Indenone Derivatives: A Novel Template for Peroxisome Proliferator-Activated Receptor γ (PPARγ) Agonists

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Agonists of peroxisome proliferator-activated receptor γ (PPAR γ) are of interest as a treatment for diabetes, which prompted the identification of a new class of non-TZD PPAR γ agonist. Moreover, compound **14c** has displayed the most active agonistic activity with an EC_{50} value of 50 nM, in addition to exhibiting a new binding mode in the X-ray cocrystal structure.

Introduction

Type 2 diabetes mellitus, also known as non-insulin-dependent diabetes mellitus, accounts for >90% of the cases of diabetes. This condition is characterized by high levels of glucose resulting from progressive insulin resistance and, at later stages of the disease, impairment of insulin secretion.

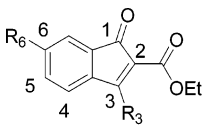
Peroxisome proliferator-activated receptors (PPARs[a]), which are one of the attractive diabetes target proteins, are members of the nuclear hormone receptor superfamily, which include three receptor isoforms, PPARα, PPARγ, and PPARδ. Among them, PPARγ has been the subject of extensive research,[1] and as a result, its activation has played a prominent role in the treatment for type 2 diabetes. The receptor is widely distributed in the spleen, colon, adipose tissue, and macrophages and found to a lesser extent in the liver, pancreas, and skeletal muscle.[2] Activation of PPARγ in the cell nucleus initiates heterodimerization with another nuclear receptor, the retinoid X receptor (RXR), with subsequent recruitment of coactivators and induction of genes that are involved in adipogenesis and insulin sensitivity. Target genes that are upregulated or downregulated have been identified from white and brown adipose tissues, skeletal muscle, and the liver.[3] However, the details corroborating the process through which the activation leads to glucose homeostasis are not fully understood. Convincingly, studies suggest that adipogenesis provides increased lipid metabolism and free fatty acid uptake in adipose tissue, thereby leading to increased insulin sensitivity and glucose metabolism in the muscle and liver.[1a,4,5]

PPARγ agonists containing the thiazolidinedione (TZD) structure for the treatment of type 2 diabetes have proven successful for glucose control and reduction of HbA_{1c}, along with the marketed compounds, rosiglitazone[6] and pioglitazone.[7,6b] However, edema, weight gain, and hepatotoxicity have been reported in patients after treatment with PPARγ agonists.[6b]

Recently, much attention has been focused on PPARα/γ dual agonists[8] (mainly, carboxylic acid derivatives), since the high PPARγ selectivity of the TZD structure is thought to be a cause of their side effects. However, PPARα/γ dual agonists in late clinical development so far have had side effect issues.[8c]

More recently, new classes of selective PPARγ modulators (SPPARγM) have been reported.[9] Indole-derived PPARγMs exhibited glucose lowering with partial agonistic activity compared to rosiglitazone. These situations prompted us to develop a new PPARγ agonist with a new skeleton as well as new binding mode in the X-ray crystal structure.

We therefore initiated a search for non-TZD PPARγ ligands. In the course of the search for PPARγ agonists through HTS (high throughput screening) using the chemical library of the Korea Chemical Bank, the indenone skeleton was discovered as a hit toward PPARγ agonists. We now report the synthesis of indenone derivatives, possessing a quite unique structure containing neither TZD nor the carboxylic acid moiety, their biological activities, and their binding mode.



indenone derivatives

Results and Discussions

Chemistry. A series of indenone derivatives was synthesized according to the synthetic Schemes 1−3. 3-Methoxybenzyl chloride (**1**) reacted with ethyl aryl- or alkyl acylacetates **2** in the presence of K_2CO_3 and KI in DMF to produce the coupling compound **3**, which was converted to the corresponding indene **4** via cyclization by treatment with polyphosphoric acid. Oxidation of indenes **4** using SeO_2 afforded the desired indenones (**5**, X = O) in moderate yields. Indenone oxime (**5b**, X = NHOH) was easily prepared with hydroxylamine.

