Full Paper

Resveratrol Derived Butyrylcholinesterase Inhibitors

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Novel polyhydroxylated (*E*)-stilbenes were synthesized by Mizoroki–Heck reactions and tested for their ability to inhibit the enzymes acetyl- and butyrylcholinesterase. Several of them are good inhibitors of butyrylcholinesterase; one of them carrying an extra fluorine substituent is a 94-fold stronger inhibitor of butyrylcholinesterase than of acetylcholinesterase.

Keywords: Acetylcholinesterase / Alzheimer disease / Butyrylcholinesterase / Resveratrol analogs

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Introduction

Neurodegenerative diseases are the sixth-leading cause of death in Europe and North-America. Worldwide up to 40 million people suffer from these diseases. Up to 8–10% of all elderly people have some sort of dementia, and dementia prevalence doubles for every five years of age starting at the age of 60 [1]. However, there are only a handful of drugs available for treating dementia, especially for the treatment of Alzheimer's disease (AD). AD strikes nearly a half million new patients each year; by 2050 approximately 115–116 million people will be affected by AD or another neurodegenerative disease. For a new drug to reduce memory loss annual sales exceeding $ 5 billion are expected. None of the drugs presently used, however, stops the underlying disease or delays the cell damage. Each of these drugs works by slowing down the disease progress by breaking down the key neurotransmitter acetylcholine (AcCh) or by regulating the activity of glutamate [2, 3].

AD patients suffer from an impaired memory, and the decline in memory and cognition is accompanied by a progressive deposition of aggregated amyloid beta-peptides (Aβ-peptides) forming amyloid plaques. This leads to neuronal degeneration and cholinergic dysfunctions in the brain [4]. The application of reversible acetylcholine esterase (ACE) inhibitors seems helpful in restoring AcCh levels and therefore cholinergic brain activity. Patients treated with ''classical'' ACE inhibitors often suffer from side effects like nausea and vomiting. These side effects have been attributed to an accompanying undesirable inhibition of butyrylcholine esterase (BCE) [5, 6]. In addition, the concentration of AcCh seems to be controlled by the action of ACE and BCE, since during AD the activity of ACE is decreased while that of BCE is high. Hence, it was suggested that BCE may *in vivo* also catalyze the hydrolysis of AcCh during this stage of disease. In summary, a specific inhibition of the BCE can raise the level of AcCh and improve recognition [7].

Phenols like curcumin (**1**) [8–10] and resveratrol (**2**, Fig. 1) [11–13] have been in the focus of scientific interest for to treat AD for several years, and stilbenes [14–17] seem of particular interest because these molecules are known for their various biological activities. Recently, we have accessed several different (*E*)-configurated stilbenes and explored their antibacterial/antifungal as well as their cytotoxic activity [18, 19]. Here, we describe the synthesis and cholinesterase inhibitory activity of several substituted resveratrol analogs.

Results and discussion

The straightforward synthesis of stilbenes has been carried out by many synthetic routes [20]. As previously shown, the use of Mizoroki–Heck reactions to synthesize (*E*)-configurated stilbenes from styrenes seems most rewarding [18, 19].

Thus, Wittig reaction of suitable substituted aldehydes with methyl triphenylphosphonium iodide and ^{t}BuOK in THF yielded styrenes [21] that were subjected to Mizoroki–Heck coupling reactions to yield the stilbenes. The use of triethanolamine (acting as well as a base and as a solvent) allows the economic synthesis of these compounds (Scheme 1) [22, 23].

