A Novel Type of Retinoic Acid Receptor Antagonist: Synthesis and Structure-Activity Relationships of Heterocyclic Ring-Containing Benzoic Acid Derivatives

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A new series of heterocyclic ring-containing benzoic acids was prepared, and the binding affinity and antagonism of its members against *all-trans*-retinoic acid were evaluated by *in vitro* assay systems using human promyelocytic leukemia (HL-60) cells. Structure–activity relationships indicated that both an N-substituted pyrrole or pyrazole (1-position) and a hydrophobic region, with these linked by a ring system, were indispensable for effective antagonism. Among the compounds evaluated, optimal antagonism was exhibited by 4-[4,5,7,8,9,10-hexahydro-7,7,10,-10-tetramethyl-1-(3-pyridylmethyl)anthra[1,2-*b*]pyrrol-3-yl]benzoic acid (**31**), 4-[4,5,7,8,9,10-hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)-5-thiaanthra[1,2-*b*]pyrrol-3-yl]benzoic acid (**40**), and 4-[4,5,7,8,9,10-hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)anthra[2,1-*d*]pyrazol-3-yl]benzoic acid (**55**), all of which possess a 3-pyridylmethyl group at the five-membered ring nitrogen atom.

Introduction

Retinoic acid (RA) is a substance essential for several life processes, including differentiation, reproduction, hematopoiesis, bone development, and pattern formation during embryogenesis.[1] Deficiency of RA causes hypovitaminosis A, which has been a serious nutritional problem in areas where malnutrition prevails. Xerophthalmia is one clinically observed symptom due to deficiency of RA. On the other hand, overloading of RA and/or its synthetic derivatives is known to cause hypervitaminosis A, whose manifestations include cornification disorder, alopecia, and metabolic disorders.

RA is recognized to be a pivotal regulatory ligand in retinoidal actions such as cell differentiation and proliferation, directly controlling gene expression through retinoid receptors (RARs,[2–5] RXRs[6]) existing in the nucleus of mammalian cells. Abnormalities in retinoid receptors at the genetic level have been reported in several pathological conditions. For example, chromosomal translocation takes place on the RAR-α gene in acute promyelocytic leukemia,[7,8] and aberrant expression of RAR-β has been reported in squamous cell carcinoma of the head and neck[9] and in pulmonary carcinoma.[10] In addition to a number of agonists, a few retinoid receptor antagonists[11–14] have previously been prepared to help in the understanding of retinoidal actions and/or as candidates for clinical application. However, these compounds are of only moderate potency, and they have proved inadequate for playing these roles. A need therefore exists for finding more potent antagonists.

In the course of researching such potent antagonists, we have discovered a new series of benzoic acid derivatives. We investigated the structure–activity relationships of these compounds by evaluation of the binding ability and antagonism using human promyelocytic leukemia (HL-60) cells. In this paper, we describe the design, synthesis, and structure–activity relationships of these novel compounds.

Table 1. Binding Affinity and Differentiation-Inducing Activities of 1–5 in HL-60 Cells[a]

compd	binding IC_{50},[b] M	differentiation $ED_{1/3}$,[c] M
ATRA (1)	6.3×10^{-10}	3.4×10^{-10}
2	1.9×10^{-8}	9.0×10^{-10}
3	1.7×10^{-8}	inactive[d] (antagonist)
4	1.6×10^{-8}	inactive[d] (antagonist)
5	8.0×10^{-8}	inactive[d]

[a] Human promyelocytic leukemia cell. [b] Concentration of the test compound inhibiting the binding of [^{3}H]ATRA. IC_{50} values were obtained from plots of binding affinity at 5.0×10^{-10} M [^{3}H]ATRA vs the logarithmic concentration of the test compound. Values are the mean of two experiments. [c] Differentiation-inducing activity of the test compound. $ED_{1/3}$ values were obtained from the percentage of the differentiated cells (CD11b-positive cells). Values are the mean of two experiments. [d] "Inactive" means there was no activity at concentrations below 3.0×10^{-6} M.

Design and Chemistry

In searching for compounds with reduced unwanted side effects due to "hypervitaminosis A" as caused by *all-trans*-retinoic acid (ATRA, **1**), some groups have examined the preparation of compounds such as **2**,[15] containing a heteroaryl group, in order to decrease lipophilicity of the molecule (Chart 1). However, the effects of rotational orientation of the three aryl groups on activity have not been reported. We hypothesized that fixing the rotation would have an effect on the binding ability and retinoidal activities.

Of the several ways of fixing the rotation between the three aryl groups, we have chosen one enabling us to examine the effect of preventing rotation between the hydrophobic region and the pyrazole group on binding affinity and biological activities. For this purpose, we designed a conformationally restricted analogue, **3**, by introducing a ring system. As shown in Table 1, while binding to the receptor as strongly as compound **2**, analogue **3** had an unexpected and interesting activity. Instead of showing agonism, as did compound **2**, it was antagonistic to ATRA in the HL-60 assay. It should be

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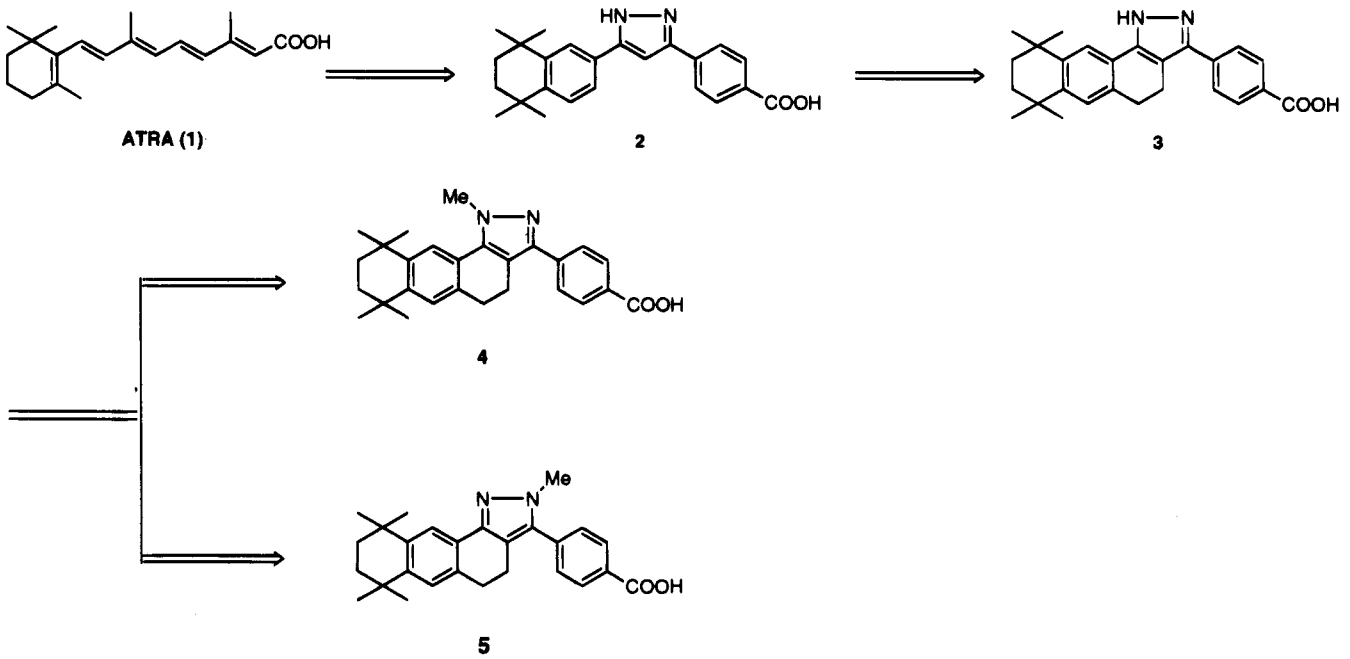
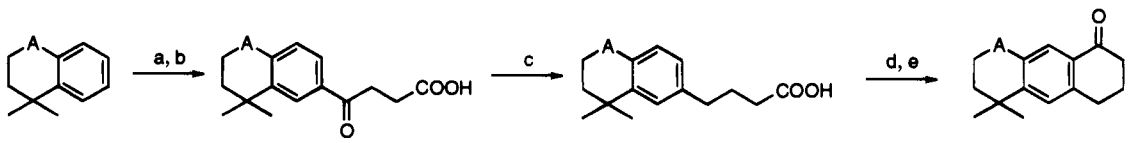
Chart 1



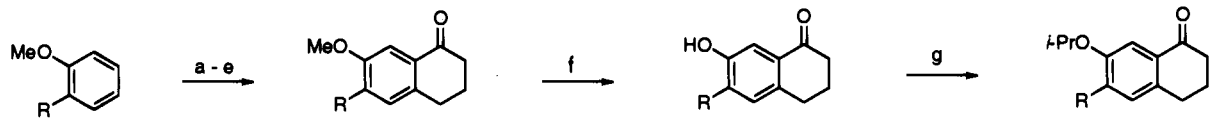
Scheme 1[a]



6a	A = S	**7a**	A = S	**8a**	A = S	**9a**	A = S
b	A = O	**b**	A = O	**b**	A = O	**b**	A = O
c	A = $C(Me)_2$	**c**	A = $C(Me)_2$	**c**	A = $C(Me)_2$	**c**	A = $C(Me)_2$

[a] (a) $ClCOCH_2CH_2COOEt/AlCl_3$; (b) NaOH/EtOH; (c) $NH_2NH_2{\cdot}H_2O$/KOH; (d) $SOCl_2$; (e) $AlCl_3$.

Scheme 2[a]



10a	R = *i*-Pr	**9d**	R = *i*-Pr	**11a**	R = *i*-Pr	**9h**	R = *i*-Pr
b	R = Me	**e**	R = Me	**b**	R = Me	**i**	R = Me
c	R = Cl	**f**	R = Cl	**c**	R = Cl	**j**	R = Cl
d	R = Ph	**g**	R = Ph	**d**	R = Ph	**k**	R = Ph

[a] (a) $ClCH_2CH_2COOEt/AlCl_3$; (b) NaOH/EtOH; (c) $NH_2NH_2{\cdot}H_2O$/KOH; (d) $SOCl_2$; (e) $AlCl_3$; (f) EtSH/$AlCl_3$; (g) K_2CO_3/*i*-PrI.

pointed out here that **3**, which has a novel skeleton, was the key compound in searching for stronger antagonists.

