(free base), 86663-23-2; **59**, 118269-99-1; **59** (free base), 118270-47-6; **60**, 94221-58-6; **60** (free base), 94221-57-5; **61**, 118270-00-1; **61** (free base), 118270-48-7; **62**, 118270-01-2; **62** (free base), 118270-49-8; **63**, 40064-41-3; **63** (free base), 40064-46-8; **64**, 94221-54-2; **64** (free base), 94221-53-1; **65**, 94275-65-7; **65** (free base), 94275-66-8; **66**, 20153-14-4; **67**, 58050-61-6; **68**, 66122-39-2; **69**, 118270-02-3; **70**, 32193-12-7; **71**, 28657-56-9; **72**, 28657-55-8; **73**, 68612-32-8; **74**, 118270-03-4; **75**, 21004-61-5; **76**, 118270-04-5; **77**, 118270-05-6; **78**, 28657-53-6; **79**, 118270-06-7; **80**, 118270-07-8; **81**, 118270-08-9; **82**, 118270-09-0; **83**, 118270-10-3; **84**, 118270-11-4; **85**, 118270-12-5; **86**, 7007-92-3; **87**, 94221-59-7; **88**, 118270-13-6; **89**, 28657-58-1; **90**, 28734-27-2; **91**, 28657-57-0; **92**, 94221-55-3; **93**, 64657-83-6; **94**, 118270-14-7; **95**, 118270-15-8; **96**, 118270-16-9; **97**, 28657-38-7; **98**, 28657-40-1; **99**, 32176-53-7; **100**, 68415-29-2; **101**, 118270-17-0; **102**, 60855-47-2; **103**, 60855-49-4; **104**, 60855-51-8; **105**, 28734-31-8; **106**, 60855-46-1; **107**, 106982-18-7; **108**, 118270-18-1; **109**, 118270-19-2; **110**, 60855-53-0; **111**, 118270-20-5; **112**, 118270-21-6; **113**, 17258-26-3; **114**, 94221-60-0; **115**, 118270-22-7; **116**, 28657-42-3; **117**, 28734-28-3; **118**, 32176-55-9; **119**, 94221-56-4; **120**, 13294-93-4; **121**, 94011-50-4; pyruvic acid, 127-17-3; 4′-chloroacetophenone, 99-91-2; 4′-fluoroacetophenone, 403-42-9; 2′-fluoroacetophenone, 445-27-2; 3′-methylacetophenone, 585-74-0; 2′-methylacetophenone, 577-16-2; 3′-methoxyacetophenone, 586-37-8; 2′-methoxyacetophenone, 579-74-8; acetone, 67-64-1; 1-phenyl-2-propanone, 103-79-7; cyclohexyl methyl ketone, 823-76-7; 2-acetylnaphthalene, 93-08-3; 2-acetylthiophene, 88-15-3; 3-acetylthiophene, 1468-83-3; benzaldehyde, 100-52-7; 4-chlorobenzoic acid, 74-11-3; 2-chlorobenzoic acid, 118-91-2; 2-naphthalenecarboxaldehyde, 66-99-9; β-benzoylpropionic acid, 2051-95-8; β-morpholinoethylamine hydrochloride, 90746-30-8; β-morpholinoethylamine, 2038-03-1; ethylenediamine, 107-15-3; propylenediamine, 78-90-0; 1,4-butanediamine, 110-60-1.

# Fluoronaphthyridines and Quinolones as Antibacterial Agents. 1. Synthesis and Structure–Activity Relationships of New 1-Substituted Derivatives

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A series of novel 7-piperazinyl-1-substituted-6-fluoroquinolones and naphthyridines have been prepared and their antibacterial activities evaluated. These derivatives are characterized by having alkyl, alkenyl, arylalkyl, cycloalkyl, and cycloalkenyl groups at the 1-position. As a result of this study, derivatives **7** and **26**, which are substituted with *tert*-butyl groups at N-1, were found to possess excellent in vitro and in vivo potency, particularly against *Staphyloccus aureus*, comparable to that of norfloxacin (**1**) or ciprofloxacin (**10**). Structure–activity relationships of N-1 substituted alkyls and cycloalkyls are also discussed.

In the intense work on the class of quinolone antibacterials, basically two types of compounds can clearly be distinguished: the first group, typified by oxolinic acid and nalidixic acid, lack Gram-positive activity, while the second type, including norfloxacin[2] and enoxacin,[3] are compounds with relatively broad spectra. A number of new compounds, such as ciprofloxacin,[4] ofloxacin,[5] CI 934,[6] and difloxacin,[7] were prepared and tested, and many of them were found to be useful antibacterial agents and are in advanced development or already marketed.

These compounds share common structural features. Earlier[1] and more recent structure–activity relationship (SAR) studies[8,9] concluded that the optimal aliphatic group to attach to N-1 should be ethyl, vinyl, or a bioisostere of ethyl. Recently, several highly potent analogues have been developed that bring doubts and induce questions on the universality of this concept. Ciprofloxacin (*N*-cyclopropyl), ofloxacin (tricycle), and difloxacin (*N*-aryl) are examples of such compounds.

