Bioorganic & Medicinal Chemistry 19 (2011) 5155–5166

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and antimicrobial activity of (*E*) stilbene derivatives

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ARTICLE INFO

Article history:
Received 5 June 2011
Revised 7 July 2011
Accepted 10 July 2011
Available online 19 July 2011

Keywords:
Antimicrobial compounds
Phytoalexins
Stilbenes
Mizoroki–Heck reaction

ABSTRACT

Plants use multiple defence mechanisms comprising both constitutive and inducible barriers to prevent entering of phytopathogenic micro-organisms. In many plant species one of the most efficient responses to combat attacking microbes is the rapid synthesis of antimicrobial low molecular weight phytoalexins, for example, resveratrol, 3,5,4′-trihydroxystilbene (**1**). Resveratrol and its natural derivatives, however, display only moderate antimicrobial effects. Nevertheless, resveratrol may be a useful lead structure for the chemical synthesis of antimicrobials. In this study, several series of stilbenes have been synthesized, starting from the aldehydes using Wittig reactions to access the corresponding styrenes that were subjected to Mizoroki–Heck reactions to yield the stilbenes in good yields. The stilbenes were tested in an agar diffusion assay against several bacteria and fungi. For some of these compounds the inhibiting zones for bacteria and fungi were comparable with those of the antibiotics tetracycline, streptomycin, ampicillin, or kanamycin, directed against prokaryotes, and nourseothricin or hygromycin controlling fungi, respectively.

1. Introduction

Plants in their natural environment are challenged by many potentially damaging organisms including viruses, nematodes, bacteria, fungi and insects. To perceive and combat biotic attack plants have devised sophisticated constitutive and inducible defence mechanism. As part of a preformed front-line defence plants produce cutin, suberin, waxes, lignin, cellulose and cell wall proteins which form a structural barrier preventing the invasion of microbial pathogens.[1] In addition, preformed compounds like saponins, glucosinolates or cyanogenic glycosides, some of which occur as inactive precursors that are immediately activated in response to tissue damage or pathogen attack, confer basic resistance.[2]

As a second line of defence, post-infectional mechanisms are activated which depend on specific receptors that recognize pathogen-associated molecular pattern (PAMPs), and transduce the information by signal cascades. This results in rapid stress responses such as forming reactive oxygen species (ROS), the initiation of hypersensitive cell death, and the de novo synthesis of pathogenesis-related proteins and toxic phytoalexins.[3–6]

The stilbene *trans*-resveratrol (**1**, Fig. 1) is a phytoalexin being produced in response to environmental stresses such as wounding or pathogen attack. It was first isolated from the White hellebore (*Veratrum grandiflorum O. Loes*) but can also be found in Japanese knotweed (*Polygonum cuspidatum syn. Fallopia japonica*) and about

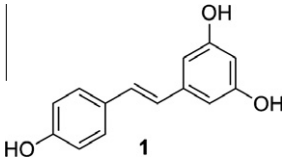

Figure 1. Structure of *trans*-resveratrol (**1**).

70 further species.[7–9] In wood, however, **1** is produced constitutively and acts as a phytoanticipin.[10]

Antifungal properties of **1** and its naturally occurring derivatives against various pathogens including *Cladosporium cuccumerinum*, *Pyricularia oryzae*, *Plasmopara viticola*, *Botrytis cinerea* and *Sphaeropsis sapinea* have been described. MIC values of up to 200 μg/ml, however, raised the question whether **1** should be considered as a precursor of compounds displaying higher fungitoxicity, for example of viniferins or pterostilbenes, rather than as a phytoalexin [[11] and reference citations therein].

Fungal pathogens may avoid the inhibitory effect of stilbenes by oxidative degradation. Resveratrol detoxification by extracellular laccases has been reported[12] and may represent a mechanism that contributes to fungal virulence. Conceivably, the natural stilbenes appear to be not suitable for the chemical control of pathogenic fungi. To overcome this problem, however, substituted resveratrol analogues that are not prone to oxidative degradation may represent excellent lead structures to develop agents allowing efficient control of various plant pathogenic bacteria and fungi.

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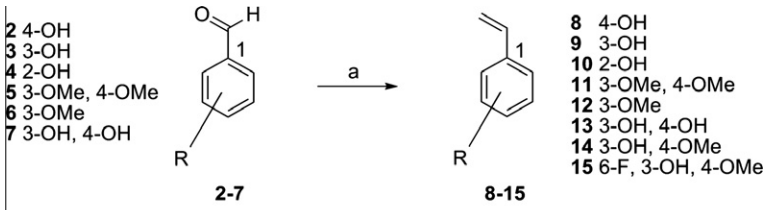
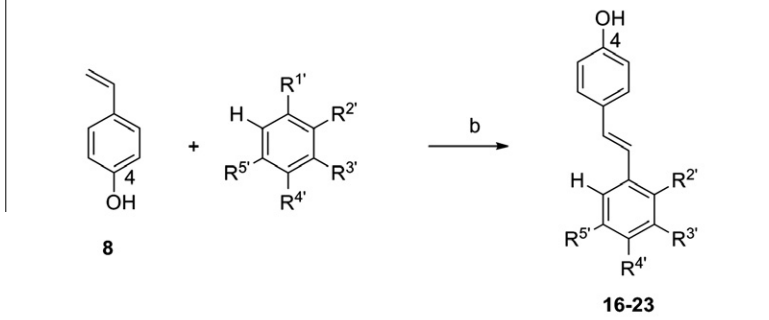
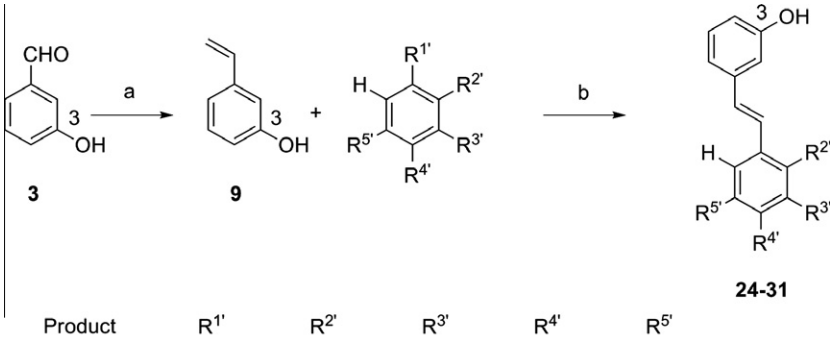
doi:10.1016/j.bmc.2011.07.015





Product	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
16	I	H	OMe	H	OMe
17	I	H	OH	H	OH
18	Br	H	OMe	F	OMe
19	Br	H	F	F	F
20	Br	H	OH	F	OH
21	I	OMe	H	H	OMe
22	I	OH	H	H	OH
23	I	OMe	H	OMe	H

Scheme 1. Synthesis of substituted styrenes by Wittig olefination and of the 4-hydroxy substituted stilbenes **16**–**23** by Mizoroki–Heck reactions. Reagents and conditions: (a) $H_3CP(C_6H_5)_3I$, ^tBuOK, THF, 24 h, 25 °C; (b) triethanolamine, Pd(II) acetate, 24 h, 100 °C.



Product	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
24	I	H	OMe	H	OMe
25	I	H	OH	H	OH
26	Br	H	OMe	F	OMe
27	Br	H	F	F	F
28	Br	H	OH	F	OH
29	I	OMe	H	H	OMe
30	I	OH	H	H	OH
31	I	OMe	H	OMe	H

Scheme 2. Synthesis of substituted styrenes by Wittig olefination and of 3-hydroxy substituted stilbenes **24**–**31** by Mizoroki–Heck reactions. Reagents and conditions: (a) $H_3CP(C_6H_5)_3I$, ^tBuOK, THF, 24 h, 25 °C; (b) triethanolamine, Pd(II) acetate, 24 h, 100 °C.

2. Chemistry

Stilbenes and stilbenoids have long been in the focus of scientific interest, and the number of publications on stilbenes exceeds 32.000.[13] Therefore, many synthetic routes to stilbene derivatives have been elaborated, among them Aldol-type condensations,[14] Perkin reactions,[15,16] Wittig-type reactions,[17,18] the reductive coupling of carbonyl compounds (e.g., by McMurry reactions[19]), and more recently precious metal catalysed Negishi–Stille couplings[20] and Mizoroki–Heck reactions.[21,22]

Mizoroki–Heck reactions can be performed under a great variety of conditions.[23–25] The use of triethanolamine acting simultaneously as a base, a ligand and as a solvent allows the straightforward and economic synthesis of substituted stilbenes-mainly of (*E*) configuration.[26,27]

Thus, reaction of substituted benzaldehydes **2–7** with methyltriphenylphosphonium bromide in the presence of ^{t}BuOK[28] in a Wittig reaction (Scheme 1) provided the matching styrene derivatives **8–13** and **15**; styrene **14** and **15** was prepared according to literature.[28] Their Mizoroki–Heck reactions with substituted iodo (or bromo) benzenes gave the matching (*E*) stilbenes in good yields. Scheme 1 depicts the synthesis of the 4-hydroxy substituted stilbenes **16–23**.

3-Hydroxybenzaldehyde (**3**, Scheme 2) served as a starting material for the synthesis of 3-hydroxystyrene (**9**) and was obtained by a Wittig reaction in 68% isolated yield. Compound **9** was used as a starting material for Mizoroki–Heck reactions using iodo (or bromo) benzenes, and stilbenes **24–31** were obtained.

In a similar manner, from 2-hydroxybenzaldehyde (**4**, Scheme 3) 2-hydroxystyrene (**10**) was obtained in 65% yield whose Mizoroki–Heck reaction with substituted iodo (or bromo) benzenes yielded the stilbenes **32**–**35**.

For comparison, the 2′,5′-dihydroxylated stilbenes **36** and **37** (Scheme 4, from 2,5-dihydroxy-iodobenzene and 6-fluoro-3-hydroxy-4-methoxystyrene (**15**) or from 3,4-dihydroxystyrene (**13**), respectively), as well as analogs **38**–**40** were prepared.

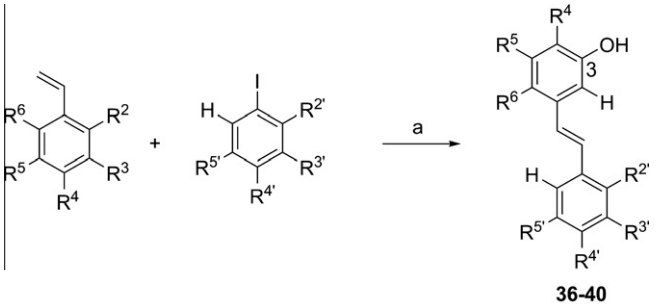
3. Results and discussion

To compare the antibacterial/antifungal activity of the stilbenes, the effect of the compounds on the growth of several bacteria and fungi was evaluated in agar diffusion tests.

