Me). Anal. ($C_{21}H_{25}N$·HCl) C, H, N, Cl.

Compound **8c**: NMR identical with **2c** except for δ 6.05 (dt, J = 10 and 2 × 6.5 Hz, (*Z*)-CH_2CH=CH), 5.67 (dt, J = 10 and 2 × 1.5 Hz, (*Z*)-CH=C*H*C≡), 3.4 (dd, J = 6.5 and 1.5 Hz, NCH_2CH=); MS, m/e 291.

(*E*,*E*)-*N*-Methyl-*N*-2,4-nonadienyl-1-naphthalenemethanamine (2). A solution of (*E*,*E*)-2,4-nonadienal (20 g, 127 mmol) and 1-naphthalenemethanamine (20.4 g, 127 mmol) in benzene was boiled in a Dean–Stark apparatus until the calculated amount of water had separated. After removal of solvent, the Schiff base was taken up in methanol, treated with solid $NaBH_4$ (4,8 g, 127 mmol) in several portions at 40 °C, and stirred for 1 h at this temperature. This reaction mixture was used directly for reductive methylation[17] following the procedure of Sondengam.[18] Aqueous 35% formaldehyde solution (57 mL, 636 mmol) was added and the reaction mixture refluxed for 1 h. The mixture was then treated under ice cooling with solid $NaBH_4$ (24 g, 636 mmol) in several portions and stirred at room temperature overnight. After concentration, the residue was partitioned between aqueous $NaHCO_3$ solution and ethyl acetate and the organic phase dried and concentrated. The crude **7** (37.2 g, quant) thus obtained was shown by TLC and NMR to be of about 80% purity. Chromatography (toluene/ethyl acetate = 9/1) over silica furnished pure **2** (25 g, 67%) as a colorless oil: NMR for NCH_2-(*E*)-CH_α=CH_β-(*E*)-CH_γ=$CH_\delta CH_2$, 6.18 (H_β), 6.08 (H_γ), 5.72 (H_α), 5.65 (H_δ); $J_{H_\alpha CH_2N}$ = 6.75 Hz, $J_{H_\alpha H_\beta}$ = 14.5 Hz, $J_{H_\delta CH_2N}$ = 1.2 Hz, $J_{H_\beta H_\gamma}$ = 10.3 Hz, $J_{H_\gamma H_\delta}$ = 14.5 Hz, $J_{H_\alpha CH_2}$ = 1.35 Hz, $J_{H_\delta CH_2}$ = 6.9 Hz; 3.87 (s, Ar CH_2N), 3.13 (dd, NCH_2CH=), 1.9–2.2 (m, =CCH_2). Anal. ($C_{21}H_{27}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-4-nonen-2-ynyl-1-naphthalenemethanamine (9a) and Its *Z* Isomer 9b. 3-Octen-1-yne[19] (3.2 g, 15.8 mmol, *E*/*Z* = 1:2), *N*-methyl-1-naphthalenemethanamine (2.7 g, 15.8 mmol), paraformaldehyde (0.47 g, 15.8 mmol), and CuCl (0.16 g, 1.58 mmol) were reacted as described for the preparation of **3a** by Mannich condensation. By chromatography (hexane/butyl acetate = 10/1) of the crude reaction mixture the stereoisomers could be separated. Z isomer **9b** (1.58 g, 34%, DC R_f 0.46, oil) was isolated first, followed by a 1:1 mixture of **9a** and **9b** (1.72 g, 37%) and a pure sample of **9a** (0.19 g, 4%, DC R_f 0.42, oil).

Compound **9a**: NMR δ 6.22 (dt, J = 16 and 2 × 7 Hz, (*E*)-CH=C*H*CH_2), 5.58 (dm, J = 16 Hz, ≡C-(*E*)-C*H*=CH), 4.0 (s, Ar CH_2N), 3.44 (d, J = 1.5 Hz, NCH_2C≡), 2.38 (s, NCH_3), 2.0–2.3 (m, =CCH_2); mp (hydrochloride) 103–106 °C. Anal. ($C_{21}H_{25}$-N·HCl) C, H, N, Cl.

Compound **9b**: NMR identical with **8a** except for δ 5.95 (dt, J = 11 and 7 Hz, (*Z*)-CH=C*H*CH_2), 5.55 (dm, J = 11 Hz, ≡C-(*Z*)-C*H*=CH), 3.49 (d, J = 1.5 Hz, NCH_2C≡), 2.2–2.5 (m, =CCH_2).

Acknowledgment. We thank W. Granitzer, I. Leitner, A. Pruckner, and S. Roth for competent technical assistance, Dr. G. Schulz for the interpretation of NMR spectra, and Dr. G. Seidl for HPLC and GC analyses. We also thank Drs. M. Grassberger, N. Ryder, A. Stephen, and H. Vyplel for critical comments and their help in the preparation of the manuscript.

Registry No. **2**, 92525-78-5; **3a**, 92525-79-6; **3a**·HCl, 92525-80-9; **3b**, 78628-65-6; **4a**, 91161-71-6; **4b**, 78628-64-5; **4b**·HCl, 78628-66-7; **4c**, 92525-81-0; **5a**, 92525-82-1; **5b**, 92525-83-2; **6a**, 78629-20-6; **6b**, 67978-48-7; **6c**, 78629-22-8; (*E*)-**7a**, 78629-21-7; (*Z*)-**7a**, 78629-19-3; (*E*)-**7b**, 67978-51-2; (*Z*)-**7b**, 67978-52-3; (*E*)-**7c**, 78629-28-4; (*Z*)-**7c**, 78629-29-5; **8a**, 78628-81-6; **8b**, 78628-73-6; **8c**, 78628-85-0; **9a**, 92525-84-3; **9b**, 92525-85-4; R_1NHCH_3, 14489-75-9; $R_1N(CH_3)$-CH_2C≡CH, 2321-99-5; R_1NH_2, 118-31-0; *t*-BuC≡CC≡CH, 4911-56-2; *n*-BuC≡CBr, 1119-64-8; *t*-BuC≡CH, 917-92-0; CH_2=CHCHO, 107-02-8; *n*-BuC≡CH, 693-02-7; *sec*-BuC≡CH, 922-59-8; (*E*,*E*)-*n*-BuCH=CHCH=CHCHO, 5910-87-2; (*E*)-*n*-BuCH=CHC≡CH, 42104-42-7; (*Z*)-*n*-BuCH=CHC≡CH, 42091-89-4.

