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Synthesis of a new 2-prenylated quinoline as potential drug for metabolic syndrome with pan-PPAR activity and anti-inflammatory effects

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ABSTRACT

We have previously reported the total synthesis and structure–activity relationships (SAR) of 2-prenylated benzopyrans with PPAR agonist activity. Herein, we have described the synthesis and PPAR activity of 2-prenylated benzopyrans and 2-prenylated quinolines. The benzopyran nucleus was generated via enamine-catalyzed Kabbe condensation, and the quinoline nucleus via Friedländer condensation. Results demonstrated that both benzopyran (**5a**) and quinoline (**4b**) derivatives bearing a γ,δ-unsaturated ester displayed a pan-PPAR agonism. They were full PPARα agonists, but showed different preferences for PPARγ and PPARβ/δ activation. It was noteworthy that quinoline **4b** displayed full hPPARα activation (2-fold than WY-14,643), weak PPARβ/δ and partial PPARγ activation. In addition, quinoline **4b** showed anti-inflammatory effects on macrophages by reducing LPS-induced expression of both *MCP-1* and *IL-6*. Therefore, **4b** emerges as a first-in-class promising hit compound for the development of potential therapeutics aimed at treating metabolic syndrome, metabolic dysfunction-associated fatty liver disease (MAFLD), and its associated cardiovascular comorbidities.

Metabolic syndrome, a disorder characterized by the concurrent presence of several cardiovascular risk factors, is highly prevalent in Western countries. This multifactorial disorder is associated with the development of type 2 diabetes, cardiovascular disease, and cancer among other chronic diseases.[1] Research suggests that metabolic syndrome is associated with low-grade systemic inflammation,[2] which is a key factor in the development of premature atherosclerosis. In turn, this contributes to the pathogenesis of both myocardial and cerebral ischemic disorders. Peroxisome proliferator-activated receptors (PPARs), a class of transcription factors belonging to the nuclear receptor superfamily, comprise three isoforms: PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3),[3] which play crucial roles in regulating lipid and glucose metabolism as well as inflammatory processes.[4] Upon activation by endogenous ligands (fatty acids and derivatives) or synthetic agonists (fibrates and thiazolidinediones), PPARs heterodimerize with 9-*cis*-retinoic acid receptors (RXRs) to regulate the expression of multiple target genes involved in adipogenesis, lipid and glucose metabolism, metabolic homeostasis, cell growth, differentiation and apoptosis.[5,6] Consequently, PPARs have attracted considerable attention because of their ability to manage metabolic diseases, including metabolic syndrome, type 2 diabetes, atherogenic dyslipidemia, but also metabolic dysfunction-associated fatty liver disease (MAFLD).[5,7] Studies have demonstrated that dual- or pan-PPAR activators are more effective than selective PPAR agonists for treating both lipid and glycaemic imbalances in individuals with type 2 diabetes and metabolic syndrome.[8,9] Clinical trials have indicated that PPARγ-selective agonists or dual-PPAR agonists with strong PPARγ activation produce adverse effects, resulting in their removal from the market or their restricted use. These adverse effects have been attributed primarily to off-target responses or excessive PPARγ activation and have prompted the development of partial agonists of this receptor subtype. Recently, the beneficial effects of pan-PPAR activators have been observed in the treatment of MAFLD

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and non-alcoholic steatohepatitis (NASH),[10] two unfulfilled clinical needs. Nowadays, the discovery of new pan-PPAR agonists, as safer and more effective drugs for metabolic syndrome-related pathologies, is attracting the attention of medicinal chemists.

We have previously reported that polycerasoidol (Fig. 1) exerts dual PPARα/γ full agonism with anti-inflammatory effects,[11] and also explored the structure–activity relationship (SAR) of 2-prenylated benzopyrans for PPAR activity.[12–14] We recently described a new 2-prenylated benzopyran (BP-2) (Fig. 1) with pan-PPAR activity, a potent anti-inflammatory effect and capable of improving metabolic derangements in *ob/ob* mice.[15] Benzopyran is analogous to quinoline nucleus, being related by replacement of oxygen atom by nitrogen. The quinoline heterocycle or benzo[*b*]pyridine is a valuable drug chemical scaffold that has demonstrated a wide range of biological functions.[16] In this study, we report the synthesis and PPAR activity of both 2-prenylated benzopyrans (*series a*) and 2-prenylated quinolines (*series b*) bearing a chroman-6-ol or quinoline-6-ol nucleus, respectively, linked at 2-position to a hydrocarbon side chain which contains one isoprenoid unit.

