Syntheses and Structure−Activity Relationships of Novel Retinoid X Receptor Agonists

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As part of our studies to develop novel retinoids with increased affinity and selectivity for the retinoid X receptor (RXR) subfamily, we have designed and synthesized a series of (*E*,*E*,*E*)-7-(1,2,3,4-tetrahydroquinolin-6-yl)-7-alkyl-6-fluoro-3-methylhepta-2,4,6-trienoic acid derivatives. These tetrahydroquinolines, generated by introducing a polar N atom into the hydrophobic part of the retinoid skeleton, showed high binding affinity to RXRs. Addition of fluorine at the 6-position of the 2,4,6-trienoic acid moiety afforded compounds which elicit potent and selective transactivation of the RXRs. Compound **14b** (ER-35794), which possesses an ethyl substituent at the 7-position and fluorine at the 6-position of the triene moiety, is one of the most potent and selective RXR agonists reported to date.

Introduction

Retinoids play important roles in a variety of biological processes, including mediation of cell growth and differentiation in both normal and neoplastic cells.[1] The ability of retinoids to modulate proliferation and differentiation of both normal and malignant cells in vitro and in vivo has significant implications for the treatment of dermatological diseases, such as psoriasis[2,3] and cancer, for which retinoids may have both chemotherapeutic and chemopreventive applications.[4−8]

The retinoid receptors, members of the superfamily of nuclear receptors, have been classified into two subfamilies, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). These receptors function as ligand-dependent transcription factors.[1,9] The natural ligands for the RARs are *all-trans*-retinoic acid (ATRA), 9-*cis*-retinoic acid (9-*cis*-RA), and 3,4-dehydro-*all-trans*-retinoic acid, while 9-*cis*-retinoic acid (9-*cis*-RA) is a potent activator of the RXRs.[10] The classification of the subfamilies is based primarily on differences in amino acid sequence, responsiveness to synthetic retinoids, and the ability to modulate expression of different target genes. Each subfamily is made up of three distinct subtypes designated RAR-α, *β*, and *γ* and RXR-α, *β*, and *γ*.

RXRs form homodimers which bind to direct repeats called retinoid X response elements. They also form heterodimers with RARs as well as with other members of the nuclear receptor superfamily,[10] namely, the peroxisome proliferator-activated receptors (PPARs), the thyroid hormone receptor (TR), the vitamin D receptor (VDR), and the orphan receptor (LXR). Only RAR-specific ligands activate the RAR/RXR heterodimers,[11] whereas RXR/RXR homodimers are activated by RXR-specific ligands.[12]

A few RXR-selective retinoid agonists have been reported.[13−20] Such compounds are of interest because they may elicit the beneficial pharmacological activities of retinoids without toxic side effects such as teratogenicity and hypervitaminosis. A selective RXR agonist (LGD 1069[15]) is under development for use in the treatment of various cancers[21] and diabetes[22] (Chart 1). In addition, it was recently reported that LGD 1069 showed an efficacy equivalent to that of tamoxifen as a chemopreventive agent in a rat mammary carcinoma model.[23]

In the course of our search for novel retinoids with increased affinity and selectivity for the RXRs, we have designed and synthesized a series of (*E*,*E*,*E*)-7-(1,2,3,4-tetrahydroquinolin-6-yl)-7-alkyl-6-fluoro-3-methyl-hepta-2,4,6-trienoic acid derivatives. These compounds were evaluated for the ability to regulate gene expression and to bind to retinoid receptors by using a transient receptor/reporter cotransfection assay system in COS-1 cells[24−26] and a competitive binding assay with [^{3}H]-9-*cis*-retinoic acid ([^{3}H]-9-*cis*-RA) and [^{3}H]-*all-trans*-retinoic acid ([^{3}H]-ATRA) as radioligands.[27]

Drug Design

It is known that 9-*cis*-RA binds to and transactivates both the RARs and RXRs. To obtain novel selective RXR agonists, we planned to introduce a N atom into the hydrophobic part of the molecule, since this was found by the Roche group to reduce retinoid activities.[28,29] Since conformation is important for RXR affinity, we introduced fluorine into the triene part in order to stabilize the 9-cis form (Chart 2).

Chemistry

The general synthetic pathways for preparation of the compounds listed in Table 3 are shown in Scheme 1.

Formylation of 1-(1-methylethyl)-1,2,3,4-tetrahydroquinoline (**2**), which was derived from 1,2,3,4-tetrahydroquinoline (**1**) by treatment with *N*,*N*-dimethylformamide and phosphorus oxychloride complex, afforded only the 6-substituted carbaldehyde derivative (**3**), which was transformed to the ketone derivative (**5a**). The olefination of the ketone derivative (**5a**) with triethyl phosphonoacetate was performed in the presence of an appropriate base, such as NaH, affording the