(17) For a new modification of reductive methylation using salts of phosphorus acid as reducing agent, see: Loibner, H.; Pruckner, A., Stütz, A. *Tetrahedron Lett.* **1984**, 2535.
(18) Sondengam, B. L.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Lett.* **1973**, *3*, 261.
(19) Pages 109, 125 in ref 16.

Pyridonecarboxylic Acids as Antibacterial Agents. 4.[1] Synthesis and Antibacterial Activity of 7-(3-Amino-1-pyrrolidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid and Its Analogues

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The title compounds (**28–56**) with an amino- and/or hydroxy-substituted cyclic amino group at C-7 were prepared with 1-substituted 7-chloro-, 7-(ethylsulfonyl)-, and 7-(tosyloxy)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and their ethyl esters (**3–7**) with cyclic amines such as 3-aminopyrrolidine. The N-1 substituent includes ethyl, vinyl, and 2-fluoroethyl groups. As a result of in vitro and in vivo antibacterial screenings, three compounds, 1-ethyl- and 1-vinyl-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**33a** and **33b**) and 1-vinyl-7-[3-(methylamino)-1-pyrrolidinyl] analogue **34b**, were found to be more active than enoxacin (**2**) and to be worthy of further biological study. Structure–activity relationships are discussed.

As exemplified by pipemidic acid (**1**),[2] we showed first that a piperazinyl group was of much importance for the improvement of antibacterial activity and pharmacokinetic properties of a class of pyridonecarboxylic acid antibacterial agents. During the last few years, several analogues having both fluoro and piperazinyl groups in their molecules were reported successively;[3,4] their antibacterial activities are noticeably much more potent and broader than

(1) Paper 3: Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Heterocycl. Chem.*, **1984**, *21*, 673.
(2) Matsumoto, J.; Minami, S. *J. Med. Chem.* **1975**, *18*, 74.
(3) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358. Goueffon, Y.; Montay, G.; Roquet, F.; Pesson, M. *C. R. Hebd. Seances Acad. Sci.* **1981**, 37. Grohe, K.; Zieiler, H.; Metzger, K. G. German Offen. 3 033 157, 1982; *Chem. Abstr.* **1982**, *97*, 55790u. Hayakawa, I.; Hiramitsu, T. European Patent Appl. 47 005, 1982; *Chem. Abstr.* **1982**, *97*, 55821b.
(4) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Med. Chem.* **1984**, *27*, 292.

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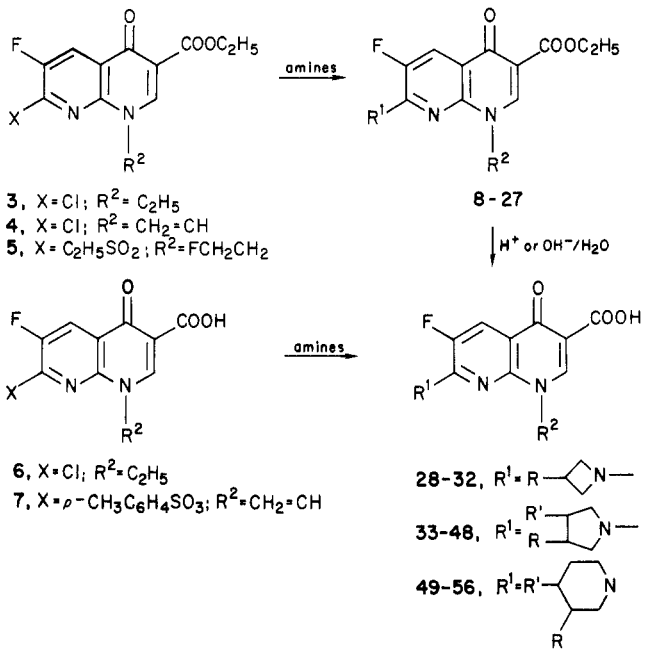
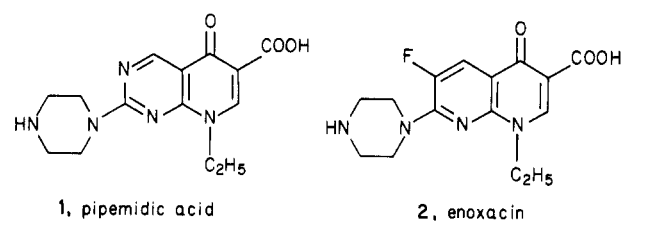
Scheme I[a]



[a] For 28-56: a, $R^2 = C_2H_5$; b, $R^2 = CH_2{=}CH$; c, $R^2 = FCH_2CH_2$; see Table II for R and R'.

those of the precedents[5] in this class. One of them, enoxacin (2, originally called AT-2266), was described in