In a first approach (*series a*), we prepared the benzopyran-4-one nucleus by conventional methods[17] via an aldol condensation followed by an intramolecular *oxo*-Michael addition (Scheme 1). The reaction between 2,5-dihydroxyacetophenone and ethyl levulinate in the presence of pyrrolidine afforded 2-substituted chroman-4-one **1a**, which was reduced under modified Clemmensen conditions to give the benzodihydropyran (chromane) **2a**. The phenol group at the 6-position was *O*-protected by benzyl chloride under basic conditions to give *O*-benzylated benzopyran ester **3a**, which was treated with DIBAL-H at −78 °C to achieve the aldehyde **4a**. The aldehyde **4a** reacted with the Grignard reagent, propenylmagnesium bromide, to obtain an allylic alcohol intermediate, which, after heating with trialkyl orthoacetate under mildly acidic conditions, produced the γ,δ-unsaturated ester **5a** *via* a Jonson-Claisen rearrangement. Next, we prepared its *O*-alkoxylated analogue via Horner-Wadsworth-Emmons (HWE) olefination. The aldehyde **4a** reacted with the *O*-alkoxyphosphonate derivative using NaH. The *O*-alkoxyphosphonates (**6a** and **7a**) were prepared in two steps from triethyl phosphonoacetate, which was treated with tosyl azide (diazo transfer) to obtain the ethyl α-diazo-α-(diethoxyphosphoryl)acetate, and subsequently, the α-diazo-β-ketophosphonates reacted with ethanol or trifluoroethanol in the presence of rhodium (II) acetate dimer as catalysts.[18].

In a second approach (*series b*), we synthetised a 2-prenylated quinoline analogue *via* Friedländer condensation to generate the benzo[*b*]pyridine nucleus (Scheme 2). The synthesis was initiated by the *O*-benzylation of the 5-hydroxy-2-nitrobenzaldehyde using benzyl chloride in a basic medium to obtain the 5-benzyloxy-2-nitrobenzaldehyde. Next, the *ortho*-nitrobenzaldehyde was reduced to *ortho*-aminobenzaldehyde (**1b**) using iron powder in aqueous HCl (5 mol %). The quinoline nucleus was then obtained through a Friedländer reaction, which involves the condensation of the *ortho*-aminobenzaldehyde intermediate **1b** with ethyl levulinate (enolizable ketone) in the presence of pyrrolidine as catalyst.[19] Previously, Friedländer condensation was tried with various catalysts such as pyrrolidine, TABO (1,3,3-trimethyl-6-azabicyclo [3.2.1] octane), NaOH or KOH, and under acidic conditions such as H_2SO_4 or HCl.[20] Optimal results were obtained by previous centrifugation (2,500 rpm) of the *nitro*-reduction mixture reaction, which allowed the elimination of iron solids, and next treating the supernatant with ethyl levulinate and pyrrolidine.[19,21] Under the specified conditions, the enamine promoted Friedländer condensation giving a mixture of the 2-substituted quinoline **2b** (50 %) and its 3-substituted-2-methyl quinoline (36 %) regioisomer in a ratio 1.4:1 via (*E*)- and (*Z*)-Schiff bases, respectively. Quinoline ester **2b** was reduced using the DIBAL-H reagent to obtain aldehyde **3b**.[12] Next, the prenylated hydrocarbon side chain was introduced through an efficient Grignard reaction with isopropenylmagnesium bromide, followed by Johnson-Claisen rearrangement with triethyl orthoacetate and catalytic amounts of isobutyric acid,[12,15] yielding 2-prenylated quinoline **4b**.

