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Resveratrol-Related Dehydrodimers: Laccase-Mediated Biomimetic Synthesis and Antiproliferative Activity

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Dedicated to the memory of Ernesto Fattorusso

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Seven resveratrol-related monomeric stilbenoids were submitted to biomimetic oxidative coupling in the presence of laccase from *Trametes versicolor* (TvL), and gave racemic dihydrobenzofuran dehydrodimers (±)-**15** to (±)-**21**. These products, after spectral characterization, were submitted to an antiproliferative activity bioassay against SW480 human colon cancer cells. Five racemates were found to be active, and were resolved by chiral HPLC. The pure enantiomers were subjected to circular dichroism measurements to establish their absolute configurations at C-7 and C-8. These enantiomerically pure compounds were submitted to the antiproliferative activity assay towards SW480 cells, and were all shown to be active with IC_{50} values in the approximate range 20–90 μM. In some cases, a significant difference between the activity of the 7*R*,8*R* and 7*S*,8*S* enantiomers was observed, but a defined configuration of the stereogenic centers does not appear to be a structural requirement for the activity. The comparison between the most active compounds and the inactive ones strongly suggests that the presence of a methoxy group in the position *ortho* to the C-4 hydroxy group is highly detrimental to the activity.

Introduction

Resveratrol – (*E*)-3,5,4′-trihydroxystilbene (**1**) – a stilbenoid originally isolated from *Veratrum grandiflorum*,[1] and later obtained from the roots of the Asian medicinal plant *Polygonum cuspidatum*,[2] has, in recent times, become one of the most cited natural products. This impressive growth of popularity started with the possible correlation between its presence in grapes and the so-called "French paradox", which refers to the inverse correlation between a high-fat diet and low mortality risk from heart disease observed in some southern regions of France, and attributed to red wine consumption.[3] The subsequent evidence in favor of its possible role in the prevention of cancer and other degenerative diseases has stimulated a wide variety of studies, including in vivo studies, which have been summarized by recent books and reviews.[4] Less attention has been dedicated to the study of natural or synthetic oligomers of resveratrol, even though this group of compounds of natural origin includes many biologically active members. Examples of dimers of this class are: ε-viniferin (**2**), a resveratrol dehydrodimer found in *Vitis vinifera* and other natural sources,[5] which is known for its antifungal,[6] antimicrobial,[7] antiinflammatory,[8] and antiproliferative activities;[9] its glucoside (**3**), and the related compound scirpusin A (**4**), both of which have recently been reported to show extremely efficient inhibition of β-amyloid peptide aggregation, a phenomenon that is observed in the progression of Alzheimer's disease;[10] the dehydrodimer δ-viniferin (**5**), identified as a metabolite of *Vitis vinifera* cultures[11] and as a product of resveratrol biotransformation by *Botritis cinerea* fungal cultures,[12] which has been shown to be moderately cytotoxic against CEM (human lymphoblastoid) cells;[12] pallidol (**6**), originally isolated from *Cissus pallida*,[13] which has also been reported to be active against CEM and, more recently, to be an inhibitor of tumorigenic colon cell growth;[14] and its hexaacetate (**7**), which has also shown significant cytotoxicity against KB cells.[15]

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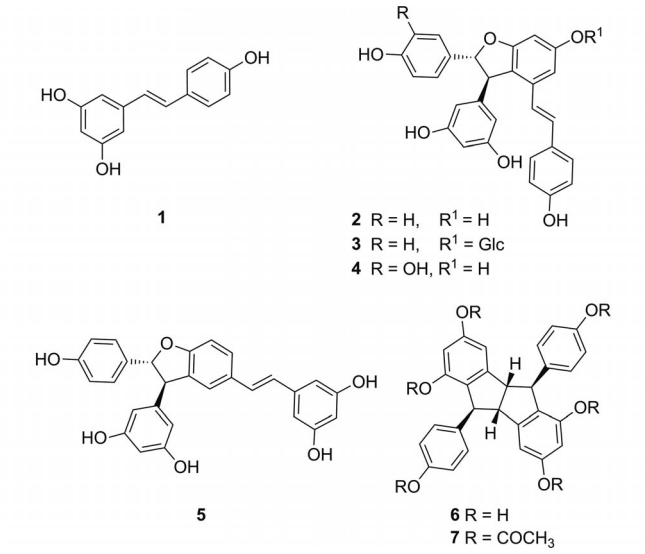


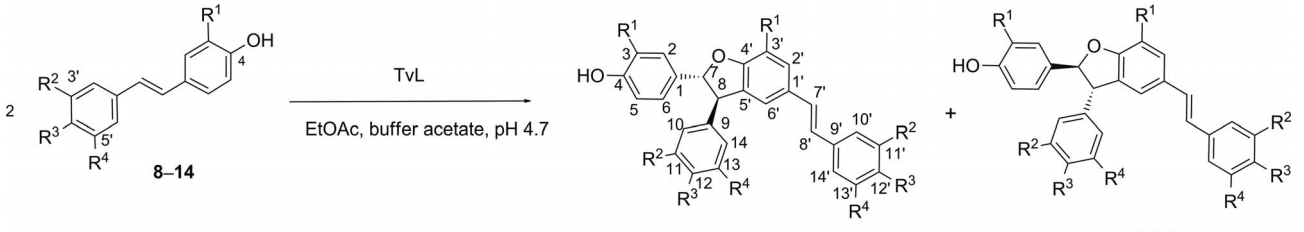
The interesting properties of the natural resveratrol dimers have stimulated the preparation of synthetic analogues by both chemical and enzymatic methods.[16] Nevertheless, to the best of our knowledge, none of these synthetic efforts has been accompanied by a biological evaluation of the products. Thus, as a continuation of our studies on antitumor resveratrol analogues,[17] we have now synthesized a small library of resveratrol-related dimers by a biomimetic route based on enzyme-mediated oxidative coupling using the laccase from *Trametes versicolor*. The products were purified and evaluated for antiproliferative activity against SW480 colon cancer cells. The results and some structure–activity relationship considerations are presented in this paper.

