Imidazo- and Triazoloquinolones as Antibacterial Agents. Synthesis and Structure–Activity Relationships[1)]

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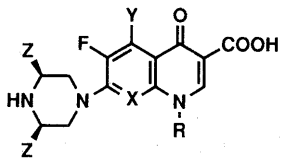
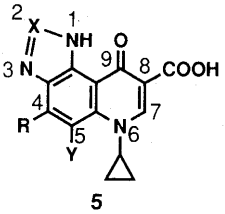
4,5-Disubstituted 6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-imidazo- (30—32) and triazolo[4,5-*f*]quinoline-8-carboxylic acids (33—35) were synthesized starting from 5,6-diaminoquinolones 25. The imidazoquinolones 30—32 were equal or superior to the corresponding triazoloquinolone analogues 33—35 in *in vitro* antibacterial activity. As for the C-5 substituents, a fluorine atom was the most favorable of the three groups, H, F, and Cl. Among the compounds prepared, 4-(cyclic amino)-5-fluoro-imidazoquinolones 31a-d showed potent and well-balanced antibacterial activity against both gram-positive and gram-negative bacteria. Structure–activity relationships for the C-4 substituents (cyclic amino groups) were also examined in detail.

Key words quinolone; 1*H*-imidazo[4,5-*f*]quinoline; 1*H*-triazolo[4,5-*f*]quinoline; synthesis; antibacterial activity; structure–activity relationship

Quinolone antibacterial agents, bacterial topoisomerase (DNA gyrase) inhibitors, occupy at present an important position in chemotherapy against bacterial infections. The newer quinolones, represented by ciprofloxacin (**1**)[2)] and sparfloxacin (**2**),[3,4)] mostly contain a fluorine atom at C-6 and a cyclic amino group at C-7 of 1-substituted 4-oxoquinoline-3-carboxylic acid. It is generally believed that the combination of C-6 fluorine and C-7 cyclic amino group affords potent antibacterial activity with an excellent pharmacokinetic properties. Much effort has been devoted to the study of 6-fluoroquinolones having a cyclic amino group at C-7 during the last decade. An additional amino group at C-5, as in sparfloxacin (**2**) also contributes to broadening the antibacterial spectrum to include Mycobacteria, Mycoplasma and Chlamydia, which are resistant to most of the current quinolones. Azole-fused quinolones, for example, thiazoloquinolones **3**,[5)] imidazoquinolones **4**,[6)] and pyrazoloquinolones **5**[7)] were reported by several research groups, before 6-fluoroquinolones had been developed. These azoloquinolones had neither fluorine nor a C-7 cyclic amino group, but some of them were noted at that time to be significantly potent in *in vitro*.



norfloxacin (**1**) : X = CH, Y = Z = H, R = Et
enoxacin (**2**) : X = N, Y = Z = H, R = Et
ciprofloxacin (**3**) : X = CH, Y = Z = H, R = *c*-C_3H_5
sparfloxacin (**4**) : X = CF, Y = NH_2, Z = Me, R = *c*-C_3H_5



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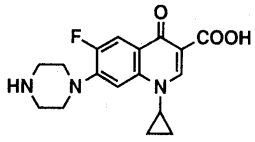
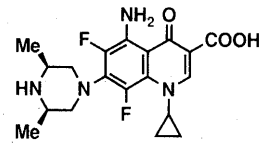
X = CH, N
Y = H, F, Cl
R = cyclic amine

In our search for a replacement for the C-6 fluorine, we designed novel quinolone molecules, *i.e.*, 4-substituted 6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-imidazo- (A) and 1*H*-triazolo[4,5-*f*]quinoline-8-carboxylic acids (B). Compounds A and B are considered to be hybrid molecules of sparfloxacin (**2**) with azole-fused quinolones such as **4** and **5**, containing a nitrogen atom (NH) (involved in the azole ring) and a cyclic amino group (R) at the positions corresponding to C-5 and C-7, respectively, of the conventional quinolone ring. This paper reports the synthesis and structure-antibacterial activity relationships of a novel series of azole-fused quinolones A and B.

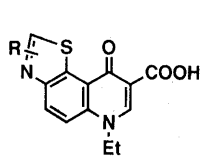
Chemistry On the basis of *retro*-synthetic consideration for compounds A and B, we planned to prepare firstly the 5,6-diaminoquinolone derivatives **25** as key inter-



ciprofloxacin (**1**)



sparfloxacin (**2**)



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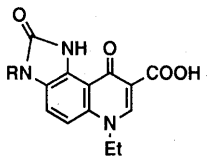

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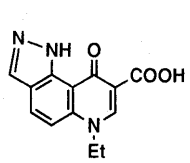

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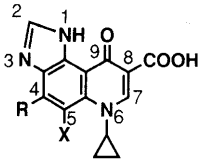
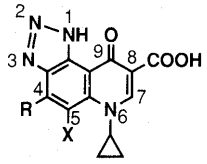


A



B

X = H, F, Cl
R = cyclic amino group

Chart 1

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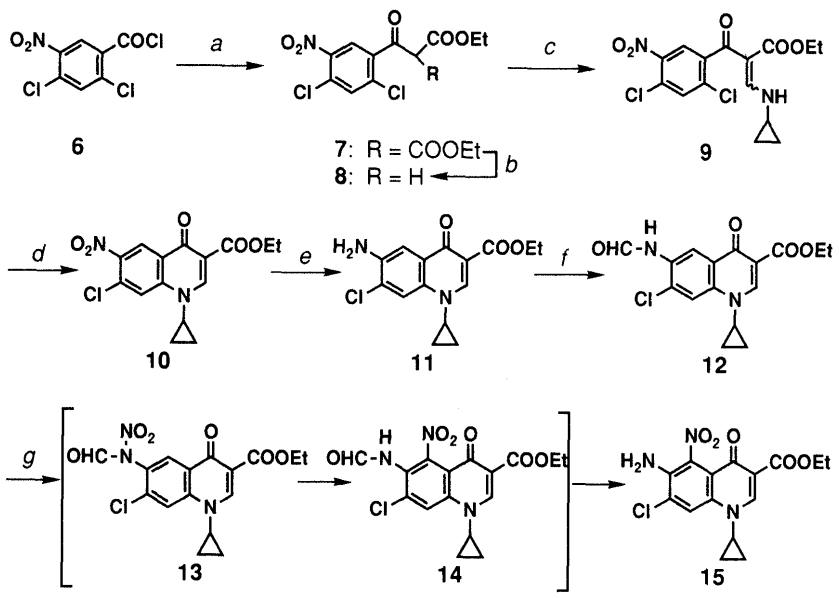

Reagents: *a* $Mg(OEt)_2$, $CH_2(COOEt)_2$; *b* *p*-TsOH; *c* 1, $HC(OEt)_3$, Ac_2O; 2, *c*-$C_3H_5NH_2$; *d* *t*-BuOK; *e* $SnCl_2 \cdot 2H_2O$, conc. HCl; *f* HCOOH, Ac_2O; *g* HNO_3, Ac_2O, AcOH, $(H_2N)_2CO$.

Chart 2

mediates, *via* an appropriately functionalized quinolone **15** or **24**.

The requisite compound **15** was prepared principally according to Grohe's method.[2] The treatment of 2,4-dichloro-5-nitrobenzoyl chloride (**6**) with diethyl malonate gave diethyl 2,4-dichloro-5-nitrobenzoyl malonate (**7**) as an oil (Chart 2). Under conditions employed for the proton nuclear magnetic resonance (^{1}H-NMR) measurement (in $CDCl_3$), the product **7** was found to exist as an equilibrium mixture with its enolic isomer in a 3:7 ratio, based on the integrated intensity of the C-6 proton signals. Reflux of **7** with a catalytic amount of *p*-toluenesulfonic acid in water gave the *β*-keto ester **8**, which also existed as an equilibrium mixture with its enolic isomer. The reaction of **8** with triethyl orthoformate in acetic anhydride, followed by treatment with cyclopropylamine, afforded the enamine **9**[8] in good yield. Cyclization of **9** to the quinolone **10**[8] by the conventional method using potassium *tert*-butoxide as a base smoothly proceeded at low temperature (even under ice-cooling), probably owing to the leaving chlorine group being activated by both *para*-nitro and *ortho*-carbonyl substituents. Reduction of the C-6 nitro group of **10** with stannous dichloride in hydrochloric acid, followed by *N*-formylation of the C-6 amino group of the resulting quinolone **11**,[8] gave the formamide **12**. The nitration of **12** was carried out under mild conditions using nitric acid in a mixture of acetic acid and acetic anhydride at 0 °C to give 6-amino-5-nitroquinolone **15** as a sole product. This nitration would occur initially at the formylated nitrogen to give the intermediate **13**, and the *N*-nitro group would subsequently migrate to the neighboring C-5 position with concurrent hydrolysis of the formyl group of 6-formylamino-5-nitroquinolone **14**, thus generating in **15**.[9,10] The C-6 amino group of **15** is acidic; in fact, **15** dissolves in aqueous sodium bicarbonate. Hence, the formyl moiety of **14** is so labile that it cleaves easily to produce **15** during the reaction process and/or the work-up.

