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Synthesis and biological studies of “Polycerasoidol” and “*trans*- δ -Tocotrienolic acid” derivatives as PPAR α and/or PPAR γ agonists

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Abstract

2-Prenylated benzopyrans represent a class of natural and synthetic compounds showing a wide range of significant activities. Polycerasoidol is a natural prenylated benzopyran isolated from the stem bark of *Polyalthia cerasoides* (Annonaceae) that exhibits dual PPAR α/γ agonism and an anti-inflammatory effect by inhibiting mononuclear leukocyte adhesion to the dysfunctional endothelium. Herein, we report the synthesis of three new series of prenylated benzopyrans containing one (series 1), two (series 2, “polycerasoidol” analogs) and three (series 3, “*trans*- δ -tocotrienolic acid” analogs) isoprenoid units in the hydrocarbon side chain at the 2-position of the chroman-6-ol (6-hydroxy-dihydrobenzopyran) scaffold. Isoprenoid moieties were introduced through a Grignard reaction sequence, followed by Johnson-Claisen rearrangement and subsequent Wittig olefination. hPPAR transactivation activity and the structure activity relationships (SAR) of eleven novel synthesized 2-prenylated benzopyrans were explored. PPAR transactivation activity demonstrated that the seven-carbon side chain analogs (series 1) displayed selectivity for hPPAR α , while the nine-carbon side chain analogs (polycerasoidol analogs, series 2) did so for hPPAR γ . The side chain elongation to 11 or 13 carbons (series 3) resulted in weak dual PPAR α/γ activation. Therefore, 2-prenylated benzopyrans of seven- and nine-carbon side chain (polycerasoidol analogs) are good lead compounds for developing useful candidates to prevent cardiovascular diseases associated with metabolic disorders.

Keywords: 2-Prenylated benzopyrans, polycerasoidol analogs, tocotrienol analogs, Grignard/Johnson-Claisen rearrangement, Wittig olefination, hPPAR activity.

1. Introduction

2-Prenylated benzopyrans represent a class of natural and synthetic compounds with significant biological activity, including hypocholesterolemic,¹ antioxidant,¹⁻³ anti-HIV,⁴ cytotoxic,⁵⁻⁷ antibacterial,⁷ and neuroprotective⁸ properties. The 2-prenylated benzopyran moiety, consisting in a chroman-6-ol ring linked with an isoprenoid side chain at the C-2 position, is limited to a few natural products.⁹ In 1995, we isolated the first members of a new class of 2-prenylated benzopyrans with a terminal carboxylic group, polycerasoidol and polycerasoidin, from the stem bark of *Polyalthia cerasoides* (Annonaceae) (Roxb.) Benth. & Hook.f. ex Bedd. and *P. sclerophylla* Hook.f. ex Thomson (Annonaceae) (Figure 1).^{10,11} We have reported that polycerasoidol and its analogs are dual peroxisome proliferator-activated receptors (PPAR) α and γ agonists that displayed a potent anti-inflammatory effect by inhibiting mononuclear leukocyte adhesion to the dysfunctional endothelium.¹² Structure-activity relationship (SAR) studies, together with a docking analysis of the polycerasoidol and semisynthetic analogs, revealed that the oxygenated atom at the C-6 position on the chromanol nucleus and the carboxylic acid at C-9' of the side chain act as key groups/ atoms to optimally interact with PPAR α - and PPAR γ -binding domains.¹² It is noticeable that the chroman-6-ol core is also present in the synthetic troglitazone, which is a dual PPAR α/γ agonist with a thiazolidinedione moiety capable of regulating lipid metabolism, insulin sensitivity, glucose homeostasis and atherosclerosis (Figure 1).^{13,14} Recently, we have also described the synthesis and hPPAR α/γ agonist activity of 2-prenylated benzopyrans bearing an original α -alkoxy- α,β -unsaturated ester instead of the carboxylic acid on the side chain [ACS Med Chem Lett 2021].

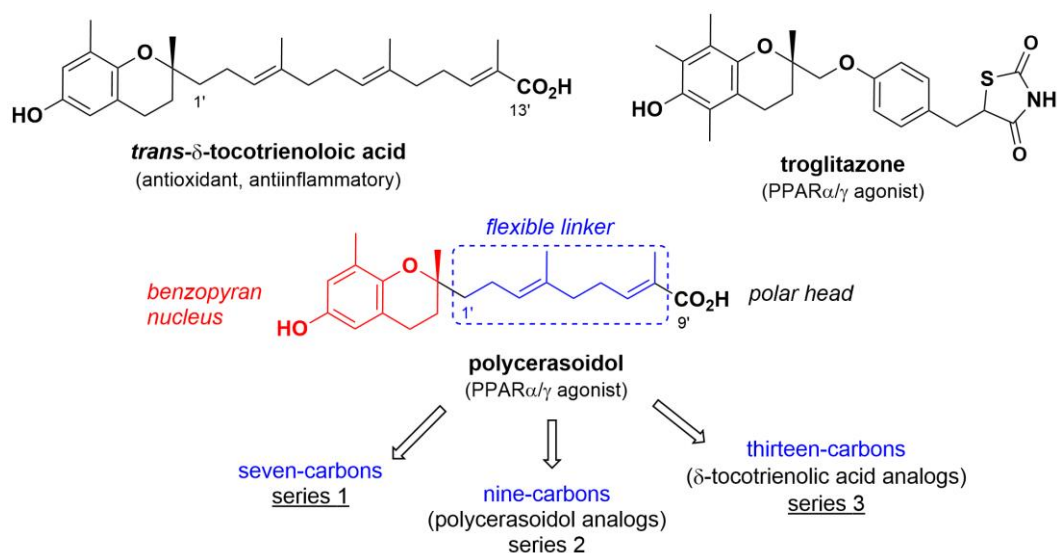


Figure 1. Bioactive prenylated benzopyrans

PPARs are ligand-activated transcription factors of the nuclear hormone receptor superfamily. Upon ligand activation, the PPAR-RXR heterodimer activate the transcription of the target genes involved in the control of lipid and carbohydrate metabolism.¹⁵ Consequently, PPARs have attracted much attention to be able to manage metabolic diseases, including metabolic syndrome, type 2 diabetes, atherogenic dyslipemia and non-alcoholic fat liver disease (NAFLD).^{15,16} PPARs are activated by a wide range of naturally occurring or metabolized lipids that derive from diet and/or result from metabolic pathways of fatty acids. Endogenous ligands include mainly saturated or unsaturated FA and FA-derived compounds, eicosanoids (e.g., leukotriene B4 and 8(S)-HETE), phospholipids (e.g., azelaoyl phosphatidylcholine, 16:0/18:1 GPC) and certain prostaglandins (e.g., 15-deoxy- Δ 12,14-prostaglandin-J₂, prostaglandin PGJ₂).¹⁷ Fibrates, which are the most representative synthetic PPAR α agonists, are clinically used to treat dyslipidemia. They reduce triglycerides, increase plasma HDL-cholesterol (HDL-C) and can improve glucose homeostasis in prediabetic patients.^{16,18} Glitazones, also called thiazolidinediones (TZDs), are oral anti-diabetic PPAR γ agonists with beneficial effects on glucose homeostasis as they enhance insulin sensitivity.^{16,18} Both PPAR isotypes (α , γ) may have synergistic therapeutic

effects to improve both glucose and lipid metabolism in patients with metabolic syndrome and/or type 2 diabetes.^{18,19} However, full PPAR γ activators have shown negative effects, including such as weight gain, fluid retention, bone fracture and cardiac hypertrophy. Therefore, there is a great interest to identify new partial PPAR γ agonists or PPAR γ modulators (PPAR γ Ms) lacking of adverse effects associated to full activation.¹⁵

Given the structural similarity between the benzopyran core and the dual PPAR α/γ agonist troglitazone, we were encouraged to explore the PPAR activity of polycerasoidol and its analogs.^{12,20,21} Polycerasoidol contains a flexible linker which is a prenylated chain formed by two isoprenoid units connecting the polar head (carboxylic acid) and the hydrophobic tail (benzopyran nucleus) like most PPAR ligands, including endogenous ligands, fibrates and TZDs.¹⁷ *Trans*- δ -tocotrienolic acid (garcinoic acid) from *Garcinia kola* is structurally related to polycerasoidol, and a bioactive metabolite with anti-inflammatory properties that contains farnesyl isoprenoid moiety as an unsaturated hydrocarbon chain (Figure 1).^{22,23}

In order to expand the arsenal of PPAR agonists, we describe herein the synthesis and hPPAR transactivation activity of novel polycerasoidol analogs characterized by a variable linker length containing one (series 1), two (series 2) or three (series 3) isoprenoid units. We perform SAR studies between the prenylated benzopyrans bearing a side chain of seven-carbons (the shortest ones, series 1), nine-carbons (“polycerasoidol” analogs, series 2) and thirteen-carbons (“*trans*- δ -tocotrienolic acid”, series 3). Further modifications are also explored by varying the substituents in the phenolic group at the C-6 position (lipophilic tail), such as alkyloxy or aryloxy groups, as well as the carboxylic function on the isoprenoid side chain (polar head), such as ester and amide bioisosteres.