The functional activities of 2-prenylated benzopyrans **5a**, **6a**, **7a**, and quinoline **4b** were evaluated by transient transfection assays with pGAL4hPPARα, pGAL4hPPARβ/δ, and pGAL4hPPARγ (Table 1). Activity was defined as the maximal activity (E_{max}) obtained for synthesised compounds at 10 μM, and expressed as a percentage of maximal activity of the reference compounds: WY-14,643 at 10 μM for hPPARα and rosiglitazone or GW501516 at 1 μM for hPPARγ or hPPARβ/δ, respectively. The 2-prenylated benzopyran ethyl ester **5a** (*series a*) and its quinoline analogue **4b** (*series b*) showed pan-PPAR agonism, but different selectivity for hPPARβ/δ and PPARγ isoforms (Table 1, Fig. 2). However, *the O*-alkoxylated derivatives (*series a*: **6a** and **7a**) were inactive. Both benzopyran **5a** and quinoline **4b** were full PPARα agonists, and it is noteworthy that quinoline **4b** showed 2-fold efficacy for hPPARα compared to WY-14,643. Benzopyran **5a** was also able to activate hPPARβ/δ and barely activated hPPARγ, whereas quinoline **4b** partially activated hPPARγ and slightly activated hPPARβ/δ. According to the findings, both benzopyran **5a** exhibited PPAR activity comparable to its previously reported analogue BP-2 (Fig. 1), and replacing an oxygen atom with a nitrogen atom in the quinoline nucleus (**4b**) significantly impacted the affinity for the ligand binding domain (LBD) of hPPARβ/δ, thereby validating the interaction with hPPARγ. Therefore, 2-prenylated quinoline **4b** emerges as a new pan-hPPAR activator, which could be useful in managing lipid and glucose metabolism or MAFDL, without causing serious adverse effects because of its partial hPPARγ agonism.