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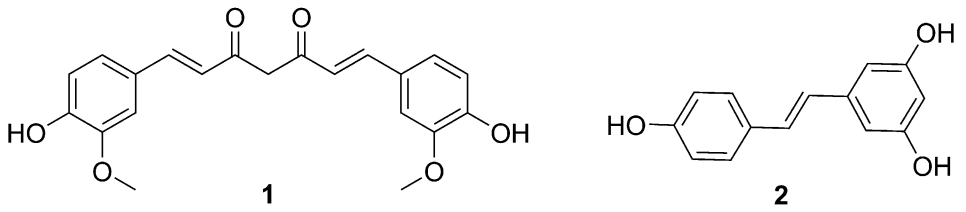
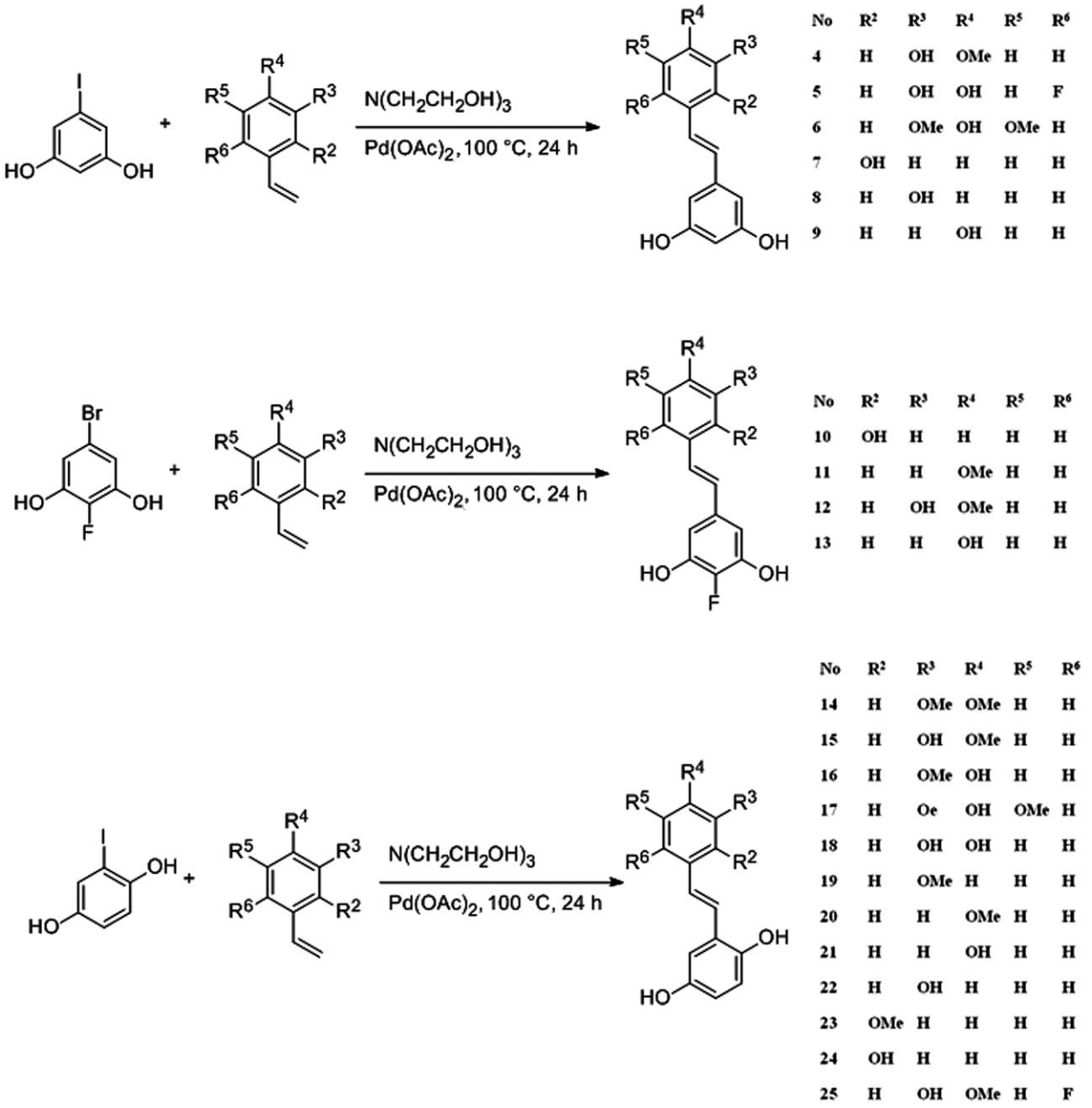


Figure 1. Structures of curcumine (**1**) and resveratrol (**2**).



