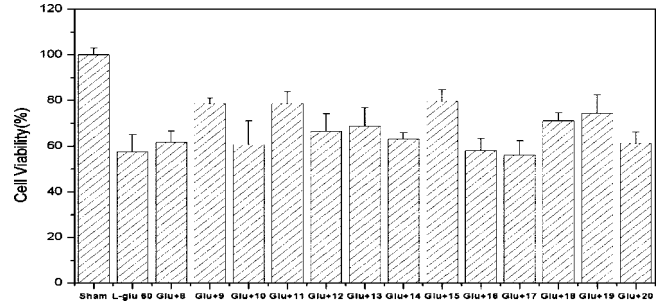


Figure 3. Inhibition of glutamate-induced neurotoxicity in cultured cortical neurons. Glutamate (60 μM) and **8**−**20** were applied for 24 h at 37 °C. After incubation of neurons with water soluble tetrazolium salts WST-1 for 2 h, the compounds were quantified spectrophotometrically. All values represent the mean ± SE of three independent experiments performed in triplicate.

the substituted high radical scavenging 1,3-diphenyl-2-propen-1-ones **8**−**20**, particularly **11**, could eventually be developed as antioxidant and antiexcitotoxicity drug candidates.

Conclusion

An efficient synthesis and biological evaluation of 1,3-diphenyl-2-propen-1-ones **8**−**20** has been described. The synthetic approach involves aldol condensation of aldehydes **4**−**6** and acetophenones **7** in the presence of LiOH to generate 1,3-diphenyl-2-propen-1-ones in high yields. The prepared compounds **8**−**20** were evaluated for free radical scavenging, suppression of LPS-induced NO generation, and antiexcitotoxicity in vitro. The activity for DPPH radical scavenging of **10**, **11**, and **17** was 6−10 times higher than 4-hydroxy-3-methoxycinnamaldehyde in the in vitro concentration range of 10−100 μM. Compounds **10** and **11** were 2-fold higher than resveratrol under lower (10−50 μM) concentrations. The compounds have also exhibited a suppression effect on NO generation after LPS stimulation in microglial cells and inhibitory action on glutamate-induced neurotoxicity in cultured neurons. Among the 1,3-diphenyl-2-propen-1-ones **8**−**20**, compound **11** showed the most potent neuroprotective effects compared with 1,3-diphenyl-2-propen-1-ones **8**, **10**, **12**−**20**. These results coupled with

Table 3. Calculated Chemical Descriptors and Biological Activities of 1,3-Diphenyl-2-propen-1-ones **8**−**20**

group	product	dipole moment (μ)	E LUMO[a] (eV)	E HOMO[b] (eV)	cell viabillity (%)	nitrite[c] 10 (μM)	nitrite[c] 20 (μM)
A	**8**	3.53	−1.95	−5.84	62	16.14	13.16
	9	3.05	−1.86	−5.69	79	12.63	11.32
	10	6.19	−2.27	−6.05	61	19.82	12.11
	11	2.07	−1.91	−5.81	79	14.21	6.23
B	**12**	4.63	−1.90	−5.70	67	18.93	16.04
	13	3.85	−1.82	−5.60	69	21.30	12.44
	14	7.48	−2.22	−5.89	63	25.07	22.00
	15	2.87	−1.86	−5.68	80	23.40	19.98
C	**16**	2.79	−2.10	−5.77	58	17.62	15.69
	17	5.56	−1.76	−5.65	56	22.62	16.44
	18	7.78	−2.16	−6.03	71	18.05	14.72
	19	3.62	−1.80	−5.81	75	19.55	14.19
	20	3.41	−1.96	−5.80	61	25.69	20.60

[a] Energy of lowest unoccupied molecular orbital (LUMO). [b] Energy of highest occupied molecular orbital (HOMO). [c] The amount of nitrite in the presence of each compound (10 or 20 μM) in LPS-treated BV-2 microglia cells, presented as concentration of LPS-activated BV-2 microglia cells. A, B, and C represent vanillin, isovanillin, and *o*-vanillin moieties, respectively.

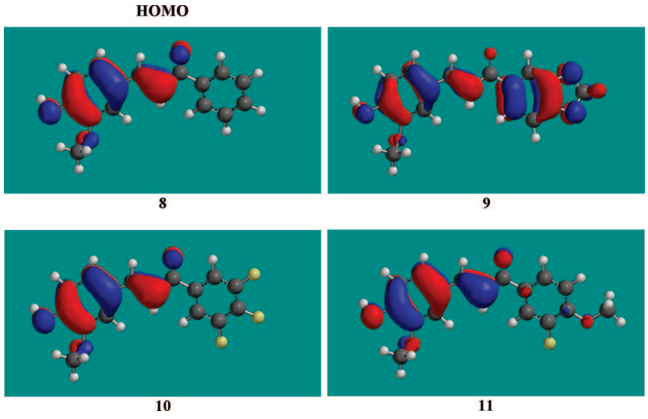


Figure 4. Frontier orbital maps of vanillin moieties **8**−**11**. Compounds **9** and **11** showed delocalization throughout all the structures of substituted 1,3-diphenyl-2-propen-1-ones.

molecular modeling will be useful to further design and develop potential antioxidant agents and neuroprotective compounds.

