Synthesis and Biological Activity of Carboxyphenylquinolines and Related Compounds as New Potent Retinoids. Retinobenzoic Acids. VII

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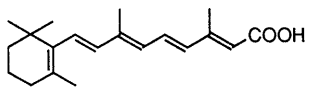
A series of new quinoline, quinolone, and quinazolinedione derivatives was synthesized and tested for retinoid activity in the human promyelocytic cell line HL-60 differentiation assay. All the quinoline compounds exhibited significant activity, depending on the substituent on the heterocycle. However, the quinolone and quinazolinedione derivatives were poor inducers of the differentiation of the HL-60 cells, the activity depending strongly on the polarity of the molecule.

Keywords retinoic acid; retinobenzoic acid; HL-60 cell differentiation; retinoid

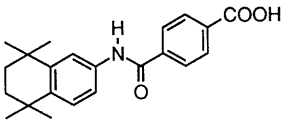
All-*trans*-retinoic acid (**1**; RA), a metabolite of vitamin A (retinol), is able to control the proliferation and differentiation of various cells: epithelial cells, hematopoietic cells, embryonal cells, and other tumor cells.[1] The action of RA is mediated by two families of nuclear receptors: the retinoic acid receptors (RAR), of which three subtypes, α, β, and γ,[2-6] have been identified, and the retinoid X receptors (RXR),[7,8] which do not bind RA but bind its 9-*cis* isomer.[9,10] These receptors belong to the steroid/thyroid nuclear receptor superfamily: they act as ligand-inducible factors and control gene expression. Thus, retinoids, the natural and synthetic analogs of RA, were defined as "substances that elicit the specific responses of RA through binding to the specific receptors."[1]

Retinoids have already proven their efficacy in the treatment of dermatological diseases as well as skin cancer and leukemia. Complete clinical remissions in the treatment of acute promyelocytic leukemia (APL) have already been obtained with RA.[11] However, RA has the disadvantage of being highly toxic: teratogenicity and hypervitaminosis A are the major side effects.[12] Therefore, development of new compounds seems to be of major importance (1) to obtain compounds with a better therapeutic index, and (2) in order to improve our understanding of the mechanism of action.

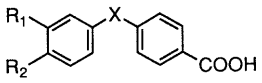
In 1984, we reported that 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (Am80, **2**) exhibited a potent differentiation-inducing activity on



1 (retinoic acid)

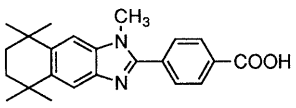


2 (Am80)

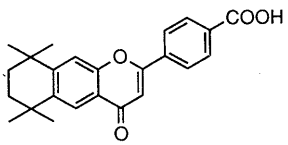


3

R_1, R_2 alkyl groups
X = CONH, NHCO, N=N *etc.*

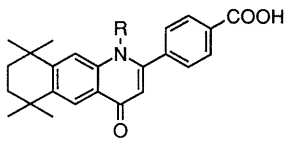


4 (Bz79)

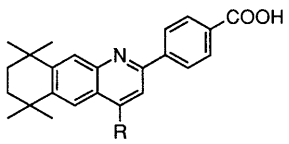


5 (Fv80)

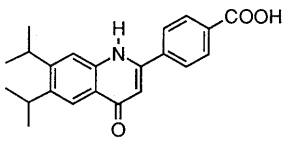
Fig. 1



6 : R = H
14 : R = CH_3



13a: R = OCH_3
13b: R = OC_2H_5
13c: R = OCH_2Ph
17 : R = Cl
18 : R = H



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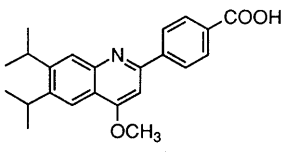
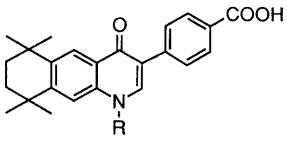
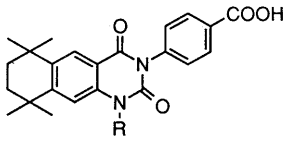


16



19: R = H
28: R = CH_3



31: R = H
32: R = CH_3

Fig. 2

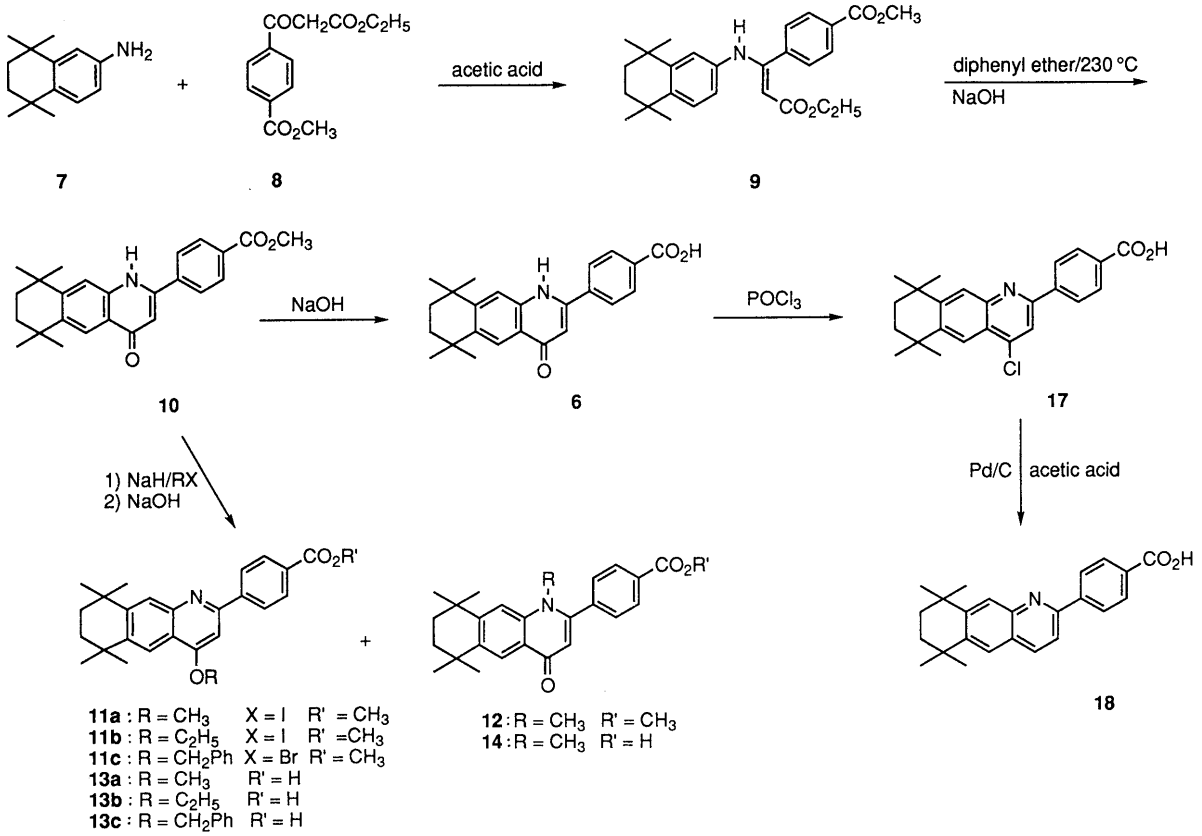
human promyelocytic leukemia cells HL60.[13] Subsequently, we found that various benzoic acid derivatives showed strong retinoidal activities,[14-17] and they were referred to as retinobenzoic acids (Fig. 1, 3). Retinobenzoic acids are defined as compounds with a *para*-substituted benzoic acid moiety and a phenyl ring moiety substituted with hydrophobic alkyl groups.[18] The two aromatic rings are linked by an X group, such as amide, azo and so on. Among them, Am80 (**2**) has already proven to be a useful probe in the elucidation of the mechanism of action of retinoids.[18] Recently, we reported a new class of retinobenzoic acids possessing a polar heterocyclic ring as the linking group.[19] For example, the benzimidazole derivative (**4**) is regarded as a conformationally restricted analog of Am80. These findings and the potent retinoidal activity of the flavone derivative Fv80 (**5**),[15] led us to synthesize candidate retinoids of another type, with a six-membered nitrogen-containing heterocyclic ring as the linking group. In this paper, we report the synthesis and the biological activity of the new heterocyclic compounds, shown in Fig. 2.

