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Synthesis and Antibacterial Activities of Substituted 7-Oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acids

ISAO HAYAKAWA,* TOKIYUKI HIRAMITSU, and YOSHIAKI TANAKA

Research Institute, Daiichi Seiyaku Co., Ltd., Kita-kasai, Edogawa-ku, Tokyo 134, Japan

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As part of a search for new synthetic antibacterial agents to combat systemic infection, various analogues of 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acids were synthesized. Among the compounds newly synthesized, 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (DL-8280) showed potent antibacterial activity against Gram-positive and -negative pathogens, including *Psedomonas aeruginosa*, and its metabolic disposition was shown in separate experimentals to be favorable.

Keywords——4-oxopyridine-3-carboxylic acid; pyrido[1,2,3-*de*][1,4]benzoxazine; fluorine; *N*-methylpiperazine; oxazine ring formation; *Pseudomonas aeruginosa*; antibacterial activity; systemic infection

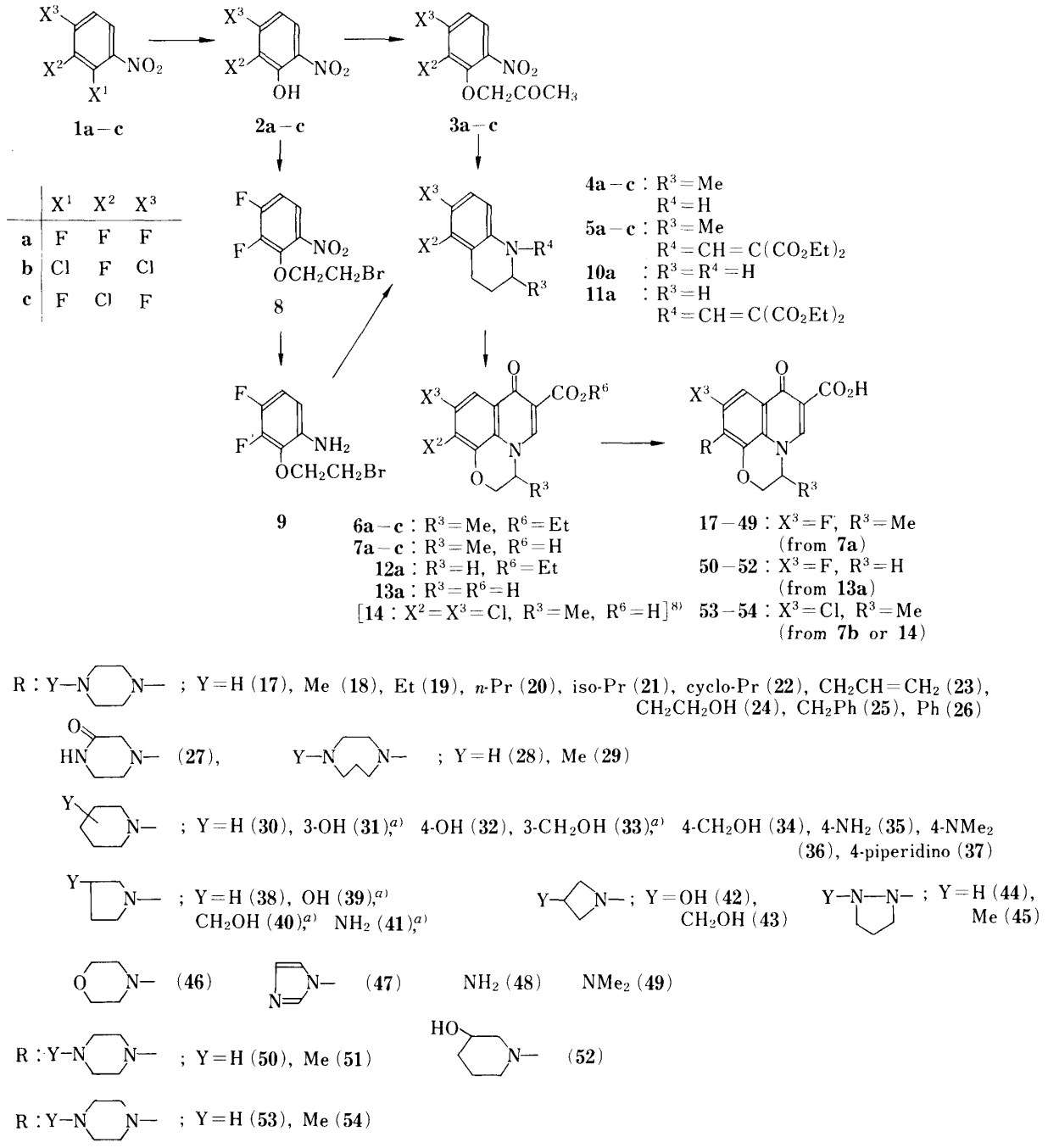
Among synthetic antimicrobial agents, oxopyridinecarboxylic acid derivatives (PCA-antibacterials) exhibit no serious side effects and do not induce significant drug resistance in the target microorganisms. Since nalidixic acid[1] was first reported by Lesher *et al.* in 1962 as a PCA-antibacterial agent, many analogues having a 4-oxopyridine-3-carboxylic acid moiety have been synthesized. Some of them have been introduced into clinical use, but their use has been limited mainly to urinary tract infections.

