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Synthesis of Antimicrobial Agents. 1. Syntheses and Antibacterial Activities of 7-(Azole substituted)quinolones

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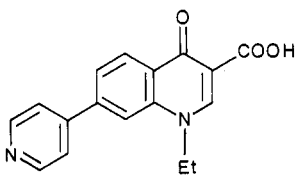
A series of 6-fluoro- and 6,8-difluoro-7-(azole substituted)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids were prepared. Structure–activity relationship studies indicated that the antibacterial potency was better when the 6,8-substituents were fluorine atoms and the 7-substituent was either 1-imidazolyl, **20**, or 4-methyl-1-imidazolyl, **25**. From the results of studies on pharmacokinetic profile and toxicity, **20** and **25** were found to possess excellent antibacterial activities and to show high blood levels after oral administration to mice with low toxicity.

Since nalidixic acid was first reported by Lesher et al.[1] in 1962 as an antibacterial agent, many analogues having a pyridonecarboxylic acid moiety (PCA antibacterials) have been synthesized.

Among these compounds, rosoxacin (**1**),[2] whose structure consists of a heteroatomic substituent (4-pyridinyl group) at the 7-position of 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (quinolone), is known to exhibit high antibacterial activity and to show good bioavailability after oral administration to animals.[3]



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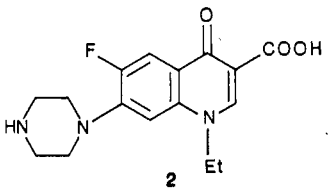

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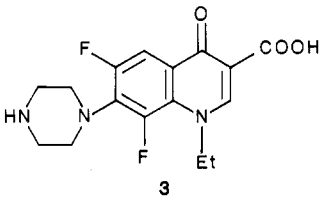
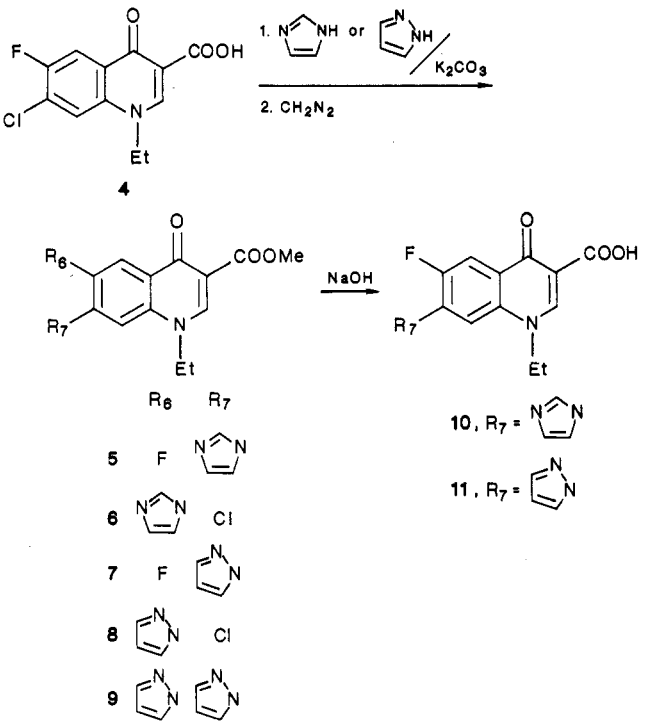


3

On the other hand, norfloxacin (NFLX, **2**)[4] containing a fluorine atom and a piperazinyl group at the 6- and 7-position of quinolone, respectively, and its 8-fluoro derivative (**3**)[5a,b] were found to show excellent antibacterial activities and a broad antibacterial spectrum. But the former has been reported to show low blood concentrations and low urinary recoveries after oral administration to animals,[6] and the latter was confirmed to show significantly greater toxicities after oral administration and intravenous injection to mice in comparison with NFLX, as shown in Table V.

Scheme I



These two findings indicate that heteroaromatics at the 7-position can bring about improved bioavailability and the introduction of fluorine atoms at the 6- or 6,8-position of the quinolones can produce enhanced antibacterial activity. Therefore, we thought that introduction of these two substituents into one molecule would result in a compound with these two preferable features. The above thought prompted us to investigate fluorinated quinolones with azoles, such as pyrrole, imidazole, pyrazole, and triazole, at the 7-position.

(1) Lesher, G. Y.; Froelich, E. J.; Gruett, M. D.; Bailey, J. H.; Brundage, R. D. *J. Med. Chem.* **1962**, *15*, 1063.
(2) Lesher, G. Y.; Carabateas, P. M. U.S. Patent 3 907 808, 1975.
(3) O'Connor, J. R.; Dobson, R. A.; Came, P. E.; Wagner, R. B. *Curr. Chemother. Infect. Dis.* **1980**, *1*, 440.
(4) Koga, h.; Ito, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358.
(5) (a) Irikura, T.; Suzue, S.; Ito, A.; Koga, H. Japan Kokai 55-47658, 1980. Irikura, T.; Koga, H.; Murayama, T. Japan Kokai 56-30964, 1981. (b) Cornett, J. B.; Wentland, M. P. *Annu. Rep. Med. Chem.* **1986**, *21*, 138.
(6) Irikura, T. U.S. Patent 4 146 719, 1979. Murayama, S.; Hirai, K.; Ito, A.; Abe, Y.; Irikura, T. *Chemotherapy* **1981**, *29* (S-4), 98.

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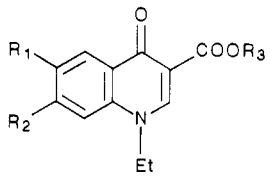
Table I. Azole-Substituted Quinolones



compd	R_1	R_2	R_3	recryst solvent	yield,[a] %	mp, °C	formula[b]
5	F	Im[c]	CH_3	EtOH	8.9	260–264	$C_{16}H_{14}FN_3O_3$
6	Im	Cl	CH_3	EtOH	22.	226–228 dec	$C_{16}H_{14}ClN_3O_3$
7	F	Py[d]	CH_3	$CHCl_3$–AcOEt	5.9	255–262	$C_{16}H_{14}FN_3O_3$
8	Py	Cl	CH_3	AcOEt	33.5	195–199	$C_{16}H_{14}ClN_3O_3 \cdot H_2O$
9	Py	Py	CH_3	AcOEt	17.1	264–267	$C_{19}H_{17}N_5O_3$
10	F	Im	H	$CHCl_3$–MeOH	69.1	300	$C_{15}H_{12}FN_3O_3$
11	F	Py	H	MeOH–H_2O	65.6	274–276	$C_{15}H_{12}FN_3O_3 \cdot {}^1/_2H_2O$
13	F	Pr[e]	H	DMF–EtOH	67.7	253–256 dec	$C_{16}H_{13}FN_2O_3$
14	F	Tr[f]	CH_3	MeOH	11.4	268–274 dec	$C_{15}H_{13}FN_4O_3$
15	F	Dm[g]	CH_3	$CHCl_3$–AcOEt	25.7	216–219	$C_{16}H_{18}FN_3O_3 \cdot {}^1/_4H_2O$
16	F	Tr	H		79.4	300	$C_{14}H_{11}FN_4O_3 \cdot {}^1/_4H_2O$

