Synthesis and Structure−Activity Relationships of Retinoid X Receptor Selective Diaryl Sulfide Analogs of Retinoic Acid

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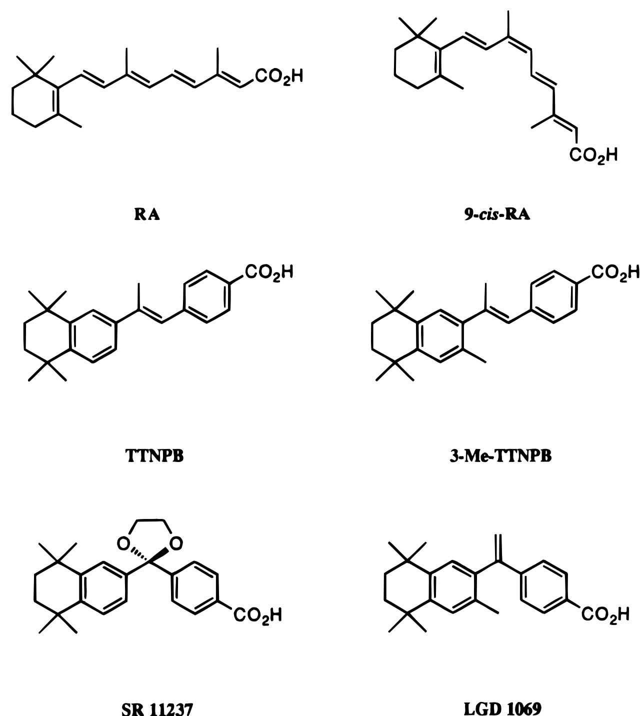
Retinoids exert their biological effects by binding to and activating nuclear receptors that interact with responsive elements on DNA to promote gene transcription. There are two families of retinoid receptors, the retinoic acid receptor (RAR) family and the retinoid X receptor (RXR) family, which are each further divided into three subclasses: $RAR_{\alpha,\beta,\gamma}$ and $RXR_{\alpha,\beta,\gamma}$. Herein we describe the synthesis and structure−activity relationships of a new series of diaryl sulfide retinoid analogs that specifically bind and transactivate the RXRs. Furthermore, the sulfoxide and sulfone derivatives of these analogs are partial agonists which activate the RXRs only at high concentrations. Thus, these compounds possess a potential site of metabolic deactivation and may have less prolonged systemic effects than other compounds with arotinoid-like structures. We show also that these compounds have activity in nontransfected cells as demonstrated by their ability to induce TGase activity in HL-60 cells. Finally, we corroborate our earlier report that RXR-specific agonists may possess reduced teratogenic toxicity compared to RAR-specific agonists since these compounds are much less potent inhibitors of chondrogenesis than RAR-specific agonists such as TTNPB.

Introduction

Retinoids are natural and synthetic analogs of vitamin A that are involved in the regulation of several biological functions including cell differentiation and proliferation.[1] Clinically, retinoids are useful for the treatment of skin disorders[2] and cancer[3] and are currently being investigated in several other therapeutic areas, including arthritis,[4] dyslipidemias,[5] and the prevention of HIV-induced lymphopenia.[6] However, retinoids are of limited therapeutic value because they cause a number of undesirable side effects such as mucocutaneous toxicity and teratogenicity. Retinoids are believed to function by binding to nuclear receptors which regulate gene transcription.[7] The six known retinoid receptors are divided into two families: the retinoic acid receptor family (RARα,β,γ)[8] and the retinoid X receptor family (RXRα,β,γ).[9] *all-trans*-Retinoic acid (RA) specifically transactivates only the RARs, whereas 9-*cis*-retinoic acid (9-*cis*-RA) binds to and transactivates both RXRs and RARs.[10] Under physiological conditions, the RARs and RXRs form heterodimers which can bind to the promoter regions of genes to modulate gene transcription.[11] The RAR hormonal pathways can be activated by RAR-specific ligands which bind to the RAR component of the RAR−RXR heterodimer, but RXR-specific ligands appear unable to activate these pathways by binding to the RXR component. However, RXR ligands display synergistic activation of RA responsive genes when they are used in combination with RAR-specific ligands.[12] In addition, it is known that RXRs form homodimers in the presence of RXR ligands and regulate gene transcription through promoters that are distinct from those utilized by RAR−RXR heterodimers.[13] RXRs also form heterodimers with the thyroid, vitamin D, and other receptors.[11] Thus, the biology associated with the RXR family is still being elucidated.