Synthesis

Our first target molecule was the quinolone derivative **6**, which is a 1′-aza analog of Fv80 (**5**). The synthetic route is shown in Chart 1. 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine **7**[14] was condensed with ethyl 4-(methoxycarbonyl)benzoylacetate **8**[19] in acetic acid to give the enamine **9**. The thermal cyclization of **9** was performed in diphenyl ether[20] at 230 °C to afford **10** in 55% yield. The structure of **10** was elucidated by ^{1}H- and ^{13}C-NMR analyses. Since the carbonyl carbon of an enone part was observed at 178.7 ppm in the ^{13}C-NMR, we concluded that **10** exists in a keto form in $CDCl_3$. It was hydrolyzed to **6** in EtOH.

Methylation of **10** (Chart 1), with methyl iodide and NaH as a base, afforded two methylated compounds, as deduced from ^{1}H-NMR and elemental analysis, in a ratio of 9 : 1. The major product **11a** showed in the ^{1}H-NMR a methyl proton at 4.13 ppm and a methine proton at 7.09 ppm, while the minor product **12** showed these protons at 3.57 ppm and at 6.19 ppm. The minor compound showed a ^{13}C-NMR signal at 177.3 ppm, corresponding to a keto form carbon–oxygen bond, and the corresponding signal of the major compound was observed at 162.5 ppm. Thus, the major product was deduced to be the *O*-methylquinoline derivative **11a**, and the minor product **12** the *N*-methylquinolone compound. These results are well correlated with those in the literature.[20,21] The final products **13a** and **14** were obtained after hydrolysis under a basic condition. In two other alkylation reactions, using bulkier alkyl halides, only the *O*-alkylated products **11b** and **11c** were obtained, which were hydrolyzed to **13b** and **13c**, respectively.

We also synthesized the structurally closely related quinolones bearing two isopropyl substituents (**15**, **16**), instead of the tetramethylbutano group (Fig. 2). The synthesis was performed in a similar way, from 3,4-diisopropylaniline,[14] except that the intermediate enamine was cyclized to the corresponding quinolone skeleton by heating in polyphosphoric acid (PPA). In order to study the influence of the substituents on the heterocycle,