Results and Discussion

Monomeric resveratrol analogues **8**–**14** were obtained by Wittig and/or Heck reactions, and their synthesis has previously been reported in detail by some of us.[18]

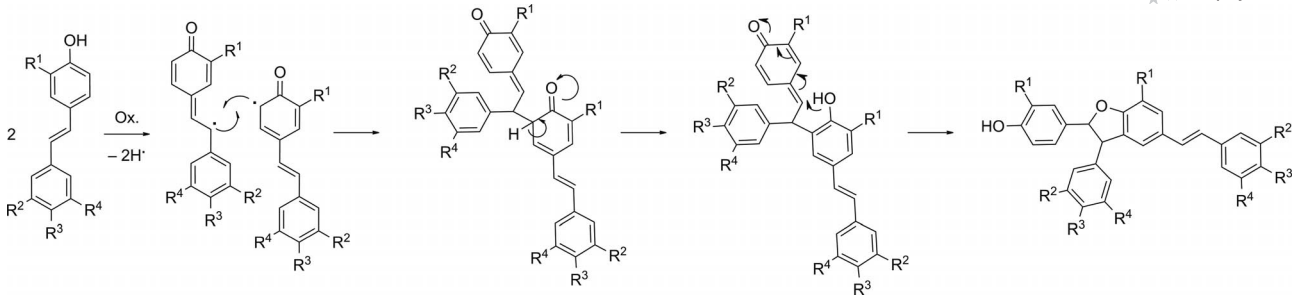
These stilbenoids were used as substrates for oxidative coupling according to the general Scheme 1, and gave dehydrodimers (±)-**15** to (±)-**21**, incorporating a dihydrobenzofuran moiety, as major products. It is worth emphasizing that the stilbenoid dimerization reactions, even the enzyme-mediated reactions, occured with regio- and diastereoselectivity, but not enantioselectivity,[16e,19] and consequently gave racemic mixtures.

The mechanism of formation of resveratrol oligomers by oxidative coupling has been investigated by several authors, and the involvement of radical species is widely accepted. The hypothesis of a radical attack on the unactivated starting material has been considered as an alternative to a radical–radical coupling mechanism.[16d,16f,19,20] However, the involvement of a quinone–methide radical is frequently claimed, and the mechanism illustrated in Scheme 2, supported by experimental evidence,[16e] seems reasonable for the laccase-mediated formation of resveratrol dehydrodimers with the δ-viniferin skeleton. The observed regioselectivity of these reactions is in agreement with this mechanism. A plausible explanation of the diastereoselectivity in favor of the 7,8-*trans*-substituted diastereomers, which has also been observed in all previous syntheses of dihydrobenzofuran-based stilbene dimers,[21] is that the less hindered transition state (TS) leading to the *trans* product is largely favoured. Moreover, recently reported AM1 calculations on compound **19**[16f] indicated that the *trans* diastereomer is more stable than its *cis* isomer. This was supported by our recently published data on the oxidative coupling of caffeic acid esters to give benzoxanthene and *trans*-aryldihydronaphthalene lignans.[22] The calculated ΔH_f values for the possible TS originating from a quinone–methide intermediate clearly indicated that the TS leading to the *trans* aryldihydronaphthalene racemate is by far the most stable. With regard to the lack of enantioselectivity in the enzyme-mediated oxidative coupling, it is worth noting that in the biosynthesis of lignans, where the proposed mechanism is the oxidative coupling of two phenylpropanoid units followed by quinone–methide cyclization, it has been proved that the



8, **15** $R^1 = R^2 = R^3 = R^4 = H$
9, **16** $R^1 = R^2 = R^4 = H$, $R^3 = -CH=CH_2$
10, **17** $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
11, **18** $R^1 = R^3 = OMe$, $R^2 = R^4 = H$
12, **19** $R^1 = R^3 = H$, $R^2 = R^4 = OMe$
13, **20** $R^1 = R^2 = R^3 = R^4 = OMe$
14, **21** $R^1 = R^2 = R^4 = H$, $R^3 = Br$

Scheme 1. Oxidative coupling of compounds **8**–**14**.



Scheme 2. Mechanism of formation of compounds (±)**15**–(±)-**21**.

oxidase enzyme only generates the radical species, and that the stereochemistry is controlled by a "dirigent protein".[21] In the absence of this protein, racemic mixtures are obtained.[23]

We used a biomimetic oxidative coupling methodology that mimics the biosynthesis of natural dihydrobenzofuran dimers,[21] as outlined in the literature.[6,16d,21] Although various synthetic methodologies have been used for the synthesis of stilbenoid oligomers, the biomimetic approach has the advantage of simplicity and brevity. An enzyme-mediated reaction is also a sustainable chemical process. Reaction conditions were evaluated in preliminary experiments on an analytical scale, using both chemical and enzymatic methods.

The reactions were carried out on three resveratrol analogues, **9**, **10** and **14**, using either $Mn(OAc)_3$ or laccase from the fungus *Trametes versicolor* (TvL). In the enzymatic reactions, a shaken biphasic system with an acetate buffer and a co-solvent was used at room temperature. In the Mn-mediated reactions, dichloromethane and chloroform gave better results than ethyl acetate. In the TvL-mediated reactions, poor conversions were observed when dichloromethane and chloroform were used as co-solvents, whereas ethyl acetate gave good conversion rates. In a further preliminary evaluation of the metal-mediated methodology, the substrate/$Mn(OAc)_3$ ratio was evaluated, and a 1:4 ratio gave the best results. In summary, the TvL-mediated conditions appeared to be the most promising, both in terms of the higher conversion of the substrate, and for giving essentially one major product. Thus, the enzymatic methodology was selected for the preparative reactions, also in view of its simple work-up and of its "eco-friendly" and heavy-metal-free features.

