Studies on Antibacterial Agents. I. Synthesis of Substituted 6,7-Dihydro-1-oxo-1*H*,5*H*-benzo[*i*,*j*]-quinolizine-2-carboxylic Acids

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A series of substituted 6,7-dihydro-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acids was synthesized and tested for antibacterial activities. Among them, 9-fluoro-6,7-dihydro-5-methyl-8-(4-methyl-1-piperazinyl)-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (OPC-7241) exhibited potent antibacterial activity against gram-positive and -negative bacteria, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and 9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (OPC-7251) showed potent activity characteristically against *Propionibacterium acnes*.

Keywords 4-oxoquinoline-3-carboxylic acid; benzo[*i*,*j*]quinolizine; tetrahydroquinoline; *N*-methylpiperazine; 4-hydroxypiperidine; *Propionibacterium acnes*; antibacterial activity

The synthetic antibiotics include the sulfa drugs, nitrofuran derivatives, pyridonecarboxylic acids analogues and so on. Among them, the sulfa drugs and nitrofuran derivatives are scarcely used in clinical therapy, since the former suffer from high rate of appearance of resistant mutants and the latter are carcinogenic. Therefore the pyridonecarboxylic acids analogues occupy the main stream in current research on synthetic antibiotics. Nalidixic acid (NA),[1] the first pyridonecarboxylic acid drug, has oral potency against gram-negative bacilli. Research on pyridonecarboxylic acids is now mainly aimed at extending the antibacterial spectrum, increasing the antibacterial potency, improving the stability to metabolic processes, and improving the tissue transmigration properties. We have investigated the improvement of the pharmacological properties of NA from the viewpoint of the balance of lipophilicity and hydrophilicity of the molecule. First, the effect of an increase of lipophilicity was studied. Namely the nitrogen atom of NA at the 8-position was exchanged to a carbon atom, and a methyl group was substituted at the 8-position. With this modification, 7-chloro-1-ethyl-1,4-dihydro-8-methyl-4-oxo-3-quinolinecarboxylic acid (OPC-7594)[2] was found to have moderately high antibacterial potency.

Therefore we speculated that piperidine ring formation at the *ij*-bonds of the quinoline ring might enhance the activity and broaden the antibacterial spectrum. Next, hydrophilic groups were substituted at the 8-position of the lipophilic benzo[*i*,*j*]quinolizine skeleton.

We wish to report here the synthesis and antibacterial activity of tricyclic quinolonecarboxylic acid derivatives which contain both lipophilic and hydrophilic moieties.

Synthesis First, the tetrahydroquinoline derivatives (**6a**,**b** and **12a**, **b**), which are key intermediates in the synthesis of the benzo[*i*,*j*]quinolizine derivatives (**13**—**16**), were prepared. Diazotization of 5-amino-3,4-dihydro-2(1*H*)-quinoline (**1**)[3] with sodium nitrite ($NaNO_2$) in concentrated HCl, followed by successive treatment with cuprous chloride (CuCl) afforded 5-chloro-3,4-dihydro-2(1*H*)-quinolinone (**2**), which was nitrated with fuming nitric acid to give the 6-nitro compound (**3**). The reduction of **3** with stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$) in concentrated HCl gave the 6-amino compound (**4**), and the crude **4** without isolation was converted to the 6-chloro compound (**5**) in the same manner as described for the synthesis of **2**. Tetrahydroquinolines (**6a**,[4] **b**) were synthesized by reduction of **2** and **5** with $NaBH_4$, respectively (Chart 1). The nitration of 6-chloro-2-methylquinoline (**7a**)[5] with potassium nitrate (KNO_3) in concentrated H_2SO_4 and the

