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Synthesis of 2-Prenylated Alkoxyated Benzopyrans by Horner-Wadsworth-Emmons olefination with PPAR α / γ Agonist Activity

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ABSTRACT: We have synthesized series of 2-prenylated benzopyrans as analogs of the natural polycerasoidol, a dual PPAR α / γ agonist with anti-inflammatory effect. The prenylated side chain consists of five- or nine-carbons with an α -alkoxy- α,β -unsaturated ester moiety. Prenylation was introduced via Grignard reaction, followed by Johnson-Claisen rearrangement, and the α -alkoxy- α,β -unsaturated ester moiety by the Horner-Wadsworth-Emmons reaction. Synthetic derivatives showed high efficacy to activate both hPPAR α and hPPAR γ as dual PPAR α / γ agonists. These prenylated benzopyrans emerge as lead compounds potentially useful for preventing cardiometabolic diseases.

KEYWORDS: Prenylated benzopyrans, Horner-Wadsworth-Emmons reaction, PPAR α / γ activity

Among nuclear receptor family, peroxisome proliferator activated receptors (PPARs) are transcription factors activated by ligands, which are implicated in numerous cell functions including glucose and lipid metabolism, and inflammation.¹ Dual PPAR α / γ activators can improve atherogenic dyslipidemia and insulin resistance.¹ Polycerasoidol is a *trans*- δ -tocotrienolic acid analog² isolated from *Polyalthia cerasoides* (Annonaceae).^{3,4} Polycerasoidol, containing a 6-chromanol nucleus and a 2-prenylated side chain, is biosynthesized from homogentisate and geranylgeranyl pyrophosphate via the shikimate and the mevalonate pathway, respectively. Pharmacologically, it displays dual PPAR α / γ agonist activity and ameliorates inflammation of dysfunctional endothelium.⁵ In structural terms, this natural benzopyran possesses a benzopyran nucleus (lipophilic tail), a prenylated chain (flexible linker), and a carboxylic acid (polar head), as other natural and synthetic PPAR α and/or PPAR γ agonists.⁶ The structure-activity relationships (SAR) of polycerasoidol and semisynthetic analogs revealed that the 6-oxygenated dihydrobenzopyran core and the linker hydrocarbon chain of at least a five-carbon length are essential moieties to activate PPAR α and/or PPAR γ .⁷ It is noteworthy that chroman-6-ol pharmacophore is present in troglitazone, the first PPAR γ agonist belonging to the class of thiazolidinediones, which was approved as anti-diabetic agent.^{8,9} Currently, rosiglitazone and pioglitazone are selective PPAR γ agonists used to manage hyperglycemia in type 2 diabetes, while saroglitazar and lobeglitazone are PPAR α / γ activators (agonists) approved against diabetes in India and South Korea, respectively.⁹ In order to find new active and safer PPAR activators, we describe

the synthesis and PPAR activity of 2-prenylated benzopyrans that bear an α -alkoxy- α,β -unsaturated ester as a tri-oxygenated polar head on the prenylated side chain.

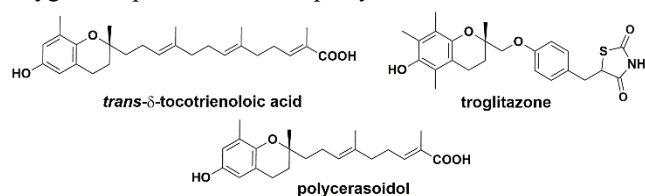
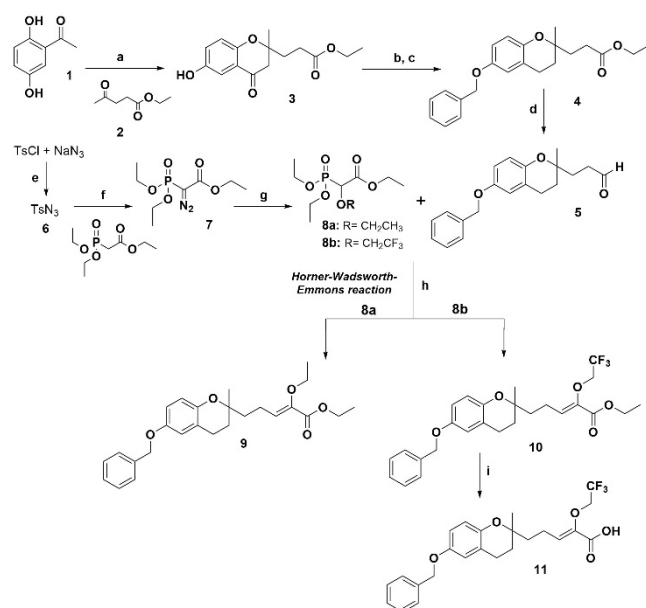