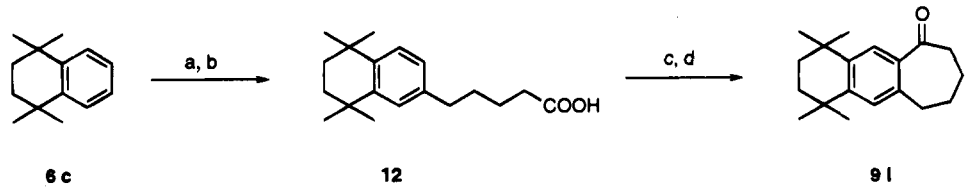
Next, compounds **4** and **5** were synthesized to evaluate the effect of a substituent at the nitrogen atom of the pyrazole. It was found that the antagonism of **4** was stronger than that of **3**, but no antagonism was seen in **5**.

On the basis of these findings, we concentrated on synthesizing compounds which possess both a conformation-restricting ring system and a 1-substituted pyrazole or pyrrole group.[16]

The requisite intermediate cyclic ketones for introduction of a ring system into the molecule were prepared as shown in Schemes **1**–6. **6a**–**c** were subjected to Friedel–Crafts acylation ($ClCOCH_2CH_2COOEt/AlCl_3$), and the intermediates were hydrolyzed under alkaline conditions (NaOH/aqueous EtOH) to give **7a**–**c**, respectively. Reduction of **7a**–**c** was achieved by the Wolff–Kishner reaction to afford **8a**–**c**. Reaction of the latter with $SOCl_2$ gave acid chlorides, which were treated with $AlCl_3$ to yield the desired ketones **9a**–**c**. **10a**–**d** were treated by this same procedure to afford **9d**–**g**.

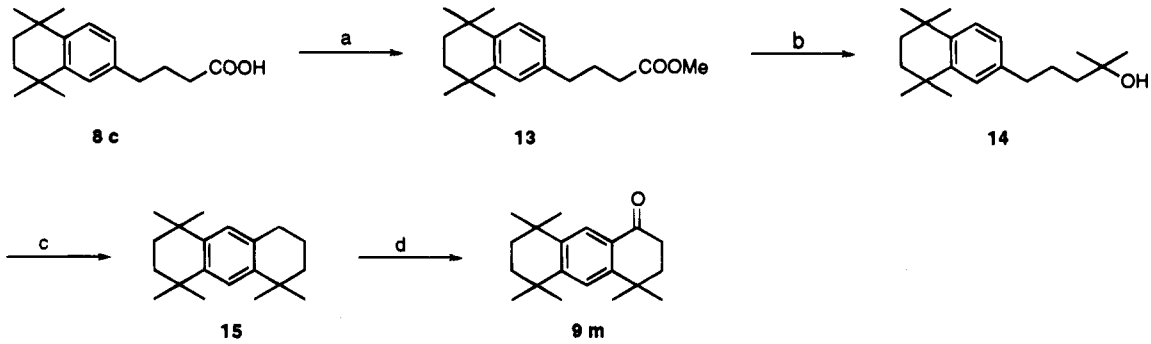
In the case of 7-isopropoxy derivatives, Friedel–Crafts acylation was unsuccessful because the isopropyl group was removed in the presence of $AlCl_3$. Therefore, the 7-isopropoxytetralones **9h**–**k** had to be prepared by another route, as shown in Scheme 2. Demethylation of **9d**–**g** was achieved by the combination of EtSH and $AlCl_3$[17] to afford the 7-hydroxy derivatives **11a**–**d** in moderate yield, which were then alkylated with 2-iodopropane in the presence of anhydrous K_2CO_3 to give **9h**–**k**. Naphthocycloheptanone **9l** was obtained from **6c** by almost the same procedure as described in the preparation of **9a**–**c** (Scheme 3).

Scheme 3[a]



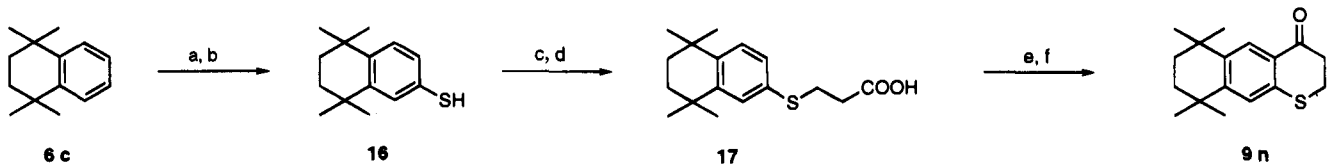
[a] (a) Glutaric anhydride/$AlCl_3$; (b) $NH_2NH_2{\cdot}H_2O$/KOH; (c) $SOCl_2$; (d) $AlCl_3$.

Scheme 4[a]



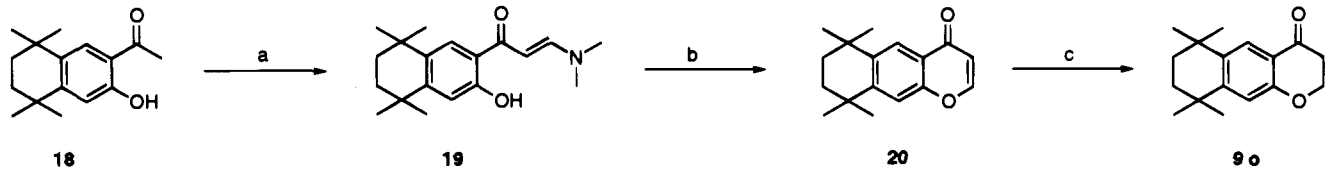
[a] (a) Concentrated H_2SO_4/MeOH; (b) MeMgBr/ether; (c) $AlCl_3$; (d) CrO_3/AcOH.

Scheme 5[a]



[a] (a) $ClSO_3H$; (b) Zn/HCl; (c) methyl acrylate/NaOMe; (d) NaOH/MeOH; (e) $SOCl_2$; (f) $AlCl_3$.

Scheme 6[a]



[a] (a) $Me_2NCH(OMe)_2$/DMF; (b) aqueous H_2SO_4; (c) H_2/10% Pd-C.

Preparation of the 4,4-dimethyl derivative **9m** is shown in Scheme 4. The methyl ester of **8c**, **13**, was prepared, and this was treated with 2.2 equiv of MeMgBr to afford the tertiary alcohol **14**. Intramolecular cyclization in the presence of $AlCl_3$ provided **15**, which was then oxidized with CrO_3 in AcOH to afford **9m**.

Preparation of **9n** is shown in Scheme 5. Introduction of the SH group was achieved by chlorosulfonation of **6c** followed by reduction with Zn/HCl to afford **16**. Michael condensation of **16** with methyl acrylate in the presence of NaOMe followed by hydrolysis gave **17**. This was treated according to the same procedure described in the preparation of **9a–c** to yield the desired ketone **9n**.

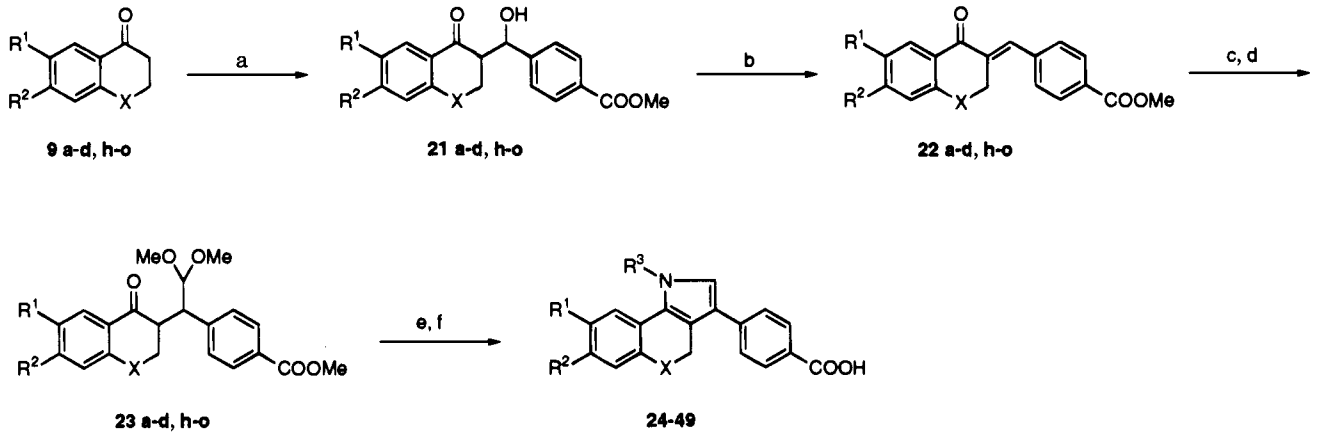
3-Acetyl-5,6,7,8-tetrahydro-2-hydroxy-5,5,8,8-tetramethylnaphthalene (**18**) was the starting compound in the preparation of **9o** (Scheme 6). Compound **18** was treated with *N,N,*-dimethylformamide dimethyl acetal to afford **19**. Intramolecular cyclization of this under acidic conditions gave **20**,[18] which was hydrogenated over 10% palladium on carbon to afford **9o**.

Scheme 7 shows the preparation of pyrrole-containing benzoic acid derivatives **24–49**. Condensation of **9a–d,h–o** with methyl 4-formylbenzoate in the presence of a catalytic amount of NaOH in MeOH provided β-keto alcohols **21a–d,h–o**. When this intermediate could be isolated by filtration, it was first collected and then converted to enone **22** by treatment with concentrated H_2SO_4. Otherwise, standing the solution of **21** led to *in situ* dehydration and then to crystallization of **22**. Oxo acetals **23a–d,h–o** were obtained from **22a–d,h–o** by conjugate addition of nitromethane anion and reaction with NaOMe (Nef reaction) to yield the aldehydes followed by acetalization. Treatment of **23a–d,h–o** with primary amines in AcOH at 100 °C yielded N-substituted pyrrole derivatives, which were then hydrolyzed under alkaline conditions to afford the desired compounds **25–49**. In the case of R^3 = H, ammonium acetate was used instead of a primary amine in the pyrrole ring-forming reaction.