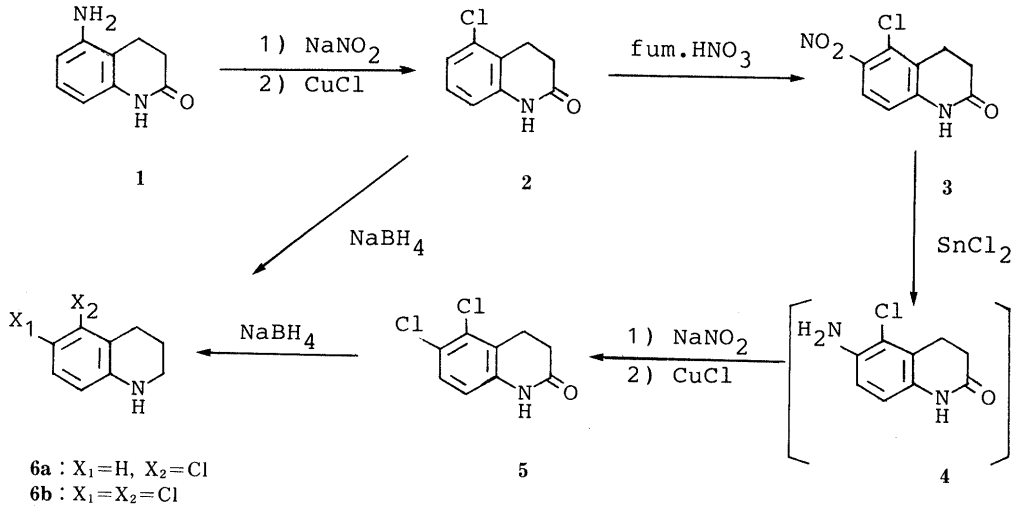


Chart 1

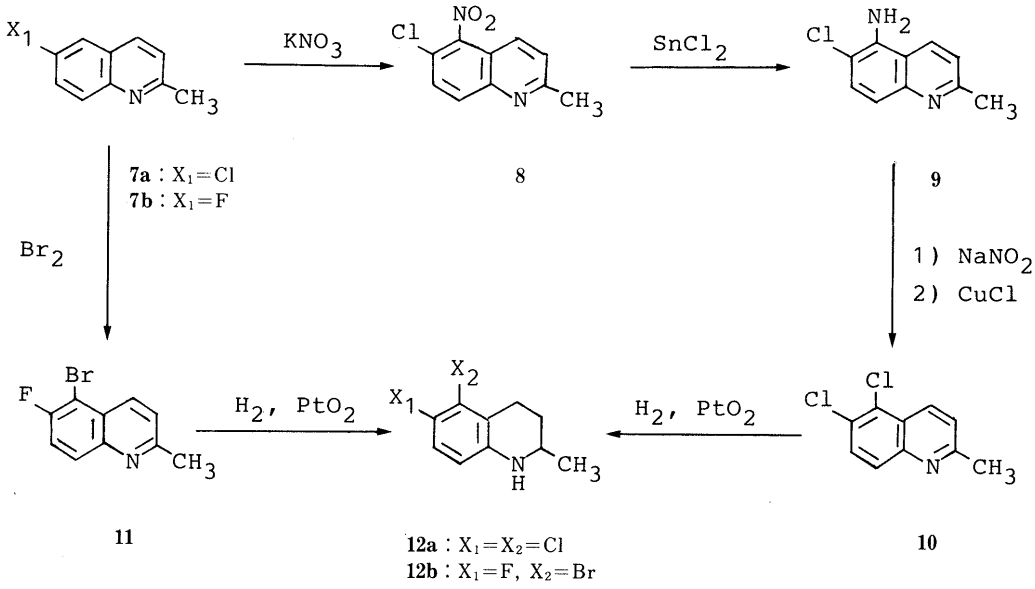


Chart 2

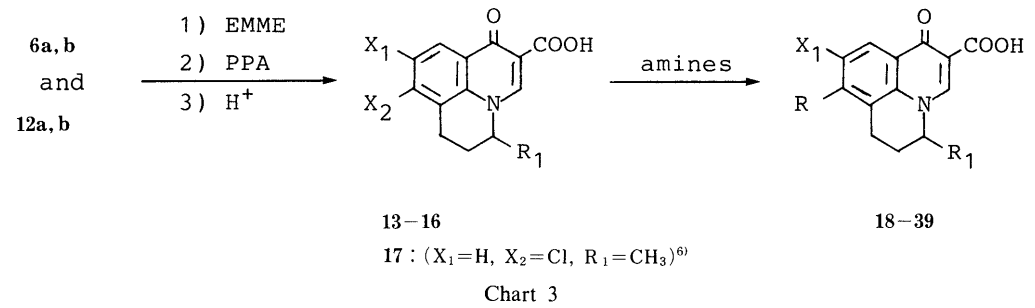


Chart 3

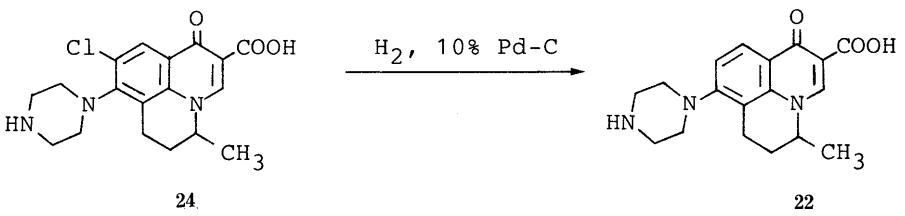


Chart 4

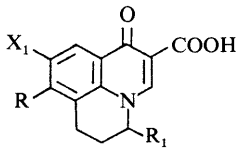
bromination of 6-fluoro-2-methylquinoline (**7b**)[6] with bromine in the presence of aluminum chloride or silver sulfate in concentrated H_2SO_4 occurred at the 5-position to give the 5-nitro compound (**8**) and the 5-bromo compound (**11**), respectively. 5,6-Dichloro-2-methylquinoline (**10**) was prepared from **8** in the same manner as described for the synthesis of **5**. Catalytic hydrogenation of the dihalogenoquinolines (**10** and **11**) with platinum oxide (PtO_2) afforded the 2-methyltetrahydroquinoline derivatives (**12a**, **b**) (Chart 2).

The halogenotetrahydroquinoline derivatives (**6a**, **b** and **12a**, **b**) were treated with diethyl ethoxymethylenemalonate (EMME) at 150 °C for 1 h and then cyclized in polyphosphoric acid (PPA) at 150 °C for 30 min. The crude esters were hydrolyzed with concentrated HCl in 90% AcOH to give the corresponding acids (**13**—**16**). Finally, the acids (**13**—**16** and **17**[7]) were allowed to react with various cyclic amines in hexamethylphosphoric triamide (HMPA) to afford the desired 8-amino derivatives (**18**—**39**) (Chart 3, see Table I). The structure of **24** was supported by the fact that **22** could be synthesized by catalytic reduction of **24** with 10% palladium on carbon (10% Pd–C) (Chart 4).

However, for kilogram scale synthesis the yield of the substitution reaction with amines was found to be unsatisfactory, so we investigated an alternative route. The nitration of **11** occurred selectively at the 8-position to give 5-bromo-6-fluoro-2-methyl-8-nitroquinoline (**40**). The displacement of the bromine atom of **40** with *N*-methylpiperazine in *N*-methyl-2-pyrrolidinone (NMP) afforded the 5-piperazinyl compound (**41**) in a satisfactory yield. The reduction of **41** with $SnCl_2 \cdot 2H_2O$ gave the 8-aminoquinoline derivative (**42**). Diazotization of **42** with $NaNO_2$ in concentrated HCl, followed by successive treatment with 50% hypophosphorous acid provided the deamino compound (**43**). Hydrogenation of **43** with 5% platinum on carbon (5% Pt–C) afforded the tetrahydroquinoline derivative (**44**). The desired compound (**27**) was prepared from **44** in the same manner as described for the synthesis of **13**—**16** in excellent yield (Chart 5).