Bacillus subtilis and *Bacillus brevis* were chosen as representatives of Gram-positive bacteria, *Enterobacter dissolvens* as an example for a Gram-negative bacterium, and *Micrococcus luteus* as representative of actinobacteria. The activity of the stilbenes was compared with well-established antibiotics, that is, streptomycin, tetracycline and the aminoglycoside antibiotic kanamycin as well as the β-lactame antibiotic ampicillin. As shown in Figure 2 all the 4-hydroxylated stilbenes **16–23** (except compound **17**) show antibacterial activity against *B. brevis*. The inhibiting areolae are comparable with those obtained from treating the bacteria with tetracycline. Compound **17** acts in a selective manner against *M. luteus* whereas compound **23** is a selective antibiotic against bacteria. None of these compounds, however, displays activity against Gram-negative *Enterobacter*.

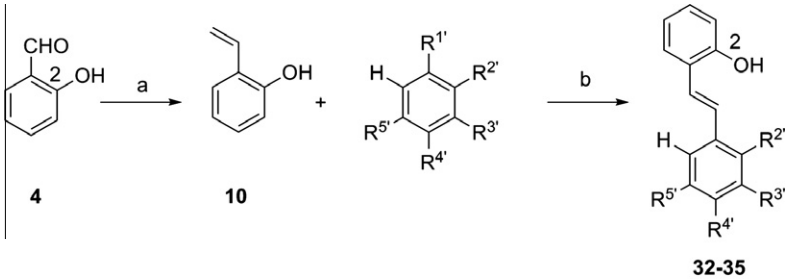
The 3-hydroxystilbenes **24–31** are active (Fig. 3) against *bacilli* and *M. luteus*. The highest activity is found for the trifluoro compound **27**. The corresponding 2-hydroxystilbenes **32**–**35**, however, show similar activity against all the strains (Fig. 4).

These data suggest that all stilbenes that do not show a monohydroxy-substitution on ring A are only active when the compounds have a 2′,5′-dihydroxy substitution in ring B. Figure 5 summarizes6 the activity of all 2′,5′-dihydroxylated stilbenes in this study (**22**, **30**, **34**, **36**, **37** and **39**). The highest activity is found for compound **36**.



Prod	R^2	R^3	R^4	R^5	R^6	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
36	H	OH	OMe	H	F	OH	H	H	OH
37	H	OH	OH	H	H	OH	H	H	OH
38	H	OH	OMe	H	H	H	OMe	H	OMe
39	H	OH	OMe	H	H	OH	H	H	OH
40	H	OH	OMe	H	H	OMe	H	OMe	H

Scheme 4. Synthesis of the 3-hydroxy substituted stilbenes **36–40** by Mizoroki–Heck reactions. Reagents and conditions: (a) triethanolamine, Pd(II) acetate, 24 h, 100 °C.



Product	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
32	Br	H	OMe	F	OMe
33	Br	H	F	F	F
34	I	OH	H	H	OH
35	I	OMe	H	H	OMe

Scheme 3. Synthesis of substituted styrenes by Wittig olefination and of 2-hydroxy substituted stilbenes **32**–**35** by Mizoroki–Heck reactions. Reagents and conditions: (a) $H_3CP(C_6H_5)_3I$, ^{t}BuOK, THF, 24 h, 25 °C; (b) triethanolamine, Pd(II) acetate, 24 h, 100 °C.

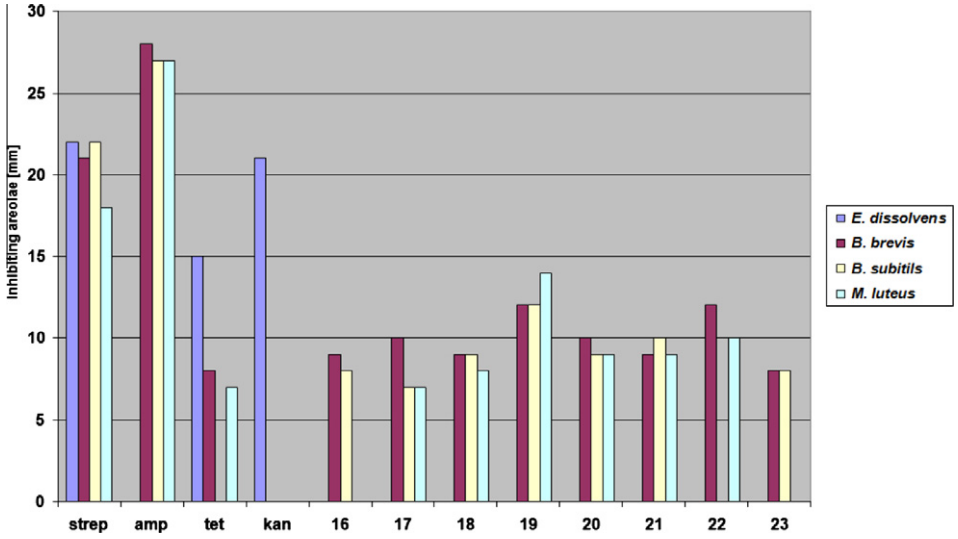


Figure 2. Inhibition zone [diameter in mm] of 4-hydroxystilbenes **16–23** against bacteria (standards: streptomycin, ampicillin, tetramycin, kanamycin).

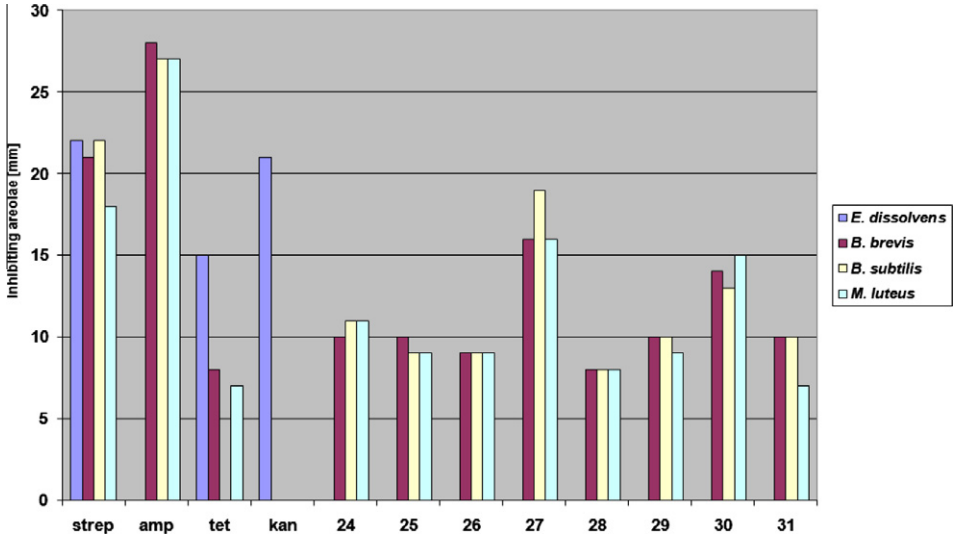


Figure 3. Inhibition zone [diameter in mm] of 3-hydroxystilbenes **24–31** against bacteria (standards: streptomycin, ampicillin, tetramycin, kanamycin).

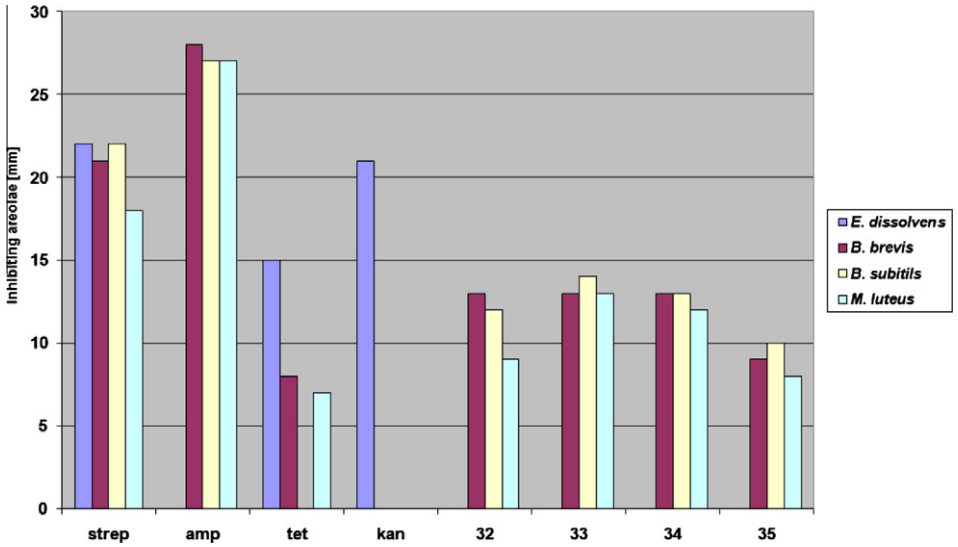


Figure 4. Inhibition zone (diameter in mm) of 2-hydroxystilbenes **32–35** against bacteria (standards: streptomycin, ampicillin, tetramycin, kanamycin).

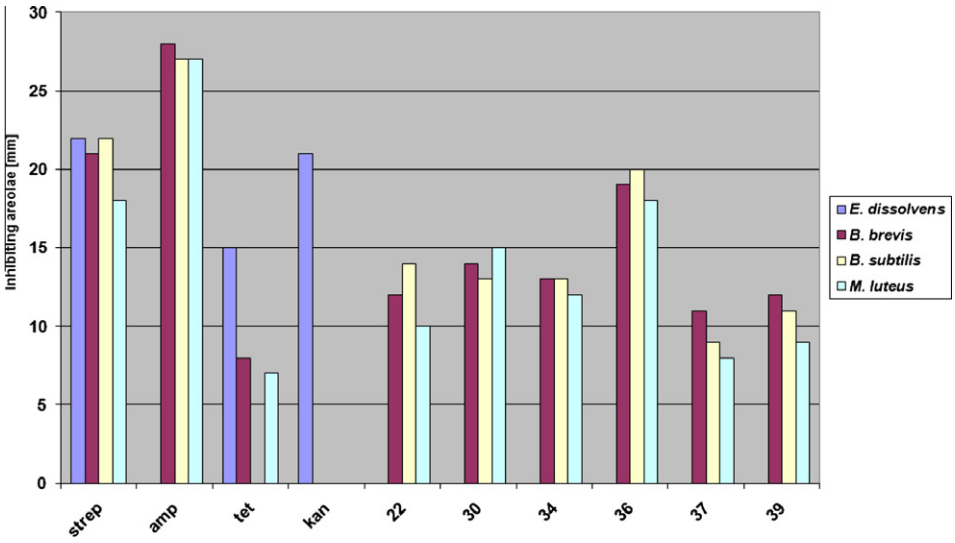


Figure 5. Inhibition zone (diameter in mm) of 2′,5′di-hydroxystilbenes **22**, **30**, **34**, **36**, **37** and **39** against bacteria (standards: streptomycin, ampicillin, tetramycin, kanamycin).