No	R^2	R^3	R^4	R^5	R^6
4	H	OH	OMe	H	H
5	H	OH	OH	H	F
6	H	OMe	OH	OMe	H
7	OH	H	H	H	H
8	H	OH	H	H	H
9	H	H	OH	H	H

No	R^2	R^3	R^4	R^5	R^6
10	OH	H	H	H	H
11	H	H	OMe	H	H
12	H	OH	OMe	H	H
13	H	H	OH	H	H

No	R^2	R^3	R^4	R^5	R^6
14	H	OMe	OMe	H	H
15	H	OH	OMe	H	H
16	H	OMe	OH	H	H
17	H	Oe	OH	OMe	H
18	H	OH	OH	H	H
19	H	OMe	H	H	H
20	H	H	OMe	H	H
21	H	H	OH	H	H
22	H	OH	H	H	H
23	OMe	H	H	H	H
24	OH	H	H	H	H
25	H	OH	OMe	H	F

Scheme 1. Synthesis of the stilbenes by Mizoroki–Heck reactions; yields: 60–85% (cf. [18, 19, 23]).

Only (*E*) configurated stilbenes were obtained from these reactions. The coupling constant $^3J_{H,H}$ for the olefinic protons was found to be approx. 16 Hz for all products, thus showing a *trans* configuration of the double bond.

To screen the compounds for an inhibitory activity towards acylcholine esterase, Ellman's method was applied [24]. Thus, acetyl- or butyrylthiocholine iodide was used as a substrate for the corresponding esterase. On incubation of the substrate with the enzyme, thiocholine is released which can be measured by its reaction with Ellman's reagent, 5,5′-dithiobis(nitrobenzoic acid) leading to the subsequent formation of yellow 5-thio-2-nitrobenzoate. ACE from the electric eel and BCE from equine serum were used as enzymes. The enzyme BCE from equine serum shows high homology with human BCE; it was estimated that the rate of evolution for this enzyme was about 2.2 million years for 1% amino acid change [25]. The ACE from the electric eel shows high homology with the human nerve system ACE subtype. Thus, it has been widely established as a model of CNS-located inhibition of human ACE (which can be obtained only at very high costs) [7, 26].

For comparison, α-pinene (for the ACE), galantamine hydrobromide (for ACE and BCE) and testosterone (for the BCE) were used as known inhibitors in these assays. α-Pinene is a component of essential oils; many of them are known to have some beneficial effects on memory disorders or depression [29, 30]. Evaluation of the results (Table 1) showed that only a few stilbenes act as inhibitors for the enzymes.

Compounds **18** and **19** were found to be good inhibitors for the ACE; they are weaker inhibitors for the BCE. Compounds **7**, **10**, and **24** are excellent inhibitors for the BCE. Common feature of these compounds is the presence of one free hydroxyl group at the *ortho*-position. Comparing the results from both assays for compound **10** shows this compound a 94-fold stronger inhibitor for the BCE than for the ACE. Testing of the compounds in photometric SRB assays [27] for cytotoxic activity (using a panel of several human tumor cell lines as well as mouse fibroblasts) gave IC_{50} values >30 μM for each cell line, therefore indicating that only a low cytotoxicity can be established for these compounds.

In summary, several of the stilbenes show noteworthy differences concerning the inhibition of ACE and BCE. Thus, fluoro-substituted **10** is a >90-fold stronger inhibitor for BCE than for ACE. The compounds possess only low cytotoxicity. These biological properties and activities make substitutes stilbenes interesting candidates for further biological evaluation especially with respect to AD.

Table 1. IC_{50} values (in mM) for compounds **4**–**25** inhibiting ACE or BCE [from Ellman's assay [28], averaged from three independent measurements each performed at least in triplicate; error ± 10%; selectivity = IC_{50} (ACE)/IC_{50} (BCE); internal standards α-pinene (IC_{50} for ACE = 0.51 mM) and testosterone (IC_{50} = 0.06 mM for BCE) and galantamine hydrobromide (IC_{50} = 0.60 μM for ACE and IC_{50} = 1.55 μM for BCE)].