Preparation of the dehydrogenated derivative **51** is shown in Scheme 8. Compound **50**, prepared from **23c** by reaction with 3-(aminomethyl)pyridine, was dehydrogenated with DDQ in benzene at reflux temperature, and the intermediate was hydrolyzed to afford **51**.

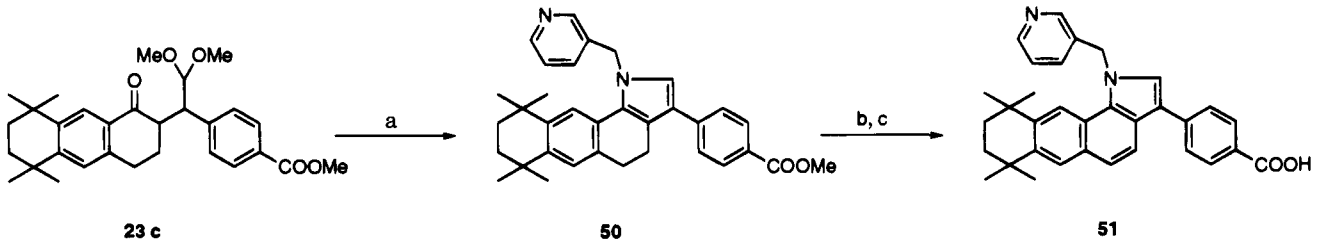
Pyrazole-containing benzoic acid derivatives **3–5** and **54–57** were prepared as shown in Scheme 9. Condensation of the anion of 3,4,5,6,7,8-hexahydro-5,5,8,8-tetramethyl-1(2*H*)-anthracenone (**9c**), formed in the

Scheme 7[a]



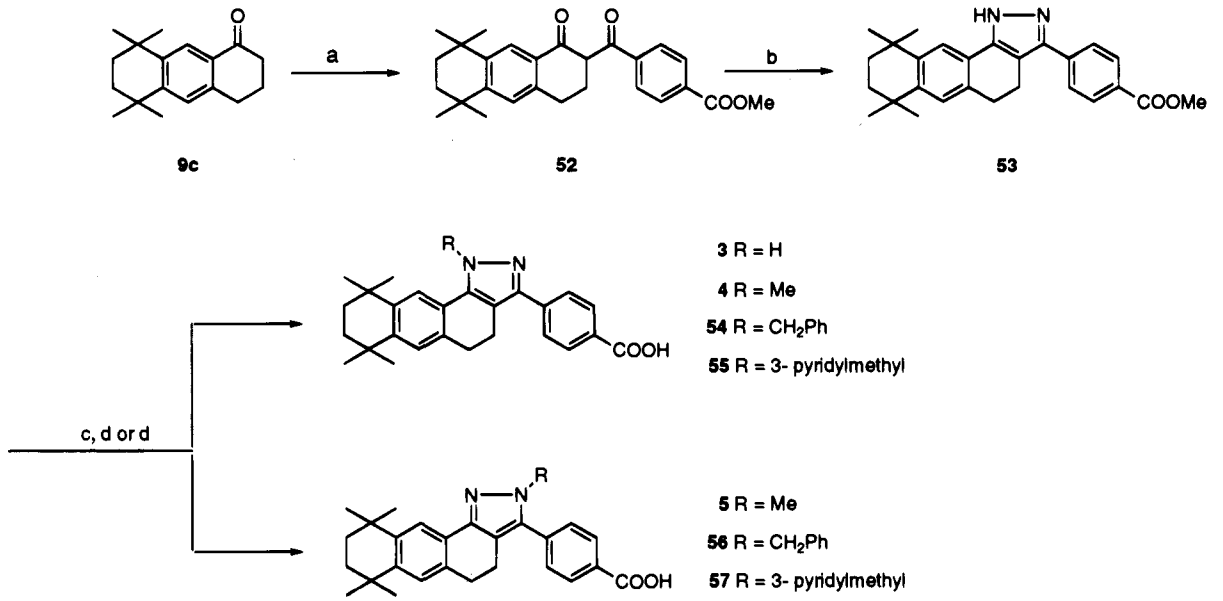
[a] (a) *p*-OHC-Ph-COOMe/catalytic NaOH; (b) concentrated H_2SO_4/dioxane; (c) $MeNO_2/PhCH_2NMe_3OH$; (d) NaOMe; concentrated H_2SO_4/MeOH; (e) R^3NH_2/AcOH; (f) NaOH/MeOH–THF.

Scheme 8[a]



[a] (a) 3-(Aminomethyl)pyridine/AcOH; (b) DDQ/benzene; (c) NaOH/MeOH–THF.

Scheme 9[a]

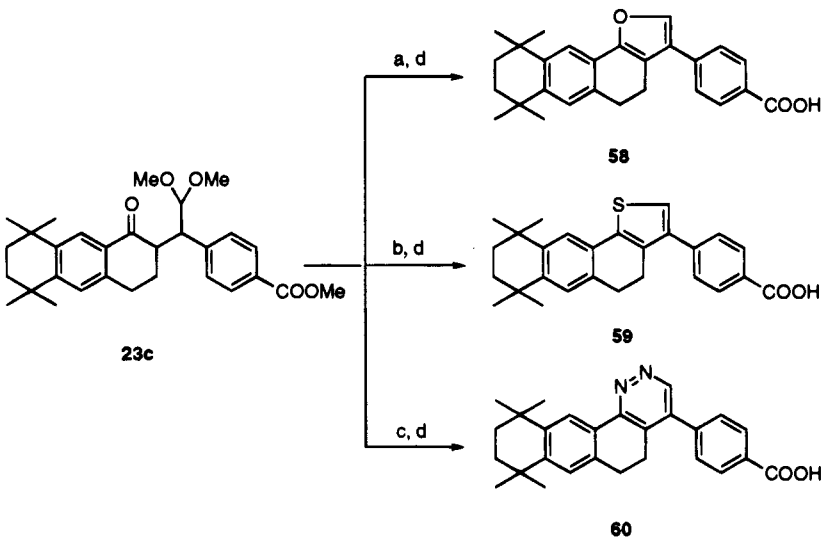


[a] (a) *p*-ClCO-Ph-COOMe/LDA; (b) $NH_2NH_2{\cdot}H_2O$; (c) NaH/MeI for **4** and **5**, NaH/$PhCH_2Br$ for **54** and **56**; NaH/3-picolyl chloride·HCl for **55** and **57**; (d) NaOH/MeOH–THF.

presence of a slight excess of LDA, with methylterephthaloyl chloride gave β-diketone **52** in moderate yield. Construction of the pyrazole ring was achieved by treatment of **52** with hydrazine monohydrate in MeOH at reflux temperature, the intermediate being hydrolyzed to yield **3**. Alkylation of **53** with iodomethane in the presence of NaH gave a mixture of 1-methyl and 2-methyl isomers. The solid residue left after evaporating the organic extract during workup was recrystallized from MeOH to afford the 1-methyl isomer. The structure was determined on the basis of an NOE experiment, in which the NOE between the methyl proton (1-position) and an aromatic proton of the anthracene ring (11-position) was observed. This methyl ester was hydrolyzed to afford **4**. Compounds **54** and **55** were obtained by the same procedure. The 2-methyl isomer was obtained from the filtrate (purified by column chromatography on silica gel) and then hydrolyzed to yield **5**. Compounds **56** and **57** were obtained by the same procedure.

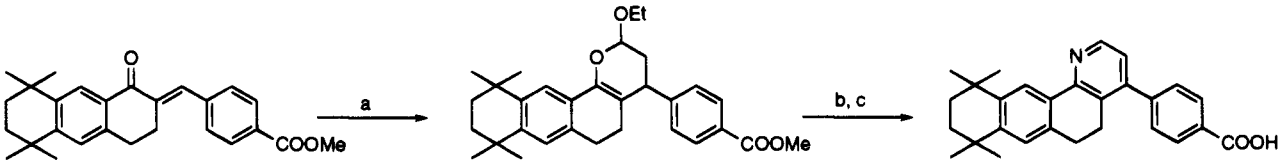
Scheme 10 shows the preparation of the furan, thiophene, and pyridazine derivatives. Construction of the furan ring was achieved by an acid-catalyzed cyclization of oxo acetal **23c**. Treatment of **23c** with

Scheme 10[a]



[a] (a) Concentrated H_2SO_4; (b) P_4S_{10}/xylene; (c) $NH_2NH_2 \cdot H_2O$/AcOH; (d) NaOH/MeOH–THF.

Scheme 11[a]



[a] (a) Ethyl vinyl ether/Yb(fod)$_3$/$ClCH_2CH_2Cl$; (b) $NH_2OH \cdot HCl/CH_3CN$; (c) NaOH/MeOH.

P_4S_{10} in xylene at reflux temperature yielded the thiophene derivative, whereas treatment with hydrazine monohydrate in AcOH at 100 °C yielded the pyridazine derivative. Hydrolysis of these gave **58**–**60**, respectively.

Construction of the pyridine ring was achieved by the method of Ciufolini et al.[19] Dihydropyran **61**, obtained by cycloaddition of **22c** with ethyl vinyl ether in the presence of ytterbium complex, was treated with hydroxylamine hydrochloride in CH_3CN at reflux temperature, forming the pyridine ring. The methyl ester was then hydrolyzed to yield the desired benzoic acid **62** (Scheme 11).