To evaluate antifungal activity, agar diffusion tests using the following fungi were performed: *Nematospora coryli* (a plant pathogen infesting fruit trees, cotton and vegetables (e.g., tomatoe), *Rhizomucor miehei*, *Penicillium notatum*, *Colletotrichum graminicola* (a fungus causing anthracnosis of maize) as well as *B. cinerea*.

Figure 6 shows the results for the 4-hydroxystilbenes **16–23**; all compounds (except **17**) show activity comparable to that of well-established noursethricin and hygromycin. Compound **22** is even more active than the commercial antifungals. Compound **19** shows activity against *N. coryli*, too. None of these compounds, however, shows significant activity against *B. cinerea*.

In the series of the 3-hydroxystilbenes, compound **27** (Fig. 7) is active against *Mucor miehei*. The activities of the 2-hydroxystilbenes are lower (Fig. 8); compound **33**, however, exhibits significant activity against all the strains. Compounds **38**–**40** are selective inhibitors; the same seems true for the 2′,5′-dihydroxylated stilbenes **22**, **30**, **34** and **35** (Fig. 9).

Little is known about the antimicrobial action of stilbenes on a molecular level. As far as an antifungal activity is concerned it has been shown that the activity of a fungal tyrosinase is inhibited by resveratrol and some of its analogs.[29,30] Whereas methoxylated derivatives exhibited a significant antifungal activity, activity of these compounds is low against bacteria. Stilbenes containing at least one hydroxyl group exhibited inhibitory activity against bacteria—but this result is not surprising because phenolic compounds are viewed as one of the major classes of natural antimicrobial agents. The mechanisms thought to be responsible include enzyme inhibition through reaction with sulfhydryl groups and through more non-specific interactions with the proteins.[31,32] Our results parallel some recent findings observed for stilbenes and their ability to inhibit methicillin-resistant *Staphylococcus aureus* strains.[33]

Addition of fluorine substituents enhanced the antibacterial effect compared to other compounds; this may be due to the overall change in the partion coefficient resulting in a higher permeability of the compounds into the membrane rather than a direct effect of the substitution.[34,35] Direct damage of the bacteria cell membrane, however, cannot be excluded since several wine phenolics[36] were

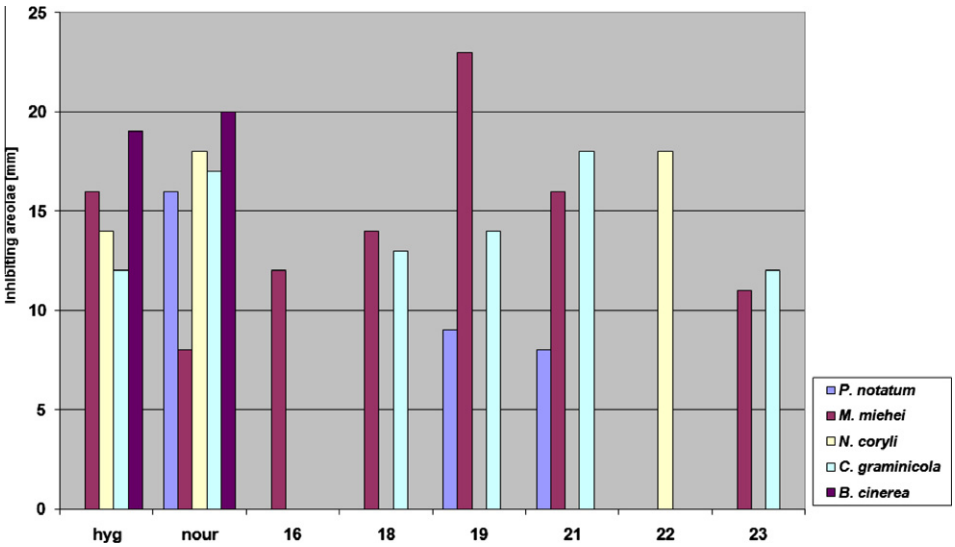


Figure 6. Inhibition zone [diameter in mm] of selected 4-hydroxystilbenes **16**, **18**, **19**, **21**, **22** and **23** against fungi (standards: noursethricin and hygromycin).

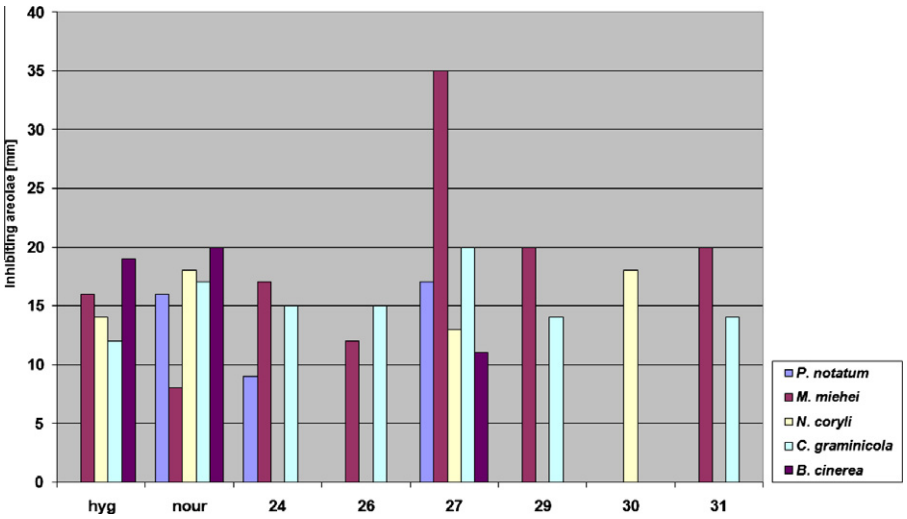


Figure 7. Inhibition zone [diameter in mm] of selected 3-hydroxystilbenes **24**, **26**, **27**, **29**–**31** against fungi (standards: noursethricin and hygromycin).

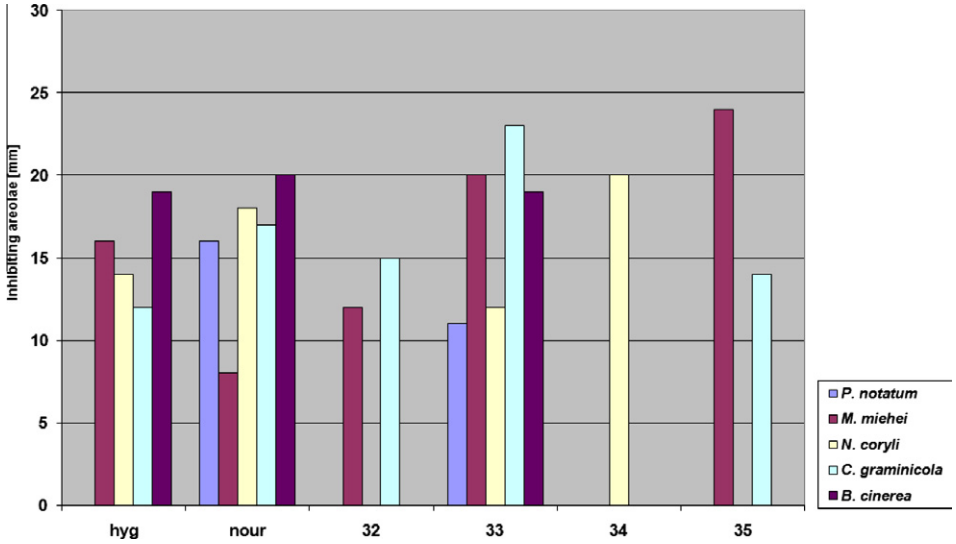


Figure 8. Inhibition zone [diameter in mm] of selected 2-hydroxystilbenes **32**–**35** against fungi (standards: noursethricin and hygromycin).

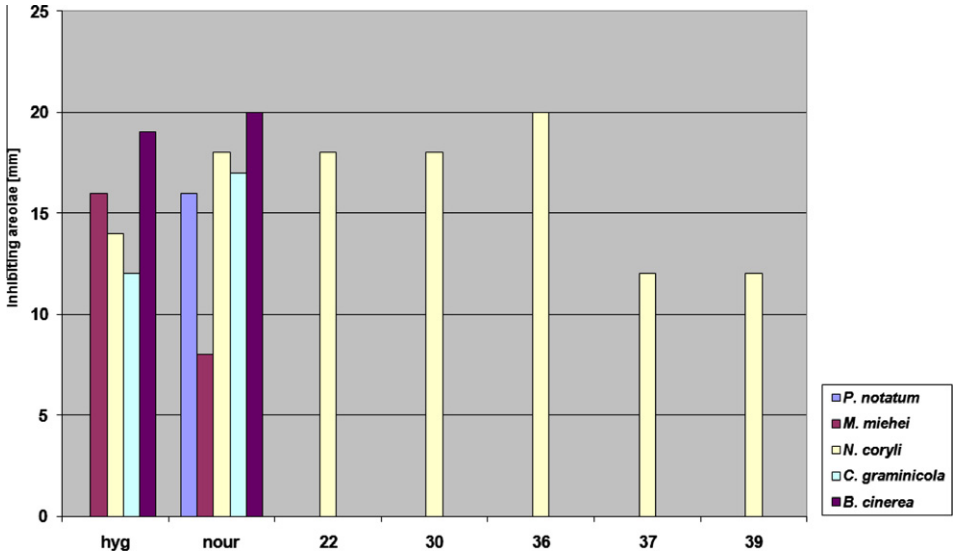


Figure 9. Inhibition zone [diameter in mm] of selected 2′,5′di-hydroxystilbenes **22**, **30**, **36**, **37** and **39** against fungi (standards: noursethricin and hygromycin).

Table 1
Biological activity (cytotoxicity, NiH3T3 mouse embryonic fibroblasts, IC_{50} in μm, from SRB assay) of compounds **1** and **16–40** (error: ±5%)

1	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
>30	12.2	24.2	11.5	6.9	>30	7.4	9.6	8.2
24	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
>30	>30	11.8	>30	>30	25.8	10.5	19.6	14.8
33	**34**	**35**	**36**	**37**	**38**	**39**	**40**	
>30	12.4	>30	21.1	>30	0.2	>30	2.1	

shown to damage bacterial cell membranes or to lead to cell aggregation.

The compounds **1** and **16–40** were tested for their cytotoxic activity (NiH3T3 cells, mouse embryonic fibroblasts) using a sulforhodamine B assay (SRB).[37] The results (IC_{50} values, three independent experiments for each compound) from these tests are summarized in Table 1. Whereas some of the compounds exhibit low toxicity (e.g., **20**, **24**, **25**, **27**, **28**, **33**, **35**, **37** and **39**), other analogs are cytotoxic with IC_{50} <10 μM (e.g., **21–23**, **38** and **40**) making them interesting (lead) structures for the development of stilbene derived antitumor active compounds.