[a] Yields were not optimized. [b] Carbon, hydrogen, and nitrogen analyses were within ±0.3% of the theoretical values. [c] Im, 1-imidazolyl. [d] Py, 1-pyrazolyl. [e] Pr, 1-pyrrolyl. [f] Tr, 1,2,4-triazol-4-yl. [g] Dm, [(dimethylamino)methylene]amino.

During our investigations, a few PCA antibacterials containing azoles have been reported,[7a-d] but there have been no reports of the systematic evaluation of these compounds.

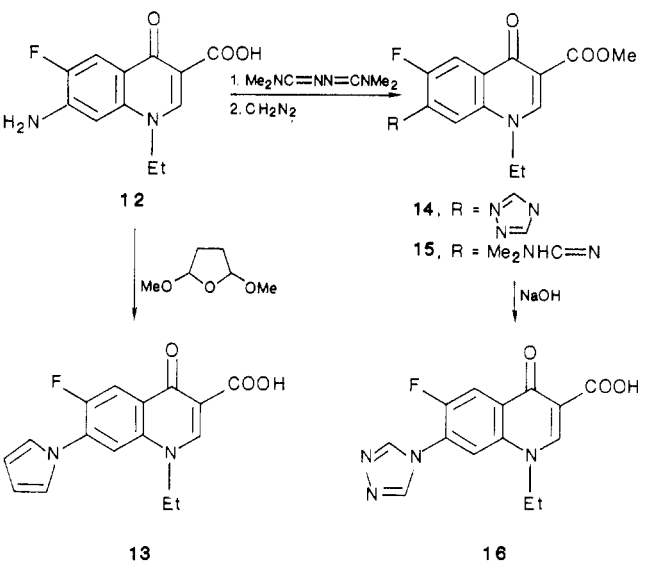
In this paper, we report the syntheses and evaluations of fluorinated quinolones containing azoles at the 7-position and, in particular, the discovery of 1-ethyl-6,8-difluoro-1,4-dihydro-7-(1-imidazolyl)-4-oxo-3-quinolinecarboxylic acid (**20**) and 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-methyl-1-imidazolyl)-4-oxo-3-quinolinecarboxylic acid (**25**), which have excellent antibacterial activities and sufficient oral absorption with low toxicity.[8]

Chemistry

Imidazole was condensed with 7-chloro-6-fluoroquinoline **4**[5] by heating in *N,N*-dimethylformamide (DMF), followed by esterification with diazomethane to afford a mixture of 6-fluoro-7-(1-imidazolyl) derivative **5** and 7-chloro-6-(1-imidazolyl) derivative **6**, as shown in Scheme I. In the case of the reaction with pyrazole in the presence of potassium carbonate, a mixture of 6-fluoro-7-(1-pyrazolyl) derivative **7**, 7-chloro-6-(1-pyrazolyl) derivative **8**, and 6,7-di-1-pyrazolyl derivative **9** was obtained after esterification with diazomethane. These esters (**5–9**) were isolated by preparative thin-layer chromatography on silica gel and their structures were confirmed with NMR and mass spectral data. The desired esters **5** and **7** were converted to the corresponding acids **10** and **11** by alkaline hydrolysis.

On the other hand, 6-fluoro-7-(1-pyrrolyl)quinoline **13**[7d] was synthesized by condensation of 7-amino-6-fluoroquinolone **12**[4] with 2,5-dimethoxytetrahydrofuran, as shown in Scheme II. During our investigation, a patent[7d] describing **13** was disclosed, in which it was synthesized

Scheme II



by the same method. 6-Fluoro-7-(1,2,4-triazol-4-yl) derivative **16** was obtained by alkaline hydrolysis of its ester **14**, which was prepared in low yield by condensation of **12** with *N,N*-dimethylformamide azine[9] followed by esterification with diazomethane. In this reaction, 6-fluoro-7-[(dimethylamino)methylene]amino] derivative **15** was obtained as the main product. The physical properties of these compounds are listed in Table I.

The preparation of 6,8-difluoro-7-(azole substituted)-quinolones is shown in Scheme III. Thus, 6,8-difluoro-7-(1-pyrrolyl)quinolone **19** was prepared by condensation of 7-amino-6,8-difluoroquinolone **18**, which was derived from 6,7,8-trifluoroquinolone **17**[5] with 2,5-dimethoxytetrahydrofuran. On the other hand, 6,8-difluoro-7-imidazolyl derivatives **20** and **24–35** were prepared by the reacton of **17** with the corresponding imidazoles.

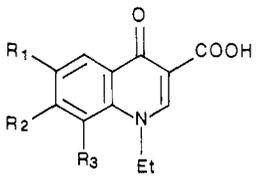
In order to clarify the effect of the 8-position substituent on antibacterial activity, nucleophilic substitutions at the fluorine atoms of **20** with sodium methoxide, sodium methanethiol, and dimethylamine were examined. The sodium salts were obtained of the corresponding 8-substituted 6-fluoro-7-(1-imidazolyl)quinolones **21** and **22**.

(7) (a) Strehlke, P. German Patent Offenlegungsschrift 2656574, 1978. 1-Ethyl-1,4-dihydro-7-(1-imidazolyl)-4-oxo-1,6-naphthyridine-3-carboxylic acid. (b) Tanaka, Y.; Hayakawa, I.; Hiramitsu, T. Japan Kokai 57-88182, 1982. 2,3-Dihydro-9-fluoro-10-(1-imidazolyl)-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-[1,4]benzoxazine-6-carboxylic acid. (c) Gerster, J. F. U.S. Patent 441246, 1982. 9-Fluoro-6,7-dihydro-8-(1-imidazolyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid. (d) Esteve, S. J. European Patent 0134165, 1984. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-pyrrolyl)-3-quinolinecarboxylic acid.