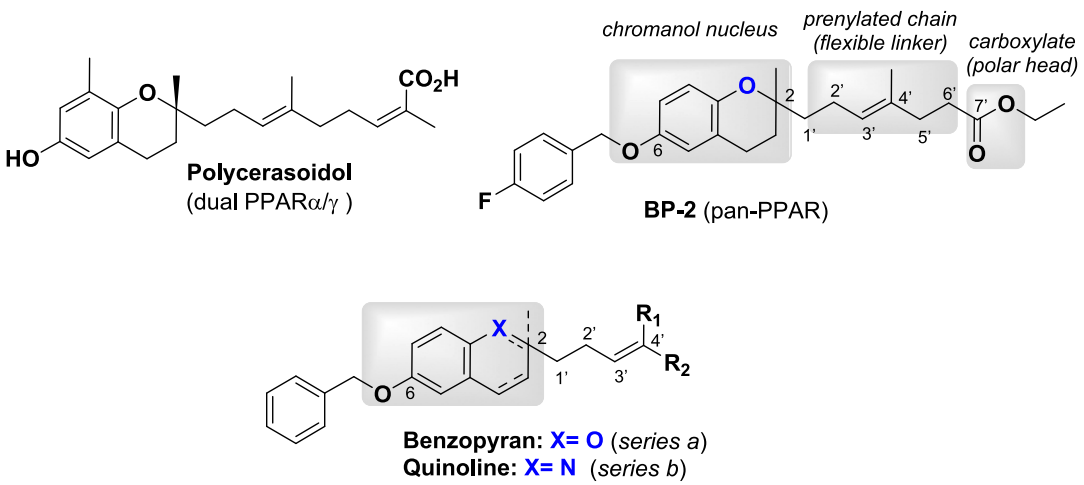
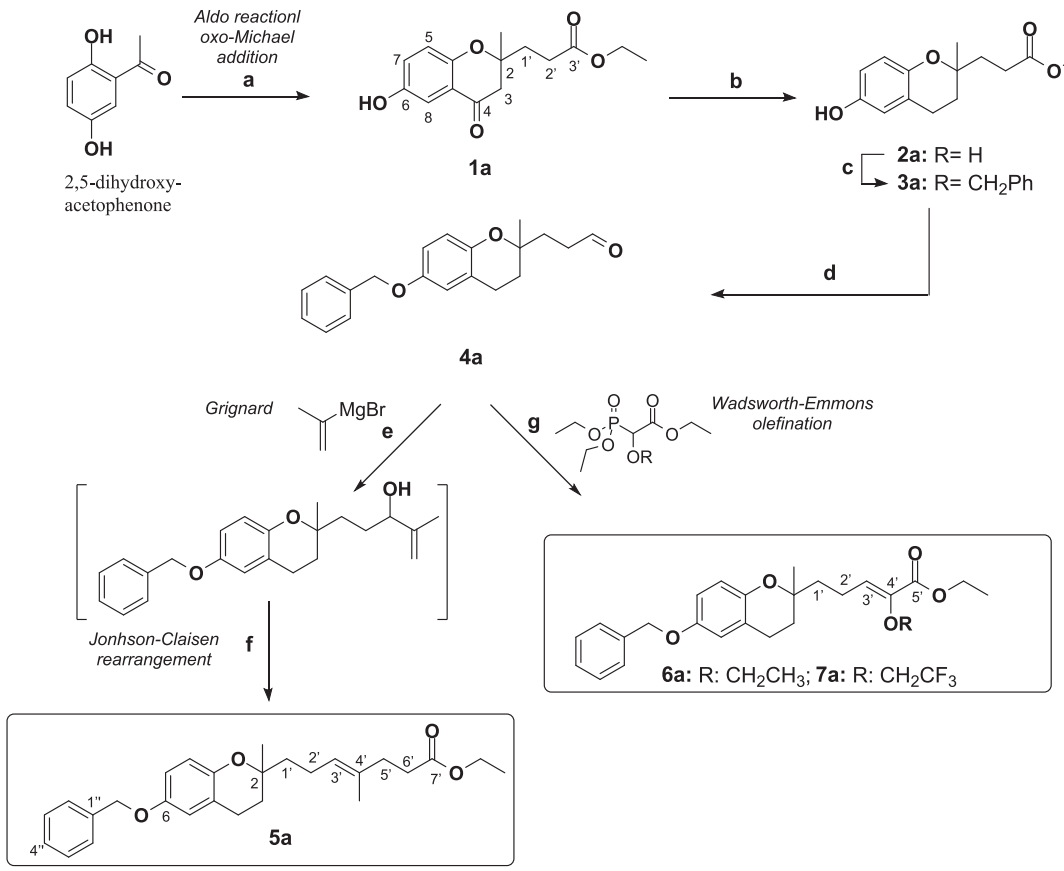
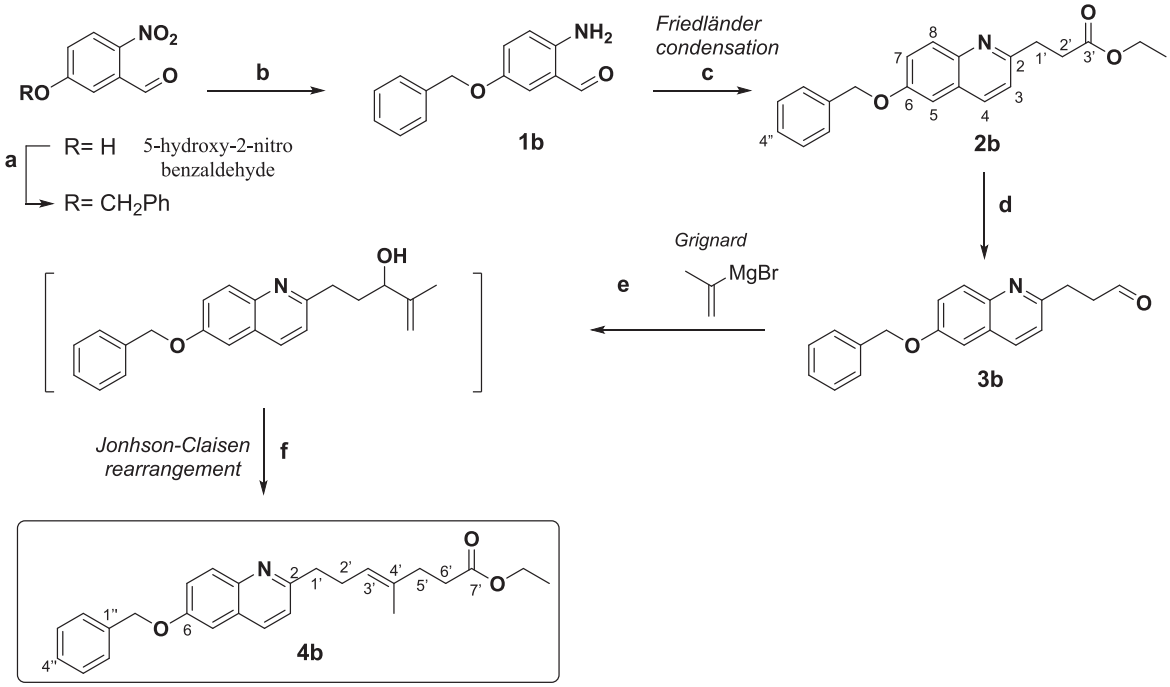


Fig. 1. Natural and synthetic 2-prenylated benzopyrans with PPAR activity, and potential quinoline analogues.