4. Conclusion

Several series of stilbenes were synthesized starting from the aldehydes using Wittig reactions to access the corresponding styrenes that were subjected to Mizoroki–Heck reactions to yield the stilbenes in good yields. The stilbenes were tested in an agar diffusion assay against several bacteria and fungi. For several of these compounds the inhibiting areolae are comparable with those obtained from treating the bacteria with tetracycline, streptomycin, ampicillin or kanamycin or noursethricin or hygromycin for the antifungal assay. As far as the antibacterial activity is concerned, all stilbenes that do not show a monohydroxy-substitution on ring A are only active when the compounds have a 2′,5′-dihydroxy substitution in ring B.

5. Experimental

5.1. Chemistry

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 freon-11 for ^{19}F NMR spectra), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used; TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium(IV) sulfate) followed by gentle heating. The solvents were dried according to usual procedures.

5.1.1. General procedure for the synthesis of styrenes

To a solution methyltriphenylphosphonium iodide (37 mmol) in dry THF (60 ml), ^{t}BuOK (40 mmol) was added in several portions, and stirring under argon was continued for 1 h. The aldehyde (14 mmol) was added, and stirring was continued for another 24 h. The reaction mixture was diluted with dichloromethane (150 ml), washed with water and brine (2 × 10 ml each), dried (Na_2SO_4), and the solvents were evaporated under diminished pressure. The crude product was purified by chromatography (silica gel, hexane/ethyl acetate mixtures).

5.1.2. 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).

5.1.3. 4-Hydroxystyrene (8)

Following the general procedure, **8** was obtained from 4-hydroxybenzaldehyde (**2**) as a slightly yellowish solid; yield: 58.0%; mp 63–65 °C (lit.: 73.5 °C,[38] 71–72.5 °C,[39] 67–69 °C,[40] 55–65 °C[41]).

5.1.4. 3-Hydroxystyrene (9)

Following the general procedure, **9** was obtained from 3-hydroxybenzaldehyde (**3**) as a slightly yellowish oil; yield: 67.6%.

5.1.5. 2-Hydroxystyrene (10)

Following the general procedure, **10** was obtained from 2-hydroxybenzaldehyde (**4**) as a colorless oil; yield: 64.8%.

5.1.6. 3,4-Dimethoxystyrene (11)

Following the general procedure, **11** was obtained from 3, 4-dimethoxybenzaldehyde (**5**) as a yellowish oil; yield: 75.2%.

5.1.7. 3-Methoxystyrene (12)

Following the general procedure, **12** was obtained from 3-methoxybenzaldehyde (**6**) as a yellowish oil; yield: 70.1%.

5.1.8. 3,4-Dihydroxystyren (13)

Following the general procedure, **13** was obtained from 3, 4-dihydroxybenzaldehyde (**7**) as an off-white, highly viscous oil; yield: 59.9%.

5.1.9. 3-Hydroxy-4-methoxystyrene (14)

Compound **14** was prepared according to 28, and obtained as colorless sold; mp 56–58 °C (lit.: 57–58 °C.[40]

5.1.10. 6-Fluoro-3-hydroxy-4-methoxystyrene (15)

Following the general procedure, **15** was obtained as an amorphous, slightly yellow powder; yield: 72.3%; R_f = 0.44 (silica gel, hexane/ethyl acetate, 8:2); IR (KBr): ν = 3388br, 3077m, 2985m, 2938m, 2849m, 1809w, 1632s, 1587w, 1508s, 1444s, 1418m, 1361s, 1315m, 1285s, 1206s, 1164s, 1102s, 1049m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 207 (4.37), 254 (4.18), 306 (3.87); ^1H NMR (400 MHz, acetone-d_6): δ = 7.58 (br s, 1H, O*H*), 7.01 (d, 1H, $^4J_{H,F}$ = 7.5 Hz, C*H* (6)), 6.75 (dd, 1H, ^3J (trans) = 17.7 Hz, ^3J (cis) = 11.2 Hz, C*H* (7)), 6.74 (d, 1H, $^3J_{H,F}$ = 11.8 Hz, C*H* (3)), 5.67 (d, 1H, ^3J (trans) = 17.7 Hz, CH_a (8)), 5.20 (d, 1H, ^3J (cis) = 11.2 Hz, CH_b (8)), 3.85 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6): δ = 153.7 (d, $^1J_{C,F}$ = 264.3 Hz, C2, $C_{quart.}$), 148.1 (d, $^3J_{C,F}$ = 26.9 Hz, C4, $C_{quart.}$), 142.9 (d, $^4J_{C,F}$ = 2.0 Hz, C5, $C_{quart.}$), 128.7 (d, $^3J_{C,F}$ = 3.3 Hz, C7, C*H*), 116.6 (d, $^2J_{C,F}$ = 13.4 Hz, C1, $C_{quart.}$), 113.2 (d, $^4J_{C,F}$ = 1.0 Hz, C8, C*H*), 111.4 (d, $^3J_{C,F}$ = 4.8 Hz, C6, C*H*)), 99.7 (d, $^2J_{C,F}$ = 28.8 Hz, C3, C*H*), 55.7 (OCH_3); ^{19}F NMR (188 MHz, acetone-d_6): δ = −129.6 (dd, $^3J_{F,H}$ = 11.8 Hz, $^4J_{F,H}$ = 7.5 Hz , –*F*); MS (e.i., 70 eV): *m*/*z* (%) = 168 (92), 153 (100), 125 (39), 97 (11), 77 (16); Anal. Calcd for $C_8H_7O_3$ (170.14): C, 56.48; H, 4.15. Found: C, 56.31; H, 4.36.

5.1.11. (*E*) 3′,5′-Dimethoxy-4-hydroxystilbene (16)

From **8** and 3,5-dimethoxyiodobenzene; yield: 55.0%; white solid; mp 83–84 °C (lit.: 88 °C,[41] 86–88 °C,[42] 55–64 °C.[43]

5.1.12. (*E*) 3′,4,5′-Trihydroxystilbene (17)

From **8** and 3,5-dihydroxyiodobenzene; yield: 41.4%; white solid; mp >260 °C (lit.: 275–276 °C,[35] 260 °C,[44] 256–258 °C[45]).

5.1.13. (*E*) 3′,5′-Dimethoxy-4′-fluoro-4-hydroxystilbene (18)

From **8** and 3,5-dimethoxy-4-fluoro-bromobenzene; yield: 47.6%; off-white solid; mp 123–125 °C; R_f = 0.49 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3419br, 2940w, 1606m, 1585w, 1519m, 1455w, 1420w, 1330w, 1265w, 1249w, 1219w, 1171w, 1124m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 209 (4.49), 306 (4.53) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, 2H, ^3J = 8.5 Hz, C*H* (2) + C*H* (6)), 6.92 (d, 1H, ^3J (trans) = 16.2 Hz, C*H*= (1)), 6.84 (d, 1H, ^3J (trans) = 16.2 Hz, C*H*= (2)), 6.81 (d, 2H, ^3J = 8.5 Hz, C*H* (3) + C*H* (5)), 6.70 (d, 2H, $^4J_{H,F}$ = 7.1 Hz, C*H* (2′) + C*H* (6′)), 3.91 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3 (C4, $C_{quart.}$), 148.4 (d, $^2J_{C,F}$ = 8.8 Hz, C3′ + C5′, $C_{quart.}$), 142.1 (d, $^1J_{C,F}$ = 245.8 Hz, C4′, $C_{quart.}$), 133.0 (d, $^4J_{C,F}$ = 5.0 Hz, C1′, $C_{quart.}$) 130.0 (C1, $C_{quart.}$), 128.1 (*C*H=), 127.8 (C2 + C6, *C*H), 126.1 (*C*H=), 115.6 (C3 + C5, *C*H), 103.9 (C2′ + C6′, *C*H), 56.5 (OCH_3) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −159.1 (t, $^4J_{F,H}$ = 7.1 Hz, *–F*) ppm; MS (ESI, MeOH): *m*/*z* = 273.6 (100% [M−H]$^-$), 319.2 (10% [M+HCO_2]$^-$), 547.0 (17% [2M−H]$^-$); Anal. Calcd for $C_{16}H_{15}FO_3$ (274.28): C, 70.06; H, 5.51. Found: C, 69.85; H, 5.62.

5.1.14. (*E*) 4-Hydroxy-3′,4′,5′-trifluorostilbene (19)

From **8** and 3,4,5-trifluorobromobenzene; yield: 56.9%; white solid; mp 149–151 °C; R_f = 0.30 (silica gel, hexane/ethyl acetate, 9:1); IR (KBr): ν = 3266br, 2361w, 1889w, 1638w, 1594s, 1529s, 1508s, 1442s, 1360m, 1321m, 1269m, 1231s, 1174m, 1131w, 1106w, 1043s cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 230 (4.19), 321 (4.50) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, 2H, ^3J = 8.5 Hz, C*H* (2) + C*H* (6)), 7.03 (dt, 1H, $^3J_{H,F}$ = 9.2 Hz, $^4J_{H,F}$ = 6.6 Hz, C*H* (2′) + C*H* (6′)), 6.92 (d, 1H, ^3J (trans) = 16.2 Hz, C*H*= (1)), 6.81 (d, 2H, ^3J = 8.5 Hz, C*H* (3) + C*H* (5)), 6.75 (d, 1H, ^3J (trans) = 16.2 Hz, C*H*= (2)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (C4, $C_{quart.}$), 151.4 (ddd, $^1J_{C,F}$ = 252.3 Hz, $^2J_{C,F}$ = 10.1 Hz, $^3J_{C,F}$ = 4.3 Hz, C3′ + C5′, $C_{quart.}$), 138.7 (m, $^1J_{C,F}$ = 250.7 Hz, C4′, $C_{quart.}$), 133.9 (dd, $^3J_{C,F}$ = 12.2 Hz, $^4J_{C,F}$ = 7.7 Hz, C1′, $C_{quart.}$), 130.4 (d, $^5J_{C,F}$ = 2.4 Hz, *C*H=), 129.2 (C1, $C_{quart.}$), 128.2 (C2 + C6, *C*H), 123.6 (d, $^4J_{C,F}$ = 2.8 Hz, *C*H=), 115.7 (C3 + C5, *C*H), 109.8 (dd, $^2J_{C,F}$ = 16.8 Hz, $^3J_{C,F}$ = 4.9 Hz, C2′ + C6′, *C*H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −135.2 (dd, $^3J_{F,F}$ = 19.7 Hz, $^3J_{F,H}$ = 9.2 Hz, *F* (3′) + *F* (5′)), −161.7 (tt, $^3J_{F,F}$ = 19.7 Hz, $^4J_{F,H}$ = 6.6 Hz, *F* (4′)) ppm; MS (ESI, MeOH): *m*/*z* = 249.6 (55% [M−H]$^-$), 498.9 (100% [2M−H]$^-$); Anal. Calcd for $C_{14}H_9F_3O$ (250.22): C, 67.20; H, 3.63. Found: C, 66.98; H, 3.83.