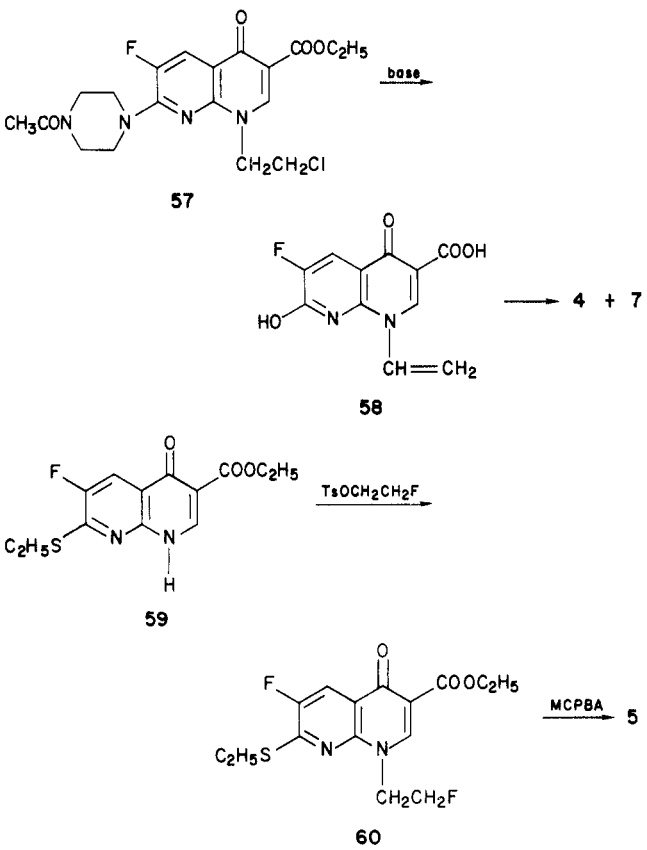


previous papers.[1,4] Our next effort in this area was mainly directed at a search for analogues with a substituent that might cause a greater enhancement in activity than the piperazinyl group. Amino-substituted alicyclic amino groups such as 3-aminopyrrolidinyl or 3-aminoazetidinyl may be expected to offer such an enhancement of activity since the physicochemical properties of these groups seem to be generally similar to those of the piperazinyl group. The present paper deals with a synthesis of 1-substituted 6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**28–56**) with an amino- and/or hydroxy-substituted alicyclic amino group at C-7 and includes a discussion of structure–activity relationships of these compounds.

Chemistry. The main routes utilized for the preparation of the carboxylic acids **28–56** are shown in Scheme I. Upon treatment of ethyl 1,7-disubstituted 6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates **3**, **4**, and **5** with an appropriate amine (method A), the displacement reaction proceeded regioselectively at C-7 to give the corresponding esters **8–27**. The esters were then hydrolyzed under either acidic (method B) or alkaline (method C) conditions, giving the corresponding carboxylic acids. Displacement of the 7-chloro and 7-tosyloxy groups of **6** and **7**, respectively, by an amine (method D) gave the carboxylic acids **31a**, **32a**, **38a,b**, **40a**, **42a**, **44a**, **46a**, **52a**, **54a**, and **56a**.

Acylation of **33a,b,c**, **34b,c**, **46a**, and **52a** with acetic anhydride, trifluoroacetic anhydride, or a formic acid–formamide mixture (method E) gave the corresponding acyl compounds **39a,b**, **40b,c**, **41a**, **42b,c**, **47a**, and **53a**. Alkaline hydrolysis of **42a** gave **34a** (method F). Reductive N-methylation of **34c** with a mixture of formic acid and 37% formalin (method G) afforded 7-[3-(dimethylamino)-1-pyrrolidinyl] derivative **38c**. The compounds prepared thus by the methods A–G are summarized in Table II.

Scheme II



Among the starting compounds (**3–5** and **7**), **3** was prepared by esterification of the carboxylic acid **6**, which had previously been reported,[4] and **4**, **5**, and **7** were derived as shown in Scheme II. Thus, alkaline treatment of the 1-(2-chloroethyl) derivative **57**,[4] followed by chlorination of the 7-hydroxy-1-vinyl derivative **58** and successive treatment with ethanol, afforded the 7-chloro-1-vinyl compound **4**. Tosylation of **58** gave 7-(tosyloxy)-1-vinyl analogue **7**. Compound **5** was derived from **59**[1] by treatment with 2-fluoroethyl tosylate, followed by oxidation of the resultant 1-(2-fluoroethyl) derivative **60** with *m*-chloroperbenzoic acid; the site of alkylation in this case was assigned on the basis of ^{13}C NMR spectral analysis.

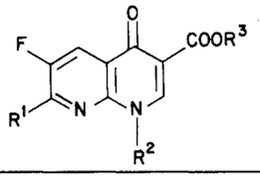
Biological Results and Discussion

The results of the in vitro antibacterial activity for compounds prepared in the present study against Gram-positive (*Staphylococcus aureus* 209P JC-1) and Gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* Tsuchijima) are summarized in Table II. The data for enoxacin (**2**) are included for comparison.

It is noteworthy that the replacement of the piperazinyl group at C-7 of **2** by the 3-aminopyrrolidinyl group (**33a**) causes an enhancement in activity against all the bacteria tested. The replacement of the 3-aminopyrrolidinyl ring by a larger membered ring, such as 3- and 4-aminopiperidine (**49a** and **50a**), results in a retention or increase in activity against *S. aureus*, whereas it causes a decrease in activity against *P. aeruginosa*. On the contrary, the

(5) For example, see: Albrecht, R. *Prog. Drug Res.* **1977**, *21*, 9.