Figure 1. Bioactive prenylated benzopyrans.

We first prepared the benzopyran-4-one nucleus (γ -benzopyrone **3**) by conventional methods.¹⁰ The reaction mechanism consists of an aldol condensation between the enolate from an *ortho*-hydroxyacetophenone and the carbonyl group from an alkyl ketone. This is followed by an intramolecular cyclisation via Michael addition, which is promoted by the *ortho*-phenol group.¹¹ Thus, 2,5-dihydroxyacetophenone (**1**) and ethyl levulinate (**2**) in the presence of pyrrolidine gave the chroman-4-one **3** as a racemic mixture in a single step with a good yield (80 %) (Figure 2).^{7,10} γ -Benzopyrone **3** was reduced under Clemmensen conditions and the phenol hydroxyl group at 6-position was protected by *O*-benzylation to give compound **4** with a good overall yield. The controlled reduction of the ester function by DIBAL-H at -78°C gave the aldehyde **5** with a 92 % yield. In a first approach, we synthesized five-carbon side chain alkoxyated prenylated benzopyrans (series 1) from aldehyde intermediate **5** by Horner-Wadsworth-Emmons olefination. For this purpose, appropriate

alkylphosphonates, e.g., ethyl 2-(diethoxyphosphoryl)-2-ethoxyacetate (**8a**) and ethyl 2-(diethoxyphosphoryl)-2-(2,2,2-trifluoroethoxy)acetate (**8b**), were previously prepared from (ethoxyacetate) diethoxyphosphorane and TsN₃ (**6**) in the presence of NaH.¹² Then, aldehyde intermediate **5** was reacted with phosphonate **8a** or **8b** to afford the α -alkoxy- α,β -unsaturated esters of prenylated benzopyrans **9** (20 %, *Z/E*= 60:40) or **10** (84 %, *Z/E*= 35:65), respectively. The saponification of ethyl ester (**10**) quantitatively afforded carboxylic acid (**11**, *Z/E*= 40:60) (Scheme 1).