5.1.15. (*E*) 4′-Fluoro-3′,4,5′-trihydroxystilbene (20)

From **8** and 3,5-dihydroxy-4-fluoro-bromobenzene; yield: 39.8%; white solid; mp >250 °C; R_f = 0.52 (silica gel, hexane/ethyl acetate, 1:1); IR (KBr): ν = 3346br, 1604w, 1554w, 1521w, 1442w, 1369w, 1255w, 1192w, 1175w, 1104w, 1048w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 217 (4.30), 305 (4.39) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.30 (d, 2H, ^3J = 8.3 Hz, C*H* (2) + C*H* (6)), 6.84 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 6.73 (d, 2H, ^3J = 8.3 Hz, C*H* (3) + C*H* (5)), 6.72 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.52 (d, 2H, $^4J_{H,F}$ = 7.1 Hz, C*H* (2′) + C*H* (6′)) ppm; ^{13}C NMR (100 MHz, methanol-d_4): δ = 156.8 (C4, $C_{quart.}$), 145.5 (d, $^2J_{C,F}$ = 7.9 Hz, C3′ + C5′, $C_{quart.}$), 140.5 (d, $^1J_{C,F}$ = 248.7 Hz, C4′, $C_{quart.}$), 133.5 (d, $^4J_{C,F}$ = 5.0 Hz, C1′, $C_{quart.}$) 128.9 (C1, $C_{quart.}$), 127.6 (*C*H=), 127.2 (C2 + C6, *C*H), 124.9 (*C*H=), 115.0 (C3 + C5, *C*H), 105.7 (C2′ + C6′, *C*H) ppm; ^{19}F NMR (188 MHz, methanol-d_4): δ = −165.3 (t, $^4J_{F,H}$ = 7.1 Hz, *–F*) ppm; MS (ESI, MeOH): *m*/*z* = 245.4 (98% [M−H]$^-$), 291.0 (23% [M+HCO_2]$^-$), 490.9 (100% [2M−H]$^-$); Anal. Calcd for $C_{14}H_{11}FO_3$ (246.23): C, 68.29; H, 4.50. Found: C, 67.98; H, 4.67.

5.1.16. (*E*) 2′,5′-Dimethoxy-4-hydroxystilbene (21)

From **8** and 2,5-dimethoxyiodobenzene; yield: 52.2%; off-white solid; mp 81–82 °C; R_f = 0.27 (silica gel, hexane/ethyl acetate/acetic acid, 8:2:0.01); IR (KBr): ν = 3341br, 2867m, 1605m, 1515m, 1497m, 1460m, 1436m, 1416w, 1359w, 1316w, 1299w, 1271w, 1215m, 1172m, 1099w, 1039m, 1009w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 208 (4.41), 284 (4.34), 341 (4.30) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, 2H, ^3J = 8.5 Hz, C*H* (2) + C*H* (6)), 7.28 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.11 (d, 1H, ^4J = 2.9 Hz, C*H* (6′)), 7.00 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.81 (d, 1H, ^3J = 9.0 Hz, C*H* (3′)), 6.79 (d, 2H, ^3J = 8.5 Hz, C*H* (3) + C*H* (5)), 6.76 (dd, 1H, ^3J = 9.0 Hz, ^4J = 2.9 Hz, C*H* (4′)), 4.92 (br s, 1H, O*H*), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1 (C4, $C_{quart.}$), 153.8 (C5′, $C_{quart.}$), 151.3 (C2′, $C_{quart.}$), 130.8 (C1, $C_{quart.}$), 128.9 (*C*H=), 128.0 (C2 + C6, *C*H), 127.6 (C1′, $C_{quart.}$), 121.2 (*C*H=), 115.5 (C3 + C5, *C*H), 113.3 (C4′, *C*H), 112.4 (C3′, *C*H), 111.5 (C6′, *C*H), 56.3 (OCH_3), 55.8 (OCH_3) ppm; MS (i.e., 70 eV): *m*/*z* (%) = 256 (100), 241 (16), 213(56), 198 (11), 181 (16), 169(9); Anal. Calcd for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29. Found: C, 74.85; H, 6.51.

5.1.17. (*E*)-2′,4,5′-Trihydroxystilbene (22)

From **8** and 2,5-dihydroxybenzene; yield: 48.7%; off-white solid; mp 198–200 °C.

5.1.18. (*E*) 2′,4′-Dimethoxy-4-hydroxystilbene (23)

From **8** and 2,5-dimethoxyiodobenzene; yield: 52.2%; off-white solid; mp 118–121 °C.

5.1.19. (*E*) 3′,5′-Dimethoxy-3-hydroxystilbene (24)

From **9** and 3,5-dimethoxyiodobenzene; yield: 54.2%; white solid (lit.: oil[46]); mp 58–60 °C; R_f = 0.44 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3252br, 3936m, 2361w, 1596s, 1455m, 1425m, 1317m, 1251w, 1193s, 1155s, 1060m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 218 (4.31), 301 (4.29) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, 1H, ^3J = 7.7 Hz, C*H* (5)), 7.05 (d, 1H, ^3J = 7.7 Hz, C*H* (6)), 7.00 (d, 1H, ^3J (trans) = 16.7 Hz, C*H*= (1)), 6.98 (d, 1H, ^3J (trans) = 16.7 Hz, C*H*= (2)), 6.96 (d, 1H, ^4J = 2.3 Hz, C*H* (2)), 6.74 (dd, 1H, ^3J = 7.7 Hz, ^4J = 2.3 Hz, C*H* (4)), 6.64 (d, 2H, ^4J = 2.2 Hz, C*H* (2′) + C*H* (6′)), 6.39 (t, 1H, ^3J = 2.2 Hz, C*H* (4′)), 3.81 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (C3′ + C5′, $C_{quart.}$), 155.8 (C3, $C_{quart.}$), 139.2 (C1, $C_{quart.}$), 138.8 (C1′, $C_{quart.}$), 129.8 (C5, *C*H), 129.1 (*C*H=), 128.8 (*C*H=), 119.5 (C6, *C*H), 114.7 (C4, *C*H), 113.0 (C2, *C*H), 104.7 (C2′ + C6′, *C*H), 100.1 (C4′, *C*H), 55.4 (OCH_3) ppm; MS (ESI, MeOH): *m*/*z* = 255.4 (100% [M−H]$^-$), 301.0 (29% [M−HCO_2]$^-$), 510.9 (82% [2M−H]$^-$); Anal. Calcd for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29. Found: C, 74.74; H, 6.31.

5.1.20. (*E*) 3,3′,5′-Trihydroxystilbene (25)

From **9** and 3,5-dihydroxyiodobenzene; yield: 47.1%; white solid; mp 208–210 °C (lit.: 228–231 °C[47]); R_f = 0.43 (silica gel, hexane/ethyl acetate, 1:1); IR (KBr): ν = 3263m, 2363w, 1596s, 1491w, 1457m, 1382w, 1325m, 1282w, 1248m, 1159s, 1008w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 219 (4.42), 307 (4.43) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.13 (t, 1H, ^3J = 7.8 Hz, C*H* (5)), 6.96 (d, 1H, ^3J = 7.8 Hz, C*H* (6)), 6.94 (d, 1H, ^3J (trans) = 16.3 Hz, C*H*= (1)), 6.93 (d, 1H, ^4J = 2.0 Hz, CH (2)), 6.91 (d, 1H, ^3J (trans) = 16.3 Hz, C*H*= (2)), 6.67 (dd, 1H, ^3J = 7.7 Hz, ^4J = 2.0 Hz, C*H* (4)), 6.47 (d, 2H, ^4J = 2.2 Hz, C*H* (2′) + C*H* (6′)), 6.19 (t, 1H, ^3J = 2.2 Hz, C*H* (4′)) ppm; ^{13}C NMR (100 MHz, methanol-d_4): δ = 159.7 (C3′ + C5′, $C_{quart.}$), 158.7 (C3, $C_{quart.}$), 140.7 (C1, $C_{quart.}$), 140.1 (C1′, $C_{quart.}$), 133.0 (C5, *C*H), 129.8 (*C*H=), 129.5 (*C*H=), 119.2 (C6, *C*H), 115.7 (C4, *C*H), 113.8 (C2, *C*H), 106.1 (C2′ + C6′, *C*H), 103.2 (C4′, *C*H) ppm; MS (ESI, MeOH): *m*/*z* = 227.5 (37% [M−H]$^-$), 273.3 (44% [M+HCO_2]$^-$), 455.0 (100% [2M−H]$^-$); Anal. Calcd for $C_{14}H_{12}O_3$ (228.24): C, 73.67; H, 5.30. Found: C, 73.54; H, 5.51.

5.1.21. (*E*) 3′,5′-Dimethoxy-4′-fluoro-3-hydroxystilbene (26)

From **9** and 3,5-dimethoxy-4-fluoro-bromobenzene; yield: 53.5%; off-white solid; mp 108–111 °C; R_f = 0.59 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3241br, 2944w, 1743w, 1601m, 1518m, 1457m, 1420m, 1336m, 1279w, 1247m, 1225m, 1184w, 1159m, 1149m, 1131s cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 214 (4.41), 319 (4.44) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, 1H, ^3J = 7.7 Hz, C*H* (5)), 7.05 (d, 1H, ^3J = 7.7 Hz, C*H* (6)), 6.97 (d, 1H, ^4J = 2.3 Hz, C*H* (2)), 6.96 (d, 1H, ^3J (trans) = 16.2 Hz, C*H*= (1)), 6.90 (d, 1H, ^3J (trans) = 16.2 Hz, C*H*= (2)), 6.74 (dd, 1H, ^3J = 7.7 Hz, ^4J = 2.3 Hz, C*H* (4)), 6.72 (d, 2H, $^4J_{H,F}$ = 7.1 Hz, C*H* (2′) + C*H* (6′)), 3.91 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (C3, $C_{quart.}$), 148.4 (d, $^2J_{C,F}$ = 8.6 Hz, C3′ + C5′, $C_{quart.}$), 142.1 (d, $^1J_{C,F}$ = 243.1 Hz, C4′, $C_{quart.}$), 138.8 (C1, $C_{quart.}$), 132.7 (d, $^4J_{C,F}$ = 5.0 Hz, C1′, $C_{quart.}$), 129.9 (C5, *C*H), 128.6 (*C*H=), 128.3 (*C*H=), 119.4 (C6, *C*H), 114.8 (C4, *C*H), 112.9 (C2, *C*H), 104.4 (C2′ + C6′, *C*H), 56.7 (O*C*H_3) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −158.3 (t, $^4J_{F,H}$ = 7.1 Hz, –*F*) ppm; MS (e.i., 70 eV): *m*/*z* (%) = 274 (100), 242(10), 228 (10), 199 (15), 170 (9); Anal. Calcd for $C_{16}H_{15}FO_3$ (274.28): C, 70.06; H, 5.51. Found: C, 69.84; H, 5.73.