For the preparation of dimer **15**, monohydroxylated stilbene **8** was treated with TvL in ethyl acetate/acetate buffer. The major product was isolated by flash chromatography. Analysis of the ESI-MS, ^1H and ^{13}C NMR spectra of the product allowed its identification as the *E*-dihydrobenzofuran dimer (±)-**15**, based also on comparison with spectroscopic data previously reported in the literature.[16e] The *J*-value of the 7′-H,8′-H coupling (J = 16.3 Hz) established the *E* configuration of the double bond, and that of the 7-H,8-H coupling (J = 8.5 Hz), confirmed the *trans* relative configuration of the C-7 and C-8 substituents. Monohydroxylated stilbenoid **9**, bearing a vinyl group at C-4′, was subjected to an analogous reaction in the presence of TvL, and the major product was isolated by flash chromatography. The ESI-MS spectrum of this product showed a peak at m/z = 465.1 $[M + Na]^+$, consistent with the expected molecular weight for (±)-**16**, a previously unreported dimer. For this compound, we carried out an extensive ^1H and ^{13}C NMR spectroscopic analysis, including two-dimensional methods (COSY, HSQC and HMBC, see Supporting Information and Figure 1), in order to unambiguously establish the structure and assign all ^1H and ^{13}C NMR signals, as reported in the Experimental section. Stilbenoid **10**, bearing a methoxy group at C-4′, was treated as described above, and one major product was obtained. The product was characterized as dimer (±)-**17** on the basis of the analysis of its ESI-MS and NMR spectroscopic data and comparison with literature data.[16e] In a similar way, substrate **11**, with three oxygenated functionalities (one hydroxy group at C-4 and two methoxy groups at C-3 and C-4′), was treated with TvL in the biphasic system, and one major product was obtained. Analysis of the ESI-MS, ^1H and ^{13}C NMR spectra of the dimer led to structure (±)-**18**, in agreement with previously reported data.[16e] When this method was applied to stilbenoid **12**, bearing two methoxy groups at C-3′ and C-5′, it led to the formation of racemate (±)-**19** as the major product, whose ESI-MS and NMR spectroscopic data were in perfect agreement with those previously reported.[16e,16f] The pentasubstituted substrate **13** (bearing four methoxy groups at C-3, C-3′, C-4′ and C-5′, in addition to the C-4 hydroxy group), treated as described above, gave a major product that had not been reported previously. Analysis of its ^1H and ^{13}C NMR spectra was facilitated by using two-dimensional methods (COSY, NOESY, HSQC and HMBC, see Supporting Information and Figure 1), which allowed a complete assignment of the NMR signals and confirmed the expected structure [i.e., (±)-**20**]. In particular, due to the presence of eight methoxy groups in this compound, the NOESY spectrum was of critical importance for the assignment of the six pertinent ^1H signals (See Experimental section). Finally, brominated stilbene **14** was submitted to the dimerization reaction conditions, and the major product gave a peak at m/z = 546.9 $[M - H]^-$, which was consistent with the expected molecular weight of (±)-**21**. The structural determination of this unprecedented dimer was also supplemented by two-dimensional NMR spectroscopic methods (COSY, HSQC and

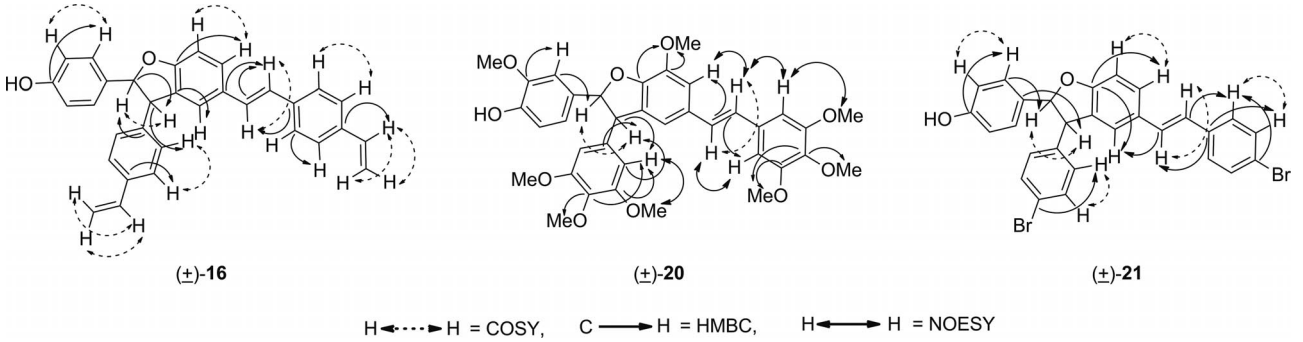


Figure 1. Selected 2D-NMR correlations for (±)-**16**, (±)-**20** and (±)-**21**.

HMBC, see Supporting Information and Figure 1), to allow the complete assignment of the NMR signals (See Experimental section).

After their structural characterization, the racemic dihydrobenzofuran dimers [i.e., (±)-**15**–(±)-**21**] were submitted to an antiproliferative activity bioassay against SW480 human colon cancer cells.

Resveratrol (**1**) was used as a reference compound, taking into account its structural relationship with the dimers and the antitumor properties of this well-known stilbenoid. The results are reported in Table 1.

Table 1. Antiproliferative activity towards SW480 cells of compounds (±)-**15**–(±)-**21**.