On the basis of former conclusions, systematic modification of the alkyl N-1 substituent received little attention. This laboratory explored and complemented data on the effect of the N-1 substituent on the antibacterial activity to update the SAR on quinolone antibacterials (see Figure 1a,b). In this paper, we report the synthesis and antibacterial activity of 7-(1-piperazinyl)-6-fluoro- and -6,8-difluoro-1-substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acids and 7-(1-piperazinyl)-6-fluoro-1-substituted-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (Tables I and II).

## Chemistry

The general method used for the preparation of 4-oxoquinolines and naphthyridines is illustrated in Scheme I and was adapted from synthetic routes reported for analogues.[7,10,14–16] Reaction of ethyl 2-(2,4-dichloro-5-

† Centre de Recherche Bristol-Myers.
‡ Bristol-Myers Research Institute Ltd.

(1) Albrecht, R. *Prog. Drug. Res.* **1977**, *21*, 9.
(2) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358.
(3) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Med. Chem.* **1984**, *27*, 292.
(4) Wise, R.; Andrews, J. M.; Edwards, L. J. *Antimicrob. Agents Chemother.* **1983**, *23*, 559.
(5) Hayakawa, I.; Tanaka, Y.; Hirimatsu, T. Eur. Pat. *Appl.* 47005; *Chem. Abstr.* **1982**, 97, 55821.
(6) Culbertson, T. P.; Mich, T. F.; Domagala, J. M.; Nichols, J. B. Eur. Pat. Appl 106489; *Chem. Abstr.* **1984**, *101*, 72740.
(7) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Pihuleac, E.; Nordeen, C. W.; Maleczka, R. E.; Pernet, A. G. *J. Med. Chem.* **1985**, *28*, 1558.
(8) Fujita, T. *The role of QSAR in drug design.* In *Drug* Design: *Fact or fantasy*? Jolles, G., Wooldridge, K. R. H., Eds.; Academic Press: New York, 1984.
(9) Matsumoto, J. I.; Nishimura, Y.; Minamida, A. *Chem. Pharm. Bull.* **1988**, *36*, 1223.
(10) During the course of this work a related patent appeared: Hokuriku Pharm. Co. Ltd., Jpn. Kohai Tokkyo Koho 60 28,964; *Chem. Abstr.* **1985**, *103*, 71202.
(11) Kyorin Pharm. Co. Ltd., Belg. Patent 899,399; *Chem Abstr.* **1985**, *102*, 45791.
(12) Following completion of this work another patent appeared: Schriewer, M.; Grohe, K.; Zeiler, H. J.; Metzger, K. G. German Patent 3,509,546; *Chem. Abstr.* **1986**, *106*, 4900.
(13) Petersen, U.; Grohe, K.; Zeiler, H. J.; Metzger, K. G. German Patent 3,508,816; *Chem. Abstr.* **1986**, *105*, 191059.
(14) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2363.

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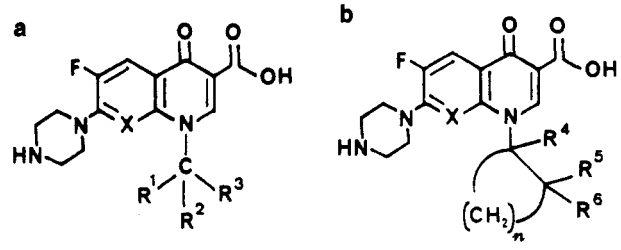
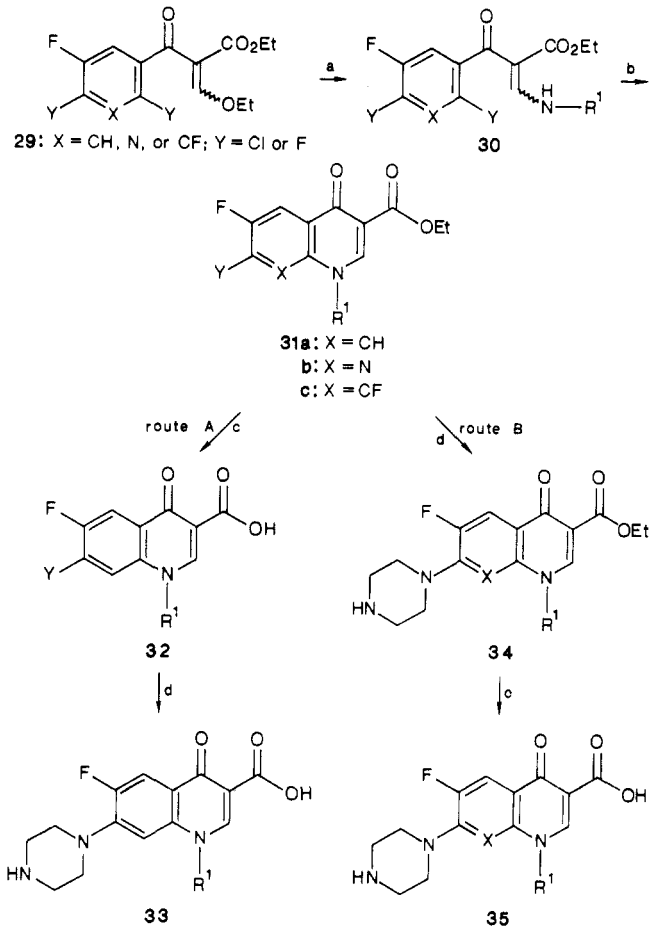


