Syntheses and Structure−Activity Relationships of 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxaline Derivatives with Retinoic Acid Receptor α Agonistic Activity

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In the course of our studies on retinoic acid receptor (RAR) agonists, we have designed and synthesized a series of quinoxaline derivatives. One of them, 4-[5-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-2-pyrrolyl]benzoic acid (**3a**), which possesses a 2,5-disubstituted pyrrole moiety, showed selectivity for the RARα receptor and exerted highly potent cell-differentiating activity on HL-60 cells.

Introduction

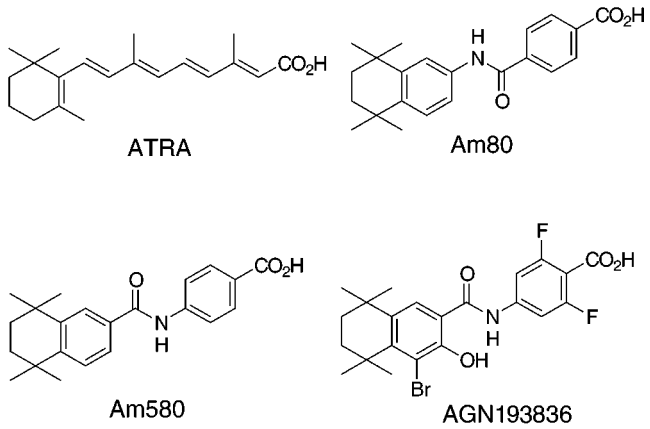
Retinoids have a variety of potent biological activities, including induction of cellular proliferation, differentiation, and death, as well as developmental changes.[1] The biological effects of retinoids are mediated by activation of retinoic acid receptors (RARs), which are ligand-dependent gene transcription factors. There are three distinct receptor subtypes (RARα, -*β*, and -*γ*), which possess considerable homology in their ligand binding domains. RARs elicit their gene transcriptional activity in the form of heterodimers with retinoid X receptors (RXRs).[2]

Although retinoids are thought to have great therapeutic potential, the clinical use of retinoids is so far limited mainly to dermatological diseases[3] and some cancers, for which retinoids may have both chemotherapeutic and chemopreventive applications.[4] The main reason for this is the wide range of toxic effects of retinoids, including mucocutaneous irritation, elevation of plasma triglycerides, headache, bone toxicity, and teratogenicity.[5] The diverse range of actions of retinoids, both desirable and undesirable, reflects the existence of multiple retinoid receptor subtypes.

Recent research has focused on the synthesis and development of subtype-selective retinoids.[6] This is because severe toxicity is thought to be due to nonspecific activation of nuclear retinoid receptor subtypes, so subtype-specific retinoids might have limited biological activities through activating only subsets of retinoid-responsive genes. Benbrook et al. recently reported[7] that heteroarotinoids were less toxic than arotinoid. On the basis of their results, we considered that the introduction of a heteroatom into the hydrophobic part of retinoids might similarly reduce the toxicity. If so, subtype-specific retinoids should show much better therapeutic indices than their nonselective counterparts and might have potential value as medical drugs.

Only a limited number of RARα agonists have been reported so far. These include Am80, Am580,[6a] and AGN193836.[6b] Am80 is more potent than ATRA (all-*trans* retinoic acid) as an in vitro differentiation inducer, and clinically Am80 was effective in leukemia patients who had relapsed from ATRA-induced complete remission.[8] Treatment of psoriasis patients with Am80 was comparable in efficacy to steroid therapy.[9] Moreover, a group at Shionogi Co. recently reported that an RARα-selective agonist (Am80) inhibited rat CII arthritis concomitantly with a decrease in the anti-CII Ab level in vivo.[10] Therefore, RARα agonists seemed to be promising compounds for the treatment of cancer, dermatological diseases, and immunological disorders.

Chart 1



The structure of retinoid analogues can be divided into three parts, i.e., a hydrophobic part, a linker, and a carboxylic part. All reported RARα-selective agonists, such as Am80, Am580, and AGN 193836, have an amide in the linker (Chart 1). In the course of our studies aimed at synthesizing novel retinoids,[11] we introduced nitrogen into the hydrophobic part to synthesize more polar novel retinoid analogues which might possess improved pharmacokinetic characteristics and show less toxicity. We hoped that such retinoid derivatives might be selective RARα agonists. Initially, we synthesized a quinoxaline-amide derivative (**1**; ER-33635),[12] which possesses a tetrahydroquinoxaline moiety at the hydro-

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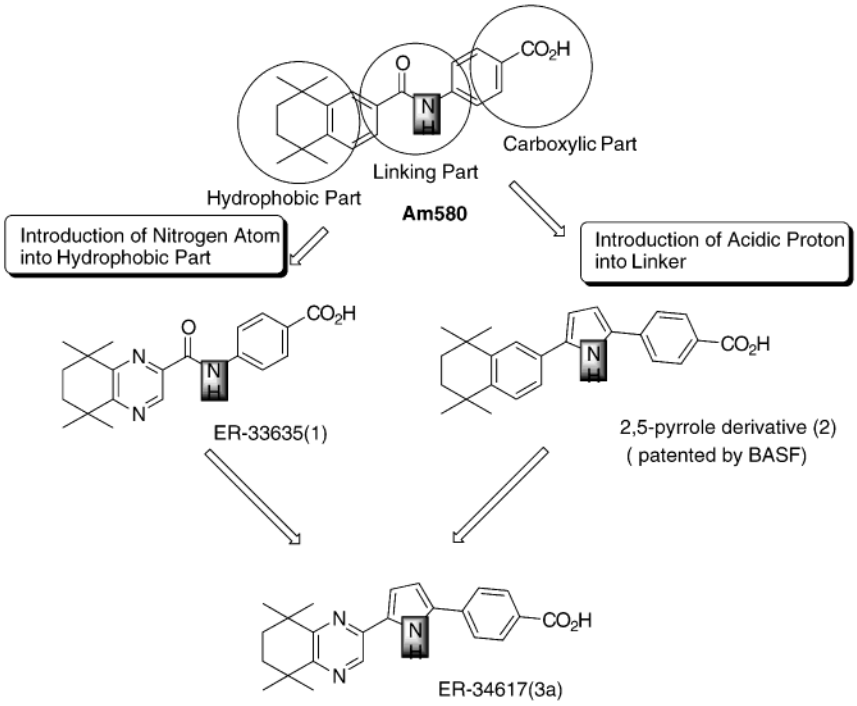
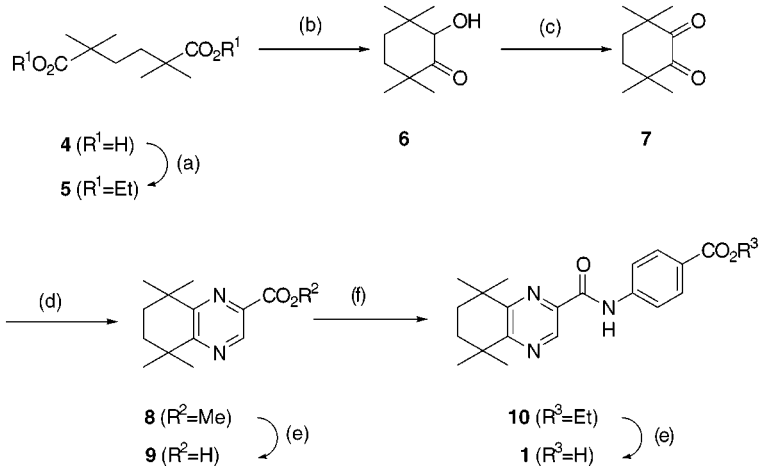
Chart 2



Scheme 1[a]



[a] Reagents: (a) conc H_2SO_4, EtOH; (b) Na, xylene; (c) CrO_3, AcOH, H_2O; (d) (i) DL-α,β-diaminopropionic acid monohydrobromide, NaOH, MeOH, (ii) conc H_2SO_4, MeOH; (e) aq NaOH, EtOH; (f) $(EtO)_2P(O)Cl$, Et_3N, ethyl 4-aminobenzoate, THF.

phobic part (Chart 2). Compound **1** showed moderate selectivity for RARα and had potent retinoid activity.