Compound	IC_{50} [μM][a]
1	68.1 ± 5.5
(±)-**15**	22.5 ± 2.0
(±)-**16**	22.3 ± 2.7
(±)-**17**	33.4 ± 2.9
(±)-**18**	> 100
(±)-**19**	27.8 ± 3.1
(±)-**20**	> 100
(±)-**21**	30.7 ± 2.8

[a] IC_{50} and standard deviation determined after 48 h of treatment; values are the mean of three experiments.

A first obvious structure–activity relationship is that two dimers (±)-**18** and (±)-**20**, the only ones bearing a methoxy group in the position *ortho* to the C-4 hydroxy group, are essentially inactive (IC_{50} > 100 μM), whereas all the other racemic dimers show antiproliferative activity with IC_{50} values in the approximate range 22–33 μM, i.e., significantly higher than that of resveratrol. It is particularly interesting that the most active dimers, (±)-**16** and (±)-**15**, are those with fewest substituents. Of course, these results do not allow the assessment of the possible consequences of different configurations at the stereogenic centers at C-7 and C-8. Thus, we carried out the chiral resolution of the five active racemates to isolate the pure enantiomers, in order to establish their absolute configuration and evaluate their specific antiproliferative activity. Each racemic mixture was subjected to chiral HPLC separation on a Chiralpack IA column (see Experimental section for details). From here on, the enantiomer with the shorter retention time of each pair is indicated as "**a**" to distinguish it from the enantiomer with the longer retention time, indicated as "**b**". The purified enantiomers were subjected to Circular Dichroism (CD) measurements to establish their absolute configuration at the stereogenic centers C-7 and C-8. The comparison of CD spectra with that of a closely related compound is one of the most useful methods for determining the absolute configuration of natural products or their synthetic analogues,[24] and it has been applied to similar cases of dihydrobenzofuran dimers.[25] For the sake of brevity, only the CD spectra of the enantiomers **17a** and **17b** are reported here (Figure 2). The CD spectra of all of the enantiomeric pairs are reported in the Supporting Information. The absolute configuration of **17a** and **17b** was determined by comparison of their CD spectra with that of (–)-ε-viniferin (**2**),[25d] whose absolute configuration has previously been established as 7*R*,8*R*.[25b] Both **17a** and 7*R*,8*R*-viniferin (**2**) show a negative Cotton effect in the range 230–240 nm, and consequently, the 7*R*,8*R* configuration was assigned to **17a**, and the 7*S*,8*S* configuration was assigned to **17b**.

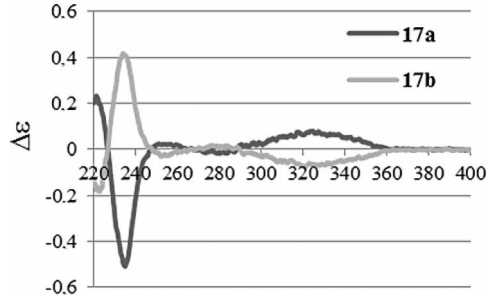


Figure 2. CD spectra of **17a** and **17b**.

The absolute configurations of the other enantiomeric pairs were determined on the basis of an analogous comparison. Thus, the ten enantiomerically pure compounds were established as follows: 7*R*,8*R*-**15a**; 7*S*,8*S*-**15b**; 7*R*,8*R*-**16a**; 7*S*,8*S*-**16b**; 7*R*,8*R*-**17a**; 7*S*,8*S*-**17b**; 7*R*,8*R*-**19a**; 7*S*,8*S*-**19b**; 7*R*,8*R*-**21a**; 7*S*,8*S*-**21b**. All of the enantiomers that eluted first from the Chiralpack IA column had the 7*R*,8*R* configuration.

The purified enantiomeric forms of **15**, **16**, **17**, **19** and **21** were submitted to the antiproliferative activity assay towards SW480 colon cancer cells. The results are summarized in Table 2.

Table 2. Antiproliferative activity towards SW480 cells of the enantiomeric forms of compounds **15**, **16**, **17**, **19**, **21**.

Compound	IC_{50} [μM][a]
7*R*,8*R*-**15a**	88.1 ± 2.1
7*S*,8*S*-**15b**	22.5 ± 0.8
7*R*,8*R*-**16a**	20.0 ± 0.4
7*S*,8*S*-**16b**	22.5 ± 0.7
7*R*,8*R*-**17a**	19.9 ± 0.6
7*S*,8*S*-**17b**	73.4 ± 2.3
7*R*,8*R*-**19a**	43.8 ± 1.5
7*S*,8*S*-**19b**	24.9 ± 0.9
7*R*,8*R*-**21a**	21.7 ± 0.4
7*S*,8*S*-**21b**	35.9 ± 0.8

[a] IC_{50} and standard deviation determined after 48 h of treatment; values are the mean of three experiments.

From these results on the inhibition of SW480 colon cancer cell growth, it is clear that all of the individual enantiomers are active, with IC_{50} values in the approximate range 20–90 μM. Although the highest activity was shown by 7*R*,8*R*-**17a**, the most active enantiomers of each pair were equally distributed between the 7*R*,8*R* and 7*S*,8*S* configurations, in the order: 7*R*,8*R*-**17a** > 7*R*,8*R*-**16a** > 7*R*,8*R*-**21a** > 7*S*,8*S*-**15b** = 7*S*,8*S*-**16b** > 7*S*,8*S*-**19b**. The most potent compound **17a** (IC_{50} = 19.9 μM) also showed the highest difference in activity with respect to its enantiomer **17b** (IC_{50} = 73.4 μM). Compound **15b** (IC_{50} = 22.5 μM) was four times more active than its enantiomer **15a** (IC_{50} = 88.1 μM), but a less marked difference was observed between **21a** and **21b** and between **19b** and **19a**, whereas **16a** and **16b** had comparable activities. On the basis of these data, a defined configuration of the stereogenic centers does not appear to be a structural determinant for the activity, although it could have a role in some cases. All of the most active dehydrodimers **17a**, **16a** and **21a**, which showed comparable IC_{50} values, bear only one substituent at C-4′ position, and their activity was close to that of **15b**, which has no substituent on the second (non-hydroxylated) ring. This corroborates the observation reported above that the compounds bearing fewer substituents show higher activity. However, other factors, such as diffusion, membrane permeability, metabolic stability, and others, may affect the activity in bioassays on cell cultures.