Compound	IC_{50} (mM, ACE)	IC_{50} (mM, BCE)
4	0.37	0.80
5	0.51	0.22
6	0.90	>1
7	0.56	0.01
8	>1	0.85
9	>1	0.40
10	0.94	0.01
11	0.21	0.46
12	>1	0.50
13	>1	0.44
14	0.58	0.41
15	0.55	0.51
16	0.34	0.29
17	0.25	0.13
18	0.06	0.33
19	0.08	0.23
20	0.32	0.35
21	0.33	0.21
22	0.37	0.10
23	0.41	0.15
24	0.56	0.01
25	0.16	0.24

Experimental

General

Melting points are uncorrected (Leica hot stage microscope), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000, or Unity 500 (δ given in ppm, J in Hz, internal Me4Si or CCl_3F), IR spectra (film or KBr pellet) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. MS spectra were taken on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. TLC was performed on silica gel (Merck 5554, detection by UV absorption). The solvents were dried according to usual procedures. The purity of the compounds was determined by HPLC and found to be >98%.

Biological testing

Ellman's assay [24] was performed in 96-well microtiter plates (Nunc) using a Spectrafluorplus instrument (Tecan) at 37°C and λ = 405 nm as outlined by Rhee et al. [28]. ACE (from electric eel, *Electrophorus electricus*) and BCE (from equine serum) were obtained from Sigma. In short, the lyophilized enzyme was dissolved in buffer (50 mM Tris–HCl, pH 8) to make a 1000 U/mL stock solution. This stock solution was further diluted (50 mM Tris–HCl, pH 8, containing 0.1% bovine serum albumine) to get 0.22 U/mL enzyme for the microtiter plate assay. For this assay the concentration of the substrate was 15 mM in water, for Ellman's reagent 3 mM in buffer (50 mM Tris–HCl, pH 8, containing 0.1 M NaCl and 0.02 M $MgCl_2 \cdot 6H_2O$). In the 96-well microtiter plates 25 μL of 15 mM substrate in water, 125 μL of 3 mM Ellman's reagent in buffer, 50 μL of additional buffer (50 mM Tris–HCl, pH 8, containing 0.1% bovine serum albumine), 25 μL of sample (10 mg/mL in MeOH diluted ten times with 50 mM Tris–HCl buffer, pH 8 to give a concentration of 1 mg/mL) were added, and the absorbance was measured at

$\lambda = 405$ nm every 12 s for five times. After 25 μL of 0.22 U/mL of the enzyme solution was added, the absorbance was again read every 12 s for ten times. The rates of reactions were calculated using JMP7 and GraphPad Prism 5 software. The results are averaged from three independent measurements each performed at least in triplicate. The cytotoxicity assay (SRB) was performed as previously described [18, 19].

General procedure for the Mizoroki–Heck reactions

A mixture of the styrene (3 mmol), the halogenated benzene (3 mmol), triethanolamine (3 mmol), and Pd(II) acetate (0.03 g) was stirred under argon at 100°C for 24 h. The reaction was cooled to 25°C, quenched by the addition of dil. aq. hydrochloric acid (2 N, 10 mL), and extracted with ether (3 × 100 mL). The organic phases were dried (Na_2SO_4), the solvents evaporated, and the crude product subjected to chromatography (silica gel, hexane/ethyl acetate mixtures).

*(E)-1-(3,5-Dihydroxyphenyl)-2-(2′-fluoro-5′-hydroxy-4′-methoxyphenyl)ethene (**5**)*