Experimental Section

General Procedures for the Preparation of the Aldol Condensation Products of Aldehyde with Acetophenones (8−20). A stirred solution of acetophenones **7a**−**d** (6.0 mmol) in MeOH (30 mL) was added to LiOH (1.2 mmol), and the mixture was stirred at room temperature for 1 h. The aldehydes **4**−**6** (6.0 mmol) were added to the mixture, and the resulting mixture was stirred at room temperature for 148 h. The mixture was concentrated under reduced pressure, and the residue was treated with water (35 mL). The aqueous mixture was neutralized by the addition of aqueous 10% HCl solution and extracted with dichloromethane (2 × 30 mL). The organic phase was washed with aqueous saturated NH_4Cl solution (30 mL) and brine (30 mL). The organic layer was separated and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product, which was purified by flash silica chromatography to produce the pure substituted 1,3-diphenyl-2-propen-1-ones **8**−**20**.

(*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-hydroxy-3-methoxyphenyl)-2-propen-1-one (9). R_f = 0.3 (30% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3349, 3007, 2955, 2876, 1645, 1554, 1477, 1243, 1186, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11−6.72 (m, 6H), 6.59 (dd, J = 7.5, 7.0 Hz, 1H), 6.38 (dd, J = 7.0, 7.0 Hz, 1H), 6.05 (s, 2H), 3.88 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.9, 151.1, 147.0, 146.3, 145.7, 138.3, 133.5, 127.9, 126.5, 125.4, 122.1, 121.4, 120.5, 112.1, 102.5, 55.9. HRMS calculated for $C_{17}H_{15}O_5$: 299.0919 $[M + H]^+$. Found: 299.0928.

(*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(3,4,5-trifluorophenyl)-2-propen-1-one (10). The title compound was obtained in 78% yield from vanillin **4** and 3,4,5-trifluoroacetophenone (**7c**). R_f = 0.3 (30% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3350, 3005, 2985, 2858, 1657, 1550, 1448, 1262, 1153, 1081 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 16.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 2H), 7.22 (d, J = 16.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.15 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 151.0, 148.2, 146.5, 132.2, 128.3, 122.9, 121.7, 119.3, 113.1, 112.2, 111.9, 55.8. HRMS calculated for $C_{16}H_{12}F_3O_3$: 309.0739 $[M + H]^+$. Found: 309.0745. Anal. ($C_{16}H_{11}F_3O_3$) C, H, O.

(*E*)-1-(3-Fluoro-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)-2-propen-1-one (11). The title compound was obtained in 82% yield from vanillin **4** and 3-fluoro-4-methoxyacetophenone (**7d**). R_f = 0.3 (40% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3359, 2987, 2875, 1662, 1578, 1455, 1278, 1164, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85−7.72 (m, 3H), 7.33 (d, J = 16.0 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.13 (s, 1H), 7.04 (t, J = 8.5 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 150.3, 148.7, 145.2, 132.4, 129.6, 124.9, 123.1, 121.8, 119.5, 115.3, 113.2, 111.8, 56.8, 55.9. HRMS calculated for $C_{17}H_{16}FO_4$: 303.1033 $[M + H]^+$. Found: 303.1020. Anal. ($C_{17}H_{15}FO_4$) C, H, O.

(*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one (13). R_f = 0.3 (40% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3340, 2969, 1671, 1460, 1265, 1176, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 15.5 Hz, 1H, vinyl), 7.64 (dd, J = 1.7, 1.7 Hz, 1H, Ar−H), 7.52 (d, J = 1.6 Hz, 1H, Ar−H), 7.37 (d, J = 15.5 Hz, 1H, vinyl), 7.32−7.26 (m, 1H, Ar−H), 7.13 (dd, J = 2.0, 2.0 Hz 1H, Ar−H), 6.89 (dd, J = 3.8, 6.0 Hz, 2H, Ar−H), 6.05 (s, 2H, CH_2), 5.69 (s, 1H, OH), 3.95 (s, 3H, OMe). HRMS calculated for $C_{17}H_{15}O_3$: 299.0919 $[M + H]^+$. Found: 299.0910.

(*E*)-3-(3-Hydroxy-4-methoxyphenyl)-1-(3,4,5-trifluorophenyl)-2-propen-1-one (14). The title compound was obtained in 75% yield from isovanillin **5** and 3,4,5-trifluoroacetophenone (**7c**). R_f = 0.3 (30% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3336, 2978, 1678, 1456, 1268, 1122, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 15.5 Hz, 1H, vinyl), 7.60 (d, J = 8.3 Hz, 2H, Ar−H), 7.36−7.16 (m, 2H, Ar−H), 7.14 (d, J = 8.4 Hz, 1H, Ar−H), 6.87 (d, J = 8.5 Hz, 1H, vinyl), 5.75 (s, 1H, OH), 3.95 (s, 3H, OMe). HRMS calculated for $C_{16}H_{12}F_3O_3$: 309.0739 $[M + H]^+$. Found: 309.0751. Anal. ($C_{16}H_{11}F_3O_3$) C, H, O.