These drugs, from a physico-chemical point of view, may be classified into two types; a hydrophilic type (A) such as pipemidic acid or norfloxacin, containing a water-soluble component in the molecule, and a lipophilic type (B) such as nalidixic acid or oxolinic acid. In the course of our search for more potent analogues which could be applied to systemic infections, we synthesized type (B) agents with a tetracyclic structure. We found that oxazine ring formation at the *ij*-bonds of the quinoline ring was more effective in terms of antibacterial activities, particularly against opportunistic pathogens, *i.e.*, *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, *Pseudomonas putida*, *etc.*, and Gram-positive bacteria, and the compound showed a lower acute toxicity (LD_{50}, *i.v.* in mice) than the corresponding compound with a piperidine ring at the *ij*-bonds of the quinoline ring.[2] On the other hand, Koga *et al.*[3] found that the combination of a fluorine atom and the piperazine substituent at the 6- and 7-positions of quinoline enhanced the antibacterial activities of type (A) compound. These two findings led us to study tricyclic compounds of type (A). This paper deals with the synthesis of pyrido[1,2,3-*de*][1,4]benzoxazine derivatives of type (A) and with their antibacterial activities.

Chemistry

Alkaline hydrolysis of 2,3,4-trihalogenonitrobenzenes (**1a**—**c**)[4-6] in dimethyl sulfoxide (DMSO) occurred selectively at the halogen atom adjacent to the nitro group to give *o*-nitrophenol derivatives (**2a**—**c**). The 2-oxopropyl ethers (**3a**—**c**) of **2a**—**c** were converted to benzoxazine derivatives (**4a**—**c**) by reductive cyclization according to the method of Hill.[7] Condensation of **4a**—**c** with diethyl ethoxymethylenemalonate (EMME) by heating at 145 °C

afforded **5a**—**c**. Pyridine ring cyclization of the condensates (**5a**—**c**) by heating at 145 °C in polyphosphoric ester (PPE) yielded the esters (**6a**—**c**), which were hydrolyzed with conc. HCl in AcOH to give the corresponding acids (**7a**—**c**).



a) Compounds, **31**, **33**, **39**, **40** and **41** were each a mixture of diastereomers.

Chart 1

An intermediate (**13**) to the 3-desmethyl derivatives (**50**—**52**) was synthesized as follows; reaction of **2a** with 1,2-dibromoethane in the presence of K_2CO_3 afforded compound **8**, which was reduced with sodium hydrosulfite in aqueous MeOH to give the aniline derivative (**9**). Oxazine cyclization of **9** was carried out by heating in *N*, *N*-dimethylformamide (DMF) in the presence of K_2CO_3 to give **10**. The intermediate (**13**) was derived from difluoro-benzoxazine (**10**) in the same manner as the 3-methyl derivatives (**7**).

