Full Paper

Synthesis and Radical Scavenging Activities of Resveratrol Analogs

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Highly substituted polyhydroxylated (*E*)-stilbenes were synthesized by Mizoroki–Heck reactions and tested for their ability to act as radical scavenger. One of the 56 stilbenes included in this study and investigated in DPPH assays gave an SC_{50} value of 11.0 μM, hence exhibiting an about 9.3 times higher activity than resveratrol. As shown in a photometric SRB assay using mouse NiH 3T3 fibroblasts, this compound is not cytotoxic up to concentrations of <30 μM.

Keywords: French paradox / Radical scavengers / Resveratrol analogs

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Introduction

Resveratrol (**1**, (*E*)-3,5,4′-trihydroxystilbene, Fig. 1) is a natural phenol and phytoalexin. It is produced by >70 different plant species, especially grapevines, pines, and legumes but also in pomegranates, soy beans, and in peanuts [1]. Since its initial discovery in 1940 [2] many biological activities have been associated [1] with this compound, including antifungal [3], antibacterial [4], antiviral [5], anticancer [6, 7], estrogenic [8], platelet anti-aggregating [9], and heart protecting activities [10, 11].

Resveratrol inhibits cyclooxygenases [6, 12, 13], and, in addition, is has been suggested that **1** is at least partly responsible for the so-called French paradox. The French paradox describes improved cardiovascular outcomes including a low incidence of coronary heart diseases [10, 14] despite the consumption of a high-fat diet by French people [15]. Although **1** is believed to be effective in preventing and treating several chronic diseases, the number of structure–activity relationships for **1** and analogs remained small. Thus, several halogenated analogs of **1** have been investigated by Chi and coworkers [16], and Kang et al. [17] evaluated several derivatives as potential antioxidants. Glycosylated resveratrol derivatives have been investigated by Orsini et al. [18], and Fauconneau et al. [19] investigated the ability of natural phenolic compounds from *Vitis vinifera* cell cultures to act as radical scavengers. Evidence from different studies suggests that the ability of these natural phenolic compounds to act as radical scavengers is one of the major reasons for the phenomenon known as French paradox.

As previously shown, highly substituted stilbenes carrying an (*E*) configurated double bond can be synthesized in good yields using a two-step sequence consisting of a Wittig olefination of substituted benzaldehydes to afford styrenes followed by a Mizoroki–Heck reaction (Scheme 1). Recently, we have accessed several different (*E*)-configurated stilbenes and explored their antibacterial/antifungal as well as their cytotoxic activity [20, 21]. Here, we describe the synthesis and radical scavenger inhibitory activity of >50 substituted stilbenes **1**–**56**.

Results and discussion

Although the straightforward synthesis of stilbenes has been carried out by many synthetic routes [22], the use of Mizoroki–Heck reactions to synthesize (*E*)-configurated stilbenes from styrenes results in short syntheses from commercially available starting materials and good yields of the products [20, 21].

Thus, Wittig reaction of suitable substituted benzaldehydes with methyl triphenylphosphonium iodide and ^{t}BuOK in THF yielded styrenes [23] that were subjected to Mizoroki–Heck coupling reactions. The use of triethanolamine (acting as well as a base and as a solvent) allowed the economic synthesis of compounds **1**–**56** [24, 25].

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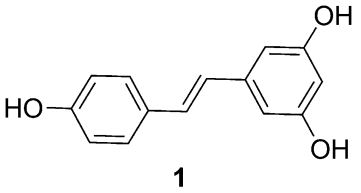

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Figure 1. Structure of resveratrol (**1**).

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging effect assays were carried out for compounds **1**–**56** following the procedure by Blois [26]. The results of these experiments are summarized in Table 1 and Figs. 2–5.

Evaluation of the results showed that 3-hydroxy-4-methoxy as well as 4-hydroxy-3-methoxy substituted stilbenes (Fig. 2) gave low SC_{50} values as long as in the second ring hydroxyl groups were present at positions 2′,5′ or 3′,5′. Compounds **7**, **9**–**11** (having been synthesized starting from isovanilline) exhibited higher SC_{50} values as compared to compounds **14**–**17** (having been synthesized starting from vanilline).

Figure 3 summarizes the SC_{50} values for 3,4-dimethoxy-substituted stilbenes as well as for stilbenes having been synthesized from syringaldehyde and for some fluorinated stilbenes. 3,5-Dimethoxy-4-hydroxy substituted stilbenes showed SC_{50} values <130 μM (130 μM being the cut-off in these experiments); for example, compounds **18** (SC_{50} = 52 μM) and **19** (SC_{50} = 43 μM) possess significantly stronger radical scavenging activity than compounds carrying a 3-hydroxy-4-methoxy substitution. Trifluoro compound **21** exhibits a lower SC_{50} value than 3′,5′-dimethoxy-4-fluoro-stilbene **20** whereas compound **8** showed SC_{50} > 130 μM and **7** gave 89 μM.

Many (Fig. 4) of the 2-hydroxy, 3-hydroxy, and 4-hydroxy stilbenes **27**–**33**, **35**–**42**, and **44**–**51**, however, showed only low activity as depicted in Fig. 4.

