Phytosterol and γ-Oryzanol Conjugates: Synthesis and Evaluation of their Antioxidant, ~~Anticancer~~ Antiproliferative and Anticholesterol Activities

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~~Abstract~~ **ABSTRACT**

Fifteen new multifunctional conjugates were designed and synthesized~~,~~ by chemically linking the steroidal framework of natural occurring γ-oryzanol and γ-oryzanol-derived phytosterols to a wide range of bioactive natural compounds (fatty acids, phenolic acids, amino acids, lipoic acid, retinoic acid, curcumin and resveratrol). ~~The purpose of this study was to evaluate the synergistic effect of the conjugation, starting from the main component of rice bran oil and aiming to enhance some of its relevant bioactivities~~ Starting from γ-oryzanol, which is the main component of rice bran oil, this study was aimed at assessing if the conjugation strategy might enhance some γ-oryzanol bioactivities. The antioxidant activity was evaluated through three different mechanisms, namely the DPPH scavenging activity, the metal chelating activity and the β-carotene bleaching inhibition. Measurement of the *in vitro* cell growth inhibitory effects on three different human cancer cellular lines was also carried out~~, as well as~~ and the potential hypocholesterolemic effect was studied. Compounds **10** and **15** displayed an antioxidant activity comparable to that of γ-oryzanol. Compounds **2**, **6** and **12** exerted an antiproliferative activity in the low μmolar range against HeLa and DAOY cells (GI_{50}<10 μM). As for the claimed hypocholesterolemic effect of γ-oryzanol, none of the synthesized compounds could inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCoAR), a key enzyme in cholesterol biosynthesis. ~~Results of this work provided a better insight into the many aspects of oryzanol's bioactivity, highlighting some conjugates as promising compounds for further development.~~

~~**Keywords**~~

~~oryzanol, phytosterol, antioxidant, anticancer, anticholesterol.~~

~~Introduction~~

Phytosterols ~~(PS)~~ are a large group of compounds that are found exclusively in plants, being essential components of plant membranes. In addition to their primary function of controlling membrane-associated metabolic processes, ~~PS~~ phytosterols are also precursors of plant growth factors, thus playing a role in cellular differentiation and proliferation.[1] ~~From a structural point of view, PS~~ Phytosterols are triterpenes structurally related to cholesterol~~,~~ which differ ~~differing~~ from it in ~~the structure of~~ the side chain. Due to this chemical similarity, ~~PS~~ phytosterols effectively reduce the levels of total cholesterol and low density cholesterol in blood, by inhibiting its absorption from the intestine in humans.[2,3] Considerable emerging evidence supports also the ~~anticancer~~ antiproliferative effect of ~~PS~~ phytosterols through multiple mechanisms of action, ranging from inhibition of carcinogen production, cancer-cell growth and angiogenesis, to the promotion of cancerous cells apoptosis.[4] ~~PS~~ Phytosterols action seems to be related to an increased activity of antioxidant enzymes and thereby oxidative stress reduction.[5] Further applications for ~~PS~~ phytosterols in the fields of pharmaceuticals, health products, and cosmetics are being developed, although ~~they are heavily hampered by~~ the poor solubility of ~~PS~~ phytosterols in water and fat is a critical issue.

Besides free ~~PS~~ phytosterols, plant materials and vegetable oils contain phytosterol esters ~~(PSE)~~, that are derived from esterification of the C3 hydroxyl group of ~~PS~~ phytosterols with fatty acids. Phytosterol esters ~~(PSE)~~ possess the same physiological activity as ~~PS~~ phytosterols and, at the same time, the advantage of a better lipid solubility as well as an easy hydrolysis in the human body. Steryl ferulates ~~(SF)~~ are the esters of ~~PS~~ phytosterols and ferulic acid. They are present in the bran of some grains such as rice (*Oryza sativa* L.), wheat (*Triticum aestivum* L.) and corn (*Zea mays* L.).[6,7] The sterol component from rice bran oil (RBO), which is called γ-oryzanol (ORY), is mainly composed of cycloartenyl ferulate, 24-methylenecycloartanyl ferulate and campesteryl ferulate, generally accounting for approximately 80% of ORY in RBO.[8,9]

To date, many papers have reported the benefit of RBO and ORY in treating dyslipidemia, by lowering cholesterol.[10,11,12] With regard to the antioxidant effect, as for all steryl ferulates ~~(SF)~~, it is

likely the result of the radical scavenging activity of the phenolic component of ORY.[13] It has been reported that ORY can inhibit the oxidation of linoleic acid to a higher extent than vitamin E and that it can also prevent peroxide formation by inhibiting reactive oxygen species (ROS).[14,15] Many studies have demonstrated that the main biologically active components in RBO are responsible for inducing apoptosis in colon cancer, breast and pancreatic cancer cells.[16,17] ORY seems also to be of interest for adjuvant chemotherapy, affecting prostate cancer cells through the down regulation of some antioxidant genes.[18]

An up to date approach to the design of new therapeutic agents is based on the conjugation of compounds whose biological activity is known.[19,20,21] This may lead to new biologically relevant properties or to synergistic effects either on single or dual targets. Multifunctional conjugates may also bring their therapeutic effects at lower concentrations compared to the single molecules alone. ~~PS~~ Phytosterols and steryl ferulates ~~(SF)~~ exhibited biological activity only at a high concentration and, therefore, they cannot be considered as the main components of medicinal preparations.

We envisioned ORY being an attractive candidate for this conjugation/hybrid strategy, based on both its chemical and biological properties. In continuation of our previous work, aimed ~~to develop~~ at developing diversified, bioactive steroidal compounds,[22] we herein report the synthesis of ~~PS~~ phytosterols and ORY conjugates, in which various relevant, naturally occurring compounds are chemically linked to the steroidal framework. For preparing new hybrid molecules, fatty acids, phenolic acids, amino acids, lipoic acid, retinoic acid, curcumin and resveratrol were selected as ligands, with the aim to enhance some of the relevant bioactivities of ~~PS~~ phytosterols and ORY. All conjugates were screened for their antioxidant, ~~anticancer~~ antiproliferative and anticholesterol activity.

~~Results and Discussion~~ RESULTS AND DISCUSSION

~~*Synthesis*~~

~~For~~ To the aim of the present study, commercially available ORY was employed. It consists of a mixture of cycloartenyl ferulate (**a**), 24-methylene-cycloartanyl ferulate (**b**), campesteryl ferulate (**c**)

and sitosteryl ferulate (**d**) (**a**/**b**/**c+d**:1/3/1, as confirmed ~~from~~ by ^{1}H NMR). The molecular structures of the main phytosterols, present in ORY as ferulate esters, are shown in Figure 1.

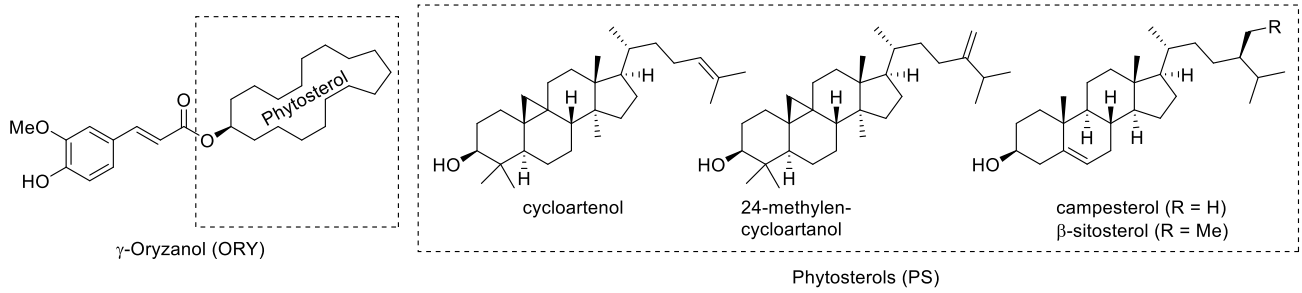


Figure 1. Chemical structure of ORY

We identified the phenolic group of ORY and the C3-hydroxy group of ~~PS~~ phytosterols as ideal sites for chemical variations through covalent linkages with naturally occurring bioactive compounds (Figure 2).

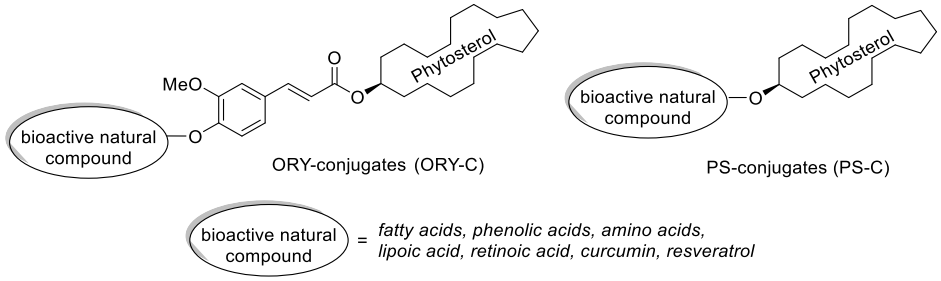
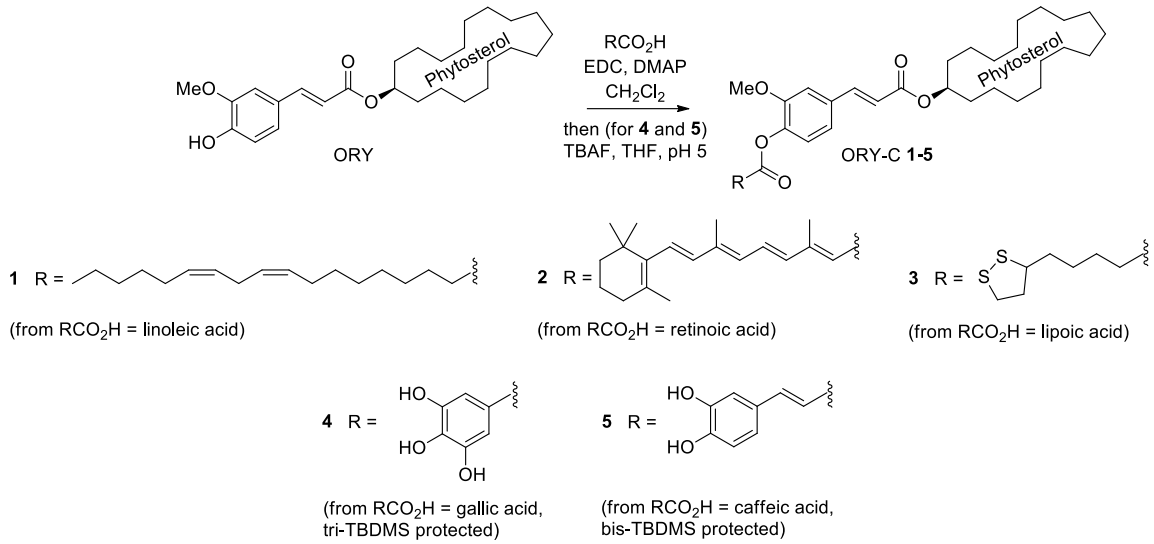


Figure 2. General chemical structures of synthesized oryzanol- and ~~**PS**~~ phytosterol-conjugates (ORY-C and PS-C, respectively)

The choice of bioactive natural compounds for conjugation was addressed by their inherent biological relevance. Among important good health associated metabolic agents, we selected a polyunsaturated fatty acid such as linoleic acid and the vitamine A metabolite retinoic acid. ~~Further~~ Moreover, lipoic acid and two phenolic acids (gallic acid and caffeic acid) were chosen as antioxidant compounds. The conjugation of ORY with these bioactive components was carried through an ester linkage, as reported in Scheme 1.