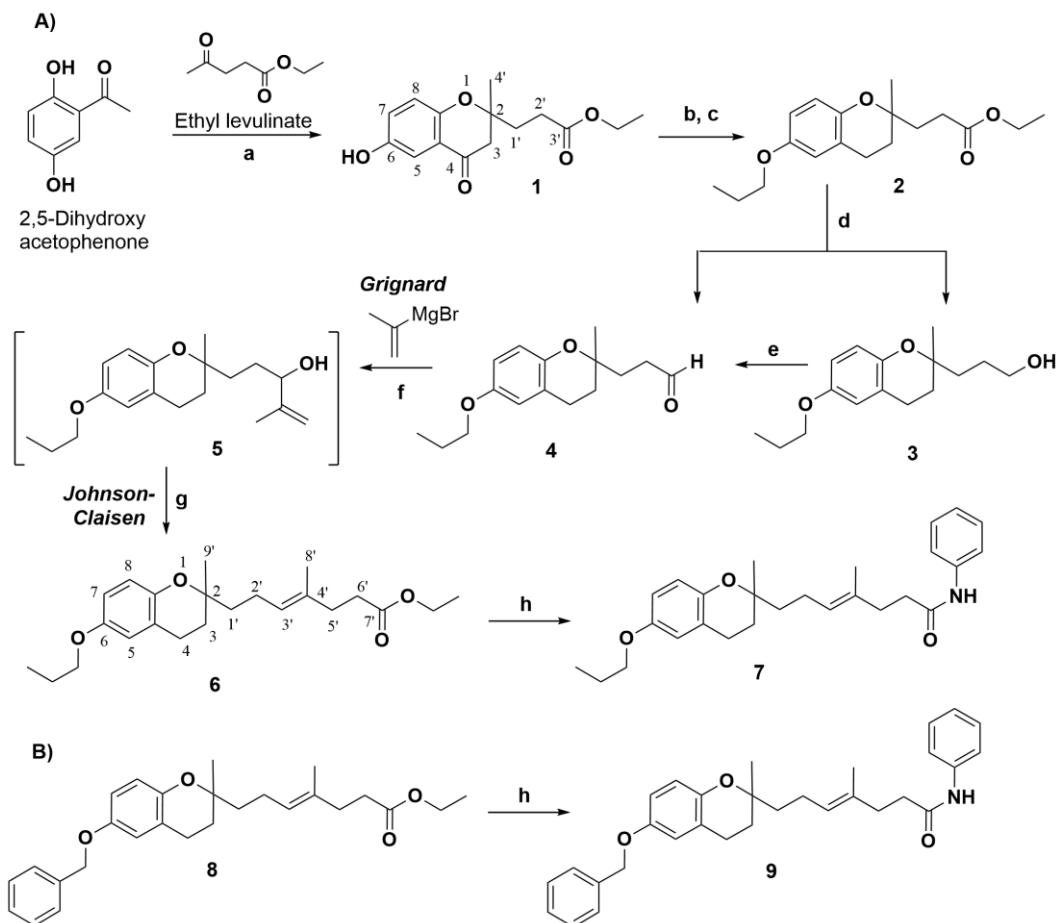
2. Results and discussion

2.1. Synthesis of 2-prenylated benzopyrans

2-Alkyl chromans (dihydrobenzopyrans) were prepared via a chroman-4-one scaffold, which is usually obtained by the aldol condensation between *ortho*-hydroxyacetophenones and ketones or aldehydes in the presence of a secondary amine (e.g., pyrrolidine, piperidine or morpholine) via enamino intermediate followed by oxa-Michael addition.^{1,20,21} Thus, the chroman-4-one or γ -benzopyrone skeleton was prepared in accordance with Pearce¹ and Kabbe's method²⁴ as briefly described in our previous report.^{20,21} The first key step involves a single condensation between the commercially available 2,5-dihydroxyacetophenone and an appropriate methyl ketone, the ethyl levulinate in the presence of pyrrolidine (Scheme 1). The obtained γ -benzopyrone **1** was reduced in one step to give the chroman-6-ol ring of the dihydrobenzopyran ester by Clemmensen conditions using dust zinc in acid medium. Subsequently, the phenolic hydroxyl group of dihydrobenzopyran was protected using propyl bromide in the presence of an appropriate base to afford *O*-propyloxy-dihydrobenzopyran **2** with a good yield.^{20,21} The aldehyde **4** intermediate was prepared by the controlled reduction of the ester function to give a good yield by using DIBAL-H reagent²¹ along with small amounts of the corresponding alcohol **3** which after pyridinium dichromate (PDC) oxidation could turn into aldehyde **4**.

By elongating the hydrocarbon side chain from aldehyde **4**, we achieved the synthesis of a series 1 of benzopyrans containing a flexible hydrocarbon linker length of seven-carbons. This elongation was performed by an efficient Grignard reaction, followed by Johnson-Claisen rearrangement to obtain the desired 2-prenylated benzopyran **6**.²⁵ The Grignard reaction consisted in the nucleophilic attack of propenyl magnesium bromide to the electrophilic carbon of aldehyde intermediate **4** to form a carbon-carbon bond. Prenylated benzopyran ester **6** was prepared by Johnson-Claisen rearrangement, using allylic alcohol

intermediate **5**, which quickly reacted with 1,1,1-triethoxyethane and catalytic amounts of isobutyric acid (Scheme 1).



Scheme 1. Synthesis of prenylated benzopyrans with seven-carbon side chain (**6-9**): Series

1. Reagents and conditions: (a) Pyrrolidine, EtOH, 60 °C, molecular sieve 3A, 24h; (b) Zn / HCl, AcOH-H₂O, rt, 2h; (c) PrBr, K₂CO₃, CH₃CN, reflux, 5h; (d) DIBAL-H, CH₂Cl₂, -78 °C, N₂, 20 min; (e) PDC, CH₂Cl₂, reflux, 2h; (f) THF, -78 °C, N₂, 60 min; (g) MeC(OEt)₃, isobutyric acid, 140 °C, 2h; (h) KOH 20 %, MeOH, reflux, 2h; SOCl₂ / CH₂Cl₂, reflux, 3h; aniline, 4-DMAP, Et₃N, N₂, rt, overnight.

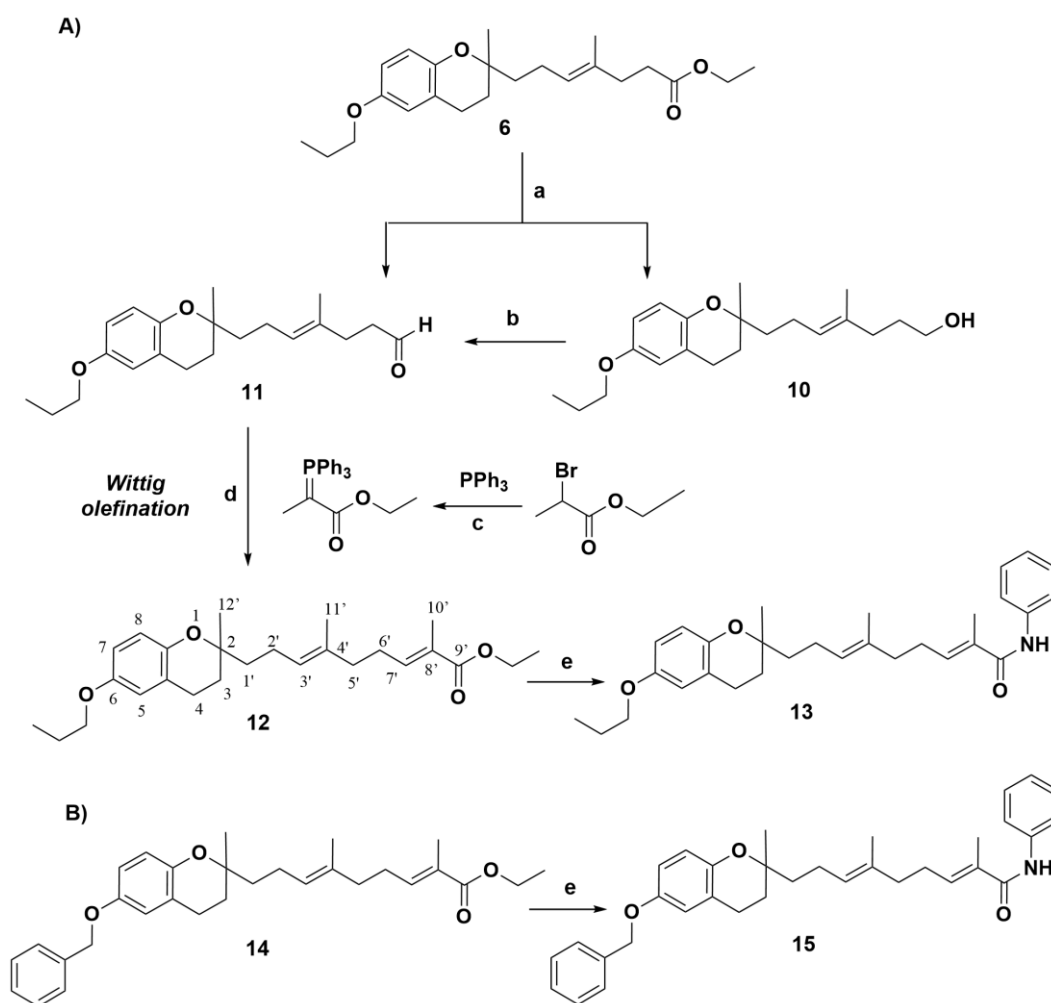
After saponification of ethyl ester **6** with basic conditions, the residue was treated with SOCl₂ at reflux to obtain the corresponding acid chloride intermediate, which was added

dropwise to a solution of aniline in the presence of catalytic amounts of 4-DMAP and Et₃N to give amide **7**. In order to explore the benzyloxy group *versus* the propyloxy substituent at the C-6 position on the chromanol ring, we prepared the corresponding 6-benzyloxybenzopyran homologs, ester **8** and amide **9**, following the same procedure as described above for **6** and **7** (Scheme 1).