Biological Results The compounds (**18**—**39**) prepared in

TABLE I. Substituted 6,7-Dihydro-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acids



Compd. No.	R	X_1	R_1	Recryst. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
13	Cl	H	H	DMF	78[a]	>300	$C_{13}H_{10}ClNO_3$	59.22 (59.08)	3.82 3.91	5.31 5.23)
14	Cl	Cl	H	DMF	73[a]	>300	$C_{13}H_9Cl_2NO_3$	52.38 (52.31)	3.04 2.95	4.70 4.78)
15	Cl	Cl	CH_3	DMF	58[a]	269—271	$C_{14}H_{11}Cl_2NO_3$	53.87 (53.90)	3.55 3.49	4.49 4.51)
16	F	Br	CH_3	DMF	75[a]	288—289	$C_{14}H_{11}BrFNO_3$	49.44 (49.15)	3.26 2.99	4.12 4.08)
18	HN N–	H	H	DMF	46	267—268 (dec.)	$C_{17}H_{19}N_3O_3$	65.16 (65.04)	6.11 5.98	13.41 13.30)
19	CH_3–N N–	H	H	DMF	40	278—281 (dec.)	$C_{18}H_{21}N_3O_3$	65.04 (65.95)	6.47 6.44	12.84 12.74)
20	HN N–	Cl	H	EtOH–H_2O	25	>300	$C_{17}H_{18}ClN_3O_3 \cdot HCl \cdot H_2O$	50.76 (50.70)	5.26 5.23	10.45 10.33)
21	CH_3–N N–	Cl	H	EtOH	22	276—280 (dec.)	$C_{18}H_{20}ClN_3O_3$	59.75 (59.66)	5.57 5.51	11.61 11.70)
22	HN N–	H	CH_3	DMF	41	260—262	$C_{18}H_{21}N_3O_3 \cdot 1/2\,H_2O$	64.27 (64.68)	6.59 6.35	12.49 12.52)
23	CH_3–N N–	H	CH_3	DMF	38	258—262	$C_{19}H_{23}N_3O_3$	66.84 (66.82)	6.79 6.67	12.31 12.19)
24	HN N–	Cl	CH_3	DMF	28	246—247 (dec.)	$C_{18}H_{20}ClN_3O_3 \cdot 1/2\,H_2O$	58.30 (58.32)	5.71 5.40	11.33 11.31)
25	CH_3–N N–	Cl	CH_3	DMF	24	290—293 (dec.)	$C_{19}H_{22}ClN_3O_3$	60.72 (60.66)	5.90 5.98	11.18 11.15)
26	HN N–	F	CH_3	DMF	48	260—261 (dec.)	$C_{18}H_{20}FN_3O_3 \cdot H_2O$	59.50 (59.23)	6.10 6.31	11.56 11.45)
27	CH_3–N N–	F	CH_3	CH_3OH–H_2O	30	256—258 (dec.)	$C_{19}H_{22}FN_3O_3$	63.50 (63.32)	6.17 6.22	11.69 11.76)
28	C_2H_5–N N–	F	CH_3	EtOH	26	253—255	$C_{20}H_{24}FN_3O_3 \cdot H_2O$	61.36 (61.41)	6.70 6.38	10.74 10.81)
29	OHC–N N–	F	CH_3	DMF	65[b]	>300	$C_{19}H_{20}FN_3O_4$	61.12 (61.05)	5.40 5.41	11.25 11.43)
30	CH_3CO–N N–	F	CH_3	DMF	72[c]	247—249	$C_{20}H_{22}FN_3O_4 \cdot 1/2\,H_2O$	60.60 (60.64)	5.85 5.79	10.60 10.75)
31	N–	F	CH_3	DMF–H_2O	18	258—261	$C_{19}H_{21}FN_2O_3$	66.27 (66.37)	6.15 6.10	8.13 8.29)
32	CH_3– N–	F	CH_3	DMF–EtOH	28	266—268	$C_{20}H_{23}FN_2O_3$	67.02 (66.98)	6.47 6.29	7.82 7.80)
33	CH_3, CH_3 N–	F	CH_3	DMF	32	214—216	$C_{21}H_{25}FN_2O_3$	67.72 (67.59)	6.77 6.54	7.52 7.56)
34	HO– N–	F	CH_3	EtOH–H_2O	25	245—247 (dec.)	$C_{19}H_{21}FN_2O_4$	63.32 (63.56)	5.87 5.85	7.77 7.82)
35	CH_3O– N–	F	CH_3	DMF	27	249—251	$C_{20}H_{23}FN_2O_4$	64.16 (63.96)	6.19 6.02	7.48 7.34)
36	AcO– N–	F	CH_3	DMF	57[d]	250—253	$C_{21}H_{23}FN_2O_5$	62.68 (62.64)	5.76 5.80	6.96 6.90)
37	N–	F	CH_3	EtOH	32	248—250	$C_{18}H_{19}FN_2O_3$	65.44 (65.18)	5.80 5.72	8.48 8.27)
38	S N–	F	CH_3	DMF	23	292—294	$C_{18}H_{19}FN_2O_3S$	59.65 (52.22)	5.28 5.07	7.73 7.75)
39	O N–	F	CH_3	DMF	39	279—280	$C_{18}H_{19}FN_2O_4$	62.42 (62.44)	5.53 5.53	8.09 8.16)

a) Yield from **6a**, **b** and **12a**, **b**. *b*) Prepared by formylation of **26**. *c*) Prepared by acetylation of **26**. *d*) Prepared by acetylation of **34**.