The other intermediates, 5-benzylamino-6-nitroquinolone derivatives **24a, b**, were prepared according to the route given in Chart 3. 2,4,5,6-Tetrafluoroisophthalic acid (**16a**) was heated in dimethyl sulfoxide (DMSO) to give the benzoic acid derivative **17a** in a low yield. Addition of dioxane to this reaction mixture caused an improvement in the yield of **17a** to 58%. In the decarboxylation of 5-chloro-2,4,6-trifluoroisophthalic acid (**16b**), triethylamine served as an accelerator, giving a 74% yield of **17b**. The carboxylic acids **17a, b** were converted to the acyl chlorides **18a, b**, which were successively converted *via* **19a, b** to the enamines **20a, b**, respectively, in a similar manner to that applied for the conversion of **6** to **9**. Cyclization of **20** is expected to proceed through nucleophilic attack of the enamino nitrogen on C-2 (giving **21**) or C-6 (giving **22**). On treatment of **20a, b** with potassium *tert*-butoxide under ice-cooling, the reaction proceeded regioselectively at C-2 to give the required quinolones **21a, b**, respectively, in more than 90% yield. When carried out with triethylamine as a base in paraffin oil at 180—190 °C, the cyclization of **20a** afforded the product **21a** in 90% yield, accompanied with **22a** in 10% yield. The structures of the quinolones **21a, b** and **22a** were assigned on the basis of ^{1}H-NMR analysis. Thus, the C-6 proton of **21a** was observed at δ 6.90 as a triple doublet due to coupling to the *ortho* C-5 and C-7 fluorines (ddd, $J_{6H,5F} = 10.0$, $J_{6H,7F} = 10.0$) and the *meta* C-8 fluorine ($J_{6H,8F} = 6.0$ Hz); the observed coupling pattern permitted the assignment of the positions of fluorines, and hence proved the structure to be **21a**. This was also the case with the 8-chloro-substituted **21b**, whose C-6 proton appeared at δ 6.92 with two *ortho*-coupling constants of 11.0 ($J_{6H,5F}$) and 9.0 Hz ($J_{6H,7F}$). The C-8 proton (δ 7.50) of the regioisomer **22a** showed the *ortho*- ($J_{8H,7F} = 12.0$ Hz), *meta*- ($J_{8H,6F} = 6.0$ Hz), and *para*-coupling constants

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Table 1. Intermediates of Cyclic Amine-Substituted Imidazoquinolones and Triazoloquinolones

Compound	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)				
			C	H	Cl	F	N
8	65—67	$C_{11}H_9Cl_2NO_5$	43.16	2.96	23.16		4.58
	(Et_2O–*n*-Hex)		(43.24	2.86	23.04		4.61)
9	118—119[a]	$C_{15}H_{14}Cl_2N_2O_5$	48.28	3.78	19.00		7.51
	(EtOH)		(48.28	4.00	18.76		7.53)
10	258—260[b]	$C_{15}H_{13}ClN_2O_5$	53.50	3.89	10.53		8.32
	($CHCl_3$)		(53.39	3.78	10.67		8.20)
11	>300	$C_{15}H_{15}ClN_2O_3$	58.73	4.93	11.56		9.13
	(DMF–EtOH)		(58.64	5.06	11.35		9.12)
12	268—269	$C_{16}H_{15}ClN_2O_4$	57.41	4.52	10.59		8.37
	(CH_2Cl_2–CH_3CN)		(57.19	4.43	10.63		8.56)
17a	100—101	$C_7H_2F_4O_2$	43.32	1.04		39.15	
	(AcOEt–*n*-Hex)		(43.03	1.06		38.98)	
20a	107—108	$C_{15}H_{13}F_4NO_3$	54.39	3.96		22.94	4.23
	(iso-Pr_2O)		(54.50	3.98		22.70	4.23)
20b	150—151	$C_{15}H_{13}ClF_3NO_3$	51.81	3.77	10.20	16.39	4.03
	(iso-Pr_2O)		(51.84	3.82	10.07	16.27	4.07)
21a	211—212	$C_{15}H_{12}F_3NO_3$	57.88	3.89		18.31	4.50
	(CH_3CN)		(57.69	3.71		18.52	4.38)
21b	218—220	$C_{15}H_{12}ClF_2NO_3$	54.98	3.69	10.82	11.59	4.27
	($CHCl_3$–EtOH)		(54.84	3.70	10.93	11.89	4.31)
22a	220—221	$C_{15}H_{12}F_3NO_3$	57.88	3.89		18.31	4.50
	(CH_3CN–iso-Pr_2O)		(58.04	3.65		18.15	4.57)
23a	165—166	$C_{22}H_{20}F_2N_2O_3$	66.32	4.06		9.54	7.04
	(AcOEt)		(66.23	4.83		9.79	6.76)
23b	124—125	$C_{22}H_{20}ClFN_2O_3$	63.69	4.86	8.55	4.58	6.75
	(CH_2Cl_2–AcOEt)		(63.81	4.97	8.66	4.56	6.54)
24a	192—194 dec.	$C_{22}H_{19}F_2N_3O_5$	59.59	4.32		8.57	9.48
	($CHCl_3$–EtOH)		(59.36	4.48		8.64	9.55)
24b	215—217	$C_{22}H_{19}ClFN_3O_5$	57.46	4.16	7.71	4.13	9.14
	($CHCl_3$–EtOH)		(57.65	4.22	7.81	4.22	9.16)
26a	>300	$C_{19}H_{14}ClN_3O_3$	57.93	4.25	10.69		12.67
	($CHCl_3$)		(58.18	4.36	10.65		12.40)
26b	293—294	$C_{19}H_{13}F_2N_3O_3$	57.66	3.93		11.40	12.61
	(DMF–EtOH)		(57.81	4.03		11.18	12.49)
26c	280—282	$C_{19}H_{13}ClFN_3O_3$	54.95	3.75	10.14	5.43	12.01
	($CHCl_3$–EtOH)		(54.67	3.75	10.34	5.26	11.75)
27a	275—277	$C_{15}H_{13}ClN_4O_3$	54.14	3.94	10.65		16.84
	($CHCl_3$–EtOH)		(53.70	4.01	10.03		16.71)
27b	253—256 dec.	$C_{15}H_{12}F_2N_4O_3$	53.90	3.62		11.37	16.76
	($CHCl_3$–EtOH)		(54.14	3.65		11.29	16.64)
27c	250—252 dec.	$C_{15}H_{12}ClFN_4O_3$	51.37	3.45	10.11	5.42	15.97
	($CHCl_3$–EtOH)		(51.59	3.54	10.05	5.38	15.92)
28a	>300	$C_{14}H_{10}ClN_3O_3$	55.37	3.32	11.67		13.84
	(DMF–EtOH)		(55.39	3.52	11.57		13.63)
28b	>300	$C_{14}H_9F_2N_3O_3$	55.09	2.97		12.45	13.77
	(DMF–EtOH)		(55.10	2.97		12.62	13.94)
28c	>300	$C_{14}H_9ClFN_3O_3$	52.27	2.82	11.02	5.91	13.06
	(DMF–EtOH)		(52.25	3.03	11.00	5.76	12.66)
29a	>300	$C_{13}H_9ClN_4O_3$	51.25	2.98	11.64		18.39
	(DMF–EtOH)		(51.50	3.04	11.40		18.41)
29b	>300 dec.	$C_{13}H_8F_2N_4O_3$	50.99	2.63		12.41	18.30
	(DMF–EtOH)		(51.39	2.70		12.07	18.14)
29c	294—297 dec.	$C_{13}H_8ClFN_4O_3$	48.39	2.50	10.99	5.89	17.36
	(DMF–EtOH)		(48.47	2.56	10.78	5.71	17.21)

a) Ref. 8 mp 123—125 °C. *b*) Ref. 8 mp 255—257 °C.

($J_{8H,5F}=2.0$ Hz), which fully supported the assigned structure of **22a**.

For the regioselective introduction of an amine at C-5 of **21**, we employed the procedure that had been developed in our previous study[11] for the synthesis of sparfloxacin (**2**). The treatment of **21a, b** with benzylamine in a refluxing aprotic nonpolar solvent such as trichloroethylene gave 5-benzylaminoquinolones **23a, b**, as expected. The structures of the products were confirmed on the basis, in particular, of the fluorine-19 nuclear magnetic resonance (^{19}F-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **23a** and **23b**, respectively. The nitration of **23a, b** under mild conditions occurred at C-6 to give 6-nitroquinolones **24a, b**.

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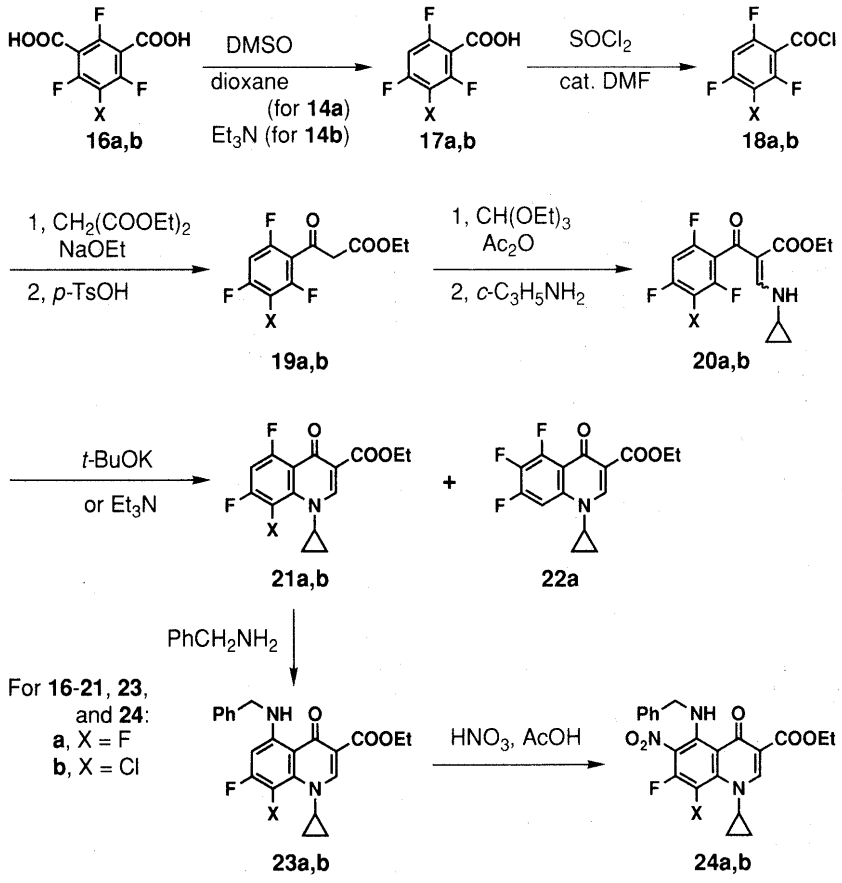