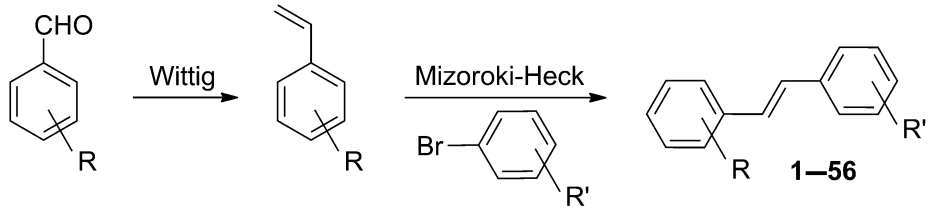
Noteworthy seems compound **54** (Fig. 3) with an SC_{50} = 13 μM. Finally, compound **56** (Fig. 5) has the lowest SC_{50} value (SC_{50} = 11.0 μM), which corresponds to the highest free radical scavenging activity. Thus, this compound exhibited a ca. 9.3 times higher activity than resveratrol (**1**) itself.

Table 1. Radical scavenging activity (DPPH assay [26] SC_{50} in μM); all experiments were carried out in triplicate on 96-well microtiter plates and repeated three times. Variation was generally ±7%; cut-off: 130 μM.

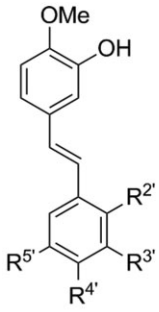
Compound	SC_{50} (μM)	IC_{50} (μM)	Compound	SC_{50} (μM)	IC_{50} (μM)
1	102	24.2	**30**	>130	>30
2	105	>30	**31**	73	7.5
3	129	>30	**32**	68	9.6
4	50	>30	**33**	52	8.2
5	>130	>30	**34**	30	7.2
6	>130	0.2	**35**	>130	29.8
7	89	0.9	**36**	>130	>30
8	>130	>30	**37**	>130	11.8
9	73	1.5	**38**	>130	>30
10	39	>30	**39**	>130	>30
11	56	2.1	**40**	>130	25.8
12	64	>30	**41**	29	10.5
13	49	17.4	**42**	52	19.6
14	76	15.0	**43**	22	11.1
15	52	>30	**44**	>130	26.0
16	19	9.5	**45**	>130	>30
17	46	>30	**46**	>130	14.8
18	52	15.0	**47**	>130	>30
19	43	10.8	**48**	>130	>30
20	108	10.6	**49**	>130	>30
21	53	>30	**50**	22	12.4
22	70	1.9	**51**	118	>30
23	17	>30	**52**	>130	0.2
24	24	>30	**53**	119	2.7
25	>130	>30	**54**	13	21.1
26	26	4.5	**55**	81	0.05
27	>130	12.2	**56**	11	>30
28	>130	11.5	(+)-Catechin*	20.2	n.d.
29	>130	6.9	(−)-Epicatechin*	15.7	n.d.

Cytotoxicity (IC_{50} values (in μM) from SRB assays [27]; n.d. not determined) for compounds **1**–**56** using mouse fibroblasts NiH 3T3 [21]. Values are derived from dose response curves obtained by measuring the percentage of viable cells relative to untreated controls after 96 h exposure of the test compounds to the cell line. The IC_{50} value was estimated by linear regression between the value before and after the 50% line is crossed in a dose–response curve. Values are the average from at least five independent experiments; cut-off: 30 μM, variation was generally ±7%.

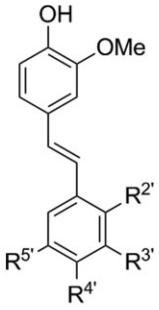
* These values were taken from Ref. [16].



Scheme 1. General scheme for the synthesis of the stilbenes **1**–**56** by a sequence consisting of a Wittig olefination followed by a Mizoroki–Heck reaction.



No	R2'	R3'	R4'	R5'
2	H	OGlc	H	OH
3	H	OH	H	OH
4	H	OH	F	OH
6	H	OMe	H	OMe
7	H	OMe	F	OMe
8	H	F	F	F
9	OMe	H	H	OMe
10	OH	H	H	OH
11	OMe	H	OMe	H



No	R2'	R3'	R4'	R5'
14	H	OMe	F	OMe
15	OMe	H	H	OMe
16	OH	H	H	OH
17	OMe	H	OMe	H

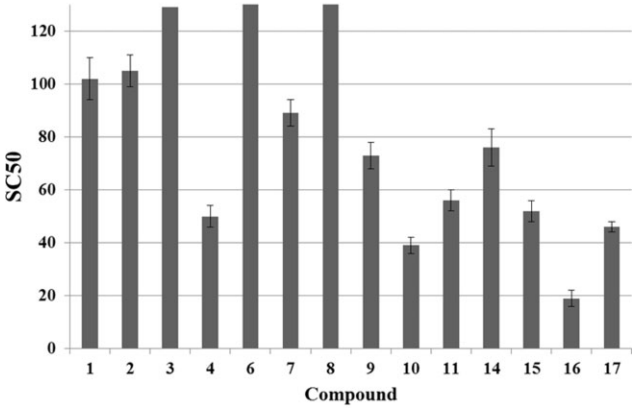
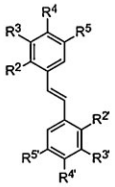


Figure 2. Structures and SC_{50} values (in μM, from DPPH assay) for compounds **1**–**4**, **7**–**11**, and **14**–**17**.



