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antibacterial activities.⁶⁾ c) Reduction of the bulkiness of the N-substituent by cyclization of the N-alkyl group to the *peri*-position of the quinoline ring may affect the antibacterial activities.

Chemistry

The Target Compounds

The secondary amines (**1a—c**) were heated with diethyl ethoxymethylenemalonate (EMME) to afford the corresponding condensates (**2a—c**). Thermal cyclization of **2a—c** in polyphosphoric ester (PPE) gave the esters (**3a—c**). The esters thus obtained were hydrolyzed by HCl to give the desired carboxylic acids (**4a—c**).

The 2,3-dihydrofuro derivatives (**6a—c**) were obtained by catalytic reduction of the esters (**3a—c**) using Pd-C as a catalyst, followed by hydrolysis of the resulting 2,3-dihydrofuro esters (**5a—c**) with 10% NaOH.

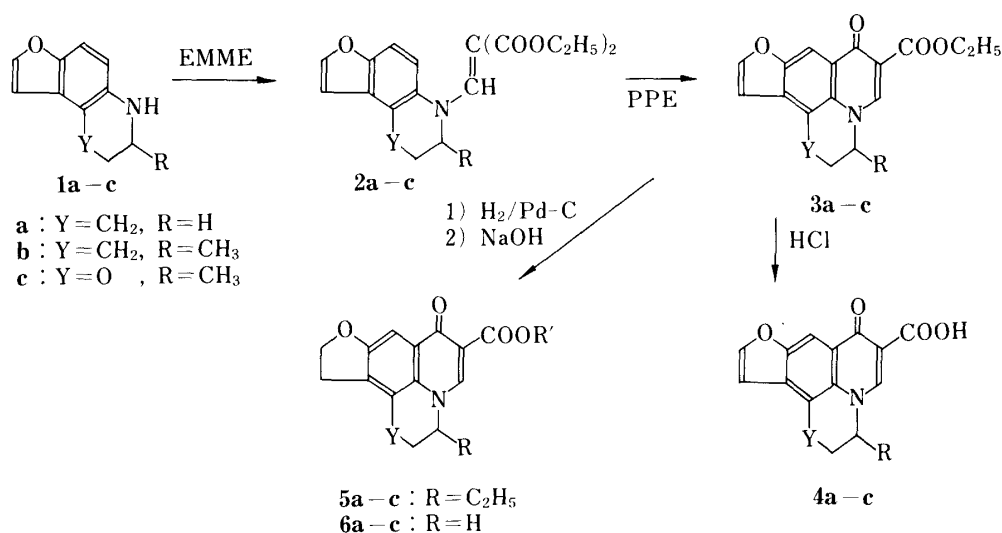


Chart 1

Intermediates of Benzofuro[4,5,6-*ij*]quinolizine Derivatives

5-Aminobenzofuran (**7**)⁸⁾ was used as the starting material for the synthesis of the 2,3-dihydro-7-oxo-1*H*,7*H*-benzofuro[4,5,6-*ij*]quinolizine-6-carboxylic acid derivatives (**4a—b**) and the corresponding 2,3-dihydrofuro derivatives (**6a, b**). Compound **7** was heated with methyl acrylate or crotonic acid to give the condensate **8** or **11**, respectively. In the case of the ester (**8**), the amino group was protected by treatment with *p*-toluenesulfonyl chloride in pyridine to give the tosylate (**9**), which was hydrolyzed with KOH to the carboxylic acid (**10**). Treatment of **10** with PCl₅, followed by AlCl₃ gave the cyclized compound (**12a**). Compound **12b** was obtained by heating **11** in polyphosphoric acid (PPA). The oxo group of the tricyclic compounds (**12a, b**) thus obtained was reduced to a methylene group with LiAlH₄ to give the desired intermediates (**1a, b**).