A number of groups have reported[13−17] the development of ligands that display varying degrees of selectivity for the RXRs. One important class of RXR selective compounds are 3-substituted stilbenes,[14] such as (*E*)-

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Table 1. Cotransfection Assay Data for Diaryl Sulfide Retinoids[a]

entry	Structure	number/ name	EC50 (nM) Efficacy (% RA)					
			RAR_{α}	RAR_{β}	RAR_{γ}	RXR_{α}	RXR_{β}	RXR_{γ}
i		RA	350	80	10	900	1400	1100
ii		9-*cis* RA	191	50	45	100	200	140
iii		1	NA (3)	570 (66)	340 (37)	770 (51)	1600 (80)	1600 (75)
iv		2	NA (3)	NA (4)	NA (6)	280 (57)	300 (74)	280 (112)
v		3	NA (5)	NA (4)	NA (3)	NA (17)	3000 (29)	1600 (28)
vi		4	NA (2)	NA (6)	NA (0)	2800 (55)	2600 (52)	2600 (45)
vii		5	NA (1)	NA (4)	NA (0)	54 (91)	57 (100)	42 (85)
viii		6	NA (1)	NA (0)	NA (7)	2300 (85)	1300 (117)	1900 (70)

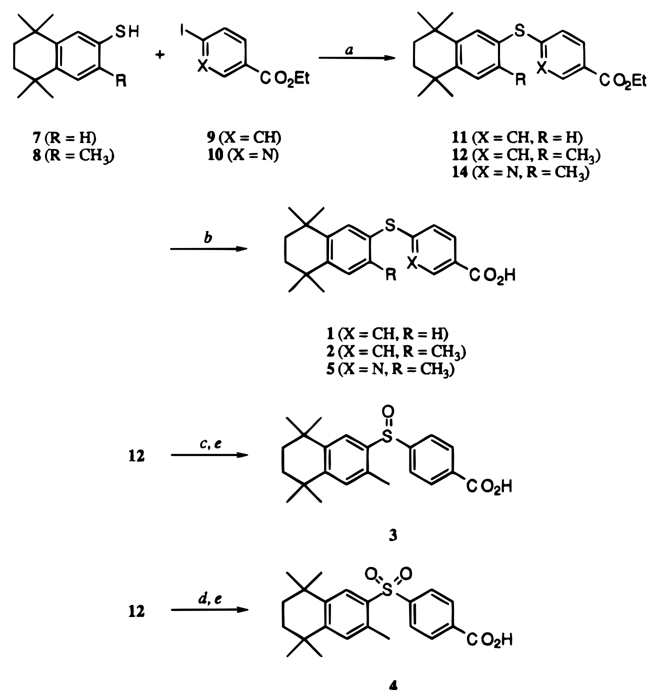
[a] NA indicates *not active* (*i.e.*, $EC_{50} > 10^4$ nmol). EC_{50} values were determined from full dose-response curves ranging from 10^{-12} to 10^{-5} M. Retinoid activity was normalized to that of *all-trans* RA and is expressed as potency (EC_{50}), which is the concentration of retinoid required to produce 50% of the maximal observed response. Values represent the EC_{50} determination of a single experiment with triplicate determinations. Standard errors for this assay system are, on average, approximately 15% of the mean values.

4-[2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)propen-1-yl]benzoic acid (3-methyl-TTNPB). 3-Methyl-TTNPB is a pan-agonist (activates both RAR and RXR receptors), while its desmethyl analog, (*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propen-1-yl]benzoic acid (TTNPB), is a highly potent and specific activator of the RARs. Recently, we reported[15] that substitution of the benzoate moiety of 3-methyl-TTNPB with heteroaromatic carboxylic acids resulted in analogs with greater RXR selectivity as well as those with pan-agonist activities. A second class of RXR selective agonists are benzophenonecarboxylic acid derivatives such as SR 11237[16a] and LGD 1069,[16b,c] of which the latter is currently in phase I/IIA clinical trial for the treatment of cancer. In this report, we discuss the synthesis and structure–activity relationships (SAR) of RXR-specific compounds in which the tetrahydronaphthalene ring and the benzoic acid moieties are bridged by a sulfur atom. Further, we show that the sulfoxide and sulfone derivatives of these compounds have significantly reduced retinoid activity compared to the parent diaryl sulfide analogs. Thus, these compounds possess a potential site of metabolic deactivation and thus may have fewer prolonged systemic effects than other arotinoid-like derivatives.

Results and Discussion

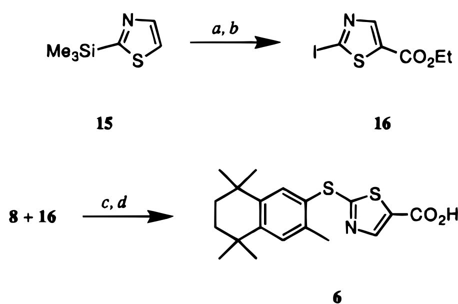
Chemistry. The analogs used in this study are summarized in Table 1. RA was purchased from Sigma Chemical Co. 9-*cis*-RA was synthesized according to literature procedures.[17] Analogs **1**–**5** were prepared as depicted in Scheme 1. Thus, 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-thiol (**7**)[18] was deprotonated with NaH and heated in the presence of CuI and ethyl 4-iodobenzoate (**9**) to give the coupled product, diaryl sulfide **11**, in 27% yield. The ester of **11** was saponified with LiOH in methanol to produce diaryl sulfide **1** in 62% yield. The same protocol was applied to 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-thiol (**8**)[19] to prepare ester **12**, which was saponified with KOH in ethanol to give **2** in 50% overall yield. Sulfide **12** was oxidized either with $NaIO_4$ to produce sulfoxide **3** in 37% overall yield after ester hydrolysis or with *m*-CPBA to

Scheme 1[a]



[a] (a) NaH, CuI, HMPA; (b) aqueous KOH, EtOH, 10% HCl; (c) **12**, $NaIO_4$; (d) **12**, *m*-CPBA; (e) aqueous LiOH, THF, 10% HCl.