7 8 9 10 6 17 18

Chart 1

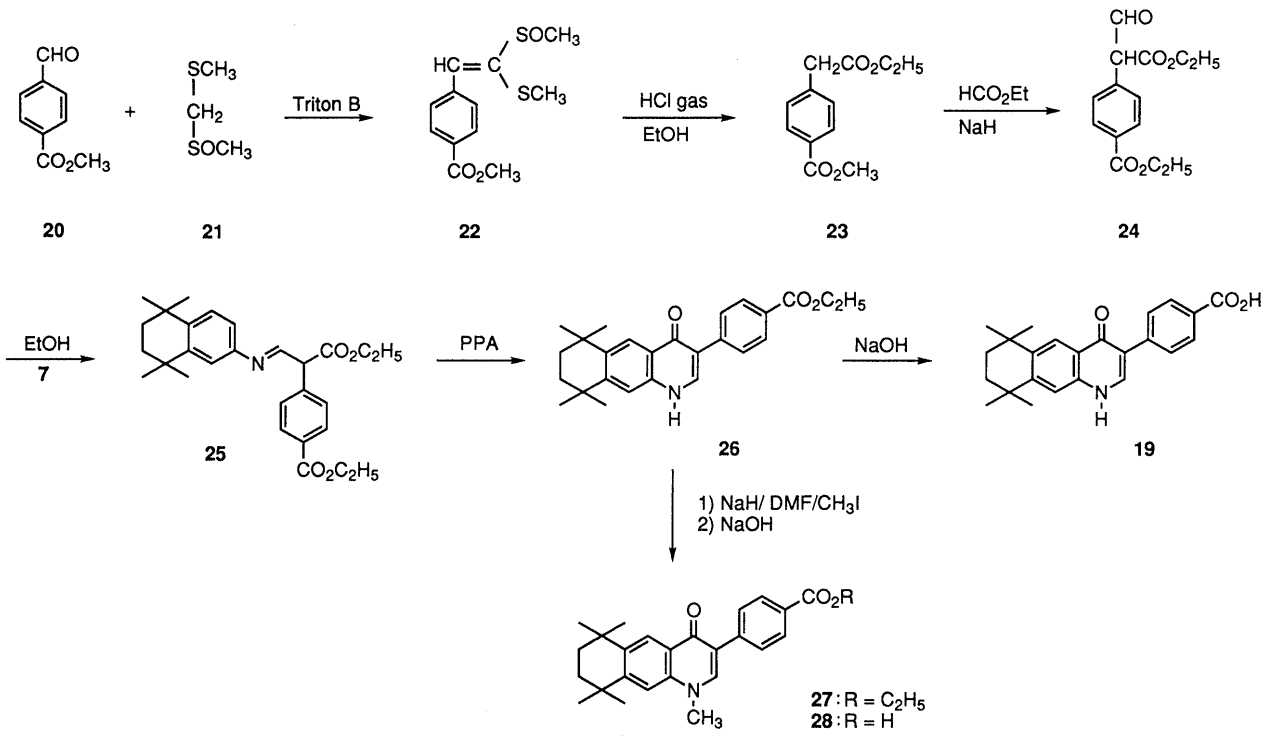


Chart 2

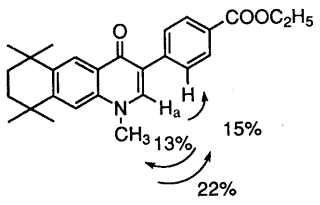


Fig. 3. NOE Enhancement of **27** in $CDCl_3$

the unsubstituted quinoline **18** was prepared from **6**, by heating in phosphoryl chloride[22] to afford the 4-chloro derivative **17**, followed by hydrogenolysis in the presence of Pd/C and acetic acid at 30 °C (Chart 1).

Compound **19**, an isomer of **6** bearing the benzoic acid group at position 3 instead of position 2 on the quinolone ring, was also synthesized (Chart 2). Terephthalaldehydic acid methyl ester **20** and methyl methylthiomethyl sulfoxide **21** were condensed by means of a Knoevenagel type reaction[23] to give **22**, which was converted to ethyl (4-methoxycarbonylphenyl)acetate **23** in acidic ethanol. Compound **24**, obtained by formylation reaction of **23**,[24] was condensed with the aniline derivative **7** to give the Schiff base **25**. Cyclodehydration of **25** in PPA afforded **26** in 59% yield, and this was hydrolyzed to **19** under a basic condition. Methylation of **26**, in the presence of NaH, gave only one product (**27**), which shows in the ^{1}H-NMR a methyl proton singlet at 3.88 ppm. The structure was elucidated by nuclear Overhauser effect (NOE) (Fig. 3) and ^{13}C-NMR analyses. A large NOE enhancement was observed between the methyl proton and H_a (22%). Besides, a signal assigned to the carbonyl carbon appeared at 175.4 ppm in the ^{13}C-NMR. From these results, **27** was identified as the *N*-methyl derivative of **26**. It was hydrolyzed to **28** by the usual method.

The quinazolinediones series consists of six-membered heterocyclic compounds of another type, which can be regarded as related to the amide Am80 (**2**). The quinazolinedione **30** was formed by reaction of **29**[19] and triphosgene (Chart 3). Hydrolysis afforded **31**, which was methylated to **32**. The methyl protons of **32** were observed at 3.54 ppm in the ^{1}H-NMR, and the structure was determined as the *N*-methyl derivative.

Biological Results and Discussion

The retinoidal activity was evaluated by assaying the ability of the compounds to induce differentiation of the human promyelocytic leukemia cell line HL-60 to mature granulocytes. The morphological changes were examined after Wright–Giemsa staining, and the nitro-blue tetrazolium (NBT) reduction assay was employed as a functional marker of differentiation, as described previously.[25] Both evaluations are quantitatively well correlated.[13] The results are listed in Table I. Interestingly, the quinolone derivative **6**, a 1′-aza analog of the potent retinoid Fv80 (**5**),[15] exhibited a very weak activity in this assay. This is an unexpected result. Conformational differences between these two compounds should not be significant, since only the aryl–aryl single bond can easily rotate. Therefore, the drastic decrease of the activity in **6** seems to be attributable to the electronic properties of the quinoline ring. A simple explanation may be the presence of an acidic proton on the nitrogen. However, the potent retinoid Am80 (**2**) has an amide proton at the corresponding position. Moreover, the replacement of the acidic proton with a methyl group, yielding **14**, did not cause an increase of the activity, although a steric effect of the *N*-methyl group in **14** on the twisting angle of the aryl–aryl bond cannot be ruled out. Another possibility

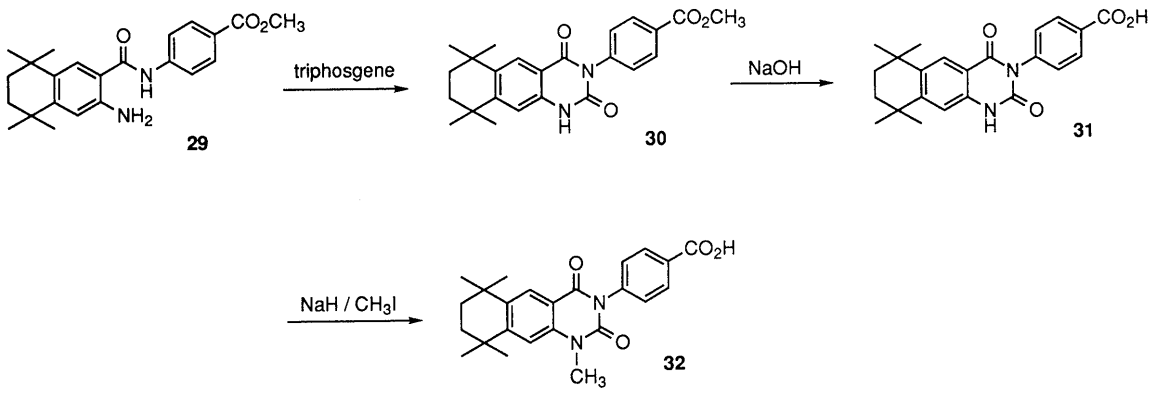


Chart 3

TABLE I. Differentiation Activity of Quinoline Derivatives and Related Compounds towards HL-60 Cells

	Compound	EC_{50} (M)
	RA (**1**)	2.4×10^{-9}
	Am80 (**2**)	7.9×10^{-10}
	Fv80 (**5**)	4.6×10^{-11}
Quinolones	**6**	2.0×10^{-6}
	14	Inactive
	15	Inactive
	19	Inactive
	28	8.0×10^{-7}
Quinolines	**13a**	2.2×10^{-9}
	13b	1.2×10^{-7}
	13c	5.3×10^{-7}
	16	5.5×10^{-9}
	17	4.6×10^{-11}
	18	2.0×10^{-11}
Quinazolinediones	**31**	Inactive
	32	5.5×10^{-7}

is the enolization of **6**, which results in the formation of a quinoline ring, possessing a polar hydroxyl group at the 4 position. However, no enol form was detected in various solvents ($CDCl_3$, DMSO-d_6, CD_3OD) by ^{1}H-NMR, though the enol form may also be active (see below). Consequently, the reason for the low potency of **6** is not clear.