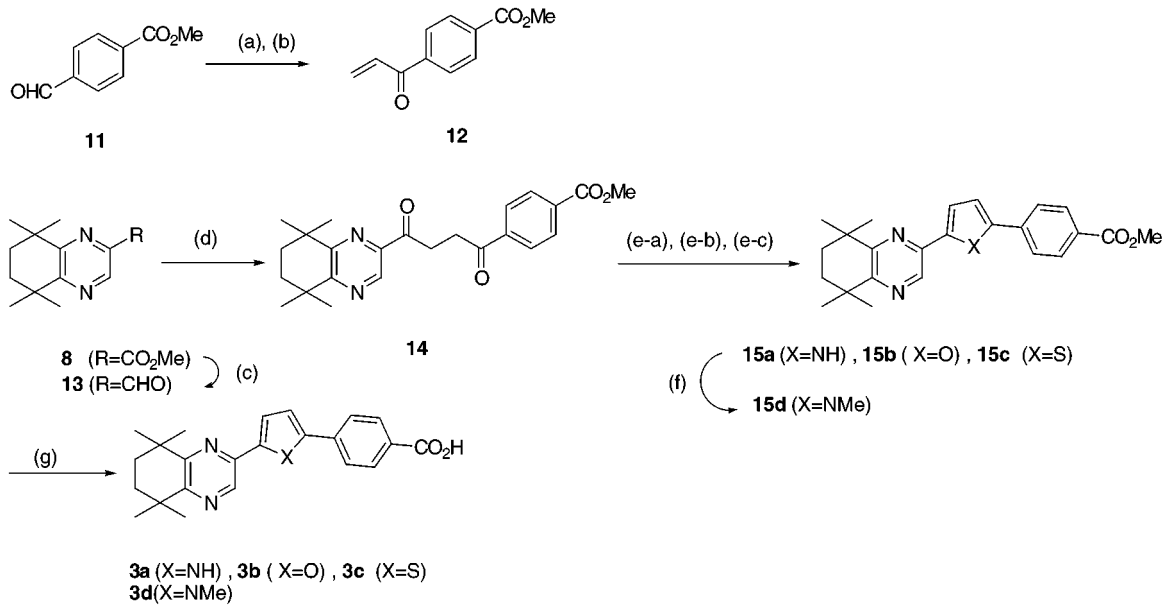
Subsequently, we focused on an acidic proton in the amide structure of the linker. We found that the 2,5-substituted pyrrole derivative (**2**),[13] a BASF-patented compound which has an acidic proton, showed RARα selectivity. On the basis of these results, we designed and synthesized quinoxaline-pyrrole derivatives with the aim of obtaining novel RARα-selective retinoids. Here we discuss the synthesis and structure−activity relationships (SAR) of retinoids which possess hydroquinoxaline and various heterocycles as the hydrophobic part and linker, respectively.

Chemistry

The synthesis of **1** (ER-33635) is shown in Scheme 1. The diester (**5**), derived from a commercially available carboxylic acid (**4**), was subjected to acyloin condensation with sodium to afford the keto alcohol (**6**). Compound (**6**) was oxidized with CrO_3 to give the diketone (**7**).[14] Condensation[11a] of the ketone (**7**) with DL-α,β-diaminopropionic acid monohydrobromide afforded the quinoxaline methyl ester (**8**), which was hydrolyzed to give the carboxylic acid (**9**). The ethyl ester (**10**), obtained by condensation of the carboxylic acid (**9**) with ethyl 4-aminobenzoate, was hydrolyzed with NaOH to afford the free acid (**1**; ER-33635).

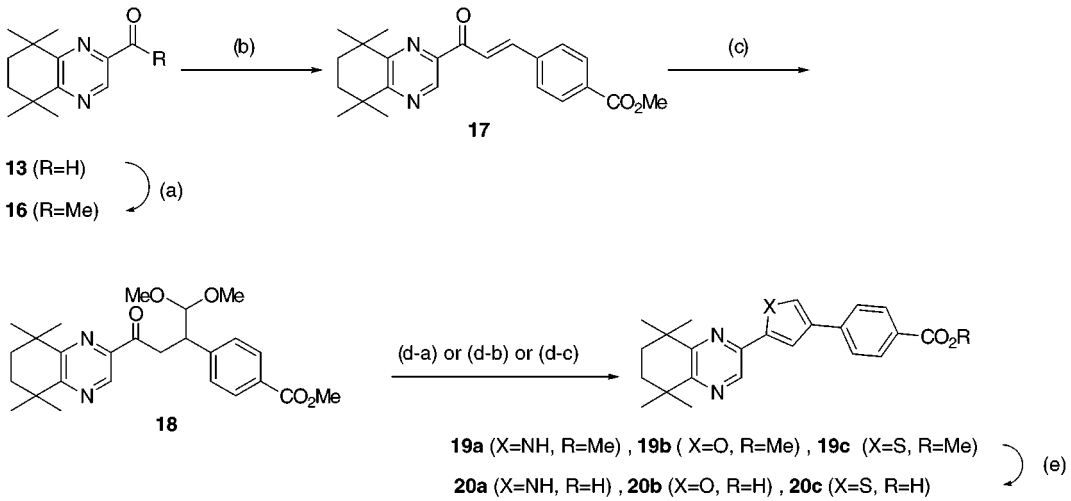
2,5-Disubstituted pyrrole derivatives were prepared as shown in Scheme 2. Synthesis of the 1,4-diketone (**14**) was achieved by means of a thiazolium salt-catalyzed benzoin condensation type reaction. A commercially available benzaldehyde derivative (**11**) was treated with vinyl Grignard reagent followed by PDC oxidation to give the enone derivative (**12**). The counterpart aldehyde (**13**) was synthesized as follows. The methyl ester (**8**) described above was reduced with diisobutylaluminum

Scheme 2[a]



[a] Reagents: (a) vinylmagnesium bromide, THF; (b) PDC, MS 3A, CH_2Cl_2; (c) (i) DIBAL-H, CH_2Cl_2, (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) **12**, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N, DMF; (e−a) $AcONH_4$, MeOH; (e−b) conc H_2SO_4; (e−c) P_2S_5, xylene; (f) NaH, MeI, DMF; (g) aq NaOH, EtOH.