Chart 3

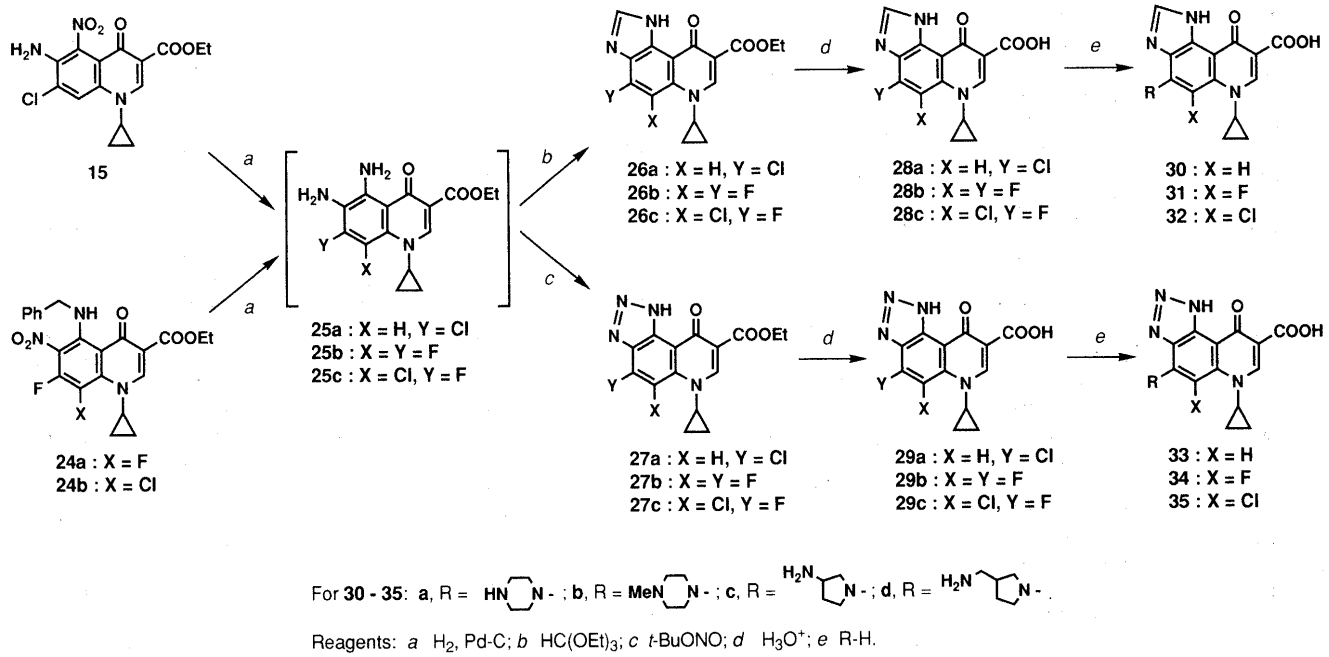

Chart 4

Hydrogenation of the quinolines **15** and **24a, b** gave the corresponding 5,6-diamino derivatives **25a, b, c** (Chart 4). These were unstable and hence, without isolation, were used immediately for the azole ring construction. Thus, successive treatment of **25** with triethyl orthoformate and *tert*-butyl nitrite afforded 1*H*-imidazo[4,5-*f*]quinolone **26** and 1*H*-triazolo[4,5-*f*]quinolone **27**, respectively. The 1*H*-imidazo and 1*H*-triazolo structures are given in Chart 4, although 3*H*-imidazo- and 3*H*-triazolo[4,5-*f*]quinolone structures are also possible as other tautomers of **26** and **27**, respectively. Acid hydrolysis of **26a, b, c** and **27a, b, c** afforded the corresponding carboxylic acids **28a, b, c** and **29a, b, c** in high yields.

The nucleophilic displacement reaction of **28a, b, c** and

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Table 2. Physical Data for the 4,5-Disubstituted Imidazoquinolones and Triazoloquinolones

Compound[a]	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
				C	H	Cl	F	N
30a	275—280 dec. (HCl–EtOH)	62	$C_{18}H_{19}N_5O_3 \cdot HCl \cdot H_2O$	53.01 (52.77	5.44 5.55	8.69 8.47		17.17 17.14)
30b	>300 dec. (HCl)	15	$C_{19}H_{21}N_5O_3 \cdot HCl \cdot 3/2H_2O$	52.96 (53.25	5.85 5.81	8.23 7.98		16.25 16.26)
30c	>300 dec. (NH_4OH)	74	$C_{18}H_{19}N_5O_3$	61.18 (61.05	5.42 5.33			19.82 19.66)
30d	293—297 dec. (HCl–EtOH)	31	$C_{19}H_{21}N_5O_3 \cdot 2HCl \cdot 5/2H_2O$	47.02 (47.21	5.81 5.52	14.61 14.43		14.43 14.49)
31a	275—278 dec. (NH_4OH)	65	$C_{18}H_{18}FN_5O_3 \cdot 9/4H_2O$	52.49 (52.55	5.51 5.21		4.61 4.36	17.00 17.11)
31b	279—283 dec. (NH_4OH)	64	$C_{19}H_{20}FN_5O_3 \cdot 3/4H_2O$	57.21 (57.11	5.43 5.14		4.76 4.51	17.56 17.47)
31c	276—278 dec. (NaOH/AcOH)	70	$C_{18}H_{18}FN_5O_3 \cdot 1/2H_2O$	56.84 (57.06	5.03 5.03		4.99 4.92	18.41 18.39)
31d	240—242 dec. (NaOH/AcOH)	87	$C_{19}H_{20}FN_5O_3 \cdot 1/4H_2O$	58.53 (58.34	5.30 5.30		4.87 4.77	17.96 17.79)
32a	>300 dec. (EtOH)	28	$C_{18}H_{18}ClN_5O_3 \cdot HCl$	50.96 (50.95	4.51 4.59	16.71 16.52		16.51 16.16)
32b	260—262 dec. ($CHCl_3$–EtOH)	43	$C_{19}H_{20}ClN_5O_3$	56.79 (56.71	5.02 5.20	8.82 8.67		17.43 17.15)
32c	215—220 dec. (NH_4OH)	28	$C_{18}H_{18}ClN_5O_3$	55.75 (55.70	4.68 4.60	9.14 8.89		18.06 17.88)
33b	285—286 dec. (NH_4OH)	38	$C_{18}H_{20}N_6O_3$	58.69 (58.50	5.47 5.46			22.81 22.94)
34a	>300 dec. ($CHCl_3$–EtOH)	35	$C_{17}H_{17}FN_6O_3 \cdot 1/2H_2O$	53.54 (53.86	4.76 4.69		4.98 4.88	22.04 22.07)
34b	281—284 dec. (AcOH/NH_4OH)	44	$C_{18}H_{19}FN_6O_3 \cdot HCl \cdot H_2O$	49.04 (48.96	5.03 5.07	8.04 7.86	4.31 4.34	19.06 19.07)
34c	>300 dec. (AcOH/NH_4OH)	86	$C_{17}H_{17}FN_6O_3 \cdot 1/2H_2O$	53.54 (53.21	4.76 5.02		4.98 4.94	22.04 22.03)
34d	282–284 dec. (AcOH/NH_4OH)	80	$C_{18}H_{19}FN_6O_3 \cdot 1/4H_2O$	55.31 (55.08	5.03 5.43		4.86 4.72	21.50 21.78)
35b	270—275 dec. ($CHCl_3$–EtOH)	61	$C_{18}H_{19}ClN_6O_3$	53.67 (53.81	4.75 4.79	8.80 8.53		20.86 20.64)
35c	>300 dec. (AcOH/NH_4OH)	77	$C_{17}H_{17}ClN_6O_3 \cdot 1/2H_2O$	51.33 (51.54	4.56 4.78	8.91 8.90		21.13 21.43)

a) Compounds **31c, d**, **34b—d**, and **35c** were purified by reprecipitation, by treatment with the acid and subsequently with the base indicated or *vice versa*.

29a, b, c with an appropriate cyclic amine gave the target compounds **30—35**. The cyclic amines used here include piperazine, 1-methylpiperazine, 3-aminopyrrolidine, and 3-aminomethylpyrrolidine, which are thought to have potential for enhancing antibacterial activity, and hence are frequently used as a C-7 appendage for antibacterial quinolons. The displacement reaction by refluxing in pyridine proceeded regioselectively at C-4, when the leaving group at C-4 was fluorine (**28b, c** and **29b, c**). In the case of C-4 chlorine (**28a** and **29a**), however, the reaction required dimethyl sulfoxide instead as a reaction medium, at higher temperature.

Antibacterial Activity The *in vitro* antibacterial activity of compounds **30—35** was tested against one gram-positive (*Staphylococcus aureus* 209P JC-1) and two gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* 12) as representatives. The results are summarized in Table 3, which includes data for ciprofloxacin (**1**) and sparfloxacin (**2**) for comparison.