The activities of the alkylated derivatives of the enol form of **6** (*i.e.* 4-alkoxyquinolines) were examined. The major product of the direct methylation of **6** is the *O*-methylated compound **13a**, which exhibits a strong activity, similar to that of RA. Similarly, *O*-methylation of the inactive quinolone **15** resulted in the potent differentiation-inducer **16**, whose EC_{50} value is 5.5×10^{-9} M. On the other hand, as the *O*-alkyl group becomes bulkier (compounds **13b**, **13c**), the activity becomes weaker.

Replacement of the alkoxy group at the 4 position of the quinoline ring with a chlorine or hydrogen atom yielded **17** and **18**, respectively. These compounds are more hydrophobic and/or less hindered than the *O*-alkyl compounds, and they are very strong inducers of differentiation of HL-60 cells. Thus, the EC_{50}s of **17** and **18** are 4.6×10^{-11} and 2.0×10^{-11} M, respectively, and they are as potent as Fv80 (**5**).

Next, we examined the effects of the polarity on the heterocyclic ring of compounds **19** and **31**. These have a polar group, –NH–C= in **19** and –NHCO– in **31**, at the position corresponding to the 3,4-position of the quinolone ring (–(C=O)C=C– or –C(OH)=C– in the possible enol form of **6**). These compounds are completely inactive at concentrations below 10^{-6} M. In order to remove the hydrophilicity of these regions, *N*-methylation of **19** and **31** was performed, affording **28** and **32**, respectively. Both compounds exhibited differentiation-inducing activity, with EC_{50} values of 8.0×10^{-7} M and 5.5×10^{-7} M respectively, though the activities were somewhat less than expected. A similar tendency of the methylation effect was observed in a retinoidal benzodiazepine series too.[19] These results, as well as the strong activity of **18**, suggest that this region of the molecule requires some hydrophobicity. This is consistent with the potent activity of anthracenyl derivatives: 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)benzoic acid[26] showed a strong retinoid activity. However, in view of the high activity of the hydroxy derivative of the flavone Fv80 and the hydroxylated chalcone derivative Re80,[15] this hypothesis does not seem to be generally applicable.

In conclusion, we have synthesized some quinoline derivatives that are very potent inducers of the differentiation of the HL-60 cells. On the basis of their molecular shape and their biological activity, we can include them in the retinobenzoic acid series. Further experiments, especially evaluation of the binding to the different RAR, are still necessary to understand their structure–activity relationships and to elucidate their modes of interaction with the receptors.

Experimental

Chemistry Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo, and values obtained were within ±0.3% of the theoretical values. NMR spectra were recorded on a JEOL GX400 (400 MHz) NMR spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded on a JEOL SX-102 spectrometer. IR spectra were taken with a Shimadzu IR-408 IR spectrometer and are expressed in cm^{-1}.

General Procedure for the Hydrolysis of Ester Compounds The esters were hydrolyzed with 2 N NaOH (10 eq) in EtOH or MeOH at room temperature, except **11a**, which was hydrolyzed in MeOH at 60 °C for 4 h. The mixture was acidified with 2 N HCl, and extracted with AcOEt. The organic layer was washed with water, and dried over Na_2SO_4. After

removal of the solvent, the crude product was recrystallized.

Methyl 4-[2-Ethoxycarbonyl-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamino)ethenyl]benzoate (9) A solution of **7**[14] (4.5 g, 22 mmol) and **8**[19] (5.55 g, 22 mmol) in acetic acid (20 ml) was stirred at room temperature for 3 d. The resulting yellow solution was poured into ice-water, and made alkaline with 1 N Na_2CO_3. The crude product was extracted with CH_2Cl_2, and the organic layer was washed twice with water, and dried over Na_2SO_4. After evaporation, the yellow oil was purified by silica gel column chromatography (hexane–CH_2Cl_2, 6:4) to give **9** (5.3 g, 56%). **9**: Yellow oil. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 0.91 (6H, s), 1.17 (6H, s), 1.31 (3H, t, J=7.2 Hz), 1.55 (4H, s), 3.91 (3H, s), 4.20 (2H, q, J=7.2 Hz), 4.95 (1H, s), 6.43 (1H, d, J=2.8 Hz), 6.52 (1H, dd, J=2.8, 8.8 Hz), 7.03 (1H, d, J=8.8 Hz), 7.42 (2H, d, J=8.3 Hz), 7.96 (2H, d, J=8.3 Hz), 10.24 (1H, s). IR (neat): 3250, 1720, 1650, 1600 cm^{-1}. MS m/z: 435 (M^+).

4-(1,4,6,7,8,9-Hexahydro-6,6,9,9-tetramethyl-4-oxonaphtho[2,3-*b*]pyridin-2-yl)benzoic Acid (6) A solution of **9** (565 mg) in phenyl ether (2 ml) was added to 2 ml of phenyl ether at 180 °C, and the mixture was progressively heated to 220 °C over 1.5 h. After cooling, hexane was added, and precipitation occurred. The solid was collected by filtration, washed with hexane, and recrystallized from hexane/AcOEt/MeOH to give **10** (55%). **10**: Pale yellow needles, mp 187 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.28 (6H, s), 1.29 (6H, s), 1.71 (4H, s), 3.92 (3H, s), 6.39 (1H, s), 7.59 (1H, s), 7.75 (2H, d, J=8.3 Hz), 8.10 (2H, d, J=8.3 Hz), 8.27 (1H, s), 10.20 (1H, s). ^{13}C-NMR (100 MHz; $CDCl_3$) δ: 32.1, 34.4, 34.6, 34.8, 50.8, 52.3, 107.6, 116.2, 122.7, 123.4, 127.3, 130.1, 131.4, 138.8, 142.5, 149.5, 151.2, 166.2, 178.7. IR (KBr): 3050, 1720, 1630, 1590 cm^{-1}. **10** was hydrolyzed to **6** by the general method. **6**: Colorless flakes (from EtOH). mp > 300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.32 (6H, s), 1.33 (6H, s), 1.71 (4H, s), 6.33 (1H, s), 7.76 (1H, s), 7.92 (2H, d, J=8.3 Hz), 8.04 (1H, s), 8.11 (2H, d, J=8.3 Hz), 11.62 (1H, s). IR (KBr): 3100, 1705, 1630, 1590 cm^{-1}. *Anal.* Calcd for $C_{24}H_{25}NO_3$: C, 74.97; H, 6.82; N, 3.64. Found: C, 74.80; H, 6.55; N, 3.90.