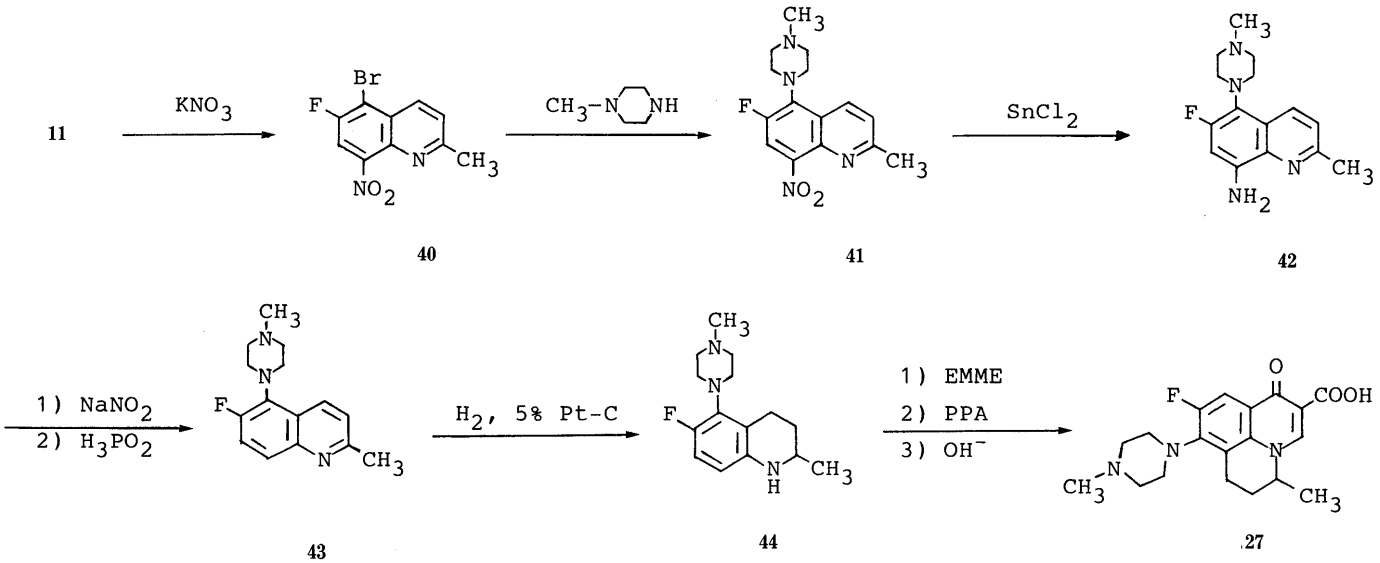


Chart 5

Table II. *In Vitro* Antibacterial Activity (Minimum Inhibitory Concentration, μg/ml)

Compd. No.	*S. aureus* 209p	*E. coli* NIHJ JC-2	*Ps. aeruginosa* ATCC 10145	*P. acnes* ATCC 6919
18	12.5	3.13	6.25	12.5
19	6.25	1.56	6.25	25
20	3.13	0.78	3.13	6.25
21	0.78	0.39	6.25	25
22	6.25	1.56	6.25	6.25
23	3.13	3.13	12.5	3.13
24	0.78	0.39	1.56	3.13
25	0.39	0.39	3.13	3.13
26	0.39	0.2	0.78	0.78
27	0.2	0.2	3.13	3.13
28	0.2	0.2	3.13	3.13
29	0.05	0.39	3.13	0.2
30	0.05	0.39	3.13	0.78
31	0.1	1.56	12.5	1.56
32	0.2	0.78	12.5	1.56
33	0.39	3.13	25	6.25
34	0.024	0.39	3.13	0.2
35	0.1	1.56	12.5	0.39
36	0.1	0.39	3.13	0.78
37	0.1	0.39	3.13	1.56
38	0.05	0.2	3.13	0.78
39	0.05	0.2	3.13	0.2
Ofloxacin	0.2	0.1	1.56	0.78

this investigation were tested for *in vitro* antibacterial activities against gram-positive (*Staphylococcus aureus* 209p and *Propionibacterium acnes* ATCC 6919) and Gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* ATCC 10145) by the serial dilution method.[8] The results are summarized in Table II. The antibacterial activities of ofloxacin[9] are included for comparison.

Introduction of a chlorine atom (**20** and **24**) at the 9-position significantly increased the activities against all the bacteria tested, as compared with the corresponding unsubstituted compounds (**18** and **22**). The replacement of the chloro group of **24** by a fluoro group (**26**) increased the activities against both gram-positive and -negative bacteria. Introduction of a methyl group (**22** and **24**) at the 5-position of the benzoquinolizine skeleton (**18** and **20**) caused an increase in activity. The substitution of the hydrogen of the piperazinyl group in **26** by acyl groups (**29** and **30**) markedly enhanced the activity against gram-positive bacteria, particularly *S. aureus*, but it caused a decrease in the activity against *Ps. aeruginosa*.

Compound **27** (OPC-7241) has outstanding properties of absorption, distribution, metabolism, and excretion, besides antibacterial activity, and compound **34** (OPC-7251) exhibited potent antibacterial activity against gram-positive bacteria, characteristically *P. acnes*.

Experimental

All the melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or JEOL JNM-FX200 NMR spectrometer using tetramethylsilane as an internal standard.

5-Chloro-3,4-dihydro-2(1*H*)-quinoline (2) A solution of $NaNO_2$ (2.3 g, 33 mmol) in H_2O (33 ml) was added dropwise to a suspension of 5-amino-3,4-dihydro-2(1*H*)-quinolinone hydrochloride (**1**) (5.9 g, 30 mmol) in 20% HCl (36 ml) at 5—10 °C. After the addition, the mixture was stirred at room temperature for 1 h. The reaction mixture was added dropwise to a solution of CuCl (5.4 g, 55 mmol) in concentrated HCl (51 ml) and heated at 50—60 °C for 1 h. After cooling, the resulting precipitates were collected by filtration and washed with water. Recrystallization from EtOH gave **2** (4.1 g, 76%) as colorless flakes, mp 193—194 °C. NMR ($CDCl_3$) δ: 2.55—2.74 (2H, m), 2.98—3.20 (2H, m), 6.78 (1H, dd, J=7.2, 1.8 Hz), 6.88—7.20 (2H, m), 9.51 (1H, br s). *Anal.* Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.52; H, 4.48; N, 7.75.