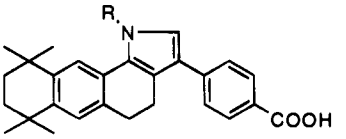
Results and Discussion

We have examined the binding ability and retinoidal activity of the synthetic compounds, the former by competitive binding experiments with ^{3}H-labeled ATRA in a nuclear extract of HL-60 cells and the latter by evaluating potency in effecting induction of the differentiation of HL-60 cells to mature granulocytes.[20,21] Generally, a cell forms a specific antigen on its surface when it has achieved differentiation. When an HL-60 cell differentiates into a mature granulocyte, CD11b, a differentiation marker of granulocytes/monocytes is expressed on its surface.[22] In this study, morphological changes were examined by flow cytometry to determine the percentage of CD11b-positive cells as the marker of differentiation.[23] As compounds evaluated in this study did not show differentiation-inducing activity at concentrations below 3.0×10^{-6} M, no further dicussion of any agonistic activity will be made. Antagonism was evaluated by the ability to inhibit the differentiation of ATRA (1.0×10^{-8} M) in HL-60 cells. Structure–activity relationships were investigated on the basis of the receptor binding assay and the evaluation of antagonism. In both cases, the relative potencies were expressed as IC_{50} values. With the exception of one or two compounds, we observed a strong correlation between binding ability and antagonism.

The effects of substitution at the nitrogen atom of the pyrrole are summarized in Table 2. Introducing various substituents affected both the binding ability and the antagonism. Substituted compounds were generally stronger antagonists than the unsubstituted compound **24**. Among these compounds substituted with an alkyl group, **25** showed the strongest antagonism. On the other hand, substitution with a bulky group, as in compound **28**, adversely affected both the binding affinity and the antagonism. Introduction of aryl groups gave good results in this system. In particular, compound **31** having a 3-pyridylmethyl substituent showed strong binding affinity and antagonism. The isomeric pyridine **32** had lower antagonism, although the 2-position analogue retained almost the same potency in both systems. Elongation of the substituent side chain, as in **34**, caused a dramatic reduction in antagonism. Introduction of methoxy or chloro groups into the pyridine (compounds **35** and **36**) resulted in loss of potency in both assays. Comparing compounds **37** and **38** with **31**, it can be seen that replacing the pyridine by a different heteroaryl group such as furan (**37**) or thiophene (**38**) reduced the binding affinity and the antagonism.

Table 3 shows the effects of substituents at the nitrogen atoms of the pyrazole. The results for 1-substituted compounds coincided with the results shown in Table 2. By introducing a methyl group (**4**), antago-

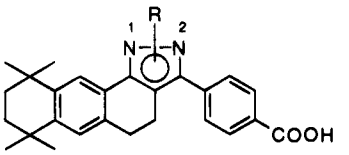
Table 2. Effects of Substituents at the Nitrogen Atom of the Pyrrole-Containing Benzoic Acid Derivatives



compd	R	mp, °C	formula[b]	HL-60[a] IC_{50}, M binding[c]	HL-60[a] IC_{50}, M antagonism[d]
24	H	254 dec	$C_{27}H_{29}NO_2 \cdot 0.9H_2O$	3.2×10^{-8}	$>3.0 \times 10^{-6}$
25	Me	291 dec	$C_{28}H_{32}NO_2$[e]	$>5.0 \times 10^{-8}$	2.0×10^{-7}
26	c-Pr	262 dec	$C_{30}H_{33}NO_2 \cdot 0.5H_2O$	1.4×10^{-8}	3.6×10^{-7}
27	*n*-pentyl	236–238	$C_{32}H_{39}NO_2 \cdot H_2O$	1.9×10^{-8}	5.2×10^{-7}
28	1-adamantylmethyl	264–266	$C_{38}H_{45}NO_2 \cdot 0.4H_2O$	$>5.0 \times 10^{-8}$	$>3.0 \times 10^{-6}$
29	benzyl	>300	$C_{34}H_{35}NO_2 \cdot 0.6H_2O$	1.2×10^{-9}	2.1×10^{-7}
30	3-pyridyl	226–227	$C_{32}H_{32}N_2O_2 \cdot 0.4H_2O$	5.9×10^{-10}	3.3×10^{-8}
31	3-pyridylmethyl	282 dec	$C_{33}H_{34}N_2O_2$	3.4×10^{-10}	4.9×10^{-9}
32	4-pyridylmethyl	264–265 dec	$C_{33}H_{34}N_2O_2 \cdot H_2O$	2.3×10^{-9}	8.4×10^{-8}
33	2-pyridylmethyl	287 dec	$C_{33}H_{34}N_2O_2 \cdot 0.4H_2O$	1.4×10^{-10}	1.7×10^{-8}
34	2-pyridylethyl	247–249	$C_{34}H_{36}N_2O_2 \cdot 0.2H_2O$	1.6×10^{-8}	1.3×10^{-6}
35	3-(4-OMe)pyridyl	269 dec	$C_{33}H_{35}N_2O_3$[f]	5.6×10^{-9}	6.5×10^{-7}
36	3-(4-Cl)pyridyl	291–292	$C_{32}H_{31}N_2O_2Cl \cdot 0.5H_2O$	3.2×10^{-9}	4.9×10^{-7}
37	2-furylmethyl	262–264 dec	$C_{32}H_{33}NO_3 \cdot 0.8H_2O$	3.4×10^{-9}	5.1×10^{-8}
38	2-thienylmethyl	288 dec	$C_{32}H_{33}NO_2 \cdot 0.4H_2O$	4.5×10^{-9}	5.4×10^{-7}

[a] Human promyelocytic leukemia cell. [b] Analytical results were within ±0.4% of the theoretical value. [c] Concentration of the test compound inhibiting the binding of [^{3}H]ATRA. IC_{50} values were obtained from plots of binding affinity at 5.0×10^{-10} M [^{3}H]ATRA vs the logarithmic concentration of the test compound. Values are the mean of two experiments. [d] Concentration of the test compound inhibiting the differentiation-inducing activity of ATRA (1.0×10^{-8} M). IC_{50} values were obtained from plots of activity at 1.0×10^{-8} M ATRA vs the logarithmic concentration of the test compound. Values are the mean of two experiments. [e,f] The formula was obtained by high-resolution mass spectroscopy: (e) calcd, 414.2433 (MH^+); found, 414.2385; (f) calcd, 507.2648 (MH^+); found, 507.2651.

Table 3. Effects of Substituents at the Nitrogen Atom of the Pyrazole-Containing Benzoic Acid Derivatives



compd	R	mp, °C	formula[b]	HL-60[a] IC_{50}, M binding[c]	HL-60[a] IC_{50}, M antagonism[d]
3	H	>300	$C_{26}H_{28}N_2O_2 \cdot 0.2H_2O$	1.7×10^{-8}	5.0×10^{-7}
4	1-Me	284 dec	$C_{27}H_{30}N_2O_2 \cdot 0.15H_2O$	1.6×10^{-8}	1.2×10^{-7}
5	2-Me	288 dec	$C_{27}H_{30}N_2O_2 \cdot 0.2H_2O$	$>5.0 \times 10^{-8}$	$>3.0 \times 10^{-6}$
54	1-benzyl	>300	$C_{33}H_{34}N_2O_2 \cdot 0.6H_2O$	1.5×10^{-9}	5.6×10^{-8}
55	1-(3-pyridylmethyl)	294–295	$C_{32}H_{33}N_3O_2 \cdot 0.7H_2O$	9.1×10^{-10}	1.3×10^{-9}

[a–d] See Table 2.

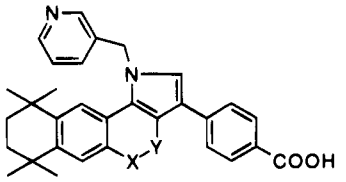
nism was increased 5-fold over that of the unsubstituted compound **3**. The 3-pyridylmethyl group (**55**) gave the greatest increase in potency in both systems and showed optimal antagonism among the compounds evaluated. On the other hand, introduction of a substituent at the 2-position, as in compound **5**, abolished both the binding affinity and the antagonism.

In order to examine the influence of the polycyclic system, compounds **39–42** and **51** were evaluated. These results are summarized in Table 4. Replacement of a ring atom of **31** with sulfur (**40**) resulted in no change in the potency of antagonism. However the oxygen derivative **39** was less active in both systems. Introduction of a dimethyl group caused a dramatic reduction of the binding affinity, and changing the six- to a seven-membered ring (**42**) also reduced the binding affinity. Comparing **31** with **51**, we assume that the higher antagonism of **31** is due to the fact that the benzene ring of the hydrophobic region and the pyrazole are not in the same plane. With respect to the polycyclic system, it seems that a six-membered, nonaromatized ring is necessary for potent antagonism, and hydrophilicity or steric bulk in this region prevents the compound from binding strongly to the receptor.

The effects of other heteroaryl groups are summarized in Table 5. Among the compounds containing a five-membered heteroaryl group, **3** and **58** displayed moderate antagonism, although their potencies were much lower than that of compound **31**. On the other hand, six-membered heteroaryl groups such as pyridazine (**60**) and pyridine (**62**) interfered with binding to the receptor, probably due to the changed position of the carboxylic acid.

Table 6 shows the results for derivatives designed to examine the effects of the hydrophobic region. Conformational restriction of the alkyl groups by a ring system (**31**) gave the highest potency in both systems. The diminished binding affinity resulting from introduction of oxygen (**44**) indicates that hydrophilicity disturbs binding of the compound to the receptor. This phenomenon has previously been observed by Kagechika et al. while examining the structure–activity relationships of a class of agonists.[24] Nevertheless, among the ring-opening derivatives **45–49**, compound **45** showed a

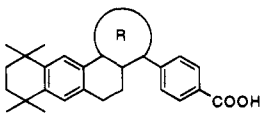
Table 4. Effects of the Ring Systems



compd	X	Y	mp, °C	formula[b]	HL-60[a] IC_{50}, M binding[c]	HL-60[a] IC_{50}, M antagonism[d]
31	CH_2	CH_2	282 dec	$C_{33}H_{34}N_2O_2$	3.4×10^{-10}	4.9×10^{-9}
39	O	CH_2	271 dec	$C_{32}H_{32}N_2O_3 \cdot 0.8H_2O$	1.9×10^{-8}	1.0×10^{-7}
40	S	CH_2	289 dec	$C_{32}H_{33}N_2O_2S$[e]	1.6×10^{-10}	5.6×10^{-9}
41	$C(Me)_2$	CH_2	273 dec	$C_{35}H_{38}N_2O_2 \cdot 1.2H_2O$	$>5.0 \times 10^{-8}$	1.0×10^{-6}
42	$-(CH_2)_3-$		280–281	$C_{34}H_{36}N_2O_2 \cdot 0.15H_2O$	4.7×10^{-9}	7.8×10^{-8}
51	$-CH=CH-$		>300	$C_{33}H_{32}N_2O_2 \cdot 1.2H_2O$	1.1×10^{-8}	7.7×10^{-8}

[a–d] See Table 2. [e] The formula was obtained by high-resolution mass spectroscopy: calcd, 509.2263 (MH^+); found, 509.2235.