We designed the synthesis of a series 2 of benzopyrans containing a flexible hydrocarbon linker length of nine-carbons like polycerasoidol (Figure 1). Starting from *O*-propyloxy-benzopyran ester **6**, we performed an initial controlled reduction using DIBAL-H²¹ to provide the key aldehyde **11**, which was also provided by the oxidation of alcohol **10**. The side chain of seven-carbons was elongated to synthesize **12** through Wittig olefination²⁶ between aldehyde **11** and the ylide. For this purpose, (carbethoxyethylidene) triphenylphosphorane was freshly prepared from 2-bromoethyl propanoate and triphenylphosphine. Then, aldehyde **11** was treated with the ylide to obtain the desired vinyl ester **12** (Scheme 2). By following the same procedure starting from *O*-benzyloxy ester **8**, we prepared its homolog *O*-benzyloxy-benzopyran ester **14**. Both polycerasoidol analogs **12** and **14** were reacted with aniline under the same conditions as those described above for compound **7** to obtain amide **13** and amide **15**, respectively (Scheme 2).

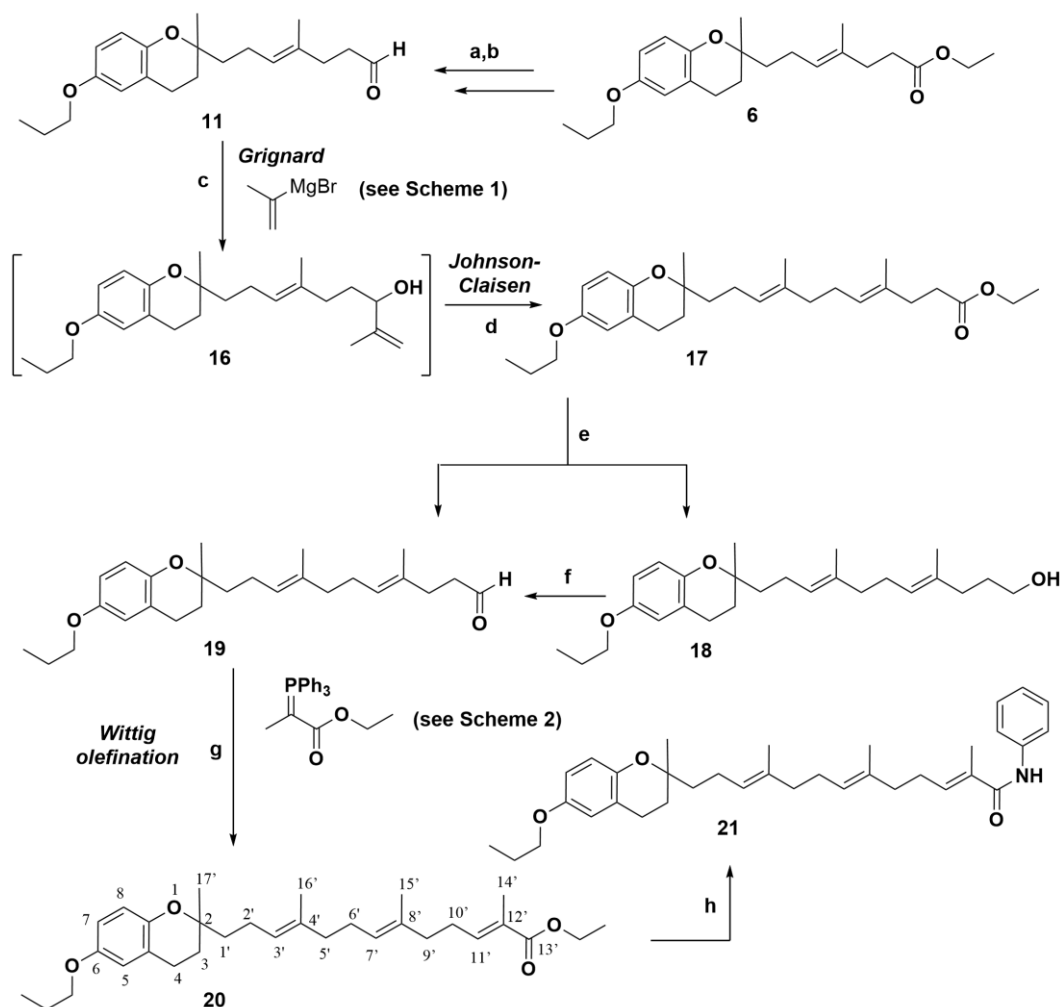
The synthesis of series 3 was achieved from the benzopyrans containing a flexible hydrocarbon linker length of thirteen-carbons like *trans*- δ -tocotrienolic acid (Figure 1). As described above, aldehyde **11** was prepared by either a controlled reduction of ester **6** or the oxidation of alcohol **10**. Aldehyde **11** was subjected to Grignard reaction by adding organomagnesium reagent, followed by Johnson-Claisen rearrangement using 1,1,1-triethoxyethane to provide the benzopyran ester **17** bearing an eleven-carbon side chain. A controlled reduction of **17** with DIBAL-H resulted in aldehyde intermediate **19**, which was also obtained by the oxidation of alcohol **18**. The side chain was elongated via Wittig

olefination between aldehyde **19** and the (carboethoxyethylidene)triphenylphosphorane to give the desired vinyl ester **20** as the “*trans*- δ -tocotrienolic acid” analog (Scheme 3). Saponification of **20** with KOH, followed by the preparation of acid chloride by SOCl₂ and its treatment with aniline, gave *O*-propyloxy benzopyran amide **21** according to the same procedure reported for the synthesis of compound **7** (Scheme 3).



Scheme 2. Synthesis of prenylated benzopyrans as “polycerasoidol” analogs (**12-15**): Series

2. Reagents and conditions: (a) DIBAL-H, CH₂Cl₂, -78 °C, N₂, 20 min; (b) PDC, CH₂Cl₂, reflux, 2h; (c) AcOEt, reflux, 5h; NaOH, EtOH, 20 min; (d) THF, rt, N₂, 24h; (e) KOH 20 %, reflux, 2h; SOCl₂/CH₂Cl₂, reflux, 3h; aniline, 4-DMAP, Et₃N, N₂, rt, overnight.



Scheme 3. Synthesis of prenylated benzopyrans as “*trans*- δ -tocotrienoloic acid” analogs (**20**, **21**): Series 3. **Reagents and conditions:** (a) DIBAL-H, CH₂Cl₂, -78 °C, N₂, 20 min; (b) PDC, CH₂Cl₂, reflux, 2h; (c) THF, -78 °C, N₂, 60 min.; (d) MeC(OEt)₃, isobutyric acid, 140 °C, 2h; (e) DIBAL-H, CH₂Cl₂, -78 °C, N₂, 20 min; (f) PDC, CH₂Cl₂, reflux, 2h; (g) THF, rt, N₂, 24h; (h) KOH 20 %, reflux, 2h; SOCl₂/CH₂Cl₂, reflux, 3h; aniline, 4-DMAP, Et₃N, N₂, rt, overnight.

2.2. PPAR α and PPAR γ Agonist Activity

All the synthesized compounds were assayed *in vitro* for hPPAR α and hPPAR γ transactivation activity by means of an established cell-based transcription assay in Cos-7 cells transiently transfected with a luciferase-reported plasmid in the presence of expression

vectors pGAL4hPPAR α and pGAL4hPPAR γ .^{12,20,21,27} The synthesized compounds were tested at the 10 μ M dose and compared to the reference compounds such as WY-14,643 at 10 μ M and rosiglitazone at 1 μ M for hPPAR α and hPPAR γ , respectively. The activating efficacy of compounds was calculated as the maximal transactivation response, expressed as a percentage of the maximum activity of the reference compounds for each receptor subtype (Figure 2). Natural polycerasoidol showed full agonist activity for both hPPAR α and hPPAR γ , exhibiting the maximal transactivation percentage (107% and 95% for hPPAR α and hPPAR γ , respectively).¹³ The benzopyrans containing a shorter side chain of seven-carbons (series 1: **6-9**) (series 1, Scheme 1) were able to activate both hPPAR α and γ isotypes. It is noteworthy that the *O*-benzyloxy-ester **8** displayed a full agonism for hPPAR α with high selectivity (123 % and 38% for α and γ , respectively). By contrast, the polycerasoidol analogs (series 2, Scheme 2) containing a side chain of nine-carbons, ester **12** (61 %, ester) and principally amide **15** (73 %), showed the highest efficacy for PPAR γ . Finally, long-chain derivatives, such as the *trans*- δ -tocotrienolic acid analogs (series 3, Scheme 3) containing a side chain of eleven- or thirteen-carbons, showed weak dual PPAR α/γ agonism (Figure 2).