In the structure–activity relationships of imidazoquinolones **30a—d**, the pyrrolidinyl series (**30c, d**) is more active than the piperazinyl series (**30a, b**) against gram-positive *S. aureus*, whereas in terms of activity against gram-negative bacteria, the latter (**30a, b**) is superior to the former (**30c, d**). The most active members are the 4-methylpiperazinyl derivative **30b** against *E. coli* and the 3-aminomethylpyrrolidinyl derivative **30d** against *S. aureus*. The piperazinyl (**30a**), 4-methylpiperazinyl (**30b**), and 3-aminopyrrolidinyl (**30c**) derivatives show essentially the same antipseudomonal activity and the 3-aminomethylpyrrolidinyl derivative **30d** is the least active. In general, a similar tendency is observed with 5-fluoroimidazoquinolones **31a—d** and 5-fluorotriazoloquinolones **34a—d**.

It is currently recognized that the introduction of a halogen (F or Cl) into C-8 of conventional bicyclic quinolone antibacterial molecules causes an increase in *in vitro* activity.[12] Accordingly, a fluoro or chloro group was introduced into the C-5 positions of the tricyclic quinolones **30a—d**, which positions correspond to C-8 of the conventional bicyclic quinolones. Comparison of the imidazoquinolones **30** (5-H), **31** (5-F), and **32** (5-Cl) shows that the antibacterial activity against *S. aureus* decreases in the order Cl (**32a, b**) > F (**31a, b**) > H (**30a, b**), and

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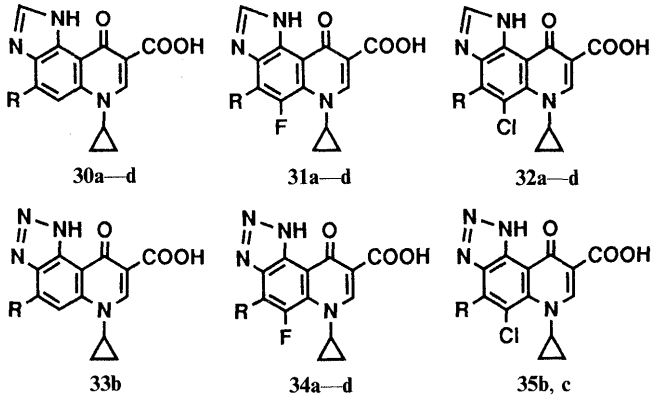
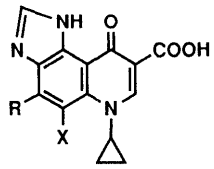
Table 3. *In Vitro* Antibacterial Activity of 4,5-Disubstituted Imidazo- and Triazoloquinolones

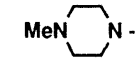
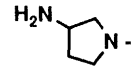
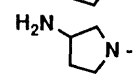


Compd.	R	Minimum inhibitory conc.[a] (μg/ml)		
		S. aureus 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* 12
30a		0.39	0.2	0.39
30b		0.78	0.05	0.39
30c		0.2	0.39	0.39
30d		0.1	6.25	12.5
31a		0.2	0.05	0.39
31b		0.2	0.05	0.2
31c		0.05	0.025	0.2
31d		0.025	0.1	0.78
32a		0.1	0.05	0.78
32b		0.1	0.025	0.78
32c		0.025	0.025	0.2
33b		0.78	0.05	0.39
34a		0.78	0.1	1.56
34b		0.39	0.05	0.39
34c		0.39	0.1	0.78
34d		0.2	0.78	12.5
35b		0.2	0.05	1.56
35c		0.2	0.2	0.78
1	Ciprofloxacin	0.1	0.0063	0.1
2	Sparfloxacin	0.05	0.0125	0.39

a) See Experimental.

Table 4. *In Vivo* Efficacy on Systemic Infections and Water Solubility of Selected Compounds



Compd.	X	R	*P. aeruginosa* 12			Water solubility at pH 7.20[c]
			MIC[a]	ED_{50} (*p.o.*)[b]	ED_{50} (i.v.)[b]	
31b	F		0.2	8.42	0.982	136.5
31c	F		0.2	36.0	0.443	19.9
32c	Cl		0.2	>25	0.292	6.2
1		Ciprofloxacin	0.1	2.78	0.366	97
2		Sparfloxacin	0.39	1.57	0.962	118

a) Minimum inhibitory concentration (μg/ml). *b*) Shown in milligrams per kilogram. See Experimental. *c*) Obtained by measuring the UV absorption of a saturated solution of the compound in phosphate buffer (pH 7.20) at 25 °C. Data are shown in micrograms per milliliter.

the activity against *E. coli* decreases in the order Cl (**32a**,**b**) ≧ F (**31a**, **b**) ≧ H (**30a**, **b**). The C-5 chlorine substitution thus tended to enhance the activity against *S. aureus* and *E. coli*. The activity against *P. aeruginosa*, however, was slightly reduced by the chlorine substitution, with the order F (**31a**, **b**) ≧ H (**30a**, **b**) > Cl (**32a**, **b**). Among the three C-5 substituents, H, F, and Cl, the C-5 fluorine is the most effective in providing a potent and well-balanced antibacterial activity against the three strains of bacteria tested. The structure–activity relationships observed in the imidazoquinolones **30**, **31**, and **32** thus also hold true for the triazoloquinolones **33**, **34**, and **35**.

The imidazoquinolones **30**—**32** are, in general, more active than the corresponding triazoloquinolones **33**—**35**. Among the 4-methylpiperazinyl series **b**, the imidazoquinolones **31b** and **32b** are 2-fold more active than the triazoloquinolones **34b** and **35b**, respectively, with the exception of **30b**, whose activity is equipotent to that of **33b**. In a comparison of other pairs with a common C-4 substituent (**31a** *vs.* **34a**, **31c** *vs.* **34c**, **31d** *vs.* **34d**, and **32c** *vs.* **35c**), the imidazoquinolone compounds **31a**, **c**, **d** and **32c** are 2- to 16-fold more active than the triazoloquinolone counterparts.

Among azole-fused quinolones reported thus far, tioxacin[5] (6-ethyl-2,3,6,9-tetrahydro-3-methyl-2,9- dioxothiazolo[5,4-*f*]quinoline-8-carboxylic acid), having the general structure **3**, was reported to show potent *in vitro* antibacterial activity. Most compounds synthesized in the present study seem to be more active than tioxacin against *S. aureus* and *P. aeruginosa*; the minimum inhibitory concentrations (MICs)[5b] reported are 3.13, <0.2, and 50 μg/ml for *S. aureus*, *E. coli*, and *P. aeruginosa*, respectively, although the strains of the bacteria tested were not described in the literature. The enhanced activity of **30a** and **30b** without a C-5 substituent would be, to some extent, owing to the cyclic amino groups introduced

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at C-4, besides the contribution of the N-6 cyclopropyl group.

Compounds **31b**, **31c**, and **32c** with the highest *in vitro* activity *versus P. aeruginosa* were selected for testing of their efficacy on systemic infection due to *P. aeruginosa* 12 in mice. The results are listed in Table 4, which includes, for reference, data for ciprofloxacin (**1**) and sparfloxacin (**2**); *in vivo* efficacy is expressed as a median effective dose (ED_{50}, mg/kg). When administered intravenously, the 4-methylpiperazinyl derivative **31b** exhibited essentially the same efficacy as sparfloxacin (**2**). The 3-aminopyrrolidinyl derivatives **31c** and **32c** were comparable to ciprofloxacin (**1**) and superior to sparfloxacin (**2**) in *in vivo* efficacy. Thus, their efficacy on the pseudomonal infection well reflects their *in vitro* activity. The oral efficacy of **31b**, however, is less than one-ninth as potent as its intravenous efficacy. The 3-aminopyrrolidinyl derivatives **31c** and **32c**, when orally administered, displayed a remarkable decrease in efficacy as compared to their intravenous efficacy. The greatly reduced efficacy with oral administration, despite good activity in *in vitro*, may reflect poor absorption from the intestinal tract, probably owing to the low solubility of compounds **31b**, **31c**, and **32c**.

In summary, the annelation of an imidazole ring at C-5/C-6 of the conventional quinolones was shown to cause an *in vitro* activity enhancement comparable to the case of the introduction of an amino group and a fluorine atom into C-5 and C-6, respectively, as in sparfloxacin (**2**). The imidazoquinolones **31b**, **31c**, and **32c** exhibited excellent intravenous efficacy, as anticipated from their *in vitro* activities. The *in vitro* activities of the imidazoquinolones, however, were not reflected in their oral protective efficacy against pseudomonal infection in mice. Further modification of this series of imidazoquinolones will be needed for enhancement of the *in vivo* oral efficacy.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 or Perkin Elmer 1600 Series FTIR spectrophotometer. ^{1}H-NMR spectra were taken at 80 MHz on a Varian FT-80A spectrometer unless otherwise indicated, or at 200 MHz on a Varian Gemini-200 spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were taken at 75 MHz on a Varian XL-300 spectrometer; chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. ^{19}F-NMR spectra were measured at 282 MHz with a Varian XL-300 spectrometer; chemical shifts are expressed in ppm (δ) with hexafluorobenzene ($\delta = -162.9$) as an internal standard. Mass spectra were obtained on a JEOL JMS D-300 or Hitachi M-80B spectrometer. The spectral data for all compounds were consistent with the assigned structures. All compounds which were stable solids were analyzed for C, H, Cl, F, and N.

2,4,5,6-Tetrafluoroisophthalic acid (**16a**), piperazine, and 1-methylpiperazine were purchased from commercial suppliers. 3-Aminopyrrolidine was prepared from the corresponding 1-benzyl derivative[13] by hydrogenation on 5% Pd–C and used without further purification. 3-Aminomethylpyrrolidine was prepared by reduction of the nitrile moiety of 1-benzyl-3-cyanopyrrolidine[14] with Raney Ni, followed by deprotection of the benzyl group with 5% Pd–C.