Scheme 1. Synthesis of 2-prenylated benzopyrans (*series a*). *Reagents and conditions:* (a) Pyrrolidine, EtOH, 60 °C, molecular sieve 3A, 24 h (80 %); (b) Zn dust/conc HCl (2:1, v/v), AcOH-H_2O, rt, 2 h; (c) $PhCH_2Cl$, K_2CO_3, CH_3CN, reflux, 5 h (90 %); (d) DIBAL-H, CH_2Cl_2, −78 °C, N_2, 20 min (92 %); (e) THF, −78 °C, N_2, 1 h; (f) MeC$(OEt)_3$, isobutyric acid, 140 °C, 2 h (50 %); (g) Phosphonate (R = CH_2CH_3 or CH_2CF_3), THF, NaH, N_2, 0 °C, 1 h to rt, overnight (30 % for **6a**; 80 % for **7a**).



Scheme 2. Synthesis of 2-prenylated quinoline 3b (*series b*). *Reagents and conditions:* (a) K_2CO_3, $PhCH_2Cl$, DMF, reflux, 4 h (75 %); (b) Fe/HCl, EtOH, reflux, 30 min; (c) Pyrrolidine, EtOH, reflux, 4 h (50 %); (d) DIBAL-H, CH_2Cl_2, −78 °C, 15 min (50 %); (e) 0.5 M $CH_2=C(CH_3)MgBr$, THF, −78 °C, 1 h; (f) MeC$(OEt)_3$, isobutyric acid, 140 °C, 2 h (47 %).

Table 1
Evaluation of agonist activity in cell-based transactivation assays of human PPAR/Gal_4 receptors. EC_{50} values against human PPARα/Gal_4, PPARβ/δ/Gal_4, and PPARγ/Gal_4 receptors.

	Efficacy (%) at 10 μmol/L			EC_{50} (μmol/L)		
Compd	**PPARα**	**PPARβ/δ**	**PPARγ**	**PPARα**	**PPARβ/δ**	**PPARγ**
5a	97	58	28	2.95	2.16	1.59
6a	NA	NA	NA	NA	NA	NA
7a	NA	NA	NA	NA	NA	NA
4b	236	21	73	3.20	1.51	1.92
WY-14,643	100	NA	NA	1.3	NA	NA
GW501516	NA	100	NA	NA	0.9	NA
Rosiglitazone	NA	NA	100	NA	NA	0.1

Efficacy: Emax is the maximal PPAR fold activation relative to the maximum activation obtained with WY-14,643 (10 μM), GW501516 (1 μM), and rosiglitazone (1 μM), corresponding to 100 % activation in the GAL4 chimeric hPPARα, hPPARβ/δ, and hPPARγ systems. NA: not active.

To provide a comprehensive understanding of the binding pattern of quinoline **4b** to PPAR receptor subtypes, we performed molecular modelling studies (Fig. 3) and molecular dynamics (MD) simulations (Fig. 1S). Our findings indicated that the compound **4b**/PPARα complex exhibited a spatial arrangement similar to that of the benzopyran analogue BP-2.[15] Quinoline **4b** demonstrated strong interactions with Ser280, Leu321, Cys276 and His440 residues which are somewhat lower but still comparable to those interactions displayed by the complex of reference compound WY-14,643/PPARα (Fig. 3A and Fig. 1S). In turn, quinoline **4b**/PPARβ/δ complex showed interactions with Cys249, Lys331 and His412 (Fig. 3B and Fig. 1S) which are closely related to those interactions obtained for the reference compound GW501516. In the case of receptor PPARγ, quinoline **4b** displayed affinity for Ile341, Arg288 and Leu330, similar to the residues involved in rosiglitazone/PPARγ complex interactions (Fig. 3C and Fig. 1S).

Macrophages are phagocytic immune cells that play a crucial role in immunity, tissue remodelling, and lipid homeostasis, are present in all tissues, and highly express the three PPAR isoforms.[22–24] The infiltration of macrophages into tissues leads to the release of proinflammatory cytokines and chemokines, including MCP-1 and IL-6, which contribute to the inflammatory state. MCP-1 is involved in the recruitment and activation of monocytes,[25] and its downregulation has been linked to improvement in metabolic disorders.[26,27] IL-6 is an inflammatory cytokine, the overproduction of which is associated with obesity, diabetes and cardiovascular disorders.[28] PPAR agonists have been reported to suppress the immunoreactive state of macrophages by suppressing immune-reactive cytokine and chemokine markers, including MCP-1