(8) Uno, T.; Takamatsu, M.; Iuchi, K.; Tsukamoto, G. European Patent 0115049, 1984.

(9) Bartett, R. K.; Humphrey, I. R. *J. Chem. Soc.* **1967**, 1664.

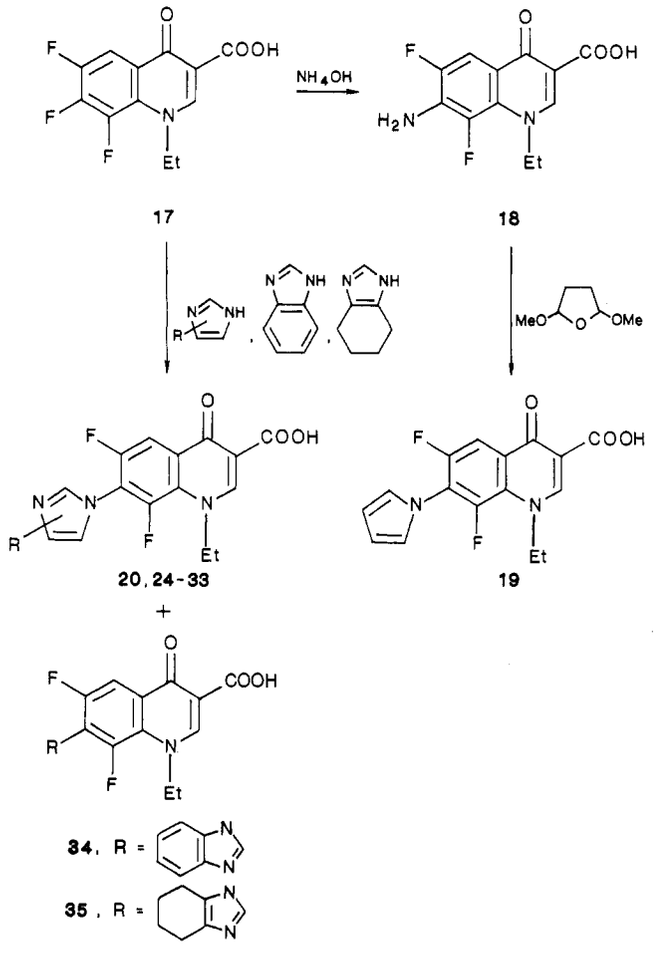
Table II. Substituted 1-Ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids



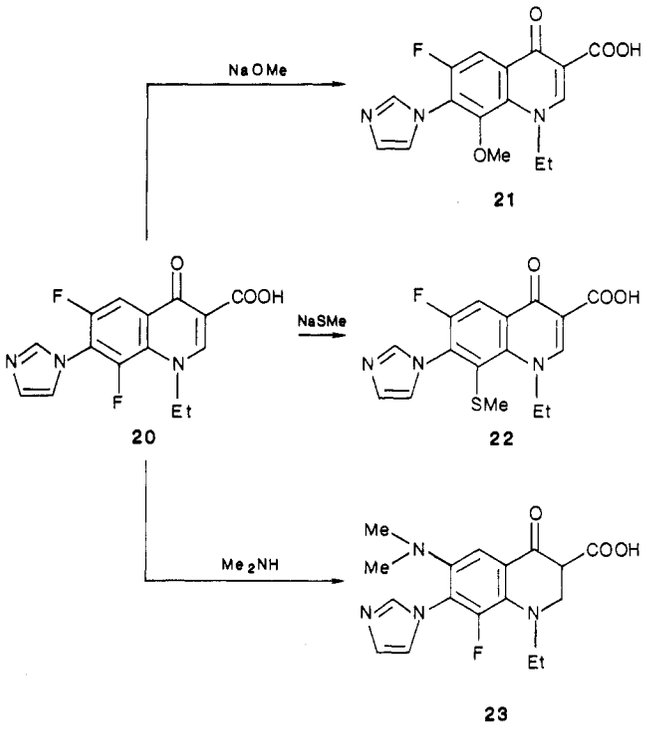
compd	R_1	R_2	R_3	recryst solvent	yield,[a] %	mp, °C	formula[b]
18	F	NH_2	F	DMF–H_2O	48.5	>300	$C_{12}H_{10}F_2N_2O_3$
19	F	Pr[c]	F	DMF–EtOH	55.0	289–290 dec	$C_{16}H_{12}F_2N_2O_3$
20	F	Im[d]	F	DMF	48.1	283–288 dec	$C_{15}H_{11}F_2N_3O_3$
21	F	Im	OMe	DMSO	54.7	270–278 dec	$C_{16}H_{14}FN_3O_4$
22	F	Im	SMe	EtOH	50.1	253–256	$C_{16}H_{14}FN_3O_3S$
23	NMe_2	Im	F	EtOH	22.0	276–280 dec	$C_{17}H_{17}FN_4O_3$

[a,b] See Table I, footnotes *a* and *b*. [c] Pr, 1-pyrrolyl. [d] Im, 1-imidazolyl.

Scheme III



Scheme IV



However, in the case of the reaction with dimethylamine, 8-fluoro-7-(1-imidazolyl)-6-(dimethylamino)quinolone **23** was obtained, as shown in Scheme IV. The physical properties of these compounds **18–35** are listed in Tables II and III.

Results and Discussion

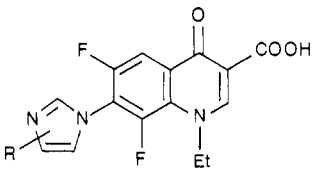
Table IV summarizes the in vitro antibacterial activities of the 7-(azole substituted) derivatives against eight organisms. The results for NFLX and its 8-fluoro derivative **3** are also included for comparison.

The data for the first four entries (compounds **10**, **11**, **13**, and **16**) indicate that 7-(1-pyrrolyl) derivative **13** was the most potent compound among the monofluoroquinolones against Gram-positive organisms, and its activity was similar to that of NFLX. However, against Gram-negative organisms, **13** and 7-(1-imidazolyl) derivative **10** showed similar activity with potencies about 2–8 times lower than that of NFLX. 7-(1-Pyrazolyl) derivative **11** showed lower activity than **10** and **13**, and 7-(1,2,4-triazol-4-yl) derivative **16** was the least active of these four compounds.