No	R2	R3	R4	R5	R2'	R3'	R4'	R5'
12	H	H	OMe	OMe	H	OH	F	OH
13	H	H	OMe	OMe	OH	H	H	OH
18	H	OMe	OH	OMe	H	OMe	H	OMe
19	H	OMe	OH	OMe	H	OH	H	OH
20	H	OMe	OH	OMe	H	OMe	F	OMe
21	H	OMe	OH	OMe	H	F	F	F
22	H	OMe	OH	OMe	OMe	H	H	OMe
23	H	OMe	OH	OMe	OH	H	H	OH
24	H	OMe	OH	OMe	OMe	H	OMe	H
5	F	H	OMe	OH	H	OH	H	OH
52	F	H	OMe	OH	H	OMe	F	OMe
53	F	H	OMe	OH	OMe	H	H	OMe
54	F	H	OMe	OH	OH	H	H	OH
55	F	H	OMe	OH	OMe	H	OMe	H

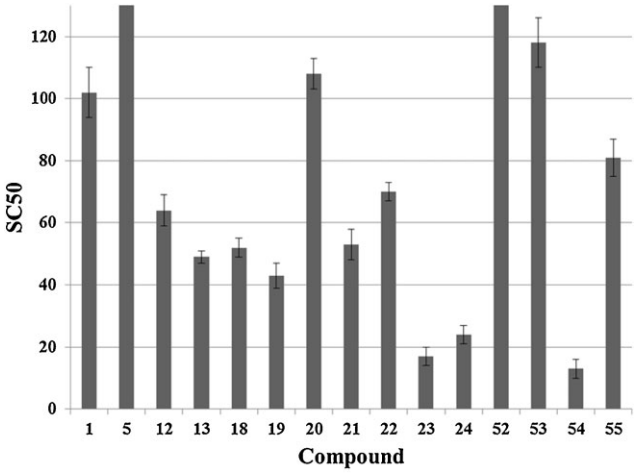
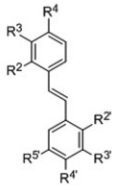


Figure 3. SC_{50} values (in μM, from DPPH assay) for compounds resveratrol (**1**), **5**, **12**, **13**, **18**–**24**, and **52**–**54**.

Besides the stilbenes, several flavonoids are known for their high free radical scavenging activities. Thus, for (+)-catechin and (−)-epicatechin SC_{50} values of 20.2 and 15.7 μM have been reported [16]. Compounds **16**, **23**, **26**, **29**, and **43** showed similar high activity. Compounds **54** and **56** showed an even better radical scavenging activity.

As a prerequisite to extended biological testing of these compounds, cytotoxicity has to be low. For all compounds reported here, cytotoxicity has been determined using the photometric SRB assay [27] employing the mouse fibroblast cell line NiH 3T3 [21]. In this assay resveratrol (**1**) showed a cytotoxicity $IC_{50} = 24.2$ μM. Most active compounds **54** and **56** gave in this assay similar high IC_{50} values ($IC_{50} = 21.1$ μM for **54**) or showed even less cytotoxicity ($IC_{50} > 30$ μM for **56**). These biological properties and activities make substituted stilbenes interesting candidates for further biological evaluation. Interestingly enough, the (*Z*) analog of **56** has been suggested [28] as a cellular rejuvenation compound to be used in skin cosmetics, and the bis(bibenzyl) analogs of **56** were found to act as inhibitors of the nitric acid synthase [29]. Inhibition of this enzyme seems very important to control inflammatory diseases. In addition, for some of the same class of compounds antitrypanosomal activity [30] as well as the induction of vasorelaxation [31] has been reported quite recently. Thus, syntheses of analogs of **54** and **56** are currently pursued, and further biological evaluation is in progress.



No	R^2	R^3	R^4	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
1	H	H	OH	H	OH	H	OH
27	H	H	OH	H	OMe	H	OMe
28	H	H	OH	H	OMe	F	OMe
29	H	H	OH	H	F	F	F
30	H	H	OH	H	OH	F	OH
31	H	H	OH	OMe	H	H	OMe
32	H	H	OH	OH	H	H	OH
33	H	H	OH	OMe	H	OMe	H
35	H	OH	H	H	OMe	H	OMe
36	H	OH	H	H	OH	H	OH
37	H	OH	H	H	OMe	F	OMe
38	H	OH	H	H	F	F	F
39	H	OH	H	H	OH	F	OH
40	H	OH	H	OMe	H	H	OMe
41	H	OH	H	OH	H	H	OH
42	H	OH	H	OMe	H	OMe	H
44	OH	H	H	H	OMe	H	OMe
45	OH	H	H	H	OH	H	OH
46	OH	H	H	H	OMe	F	OMe
47	OH	H	H	H	F	F	F
48	OH	H	H	H	OH	F	OH
49	OH	H	H	OMe	H	H	OMe
50	OH	H	H	OH	H	H	OH
51	OH	H	H	OMe	H	OMe	H

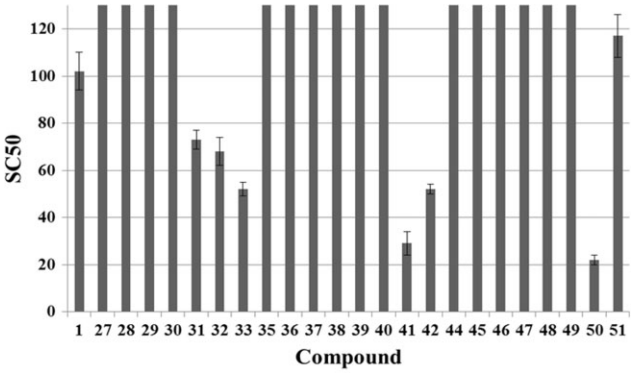
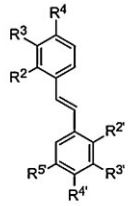


Figure 4. SC_{50} values (in μM, from DPPH assay) for compounds resveratrol (**1**) and 2-hydroxy-, 3-hydroxy- and 4-hydroxy-substituted stilbenes **27**–**33**, **35**–**42**, and **44**–**51**.