Diethyl 2,4-Dichloro-5-nitrobenzoylmalonate (7) and Ethyl 2,4-Dichloro-5-nitrobenzoylacetate (8) A mixture of Mg (10.0 g, 0.412 mol) in CCl_4 (2.0 ml) and EtOH (6.0 ml) was heated at 50 °C until hydrogen evolution ceased. To this mixture was added a solution of diethyl malonate (63 ml, 66.4 g, 0.415 mol) in a mixture of EtOH (40 ml), toluene (150 ml), and tetrahydrofuran (THF) (50 ml). The resulting mixture was heated at 60 °C for 30 min and cooled. A solution of 2,4-dichloro-5-nitrobenzoyl chloride[15] (**6**, 100.0 g, 0.393 mol) in THF (90 ml) was added during a 50-min period under ice-cooling. The reaction mixture was kept at 20 °C for 1 h, acidified with 1 N HCl (412 ml), and extracted with toluene (200 ml). The organic layer was washed with water (containing a small amount of $NaHCO_3$), dried over Na_2SO_4, and concentrated *in vacuo* to give **7** as an oil. IR (neat) cm^{-1}: 1720, 1610. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.5 (6H, m, $2 \times CH_2C\underline{H}_3$), 3.9—4.5 (4H, m, $2 \times C\underline{H}_2CH_3$), 7.63 (1H, s, 3-H), 7.94 and 8.44 (each 0.3H, 0.7H, s, 6-H). MS *m/z*: 342 ($M^+ - Cl$).

A mixture of the resultant oil **7** and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) (0.50 g, 2.6 mmol) in water (600 ml) was refluxed for 2 h, then cooled, and extracted with CH_2Cl_2. The organic extract was washed twice with water (containing a small amount of $NaHCO_3$), dried over Na_2SO_4, and concentrated *in vacuo*. After addition of *n*-hexane, the resulting solid was collected by filtration, washed with *n*-hexane, and dried to give 77.9 g (65% from **6**) of **8**. IR (KBr) cm^{-1}: 1640, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.25 and 1.35 (each 0.6×3H, 0.4×3H, t, $J = 7.0$ Hz, $CH_2C\underline{H}_3$), 4.02 (0.4×2H, s, CH_2COO), 4.20 and 4.30 (each 0.6×2H, 0.4×2H, q, $J = 7.0$ Hz, $C\underline{H}_2CH_3$), 5.66 (0.6H, s, Ar-C=CH–COO), 7.66 (1H, s, 3-H), 8.20 and 8.22 (each 0.4H, 0.6H, s, 6-H), 12.5 (0.6H, br s, HO-C=C–COO). MS *m/z*: 305 (M^+), 270, 260.

Ethyl 3-Cyclopropylamino-2-(2,4-dichloro-5-nitrobenzoyl)acrylate (9) A mixture of **8** (9.60 g, 0.0314 mol), triethyl orthoformate (6.95 g, 0.0470 mol), and Ac_2O (7.99 g, 0.0784 mol) was heated at 130—140 °C for 1 h, during which period the resulting AcOEt was distilled off under atmospheric pressure. After concentration *in vacuo*, the residue was diluted with EtOH (40 ml). To this mixture was added a solution of cyclopropylamine (1.86 g, 0.0326 mol) in EtOH (10 ml) under ice-cooling. The resulting mixture was stirred at room temperature for 1 h. The resulting solid was collected by filtration, washed with iso-Pr_2O, and dried to give 9.00 g (77%) of 9.[8] IR (KBr) cm^{-1}: 1700, 1635. ^{1}H-NMR ($CDCl_3$) δ: 0.75—1.1 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.05 (3H, t, $J = 7.0$ Hz, $CH_2C\underline{H}_3$), 2.8—3.2 (1H, m, cyclopropyl CH), 4.02 (2H, q, $J = 7.0$ Hz, $C\underline{H}_2CH_3$), 7.53 (1H, s, aromatic 3-H), 7.75 (1H, s, aromatic 6-H), 8.22 and 8.40 (both 0.5H, d, $J = 6.0$ Hz, C=CH–N), 11.0 and 11.1 (both 0.5H, br d, NH). MS *m/z*: 327 (M^+), 292.

Ethyl 7-Chloro-1-cyclopropyl-1,4-dihydro-6-nitro-4-oxoquinoline-3-carboxylate (10) A stirred solution of **9** (64.7 g, 0.173 mol) in dioxane (250 ml) was treated with *tert*-BuOK (20.0 g, 0.179 mol) under ice-cooling. The mixture was stirred for 1 h at the same temperature and diluted with water (300 ml). The resulting precipitates were collected by filtration, washed successively with water, MeOH, and Et_2O, and then dried to give 46.2 g (79%) of **10**.[8] IR (KBr) cm^{-1}: 1720, 1620, 1590. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.5 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.29 (3H, t, $J = 7.5$ Hz, $CH_2C\underline{H}_3$), 3.5—3.8 (1H, m, cyclopropyl CH), 4.25 (2H, q, $J = 7.5$ Hz, $C\underline{H}_2CH_3$), 8.33 (1H, s, 8-H), 8.53 (1H, s, 2-H), 8.73 (1H, s, 5-H). MS *m/z*: 336 (M^+), 301, 264.

Ethyl 6-Amino-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (11) Compound **10** (15.0 g, 0.046 mol) was added to a stirred solution of $SnCl_2 \cdot 2H_2O$ (30 g, 0.133 mol) in 36% HCl (60 ml) over a 20-min period at room temperature. The reaction mixture was stirred for 4 h and diluted with water. The precipitates were collected by filtration, washed with water, and dissolved in 60 ml of concentrated H_2SO_4. This solution was poured into ice water under stirring. The resulting solid was collected by filtration, washed successively with water, EtOH, and Et_2O, and then dried to give 12.6 g (92%) of **11**.[8] IR (KBr) cm^{-1}: 3470, 3300, 1700. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.4 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.27 (3H, t, $J = 7.0$ Hz, $CH_2C\underline{H}_3$), 3.4—3.8 (1H, m, cyclopropyl CH), 4.20 (2H, q, $J = 7.0$ Hz, $C\underline{H}_2CH_3$), 5.73 (2H, br s, NH_2), 7.59 (1H, s, 8-H), 7.94 (1H, s, 5-H), 8.33 (1H, s, 2-H). MS *m/z*: 306 (M^+), 271, 261.

Ethyl 7-Chloro-1-cyclopropyl-1,4-dihydro-6-formylamino-4-oxoquinoline-3-carboxylate (12) Compound **11** (10.5 g, 0.0343 mol) was added to a stirred solution of HCOOH (52 ml) and Ac_2O (10 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 2.5 h and then diluted with methyl ethyl ketone (150 ml). The precipitates were collected by filtration, washed with methyl ethyl ketone, and dried *in vacuo* to give 10.9 g (95%) of **12**. IR (KBr) cm^{-1}: 3300, 1715, 1680. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.4 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.28 (3H, t, $J = 7.0$ Hz, $CH_2C\underline{H}_3$), 3.4—3.8 (1H, m, cyclopropyl CH), 4.21 (2H, q, $J = 7.0$ Hz, $C\underline{H}_2CH_3$), 8.13 (1H, s, 8-H), 8.42 and 8.44 (both 1H, s, 2-H and 5-H), 8.85 (1H, br s, CHO), 10.05 (1H, br s, NH). MS *m/z*:

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334 (M^+), 299, 289.

Ethyl 6-Amino-7-chloro-1-cyclopropyl-1,4-dihydro-5-nitro-4-oxoquinoline-3-carboxylate (15) A mixture of urea (93 mg, 1.55 mmol) and AcOH (4.0 ml) was treated with HNO_3 (density 1.52 g/ml, 2.6 ml) under ice-cooling. The resulting solution was added dropwise to a mixture of **12** (2.00 g, 6.84 mmol) in AcOH (4.0 ml) and Ac_2O (6.0 ml) under ice-cooling. The whole was stirred at room temperature for 1 h and then diluted with Et_2O. The precipitates were collected by filtration, and washed twice with Et_2O to give crude **15**, which was dissolved in aqueous $NaHCO_3$. The solution was treated with charcoal, and filtered. The filtrate was acidified with 15% HCl. The resultant solid was collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 920 mg (42%) of **15**. This compound was unstable even at room temperature[16] and hence elemental analysis was not performed. Compound **15**: mp <130 °C (dec.). IR (KBr) cm^{-1}: 3400, 1715, 1625. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.5 (4H, m, cyclopropyl CH_2CH_2), 1.27 (3H, t, $J=7.0$ Hz, CH_2CH_3), 3.5—3.9 (1H, m, cyclopropyl CH), 4.22 (2H, q, $J=7.0$ Hz, CH_2CH_3), 7.5—6.2 (2H, br s, NH_2), 8.52 and 8.54 (both 1H, s, 2-H and 8-H). High-resolution MS: Calcd 351.0620, Found 351.0555.

2,3,4,6-Tetrafluorobenzoic Acid (17a) A solution of 2,4,5,6-tetrafluoroisophthalic acid (**16a**, 350 g, 1.471 mol) in DMSO (700 ml) and dioxane (525 ml) was heated at 130—140 °C for 4 h and then at 150 °C for 30 min.[17] The mixture was poured into water (2.5 l) and extracted successively with toluene and Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The solid residue was triturated with a 1:2 mixture of AcOEt and *n*-hexane. The resultant crystals were collected by filtration, washed with *n*-hexane, and dried to give 121 g (42%) of **17a**. The filtrate was concentrated to dryness and the resulting solid was triturated with a 1:10 mixture of AcOEt and *n*-hexane to give an additional 45.2 g (16%) of **17a**. mp 100—101 °C (lit.[18] 143—145 °C). IR (KBr) cm^{-1}: 3000, 1720, 1640. MS *m/z*: 194 (M^+), 177, 149.