Scheme 3[a]



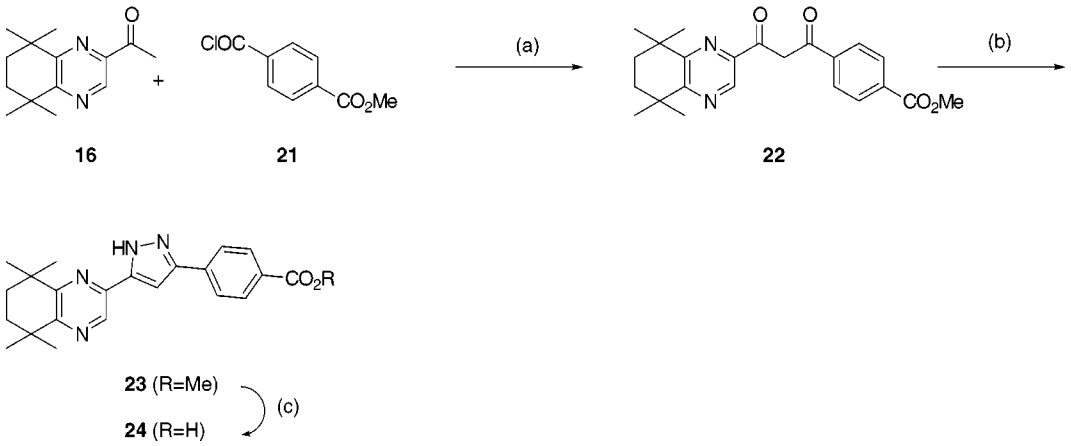
[a] Reagents: (a) (i) MeMgBr, Et_2O, (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) methyl 4-formylbenzoate, NaOH, MeOH; (c) (i) $MeNO_2$, Triton B, THF, (ii) NaOMe, MeOH−THF−CH_2Cl_2, (iii) conc H_2SO_4, MeOH; (d−a) $AcONH_4$, AcOH; (d−b) conc H_2SO_4; (d−c) P_2S_5, xylene; (e) aq NaOH, EtOH.

hydride (DIBAL-H), followed by Swern oxidation to give the aldehyde (**13**). Condensation of the aldehyde (**13**) with the enone (**12**) in the presence of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride and triethylamine gave the 1,4-diketone (**14**).[15] This was treated with ammonium acetate to afford the pyrrole derivative (**15a**), which was hydrolyzed to the quinoxaline derivative (**3a**). Treatment of the 1,4-diketone (**14**) with concentrated sulfuric acid yielded the furan derivative (**15b**), which was then hydrolyzed to the acid (**3b**), whereas treatment with P_2S_5 in xylene at reflux temperature gave the thiophene derivative (**15c**) and hydrolysis of this yielded **3c**. N-Alkylation of the 2,5-substituted pyrrole derivative (**15a**) was carried out with sodium hydride and methyl iodide, followed by hydrolysis to give the *N*-methyl pyrrole derivative (**3d**) (Scheme 2).

Preparation of the 2,4-disubstituted heterocyclic derivatives (**20**) is shown in Scheme 3. Grignard reaction of the aldehyde (**13**) followed by Swern oxidation gave the methyl ketone (**16**), which was condensed with methyl 4-formylbenzoate in the presence of NaOH to afford the enone (**17**). Conjugate addition of nitromethane anion to compound **17** followed by reaction with NaOMe gave the aldehyde, which was acetalized to give compound **18**. Treatment of the acetal (**18**) with ammonium acetate gave the 2,4-substituted pyrrole derivative (**19a**), which was hydrolyzed with NaOH to give the acid (**20a**). Transformation of the acetal (**18**) into the furan (**20b**) and the thiophene (**20c**) were accomplished with H_2SO_4 and P_2S_5, respectively (Scheme 3).

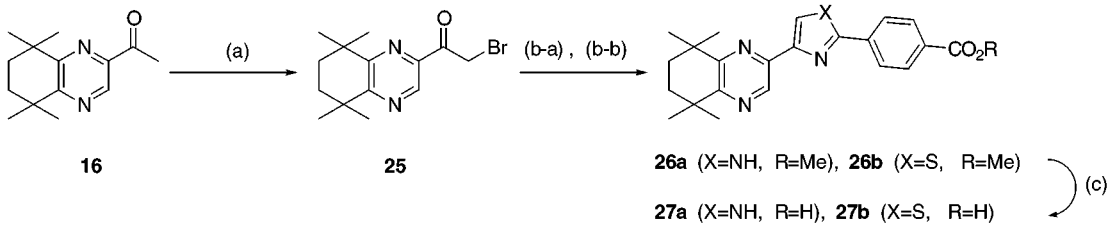
Preparation of the pyrazole derivatives is shown in Scheme 4. The pyrazole moiety was constructed in a usual manner, by condensation of hydrazine with the

Scheme 4[a]



[a] Reagents: (a) LDA, THF; (b) hydrazine, AcOH; (c) aq NaOH, EtOH.

Scheme 5[a]



[a] Reagents: (a) $CuBr_2$, AcOEt, $CHCl_3$; (b−a) methyl 4-amizinobenzoate acetate, K_2CO_3, DMF; (b−b) 4-carbomethoxybenzthioamide, pyridine, IPA; (c) aq NaOH, EtOH.

1,3-diketone derivative (**22**), which was prepared from the anion of the ketone (**16**) and terephthalic acid monomethyl ester chloride (**21**), followed by hydrolysis to afford the pyrazole derivative (**24**).

Preparation of the imidazole derivative was accomplished as follows. The α-bromo ketone (**25**), obtained by bromination of the ketone (**16**) with $CuBr_2$, was condensed with methyl 4-amizinobenzoate followed by hydrolysis to give the imidazole derivative (**27a**). Condensation of the α-bromo ketone with 4-carbomethoxybenzthioamide in the presence of pyridine followed by hydrolysis gave the thiazole (**27b**) (Scheme 5).

Results and Discussion

The above retinoids were synthesized and assayed in vitro for the ability to bind to the individual RARs and to induce gene transcription in the cotransfection assay. Cotransfection assays were performed as described in the Experimental Section, and relative ED_{30} values were calculated (see footnotes to Tables 1 and 2). Binding assays for RAR receptor isoforms were performed in a manner similar to that described by Boehm et al.[16] using [^{3}H]ATRA. The results are summarized in Tables 1 and 2. RXRα transactivation was also studied, but none of these compounds activated RXR (data not shown).

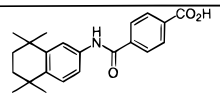
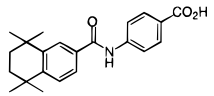
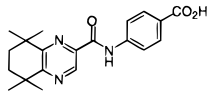
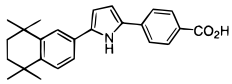
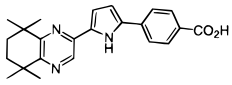
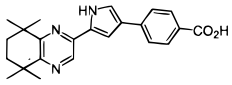
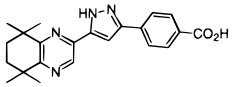
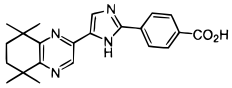
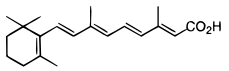
We initially introduced a nitrogen atom into the hydrophobic part of the retinoid structure to obtain more polar retinoids which might possess improved pharmacokinetic characteristics. Moreover, we hoped to find retinoids with potent and selective retinoid activity among the quinoxaline derivatives. Although ER-33635 (**1**) had low RARα selectivity, this compound is more potent than Am580 and Am80 at RARα, -β, and -γ.