Conclusions

In this work, we have synthesized seven racemic resveratrol-related dehydrodimers incorporating a dihydrobenzofuran moiety (i.e., **15**–**21**), using an eco-friendly, biomimetic methodology based on laccase-mediated oxidative coupling of synthetic stilbenoids **8**–**14**. Three previously unreported dimers (i.e., **16**, **20**, and **21**) were obtained; the other products (i.e., **15**, **17**, **18**, and **19**) have been reported previously, but using the laccase from *Trametes versicolor*, we obtained both higher yields and shorter reaction times (for compounds **15**, **17** and **19**), or at least a shorter reaction time (for compound **18**), than had previously been obtained using the laccase from *Trametes pubescens*.[16e]

The racemates were submitted to an antiproliferative activity bioassay towards SW480 human colon cancer cell cultures, and from this assay, five dimers showed significant activity, in the order (±)-**16** > (±)-**15** > (±)-**19** > (±)-**21** > (±)-**17**. The racemic mixtures were resolved by chiral HPLC, and the pure enantiomers were submitted to CD measurements in order to establish their absolute configuration. The enantiomerically pure compounds were also evaluated for their antiproliferative activity. The results of the bioassays are not simple to interpret, but the following observations on possible structure–activity relationships can be made: (a) A comparison between the most active compound (i.e., **17a**) and inactive (±)-**18** strongly suggests that the methoxy group *ortho* to the C-4 hydroxy group is highly detrimental to the activity. The data also suggest a critical role for the C-4 hydroxy group, for instance in establishing hydrogen bonds with a biological target;

(b) Although the three most active compounds (i.e., **17a**, **16a** and **21a**) have a 7*R*,8*R* configuration, the configuration of the stereogenic centers does not appear to be a vital structural determinant for activity. However, it could become important when other factors have a minor role, as suggested by the marked difference in activity between some pairs of enantiomers. For instance, in dimers without hindering substituents close to the C-4 hydroxy group, further interactions involving the stereogenic centers could be established with the biological target.

In conclusion, although only a small library of compounds was evaluated, and a more detailed definition of the structural determinants for resveratrol-related dihydrobenzofuran dimers will require further structure–activity relationship studies, the results discussed here offer first indications for further optimization of these promising lead compounds.

Experimental Section

General: NMR spectra were obtained with a Varian Unity Inova spectrometer operating at 499.86 (^{1}H) and 125.70 MHz (^{13}C), equipped with gradient-enhanced, reverse-detection probe. Chemical shifts (δ) are indirectly referenced to TMS using solvent signals. All NMR experiments, including two-dimensional spectra, were performed using software supplied by the manufacturers and acquired at constant temperature (298 K) using $CDCl_3$ as solvent. NMR spectroscopic data of the previously unreported compounds (**16**, **20** and **21**) are reported below, copies of the pertinent spectra are included in the Supporting Information.

Electrospray ionization mass spectra (ESI-MS) were recorded with a Thermo-Finnigan LCQ-DECA ion-trap mass spectrometer equipped with an ESI ion source, operating in MS negative- or positive-ion mode under the following conditions: capillary temperature, 180 °C; sheath gas 20 a.u.; spray voltage 4 kV. Elemental analyses were performed with a Perkin–Elmer 240B microanalyzer.

High-performance liquid chromatography (HPLC) was carried out using an Agilent Series G1354A pump and a photodiode array detector Agilent Series 1200 G1315C/D. An auto-sampler Agilent Series 1100 G1313A was used for sample injection. The chiral HPLC-UV of racemates was carried out on a Chiralpak IA (5 μm; 4.6 × 250 mm) column; details of elution and flow rate are reported

below for each separation. The separation protocol was repeated a sufficient number of times to achieve the amount (3–5 mg) required for CD measurements and bioassays.

CD spectra were run in methanol on a Jasco J610 spectrometer. The CD spectra of pure enantiomers are included in the Supporting Information.

Flash chromatography was performed on Silica gel 60 (Merck) and DIOL Silica gel (Merck) using different solvent systems, as reported for each compound. TLC was carried out using pre-coated silica gel F_{254} plates (Merck); cerium sulfate and phosphomolybdic acid were used as chromogenic spray reagents.

Materials and Methods: All chemicals were of reagent grade and were used without further purification. Laccase from *Trametes versicolor* (TvL) and manganese acetate were purchased from Sigma (Milan, Italy).

Synthesis of the Stilbenoids 8–14: The monomeric resveratrol analogues **8**–**14** were synthesized by Wittig and/or Heck reactions according to the procedures previously reported by some of us.[18]

Biomimetic Synthesis of Compounds (±)-15 to (±)- 21

Preliminary Experiments. Metal-Mediated Reactions: Each substrate (**9**, **10**, and **14**; 2 mg) was dissolved in three different solvents, namely dichloromethane, chloroform and ethyl acetate (2 mL). Subsequently, $Mn(OAc)_3$ (1 equiv.) was added to the solutions. The reaction mixture was stirred at room temperature and monitored by TLC. After 24 h, the reaction was quenched with a solution of ascorbic acid in water, and a further amount (3× 2 mL) of the pertinent organic solvent (dichloromethane, chloroform or ethyl acetate) was added. After extraction, the dried organic phase was evaporated to dryness under vacuum, and the residue was analyzed by TLC. Two further substrate/oxidant ratios (1:2 and 1:4) were also evaluated in chloroform and dichloromethane.