Scheme 1. Synthesis of prenylated benzopyrans **9-11** (series 1).^a

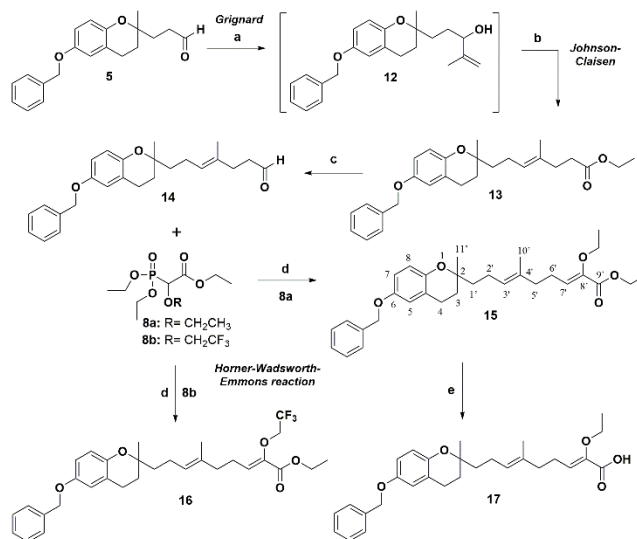


^a Reaction conditions: (a) Pyrrolidine, EtOH, 60 °C, molecular sieve 3Å, 24h, 80 %; (b) Zn/HCl, AcOH-H₂O, rt, 2h; (c) ClCH₂C₆H₅, K₂CO₃, EtOH, 60 °C, 5h, 90 %; (d) DIBAL-H, CH₂Cl₂, -78 °C, N₂, 20 min, 92 %; (e) 0 °C, acetone, 2h, 81 %; (f) 60 % NaH, THF, 0 °C, N₂, 16h, 65 %; (g) EtOH, Rh(OAc)₂, toluene, 45 °C, overnight, **8a** (R = CH₂CH₃), 40.2 % or **8b** (R = CH₂CF₃), 51 %; (h) Phosphonate **8a** or **8b**, THF, NaH, 0 °C, N₂, 1h + **5**, THF, rt, overnight: **9**, 20 % or **10**, 84 %; (i) 20 % KOH, reflux, 5h, 99 %.

In a second approach, we synthesized the nine-carbon side chain *O*-alkoxylated prenylated benzopyrans (series 2) **15**, **16** and **17** from aldehyde intermediate **5**. The prenylated side chain at the 2-position of the dihydrobenzopyran nucleus was elongated with a sequence of Grignard reaction, Johnson-Claisen rearrangement and Horner-Wadsworth-Emmons olefination (Scheme 2). The aldehyde synthon **5** was treated with isoprenylmagnesium bromide as the vinyl Grignard reagent, followed by Johnson-Claisen rearrangement of allylic alcohol **12** using ethyl orthoacetate to produce unsaturated ester **13** with a 50 % yield in the last two steps. Ester **13** was subjected to a controlled reduction using DIBAL-H at -78 °C to give the aldehyde intermediate **14** in 89 % yield. The α -alkoxy- α,β -unsaturated ester on the prenylated side chain was introduced by a Horner-Wadsworth-Emmons reaction.¹³ Thus, aldehyde **14** was treated with phosphonates **8a** and **8b** to afford esters **15** (85

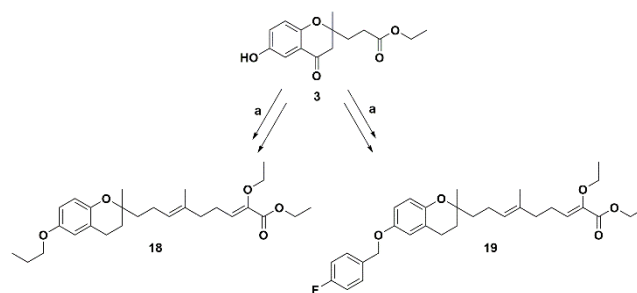
%) and **16** (82 %), respectively.¹⁴ It is noteworthy that ester **15** was obtained as *Z*-alkene isomer exclusively. Once again, the saponification of ethyl ester **15** quantitatively yielded carboxylic acid **17** (Scheme 2). In addition to *O*-benzyloxy benzopyrans bearing a nine-carbon prenylated alkoxy side chain (series 2), we accomplished the synthesis of its *O*-propyloxy and *O*-*p*-fluorobenzyloxy benzopyran analogs. According to the second approach followed to prepare ester **15**, but starting from the chroman-4-one **3**, we synthesized *O*-propyloxy ester **18** and *O*-*p*-fluorobenzyloxy ester **19** (Scheme 3).

Scheme 2. Synthesis of prenylated benzopyrans **15-17** (series 2).^a



^a Reaction conditions: (a) CH₃C(MgBr)=CH₂, THF, -78 °C, N₂, 1h, 84 %; (b) MeC(OEt)₃, isobutyric acid, 140 °C, 2h, 50 %; (c) DIBAL-H, CH₂Cl₂, -78 °C, N₂, 20 min, 89 %; (d) Phosphonate **8a** or **8b**, THF, NaH, 0 °C, N₂, 1h + **14** in THF, rt, overnight: **15** (R = CH₂CH₃), 85 % or **16** (R = CH₂CF₃), 82 %; (e) 20 % KOH, reflux, 5h, 99 %.