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Chart 1

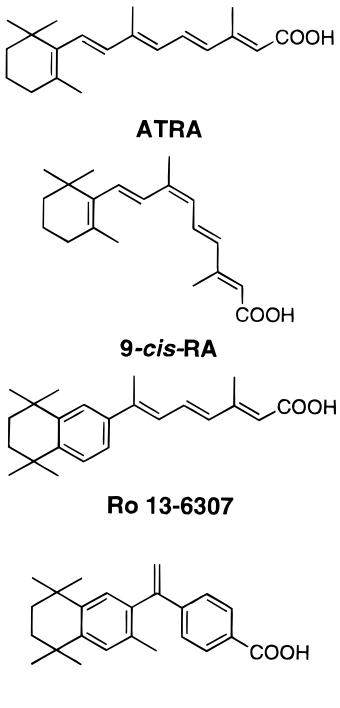
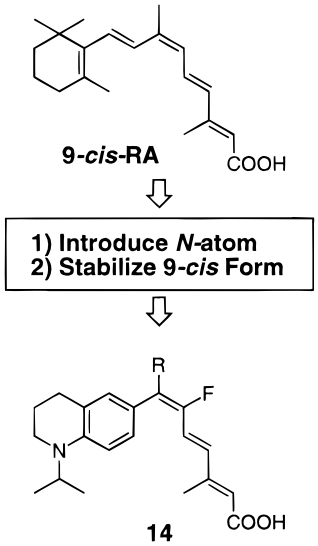


Chart 2



E and *Z* isomers (**6**) in a ratio of approximately 85:15, in a good yield. Reduction of the separated (*E*)-α,*β*-unsaturated ester (**6**) with diisobutylaluminum hydride (DIBAL-H) at −70 °C and oxidation with activated manganese(IV) oxide afforded the (*E*)-α,*β*-unsaturated aldehyde (**8**). The (*E*)-aldehyde (**8**) was coupled with phosphonate ester to afford the 2,4,6-octatrienoic ester (**9**), which was hydrolyzed to give the 2,4,6-octatrienoic acid (**10**).

Initial experiments were aimed at construction of the 9-cis form of compound **10**. After the Horner−Emmons reaction, the (*Z*)-butenoic acid ester **6** was separated by flash column chromatography with silica gel. The (*Z*)-ester **6** was reduced with DIBAL-H at −70 °C to obtain the (*Z*)-alcohol **7**. All attempts at oxidation of the (*Z*)-butenol **7** using manganese(IV) oxide, Dess−Martin reagent and Swern oxidation reagent resulted in isomerization to the to *E* isomer, so that the unstable (*Z*)-butenal **8** could not be isolated.

To construct the stable 9-cis form, we used the synthetic route employed for fluorinated vitamin A analogues.[30−35] According to these reports, the Horner−Emmons reaction using triethyl 2-fluoro-2-phosphonoacetate for coupling with the ketone (**5**) should mainly afford the *E*-form ester (**11a**−**d**).

The configuration of the 2-fluorobutenoic ester (**11**) was established by the magnitude of the four-bond H (3-Me), F coupling constants, and the proton chemical shifts.[33] The ^{1}H NMR data for **11a**, **12a**, and **13a** are listed in Table 1. According to Pawson's method,[30] we assigned the stereochemistry of the double bond from the chemical shifts and coupling constants of the intermediates (**11a**, **12a**, and **13a**), and this assisted in the assignment of the stereochemistry of the final retinoids. In the esters **11** and the aldehyde **12**, the methyl group at C-3 of the *Z* isomers is deshielded, as expected, by more than 0.17 ppm.[36] We also found that four-bond coupling constants ($^4J_{^1H-^{19}F}$) (Table 1) between C-2 fluorine and C-3 methyl protons in compounds **11**, **12**, and **13** follow a pattern of $^4J_{^1H-^{19}F}$ (*E* isomer) > $^4J_{^1H-^{19}F}$ (*Z* isomer).[33,37]

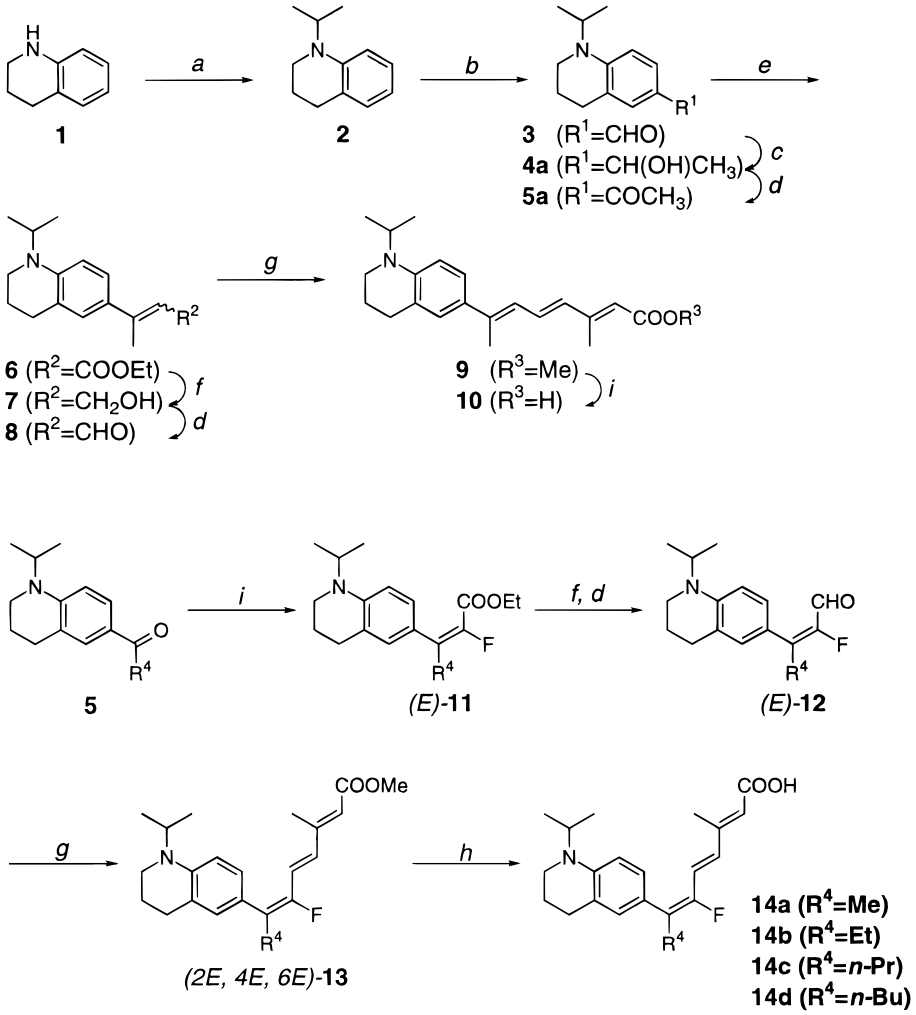
Horner−Emmons reaction of the α,*β*-unsaturated aldehyde (**12a**−**d**) afforded the 6-fluoro-3-methylhepta-2,4,6-trienoic acid ester (**13a**−**d**), in which the major isomer had the 2*E*,4*E*,6*E* stereochemistry. This assignment was based largely on the ^{1}H NMR data for the free acid derivatives (**14**), which were obtained by hydrolysis of the esters (**13**) followed by crystallization (Table 2).[33]