No	R^2	R^3	R^4	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
25	H	H	OMe	H	OH	F	OH
26	H	H	OMe	OH	H	H	OH
34	H	OMe	H	OH	H	H	OH
43	OMe	H	H	OH	H	H	OH
56	H	OH	OH	OH	H	H	OH

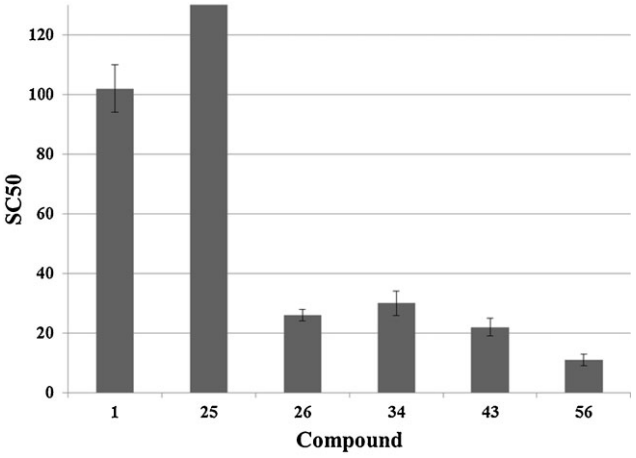


Figure 5. SC_{50} values (in μM, from DPPH assay) for compounds **1**, **25**, **26**, **34**, **43**, and **56**.

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 Me_4Si 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%.

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). The synthesis of compounds **1**–**3**, **6**, **7**, **9**–**11**, **14**, **16**–**20**, **26**–**47**, and **48**–**55** has already been described [20, 21, 24, 32, 33].

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

According to the general procedure from 3,5-dihydroxyiodobenzene and 4-fluoro-3,5-dihydroxybromobenzene compound **4** (72.3%) was obtained as an off-white solid; mp 177–179°C; $R_f = 0.11$ (silica gel, hexanes/ethyl acetate, 3:1); IR (KBr): $\nu = 3330$ br, 1606m, 1539m, 1513m, 1438m, 1376m, 1267m, 1187m, 1128m, 1053m, 1025m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 239 (4.23), 343 (4.24) nm; ^1H NMR (400 MHz, acetone-d_6): $\delta = 7.06$ (*d*, 1H, $J = 1.7$ Hz, C*H*(2)), 6.94 (*dd*, 1H, $J = 8.5$, 2.0 Hz, C*H*

(6)), 6.89 (*d*, 1H, J_{trans} = 16.4 Hz, C*H*= (2)), 6.88 (*d*, 1H, J = 8.5 Hz, C*H* (5′)), 6.83 (*d*, 1H, J_{trans} = 16.4 Hz, C*H*= (1)), 6.68 (*d*, 2H, $^4J_{H,F}$ = 7.5 Hz, C*H* (6′) + C*H* (2′)), 3.82 (s, 3H, OC*H*3) ppm; ^{13}C NMR (100 MHz, acetone-d$_6$): δ = 148.2 (C4), 147.5 (C3), 146.5 (*d*, $^2J_{C,F}$ = 9.1 Hz, C3′ + C5′), 141.4 (*d*, $^1J_{C,F}$ = 237.0 Hz, C4′), 134.4 (*d*, $^4J_{C,F}$ = 4.1 Hz, C1′), 131.6 (C1), 128.8 (*C*H=), 126.7 (*C*H=), 119.6 (C5), 113.1 (C6), 112.3 (C2), 107.1 (C2′ + C6′), 56.2 (O*C*H$_3$) ppm; ^{19}F NMR (188 MHz, CDCl$_3$): δ = −163.7 (*t*, $^4J_{F,H}$ = 7.5 Hz) ppm; MS (ESI, MeOH): *m*/*z* = 275.3 (100% [M−H]$^-$), 320.9 (15% [M+HCO$_2$]$^-$); 550.7 (38% [2M−H]$^-$); analysis for $C_{15}H_{13}FO_4$ (276.26): C, 65.21; H, 4.74; found: C, 65.01; H, 4.93.

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

According to the general procedure from dihydroxyiodobenzene compound **5** (71.2%) 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 (methanol): λ_{max} (log ε) = 218 (4.24), 331 (4.36) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.22 (br s, 3H, O*H*), 7.13 (*d*, 1H, $^4J_{H,F}$ = 7.5 Hz, C*H* (6′)), 7.08 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (2)), 6.95 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (1)), 6.78 (*d*, 1H, $^3J_{H,F}$ = 11.8 Hz, C*H* (3′)), 6.55 (*d*, 2H, ^4J = 2.0 Hz C*H* (2) + C*H* (6)), 6.29 (s, 1H, C*H* (4)), 3.86 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ = 158.7 (C3 + C5), 153.5 (*d*, $^1J_{C,F}$ = 236.9 Hz, C2′), 147.9 (*d*, $^3J_{C,F}$ = 10.6 Hz, C4′), 143.0 (*d*, $^4J_{C,F}$ = 2.0 Hz, C5′), 139.6 (C1′), 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′), 111.5 (*d*, $^3J_{C,F}$ = 4.8 Hz, C6′), 104.9 (C2 + C6), 102.2 (C4), 99.8 (*d*, $^2J_{C,F}$ = 28.8 Hz, C3′), 55.7 (s, OCH_3) ppm; ^{19}F NMR (188 MHz, acetone-d_6): δ = −128.8 (*dd*, $^4J_{F,H}$ = 7.5 Hz, $^3J_{F,H}$ = 11.8 Hz); MS (ESI, MeOH): *m*/*z* = 275.5 (79% [M−H]$^-$), 321.3 (100% [M+HCO$_2$]$^-$), 550.9 (70% [M(M−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) 3-Hydroxy-4-methoxy-3′,4′,5′-trifluorostilbene (**8**)*