5.1.22. (*E*)-3-Hydroxy-3′,4′,5′-trifluorostilbene (27)

From **9** and 3,4,5-trifluorobromobenzene; yield: 58.4%; white solid; mp 132–134 °C; R_f = 0.30 (silica gel, hexane/ethyl acetate, 9:1); IR (KBr): ν = 3285m, 1638w, 1594w, 1529m, 1508w, 1442w, 1360w, 1331w, 1269w, 1231m, 1174w, 1106w, 1043m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 230 (4.15), 320 (4.47) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, 1H, ^3J = 7.7 Hz, C*H* (5)), 7.08–7.02 (m, 3H, C*H* (2′) + C*H* (6) + C*H* (6′)), 6.95 (d, 1H, ^4J = 2.1 Hz, C*H* (2)), 6.94 (d, 1H, ^3J (trans) = 16.0 Hz, C*H*= (1)), 6.86 (d, 1H, ^3J (trans) = 16.0 Hz, C*H*= (2)), 6.81(dd, 2H, ^3J = 7.7 Hz, ^4J = 2.1 Hz, C*H* (4)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (C3, $C_{quart.}$), 151.4 (ddd, $^1J_{C,F}$ = 251.6 Hz, $^2J_{C,F}$ = 11.3 Hz, $^3J_{C,F}$ = 5.0 Hz, C3′ + C5′, $C_{quart.}$), 139.1 (m, $^1J_{C,F}$ = 250.7 Hz, C4′, $C_{quart.}$), 137.4 (C1, $C_{quart.}$), 133.4 (dd, $^3J_{C,F}$ = 12.2 Hz, $^4J_{C,F}$ = 7.7 Hz, C1′, $C_{quart.}$), 130.5 (d, $^5J_{C,F}$ = 2.4 Hz, C*H*= (1)), 130.0 (C5, *C*H), 126.1 (d, $^4J_{C,F}$ = 3.0 Hz, *C*H=), 119.7 (C6, *C*H), 115.5 (C4, *C*H), 113.2 (C2, *C*H), 110.1 (dd, $^2J_{C,F}$ = 17.1 Hz, $^3J_{C,F}$ = 5.0 Hz, C2′ + C6′, *C*H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −134.9 (dd, $^3J_{F,F}$ = 19.5 Hz, $^3J_{F,H}$ = 9.0 Hz, *F* (3′) + *F* (5′)), −161.7 (tt, $^3J_{F,F}$ = 19.5 Hz, $^4J_{F,H}$ = 6.0 Hz, *F* (4′)) ppm; MS (ESI, MeOH): *m*/*z* = 249.5 (24% $[M-H]^-$), 295.3 (25% $[M+HCO_2]^-$), 499.1 (100% $[2M-H]^-$), 545.1 (12% $[2M+HCO_2]^-$); Anal. Calcd for $C_{14}H_9F_3O$ (250.22): C, 67.20; H, 3.63. Found: C, 66.96; H, 3.83.

5.1.23. (*E*) 4′-Fluoro-3,3′,5′-trihydroxystilbene (28)

From **9** and 3,5-dihydroxy-4-fluoro-bromobenzene; yield: 46.8%; off-white solid; mp >250 °C; R_F = 0.57 (silica gel, hexane/ethyl acetate, 1:1); IR (KBr): ν = 3340br, 2605w, 2465m, 1606m, 1581m, 1518s, 1455m, 1368m, 1278m, 1213w, 1159m, 1069m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 219 (4.47), 300 (4.50) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.50 (t, 1H, ^3J = 7.9 Hz, C*H* (5)), 7.32 (d, 1H, ^3J = 7.9 Hz, C*H* (6)), 7.28 (d, 1H, ^4J = 1.9 Hz, C*H* (2)), 7.26 (d, 1H, ^3J (trans) = 16.6 Hz, C*H*= (1)), 7.22 (d, 1H, ^3J (trans) = 16.6 Hz, C*H*= (2)), 7.03 (dd, 1H, ^3J = 7.7 Hz, ^4J = 1.9 Hz, C*H* (4)), 6.94 (d, 2H, $^4J_{H,F}$ = 7.3 Hz, C*H* (2′) + C*H* (6′)) ppm; ^{13}C NMR (100 MHz, methanol-d_4): δ = 158.7 (C3, $C_{quart.}$), 147.0 (d, $^2J_{C,F}$ = 8.6 Hz, C3′ + C5′, $C_{quart.}$), 142.3 (d, $^1J_{C,F}$ = 237.6 Hz, C4′, $C_{quart.}$), 140.1 (C1, $C_{quart.}$), 134.5 (d, $^4J_{C,F}$ = 4.3 Hz, C1′, $C_{quart.}$), 130.6 (C5, *C*H), 129.2 (*C*H=), 129.1 (*C*H=), 119.2 (C6, *C*H), 115.6 (C4, *C*H), 113.8 (C2, *C*H), 107.5 (C2′ + C6′, *C*H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −164.5 (t, $^4J_{F,H}$ = 7.3 Hz, *F*) ppm; MS (ESI, MeOH): *m*/*z* = 245.4 (68% $[M-H]^-$), 291.0 (40% $[M+HCO_2]^-$), 490.9 (100% $[2M-H]^-$); Anal. Calcd for $C_{14}H_{11}FO_3$ (246.23): C, 68.29; H, 4.50. Found: C, 68.00; H, 4.63.

5.1.24. (*E*) 2′,5′-Dimethoxy-3-hydroxystilbene (29)

From **9** and 2,5-dimethoxyiodobenzene; yield: 51.1%; off-white solid; mp 66–68 °C; R_F = 0.26 (silica gel, hexane/ethyl acetate, 8:2); IR (KBr): ν = 3415br, 2955m, 1633w, 1609m, 1581m, 1496s, 1462m, 1414m, 1384m, 1313m, 1277m, 1250m, 1216s, 1179m, 1157m, 1102w, 1039s, 1008m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 291 (4.44), 338 (4.35) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.19 (t, 1H, ^3J = 7.9 Hz, C*H* (5)), 7.12 (d, 1H, ^4J = 3.0 Hz, C*H* (6′)), 7.07 (d, 1H, ^3J = 7.9 Hz, C*H* (6)), 7.00 (d, 1H, ^4J = 1.7 Hz, C*H* (2)), 6.99 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.82 (d, 1H, ^3J = 8.9 Hz, C*H* (3′)), 6.78 (dd, 1H, ^3J = 8.9 Hz, ^4J = 3.0 Hz, C*H* (4′)), 6.71 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.7 Hz, C*H* (4)), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (C3, $C_{quart.}$), 153.7 (C5′, $C_{quart.}$), 151.5 (C2′, $C_{quart.}$), 139.5 (C1, $C_{quart.}$), 129.8 (C5, *C*H), 128.9 (*C*H=), 127.1 (C1′, $C_{quart.}$), 123.7 (*C*H=), 119.6 (C6, *C*H), 114.5 (C4, *C*H), 113.9 (C4′, *C*H), 112.9 (C2, *C*H), 112.4 (C3′, *C*H), 111.7 (C6′, *C*H), 56.3 (O*C*H_3), 55.8 (O*C*H_3) ppm; MS (ESI, MeOH): *m*/*z* = 255.4 (100% $[M-H]^-$), 301.1 (19% $[M+HCO_2]^-$), 510.9 (50% $[2M-H]^-$); Anal. Calcd for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29. Found: C, 74.86; H, 6.41.

5.1.25. (*E*) 2′,3,5′-Trihydroxystilbene (30)[48,49]

From **9** and 2,5-dihydroxyiodobenzene; yield: 47.9%; off-white solid; mp 208–210 °C; R_F = 0.13 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3300br, 1613w, 1582w, 1505w, 1457m, 1377w, 1305w, 1254w, 1199w, 1156w, 1095w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 211 (4.57) , 291 (4.42), 345 (4.31) nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.44 (br s, 1H, O*H*), 9.07 (br s, 1H, O*H*), 8.81 (br s, 1H, O*H*), 7.27 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.13 (t, 1H, ^3J = 7.8 Hz, C*H* (5)), 6.96 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.94–6.92 (m, 3H, C*H* (2) + C*H* (6) + C*H* (6′)), 6.66 (d, 1H, ^3J = 8.5 Hz, C*H* (3′)), 6.64 (d, 1H, ^3J = 7.8 Hz, C*H* (4)), 6.53 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.9 Hz, C*H* (4′)) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.7 (C3, $C_{quart.}$), 150.2 (C5′, $C_{quart.}$), 148.0 (C2′, $C_{quart.}$), 139.2 (C1, $C_{quart.}$), 129.9 (C5, *C*H), 127.7 (*C*H=), 124.3 (C1′, $C_{quart.}$), 123.7 (*C*H=), 117.8 (C6, *C*H), 116.8 (C3′, *C*H), 116.1 (C4′, *C*H), 114.8 (C4, *C*H), 112.7 (C6′, *C*H), 112.0 (C2, *C*H) ppm; MS (ESI, MeOH): *m*/*z* = 227.4 (25% $[M-H]^-$), 273.1 (100% $[M+HCO_2]^-$), 454.9 (27% $[2M-H]^-$); Anal. Calcd for $C_{14}H_{12}O_3$ (228.24): C, 73.67; H, 5.30. Found: C, 73.49; H, 5.35.

5.1.26. (*E*) 2′,4′-Dimethoxy-3-hydroxystilbene (31)

From **9** and 2,4-dimethoxyiodobenzene; yield: 53.7%; off-white solid; mp 106–108 °C; R_F = 0.30 (silica gel, dichloromethane/hexane, 3:1); IR (KBr): ν = 3397br, 2945m, 1603m, 1577m, 1505m, 1468m, 1434w, 1419w, 1296m, 1277m, 1200m, 1152m, 1107w, 1023 cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 213 (4.34), 326 (4.36) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, 1H, ^3J = 8.5 Hz, C*H* (6′)), 7.35 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.18 (t, 1H, ^3J = 7.9 Hz, C*H* (5)), 7.05 (d, 1H, ^3J = 7.9 Hz, C*H* (6)), 6.97 (d, 1H, ^4J = 1.7 Hz, C*H* (2)), 6.92 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.68 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.7 Hz, C*H* (4)), 6.50 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.3 Hz, C*H* (5′)), 6.46 (d, 1H, ^4J = 2.3 Hz, C*H* (3′)), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (C4′, $C_{quart.}$), 158.1 (C2′, $C_{quart.}$), 155.7 (C3, $C_{quart.}$), 140.0 (C1, $C_{quart.}$), 129.7 (C5, *C*H), 127.3 (C6′, *C*H), 126.5 (*C*H=), 123.8 (*C*H=), 119.4 (C1′, $C_{quart.}$), 119.3 (C6, *C*H), 114.0 (C4, *C*H), 112.6 (C2, *C*H), 105.6 (C5′, *C*H), 98.5 (C3′, *C*H), 55.5 (O*C*H_3), 55.4 (O*C*H_3) ppm; MS (ESI, MeOH): *m*/*z* = 255.3 (100% $[M-H]^-$), 510.8 (21% $[2M-H]^-$); Anal. Calcd for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29. Found: C, 74.69; H, 6.42.