Table 5. Effects of Heteroaryl Groups



compd	R	mp, °C	formula[b]	HL-60[a] IC_{50}, M Binding[c]	HL-60[a] IC_{50}, M Antagonism[d]
3		> 300	$C_{26}H_{28}N_2O_2 \cdot 0.2H_2O$	1.7×10^{-8}	5.0×10^{-7}
24		254 (dec)	$C_{27}H_{29}NO_2 \cdot 0.9H_2O$	3.2×10^{-8}	$> 3.0 \times 10^{-6}$
58		248 (dec)	$C_{27}H_{28}O_3 \cdot 0.7H_2O$	$> 5.0 \times 10^{-8}$	3.0×10^{-7}
59		261-262	$C_{27}H_{28}SO_2 \cdot 0.3H_2O$	$> 5.0 \times 10^{-8}$	2.4×10^{-6}
60		291 (dec)	$C_{27}H_{28}N_2O_2 \cdot 0.4H_2O$	$> 5.0 \times 10^{-8}$	$> 3.0 \times 10^{-6}$
62		286-289	$C_{28}H_{29}NO_2 \cdot 0.6H_2O$	$> 5.0 \times 10^{-8}$	$> 3.0 \times 10^{-6}$

[a–d] See Table 2.

strong binding affinity in spite of having a hydrophilic oxygen. This result suggests that further research needs to be carried out to find the most appropriate combination of substituents in the hydrophobic region for strong binding affinity and antagonism.

Overall, among the compounds evaluated, compounds **31**, **40**, and **50**, which possess a 3-pyridylmethyl group at the nitrogen atom, were the most potent antagonists (IC_{50}: $<(1.0 \times 10^{-8})$ M).

Conclusion

We succeeded in discovering potent retinoid antagonists by using two key strategies: (1) restriction of conformational change by introduction of a ring system and (2) introduction of a pyridylmethyl group at the nitrogen atom of the pyrrole or the pyrazole. The most potent antagonists we found were 4-[4,5,7,8,9,10-hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)-anthra[1,2-*b*]pyrrol-3-yl]benzoic acid (**31**), 4-[4,5,7,8,9,10-hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)-5-thiaanthra[1,2-*b*]pyrrol-3-yl]benzoic acid (**40**), and 4-[4,5,7,8,9,10-hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)anthra[2,1-d]pyrazol-3-yl]benzoic acid (**55**). To further characterize **31**, **40**, and **55**, additional research, including a subtype specific binding assay, is currently being carried out and will be reported elsewhere.

We have reported an interesting phenomenon caused by fixing the rotation between the hydrophobic region and the heteroaryl group. This approach, which leads to the finding of antagonists, opens the door for further study. We need to uncover the cause of this phenomenon and also investigate other ways of fixing the rotation and their effects on binding affinity and retinoidal activity.

Experimental Section

Chemistry. All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian UNITY 400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra (MS) were obtained on a JEOL JMS-HX100 mass spectrometer. All organic extracts were dried over anhydrous $MgSO_4$, and solvents were removed with a rotary evaporator under reduced pressure. Merck silica gel 60, 70–230 mesh or 230–400 mesh, was used for flash column chromatography.

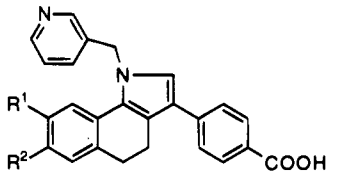
3-[6-(4,4-Dimethylthiochromanoyl)]propionic Acid (7a). To an ice-cooled suspension of 4,4-dimethylthiochroman (**6a**; 18.8 g, 105.5 mmol) and $AlCl_3$ (21 g, 157 mmol) in CH_2Cl_2 (150 mL) was added dropwise monoethylsuccinyl chloride (18.1 mL, 126.5 mmol). After being stirred for 6 h at room temperature, the mixture was poured into ice–water and extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated.

To a solution of the resulting residue in EtOH (100 mL) was added 5 N NaOH (50 mL), and this mixture was stirred at room temperature for 3 h. After being acidified with 1 N HCl, the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid was recrystallized from AcOEt/hexane to afford **7a** (11.4 g, 39%) as colorless crystals: mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6 H), 1.96 (t, 2 H, J = 9.0 Hz), 2.78 (t, 2 H, J = 7.0 Hz), 3.04 (t, 2 H, J = 9.0 Hz), 3.25 (t, 2 H, J = 7.0 Hz), 7.15 (d, 1 H, J = 8.9 Hz), 7.61 (dd, 1 H, J = 2.5 Hz, 8.9 Hz), 8.00 (d, 1 H, J = 2.5 Hz).

3,4,5,6,7,8-Hexahydro-5,5-dimethyl-8-thia-1(2*H*)anthracenone (9a). To a suspension of **7a** (11.4 g, 40.9 mmol) in diethylene glycol (100 mL) were added successively NaOH (8.2 g, 205 mmol) and hydrazine monohydrate (6 mL, 123 mmol). This mixture was vigorously stirred at 140 °C for 6 h under a nitrogen atmosphere and then cooled and poured into cold, aqueous HCl. The mixture was extracted with AcOEt, and the organic extract was washed with brine, dried, and evaporated to afford crude **8a**.

To a solution of **8a** (11 g) in dry benzene (11 mL) was added thionyl chloride (9 mL, 123 mmol), and this mixture was

Table 6. Effects of Substituents in the Hydrophobic Region



compd	R^1	R^2	mp, °C	formula[b]	HL-60[a] IC_{50}, M binding[c]	HL-60[a] IC_{50}, M antagonism[d]
31	$-Me_2CH_2CH_2Me_2-$		282 dec	$C_{33}H_{34}N_2O_2$	3.4×10^{-10}	4.9×10^{-9}
43	$-SCH_2CH_2Me_2-$		270–271	$C_{30}H_{28}N_2O_2S \cdot 0.5H_2O$	1.3×10^{-8}	1.1×10^{-6}
44	$-OCH_2CH_2Me_2-$		206 dec	$C_{30}H_{28}N_2O_3 \cdot H_2O$	$>5.0 \times 10^{-8}$	1.6×10^{-6}
45	*Oi*-Pr	*i*-Pr	265–266	$C_{31}H_{32}N_2O_3 \cdot 0.5H_2O$	9.7×10^{-10}	6.9×10^{-8}
46	OMe	*i*-Pr	152–154	$C_{29}H_{28}N_2O_3 \cdot 1.2H_2O$[e]	2.2×10^{-8}	1.7×10^{-7}
47	*Oi*-Pr	Me	261–263	$C_{29}H_{28}N_2O_3 \cdot 0.3H_2O$	3.7×10^{-9}	3.7×10^{-8}
48	*Oi*-Pr	Cl	272–273	$C_{28}H_{25}N_2O_3Cl \cdot 0.5H_2O$	2.9×10^{-9}	2.3×10^{-7}
49	*Oi*-Pr	Ph	275–278	$C_{34}H_{30}N_2O_3 \cdot 0.3H_2O$	3.0×10^{-8}	3.0×10^{-7}

[a–d] See Table 2. [e] H: calcd, 6.46; found, 5.95.

refluxed for 40 min. After allowing it to cool to room temperature, the solvent was evaporated and the residue was dissolved in CS_2 (30 mL). This solution was added to a suspension of $AlCl_3$ (7.2 g, 54 mmol) in CS_2 (100 mL), and the mixture was refluxed for 4 h. The mixture was allowed to cool to room temperature and then poured into ice–water and extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated. The resulting solid residue was washed with isopropyl ether to afford **9a** (5.0 g, 50%) as a pale brown solid: mp 88–89 °C; ^1H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.93 (t, 2 H, J = 9.0 Hz), 2.05–2.14 (m, 2 H), 2.59 (t, 2 H, J = 8.8 Hz), 2.85 (t, 2 H, J = 9.0 Hz), 3.02 (t, 2 H, J = 8.8 Hz), 7.22 (s, 1 H); MS M^+ 246. Anal. ($C_{15}H_{18}OS$) C, H.

3,4,5,6,7,8-Hexahydro-5,5-dimethyl-8-oxo-1(2*H*)anthracenone (9b). 4,4-Dimethylchroman (**6b**) was treated according to the same procedure described in the preparation of **9a** to afford **9b** as a pale yellow oil in 10% total yield, which was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.83 (t, 2 H, J = 7.0 Hz), 2.06–2.14 (m, 2 H), 2.58 (t, 2 H, J = 7.0 Hz), 2.86 (t, 2 H, J = 7.0 Hz), 4.16 (t, 2 H, J = 7.0 Hz), 7.12 (s, 1 H), 7.43 (s, 1 H).

3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1(2*H*)anthracenone (9c). 1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalene (**6c**) was treated according to the same procedure described in the preparation of **9a** to afford **9c** as a pale brown solid in 46% total yield: mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 1.29 (s, 1 H), 1.68 (s, 4 H), 2.06–2.16 (m, 2 H), 2.61 (t, 2 H, J = 7.0 Hz), 2.88 (t, 2 H, J = 7.0 Hz), 7.16 (s, 1 H), 8.00 (s, 1 H); MS MH^+ 257. Anal. ($C_{18}H_{24}O \cdot 0.2H_2O$) C, H.