Table I. 1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids



no.	R^1	R^2	R^3	mp, °C	recrystn solvent	yield,[a] %	formula[b]
3	Cl	C_2H_5	C_2H_5	191–194	AcOEt	96	$C_{13}H_{12}ClFN_2O_3$
4	Cl	CH_2=CH	C_2H_5	150–151	AcOEt	77	$C_{13}H_{10}ClFN_2O_3$
5	$C_2H_5SO_2$	FCH_2CH_2	C_2H_5	176–178	EtOH	74	$C_{15}H_{16}F_2N_2O_5S$
7	p-$CH_3C_6H_4SO_3$	CH_2=CH	H	190–192	EtOH–$CHCl_3$	62	$C_{18}H_{13}FN_2O_6S$
8	3-CH_3CONH-1-azet[c]	C_2H_5	C_2H_5	229–230	EtOH	63	$C_{18}H_{21}FN_4O_4$
9	3-CF_3CONH-1-azet	CH_2=CH	C_2H_5	251–253	EtOH–$CHCl_3$	75	$C_{18}H_{16}F_4N_4O_4$
10	3-morpholino-1-azet	C_2H_5	C_2H_5	195–196	MeCN	90	$C_{20}H_{25}FN_4O_4$
11	3-HO-1-azet	C_2H_5	C_2H_5	265–268	EtOH–$CHCl_3$	97	$C_{16}H_{18}FN_3O_4$
12	3-CH_3CONH-1-pyr[d]	C_2H_5	C_2H_5	267–270	EtOH–$CHCl_3$	90	$C_{19}H_{23}FN_4O_4$
13	3-CF_3CONH-1-pyr	CH_2=CH	C_2H_5	280–282	EtOH-$CHCl_3$	92	$C_{19}H_{18}F_4N_4O_4$
14	3-CH_3CONH-1-pyr	FCH_2CH_2	C_2H_5	269–270	EtOH–$CHCl_3$	73	$C_{19}H_{22}F_2N_4O_4$
15	3-$CF_3CON(CH_3)$-1-pyr	CH_2=CH	C_2H_5	160–161	AcOEt–$(i\text{-}Pr)_2O$	73	$C_{20}H_{20}F_4N_4O_4$
16	3-$CH_3CON(CH_3)$-1-pyr	FCH_2CH_2	C_2H_5	227–229	EtOH–$CHCl_3$	80	$C_{20}H_{24}F_2N_4O_4$
17	3-$CH_3CON(C_2H_5)$-1-pyr	C_2H_5	C_2H_5	205–206	EtOH	92	$C_{21}H_{27}FN_4O_4$
18	3-$CH_3CON(CH_2CF_3)$-1-pyr	C_2H_5	C_2H_5	226–228	EtOH	81	$C_{21}H_{24}F_4N_4O_4$
19	3-$CF_3CON(CH_2CF_3)$-1-pyr	CH_2=CH	C_2H_5	138–140	AcOEt–Et_2O	89	$C_{19}H_{19}F_7N_4O_3$
20	3-$CH_3CON(C_3H_7)$-1-pyr	C_2H_5	C_2H_5	180–181	EtOH–AcOEt	76	$C_{22}H_{29}FN_4O_4$
21	3-$CH_3CONHN(COCH_3)$-1-pyr	C_2H_5	C_2H_5	277–279	EtOH–$CHCl_3$	82	$C_{21}H_{26}FN_5O_5$
22	3-CH_3CONH-4-CH_3COO-1-pyr	C_2H_5	C_2H_5	254–255	EtOH	77	$C_{21}H_{25}FN_4O_6$
23	3-Cl-1-pyr	C_2H_5	C_2H_5	207–208	EtOH	90	$C_{17}H_{19}ClFN_3O_3$
24	3-CH_3CONH-piper[e]	C_2H_5	C_2H_5	202–203	EtOH	90	$C_{20}H_{25}FN_4O_4 \cdot {}^1/_2H_2O$
25	4-CH_3CONH-piper	C_2H_5	C_2H_5	195–196	EtOH–MeCN	90	$C_{20}H_{25}FN_4O_4$
26	4-C_6H_5CONH-piper	C_2H_5	C_2H_5	246–247	EtOH–$CHCl_3$	86	$C_{25}H_{27}FN_4O_4$
27	3-HO-piper	C_2H_5	C_2H_5	189–190	EtOH	81	$C_{18}H_{22}FN_3O_4 \cdot {}^1/_5H_2O$

[a] Yields are of purified products by method A except for **3–5** and **7** and are not maximal. [b] All compounds were analyzed for C, H, N and where present Cl, F, and S; analytical results were within ±0.4% of theoretical values. [c] Azetidinyl = azet. [d] Pyrrolidinyl = pyr. [e] Piperidinyl = piper.

replacement by a smaller ring such as 3-aminoazetidine (**28a**) shows the same level of activity as that of **2** against all the organisms.

The replacement of the amino group of **28a**, **33a**, **49a**, and **50a** by a hydroxyl group (giving **30a**, **46a**, **55a**, and **56a**, respectively) causes a significant decrease in Gram-negative activity compared with the corresponding amino-substituted compounds. Alkylation or formylation of the hydroxyl group (giving **31a**, **32a**, and **47a**) reduces furthermore the activity against Gram-negative bacteria.

Compounds **52a** and **53a**, which have a methylene group between the amino group and the piperadinyl ring, are less active than **50a**. Compound **54a** with a carbamoyl group is also inferior to **49a**.

Introduction of an alkyl group such as a methyl, ethyl, 2,2,2-trifluoroethyl, or propyl group to the amino nitrogen atom on the pyrrolidinyl ring of **33a** (giving **34a–37a**) reduces generally the activity against the organisms in this order. The dimethylamino compound **38a** shows activity similar to that of the ethylamino congener **35a**.