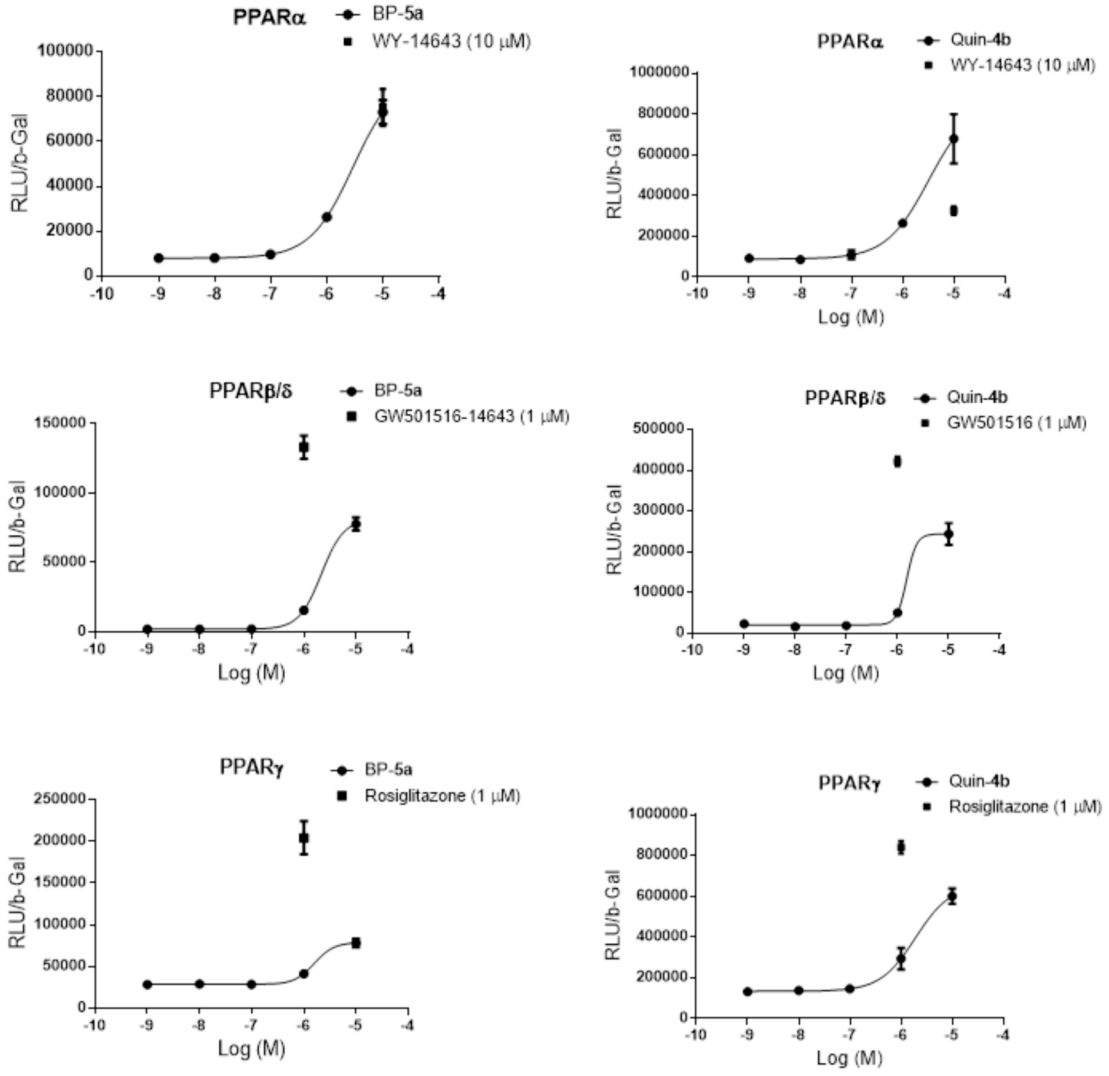


Fig. 2. Dose-response curves of benzopyran **5a** and quinoline **4b**, which were tested across a range of concentrations up to 10 μM, and luciferase activity was measured for pGAL4hPPARα pGAL4hPPARβ/δ and pGAL4hPPARγ.