According to the general procedure from 3,4,5-tribromofluorobenzene and 3-hydroxy-5-methoxystyrene compound **8** (85.6%) was obtained as a colorless solid; mp 137–138°C; R_f = 0.29 (silica gel, hexanes/ethyl acetate, 9:1); IR (KBr): ν = 3528br, 3030m, 1616w, 1604m, 1582w, 1528m, 1508m, 1459m, 1441m, 1367w, 1341w, 1307w, 1293w, 1263m, 1238m, 1205m, 1158w, 1180w, 1158w, 1128m, 1039m, 1022m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 204 (4.34), 326 (4.41) nm; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.09 (*d*, 1H, ^4J = 2.1 Hz, C*H* (2)), 7.05–7.01 (m, 2H, C*H* (2′) + C*H* (6′)), 6.93 (*dd*, 1H, ^3J = 8.3 Hz, ^4J = 2.1 Hz, C*H* (6)), 6.88 (*d*, 1H, $^3J_{trans}$ = 16.2 Hz, C*H*= (1)), 6.81 (*d*, 1H, ^3J = 8.3 Hz, C*H* (5)), 6.74 (*d*, 1H, $^3J_{trans}$ = 16.2 Hz, C*H*= (2)), 5.60 (br s, 1H, O*H*), 3.89 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ = 151.7 (m, $^1J_{C,F}$ = 214.0 Hz, C3′ + C5′), 146.9 (C4), 145.9 (C3), 138.7 (m, $^1J_{C,F}$ = 247.7 Hz, C4′), 133.8 (m, C1′), 130.6 (*C*H=), 129.9 (C1), 124.0 (*C*H=), 119.7 (C6), 111.8 (C2), 110.6 (C5), 109.8 (C2′ + C6′), 55.9 (O*C*H$_3$), 56.1 (O*C*H$_3$), 55.7 (O*C*H$_3$) ppm; ^{19}F NMR (188 MHz, CDCl$_3$): δ = −135.2 (m, −*F* (4′)), −160.5 (m, −*F* (3′;5′)) ppm; MS (ESI, MeOH): *m*/*z* = 279.3 (100% [M−H]$^-$), 325.0 (12% [M+HCO$_2$]$^-$), 558.9 (12% [2M−H]$^-$); analysis for $C_{15}H_{11}F_3O_2$ (280.24): C, 64.29; H, 3.96; found: C, 64.13; H, 4.09.

*(E) 3′,5′-Dimethoxy-3,4-dihydroxy-4′-fluorostilbene (**12**)*

According to the general procedure from 2,5-dihydroxy-4-fluorobromobenzene and 3,4-dimethoxystyrene compound **12** (63.7%) was obtained as a colorless solid; mp 166–168°C; R_f = 0.38 (silica gel, hexanes/ethyl acetate, 3:1); IR (KBr): ν = 3385 br, 2989w, 2845w, 1598w, 1518w, 1454w, 1423w, 1378w, 1331w, 1295w, 1264w, 1192w, 1160w, 1138w, 1052w, 1021w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 236 (4.35), 341 (4.44) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.22 (*d*, 1H, ^4J = 1.9 Hz, C*H* (2)), 7.09 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (1)), 7.07 (*dd*, 1H, ^3J = 8.1 Hz, ^4J = 1.9 Hz, C*H* (6)), 7.01–6.97 (m, 3H, C*H*= (2) + C*H* (2′) + C*H* (6′)), 6.93 (*d*, 1H, ^3J = 8.1 Hz, C*H* (5)), 3.45 (s, 3H, OC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, acetone-d$_6$): δ = 153.2 (C4), 151.3 (C3), 150.6 (*d*, $^2J_{C,F}$ = 11.9 Hz C3′ + C5′), 140.0 (*d*, $^1J_{C,F}$ = 243.0 Hz, C4′), 135.2 (*d*, $^4J_{C,F}$ = 8.9 Hz, C1′), 130.8 (C1) 130.6 (*C*H=), 125.4 (*C*H=), 121.7 (C6), 112.7 (C5 + C2), 105.6 (*d*, $^3J_{C,F}$ = 17.6 Hz, C2′ + C6′), 56.0 (O*C*H$_3$) ppm; ^{19}F NMR (188 MHz, acetone-d_6): δ = −162.3 (*t*, $^4J_{F,H}$ = 7.8 Hz); MS (ESI, MeOH): *m*/*z* = 291.3 (100% [M−H]$^-$), 336.9 (20% [M+HCO$_2$]$^-$), 582.7 (77% [2M−H]$^-$); analysis for $C_{16}H_{15}FO_4$ (290.29): C, 66.20; H, 5.21; found: C, 66.17; H, 5.29.