Intermediates of Furo[2,3-*h*]pyrido[1,2,3-*de*][1,4]benzoxazine Derivatives

4-Hydroxybenzofuran-6-carboxylic acid (**13**)⁹⁾ was used as a starting material for the synthesis of 2,3-dihydro-7-oxo-7*H*-furo[2,3-*h*]pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid derivatives. Nitration of **13** was conducted by using various nitrating agents, among which aluminum nitrate nonahydrate was the most efficient. After decarboxylation of **14** and successive acetylation of the hydroxyl group of **15**, catalytic reduction of **16** by the method

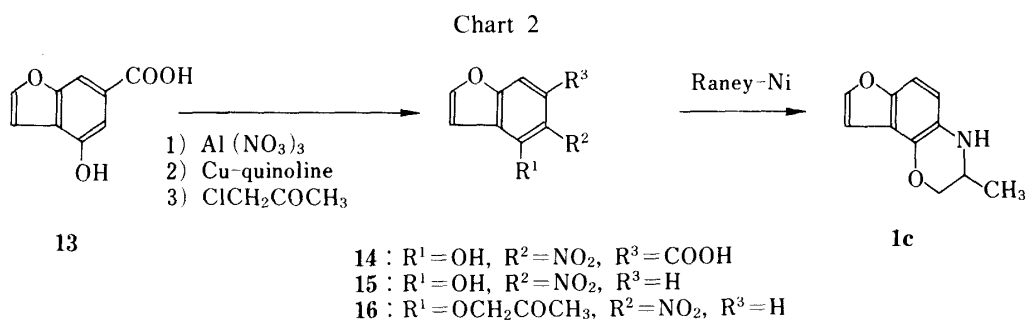
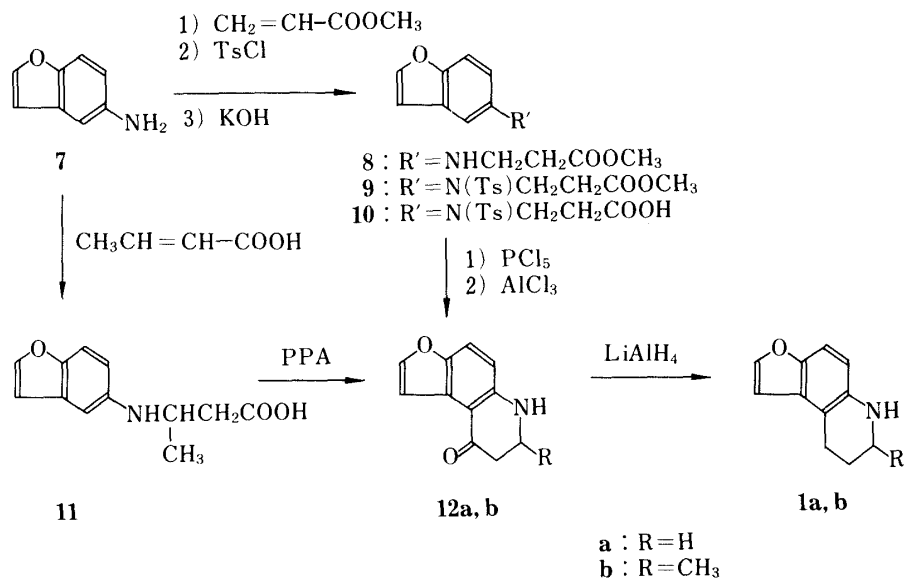


Chart 3

 TABLE I. The *in Vitro* Antibacterial Activity (MIC, $\mu\text{g/ml}$) and Acute Toxicity (LD_{50} , *i.v.*, in Mice, mg/kg) Data

Organisms	Compd. No.						
	4a	6a	4b	6b	4c	6c	Droxacin
MIC ($\mu\text{g/ml}$) <i>E. coli</i> , NIHJ	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	0.39	≤ 0.2
<i>Sh. flexneri</i> , 2a-5503	≤ 0.2	0.39	≤ 0.2	0.39	≤ 0.2	≤ 0.2	0.39
<i>Sal. typhimurium</i> , W-118	0.78	0.78	0.39	0.78	≤ 0.2	0.39	0.78
<i>Pr. vulgaris</i> , 3167	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	0.39	≤ 0.2
<i>Pr. mirabilis</i> , 1287	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	≤ 0.2	0.39	≤ 0.2
<i>K. pneumoniae</i> , Type 1	1.56	3.13	3.13	3.13	0.78	1.56	3.13
<i>Ent. cloacae</i> , 12001	1.56	0.78	0.78	3.13	≤ 0.2	0.78	0.78
<i>Ser. marcescens</i> , 13014	1.56	3.13	1.56	3.13	0.78	0.78	0.39
<i>Ps. aeruginosa</i> , 2063	12.5	50	12.5	50	1.56	3.13	25
<i>Sta. aureus</i> , 209 p	0.78	3.13	0.39	0.78	≤ 0.2	0.39	6.25
<i>Str. pyogenes</i> , G-36	6.25	50	3.13	25	3.13	12.5	100
LD_{50} , <i>i.v.</i> , in mice (mg/kg)	77	184	70	131	310	300	170

of Hill¹⁰) afforded the cyclized furo[2,3-*h*][1,4]benzoxazine derivative (**1c**), which was used for the condensation reaction with EMME without further purification.