Am80 and Am580 are retinoid analogues in which the linker moiety possesses an amide structure. Since usual nonselective retinoids such as ATRA and arotinoid (TTNPB)[17] do not have such an amide structure, we hypothesized that the RARα receptor possesses a strong binding site for the acidic proton of the linker; in other words, ligands which have such an acidic proton would activate RARα-mediated transactivation. On the basis of this hypothesis, we introduced various heterocycles, such as 2,4-substituted pyrrole, 2,5-substituted pyrrole, pyrazole, and imidazole, as the linker moiety.

In the cotransfection assay, the 2,5-substituted pyrrole derivative (**3a**) showed more potent activity than ATRA at RARα. However, this compound (**3a**) showed weak affinity for RARβ and RARγ and was less potent than ATRA at these receptors (Figure 1). It was 8-fold more potent than ATRA in terms of HL-60 differentiation-inducing activity. Compound **2**, which has tetramethyl-tetrahydronaphthalene and 2,5-disubstituted pyrrole moieties, also showed potent RARα agonistic activity. However, compound **3a** was less potent than **2** in terms of RARγ transcription activity and binding affinity. In contrast, other heterocyclic derivatives (**20a**, **24**, and **27a**) with an acidic proton were less potent than compound **3a** and less selective for RARα.

To test the effect of the acidic proton of the 2,5-substituted pyrrole (**3a**), the pyrrole linker was replaced with other heterocycles, which do not possess an acidic proton. When the 2,5-substituted pyrrole moiety of compound **3a** was replaced with furan (**3b**), the activities at RARα, -β, and -γ were comparable to those of ATRA. The thiophene derivative (**3c**) showed weak potency at RARα whereas this compound was comparable to ATRA at RARβ and -γ. Thus, compounds **3b**

Table 1. Competitive Binding, Transactivation, and Induction of Differentiation

		binding affinity[a] relative IC_{50}[b]			subtype-specific transactivation[e] relative EC_{30}[f]			HL-60 Differentiation-inducing activity
Comp. No.	Structure	RARα	RARβ	RARγ	RARα	RARβ	RARγ	ED_{30} (nM)
Am80		78±20	nd[c]	nd[c]	1.3±0	48±13	150±90	0.67±0.32
Am 580		41±9	nd[c]	nd[c]	0.30±0.01	12±3	33±5	0.34±0.08
1 (ER-33635)		40±2	140±20	nd[c]	0.15±0.04	0.40±0	1.6±0.8	0.87±0.41
2		0.45±0.15	100±8	21±5	0.34±0.10	3.9±1.4	3.5±0.5	0.54±0.27
3a (ER-34617)		2.2±1.5	230±120	310±40	0.32±0.03	2.5±0.3	20±6	0.11±0.04
20a		nd[c]	nd[c]	150±120	11±3	4.5±0.3	1.6±0.3	140±43
24		nd[c]	290±190	nd[c]	1.7±0	0.85±0.16	3.9±1.0	2.1±0.2
27a		nd[c]	nd[c]	nd[c]	80±34	40±19	39±14	20±3
ATRA		1.0	1.0	1.0	1.0	1.0	1.0	0.94±0.20
		0.64±0.04[d]	0.71±0.05[d]	0.47±0.04[d]	0.92±0.09[g]	0.70±0.06[g]	0.18±0.02[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. 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). [b] Mean of IC_{50}/ATRA IC_{50} ± SEM. [c] nd: not detectable (relative IC_{50} > 1000). [d] Mean of ATRA IC_{50} (nM) ± SEM. [e] 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_{30}, which is the concentration of retinoid required to produce 30% of the maximal observed response, normalized relative to that of ATRA. [f] Mean of EC_{30}/ATRA EC_{30} ± SEM. [g] Mean of ATRA EC_{30} (nM) ± SEM.

and **3c** did not show any selectivity for RARα. The 2,4-substituted pyrrole moiety of compound **20a** was also replaced with furan (**20b**) and thiophene (**20c**). Compounds **20b**,**c** both possess comparable activity to ATRA at RARα, -β, and -γ.

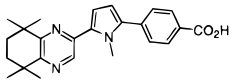
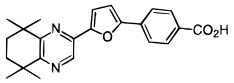
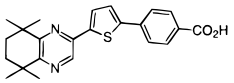
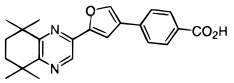
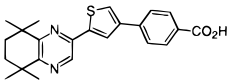
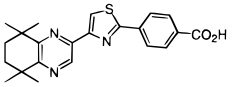
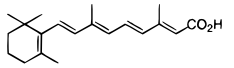
In conclusion, we have described the syntheses and SAR of a new series of quinoxaline derivatives. We found out that the quinoxaline derivatives have retinoid activities. One of them, 4-[5-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-quinoxalinyl)-1*H*-2-pyrrolyl]benzoic acid (**3a**; ER-34617) has selectivity for the RARα receptor and shows highly potent cell differentiation-inducing activity. Thus, ER-34617 should be useful as a tool to study the physiological role of RARα. It may also be useful as a lead compound for more highly RARα selective retinoids, which might have fewer toxic effects and better therapeutic indices than nonselective retinoid drugs.

Experimental Section

Chemistry. Reagents and solvents were purchased from 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 $MgSO_4$, and solvents were removed with a rotary evaporator under reduced pressure.

Diethyl 2,2,5,5-Tetramethylhexanedioate (5). To a solution of 2,2,5,5-tetramethylhexanedioic acid (25 g, 123 mmol) in ethanol (300 mL) was added concentrated sulfuric acid (25 mL) at room temperature, and the mixture was stirred under reflux for 16 h. Ethanol was removed under reduced pressure, and residue was poured into saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **5** (31.7 g, 123 mmol, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 12H), 1.24 (t, J = 7.2 Hz, 6H), 1.44 (s, 4H), 4.11 (q, J = 7.2 Hz, 4H).

Table 2. Competitive Binding, Transactivation, and Induction of Differentiation

		binding affinity[a] relative IC_{50}[b]			subtype-specific transactivation[e] relative EC_{30}[f]			HL-60 Differentiation-inducing activity
Comp. No.	Structure	RARα	RARβ	RARγ	RARα	RARβ	RARγ	ED_{30} (nM)
3d		nd[c]	nd[c]	nd[c]	38±1.0	14±1.0	120±65	240±60
3b		32±1	39±18	4.6±0.9	1.8±0.1	0.38±0.06	1.5±0.4	2.1±0.4
3c		130±40	36±3	17±4	15±2	0.73±0.17	2.1±0.5	40±16
20b		19±5	2.5±0.5	27±4	0.35±0.20	0.18±0.10	0.76±0.34	0.21±0.02
20c		2.4±1.4	4.5±1.2	2.0±0.5	0.87±0.42	0.50±0.17	0.72±0.18	9.5±3.5
27b		83±9	21±3	3.6±0.7	5.2±0.7	0.39±0.22	0.34±0.03	11±2
ATRA		1.0	1.0	1.0	1.0	1.0	1.0	0.94±0.20
		0.64±0.04[d]	0.71±0.05[d]	0.47±0.04[d]	0.92±0.09[g]	0.70±0.06[g]	0.18±0.02[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. 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). [b] Mean of IC_{50}/ATRA IC_{50} ± SEM. [c] nd: not detectable (relative IC_{50} > 1000). [d] Mean of ATRA IC_{50} (nM) ± SEM. [e] 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_{30}, which is the concentration of retinoid required to produce 30% of the maximal observed response, normalized relative to that of ATRA. [f] Mean of EC_{30}/ATRA EC_{30} ± SEM. [g] Mean of ATRA EC_{30} (nM) ± SEM.