According to the general procedure, from 6-fluoro-3-hydroxy-4-methoxystyrene, 3,5-dihydroxyiodobenzene **5** (81.2%) was obtained as an off-white solid; mp 175–176°C; $R_f = 0.11$ (silica gel, hexanes/ethyl acetate, 3:1); IR (KBr): ν = 3345br, 2934m, 1699w, 1598s, 1513s, 1445s, 1339s, 1289s, 1195s, 1144s, 1014m cm^{-1}; UV–Vis (MeOH): λ_{max} (log ε) = 218 (4.24), 331 (4.36) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.22 (br s, 3 H, O*H*), 7.13 (d, 1 H, $^4J_{H,F}$ = 7.5 Hz, C*H* (6′)), 7.08 (d, 1 H, ^3J (trans) = 16.6 Hz, C*H* = (2)), 6.95 (d, 1 H, ^3J (trans) = 16.6 Hz, C*H* = (1)), 6.78 (d, 1 H, $^3J_{H,F}$ = 11.8 Hz, C*H* (3′)), 6.55 (d, 2 H, ^4J = 2.0 Hz, C*H* (2) + C*H* (6)), 6.29 (s, 1 H, C*H* (4)), 3.86 (s, 3 H, OCH_3) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ = 158.7 (C3 + C5, $C_{quart.}$), 153.5 (d, $^1J_{C,F}$ = 236.9 Hz, C2′, $C_{quart.}$), 147.9 (d, $^3J_{C,F}$ = 10.6 Hz, C4′, $C_{quart.}$), 143.0 (d, $^4J_{C,F}$ = 2.0 Hz, C5′, $C_{quart.}$), 139.6 (C1′, $C_{quart.}$), 128.7 (d, $^3J_{C,F}$ = 4.8 Hz, *C*H=), 119.9 (d, $^4J_{C,F}$ = 3.9 Hz, *C*H=), 116.6 (d, $^2J_{C,F}$ = 12.5 Hz, C1′, $C_{quart.}$), 111.5 (d, $^3J_{C,F}$ = 4.8 Hz, C6′, *C*H), 104.9 (C2 + C6, *C*H), 102.2 (C4, *C*H), 99.8 (d, $^2J_{C,F}$ = 28.8 Hz, C3′, *C*H), 55.7 (s, O*C*H_3) ppm; ^{19}F NMR (188 MHz, acetone-d_6): δ = −128.8 (dd, $^4J_{F,H}$ = 7.5, $^3J_{F,H}$ = 11.8 Hz, -*F*) ppm; MS (ESI, MeOH): *m*/*z* = 275.5 (79% [M−H]$^-$); 321.3 (100% [M+HCO_2]$^-$); 550.9 (70% [2M−H)]$^-$); analysis for $C_{15}H_{13}FO_4$ (276.26): C, 65.21; H, 4.74; found C, 64.99; H, 4.83.

*(E)-4′-Fluoro-2,3′,5′-trihydroxystilbene (**10**)*

According to the general procedure, from 2-hydroxystyrene, 3,5-dihydroxy-4-fluorobromobenzene **10** (69.8%) was obtained as a beige-colored solid; mp 193–194°C; $R_f = 0.21$ (silica gel, hexanes/ethyl acetate, 3:1); IR (KBr): ν = 3395br, 1638w, 1604m, 1576m, 1523s, 1486m, 1457w, 1369m, 1340m, 1292m, 1261m, 1191s, 1135m, 1088w, 1055s cm^{-1}; UV–Vis (MeOH): λ_{max} (log ε) = 236 (4.30), 291 (4.30), 325 (4.36) nm; ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.46 (d, 1 H, ^3J = 7.7 Hz, C*H* (6)), 7.24 (d, 1 H, ^3J (trans) = 16.6 Hz, C*H* = (1), 7.04–7.01 (m, 1 H, C*H* (4)), 6.90 (d, 1 H, ^3J (trans) = 16.6 Hz, C*H* = (2)), 6.79–6.77 (m, 2 H, C*H* (3) + C*H* (5)), 6.55 (d, 2 H, $^4J_{H,F}$ = 8.0 Hz, C*H* (2′) + C*H* (6′)) ppm; ^{13}C NMR (100 MHz, MeOH-d_4): δ = 156.0 (C2, $C_{quart.}$), 146.9 (d, $^2J_{C,F}$ = 10.7 Hz, C3′ + C5′, $C_{quart.}$), 142.1 (d, $^1J_{C,F}$ = 236.8 Hz, C4′, $C_{quart.}$), 135.2 (d, $^4J_{C,F}$ = 4.4 Hz, C1′, $C_{quart.}$), 129.3 (C6, *C*H), 128.7 (*C*H=), 127.4 (C4, *C*H), 125.7 (C1, $C_{quart.}$), 124.4 (*C*H=), 120.7 (C5, *C*H), 116.6 (C3, *C*H), 107.4 (d, $^3J_{C,F}$ = 4.5 Hz, C2′ + C6′, *C*H) ppm; ^{19}F NMR (188 MHz, acetone-d_6): δ = −165.0 (*t*, $^4J_{F,H}$ = 8.0 Hz, *F*) ppm; MS (ESI, MeOH): *m*/*z* = 245.6 (100% [M−H]$^-$); 291.5 (60% [M+HCO_2]$^-$); 491.3 (52% [2M−H]$^-$); analysis for $C_{14}H_{11}FO_3$ (246.23): C, 68.29; H, 4.50; found C, 68.01; H, 4.73.