3-Chloro-2,4,6-trifluorobenzoic Acid (17b) A mixture of 5-chloro-2,4,6-trifluoroisophthalic acid[19] (**16b**, 235 g, 0.923 mol), Et_3N (120 ml, 0.862 mol), and DMSO (250 ml) was heated at 100 °C for 3 h. It was diluted with water (250 ml), acidified with 36% HCl (100 ml), and then extracted with AcOEt. The organic extract was washed with diluted HCl, dried over Na_2SO_4, and concentrated *in vacuo*. The solid residue was triturated with hot *n*-hexane, collected by filtration, and dried to give 144 g (74%) of **17b**. mp 106—108 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 2532.8, 1694.9, 1623.6. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.64 (1H, ddd, $J=10.0$, 10.0, 2.0 Hz, 5-H), 14.3 (1H, br s, COOH). MS *m/z*: 210 (M^+), 193. High-resolution MS: Calcd 209.9694, Found 209.9692.

2,3,4,6-Tetrafluoro- and 3-Chloro-2,4,6-trifluorobenzoyl Chlorides (18a[20] and 18b) A stirred mixture of **17a** (474 g, 2.44 mol), $SOCl_2$ (378 g, 3.18 mol) and *N,N*-dimethylformamide (DMF) (1.78 g, 0.0244 mol) was heated at 90 °C for 2 h, at 120 °C for 1 h, and then at 140 °C for 2.5 h. After removal of excess reagent under reduced pressure, the residue was fractionally distilled to give 496 g (96%) of **18a**, bp 94—97 °C (61 mmHg). IR (neat) cm^{-1}: 1784.1.

According to this procedure, the reaction with 144 g (0.686 mol) of **17b** gave 103 g (66%) of **18b**, bp 94—95 °C (20—21 mmHg). IR (neat) cm^{-1}: 1795.

Ethyl 2,3,4,6-Tetrafluoro- and 3-Chloro-2,4,6-trifluorobenzoylacetates (19a[20] and 19b) A mixture of diethyl malonate (162 g, 1.01 mol) and NaOEt (65.9 g, 0.969 mol) in toluene (800 ml) was stirred for 1 h at room temperature. To the reaction mixture was added a solution of **18a** (103 g, 0.485 mol) in toluene (200 ml) under water-cooling. The mixture was stirred for 1 h, and extracted twice with dilute aqueous NaOH. The aqueous layers were combined, washed with *n*-hexane, acidified with 20% HCl, and extracted twice with $CHCl_3$. The combined extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give 141 g (87%) of diethyl 2,3,4,6-tetrafluorobenzoylmalonate as an oil: IR (neat) cm^{-1}: 2700, 1710, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.10 and 1.37 (both 3H, t, $J=7.0$ Hz, CH_2CH_3), 4.07 and 4.37 (both 2H, q, $J=7.0$ Hz, CH_2CH_3), 7.0—6.6 (1H, m, aromatic H). MS *m/z*: 336 (M^+), 290, 177.

A stirred mixture of the resultant oil (141 g, 0.420 mol) and *p*-TsOH·H_2O (515 mg, 2.71 mol) in water (515 ml) was heated to reflux for 3 h. After addition of saturated $NaHCO_3$ (15 ml), the reaction mixture was extracted twice with $CHCl_3$. The combined $CHCl_3$ extract was dried over Na_2SO_4, and concentrated *in vacuo* to leave an oil, which was distilled to give 78.2 g (61% from **18a**) of **19a**, bp 98—100 °C (3 mmHg). IR (neat) cm^{-1}: 1740, 1705, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.25 and 1.33 (both 0.5×3H, t, $J=7.0$ Hz, CH_2CH_3), 3.86 (0.5×2H, dd, $J=1.5$, 1.5 Hz, CH_2COO), 4.18 and 4.27 (both 0.5×2H, q, $J=7.0$ Hz, CH_2CH_3), 5.38 (0.5H, dd, $J=1.5$, 1.5 Hz, Ar-C=CH–COO), 7.05—6.65 (1H, m, aromatic H), 12.35 (0.5H, br s, HO–C=C). MS *m/z*: 264 (M^+), 219, 177.

According to this procedure, the reaction with **18b** (103 g, 0.449 mol) gave 76.4 g (61%) of **19b**. bp 115—117 °C (2 mmHg). IR (neat) cm^{-1}: 1740, 1705, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.23 and 1.33 (total 3H, both t, $J=7.0$ Hz, CH_2CH_3), 3.81 (0.6×2H, dd, $J=1.4$, 1.4 Hz, CH_2COO), 4.18 and 4.27 (total 2H, both q, $J=7.0$ Hz, CH_2CH_3), 5.38 (0.4H, dd, $J=1.0$, 1.0 Hz, Ar-C=CH–COO), 6.7—7.0 (1H, m, aromatic H), 12.30 (0.4H, br s, HO–C=C–COO). MS *m/z*: 280 (M^+), 252, 245, 208.

Ethyl 2-(2,3,4,6-Tetrafluorobenzoyl)- and 2-(3-Chloro-2,4,6-trifluorobenzoyl)-3-cyclopropylaminoacrylates (20a[20] and 20b) A stirred mixture containing **19a** (78.2 g, 0.296 mol), Ac_2O (69.9 ml, 75.5 g, 0.740 mol), and triethyl orthoformate (73.8 ml, 65.8 g, 0.444 mol) was heated at 130—140 °C for 2 h, during which period the resulting AcOEt was removed by distillation. The mixture was concentrated *in vacuo*. The residue was taken up with EtOH (150 ml). To the EtOH solution was added a solution of cyclopropylamine (18.8 g, 0.330 mol) in EtOH (30 ml) under ice-cooling. The reaction mixture was stirred at room temperature overnight. The resultant solid was collected by filtration, washed successively with EtOH and *n*-hexane, and then dried to give 71.8 g (73%) of **20a**. After concentration of the filtrate, the residue was crystallized with EtOH–*n*-hexane to give an additional 15.2 g (16%) of **20a**. IR (KBr) cm^{-1}: 1700, 1630. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.1 (4H, m, cyclopropyl CH_2CH_2), 1.08 (3H, t, $J=7.0$ Hz, CH_2CH_3), 2.8—3.1 (1H, m, cyclopropyl CH), 4.05 (2H, q, $J=7.0$ Hz, CH_2CH_3), 6.9—6.5 (1H, m, aromatic H), 8.27 (1H, d, $J=14.0$ Hz, C=CH–N). MS *m/z*: 331 (M^+), 302, 285.

According to this procedure, the reaction with **19b** (76.0 g, 0.271 mol) gave 79.2 g (84%) of **20b**. IR (KBr) cm^{-1}: 3200, 1685, 1635, 1620. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.0 (4H, m, cyclopropyl CH_2CH_2), 1.06 (3H, t, $J=7.0$ Hz, CH_2CH_3), 2.8—3.2 (1H, m, cyclopropyl CH), 4.04 (2H, q, $J=7.0$ Hz, CH_2CH_3), 6.75 (1H, ddd, $J=9.0$, 9.0, 2.0 Hz, aromatic H), 8.26 and 8.27 (both 0.5H, d, $J=14.0$ Hz, C=CH–N), 11.0 (1H, m, NH). MS *m/z*: 347 (M^+), 318.

Ethyl 5,7,8-Trifluoro-, 8-Chloro-5,7-difluoro- and 5,6,7-Trifluoro-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylates (21a,[20] 21b, and 22a[20]) (a) A stirred solution of **20a** (172 g, 0.519 mol) in a mixture of dioxane (340 ml) and THF (340 ml) was treated with *tert*-BuOK (61.2 g, 0.545 mol) over a 15-min period under ice-cooling. The mixture was stirred for an additional 40 min and poured into ice water. The resulting solid was collected by filtration, washed with water, and dried to give 150 g (93%) of **21a**. IR (KBr) cm^{-1}: 1680, 1650, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.38 (3H, t, $J=7.5$ Hz, CH_2CH_3), 3.7—4.0 (1H, m, cyclopropyl CH), 4.36 (2H, q, $J=7.5$ Hz, CH_2CH_3), 6.90 (1H, ddd, $J=10.0$, 10.0, 6.0 Hz, 6-H), 8.45 (1H, s, 2-H). ^{19}F-NMR ($CDCl_3$) δ: -150.95 (1F, m, 8-F), -127.82 (1F, ddd, $J_{7F-8F}=19.8$ Hz, $J_{5F-7F}=15.8$ Hz, $J_{6H-7F}=10.0$ Hz, 7-F), -112.38 (1F, ddd, $J_{5F-7F}=15.8$ Hz, $J_{5F-6H}=10.0$ Hz, $J_{5F-8F}=8.7$ Hz, 5-F).[21] MS *m/z*: 311 (M^+), 292, 266, 239.

According to this procedure, the reaction with **20b** (77.7 g, 0.224 mol) gave 69.0 g (94%) of **21b**: IR (KBr) cm^{-1}: 1680, 1660, 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.38 (3H, t, $J=7.0$ Hz, CH_2CH_3), 4.0—4.3 (1H, m, cyclopropyl CH), 4.35 (2H, q, $J=7.0$ Hz, CH_2CH_3), 6.92 (1H, dd, $J=11.0$, 9.0 Hz, 6-H), 8.52 (1H, s, 2-H). ^{19}F-NMR ($CDCl_3$) δ: -108.53 (1F, dd, $J_{5F-7F}=13.6$ Hz, $J_{5F-6H}=10.7$Hz, 5-F), -100.07 (1F, dd, $J_{5F-7F}=13.6$ Hz, $J_{6H-7F}=8.9$ Hz, 7-F). MS *m/z*: 327 (M^+), 292, 282.