7-Hydroxy-6-isopropyl-1-tetralone (11a). To a suspension of $AlCl_3$ (28 g, 0.21 mol) in CH_2Cl_2 (100 mL) was added EtSH (20 mL, 0.27 mol) at 0 °C. To this mixture was added dropwise a solution of 6-isopropyl-7-methoxy-1-tetralone (**9d**) (15.3 g, 70 mmol) in CH_2Cl_2 (50 mL). The mixture was allowed to warm to room temperature and then stirred for 3 h. The reaction mixture was poured into ice–water and extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated. The resulting solid residue was washed with hexane to afford **11a** (8.5 g, 59%) as a colorless solid: mp 149–150 °C; ^1H NMR ($CDCl_3$) δ 1.25 (d, 6 H, J = 6.5 Hz), 2.06–2.15 (m, 2 H), 2.63 (t, 2 H, J = 7.0 Hz), 2.88 (t, 2 H, J = 7.0 Hz), 3.29–3.38 (m, 1 H), 6.42 (s, 1 H), 7.05 (s, 1 H), 7.63 (s, 1 H); MS M^+ 205. Anal. ($C_{13}H_{16}O_2 \cdot 0.1H_2O$), C, H.

7-Isopropoxy-6-isopropyl-1-tetralone (9h). A mixture of **11a** (5.4 g, 26.4 mmol), 2-bromopropane (4.3 mL, 39.6 mmol), and anhydrous K_2CO_3 (7.3 g, 52.8 mmol) in dry DMF (50 mL) was stirred at 80 °C for 8 h. After cooling of the reaction mixture to room temperature, water was added and the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (5:95), to afford **9h** (6.0 g, 92%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.21 (d, 6 H, J = 6.5 Hz), 1.33 (d, 6 H, J = 6.5 Hz), 2.06–2.14 (m, 2 H), 2.60 (t, 2 H, J = 7.0 Hz), 2.88 (t, 2 H, J = 7.0 Hz), 3.28–3.38 (m, 1 H), 4.62–4.70 (m, 1 H), 7.03 (s, 1 H), 7.45 (s, 1 H).

Compounds **9e–g** were treated according to the same procedure described in the preparation of **9h** to afford **9i–k**, respectively.

4-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthyl)]-valeric Acid (12). To a solution of **6c** (10 g, 53.1 mmol) and glutaric anhydride (6.0 g, 52.6 mmol) in CH_2Cl_2 (100 mL) was added $AlCl_3$ (14.2 g, 106 mmol) at 0 °C. After being stirred at room temperature for 3.5 h, the mixture was poured into ice–water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid residue was washed with hexane to afford a colorless solid (5.1 g).

To a suspension of this solid in diethylene glycol (100 mL) were added in succession NaOH (3.3 g, 82.5 mmol) and hydrazine monohydrate (2.5 g, 49.9 mmol). After being vigorously stirred at 180 °C for 6 h under a nitrogen atmosphere, the reaction mixture was cooled to room temperature and then poured into cold aqueous HCl and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated to afford **12** (4.3 g, 28%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.23 (s, 6 H), 1.26 (s, 6 H), 1.60–1.76 (m, 4 H), 1.66 (s, 4 H), 2.38 (t, 2 H, J = 7.2 Hz), 2.57 (t, 2 H, J = 7.2 Hz), 6.92 (dd, 1 H, J = 2.5, 8.8 Hz), 7.08 (d, 1 H, J = 2.5 Hz), 7.20 (d, 1 H, J = 8.8 Hz).

7,8,9,10-Tetrahydro-7,7,10,10-tetramethylnaphtho[2,3-*b*]cycloheptan-1-one (9l). Compound **12** was treated according to the same procedure described in the preparation of **9a** to afford **9l** as a pale brown solid in 87% yield: mp 102–105 °C; ^1H NMR ($CDCl_3$) δ 1.28 (s, 1 H), 1.67 (s, 4 H), 1.76–1.90 (m, 4 H), 2.66–2.74 (m, 2 H), 2.83–2.92 (m, 2 H), 7.09 (s, 1 H), 7.71 (s, 1 H); MS MH^+ 271. Anal. ($C_{19}H_{26}O$) C, H.

5-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthyl)]-2-methyl-2-pentanol (14). To a solution of **13** (15 g, 52 mmol) in anhydrous Et_2O (200 mL) at 0 °C was added MeMgBr (3 M in Et_2O; 38 mL, 114 mmol) dropwise. After being stirred at room temperature for 6 h, the reaction mixture was poured into cold, aqueous ammonium chloride. The organic extract was washed with brine, dried, and evaporated to afford **14** (14 g, 93%) as a colorless solid: mp 75 °C; ^1H NMR ($CDCl_3$) δ 1.21 (s, 6 H), 1.26 (s, 4 H), 1.27 (s, 6 H), 1.48–1.56 (m, 2 H), 1.62–1.73 (m, 3 H), 1.65 (s, 4 H), 2.56 (t, 2 H, J = 7.6 Hz), 6.99 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 7.10 (d, 1 H, J = 2.5 Hz), 7.20 (d, 1 H, J = 8.8 Hz).

1,2,3,4,5,6,7,8-Octahydro-1,1,4,4,5,5-hexamethylanthracene (15). To a suspension of $AlCl_3$ (10 g, 74.9 mmol) in nitromethane (100 mL) was added **14** (14 g, 48.5 mmol) at 0 °C. After being stirred for 3 h at room temperature, the mixture was poured into ice–water and extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated.

The crude residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (1:99), to afford **15** (12 g, 91%) as a pale yellow solid: mp 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 H), 1.25 (s, 12 H), 1.54–1.80 (m, 4 H), 1.64 (s, 4 H), 2.70 (t, 2 H, J = 7.0 Hz), 6.93 (s, 1 H), 7.22 (s, 1 H).

3,4,5,6,7,8-Hexahydro-4,4,5,5,8,8-hexamethyl-1(2*H*)anthracenone (9m). To a solution of **15** (12 g, 44.3 mmol) in AcOH (80 mL) and acetone (80 mL) at 0 °C was added a solution of chromic anhydride (11 g, 110 mmol) in 80% AcOH (50 mL). After being stirred at room temperature for 10 h, the reaction mixture was cooled with ice–water, and then an aqueous solution of sodium sulfite was added. Water (300 mL) was added to this mixture to precipitate a solid which was collected by filtration and then washed with water to afford **9m** (11 g, 87%) as a pale brown solid: mp 136–138 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 12 H), 1.36 (s, 6 H), 1.67 (s, 4 H), 1.97 (t, 2 H, J = 7.0 Hz), 2.68 (t, 2 H, J = 7.0 Hz), 7.32 (s, 1 H), 7.96 (s, 1 H); MS MH$^+$ 285. Anal. ($C_{20}H_{28}O$·0.3H_2O) C, H.

5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalene-2-thiol (16). To chlorosulfonic acid (50 mL) at 0 °C was added **6c** (30 g, 0.16 mol) dropwise over a period of 10 min. After being stirred at room temperature for 3 h, this mixture was poured into ice–water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting residue was dissolved in EtOH (200 mL), and then zinc powder (50 g, 0.76 mol) was added. To this mixture was added concentrated HCl (200 mL) over a period of 30 min, and the suspension was refluxed for 1 h. After cooling of the mixture to room temperature, undissolved materials were filtrated off through Celite and then the solution was evaporated. The residue was dissolved in AcOEt, and the organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated to afford **16** (30.5 g, 86%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 H), 1.25 (s, 6 H), 1.65 (s, 4 H), 3.36 (s, 1 H), 7.03 (dd, 1 H, J = 2.5, 8.9 Hz), 7.17 (d, 1 H, J = 8.9 Hz), 7.22 (d, 1 H, J = 2.5 Hz).

3-[[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthyl)]thio]propionic Acid (17). To a mixture of **16** (26 g, 0.12 mol) and methyl acrylate (14 mL, 0.15 mol) was added NaOMe (28% solution in MeOH; 1.1 mL, 5.7 mmol) at room temperature. After being stirred at this temperature for 1 h, this mixture was poured into cold aqueous HCl and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (2:98), to afford a yellow oil (24 g).

To a solution of this oil in MeOH (100 mL) was added 5 N NaOH (100 mL) at room temperature. After being stirred at this temperature for 2 h, this mixture was poured into cold aqueous HCl and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid residue was washed with hexane to afford **17** (15.4 g, 44%) as a colorless solid: mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 H), 1.26 (s, 6 H), 1.66 (s, 4 H), 2.66 (t, 2 H, J = 7.0 Hz), 3.10 (t, 2 H, J = 7.0 Hz), 7.14 (dd, 1 H, J = 2.5, 8.9 Hz), 7.23 (d, 1 H, J = 8.9 Hz), 7.32 (d, 1 H, J = 2.5 Hz).

3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-4-thia-1(2*H*)anthracenone (9n). Compound **17** was treated according to the same procedure described in the preparation of **9a** to afford **9n** as a pale yellow solid in 66% yield: mp 144–145 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.26 (s, 6 H), 1.66 (s, 4 H), 2.94 (t, 2 H, J = 9.0 Hz), 3.20 (t, 2 H, J = 9.0 Hz), 7.19 (s, 1 H), 8.08 (s, 1 H); MS MH$^+$ 275. Anal. ($C_{17}H_{22}OS$·0.1H_2O) C, H.

5,6,7,8-Tetrahydro-2-hydroxy-5,5,8,8-tetramethyl-3-[[(*N*,*N*-dimethylamino)ethynyl]carbonyl]naphthalene (19). To a solution of 3-acetyl-5,6,7,8-tetrahydro-2-hydroxy-5,5,8,8-tetramethylnaphthalene (**18**; 25 g, 0.10 mol) in DMF (100 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (27 mL, 0.20 mol). After being stirred at 100 °C for 40 min, this mixture was poured into ice–water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid residue was washed with hexane to afford **19** (13.4 g, 44 %) as a yellow solid: mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6 H), 1.28 (s, 6 H), 1.67 (s, 4 H), 3.00 (brs, 3 H), 3.18 (brs, 3 H), 5.75 (d, 1 H, J = 13.0 Hz), 6.85 (s, 1 H), 7.59 (s, 1 H), 7.86 (d, 1 H, J = 13.0 Hz), 13.44 (s, 1 H).