*(E) 2′,5′-Dihydroxy-3,4-dimethoxystilbene (**13**)*

According to the general procedure from 2,5-dihydroxyiodobenzene and 3,4-dimethoxystyrene compound **13** (69.0%) 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 (methanol): 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, 1H, O*H*), 7.76 (br s, 1H, O*H*), 7.33 (*d*, 1H, 3J_{trans} = 16.4 Hz, C*H*= (1)), 7.18 (*d*, 1H, ^4J = 1.9 Hz, C*H* (2)), 7.06 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (2)), 7.06–7.04 (m, 2H, C*H* (6) + C*H* (6′)), 6.91 (*d*, 1H, ^3J = 8.3 Hz, C*H* (5)), 6.72 (*d*, 1H, ^4J = 8.8 Hz, C*H* (3′)), 6.58 (*dd*, ^3J = 8.8 Hz, ^4J = 1.9 Hz, C*H* (4′)), 3.85 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ = 151.3 (C5′), 150.5 (C3), 150.1 (C3′), 148.7 (C4), 132.1 (C1), 128.9 (*C*H=), 126.0 (C1′) 122.5 (*C*H=), 120.5 (C2), 117.3 (C3′), 116.0 (C4′), 113.0 (C5 + C6′), 110.3 (C2), 56.1 (O*C*H$_3$), 56.0 (O*C*H$_3$); 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) 4-Hydroxy-2′,3,5′-trimethoxystilbene (**15**)*

According to the general procedure from 2,5-dimethoxyiodobenzene and 4-hydroxy-3-methoxystyrene compound **15** (68.6%) was obtained as an off-white solid; mp 75–77°C; R_f = 0.25 (silica gel, hexanes/ethyl acetate, 8:2); IR (KBr): ν = 3418br, 2938m, 2834m, 2062w, 1594m, 1514s, 1463s, 1427s, 1372m, 1218s, 1161m, 1120s, 1045s cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 339 (4.21) nm; ^{1}H NMR (400 MHz, CDCl3): δ = 7.26 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (1)), 7.11 (*d*, 1H, ^4J = 2.9 Hz, C*H* (6′)), 7.04 (*d*, 1H, ^4J = 2.0 Hz, C*H* (2)), 7.02 (*dd*, 1H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, C*H* (6)), 7.00 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (2)), 6.87 (*d*, 1H, ^3J = 8.0 Hz, C*H* (5)), 6.81 (*d*, 1H, ^3J = 8.9 Hz, C*H* (3′)), 6.75 (*dd*, 1H, ^3J = 8.9 Hz, ^4J = 2.9 Hz C*H* (4′)), 3.93 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 153.8 (C5′), 151.3 (C2′), 146.7 (C3), 145.5 (C4), 130.5 (C1), 129.4 (*C*H=), 127.5 (C1′), 121.0 (*C*H=), 120.6 (C6), 114.5 (C5), 113.3 (C4′), 112.3 (C3′), 111.5 (C2), 108.4 (C6′), 56.3 (O*C*H$_3$), 56.0 (O*C*H3), 55.8 (O*C*H$_3$) ppm; MS (ESI, MeOH): *m*/*z* = 285.3 (100% [M−H]$^-$); analysis for $C_{17}H_{18}O_4$ (286.32): C, 71.31; H, 6.34; found: C, 71.15; H, 6.54.

*(E) 4-Hydroxy-2′,3,4′-trimethoxystilbene (**17**)*

According to the general procedure from 2,4-dimethoxyiodobenzene and 4-hydroxy-3-methoxystyrene compound **17** (62.7%) was

obtained as a beige colored solid; mp 98–100°C; $R_f = 0.25$ (silica gel, hexanes/ethylacetate 8:2 + 0.01% acetic acid); IR (KBr): ν = 3405br, 2940w, 1607w, 1576w, 1513w, 1455w, 1417w, 1365w, 1336w, 1264w, 1202w, 1155w, 1118w, 1034w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 207 (4.61), 292 (4.40), 331 (4.58) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (*d*, 1H, ^3J = 8.4 Hz, C*H* (6′)), 7.22 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (1)), 7.03 (*d*, 1H, ^4J = 1.6 Hz, C*H* (2)), 7.00 (*dd*, 1H, ^3J = 8.2 Hz, ^4J = 1.6 Hz, C*H* (6)), 6.93 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (2)), 6.88 (*d*, 1H, ^3J = 8.2 Hz, C*H* (5)), 6.51 (*dd*, 1H, ^3J = 8.4 Hz, ^4J = 2.3 Hz, C*H* (4′)), 6.47 (*d*, 1H, 4*J* = 2.3 Hz, C*H* (3′)), 3.95 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C4′), 157.8 (C2′), 146.6 (C3), 145.0 (C4), 131.0 (C1), 127.1 (*C*H=), 126.9 (C6′), 121.1 (*C*H=), 120.1 (C6), 119.8 (C1′), 114.4 (C5), 108.1 (C2), 104.9 (C5′), 98.5 (C3′), 55.9 (O*C*H_3), 55.5 (O*C*H_3), 55.4 (O*C*H_3) ppm; MS (e.i. 70 eV): *m*/*z* (%) = 286 (100); 274 (37), 243 (26), 228 (11), 211 (14), 150 (16), 137 (19); analysis for $C_{17}H_{18}O_4$ (286.32): C, 71.31; H, 6.34; found: C, 71.08; H, 6.55.