Result and Discussion

The above retinoids were evaluated in vitro for the ability to bind the individual RARs and RXR-α and to induce gene transcription in the cotransfection assay at each of the six retinoid receptors. Binding assays for receptor subtypes were performed in a manner similar to that described by Boehm et al.,[15] using [^{3}H]-9-*cis*-RA as the radioligand for RXR-α and [^{3}H]-ATRA for the RARs. The relative IC_{50} values are reported based on ATRA = 1.0 for RARs, and 9-*cis*-RA = 1.0 for RXR-α (see Table 3). Cotransfection assays were performed as described in the Experimental Section, with relative EC_{30} values being reported (see footnote to Table 3). In our investigation, it was found that the response to some RAR-, and RXR-selective retinoids tended to reach a plateau near 50% of that to the natural ligands. Therefore, EC_{30} values were used to represent the transcriptional activity for the evaluation of retinoid derivatives, including low activity compounds.

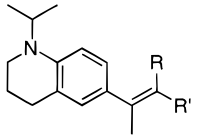
Binding activity data showed that (*E*,*E*,*E*)-7-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-3-methylocta-2,4,6-trienoic acid (**10**) exhibits a potent and selective affinity for RXR-α, with affinity for RARs weaker than that of (*E*,*E*,*E*)-7-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-3-methylocta-2,4,6-trienoic acid (Ro 13-6307[38]). Although Ro 13-6307 has no affinity for RXR-α, compound **10**, which has a N atom in the hydrophobic part, binds strongly to RXR-α and is a correspondingly potent activator of RXRs. Addition of fluorine at the 6-position of the triene moiety of **10** afforded compounds **14a**−**14c**, which bind with even

Scheme 1[a]



[a] Reagents: (a) *i*-PrI, K_2CO_3, DMF; (b) $POCl_3$, DMF; (c) R^4MgBr, ether; (d) MnO_2, acetone; (e) $(EtO)_2P(O)CH_2COOEt$, NaH, DMF; (f) DIBAL-H, THF; (g) $(EtO)_2P(O)CH_2C(Me)=CHCOOMe$, NaH, DMF; (h) NaOH aqueous EtOH: (i) $(EtO)_2P(O)CHFCOOEt$, NaH, DMF and separation.

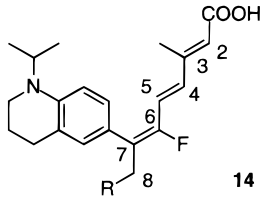
Table 1. Chemical Shifts and $^1H-^{19}F$ Coupling Constants of C-3 (**11a** and **12a**) and C-7 (**13a**) Methyl Proton



compd	R	R′	δ	$^4J_{^1H-^{19}F}$
(*E*)-**11a**	-COOEt	-F	2.12	4.8
(*Z*)-**11a**	-F	-COOEt	2.43	3.2
(*E*)-**12a**	-CHO	-F	2.25	3.6
(*Z*)-**12a**	-F	-CHO	2.42	3.2
(6*E*)-**13a**	-A[a]	-F	2.12	3.6
(6*Z*)-**13a**	-F	-A[a]	2.13	2.8

[a] A = (*E*,*E*)-CH=CH−C(CH_3)=CH−COOMe.