The indenone with the acetate at the R_2 position was prepared by a modified literature method[10] (Scheme 2). The condensation of 4-methoxybenzophenone with diethyl succinate in the presence of potassium *tert*-butoxide in *t*-BuOH produced the coupled half-ester, followed by hydrolysis using KOH, and anhydride formation with acetyl chloride to afford compound **8**. Compound **8** was cyclized with aluminum chloride to give the indenone, which was converted to the desired ester **10** by esterification.

Phenylalkyl substituents at R_6 could be obtained by four-step synthesis as shown in Scheme 3. 3-Hydoxybenzyl chloride (**11**) was coupled with ethyl benzoylacetate to produce the

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[a] Abbreviations: PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione; RXR, retinoid X receptor; HbA_{1c}, hemoglobin A_{1c}; LBD, ligand binding domain; HTS, high throughput screening; Ac, acetyl; AF2 helix, activation function 2 helix; SRC-1, steroid receptor coactivator-1; DMF, *N*,*N*-dimethylformamide.

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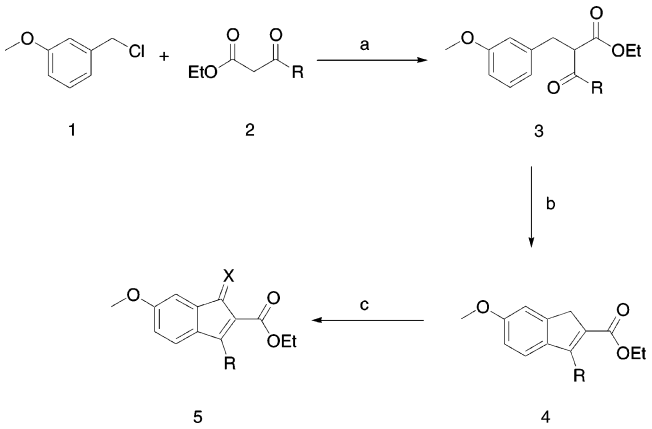
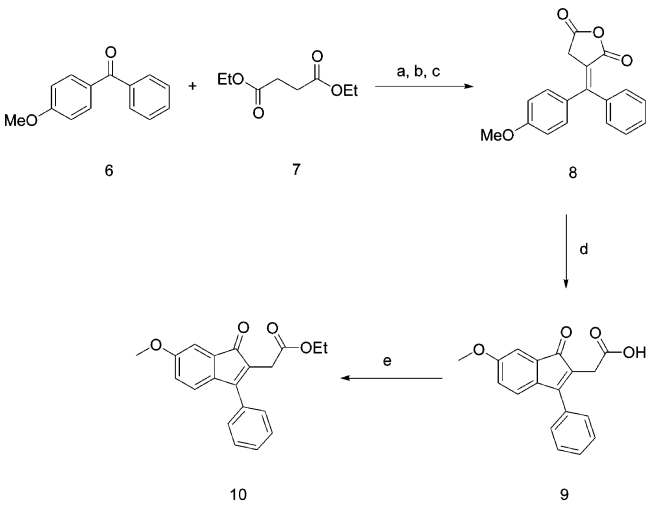
Scheme 1[a]



[a] Reagent and conditions: (a) R = phenyl, furyl, adamantyl, K_2CO_3, KI, DMF, room temperature (78−94%); (b) polyphosphoric acid, 30−45 °C (37−60%); (c) X = O; SeO_2, dioxane, reflux (25−72%); X = NHOH; SeO_2, dioxane, reflux, and then NH_2OH, pyridine, ethanol (overall 41%).