*(E) 3,5-Dimethoxy-4-hydroxy-,3′,4′,5′-trifluorstilbene (**21**)*

According to the general procedure from 3,4,5-trifluorobromobenzene and 3,5-dimethoxy-4-hydroxystyrene compound **21** (75.3%) was obtained as a colorless solid; mp 161–162°C; $R_f = 0.09$ (silica gel, hexanes/ethyl acetate, 9:1); IR (KBr): ν = 3511 br, 2950w, 2847w, 1609m, 1529s, 1518s, 1458m, 1441m, 1425w, 1353m, 1372m, 1351s, 1257s, 1329m, 1259w, 1220m, 1160w, 1107s, 1046m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 244 (4.20), 326 (4.39) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (*dt*, 1H, $^3J_{H,F}$ = 8.3 Hz, $^4J_{H,F}$ = 2.2 Hz, C*H* (2′) + C*H* (6′)), 6.89 (*d*, 1H, $^3J_{trans}$ = 16.2 Hz, C*H*= (1)), 6.75 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (2)), 6.70 (s, 2H, C*H* (2) + C*H* (6)), 5.60 (br s, 1H, O*H*), 3.92 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4 (*ddd*, $^1J_{C,F}$ = 249.0 Hz, $^2J_{C,F}$ = 10.1 Hz, $^3J_{C,F}$ = 4.3 Hz, C3′ + C5′), 147.3 (C3 + C5), 138.7 (m, $^1J_{C,F}$ = 251.9 Hz, C4′), 135.5 (C4), 133.8 (*dd*, $^3J_{C,F}$ = 12.4 Hz, $^4J_{C,F}$ = 7.6 Hz, C1′), 131.1 (*d*, $^5J_{C,F}$ = 2.4 Hz, *C*H=), 127.8 (C1), 123.7 (*d*, $^4J_{C,F}$ = 2.8 Hz, *C*H=), 109.8 (*dd*, $^2J_{C,F}$ = 16.8 Hz, $^3J_{C,F}$ = 4.9 Hz, C2′ + C6′), 103.6 (C2 + C6), 56.3 (O*C*H_3) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −135.1 (*dd*, $^3J_{F,F}$ = 25.6 Hz, $^3J_{F,H}$ = 8.3 Hz, *F* (3′) + *F* (5′)), −162.5 (*tt*, $^3J_{F,F}$ = 25.6 Hz, $^4J_{F,H}$ = 2.2 Hz, *F* (4′)) ppm; MS (ESI, MeOH): *m*/*z* = 309.5 (100% [M−H]$^-$); analysis for $C_{16}H_{13}F_3O_3$ (310.27): C, 61.94; H, 4.22; found: C, 61.75; H, 4.44.

*(E) 3,5-Dimethoxy-4,2′,5′-trihydroxystilbene (**23**)*

According to the general procedure from 2,5-dihydroxyiodobenzene and 3,5-dimethoxy-4-hydroxystyrene compound **23** (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 (methanol): λ_{max} (log ε) = 218 (4.45), 309 (4.05) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.21 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (1)), 7.02 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (2)), 6.96 (*d*, 1H, ^4J = 2.9 Hz, C*H* (6′)), 6.83 (s, 2H, C*H* (2) + C*H* (6)), 6.68 (*d*, 1H, ^3J = 8.7 Hz, C*H* (3′)), 6.55 (*dd*, ^3J = 8.7 Hz, ^4J = 2.9 Hz, C*H* (4′)), 3.86 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ = 149.9 (C5′), 147.9 (C3 + C5), 147.6 (C2′), 135.1 (C4), 131.6 (*C*H=), 129.54 (C1), 125.2 (C1′), 120.9 (*C*H=), 116.0 (C3′), 114.7 (C4′), 111.3 (C6′), 103.4 (C2 + C6), 55.3 (O*C*H_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.

*(E) 4-Hydroxy-2′,3,4′,5-tetramethoxystilbene (**24**)*

According to the general procedure from 2,4-dimethoxyiodobenzene and 3,5-dimethoxy-4-hydroxystyrene compound **24** (72.8%) was obtained as a colorless solid; mp 121–122°C; $R_f = 0.13$ (silica gel, hexanes/ethyl acetate, 8:2 + 0.01% acetic acid); IR (KBr): ν = 3445br, 2999w, 2941w, 2840w, 1602m, 1574w, 1515m, 1462m, 1426w, 1359w, 1332w, 1314w, 1293m, 1250w, 1199m, 1163w, 1110m, 1024w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 214 (4.36), 241 (4.24), 332 (4.47) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (*d*, 1H, ^3J = 8.6 Hz, C*H* (6′)), 7.20 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (2)), 6.90 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (1)), 6.72 (s, 2H, C*H* (2) + C*H* (6)), 6.49 (*dd*, 1H, ^3J = 8.6 Hz, ^4J = 2.5 Hz, C*H* (5′)), 6.46 (*d*, 1H, ^4J = 2.5 Hz, C*H* (3′)), 3.92 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (C4′), 157.9 (C2′), 147.1 (C3 + C5) 134.4 (C4), 129.9 (C1), 127.3 (*C*H=), 127.0 (C6, *C*H), 121.5 (*C*H=), 119.6 (C1′), 104.9 (C5′), 103.2 (C2 + C6), 98.5 (C3′), 56.3 (O*C*H_3), 55.4 (O*C*H_3), 54.8 (O*C*H_3) ppm; MS (e.i. 70 eV): *m*/*z* (%) = 316 (100), 273 (14), 241 (10), 180 (14), 137 (7); analysis for $C_{18}H_{20}O_5$ (316.35): C, 68.34; H, 6.37; found: C, 68.13; H, 6.54.