Enzyme-Mediated Reactions: Each substrate (**9**, **10**, and **14**; 2 mg) was dissolved in three different solvents, namely dichloromethane, chloroform and ethyl acetate (1 mL). A solution of TvL (2 mg) in acetate buffer (1 mL, 0.1 M, pH = 4.7) was added, the mixture was stirred at room temperature, and the reaction was monitored by TLC. After 24 h, the product was obtained by phase-separation.

Synthesis of (±)-15: Substrate **8** (140 mg, 0.71 mmol) was dissolved in ethyl acetate (35 mL), and TvL (10 U, 30 mg) was dissolved in acetate buffer, (pH 4.7; 15 mL). The biphasic system was stirred at room temperature for 10 h and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The dried organic extracts were evaporated, and the crude residue was purified by flash chromatography using petroleum ether/dichloromethane (6:4) as the eluent to give (±)-**15** (38 mg, 28%). ^{1}H and ^{13}C NMR spectroscopic data were in agreement with previous data reported in the literature.[16e] ESI-MS: m/z = 413.1 $[M + Na]^+$. The resolution of racemic (±)-**15** was carried out by chiral HPLC-UV using a Chiralpak IA column (5 μm; 4.6×250 mm), with an isocratic elution (2-propanol/*n*-hexane, 8:2, flow rate 0.4 mL/min). Pure enantiomer 7*R*,8*R*-**15a** was isolated with a retention time of 14.3 min, and 7*S*,8*S*-**15b** was isolated with a retention time of 18.1 min. 7*R*,8*R*-**15a**: CD (c = 2.5×10^{-4} M, MeOH) nm ($\Delta\varepsilon$): 230 (–0.334); 7*S*,8*S*-**15b**: CD (c = 2.7×10^{-4} M, MeOH) nm ($\Delta\varepsilon$): 230 (0.421).

Synthesis of (±)-16: Substrate **9** (30 mg, 0.13 mmol) was dissolved in ethyl acetate (20 mL), and TvL (10 U, 15 mg) was dissolved in acetate buffer, (pH 4.7; 15 mL). The biphasic system was stirred at room temperature for 24 h and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The dried organic extracts were evaporated, and the crude residue was purified by flash chromatography (petroleum ether/dichloromethane, 6:4) to give (±)-**16** (9 mg, 24%) as an amorphous white powder. R_f (TLC) = 0.41 (25% EtOAc/*n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.41 (d, $^3J_{H,H}$ = 8.5 Hz, 4 H, 11-H, 13-H, 11′-H, and 13′-H), 7.38* (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 2′-H), 7.37* (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 10′-H and 14′-H), 7.23 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 2-H, 6-H), 7.19# (br. s, 1 H, 6′-H), 7.18# (d, $^3J_{H,H}$ = 8.5 Hz, 4 H, 10-H and 14-H), 7.04 (d, $^3J_{H,H}$ = 16.2 Hz, 1 H, 7′-H), 6.94 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 3′-H), 6.90 (d, $^3J_{H,H}$ = 16.2 Hz, 1 H, 8′-H), 6.82 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 3-H and 5-H), 6.74 (dd, $^3J_{H,H}$ = 16.2, 10.5 Hz, 1 H, 15-H), 6.70 (dd, $^3J_{H,H}$ = 16.2, 10.5 Hz, 1 H, 15′-H), 5.78 (d, $^3J_{H,H}$ = 16.2 Hz, 1 H, 16b-H), 5.75 (d, $^3J_{H,H}$ = 16.2 Hz, 1 H, 16b′-H), 5.49 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 7-H), 5.28 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, 16a-H), 5.24 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, 16a′-H), 4.90 (br. s, 1 H, OH), 4.56 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 8-H) ppm. The signals with identical superscripts (* or #) were partially overlapping. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 159.6 (C-4′), 155.6 (C-4), 140.9 (C-9), 137.2 (C-5′), 136.7 (C-12′), 136.5 (C-15), 136.4 (C-15′), 132.5 (C-1), 131.0 (C-1′), 130.9 (C-9′), 128.6 (C-7′), 128.3 (C-6′), 127.9 (C-2′), 127.6 (C-2 and C-6), 126.7 (C-10′ and C-14′), 126.5 (C-11, C-13, C-11′ and C-13′), 126.3 (C-12), 125.9 (C-8′), 122.8 (C-10 and C-14), 115.5 (C-3 and C-5), 113.9 (C-16), 113.4 (C-16′), 109.7 (C-3′), 93.2 (C-7), 57.4 (C-8) ppm. For selected COSY and HMBC correlations, see Figure 1. ESI-MS: m/z = 465.1 $[M + Na]^+$. $C_{32}H_{26}O_2$ (442.5): calcd. C 86.85, H 5.92; found C 86.91, H 5.86. The chiral HPLC of racemic (±)-**16** was carried out by HPLC-UV using a Chiralpak IA (5 μm; 4.6×250 mm) column and an isocratic elution (2-propanol/*n*-hexane, 6:4, flow rate 0.6 mL/min). Pure enantiomer 7*R*,8*R*-**16a** was isolated with a retention time of 12.0 min, and 7*S*,8*S*-**16b** was isolated with a retention time of 14.0 min. 7*R*,8*R*-**16a**: CD (c = 1.8×10^{-4} M, MeOH) nm ($\Delta\varepsilon$): 235 (–0.508); 7*S*,8*S*-**16b**: CD (c = 2.2×10^{-4} M, MeOH) nm ($\Delta\varepsilon$): 235 (0.417).