Scheme 2[a]



[a] (a) *n*-BuLi, −78 °C, EtO_2CCl; (b) I_2, THF; (c) NaH, CuI, HMPA; (d) aqueous LiOH, THF, 10% HCl.

furnish sulfone **4** (92% after hydrolysis). The nicotinic acid derivative **5** was prepared in 39% yield by coupling **8** and ethyl 6-iodonicotinate (**10**) followed by saponification of the resulting ester **14**.

The synthesis of the thiazole derivative **6** is presented in Scheme 2. Thus, 2-(trimethylsilyl)thiazole (**15**) was carboxylated in the 5-position (*n*-BuLi, THF, −78 °C, EtO_2CCl) and the 2-trimethylsilyl group iodinated (I_2, THF) to give ethyl 2-iodo-5-thiazolecarboxylate (**16**). Compound **16** was coupled to **8** and saponified as described above to produce **6** in 32% yield.

Biological Studies. The retinoid analogs in Table 1 were tested separately for activity at each of the six retinoid receptors in a cotransfection assay,[9a,20,21] which measures the ability of compounds to induce transcription in CV-1 cells transiently cotransfected with a specific receptor gene construct and an appropriate reporter gene. The binding affinities of the compounds to each of the receptor subtypes were measured in competitive binding assays[13b,c] and are reported in Table 2. In the cotransfection assay, RA activates each of the RAR subtypes with high potency and each of the RXR subtypes with low potency, consistent with its ability to bind to each of these receptors. In contrast, 9-*cis*-RA binds to and activates each of the RAR and RXR subtypes with high affinity. In the cotransfection assay, the desmethyl analog **1** has no activity at RARα but effectively activates the other five retinoid receptors, albeit at high concentrations at RXRβ and RXRγ. In contrast, the 3-methyl derivative **2** is an RXR-specific transactivator which is 3−5-fold more potent than **1** at the RXRs and with absolutely no activity at the RARs. These results were confirmed in the competitive binding assay in which **1** has little affinity to any of the retinoid receptors, while **2** binds exclusively to the RXRs, with K_d values of approximately 300 nM. The sulfoxide and sulfone derivatives of **2**, compounds **3** and **4**, are lowered in their affinity to the RXRs relative to **2**. In addition, they are lowered in both efficacy and potency in the cotransfection assays, having only partial agonist activity at the RXRs even at high concentrations. The effects of heterocyclic carboxylic acid substitution on receptor binding and transactivation properties of these compounds was examined using the nicotinic acid isostere **5** and the thiazolecarboxylic acid analog **6**. The nicotinic acid moiety has a favorable effect on RXR transactivation and binding since **5** is at least 5-fold more potent than **2** in the transactivation assay and binds to the RXRs with about 4-fold higher affinity. Thus, the RXR-specific agonist **5** has receptor-binding and transactivation properties that are comparable to those of LGD 1069.[16b] However, the thiazole derivative **6** is 4−8-fold less potent than **2** in the cotransfection assays, having EC_{50} values of >1300 nM at all three RXRs. Both compounds are, however, specific for the RXRs having no RAR activity.

Previous studies have established that RXR selective retinoids induce tissue transglutaminase (TGase) in a human promyelocytic leukemia cell line (HL-60 cdm-1).[15a,1b,22] As a measure of their activity in a nontransfected cell line, we tested **2** and **5**, along with selected reference compounds, in the TGase assay (Table 3). As reported previously,[15a] while the RAR-specific agonist TTNPB is inactive in this assay, the RXR-specific diaryl sulfides **2** and **5** induced TGase activity effectively. We also wanted to determined the activity of these analogs in an assay of retinoid toxicity, namely, that of inhibition of chondrogenesis in mouse embryo limb bud mesenchymal cells (Table 2).[23] This assay is highly predictive of the *in vivo* teratogenic potential of retinoids in ICR mice.[24] We had previously reported that RXR selective analogs appear to be reduced in their teratogenic potential.[15a] In keeping with these observations and consistent with its RXR specificity, the diaryl sulfides **2** and **5** display very little activity in this assay, being more than 10000-fold less potent than the RAR-specific analog TTNPB.

Discussion

The data presented in Tables 1 and 2 demonstrate several interesting characteristics of these compounds. First, all of the compounds that were tested in this series that have a 3-methyl group on the tetrahydronaphthalene ring do not bind to or transactivate any of the RARs. Thus, it appears that a 3-methyl group on the tetrahydronaphthalene ring is necessary for RXR specificity and activity. This finding is consistent with our earlier results in the stilbene series in that a 3-substituent on the tetrahydronaphthalene ring resulted in significantly increased transactivational po-