*(E)-3′,5′-Dihydroxy-4′-fluoro-4-methoxystilbene (**11**)*

According to the general procedure, from 4-methoxystyrene, 3,5-dihydroxy-4-fluoro-bromobenzene **11** (82.3%) was obtained as a colorless solid; mp 173–174°C; $R_f = 0.38$ (silica gel, hexanes/ethyl acetate, 3:1); IR (KBr): ν = 3424s, 1601m, 1575w, 1539s, 1510m, 1452w, 1417w, 1378m, 1365m, 1329w, 1301m, 1247m, 1177s, 1112w, 1051s, 1013m, 1003m cm^{-1}; UV–Vis (MeOH): λ_{max} (log ε) = 217 (4.45), 305 (4.57) nm; ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.41 (d, 2 H, ^3J = 8.7 Hz, C*H* (2) + C*H* (6)), 6.89 (d, 1 H, ^3J (trans) = 16.4 Hz, C*H* = (1)), 6.88 (d, 2 H, ^3J = 8.7 Hz, C*H* (3) + C*H* (5)), 6.78 (d, 1 H, ^3J (trans) = 16.4 Hz, C*H* = (2)), 6.55 (d, 2 H, $^4J_{H,F}$ = 7.1 Hz, C*H* (2′) + C*H* (6′)), 4.82 (br s, 2 H, O*H*), 3.79 (s, 3 H, OCH_3) ppm; ^{13}C NMR (100 MHz, MeOH-d_4): δ = 160.8 (C4, $C_{quart.}$), 147.0 (d, $^2J_{C,F}$ = 11.0 Hz, C3′ + C5′, $C_{quart.}$), 142.1 (d, $^1J_{C,F}$ = 236.6 Hz, C4′, $C_{quart.}$), 134.8 (d, $^4J_{C,F}$ = 4.6 Hz, C1′, $C_{quart.}$), 131.5 (C1, $C_{quart.}$), 128.7 (*C*H=), 128.6 (C2 + C6, *C*H), 127.1 (*C*H=), 115.1 (C3 + C5, *C*H), 107.3 (C2′ + C6′, *C*H), 55.7 (O*C*H_3) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −165.1 (*t*, $^4J_{F,H}$ = 7.1 Hz, -*F*) ppm; MS (ESI, MeOH): *m*/*z* = 259.3 (100% [M−H]$^-$), 304.9 (19% [M+HCO_2]$^-$), 518.8 (71% [2M−H]$^-$); analysis for $C_{15}H_{13}FO_3$ (260.26): C, 69.22; H, 5.03; found C, 68.97; H, 5.15.