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-4-oxo-1(4*H*)-anthracenone (20). A suspension of **19** (13.4 g, 44.4 mmol) in 3 N H_2SO_4 (200 mL) was refluxed for 1.5 h. After allowing it to cool to room temperature, this mixture was extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The resulting solid residue was washed with hexane to afford **20** (10 g, 88%) as a pale brown solid: mp 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.33 (s, 6 H), 1.73 (s, 4 H), 6.27 (d, 1 H, J = 5.6 Hz), 7.36 (s, 1 H), 7.78 (d, 1 H, J = 5.6 Hz), 8.12 (s, 1 H).

3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-4-oxo-1(2*H*)-anthracenone (9o). A solution of **20** (10 g, 39 mmol) in EtOH (100 mL) and AcOEt (100 mL) was hydrogenated over 10% palladium on carbon (water content–50%; 1.0 g) at 1 atm for 1.5 h. The catalyst was filtered off, and the filtrate was evaporated to give the crude product, which was purified by column chromatography on silica gel, eluting with AcOEt/hexane (5:95), to afford **9o** (6.2 g, 62%) as a colorless solid: mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 12 H), 1.66 (s, 4 H), 2.77 (t, 2 H, J = 6.4 Hz), 4.48 (t, 2 H, J = 6.4 Hz), 6.89 (s, 1 H), 7.84 (s, 1 H); MS MH$^+$ 259. Anal. ($C_{17}H_{22}O_2$) C, H.

Methyl 4-[(3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1(2*H*)-oxoanthracen-2-yl)hydroxymethyl]benzoate (21c). To a solution of **9c** (8.0 g, 31.2 mmol) and methyl 4-formylbenzoate (5.1 g, 31.1 mmol) in MeOH (200 mL) was added NaOH (0.3 g, 7.5 mmol). This mixture was stirred at room temperature for 24 h precipitating a solid. This was collected by filtration and then washed with MeOH to afford **21c** (8.4 g, 64%) as a colorless solid: mp 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 6 H), 1.32 (s, 6 H), 1.33 (s, 3 H), 1.75–1.84 (m, 1 H), 1.98–2.13 (m, 1 H), 2.76–2.92 (m, 3 H), 3.08 (d, 1 H, J = 5.0 Hz), 3.93 (s, 3 H), 5.70–5.76 (m, 1 H), 7.13 (s, 1 H), 7.45 (d, 2 H, J = 8.4 Hz), 8.02 (s, 1 H), 8.04 (d, 2 H, J = 8.4 Hz).

Methyl 4-(3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1-oxoanthracen-2-ylidene)benzoate (22c). To a suspension of **21c** (8.4 g, 20 mmol) in 1,4-dioxane (100 mL) was added concentrated H_2SO_4 (5 mL) at room temperature. After being stirred at the same temperature for 3 h, the mixture was poured into water and extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated. The resulting solid residue was washed with hexane to afford **22c** (7.1 g, 85%) as a colorless solid: mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.33 (s, 6 H), 1.70 (s, 4 H), 2.90 (t, 2 H, J = 6.4 Hz), 3.08 (t, 2 H, J = 6.4 Hz), 3.93 (s, 3 H), 7.17 (s, 1 H), 7.48 (d, 2 H, J = 8.4 Hz), 7.81 (s, 1 H), 8.08 (d, 2 H, J = 8.4 Hz), 8.10 (s, 1 H); MS MH$^+$ 403. Anal. ($C_{27}H_{30}O_3$) C, H.

Methyl 4-[1-(3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1(2*H*)-oxoanthracen-2-yl)-2,2-dimethoxyethyl]benzoate (23c). To a solution of **22c** (5.0 g, 11.9 mmol) in THF (20 mL) were added nitromethane (40 mL) and benzyltrimethylammonium hydroxide (40% methanolic solution; 0.5 g, 1.1 mmol) successively at room temperature. After being stirred at this temperature for 4 h, this mixture was extracted with AcOEt. The organic extract was washed successively with 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated to afford the crude nitrate as a pale orange powder (6.3 g).

A solution of this nitrate (6.3 g) in CH_2Cl_2 (20 mL) and THF (20 mL) was added dropwise to a sodium methoxide solution (28% solution in MeOH; 6.6 mL, 34.2 mmol) at –35 °C. The resultant mixture was then added dropwise at –35 °C to a separately prepared mixture of concentrated H_2SO_4 (35 mL) and MeOH (100 mL). The mixture was allowed to warm to room temperature, poured into saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated to afford **23c** (5.7 g, quantitative) as a pale brown powder. This powder was used in the subsequent reactions without being further purified.

Methyl 4-[4,5,7,8,9,10-Hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)anthra[1,2-*b*]pyrrol-3-yl]benzoate (50). A mixture of **23c** (0.5 g, 1.0 mmol) and 3-(aminomethyl)-pyridine (0.14 g, 1.3 mmol) in AcOH (10 mL) was heated at 100 °C for 30 min. After allowing to cool to room temperature,

this mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid residue was washed with MeOH to afford **50** (0.34 g, 67%) as a colorless solid: mp 241–242 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 6 H), 1.27 (s, 6 H), 1.52 (s, 4 H), 2.83–2.94 (m, 4 H), 3.93 (s, 3 H), 5.50 (s, 2 H), 6.94 (s, 2 H), 7.17 (s, 1 H), 7.24–7.29 (m, 1 H), 7.35–7.40 (m, 1 H), 7.49 (d, 2 H, J = 8.4 Hz), 8.04 (d, 2 H, J = 8.4 Hz), 8.54–8.60 (m, 2 H); MS M^+ 504. Anal. ($C_{34}H_{36}N_2O_2$·0.15H_2O) C, H, N.

4-[4,5,7,8,9,10-Hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)anthra[1,2-*b*]pyrrol-3-yl]benzoic Acid (31). To a solution of **50** (0.34 g, 0.67 mmol) in MeOH (5 mL) and THF (5 mL) was added 5 N NaOH (5 mL), and then this mixture was refluxed for 30 min. After allowing it to cool to room temperature, the pH of the mixture was adjusted to 4 with 1 N HCl to precipitate a solid. This solid was collected by filtration and then washed with water to afford **31** (0.25 g, 75%) as a colorless solid: mp 282 °C dec; ^{1}H NMR (DMSO-d_6) δ 0.91 (s, 6 H), 1.17 (s, 6 H), 1.50 (s, 4 H), 2.68–2.85 (m, 4 H), 5.58 (s, 2 H), 6.90 (s, 1 H), 7.15 (s, 1 H), 7.34–7.43 (m, 3 H), 7.53 (d, 2 H, J = 8.4 Hz), 7.92 (d, 2 H, J = 8.4 Hz), 8.37 (brs, 1 H), 8.46 (brs, 1 H); MS M^+ 490. Anal. ($C_{33}H_{34}N_2O_2$) C, H, N.

Compounds **9a,b,d,h–o** were treated according to the same procedure described in the preparation of **31** to afford **24–30** and **32–49**, respectively.

4-[7,8,9,10-Tetrahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)anthra[1,2-*b*]pyrrol-3-yl]benzoic Acid (51). A mixture of **50** (0.62 g, 1.2 mmol) and DDQ (0.56 g, 2.4 mmol) in benzene (50 mL) was refluxed for 4 h. After being allowed to cool to room temperature, the solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (30:70), to afford a pale yellow solid.

This solid was treated according to the same procedure described in the preparation of **31** to afford **51** (0.2 g, 33%) as a colorless solid: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 1.03 (s, 6 H), 1.30 (s, 6 H), 1.62 (s, 4 H), 6.05 (s, 2 H), 7.30 (brs, 2 H), 7.56 (d, J = 8.9 Hz, 1 H), 7.81–7.86 (m, 3 H), 7.90 (s, 1 H), 7.94 (d, J = 8.9 Hz, 1 H), 7.98–8.07 (m, 3 H), 8.40 (s, 1 H), 8.42 (brs, 1 H). Anal. ($C_{33}H_{32}N_2O_2$·1.2H_2O) C, H, N.

Methyl 4-[(3,4,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1(2*H*)-oxoanthracen-2-yl)carbonyl]benzoate (52). Diisopropylamine (1.5 g, 14.8 mmol) was dissolved in anhydrous THF (50 mL), and then *n*-BuLi (1.6 M in hexane; 8.8 mL, 14.1 mmol) was added at 0 °C. The mixture was stirred for 10 min and then cooled to −78 °C followed by the addition of a solution of **9c** (3.0 g, 11.7 mmol) in anhydrous THF (20 mL). After being stirred for 30 min at this temperature, the mixture was treated by dropwise addition of a solution of methylterephthaloyl chloride (2.8 g, 14.1 mmol) in anhydrous THF (20 mL). The mixture was allowed to warm to room temperature, poured into cold aqueous HCl, and extracted with AcOEt. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (5:95), and the resulting solid residue was washed with MeOH to afford **52** (2.5 g, 51%) as a pale yellow solid: mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.34 (s, 6 H), 1.70 (s, 4 H), 2.67–2.80 (m, 4 H), 3.95 (s, 3 H), 7.14 (s, 1 H), 7.63 (d, 2 H, J = 8.4 Hz), 7.99 (s, 1 H), 8.12 (d, 2 H, J = 8.4 Hz); MS MH^+ 419. Anal. ($C_{27}H_{30}O_4$) C, H.

Methyl 4-(4,5,7,8,9,10-Hexahydro-7,7,10,10-tetramethylanthra[2,1-*d*]pyrazol-3-yl)benzoate (53). To a suspension of **49** (2.5 g, 6.2 mmol) in MeOH (80 mL) was added hydrazine monohydrate (0.4 g, 8.0 mmol), and this mixture was refluxed for 2 h. After cooling of the reaction mixture to room temperature, the resulting precipitate was collected by filtration and then washed with MeOH to afford **53** (2.0 g, 78%) as a pale yellow solid: mp 241–243 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.26 (s, 6 H), 1.62 (s, 4 H), 2.80–2.96 (m, 4 H), 3.85 (s, 3 H), 7.24 (s, 1 H), 7.66 (s, 1 H), 7.84 (d, 2 H, J = 8.4 Hz), 8.02 (d, 2 H, J = 8.4 Hz); MS MH^+ 415. Anal. ($C_{27}H_{30}N_2O_2$) C, H, N.