Acylation of the amino group on the pyrrolidinyl ring, giving **39a–42a** (see Table II), results in a decrease in activity. The decrease is greater with Gram-negative activity than with Gram-positive activity.

Compounds **43a** and **48a** with a hydrazino and chloro group, respectively, on the pyrrolidinyl ring are comparable to **33a** in activity against Gram-positive bacteria, whereas they are much less active against Gram-negative organisms, particularly *P. aeruginosa*.

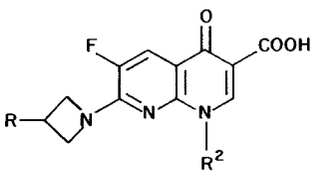
When the N-1 substituent is varied while the C-7 substituent is kept constant as the most active 3-aminopyrrolidinyl group, introduction of a vinyl group (**33b**) influences markedly the antibacterial activity. Thus, the vinyl group significantly enhances Gram-negative activity without a decrease of Gram-positive activity. On the other hand, introduction of a fluoroethyl group (**33c**) reduces Gram-positive activity, whereas Gram-negative activity remains unchanged. Either alkylation or acylation of compounds **33b,c** (giving **34b,c–42b,c**) causes a decrease in activity. This is consistent with the case of the same modification of the 1-ethyl compound **33a** as discussed above.

In each comparison between the ethyl compounds (series **a**) and their vinyl analogues (series **b**) of **28**, **33**, **34**, **36**, **38–40**, and **42**, the vinyl group enhances Gram-negative activity, whereas it reduces Gram-positive activity; this relationship is in agreement with that observed in our previous works.[2,4] The fluoroethyl group shows a tendency to enhance Gram-negative activity and to reduce Gram-positive activity (compare **33a**, **34a**, **38a**, **40a**, and **42a** with **33c**, **34c**, **38c**, **40c**, and **42c**, respectively).

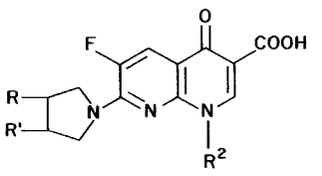
Thus, the 10 compounds **28a,b**, **33a–c**, **34a–c**, **46a**, and **50a**, being equal or superior to **2** in the in vitro antibacterial activity, were tested with oral administration upon systemic infections due to *S. aureus* 50774, *E. coli* P-5101, and *P. aeruginosa* 12 in mice. The results are listed in Table III, which includes, for reference, the minimal inhibitory concentration (MIC) against the organisms employed.

The therapeutic efficacies of **28a**, **34a**, **46a**, and **50a** are obviously inferior to those of **2**. Compounds **28b**, **33a–c**, and **34a,b** compare very favorably with **2**. Of much interest are **33a,b** and **34b**, which are much more efficient than **2**, particularly against staphylococcal and pseudomonal infections. In conclusion, the 3-aminopyrrolidinyl group proved to be equivalent to or more efficient than the piperazinyl group. In variation of the N-1 substituent of **28a**, **33a**, and **34a**, the vinyl group causes an outstanding increase in efficacy on all the infections tested, whereas the 2-fluoroethyl group tends to reduce the efficacy in general.

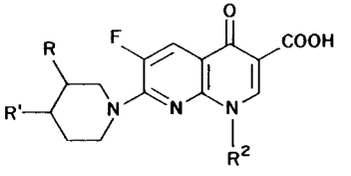
Table II. 1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids and Their in Vitro Antibacterial Activity