Table 2. ^1H NMR Signals and $^1H-^{19}F$ Coupling Constants for the 6-Fluoro-Substituted Compounds (**14a**−**d**)



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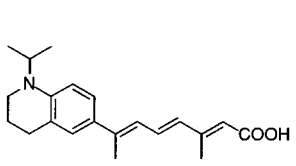
		^1H NMR chemical shifts, δ					coupling constants, Hz		
compd	R	C-2 H	C-3 CH_3	C-4 H	C-5 H	C-8 CH_2	$J_{4,5}$	$^4J_{H-F}$	$^3J_{H-F}$
14a	H	5.86	2.21	6.52	6.71	2.12	15.6	3.2	26.4
14b	Me	5.85	2.19	6.51	6.63	2.55	15.6	2.8	25.6
14c	Et	5.85	2.19	6.51	6.64	2.55	16.0	2.8	26.0
14d	*n*-Pr	5.85	2.19	6.51	6.64	2.55	16.0	2.8	26.0

higher affinity to RXR-α and elicit potent and selective activation of the RXRs. Although the "stable 9-cis form" analogues **14a**−**c** have a binding affinity for RXR-α higher than that of the parent compound **10** (Table 3), introduction of an *n*-butyl substituent at the 7-position of the 2,4,6-heptatrienoic moiety (**14d**) reduced the affinity for RXR-α approximately 10-fold.

The 7-alkyl-6-"*cis*"-3-methylhepta-2,4,6-trienoic acid derivatives (compounds **14a**−**d**) were also potent activators of RXRs. The *n*-propyl analogue (**14c**) had relative EC_{30} values for activation of the RXRs that were somewhat higher than those of the parent 7-methyl analogue (**14a**), whereas the 7-ethyl analogue (**14b**) had relative EC_{30} values lower than that of **14a**. Although **14a** was capable of activating the RARs (especially RAR-β, γ), analysis of the relative EC_{30} and efficacy (%) of transactivation suggested that **14b** and **14c** function

Table 3. Competitive Binding and Transactivation Data for Compound **10** and (*E*,*E*,*E*)-7-(1,2,3,4-Tetrahydroquinolin-6-yl)-7-alkyl-6-fluoro-3-methylhepta-2,4,6-trienoic Acid Derivatives (**14**)



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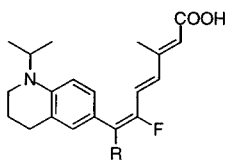

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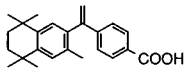
		binding affinity[a] relative IC_{50} (IC_{50}/natural ligand IC_{50})				subtype specific transactivation[b] relative EC_{30} (EC_{30}/natural ligand EC_{30}) (Efficacy)[c]					
No.	R	RAR-α	RAR-β	RAR-γ	RXR-α	RAR-α	RAR-β	RAR-γ	RXR-α	RXR-β	RXR-γ
10		372	432	187	12.7	21 (93%)	11 (104%)	25 (100%)	5.2 (119%)	7.4 (91%)	3.3 (125%)
14a	Me	nd[d]	nd[d]	nd[d]	4.7	6100 (26%)	40 (94%)	230 (107%)	0.16 (104%)	0.12 (98%)	0.081 (158%)
14b	Et	nd[d]	nd[d]	nd[d]	6.6	-[e]	1600 (36%)	-[e]	0.067 (121%)	0.068 (129%)	0.033 (233%)
14c	*n*-Pr	nd[d]	nd[d]	nd[d]	9.0	-[e]	660 (37%)	-[e]	0.68 (146%)	0.45 (139%)	0.30 (205%)
14d	*n*-Bu	nd[d]	nd[d]	nd[d]	121	-[e]	-[e]	-[e]	110 (125%)	59 (34%)	32 (92%)
 **LGD 1069**		nd[d]	nd[d]	nd[d]	3.0	3900 (28%)	450 (53%)	3400 (47%)	1.2 (139%)	0.86 (117%)	0.61 (132%)
ATRA		1.0 0.5 nM[f]	1.0 0.5 nM[f]	1.0 0.3 nM[f]	43.4	1.0 0.74 nM[g]	1.0 0.38 nM[g]	1.0 0.08 nM[g]	1.2	38	21
9-*cis*-RA		5.4	3.9	7.0	1.0 11.5 nM[f]	2.4	1.6	1.9	1.0 2.8 nM[g]	1.0 40 nM[g]	1.0 15 nM[g]

[a] Specific binding affinity was defined as the total binding minus the nonspecific binding, and the 50% inhibitory dose (IC_{50}) values were obtained from logarithmic plots. In some cases, Scatchard plot analysis was performed. The selectivity of test compounds for each receptor is indicated as relative IC_{50}, where the IC_{50} value for each receptor was divided by that of the natural ligand (ATRA or 9-*cis*-RA). [b] EC_{30} values were determined from full dose−response curves ranging from 0.1 nM to 3 μM. Retinoid activity is expressed in terms of relative EC_{50}, which is the concentration of retinoid required to produce 30% of the maximal observed response, normalized relative to that of ATRA or 9-*cis*-RA. [c] Efficacy was calculated as percent maximal induction normalized to 9-*cis*-RA for the RXRs and to ATRA for the RARs. [d] Not detected at 500 nM. [e] Test compounds showing less than 30% of the maximal activity of ATRA or 9-*cis*-RA at 3 μM were considered inactive. [f] Binding affinity (IC_{50}). [g] Transactivation (EC_{30}).

only as RXR agonists. Introduction of an *n*-butyl substituent at the 7-position of the triene moiety (**14d**) significantly decreased the potency at RXRs. These findings can be more clearly depicted by a graphical representation of the cotransfection data (Figure 1). Thus, in this series, the nature of the 7-alkyl group critically determines the agonist activity of these retinoid ligands.