Scheme 1. Synthesis of ORY-Conjugates (ORY-C) 1-5



~~**Scheme 1. Synthesis of ORY-Conjugates (ORY-C) 1-5**~~

ORY-conjugates (ORY-C) **1-5** were obtained in good to excellent yields (67-98%) and fully characterized by ~~means of~~ ^{1}H NMR, ^{13}C NMR, 2D NMR techniques and ESI mass spectrometry. The ^{1}H and ^{13}C NMR spectra of **1-5** ~~are given in the Supporting Information and~~ are in good agreement with the ~~proposed~~ expected structures. In the experimental section, ^{1}H NMR selected ~~spectral~~ spectroscopic data are provided~~, useful~~ to establish the formation of the product and to assess the actual ratio of components, for what concerns the ~~PS~~ phytosterol moiety. In all products, the original **a**/**b**/**cd**:1:3:1 ratio is substantially retained. Full assignment of ^{13}C NMR signals is also provided for the dominant cycloartenol-based **a,b** component.

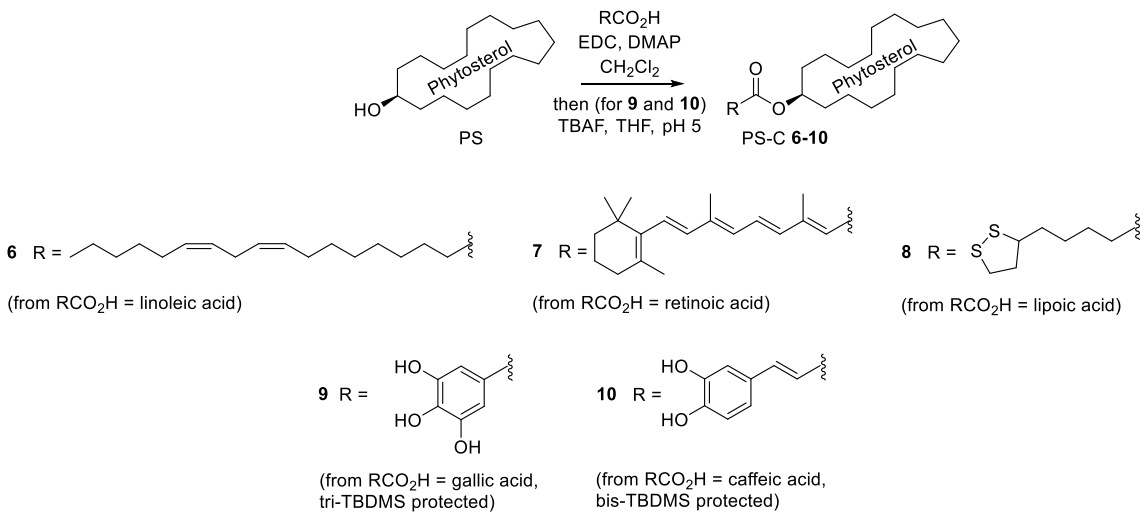
In order to modulate the potential dual action of the target compounds, by varying the distance between the phytosterol pharmacophore and the linked bioactive natural organic acid, ~~PS~~ phytosterol-conjugates ~~(PS-C)~~ were also synthesized, lacking the ferulic acid linker component.

Basic hydrolysis of ORY afforded ~~PS~~ phytosterols in high yield, with the complete maintenance of the ~~same~~ **a**/**b**/**cd**:1:3:1 ratio among phytosterol components, as in native ORY. ~~PS-C~~ Phytosterol-

conjugates **6-10** were obtained in good yields (67-94%, Scheme 2) and fully characterized, as described above for **1-5**.

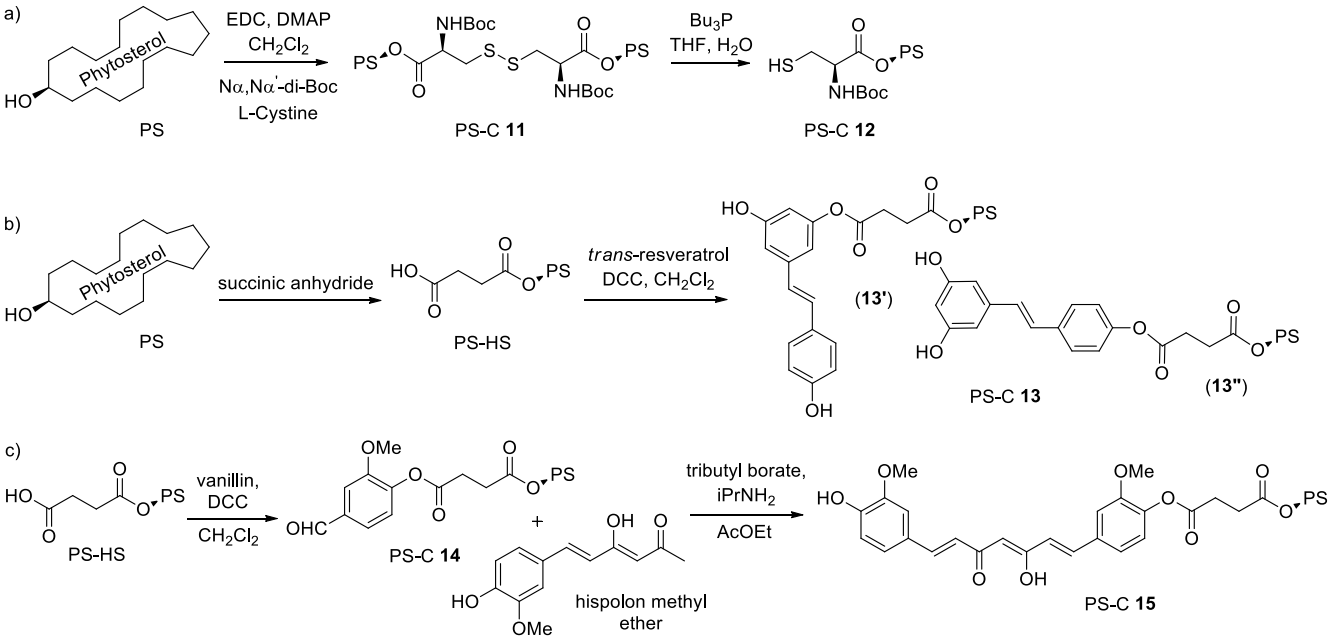
Finally, starting from ~~PS~~ phytosterols, the small library was completed with the synthesis of the cysteine derivative **12** (synthesized through Bu_3P-mediated reduction of cystine-based intermediate **11**, Scheme 3a) and of hybrid compounds **13**, **14** and **15**, ~~respectively~~ containing resveratrol, vanillin ~~and~~ or curcumin moieties, respectively (Scheme 3b,c).

Scheme 2. Synthesis of ~~PS-C~~ Phytosterol-Conjugates (PS-C) 6-10



~~**Scheme 2. Synthesis of PS-C Phytosterol-Conjugates (PS-C) 6-10**~~

Scheme 3. ~~a)~~ Synthesis of ~~PS-C~~ Phytosterol-Conjugates (PS-C) a) 11-12 b) ~~Synthesis of PS-C~~ 13 (as 1:1.5 inseparable mixture of 13' and 13") c) ~~Synthesis of PS-C~~ 14-15



~~**Scheme 3. a) Synthesis of PS-C Phytosterol-Conjugates (PS-C) a) 11-12 b) Synthesis of PS-C 13 (as 1:1.5 inseparable mixture of 13' and 13") c) Synthesis of PS-C 14-15**~~

For the preparation of ~~PS-C~~ **13-15**, a succinic acid-based linker was selected. ~~PS~~ Phytosterol was ~~subjected to reaction~~ reacted with succinic anhydride to give the phytosteryl hemisuccinate intermediate (PS-HS) in high yield. Condensation of PS-HS with *trans*-resveratrol afforded ~~PS-C~~ **13**~~,~~ as a 1:1.5 inseparable mixture of **13'** and **13"** isomers.

From PS-HS and vanillin, the conjugate ~~PS-C~~ **14** could be easily obtained. Finally, condensation of ~~PS-C~~ **14** with naturally derived hispolon methyl ether afforded the curcumin conjugate ~~PS-C~~ **15** in ~~moderate~~ 44% yield.

~~*Antioxidant activity*~~[23]

The knowledge of the complex system of natural enzymatic and non-enzymatic antioxidant defenses of the human body led to develop a large array of methods for antioxidant activity[23]

evaluation. Being aware that such an activity should not be concluded from a single antioxidant test model, we performed three different *in vitro* assays~~screenings~~, aimed ~~to evaluate~~ at evaluating the potential of ~~our~~ newly synthesized compounds to contrast the harmful effects of free radicals and other oxidants, through various mechanisms.

~~*DPPH scavenging activity.*~~ The potential free radical scavenging capacity of conjugates **1-15** was evaluated by using the DPPH method, ~~by~~ thus UV monitoring the change in optical density of DPPH radicals. The results are given as percentage of radical inhibition, using butylated hydroxyanisole (BHA) as the standard positive control (Table 1, first column). ORY proved to be effective in DPPH inhibition (58%), thus confirming the recently reported data[24] and supporting the interest in ORY for adjuvant chemotherapy in some types of cancer, where an imbalance of the oxidant-antioxidant system is recognized as an important feature.[18] Among conjugates, it clearly emerged that many of them were even more effective than ORY, with in particular compounds **10** and **15** showing inhibition percentages similar to those of the positive control ~~butylated hydroxyanisole (~~BHA~~)~~.