Biological Studies

The target compounds (**4a**—**c** and **6a**—**c**) prepared in this work were tested for *in vitro*

antibacterial activities¹¹⁾ (MIC, $\mu\text{g/ml}$) and acute toxicity (LD_{50} mg/kg) on intravenous administration to mice. These results are presented in Table I. Droxacin was chosen as a reference compound because of its structural resemblance to the test compounds. The furo derivatives (**4a—c**) showed higher activity than the corresponding 2,3-dihydrofuro derivatives (**6a—c**). Antibacterial activity was little affected by the introduction of a methyl group at the 3-position. Compound **4c** exhibited the highest antimicrobial activity against Gram-positive and -negative pathogens tested, including *Ps. aeruginosa*. In addition, replacement of methylene (Y) in **4b** by oxygen (Y) in **4c** significantly decreased the acute toxicity to mice.

Experimental

N-(5-Benzofuryl)-N-tosyl- β -alanine (10) — A mixture of 5-aminobenzofuran (10 g), methyl acrylate (6.8 g) and a catalytic amount of AcOH (0.1 ml) was heated under reflux for 20 h, then concentrated *in vacuo*. The oily residue was dissolved in pyridine (100 ml). *p*-Toluenesulfonyl chloride (17 g) was added portionwise to the solution at room temperature during 30 min, then the reaction mixture was heated at 80–90 °C for 1 h with stirring. After being cooled, the solution was poured into ice-water (200 ml), and extracted with ether. The ether layer was washed successively with 10% HCl, 5% KOH and water. After evaporation of the solvent, the crude product was purified by silica-gel column chromatography using CHCl_3 as an eluent to give the oily methyl ester (**9**). A solution of the ester in 10% KOH (40 ml) and 80% MeOH (100 ml) was stirred for 1 h at room temperature. The reaction mixture was poured into ice-water (200 ml), then neutralized with 10% HCl and extracted with CHCl_3 . After removal of the solvent, the residue was purified by silica-gel column chromatography using CHCl_3 as an eluent to give **10** (4.8 g, 18%), mp 129–130 °C. *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_5\text{S}$: C, 60.15; H, 4.76; N, 3.89. Found: C, 59.84; H, 4.82; N, 3.92.

9-Oxo-6,7,8,9-tetrahydrofuro[3,2-*f*]quinoline (12a) — Phosphorus pentachloride (3.0 g) was added to a solution of **10** (5.4 g) in benzene (30 ml) at 0–5 °C, and the mixture was heated at 100 °C for 30 min. Aluminum chloride (2.5 g) was added to the solution at 5 °C during 30 min. The whole was stirred for 3 h at room temperature, then most of the benzene solution was removed by decantation, and water was added to the residue, which was extracted with CHCl_3 . The combined benzene and CHCl_3 solution was washed with water and concentrated to dryness. The crude product was subjected to silica-gel column chromatography using CHCl_3 as an eluent to give **12a** (1.5 g, 54%), mp 130–134 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{NO}_2$: C, 70.57; H, 4.84; N, 7.47. Found: C, 70.54; H, 4.87; N, 7.38.

6-[2,2-Bis(ethoxycarbonyl)ethenyl]-6,7,8,9-tetrahydrofuro[3,2-*f*]quinoline (2a) — A mixture of **12a** (1.0 g) and LiAlH_4 (0.4 g) in tetrahydrofuran (THF) (100 ml) was heated under reflux for 1 h. Excess LiAlH_4 was decomposed by adding water cautiously, and the solvent was evaporated off. The residue was mixed with CHCl_3 and water. The CHCl_3 layer was separated, washed and dried. After removal of the solvent, the residue was subjected to silica-gel column chromatography using CHCl_3 as an eluent to give **1a** as an oil (0.8 g). EMME (1.1 g) was added to the oily intermediate (**1a**) and the mixture was heated at 120–125 °C for 1.5 h, then cooled. The reaction mixture was triturated with ether. The insoluble material was collected by filtration and recrystallized from petroleum ether to give **2a** (1.0 g, 55%) as colorless needles, mp 83–84 °C. *Anal.* Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: C, 66.45; H, 6.16; N, 4.07. Found: C, 66.44; H, 6.19; N, 4.14.