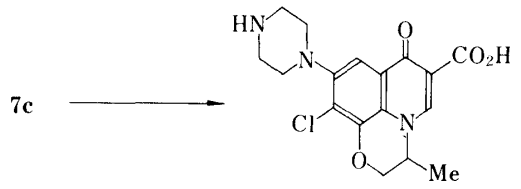


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Chart 2

Finally, the acid (**7a**) was condensed with various secondary amines by heating in DMSO to afford the desired compounds (**17**—**49**) without accompanying isomer formation. 3-Desmethyl derivatives (**50**—**52**) were synthesized from **13** in the same manner as described for the 3-methyl derivatives. Compounds **53** and **54** were obtained from the 9,10-dichloro-(**14**)[8] or 9-chloro-10-fluoro-(**7b**) derivatives. On the other hand, a 9-fluoro-10-chloro intermediate (**7c**) was converted to a 9-substituted 10-chloro compound (**55**) which showed no antimicrobial activity, as described below. 9-Dehalogenated derivatives (**56**—**60**) were obtained from the 10-fluoro derivative (**15**)[8] by heating with amines, while the 10-chloro derivative (**16**)[8] did not react with amines under the same conditions.

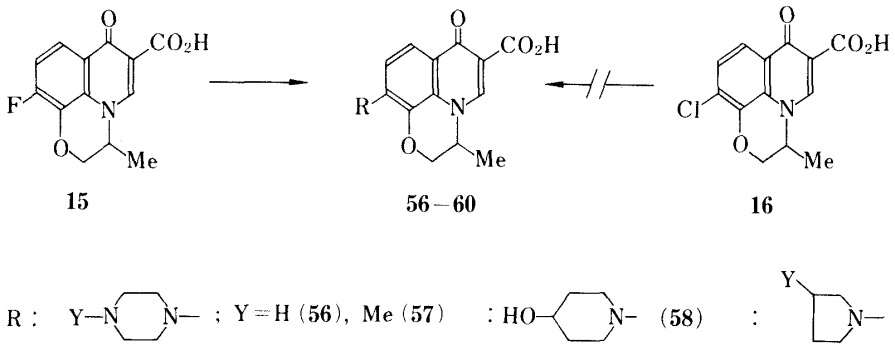

Chart 3

Biological Results

All the carboxylic acids (**17**—**60**) prepared in this work were tested for antibacterial activities *in vitro* by the serial dilution method.[9] Their minimum inhibitory concentrations are summarized in Table II. Most of the compounds synthesized exhibited more potent activities than the related drug, pipemidic acid.[11]

The following relationships were found. a) Introduction of a fluorine atom at the 9-position of the pyrido[1,2,3-*de*][1,4]benzoxazine ring markedly enhanced the antibacterial activities, in accordance with the result reported by Koga.[3] b) Introduction of a methyl group at the 3-position of the ring increased the activities, particularly against Gram-positive bacteria, as compared with those of the corresponding desmethyl derivatives. c) The piperazinyl derivatives generally showed potent and balanced antibacterial activities against Gram-positive and -negative bacteria, including *Pseudomonas aeruginosa*. Antibacterial activity decreased with increasing bulkiness of the substituent at the 4-position of the piperazine ring. d) The pyrrolidinyl derivatives exhibited potent activity, particularly against Gram-positive bacteria. The practical usefulness of oral antibacterial agents in the treatment of infectious disease depends on absorption, distribution, metabolism and excretion, besides antibacterial activity. Compound **18** (DL-8280)[12] has outstanding characteristics with respect

TABLE I. Substituted 7-Oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acids