~~*Metal chelating activity.*~~ As excess free irons have been implicated in the induction and formation of free radicals in biological systems, we tested ~~our~~ compounds **1-15** in a metal chelating assay. We used the Mohr's salt/ferrozine system and measured the absorbance at 545 nm, thus evaluating the decrease of the red colour of the ferrozine-Fe^{2+} complexes (Table 1, second column). ~~Expressing~~ The results, expressed as percentage of chelated ferrous ions ~~and~~ and compared with ~~using~~ quercetine (used as the reference standard), showed that ORY ~~proved to be~~ was inactive. Compound **10** demonstrated a surprisingly high activity, while compound **15** showed to be as active as the reference.

~~*β-Carotene bleaching inhibition.*~~ The antioxidant activity ~~of extracts~~ was also evaluated by using the β-carotene-linoleic acid method. This protocol is mainly based on the principle that linoleic acid, which is an unsaturated fatty acid, gets oxidized by reactive oxygen species produced by oxygenated water. The products formed initiate the β-carotene oxidation, which leads to discoloration. Antioxidants decrease the extent of discoloration, which is measured at 450 nm, thus determining the bleaching inhibition percentage (Table 1, third column). Both ORY and all synthesized compounds

were less active than the reference BHA. However, ~~interestingly~~ almost all tested compounds inhibited linoleic acid oxidation, ~~at~~ although to a ~~various~~ different extent~~s~~.

From the above data, conjugation of ORY and phytosterols with natural compounds resulted in an increased antioxidant activity, in particular for the inhibition of the DPPH radical and for the Fe^{2+} chelating activity. Some newly synthesized compounds performed better than ORY, equaling or even surpassing the activity of the positive control at the same concentration. The most active compounds are **10** and **15**, bearing a caffeic acid and a curcumin unit, respectively. Even if it is not possible to draw conclusive information about structure-activity relationships, phenolic hydroxyl groups and aromatic-double bond conjugation can be recognized to play a role in antioxidant activity.

~~*Anticancer Antiproliferative activity*~~

The antiproliferative effects of ORY (used as the reference compound) and conjugates **1-15** against a panel of three human cancer cell lines~~, using ORY as the reference compound,~~ are summarized in Table 1 (from fourth to sixth column). ORY was practically ineffective in HeLa and MDA-MB-468~~MCF-7~~ cells (GI_{50}>100 µM), whereas it was moderately active in medulloblastoma cells DAOY. Three out of the synthesized compounds **2, 6** and ~~**15**~~ **12** possessed the highest overall potency, with GI_{50} values ~~of 6.4-33.0, 2.9-16.1 and 13.3-20.0~~ranging from 1.4 to 8.3 µM against HeLa and DAOY ~~the three~~ cell lines ~~investigated~~.

Table 1. Biological ~~evaluation~~ Evaluation of ~~conjugates~~ Conjugates 1-15

~~C~~compound	Iinhibition of DPPH radical [%][a]	Fe^{2+} chelated [%][a]	β-carotene bleaching inhibition [%][a]	GI_{50} (μM) [b] HeLa	MDA-MB-468	DAOY
positive control	95 (BHA)	22 (quercetine)	97 (BHA)	0.093±0.005 (doxorubicin)	0.046±0.009 (doxorubicin)	0.016±0.008 (doxorubicin)
ORY	58	0	54	>100	>100	>10
1	9	0	11	>10	>10	>10
2	13	0	27	8.3±6.3	>10	6.4±4.4
3	0	0	36	>10	>10	8.3±4.4
4	89	10	53	>100	>100	>10
5	81	0	40	>100	>10	>10
6	0	0	20	2.9±0.6	>10	6.0±3.8
7	0	0	18	>10	>100	>10
8	2	0	0	>100	>100	>100
9	89	6	44	>100	>100	>100
10	91	72	51	>100	>100	>100
11	0	0	5	>100	>10	>10
12	76	0	24	>10	>10	1.4±0.5
13	41	0	17	>100	>10	>100
14	0	0	29	>10	>10	8.7±2.4
15	93	23	46	>10	>10	>10

[a]Compound (or positive control) concentration in the native solution: 0.18 μmol/mL (see Experimental Section for details). [b]GI_{50}= compound concentration required to inhibit tumor cell proliferation by 50%. Data are expressed as the mean ± SE from the dose-response curves of at least three independent experiments.

~~*Anticholesterol activity*~~

As for the hypocholesterolemic activity, although the ~~hypocholesterolemic~~ effect of ORY has been widely demonstrated in various animal and human studies,[25,26,27] the mechanisms responsible for this activity remain unclear.[28] Recently, it has been reported[29] that ORY can inhibit hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCoAR) in a dose-dependent manner. HMGCoAR is the key enzyme of the mevalonate synthetic pathway that produces cholesterol. Inhibition of HMGCoAR reduces cholesterol biosynthesis in the liver. Statins are HMGCoAR inhibitors used as first-line drugs in the treatment of hypercholesterolemia.[30]

Compounds **1-15** and ORY were evaluated as potential inhibitors of HMGCoAR through an *in vitro* assay by using the purified catalytic domain of this enzyme (see Experimental Section for details). The activity assay is based on the spectrophotometric measurement of the rate of oxidation of the cofactor (NADPH) at 340 nm. At the highest concentrations assayed, dictated by the poor water solubility of the tested compounds, no enzyme inhibition was detected (a decrease of NADPH absorbance was observed, thus indicating that the enzyme was active; data not shown). It is worth mentioning, however, that the concentration of the tested compounds was at least 20-fold higher than the concentration of the reference inhibitor (pravastatin). We hypothesized that the inconsistency between our data and the previous investigation[29] might be attributed to multiple concurrent factors. ~~First, the measurement of NADPH/NADP$^+$ kinetics in the assay described by Mäkynen *et al.*[29] could be partly affected by non-specific effects owing to the heterogeneity of the enzymatic preparation. In other words, it can be speculated that the hepatic homogenate used can contain oxidoreductase activities other than HMGCoAR that may interfere with the HMGCoAR assay. The lack of a comparison with a reference inhibitor does not allow to drop this hypothesis. Second, the commercial enzyme here used contains only the catalytic domain.~~ It can be postulated that ORY may react through a different mechanism that does not involve the catalytic site targeted by statins.[31] ~~These~~ This evidence~~s~~ suggests that the anticholesterol activity exerted by ORY may depend on other mechanisms that do not involve necessarily HMGCoAR.

~~**Conclusions**~~

~~A number of γ-oryzanol and phytosterol hybrids were chemically synthesized at a laboratory scale with the aim to assess if these compounds might exert synergistic effects in the investigated bioactivities. All compounds were fully characterized and then tested for their antioxidant, anticancer antiproliferative and anticholesterol activities, providing in many cases evidence of the positive effect of the conjugation strategy. The antioxidant potential was evaluated through three different mechanisms, namely the DPPH scavenging activity, the metal chelating activity and the β-carotene bleaching inhibition. Compounds **10** and **15** emerged as the most promising agents, outclassing γ-~~

~~oryzanol and positioning themselves as active as the positive control compounds. Measurement of the *in vitro* cell growth inhibitory effects on three different human cancer cellular lines established compounds **2**, **6** and **15** **12** as the most active, displaying antiproliferative effects in the μmolar range, against all the three cell lines investigated. Finally, with regard to the recognized hypocholesterolemic activity of γ-oryzanol, all compounds were evaluated as potential inhibitors of HMGCoAR, the key enzyme targeted by statins. Since no enzyme inhibition was detected, not even for γ-oryzanol, a still unknown mechanism, not necessarily involving HMGCoAR, must presumably be taken into consideration. Further work is currently underway in order to deepen these aspects and to exploit the numerous implications of the most promising compounds' biological activity.~~

~~Experimental Section~~ EXPERIMENTAL SECTION

General ~~Information~~ Experimental Procedures. γ-Oryzanol was purchased from TCI Chemicals. ~~All c~~Commercial ~~materials~~ reagents were purchased from Sigma-Aldrich Chemical Co. and used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel 60 F254; spots were visualized with UV light or by treatment with a 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on silica gel 60 (230−400 mesh). ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 101 or 75 MHz (Bruker spectrometers). Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High resolution mass spectra were obtained in the ESI positive mode ((+)-HRESIMS), from a Waters Micromass Q-Tof micro Mass spectrometer.

~~γ-Oryzanol (**ORY**, CAS number 11042-64-1) was purchased from TCI Chemicals and it consists of a mixture of cycloartenyl ferulate (**a**), 24-methylene-cycloartenyl ferulate (**b**), campesteryl ferulate (**c**) and sitosteryl ferulate (**d**) (**a**/**b**/**c**,**d**:1:3:1). ORY concentration is expressed as molarity of~~

~~cycloarthenyl ferulates, the most represented components of the mixture (M.W. 602,89). White solid; mp 135.2-137.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$, selected signals): δ 7.59 (1H, d, *J* = 15.6 Hz), 7.12-7.00 (2H, m), 6.90 (1H, d, *J* = 8.6 Hz), 6.29 (0.8H, d, *J* = 15.6 Hz), 6.26 (0.2H, d, *J* = 15.6 Hz), 5.83 (1H, s, br), 5.38 (0.2H, m, H-6c,d), 5.09 (0.2H, t, br, *J* = 6.8 Hz, H-24a), 4.75 (0.1H, m, H-3d), 4.73-4.60 (2.1H, m), 3.93 (2.4H, s), 3.91 (0.6H, s), 2.42-2.35 (0.4H, m), 2.23 (0.6H, sept, *J* = 6.9 Hz), 0.68 (0.6H, s), 0.59 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.36 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2 (1'), 156.9 (24b), 147.9 (7'), 146.8 (8'), 144.4 (3'), 130.9 (25a), 127.2 (4'), 125.3 (24a), 123.1 (5'), 116.3 (6'), 114.8 (2'), 109.3 (9'), 106.0 (24$_1$b), 80.6 (3), 56.0 (10'), 52.3 (17), 48.8 (14), 47.9 (8), 47.2 (5), 45.3 (13), 39.7 (4), 36.3 (22a), 36.2 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.6 (1), 31.3 (23b), 29.8 (19), 28,2 (7), 27.0 (2), 26.5 (16), 26.0 (10), 25.8 (11), 25.7 (26a), 25.5 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 20.9 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.4 (29).~~

All ORY conjugates (ORY-C) and PS conjugates (PS-C), obtained starting from commercial ORY, are described as a mixture of cycloartenyl (**a**), 24-methylene-cycloartanyl (**b**), campesteryl (**c**) and sitosteryl (**d**) derivatives, in **a**/**b**/**c**+**d**:1/3/1 relative ratio, as determined by NMR analysis. In ^{1}H NMR spectra, key ^{1}H signals are unambiguously assigned for all **a**, **b**, **c** and **d** components, in order to confirm both the chemical structure and the components ratio. For reasons of brevity and clarity, in ^{13}C NMR spectra, signals are fully assigned exclusively for predominant (≥ 80%) **a** and **b** components. Reported, but not assigned, ^{13}C NMR signals are to be ascribed to minor **c** and **d** components. In mass spectra, the exact mass assignment is reported exclusively for predominant **a** and **b** components.