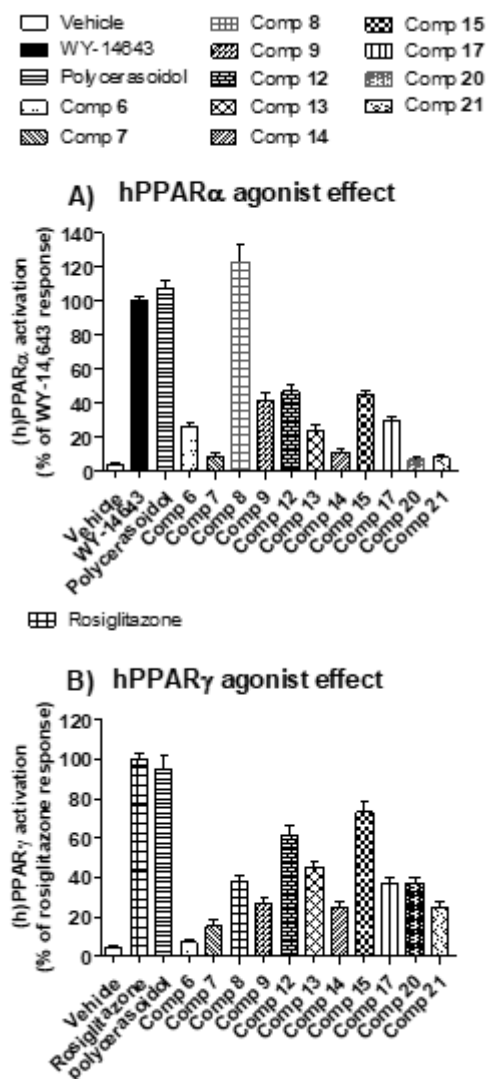


Figure 2. *In vitro* hPPAR α (A) and hPPAR γ activation (B) for active benzopyrans at 10 μ M. Results refer to the maximal PPAR fold activation of each compound relative to the maximum activation of reference compounds, WY-14,643 (10 μ M) and rosiglitazone (1 μ M), which corresponded to 100% in GAL4 chimeric hPPAR α and hPPAR γ system.

In order to provide a structural understanding of how benzopyran **15** and **8** activate PPAR γ and PPAR α , respectively, we carried out molecular docking analysis. Compound **15**/PPAR γ complex showed a nearby spatial location to the natural polycerasoidol, which was previously reported.¹² Compound **15** showed a hydrogen bond between nitrogen of amide group and Cys285, and also strong interactions with Tyr473, Tyr327, Leu330 and Ile

341 of PPAR γ (Figure 3A). Benzopyran **8**/PPAR α complex exhibited strong interactions with Ala333, Ser280, Thr283, Tyr314 and His440. This analysis indicated that molecule **8** adopted a spatial ordering slightly different than polycerasoidol for PPAR α (Figure 3B).¹²

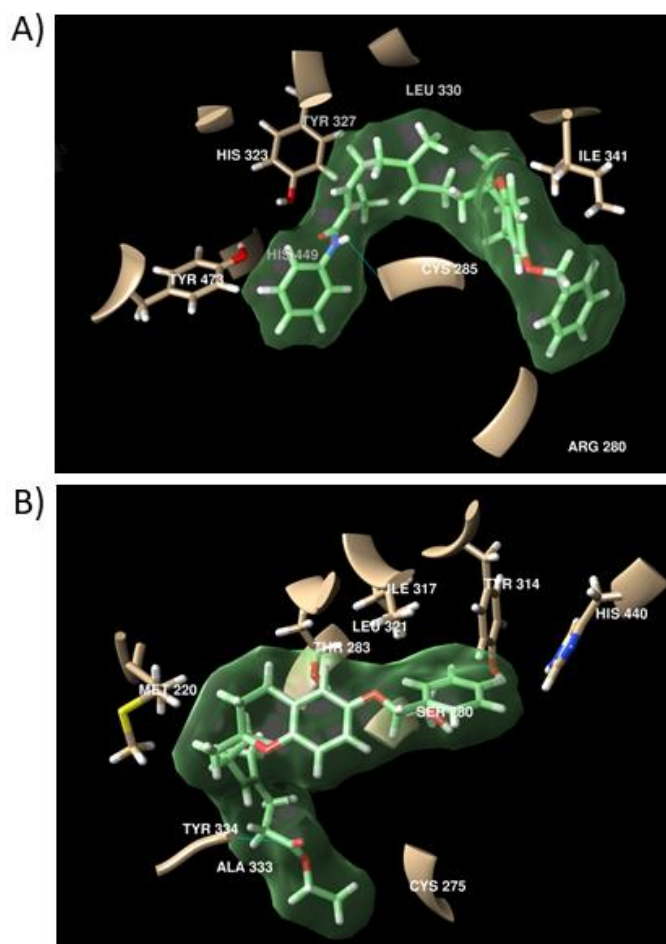


Figure 3. Spatial view obtained for the benzopyran **15**/ PPAR γ complex (A) and **8**/ PPAR α complex (B). Molecules **15** and **8** are depicted in green, and the hydrogen bonds established with the different amino acids in these conformations are also shown. Benzopyran **15** establishes strong hydrogen bond interactions with Cys285, Tyr473, Tyr327, Leu330 and Ile 341 of PPAR γ , while benzopyran **8** establishes strong hydrogen bond interactions with Ala333, Ser280, Thr283, Tyr314 and His440 of PPAR α .

3. Conclusion

Herein, we efficiently prepared three series of prenylated benzopyrans with a sequence of reactions, including Grignard reaction followed by Johnson-Claisen rearrangement, as well as Wittig olefination with (carbethoxyethylidene) triphenylphosphorane to introduce one, two or three prenylated moieties in the side chain. Seven-carbon side chain analogs like **8** (series 1), displayed selectivity for hPPAR α . By contrast, nine-carbon side chain analogs, like **15** (series 2), showed high efficacy to activate hPPAR γ without raising a full agonism and probably avoiding adverse effects. Therefore, these novel molecules are good lead compounds for developing useful candidates to prevent cardiovascular diseases associated with metabolic disorders.

4. Experimental section

4.1. General instrumentation

EIMS and HREIMS, were recorded on a VG Auto Spec Fisons spectrometer instruments. Liquid chromatography with mass spectrometry detection (LC-MSD) with API (atmospheric pressure ionization) source configured as APIES (electrospray ionisation) in positive or negative mode were determined on a Hewlett-Packard (HP-1100). Liquid chromatography-mass spectrometry detection was performed on a liquid chromatography UHPLC apparatus (Shimadzu, LCMS-8040) coupled to a tandem mass spectrometry (MS/MS) triple quadrupole equipped with electrospray ionization (ESI) ion source (Shimadzu, Kyoto, Japan). ^1H NMR and ^{13}C NMR spectra were recorded with CDCl_3 as solvent on a Bruker AC-300, AC-400 or AC-500. Multiplicities of ^{13}C NMR resonances were assigned by DEPT experiments. The assignments in proton and carbon NMR were made by COSY 45, HSQC and HMBC correlations recorded at 400 or 500 MHz. All reactions were monitored by analytical TLC with silica gel 60 F254 (Merck 5554). The residues were purified through 60H silica gel column (5-40 μm , Merck 7736) and by flash chromatography (230-400 μm , Merck 9385). Solvents and reagents were used as purchased

from commercial sources. Quoted yields are of purified material.

4.1.1. General procedure for synthesis of prenylated benzopyrans **1** and **2**

2-(Ethylpropanoate)-6-hydroxy-2-methyldihydrobenzopyran-4-one (**1**) and 2-(ethylpropanoate)-2-methyl-6-propoxydihydrobenzopyran (**2**) were prepared from 2,5-dihydroxy acetophenone and ethyl levulinate as previously described.^{20,21}

4.1.2. General procedure for synthesis of alcohol **3** and aldehyde **4**

A solution of (250 mg, 0.816 mmol) of **2** in anhydrous CH₂Cl₂ (10 mL) at -78°C under nitrogen atmosphere was stirred for 10 min. To this solution was added dropwise 4.4 mL of 1.0 M DIBAL-H solution in THF. After 20 min, the mixture was quenched by addition of 5 mL of MeOH and 10 mL of halfsat aqueous NH₄Cl solution. The reaction mixture was stirred for additional 10 min at room temperature and concentrated in vacuo. Then, water was added and extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄ and evaporated to dryness. The residue was purified by silica gel column chromatography (hexane/EtOAc, 90:10) to afford 80 mg of the corresponding alcohol **3** (35%) and 120 mg of the aldehyde **4** (53%).²¹ Alcohol **3** (80 mg, 0.303 mmol) in anhydrous CH₂Cl₂ (4 mL) was treated with pyridinium dichromate (PDC) (230 mg, 0.611 mmol). The reaction mixture was stirred under reflux for 2 h. The mixture was diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure, and the crude purified as above described to give 71 mg of aldehyde **4** (89%) as a colorless oil.

2-Methyl-2-propanol-6-propoxydihydrobenzopyran (3): ¹H NMR (300 MHz, CDCl₃): δ_H 6.63 (m, 3H, H-5, 7, 8), 3.83 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 3.65 (m, 2H, CH₂-3'), 2.74 (m, 2H, CH₂-4), 1.72 (m, 8H, CH₂-1', CH₂-2', CH₂-3, OCH₂CH₂CH₃), 1.27 (s, 3H, CH₃-4'), 1.01 (t, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 152.4 (C-6), 147.8 (C-8a), 121.5 (C-4a), 117.5 (CH-7), 114.7 (CH-5), 114.0 (CH-8), 75.5 (C-2), 70.0

(OCH₂CH₂CH₃), 63.1 (CH₂-3'), 35.8 (CH₂-2'), 31.2 (CH₂-3), 26.8 (CH₂-1'), 24.3 (CH₃-4'), 22.6 (OCH₂CH₂CH₃), 22.3 (CH₂-4), 10.9 (OCH₂CH₂CH₃). MS (ESI) *m/z*: 265 [M+H]⁺.