5.1.27. (*E*) 3′,5′-Dimethoxy-4′-fluoro-2-hydroxystilbene (32)

From **10** and 3,5-dimethoxy-4-fluoro-bromobenzene; yield: 51.1%; white solid; mp 63–65 °C; R_F = 0.16 (silica gel, hexane/

ethyl acetate, 8:2); IR (KBr): ν = 3418br, 2940m, 2842w, 1704m, 1605s, 1519s, 1455s, 1421s, 1349s, 1243s, 1128s, 1042m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 290 (4.12), 326 (4.18) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, 1H, ^3J = 7.7 Hz, C*H* (6)), 7.28 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.11 (t, 1H, ^3J = 7.7 Hz, C*H* (4)), 7.01 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.92 (t, 1H, ^3J = 7.7 Hz, C*H* (5)), 6.80 (d, 1H, ^3J = 7.7 Hz, C*H* (3)), 6.74 (d, 2H, $^4J_{H,F}$ = 7.0 Hz, C*H* (2′) + C*H* (6′)) 3.88 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (C2, $C_{quart.}$), 148.3 (d, $^2J_{C,F}$ = 8.7 Hz, C3′ + C5′, $C_{quart.}$), 142.2 (d, $^1J_{C,F}$ = 245.7 Hz, C4′, $C_{quart.}$), 133.3 (d, $^4J_{C,F}$ = 4.8 Hz, C1′, $C_{quart.}$) 129.1 (*C*H=), 128.8 (C4, *C*H), 127.0 (C6, *C*H), 124.4 (C1, $C_{quart.}$), 123.3 (*C*H=), 121.0 (C5, *C*H), 116.0 (C3, *C*H), 104.3 (C2′ + C6′, *C*H), 56.5 (OCH_3) ppm; ^{19}F NMR (188 MHz, CD_3CN): δ = −158.8 (t, $^4J_{F,H}$ = 7.0 Hz, *F*) ppm; MS (ESI, MeOH): *m*/*z* = 273.3 (100% [M−H]$^-$); 319.0 (16.3% [M+HCO_2]$^-$); 546.8 (52% [2M−H]$^-$); Anal. Calcd for $C_{16}H_{15}FO_3$ (274.28): C, 70.06; H, 5.51. Found: C, 69.89; H, 5.71.

5.1.28. (*E*) 2-Hydroxy-3′,4′,5′-trifluorostilbene (33)

From **10** and 3,4,5-trifluoro-bromobenzene; yield: 52%; white solid; mp 98–100 °C; R_F = 0.52 (silica gel, hexane/ethyl acetate, 9:1); IR (KBr): ν = 3489m, 3383br, 1636w, 1613w, 1598w, 1585w, 1528s, 1498w, 1455m, 1441m, 1358m, 1319m, 1270w, 1230m, 1181w, 1153w, 1091w, 1062w, 1042m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 204 (4.34), 287 (4.27), 326 (4.25) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, 1H, ^3J = 7.8 Hz, C*H* (6)), 7.27 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.15 (t, 1H, ^3J = 7.8 Hz, C*H* (4)), 7.07(dt, 1H, $^3J_{H,F}$ = 11.0 Hz, $^4J_{H,F}$ = 6.6 Hz, C*H* (2′) + C*H* (6′)), 6.96 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.94 (t, 1H, ^3J = 7.8 Hz, C*H* (5)), 6.77 (d, 1H, ^3J = 7.8 Hz, C*H* (3)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (C2, $C_{quart.}$), 151.2 (ddd, $^1J_{C,F}$ = 249.5 Hz, $^2J_{C,F}$ = 10.5 Hz, $^3J_{C,F}$ = 4.3 Hz, C3′ + C5′, $C_{quart.}$), 139.9 (m, $^1J_{C,F}$ = 252.7 Hz, C4′, $C_{quart.}$), 134.1 (dd, $^3J_{C,F}$ = 12.5 Hz, $^4J_{C,F}$ = 7.7 Hz, C1′, $C_{quart.}$), 129.2 (C4, *C*H), 127.3 (C6, *C*H), 126.6 (d, $^5J_{C,F}$ = 2.4 Hz, *C*H=), 125.5 (d, $^4J_{C,F}$ = 2.4 Hz, *C*H=), 123.6 (C1, $C_{quart.}$), 121.3 (C5, *C*H), 116.0 (C3, *C*H), 110.0 (dd, $^2J_{C,F}$ = 16.3 Hz, $^3J_{C,F}$ = 4.8 Hz, C2′ + C6′, *C*H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ = −135.1 (dd, $^3J_{F,F}$ = 19.5 Hz, $^3J_{F,H}$ = 11.0 Hz, *F* (3′) + *F* (5′)), -161.7 (tt, $^3J_{F,F}$ = 19.5 Hz, $^4J_{F,H}$ = 6.6 Hz, *F* (4′)) ppm; MS (ESI, MeOH): *m*/*z* = 249.6 (21% [M−H]$^-$); 499.1 (100% [2M−H]$^-$); Anal. Calcd for $C_{14}H_9F_3O$ (250.22): C, 67.20; H, 3.63. Found: C, 67.00; H, 3.87.

5.1.29. (*E*) 2,2′,5′-Trihydroxystilbene (34)

From **10** and 2,5-dihydroxy-iodobenzene; yield: 49.8%; off-white solid; mp 218–220 °C; R_F = 0.67 (silica gel, hexane/ethyl acetate, 1:1); IR (KBr): ν = 3287br, 2362w, 1603w, 1581w, 1508w, 1455w, 1376w, 1236w, 1197w, 1156w, 1097w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 284 (4.17), 341 (4.24) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 7.52 (d, 1H, ^3J = 7.7 Hz, CH (6)), 7.40 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.35 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 7.03 (t, 1H, ^3J = 7.4 Hz, C*H* (4)), 7.01 (d, 1H, ^4J = 2.9 Hz, C*H* (6′)), 6.81 (t, 1H, ^3J = 7.4 Hz, C*H* (5)), 6.78 (d, 1H, ^3J = 7.4 Hz, C*H* (3)), 6.64 (d, 1H, ^3J = 8.5 Hz, C*H* (3′)), 6.53 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.9 Hz, C*H* (4′)), 4.81 (br s, 3H, O*H*) ppm; ^{13}C NMR (100 MHz, methanol-d_4): δ = 155.8 (C2, $C_{quart.}$), 151.2 (C5′, $C_{quart.}$), 148.9 (C2′, $C_{quart.}$), 129.0 (C4, *C*H), 127.1 (C1′, $C_{quart.}$), 127.0 (C6, *C*H), 126.4 (C1, $C_{quart.}$), 124.0 (*C*H=), 123.8 (*C*H=), 120.7 (C5, *C*H), 117.4 (C3′, *C*H), 116.5 (C3, *C*H), 116.1 (C4′, *C*H), 112.7 (C6′, *C*H) ppm; MS (ESI, MeOH): *m*/*z* = 227.4 (48% [M−H]$^-$), 273.1 (58% [M+HCO_2]$^-$), 455.0 (100% [2M−H]$^-$); Anal. Calcd for $C_{14}H_{12}O_3$ (228.24): C, 73.67; H, 5.30. Found: C, 73.56; H, 5.44.

5.1.30. (*E*) 2′,4′-Dimethoxy-2-hydroxystilbene (35)

From **10** and 2,4-dimethoxyiodobenzene: yield: 57.7%; white solid; mp 85–88 °C; R_F = 0.50 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3428br, 3063w, 2995m, 2932w, 1743w, 1602s, 1518m, 1457s, 1425m, 1381m, 1235m, 1198w, 1176m, 1140m, 1120s cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 214 (4.42), 319 (4.45) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, 1H, ^3J = 8.5 Hz, C*H* (6′)), 7.49 (d, 1H, ^3J = 7.4 Hz, C*H* (6)), 7.34 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.23 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 7.09 (t, 1H, ^3J = 7.4 Hz, C*H* (4)), 6.91 (t, 1H, ^3J = 7.4 Hz, C*H* (5)), 6.79 (d, 1H, ^3J = 7.4 Hz, C*H* (3)), 6.50 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.3 Hz, C*H* (5′)), 6.46 (d, 1H, ^4J = 2.3 Hz, C*H* (3′)), 5.28 (br s, 1H, O*H*), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (C4′, $C_{quart.}$), 158.0 (C2′, $C_{quart.}$), 152.8 (C2, $C_{quart.}$), 128.0 (C4, *C*H), 127.1 (C6′, *C*H), 126.7 (C6, *C*H), 125.6 (C1, $C_{quart.}$), 124.8 (*C*H=), 121.1 (*C*H=), 120.9 (C5, *C*H), 119.7 (C1′, $C_{quart.}$), 115.8 (C3, *C*H), 105.0 (C5′, *C*H), 98.5 (C3′, *C*H), 55.5 (OCH_3), 55.4 (OCH_3) ppm; MS (ESI, MeOH): *m*/*z* = 255.3 (100% [M−H]$^-$), 300.9 (8% [M+HCO_2]$^-$), 510.9 (11% [2M−H]$^-$); Anal. Calcd for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29. Found: C, 74.84; H, 6.42.

5.1.31. (*E*) 6-Fluoro-4-methoxy-2′,3,5′-trihydroxystilbene (36)

From 6-fluoro-3-hydroxy-4-methoxystyrene (**15**) and 2,5-dihydroxy-iodobenzene; yield: 44.4%; off-white solid; mp 158–160 °C; R_F = 0.08 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3383br, 2942w, 1627w, 1508w, 1448w, 1384w, 1303w, 1195w, 1094w, 1017w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 291 (4.11), 349 (4.06) nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.16 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (1)), 7.01 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*= (2)), 6.88 (d, 1H, ^4J = 2.3 Hz, C*H* (6′)), 6.82 (d, 1H, $^3J_{H,F}$ = 12.2 Hz, C*H* (5)), 6.73 (d, 1H, ^3J = 8.7 Hz, C*H* (3′)), 6.65 (d, 1H, $^4J_{H,F}$ = 8.9 Hz, C*H* (2)), 6.51 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.3 Hz, C*H* (4′)), 3.77 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.3 (d, $^1J_{C,F}$ = 244.3 Hz, C6, $C_{quart.}$), 150.1 (C5′, $C_{quart.}$), 148.1 (d, $^3J_{C,F}$ = 11.3 Hz, C4, $C_{quart.}$), 147.8 (C2′, $C_{quart.}$), 143.1 (d, $^4J_{C,F}$ = 2.2 Hz, C3, $C_{quart.}$), 124.3 (C1′, $C_{quart.}$), 123.7 (d, $^4J_{C,F}$ = 3.0 Hz, *C*H=), 119.2 (d, $^3J_{C,F}$ = 3.4 Hz, *C*H=), 116.8 (C4′, *C*H), 116.5 (d, $^2J_{C,F}$ = 13.2 Hz, C1, $C_{quart.}$), 115.8 (C3′, *C*H), 115.3 (C6′, *C*H), 111.7 (d, $^3J_{C,F}$ = 4.7 Hz, C2, *C*H), 100.6 (d, $^2J_{C,F}$ = 28.0 Hz, C5, *C*H), 56.1 (OCH_3) ppm; ^{19}F NMR (188 MHz, DMSO-d_6): δ = −128.2 (dd, $^3J_{F,H}$ = 12.2 Hz, $^4J_{F,H}$ = 8.9 Hz, *F*) ppm; MS (ESI, MeOH): *m*/*z* = 275.3 (45% [M−H]$^-$), 321.2 (100% [M+HCO_2]$^-$), 550.8 (16% [2M−H]$^-$); Anal. Calcd for $C_{15}H_{13}FO_4$ (276.26): C, 65.21; H, 4.74. Found: C, 65.03; H, 4.96.