Scheme 2[a]



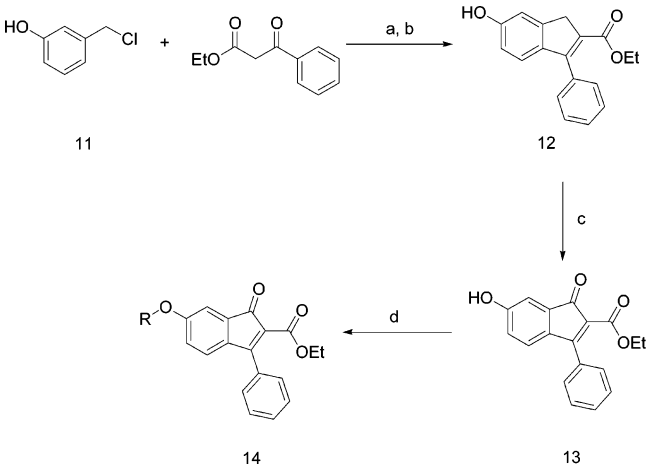
[a] Reagent and conditions: (a) K, t-BuOH, reflux (32%); (b) KOH, MeOH, H_2O, reflux (38%); (c) AcCl, reflux (99%); (d) $AlCl_3$, nitrobenzene, room temperature (92%); (e) TsOH, EtOH, reflux (15%).

coupling product, followed by cyclization using polyphosphoric acid to afford the corresponding indene **12**. Further, **12** was oxidized by SeO_2 to produce the indenone **13**, which was alkylated with RBr to afford the final R_6-substituted indenone derivatives **14**.

Biological Activity. All compounds prepared were evaluated for their activity for PPARγ activation. The vector fused with the ligand binding domain of a human PPARγ gene and the DNA binding site of a yeast GAL-4 gene, and the luciferase reporter vector, were simultaneously transfected in NIH/3T3 cells. Then, each of the test compounds or the vehicle alone was added thereto. After incubation for 24 h, the cells were subjected to lysis. Then the luciferase activity was measured and the potency of the test compound was expressed as EC_{50} (the concentration at which 50% of the maximum activation was observed) to compute the activation potencies of the test compounds and the comparative compound, rosiglitazone, on PPARγ.

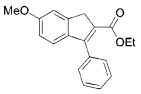
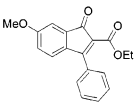
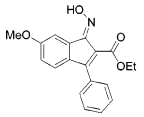
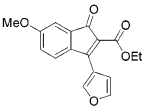
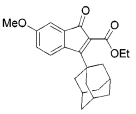
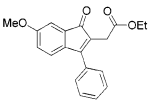
Our efforts began by screening the Korea Chemical Bank library to identify a new agonist of PPARγ, and as a result, the indenone skeleton was discovered as a novel hit. Indenone is a neutral molecule without a TZD moiety, and it is also well suited to derivatization. Several indenone analogues were synthesized

Scheme 3[a]



[a] Reagent and conditions; (a) K_2CO_3, KI, DMF, room temperature (96%); (b) polyphosphoric acid, room temperature (45%); (c) SeO_2, dioxane, reflux (25−72%); (d) R = benzyl, phenethyl, phenylpropyl, K_2CO_3, KI, DMF, room temperature (75−90%)

Table 1. Activity of Indenone Derivatives on Human PPARs

compound	structure	PPARγ EC_{50}, μM[a]	PPARα EC_{50}, μM[a]
4		> 10	
5a		0.3	>100
5b		> 10	
5c		1.0	
5d		2.5	
10		0.3	
Rosiglitazone		0.32	

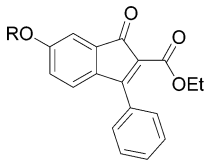
[a] EC_{50} values were determined from direct regression curve analysis.

and evaluated for their biological activities as shown in Table 1. Indeed, indene compound **4** was significantly less active (>10 μM), whereas indenone **5a** showed good activity for PPARγ activation with an EC_{50} value of 0.3 μM. This is the first of our compounds to show nanomloar activity.