Synthesis of ORY-C 1-5

General Procedure A (GP-A) for Esterification of ORY. To a stirred solution of ORY (0.2 mmol) and the appropriate carboxylic acid (0.24 mmol) in anhydrous dichloromethane (2.5 mL), under a nitrogen atmosphere at 0 °C, *N*,*N*′-dimethylaminopyridine (3 mg, 0.024 mmol) and EDC (38 mg, 0.24 mmol) were added. The resulting mixture was stirred at room temperature for 8-24 hrs, until the

conversion was found to be complete by TLC analysis. The resulting solution was diluted with EtOAc (20 mL) and washed with 5% aq. H_3PO_4 (3x10 mL), saturated aq. $NaHCO_3$ (3x10 mL) and brine (3x10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The resulting crude product was purified, if necessary, by flash column chromatography (FC) on silica gel, as described below.

Compound 1. Prepared according to GP-A using linoleic acid; FC (*n*-hexane-EtOAc, 9:1); ~~yield:~~ 67% yield; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 7.65 (1H, d, *J* = 15.7 Hz), 7.18-7.11 (2H, m), 7.06 (1H, d, *J* = 7.9 Hz), 6.42 (0.8H, d, *J* = 15.7 Hz), 6.39 (0.2H, d, *J* = 15.7 Hz), 5.44-4.26 (4.2H, m), 5.13 (0.2H, t, br, *J* = 7.2 Hz, H-24**a**), 4.79 (0.1H, m, H-3**d**), 4.77-4.72 (1.5H, m, H-3**a,b,c** and H-24$_1$**b**), 4.70 (0.6H, s, br, H-24$_1$**b**), 3.89 (2.4H, s), 3.87 (0.6H, s), 2.80 (2H, m), 2.61 (2H, t, *J* = 7.3 Hz), 2.45-2.41 (0.4H, m), 2.27 (0.6H, sept, *J* = 6.8 Hz), 1.07 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.92 (3H, t, *J* = 6.8 Hz), 0.71 (0.6H, s), 0.63 (0.8H, d, *J* = 4.1 Hz, H-19**a,b** *endo*), 0.39 (0.8H, d, *J* = 4.1 Hz, H-19**a,b** *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 171.7, 168.8 (1'), 156.9 (24**b**), 151.4 (7' and 8'), 143.6 (3'), 133.4 (4'), 130.9 (25**a**), 130.2, 130.0, 128.1, 127.9, 125.3 (24**a**), 123.2 (5'), 121.3 (6'), 119.0 (2'), 111.2 (9'), 106.0 (24$_1$**b**), 80.9 (3), 55.9 (10'), 52.3 (17), 48.8 (14), 47.9 (8), 47.2 (5), 45.3 (13), 39.7 (4), 36.3 (22**a**), 36.1 (20**b**), 35.9 (20**a**), 35.5 (12), 35.0 (22**b**), 34.1, 33.8 (25**b**), 32.9 (15), 31.7 (1), 31.5 (23**b**), 31.3, 29.8 (19), 29.0, 28,1 (7), 27.2 (3C), 26.9 (2), 26.5 (16), 26.0 (10), 25.8 (11), 25.7 (4C), 25.6 (26**a**), 25.5 (28), 25.0 (23**a**), 24.7, 22.6, 22.0 (27**b**), 21.9 (26**b**), 21.0 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27**a**), 15.4 (29), 14.1; (+)-HRESIMS~~:~~ *m/z* 887.6531 $[M+Na]^+$ (calcd for $C_{58}H_{88}NaO_5$, **1(a)**, 887.6524); *m/z* 901.6688 $[M+Na]^+$ (calcd for $C_{59}H_{90}NaO_5$, **1(b)**, 901.6680).

Compound 2. Prepared according to GP-A using retinoic acid; 97% yield~~: 97%~~; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 7.66 (d, *J* = 15.9 Hz, 1H), 7.20-7.05 (4H, m), 6.42 (1H, d, *J* = 15.9 Hz), 6.40 (1H, d, *J* = 15.4 Hz), 6.33 (1H, d, br, *J* = 16.1 Hz), 6.21 (1H, d, *J* = 11.5 Hz), 6.19 (1H, d, *J* = 16.1 Hz), 6.07 (1H, s, br), 5.43 (0.2H, d, br, *J* = 4.2 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.9 Hz, H-24a), 4.79 (0.1H, m, H-3d), 4.77-4.71 (1.5H, m, H-3a,b,c and H-24$_1$b), 4.69 (0.6H, s, br, H-24$_1$b),

3.90 (2.4H, s), 3.88 (0.6H, s), 2.43 (3H, s, br), 2.05 (3H, s), 1.75 (3H, s), 1.08-1.03 (12H, m), 0.71 (0.6H, s), 0.63 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.40 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (101 MHz, $CDCl_3$)~~:~~ δ 166.8 (1'), 164.7, 156.9 (24b), 155.9, 151.7 (7'), 143.8 (3'), 141.5 (8'), 140.5, 137.7, 137.2, 134.8, 133.2 (4'), 132.1, 130.9 (25a), 130.3, 129.4, 129.2, 125.3 (24a), 123.6 (5'), 121.3 (6'), 118.9 (2'), 116.6, 111.2 (9'), 106.0 (24_1b), 80.9 (3), 56.0 (10'), 52.3 (17), 48.9 (14), 47.9 (8), 47.3 (5), 45.3 (13), 39.7 (4), 39.8, 36.2 (22a, 20b), 35.9 (20a), 35.6 (12), 35.0 (22b), 34.3, 33.8 (25b), 33.2, 32.9 (15), 31.7 (1), 31.4 (23b), 29.8 (19), 29.0 (2C), 28,2 (7), 27.0 (2), 26.6 (16), 26.0 (10), 25.9 (11), 25.8 (26a), 25.5 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 21.8, 21.0 (6), 20.2 (9), 19.4 (28), 19.2, 18.4 (21), 18.0 (18), 17.7 (27a), 15.4 (29), 14.2, 13.0; (+)-HRESIMS~~:~~ *m/z* 907.6204 $[M+Na]^+$ (calcd for $C_{60}H_{84}NaO_5$, **2**a, 907.6211); *m/z* 921.6374 $[M+Na]^+$ (calcd for $C_{61}H_{86}NaO_5$, **2**b, 921.6367).

Compound 3. Prepared according to GP-A using lipoic acid; FC (*n*-hexane-EtOAc, 9:1); 73% yield~~: 73%~~; thick pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 7.65 (1H, d, *J* = 15.7 Hz), 7.18-7.11 (2H, m), 7.06 (1H, d, *J* = 7.8 Hz), 6.42 (0.8H, d, *J* = 15.9 Hz), 6.40 (1H, d, *J* = 15.9 Hz), 5.44 (0.2H, d, br, *J* = 4.2 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.8 Hz, H-24a), 4.79 (0.1H, m, H-3d), 4.77-4.72 (1.5H, m, H-3a,b,c and H-24_1b), 4.69 (0.6H, s, br, H-24_1b), 3.89 (2.4H, s), 3.88 (0.6H, s), 3.63 (1H, quint, br, *J* = 6.8 Hz), 3.22 (1H, ddd, br, *J* = 10.9, 6.8, 5.5 Hz), 3.15 (1H, dt, *J* = 10.9 and 6.8 Hz), 2.63 (2H, t, *J* = 7.3 Hz), 2.51 (1H, sext, br, *J* = 6.3 Hz), 2.45-2.41 (0.4H, m), 2.27 (0.6H, sept, *J* = 6.8 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.71 (0.6H, s), 0.63 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.40 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 171.3, 166.6 (1'), 156.9 (24b), 151.4 (7'), 143.6 (3'), 141.4 (8'), 133.5 (4'), 130.9 (25a), 125.3 (24a), 123.2 (5'), 121.3 (6'), 119.1 (2'), 111.2 (9'), 106.0 (24_1b), 80.8 (3), 56.4, 55.9 (10'), 52.2 (17), 48.8 (14), 47.8 (8), 47.2 (5), 45.3 (13), 40.3 (2C), 39.7 (4), 38.5, 36.3 (22a), 36.1 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 34.6, 33.8 (25b), 32.9 (15), 31.7 (1), 31.3 (23b), 29.8 (19), 28.7, 28,1 (7), 26.9 (2), 26.5 (16), 26.0 (10), 25.8 (11), 25.8 (26a), 25.5 (28), 25.0 (23a), 24.7, 22.0 (27b), 21.9 (26b), 21.0 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.7 (27a), 15.4 (29); (+)-HRESIMS~~:~~ *m/z* 813.4561 $[M+Na]^+$ (calcd for $C_{48}H_{70}NaO_5S_2$, **3**a, 813.4557); *m/z* 827.4717 $[M+Na]^+$ (calcd for $C_{49}H_{72}NaO_5S_2$, **3**b, 827.4713).