4-(4-Chloro-6,7,8,9-tetrahydro-6,6,9,9-tetramethylnaphtho[2,3-*b*]pyridin-2-yl)benzoic Acid (17) Compound **6** (112 mg) was heated with $POCl_3$ at 130 °C for 3.5 h. After cooling, the mixture was poured into ice-water, and extracted with AcOEt. The organic layer was washed with water, and dried over Na_2SO_4. After evaporation of the solvent, almost pure acyl chloride form of **17** was obtained (100 mg). The carboxylic acid was liberated by treatment with NaOH (25 eq) and acidification with 2 N HCl, extracted, and recrystallized from MeOH (50%). **17**: Colorless flakes (from MeOH), mp 245 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.41 (6H, s), 1.42 (6H, s), 1.78 (4H, s), 8.10 (2H, d, J=8.3 Hz), 8.11 (1H, s), 8.13 (1H, s), 8.36 (1H, s), 8.43 (2H, d, J=8.3 Hz), 13.1 (1H, s). IR (KBr): 1685, 1605, 1560 cm^{-1}. MS m/z: 393 (M^+). *Anal.* Calcd for $C_{24}H_{24}ClNO_2$: C, 73.18; H, 6.14; N, 3.56. Found: C, 72.98; H, 5.99; N, 3.32.

4-(6,7,8,9-Tetrahydro-6,6,9,9-tetramethylnaphtho[2,3-*b*]pyridin-2-yl) benzoic Acid (18) Compound **17** (50 mg) was stirred in acetic acid in the presence of Pd/C (5 mg) under hydrogen for 2 d at 30 °C. The solution was filtered, and acetic acid was removed under vacuum. The residue was dissolved in AcOEt, and the organic layer was washed with water to remove traces of acetic acid. The solution was dried over Na_2SO_4, and the solvent was removed to leave 50 mg of a pale yellow solid, which was recrystallized from MeOH. **18**: Yellow needles, mp 295 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.39 (6H, s), 1.41 (6H, s), 1.77 (4H, s), 7.99 (1H, s), 8.05 (1H, s), 8.10 (3H, d, J=8.5 Hz), 8.38 (1H, d, J=8.5 Hz), 8.39 (2H, d, J=8.5 Hz). IR (KBr): 1680, 1600 cm^{-1}. MS m/z: 359 (M^+). *Anal.* Calcd for $C_{24}H_{25}NO_2 \cdot 1/3H_2O$: C, 78.87; H, 7.08; N, 3.83. Found: C, 78.84; H, 6.90; N, 4.13.

Methylation of 10 A solution of **10** (287 mg, 0.74 mmol) dissolved in dry dimethylformamide (DMF) (7 ml) was added to a suspension of NaH (60% in oil, 32 mg, 0.8 mmol) in dry DMF (2 ml), under Ar. After 30 min, methyl iodide (0.05 ml, 0.8 mmol) was added, and the mixture was stirred at room temperature for 2 h. The resulting yellow suspension was poured into ice-water, and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4, filtered, and the solvent removed. The two products were separated by silica gel column chromatography. **11a** (229 mg, 77%) was eluted with CH_2Cl_2–hexane (6:3), and **12** (30 mg, 10%) was eluted with CH_2Cl_2–AcOEt (6:3). **11a**: Colorless flakes (from AcOEt), mp 260 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.42 (6H, s), 1.43 (6H, s), 1.79 (4H, s), 3.96 (3H, s), 4.13 (3H, s), 7.09 (1H, s), 8.08 (1H, s), 8.13 (1H, s), 8.16 (4H, m). ^{13}C-NMR (100 MHz; $CDCl_3$) δ: 32.3, 32.6, 34.8, 34.9, 35.0, 52.2, 55.6, 97.1, 118.6, 118.7, 126.4, 127.4, 130.0, 130.3, 144.6, 144.9, 147.6, 149.1, 157.0, 162.5, 167.0. IR (KBr): 1710, 1590, 1540 cm^{-1}. *Anal.* Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.11; H, 7.20; N, 3.75. **12**: Colorless powder. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.39 (6H, s), 1.40 (6H, s), 1.78 (4H, s), 3.57 (3H, s), 3.98 (3H, s), 6.19 (1H, s), 7.44 (1H, s), 7.49 (2H, d, J=8.4 Hz), 8.17 (2H, d, J=8.4 Hz), 8.44 (1H, s). ^{13}C-NMR (100 MHz; $CDCl_3$) δ: 32.2, 32.3, 34.4, 34.8, 35.2, 37.0, 52.4, 111.8, 113.2, 124.5, 125.0, 128.7, 130.0, 131.1, 140.0, 140.3, 142.2, 151.1, 153.2, 166.2, 177.3. **11a** and **12** were hydrolyzed to **13a** and **14**, respectively. **13a**: Colorless flakes (from MeOH), mp 258 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.36 (6H, s), 1.39 (6H, s), 1.75 (4H, s), 4.16 (3H, s), 7.51 (1H, s), 7.97 (1H, s), 8.05 (1H, s), 8.08 (2H, d, J=8.4 Hz), 8.41 (2H, d, J=8.4 Hz). MS m/z: 389 (M^+). IR (KBr): 1690, 1580 cm^{-1}. *Anal.* Calcd for $C_{25}H_{27}NO_3 \cdot 1/2H_2O$: C, 75.35; H, 7.08; N, 3.52. Found: C, 75.30; H, 7.19; N, 3.42. **14**: Colorless flakes (from MeOH), mp > 300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.33 (6H, s), 1.39 (6H, s), 1.74 (4H, s), 3.56 (3H, s), 5.93 (1H, s), 7.63 (1H, s), 7.65 (2H, d, J=8 Hz), 8.09 (2H, d, J=8 Hz), 8.16 (1H, s). IR (KBr): 1700, 1590 cm^{-1}. *Anal.* Calcd for $C_{25}H_{27}NO_3 \cdot 1/5H_2O$: C, 76.38; H, 7.03; N, 3.56. Found: C, 76.32; H, 6.99; N, 3.71.