Ethyl 2,3-Dihydro-7-oxo-1*H*,7*H*-benzofuro[4,5,6-*ij*]quinolizine-6-carboxylate (3a) — A mixture of **2a** (5.0 g) and PPE (45 g) was heated at 120 °C for 20 min. After the mixture had cooled, water was added to the viscous oil and stirring was continued until a homogeneous suspension was formed. The product was extracted with CHCl_3 . The CHCl_3 solution was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from EtOH to give **3a** (3.4 g, 79%) as colorless needles, mp 256–259 °C. *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_4$: C, 68.67; H, 5.08; N, 4.70. Found: C, 68.57; H, 5.21; N, 5.09.

7-Methyl-9-oxo-6,7,8,9-tetrahydrofuro[3,2-*f*]quinoline (12b) — A solution of 5-aminobenzofuran (9.0 g) and crotonic acid (6.4 g) in benzene (35 ml) was heated under reflux for 16 h. Benzene (35 ml) and 2.5% KOH (175 ml) were added to the cooled reaction mixture with stirring. The aqueous layer was separated, neutralized with conc. HCl and extracted with CHCl_3 . The CHCl_3 solution was washed with water, dried over Na_2SO_4 and concentrated to dryness. PPA (40 g) was added to the residue and the mixture was heated at 110–115 °C for 30 min with stirring. Water (200 ml) was added to the cooled viscous oil and the product was extracted with CHCl_3 . The crude product obtained from the CHCl_3 extract was purified by silica-gel column chromatography using CHCl_3 as an eluent to give **12b** (2.9 g, 21%) as light yellow needles, mp 108–110 °C. *Anal.* Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_2$: C, 71.63; H, 5.50; N, 6.95. Found: C, 71.42; H, 5.63; N, 6.79.

Ethyl 2,3-Dihydro-3-methyl-7-oxo-1*H*,7*H*-benzofuro[4,5,6-*ij*]quinolizine-6-carboxylate (3b) — A mixture of **12b** (3.0 g) and LiAlH_4 (1.5 g) in THF (150 ml) was heated under reflux for 2 h. Excess LiAlH_4 was decomposed by adding water cautiously, and the solvent was evaporated off. The residue was mixed with CHCl_3 and water. EMME (3.2 g) was added to the crude product (**1b**) obtained from the separated CHCl_3 layer. The mixture was heated at 120–130 °C for 2.5 h, followed by addition of PPE (50 g), and the whole was heated at 120 °C for an additional 20 min.

Water was added to the cooled reaction mixture and the product was extracted with CHCl_3 . The crude **3b** obtained from the CHCl_3 extract was recrystallized from EtOH to afford **3b** (2.2 g, 47%) as colorless prisms, mp 260–262 °C. *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_4$: C, 69.44; H, 5.50; N, 4.49. Found: C, 69.78; H, 5.60; N, 4.64.

4-Hydroxy-5-nitrobenzofuran-6-carboxylic Acid (14)—Aluminum nitrate nonahydrate (9.1 g) was added portionwise to a suspension of **13** (15.0 g) in AcOH (300 ml) at 20–23 °C during 1 h. After being stirred for an additional 1 h, the reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4 and concentrated until the product was deposited. The precipitate was collected by filtration and washed with ether to give **14** (6.8 g, 36%), mp 231–233 °C (dec.). *Anal.* Calcd for $\text{C}_9\text{H}_5\text{NO}_6$: C, 48.44; H, 2.26; N, 6.28. Found: C, 48.32; H, 2.33; N, 6.07.

4-Hydroxy-5-nitrobenzofuran (15)—Copper powder (6 g) was added to a solution of **14** (6.7 g) in quinoline (70 ml) at 180 °C with vigorous stirring, and heating was continued for 10 min. AcOEt was added to the cooled reaction mixture and insoluble materials were filtered off. The filtrate was shaken with 3 N HCl to remove quinoline. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was subjected to silica-gel column chromatography using benzene as an eluent to give **15** (3.1 g, 58%), mp 170 °C. *Anal.* Calcd for $\text{C}_8\text{H}_5\text{NO}_4$: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.42; H, 2.96; N, 7.63.