6-Hydroxy-2,2,5,5-tetramethyl-1-cyclohexanone (6). To a suspension of Na (40% dispersion in xylene, 44.6 g, 776 mmol) in xylene (500 mL) was added dropwise over 30 min a solution of **5** (50 g, 194 mmol) in xylene (100 mL) under a nitrogen atmosphere at 100 °C. The mixture was stirred for 2 h at the same temperature, then cooled in an ice bath, and a solution of sulfuric acid (50 mL) in water (50 mL) was added dropwise to it. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **6** (28 g, 164 mmol, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (s, 3H), 1.09 (s, 3H), 1.13 (s, 3H), 1.20 (s, 3H), 1.43 (ddd, J = 2.8, 4.0, 14.0 Hz, 1H), 1.62 (ddd, J = 2.8, 4.8, 14.0 Hz, 1H), 1.70 (ddd, J = 4.0, 14.0, 14.0 Hz, 1H), 1.87 (ddd, J = 4.8, 14.0, 14.0 Hz, 1H), 3.58 (d, J = 4.6 Hz, 1H), 4.13 (d, J = 4.0 Hz, 1H).

3,3,6,6-Tetramethyl-1,2-cyclohexanedione (7). To a solution of **6** (28 g, 164 mmol) in acetic acid (70 mL) was added dropwise a solution of chromium(VI) oxide (18 g, 180 mmol) in acetic acid (70 mL)−water (9 mL) at 15 °C, and the mixture was stirred for 3 h at the same temperature. It was poured into water, and the resulting precipitate was collected by filtration, washed with water, and dried under reduced pressure to afford **7** (19.5 g, 116 mmol, 70%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 12H), 1.86 (s, 4H).

Methyl 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinecarboxylate (8). To a solution of **7** (2.5 g, 14.9 mmol) and DL-α,β-diaminopropionic acid monohydrobromide (2.76 g, 14.9 mmol) in methanol (100 mL) was added sodium hydroxide (2.4 g, 59.6 mmol) at room temperature, and then the mixture was stirred under reflux for 48 h. It was cooled in an ice bath, concentrated sulfuric acid (12 mL) was added dropwise, and the whole was stirred under reflux for 6 h. Methanol was removed under reduced pressure, and the residue was poured into saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **8** (2.65 g, 10.7 mmol, 72%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.36 (s, 6H), 1.82 (s, 4H), 3.98 (s, 3H), 9.00 (s, 1H).

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinecarboxylic Acid (9). A solution of **8** (35 mg, 0.141 mmol) in ethanol (2 mL) was treated with 5 N aqueous sodium hydroxide solution (0.2 mL) at room temperature and stirred for 1 h at the same temperature. The reaction mixture was diluted with water, and the pH was adjusted to 5 with 2 N aqueous hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, then dried, and evaporated to afford **9** (32 mg, 0.137 mmol, 97%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 1.85 (s, 4H), 9.18 (s, 1H).

Ethyl 4-{[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboyl]amino}benzoate (10). To a solution of **9** (40 mg, 0.171 mmol) in tetrahydrofuran (2 mL) was added diethylchlorophosphate (30 μL, 0.205 mmol), triethylamine (29 μL, 0.205 mmol), and a solution of ethyl 4-aminobenzoate (28.2 mg, 0.171 mmol) in tetrahydrofuran (1 mL) under a nitrogen atmosphere at 0 °C. The mixture was stirred for 12 h at room temperature, then water was added, and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **10** (45 mg, 0.118 mmol, 69%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 6H), 1.41 (s, 6H), 1.41 (t, J = 7.2 Hz, 3H),

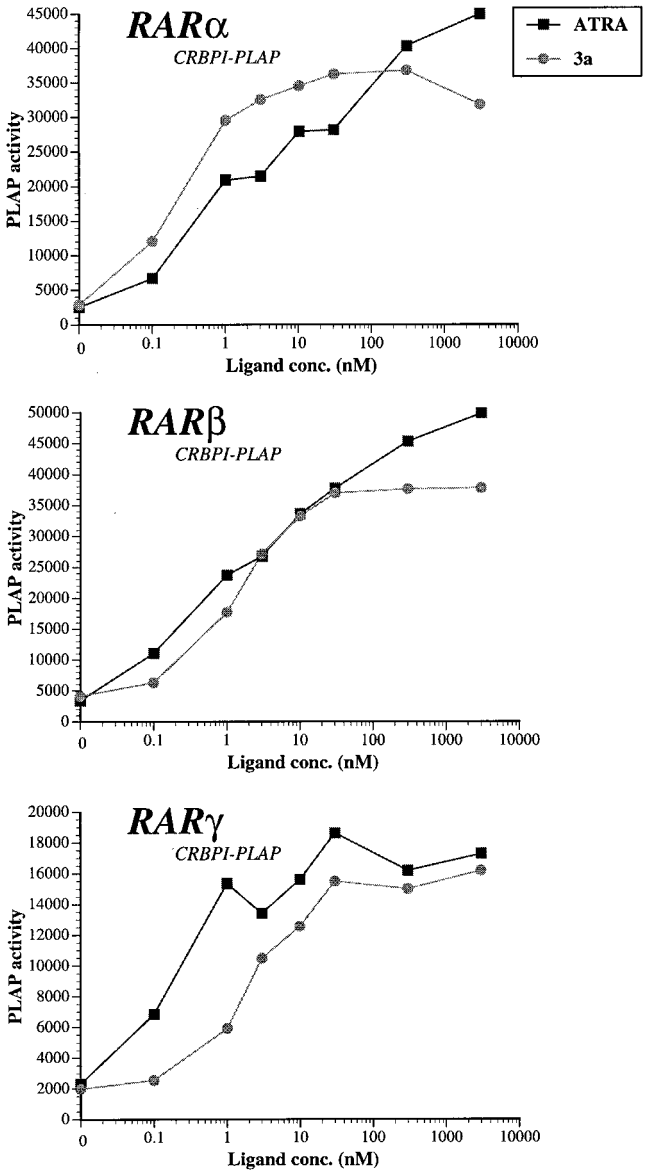


Figure 1. Dose−response curves for RAR-mediated transactivation activity of **3a** and ATRA at each RAR subtype.

1.86 (s, 4H), 4.38 (q, J = 7.2 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H), 9.25 (s, 1H), 9.83 (br s, 1H).

4-{[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboyl]amino}benzoic Acid (1). A solution of **10** (250 mg, 0.66 mmol) in ethanol (30 mL) was treated with 5 N aqueous sodium hydroxide solution (3 mL) at room temperature, and the mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with water, and the pH was adjusted to 5 with 6 N aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried under reduced pressure to afford **1** (146 mg, 0.41 mmol, 63%) as a colorless solid: mp 257−259 °C (EtOH − water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 6H), 1.40 (s, 6H), 1.81 (s, 4H), 7.96 (s, 4H), 9.05 (s, 1H), 10.42 (br s, 1H). Anal. ($C_{20}H_{23}N_3O_3 \cdot 1.2H_2O$) C, H, N.