Similarly, compound **5a** was also tested toward PPARα to find out whether it was a PPARγ-selective or a PPARα/γ dual agonist, and the subsequent result showed that compound **5a** was a PPARγ-selective agonist without PPARα agonistic activity (>100 μM).

Introduction of an oxime moiety on the carbonyl group at R_1 resulted in the loss of the activity (compound **5b**, >10 μM).

Table 2. Activity of Indenone Derivatives on Human PPARγ



compound	R	EC_{50}, μM[a]	% max. activation at 10 μM
5a	CH_3	0.30	
14a	$C_6H_5CH_2$	0.22	91
14b	$C_6H_5CH_2CH_2$	0.21	88
14c	$C_6H_5CH_2CH_2CH_2$	0.05	113
rosiglitazone		0.32	100

[a] EC_{50} values were determined from direct regression curve analysis.

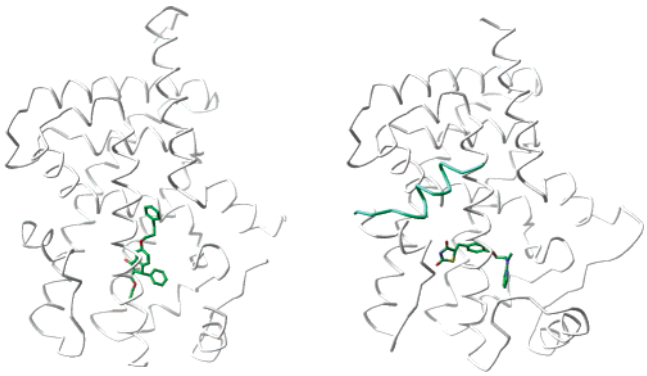


Figure 1. A comparison of the ligand binding pattern of PPARγ with compound **14c** (left) and with rosiglitazone (right; pdb code: 2PRG). PPARγ was represented as worm model and colored gray whereas both compounds (**14c** and rosiglitazone) were depicted as ball-and-stick models. In the 2PRG structure, coactivator SRC-1 peptide was colored cyan. The point of view is the same for both left and right parts.

On the other hand, the substitution effect of the R_3 position indicated that heteroaryl and alkyl groups such as furyl and adamantyl (compounds **5c** and **5d**) were less active than the phenyl substituent (**5a**). The insertion of methylene group at R_2 position exhibited a potent activity similar to compound **5a** (**10**, EC_{50} = 0.3 μM). However, the corresponding acid (compound **9**) was not active (data not shown).

Furthermore, we set out to study the effects of substituents on the R_6 position, and the results are summarized in Table 2. Indenone derivatives with a benzyl or phenethyl substituent at R_6 (compounds **14a** and **14b**) were found to be slightly more potent than **5a**, while compound **14c** having a phenylpropyl group at R_6 was the most active in this series, with an EC_{50} value of 0.05 μM and 6-fold greater potency than the referred rosiglitazone. This apparently suggested that the phenylpropyl moiety had an additional binding to PPARγ.

Indenone derivatives with substituents on the R_6 position (**14a**, **14b**, and **14c**) are potent full agonists of PPARγ with maximum activation ranging from 88% to 113% at 10 μM compared to full agonist rosiglitazone (Table 2).

X-ray Cocrystal Structure. To further elucidate our postulation, we determined a crystal structure of the ligand binding domain (LBD) of PPARγ complexed with the compound **14c**. The crystal structure (Figure 1) revealed nearly identical Cα conformations with that of PPARγ LBD complexed with rosiglitazone.[11] However, the complexed structure of compound **14c** exhibited completely different binding modes as compared to rosiglitazone. In the 2PRG structure, rosiglitazone occupied the left and right portion of the active site pocket in PPARγ LBD.

Notably, the headgroup of rosiglitazone stretched deep into the left stem of the cavity and tethered the AF2 helix of PPARγ, which is known to be important in coactivator binding. In contrast, the indenone moiety of compound **14c** occupied the base part and the phenylpropyl group stretched deep into the upper part of cavity as shown in Figure 1.