Table 2. Competitive Binding Assay Data for Diaryl Sulfide Retinoids[a]

entry	Structure	number/name	K_d (nM)					
			RARα	RARβ	RARγ	RXRα	RXRβ	RXRγ
i		RA	15	13	18	>10³	>10³	350
ii		9-*cis* RA	7	7	17	32	12	4
iii		1	4081	4239	>10⁴	3868	3087	2846
iv		2	>10⁴	>10⁴	>10⁴	296	302	304
v		3	>10⁴	>10⁴	>10⁴	>10⁴	>10⁴	>10⁴
vi		4	>10⁴	>10⁴	>10⁴	2518	4122	3993
vii		5	NA	NA	NA	32	87	73
viii		6	>10³	>10³	>10³	>10³	>10³	>10³

[a] NA indicates *not active* (*i.e.*, K_d > 30000 nmol).

tencies at the RXRs and decreased potencies at the RARs. Second, the oxidized derivatives of **2**, sulfoxide **3** and sulfone **4**, are characterized by reduced transactivational potencies and lower binding affinities relative to sulfide **2**, suggesting that the sulfides have a potential site of metabolic deactivation that is not available to other RXR-specific compounds with arotinoid-like structures. Third, we recently reported that stilbenes substituted with nicotinic acid isosteres were of comparable potencies in the RXR cotransfection assays to the corresponding benzoic acid derivatives, whereas the thiazolecarboxylic acids had dramatically increased potencies. In the case of diaryl sulfides, however, the effect is altered; replacement of the benzoic acid group with a thiazolecarboxylic acid (compound **6**) significantly decreases the transactivational potencies for the RXRs, while replacement of the benzoic acid with a nicotinic acid increases RXR transactivational potencies. Thus, five-membered heteroaromatic carboxylic acid groups are detrimental to the RXR transactivational and binding properties of these compounds.

The data in Table 3 corroborate our earlier inference that RAR and RXR selective compounds possess different biological properties in nontransfected cells. The RXR-specific compounds **2** and **5** both appear to be able to induce TGase activity in HL-60 cells effectively, providing additional evidence that ligand-dependent RXR activation is necessary for the induction of TGase activity in these cells. In the chondrogenesis assay, the RXR-specific diaryl sulfides **2** and **5** are some of the least active retinoids tested, being about 10000-fold less potent than the RAR-specific arotinoid TTNPB. These data support our earlier suggestion[15a,24b] that the teratogenic potency of RXR selective agonists is decreased relative to RAR agonists.

Conclusions

In summary, we have described the synthesis and SAR of a new series of diaryl sulfide retinoid analogs that specifically bind to and transactivate RXRs. We have shown that a 3-methyl substituent on the tetrahydronaphthalene ring of these compounds is required for RXR specificity in receptor cotransfection and competitive binding assays. RXR transactivational potencies and binding affinities were increased further by replacement of the benzoic acid group of **2** with a nicotinic acid group as in compound **5**, a potent and specific RXR agonist. In addition, the sulfoxide and sulfone derivatives of **2**, compounds **3** and **4**, were shown to be partial agonists which activate the RXRs only at high concentrations. Thus, these compounds possess a potential site of metabolic deactivation and may have less pro-

Table 3. Biological Assay Data for Representative Retinoid Analogs

Compound number	Compound structure	Tgase Induction EC_{50} (nM)	Chondrogenesis Inhibition IC_{50} (nM)
RA		5	31
9-*cis*-RA		2	58
TTNPB		>1000	0.06
2		200	910
5		100	1000

longed systemic effects than compounds with arotinoid-like structures. Furthermore, the activity of these compounds in nontransfected cells was demonstrated by the ability of **2** and **5** to induce TGase activity in HL-60 cells. Finally, we have shown that these compounds are much less potent inhibitors of chondrogenesis than RAR-specific agonists such as TTNPB, thus corroborating our earlier suggestion that RXR-specific agonists possess reduced toxicity relative to RAR-specific agonists.

Experimental Section

General Procedures. RA was obtained from Sigma Chemical Co. 9-*cis*-RA was prepared by the procedure of Jong *et al.*[17] Solvents were used as purchased unless otherwise noted. When deemed necessary, reaction flasks containing magnetic stir bars were flame-dried, cooled under vacuum (<3 Torr), and flushed several times with dry argon before any reagents were added. Most reactions were monitored by analytical thin-layer chromatography (TLC) using Merck TLC glass plates precoated with silica gel 60 F_{254} (0.2 mm thick). Flash chromatography was performed using Merck silica gel 60. Melting points and boiling points are uncorrected. Unless the use of an internal thermometer is indicated, temperatures are reported as bath temperatures. IR spectra were obtained on a Mattson Galaxy Series 3000 FTIR spectrophotometer. NMR spectra were recorded on Gemini 300 (300 MHz) and XL 300 (300 MHz) Varian spectrometers. Mass spectral analyses were conducted on an EG 7070E organic mass spectrometer. Elemental analyses were conducted at Robertson Microlit Laboratories, Inc., Madison, NJ.