28-32



33-48



49-56

no.	R	R′	R^2	mp, °C	recrystn solvent	method[a] (starting material)	yield,[b] %	formula[c]	min inhibitory concn[d] μg/mL: *S. aureus* 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* Tsuchijima
2[e]									0.78	0.2	0.78
28a	H_2N		C_2H_5	266–269 dec	NaOH–$AcONH_4$[f]	C (8)	38	$C_{14}H_{15}FN_4O_3$	0.78	0.1	0.78
28b	H_2N		CH_2=CH	250–255 dec	NaOH–AcOH[f]	C (9)	63	$C_{14}H_{13}FN_4O_3$	1.56	0.1	0.39
29a	$O(CH_2CH_2)_2N$		C_2H_5	260–262	MeCN–$CHCl_3$	C (10)	86	$C_{18}H_{21}FN_4O_4$	1.56	6.25	50
30a	HO		C_2H_5	284–286	DMF	C (11)	91	$C_{14}H_{14}FN_3O_4$	0.78	0.78	3.13
31a	CH_3O		C_2H_5	233–235	MeCN	D (6)	48	$C_{15}H_{16}FN_3O_4$	0.78	3.13	6.25
32a	C_2H_2O		C_2H_5	201–203	MeCN	D (6)	77	$C_{16}H_{18}FN_3O_4$	0.78	3.13	25
33a	H_2N	H	C_2H_5	272–290 dec	EtOH–H_2O	B (12)	84	$C_{15}H_{17}FN_4O_3$·HCl	0.2	0.1	0.39
33b	H_2N	H	CH_2=CH	253–257	NaOH–AcOH[f]	C (13)	83	$C_{15}H_{15}FN_4O_3$	0.2	0.025	0.2
33c	H_2N	H	FCH_2CH_2	251–255	HCl–NH_4OH[f]	B (14)	73	$C_{15}H_{16}F_2N_4O_3$	0.39	0.1	0.39
34a	CH_3NH	H	C_2H_5	242–245	NaOH–$AcONH_4$[f]	F (42a)	71	$C_{16}H_{19}FN_4O_3$	0.39	0.2	1.56
34b	CH_3NH	H	CH_2=CH	265–267 dec	NaOH–AcOH[f]	C (15)	87	$C_{16}H_{17}FN_4O_3$	0.78	0.1	0.78
34c	CH_3NH	H	FCH_2CH_2	243–245	HCl–NH_4OH[f]	B (16)	65	$C_{16}H_{18}F_2N_4O_3$	0.78	0.2	0.78
35a	C_2H_5NH	H	C_2H_5	>290 dec	EtOH–H_2O	B (17)	82	$C_{17}H_{21}FN_4O_3$·HCl	0.78	0.78	3.13
36a	CF_3CH_2NH	H	C_2H_5	203–204	EtOH	B (18)	67	$C_{17}H_{18}F_4N_4O_3$	0.78	1.56	50
36b	CF_3CH_2NH	H	CH_2=CH	183–185	MeCN	C (19)	87	$C_{17}H_{16}F_4N_4O_3$	1.56	6.25	100
37a	C_3H_7NH	H	C_2H_5	268–269 dec	H_2O	B (20)	91	$C_{18}H_{23}FN_4O_3$·$HCl^{.3}/_2H_2O$	25	6.25	>100
38a	$(CH_3)_2N$	H	C_2H_5	234–236	MeCN–$CHCl_3$	D (6)	84	$C_{17}H_{21}FN_4O_3$	1.56	0.78	6.25
38b	$(CH_3)_2N$	H	CH_2=CH	199–201	EtOH–$CHCl_3$	D (7)	86	$C_{17}H_{19}FN_4O_3$	3.13	0.39	3.13
38c	$(CH_3)_2N$	H	FCH_2CH_2	247–249	EtOH–$CHCl_3$	G (34c)	45	$C_{17}H_{20}F_2N_4O_3$	0.78	0.2	6.25
39a	OHCNH	H	C_2H_5	285–286	HCOOH–Me_2CO	E (33a)	81	$C_{16}H_{17}FN_4O_4$	0.78	0.78	3.13
39b	OHCNH	H	CH_2=CH	287–289	DMF	E (33b)	78	$C_{16}H_{15}FN_4O_4$	0.78	0.39	3.13
40a	CH_3CONH	H	C_2H_5	283–284	DMF–EtOH	D (6)	97	$C_{17}H_{19}FN_4O_4$	0.78	6.25	6.25
40b	CH_3CONH	H	CH_2=CH	287–289 dec	DMF	E (33b)	88	$C_{17}H_{17}FN_4O_4$	1.56	0.78	12.5
40c	CH_3CONH	H	FCH_2CH_2	294–297	DMF–EtOH	E (33c)	74	$C_{17}H_{18}F_2N_4O_4$	1.56	1.56	25
41a	CF_3CONH	H	C_2H_5	290–292	CF_3COOH–H_2O	E (33a)	79	$C_{17}H_{16}F_4N_4O_4$	0.78	1.56	6.25
42a	$CH_3CON(CH_3)$	H	C_2H_5	287–289	DMF	D (6)	98	$C_{18}H_{21}FN_4O_4$	0.78	6.25	25
42b	$CH_3CON(CH_3)$	H	CH_2=CH	274–275	DMF–EtOH	E (34b)	89	$C_{18}H_{19}FN_4O_4$	1.56	3.13	25
42c	$CH_3CON(CH_3)$	H	FCH_2CH_2	291–294	DMF	E (34c)	42	$C_{18}H_{20}F_2N_4O_4$	0.39	1.56	25
43a	H_2NNH	H	C_2H_5	249–250	EtOH–H_2O	B (21)	84	$C_{15}H_{18}FN_5O_3$·$HCl^{.1}/_5H_2O$	0.39	1.56	12.5
44a	H_2NCONH	H	C_2H_5	266–267	DMF–EtOH	D (6)	91	$C_{16}H_{18}FN_5O_4$	6.25	3.13	25
45a	H_2N	HO	C_2H_5	280–285 dec	EtOH–H_2O	B (22)	96	$C_{15}H_{17}FN_4O_4$·HCl	1.56	1.56	3.13
46a	HO	H	C_2H_5	291–293	DMF–EtOH	D (6)	79	$C_{15}H_{16}FN_3O_4$	0.39	0.78	0.78
47a	OHCO	H	C_2H_5	234–236	EtOH–$CHCl_3$	E (46a)	74	$C_{16}H_{16}FN_3O_5$	0.39	1.56	3.13
48a	Cl	H	C_2H_5	274–275	EtOH–$CHCl_3$	C (23)	87	$C_{15}H_{15}ClFN_3O_3$	0.2	0.39	12.5

49a	H_2N	H	C_2H_5	169–170	EtOH	B (24)	61	$C_{16}H_{19}FN_4O_3{}^{\cdot 1}/_2H_2O$	0.78	0.78	6.25
50a	H	H_2N	C_2H_5	268–272	HCl–AcONa[f]	B (25)	74	$C_{16}H_{19}FN_4O_3$	0.2	0.2	1.56
51a	H	C_6H_5CONH	C_2H_5	287–288	AcOH	B (26)	89	$C_{23}H_{23}FN_4O_4$	1.56	12.5	>100
52a	H	H_2NCH_2	C_2H_5	213–214	EtOH–$CHCl_3$	D (6)	88	$C_{17}H_{21}FN_4O_3{\cdot}H_2O$	0.39	1.56	12.5
53a	H	$CH_3CONHCH_2$	C_2H_5	267–268	EtOH–$CHCl_3$	E (52a)	73	$C_{19}H_{23}FN_4O_4$	0.78	1.56	25
54a	H_2NCO	H	C_2H_5	>300	DMF	D (6)	96	$C_{17}H_{19}FN_4O_4$	6.25	12.5	50
55a	HO	H	C_2H_5	208–209	EtOH	C (27)	33	$C_{16}H_{18}FN_3O_4$	1.56	3.13	25
56a	H	HO	C_2H_5	217–218	EtOH–$CHCl_3$	D (6)	89	$C_{16}H_{18}FN_3O_4$	0.78	3.13	6.25

[a] Capital letters refer to the method described in the Experimental Section. [b,c] See footnotes in Table I. [d] See the Experimental Section. [e] Enoxacin; see ref 4. [f] Purified by reprecipitation on treatment with the acid and subsequently with the base or vice versa.