Compound **14b**, which has an ethyl substituent at the 7-position and fluorine at the 6-position of the triene moiety, is one of the most potent and selective RXRs agonists reported to date. It causes transactivation of RXRs approximately 10-fold more potent than Targretin (LGD 1069), which is under development for the treatment of cancer[21] and diabetes.[22]

It is evident that the stable 9-cis conformation plays a critical role in orienting the triene moiety with respect to the tetrahydroquinoline nucleus. Compound **14b** (ER-35794) showed good absorption into the systemic circulation after oral administration in preclinical studies (data not shown). In view of its specific agonist

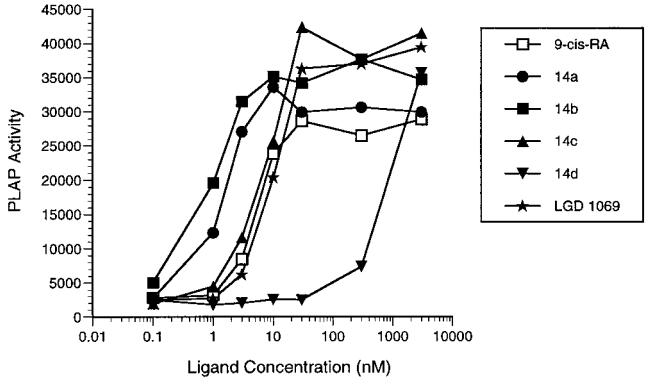


Figure 1. Transactivation dose−response curves for RXR-α of 9-*cis*-RA, **14a**−**d**, and LGD 1069.

activities for RXRs, **14b** could be a candidate for clinical application.

Experimental Section

Chemistry. Reagents and solvents were purchased from the usual commercial sources. Silica gel (Kieselgel 60, Merck) was used for column chromatography and silica gel (Kieselgel 60 F_{254}, Merck) for analytical thin-layer chromatography (TLC). Compounds were detected on TLC plates by exposure to UV light (254 nm). Melting points were measured on a Yanagimoto micro melting point apparatus without correction. ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were obtained on a JEOL JMS-HX100 mass spectrometer. All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure.

1-(1-Methylethyl)-1,2,3,4-tetrahydroquinoline-6-carbaldehyde (3). To a flask containing 29.2 g (0.4 mol) of *N*,*N*-dimethylformamide cooled to 10 °C and protected from moisture was added 18.6 g (0.12 mol) of phosphorus oxychloride. 1-(1-Methylethyl)-1,2,3,4-tetrahydroquinoline (**2**) (17.5 g, 0.10 mol) in *N*,*N*-dimethylformamide (3 mL) was then added slowly with stirring at such a rate to keep the temperature at 20−35 °C. The mixture was kept at 35 °C for 30 min, and then it was poured onto crushed ice. The whole was neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate twice. The organic layer was washed with brine, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent, *n*-hexane−ethyl acetate = 1:9) to afford **3** (11.4 g, 0.056 mol, 56%) as a red-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 6.5 Hz, 6H), 1.90 (tt, J = 6.0, 6.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 3.27 (t, J = 6.0 Hz, 2H), 4.20 (hept, J = 6.5 Hz, 1H), 6.69 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 2.0, 9.0 Hz, 1H), 9.63 (s, 1H).

1-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-ethanol (4a). To a 3.0 M solution of methylmagnesium bromide (4.9 mL, 15 mmol) in diethyl ether (15 mL) was added 1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-carbaldehyde (**3**) (2.0 g, 9.8 mmol) in diethyl ether (10 mL) over a period of 10 min while the ether refluxed as a result of the heat reaction. After the mixture had been stirred at room temperature for 1 h, the mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to afford **4a** (2.1 g, 9.6 mmol, 98%) as a red-brown oil which was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.5 Hz, 6H), 1.48 (d, J = 6.5 Hz, 3H), 1.91 (tt, J = 6.0, 6.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H), 4.11 (hept, J = 6.5 Hz, 1H), 4.76 (q, J = 6.0 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 2.0, 9.0 Hz, 1H).

1-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-ethanone (5a). To a solution of 1-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-ethanol (**4a**) (2.1 g, 9.6 mmol) in acetone (10 mL) was added manganese(IV) oxide (activated, <5 μm) (10 g) at room temperature. The mixture was stirred for 12 h at the same temperature, and manganese(IV) oxide was filtered out with Celite. The organic solution was evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent, *n*-hexane−ethyl acetate = 1:9) to afford **5a** (1.3 g, 6.0 mmol, 63%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.5 Hz, 6H), 1.89 (tt, J = 6.0, 6.0 Hz, 2H), 2.48 (s, 3H), 2.75 (t, J = 6.0 Hz, 2H), 3.24 (t, J = 6.0 Hz, 2H), 4.19 (hept, J = 6.5 Hz, 1H), 6.63 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.69 (dd, J = 2.0, 9.0 Hz, 1H).

Ethyl (*E*)-3-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-butenoate (6). To a suspension of 60% sodium hydride (2.0 g, 51 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise a solution of triethyl phosphonoacetate (11.3 g, 51 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0 °C. After the addition was completed, the mixture was stirred at room temperature for 30 min, and then a solution of 1-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-ethanone (**5a**) (5.5 g, 25.3 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise. The reaction mixture was stirred for 48 h under heating at 60 °C and then poured onto 100 mL of ice−water. The whole mixture was extracted with ethyl acetate twice. The organic layer was separated, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent, *n*-hexane−ethyl acetate = 96:4) to afford **6** (4.0 g, 13.9 mmol, 55%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.5 Hz, 6H), 1.31 (t, J = 6.5 Hz, 3H), 1.90 (tt, J = 6.0, 6.0 Hz, 2H), 2.55 (d, J = 1.0 Hz, 3H), 2.74 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 4.13 (hept, J = 6.5 Hz, 1H), 4.19 (q, J = 6.5 Hz, 2H), 6.09 (q, J = 1.0 Hz, 1H), 6.64 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 2.0, 9.0 Hz, 1H).