Ethyl 4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)thio]benzoate (11). Sodium hydride (0.807 g, 60% dispersion in oil, 20 mmol) was rinsed three times with hexane and dried under vacuum. The vacuum was broken with dry argon, to this was added 10.0 mL of dimethylformamide, and the mixture was cooled to 0 °C. 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenethiol[18] (702 mg, 3.2 mmol) was added, and the resulting mixture was stirred at 0−10 °C for 1.25 h. Copper(I) iodide (0.592 g, 3.1 mmol) was added, and the mixture was stirred at 0 °C for 45 min. A solution of ethyl 4-iodobenzoate (0.839 g, 3.04 mmol) and 2.0 mL of dimethylformamide was added, and the mixture was heated to 75 °C for 48 h, cooled to room temperature, and stirred for 48 h. The reaction mixture was then poured onto ice, and the products were extracted with ether (4×). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed *in vacuo* to give an orange solid. The crude product was purified by flash chromatography on silica gel (2% ethyl acetate in hexanes) to give **11** as a clear oil (0.32 g, 27%): IR (salt plate) 1716 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6 H), 1.30 (s, 6 H), 1.37 (t, 3 H, J = 7.1 Hz), 1.70 (s, 4 H), 4.34 (q, 2 H, J = 7.1 Hz), 7.17 (d, 2 H, J = 8.5 Hz), 7.22 (dd, 1 H, J = 2.0, 8.2 Hz), 7.32 (d, 1 H, J = 8.2 Hz), 7.44 (d, 1 H, J = 2.0 Hz), 7.89 (d, 2 H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 31.7, 34.3, 34.4, 34.9, 60.8, 126.7, 127.3, 128.0, 130.0, 131.0, 132.4, 137.6, 145.2, 146.0, 146.6, 166.3; MS (EI, 70 eV) m/z 368 (M^+, 58), 353 (100).

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)thio]benzoic Acid (1). To a solution of 70 mg (0.19 mmol) of ethyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)thio]benzoate (**11**) and 4.0 mL of THF were added 1.0 mL of LiOH (1.9 M aqueous solution) and 1.5 mL of MeOH. The solution was heated at 55 °C for 3 h, cooled to room temperature, and concentrated *in vacuo*. The residue was diluted with water and washed with hexanes. The aqueous layer was separated and acidified to pH = 1 with 10% aqueous HCl, and the products were extracted with ether (2×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (30% ethyl acetate in hexanes) to give **1** as a white solid (40 mg, 62%): mp 174−178 °C; IR (salt plate) 3500−2500 (COO*H*), 1689 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6 H), 1.31 (s, 6 H), 1.71 (s, 4 H), 7.18 (d, 2 H, J = 8.6 Hz), 7.25 (dd, 1 H, J = 2.0, 8.2 Hz), 7.34 (d, 1 H, J = 8.2 Hz), 7.47 (d, 1 H, J = 2.0 Hz), 7.95 (d, 2 H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8, 34.3, 34.5, 34.9, 126.4, 127.5, 128.1, 130.6, 131.3, 132.8,

146.2, 146.8, 146.9, 166.2; MS (EI, 70 eV) 340 (M^+, 55), 325 (100); HRMS calcd for $C_{21}H_{24}O_2S$ 340.1497, found 340.1493.

Ethyl 4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]benzoate (12). Sodium hydride (65 mg, 60% dispersion in oil, 1.62 mmol) was rinsed three times with hexane and dried under vacuum. The vacuum was broken with dry argon, and 2.5 mL of HMPA and 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenethiol[17] (0.38 g, 1.62 mmol) were added sequentially. After 30 min at 50 °C, copper(I) iodide (257 mg, 1.35 mmol) was added, which caused the solution to become deep green. The solution was stirred for 15 min, and ethyl 4-iodobenzoate (373 mg, 1.35 mmol) was added. The solution was heated to 90 °C for 5 h, the bath was removed, and stirring was continued overnight at room temperature. Water was added, and the products were extracted with diethyl ether (3×). The combined ether layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes) to give **12** as a light yellow solid (260 mg, 50%): mp 106–107.5 °C; IR 1716 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6 H), 1.30 (s, 6 H), 1.36 (t, 3 H, J = 7.1 Hz), 1.69 (s, 4 H), 2.28 (s, 3 H), 4.33 (q, 2 H, J = 7.1 Hz), 7.05 (d, 2 H, J = 8.6 Hz), 7.23 (s, 1 H), 7.26 (s, 1 H), 8.87 (d, 2 H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.3, 31.7, 31.8, 34.0, 34.2, 34.9, 35.0, 60.8, 125.7, 126.7, 126.9, 129.1, 129.9, 134.4, 138.8, 144.1, 145.2, 145.8, 166.3; MS (EI, 70 eV) *m/z* 382 (M^+, 42), 367 (67), 171 (100). Anal. ($C_{24}H_{30}O_2S$) C, H, S.

4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]benzoic Acid (2). Ethyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]benzoate (**12**; 170 mg, 0.44 mmol) was dissolved in ethyl alcohol (4 mL) and the solution treated with 2 M aqueous KOH (2 mL). The solution was heated to 50 °C for 4 h and concentrated *in vacuo*. The residue was treated with diethyl ether, cooled to 0 °C, and acidified with 10% aqueous HCl. The product was extracted with ether, washed with water and brine, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give **2** as a yellow solid (158 mg, 100%): mp 249–250 °C; IR 3300–2400 (COO*H*), 1672 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6 H), 1.31 (s, 6 H), 1.69 (s, 4 H), 2.29 (s, 3 H), 7.05 (d, 2 H, J = 8.5 Hz), 7.25 (s, 1 H), 7.26 (s, 1 H), 7.92 (d, 2 H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 31.7, 31.8, 34.1, 34.2, 34.9, 35.0, 125.4, 125.5, 126.3, 129.1, 130.6, 134.6, 139.0, 144.2, 146.9, 147.1, 171.0; MS (EI, 70 eV) *m/z* 354 (M^+, 41), 335 (67), 173 (100). Anal. ($C_{22}H_{26}O_2S$) C, H, S.