(*E*)-1-(3-Fluoro-4-methoxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one (15). The title compound was obtained in 80% yield from isovanillin **5** and 3-fluoro-4-methoxyacetophenone (**7d**). R_f = 0.3 (25% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3355, 2976, 1682, 1458, 1276, 1120, 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95−7.78 (m, 2H, Ar−H), 7.76 (d, J = 15.5 Hz, 1H, vinyl), 7.39−7.27 (m, 2H, Ar−H), 7.15−7.04 (m, 2H, Ar−H), 6.84 (d, J = 4.8 Hz, 1H, vinyl), 5.77 (s, 1H, OH), 3.97 (s, 3H, OMe), 3.94 (s, 3H, OMe); HRMS calculated for $C_{17}H_{16}FO_4$: 303.1033 $[M + H]^+$. Found: 303.1045. Anal. ($C_{17}H_{15}FO_4$) C, H, O.

(*E*)-3-(2-Hydroxy-3-methoxyphenyl)-1-(3,4,5-trifluorophenyl)-2-propen-1-one (18). The title compound was obtained in 77% yield from *o*-vanillin **6** and 3,4,5-trifluoroacetophenone (**7c**). $R_f = 0.3$ (30% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3405, 2987, 1675, 1540, 1455, 1247, 1130, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, $J = 15.5$ Hz, 1H, vinyl), 7.76 (d, $J = 7.5$ Hz, 2H, Ar−H), 7.34 (d, $J = 15.5$, Hz, 1H, vinyl), 7.23 (dd, $J = 3.5$, 3.5 Hz, 1H, Ar−H), 7.18 (d, $J = 6.5$ Hz, 1H, Ar−H), 6.93 (d, $J = 7.5$ Hz, 1H, Ar−H), 5.54 (s, 1H, OH), 3.91 (s, 3H, OMe); HRMS calculated for $C_{16}H_{12}F_3O_3$: 309.0739 $[M + H]^+$. Found: 309.0722. Anal. ($C_{16}H_{14}F_3O_3$) C, H, O.

(*E*)-1-(3-Fluoro-4-methoxyphenyl)-3-(2-hydroxy-3-methoxyphenyl)-2-propen-1-one (19). The title compound was obtained in 81% yield from *o*-vanillin **6** and 3-fluoro-4-methoxyacetophenone (**7d**). $R_f = 0.3$ (25% ethyl acetate/hexanes, v/v); IR (neat, NaCl) 3352, 2979, 1687, 1466, 1285, 1122, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, $J = 15.5$ Hz, 1H, vinyl), 8.11−8.06 (m, 2H, Ar−H), 7.96 (d, $J = 15.5$ Hz, 1H, vinyl), 7.41 (dd, $J = 3.5$, 3.5 Hz, 1H, Ar−H), 7.22 (t, $J = 8.4$ Hz, 1H, Ar−H), 7.16−7.03 (m, 2H, Ar−H), 6.56 (s, 1H, OH), 4.21 (s, 3H, OMe), 4.17 (s, 3H, OMe); HRMS calculated for $C_{17}H_{16}FO_4$: 303.1033 $[M + H]^+$. Found: 303.1053. Anal. ($C_{17}H_{15}FO_4$) C, H, O.

Measurement of Cell Viability. Cortical neuronal cell number and viability were assessed by using the reagent WST-1 (Roche, Indianapolis, IN). This colorimetric assay measures the metabolic activity of viable cells based on cleavage of the tetrazolium salt WST-1 substrate 4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2*H*-5-tetrazolio-1,3-benzene disulfonate] into formazan by mitochondria dehydrogenase in live cells. This was followed by incubation with WST-1 reagent at a dilution of 1:10 in the original conditioned media at 37 °C for 2 h. After thorough shaking, the formazan produced by the metabolically active cells in each sample was measured at a wavelength of 450 nm and a reference wavelength of 650 nm. Absorbance readings were normalized against control wells with untreated cells. Neuronal death was analyzed 24 h later, and the percentage of neurons undergoing actual neuronal death was normalized to the mean value found after a 24 h exposure to 300 μM NMDA (defined as 0) or a sham control (defined as 100).

Molecular Modeling. The lower energy conformers for **8**−**20** were searched by a molecular mechanics force field (MMFF) analysis[19] and were submitted to a geometry optimization and energy calculations by density functional theories (DFT) model[20] calculation at the B3LYP 6-31G** level. The HOMO, LUMO, and dipole values of the selected conformers were also calculated. All calculations and graphical representations were performed by using the SPARTAN 06 for Windows software package.

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Supporting Information Available: Spectral data of **8**, **12**, **16**, **17**, and **20**, experimental procedures for synthesis, frontier orbital maps of **8**−**20**, and biological evaluations (radical scavenging test, cell cultures, and DPPH bleaching kinetics). This material is available free of charge via the Internet at http://pubs.acs.org.

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