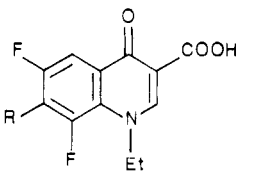
On the other hand, 6,8-difluoro-7-(1-imidazolyl)-quinolone **20** was found to possess almost similar activity to that of NFLX and **3**, while it was 4 and 8 times less potent than these compounds, respectively, against *Pseudomonas aeruginosa*. These data suggested that the introduction of a fluorine atom at the 8-position of **10** enhanced the antibacterial potency. But the activity of 6,8-difluoro-7-(1-pyrrolyl)quinolone **19** showed similar activity to that of **13**, which indicated that a fluorine atom at the 8-position of **19** plays no effect on in vitro potency. From these results, it is concluded that the introduction of a fluorine atom at the 8-position does not always enhance the in vitro activity.

To clarify the effect of other substituents at the 8-position on antibacterial activity, 6-fluoro-7-(1-imidazolyl)-8-methoxyquinolone **21** and 6-fluoro-7-(1-imidazolyl)-8-(methylthio)quinolone **22** were tested. But they were less active than **20**. The above results indicate that the most preferable substituent at the 8-position is a fluorine atom

Table III. 6,8-Difluoro-7-(substituted 1-imidazolyl)quinolones



24-33



34, 35

compd	R	react. solvent	react. temp., °C (react. time, h)	recryst	yield,[a] %	mp, °C	formula[b]
24	2-CH_3	pyridine	100 (0.5)	MeOH	69	280–283	$C_{16}H_{13}F_2N_3O_3$
25	4-CH_3	DMSO	110 (1.0)	EtOH	88	247–253	$C_{16}H_{13}F_2N_3O_3 \cdot {}^1/_2H_2O$
26	4-NO_2	DMSO	165 (7.0)	DMSO–MeOH	35	300	$C_{15}H_{10}F_2N_4O_5$
27	4-Br	DMSO	165 (4.0)	MeOH	60	275–280	$C_{15}H_{10}BrF_2N_3O_3$
28	4-$COOCH_3$	DMSO	165 (5.0)	MeOH	52	281–286	$C_{17}H_{13}F_2N_3O_5$
29	4-$CON(CH_3)_2$	pyridine	100 (5.0)	MeOH	13	278–283	$C_{18}H_{16}F_2N_4O_4$
30	4-CHO	DMSO	135 (7.0)	DMSO–MeOH	61	279–284	$C_{16}H_{11}F_2N_3O_4$
31	4-CH_2OH	pyridine	100 (0.5)	DMSO–MeOH	71	275–280	$C_{16}H_{13}F_2N_3O_4$
32	4-$CH_2N(CH_3)_2$	DMSO	110 (0.5)	DMSO–acetone	60	219–223	$C_{18}H_{18}F_2N_4O_3$
33	4-CH=NOH	DMSO	135 (2.0)	MeOH	73	260–264	$C_{16}H_{12}F_2N_4O_4$
34	BzIm[c]	DMSO	105 (0.75)	DMF–H_2O	45	280 dec	$C_{19}H_{13}F_2N_3O_3$
35	ThIm[d]	DMSO	100 (0.25)	MeOH	66	265–273 dec	$C_{19}H_{17}F_2N_3O_3$

[a,b] See Table I, footnotes *a* and *b*. [c] BzIm, 1-benzimidazolyl. [d] ThIm, 4,5,6,7-tetrahydrobenzimidazol-1-yl.

Table IV. In Vitro Antibacterial Activity of 7-(Azole substituted)quinolones

	organism; minimum inhibitory concentration (MIC),[a] μg/mL							
compd	Sa	Se	Bs	Ec	Kp	Pv	St	Pa
10	6.25	25	0.78	1.56	0.20	0.20	0.10	12.5
11	6.25	25	0.78	12.5	0.78	0.39	0.39	25
13	0.39	1.56	0.05	3.13	0.20	0.10	0.10	12.5
16	25	25	25	25	12.5	25	3.13	25
19	0.39	1.56	0.05	3.13	0.20	0.10	0.20	12.5
20	0.39	3.13	0.10	0.20	0.05	0.025	0.05	6.25
21	0.39	1.56	0.10	1.56	0.10	0.10	0.10	25
22	3.13	12.5	0.39	6.25	0.39	0.39	0.39	25
24	6.25	25	0.78	3.13	0.39	0.20	0.39	25
25	0.78	3.13	0.05	0.39	0.10	0.025	0.10	6.25
26	1.56	6.25	0.39	6.25	0.39	3.13	1.56	25
27	0.78	6.25	0.20	1.56	0.20	0.20	0.20	25
28	25	25	12.5	25	3.13	1.56	3.13	25
29	12.5	25	6.25	25	1.56	3.13	3.13	25
30	3.13	25	0.78	0.78	0.20	0.20	0.20	25
31	25	25	6.25	6.25	0.78	0.78	0.39	25
32	6.25	25	6.25	25	3.13	6.25	6.25	25
33	3.13	25	0.78	6.25	0.39	0.78	0.39	25
34	0.20	1.56	0.05	1.56	0.39	0.78	0.78	12.5
35	1.56	6.25	0.39	12.5	1.56	3.13	6.25	25
NFLX	0.39	3.13	0.39	0.39	0.10	0.10	0.10	1.56
3	0.39	3.13	0.39	0.20	0.10	0.10	0.10	0.78

[a] The MICs were determined by the twofold agar dilution on sensitivity test agar. Organisms selected for inclusion in the table: Sa, *Staphlococcus aureus* FDA 209P JC-1; Se, *Staphylococcus epidermidis* IAM 1576; Bs, *Bacillus subtilis* ATCC 6633; Ec, *Escherichia coli* NIHJ JC-2; Kp, *Klebsiella pneumoniaew* PCI-602; Pv, *Proteus vulgaris* HX-19; St, *Salmonella paratyphi* 1015; Pa, *Pseudomonas aeruginosa* IFO 3445.

in the case of 7-(1-imidazolyl) derivatives.

Among the 6,8-difluoro-7-(substituted 1-imidazolyl)-quinolones **24–33**, the 7-(4-methyl-1-imidazolyl) derivative **25** showed as high activity as **20**, while 7-(2-methyl-1-imidazolyl) derivative **24** had moderate activity. The other 7-(4-substituted 1-imidazolyl) derivatives **26–33** were less potent than **20**. The 7-(1-benzimidazolyl) derivative **34** and the 7-(4,5,6,7-tetrahydro-1-benzimidazolyl) derivative **35** showed lower activities than that of **20**.