Because of the unique structure and binding mode, compounds within this indenone structural motif may have differing biochemical and pharmacological properties compared to the TZD and carboxylated PPARγ full agonists. Further exploration of the potential of this compound class will require structural modification and biological evaluation in order to discover any unexpected side-effect advantage.

Conclusion

The indenone derivatives were discovered as a unique template for the activation of PPARγ. Compound **14c** displayed the most active agonistic activity with an EC_{50} value of 50 nM and exhibited a new binding mode in the X-ray cocrystal structure. The indenones are a novel and interesting chemical class, which could be further optimized for the treatment of diabetes.

Experimental Section

General. All reported yields are isolated yields after column chromatography or crystallization. ^{1}H NMR spectra were obtained on a FT-NMR Varian GEMINI-200FT with TMS as internal reference. MS spectra were obtained on a Shimadzu QP5050 spectrograph. Elemental analysis was performed by the ThermoFinnigan Flash 1112.

6-Methoxy-3-phenyl-1*H*-indene-2-carboxylic Acid Ethyl Ester (4). To a mixture of ethyl benzoylacetate (7 g, 36.42 mmol), K_2CO_3 (15.1 g, 109.26 mmol), and NaI (6.55 g, 43.70 mmol) in DMF was added 3-methoxybenzyl chloride (6.27 g, 40.06 mmol). After 1 h at room temperature, sat NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by silica gel column chromatography to give 2-(3-methoxybenzyl)-3-oxo-3-phenylpropionic acid ethyl ester (10.69 g, 94%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.1 Hz, 1.8 Hz, 2H), 7.60−7.40 (m, 3H) 7.24 (t, J = 7.1 Hz, 1H), 6.84−6.69 (m, 3H), 4.63 (t, J = 7.3 Hz, 1H), 4.11 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 3.31 (d, J = 7.3 Hz, 2H), 1.13 (t, J = 7.3 Hz, 3H); mass spectrum *m*/*e* (relative intensity) 312 (M^+, 20), 105 (100), 77 (65). A mixture of 2-(3-methoxybenzyl)-3-oxo-3-phenylpropionic acid ethyl ester (10.69 g, 34,26 mmol) and polyphosphoric acid (100 g) was stirred for 1 h at 30−45 °C. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by silica gel column chromatography to give 6-methoxy-3-phenyl-1*H*-indene-2-carboxylic acid ethyl ester (4.064 g, 40%): ^{1}H NMR (200 MHz, $CDCl_3$) δ7.46−7.40 (m, 5H), 7.20−7.11 (m, 2H), 6.87 (dd, J = 8.6 Hz, 2.3 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 2H), (t, J = 7.2 Hz, 3H); mass spectrum *m*/*e*(relative intensity) 294 (M^+, 33), 221 (100), 178 (25); Anal. ($C_{19}H_{18}O_3$) C, H, N: calcd, C 77.53, H 6.16; found, C 77.23, H 6.32.

6-Methoxy-1-oxo-3-phenyl-1*H*-indene-2-carboxylic Acid Ethyl Ester (5a). A mixture of 6-methoxy-3-phenyl-1*H*-indene-2-carboxylicacidethyl ester (1 g, 3.40 mmol) and SeO_2 (5.655 g, 50.96 mmol) in 1,4-dioxane was refluxed for 24 h. The reaction mixture was cooled to room temperature and diluted with 1 M $NaHCO_3$ and ether. The organic layer was dried and evaporated. The residue was purified by silica gel column chromatography to give 6-methoxy-1-oxo-3-phenyl-1*H*-indene-2-carboxylic acid ethyl ester (756 mg, 72%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (s, 5H), 7.19 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.83 (dd, J = 8.2 Hz, 2.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); mass spectrum *m*/*e* (relative intensity) 308 (M^+, 52), 236

(100). Anal. ($C_{19}H_{16}O_4$) C, H, N: calcd, C 74.01, H 5.23; found, C 73.64, H 5.38.