Ethyl 4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)sulfoxy]benzoate. To a solution of **12** (0.12 g, 0.31 mmol) and 4 mL of dioxane was added 1.0 mL of a 0.42 M solution of sodium periodate (prepared by dissolving 180 mg of sodium periodate in 0.7 mL of water and 1.3 mL of methanol). An additional 6.0 mL of methanol was added, and the resulting mixture was stirred at room temperature for 42 h and then heated to 50 °C for 8 days. Additional sodium periodate (80 mg, 0.38 mmol) and 2.0 mL of dioxane were added periodically during this time. The reaction mixture was cooled to room temperature, brine was added, and the mixture was extracted with ether (2×). The organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes) to give the title compound as a clear oil (65 mg, 52%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.24 (s, 3 H), 1.26 (s, 3 H), 1.30 (s, 3 H), 1.39 (t, 3 H, J = 7.1 Hz), 1.67 (s, 4 H), 2.31 (s, 3 H), 4.38 (q, 2 H, J = 7.1 Hz), 7.08 (s, 1 H), 7.66 (d, 2 H, J = 8.4 Hz), 7.76 (s, 1 H), 8.12 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.2, 31.6, 31.8, 34.3, 34.4, 34.8, 61.4, 123.7, 125.4, 129.5, 130.2, 132.5, 132.7, 139.1, 144.4, 148.8, 149.8, 165.6; MS (EI, 70 eV) *m/z* 398 (M^+, 12), 382 (23), 367 (34), 352 (100).

4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)sulfoxy]benzoic Acid (3). To a solution of 58 mg (0.15 mmol) of ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)sulfoxy]benzoate and 4.0 mL of THF were added 1.0 mL of 2 M aqueous LiOH and 2.0 mL of MeOH. The solution was heated at 55 °C for 2 h, cooled to room temperature, and stirred for 8 h. The reaction mixture was concentrated *in vacuo*, the residue was treated with brine and acidified with 10% aqueous HCl, and the product was extracted with ether (2×). The combined ether layers were dried ($MgSO_4$) and filtered, and the solvents were removed *in vacuo* to give **3** as a white solid (0.39 mg, 72%): mp 235–240 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.24 (s, 3 H), 1.26 (s, 3 H), 1.29 (s, 3 H), 1.66 (s, 4 H), 2.34 (s, 3 H), 7.10 (s, 1 H), 7.70 (d, 2 H, J = 8.3 Hz), 7.76 (s, 1 H), 8.17 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 31.5, 31.6, 31.8, 34.3, 34.4, 34.7, 124.0, 125.6, 129.6, 130.8, 131.6, 132.9, 138.5, 144.6, 149.1, 150.2, 169.9; MS (EI, 70 eV) *m/z* 370 (M^+, 25), 357 (100). Anal. ($C_{22}H_{26}O_3S$) C, H.

Ethyl 4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)sulfonyl]benzoate. To a solution of 69 mg (0.18 mmol) of **12** in 2.0 mL of methylene chloride was added a solution of *m*-chloroperoxybenzoic acid (80 mg, 50–60%, 0.27 mmol) and 2.0 mL of methylene chloride. The resulting solution was stirred at room temperature for 3 h and diluted with water, and the products were extracted with methylene chloride (2×). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes) to give the title compound as a white solid (51 mg, 94%): mp 130–131 °C; IR 2962, 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6 H), 1.34 (s, 6 H), 1.39 (t, 3 H, J = 7.1 Hz), 1.70 (s, 4 H), 2.33 (s, 3 H), 4.40 (q, 2 H, J = 7.1 Hz), 7.11 (s, 1 H), 7.90 (d, 2 H, J = 8.5 Hz), 8.15 (s, 1 H), 8.16 (d, 2 H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.8, 31.5, 31.7, 34.3, 34.5, 34.7, 61.7, 127.5, 128.1, 130.1, 131.0, 134.1, 134.3, 135.0, 143.9, 145.5, 151.7, 165.1; MS (EI, 70 eV) *m/z* 416 (MH^+, 9), 414 (9), 399 (76), 305 (86), 77 (100). Anal. ($C_{24}H_{30}O_4S$) C, H.