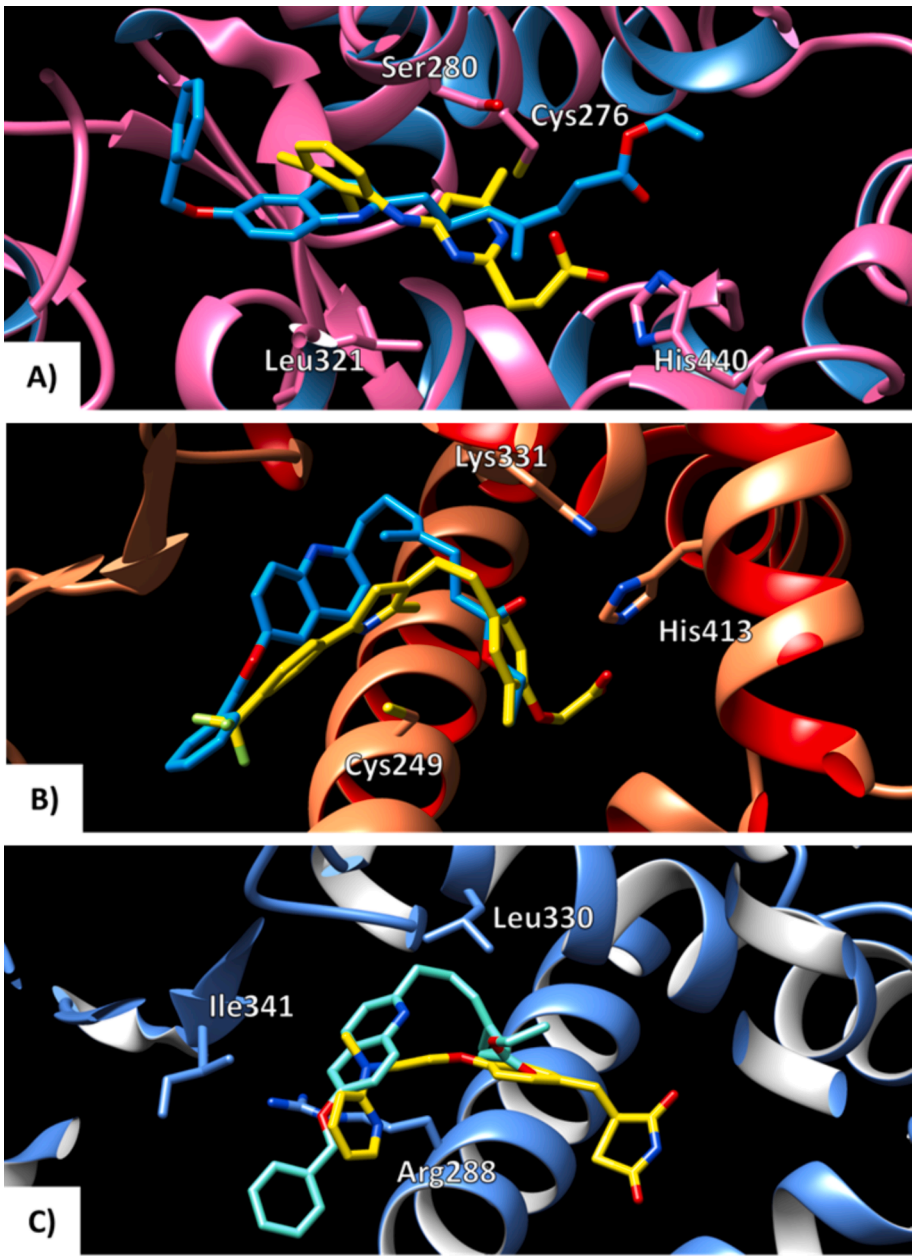


Fig. 3. Spatial view of interactions with PPARs using docking studies. Spatial views of synthetic quinoline **4b** (blue)/PPARα (A), **4b** (blue)/PPARβ/δ (B), and **4b** (blue)/ PPARγ (C) complex interactions overlapping reference compounds WY-14,643 (yellow), GW501516 (yellow), and rosiglitazone (yellow), respectively. The names of residues involved in the main interactions are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and IL-6.[5,29].

To evaluate the potential anti-inflammatory effects of quinoline **4b**, we differentiated THP-1 human monocytes (ATCC, TIB-202™, Manassas, VA, USA) into macrophages to study the mRNA levels of the pro-inflammatory markers *CCL-2* and *IL-6*. Cells were pretreated with **4b** at 10 μM prior to stimulation with LPS (10 ng/mL) for a total induction time of 4 and 24 h. Dexamethasone (1 μM) was used as the positive control. As expected, LPS stimulation increased the expression of both inflammatory markers, as revealed by RT-qPCR results. Notably, treatment with quinoline **4b** diminished the LPS-induced expression of *CCL-2* at 4 and 24 h and the expression of *IL-6* at 24 h (Fig. 4). These results suggested the potential beneficial effects of **4b** in ameliorating low-grade systemic inflammation associated with metabolic syndrome, thereby preventing cardiovascular comorbidities.