Synthesis of (±)-17: Substrate **10** (100 mg, 0.44 mmol) was dissolved in ethyl acetate (40 mL), and TvL (10 U, 15 mg) was dissolved in acetate buffer, (pH 4.7; 15 mL). The biphasic system was stirred at room temperature for 20 h and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The dried organic extracts were evaporated. The crude residue was purified by flash chromatography using petroleum ether/ethyl acetate (8:2) as eluent to give (±)-**17** (65 mg, 65%). ^{1}H and ^{13}C NMR spectroscopic data were in agreement with previous data reported in the literature.[16e] ESI-MS: m/z = 449.3 $[M - H]^-$. The chiral HPLC of racemic (±)-**17** was carried out by HPLC-UV using a column Chiralpak IA (5 μm; 4.6×250 mm) and an isocratic elution with (2-propanol/*n*-hexane, 3:7, flow rate 0.5 mL/min). Pure enantiomer 7*R*,8*R*-**17a** was isolated with a retention time of 21.0 min, and 7*S*,8*S*-**17b** was isolated with a retention time of 25.1 min. 7*R*,8*R*-**17a**: CD (c = 1.1×10^{-4} M, MeOH) nm ($\Delta\varepsilon$): 235 (–0.508); 7*S*,8*S*-**17b**: CD (c = 1.2×10^{-4} M, MeOH) nm ($\Delta\varepsilon$): 235 (0.417).

Synthesis of (±)-18: Substrate **11** (30 mg, 0.11 mmol) was dissolved in EtOAc (15 mL), and TvL (10 U, 10 mg) was dissolved in of acetate buffer (pH 4.7; 10 mL). The biphasic system was stirred at room temperature for 24 h and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The dried organic extracts were evaporated. The crude residue was purified by flash chromatography using petroleum ether/ethyl acetate (8:2) as eluent to give (±)-**18** (19 mg, 67%). ^{1}H and ^{13}C NMR spectroscopic data were in agreement with previous data reported in the literature.[16e] ESI-MS: m/z = 509 $[M - H]^-$.

Synthesis of (±)-19: Substrate **12** (80 mg, 0.31 mmol) was dissolved in EtOAc (35 mL), and TvL (10 U, 15 mg) was dissolved in acetate buffer (pH 4.7; 15 mL). The biphasic system was stirred at room temperature for 10 h and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The dried organic extracts were evaporated. The residue was subjected to column chromatography using DIOL silica gel and petroleum ether/ethyl acetate (8:2) as eluent to give (±)-**19** (12 mg, 25%). ^{1}H NMR spectroscopic data were in perfect agreement with those previously reported.[16f] ESI-MS: *m*/*z* = 509 [M – H]$^-$. The chiral HPLC of racemic (±)-**19** was carried out by HPLC-UV using a column Chiralpak IA (5 μm; 4.6 × 250 mm) and an isocratic elution with (2-propanol/*n*-hexane, 6:4, flow rate 0.6 mL/min). Pure enantiomer 7*R*,8*R*-**19a** was isolated with a retention time of 13.4 min, and 7*S*,8*S*-**19b** was isolated with a retention time of 16.0 min. 7*R*,8*R*-**19a**: CD ($c = 2.7 \times 10^{-4}$ M, MeOH) nm (Δε): 234 (–0.378); 7*S*,8*S*-**19b**: CD ($c = 3.3 \times 10^{-4}$ M, MeOH) nm (Δε): 234 (0.392).

Synthesis of (±)-20: Substrate **13** (100 mg, 0.32 mmol) was dissolved in EtOAc (25 mL), and TvL (10 U, 15 mg) was dissolved in acetate buffer (pH 4.7; 15 mL). The biphasic system was stirred at room temperature for 8 h and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The organic solvents were evaporated. The crude residue was purified by flash chromatography using petroleum ether/ethyl acetate (6:4) as eluent to give (±)-**20** (30 mg, 30%) as an amorphous white powder. R_f (TLC) = 0.58 (40% EtOAc/*n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.03 (s, 1 H, 2′-H), 6.95 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, 7′-H), 6.90 (d, $^3J_{H,H}$ = 2.0 Hz, 1 H, 6′-H), 6.88 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 5-H), 6.86 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, 8′-H), 6.82 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.5 Hz, 1 H, 6-H), 6.80 (d, $^3J_{H,H}$ = 1.5 Hz, 1 H, 2-H), 6.70 (s, 2 H, 10′-H and 14′-H), 6.38 (s, 2 H, 10-H and 14-H), 5.52 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 7-H), 4.52 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 8-H), 4.01 (s, 3 H, 3′-OCH_3), 3.90 (s, 6 H, 11′-OCH_3 and 13′-OCH_3), 3.874 (s, 3 H, 3-OCH_3), 3.872 (s, 3 H, 12′-OCH_3), 3.86 (s, 3 H, 12-OCH_3), 3.78 (s, 6 H, 11-OCH_3 and 13-OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 153.5 (C-11, C-13), 153.4 (C-11′ and C-13′), 148.1 (C-3), 146.6 (C-4′), 145.8 (C-4), 144.5 (C-3′), 137.7 (C-12′), 137.2 (C-12), 136.8 (C-5′), 133.2 (C-1′), 131.9 (C-1), 131.7 (C-9), 131.5 (C-9′), 128.2 (C-7′), 126.6 (C-8′), 119.6 (C-2), 115.6 (C-6), 114.2 (C-5), 109.9 (C-2′), 108.7 (C-6′), 105.4 (C-10 and C-14), 103.3 (C-10′ and C-14′), 94.2 (C-7), 60.9 (12-OCH_3), 60.8 (12′-OCH_3), 58.5 (C-8), 56.2 (3′-OCH_3), 56.1 (11-OCH_3, 13-OCH_3), 56.05 (11′-OCH_3, 13′-OCH_3), 56.01 (3-OCH_3) ppm. For selected COSY, NOESY and HMBC correlations, see Figure 1. ESI-MS: *m*/*z* = 629.2 [M – H]$^-$. $C_{36}H_{38}O_{10}$ (630.7): cald. C 68.56, H 6.07; found C 68.34, H 6.21.