4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)sulfonyl]benzoic Acid (4). To a solution of 50 mg (0.12 mmol) of ethyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)sulfonyl]benzoate and 3.0 mL of THF was added 1.0 mL of 1 N aqueous LiOH. The solution was heated to 50 °C for 3 h, cooled to room temperature, and concentrated *in vacuo*. The residue was diluted with brine and acidified with 10% aqueous HCl, and the products were extracted with ether (2×). The combined ether layers were dried ($MgSO_4$) and filtered, and the solvents were removed *in vacuo* to give **4** as a white solid (45 mg, 98%): mp 228–231 °C; IR 3300–2500, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6 H), 1.34 (s, 6 H), 1.70 (s, 4 H), 2.33 (s, 3 H), 7.12 (s, 1 H), 7.95 (d, 2 H, J = 8.4 Hz), 8.15 (s, 1 H), 8.22 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 31.5, 31.7, 34.3, 34.5, 34.7, 127.7, 128.2, 130.8, 131.1, 134.1, 134.8, 144.0, 146.5, 151.9, 165.0; MS (EI, 70 eV) 387 *m/z* 387 (MH^+, 33), 371 (100). Anal. ($C_{22}H_{26}O_4S$) C, H, S.

Ethyl 6-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]nicotinate (14). Sodium hydride (171 mg, 60% dispersion in oil, 4.3 mmol) was rinsed three times with hexane and dried under vacuum. The vacuum was broken with dry argon, and 6.6 mL of HMPA and 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenethiol (1.0 g, 4.27 mmol) were added sequentially. After 30 min at 50 °C, copper(I) iodide (678 mg, 3.56 mmol) was added, which caused the solution to become deep green. The solution was stirred for an additional 15 min at 50 °C, ethyl 2-iodonicotinate (986 mg, 3.56 mmol) was added, and the solution was heated to 90 °C for 5 h. The heating bath was removed, and the reaction mixture was stirred overnight at room temperature. Water was added, and the products were extracted with diethyl ether (3×). The combined ether layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (5% ethyl acetate in hexanes) to give **14** as a light yellow solid (642 mg, 47%): mp 110–111 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6 H), 1.31 (s, 6 H), 1.37 (t, 3 H, J = 7.1 Hz), 1.69 (s, 4 H), 2.32 (s, 3 H), 4.36 (q, 2 H, J = 7.1 Hz), 6.68 (d, 1 H, J = 8.0 Hz), 7.23 (s, 1 H), 7.53 (s, 1 H), 7.99 (dd, 1 H, J = 2.3, 8.0 Hz), 9.00 (d, 1 H, J = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.4, 31.7, 31.8, 34.1, 34.2, 34.9, 34.9, 61.1, 118.9, 121.8, 125.3, 129.3, 135.1, 137.2, 139.2, 144.4, 147.6,

150.7, 165.3, 167.9; MS (EI, 70 eV) *m/z* 383 (M^+, 47), 368 (83), 350 (100). Anal. ($C_{23}H_{29}NO_2S$) C, H, N, S.

6-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]nicotinic Acid (5). To a solution of ethyl 2-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]nicotinate (300 mg, 0.78 mmol) and ethanol (8 mL) was added 2 *N* KOH (2 mL), and the resulting solution was stirred at 50 °C for 34 h. The solution was concentrated *in vacuo*, water was added, and the mixture was acidified with 10% aqueous HCl. The product was extracted with methylene chloride (3×), and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The solid residue was recrystallized from acetonitrile/methanol (4:1) to give the title compound (233 mg, 84%) as light yellow crystals: mp 259−260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21 (s, 6 H), 1.26 (s, 6 H), 1.63 (s, 4 H), 2.23 (s, 3 H), 6.81 (d, 1H, *J* = 8.2 Hz), 7.39 (s, 1 H), 7.50 (s, 1 H), 7.05 (dd, 1 H, *J* = 2.1, 8.2 Hz), 8.84 (d, 1H, *J* = 2.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.9, 31.4, 31.4, 33.7, 33.9, 34.4, 119.0, 122.6, 124.8, 129.2, 134.4, 137.7, 138.9, 143.9, 147.1, 150.3, 165.7, 166.0; MS (EI, 70 eV) *m/z* 355 (M^+, 31), 340 (80), 322 (100). Anal. ($C_{21}H_{25}NO_2S$) C, H, N, S.

Ethyl 2-Iodo-5-thiazolecarboxylate (16). To a solution of 4.96 g (31.5 mmol) of 2-(trimethylsilyl)thiazole in 100 mL of ether at −78 °C under argon was added *n*-BuLi (23.0 mL, 36.8 mmol, 1.6 M in hexanes), and the resulting mixture was stirred at −78 °C for 30 min. Ethyl chloroformate (7.60 mL, 10.6 g, 98 mmol) was added, and the reaction mixture was stirred at −78 °C for 30 min and then at room temperature for 30 min. The solution was recooled to −78 °C, and a solution of 10.8 g (42.5 mmol) of iodine and 50 mL of THF was added via canula. The reaction mixture was warmed slowly to room temperature and stirred for 15 h. The reaction mixture was then recooled to −78 °C and the reaction quenched with 20% aqueous sodium thiosulfate. The products were extracted with ether (3×), the organic layers were combined, washed with brine, dried (Na_2SO_4), and filtered, and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes) to give **16** as a yellow oil (0.89 g, 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3 H, *J* = 7.1 Hz), 4.36 (q, 2 H, *J* = 7.1 Hz), 8.11 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 61.9, 135.6, 149.4, 159.7.