Compound 4. Prepared according to GP-A using 3,4,5-tri[(*tert*-butyldimethylsilyl)oxy]benzoic acid,[32] followed by treatment of the crude TBDMS protected intermediate as follows. The crude material, dissolved in THF (0.5 mL), was added to a solution of tetrabutylammonium fluoride trihydrate (189 mg, 0.6 mmol) in THF (2 mL). The pH was adjusted to 5 by addition of acetic acid and the resulting mixture was allowed to stir overnight at room temperature. Then it was diluted with EtOAc (20 mL), washed with saturated aq. NH_4Cl (3x15 mL), H_2O (3x15 mL) and brine (3x15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The resulting crude product was dissolved in acetone and the insoluble solid discarded. The acetone was evaporated *in vacuo* to afford **4**; 95% yield ~~95%~~; pale brown solid; ^{1}H NMR (400 MHz, acetone-d_6)~~:~~ δ 8.68-8.13 (1.3H, m, br), 7.69 (0.8H, d, *J* = 15.7 Hz), 7.67 (0.2H, d, *J* = 16.0 Hz), 7.50 (1H, m), 7.31(1H, dd, *J* = 7.8, 1.7 Hz), 7.26 (2H, s), 7.21 (1H, d, *J* = 7.8 Hz), 6.60 (0.8H, d, *J* = 15.7 Hz), 6.56 (0.2H, d, *J* = 16.0 Hz), 5.42 (0.2H, d, br, *J* = 4.6 Hz, H-6c,d), 5.11 (0.2H, t, br, *J* = 7.2 Hz, H-24a), 4.77-4.66 (2.1H, m), 4.64 (0.1H, m, H-3d), 3.89 (0.6H, s), 3.88 (2.4H, s), 2.96-2.62 (1.7H, m, br), 2.42-2.37 (0.4H, m), 2.26 (0.6H, sept, *J* = 6.9 Hz), 0.73 (0.6H, s), 0.64 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.45 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, acetone-d_6)~~:~~ δ 166.0, 163.9 (1'), 156.5 (24b), 152.1 (7'), 145.4 (2C), 143.7 (3'), 142.2 (8'), 138.7, 133.4 (4'), 130.4 (25a), 125.2 (24a), 123.6 (5'), 121.4 (6'), 119.8, 118.9 (2'), 111.6 (9'), 109.7 (2C), 106.0 (24_1b), 80.2 (3), 55.6 (10'), 52.2 (17), 48.8 (14), 48.1 (8), 47.3 (5), 45.3 (13), 39.5 (4), 36.3 (22a), 36.0 (20b), 35.8 (20a), 35.5 (12), 35.0 (22b), 33.6 (25b), 32.9 (15), 31.6 (1), 31.2 (23b), 29.5 (19), 29.0 (7), 28.0 (2), 26.9 (16), 26.0 (10), 25.8 (11), 25.1 (28 and 26a), 24.7 (23a), 21.5 (27b), 21.4 (26b), 20.9 (6), 20.0 (9), 19.0 (28), 17.9 (21), 17.8 (18), 17.1 (27a), 15.0 (29); (+)-HRESIMS~~:~~ *m/z* 777.4330 $[M+Na]^+$ (calcd for $C_{47}H_{62}NaO_8$, **4**a, 777.4337); *m/z* 791.4488 $[M+Na]^+$ (calcd for $C_{48}H_{64}NaO_8$, **4**b, 791.4493).

Compound 5. Prepared according to GP-A using (*E*)-3-(3,4-bis((*tert*-butyldimethylsilyl)oxy) phenyl)acrylic acid,[33] followed by treatment of the crude TBDMS protected intermediate, as described above for compound **4**. The resulting crude product was dissolved in acetone and the insoluble solid discarded. The acetone was evaporated *in vacuo* to afford **5**; 98% yield ~~98%~~; pale

yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$)÷ δ 7.77 (1H, d, *J* = 16.0 Hz), 7.67 (1H, d, *J* = 16.0 Hz), 7.22-7.09 (4H, m), 7.05(1H, d, br, *J* = 7.5 Hz), 6.90 (1H, d, *J* = 7.8 Hz), 6.51 (2H, m, br), 6.46 (1H, d, *J* = 16.0 Hz), 6.43 (0.8H, d, *J* = 16.0 Hz), 6.41 (0.2H, d, *J* = 16.0 Hz), 5.43 (0.2H, d, br, *J* = 4.2 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.9 Hz, H-24a), 4.84-4.72 (1.6H, m, H-3a,b,c,d and H-24$_1$b), 4.70 (0.6H, s, br, H-24$_1$b), 3.87 (2.4H, s), 3.86 (0.6H, s), 2.49-2.40 (0.4H, m), 2.27 (0.6H, sept, *J* = 6.7 Hz), 0.72 (0.6H, s), 0.63 (0.8H, d, *J* = 3.9 Hz, H-19a,b *endo*), 0.40 (0.8H, d, *J* = 3.9 Hz, H-19a,b *exo*); ^{13}C NMR (101 MHz, $CDCl_3$)÷ δ 167.2, 165.7 (1'), 156.9 (24b), 151.5 (7'), 147.5, 147.2, 144.2, 144.0 (3'), 141.5 (8'), 133.4 (4'), 130.9 (25a), 127.1, 125.3 (24a), 123.4 (5'), 123.0, 121.4 (6'), 118.9 (2'), 115.5, 114.4, 113.7, 111.3 (9'), 106.0 (24$_1$b), 81.3 (3), 56.0 (10'), 52.3 (17), 48.8 (14), 47.9 (8), 47.3 (5), 45.3 (13), 39.8 (4), 36.4 (22a), 36.2 (20b), 35.9 (20a), 35.6 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.7 (1), 31.4 (23b), 29.9 (19), 29.0 (7), 28.2 (2), 27.0 (16), 26.5 (10), 26.0 (11), 25.6 (26a), 25.1 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 21.0 (6), 20.2 (9), 19.4 (28), 18.4 (21), 18.0 (18), 17.7 (27a), 15.4 (29); (+)-HRESIMS÷ *m/z* 787.4549 $[M+Na]^+$ (calcd for $C_{49}H_{64}NaO_7$, **5**a, 787.4544); *m/z* 801.4709 $[M+Na]^+$ (calcd for $C_{50}H_{66}NaO_7$, **5**b, 801.4701).

Hydrolysis of ORY to Phytosterol Mixtures (PS). To a solution of ORY (3.0 g, 5.0 mmol) in 94% aq. EtOH (32 mL), KOH (2.5 g, 44 mmol) was added and the resulting mixture was stirred under reflux. After 8 hrs the reaction was concentrated under reduced pressure and the residue was treated with 25 mL of water. The product was extracted into EtOAc (3x30 mL), the extract was dried over Na_2SO_4 and evaporated to give PS (2.1 g, 99% yield); white solid; ^{1}H NMR (400 MHz, $CDCl_3$)÷ δ 5.38 (0.2H, m, H-6c,d), 5.13 (0.2H, t, br, J = 7.1 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.69 (0.6H, s, br, H-24$_1$b), 3.55 (0.2H, tt, J = 11.3, 4.8 Hz, H-3c,d), 3.35-3.27 (0.8H, m, H-3a,b), 2.26 (0.6H, sept, J = 7.1 Hz), 1.71 (0.6H, s, br), 1.06 (1.8H, d, J = 6.8 Hz), 1.05 (1.8H, d, J = 6.8 Hz), 0.71 (0.6H, s), 0.58 (0.8H, d, J = 4.1 Hz, H-19a,b endo), 0.36 (0.8H, d, J = 4.1 Hz, H-19a,b exo); ^{13}C NMR (75 MHz, $CDCl_3$)÷ δ 156.9 (24b), 130.9 (25a), 125.3 (24a), 106.8 (24$_1$b), 78.8 (3), 52.3 (17), 48.8 (14), 48.0 (8), 47.1 (5), 45.3 (13), 39.8 (4), 37.3, 35.9 (20a), 36.1 (20b), 35.6 (12), 35.0 (22), 33.8 (25b), 32.9 (15),

32.0 (1), 31.6 (23b), 31.3 (2), 30.4 (16), 29.9 (19), 28.2 (7), 26.5 (10), 26.0 (11), 25.7 (26a), 25.5 (28), 25.0 (23a), 22.0 (26b), 21.9 (27b), 21.1 (6), 20.0 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 14.0 (29); (+)-HRESIMS~~:~~ m/z 449.3746 $[M+Na]^+$ (calcd for $C_{30}H_{50}NaO$, PSa, 449.3754); m/z 463.3902 $[M+Na]^+$ (calcd for $C_{31}H_{52}NaO$, PSb, 463.3910).

Synthesis of PS-C 6-11

General Procedure B (GP-B) for Esterification of Phytosterols (PS). To a stirred solution of PS (0.2 mmol) and the appropriate carboxylic acid (0.24 mmol, or 0.12 mmol in the case of N_α, N_α′-di-Boc-L-cystine) in anhydrous dichloromethane (2.5 mL), under a nitrogen atmosphere at 0 °C, *N*,*N*′-dimethylaminopyridine (3 mg, 0.024 mmol) and EDC (38 mg, 0.24 mmol) were added. The resulting mixture was stirred at room temperature for 8-24 hrs, until the conversion was found to be complete by TLC analysis. The resulting solution was diluted with EtOAc (20 mL) and washed with 5% aq. H_3PO_4 (3x10 mL), saturated aq. $NaHCO_3$ (3x10 mL) and brine (3x10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The resulting crude product was purified, if necessary, by flash column chromatography (FC) on silica gel, as described below.

Compound 6. Prepared according to GP-B using linoleic acid; FC (*n*-hexane-EtOAc, 19:1); 67% yield~~: 67%~~; colourless wax; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 5.46-5.31 (4.2H, m), 5.13 (0.2H, t, br, *J* = 7.0 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.69 (0.6H, s, br, H-24$_1$b), 4.67-4.54 (1H, m, H-3), 2.80 (2H, t, *J* = 6.5 Hz), 2.40-2.34 (0.4H, m), 2.33 (2H, t, *J* = 7.2 Hz), 2.27 (0.6H, sept, *J* = 6.8 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.71 (0.6H, s), 0.60 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.37 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 173.7, 156.9 (24b), 130.9 (25a), 130.2, 130.1, 128.0, 127.9, 125.3 (24a), 106.0 (24$_1$b), 80.4 (3), 52.2 (17), 48.8 (14), 47.9 (8), 47.2 (5), 45.3 (13), 39.5 (4), 36.3 (22a), 36.1 (20b), 35.9 (20a), 35.5 (12), 34.8 (22b), 34.1, 33.8 (25b), 32.9 (15), 31.6 (1), 31.5 (23b), 31.3, 29.6 (19), 29.2, 28,1 (7), 27.2 (3C), 26.9 (2), 26.5 (16), 26.0 (10), 25.8 (11), 25.7 (4C), 25.4 (26a), 25.5 (28), 25.1 (23a), 24.7, 22.6, 22.0 (27b), 21.9 (26b), 20.9 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.2 (29), 14.1; (+)-HRESIMS~~:~~ *m/z*

711.6058 [M+Na]$^+$ (calcd for $C_{48}H_{80}NaO_2$, **6**a, 711.6051); *m/z* 725.6212 [M+Na]$^+$ (calcd for $C_{49}H_{82}NaO_2$, **6b**, 725.6207).