Methyl 4-Acryloylbenzoate (12). To a solution of methyl terephthalaldehydate (13.6 g, 82.8 mmol) in tetrahydrofuran (150 mL) was added a 1 M solution of vinylmagnesium bromide in tetrahydrofuran (100 mL, 100 mmol) at −78 °C. The mixture was stirred for 30 min at the same temperature and then quenched with saturated aqueous ammonium chloride solution, and the whole was extracted with ethyl acetate. The organic layer was washed with brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford methyl 4-(1-hydroxyallyl)benzoate (11.6 g, 60.4 mmol, 73%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (br s, 1H), 3.91 (s, 3H), 5.23 (d, J = 10.8 Hz, 1H), 5.25−5.29 (m, 1H), 5.37 (d, J = 17.6 Hz, 1H), 6.02 (ddd, J = 6.8, 10.8, 17.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H).

To a solution of methyl 4-(1-hydroxyallyl)benzoate (11.6 g, 60.4 mmol) in dichloromethane (600 mL) were added pyridinium dichromate (27 g, 71.8 mmol) and molecular sieve 3A at room temperature, and the mixture was stirred for 4 h at the same temperature. It was filtered on Celite, and the filtrate was evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **12** (5.5 g, 28.9 mmol, 48%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.00 (d, J = 10.4 Hz, 1H), 6.46 (d, J = 17.2 Hz, 1H), 7.14 (dd, J = 10.4, 17.2 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H).

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinecarbaldehyde (13). To a solution of **8** (23.2 g, 93.4 mmol) in dichloromethane (500 mL) was added dropwise a 1 M solution of DIBAL-H in toluene (280 mL, 280 mmol) under a nitrogen atmosphere at −78 °C, and the mixture was stirred for 1 h at the same temperature. It was quenched with saturated aqueous ammonium chloride solution, and the resulting precipitate was filtered off on Celite. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash column chromatography on silica gel (solvent: 20% ethyl acetate−*n*-hexane) to afford (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)methanol (12.4 g, 56.3 mmol, 60%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 6H), 1.33 (s, 6H), 1.80 (s, 4H), 3.62 (t, J = 5.1 Hz, 1H), 4.74 (d, J = 5.1 Hz, 2H), 8.31 (s, 1H).

To a solution of oxalyl chloride (4.58 mL, 52.5 mmol) in dichloromethane (250 mL) was added dropwise a solution of dimethyl sulfoxide (7.45 mL, 105 mmol) in dichloromethane (17 mL) at −60 °C, and the mixture was stirred for 10 min at the same temperature. To this solution was added dropwise a solution of (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)methanol (7.7 g, 35 mmol) in dichloromethane (120 mL) at a rate sufficient to keep the temperature at −60 °C. After the reaction mixture had been stirred for 15 min at this temperature, triethylamine (35.1 mL, 252 mmol) was added and the whole was stirred for 5 min at −60 °C and for 15 min at room temperature. Water was added, and the whole was extracted with dichloromethane. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 3% ethyl acetate−*n*-hexane) to afford **13** (6.8 g, 31.1 mmol, 89%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.38 (s, 6H), 1.84 (s, 4H), 8.91 (s, 1H), 10.10 (s, 1H).

Methyl 4-[4-Oxo-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)butanoyl]benzoate (14). A solution of **13** (300 mg, 1.37 mmol), **12** (260 mg, 1.58 mmol), triethylamine (0.23 mL, 1.65 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (74 mg, 0.27 mmol) in *N*,*N*-dimethylformamide (10 mL) was stirred for 30 min at 100 °C. The mixture was extracted with ethyl acetate, and the organic layer was washed with 1 N aqueous hydrochloric acid and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 7% ethyl acetate−*n*-hexane) to afford **14** (420 mg, 1.03 mmol, 75%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.38 (s, 6H), 1.84 (s, 4H), 3.46 (t, J = 6.4 Hz, 2H), 3.68 (t, J = 6.4 Hz, 2H), 3.96 (s, 3H), 8.08 (d, J = 8.0 Hz, 2H), 8.15 (d, J = 8.0 Hz, 2H), 8.96 (s, 1H).

Methyl 4-[5-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-2-pyrrolyl]benzoate (15a). A solution of **14** (380 mg, 0.93 mmol) and ammonium acetate (358 mg, 4.65 mmol) in methanol (50 mL) was stirred under reflux for 8 h. Methanol was removed under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated.

The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **15a** (260 mg, 0.67 mmol, 72%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.40 (s, 6H), 1.82 (s, 4H), 3.94 (s, 3H), 6.73 (dd, J = 2.8, 4.0 Hz, 1H), 6.82 (dd, J =2.4, 4.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 8.66 (s, 1H).

Methyl 4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-2-furyl]benzoate (15b). A solution of **14** (200 mg, 0.49 mmol) in concentrated sulfuric acid (2 mL) was stirred for 15 h at room temperature, then poured into saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **15b** (120 mg, 0.31 mmol, 63%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.36 (s, 6H), 1.82 (s, 4H), 3.94 (s, 3H), 6.92 (d, J = 3.6 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 8.0 Hz, 2H), 8.83 (s, 1H).

Methyl 4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-2-thienyl]benzoate (15c). To a solution of **14** (200 mg, 0.49 mmol) in xylene (10 mL) was added phosphorus pentasulfide (109 mg, 0.49 mmol) at room temperature, and the mixture was stirred under reflux for 2 h, then purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **15c** (90 mg, 0.22 mmol, 45%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.38 (s, 6H), 1.82 (s, 4H), 3.94 (s, 3H), 7.43 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 4.0 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 8.06 (d, J = 8.6 Hz, 2H), 8.72 (s, 1H).

Methyl 4-[1-Methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-5-pyrrolyl}benzoate (15d). To a solution of **15a** (120 mg, 0.31 mmol) in *N*,*N*-dimethylformamide (10 mL) was added sodium hydride (60% in mineral oil) (19 mg, 0.48 mmol) and iodomethane (38 μL, 0.61 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. A saturated aqueous ammonium chloride solution was added, and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **15d** (110 mg, 0.27 mmol, 88%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.36 (s, 6H), 1.82 (s, 4H), 3.94 (s, 3H), 3.95 (s, 3H), 6.39 (d, J = 3.8 Hz, 1H), 6.70 (d, J = 3.8 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 8.09 (d, J = 8.2 Hz, 2H), 8.64 (s, 1H).

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-2-pyrrolyl]benzoic Acid (3a). Compound **3a** was synthesized from **15a** following the representative procedure described for **1** and obtained as a yellow solid in 93% yield: mp 280−283 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.40 (s, 6H), 1.82 (s, 4H), 6.76 (dd, J = 2.8, 3.8 Hz, 1H), 6.84 (dd, J = 2.4, 3.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H), 8.68 (s, 1H), 9.66 (br s, 1H). Anal. ($C_{23}H_{25}N_3O_2 \cdot 0.2H_2O$) C, H, N.

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-2-furyl]benzoic Acid (3b). Compound **3b** was synthesized from **15b** following the representative procedure described for **1** and obtained as a orange solid in 78% yield: mp 275 °C (decomp.) (EtOH−water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.20 (s, 6H), 1.66 (s, 4H), 6.77 (d, J = 3.6 Hz, 1H), 7.03 (d, J = 3.6 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 8.66 (s, 1H). Anal. ($C_{23}H_{24}N_2O_3 \cdot 0.2H_2O$) C, H, N.