(*E*)-3-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-butenol (7). To a solution of ethyl (*E*)-3-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-butenoate (**6**) (1.0 g, 3.5 mmol) in THF (20 mL) was added dropwise a 1.5 M solution of diisobutylaluminum hydride in *n*-hexane (7.0 mL, 10.5 mmol) at −70 °C. The reaction mixture was stirred for 3 h at the same temperature, quenched with a saturated aqueous solution of ammonium chloride, stirred for 2 h, and then extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to afford **7** (650 mg, 2.6 mmol, 74%) as a colorless oil which was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 6.5 Hz, 6H), 1.90 (tt, J = 6.0, 6.0 Hz, 2H), 2.04 (s, 3H), 2.74 (t, J = 6.0 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H), 4.11 (hept, J = 6.5 Hz, 1H), 4.18 (br. d, J = 5.0 Hz, 1H), 4.33 (d, J = 6.5 Hz, 2H), 5.89 (t, J = 6.5 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 2.0, 8.5 Hz, 1H).

(*E*)-3-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-butenal (8). To a solution of (*E*)-3-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-butenol (**7**) (650 mg, 2.6 mmol) in acetone (10 mL) was added manganese(IV) oxide (activated, <5 μm) (3.5 g) at room temperature. The mixture was stirred for 12 h at the same temperature, and manganese(IV) oxide was filtered out with Celite. The organic solution was evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent, *n*-hexane−ethyl acetate = 1:9) to afford **8** (400 mg, 1.6 mmol, 62%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.5 Hz, 6H), 1.91 (tt, J = 6.0, 6.0 Hz, 2H), 2.50 (s, 3H), 2.75 (t, J = 6.0 Hz, 2H), 3.23 (t, J = 6.0 Hz, 2H), 4.16 (hept, J = 6.5 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 2.0, 9.0 Hz, 1H), 10.10 (d, J = 8.0 Hz, 1H).

Methyl (*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-3-methylocta-2,4,6-trienoate (9). To a suspension of 60% sodium hydride (98 mg, 2.46 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise a solution of methyl 3-methyl-4-diethylphosphonocrotonate (560 mg, 2.14 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0 °C. After the addition was completed, the mixture was stirred at room temperature for 30 min, and then a solution of (*E*)-3-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-butenal (**8**) (400 mg, 1.64 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise. The reaction mixture was stirred for 1 h and then poured onto 100 mL of ice−water. The whole mixture was extracted with ethyl acetate twice. The organic layer was separated, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent, *n*-hexane−ethyl acetate = 85:15) to afford **9** (330 mg, 0.97 mmol, 59%) as a red-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 6H), 1.91 (tt, J = 6.0, 6.0 Hz, 2H), 2.20 (s, 3H), 2.38 (d, J = 0.8 Hz, 3H), 2.75 (t, J = 6.0 Hz, 2H), 3.19 (t, J = 6.0 Hz, 2H), 3.72 (s, 3H), 4.15 (hept, J = 6.8 Hz, 1H), 5.77 (s, 1H), 6.32 (d, J = 15.2 Hz, 1H), 6.53 (d, J = 11.2 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 7.06 (dd, J = 11.2, 15.2 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 2.4, 8.8 Hz, 1H).

(*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-3-methylocta-2,4,6-trienoic Acid (10). A solution of methyl (*E*,*E*,*E*)-7-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-3-methylocta-2,4,6-trienoate (**9**) (330 mg, 0.97 mmol) in ethanol (10 mL) was treated with 5 N sodium hydroxide solution (1.0 mL). The mixture was heated under a nitrogen atmosphere at 60 °C for 1 h followed by the addition of 3 g of ice. The pH thereof was adjusted to 5 with 6 N hydrochloric acid. The precipitate was collected by filtration and washed with water. This product was recrystallized from ethanol to afford **10** (100 mg, 0.31 mmol, 32%) as an orange solid: mp 172−173 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.5 Hz, 6H), 1.91 (tt, J = 6.0, 6.0 Hz, 2H), 2.21 (s, 3H), 2.39 (s, 3H), 2.75 (t, J = 6.0 Hz, 2H), 3.19 (t, J = 6.0 Hz, 2H), 4.13 (hept, J = 6.5 Hz, 1H), 5.79 (s, 1H), 6.35 (d, J = 15.0 Hz, 1H), 6.55 (d, J = 11.0 Hz, 1H), 6.66 (d, J = 9.0 Hz, 1H), 7.10 (dd, J = 15.0, 11.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 9.0, 2.0 Hz, 1H). Anal. ($C_{21}H_{27}NO_2 \cdot H_2O$) C, N; H: calcd, 8.51; found, 7.95. HRMS Calcd for $C_{21}H_{27}NO_2$: 325.2042. Found: 325.2040.