4-(4-Ethoxy-6,7,8,9-tetrahydro-6,6,9,9-tetramethylnaphtho[2,3-*b*]pyridin-2-yl)benzoic Acid (13b) A solution of **10** (120 mg, 0.31 mmol) in dry DMF (4 ml) was alkylated with 14 mg of NaH (60% in oil, 0.34 mmol) in dry DMF (2 ml) and ethyl iodide (0.03 ml) to give **11b** (80%), which was hydrolyzed to **13b**. **11b**: Colorless needles (from EtOH); mp 193—194 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.42 (12H, s), 1.62 (3H, t, J=7 Hz), 1.79 (4H, s), 3.96 (3H, s), 4.37 (2H, q, J=7 Hz), 7.07 (1H, s), 8.07 (1H, s), 8.15 (5H, m). IR (KBr): 1710, 1590 cm^{-1}. *Anal.* Calcd for $C_{27}H_{31}NO_3$: C, 77.66; H, 7.48; N, 3.36. Found: C, 77.36; H, 7.49; N, 3.59. **13b**: Colorless flakes (from EtOH), mp 280 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.37 (6H, s), 1.40 (6H, s), 1.54 (3H, t, J=7 Hz), 1.76 (4H, s), 4.47 (2H, q, J=7 Hz), 7.48 (1H, s), 7.96 (1H, s), 8.06 (1H, s), 8.08 (2H, d, J=8.8 Hz), 8.38 (2H, d, J=8.4 Hz). IR (KBr): 1680, 1580 cm^{-1}. MS m/z: 403 (M^+). *Anal.* Calcd for $C_{26}H_{29}NO_3 \cdot 1/3H_2O$: C, 76.25; H, 7.30; N, 3.42. Found: C, 76.32; H, 7.54; N, 3.15.

4-(4-Benzyloxy-6,7,8,9-tetrahydro-6,6,9,9-tetramethylnaphtho[2,3-*b*]pyridin-2-yl)benzoic Acid (13c) Compound **10** (120 mg, 0.3 mmol) was alkylated with 12 mg of NaH (60% in oil, 0.3 mmol) in dry DMF (4 ml), and benzyl bromide (0.04 ml, 0.36 mmol) to give **11c** (65%), which was hydrolyzed to **13c**. **11c**: Colorless needles (from hexane), mp 104 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.42 (6H, s), 1.43 (6H, s), 1.80 (4H, s), 3.96 (3H, s), 5.41 (2H, s), 7.15 (1H, s), 7.39 (1H, m), 7.46 (2H, m), 7.55 (2H, d, J=7 Hz), 8.09 (1H, s), 8.10 (2H, d, J=8.8 Hz), 8.16 (2H, d, J=8.8 Hz), 8.21 (1H, s). IR (KBr): 1715, 1590 cm^{-1}. *Anal.* Calcd for $C_{32}H_{33}NO_3$: C, 80.13; H, 6.94; N, 2.92. Found: C, 80.11; H, 7.24; N, 3.20. **13c**: Pale yellow prisms (from MeOH), mp 230—231 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.36 (6H, s), 1.40 (6H, s), 1.76 (4H, s), 5.58 (2H, s), 7.39 (1H, t, J=7 Hz), 7.48 (2H, t, J=7 Hz), 7.60 (2H, d, J=7 Hz), 7.64 (1H, s), 7.99 (1H, s), 8.09 (2H, d, J=8.4 Hz), 8.11 (1H, s), 8.38 (2H, d, J=8.4 Hz). IR (KBr): 1685, 1570 cm^{-1}. MS m/z: 465 (M^+). *Anal.* Calcd for $C_{31}H_{31}NO_3$: C, 79.97; H, 6.71; N, 3.01. Found: C, 80.05; H, 6.70; N, 3.28.

4-(1,4-Dihydro-6,7-diisopropyl-4-oxoquinolin-2-yl)benzoic Acid (15) Diisopropylaniline[14] (212 mg, 1.2 mmol) and **8**[19] (304 mg, 1.2 mmol) were dissolved in acetic acid (1 ml), and the reaction mixture was stirred at room temperature for 3 d. The solution was poured into ice-water, made alkaline with saturated Na_2CO_3, extracted with AcOEt, washed twice with water, and dried over Na_2SO_4. The solvent was removed, and the crude product was purified by silica gel column chromatography (hexane–AcOEt, 10:1) to give methyl 4-[2-ethoxycarbonyl-1-(3,4-diisopropylphenylamino)ethenyl]benzoate as a yellow oil (47%). ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 0.91 (6H, d, J=6.6 Hz), 1.14 (6H, d, J=6.6 Hz), 1.32 (3H, t, J=7 Hz), 3.06 (2H, hept, J=6.6 Hz), 3.91 (3H, s), 4.21 (2H, q, J=7 Hz), 4.96 (1H, s), 6.42 (1H, d, J=2 Hz), 6.52 (1H, dd, J=8.4, 2 Hz), 6.97 (1H, d, J=8.4 Hz), 7.42 (2H, d, J=8.4 Hz), 7.95 (2H, d, J=8.4 Hz), 10.26 (1H, s). IR (neat): 3250, 1720, 1650, 1600 cm^{-1}. MS m/z: 409 (M^+). Methyl 4-[2-ethoxycarbonyl-1-(3,4-diisopropylphenylamino)ethenyl]benzoate (207 mg) and PPA (Wako Chemicals, approx. $H_6P_4O_{13}$) (1.3 g) were heated at 110 °C for 30 min. The residue was poured into ice-water, and the solution made alkaline with saturated Na_2CO_3. The aqueous layer was extracted with AcOEt, and the organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the crude product was purified by silica gel column chromatography (hexane–AcOEt, 4:6) to afford methyl 4-(1,4-dihydro-6,7-diisopropyl-4-oxoquinolin-2-yl)benzoate (64%). Methyl 4-(1,4-dihydro-

6,7-diisopropyl-4-oxoquinolin-2-yl)benzoate: Colorless needles (from MeOH), mp >300 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.26 (6H, d, J=7 Hz), 1.27 (6H, d, J=7 Hz), 3.29 (1H, hep, J=7 Hz), 3.35 (1H, hep, J=7 Hz), 3.93 (3H, s), 6.44 (1H, s), 7.46 (1H, s), 7.75 (2H, d, J=8.8 Hz), 8.12 (2H, d, J=8.8 Hz), 8.22 (1H, s), 9.67 (1H, s). IR (KBr): 3050, 1730, 1630, 1590 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 76.06; H, 7.05; N, 3.98. **15** was obtained by hydrolysis of methyl 4-(1,4-dihydro-6,7-diisopropyl-4-oxoquinolin-2-yl)benzoate. **15**: Colorless flakes (from AcOEt–MeOH), mp >300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.27 (6H, d, J=6.6 Hz), 1.28 (6H, d, J=6.6 Hz), 3.3 (1H, m), 6.37 (1H, s), 7.68 (1H, s), 7.96 (3H, m), 8.11 (2H, d, J=8.3 Hz), 11.68 (1H, s), 13.2 (1H, br s). IR (KBr): 3250, 1630, 1590, 1470 cm^{-1}. *Anal.* Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.64; N, 4.01. Found: C, 75.67; H, 6.34; N, 4.29.