4-(4,5,7,8,9,10-Hexahydro-7,7,10,10-tetramethylanthra[2,1-*d*]pyrazol-3-yl)benzoic Acid (3). Compound **53** was treated according to the same procedure described in the preparation of **31** to afford **3** as a pale yellow solid in 80% yield: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 6 H), 1.26 (s, 6 H), 1.64 (s, 4 H), 2.82–2.96 (m, 4 H), 7.24 (s, 1 H), 7.65 (s, 1 H), 7.80 (d, 2 H, J = 8.4 Hz), 8.00 (d, 2 H, J = 8.4 Hz); MS MH^+ 401. Anal. ($C_{26}H_{28}N_2O_2$·0.2H_2O) C, H, N.

4-(4,5,7,8,9,10-Hexahydro-1,7,7,10,10-pentamethylanthra[2,1-*d*]pyrazol-3-yl)benzoic Acid (4) and 4-(4,5,7,8,9,-10-Hexahydro-2,7,7,10,10-pentamethylanthra[2,1-*d*]pyrazol-3-yl)benzoic Acid (5). To a solution of **53** (4.5 g, 10.9 mmol) in DMF (20 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil; 0.52 g, 13.1 mmol) followed by the addition of iodomethane (1.0 mL, 16.4 mmol) at the same temperature. After being stirred at room temperature for 30 min, the mixture was poured into ice water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid residue was recrystallized from MeOH to afford a pale yellow solid (2.8 g).

This solid was treated according to the same procedure described in the preparation of **31** to afford **4** (2.1 g, 46%) as a pale yellow solid: mp 284 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 6 H), 1.30 (s, 6 H), 1.64 (s, 4 H), 2.82 (s, 4 H), 4.17 (s, 3 H), 7.31 (s, 1 H), 7.54 (s, 1 H), 7.77 (d, 2 H, J = 8.4 Hz), 7.98 (d, 2 H, J = 8.4 Hz); MS MH^+ 415. Anal. ($C_{27}H_{30}N_2O_2$·0.15H_2O) C, H, N.

Compounds **54** and **55** were obtained by the same procedure described in the preparation of **4**.

The filtrate of the methyl ester of **4** was evaporated, and the residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (10:90), to afford a colorless solid (0.88 g). This solid was treated according to the same procedure described in the preparation of **31** to afford **5** (0.7 g, 15%) as a colorless solid: mp 288 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.22 (s, 6 H), 1.23 (s, 6 H), 1.62 (s, 4 H), 2.58–2.68 (m, 2 H), 2.74–2.83 (m, 2 H), 3.84 (s, 3 H), 7.20 (s, 1 H), 7.58 (s, 1 H), 7.60 (d, 2 H, J = 8.4 Hz), 8.04 (d, 2 H, J = 8.4 Hz). Anal. ($C_{27}H_{30}N_2O_2$·0.2H_2O) C, H, N.

Compounds **56** and **57** were obtained by the same procedure described in the preparation of **5**.

4-(4,5,7,8,9,10-Hexahydro-7,7,10,10-tetramethylanthra-[1,2-*b*]furan-3-yl)benzoic Acid (58). To concentrated H_2SO_4 (10 mL) was added **23c** (0.4 g, 0.8 mmol) at room temperature. After being stirred at this temperature for 20 h, the mixture was poured into cold water and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (5:95), to afford the furan as a colorless solid (0.1 g).

To a solution of this solid (0.1 g) in MeOH (5 mL) and THF (5 mL) was added 5 N NaOH (5 mL), and then this mixture was refluxed for 30 min. After being allowed to cool to room temperature, the reaction mixture was acidified with 1 N HCl to precipitate a solid. This solid was collected by filtration and then washed with water to afford **58** (0.09 g, 27%) as a colorless solid: mp 248 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 6 H), 1.25 (s, 6 H), 1.62 (s, 4 H), 2.84–2.95 (m, 4 H), 7.22 (s, 1 H), 7.32 (s, 1 H), 7.62 (d, 2 H, J = 8.4 Hz), 7.96 (d, 2 H, J = 8.4 Hz), 8.14 (s, 1 H); MS M^+ 400. Anal. ($C_{27}H_{28}O_3$·0.7H_2O) C, H.

4-(4,5,7,8,9,10-Hexahydro-7,7,10,10-tetramethylanthra-[1,2-*b*]thiophene-3-yl)benzoic Acid (59). To a solution of **23c** (1.0 g, 2.1 mmol) in xylene (50 mL) was added phosphorus pentasulfide (0.6 g, 1.3 mmol) at room temperature, and this mixture was refluxed for 20 min. After being allowed to cool to room temperature, this mixture was evaporated and purified by column chromatography on silica gel, eluting with AcOEt/hexane (3:97), to afford the thiophene as a yellow solid (0.25 g).

This solid was treated according to the same procedure described in the preparation of **58** (in part) to afford **59** (0.22 g, 25%) as a pale yellow solid: mp 261–262 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 6 H), 1.26 (s, 6 H), 1.63 (s, 4 H), 2.75–2.84 (m, 4 H), 7.23 (s, 1 H), 7.24 (s, 1 H), 7.55 (d, 2 H, J = 8.4 Hz), 7.59 (s, 1 H), 7.99 (d, 2 H, J = 8.4 Hz); MS M^+ 416. Anal. ($C_{27}H_{28}SO_2$·0.3H_2O), C, H.

4-(5,6,8,9,10,11-Hexahydro-8,8,11,11-tetramethylanthra-[2,1-*e*]pyridazin-4-yl)benzoic Acid (60). A solution of **23c** (0.4 g, 0.84 mmol) and hydrazine monohydrate (0.1 g, 2.6

mmol) in AcOH (20 mL) was refluxed for 1.5 h. After being allowed to cool to room temperature, this mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The crude residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (20:80), to afford the pyridazine as a colorless solid (0.2 g).

This solid was treated according to the same procedure described in the preparation of **58** (in part) to afford **60** (0.15 g, 43%) as a colorless solid: mp 291 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 6 H), 1.33 (s, 6 H), 1.69 (s, 4 H), 2.72–2.82 (m, 2 H), 2.86–2.95 (m, 2 H), 7.28 (s, 1 H), 7.63 (d, 2 H, J = 8.4 Hz), 8.06 (d, 2 H, J = 8.4 Hz), 8.37 (s, 1 H), 9.04 (s, 1 H); MS MH^+ 413. Anal. ($C_{27}H_{28}N_2O_2 \cdot 0.4H_2O$) C, H, N.

4-(5,6,8,9,10,11-Hexahydro-8,8,11,11-tetramethylanthra-[1,2-*b*]pyridin-4-yl)benzoic Acid (62). To a solution of **22c** (0.5 g, 1.2 mmol) in 1,2-dichloroethane (15 mL) were added ethyl vinyl ether (5 mL) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (0.063 g, 0.06 mmol). This mixture was refluxed for 48 h and then evaporated. The residue was dissolved in acetonitrile (20 mL), and then hydroxylamine hydrochloride (0.25 g, 3.6 mmol) was added. The mixture was refluxed for 9 h, and then water was added, and the mixture was extracted with AcOEt. The organic extract was washed with brine, and evaporated. The crude residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane (20:80), to afford the pyridine as a pale yellow foam (0.3 g).

This foam (0.3 g) was treated according to the same procedure described in the preparation of **31** to afford **62** (0.19 g, 38%) as a colorless solid: mp 286–289 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 6 H), 1.28 (s, 6 H), 1.64 (s, 4 H), 2.68–2.84 (m, 4 H), 7.18 (d, 1 H, J = 5.4 Hz), 7.20 (s, 1 H), 7.54 (d, 2 H, J = 8.4 Hz), 8.03 (d, 2 H, J = 8.4 Hz), 8.18 (s, 1 H), 8.56 (d, 1 H, J = 5.4 Hz); MS MH^+ 412. Anal. ($C_{28}H_{29}NO_2 \cdot 0.6H_2O$) C, H, N.

Pharmacology. Receptor Binding Assay Using Human Promyelocytic Leukemia (HL-60) Cell. The nuclear extract of HL-60 was prepared according to the procedure of C. Nervi et al.[25] In each well of a 96-well poly(propylene) plate were put 180 μL of this extract and 10 μL of a solution of a test compound followed by 10 μL of 1.0×10^{-8} M [^{3}H]ATRA. After incubating this mixture at 4 °C for 16 h, a solution containing 3% charcoal and 0.3% dextran was added. The mixture was then centrifuged to remove free [^{3}H]ATRA, and the intensity of radiation of the supernatant was determined with a scintillation counter. The extent of specific binding of the test compounds was determined by taking the intensity of radiation observed when 200–1000-fold excess of ATRA was added (nonspecific binding) and subtracting the intensity from the one determined above. The 50% inhibitory concentrations of test compounds were calculated as an inhibiting ability against the binding of [^{3}H]ATRA.

Antagonism against the Differentiation-Inducing Activity of ATRA in HL-60. ATRA (1.0×10^{-8} M) and various amounts of test compounds were added to an HL-60 cell suspension (1×10^5 cells/mL) in the wells of a 48-well plate in an amount of 1 mL/well. After incubation in an incubator (5% CO_2/air) for 5 days, the cells in each individual well were transferred to a test tube, and then an FITC-labeled monoclonal antibody reactive with CD11b, a marker of differentiation, was added. The resulting cells were immobilized with 0.2% paraformaldehyde. The immobilized cell suspension was examined by flow cytometry for the percentage of CD11b-positive cells. The test compounds lowered the percentage of CD11b-positive cells induced by ATRA (1.0×10^{-8} M) dose dependently, and the 50% inhibitory concentrations were calculated.

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