2-Methyl-2-propanal-6-propoxydihydrobenzopyran (4): ¹H NMR (300 MHz, CDCl₃): δ_H 9.73 (s, CHO), 6.67 (m, 3H, H-5, H-7, H-8), 3.84 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 2.76 (m, 2H, CH₂-4), 2.60 (m, 2H, CH₂-2'), 2.02, 1.89 (m, 2H, CH₂-1'), 1.77 (m, 4H, CH₂-3, OCH₂CH₂CH₃), 1.25 (s, 3H, CH₃-4'), 1.01 (t, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 202.3 (CHO), 152.6 (C-6), 147.2 (C-8a), 121.2 (C-4a), 117.6 (CH-7), 114.7 (CH-5), 114.2 (CH-8), 74.5 (C-2), 70.0 (OCH₂CH₂CH₃), 38.4 (CH₂-2'), 31.7 (CH₂-1'), 31.2 (CH₂-3), 23.7 (CH₃-4'), 22.6 (OCH₂CH₂CH₃), 22.2 (CH₂-4), 10.5 (OCH₂CH₂CH₃); MS (ESI) *m/z*: 263 [M+H]⁺.

4.1.3. General Procedure for Synthesis of Seven-Carbons Side Chain Prenylated Benzopyrans: Compounds **6-9** (series 1)

A mixture of aldehyde **4** (300 mg, 1.14 mmol) and 13.7 mL of 0.5 M isopropenylmagnesium bromide solution (6.84 mmol) in THF (30 mL) at -78°C was stirred for 1 h under nitrogen atmosphere. The resulting mixture reaction was quenched by addition of half-saturated aqueous NH₄Cl solution. The reaction was stirred for 15 min at room temperature. Then, water was added and extracted with ethyl acetate. The combined organic layers were washed with water, dried with anhydrous Na₂SO₄ and evaporated to dryness. The residue obtained, 174 mg of **5** (not isolated), was directly treated with 10 mL of triethylorthoacetate and a catalytic amount of isobutyric acid. The mixture was stirred at 140 °C for 2 h, and then, cooled and concentrated under reduced pressure to remove the excess of ethylorthoacetate. The residue diluted with hexane, and successively washed with water, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 80:20) to afford 135 mg of benzopyran **6** (31.6 %). Amide **7** was obtained from **6** (100 mg, 0.27 mmol) by KOH 20% solution at reflux for

2 h and SOCl₂ (0.15 mL, 2.06 mmol) in anhydrous CH₂Cl₂ refluxed for 3h. Then, the solvent was removed to obtain quantitatively the acid chloride which was used in the next step without further purification. The crude of acid chloride in dry CH₂Cl₂ (1 mL) was added dropwise to a solution of aniline (32 μL, 0.35 mmol), 4-DMAP (2.4 mg, 0.02 mmol) and Et₃N (19 μL, 0.14 mmol) under N₂ atmosphere and in a cooling ice bath. After stirring at room temperature for 1 h, 5% aq HCl (1.5 mL) solution was added and extracted with CH₂Cl₂. The organic layer was washed with 5% aq NaHCO₃ solution, brine, water, dried and the solvent was removed under reduced pressure to give 23 mg of amide **7** (37.5 %) as a colorless oil. The 6-benzylated homologs of type **6**, compounds **8** and **9** were prepared according to the procedure for the synthesis of **6** and **7**.

2-Methyl-2-((4'-methyl)ethylhept-3'-enoate)-6-propoxydihydrobenzopyran (6). ¹H NMR (300 MHz, CDCl₃): δ_H 6.67 (m, 3H, H-5, 7, 8), 5.15 (t, *J* = 7 Hz, 1H, CH-3'), 4.11 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 3.84 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 2.72 (t, *J* = 6.6, 2H, CH₂-4), 2.32 (m, 4H, CH₂-5', CH₂-6'), 2.09 (q, *J* = 7.8 Hz, 2H, CH₂-2'), 1.68 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.61 (s, 3H, CH₃-8'), 1.26 (s, 3H, CH₃-9'), 1.24 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.01 (t, *J* = 7.3 Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 173.3 (CO), 152.3 (C-6), 147.7 (C-8a), 133.4 (C-4'), 124.9 (CH-3'), 121.4 (C-4a), 117.6 (CH-7), 114.7 (CH-5), 114.0 (CH-8), 75.3 (C-2), 70.0 (OCH₂CH₂CH₃), 60.1 (OCH₂CH₃), 39.1 (CH₂-1'), 34.6 (CH₂-5'), 34.5 (CH₂-6'), 33.1 (CH₂-3), 24.0 (CH₃-9'), 22.6 (CH₂-4), 22.3 (OCH₂CH₂CH₃, CH₂-2'), 15.7 (CH₃-8'), 14.1 (OCH₂CH₃), 10.4 (OCH₂CH₂CH₃); HREIMS *m/z* 375.5233 [M+H]⁺ (375. 5216, calcd. for C₂₃H₃₅O₄).

2-Methyl-2-((4'-methyl)-N-phenylhept-3'-enamamide)-6-propoxydihydrobenzopyran (7). ¹H NMR (300 MHz, CDCl₃): δ_H 7.47 (d, *J* = 7.8 Hz, 2H, H-2'', 6''), 7.30 (t, *J* = 7.8 Hz, 2H, H-3'', 5''), 7.09 (t, *J* = 7.4 Hz, 1H, H-4''), 6.70 (m, 3H, H-5, H-7, H-8), 5.25 (t, *J* = 7 Hz, 1H, CH-3'), 3.84 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 2.73 (t, *J* = 6.6, 2H, CH₂-4), 2.38 (m, 4H,

CH₂-5', CH₂-6'), 2.12 (q, $J = 7.8$ Hz, 2H, CH₂-2'), 1.75 (m, 4H, CH₂-3, OCH₂CH₂CH₃), 1.65 (s, 3H, CH₃-8'), 1.58 (m, 2H, CH₂-1'), 1.27 (s, 3H, CH₃-9'), 1.01 (t, $J = 7.3$ Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_c 173.7 (CO), 152.4 (C-6), 147.7 (C-8a), 137.8 (C-1'), 133.7 (C-4'), 129.3 (C-3', 5'), 129.0 (C-4'), 125.8 (C-3'), 121.6 (C-4a), 117.6 (CH-7), 115.1 (CH-5), 114.8 (CH-8), 75.4 (C-2), 70.1 (OCH₂CH₂CH₃), 39.1 (CH₂-1'), 36.2 (CH₂-6'), 35.1 (CH₂-5'), 31.1 (CH₂-3), 24.1 (CH₃-9'), 22.7 (CH₂-4), 22.2, 22.4 (OCH₂CH₂CH₃) and (CH₂-2'), 15.9 (CH₃-8'), 10.5 (OCH₂CH₂CH₃); HREIMS m/z 421.2620 [M]⁺ (421.2457 calcd. for C₂₇H₃₅NO₃).

6-Benzoyloxy-2-methyl-2-((4'-methyl)ethylhept-3'-enoate)-dihydrobenzopyran (8). ¹H NMR (400 MHz, CDCl₃): δ_H 7.35 (m, 5H, H-2'' to H-6''), 6.72 (m, 3H, H-5, H-7, H-8), 5.20 (t, $J = 7$ Hz, 1H, CH-3'), 4.99 (s, 2H, OCH₂Ar), 4.11 (q, $J = 7.4$ Hz, 2H, OCH₂CH₃), 2.75 (t, $J = 6.7$, 2H, CH₂-4), 2.38 (m, 4H, CH₂-6', CH₂-5'), 2.09 (m, 2H, CH₂-2'), 1.68 (m, 4H, CH₂-3, CH₂-1'), 1.61 (s, 3H, CH₃-8'), 1.27 (s, 3H, CH₃-9'), 1.23 (t, $J = 7.3$ Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_c 173.4 (CO), 152.1 (C-6), 148.1 (C-8a), 137.5 (C-1''), 133.5 (C-4'), 128.5, 127.8, 127.4 (CH-2'' to CH-6''), 125.0 (CH-3'), 121.6 (C-4a), 117.7 (CH-7), 115.1 (CH-5), 114.4 (CH-8), 75.5 (C-2), 70.6 (OCH₂Ar), 60.2 (OCH₂CH₃), 39.2 (CH₂-1'), 34.6 (CH₂-6'), 33.2 (CH₂-5'), 30.9 (CH₂-3), 24.1 (CH₃-9'), 22.3 (CH₂-4), 22.1 (CH₂-2'), 15.8 (CH₃-8'), 14.2 (OCH₂CH₃); HREIMS m/z 422.2473 [M]⁺ (422.2457 calcd. for C₂₇H₃₄O₄).