(b) When the reaction with **20a** was carried out at 180—190 °C (in paraffin oil (bp 220—240 °C)) with Et_3N (1.0 equimole) as a base, a small amount (10%) of the isomer **22a** could be isolated, together with **21a** (90%). Compound **22a**: IR (KBr) cm^{-1}: 1725, 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, $J=7.0$ Hz, CH_2CH_3), 3.1—3.5 (1H, m, cyclopropyl CH), 4.37 (2H, q, $J=7.0$ Hz, CH_2CH_3), 7.50 (1H, ddd, $J=12.0$, 6.0, 2.0 Hz, 8-H), 8.47 (1H, s, 2-H). ^{19}F-NMR ($CDCl_3$) δ: -163.59 (1F, ddd, $J_{6F-7F}=22.0$ Hz, $J_{5F-6F}=18.9$ Hz, $J_{6F-8H}=6.1$ Hz, 6-F), -133.75 (1F, ddd, $J_{5F-6F}=18.9$ Hz, $J_{5F-7F}=13.8$ Hz, $J_{5F-8H}=2.2$ Hz, 5-F), -125.66 (1F, ddd, $J_{6F-7F}=22.0$ Hz, $J_{5F-7F}=13.8$ Hz, $J_{7F-8H}=11.5$ Hz, 7-F). MS *m/z*: 311 (M^+), 266, 239.

Ethyl 7,8-Difluoro- and 8-Chloro-7-fluoro-5-benzylamino-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylates (23a[20] and 23b) A stirred mixture of **21a** (45.8 g, 0.147 mol) and benzylamine (91.6 ml, 89.9 g,

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0.839 mol) in trichloroethylene (916 ml) was heated to reflux for 5.5 h. The resulting precipitates were filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was triturated with EtOH (200 ml). The resultant crystals were collected by filtration, washed with EtOH, and dried to give 49.4 g (84%) of **23a**. IR (KBr) cm^{-1}: 3230, 1690, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.38 (3H, t, J=7.0 Hz, CH_2CH_3), 4.33 (2H, s, CH_2-Ph), 4.37 (2H, q, J=7.0 Hz, CH_2CH_3), 6.12 (1H, dd, J=13.0, 6.0 Hz, 6-H), 7.1—7.4 (5H, s-like m, Ph), 8.40 (1H, s, 2-H), 10.75 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ: −165.22 (1F, br dd, J_{7F-8F}=22.1 Hz, J_{6H-8F}= 6.1 Hz, 8-F), −128.37 (1F, dd, J_{7F-8F}=22.1 Hz, J_{6H-7F}=13.2 Hz, 7-F).[21] MS *m/z*: 398 (M^+), 369.

According to this procedure, the reaction with **21b** (45.8 g, 0.147 mol) gave 57.6 g (91%) of **23b**. IR (KBr) cm^{-1}: 1720, 1680, 1625. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.38 (3H, t, J=7.0 Hz, CH_2CH_3), 4.0—4.3 (1H, m, cyclopropyl CH), 4.37 (2H, q, J=7.0 Hz, CH_2CH_3), 4.38 (2H, s, CH_2-Ph), 6.20 (1H, d, J=12.5 Hz, 6-H), 7.2—7.5 (5H, s-like m, Ph), 8.46 (1H, s, 2-H), 12.0 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 93.50 (d, J_{C-7F}=27.4 Hz, C-6), 94.34 (d, J_{C-7F}=22.2 Hz, C-8), 112.24 (d, J_{C-7F}=1.2 Hz, C-4a), 112.28 (s, C-3), 142.66 (d, J_{C-7F}=5.1 Hz, C-8a), 150.72 (s, C-2), 151.90 (d, J_{C-7F}=14.3 Hz, C-5), 162.59 (d, J_{C-7F}=247.3 Hz, C-7), 177.62 (s, C-4).[22] ^{19}F-NMR ($CDCl_3$) δ: −102.06 (1F, d, J_{6H-7F}= 12.2 Hz, 7-F). MS *m/z*: 414 (M^+), 385.

Ethyl 7,8-Difluoro- and 8-Chloro-7-fluoro-5-benzylamino-1-cyclopropyl-1,4-dihydro-6-nitro-4-oxoquinoline-3-carboxylates (24a and 24b) Compound **23a** (5.00 g, 0.126 mol) was added to a stirred solution of HNO_3 (density 1.52 g/ml, 5.0 ml) and AcOH (15 ml) under ice-cooling over a period of 5 min. The reaction mixture was stirred under ice-cooling for 45 min and poured into ice water. The resulting solid was collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 3.82 g (69%) of **24a**. IR (KBr) cm^{-1}: 1690, 1635, 1605. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.35 (3H, t, J=7.0 Hz, CH_2CH_3), 3.7—4.1 (1H, m, cyclopropyl CH), 4.15 (2H, s, CH_2-Ph), 4.33 (2H, q, J=7.0 Hz, CH_2CH_3), 7.28 (5H, s-like m, Ph), 8.38 (1H, s, 2-H), 10.70 (1H, br s, NH). MS *m/z*: 443 (M^+).

According to this procedure, the reaction with **23b** (5.00 g, 12.1 mol) gave 5.00 g (90%) of **24b**. IR (KBr) cm^{-1}: 1685, 1630, 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.35 (3H, t, J=7.0 Hz, CH_2CH_3), 4.0—4.3 (1H, m, cyclopropyl CH), 4.20 (2H, d, J=5.0 Hz, CH_2-Ph), 4.34 (2H, q, J=7.0 Hz, CH_2CH_3), 7.30 (5H, s-like m, Ph), 8.46 (1H, s, 2-H), 11.95 (1H, br s, NH). MS *m/z*: 459 (M^+), 353.

Ethyl 4-Chloro-6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-imidazo[4,5-*f*]-quinoline-8-carboxylate (26a) A mixture of **15** (606 mg, 1.72 mmol) in dioxane (36 ml) was hydrogenated over 5% Pd–C (120 mg) at 60 °C for 5 h. Then triethyl orthoformate (6.0 ml) and HCOOH (6.0 ml) were added at room temperature and the resulting mixture was stirred at room temperature for 30 min. After addition of 30 ml of $CHCl_3$, the catalyst (Pd–C) was removed by filtration. The filtrate was concentrated *in vacuo* to leave a solid residue, which was triturated with EtOH. The resultant crystals were collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 369 mg (65%) of **26a**. IR (KBr) cm^{-1}: 3200, 1710, 1685. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.5 (4H, m, cyclopropyl CH_2CH_2), 1.32 (3H, t, J=7.0 Hz, CH_2CH_3), 3.6—3.9 (1H, m, cyclopropyl CH), 4.26 (2H, q, J=7.0 Hz, CH_2CH_3), 8.00 (1H, s, 5-H), 8.32 (1H, s, 2-H), 8.55 (1H, s, 7-H). MS *m/z*: 331 (M^+), 296, 286, 259.

Ethyl 6-Cyclopropyl-4,5-difluoro-6,9-dihydro-9-oxo-1*H*-imidazo[4,5-*f*]-quinoline-8-carboxylate (26b) A mixture of **24a** (4.00 g, 9.03 mmol) and HCOOH (40 ml) was hydrogenated over 5% Pd–C (400 mg) at 50 °C for 3 h. The catalyst was removed by filtration. The filtrate was allowed to react with triethyl orthoformate (12 ml, 72.1 mmol) under reflux for 30 min and the resulting mixture was concentrated *in vacuo* to dryness. The residue was triturated with EtOH. The resultant crystals were collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 2.50 g (83%) of **26b**. IR (KBr) cm^{-1}: 3270, 1715, 1605. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.30 (3H, t, J=7.5 Hz, CH_2CH_3), 3.9—4.2 (1H, m, cyclopropyl CH), 4.26 (2H, q, J=7.5 Hz, CH_2CH_3), 8.32 (1H, s, 2-H), 8.56 (1H, s, 7-H), 13.4 (1H, br s, NH). MS *m/z*: 333 (M^+), 288, 261.

Ethyl 5-Chloro-6-cyclopropyl-4-fluoro-6,9-dihydro-9-oxo-1*H*-imidazo-[4,5-*f*]quinoline-8-carboxylate (26c) A mixture of **24b** (4.30 g, 9.36 mmol) and AcOH (43 ml) was hydrogenated over 5% Pd–C (430 mg) at 40—50 °C for 1.5 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was taken up with $CHCl_3$ (20 ml) and the solution was treated with triethyl orthoformate (1.78 g, 12.0 mmol) and *p*-TsOH·H_2O (50 mg, 0.26 mmol) under reflux for 1 h. The mixture was concentrated *in vacuo* to leave a solid residue. The residue was triturated with EtOH. The resultant crystals were collected by filtration, and dried to give 2.50 g (76%) of **26c**. IR (KBr) cm^{-1}: 3250, 1725, 1620. ^{1}H-NMR (DMSO-d_6) δ: 0.9—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.32 (3H, t, J=7.0 Hz, CH_2CH_3), 4.1—4.5 (1H, m, cyclopropyl CH), 4.28 (2H, q, J=7.0 Hz, CH_2CH_3), 8.33 (1H, s, 2-H), 8.68 (1H, s, 7-H), 13.5 (1H, br s, NH). MS *m/z*: 349 (M^+), 314.