Compd. No.	Reaction time (h)	Recryst. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
17	3	EtOH	53	257—260 (dec.)	$C_{17}H_{18}FN_3O_4 \cdot 1/2H_2O$	57.30	5.37	11.79
						(57.01	5.42	11.75)
18	12	EtOH	62	250—257 (dec.)	$C_{18}H_{20}FN_3O_4$	59.82	5.58	11.63
						(59.62	5.59	11.65)
19	5	EtOH	68	263—264 (dec.)	$C_{19}H_{22}FN_3O_4$	60.79	5.91	11.19
						(60.56	5.96	11.04)
20	1	EtOH	38	257—261 (dec.)	$C_{20}H_{24}FN_3O_4$	61.69	6.21	10.79
						(61.51	6.00	10.50)
21	1	EtOH	33	255—260	$C_{20}H_{24}FN_3O_4$	61.69	6.21	10.79
						(61.48	6.08	10.70)
22	1	EtOH–$CHCl_3$	55	270—273 (dec.)	$C_{20}H_{22}FN_3O_4$	62.01	5.73	10.85
						(62.14	5.79	10.92)
23	6	EtOH–$CHCl_3$	52	255—258 (dec.)	$C_{20}H_{22}FN_3O_4$	62.01	5.73	10.85
						(61.77	5.76	10.83)
24	5	EtOH	66	282—285 (dec.)	$C_{19}H_{22}FN_3O_5$	58.30	5.67	10.74
						(58.32	5.64	10.86)
25	2	EtOH	45	257—259 (dec.)	$C_{24}H_{24}FN_3O_4$	65.89	5.53	9.61
						(65.68	5.60	9.68)
26	6	EtOH–$CHCl_3$	47	275—280 (dec.)	$C_{23}H_{22}FN_3O_4$	65.23	5.24	9.93
						(64.97	5.14	9.89)
27	6	EtOH–$CHCl_3$	51	>300	$C_{17}H_{16}FN_3O_5$	56.51	4.46	11.63
						(56.52	4.59	11.53)
28	4.5	EtOH	46	285—290 (dec.)	$C_{18}H_{20}FN_3O_4 \cdot HCl \cdot H_2O$	51.99	5.57	10.10
						(51.71	5.35	10.10)
29	5	EtOH	54	234—237 (dec.)	$C_{19}H_{22}FN_3O_4$	60.79	5.91	11.19
						(60.57	5.91	11.04)
30	5.5	EtOH	58	268—275 (dec.)	$C_{18}H_{19}FN_2O_5$	62.24	5.51	8.07
						(62.12	5.39	8.08)
31	6	EtOH	64	267—273 (dec.)	$C_{18}H_{19}FN_2O_5$	59.66	5.28	7.73
						(59.49	5.19	7.63)
32	5.5	EtOH	56	235—240 (dec.)	$C_{18}H_{19}FN_2O_5$	59.66	5.28	7.73
						(59.44	5.26	7.65)
33	4	EtOH–$CHCl_3$	63	221—222	$C_{19}H_{21}FN_2O_5$	60.63	5.62	7.44
						(60.44	5.76	7.30)
34	4	EtOH	58	265—266	$C_{19}H_{21}FN_2O_5$	60.63	5.62	7.44
						(60.36	5.42	7.54)
35[10]	3	EtOH	55	210—212	$C_{18}H_{20}FN_3O_4$	59.82	5.58	11.63
						(59.58	5.71	11.52)
36	6	EtOH	56	245—248 (dec.)	$C_{20}H_{24}FN_3O_4$	61.68	6.21	10.79
						(61.45	6.10	10.67)
37	4.5	EtOH	56	239—245 (dec.)	$C_{23}H_{28}FN_3O_4$	64.32	6.57	9.79
						(64.10	6.59	9.64)
38	4	EtOH	74	268—269	$C_{17}H_{17}FN_2O_4$	61.45	5.16	8.43
						(61.25	5.27	8.55)
39	1	EtOH–$CHCl_3$	43	278—280 (dec.)	$C_{17}H_{17}FN_2O_5$	58.61	4.92	8.04
						(58.45	5.10	7.94)
40	1	EtOH	50	236—237	$C_{18}H_{19}FN_2O_5$	59.66	5.28	7.73
						(59.70	5.29	7.67)
41[10]	3	EtOH–$CHCl_3$	48	236—241	$C_{17}H_{18}FN_3O_4$ $2HCl \cdot H_2O$	46.58	5.06	9.58
						(46.87	4.84	9.65)
42	1.5	EtOH	43	286—287 (dec.)	$C_{16}H_{15}FN_2O_5$	57.48	4.52	8.38
						(57.58	4.32	8.27)

TABLE I. (continued)