5-Chloro-3,4-dihydro-6-nitro-2(1*H*)-quinolinone (3) Fuming HNO_3 (0.8 ml, d=1.50, 18 mmol) was added dropwise to a solution of **2** (3.3 g, 18 mmol) in concentrated H_2SO_4 (17 ml) below −5 °C. After the addition, the mixture was stirred at room temperature for 30 min and poured into ice-water. The precipitates were collected by filtration and washed with water. Recrystallization from EtOH–$CHCl_3$ gave **3** (3.4 g, 83%) as colorless needles, mp 232—234 °C. NMR ($CDCl_3$) δ: 2.66—2.82 (2H, m), 3.15—3.30 (2H, m), 6.83 (1H, d, J=8.7 Hz), 7.82 (1H, d, J=8.7 Hz), 9.10 (1H, br s). *Anal.* Calcd for $C_9H_7ClN_2O_3$: C, 47.70; H, 3.11; N, 12.36. Found: C, 47.68; H, 3.12; N, 12.48.

5,6-Dichloro-3,4-dihydro-2(1*H*)-quinolinone (5) Compound **3** (4.5 g, 20 mmol) was added to a solution of $SnCl_2 \cdot 2H_2O$ (13.5 g, 60 mmol) in concentrated HCl (17 ml) at room temperature. The mixture was heated at 90 °C for 30 min and then cooled. Next, a solution of $NaNO_2$ (1.5 g, 22 mmol) in H_2O (10 ml) was added dropwise below 5 °C. After the addition, the mixture was added to a solution of CuCl (2.4 g, 24 mmol) in concentrated HCl (10 ml) and the whole was stirred at 90 °C for 1 h. After cooling, the reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over $MgSO_4$ and concentrated. The

residue was purified by silica gel column chromatography (eluent, CH_2Cl_2) and recrystallized from EtOH to give **5** (3.7 g, 84%) as colorless needles, mp 205—207 °C. NMR ($CDCl_3$) δ: 2.60—2.74 (2H, m), 3.08—3.21 (2H, m), 6.72 (1H, d, J=8.4 Hz), 7.28 (1H, d, J=8.4 Hz), 9.25 (1H, br s). *Anal.* Calcd for $C_9H_7Cl_2NO$: C, 50.03; H, 3.27; N, 6.48. Found: C, 49.92; H, 3.24; N, 6.72.

5-Chloro-1,2,3,4-tetrahydroquinoline (6a) AcOH (5.1 ml, 90 mmol) was added dropwise to a suspension of **2** (5.4 g, 30 mmol) and $NaBH_4$ (5.7 g, 90 mmol) in 1,4-dioxane (53 ml) with ice-cooling. After the addition, the mixture was heated at 90 °C for 30 min. The reaction mixture was poured into ice-water and extracted with ether. The ether solution was washed with water, dried over $MgSO_4$ and concentrated. The residue was distilled to give **6a** (3.6 g, 72%), bp 106—107 °C/0.5 mmHg (lit.[4] 110—120 °C/1 mmHg). NMR ($CDCl_3$) δ: 1.86—2.08 (2H, m), 2.69—2.87 (2H, m), 3.15—3.33 (2H, m), 3.71 (1H, br s), 6.35 (1H, dd, J=7.9, 1.1 Hz), 6.66 (1H, dd, J=7.9, 1.1 Hz), 6.87 (1H, t, J=7.9 Hz).

Compound **6b** (1.5 g, 73%) was obtained from **5** (2.2 g) in the same manner as described for **6a**. Compound **6a** was purified by silica gel column chromatography (eluent, CH_2Cl_2: hexane = 1 : 4) and recrystallized from ether–hexane to give colorless needles, mp 55—56 °C. NMR ($CDCl_3$) δ: 1.82—2.05 (2H, m), 2.67—2.88 (2H, m), 3.13—3.32 (2H, m), 3.63 (1H, br s), 6.32 (1H, d, J=8.6 Hz), 7.02 (1H, d, J=8.6 Hz). *Anal.* Calcd for $C_9H_9Cl_2N$: C, 53.49; H, 4.49; N, 6.93. Found: C, 53.39; H, 4.46; N, 6.89.

6-Chloro-2-methyl-5-nitroquinoline (8) A solution KNO_3 (7.1 g, 60 mmol) in concentrated H_2SO_4 (20 ml) was added dropwise to a solution of **7a** (10.7 g, 60 mmol) in concentrated H_2SO_4 (20 ml) at 10—15 °C. After the addition, the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and basified with 28% ammonia water. The resulting precipitates were collected by filtration and recrystallized from ethyl acetate to give **8** (12.3 g, 89%) as colorless prisms, mp 118—120 °C. NMR ($CDCl_3$) δ: 2.77 (3H, s), 7.47 (1H, d, J=8.8 Hz), 7.72 (1H, d, J=9.1 Hz), 7.93 (1H, d, J=8.8 Hz), 8.10 (1H, d, J=9.1 Hz). *Anal.* Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.82; H, 3.22; N, 12.59.

5-Amino-6-chloro-2-methylquinoline (9) A mixture of **8** (6.7 g, 30 mmol) and $SnCl_2 \cdot 2H_2O$ (25.0 g, 0.11 mol) in concentrated HCl (50 ml) was heated at 80—90 °C for 30 min. The reaction mixture was poured into ice-water, basified with 20% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2) and recrystallized from EtOH to give **9** (4.5 g, 78%) as colorless prisms, mp 194—195 °C. NMR ($CDCl_3$) δ: 2.72 (3H, s), 4.56 (2H, br s), 7.25 (1H, d, J=8.7 Hz), 7.41 (1H, d, J=9.0 Hz), 7.53 (1H, d, J=9.0 Hz), 8.03 (1H, d, J=8.7 Hz). *Anal.* Calcd for $C_{10}H_9ClN_2$: C, 62.35; H, 4.71; N, 14.54. Found: C, 62.27; H, 4.74; N, 14.47.