Ethyl (*E*)-3-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-fluoro-2-butenoate (11a). To a suspension of 60% sodium hydride (450 mg, 11.3 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise a solution of triethyl 2-fluoro-2-phosphonoacetate (3.3 g, 13.6 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0 °C. After the addition was completed, the mixture was stirred at 0 °C for 1 h, and then a solution of 1-[1-(1-methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-ethanone (**5a**) (2.0 g, 9.2 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C then poured onto ice−water. The whole mixture was extracted with ethyl acetate twice. The organic layer was separated, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent, *n*-hexane−ethyl acetate = 90:10) to afford **11a** (2.3 g, 7.5 mmol, 66%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H), 1.18 (d, J = 6.8 Hz, 6H), 1.89 (tt, J = 6.0, 6.0 Hz, 2H), 2.12 (d, J = 4.8 Hz, 3H), 2.71 (t, J = 6.0 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H), 4.12 (hept, J = 6.8 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 2.4, 8.8 Hz, 1H).

Ethyl (*E*)-3-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-fluoro-2-butenal (12a). Compound **12a** was synthesized from **11a** by following the representative procedure described for **4a** and **5a**. A colorless oil of **12a** was obtained in 39% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.8 Hz, 6H), 1.91 (tt, J = 6.0, 6.0 Hz, 2H), 2.25 (d, J = 3.6 Hz, 3H), 2.73 (t, J = 6.0 Hz, 2H), 3.22 (t, J = 6.0 Hz, 2H), 4.12 (hept, J = 6.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 2.4, 8.4 Hz, 1H), 9.35 (d, J = 19.6 Hz, 1H).

Methyl (*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-6-fluoro-3-methylocta-2,4,6-trienoate (13a). Compound **13a** was synthesized from **12a** by following the representative procedure described for **9**. A brown oil of **13a** was obtained in 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.8 Hz, 6H), 1.92 (tt, J = 6.0, 6.0 Hz, 2H), 2.12 (d, J = 3.6 Hz, 3H), 2.21 (d, J = 0.8 Hz, 3H), 2.74 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 3.70 (s, 3H), 4.13 (hept, J = 6.8 Hz, 1H), 5.84 (s, 1H), 6.50 (d, J = 15.6 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.68 (dd, J = 15.6, 26.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.95 (dd, J = 2.4, 8.4 Hz, 1H).

(*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-6-fluoro-3-methylocta-2,4,6-trienoic Acid (14a). Compound **14a** was synthesized from **13a** by following the representative procedure described for **10**. An orange solid of **14a** was obtained in 47% yield: mp 138−139 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.4 Hz, 6H), 1.92 (tt, J = 6.0, 6.0 Hz, 2H), 2.12 (d, J = 3.2 Hz, 3H), 2.21 (s, 3H), 2.74 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 4.13 (hept, J = 6.4 Hz, 1H), 5.86 (s, 1H), 6.52 (d, J = 15.6 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.71 (dd, J = 15.6, 26.4 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 2.4, 8.8 Hz, 1H). Anal. ($C_{21}H_{26}FNO_2 \cdot 0.8H_2O$) C, N; H: calcd, 7.77; found, 7.12. HRMS Calcd for $C_{21}H_{26}FNO_2$: 343.1947. Found: 343.1955.

(*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-6-fluoro-3-methylnona-2,4,6-trienoic Acid (14b). Compound **14b** was synthesized from **13b** by following the representative procedure described for **10**. An orange solid of **14b** was obtained in 26% yield: mp 161−162 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 6.8 Hz, 6H), 1.88−1.95 (m, 2H), 2.19 (s, 3H), 2.55 (dq, J = 2.8, 7.6 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 4.13 (hept, J = 6.4 Hz, 1H), 5.85 (s, 1H), 6.51 (d, J = 15.2 Hz, 1H), 6.63 (dd, J = 16.0, 25.6 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.4, 8.8 Hz, 1H). Anal. ($C_{22}H_{28}FNO_2 \cdot 0.1H_2O$) C, H, N. HRMS Calcd for $C_{22}H_{28}FNO_2$: 357.2104. Found: 357.2112.

(*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-6-fluoro-3-methyldeca-2,4,6-trienoic Acid (14c). Compound **14c** was synthesized from **13c** by following the representative procedure described for **10**. An orange solid of **14c** was obtained in 96% yield: mp 120−121 °C (EtOH−water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 3H), 1.21 (d, J = 6.8 Hz, 6H), 1.39 (tq, J = 7.6, 7.6 Hz, 2H), 1.88−1.95 (m, 2H), 2.19 (s, 3H), 2.51 (dt, J = 2.8, 7.6 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 4.12 (hept, J = 6.4 Hz, 1H), 5.86 (s, 1H), 6.51 (d, J = 16.0 Hz, 1H), 6.64 (dd, J = 16.0, 26.0 Hz, 1H), 6.64 (d, J = 9.2 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.4, 8.8 Hz, 1H). Anal. ($C_{23}H_{30}FNO_2 \cdot 0.4H_2O$) C, H, N. HRMS calcd for $C_{23}H_{30}FNO_2$: 371.2260. Found: 371.2256.