In vivo antibacterial activities of the pyrrolyl derivatives (**13** and **19**) and imidazolyl derivatives (**10**, **20**, and **25**) against an experimentally induced infection of mice after oral administration are given in Table V, together with the in vitro activity against the infecting strains. Monofluoro derivatives (**10** and **13**) were found to be essentially inactive against *Escherichia coli* KC-14 in vivo. On the other hand, difluoro derivatives (**19**, **20**, and **25**) showed good activities,

Table V. In Vivo Antibacterial Activity of 7-(Azole substituted)quinolones and Acute Toxicities

	antibacterial activity vs. *E. coli* KC-14 LD_{50},[b] mg/kg			
compd	MIC[a] μg/mL	ED_{50},[b,c] mg/kg po	po	iv
10	1.56	50	NT[d]	NT
13	3.13	50	NT	NT
19	3.13	11.7 (8.13–16.4)	NT	NT
20	0.78	4.0 (3.3–5.0)	4000	773
25	0.78	3.3 (2.4–4.7)	4000	593
NFLX	0.20	6.7 (4.8–9.4)	4000	327
3	0.20	NT	1072	193

[a] See Table IV, footnote *a*. [b] See the Experimental Section. [c] 95% confidence limits in parentheses. [d] Not tested.

which indicated the fluorine atom at the 8-position enhanced in vivo antibacterial activity. From the comparison of the activities of these compounds, imidazolyl derivatives

Table VI. Concentration in Serum after Oral Administration of 7-Imidazol-1-yl Derivatives to Mice

compd	concn in serum[a] (μg/mL) after (min): 30	60	120	240	μg h/mL (0–4 h)
10	4.20	2.30	1.10	ND[b]	5.5
13	5.53	2.20	0.84	0.55	6.8
19	10.7	7.07	3.23	1.65	17.2
20	44.8	39.3	7.6	1.7	64.9
25	49.2	29.4	10.0	6.3	67.9
NFLX	1.05	0.69	0.40	0.36	2.0

[a] See the Experimental Section. [b] Not determined.

20 and **25** were found to be about 3 times better than pyrrolyl derivative **19** and about 2 times more potent than NFLX, while in vitro activity of **20** and **25** were 4 times lower than that of NFLX.

The acute toxicities of the most active compounds **20** and **25** are summarized in Table V. It is apparent that the toxicities of **20** and **25** were significantly lower than that of piperazinyl derivative 3, which was confirmed to show higher toxicities, when administered orally to and injected intravenously in mice.

In order to clarify the reason for increased in vivo activities of imidazolyl derivatives **20** and **25**, the blood levels after oral administration to mice were investigated. The data for NFLX and the 6-fluoro-7-(1-imidazolyl) derivative **10** are included for comparison (Table VI). Compounds **20** and **25** showed higher blood concentrations after oral administration than NFLX. Therefore, the superior in vivo activities of **20** and **25** to NFLX were likely due to high blood concentration after oral administration. These higher blood levels of **20** and **25** were considered to be due to the combination of imidazole and fluorine atoms at the 7-position and 6,8-positions, respectively, from the comparison with the blood level of **10**, which showed low blood levels similar to those of NFLX.

From the above results of the microbiological, toxicological, and pharmacokinetic profile of imidazolyl derivatives **20** and **25** and other studies,[7a-c] we believe that the imidazolyl and 4-methylimidazolyl groups are beneficial groups for the PCA antibacterial agents.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus, and all melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined at 100 MHz on a Nihon Denshi PS-100 NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a Hitachi Seisakusyo M-60 instrument. Preparative thin-layer chromatography was performed with E. Merck silica gel $60F_{254}$.

4-Bromoimidazole,[10] 4-(methoxycarbonyl)imidazole,[11] 4-[(dimethylamino)carbonyl]imidazole,[12] 4-formylimidazole,[13] 4-[(dimethylamino)methyl]imidazole,[14] 4-(hydroxyimino)imidazole,[15] and 4,5,6,7-tetrahydrobenzimidazole[16] were prepared according to the literature, and other substituted imidazoles were commercially available.

In Vitro Antibacterial Activity. All the carboxylic acids prepared in this work were tested for antibacterial activity in vitro by the serial dilution method.[17]

In Vivo Antibacterial Activity. The in vivo antibacterial activity of the test compounds was determined in ddY-strain male mice (20–25 g body weight, five per group). Suspension of the test compounds was made by dispersing in 5% sodium (carboxymethyl)cellulose solution (5% CMC), and the compounds were diluted with 5% CMC to the desired concentration.

E. coli KC-14 was incubated in trypticase–soy broth at 37 °C for 18 h.

The culture was diluted in 5% (w/v) mucin to obtain 20 000 cfu/mL and 0.5 mL was injected intraperitoneally into mice. The mice were treated orally (po) with a specific amount of the test compound to be administered at 1 h after infection. ED_{50} values were calculated from the cumulative mortalities on the seventh day after infection by using the trimmed version of the Weil method.[18]

Acute Toxicity on Oral Administration to and Intravenous Injection in Mice. Oral Administration. A suspension of each test compound in a 0.5% CMC was administered orally to ddY-strain male mice (20–25 g body weight, five per group). Seven days later, LD_{50} values were determined by using the Weil method.

Intravenous Injection. Each of the compounds was dissolved in 1 N NaOH and a phosphoric acid–saline buffer (pH 7.2) was added to prepare a test solution. The test solution was injected intravenously into ddY-strain male mice (20–25 g body weight, five per group). Seven days later, the LD_{50} was determined by using the Weil method.

Blood Levels on Oral Administration to Mice. Each of the test compounds was suspended in 0.5% CMC at the concentration of 5 mg/mL.

ddY-strain male mice (22–25 g body weight, three per group) were used. The suspension of each test compound was administered orally to mice fasted for 16 h. The dose of the test compound was adjusted to 50 mg/kg of body weight of mice. Thirty, 60, 120, and 240 min after the administration of the test compound, blood was taken from each mouse, and the blood sample was centrifuged at 3000 rpm for 20 min to obtain a serum sample.

Concentration (μg/mL) of test compound in the serum sample was measured by a bioassay method on *Klebsiella pneumoniae* IFO 3512. Areas under the serum concentration–time curve (AUC, μg h/mL) was calculated from the figure of the serum concentration.