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-2-thienyl]benzoic Acid (3c). Compound **3c** was synthesized from **15c** following the representative procedure described for **1** and obtained as a pale brown solid in 77% yield: mp 292 °C (decomp.) (EtOH−water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.24 (s, 6H), 1.68 (s, 4H), 7.31 (d, J = 3.6 Hz, 1H), 7.47 (d, J = 3.6 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 8.58 (s, 1H). Anal. ($C_{23}H_{24}N_2O_2S \cdot 0.7H_2O$) C, N; H: calcd, 6.32; found, 5.89. HRMS Calcd for $C_{23}H_{25}N_2O_2S$ (MH^+): 393.1637. Found: 393.1620.

4-[1-Methyl-3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-5-pyrrolyl}benzoic Acid (3d). Compound **3d** was synthesized from **15d** following the representative procedure described for **1** and obtained as a pale yellow solid in 90% yield: mp 252−254 °C (EtOH−water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.36 (s, 6H), 1.82 (s, 4H), 3.96 (s, 3H), 6.42 (d, J = 4.0 Hz, 1H), 6.72 (d, J = 4.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H), 8.65 (s, 1H). Anal. ($C_{24}H_{27}N_3O_2 \cdot 0.3H_2O$) C, H; N: calcd, 10.64; found, 9.97. HRMS Calcd for $C_{24}H_{28}N_3O_2$ (MH^+): 390.2181. Found: 390.2190.

1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1-ethanone (16). To a solution of **13** (3.00 g, 13.7 mmol) in diethyl ether (180 mL) was added dropwise a 3 M solution of methylmagnesium bromide in diethyl ether (5.53 mL, 16.6 mmol) under a nitrogen atmosphere at 0 °C, and the mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 20% ethyl acetate−*n*-hexane) to afford 1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1-ethanol (3.20 g, 13.7 mmol, >99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 12H), 1.52 (d, J = 6.6 Hz, 3H), 1.80 (s, 4H), 4.16 (d, J = 4.9 Hz, 1H), 4.85−4.93 (m, 1H), 8.35 (s, 1H).

To a solution of oxalyl chloride (1.8 mL, 20.7 mmol) in dichloromethane (80 mL) was added dropwise a solution of dimethyl sulfoxide (2.94 mL, 41.4 mmol) in dichloromethane (3 mL) at −60 °C, and the mixture was stirred for 5 min at the same temperature. To this solution was added dropwise a solution of 1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1-ethanol (3.20 g, 13.7 mmol) in dichloromethane (40 mL) at a rate sufficient to keep the temperature at −60 °C. After the reaction mixture had been stirred for 15 min at this temperature, triethylamine (13.8 mL, 99.4 mmol) was added, and the whole was stirred for 5 min at −60 °C and for 15 min at room temperature. Water was added, and the mixture was extracted with dichloromethane. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 10% ethyl acetate−*n*-hexane) to afford **16** (1.90 g, 8.2 mmol, 60%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.36 (s, 6H), 1.82 (s, 4H), 2.68 (s, 3H), 8.96 (s, 1H).

Methyl 4-[(*E*)-3-Oxo-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1-propenyl]benzoate (17). To a solution of **16** (1.90 g, 8.2 mmol) and methyl 4-formylbenzoate (1.34 g, 8.2 mmol) in methanol (50 mL) was added a piece of solid sodium hydroxide at room temperature. After the mixture had been stirred for 12 h at room temperature, the resulting precipitate was collected by filtration and dried under reduced pressure to afford **17** (2.58 g, 6.9 mmol, 84%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 6H), 1.43 (s, 6H), 1.86 (s, 4H), 3.95 (s, 3H), 7.74 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 16.0 Hz, 1H), 8.10 (d, J = 8.2 Hz, 2H), 8.26 (d, J = 16.0 Hz, 1H), 9.11 (s, 1H).

Methyl 4-[1-(Dimethoxymethyl)-3-oxo-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)propyl]benzoate (18). To a solution of **17** (2.53 g, 6.7 mmol) in nitromethane (30 mL) and tetrahydrofuran (9 mL) was added Triton B (1.5 mL) at room temperature. The mixture was stirred for 12 h at room temperature and extracted with ethyl acetate. The organic layer was washed with diluted aqueous hydrochloric acid, water, and brine, then dried, and evaporated. The crude residue was dissolved in tetrahydrofuran: dichloromethane (1:1) (70 mL). This solution was added to a solution of sodium methoxide (3.7 mL, 18.8 mmol) in methanol (23 mL) at −35 °C, and the mixture was stirred for 40 min at the same temperature. It was then added dropwise to a solution of concentrated sulfuric acid (9.3 mL) in methanol (46 mL) at −35 °C, and the whole was stirred at room temperature for 40 min. The mixture was poured into ice and extracted with

ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated to afford **18** (2.80 g, 6.2 mmol, 90%) as a pale brown solid. This crude solid was used without further purification.

Methyl 4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-3-pyrrolyl]benzoate (19a). To a solution of **18** (250 mg, 0.55 mmol) in acetic acid (5 mL) was added ammonium acetate (220 mg, 2.85 mmol) at room temperature, and the mixture was stirred under reflux for 1 h. It was poured onto ice, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 10% ethyl acetate−*n*-hexane) to afford **19a** (190 mg, 0.49 mmol, 89%) as a dark green solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.36 (s, 6H), 1.81 (s, 4H), 3.93 (s, 3H), 7.06 (dd, J = 1.6, 2.4 Hz, 1H), 7.32 (dd, J = 1.6, 2.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 8.68 (s, 1H), 9.55 (br s, 1H).

Methyl 4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-3-furyl]benzoate (19b). A solution of **18** (2.0 g, 4.40 mmol) in concentrated sulfuric acid (10 mL) was stirred for 12 h at room temperature then poured into saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **19b** (300 mg, 0.77 mmol, 17%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.38 (s, 6H), 1.82 (s, 4H), 3.94 (s, 3H), 7.41 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.90 (s, 1H), 8.07 (d, J = 8.4 Hz, 2H), 8.75 (s, 1H).

Methyl 4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-3-thienyl]benzoate (19c). To a solution of **18** (400 mg, 0.88 mmol) in xylene (10 mL) was added phosphorus pentasulfide (196 mg, 0.88 mmol) at room temperature, and the mixture was stirred under reflux for 2 h then purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **19c** (100 mg, 0.25 mmol, 28%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.38 (s, 6H), 1.82 (s, 4H), 3.94 (s, 3H), 7.62 (d, J = 1.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.90 (d, 1H, J = 1.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 8.74 (s, 1H).

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-3-pyrrolyl]benzoic Acid (20a). Compound **20a** was synthesized from **19a** following the representative procedure described for **1** and obtained as a pale brown solid in 76% yield: mp 245−248 °C (EtOH−water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (s, 6H), 1.35 (s, 6H), 1.75 (s, 4H), 7.30−7.34 (m, 1H), 7.54−7.59 (m, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 8.79 (s, 1H). Anal. ($C_{23}H_{25}N_3O_2 \cdot 0.4H_2O$) C, H, N.