5,6-Dichloro-2-methylquinoline (10) A solution of $NaNO_2$ (2.1 g, 30 mmol) in H_2O (10 ml) was added dropwise to a solution of **9** (3.8 g, 20 mmol) in 20% HCl (40 ml) at 5—10 °C. After the addition, the mixture was added to a solution of CuCl (6.9 g, 70 mmol) in concentrated HCl (15 ml) and stirred at 50 °C for 1 h. The reaction mixture was cooled, basified with 20% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2) and recrystallized from ethyl acetate–hexane to give **10** (2.3 g, 55%) as colorless needles, mp 84—85 °C. NMR ($CDCl_3$) δ: 2.76 (3H, s), 7.42 (1H, d, J=8.8 Hz), 7.71 (1H, d, J=9.1 Hz), 7.90 (1H, d, J=9.1 Hz), 8.47 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33; N, 6.60. Found: C, 56.44; H, 3.25; N, 6.38.

5-Bromo-6-fluoro-2-methylquinoline (11) a) Bromine (5.5 ml, 0.11 mol) was added to a solution of **7b** (16.1 g, 0.1 mol) and Ag_2SO_4 (17 g, 55 mmol) in concentrated H_2SO_4 (90 ml) at 5 °C. After the addition, the mixture was stirred for 1 h and then poured into ice-water. The precipitates were filtered off and the filtrate was basified with 28% ammonia water. The resulting precipitates were collected by filtration and recrystallized from ligroin to give **11** (20.8 g, 87%) as colorless needles, mp 78—79 °C. NMR ($CDCl_3$) δ: 2.76 (3H, s), 7.41 (1H, d, J=8.7 Hz), 7.51 (1H, t, J=8.7 Hz), 7.99 (1H, dd, J=9.2, 5.1 Hz), 8.41 (1H, d, J=8.7 Hz). *Anal.* Calcd for $C_{10}H_7BrFN$: C, 50.03; H, 2.94; N, 5.83. Found: C, 50.01; H, 2.87; N, 5.81.

b) Bromine (11 ml, 0.22 mol) was added during 2 h to a melted mixture of **7b** (27.4 g, 0.17 mol) and powdered anhydrous aluminum chloride (68 g, 0.51 mol) at 110 °C. After the addition, the mixture was stirred at 120 °C for 2 h and then poured into ice-water. The solution was basified with 20% NaOH, and CH_2Cl_2 was added. Insoluble materials were removed by filtration and the CH_2Cl_2 solution was separated. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from ligroin to give **11** (31 g, 76%).

5,6-Dichloro-1,2,3,4-tetrahydro-2-methylquinoline (12a) A mixture of **10** (1.1 g, 5 mmol) and PtO_2 (50 mg) in AcOH (15 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*, basified with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2) to give **12a** as a pale orange oil. NMR ($CDCl_3$) δ: 1.20 (3H, d, J=6.3 Hz), 1.44—1.70 (1H, m), 1.92—2.05 (1H, m), 2.59—2.76 (1H, m), 3.21—3.42 (1H, m), 3.75 (1H, br s), 6.32 (1H, d, J=8.6 Hz), 7.02 (1H, d, J=8.6 Hz). *Anal.* Calcd for $C_{10}H_{11}Cl_2N$: C, 55.58; H, 5.13; N, 6.48. Found: C, 55.50; H, 5.14; N, 6.43.

Compound **12b** (30 g, 68%) was obtained from **11** (43.7 g) in the same manner as described for **12a**. Compound **12b** was purified by silica gel column chromatography (eluent, CH_2Cl_2 : hexane = 1 : 2) to give a colorless oil. NMR ($CDCl_3$) δ: 1.21 (3H, d, J=6.3 Hz), 1.44—1.70 (1H, m), 1.91—2.10 (1H, m), 2.57—3.00 (2H, m), 3.20—3.40 (1H, m), 3.65 (1H, br s), 6.37 (1H, dd, J=8.8, 4.5 Hz), 6.76 (1H, t, J=8.5 Hz). *Anal.* Calcd for $C_{10}H_{11}BrFN$: C, 49.20; H, 4.54; N, 5.74. Found: C, 49.18; H, 4.48; N, 5.69.

8-Bromo-9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (16) A mixture of **12b** (3.1 g, 13 mmol) and EMME (3.0 g, 14 mmol) was heated at 150 °C for 1 h. PPA (24 g) was added to the reaction mixture and heated at 150 °C for 30 min. The mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and concentrated *in vacuo*. Concentrated HCl (10 ml), AcOH (40 ml) and H_2O (4 ml) were added to the residue, and the mixture was refluxed for 2 h. After cooling, the resulting precipitates were collected by filtration, washed with water and recrystallized from dimethylformamide (DMF) to give **16** (3.2 g, 74%) as colorless prisms, mp 288—289 °C. NMR ($CDCl_3$) δ: 1.52 (3H, d, J=7.0 Hz), 2.21—2.24 (2H, m), 2.90—3.44 (2H, m), 4.50—4.71 (1H, m), 8.14 (1H, d, J=8.2 Hz), 8.75 (1H, s), 14.64 (1H, s). The elemental analysis data are shown in Table I.

Compound **13**—**15** were obtained by the same procedure as described for **16**; the yield, melting point and elemental analysis data are listed in Table I.