Ethyl 2-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]-5-thiazolecarboxylate. Sodium hydride (0.057 g, 60% dispersion in oil, 2.4 mmol) was rinsed three times with hexane and dried under vacuum. The vacuum was broken with dry argon and the hydride was suspended in 5.0 mL of HMPA. 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenethiol (445 mg, 1.9 mmol) was added, and the resulting mixture was heated at 50 °C for 45 min. Copper(I) iodide (0.36 g, 1.9 mmol) was added, and the mixture was heated at 55 °C for 1.5 h. A solution of ethyl 2-iodo-5-thiazolecarboxylate (0.65 g, 2.3 mmol) and 2.0 mL of HMPA was added, and the mixture was heated to 95 °C for 2 h. The reaction mixture was cooled to 0 °C, the reaction was quenched with water, and the products were extracted with ether (2×). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes) to produce the title compound as an orange oil (0.30 g, 41%): IR 1714 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 6 H), 1.32 (s, 6 H), 1.32 (t, 3 H, *J* = 7.1 Hz), 1.70 (s, 4 H), 2.41 (s, 3 H), 4.29 (q, 2 H, *J* = 7.1 Hz), 7.30 (s, 1 H), 7.60 (s, 1 H), 8.19 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.3, 31.7, 31.8, 34.1, 34.3, 34.8, 34.9, 61.4, 125.6, 128.5, 129.8, 135.1, 139.0, 144.9, 148.8, 148.9, 161.0, 177.3; MS (EI, 70 eV) *m/z* 389 (M^+, 100). Anal. ($C_{21}H_{27}NO_2S_2$) C, H, N.

2-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]-5-thiazolecarboxylic Acid (6). To a solution of 0.183 g (0.47 mmol) of ethyl 2-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)thio]-5-thiazolecarboxylate and 2.0 mL of THF were added 1.0 mL of 2.1 N aqueous LiOH and 1.0 mL of MeOH. The solution was heated at 50 °C for 1 h, cooled to room temperature, and concentrated *in vacuo*. The residue was diluted with water and acidified with 10% aqueous HCl, and the products were extracted with ether (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed *in vacuo* to give **6** as a white solid (131 mg, 78%): mp 220−224 °C dec; IR (KBr pellet) 3400−2500 (COO*H*), 1702 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.28 (s, 6 H), 1.32 (s, 6 H), 1.73 (s, 4 H), 2.40 (s, 3 H), 7.42 (s, 1 H), 7.63 (s, 1 H), 8.12 (s, 1 H); ^{13}C NMR (75 MHz, DMSO) δ 19.8, 31.4, 31.5, 31.5, 33.8, 34.1, 34.3, 125.3, 129.6, 129.7, 134.7, 138.6, 144.6, 148.5, 148.6, 161.5; MS (EI, 70 eV) *m/z* 361 (M^+, 58), 345 (57), 328 (25), 249 (26), 122 (12), 81 (53), 69 (100). Anal. ($C_{19}H_{22}NO_2S_2$) C, H, N, S.

Receptor Assays. The transactivation and binding properties of retinoid analogs were determined at Ligand Pharmaceuticals (La Jolla, CA) as previously described.[14b,c]

TGase Induction. HL-60 cdm-1 cells were cultured under conditions described in detail previously.[22] Cells in log-phase growth (2 × 10^{-5} cells/mL) in RPMI 1640 (Fisher Scientific) supplemented with insulin, transferrin, and sodium selenide (TIS; Sigma) were pretreated with 1.25% dimethyl sulfoxide (DMSO) for 18 h. Cells were then sedimented and resuspended in RPMI-TIS containing retinoids or an equivalent solvent control (0.1% ethanol). After culture for 24 h, cells were again sedimented, washed once, and lysed, and the transglutaminase activity was assayed by measuring the covalent and Ca^{2+}-dependent conjugation of [^{3}H]putrescine to *N,N*-dimethylcasein.[22] The EC_{50} value is defined as the concentration required to induce 50% of the maximal induction of transglutaminase activity achieved with that compound.

Chondrogenesis Inhibition. The *in vitro* bioassay employed high-density micromass cultures of day 11 embryonic limb bud cells as described.[23] Briefly, forelimb buds were dissociated in a trypsin-EDTA solution, and the resultant single-cell suspension was plated as 20 μL spots (200 000 cells/spot) on plastic culture dishes. Retinoid concentrations ranging from 0.3 to 3 μg/mL (1 nM−10 μM) were added to the culture medium (Eagle's MEM + 10% fetal bovine serum; GIBCO) 24 h after initial plating. Control cultures received only the vehicle (ethanol, concentration < 1% by volume). The cultures were terminated 96 h after plating, at which time the medium was removed and the cells were fixed for 1 h in 10% formalin containing 0.5% cetylpyridinium chloride. The cultures were rinsed with acetic acid and then dehydrated in ethanol and scored for chondrogenesis under the microscope. An absence or reduction in the number of cartilage nodules as compared to control cultures was taken as a measure of suppression of chondrogenesis. The number of cartilage nodules stained in the whole spot were counted by automated image scan using the N.I.H. Image-1.52 application. Mean number of nodules and standard deviations were calculated for four replicate cultures per concentration. The median concentration of each retinoid causing 50% inhibition of chondrogenesis compared with controls (IC_{50}) was calculated by logarithmic curve fitting of the dose−response data.

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