4-Acetyloxy-5-nitrobenzofuran (16)—A mixture of **15** (1.05 g), K_2CO_3 (0.83 g), KI (0.20 g) and chloroacetone (1.0 ml) in acetone (20 ml) was heated under reflux for 1.5 h. The inorganic materials were removed by filtration, and the filtrate was concentrated to dryness. The residue was triturated with isopropyl ether and the resulting precipitate was collected by filtration to give **16** (1.19 g, 86%), mp 78 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{NO}_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 55.98; H, 3.69; N, 6.04.

Ethyl 3-Methyl-7-oxo-2,3-dihydro-7H-furo[2,3-*h*]pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (3c)—Compound **16** (1.6 g) was catalytically reduced in the presence of Raney Ni (2.0 ml) in EtOH (50 ml) at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated to dryness. EMME (1.6 g) was added to the oily

TABLE II. Furo-quinoline Derivatives

Compd. No.	Y	R	Reaction time (h)	Yield (%)	mp (°C)	Formula	Analysis (%)		
							Calcd (Found)		
							C	H	N
4a	CH_2	H	3	53	> 300	$\text{C}_{15}\text{H}_{11}\text{NO}_4$	66.91 (66.72)	4.11 4.26	5.20 5.39
4b	CH_2	CH_3	4	48	253–255	$\text{C}_{16}\text{H}_{13}\text{NO}_4$	67.84 (67.65)	4.62 4.95	4.94 4.85
4c	O	CH_3	10	58	> 300	$\text{C}_{15}\text{H}_{11}\text{NO}_5$	63.16 (62.94)	3.89 4.00	4.91 5.07

TABLE III. 2,3-Dihydrofuro-quinoline Derivatives

Compd. No.	Y	R	Reaction time (h)	Yield (%)	mp (°C)	Formula	Analysis (%)		
							Calcd (Found)		
							C	H	N
5a	CH_2	H		74	213–214	$\text{C}_{17}\text{H}_{17}\text{NO}_4$	68.21 (68.10)	5.72 5.53	4.67 4.62
5b	CH_2	CH_3		73	214–216	$\text{C}_{18}\text{H}_{19}\text{NO}_4$	68.99 (68.72)	6.11 6.07	4.46 4.57
5c	O	CH_3		69	243–245	$\text{C}_{17}\text{H}_{17}\text{NO}_5$	64.75 (64.63)	5.44 5.55	4.44 4.27
6a	CH_2	H	0.5	47	> 300	$\text{C}_{15}\text{H}_{13}\text{NO}_4$	66.41 (66.36)	4.82 4.90	5.16 5.25
6b	CH_2	CH_3	0.5	52	288–290	$\text{C}_{16}\text{H}_{15}\text{NO}_4$	67.35 (67.10)	5.30 5.28	4.90 4.91
6c	O	CH_3	1	89	> 300	$\text{C}_{15}\text{H}_{13}\text{NO}_5$	62.71 (62.47)	4.56 4.62	4.88 4.73

residue and the mixture was heated at 120—130°C for 40 min. PPE (25 g) was added to the reaction mixture and heating was continued at 130—140°C for 1 h. After being cooled, the reaction mixture was poured into ice-water. The precipitate was collected by filtration and recrystallized from EtOH to give **3c** (1.3 g, 61%), mp 235—237°C. *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.46; H, 4.88; N, 4.53.

6-Carboxylic Acids (4a—c): General Procedure—An ester (**3a—c**) was dissolved in 10 volumes of conc. HCl-AcOH (1 : 11) and heated under gentle reflux. After the reaction mixture had cooled, the precipitate was collected by filtration and recrystallized from *N,N*-dimethylformamide (DMF) to give the corresponding acid (**4a—c**) (Table II).

2,3-Dihydrofuro Derivatives (6a—c): General Procedure—An ester (**3a—c**) was hydrogenated in the presence of Pd-C in MeOH at atmospheric pressure. The dihydrofuro derivative (**5a—c**) thus obtained was hydrolyzed by heating in 10% NaOH to give the corresponding acid (**6a—c**) (Table III).

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References and Notes

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