9-Chloro-6,7-dihydro-5-methyl-8-(4-methyl-1-piperazinyl)-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (25) A mixture of **15** (3.1 g, 10 mmol) and *N*-methylpiperazine (5.0 g, 50 mmol) in HMPA (30 ml) was heated at 160 °C for 6 h. The reaction mixture was concentrated *in vacuo* and ethyl acetate was added to form precipitates, which were separated by filtration. The crystals obtained were suspended in 10% HCl (20 ml) and insoluble materials were removed by filtration. The filtrate was adjusted to pH 7.8 with 10% NaOH and the resulting precipitates were collected by filtration. Recrystallization from DMF gave **25** (0.9 g, 24%) as colorless prisms, mp 290—293 °C (dec.). NMR ($CDCl_3$) δ: 1.51 (3H, s), 2.10—2.31 (2H, m), 2.42 (3H, s), 2.33—3.86 (10H, m), 4.43—4.65 (1H, m), 8.37 (1H, s), 8.70 (1H, s), 14.89 (1H, br s). The elemental analysis data are shown in Table I.

Compounds **18**—**24** and **26**—**28** were obtained by the same procedure as described for **25**; the yield, melting point and elemental analysis data are listed in Table I.

9-Fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (34) A mixture of **16** (6.8 g, 20 mmol) and 4-hydroxypiperidine (10.1 g, 0.1 mol) in HMPA (70 ml) was heated at 160 °C for 7 h. The reaction mixture was concentrated *in vacuo* and ethyl acetate was added to form precipitates. The precipitates were collected by filtration and recrystallized from EtOH–H_2O to give **34** (1.8 g, 25%) as colorless prisms, mp 245—247 °C (dec.). NMR (DMSO-d_6) δ: 1.42 (3H, d, J=6.8 Hz), 1.25—2.26 (6H, m), 2.70—3.43 (6H, m), 3.56—3.82 (1H, m), 4.75 (1H, d, J=3.2 Hz), 4.82—4.98 (1H, m), 7.85 (1H, d, J=12.8 Hz), 8.96 (1H, s), 15.29 (1H, s). The elemental analysis data are shown in Table I.

Compounds **31**—**33**, **35** and **37**—**39** were obtained by the same procedure as described for **34**. The yield, melting point and elemental analysis data are listed in Table I.

9-Fluoro-8-(4-formyl-1-piperazinyl)-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (29) A mixture of acetic anhydride (25.4 ml, 0.27 mol) and formic acid (18.1 ml, 0.48 mol) was heated at 50 °C for 20 min, then **26** (10.4 g, 30 mmol) was added and the reaction mixture was heated at 80 °C for 2 h. After cooling, the reaction mixture was poured into ether. The resulting precipitates were collected by filtration and recrystallized from DMF to give **29** (7.3 g, 65%) as colorless

prisms, mp > 300 °C. NMR ($CDCl_3$) δ: 1.54 (3H, d, J=6.8 Hz), 2.10—2.35 (2H, m), 2.75—3.90 (10H, m), 4.43—4.68 (1H, m), 8.04 (1H, d, J=12.2 Hz), 8.15 (1H, s), 8.71 (1H, s), 14.87 (1H, br s). The elemental analysis data are shown in Table I.

8-(4-Acetyl-1-piperazinyl)-9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (30) Acetic anhydride (4.6 g, 45 mmol) was added to a solution of **26** (10.4 g, 30 mmol) in 5% NaOH (240 ml) at room temperature and the mixture was stirred for 1 h, then acidified with AcOH. The resulting precipitates were collected by filtration. Recrystallization from DMF gave **30** (8.4 g, 72%) as colorless prisms, mp 247—249 °C. NMR ($CDCl_3$) δ: 1.54 (3H, d, J=6.8 Hz), 2.18 (3H, s), 2.15—2.30 (2H, m), 2.73—3.94 (10H, m), 4.50—4.69 (1H, m), 8.03 (1H, d, J=12.4 Hz), 8.71 (1H, s), 14.91 (1H, br s). The elemental analysis data are shown in Table I.

8-(4-Acetoxy-1-piperidyl)-9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (36) A mixture of **34** (1.1 g, 3 mmol), AcOH (1 ml) and concentrated H_2SO_4 (0.3 ml) in CH_2Cl_2 (15 ml) was refluxed for 5 h and then concentrated *in vacuo*. Water was added to the residue and the precipitates were collected by filtration. Recrystallization from DMF gave **36** (0.7 g, 57%) as colorless prisms, mp 250—253 °C. NMR ($CDCl_3$) δ: 1.53 (3H, d, J=6.8 Hz), 1.67—2.33 (6H, m), 2.11 (3H, s), 2.75—3.52 (6H, m), 4.48—4.68 (1H, m), 5.00 (1H, br s), 8.01 (1H, d, J=12.4 Hz), 8.70 (1H, s), 15.03 (1H, br s). The elemental analysis data are given in Table I.

6,7-Dihydro-5-methyl-8-(1-piperazinyl)-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (22) A mixture of **24** (1.8 g, 5 mmol) and 10% Pd–C (0.2 g) in 5% NaOH (14 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was adjusted to pH 7.8 with AcOH. The resulting precipitates were collected by filtration and recrystallized from DMF to give **22** (1.2 g, 74%) as colorless prisms, mp 260—262 °C. NMR (DMSO-d_6) δ: 1.39 (3H, d, J=6.7 Hz), 1.82—2.18 (2H, m), 2.60—3.22 (8H, m), 4.72—4.90 (1H, m), 7.30 (1H, d, J=8.8 Hz), 8.15 (1H, d, J=8.8 Hz), 8.89 (1H, s). The elemental analysis data are given in Table I.

5-Bromo-6-fluoro-2-methyl-8-nitroquinoline (40) A solution of KNO_3 (11.5 g, 0.11 mol) in concentrated H_2SO_4 (30 ml) was added dropwise to a solution of **11** (21.0 g, 88 mmol) in concentrated H_2SO_4 (117 ml) at −5 °C with stirring. After the addition, the mixture was stirred at room temperature for 5 h and poured into ice-water. The precipitates were collected by filtration and recrystallized from iso-PrOH to give **40** (22.9 g, 92%) as colorless needles, mp 135—137 °C. NMR ($CDCl_3$) δ: 2.79 (3H, s), 7.53 (1H, d, J=8.8 Hz), 7.83 (1H, d, J=7.4 Hz), 8.48 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{10}H_6BrFN_2O_2$: C, 42.13; H, 2.12; N, 9.83. Found: C, 41.95; H, 2.10; N, 9.74.