5.1.32. (*E*)-2′,3,4,5′-Tetrahydroxystilbene (37)[50]

From **13** and 2,5-dihydroxyiodobenzene; yield: 39.5%; off-white solid; mp 162–164 °C; R_F = 0.47 (silica gel, hexane/ethyl acetate, 1:1); IR (KBr): ν = 3356br, 1601w, 1523m, 1453m, 1363w, 1190m, 1109w cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 294 (4.15), 347 (4.21) nm; ^{1}H NMR (400 MHz, methanol-d_4): δ = 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): δ = 151.3 (C5′, $C_{quart.}$), 148.9 (C2′, $C_{quart.}$), 146.4 (C4, $C_{quart.}$), 146.2 (C3, $C_{quart.}$), 131.8 (C1′, $C_{quart.}$), 129.3 (*C*H=), 126.9 (C1, $C_{quart.}$) 121.8 (*C*H=), 120.0 (C6, *C*H), 117.4 (C3′, *C*H), 116.4 (C5, *C*H), 115.9 (C4′, *C*H), 113.8 (C2, *C*H), 112.7 (C6′, *C*H) ppm; MS (ESI, MeOH): *m*/*z* = 243.4 (48% [M−H]$^-$); 487.0 (100% [2M−H]$^-$); Anal. Calcd for $C_{14}H_{12}O_4$ (244.24): C, 68.85; H, 4.95. Found: C, 68.74; H, 5.07.

5.1.33. (*E*) 3-Hydroxy-3′,4,5′-trimethoxystilbene (38)

From 3-hydroxy-4-methoxystyrene (**14**) and 3,5-dimethyliodobenzene; yield: 58.7%; white solid; mp 94–96 °C (lit.: 90–91 °C,[35] 89–90.[50]

5.1.34. (*E*) 4-Methoxy-2′,3,5′-trihydroxystilbene (39)

From **14** and 2,5-dihydroxyiodobenzene; yield: 51.6%; mp 181–183 °C; white solid; R_F = 0.61 (silica gel, hexane/ethyl acetate, 1:1); IR (KBr): ν = 3298br, 2898w, 1636w, 1605w, 1558w, 1522m, 1453s, 1383s, 1272m, 1223m, 1195m, 1163w, 1129m, 1093w, 1022m cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 211 (4.30), 294 (4.02), 347 (4.08) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.01 (br s, 1H, O*H*), 7.79 (br s, 1H, O*H*), 7.63 (br s, 1H, O*H*), 7.30 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*═ (1)), 7.08 (d, 1H, ^4J = 1.9 Hz , C*H* (2)), 7.04 (d, 1H, ^4J = 1.9 Hz, C*H* (6′)) 7.01 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*═ (2)), 6.96 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.9 Hz, C*H* (6)), 6.90 (d, 1H, ^3J = 8.3 Hz, C*H* (5)), 6.72 (d, 1H, ^4J = 8.7 Hz, C*H* (3′)), 6.58 (dd, ^3J = 8.7 Hz, ^4J = 1.9 Hz, C*H* (6)), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ = 150.0 (C5′, $C_{quart.}$), 147.4 (C3, $C_{quart.}$), 146.8 (C2′, $C_{quart.}$), 146.2 (C4, $C_{quart.}$), 131.1 (C1, $C_{quart.}$), 127.4 (*C*H═), 124.7 (C1′, $C_{quart.}$) 121.1 (*C*H═), 118.1 (C6, *C*H), 116.0 (C3′, *C*H), 114.7 (C4′, *C*H), 111.8 (C2, *C*H), 111.3 (C6′, *C*H), 111.1 (C5, *C*H), 54.9 (O*C*H_3) ppm; MS (ESI, MeOH): m/z = 257.3 (93% $[M-H]^-$); 303.0 (100% $[M+HCO_2]^-$); 542.9 (54% $[2M-H]^-$); Anal. Calcd for $C_{15}H_{14}O_4$ (258.27); C, 69.76; H, 5.46. Found: C, 69.49; H, 5.61.

5.1.35. (*E*) 3-Hydroxy-2′,4,4′-trimethoxystilbene (40)

From **14** und 2,4-dimethoxyiodobenzene: yield: 54.7%; mp 139–140 °C; white solid; R_F = 0.46 (silica gel, hexane/ethyl acetate, 3:1); IR (KBr): ν = 3382br, 2990m, 2962m, 2932m, 2837m, 1604s, 1577s, 1517s, 1500s, 1460s, 1440m, 1416m, 1348w, 1323m, 1291s, 1250s, 1202s, 1157s, 1120s, 1038s, 1023s cm^{-1}; UV–vis (methanol): λ_{max} (log ε) = 210 (4.60), 294 (4.48), 330 (4.65) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, 1H, ^3J = 8.5 Hz, C*H* (6′)), 7.23 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*═ (1)), 7.13 (d, 1H, ^4J = 1.9 Hz, C*H* (2)), 6.94 (dd, 1H, ^3J = 8.6 Hz, ^4J = 1.9 Hz, C*H* (6)), 6.88 (d, 1H, ^3J (trans) = 16.4 Hz, C*H*═ (2)), 6.79 (d, 1H, ^3J = 8.6 Hz, C*H* (5)), 6.49 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.5 Hz, C*H* (5′)), 6.45 (d, 1H, ^4J = 2.5 Hz, C*H* (3′)), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C4′, $C_{quart.}$), 157.9 (C2′, $C_{quart.}$), 145.9 (C3, $C_{quart.}$), 145.7 (C4, $C_{quart.}$), 132.2 (C1, $C_{quart.}$), 126.9 (C6′, *C*H), 126.6 (*C*H═), 121.8 (*C*H═), 119.7 (C1′, $C_{quart.}$), 118.9 (C6, *C*H), 111.7 (C2, *C*H), 110.6 (C5, *C*H), 104.9 (C5′, *C*H), 98.5 (C3′, *C*H), 55.9 (O*C*H_3), 55.5 (O*C*H_3), 55.74 (O*C*H_3) ppm; MS (ESI, MeOH): m/z = 285.2 (100 % $[M-H]^-$); 570.7 (4% $[2M-H]^-$); Anal. Calcd for $C_{17}H_{18}O_4$ (286.32): C, 71.31; H, 6.34. Found: C, 71.11; H, 6.52.

5.2. Biology

5.2.1. Antibacterial and antifungal activity

Test organisms were obtained from the American Type Culture Collection (ATCC, Manassas, USA) or the Jena Microbial Resource Collection (JMRC, Jena, Germany), respectively. Bacteria were grown in 8 g/l nutrient broth (AppliChem, Darmstadt, Germany) at 37 °C or kept on slants (NB amended with 1.5% [w/v] agar; Roth, Karlsruhe, Germany) at 4 °C. Fungal cultures were grown in HA medium (5 g/l malt extract; AppliChem, Darmstadt, Germany/4 g/l yeast extract; Roth, Karlsruhe, Germany/4 g/l glucose; Roth, Karlsruhe, Germany or kept on slants (HA amended with 1.5% [w/v] agar) at 4 °C.

The antimicrobial activities of the test compounds and the antibiotics used as reference substances were determined according to Zähner.[51] In brief, fungal plates were prepared with HA medium supplemented with 1.5% (w/v) agar. After autoclaving and cooling to 45 °C fungal spores or yeast cells were added to a final density of 10^5 colony forming units (cfu)/ml. Twenty milliliters of this preparation were poured into each Petri dish.

Bacterial test plates were prepared with NB supplemented with 1.5% (w/v) agar. After autoclaving and cooling to 45 °C, bacterial spores or vegetative cells were added to a final density of 10^6 cfu/ml. Fifteen ml of this preparation were poured into each Petri dish.

Table 2
Organisms and growth conditions used in the agar diffusion test

Organism	Ref. number	Growth temp (°C)	Medium
Bacillus brevis	ATTC 9999	37	NB
Bacillus subtilis	ATTC6633	37	NB
Enterobacter dissolvens	ATCC222	37	NB
Micrococcus luteus	ATCC381	37	NB
Nematospora coryli	ATCC10647	28	HA
Penicillium notatum	FSU2721	28	HA
Mucor miehei	FSU769	37	HA
Colletotrichum graminicola	M2	28	HA
Botrytis cinerea	FSU 883	28	HA

The test compounds were dissolved in methanol in a final concentration of 10 mg/ml, and 5 ml of the solution were pipetted onto paper discs (6 mm diameter; Macherey-Nagel, Düren, Germany) and left for drying before they were placed onto test plates.

Test organisms and cultivation conditions are listed in Table 2. Inhibition zone measurements and types of inhibition (incomplete or complete) were determined after 24–72 h.

5.2.2. Cytotoxicity assay[29]

The cytotoxicity of the compounds was evaluated using the sulforhodamine-B (SRB) (Sigma Aldrich) microculture colorimetric assay. In short, exponentially growing cells were seeded into 96-well plates on day 0 at the appropriate cell densities to prevent confluence of the cells during the period of experiment. After 24 h, the cells were treated with serial dilutions of the compounds (0–100 μm) for 96 h. The final concentration of DMSO or DMF solvent never exceeded 0.5%, which was non-toxic to the cells. The percentages of surviving cells relative to untreated controls were determined 96 h after the beginning of drug exposure. After a 96 h treatment, the supernatant medium from the 96 well plates was thrown away, and the cells were fixed with 10% TCA. For a thorough fixation, the plates were allowed to rest at 4 °C. After fixation, the cells were washed in a strip washer. The washing was done four times with water using alternate dispensing and aspiration procedures. The plates were then dyed with 100 μL of 0.4% SRB (sulforhodamine B) for about 20 min. After dying the plates were washed with 1% acetic acid to remove the excess of the dye and allowed to air-dry overnight. One-hundred microliters of 10 mm Tris base solution were added to each well and absorbance was measured at 570 nm (using a 96 well plate reader, (Tecan Spectra, Crailsheim, Germany). The IC_{50} was estimated by linear regression between the value before and after the 50% line is crossed in a dose–response curve.

Acknowledgments

We like to thank Dr. Dieter Ströhl for the NMR measurements and Dr. Ralph Kluge for the ESI-MS spectra. *C. graminicola* strain M2 was kindly provided by R. L. Nicholson, Purdue University. We thank PD Dr. R. Paschke from Biosolutions Halle GmbH for support. We are grateful to the Hans-Böckler-Stiftung (Düsseldorf) for a scholarship to S. Albert. The cell line was kindly provided by Dr. T. Müller (Dept. of Haematology/Oncology, Univ. Halle).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.07.015.

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