1-Oxo-3-phenyl-6-(3-phenylpropoxy)-1*H*-indene-2-carboxylic Acid Ethyl Ester (14c). To a mixture of ethyl benzoylacetate (27.6 g, 161.28 mmol), K_2CO_3 (44.58 g, 322.56 mmol), and NaI (29 g, 193.54 mmol) in DMF was added 3-chloromethylphenol (27.6 g, 193.54 mmol). After 5 h at room temperature, sat. NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by silica gel column chromatography to give 2-(3-hydroxybenzyl)-3-oxo-3-phenylpropionic acid ethyl ester (46.51 g, 96%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.8 Hz, 1.2 Hz, 2H), 7.60−7.40 (m, 3H) 7.11 (t, J = 7.8 Hz, 1H), 6.80−6.60 (m, 3H), 5.37 (s, 1H), 4.62 (t, J = 7.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.26 (d, J = 7.3 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H); mass spectrum *m*/*e* (relative intensity) 298 (M^+, 6), 105 (100). A mixture of 2-(3-hydroxybenzyl)-3-oxo-3-phenylpropionic acid ethyl ester (10 g, 33.52 mmol) and polyphosphoric acid (100 g) was stirred for 2 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by silica gel column chromatography to give 6-hydroxy-3-phenyl-1*H*-indene-2-carboxylic acid ethyl ester (4.24 g, 45%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45−7.39 (m, 5H), 7.11 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.77 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 5.27 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.81 (s, 2H), 1.13 (t, J = 7.1 Hz, 3H); mass spectrum *m*/*e* (relative intensity) 280 (M^+, 11), 208 (100), 105 (82). A mixture of 6-hydroxy-3-phenyl-1*H*-indene-2-carboxylic acid ethyl ester (5 g, 17.84 mmol) and SeO_2 (19.8 g, 278.37 mmol) in 1,4-dioxane was refluxed for 24 h. The reaction mixture was cooled to room temperature and diluted with 1 M $NaHCO_3$ and ether. The organic layer was dried and evaporated. The residue was purified by silica gel column chromatography to give 6-hydroxy-3-phenyl-1*H*-indene-2-carboxylic acid ethyl ester (2.83 g, 54%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (s, 5H), 7.11 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1 Hz, 2.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H); mass spectrum *m*/*e* (relative intensity) 294 (M^+,57), 249 (99), 222 (100). To a mixture of 6-hydroxy-3-phenyl-1*H*-indene-2-carboxylic acid ethyl ester (2 g, 6.79 mmol), K_2CO_3 (1.41 g, 10.19 mmol), and NaI (0.2 g, 1.40 mmol) in DMF was added 1-bromo-3-phenylpropane (2.07 mL, 13.59 mmol). After 8 h at room temperature, sat NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by silica gel column chromatography to give 1-oxo-3-phenyl-6-(3-phenylpropoxy)-1*H*-indene-2-carboxylic acid ethyl ester (2.37 g, 85%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (s, 5H), 7.36−7.21 (m, 6H), 7.06 (d, J = 8.1 Hz, 1H), 6.83 (dd, J = 8.1 Hz, 2.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 1.14 (t, J = 7.4 Hz, 2H), 2.16−2.05 (m, 2H), 1.15 (t, J = 7.1 Hz, 3H); mass spectrum *m*/*e* (relative intensity) 412 (M^+, 14), 91 (100); Anal. ($C_{27}H_{24}O_4$) C, H, N: calcd, C 78.62, H 5.86; found, C 78.90, H 5.82.

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Supporting Information Available: Synthetic procedure for compounds including the ^{1}H NMR, mass, and elemental analysis data, biological procedures, and X-ray cocrystal structure determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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