Table III. Oral Efficacy on Systemic Infections[a]

	ED_{50}:[b] min inhibitory concn[c]		
no.	*S. aureus* 50774	*E. coli* P-5101	*P. aeruginosa* 12
2	10.0 (0.78)	1.8 (0.1)	9.0 (0.78)
28a	8.8 (0.78)	4.1 (0.1)	12.5 (0.78)
25b	5.3 (0.78)	1.3 (0.05)	4.4 (0.78)
33a	3.0 (0.39)	1.7 (0.1)	3.7 (0.78)
33b	1.6 (0.39)	0.72 (0.05)	1.6 (0.2)
33c	4.6 (0.39)	2.8 (0.1)	6.3 (0.39)
34a	4.8 (0.78)	1.4 (0.2)	6.5 (0.78)
34b	1.6 (0.78)	2.0 (0.2)	3.7 (0.78)
34c	15 (0.78)	2.8 (0.1)	19.3 (0.78)
46a	5.5 (0.39)	6.8 (0.39)	42 (3.13)
50a	>25 (0.78)	6.3 (0.39)	16.2 (1.56)

[a] For experimental details, see ref 4. Challenge dose (cells per mouse); 5×10^8 for *S. aureus*, 9×10^6 for *E. coli*, and 4×10^3 for *P. aeruginosa*. [b] In milligram per kilogram. [c] In microgram per milliliter.

Compounds **28b**, **33a–c**, and **34a–c** exhibit weak oral acute toxicity in mice, all being >2000 mg/kg of the median lethal dose (LD_{50}).

These findings indicate that 1-ethyl- and 1-vinyl-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**33a** and **33b**) and 1-vinyl-7-[3-(methylamino)-1-pyrrolidinyl] analogue **34b** are worth further biological evaluation as possible potent antibacterial agents.

Experimental Section

Chemistry. All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi Model 215 spectrophotometer. ^1H NMR spectra were taken at 60 or 100 MHz on either a Varian EM-360A or HA-100 spectrometer and ^{13}C NMR spectra were obtained with a Varian FT-80A spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi RMU-6L spectrometer. IR, NMR, and mass spectra were obtained on all compounds and were consistent with assigned structures. Elemental analyses are indicated only by symbols of the elements; analytical results were within ±0.4% of theoretical values.

Ethyl 7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (3). To a stirred suspension containing 24.9 g (0.092 mol) of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**6**),[4] 19 mL of NEt_3, and 200 mL of $CHCl_3$ was added portionwise 11 mL of ethyl chlorocarbonate, while the temperature was maintained at 5–10 °C under ice-cooling. After the mixture was stirred for 30 min at the same temperature, 50 mL of EtOH was added. The reaction mixture was allowed to stir for 4 h at room temperature and concentrated to dryness in vacuo. After addition of 50 mL of EtOH, the precipitate was collected by filtration and recrystallized from AcOEt to give 26.6 g (96%) of **3**.

Ethyl 7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylate (4). A mixture containing 20.0 g (0.08 mol) of 6-fluoro-1,4-dihydro-7-hydroxy-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylic acid (**58**) and 60 mL of $POCl_3$ was heated at 115 °C for 6 min. The excess of $POCl_3$ was evaporated in vacuo and 150 mL of $CHCl_3$ was added to the residue. After addition of 30 mL of EtOH, the mixture was allowed to stir at 40 °C for 30 min and cooled and then 100 mL of water was added. The organic phase was separated, dried over Na_2SO_4, and evaporated in vacuo. The residue was crystallized from a mixture of AcOEt and Et_2O to give 18.2 g (77%) of **4**.

Ethyl 7-(Ethylsulfonyl)-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (5). To a mixture containing 24.0 g (0.07 mol) of ethyl 7-(ethylthio)-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**60**) and 200 mL of $CHCl_3$ was added 24.1 g (0.14 mol) of *m*-chloroperbenzoic acid under ice-cooling. The mixture was allowed to stir at room temperature for 2 h. After addition of 10% Na_2CO_3, the organic phase was separated and dried over K_2CO_3, and the solvent was evaporated in vacuo. The residue

was crystallized from EtOH to give 19.4 g (74%) of **5**.

6-Fluoro-1,4-dihydro-4-oxo-7-(tosyloxy)-1-vinyl-1,8-naphthyridine-3-carboxylic Acid (7). A mixture containing 2.5 g (0.01 mol) of **58**, 3.8 g (0.02 mol) of tosyl chloride, 1.4 g (0.01 mol) of K_2CO_3, and 20 mL of MeCN was heated to reflux for 4 h. After filtration, the filtrate was concentrated to dryness in vacuo. The residue was chromatographed on silica gel with $CHCl_3$. The solid resulting from the main fraction was crystallized from a mixture of EtOH and $CHCl_3$ to give 2.5 g (62%) of **7**.

Ethyl 1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (8–27) (Table I). Method A. A mixture containing 0.01 mol of an ester (**3–5**), 0.015 mol of an appropriate amine, 1.5 mL of NEt_3, and 40 mL of EtOH was heated to reflux for 0.5–4 h and concentrated to dryness in vacuo. After addition of 80 mL of water, the residue was filtered off or extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated in vacuo. The resulting solid was crystallized from an appropriate solvent to give **8–27**.