1-Ethyl-6-fluoro-1,4-dihydro-7-(1-imidazolyl)-4-oxo-3-quinolinecarboxylic Acid (10). A mixture of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**4**; synthesized in accordance with the literature,[9] 270 mg), imidazole (408 mg), and DMF (2 mL) was heated at 150 °C for 17.5 h with stirring. After the mixture was cooled with water, water was added, and then the mixture was adjusted to pH 5 with 3 N HCl and evaporated to dryness to give a yellow solid. The solid was suspended in MeOH and esterified with diazomethane and the reaction mixture was evaporated to dryness to give a mixture of two products, which were purified by preparative TLC ($CHCl_3$–MeOH, 15:1).

The product with an R_f value of 0.5 was recrystallized to give 7-chloro-1-ethyl-1,4-dihydro-6-(1-imidazolyl)-4-oxo-3-quinolinecarboxylic acid methyl ester (**6**) as colorless needles. ^{1}H NMR ($CDCl_3$): δ 1.55 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 3.86 (3 H, s, $COOCH_3$), 4.24 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 7.13 (2 H, br s, imidazole C_5-H and C_4-H), 7.64 (1 H, br s, imidazole C_2-H), 7.59 (1 H, s, C_8-H), 8.37 (1 H, s, C_5-H), 8.44 (1 H, s, C_2-H). MS: m/e 331, 333 (M^+).

The product with an R_f value of 0.4 was recrystallized to give 1-ethyl-6-fluoro-1,4-dihydro-7-(1-imidazolyl)-4-oxo-3-quinolinecarboxylic acid methyl ester (**5**) as colorless needles. ^{1}H NMR ($CDCl_3$–CD_3OD): δ 1.60 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 3.92 (3 H, s, $COOCH_3$), 4.42 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 7.26 (1 H, br s, imidazole C_3-H or C_4-H), 7.54 (1 H, br s, imidazole C_3-H or C_4-H), 7.80 (1 H, d, J = 6 Hz, C_8-H), 8.08 (1 H, br s, imidazole C_2-H), 8.34 (1 H, d, J = 11 Hz, C_5-H), 8.69 (1 H, s, C_2-H). MS: m/e 315 (M^+).

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To a solution of **5** (200 mg) in MeOH (9 mL) and $CHCl_3$ (3 mL) was added 1 N NaOH (1 mL) and the mixture was stirred at room temperature for 2 days and then evaporated to dryness. After addition of water, the mixture was adjusted to pH 5 with 3 N HCl to yield a pale yellow solid. The solid was collected by filtration, washed with water, dried, and recrystallized to give the acid **10** as colorless needles. ^1H NMR (DMSO-d_6): δ 1.46 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 4.69 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 7.23 (1 H, br s, imidazole C_4-H or C_5-H), 7.79 (1 H, br s, imidazole C_4-H or C_5-H), 8.24 (1 H, br s, imidazole C_2-H), 8.27 (1 H, d, J = 6 Hz, C_8-H), 8.27 (1 H, d, J = 11 Hz, C_5-H), 9.05 (1 H, s, C_2-H). MS: m/e 301 (M^+).

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-pyrazolyl)-3-quinolinecarboxylic Acid (11). A mixture of acid **4** (270 mg), pyrazole (204 mg), potassium carbonate (276 mg), and pyridine (2 mL) was heated at 135 °C for 18 h with stirring. After the mixture was cooled with water, evaporation to dryness yielded a pale green residue, which was triturated with 10% CH_3COOH and washed with water. The powder obtained was suspended in methanol, esterified with diazomethane, and then evaporated to dryness to give an orange residue which contained three products. They were isolated by preparative TLC ($CHCl_3$–MeOH, 50:1, developed three times).

The product with an R_f value of 0.6 was recrystallized to give 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-pyrazolyl)-3-quinolinecarboxylic acid methyl ester (**7**) as colorless prisms. ^1H NMR ($CDCl_3$–CD_3OD): δ 1.66 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 3.95 (3 H, s, $COOCH_3$), 4.49 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 6.62 (1 H, m, pyrazole H), 7.82 (1 H, m, pyrazole H), 8.10–8.42 (3 H, m, pyrazole H, C_5-H and C_8-H), 8.62 (1 H, s, C_2-H). MS: m/e 315 (M^+).

The second product, with an R_f value 0.5, was recrystallized to give 7-chloro-1-ethyl-1,4-dihydro-4-oxo-6-(1-pyrazolyl)-3-quinolinecarboxylic acid methyl ester (**8**) as colorless needles. ^1H NMR ($CDCl_3$–CD_3OD): δ 1.59 (3 H, t, J = 7.0 Hz, NCH_2CH_3), 3.90 (3 H, s, $COOCH_3$), 4.27 (2 H, q, J = 7.0 Hz, NCH_2CH_3), 6.50 (1 H, m, pyrazole H), 7.70 (2 H, m, pyrazole H), 7.59 (1 H, s, C_2-H). MS: m/e 331, 333 (M^+).

The third product, with an R_f value of 0.4, was recrystallized to give 1-ethyl-1,4-dihydro-4-oxo-6,7-di(1-pyrazolyl)-3-quinolinecarboxylic acid methyl ester (**9**) as colorless needles. ^1H NMR ($CDCl_3$–CD_3OD): δ 1.58 (3 H, t, J = 7.0 Hz, NCH_2CH_3), 3.89 (3 H, s, $COOCH_3$), 4.32 (2 H, q, J = 7.0 Hz, NCH_2CH_3), 6.28 (1 H, m, pyrazole H), 6.40 (1 H, m, pyrazole H), 6.73 (1 H, m, pyrazole H), 7.70 (2 H, m, pyrazole H), 7.73 (1 H, m, pyrazolyl H), 7.98 (1 H, s, C_5-H), 8.60 (1 H, s, C_2-H). MS: m/e 363 (M^+).

Ester **7** (29.5 mg) was suspended in MeOH–1 N NaOH (1:1, 2 mL) and heated at 65 °C for 10 min with stirring. MeOH was evaporated, water was added, and the mixture was adjusted to pH 5 with 1 N HCl to give a white powder. The powder was collected by filtration, washed with water, dried, and recrystallized to give the acid **11** as colorless needles. ^1H NMR (DMSO-d_6): δ 1.47 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 4.66 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 6.73 (1 H, m, pyrazole H), 7.96 (1 H, m, pyrazole H), 8.26 (1 H, d, J = 12 Hz, C_5-H), 8.37 (1 H, d, J = 7 Hz, C_8-H), 8.41 (1 H, m, pyrazole H), 14.69 (1 H, br s, COO*H*). MS: m/e 301 (M^+).