*(E) 3′,5′-Dihydroxy-4′-fluoro-4-methoxystilbene (**25**)*

According to the general procedure from 3,5-dihydroxy-4-fluorobromobenzene and 4-methoxystyrene compound **25** (62.3%) 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 (methanol): λ_{max} (log ε) = 217 (4.45), 305 (4.57) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.41 (*d*, 2H, ^3J = 8.7 Hz, C*H* (2) + C*H* (6)), 6.89 (*d*, 1H, 3J_{trans} = 16.4 Hz, C*H*= (1)), 6.88 (*d*, 2H, ^3J = 8.7 Hz, C*H* (3) + C*H* (5)), 6.78 (*d*, 1H, $^3J_{trans}$ = 16.4 Hz, C*H*= (2)), 6.55 (*d*, 2H, $^4J_{H,F}$ = 7.1 Hz, C*H* (2′) + C*H* (6′)), 4.82 (br s, 2H, O*H*), 3.79 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, methanol-d_4): δ = 160.8 (C4), 147.0 (*d*, $^2J_{C,F}$ = 11.0 Hz, C3′ + C5′), 142.1 (*d*, $^1J_{C,F}$ = 236.6 Hz, C4′), 134.8 (*d*, $^4J_{C,F}$ = 4.6 Hz, C1′), 131.5 (C1), 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); 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) 4′-Fluoro-2,3′,5′-trihydroxystilbene (**48**)*

According to the general procedure from 3,5-dihydroxy-4-fluorobromobenzene and 2-hydroxystyrene compound **48** (69.8%) was obtained as an off-white 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 (methanol): λ_{max} (log ε) = 236 (4.30), 291 (4.30), 325 (4.36) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.46 (*d*, 1H, ^3J = 7.7 Hz, C*H* (6)), 7.24 (*d*, 1H, 3J_{trans} = 16.6 Hz, C*H*= (1), 7.04–7.01 (m, 1H, C*H* (4)), 6.90 (*d*, 1H, $^3J_{trans}$ = 16.6 Hz, C*H*= (2)), 6.79–6.77 (m, 2H, C*H* (3) + C*H* (5)), 6.55 (*d*, 2H, $^4J_{H,F}$ = 8.0 Hz, C*H* (2′) + C*H* (6′)) ppm; ^{13}C NMR (100 MHz, methanol-d_4): δ = 156.0 (C2), 146.9 (*d*, $^2J_{C,F}$ = 10.7 Hz, C3′ + C5′), 142.1 (*d*, $^1J_{C,F}$ = 236.8 Hz, C4′), 135.2 (*d*, $^4J_{C,F}$ = 4.4 Hz, C1′), 129.3 (C6, *C*H) 128.7 (*C*H=), 127.4 (C4, *C*H), 125.7 (C1), 124.4 (*C*H=), 120.7 (C5), 116.6 (C3), 107.4 (*d*, $^3J_{C,F}$ = 4.5 Hz, C2′ + C6′) ppm; ^{19}F NMR (188 MHz, acetone-d_6): δ = −165.0 (*t*, $^4J_{F,H}$ = 8.0 Hz) 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) 2′,5′,3,4-Tetrahydroxystilbene (**56**)*

According to the general procedure from 3,4-dihydroxystyrene and 2,5-dihydroxyiodobenzene compound **56** (62.4%) was

obtained as an off-white solid; mp 162–164°C; $R_f = 0.47$ (silica gel, hexanes/ethyl acetate, 1:1); IR (KBr): $\nu = 3356$br, 1601w, 1523m, 1453m, 1363w, 1190m, 1109w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 294 (4.15), 347 (4.21) nm; ^1H NMR (400 MHz, methanol-d_4): $\delta = 7.17$ (*d*, 1H, $^3J_{trans} = 16.4$ Hz, C*H*= (1)), 6.99 (*d*, 1H, $^4J = 1.9$ Hz, C*H* (2)), 6.93 (*d*, 1H, $^4J = 2.9$ Hz, C*H* (6′)), 6.90 (*d*, 1H, $^3J_{trans} = 16.4$ Hz, C*H*= (2)), 6.83 (*dd*, $^3J = 8.1$ Hz, $^4J = 1.9$ Hz, C*H* (6)), 6.72 (*d*, 1H, $^3J = 8.1$ Hz, C*H* (5)), 6.63 (*d*, 1H, $^4J = 8.7$ Hz, C*H* (3′)), 6.51 (*dd*, $^3J = 8.7$ Hz, $^4J = 2.9$ Hz, C*H* (4′) ppm; ^{13}C NMR (100 MHz, methanol-d_4): $\delta = 151.3$ (C5′), 148.9 (C2′), 146.4 (C4), 146.2 (C3), 131.8 (C1′), 129.3 (*C*H=), 126.9 (C1) 121.8 (*C*H=), 120.0 (C6), 117.4 (C3′), 116.4 (C5), 115.9 (C4′), 113.8 (C2), 112.7 (C6′) ppm; MS (ESI, MeOH): $m/z = 243.4$ (48% $[M-H]^-$); 487.0 (100% $[2M-H]^-$); analysis for $C_{14}H_{12}O_4$ (244.24): C, 68.85; H, 4.95; found: C, 68.74; H, 5.07.

Biological testing

DPPH assays [26] were performed in 96-well microtiter plates (Nunc) using a Spectrafluorplus instrument (Tecan) at 25°C and $\lambda = 518$ nm. Thus, 100 μL of the sample solution was added to 900 μL of an ethanolic solution of DPPH (10^{-4} M) and incubated at 25°C for 30 min. Then the absorbance of this solution was determined at $\lambda = 518$ nm, and the respective SC_{50} values (in μM) were calculated. All experiments were carried out in triplicate and repeated three times. The cytotoxicity assay (SRB) [27] was performed as previously described [21].

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