6-Fluoro-2-methyl-5-(4-methyl-1-piperazinyl)-8-nitroquinoline (41) A mixture of **40** (150.0 g, 0.53 mol) and *N*-methylpiperazine (263.0 g, 2.63 mol) in NMP (1.5 l) was heated at 80 °C for 7 h. The reaction mixture was concentrated *in vacuo* and basified with 10% NaOH. The resulting precipitates were collected by filtration and recrystallized from iso-PrOH to give **41** (136.9 g, 85%) as yellow needles, mp 115—117 °C. NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.45—2.80 (4H, m), 2.75 (3H, s), 3.20—3.50 (4H, m), 7.40 (1H, d, J=8.7 Hz), 7.81 (1H, d, J=11.3, Hz), 8.48 (1H, d, J=8.7 Hz). *Anal.* Calcd for $C_{15}H_{17}FN_4O_2$; C, 59.20; H, 5.63; N, 18.41. Found: C, 59.30; H, 5.57; N, 18.49.

8-Amino-6-fluoro-2-methyl-5-(4-methyl-1-piperazinyl)quinoline (42) A solution of $SnCl_2 \cdot 2H_2O$ (237 g, 1.07 mol) in concentrated HCl (800 ml) was added dropwise to a solution of **41** (80.0 g, 0.26 mol) in concentrated HCl (800 ml) below 40 °C. After the addition, the mixture was stirred for 2 h and the resulting precipitates were collected by filtration. Water was added to the precipitates, and the solution was basified with 40% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from hexane to give **42** (66 g, 92%) as yellow needles, mp 149—151 °C. NMR ($CDCl_3$) δ: 2.26—2.45 (2H, m), 2.39 (3H, s), 2.68 (3H, s), 2.76—2.97 (4H, m), 3.37—3.57 (2H, m), 4.98 (2H, br s), 6.58 (1H, d, J=13.6 Hz), 7.26 (1H, d, J=8.6 Hz), 8.50 (1H, d, J=8.6 Hz). *Anal.* Calcd for $C_{15}H_{19}FN_4$: C, 65.67; H, 6.98; N, 20.42. Found: C, 65.25; H, 6.91; N, 20.13.

6-Fluoro-2-methyl-5-(4-methyl-1-piperazinyl)quinoline (43) A solution of $NaNO_2$ (4.9 g, 71 mmol) in H_2O (20 ml) was added dropwise to a solution of **42** (15.0 g, 55 mmol) in 30% HCl (130 ml) at −5 to 0 °C. After the addition, the mixture was stirred at the same temperature. Then 50% hypophosphorous acid (74 ml) was added. The reaction mixture was stirred for 6 h, poured into ice-water and basified with 10% NaOH. The resulting precipitates were collected by filtration and recrystallized from hexane to give **43** (10.0 g, 71%) as pale brown needles, mp 87—90 °C. NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.72 (3H, s), 2.10—3.70 (8H, m), 7.30 (1H, d, J=8.8 Hz), 7.39 (1H, dd, J=11.9, 10.6 Hz), 7.79 (1H, dd, J=9.2, 4.5 Hz), 8.55 (1H, d, J=8.8 Hz). *Anal.* Calcd for $C_{15}H_{18}FN_3$: C, 69.47; H, 7.00; N, 16.20. Found: C, 69.54; H, 6.71; N, 16.18.

6-Fluoro-1,2,3,4-tetrahydro-2-methyl-5-(4-methyl-1-piperazinyl)quinoline (44) A mixture of **43** (6.6 g, 25 mmol) and 5% Pt–C (0.3 g) in AcOH (70 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was basified with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and concentrated. The residue was recrystallized from hexane to give **44** (6.1 g, 91%) as colorless needles, mp 64.5—65.5 °C. NMR ($CDCl_3$) δ: 1.19 (3H, d, J=6.2 Hz), 1.30—1.60 (1H, m), 1.80—3.70 (13H, m), 2.34 (3H, s), 6.22 (H, dd, J=8.7, 4.1 Hz), 6.66 (1H, dd, J=11.9, 8.7 Hz). *Anal.* Calcd for $C_{15}H_{22}FN_3$: C, 68.41; H, 8.42; N, 15.96. Found: C, 68.39; H, 8.37; N, 15.95.

9-Fluoro-6,7-dihydro-5-methyl-8-(4-methyl-1-piperazinyl)-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic Acid (27) A mixture of **44** (5.3 g, 20 mmol) and EMME (5.2 g, 24 mmol) was heated at 150 °C for 1 h. PPA (16 g) was added, and the reaction mixture was heated at 150 °C for 30 min. The mixture was poured into ice-water, adjusted to pH 7.8 with 20% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was concentrated *in vacuo* and 10% NaOH (80 ml) was added to the residue. The suspension was refluxed for 1 h, cooled and adjusted to pH 7.8 with AcOH. The resulting precipitates were collected by filtration and recrystallized from MeOH–H_2O to give **27** (5.4 g, 75%) as colorless prisms, mp 256—258 °C (dec.). NMR ($CDCl_3$) δ: 1.53 (3H, d, J=6.8 Hz), 2.13—2.28 (2H, m), 2.39 (3H, s), 2.40—3.00 (5H, m), 3.05—3.50 (5H, m), 4.45—4.65 (1H, m), 8.01 (1H, d, J=12.3 Hz), 8.69 (1H, s), 15.03 (1H, br s). The elemental analysis data are given in Table I.

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