Ethyl 4-Chloro-6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-triazolo[4,5-*f*]-quinoline-8-carboxylate (27a) A mixture of **15** (1.39 g, 3.95 mmol) and dioxane (140 ml) was hydrogenated over 5% Pd–C (250 mg) at 60 °C for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was taken up with CH_3CN (14 ml) and allowed to react with *tert*-BuONO (616 mg, 5.97 mmol) and 10% HCl (0.10 ml) for 15 min at room temperature. Water (50 ml) was added and the mixture was adjusted to pH 6 with 10% NaOH. The precipitates were collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 604 mg (46%) of **27a**. IR (KBr) cm^{-1}: 3350, 1720, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.5 (4H, m, cyclopropyl CH_2CH_2), 1.43 (3H, t, J=7.0 Hz, CH_2CH_3), 3.4—3.8 (1H, m, cyclopropyl CH), 4.46 (2H, q, J=7.0 Hz, CH_2CH_3), 8.00 (1H, s, 5-H), 8.73 (1H, s, 7-H), 14.1 (1H, br s, NH). MS *m/z*: 332 (M^+), 304, 287, 260.

Ethyl 4,5-Difluoro- and 5-Chloro-4-fluoro-6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-triazolo[4,5-*f*]quinoline-8-carboxylates (27b and 27c) A mixture of **24a** (3.00 g, 6.77 mmol) and AcOH (30 ml) was hydrogenated over 5% Pd–C (300 mg) at 50 °C for 3.5 h. The catalyst was removed by filtration and the filtrate was allowed to react with *tert*-BuONO (1.04 g, 10.1 mmol) at room temperature for 30 min. The reaction mixture was diluted with EtOH. The precipitates were collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 1.04 g (46%) of **27b**. The foregoing filtrate was concentrated to dryness *in vacuo* and the resulting residue was chromatographed on silica gel using $CHCl_3$: MeOH = 8 : 1 as an eluent to give an additional 526 mg (23%) of **27b**. IR (KBr) cm^{-1}: 3060, 1730, 1610. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.1—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.32 (3H, t, J=7.5 Hz, CH_2CH_3), 4.05—4.2 (1H, m, cyclopropyl CH), 4.29 (2H, q, J=7.5 Hz, CH_2CH_3), 8.64 (1H, s, 7-H), 16.8 (1H, br s, NH). MS *m/z*: 334 (M^+), 306.

According to this procedure, the reaction with **24b** (3.11 g, 6.77 mmol) gave 1.44 g (61%) of **27c**. IR (KBr) cm^{-1}: 3273.8, 1730.5. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.33 (3H, t, J=7.0 Hz, CH_2CH_3), 4.1—4.5 (1H, m, cyclopropyl CH), 4.30 (2H, q, J=7.0 Hz, CH_2CH_3), 8.73 (1H, s, 7-H), 16.70 (1H, br s, NH). MS *m/z*: 350 (M^+), 315.

4-Chloro-, 4,5-Difluoro-, and 5-Chloro-4-fluoro-6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-imidazo[4,5-*f*]quinoline-8-carboxylic Acids (28a, 28b, and 28c) A mixture of **26a** (1.40 g, 4.22 mmol) in a mixture of AcOH–H_2O–H_2SO_4 (8 : 6 : 1 v/v, 14 ml) was heated to reflux for 1 h. The reaction mixture was poured into ice water and adjusted to pH 4 with diluted NaOH. The precipitates were collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 1.23 g (96%) of **28a**. IR (KBr) cm^{-1}: 3350, 2550, 1700. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.5 (4H, m, cyclopropyl CH_2CH_2), 3.7—4.1 (1H, m, cyclopropyl CH), 8.18 (1H, s, 5-H), 8.45 (1H, s, 2-H), 8.80 (1H, s, 7-H), 13.5 (1H, br s, NH), 15.0 (1H, br s, COOH). MS *m/z*: 303 (M^+), 268, 259.

According to the procedure described above, **26b** (1.35 g, 4.05 mmol) and **26c** (1.89 g, 5.41 mmol) were worked up to give **28b** (1.16 g, 94%) and **28c** (1.74 g, 100%), respectively. Compound **28b**: IR (KBr) cm^{-1}: 3190, 1720, 1640. ^{1}H-NMR (NaOD–D_2O) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 3.7-4.1 (1H, m, cyclopropyl CH), 8.03 (1H, s, 2-H), 8.40 (1H, s, 7-H). MS *m/z*: 305 (M^+), 261.

Compound **28c**: IR (KBr) cm^{-1}: 3200, 2500, 1770, 1720. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 4.45—4.6 (1H, m, cyclopropyl CH), 8.49 (1H, s, 2-H), 8.93 (1H, s, 7-H), 13.61 (1H, br s, NH), 14.63 (1H, br s, COOH). MS *m/z*: 321 (M^+), 303, 286.

4-Chloro-, 4,5-Difluoro-, and 5-Chloro-4-fluoro-6-cyclopropyl-6,9-dihydro-9-oxo-1*H*-triazolo[4,5-*f*]quinoline-8-carboxylic Acids (29a, 29b, and 29c) According to the procedure described for the conversion of **26a** to **28a**, **27a** (504 mg, 1.52 mmol), **27b** (1.40 g, 4.19 mmol), and **27c** (1.05 g, 3.00 mmol) were worked up to give **29a** (303 mg, 66%), **29b**

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(1.22 g, 95%), and **29c** (919 mg, 95%), respectively. Compound **29a**: IR (KBr) cm^{-1}: 3266.0, 1716.4. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.2—1.5 (4H, m, cyclopropyl CH_2CH_2), 3.9—4.1 (1H, m, cyclopropyl CH), 8.38 (1H, s, 5-H), 8.87 (1H, s, 7-H), 14.80 (1H, br s, NH), 16.85 (1H, br s, COOH). MS *m/z*: 304 (M^+), 259.

Compound **29b**: IR (KBr) cm^{-1}: 3300, 1710, 1615. ^{1}H-NMR (NaOD–D_2O) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 3.8—4.2 (1H, m, cyclopropyl CH), 8.52 (1H, s, 7-H). MS *m/z*: 306 (M^+), 288, 278, 262.

Compound **29c**: IR (KBr) cm^{-1}: 1717.3, 1610.1. ^{1}H-NMR (NaOD–D_2O) δ: 0.9—1.4 (4H, m, cyclopropyl CH_2CH_2), 4.1—4.5 (1H, m, cyclopropyl CH), 8.60 (1H, s, 7-H). MS *m/z*: 322 (M^+), 304, 287, 278.

6-Cyclopropyl-6,9-dihydro-9-oxo-4-(1-piperazinyl)-1*H*-imidazo[4,5-*f*]-quinoline-8-carboxylic Acid (30a) A mixture of **28a** (400 mg, 1.32 mmol) and piperazine (567 mg, 6.59 mmol) in DMSO (4.0 ml) was heated at 120 °C for 1 h. The solvent was distilled off *in vacuo*. The residue was triturated with EtOH. The resultant crystals were collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 421 mg of crude crystals. Recrystallization of the crude crystals from diluted HCl–EtOH gave 332 mg (62%) of **30a**. IR (KBr) cm^{-1}: 3350, 1695, 1605. ^{1}H-NMR (D_2O) δ: 0.8—1.5 (4H, m, cyclopropyl CH_2CH_2), 3.1—3.8 (total 5H, m, 2 × $HNCH_2CH_2N$ and cyclopropyl CH), 3.8—4.2 (4H, m, 2 × $HNCH_2CH_2N$), 6.70 (1H, s, 5-H), 7.87 (1H, s, 2-H), 8.10 (1H, s, 7-H). MS *m/z*: 353 (M^+), 309.

According to this procedure, compounds **30b—d** and **33b** were prepared from **28a** and **29a**, respectively.

6-Cyclopropyl-5-fluoro-6,9-dihydro-9-oxo-4-(1-piperazinyl)-1*H*-imidazo[4,5-*f*]quinoline-8-carboxylic Acid (31a) A mixture of **28b** (150 mg, 0.492 mmol) and piperazine (127 mg, 1.48 mmol) in pyridine (3.0 ml) was heated to reflux for 45 min. The solvent was distilled off *in vacuo*. The residue was triturated with EtOH. The resultant crystals were collected by filtration, washed successively with EtOH and with iso-Pr_2O, and then dried to give 175 mg of crude crystals. Recrystallization of the crystals from aqueous NH_4OH gave 126 mg (65%) of **31a**. IR (KBr) cm^{-1}: 3300, 1620, 1580. ^{1}H-NMR (NaOD–D_2O) δ: 0.8—1.3 (4H, m, cyclopropyl CH_2CH_2), 2.8—3.1 and 3.1—3.5 (both 4H, m, 2 × $HNCH_2CH_2N$), 3.5—4.0 (1H, m, cyclopropyl CH), 7.99 (1H, s, 2-H), 8.30 (1H, s, 7-H). MS *m/z*: 371 (M^+).

According to this procedure, compounds **31b—d, 32a, b, 34a—d**, and **35b, c** were prepared from **28b**, **28c**, **29b**, and **29c**.

***In Vitro* Antibacterial Activity** According to the assay method recommended by the MIC Committee of the Japan Society of Chemotherapy,[23] the MIC (in micrograms per milliliter) was determined by the 2-fold agar dilution method using Mueller-Hinton agar (pH 7.4, Difco); the bacterial inocula contained approximately 10^6 colony-forming units and the bacterial growth was observed after a 20 h incubation at 37 °C.

***In Vivo* Efficacy on Systemic Infections** *In vivo* activity assay was carried out according to the method of Nakamura *et al.*[4] Groups of 8 or more male mice (Std-ddY, 20 ± 2 g) were infected with *P. aeruginosa* 12 (i.p., 4×10^3 cells). For evaluation of ED_{50} (*p.o.*), the test compounds were suspended in 0.4% carboxymethyl cellulose sodium salt and administered orally at 0 and 6 h postinfection. For determination of ED_{50} (i.v.), the test compounds were dissolved in water with equimolar NaOH and injected intravenously at 0 and 6 h postinfection. Survival rates were evaluated after 1 week and ED_{50} (*p.o.*) and ED_{50} (i.v.) were calculated from the rates.

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References and Notes

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