Synthesis of (±)-21: Substrate **14** (50 mg, 0.2 mmol) was dissolved in EtOAc (20 mL), and TvL (10 U, 15 mg) was dissolved in acetate buffer (pH 4.7; 10 mL). The biphasic system was stirred at room temperature for 5 d and monitored by TLC. The reaction was quenched by phase separation, and this was followed by EtOAc extraction of the water solution. The dried organic extracts were evaporated. The crude residue was purified by flash chromatography using petroleum ether/ethyl acetate (94:6) as eluent to give (±)-**21** (19 mg, 20%) as an amorphous white powder. R_f (TLC) = 0.29 (20% EtOAc/*n*-*hexane*). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.49 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 11-H and 13-H), 7.44 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 11′-H and 13′-H), 7.38 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 2′-H), 7.31 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 10′-H and 14′), 7.21 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2-H and 6-H), 7.14 (br. s, 1 H, 6′-H), 7.08 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 10-H and 14-H), 7.02 (d, $^3J_{H,H}$ = 16.3 Hz, 1 H, 7′-H), 6.94 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 3′-H), 6.836* (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 3-H and 5-H), 6.834* (d, $^3J_{H,H}$ = 16.3 Hz, 1 H, 8′-H), 5.44 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 7-H), 4.99 (s, 1 H, 4-OH), 4.53 (d, $^3J_{H,H}$ = 8.7 Hz, 8-H) ppm. The signals with identical superscript (*) were partially overlapping. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 159.8 (C-4′), 155.8 (C-4), 140.3 (C-9), 136.5 (C-9′), 132.0 (C-11′ and C-13′), 131.7 (C-11 and C-13), 130.8 (C-1), 130.6 (C-5′), 130.1 (C-10, C-14), 129.0 (C-7′), 128.24 (C-1′), 128.23 (C-2′), 127.6 (C-2 and C-6), 127.6 (C-10′ and C-14′), 125.2 (C-8′), 122.8 (C-6′), 121.3 (C-12), 120.8 (C-12′), 115.5 (C-3 and, C-5), 109.9 (C-3′), 93.3 (C-7), 57.1 (C-8) ppm. For selected COSY and HMBC correlations, see Figure 1. ESI-MS: *m*/*z* = 546.9 [M – H]$^-$. $C_{28}H_{20}Br_2O_2$ (548.3): calcd. C 61.34, H 3.68, Br 29.15; found C 61.37, H 3.58, Br 29.22. The chiral HPLC of the racemate was carried out by HPLC-UV using a column Chiralpak IA (5 μm; 4.6 × 250 mm) and an isocratic elution (2-propanol/*n*-hexane, 5:5; flow rate 0.8 mL/min). Pure enantiomer 7*R*,8*R*-**21a** was isolated with a retention time of 10.4 min, and enantiomer 7*S*,8*S*-**21b** was isolated with a retention time of 12.5 min. 7*R*,8*R*-**21a**: CD ($c = 1.8 \times 10^{-4}$ M, MeOH) nm (Δε): 235 (–1.853); 7*S*,8*S*-**21b**: CD ($c = 2.4 \times 10^{-4}$ M, MeOH) nm (Δε): 235 (1.515).

Biological Methods

Cell Culture: The human colon carcinoma cell line SW480 was obtained from ATCC (American Type Culture Collection). The cells were cultured in RPMI-Medium, supplemented with 10% (v/v) heat-inactivated fetal bovin serum and 1% antibiotics (penicillin, streptomycin); the cell cultures were maintained at 37 °C in a humidified CO_2 (5%) incubator.

Proliferation Inhibition Assays: Proliferation inhibition assays were performed in 96-well plates in triplicate. Each well was seeded with 10^5 cells, and after 24 h, the cells were incubated with the compounds under study dissolved in 0.1% dimethyl sulfoxide (DMSO), at different concentrations (0.75–100 μM). After 48 h incubation at 37 °C, the medium was carefully removed from the wells, and the PBS was warmed at room temperature before washing the plates. Then the plates were washed several times with tap water to remove the excess stain. The remaining crystal violet incorporated into the nucleus was solubilized in sodium citrate solution. Plates were agitated on an orbital shaker until the color was uniform, with no areas of dense coloration in the bottom of the wells. The absorbance was read on each plate at 540 nm with a spectrophotometer (Dynex MRX-TC Revelation). The absorbance is proportional to the density of cells adhering to the multi-well dishes relative to the absorbance of the control well-plate (5% DMSO).

Supporting Information (see footnote on the first page of this article): ESI mass, NMR and CD spectra.

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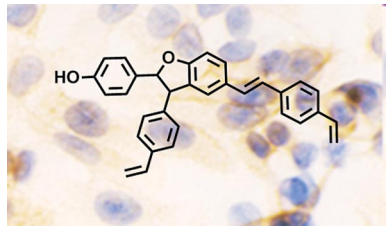
Medicinal Chemistry

Seven resveratrol-related dehydrodimers were obtained by biomimetic oxidative coupling in the presence of laccase from *Trametes versicolor*. Some of these products were found to be active in an antiproliferative bioassay against SW480 human colon cancer cells.



Keywords: Medicinal chemistry / Biomimetic synthesis / Enzyme catalysis / Antiproliferation / Antitumor agents / Structure-activity relationships