Compd. No.	Reaction time (h)	Recryst. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
43	2	MeOH	42	>300	$C_{17}H_{17}FN_2O_5$	58.61	4.92	8.04
						(58.46	5.06	8.12)
44	2	EtOH	45	218—225 (dec.)	$C_{16}H_{16}FN_3O_4$	57.65	4.84	12.61
						(57.33	4.89	12.53)
45	6	EtOH	38	233—236	$C_{17}H_{18}FN_3O_4$	58.78	5.22	12.10
						(58.53	5.33	11.89)
46	4	EtOH	66	>300	$C_{17}H_{17}FN_2O_5$	58.61	4.92	8.04
						(58.72	4.96	8.03)
47	(10 min)	EtOH	60	>300	$C_{16}H_{12}FN_2O_4$	58.36	3.67	12.76
						(58.45	3.81	12.66)
48	2	EtOH	56	>300	$C_{13}H_{11}FN_2O_4$	56.11	3.99	10.07
						(55.99	4.18	9.92)
49	3	EtOH	62	233—235	$C_{15}H_{15}FN_2O_4$	58.82	4.94	9.15
						(58.89	5.13	9.13)
50	5	H_2O	58	265—268 (dec.)	$C_{16}H_{16}FN_3O_4$	57.65	4.84	12.61
						(57.35	4.79	12.69)
51	6	EtOH	41	265—270 (dec.)	$C_{17}H_{18}FN_3O_4$	58.78	5.22	12.10
						(58.57	5.38	12.04)
52	7	MeOH	55	270—277 (dec.)	$C_{17}H_{17}FN_2O_5$	58.61	4.92	8.04
						(58.30	4.94	7.97)
53	24	H_2O–EtOH–Me_2CO	56	>300	$C_{17}H_{18}ClN_3O_4 \cdot HCl \cdot 1/2H_2O$	49.89	4.93	10.27
						(49.62	5.00	10.02)
54	6	MeOH–$CHCl_3$	63	275—276	$C_{18}H_{20}ClN_3O_4$	57.22	5.34	11.12
						(57.20	5.11	11.23)
55	4	MeOH	31	>300	$C_{17}H_{18}ClN_3O_4$	56.13	4.99	11.55
						(55.97	5.18	11.38)
56	8	EtOH	47	273—275	$C_{17}H_{19}N_3O_4 \cdot 1/2H_2O$	60.35	5.96	12.42
						(60.67	6.22	12.27)
57	2	EtOH	62	226—227	$C_{18}H_{21}N_3O_4$	62.97	6.16	12.23
						(62.95	6.29	12.03)
58	2	EtOH	84	>300	$C_{18}H_{20}N_2O_5$	62.78	5.85	8.14
						(62.62	6.00	8.06)
59	0.5	EtOH–$CHCl_3$	58	294—295	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91
						(65.09	5.91	8.84)
60	0.5	EtOH	68	>300	$C_{17}H_{18}N_2O_5$	61.81	5.49	8.48
						(61.75	5.47	8.49)

to the above factors.

The relationship between the hydrophobicities of the compounds and their biological activities will be reported in a separate paper.

Experimental

Melting points were determined on a Yanagimoto MP-1 micro melting point apparatus, and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi Perkin-Elmer R-20B (60 MHz) spectrometer using Me_4Si as an internal standard (δ value).

2,3-Difluoro-6-nitrophenol (2a)——A 10% KOH solution (70 ml) was added dropwise to a solution of **1a** (20.0 g, 0.113 mol) in DMSO (15 ml) at 18—20 °C. The mixture was stirred for 2 h, H_2O was added, and the whole was washed three times with $CHCl_3$ to remove unreacted starting materials. The aqueous layer was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated to dryness *in vacuo*.

Table II. *In vitro* Antibacterial Activities (Minimum Inhibitory Concentration, μg/ml)