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-3-furyl]benzoic Acid (20b). Compound **20b** was synthesized from **19b** following the representative procedure described for **1** and obtained as a pale brown solid in 52% yield: mp 267−269 °C (EtOH−water); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.38 (s, 6H), 1.83 (s, 4H), 7.42 (d, J = 0.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 0.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 8.77 (s, 1H). Anal. ($C_{23}H_{24}N_2O_3 \cdot 4.0H_2O$) C, N; H: calcd, 7.19; found, 5.46. HRMS Calcd for $C_{23}H_{25}N_2O_3$ (MH^+): 376.1865. Found: 377.1857.

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-3-thienyl}benzoic Acid (20c). Compound **20c** was synthesized from **19c** following the representative procedure described for **1** and obtained as a pale brown solid in 83% yield: mp 247−249 °C (EtOH−water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 6H), 1.30 (s, 6H), 1.77 (s, 4H), 7.90 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 8.17 (s, 1H), 8.42 (s, 1H), 9.06 (s, 1H). Anal. ($C_{23}H_{24}N_2O_2S \cdot 0.9H_2O$) C, H, N.

Methyl 4-[3-Oxo-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl) propanoyl]benzoate (22). To a solution of diisopropylamine (542 μL, 3.87 mmol) in tetrahydrofuran (10 mL) was added *n*-butyllithium (1.6 M solution in *n*-hexane) (1.94 mL, 3.10 mmol) at 0 °C, and the mixture was stirred for 30 min at this temperature. This solution was added to a solution of **16** (600 mg, 2.58 mmol) in tetrahydrofuran (30 mL) at −78 °C. After the mixture had been stirred for 30 min at this temperature, a solution of terephthalic acid monomethyl ester chloride (564 mg, 2.84 mmol) in tetrahydrofuran (10 mL) was added, and the whole was stirred for 30 min at −78 °C. Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **22** (375 mg, 0.951 mmol, 37%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 6H), 1.41 (s, 6H), 1.85 (s, 4H), 3.96 (s, 3H), 7.54 (s, 1H), 8.06 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 9.10 (s, 1H).

Methyl 4-[5-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-3-pyrazolyl]benzoate (23). To a solution of **22** (200 mg, 0.507 mmol) in acetic acid (2 mL) was added hydrazine monohydrate (38 mg, 0.760 mmol) at room temperature, and the mixture was stirred under reflux for 2 h, poured into a saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **23** (190 mg, 0.487 mmol, 96%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.38 (s, 6H), 1.83 (s, 4H), 3.94 (s, 3H), 7.11 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 8.74 (s, 1H).

4-[5-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-3-pyrazolyl]benzoic Acid (24). Compound **24** was synthesized from **23** following the representative procedure described for **1** and obtained as a pale yellow solid in 86% yield: mp 295−298 °C (EtOH−water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 6H), 1.35 (s, 6H), 1.78 (s, 4H), 7.44 (br s, 1H), 7.92−8.04 (m, 4H), 8.92 (s, 1H). Anal. ($C_{22}H_{24}N_4O_2 \cdot 0.9H_2O$) C, H, N.

2-Bromo-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1-ethanone (25). To a solution of copper(II) bromide (1.08 g, 4.82 mmol) in ethyl acetate (5 mL) was added a solution of **16** (700 mg, 3.01 mmol) in chloroform (5 mL) at room temperature, and the mixture was stirred under reflux for 8 h. Water was added, and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **25** (815 mg, 2.62 mmol, 87%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.36 (s, 6H), 1.84 (s, 4H), 4.75 (s, 2H), 9.01 (s, 1H).

Methyl 4-[4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-2-imidazolyl]benzoate (26a). To a solution of **25** (1.54 g, 4.95 mmol) in *N*,*N*-dimethylformamide (10 mL) was added methyl 4-amizinobenzoate acetate (1.24 g, 5.20 mmol) and potassium carbonate (2.39 g, 17.3 mmol) at room temperature, and the mixture was stirred under reflux for 2 h. Water was added, and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: 20% ethyl acetate−*n*-hexane) to afford **26a** (280 mg, 0.60 mmol, 12%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.39 (s, 6H), 1.83 (s, 4H), 3.95 (s, 3H), 7.71 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 8.15 (d, J = 8.2 Hz, 2H), 8.72 (s, 1H), 10.24 (br s, 1H).

Methyl 4-[4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1,3-thiazol-2-yl]benzoate (26b). To a solution of **25** (200 mg, 0.643 mmol) in 2-propanol (10 mL) was added 4-carbomethoxybenzthioamide (132 mg, 0.675 mmol) and pyridine (0.1 mL) at room temperature, and the mixture was stirred under reflux for 2 h. Water was added, and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, and evaporated. The crude residue was purified by flash column chromatography

on silica gel (solvent: 5% ethyl acetate−*n*-hexane) to afford **26b** (135 mg, 0.331 mmol, 52%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.38 (s, 6H), 1.83 (s, 4H), 3.95 (s, 3H), 8.10 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 2H), 8.15 (s, 1H), 9.22 (s, 1H).

4-[4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1*H*-2-imidazolyl]benzoic Acid (27a). Compound **27a** was synthesized from **26a** following the representative procedure described for **1** and obtained as a yellow solid in 85% yield: mp >300 °C (EtOH−water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 6H), 1.32 (s, 6H), 1.77 (s, 4H), 7.91 (br s, 1H), 8.03 (d, J = 8.2 Hz, 2H), 8.13 (br d, J = 8.2 Hz, 2H), 8.91 (s, 1H), 13.15 (br s, 1H). Anal. ($C_{22}H_{24}N_4O_2 \cdot 1.2H_2O$) C, H, N.

4-[4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)-1,3-thiazol-2-yl]benzoic Acid (27b). Compound **27b** was synthesized from **26b** according to the procedure described for **1** and obtained as a yellow solid in 90% yield: mp 262 °C (decomp.) (EtOH−water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 6H), 1.34 (s, 6H), 1.79 (s, 4H), 8.07 (d, J = 8.2 Hz, 2H), 8.16 (d, J = 8.2 Hz, 2H), 8.45 (s, 1H), 9.12 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N.

Biology. Binding assays were performed as previously reported.[11b] Compounds were tested in log dilutions from 5.0×10^{-7} to 5.0×10^{-11} M with duplicate determinations at each concentration. 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 receptors is indicated as relative IC_{50}, obtained by dividing the IC_{50} value of a compound for a given receptor by that of ATRA. Transient transactivation assay for each receptor were also done by the reported method.[11b] Compounds were tested in log dilutions from 3.0×10^{-6} to 1.0×10^{-10} M with duplicate determinations at each concentration. Receptor and reporter vectors were transfected into COS-1 cells by means of the Lipofection method. After 4 h of incubation, the medium was replaced with DMEM supplemented with 10% FBS and incubation was continued for an additional 20 h. The cells were then suspended in DMEM supplemented with 10% FBS and seeded at 3×10^4 per well in 96-well plates. After 6 h of incubation, test compounds at various concentrations were added to duplicate wells. The plates were incubated for a further 48 h, then the cell supernatants were assayed for PLAP activity.[18] HL60 differentiation-inducing activity was measured by the method described previously.[11a] Compounds were tested in log dilutions from 1.0×10^{-5} to 1.0×10^{-12} M with duplicate determinations at each concentration. HL60 cells (1×10^5) were suspended in 1 mL of RPMI1640, plated in 48-well plates, and exposed to compounds for 5 days. The extent of differentiation was assayed by measuring CD11b expression on the cell surface with a FACS method. The values given in the table are averages of those from at least two experiments.

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