Herein, we report the total synthesis of 2-prenylated benzopyrans (*series a*) via aldol-*oxo*-Michael cyclisation to generate the chroman-6-ol scaffold, followed by the Grignard reaction and subsequent Johnson-Claisen rearrangement or Horner-Wadsworth-Emmons (HWE) olefination to introduce the isoprenoid ethyl ester or isoprenoid *O*-alkoxylated ester, respectively. In addition, 2-prenylated quinoline **4b** was synthesized *via* Friedländer condensation to obtain the quinolin-6-ol nucleus, followed by the Grignard reaction and subsequent Johnson-Claisen rearrangement. Unexpectedly, quinoline **4b**, which is analogue to the most active benzopyran **5a**, demonstrated pan-PPAR agonism, with full activation of hPPARα, weak PPARβ/δ, and partial PPARγ activation. In addition, quinoline **4b** exerted anti-inflammatory effects on macrophages. Consequently, **4b** emerges a promising hit compound for the development of potential therapeutics aimed at treating metabolic syndrome, MAFDL, and associated cardiovascular complications.

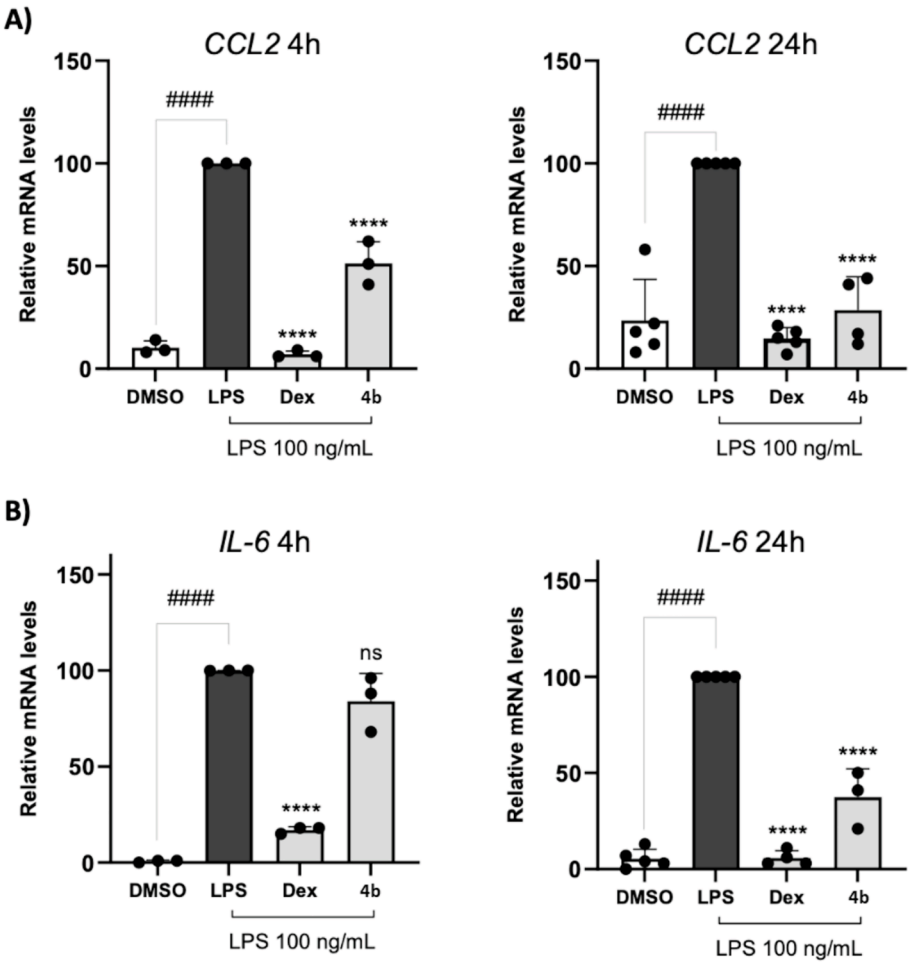


Fig. 4. Anti-inflammatory effects on CCL-2 and IL-6 mRNA levels. THP-1 human monocytes differentiated into macrophages were treated with quinoline **4b** (10 μM) for 1 h prior to LPS stimulation (100 ng/mL) for a total induction time of 4 and 24 h. mRNA was isolated, reverse-transcribed, and subjected to RT-qPCR using primers to detect *CCL-2* and *IL-6*.

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.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2024.129770.

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