Compd. No.	*S. aureus* 209 p	*E. coli* NIHJ	*Ps. aeruginosa* 2063	Compd. No.	*S. aureus* 209 p	*E. coli* NIHJ	*Ps. aeruginosa* 2063
17	0.19	<0.05	1.56	**40**	<0.05	<0.05	6.25
18	0.39	<0.05	0.78	**41**	<0.05	<0.05	0.39
19	0.39	<0.05	1.56	**42**	0.19	0.10	6.25
20	0.78	0.19	6.25	**43**	0.10	0.10	6.25
21	0.78	0.39	6.25	**44**	1.56	0.10	12.5
22	0.78	0.39	6.25	**45**	6.25	1.56	100
23	0.39	0.19	6.25	**46**	0.10	<0.05	6.25
24	0.39	0.10	6.25	**47**	0.39	<0.05	6.25
25	0.39	1.56	12.5	**48**	3.13	0.10	12.5
26	0.39	12.5	>100	**49**	0.39	0.10	6.25
27	1.56	0.39	50	**50**	1.56	<0.05	3.13
28	0.78	0.39	6.25	**51**	0.78	0.10	3.13
29	0.39	0.10	3.13	**52**	1.56	0.78	25
30	0.19	0.78	6.25	**53**	0.78	0.10	3.13
31	0.10	0.19	6.25	**54**	0.19	<0.05	0.78
32	0.10	0.19	6.25	**55**	>100	100	>100
33	0.19	<0.05	12.5	**56**	1.56	0.39	3.13
34	<0.05	0.19	6.25	**57**	3.13	0.78	25
35	0.39	0.19	6.25	**58**	0.19	0.19	6.25
36	0.39	0.19	6.25	**59**	0.39	0.78	6.25
37	1.56	0.78	25	**60**	0.39	0.19	6.25
38	0.10	0.39	1.56	Pipemidic acid	12.5	6.25	6.25
39	0.10	<0.05	1.56				

The residue was purified by silica-gel column chromatography using $CHCl_3$ as an eluent to give **2a** (5.8 g, 29%); mp 61 °C. *Anal.* Calcd for $C_6H_3F_2NO_3$: C, 41.15; H, 1.72; N, 7.99. Found: C, 40.97; H, 1.70; N, 8.14.

2-Acetonyloxy-3,4-difluoronitrobenzene (3a)——A mixture of **2a** (5.8 g, 0.033 mol), $ClCH_2COCH_3$ (5.0 g, 0.054 mol), K_2CO_3 (8.0 g, 0.058 mol) and KI (0.8 g) in acetone (100 ml) was heated under reflux for 4 h. Insoluble materials were removed by filtration and the filtrate was concentrated to dryness. The residue was mixed with $CHCl_3$ and H_2O. The $CHCl_3$ layer was separated, washed with H_2O, dried and concentrated to dryness. The oily residue was purified by silica-gel column chromatography using benzene as an eluent to yield a light yellow oil, **3a** (5.0 g, 65%). *Anal.* Calcd for $C_9H_7F_2NO_4$: C, 46.76; H, 3.05; N, 6.06. Found: C, 46.74; H, 3.12; N, 6.19.

Ethyl 9,10-Difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (6a)——A solution of **3a** (7.1 g, 0.031 mol) in EtOH (200 ml) was catalytically reduced in the presence of Raney Ni (14 ml) at atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated to dryness to give crude **4a** (5.1 g, 90%), which was used in the next reaction step without further purification.

A mixture of **4a** (4.8 g, 0.026 mol) and EMME (5.3 g, 0.025 mol) was heated at 140—145 °C for 1 h to give oily **5a**. PPE (35 g) was added to the crude **5a**, and the mixture was heated at the same temperature for an additional 1 h. After being cooled, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% K_2CO_3 and H_2O, then dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from EtOH to yield **6a** (5.1 g, 64% from **4a**); mp 261 °C. *Anal.* Calcd for $C_{15}H_{13}F_2NO_4$: C, 58.24; H, 4.24; N, 4.53. Found: C, 58.05; H, 4.30; N, 4.37.

9,10-Difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (7a)——A solution of the ester **6a** (4.0 g, 0.013 mol) in conc. HCl (10 ml)–AcOH (40 ml) was heated under reflux for 3 h, then cooled. The resulting precipitate was collected by filtration, washed with EtOH–Et_2O (1 : 4), and dried to afford **7a** (3.7 g, 94%); mp >300 °C. *Anal.* Calcd for $C_{13}H_9F_2NO_4$: C, 55.52; H, 3.23; N, 4.98. Found: C, 55.66; H, 3.01; N, 5.17.