1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids (28–56) (Table II). Method B. A mixture containing 0.01 mol of an ester (**12**, **14**, **16–18**, **20–22**, or **24–26**), and 20% HCl was heated to reflux for 3–10 h and then concentrated to dryness in vacuo. The resulting solid was filtered off and washed with EtOH. Recrystallization from the solvent given in Table II gave the corresponding compound (**33a**, **35a–37a**, **43a**, **45a**, or **51a**). Neutralization of the filtrate with aqueous ammonia afforded **33c**, **34c**, **49a**, or **50a**.

Method C. A stirred suspension containing 0.01 mol of an ester (**8–11**, **13**, **15**, **19**, **23**, or **27**), 40 mL of 5–10% NaOH, and 5–10 mL of EtOH was heated at 60–100 °C for 0.5–2 h, allowed to cool, and adjusted to pH 6–7 with 30% AcOH. The resulting solid was filtered off, washed with water, and recrystallized from an appropriate solvent to give the corresponding carboxylic acid (**28a,b**, **29a**, **30a**, **33b**, **34b**, **36b**, **48a**, or **55a**).

Method D. A stirred suspension containing 0.01 mol of **6** or **7**, 0.015 mol of an amine, 3 mL of NEt_3, and 50 mL of a solvent (EtOH, MeCN, or DMF) was heated at 100–110 °C for 1–4 h. The reaction mixture was concentrated to dryness in vacuo. The residue was taken up in 3% AcOH, and the solution was adjusted to pH 6–7. The resulting solid was filtered off, washed with water, and recrystallized from an appropriate solvent to give **31a**, **32a**, **38a,b**, **40a**, **42a**, **44a**, **46a**, **52a**, **54a**, or **56a**.

Method E. A mixture containing 0.01 mol of **33a–c**, **34b,c**, **46a**, or **52a** and an acylating agent [formic acid (30 mL)–formamide (10 mL), acetic anhydride (10 mL)–acetic acid (30 mL), or trifluoroacetic anhydride (30 mL)] was heated at 100–110 °C for 1–3 h with stirring. The reaction mixture was concentrated to dryness in vacuo. The residue was triturated with water or EtOH. The resulting solid was filtered off and recrystallized from an appropriate solvent to give the corresponding acyl compound (**39a,b**, **40b,c**, **41a**, **42b,c**, **47a**, or **53a**).

Method F. A solution of 7-[3-(*N*-methylacetamido)-1-pyrrolidinyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**42a**) (3.0 g, 0.08 mol) in 75 mL of 10% NaOH was heated to reflux for 4 h, allowed to cool, and adjusted to pH 6–7 with AcOH. The resulting solid was filtered off, washed with water, and taken up in 25 mL of 2% NaOH. The solution was neutralized with 10% AcOH to give 1.9 g (71%) of **34a**.

Method G. A mixture containing 1.9 g (0.0054 mol) of 6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-7-[3-(methylamino)-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (**34c**), 4 mL of 37% formalin, and 6 mL of formic acid was heated at 100–110 °C for 8 h with stirring. The reaction mixture was concentrated to dryness in vacuo. The residue was taken up in 10 mL of water. The mixture was adjusted to pH 8–9 with an aqueous ammonia. The resulting solid was filtered off, washed with water, and recrystallized from a mixture of $CHCl_3$ and EtOH to give 0.9 g (45%) of **38c**.

6-Fluoro-1,4-dihydro-7-hydroxy-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylic Acid (58). To a stirred mixture containing 42.5 g (0.10 mol) of ethyl 7-(4-acetyl-1-piperazinyl)-1-(2-chloroethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**57**)[4] and 300 mL of EtOH was added a solution of KOH (16.8 g, 0.30 mol) in 300 mL of EtOH. The mixture was heated to reflux for 2 h. After addition of 500 mL of 20% NaOH, the mixture was heated at 120 °C for 18 h, during which period the EtOH was removed gradually by distillation. The resulting precipitate was filtered off, washed with 10% NaOH, and dissolved in a mixture of water (250 mL) and AcOH (25 mL). The solution was treated with charcoal and acidified with concentrated HCl to give 21.2 g (85%) of **58**. Recrystallization from a mixture of EtOH and $CHCl_3$ gave an analytical sample, mp 256–259 °C. Anal. ($C_{11}H_7FN_2O_4$) C, H, F, N.

Ethyl 7-(Ethylthio)-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (60). A mixture containing 25.0 g (0.085 mol) of ethyl 7-(ethylthio)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**59**),[1] 15.2 g (0.11 mol) of K_2CO_3, and 250 mL of DMF was heated at 65 °C for 1 h with stirring. To this mixture was added 24.0 g (0.11 mol) of 2-fluoroethyl tosylate. The resulting mixture was heated at 100–105 °C for 1.5 h with stirring and then filtered to remove insoluble materials. The filtrate was concentrated to dryness in vacuo. The residue was taken up in a mixture of water (150 mL) and $CHCl_3$ (250 mL). The organic phase was separated, washed with water, and dried over Na_2SO_4. The $CHCl_3$ was evaporated in vacuo and the residue was crystallized from AcOEt to give 27.8 g (96%) of **60**. Recrystallization from a mixture of AcOEt and CH_2Cl_2 gave an analytical sample, mp 174–175 °C. Anal. ($C_{15}H_{16}F_2N_2O_3S$) C, H, N, S.

Biological Screenings. The in vitro antibacterial activity, in vivo efficacy on systemic infections, and acute toxicity were tested by the same methods reported in a previous paper.[4] Acute toxicity tests for **28a**, **46a**, and **50a** were not performed.

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