4-(6,7-Diisopropyl-4-methoxyquinolin-2-yl)benzoic Acid (16) Methyl 4-(1,4-dihydro-6,7-diisopropyl-4-oxoquinolin-2-yl)benzoate (82 mg, 0.23 mmol) in dry DMF (5 ml) was alkylated by using NaH (60% in oil, 10 mg, 0.25 mmol) in dry DMF (2 ml), and methyl iodide (0.02 ml). The product was purified by silica gel column chromatography with hexane–AcOEt (6:2) to give methyl 4-(6,7-diisopropyl-4-methoxyquinolin-2-yl)benzoate (64 mg). Methyl 4-(6,7-diisopropyl-4-methoxyquinolin-2-yl)benzoate: Colorless flakes (from hexane–CH_2Cl_2), mp 215 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.37 (6H, d, J=7 Hz), 1.38 (6H, d, J=7 Hz), 3.40 (2H, hept, J=7 Hz), 3.96 (3H, s), 4.14 (3H, s), 7.12 (1H, s), 8.00 (1H, s), 8.05 (1H, s), 8.17 (4H, m). IR (KBr): 1710, 1590, 1550 cm^{-1}. MS m/z: 363 (M^+). *Anal.* Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.45; H, 7.35; N, 3.66. Methyl 4-(6,7-diisopropyl-4-methoxyquinolin-2-yl)benzoate was hydrolyzed to **16** by the general method. **16**: Colorless prisms (from MeOH), mp 233 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.31 (6H, d, J=7 Hz), 1.34 (6H, d, J=7 Hz), 3.37 (2H, m), 4.17 (3H, s), 7.55 (1H, s), 7.88 (1H, s), 7.97 (1H, s), 8.09 (2H, d, J=8.8 Hz), 8.42 (2H, d, J=8.4 Hz). IR (KBr): 1700, 1580 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 75.76; H, 6.96; N, 4.15.

Ethyl 4-[1-Ethoxycarbonyl-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenylimino)ethyl]benzoate (25) Terephthalaldehydic acid methyl ester **20** (6.9 g, 0.04 mol) and Triton B (8 ml) were added successively to a solution of methyl methylthiomethyl sulfoxide **21** (4.4 ml, 0.04 mol) in dry tetrahydrofuran (THF) (16 ml). The mixture was heated under reflux for 8 h. After cooling, the solvent was removed and the crude product purified by silica gel column chromatography (hexane–AcOEt, 1:1) to give **22** (1.7 g, 16%). **22**: Pale yellow solid. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 2.33 (3H, s), 2.80 (3H, s), 3.94 (3H, s), 7.66 (1H, s), 7.93 (2H, d, J=8.4 Hz), 8.09 (2H, d, J=8.43 Hz). **22** (488 mg, 1.8 mmol) was dissolved in dry EtOH (10 ml), and HCl gas was bubbled into the solution for 5 min at 0 °C. The solvent was removed and the residue dissolved in CH_2Cl_2. The organic layer was washed three times with water and dried over Na_2SO_4. After evaporation, the residue was purified by silica gel column chromatography (hexane–AcOEt, 8:1.5) to give **23** (283 mg, 70%). **23**: Pale yellow oil. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 3.67 (2H, s), 3.91 (3H, s), 4.16 (2H, q, J=7 Hz), 7.36 (2H, d, J=8 Hz), 8.00 (d, 2H, d, J=8 Hz). IR (neat): 1720 cm^{-1}. A solution of **23** (271 mg, 1.2 mmol) in ethyl formate (2 ml, 0.024 mol) was treated in portions with NaH (60% in oil, 192 mg, 4.8 mmol), at room temperature. Immediately, an exothermic reaction took place, and a yellow-orange solid was obtained. The mixture was stirred for 1.5 h at room temperature, and poured into ice-water. The mixture was acidified with 2 N HCl, and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent removed. Purification by silica gel column chromatography (hexane–AcOEt, 8:1.5) afforded **24** (86%). **24**: Colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.30 (3H, t, J=7.2 Hz), 1.40 (3H, t, J=7.2 Hz), 4.30 (2H, q, J=7.2 Hz), 4.39 (2H, q, J=7.2 Hz), 7.34 (2H, d, J=8.8 Hz), 7.36 (1H, d, J=12.7 Hz), 8.01 (2H, d, J=8.8 Hz), 12.25 (1H, d, J=12.7 Hz). A solution of **7** (201 mg, 1 mmol) and **24** (262 mg, 1 mmol) in EtOH was stirred overnight at room temperature. The solvent was removed and **25** was purified by silica gel column chromatography (hexane–AcOEt, 8:1). **25**: ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.26 (6H, s), 1.27 (6H, s), 1.31 (3H, t, J=7 Hz), 1.40 (3H, t, J=7 Hz), 1.68 (4H, s), 4.27 (2H, q, J=7 Hz), 4.38 (2H, q, J=7 Hz), 6.85 (1H, dd, J=2.5, 8.4 Hz), 6.91 (1H, d, J=2.5 Hz), 7.26 (1H, d, J=8.4 Hz), 7.41 (2H, d, J=8.4 Hz), 7.45 (1H, d, J=12.8 Hz), 8.0 (2H, d, J=8.4 Hz), 10.43 (1H, d, J=12.8 Hz).

4-(1,4,6,7,8,9-Hexahydro-6,6,9,9-tetramethyl-4-oxonaphtho[2,3-*b*]pyridin-3-yl)benzoic Acid (19) Compound **25** (210 mg, 0.47 mmol) and 1.4 g of PPA were heated at 110 °C for 10 min. The residue was poured into ice-water, and extracted with AcOEt. The organic layer was washed with water, and dried over Na_2SO_4. After removal of the solvent, a yellow oil was obtained, which was washed with hexane to leave a solid, which was recrystallized from hexane–MeOH–CH_2Cl_2 to afford **26** (59%). **26**: Colorless needles, mp 263—267 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.23 (6H, s), 1.30 (6H, s), 1.35 (3H, t, J=7.1 Hz), 1.70 (4H, s), 4.32 (2H, q, J=7.1 Hz), 7.36 (1H, d, J=7 Hz), 7.41 (1H, s), 7.63 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 8.43 (1H, s), 10.83 (1H, d). ^{13}C-NMR (100 MHz; $CDCl_3$) δ: 14.4, 32.2, 32.3, 34.4, 34.8, 35.1, 40.7, 60.8, 112.5, 119.7, 125.3, 125.4, 128.2, 128.4, 129.4, 138.0, 140.6, 142.4, 142.7, 150.9, 166.7, 175.4. IR (KBr): 1705, 1605, 1540, 1495 cm^{-1}. *Anal.* Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.16; H, 7.21; N, 3.66. **26** was hydrolyzed to **19** by the usual method. **19**: Colorless needles (from MeOH), mp >300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.32 (12H, s), 1.72 (4H, s), 7.53 (1H, s), 7.89 (2H, d, J=8.8 Hz), 7.94 (2H, d, J=8.8 Hz), 8.17 (1H, s), 8.24 (1H, s), 11.97 (1H, s). IR (KBr): 1695, 1610, 1535, 1485 cm^{-1}. *Anal.* Calcd for $C_{24}H_{25}NO_3 \cdot H_2O$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.54; H, 6.68; N, 3.67.