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-pyrrolyl)-3-quinolinecarboxylic Acid (13). A mixture of 7-amino-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid[9] (**12**, 500 mg) and 2,5-dimethoxytetrahydrofuran (529 mg) was heated at 180 °C for 40 min in a sealed tube. After the mixture was cooled with water, water was added to give a yellow solid which was collected by filtration, washed with water, dried, and recrystallized to yield the acid **13** as pale yellow needles.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1,2,4-triazol-4-yl)-3-quinolinecarboxylic Acid (16). A mixture of acid **12** (125 mg), *N,N*-dimethylformamide azine[10] (142 mg), and a catalytic amount of *p*-toluenesulfonic acid (7.6 mg) was heated at 180 °C for 30 min with stirring. After cooling, the reaction mixture was triturated with benzene to give a yellow powder. The powder was esterified with diazomethane in methanol, and the solvent was evaporated. The resulting yellow residue contained two products, which were purified by preparative TLC ($CHCl_3$–MeOH, 10:1).

The product with and R_f value of 0.7 was recrystallized to give 1-ethyl-6-fluoro-1,4-dihydro-7-[[(dimethylamino)methylene]-amino]-4-oxo-3-quinolinecarboxylic acid methyl ester (**15**) as colorless needles. ^1H NMR ($CDCl_3$): δ 1.54 (3 H, t, J = 7.0 Hz, NCH_2CH_3), 3.11 (6 H, s, $N(CH_3)_2$), 3.92 (3 H, s, $COOCH_3$), 4.19 (2 H, q, J = 7.0 Hz, NCH_2CH_3), 6.96 (1 H, d, J = 6.0 Hz, C_8-H), 7.76 (1 H, d, J = 2.0 Hz, N=CHN$(CH_3)_2$), 8.11 (1 H, d, J = 12.0 Hz, C_5-H), 8.42 (1 H, s, C_2-H). MS: m/e 319 (M^+).

The product with an R_f value of 0.2 was recrystallized to give 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1,2,4-triazol-4-yl)-3-quinolinecarboxylic acid methyl ester (**14**) as yellow needles. ^1H NMR (DMSO-d_6): δ 1.58 (3 H, t, J = 7.0 Hz, NCH_2CH_3), 3.92 (3 H, s, $COOCH_3$), 4.41 (2 H, q, J = 7.0 Hz, NCH_2CH_3), 7.89 (1 H, d, J = 6.0 Hz, C_8-H), 8.40 (1 H, d, J = 13 Hz, C_5-H), 8.64 (1 H, s, C_2-H), 8.75 and 8.76 (2 H, s, triazole H). MS: m/e 316 (M^+).

A mixture of ester **14** (31 mg), methanol (2 mL), and 1 N NaOH (2 mL) was stirred at room temperature for 30 min, and the methanol was evaporated. After addition of water, the mixture was neutralized with 1 N HCl to give pale yellow needles (**16**), which were collected by filtration, washed with water, and dried. ^1H NMR (Me_2SO-d_6): δ 1.46 (3 H, t, J = 7.0 Hz, NCH_2CH_3), 4.66 (2 H, q, J = 7.0 Hz, NCH_2CH_3), 8.33 (1 H, d, J = 12.0 Hz, C_5-H), 8.45 (1 H, d, J = 6.0 Hz, C_8-H), 9.10 (2 H, s, triazole H). MS: m/e 302 (M^+).

1-Ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-pyrrolyl)-3-quinolinecarboxylic Acid (19). A mixture of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**17**; synthesized in accordance with the literature,[5] 1.08 g), NH_4OH (28%, 8 mL), and pyridine (8 mL) was heated at 120 °C for 17 h in a sealed tube. The reaction mixture was evaporated to dryness to give a yellow residue. The yellow residue was triturated with water–CH_3COOH (10:1, 44 mL), filtered, washed with water, and then recrystallized to give 7-amino-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**18**, 573 mg) as pale yellow prisms. ^1H NMR (DMSO-d_6): δ 1.43 (3 H, dt, J = 1.0 and 7.0 Hz, NCH_2CH_3), 4.30–4.70 (2 H, m, NCH_2CH_3), 6.67 (2 H, br s, 7-NH_2), 7.76 (1 H, dd, J = 2.0 and 12.0 Hz, C_5-H), 8.78 (1 H, s, C_2-H). MS: m/e 268 (M^+).

A mixture of 7-aminoquinolone **18** (54 mg), 2,5-dimethoxytetrahydrofuran (53 mg), and 3 drops of CH_3COOH was heated at 180 °C for 5 min in a sealed tube. After cooling, the reaction mixture was triturated with water to give an insoluble brown solid. The solid was recrystallized to give **19** (35 mg) as pale yellow plates. ^1H NMR (DMSO-d_6): δ 1.48 (3 H, dt, J = 1.0 and 7.5 H, NCH_2CH_3), 4.40–4.80 (2 H, m, NCH_2CH_3), 6.30–6.50 (2 H, m, pyrrole H), 7.10–7.30 (2 H, m, pyrrole H), 8.13 (1 H, dd, J = 2 and 10 Hz, C_5-H), 9.01 (1 H, s, C_2-H). MS: m/e 318 (M^+).

1-Ethyl-6,8-difluoro-1,4-dihydro-7-(1-imidazolyl)-4-oxo-3-quinolinecarboxylic Acid (20). A mixture of **17** (13.6 g), imidazole (10.2 g), and DMF (80 mL) was heated at 100 °C for 1.25 h with stirring. The reaction mixture was cooled to room temperature, and the resulting crystals were collected by filtration and washed with EtOH to yield crude product. Recrystallization gave **20** (7.7 g) as colorless needles. ^1H NMR (DMSO-d_6): δ 1.51 (3 H, br t, J = 7.5 Hz, NCH_2CH_3), 4.67 (2 H, m, NCH_2CH_3), 7.28 (1 H, br s, imidazole C_4-H or C_5-H), 7.64 (1 H, br s, imidazole C_4-H or c_5-H), 8.12 (1 H, br s, imidazole C_2-H), 8.22 (1 H, dd, J = 2.0 and 10.0 Hz, C_5-H), 9.07 (1 H, s, C_2-H). MS: m/e 319 (M^+).