6-Benzoyloxy-2-methyl-2-(N-phenyl(4'-methyl)hept-3'-enamido)-dihydrobenzopyran (9). ¹H NMR (400 MHz, CDCl₃): δ_H 7.47 (d, $J = 7.8$ Hz, 2H, H-2''', 6'''), 7.36 (m, 8H, H-3''' to H-5''' and H-2'' to H-6''), 6.72 (m, 3H, H-5, H-7, H-8), 5.26 (t, $J = 6.8$ Hz, 1H, CH-3'), 4.96 (s, 2H, OCH₂Ar), 2.73 (t, $J = 6.8$ Hz, 2H, CH₂-4), 2.42 (m, 4H, CH₂-5', 6'), 2.14 (m, 2H, CH₂-2'), 1.70 (m, 4H, CH₂-3, CH₂-1'), 1.65 (s, 3H, CH₃-8'), 1.27 (s, 3H, CH₃-9'); ¹³C NMR (100 MHz, CDCl₃): δ_c 170.9 (CO), 152.1 (C-6), 148.0 (C-8a), 137.9, 137.5 (C-1'', C-1'''), 133.7 (C-4'), 128.9-125.7 (CH-Ar), 124.2 (CH-3'), 121.7 (C-4a), 119.7 (CH-2''', 6'''),

117.7 (CH-7), 115.2 (CH-5), 114.4 (CH-8), 75.5 (C-2), 70.6 (OCH₂Ar), 39.2 (CH₂-1'), 36.2 (CH₂-6'), 35.0 (CH₂-5'), 31.0 (CH₂-3), 24.2 (CH₃-9'), 22.5 (CH₂-4), 22.2 (CH₂-2'), 15.9 (CH₃-8'); HREIMS m/z 469.2596 [M]⁺ (469.2616 calcd. for C₃₁H₃₅NO₃).

4.1.4. *General procedure for synthesis of nine-carbon side chain prenylated benzopyrans: "polycerasoidol" analogs 12-15 (series 2)*

Alcohol **10** and aldehyde **11**, obtained by controlled reduction from ethyl-ester **6**, were prepared according to the procedure for the synthesis of **3** and **4**. For Wittig olefination the carbethoxyethylidene triphenylphosphorane was previously prepared. For this purpose, triphenylphosphine dissolved was dissolved in ethyl acetate, and then splashed into 2-bromoethyl propanoate under room temperature at reflux for 5 h. The obtained white solid was dissolved in EtOH and treated with 20% NaOH during 20 min, to obtain carbethoxyethylidene triphenylphosphorane. The aldehyde **11** (200 mg, 0.60 mmol) was added to a solution of the ylide (350 mg, 0.97 mmol) in THF under N₂ atmosphere. The reaction was stirred for 24 h at room temperature. Then, water was added and extracted with ethyl acetate. The organic layer was washed with 5% aq NaHCO₃ solution, brine, water, dried and the solvent was removed under reduced pressure. The residue was purified via silica gel column chromatography (hexane/EtOAc, 85:15) to afford 237 mg of ethyl-ester polycerasoidol analog **12** (54.5%) as a colorless oil. The 6-benzylated homolog **14** was prepared according to the same procedure for the synthesis of **12** above. The corresponding amides **13** and **15** were prepared according to the procedure for the synthesis of **7** (Scheme 2).

2-Methyl-2-((4'-methyl)hept-3'-enol)-6-propoxydihydrobenzopyran (10). ¹H NMR (500 MHz, CDCl₃): δ_H 6.63 (m, 3H, H-5, 7, 8), 5.14 (t, $J = 6.5$ Hz, 1H, H-3'), 3.82 (t, $J = 6.4$ Hz, 2H, OCH₂CH₂CH₃), 3.59 (t, $J = 6.5$ Hz, 2H, CH₂-7'), 2.70 (t, $J = 6.8$ Hz, 2H, CH₂-4), 2.07 (m, 2H, CH₂-2'), 2.02 (t, $J = 7.4$ Hz, 2H, CH₂-5'), 1.75 (m, 4H, CH₂-3, OCH₂CH₂CH₃),

1.63 (m, 4H, CH₂-1, CH₂-6), 1.58 (s, 3H, CH₃-8'), 1.25 (s, 3H, CH₃-9'), 0.99 (t, $J = 7.4$ Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃): δ_C 152.4 (C-6), 147.8 (C-8a), 133.4 (C-4'), 124.6 (CH-3'), 121.5 (C-4a), 117.6 (CH-7), 114.7 (CH-5), 114.0 (CH-8), 75.5 (C-2), 70.1 (OCH₂CH₂CH₃), 62.7 (CH₂-7'), 39.2 (CH₂-1'), 35.8 (CH₂-6'), 30.9 (CH₂-3), 30.6 (CH₂-5'), 24.0 (CH₃-9'), 22.6 (CH₂-4), 22.3 (OCH₂CH₂CH₃), 22.0 (CH₂-2'), 15.7 (CH₃-8'), 10.4 (OCH₂CH₂CH₃); MS (ESI) m/z 333 [M+H]⁺.

2-Methyl-2-((4'-methyl)hept-3'-enal)-6-propoxydihydrobenzopyran (11). ¹H NMR (400 MHz, CDCl₃): δ_H 6.65 (m, 3H, H-5, 7, 8), 5.15 (t, $J = 6.5$ Hz, 1H, H-3'), 3.84 (dd, $J = 6.6$ Hz, 2H, OCH₂CH₂CH₃), 2.73 (t, $J = 6.8$ Hz, 2H, CH₂-4), 2.50 (t, $J = 6.5$ Hz, 2H, CH₂-6'), 2.30 (t, $J = 7.4$ Hz, 2H, CH₂-5'), 2.10 (dq, $J = 7.4$ Hz, 1.6 Hz, 2H, CH₂-2'), 1.78 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.57 (s, 3H, CH₃-8'), 1.27 (s, 3H, CH₃-9'), 1.01 (t, $J = 7.4$ Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ_C 202.5 (CHO), 152.4 (C-6), 147.8 (C-8a), 133.1 (C-4'), 125.3 (CH-3'), 121.6 (C-4a), 117.7 (CH-7), 114.8 (CH-5), 114.1 (CH-8), 75.4 (C-2), 70.1 (OCH₂CH₂CH₃), 42.1 (CH₂-6'), 39.2 (CH₂-1'), 31.7 (CH₂-5'), 31.1 (CH₂-3), 24.1 (CH₃-9'), 22.7 (CH₂-4), 22.4 (OCH₂CH₂CH₃), 22.2 (CH₂-2'), 16.0 (CH₃-8'), 10.5 (OCH₂CH₂CH₃); HREIMS m/z 330.2247 [M]⁺ (330.2194 calcd. for C₂₁H₃₀O₃).

2-((4',8'-Dimethyl)ethylnonan-3',7'-dienoate)-2-methyl-6-propoxydihydro-benzopyran (12). ¹H NMR (400 MHz, CDCl₃): δ_H 6.70 (m, 1H, H-7'), 6.65 (m, 3H, H-7, 8), 6.60 (m, 3H, H-5), 5.15 (t, $J = 7.2$ Hz, 1H, H-3'), 4.17 (q, $J = 7.1$ Hz, 2H, OCH₂CH₃), 3.84 (t, $J = 6.6$ Hz, 2H, OCH₂CH₂CH₃), 2.73 (t, $J = 6.8$ Hz, 2H, CH₂-4), 2.25 (q, $J = 7.5$ Hz, 2H, CH₂-6'), 2.09 (m, 4H, CH₂-2', 5'), 1.81 (d, $J = 1.2$ Hz, 3H, CH₃-10'), 1.74 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.60 (s, 3H, CH₃-11'), 1.28 (t, $J = 7.2$ Hz, 3H, OCH₂CH₃), 1.27 (s, 3H, CH₃-12'), 1.01 (t, $J = 7.4$ Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ_C 168.2 (CO), 152.4 (C-6), 147.8 (C-8a), 141.8 (CH-7'), 134.1 (C-4'), 127.8 (C-8'), 124.3 (CH-3'), 121.6 (C-4a), 117.7 (CH-7), 114.8 (CH-5), 114.1 (CH-8), 75.5 (C-2), 70.1 (OCH₂CH₂CH₃), 60.4

(OCH₂CH₃), 39.2 (CH₂-1'), 38.2 (CH₂-5'), 31.1 (CH₂-3), 27.3 (CH₂-6'), 24.2 (CH₃-12'), 22.7 (CH₂-4), 22.5 (OCH₂CH₂CH₃), 22.2 (CH₂-2'), 15.9 (CH₃-11'), 14.3 (OCH₂CH₃), 12.4 (CH₃-10'), 10.6 (OCH₂CH₂CH₃); HREIMS m/z 414.2768 [M]⁺ (414.2770 calcd. for C₂₆H₃₈O₄).

2-Methyl-2-((4',8'-dimethyl)-N-phenylnona-3',7'-dienamide)-6-propoxydihydro-benzopyran (13): ¹H NMR (300 MHz, CDCl₃): δ_H 7.52 (d, J = 8.2 Hz, 2H, H-2'', 6''), 7.36 (t, 2H, J = 8.2 Hz, H-3'', 5''), 7.12 (t, J = 8.2 Hz, 1H, H-4''), 6.72 (m, 3H, H-5, H-7, H-8), 6.38 (dt, J = 7.1 Hz, 1.3 Hz, 1H, H-7'), 5.18 (t, J = 7 Hz, 1H, CH-3'), 3.83 (t, J = 6.6 Hz, 2H, OCH₂CH₂CH₃), 2.73 (t, J = 6.7 Hz, 2H, CH₂-4), 2.28 (m, 2H, CH₂-6'), 2.13 (m, 4H, CH₂-2', 5'), 1.95 (s, 3H, CH₃-10'), 1.76 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.62 (s, 3H, CH₃-11'), 1.27 (s, 3H, CH₃-12') 1.01 (t, J = 7.4 Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 167.7 (CO), 152.4 (C-6), 147.7 (C-8a), 138.1 (C-1''), 136.2 (CH-7'), 134.0 (C-4'), 132.0 (C-8'), 129.0 (CH-3'', 5''), 125.2 (CH-4''), 124.1 (CH-3'), 121.6 (C-4a), 120.0 (CH-2'', 6''), 117.7 (CH-7), 114.8 (CH-5), 114.1 (CH-8), 75.5 (C-2), 70.1 (OCH₂CH₂CH₃), 39.2 (CH₂-1'), 38.4 (CH₂-5'), 31.0 (CH₂-3), 26.9 (CH₂-6'), 24.1 (CH₃-12'), 22.7 (CH₂-4), 22.4 (OCH₂CH₂CH₃), 22.2 (CH₂-2'), 15.9 (CH₃-11'), 12.9 (CH₃-10'), 10.6 (OCH₂CH₂CH₃); HREIMS m/z 461.2625 [M]⁺ (461.2520 calcd. for C₃₀H₃₉NO₃).