4-(1,4,6,7,8,9-Hexahydro-1,6,6,9,9-pentamethyl-4-oxonaphtho-[2,3-*b*]pyridin-3-yl)benzoic Acid (28) Compound **26** (135 mg, 0.33 mmol) was alkylated in dry DMF (6 ml) with NaH (60% in oil, 15 mg, 0.36 mmol) and methyl iodide (0.03 ml). After work-up, **27** was recrystallized (68%), and hydrolyzed to **28**. **27**: Colorless flakes (from MeOH), mp 231 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.39 (6H, s), 1.40 (6H, s), 1.41 (3H, t, J=7 Hz), 1.77 (4H, s), 3.88 (3H, s), 4.39 (2H, q, J=7 Hz), 7.32 (1H, s), 7.73 (1H, s), 7.79 (2H, d, J=8.4 Hz), 8.07 (2H, d, J=8.4 Hz), 8.53 (1H, s). IR (KBr): 1710, 1610, 1570, 1530, 1500 cm^{-1}. *Anal.* Calcd for $C_{27}H_{31}NO_3$: C, 77.66; H, 7.48; N, 3.36. Found: C, 77.46; H, 7.50; N, 3.66. **28**: Colorless flakes (from MeOH); mp >300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.33 (6H, s), 1.39 (6H, s), 1.73 (4H, s), 3.93 (3H, s), 7.54 (1H, s), 7.91 (2H, d, J=8.8 Hz), 7.95 (2H, d, J=8.8 Hz), 8.26 (1H, s), 8.37 (1H, s). IR (KBr): 1680, 1610 cm^{-1}. *Anal.* Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.00; H, 7.09; N, 3.79.

4-(1,2,3,4,6,7,8,9-Octahydro-6,6,9,9-tetramethyl-2,4-dioxonaphtho-[2,3-*d*]pyrimidin-3-yl)benzoic Acid (31) Compound **29** (300 mg, 0.8 mmol) was dissolved in dichloroethane (20 ml). Triphosgene (101 mg, 0.34 mmol) and triethylamine (3 ml) were added successively, at room temperature. By heating, a clear yellow solution was obtained, and reflux was continued for 1 h. After cooling, the reaction mixture was poured into ice-water, and acidified with 2 N HCl. The aqueous layer was extracted three times with CH_2Cl_2, the organic layer was washed with water, and dried over $MgSO_4$, and the solvent was removed to leave an oily product which solidified (320 mg). The crude product was purified by silica gel column chromatography (hexane–AcOEt, 6:2), and recrystallized from hexane–CH_2Cl_2 to afford **30** (72%). **30**: Colorless needles, mp 270 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.29 (6H, s), 1.31 (6H, s), 1.72 (4H, s), 3.96 (3H, s), 6.91 (1H, s), 7.37 (2H, d, J=8.8 Hz), 8.09 (1H, s), 8.19 (2H, d, J=8.8 Hz), 8.70 (1H, s). IR (KBr): 2950, 1720, 1660, 1620 cm^{-1}. *Anal.* Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.62; H, 6.40; N, 6.90. Compound **30** was hydrolyzed to **31** by the usual method. **31**: Colorless flakes (from MeOH), mp >300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.27 (6H, s), 1.28 (6H, s), 1.69 (4H, s), 7.18 (1H, s), 7.43 (2H, d, J=8.4 Hz), 7.86 (1H, s), 8.03 (2H, d, J=8.4 Hz), 11.36 (1H, s). IR (KBr): 3200, 1720, 1670 cm^{-1}. MS m/z: 392 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_4 \cdot 1/2H_2O$: C, 68.81; H, 6.28; N, 6.98. Found: C, 68.75; H, 6.14; N, 7.08.

4-(1,2,3,4,6,7,8,9-Octahydro-1,6,6,9,9-pentamethyl-2,4-dioxonaphtho-[2,3-*d*]pyrimidin-3-yl)benzoic Acid (32) NaH (60% in oil, 8 mg, 0.18 mmol) was washed twice with hexane, and put into THF (2 ml), then **31** (23 mg, 0.06 mmol) was added. After 30 min, methyl iodide (0.1 ml) was added. The reaction mixture was stirred at room temperature for 3 d, then poured into ice-water, acidified with 2 N HCl and extracted with AcOEt. The organic layer was washed with water, and dried over $MgSO_4$, and the solvent was removed to leave a white solid, which was recrystallized from MeOH. **32**: Colorless flakes, mp >300 °C. ^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.28 (6H, s), 1.37 (6H, s), 1.70 (4H, s), 3.54 (3H, s), 7.32 (1H, s), 7.33 (2H, d, J=8 Hz), 7.97 (1H, s), 8.03 (2H, d, J=8 Hz). IR (KBr): 3400, 1710, 1665, 1610 cm^{-1}. MS m/z: 406 (M^+). *Anal.* Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.70; H, 6.32; N, 6.75.

Cells and Culture The human promyelocytic leukemia cell line HL60 was provided by Prof. F. Takaku (Faculty of Medicine, University of

Tokyo) and was maintained in continuous suspension culture. The cells were cultured in plastic flasks in RPMI1640 medium, supplemented with 5% fetal calf serum (FCS) and antibiotics (penicillin G and streptomycin), at 37 °C in a humidified atmosphere of 5% CO_2 in air. Test compounds were dissolved in ethanol at 2 mM and added to the cells, (except **14**, which was added as a suspension) which were seeded at about 8×10^4 cells/ml; the final ethanol concentration was kept below 0.5%. Control cells were given only the same volume of ethanol. Am80, as a positive control, was always assayed at the same time. The cells were incubated for 4 d and stained with Wright–Giemsa. Differential counts were then performed under a light microscope on a minimum of 200 cells. NBT reduction was assayed as described previously.[25] Cells were incubated for 20 min at 37 °C in RPMI1640 medium (5% FCS) and an equal volume of phosphate-buffered saline (PBS) containing NBT (0.2%) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA; 200 ng/ml). The percentage of cells containing blue-black formazan was determined on a minimum of 200 cells. The results of these two evaluations were always in good agreement. The assays of test compounds were performed at least twice. EC_{50} values of active compounds were calculated from the NBT reduction assay data by means of the van der Waerden method.

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