Compound 7. Prepared according to GP-B using retinoic acid; FC (*n*-hexane-EtOAc, 19:1); 87% yield~~: 87%~~; amorphous white solid; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 7.11-6.95 (1H, m), 6.38-6.10 (4H, m), 5.83 (0.6H, s, br), 5.78 (0.1H, s, br), 5.69 (0.2H, s, br), 5.65 (0.1H, s, br), 5.41 (0.2H, d, br, *J* = 4.1 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 7.0 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.72-4.62 (1.6H, m), 2.39 (3H, s, br), 2.04 (3H, s), 1.75 (3H, s), 1.08-1.03 (12H, m), 0.71 (0.6H, s), 0.61 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.37 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 163.8, 156.9 (24b), 156.0, 141.5, 137.4, 137.1, 134.9, 132.1, 130.9 (25a), 130.4, 129.7, 129.1, 125.3 (24a),116.5, 106.0 (24$_1$b), 78.9 (3), 52.3 (17), 48.8 (14), 48.0 (8), 47.1 (5), 45.3 (13), 39.8 (4), 39.6, 36.3 (22a), 36.1 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 34.3, 33.8 (25b), 33.1, 32.9 (15), 32.0 (1), 31.3 (23b), 30.3 (2C), 29.9 (19), 28,1 (7 and 2), 26.5 (16), 26.0 (10), 25.8 (11), 25.7 (26a), 25.4 (28), 25.0 (23a), 22.0 (27b), 21.8 (26b), 21.6, 21.1 (6), 20.0 (9), 19.3 (28), 19.2, 18.3 (21), 18.0 (18), 17.6 (27a), 15.3 (29), 14.0 (2C); (+)-HRESIMS~~:~~ *m/z* 731.5731 [M+Na]$^+$ (calcd for $C_{50}H_{76}NaO_2$, **7a**, 731.5738); *m/z* 745.5890 [M+Na]$^+$ (calcd for $C_{51}H_{78}NaO_2$, **7b**, 745.5894).

Compound 8. Prepared according to GP-B using lipoic acid; FC (*n*-hexane-EtOAc, 9:1); 94% yield~~: 94%~~; pale yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 5.42-5.45 (0.2H, m, H-6c,d), 5.13 (0.2H, t, br, *J* = 7.0 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.69 (0.8H, m, br, H-24$_1$b), 4.67-4.56 (1H, m, H-3), 3.59 (1H, quint, br, *J* = 6.8 Hz), 3.20 (1H, ddd, br, *J* = 10.8, 6.8, 5.7 Hz), 3.13 (1H, dt, *J* = 10.8, 7.0 Hz), 2.48 (1H, sext, br, *J* = 6.4 Hz), 2.35 (2H, t, *J* = 7.4 Hz), 2.26 (0.6H, sept, *J* = 6.8 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.70 (0.6H, s), 0.60 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.36 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (101 MHz, $CDCl_3$)~~:~~ δ 173.3, 156.9 (24b), 130.9 (25a), 125.3 (24a), 106.0 (24$_1$b), 80.6 (3), 56.4, 52.3 (17), 48.8 (14), 47.9 (8), 47.2 (5), 45.3 (13), 40.2 (2C), 39.8 (4), 38.5, 36.4 (22a), 36.2 (20b), 35.9 (20a), 35.6 (12), 35.0 (22b), 34.7, 33.8 (25b), 32.9 (15), 32.0 (1), 31.4 (23b), 29.9 (19), 29.8, 28,2 (7), 26.9 (2), 26.5 (16), 26.0 (10),

25.9 (11), 25.8 (26a), 25.5 (28), 25.0 (23a), 24.9, 22.0 (27b), 21.9 (26b), 21.2 (6), 20.2 (9), 19.4 (28), 18.3 (21), 18.1 (18), 17.7 (27a), 15.3 (29); (+)-HRESIMS: *m/z* 637.4078 $[M+Na]^+$ (calcd for $C_{38}H_{62}NaO_2S_2$, **8a**, 637.4083); *m/z* 651.4235 $[M+Na]^+$ (calcd for $C_{39}H_{64}NaO_2S_2$, **8b**, 651.4240).

Compound 9. Prepared according to GP-B using 3,4,5-tri[(*tert*-butyldimethylsilyl)oxy]benzoic acid,[32] followed by treatment of the crude TBDMS protected intermediate, as described above for compound **4**. The resulting crude product was dissolved in acetone and the insoluble solid discarded. The acetone was evaporated *in vacuo* to afford **9**; 78% yield; pale yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (2H, m), 6.10-5.83(3H, m, br), 5.43 (0.2H, m, br, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.9 Hz, H-24a), 4.86-4.72 (1.6H, m, H-3 and H-24$_1$b), 4.70 (0.6H, s, br, H-24$_1$b), 2.49-2.42 (0.4H, m), 2.27 (0.6H, sept, *J* = 6.7 Hz), 0.72 (0.6H, s), 0.64 (0.8H, d, *J* = 3.9 Hz, H-19a,b *endo*), 0.41 (0.8H, d, *J* = 3.9 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, acetone-d_6): δ 166.3, 157.3 (24b), 146.0 (2C), 138.5, 131.3 (25a), 126.0 (24a), 123.2, 109.8 (2C), 106.8 (24$_1$b), 81.0 (3), 53.1 (17), 49.6 (14), 49.0 (8), 48.1 (5), 46.0 (13), 40.6 (4), 37.1 (22a), 36.8 (20b), 36.7 (20a), 36.3 (12), 35.8 (22b), 34.4 (25b), 33.7 (15), 32.3 (1), 31.9 (23b), 30.4 (19), 30.1 (7), 29.6 (2), 27.8(16), 27.1 (10), 26.7 (11), 26.6 (28), 25.9 (26a), 25.5 (23a), 22.3 (27b), 22.2 (26b), 21.6 (6), 20.8 (9), 19.7 (28), 18.7(21), 18.6 (18), 17.9 (27a), 15.9 (29); (+)-HRESIMS: *m/z* 601.3867 $[M+Na]^+$ (calcd for $C_{37}H_{54}NaO_5$, **9a**, 601.3863); *m/z* 615.4027 $[M+Na]^+$ (calcd for $C_{38}H_{56}NaO_5$, **9b**, 615.4020).

Compound 10. Prepared according to GP-B using (*E*)-3-(3,4-bis((*tert*-butyldimethylsilyl)oxy)phenyl)acrylic acid,[33] followed by treatment of the crude TBDMS protected intermediate, as described above for compound **4**. The resulting crude product was dissolved in acetone and the insoluble solid discarded. The acetone was evaporated *in vacuo*. The residue was purified by FC (*n*-hexane-EtOAc, 4:1); to afford **10**; 94% yield; pale brown powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (0.2H, d, *J* = 15.7 Hz), 7.60 (0.8H, d, *J* = 16.0 Hz), 7.17-7.11 (1H, m), 7.08-7.00 (1H, m), 6.94-6.86 (1H, m), 6.35-6.24 (1H, m), 6.04 (1H, m, br), 5.83 (1H, m, br), 5.45-5.36 (0.2H, m, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.9 Hz, H-24a), 4.80-4.66 (2.2H, m, H-3 and 2H-24$_1$b), 2.46-

2.39 (0.4H, m), 2.27 (0.6H, sept, *J* = 6.7 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.71 (0.6H, s), 0.63 (0.8H, d, *J* = 3.9 Hz, H-19a,b *endo*), 0.39 (0.8H, d, *J* = 3.9 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 168.1, 156.9 (24b), 146.6, 145.0, 144.0, 130.9 (25a), 127.4, 125.3 (24a), 122.4, 116.0, 115.5, 114.5, 106.0 (24_1b), 81.3 (3), 52.3 (17), 48.8 (14), 48.0 (8), 47.2 (5), 45.3 (13), 39.8 (4), 36.3 (22a), 36.2 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.6 (1), 31.3 (23b), 29.9 (19), 29.0 (7), 28.1 (2), 26.9 (16), 26.5 (10), 25.9 (11), 25.8 (26a), 25.5 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 21.0 (6), 20.2 (9), 19.4 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.3 (29); (+)-HRESIMS~~:~~ *m/z* 611.4077 $[M+Na]^+$ (calcd for $C_{39}H_{56}NaO_4$, **10a**, 611.4071); *m/z* 625.4231 $[M+Na]^+$ (calcd for $C_{40}H_{58}NaO_4$, **10b**, 625.4227).