Scheme 3. Synthesis of prenylated benzopyrans **18** and **19**.^a



^a Reaction conditions: (a) See reagents and conditions described in Scheme 1 for synthesis of **5**, and Scheme 2 for synthesis of **15** and **16**.

The transactivation studies¹⁵ of the synthesized benzopyrans were carried out and compared to the maximal efficacy of WY-14,643 (at 10 μM) or rosiglitazone (at 1 μM) as hPPAR α and hPPAR γ reference compounds, respectively. At

the 10 μM dose, compounds **10**, **15**, **16** and **18** were moderate hPPAR activators for both receptors, while compounds **11**, **17** and **19** showed high efficacy as dual hPPAR α/γ agonists. Indeed, compound **11** showed higher efficacy to activate hPPAR α than PPAR γ (α/γ ratio= 1.73), and **17** displayed slight selectivity towards hPPAR γ (α/γ ratio= 0.64). Therefore, the elongation of the side chain from five- to nine-carbons is beneficial to activate hPPAR γ . In agreement with previous docking analysis of polycerasoidol, the carboxylic moiety at the C-9' position of **17** plays a key role as an anchoring point to bind PPAR γ receptor.⁵

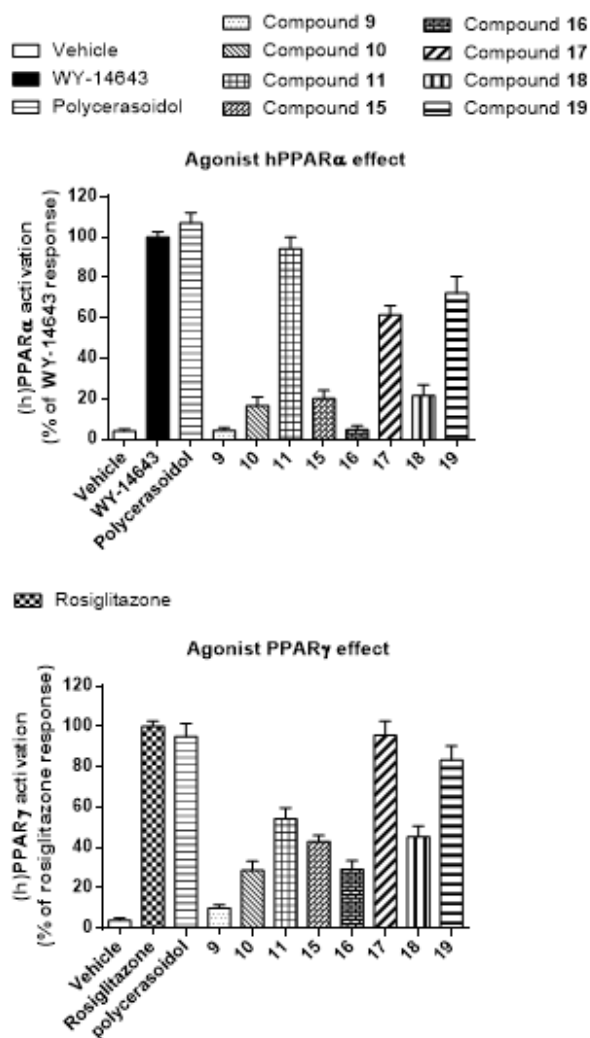


Figure 2. hPPAR α and hPPAR γ transactivation assays. Synthesized benzopyrans were tested at 10 μM , and WY-14,643 (10 μM) and rosiglitazone (1 μM), as reference compounds for α and γ , respectively.

In conclusion, we efficiently prepared new series of the 2-prenylated *O*-alkoxylated benzopyrans possessing the α -alkoxy- α,β -unsaturated moiety on the prenylated chain by the Horner-Wadsworth-Emmons reaction. Synthetic derivatives were efficient in activating both hPPAR α and hPPAR γ as dual PPAR α/γ agonists. These prenylated benzopyrans emerge as lead compounds that might be potentially useful for preventing cardiometabolic diseases.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

PPARs, Peroxisome proliferator-activated receptors; SAR, structure-activity relationships; DIBAL-H, Diisobutylaluminium hydride; TsN₃, Tosyl azide.

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