6-Benzoyloxy-2-((4',8'-dimethyl)ethylnona-3',7'-dienoate)-2-methyl-dihydro-benzopyran (14). ¹H NMR (300 MHz, CDCl₃): δ_H 7.33 (m, 5H, H-2'' to H-6''), 6.70 (m, 1H, H-7'), 6.68 (m, 3H, H-5, 7, 8), 5.14 (t, J = 6 Hz, 1H, H-3'), 4.98 (s, 2H, OCH₂Ar), 4.18 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 2.73 (t, J = 6.8 Hz, 2H, CH₂-4), 2.26 (q, J = 7.5 Hz, 2H, CH₂-6'), 2.10 (m, 4H, CH₂-2', 5'), 1.82 (s, 3H, CH₃-10'), 1.76 (q, J = 6.8 Hz, 2H, CH₂-3), 1.63 (m, 2H, CH₂-1'), 1.60 (s, 3H, CH₃-11'), 1.28 (s, 3H, CH₃-12'), 1.26 (t, J = 7.1 Hz, 3H, OCH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 168.2 (CO), 152.1 (C-6), 148.1 (C-8a), 141.8 (CH-7'), 137.5 (C-1''), 134.1 (C-4'), 128.5 (CH-2'', 6''), 127.8 (C-8'), 127.7 (CH-4''), 127.5 (CH-3'', CH-5''), 125.0 (CH-3'), 121.7 (C-4a), 117.7 (CH-7), 115.1 (CH-5), 114.3 (CH-8), 75.6 (C-2), 70.6

(OCH₂Ar), 60.3 (OCH₂CH₃), 39.2 (CH₂-1'), 38.2 (CH₂-5'), 30.9 (CH₂-3), 27.2 (CH₂-6'), 24.1 (CH₃-12'), 22.4 (CH₂-4), 22.1 (CH₂-2'), 15.9 (CH₃-11'), 14.3 (OCH₂CH₃), 12.4 (CH₃-10'); HREIMS m/z 462.2729 [M]⁺ (462.2770 calcd. for C₃₀H₃₈O₄).

6-Benzoyloxy-2-methyl-2-((4',8'-dimethyl)-N-phenylnona-3',7'-dienamide)-dihydro-benzopyran (15). ¹H NMR (300 MHz, CDCl₃): δ_H 7.54 (d, J = 8.7 Hz, 2H, H-2''', 6'''), 7.36 (m, 7H, H-3''', 5''' and H-2'' to H-6''), 7.14 (m, 1H, H-4'''), 6.72 (m, 3H, H-5, H-7, H-8), 6.37 (dt, J = 7.1 Hz, 1.3 Hz, 1H, H-7'), 5.18 (t, J = 7 Hz, 1H, CH-3'), 4.98 (s, 2H, OCH₂Ar), 2.73 (t, J = 6.7 Hz, 2H, CH₂-4), 2.28 (m, 2H, CH₂-6'), 2.12 (m, 4H, CH₂-2', 5'), 1.93 (s, 3H, CH₃-10'), 1.78 (m, 2H, CH₂-3), 1.64 (m, 2H, CH₂-1'), 1.62 (s, 3H, CH₃-11'), 1.27 (s, 3H, CH₃-12'); ¹³C NMR (75 MHz, CDCl₃): δ_C 167.6 (CO), 152.1 (C-6), 148.0 (C-8a), 138.1, 137.5 (C-1'', C-1'''), 136.1 (CH-7'), 134.0 (C-4'), 132.0 (C-8'), 129.0, 128.5, 127.8, 127.5 and 125.2 (CH-Ar), 124.2 (CH-3'), 121.7 (C-4a), 120.0 (CH-2''', 6'''), 117.1 (CH-7), 115.2 (CH-5), 114.4 (CH-8), 75.6 (C-2), 70.7 (OCH₂Ar), 39.2 (CH₂-1'), 38.4 (CH₂-5'), 31.1 (CH₂-3), 26.9 (CH₂-6'), 24.1 (CH₃-12'), 22.7 (CH₂-4), 22.5 (CH₂-2'), 15.8 (CH₃-11'), 12.9 (CH₃-10'); HREIMS m/z 509.2953 [M]⁺ (509.2930 calcd. for C₃₄H₃₉NO₃).

4.1.5. General procedure for synthesis of eleven- and thirteen-carbon side chain prenylated benzopyrans: “*trans*-δ-tocotrienolic acid” analogs **17-21** (series 3)

Following the same methodology described to synthesize compound **6**, the prenylated benzopyran **17** was prepared by reacting aldehyde **11** with a solution of isopropenylmagnesium bromide. Intermediate **16** was treated directly with triethylorthoacetate, to give compound **17** (50%) as a colorless oil. For the preparation of compounds **20**, prenylated benzopyran “*trans*-δ-tocotrienolic acid” type, the same procedure was followed as that used for the synthesis of compound **12** (63%) as a colorless oil. The amidation from compound **20** to give compound **21** (23 %) as a colorless oil was carried out following the procedure described to synthesize compound **7** (Schemes 2, 3 and 4).

2-((4',8'-Dimethyl)ethylundeca-3',7'-dienoate)-2-methyl-6-propoxydihydro-benzopyran
(17). ¹H NMR (300 MHz, CDCl₃): δ_H 6.75 (m, 3H, H-5, 7, 8), 5.10 (m, 2H, H-3', 7'), 4.11 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 3.84 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 2.73 (t, *J* = 6.8 Hz, 2H, CH₂-4), 2.30 (m, *J* = 4H, CH₂-9', 10'), 2.10 (m, 6H, CH₂-2', 5', 6'), 1.80 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.59 (s, 6H, CH₃-12', 13'), 1.27 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.24 (s, 3H, CH₃-14'), 1.00 (t, *J* = 7.4 Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 173.5 (CO), 152.3 (C-6), 147.8 (C-8a), 135.0 (C-8'), 133.3 (C-4'), 125.0 (CH-7'), 124.2 (CH-3'), 121.6 (C-4a), 117.7 (CH-7), 114.8 (CH-5), 114.0 (CH-8), 75.6 (C-2), 70.1 (OCH₂CH₂CH₃), 60.2 (OCH₂CH₃), 39.5 (CH₂-1'), 39.3 (CH₂-5'), 34.7 (CH₂-10'), 33.3 (CH₂-9'), 31.0 (CH₂-3), 26.5 (CH₂-6'), 24.1 (CH₃-14'), 22.7 (CH₂-4), 22.4 (OCH₂CH₂CH₃), 22.1 (CH₂-2'), 15.9, 15.8 (CH₃-12', 13'), 14.2 (OCH₂CH₃), 10.5 (OCH₂CH₂CH₃); HREIMS *m/z* 442.3123 [M]⁺ (442.3083 calcd. for C₂₈H₄₂O₄).

2-((4',8'-Dimethyl)undeca-3',7'-dien-11'-ol)-2-methyl-6-propoxydihydrobenzopyran
(18). ¹H NMR (500 MHz, CDCl₃): δ_H 6.70 (m, 3H, H-5, 7, 8), 5.12 (m, 2H, H-3', 7'), 3.84 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 3.61 (t, *J* = 6.4 Hz, 2H, CH₂-11), 2.73 (t, *J* = 6.7 Hz, 2H, CH₂-4), 2.30 (m, 4H, CH₂-9', 10'), 2.10 (m, 6H, CH₂-2', 5', 6'), 1.80 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.59 (s, 6H, CH₃-12', 13'), 1.28 (s, 3H, CH₃-14'), 1.01 (t, *J* = 7.4 Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃): δ_C 152.3 (C-6), 147.8 (C-8a), 135.0 (C-8'), 133.3 (C-4'), 124.7 (CH-7'), 124.3 (CH-3'), 121.6 (C-4a), 117.7 (CH-7), 114.8 (CH-5), 114.1 (CH-8), 75.6 (C-2), 70.1 (OCH₂CH₂CH₃), 62.8 (CH₂-11'), 39.5 (CH₂-1'), 39.3 (CH₂-5'), 36.0 (CH₂-9'), 31.0 (CH₂-3), 30.7 (CH₂-10'), 26.4 (CH₂-6'), 24.2 (CH₃-14'), 22.7 (CH₂-4), 22.4 (OCH₂CH₂CH₃), 22.2 (CH₂-2'), 15.9 (CH₃-12', 13'), 10.6 (OCH₂CH₂CH₃); HREIMS *m/z* 400.3048 [M]⁺ (400.2977 calcd. for C₂₆H₄₀O₃).