Compound 11. Prepared according to GP-B using N_α, N_α′-di-Boc-L-cystine; FC (*n*-hexane-EtOAc, 4:1); 91% yield~~: 91%~~; amorphous white solid; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 5.63-5.33 (2.4H, m, br, 2NH and H-6c,d), 5.13 (0.4H, t, br, *J* = 6.9 Hz, H-24a), 4.80-4.50 (6.4H, m, H-3 and 2H-24_1b), 3.38-3.12 (4H, m), 2.42-2.32 (0.8H, m), 2.27 (1.2, m), 1.48 (18H, s, br), 0.70 (1.2H, s), 0.60 (1.6H, d, *J* = 3.9 Hz, H-19a,b *endo*), 0.36 (1.6H, d, *J* = 3.9 Hz, H-19a,b *exo*); ^{13}C NMR (101 MHz, $CDCl_3$)~~:~~ δ 170.4 and 170.0 (1C), 156.8 (24b), 155.1, 130.9 (25a), 125.3 (24a), 106.0 (24_1b), 82.8 and 82.7 (3), 80.1, 56.1, 52.3 (17), 48.8 (14), 48.0 (8), 47.2 (5), 45.3 (13), 39.8 (4), 36.4 (22a), 36.1 (20b), 35.9 (20a), 35.6 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.6 (1), 31.3 (23b), 30.4, 29.9 (19), 29.8 (7), 28.4 (3C), 28.2 (2), 26.8 (16), 26.5 (10), 26.0 (11), 25.8 (26a), 25.5 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 21.2 (6), 20.2 (9), 19.4 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.3 (29); (+)-HRESIMS~~:~~ *m/z* 1307.9009 $[M+Na]^+$ (calcd for $C_{78}H_{128}N_2NaO_8S_2$, **11**, (PS=**1b**), 1307.9004);

Synthesis of PS-C 12-15

Synthesis of PS-C 12. To a solution of compound **11** (126 mg, 0.1 mmol) in degassed THF (1.5 mL), under a nitrogen atmosphere, tri-*n*-butylphosphine (24 μL, 0.11 mmol) was added at 25 ºC. After 2 min of stirring, H_2O (9.1 μL, 0.5 mmol) was added and the reaction mixture was stirred for 24 hrs at the same temperature. The solvent was removed *in vacuo* and the crude product was purified

by by FC (*n*-hexane-EtOAc, 6:1) to afford pure compound **12**; 78% yield ~~78%~~; colorless foam; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 5.52-5.36 (1.2H, m, br, NH and H-6c,d), 5.12 (0.2H, t, br, *J* = 7.1 Hz, H-24a), 4.80-4.50 (3.2H, m, SH, H-3 and 2H-24$_1$b), 3.11-2.94 (2H, m), 2.42-2.34 (0.4H, m), 2.26 (0.6H, sept, *J* = 6.7 Hz), 1.48 (9H, s, br), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.71 (0.6H, s), 0.61 (0.8H, d, *J* = 4.0 Hz, H-19a,b *endo*), 0.38 (0.8H, d, *J* = 4.0 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 170.1 and 169.7 (1C), 156.9 (24b), 155.2, 130.9 (25a), 125.3 (24a), 106.0 (24$_1$b), 82.8 (3), 80.1, 56.0, 52.3 (17), 48.8 (14), 47.8 (8), 47.2 (5), 45.3 (13), 39.7 (4), 36.3 (22a), 36.1 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.5 (1), 31.3 (23b), 30.3, 29.9 (19), 29.7 (7), 28.3 (3C), 28.1 (2), 26.9 (16), 26.5 (10), 26.0 (11), 25.8 (26a), 25.6 (28), 24.9 (23a), 22.0 (27b), 21.9 (26b), 21.1 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.3 (29); (+)-HRESIMS~~:~~ *m/z* 652.4365 $[M+Na]^+$ (calcd for $C_{38}H_{63}NNaO_4S$, **12a**, 652.4370); *m/z* 666.4521 $[M+Na]^+$ (calcd for $C_{39}H_{65}NNaO_4S$, **12b**, 666.4527).

Synthesis of PS-C 13. ~~PS~~ Phytosterols (500 mg, 1.17 mmol) and succinic anhydride (150 mg, 1.50 mmol), in dry toluene (2.5 mL), under a nitrogen atmosphere, were combined and stirred at 120 °C, until the conversion was found to be complete by TLC analysis. The resulting mixture was diluted with toluene, cooled to 4 °C and the solids were filtered off. The filtrate was evaporated on a rotary evaporator to give intermediate PS-HS (587 mg, 95%yield); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, selected signals)~~:~~ δ 5.40 (0.2H, d, br, *J* = 4.1 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 7.1 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.69 (0.6H, s, br, H-24$_1$b), 4.67 (0.1H, m, H-3d), 4.66-4.60 (0.9H, m), 2.75-2.60 (4H, m), 2.38-2.32 (0.4H, m), 2.26 (0.6H, sept, *J* = 7.0 Hz), 1.71 (0.6H, s, br), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.71 (0.6H, s), 0.61 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.37 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 178.3, 171.8, 156.9 (24b), 130.9 (25a), 125.3 (24a), 106.0 (24$_1$b), 81.3 (3), 52.2 (17), 48.8 (14), 47.9 (8), 47.2 (5), 45.3 (13), 39.5 (4), 36.3 (22a), 36.1 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.6 (1 and 23b), 29.8 (19), 29.4, 29.1, 28,1 (7), 26.8 (2), 26.5 (16), 25.8 (11 and 10), 25.7 (26a), 25.4 (28), 25.0 (23a), 22.0

(27b), 21.9 (26b), 20.9 (6), 20.1 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.1 (29); (+)-HRESIMS: *m/z* 549.3919 $[M+Na]^+$ (calcd for $C_{34}H_{54}NaO_4$, PS-HSa, 549.3914); *m/z* 563.4077 $[M+Na]^+$ (calcd for $C_{35}H_{56}NaO_4$, PS-HSb, 563.4071). To a stirred solution of the intermediate PS-HS (106 mg, 0.2 mmol) in anhydrous dichloromethane (2.0 mL) under a nitrogen atmosphere at 0 °C, *trans*-resveratrol (0.22 mmol) and DCC (45 mg, 0.22 mmol) were added. The resulting mixture was stirred at room temperature for 24 hrs, then it was diluted with Et_2O (35 mL) and filtered off to remove the precipitate. The filtrate was washed with 5% aq. H_3PO_4 (3x10 mL), saturated aq. $NaHCO_3$ (3x10 mL) and brine (3x10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The resulting crude product was purified by FC (*n*-hexane-EtOAc, 1.5:1) to give pure compound **13**, as an inseparable 1:1.5 mixture of **13'** and **13"** isomers; 91% yield: 91%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (0.4H, s), 7.47 (1.2H, d, *J* = 8.5 Hz), 7.36 (0.8H, d, *J* = 8.5 Hz), 7.09 (1.2H, d, *J* = 8.5 Hz), 7.00 (0.6H, d, *J* = 16.4 Hz), 6.97 (0.4H, d, *J* = 16.4 Hz), 6.89 (0.6H, d, *J* = 16.4 Hz), 6.86-6.77 (2H, m), 6.57 (1.2H, d, br, *J* = 2.0 Hz), 6.51 (0.4H, m), 6.31 (0.6H, t, br, *J* = 2.0 Hz), 6.17-5.46 (1.6H, m, br), 5.40 (0.2H, d, br, *J* = 4.8 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.8 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.73-4.63 (1.6H, m, H-3 and H-24$_1$b), 2.96-2.87 (2H, m), 2.82-2.72 (2H, m), 2.39-2.34 (0.4H, m), 2.27 (0.6H, sept, *J* = 6.7 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.70 (0.6H, s, br), 0.60 (0.8H, m, br, H-19a,b *endo*), 0.37 (0.8H, m, br, H-19a,b *exo*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 171.2, 157.9, 157.8, 156.9 (24b), 151.6, 149.9, 140.1, 139.4, 135.2, 130.9 (25a), 129.4, 129.0, 128.9, 127.9, 127.6, 127.4, , 125.2 (24a), 121.6, 115.6, 111.0, 110.4, 107.6, 105.9 (24$_1$b), 105.4, 102.3, 81.6 (3), 52.2 (17), 48.9 (14), 47.8 (8), 47.2 (5), 45.3 (13), 39.5 (4), 36.3 (22a), 36.1 (20b), 35.8 (20a), 35.5 (12), 35.0 (22b), 33.8 (25b), 32.8 (15), 31.5 (1), 31.3 (23b), 29.6 (19), 29.5 (7), 28.1 (2), 26.7 (16), 26.4 (10), 25.8 (11), 25.6 (26a), 25.4 (28), 24.9 (23a), 21.9 (27b), 21.8 (26b), 20.9 (6), 20.1 (9), 19.2 (28), 18.2 (21), 17.9 (18), 17.5 (27a), 15.1 (29); (+)-HRESIMS: *m/z* 759.4601 $[M+Na]^+$ (calcd for $C_{48}H_{64}NaO_6$, **13a**, 759.4595); *m/z* 773.4758 $[M+Na]^+$ (calcd for $C_{49}H_{66}NaO_6$, **13b**, 773.4752).

Synthesis of PS-C 14. To a stirred solution of the intermediate PS-HS (106 mg, 0.2 mmol), prepared as above, in anhydrous dichloromethane (2.0 mL) under a nitrogen atmosphere at 0 °C, vanilline (0.22 mmol) and DCC (45 mg, 0.22 mmol) were added. The resulting mixture was stirred at room temperature for 24 hrs, then it was diluted with Et_2O (35 mL) and filtered off to remove the precipitate. The filtrate was washed with 5% aq. H_3PO_4 (3x10 mL), saturated aq. $NaHCO_3$ (3x10 mL) and brine (3x10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The resulting crude product was purified by FC (*n*-hexane-EtOAc, 4:1) to give pure compound **14**; 93% yield~~: 93%~~; white solid; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 9.98 (0.2H, s), 9.97 (0.8H, s), 7.53-7.48 (2H, m), 7.26 (0.4H, d, *J* = 7.8 Hz), 7.25 (0.6H, d, *J* = 7.8 Hz), 5.40 (0.2H, d, br, *J* = 4.4 Hz, H-6c,d), 5.13 (0.2H, t, br, *J* = 6.8 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.73-4.58 (1.6H, m, H-3 and H-24$_1$b), 3.92 (2.4H, s), 3.91 (0.6H, s), 3.02-2.94 (2H, m), 2.82-2.73 (2H, m), 2.38-2.33 (0.4H, m), 2.26 (0.6H, sept, *J* = 6.7 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.70 (0.6H, s, br), 0.61 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.37 (d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (75 MHz, $CDCl_3$)~~:~~ δ 191.0, 171.6, 169.9, 156.9 (24b), 152.0, 144.9, 135.4, 130.9 (25a), 125.3 (24a), 124.7, 123.4, 110.8, 106.0 (24$_1$b), 81.3 (3), 56.1, 52.2 (17), 48.8 (14), 47.8 (8), 47.2 (5), 45.3 (13), 39.5 (4), 36.3 (22a), 36.1 (20b), 35.9 (20a), 35.5 (12), 35.0 (22b), 33.8 (25b), 32.8 (15), 31.6 (1), 31.3 (23b), 29.5 (19), 29.1 (7), 28.1 (2), 26.8 (16), 26.5 (10), 25.8 (11), 25.7 (26a), 25.4 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 20.9 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.6 (27a), 15.2 (29); (+)-HRESIMS~~:~~ *m/z* 683.4289 $[M+Na]^+$ (calcd for $C_{42}H_{60}NaO_6$, **14a**, 683.4282); *m/z* 697.4443 $[M+Na]^+$ (calcd for $C_{43}H_{62}NaO_6$, **14b**, 697.4439).