1-Ethyl-6,8-difluoro-1,4-dihydro-7-(substituted 1-imidazolyl)-4-oxo-3-quinolinecarboxylic Acids (24–35). These compounds (**24–35**) were synthesized by procedures similar to those described above with the corresponding imidazoles listed in Table III. The spectral properties and analytical data were consistent with their structures.

1-Ethyl-6-fluoro-1,4-dihydro-7-(1-imidazolyl)-8-methoxy-4-oxo-3-quinolinecarboxylic Acid (21). A solution of **20** (80 mg) in methanol (0.5 mL) and 28% $NaOCH_3$ methanol solution (0.14 mL) was stirred at room temperature for 3 h. The reaction mixture was evaporated to dryness and triturated with water containing CH_3COOH to give a pale yellow solid, which was collected by filtration, washed with water, and dried. The crude product was purified by preparative TLC ($CHCl_3$–MeOH, 10:1) and recrystallized to give **21** as pale yellow needles. ^1H NMR (DMSO-d_6): δ 1.44 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 3.41 (3 H, s, OCH_3), 4.72 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 7.25 (1 H, br s, imidazole H), 7.58 (1 H, br s, imidazole H), 8.04 (1 H, br s, imidazole H), 8.11 (1 H, d, J = 10.0 Hz, C_5-H), 9.00 (1 H, s, C_2-H), 14.57 (1 H, br s, COOH). MS: m/e 331 (M^+).

1-Ethyl-6-fluoro-1,4-dihydro-7-(1-imidazolyl)-8-(methylthio)-4-oxo-3-quinolinecarboxylic Acid (22). A solution of **20** (80 mg) in 1 N NaOH (0.4 mL) and a 15% $NaSCH_3$ aqueous solution (0.25 mL) were stirred at room temperature for 5 h. The reaction mixture was neutralized with CH_3COOH to yield a pale yellow solid, which was collected by filtration, washed with water, and dried. The solid was purified by preparative TLC ($CHCl_3$–MeOH, 10:1) and recrystallized to yield **22** as colorless needles. ^1H NMR (DMSO-d_6): δ 1.28 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 2.09 (3 H, s, SCH_3), 5.11 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 7.19 (1 H, br s, imidazole H), 7.52 (1 H, br s, imidazole H), 7.97 (1 H, br s, imidazole H), 8.28 (1 H, d, J = 10 Hz, C_5-H), 9.04 (1 H, s, C_2-H), 14.27 (1 H, br s, COOH). MS: m/e 347 (M^+).

1-Ethyl-8-fluoro-1,4-dihydro-7-(1-imidazolyl)-6-(dimethylamino)-4-oxo-3-quinolinecarboxylic Acid (23). A mixture of **20** (80 mg), dimethylamine hydrochloride (62 mg), and 1 N NaOH (1.2 mL) was heated at 150 °C for 6 h in a sealed tube. The reaction mixture was cooled, water was added, and the mixture was neutralized with acetic acid. The precipitated red solid was collected by filtration, purified by preparative TLC ($CHCl_3$–MeOH, 10:1), and recrystallized to yield **23** as pale yellow needles. ^1H NMR (DMSO-d_6): δ 1.46 (3 H, dt, J = 1.0 and 7.0 Hz, NCH_2CH_3), 4.40–4.80 (2 H, m, NCH_2CH_3), 7.20 (1 H, br s, imidazole H), 7.48 (1 H, br s, imidazole H), 7.68 (1 H, d, J = 2 Hz, C_5-H), 7.96 (1 H, br s, imidazole H), 8.90 (1 H, s, C_2-H), 14.75 (1 H, br s, COOH). MS: m/e 344 (M^+).

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N-Substituted 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines and 3-Phenylpiperidines: Effects on Central Dopamine and σ Receptors

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N-Substituted analogues of *trans*-7- and *trans*-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (*trans*-7- and *trans*-9-OH-OHBQ) were tested for dopamine (DA) D2 receptor affinity by using in vitro [^3H]spiperone and in vivo 5,6-di-*n*-Pr-ADTN binding assays. Potencies at central pre- (auto-) and postsynaptic DA receptors were determined by a biochemical and a behavioral method, respectively. Corresponding data were included for analogous, resolved 3-(3-hydroxyphenyl)piperidines and a few other substituted, racemic 3-phenylpiperidines. Beside the central dopaminergic effects of these compounds, previously reported σ receptor affinity data [[^3H]-(+)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine; [^3H]-(+)-3-PPP] were also taken into account for a comparison of the structure–activity/affinity relationships of these compounds at these two receptor types. Larger N-substituents in both phenylpiperidines and OHBQs increase both pre- and postsynaptic dopaminergic activity. An *n*-propyl group gives high dopaminergic efficacy at both receptor sites (pre- and postsynaptic) in all series. However, even higher dopaminergic potency is observed for *trans*-7-OH-OHBQs and (*S*)-3-(3-hydroxyphenyl)piperidines with N-substituents larger than *n*-propyl. In contrast, *trans*-4-*n*-Bu-9-OH-OHBQ is inactive, and (*R*)-3-(3-hydroxyphenyl)-*N*-*n*-butylpiperidine is less active at central DA receptors than its corresponding *n*-propyl analogue. This implies interesting differences in N-substituent sensitivity for the different classes of compounds with respect to the direction of their respective N-substituents at the drug–receptor interaction. The stereochemical and steric demands for σ receptor affinity are much less stringent. The general trend is that, up to a certain size, the more lipophilic the N-substituent, the higher the affinity for σ receptor sites.

Recently presented developments[1-3] of current dopamine (DA) receptor concepts[4-6] emphasize two different main directions, referred to as upward and downward in Figure 1, of the N-substituents of dopaminergic agonists. This new concept was developed on the basis of a study of resolved *trans*-7- and *trans*-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (*trans*-7- and *trans*-9-OH-OHBQ).[1,2] The intimate relationship between central pre- (auto-) and postsynaptic DA receptors has recently been demonstrated by Carlsson, using (*S*)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine ((*S*)-3-PPP, (*S*)-**4**) as the investigation tool.[7] *trans*-(4a*S*,10b*S*)-7-OH-OHBQ ((4a*S*,10b*S*)-HW165; (4a*S*,10b*S*)-**11**) has been demon-

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