2-((4',8'-Dimethyl)undeca-3',7'-dienal)-2-methyl-6-propoxydihydrobenzopyran (19).
¹H NMR (500 MHz, CDCl₃): δ_H 9.8 (d, *J* = 1.6 Hz, CHO-11'), 6.68 (m, 3H, H-5, 7, 8), 5.14

(m, 2H, H-3', 7'), 3.84 (t, $J = 6.6$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.73 (t, $J = 6.8$ Hz, 2H, CH_2 -4), 2.50 (dt, $J = 7.6$ Hz, 1.6 Hz, 2H, CH_2 -10'), 2.30 (t, $J = 7.5$ Hz, 2H, CH_2 -9'), 2.10 (m, 6H, CH_2 -2', 5', 6'), 1.80 (m, 6H, CH_2 -3, $\text{OCH}_2\text{CH}_2\text{CH}_3$, CH_2 -1'), 1.60 (s, 3H, CH_3 -12'), 1.57 (s, 3H, CH_3 -13'), 1.27 (s, 3H, CH_3 -14'), 1.01 (t, $J = 7.4$ Hz, 3H, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 202.6 (CO), 152.4 (C-6), 147.7 (C-8a), 133.1 (C-8' and C-4'), 125.3 (CH-7' and CH-3'), 121.6 (C-4a), 117.6 (CH-7), 114.8 (CH-5), 114.1 (CH-8), 75.5 (C-2), 70.1 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 42.1 (CH_2 -10'), 39.1 (CH_2 -1', 5'), 31.7 (CH_2 -9'), 31.0 (CH_2 -3), 30.7 (CH_2 -10'), 26.4 (CH_2 -6'), 24.2 (CH_3 -14'), 22.7 (CH_2 -4), 22.4 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 22.2 (CH_2 -2'), 16.0 (CH_3 -12', 13'), 10.5 ($\text{OCH}_2\text{CH}_2\text{CH}_3$); HREIMS m/z 398.2913 $[\text{M}]^+$ (398.2821 calcd. for $\text{C}_{26}\text{H}_{38}\text{O}_3$).

2-Methyl-6-propoxy-2-((4',8',12'-trimethyl)ethyltrideca-3',7',11'-trienoate)-dihydrobenzopyran (20). ^1H NMR (400 MHz, CDCl_3): δ_{H} 6.72 (dt, $J = 7.3$ Hz, 1.4 Hz, H-11'), 6.65 (m, 3H, H-5, 7, 8), 5.15 (dt, $J = 5.7$ Hz, 1.2 Hz, 2H, H-7', H-3'), 4.18 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.84 (t, $J = 6.6$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.73 (t, $J = 6.8$ Hz, 2H, CH_2 -4), 2.25 (q, $J = 7.5$ Hz, 2H, CH_2 -10'), 2.08 (m, 8H, CH_2 -2', 5', 6', 9'), 1.83 (s, 3H, CH_3 -14'), 1.77 (m, 6H, CH_2 -3, $\text{OCH}_2\text{CH}_2\text{CH}_3$, CH_2 -1'), 1.60 (s, 6H, CH_3 -15', 16'), 1.30 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.27 (s, 3H, CH_3 -17'), 1.02 (t, $J = 7.4$ Hz, 3H, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 168.1 (CO), 152.3 (C-6), 147.7 (C-8a), 141.8 (CH-11'), 134.9 (C-8'), 133.8 (C-4'), 127.6 (C-12'), 125.0 (CH-7'), 124.2 (CH-3'), 121.5 (C-4a), 117.7 (CH-7), 114.8 (CH-5), 114.0 (CH-8), 75.5 (C-2), 70.0 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 60.3 (OCH_2CH_3), 39.5 (CH_2 -1'), 39.3 (CH_2 -5'), 38.2 (CH_2 -9'), 31.0 (CH_2 -3), 27.3 (CH_2 -10'), 26.5 (CH_2 -6'), 24.1 (CH_3 -17'), 22.7 (CH_2 -4), 22.5 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 22.1 (CH_2 -2'), 15.9 (CH_3 -15', 16'), 14.2 (OCH_2CH_3), 12.3 (CH_3 -14'), 10.5 ($\text{OCH}_2\text{CH}_2\text{CH}_3$); HREIMS m/z 482.2538 $[\text{M}]^+$ (482.2402 calcd. for $\text{C}_{31}\text{H}_{46}\text{O}_4$).

2-Methyl-2-(N-phenyl(4',8',12'-trimethyl)trideca-3',7',11'-trienamide)-6-propyloxy-dihydrobenzopyran (21). ¹H NMR (300 MHz, CDCl₃): δ_H 7.42 (m, 5H, H-2" to 6"), 6.65 (m, 3H, H-5, 7, 8), 6.37 (dt, *J* = 7.1 Hz, 1.3 Hz, 1H, H-11'), 5.15 (t, *J* = 7.2 Hz, 2H, H-3', H-7'), 3.83 (t, *J* = 6.6 Hz, 2H, OCH₂CH₂CH₃), 2.73 (t, *J* = 6.8 Hz, 2H, CH₂-4), 2.25 (q, *J* = 7.5 Hz, 2H, CH₂-10'), 2.08 (m, 8H, CH₂-2', 5', 6', 9'), 1.83 (s, 3H, CH₃-14'), 1.77 (m, 6H, CH₂-3, OCH₂CH₂CH₃, CH₂-1'), 1.60 (s, 3H, CH₃-15'), 1.59 (s, 3H, CH₃-16'), 1.27 (s, 3H, CH₃-17'), 1.00 (t, *J* = 7.4 Hz, 3H, OCH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ_C 168.2 (CO), 152.4 (C-6), 147.8 (C-8a), 141.8 (CH-11'), 134.9 (C-8'), 133.8 (C-4'), 129.0, 127.8 and 125.2 (CH-Ar), 127.6 (C-12'), 125.0 (CH-7'), 124.2 (CH-3'), 121.5 (C-4a), 117.7 (CH-7), 114.8 (CH-5), 114.0 (CH-8), 75.5 (C-2), 70.0 (OCH₂CH₂CH₃), 39.5 (CH₂-1'), 39.3 (CH₂-5'), 38.2 (CH₂-9'), 31.0 (CH₂-3), 27.3 (CH₂-10'), 26.5 (CH₂-6'), 24.1 (CH₃-12'), 22.7 (CH₂-4), 22.5 (OCH₂CH₂CH₃), 22.1 (CH₂-2'), 15.9 (CH₃-15', 16'), 12.3 (CH₃-17'), 10.5 (OCH₂CH₂CH₃); HREIMS *m/z* 529.2416 [M]⁺ (529.2230 calcd. for C₃₅H₄₇NO₃).

4.2. Evaluation of PPAR Activity by Transactivation Assays

PPAR transcriptional activity of synthesized compounds was performed using a human chimera PPAR/Gal4 gene reporter luciferase system to obtain the maximal transactivation response for each compound at 10 μM dose and compared with WY-14,643 (pirinixic acid, Sigma-Aldrich, St. Louis, MO) at 10 μM for PPARα or rosiglitazone (Sigma-Aldrich) at 1 μM for PPARγ. Cos-7 cells (CRL-1651, ATCC, Manassas, VA) were maintained under standard culture conditions (Dulbecco's modified Eagle's minimal essential medium: DMEM supplemented with 10% fetal calf serum [FCS], Thermo Fisher Scientific, Waltham, MA) at 37°C in a humidified atmosphere of 5% CO₂. The medium was changed every 2 days. Cells (5.5 × 10⁵ cells/mL) were seeded in 60-mm dishes in DMEM supplemented with 10% FCS and incubated at 37°C for 16 h prior to transfection. Cells were transfected in DMEM with the jetPEI transfection reagent (Polyplus-Transfection S.A.,

Strasbourg, France) using the reporter plasmid pG5-TK-pGL3 in combination with one of the expression plasmids, pGal4hPPAR α or pGal4hPPAR γ . The pCMV- β -galactosidase expression plasmid was included as a control of transfection efficiency. The transfection was stopped after 16 h by the addition of DMEM supplemented with 10% FCS, and cells were detached with trypsin and re-seeded in 96-well plates and incubated for 6 h in DMEM containing 10% FCS. Cells were then incubated for 24 h in DMEM containing 0.2% FCS and increasing concentrations of the compound tested or vehicle (dimethylsulfoxide, DMSO, 0.1% final concentration). At the end of the experiment, cells were washed once with ice-cold phosphate-buffered saline (PBS) and lysed, and luciferase and β -galactosidase activity was measured. Each experiment was achieved in triplicate, and mean \pm standard error (SEM) values were calculated using GraphPad Prism 5 Software.

Molecular Modeling. Molecular docking simulation was performed to localize the ligand **15** in the binding pocket of PPAR γ and molecular interactions. The 3D crystal structure of PPAR γ in complex with rosiglitazone (PDB code: 4EMA) and PPAR α in complex with WY-14,643 (PDB code: 4BCR) were retrieved from RCSB Protein Data Bank (PDB, <https://www.rcsb.org>). USCF Chimera software²⁸ was used for ligand and protein preparation. Solvent molecules were removed, while hydrogens and Gasteiger charges were added.²⁹ Docking simulations were performed with AutoDock Vina tool, and the results obtained were analyzed with USCF Chimera. The ligand/protein complex was considered stable when the values of the binding free energy ($\Delta G_{\text{ligand-residue}}$) were lower than -5 Kcal/mol.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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