2-(2-Bromoethoxy)-3,4-difluoronitrobenzene (8)——A mixture of **2a** (7.9 g, 0.045 mol), 1,2-dibromoethane (50.1 g, 0.27 mol) and K_2CO_3 (18.7 g, 0.13 mol) in DMF (80 ml) was heated at 80—100 °C for 2.5 h, then concentrated. The residue was mixed with AcOEt and H_2O. The AcOEt layer was separated, washed with H_2O, dried and concentrated to dryness. The residue was purified by silica-gel column chromatography using benzene as an eluent to give oily **9** (7.7 g, 61%). NMR ($CDCl_3$) δ: 3.75 (2H, t, J=7 Hz, CH_2Br), 4.62 (2H, t, J=7 Hz, OCH_2), 6.92—7.40, 7.65—7.93 (each 1H, m, 5-H and 6-H).

2-(2-Bromoethoxy)-3,4-difluoroaniline (9)——An aqueous solution (15 ml) of sodium hydrosulfite (6.4 g) was added dropwise to a solution of **8** (1.74 g, 0.0062 mol) in MeOH (30 ml). The reaction mixture was stirred at room temperature for 1 h, then concentrated. The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated to give **9** as a colorless oil, (0.44 g, 28%). NMR ($CDCl_3$) δ: 3.67 (2H, t, J=6 Hz, CH_2Br), 3.90 (2H, s, NH_2), 4.42 (2H, t, J=6 Hz, OCH_2), 6.30—6.90 (2H, m, 5-H and 6-H).

7,8-Difluoro-2,3-dihydro-4*H*-1,4-benzoxazine (10)——A mixture of **9** (1.82 g, 0.0072 mol) and K_2CO_3 (3.03 g, 0.022 mol) in DMF (10 ml) was heated at 80—100 °C for 1 h. After being cooled, the reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried and concentrated to dryness to give **10** (1.21 g, 97%); mp 48—54 °C. NMR ($CDCl_3$) δ: 3.39 (2H, t, J=5.5 Hz, $NHCH_2$), 3.70 (1H, br s, NH), 4.28 (2H, t, J=5.5 Hz, OCH_2), 6.17—6.80 (2H, m, 5-H and 6-H). *Anal.* Calcd for $C_8H_7F_2NO$: C, 56.14; H, 4.12; N, 8.18. Found: C, 56.13; H, 4.09; N, 8.32.

Ethyl 9,10-Difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (12)——A mixture of **10** (1.1 g, 0.0065 mol) and EMME (1.37 g, 0.0065 mol) was heated at 130—135 °C for 2 h. PPE (20 g) was added to the viscous oil and the mixture was heated at 140—145 °C for 1.5 h, then poured onto ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated to dryness. The residue was recrystallized from AcOEt to give colorless needles, **12** (1.3 g, 68%), mp 265—266 °C. NMR (CF_3COOH) δ: 1.58 (3H, t, J=7.5 Hz, CH_3), 4.76 (2H, q, J=7.5 Hz, CH_2), 4.96 (4H, br s, CH_2CH_2), 8.17 (1H, q, 8-H), 9.35 (1H, s, 5-H). *Anal.* Calcd for $C_{14}H_{11}F_2NO_4$: C, 56.95; H, 3.76; N, 4.74. Found: C, 57.02; H, 3.81; N, 4.59.

9,10-Difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (13)——A solution of the ester **12** (1.15 g, 0.0039 mol) in conc. HCl–AcOH (1 : 4, 12 ml) was heated at 100—110 °C for 4 h. After the mixture had cooled, the resulting precipitate was collected by filtration, washed successively with H_2O and MeOH–$CHCl_3$, and then dried to give **13** (0.78 g, 75%), mp >300 °C. NMR (CF_3COOH) δ: 5.0 (4H, br s, CH_2CH_2), 8.17 (1H, q, 8-H), 9.45 (1H, s, 5-H). *Anal.* Calcd for $C_{12}H_7F_2NO_4$: C, 53.94; H, 2.64; N, 5.24. Found: C, 53.99; H, 2.71; N, 5.15.

General Procedure for the Synthesis of the Target Compounds (17—60)——A mixture of an intermediate (**7a—c**, **13**, **15**) and 2—4 eq of the amine in DMSO was heated at 100—140 °C for 1—5 h with stirring. The solvent was evaporated off *in vacuo* and the residue was washed with H_2O and recrystallized from suitable solvent to give **17—60**, as listed in Table I.

In the case of the reaction of **7c** with piperazine, the fluorine atom at the 9-position was selectively substituted by the amino group to give an unexpected compound (**55**).

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