Synthesis of PS-C 15. To a solution of hispolon methyl ether[34] (24 mg, 0.1 mmol), in EtOAc (0.3 mL), tributylborate (27 μL, 0.1 mmol) was added and the solution was stirred for 30 min at room temperature. Then, a solution of 14 (66 mg, 0.1 mmol) and *i*-propylamine (9 μL, 0.1 mmol) in EtOAc (0.4 mL) was added and the reaction mixture was stirred at room temperature for additional 2 hrs. After this, 1M aq. HCl (2 mL) was added and the mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with water until neutral and dried over sodium sulphate. After

removal of the solvent *in vacuo* the crude product was purified by FC (*n*-hexane-EtOAc, 1.5:1) to afford 15 (38 mg, 44% yield); yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$)~~:~~ δ 9.86 (1H, s), 7.56 (2H, d, *J* = 15.7 Hz), 7.11 (2H, dd, *J* = 8.2, 2.0 Hz), 7.04 (2H, d, *J* = 2.0 Hz), 6.94 (2H, d, *J* = 8.2 Hz), 6.35 (2H, d, *J* = 15.7 Hz), 5.95 (1H, m, br), 5.65 (1H, s), 5.39 (0.2H, d, br, *J* = 4.1 Hz, H-6c,d), 5.12 (0.2H, t, br, *J* = 6.8 Hz, H-24a), 4.74 (0.6H, s, br, H-24$_1$b), 4.70-4.57 (1.6H, m, H-3 and H-24$_1$b), 3.96 (6H, s), 2.73-2.63 (2H, m), 2.49-2.42 (2H, m), 2.36-2.31 (0.4H, m), 2.26 (0.6H, sept, *J* = 6.7 Hz), 1.06 (1.8H, d, *J* = 6.8 Hz), 1.05 (1.8H, d, *J* = 6.8 Hz), 0.70 (0.6H, s, br), 0.60 (0.8H, d, *J* = 4.1 Hz, H-19a,b *endo*), 0.36 (0.8H, d, *J* = 4.1 Hz, H-19a,b *exo*); ^{13}C NMR (101 MHz, $CDCl_3$)~~:~~ δ 196.9, 178.0, 172.8, 170.6, 156.9 (24b), 147.9, 146.9, 140.1, 130.9 (25a), 127.6, 125.3 (24a), 122.7, 120.3, 114.9, 109.6, 106.0 (24$_1$b), 100.7, 81.1 (3), 56.0, 52.3 (17), 48.8 (14), 47.9 (8), 47.2 (5), 45.3 (13), 39.5 (4), 36.4 (22a), 36.1 (20b), 35.9 (20a), 35.6 (12), 35.0 (22b), 33.8 (25b), 32.9 (15), 31.6 (1), 31.5, 31.4 (23b), 30.2 (19), 29.8 (7), 28.2 (2), 26.8 (16), 26.5 (10), 25.8 (11), 25.7 (26a), 25.4 (28), 25.0 (23a), 22.0 (27b), 21.9 (26b), 20.9 (6), 20.2 (9), 19.3 (28), 18.3 (21), 18.0 (18), 17.7 (27a), 15.2 (29); (+)-HRESIMS~~:~~ *m/z* 899.5076 $[M+Na]^+$ (calcd for $C_{55}H_{72}NaO_9$, **15a**, 899.5069); *m/z* 913.5228 $[M+Na]^+$ (calcd for $C_{56}H_{74}NaO_9$, **15b**, 913.5225).

Antioxidant Activity

Antiradical Activity (Scavenging DPPH). Free radical scavenging activity was evaluated by the scavenging of DPPH radicals. A ~~M~~methanolic solution of DPPH (40µL, 0.735 mg/mL) was added to a solution of the test substance in methanol or ethanol or toluene (800 µL, 0.18 µmol/mL). The absorbance was recorded at 545 nm after 30 min of incubation in the dark. Negative control was made using the appropriate solvent (e.g. methanol or ethanol or toluene) in absence of the test substance. BHA was used as the positive control. The percentage of the DPPH scavenging activity was calculated using the equation below:

% inhibition of DPPH radical = (1- ($A_{sample}/A_{negative}$)) x 100, where A_{sample} is the final absorbance of the test sample and $A_{negative}$ is the final absorbance of the negative control. All assays ~~was~~ were performed in triplicate.

Fe^{2+} Chelating Activity (Ferrozine Method). The chelating activity was evaluated by using the ferrozine protocol. To an aliquot of the methanolic or ethanolic solution of the test substance (450 µL, 0.18 µmol/mL) aq. Mohr's salt (150 µL, 0.125 mM) was added. After 5 min ~~of~~ incubation, the reaction was initiated by the addition of aq. ferrozine solution (300 µL, 0.5 mM). Absorbance ~~at 545 nm~~ was recorded at 545 nm after 10 min~~utes of~~ incubation at room temperature. A reaction mixture containing methanol or ethanol instead of the test substance solution served as the negative control. Quercetin was used as the positive control. The percentage of the iron chelating activity was calculated using the equation below:

$\%\ Fe^{2+}\ chelated = (1- (A_{sample}/A_{negative})) \times 100$, where A_{sample} is the final absorbance of the test sample and $A_{negative}$ is the final absorbance of the negative control. All assays ~~was~~ were performed in triplicate.

β-Carotene Bleaching Inhibition (β-Carotene-Linoleic Acid Assay). The antioxidant activity was evaluated by using the β-carotene-linoleic acid system. Tween 40 emulsifier (200 mg) and β-carotene solution in chloroform (1 mL, 0.2 mg/mL) were mixed. After removing the chloroform *in vacuo* for 10 min at 40 °C, linoleic acid (20 µL) and distilled water saturated with oxygen (30 mL) were added to the oily residue. The mixture was vigorously ~~agitated~~ shaken to form a stable emulsion. Aliquots of 4 mL of the emulsion were added to the test tubes containing the sample solution in ethanol (1 mL, 0.18 µmol/mL). The tubes ~~was~~ were incubated at 50 °C for 1 h. During that period, the absorbance was measured at 450 nm at 15 min intervals, starting immediately after sample preparation (t = 0 min), until the end of the experiment (t = 60 min). A reaction mixture containing ethanol instead of the test substance solution served as the negative control. BHA was used as the positive control. The percentage β-carotene bleaching inhibition was calculated using the equation below:

$\%\ \beta\text{-carotene bleaching inhibition} = (1- (m_{sample}/m_{negative}))x100$, where m_{sample} is the slope of the line (deriving from the interpolation of absorbance vs. time) of the test sample and $m_{negative}$ is the slope of the line (deriving from the interpolation of absorbance vs. time) of the negative control. All assays ~~was~~ were performed in triplicate.

~~Anticancer~~ **Antiproliferative Activity.** Human breast adenocarcinoma (MDA-MB-468), human cervix carcinoma (HeLa) and human medulloblastoma (DAOY) cells were grown in DMEM medium (Gibco, Milano, Italy). Both media were supplemented with 115 units/mL of penicillin G (Gibco, Milano, Italy), 115 μg/mL of streptomycin (Invitrogen, Milano, Italy) and 10% fetal bovine serum (Invitrogen, Milano, Italy). These cell lines were purchased from ATCC. Stock solutions (10 mM) of the different compounds were obtained by dissolving them in DMSO. Individual wells of a 96-well tissue culture microtiter plate were inoculated with 100 μL of complete medium containing $8x10^3$ cells. The plates were incubated at 37 °C in a humidified 5% CO_2 incubator for 18 h prior to the experiments. After medium removal, 100 μL of fresh medium containing the test compound at different concentrations was added to each well and incubated at 37 °C for 72 h. The percentage of DMSO in the medium never exceeded 0.25%. This was also the maximum DMSO concentration in all cell-based assays described below. Cell viability was assayed by the (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide test as previously described.[21] The IC_{50} was defined as the compound concentration required to inhibit cell proliferation by 50%, in comparison with cells treated with the maximum amount of DMSO (0.25%) and considered as 100% viability.

Anticholesterol Activity. The anticholesterol activity was measured as inhibition of the catalytic activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoAR). HMGCoAR, NADPH, the assay buffer, the substrate (HMGCoA) and the reference inhibitor (~~P~~pravastatin) solutions were used as provided in the HMGCoAR Assay Kit by Sigma-Aldrich S.r.l. (Milano, Italy). The experiments were carried out according to the manufacturer's instructions at 37 °C. Stock solutions of ORY and compounds **1**-**15** were prepared in DMSO. The final concentration in the assay of the tested compounds was 0.05 mg/mL (ORY, 83 μM) or 0.025-0.05 mg/mL (20-87 μM), depending on their solubility. The final concentration of DMSO in the assay was 1% (v/v). Specifically, each reaction (200 μL) was prepared by adding the reagents in the following order: assay buffer 1× (181 μL); ORY or compound **1**-**15** (1 μL); NADPH (4 μL); substrate solution (12 μL) and HMGCoAR

(catalytic domain; 2 µL). The samples were mixed and the absorbance of NADPH at 340 nm was detected by a microplate reader FLUOstar® Omega (BMG Labtech) over 10 min. The HMGCoA-dependent oxidation of NADPH and the inhibition properties of ~~P~~pravastatin, ORY and compounds **1-15** were measured by NADPH absorbance reduction which is directly proportional to the enzyme activity.

Each assay was performed in triplicate. Experiments were performed also without the enzyme (blank) as well as in the absence of inhibitor/sample (enzyme activity). It was experimentally demonstrated that 1% DMSO did not affect the enzyme activity.

The enzymatic activity (U/mg) was calculated by using the equation below~~Eq. 1~~:

~~Eq. 1~~

$$\text{U/mg} = \frac{(\Delta A_{340}/\text{min}_{sample} - \Delta A_{340}/\text{min}_{\text{blank}}) \times TV}{12.44 \times V \times 0.6 \times 0.55}$$

12.44 = ε^{mM}, the extinction coefficient for NADPH at 340 nm is 6.22 $mM^{-1}cm^{-1}$. 12.44 accounts for 2 NADPH moles consumed in the reaction.

TV = Total volume of the reaction in mL (0.2 mL)

V = Volume of HMGCoAR used in the assay (mL)

0.6 = HMGCoAR concentration (mg/mL)

0.55 = Light path (cm)

~~Supplementary Material~~ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ~~Supplementary data associated (~~^{1}H and ^{13}C NMR spectra of all new compounds.~~) with this article can be found, in the online version, at xxxxxxxxxxxx~~

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Notes

The authors declare no competing financial interest.

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