*(E)-2′,5′-Dihydroxy-3,4-dimethoxystilbene (**14**)*

According to the general procedure, from 3,4-dimethoxystyrene, 2,5-dihydroxyiodobenzene **14** (79.0%) was obtained as an off-white solid; mp 178–179°C; $R_f = 0.63$ (silica gel, hexanes/ethyl acetate, 1:1); IR (KBr): ν = 3418br, 2945s, 2831s, 1845w, 1636m, 1600s, 1517s, 1452s, 1417s, 1384s, 1310m, 1265s, 1237s, 1193s, 1159s, 1139s, 1092w, 1039w, 1025s cm^{-1}; UV–Vis (MeOH): λ_{max} (log ε) = 227 (4.30), 314 (3.99), 367 (4.03) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.00 (br s, 1 H, O*H*), 7.76 (br s, 1 H, O*H*), 7.33 (d, 1 H, ^3J (trans) = 16.4 Hz, C*H* = (1)), 7.18 (d, 1 H, ^4J = 1.9 Hz, C*H* (2)), 7.06 (d, 1 H, ^3J (trans) = 16.4 Hz, C*H* = (2)), 7.06–7.04 (m, 2 H, C*H* (6) + C*H* (6′)), 6.91 (d, 1 H, ^3J = 8.3 Hz, C*H* (5)), 6.72 (d, 1 H, ^4J = 8.8 Hz, C*H* (3′)), 6.58 (dd, ^3J = 8.8 Hz, ^4J = 1.9 Hz, C*H* (4′)), 3.85 (s, 3 H, OCH_3), 3.80 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ = 151.3 (C5′, $C_{quart.}$), 150.5 (C3, $C_{quart.}$), 150.1 (C3′, $C_{quart.}$), 148.7 (C4, $C_{quart.}$), 132.1 (C1, $C_{quart.}$), 128.9 (*C*H=), 126.0 (C1′, $C_{quart.}$) 122.5 (*C*H=), 120.5 (C2, *C*H), 117.3 (C3′, *C*H), 116.0 (C4′, *C*H), 113.0 (C5 + C6′, *C*H), 110.3 (C2, *C*H), 56.1 (O*C*H_3), 56.0 (O*C*H_3) ppm; MS (ESI, MeOH): *m*/*z* = 271.4 (41% [M−H]$^-$); 317.2 (74% [M+HCO_2]$^-$); 542.9 (100% [2M−H]$^-$); analysis for $C_{16}H_{16}O_4$ (272.30): C, 70.57; H, 5.92; found C, 70.38; H, 6.09.

*(E)-3,5-Dimethoxy-4,2′,5′-trihydroxystilbene (**17**)*

According to the general procedure, from 3,5-dimethoxy-4-hydroxystyrene, 2,5-dihydroxyiodobenzene **17** (65.3%) was obtained as a colorless solid; mp 89–91°C; $R_f = 0.45$ (silica gel, hexanes/ethyl acetate, 1:1); IR (KBr): ν = 3421br, 2938w, 1610w, 1517w, 1458w, 1339w, 1215w, 1113w cm^{-1}; UV–Vis (MeOH): λ_{max} (log ε) = 218 (4.45), 309 (4.05) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.21 (d, 1 H, ^3J (trans) = 16.6 Hz, C*H* = (1)), 7.02 (d, 1 H, ^3J (trans) = 16.6 Hz, C*H* = (2)), 6.96 (d, 1 H, ^4J = 2.9 Hz, C*H* (6′)), 6.83 (s, 2 H, C*H* (2) + C*H* (6)), 6.68 (d, 1 H, ^3J = 8.7 Hz, C*H* (3′)), 6.55 (dd, ^3J = 8.7 Hz, ^4J = 2.9 Hz, C*H* (4′)), 3.86 (s, 6 H, OCH_3) ppm; ^{13}C

NMR (100 MHz, acetone-d_6): $\delta = 149.9$ (C5′, $C_{quart.}$), 147.9 (C3 + C5, $C_{quart.}$), 147.6 (C2′, $C_{quart.}$), 135.1 (C4, $C_{quart.}$), 131.6 (*C*H=), 129.54 (C1, $C_{quart.}$), 125.2 (C1′, $C_{quart.}$), 120.9 (*C*H=), 116.0 (C3′, *C*H), 114.7 (C4′, *C*H), 111.3 (C6′, *C*H), 103.4 (C2 + C6, *C*H), 55.3 (OCH_3) ppm; MS (ESI, MeOH): $m/z = 287.2$ (100% $[M-H]^-$), 332.9 (15% $[M+HCO_2]^-$); analysis for $C_{16}H_{16}O_5$ (288.30): C, 66.66; H, 5.59; found C, 66.43; H, 5.71.

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The authors declare that there are no conflicts of interest.

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