(*E*,*E*,*E*)-7-[1-(1-Methylethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-6-fluoro-3-methylundeca-2,4,6-trienoic Acid (14d). Compound **14d** was synthesized from **13d** by following the representative procedure described for **10**. An orange solid of **14d** was obtained in 65% yield: mp 82−83 °C (EtOH−water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H), 1.21 (d, J = 6.4 Hz, 6H), 1.25−1.40 (m, 4H), 1.92 (tt, J = 6.0, 6.0 Hz, 2H), 2.19 (s, 3H), 2.45−2.60 (m, 2H), 2.73 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 4.12 (hept, J = 6.4 Hz, 1H), 5.85 (s, 1H), 6.51 (d, J = 15.2 Hz, 1H), 6.63 (dd, J = 16.0, 26.0 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.4, 8.8 Hz, 1H). Anal. ($C_{24}H_{32}FNO_2 \cdot 1.8H_2O$) C, N; H: calcd, 8.59; found, 7.50. HRMS Calcd for $C_{24}H_{32}FNO_2$: 385.2416. Found: 385.2415.

Biology. Plasmid Construction. Full-length human RAR-α, β, and γ and RXR-α, β, and γ cDNAs were cloned by polymerase chain reaction (PCR) from QUICK-clone cDNA (Clontech, Palo Alto, CA) derived from liver or placenta, and the correctness of the sequences was confirmed. Each cDNA was inserted into the *Pst*I/*Kpn*I site of expression vector pcDLSRα-296.[39] The reporter plasmids, CRBP I-PLAP and CRBP II-PLAP, were constructed as follows. The response element CRBPI (DR2) or CRBPII (DR1) was synthesized[13] and inserted into the 5′-*Spe*I and 3′-*Xba*I site upstream of the thymidine kinase (TK) promoter in pTK-PLAP.[40]

Binding Assay. Unlabeled ATRA was purchased from Sigma (St. Louis, MO). [^{3}H]-ATRA was purchased from DuPont/NEN. Unlabeled 9-*cis*-RA or [^{3}H]-9-*cis*-RA was synthesized from ATRA or [^{3}H]-ATRA by the method of Heyman et al.[15] The pcDLSRα296 human RAR-α, β, and γ or RXR-α and pSV2-DHFR plasmid were cotransfected into BHK cells by the calcium phosphate method. For the selection of a stable transformant, the transfected cells were maintained in the medium containing 250 nM methotrexate (MTX). We selected several clones which were resistant to MTX, and the receptor sequence was confirmed by PCR. The nuclear extracts of these stable transformants were used for the binding assay. Nuclear extracts were prepared by the method of Nervi et al.[27] A 180-μL aliquot of nuclear extract was incubated with 10 μL of 10 nM [^{3}H]-ATRA or 15 nM [^{3}H]-9-*cis*-RA and 10 μL of various concentrations of unlabeled compounds in a 96-well polypropylene plate. The plate was incubated for 16 h at 4 °C, and then 50 μL/well of a charcoal/dextran suspension (3% Norit A/0.3% dextran in 10 mM Tris-HCl pH 7.4, 0.02% sodium

azide) was added for 10 min at 4 °C. The plate was centrifuged for 5 min, and the supernatants were subjected to liquid scintillation counting. Binding in the presence of a 1000-fold excess of unlabeled ligand was defined as nonspecific binding. Specific binding was defined as the total binding minus the nonspecific binding, and the 50% inhibitory dose (IC_{50}) values were obtained from logarithmic plots. The selectivity of compounds for each receptor is indicated as relative IC_{50}, obtained by dividing the IC_{50} value for each receptor of the compound by that of the natural ligand (ATRA or 9-*cis*-RA).

Transactivation Assay. COS-1 cells at 80% confluence in a 60-mm dish were incubated with 6 μg of receptor expression plasmid, 6 μg of reporter plasmid, and 40 μL of Lipofectamine (GIBCO-BRL, Gaithersburg, MD) per dish in OPTI-MEM (GIBCO-BRL). After the cells had incubated for 4 h, the medium was replaced with D-MEM (GIBCO-BRL) supplemented with 10% FBS, and incubation was continued for 20 h. The cells were then suspended in D-MEM supplemented with 10% FBS and seeded at 3×10^4 per well in 96-well plates. After the cells had incubated for 6 h, compounds at various concentrations were added to duplicate wells. The cells were incubated for a further 48 h, and then the supernatants were assayed for PLAP activity.[40] To inactivate nonspecific activity, the samples were preheated at 65 °C for 20 min. Aliquots of 15 μL were mixed with 60 μL of assay buffer (0.28 M Na_2CO_3−$NaHCO_3$, pH 10.0, containing 8 mM $MgSO_4$) and reacted with 75 μL of substrate (Lumistain, Sumitomo, Osaka, Japan). After the reaction mixture had incubated for 30 min at 37 °C and 30 min at room temperature, steady-state chemiluminescence was measured with a microplate luminometer (LB96P, EG&G Bertold, Bad Wildbad, Germany). A 100% transactivation was defined as the value at 3 μM natural ligand (ATRA or 9-*cis*-RA), and the 30% efficacy dose (EC_{30}) values of compounds were obtained from logarithmic plots. The selectivity of compounds for each receptor is indicated as relative EC_{30}, obtained by dividing the EC_{30} value for each receptor of the compound by that of the natural ligand (ATRA or 9-*cis*-RA).

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Supporting Information Available: Descriptions of syntheses of intermediates (**5b**−**d**, **11b**−**d**, **12b**−**d**, and **13b**−**d**) (4 pages). Ordering information is given on any current masthead page.

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