Figure 1.

Scheme I[a]

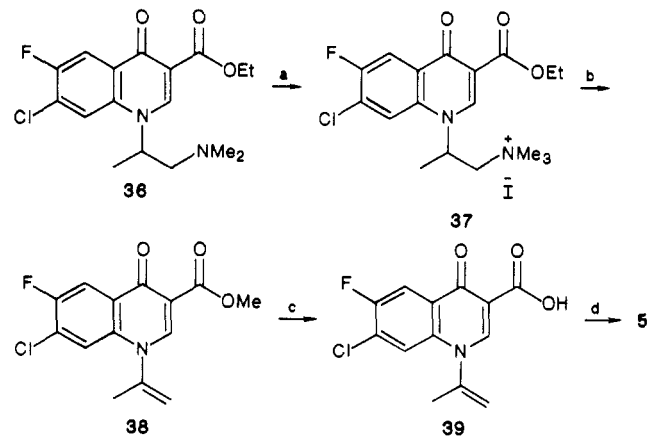


[a] (a) $R^1NH_2$, EtOH, room temperature; (b) NaH in dioxane or $K_2CO_3$ in acetone, or $NBu_4F$ in THF; (c) NaOH, $H_2O$; (d) piperazine, DBU, $CH_3CN$.

fluoroaroyl)-3-ethoxyacrylate **29** with a slight excess of an appropriate amine in ethanol at room temperature gives the corresponding enamino keto ester **30**, usually as a crystalline product. Cyclization of **30** (X = CH), by heating with sodium hydride in dioxane, gives ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate **31a** (X = CH). Cyclizations of **30** (X = N) are performed by using three different procedures: sodium hydride in dioxane, potassium carbonate in $CH_3CN$, or tetrabutylammonium fluoride in THF.[17] Substitution of the 7-halogen atom of the carboxylates **31** is accomplished by two procedures: Route A was used in the quinoline derivatives series; the ester **31a** (X = CH) is hydrolyzed by heating with aqueous NaOH to give the corresponding acid **32**. Subsequent

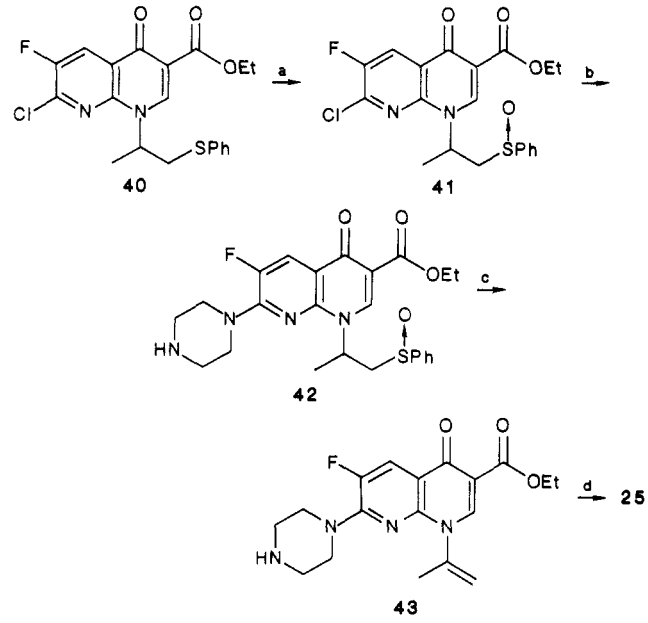
(15) Petersen, U.; Grohe, K.; Zeiler, H. J.; Metzger, K. G. German Patent 3,248,506; *Chem. Abstr.* **1985**, *102*, 6526.
(16) Chu, D. T. W. *J. Heterocycl. Chem.* **1985**, *22*, 1033.
(17) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Remuzon, P. *Tetrahedron Lett.* **1988**, *29*, 1931.

Scheme II[a]



[a] (a) $CH_3I$, acetone; (b) DOWEX (OH form), MeOH, 190 °C; (c) 1 N NaOH, reflux; (d) piperazine, pyridine.

Scheme III[a]



[a] (a) mCPBA, $CH_2Cl_2$; (b) piperazine, $CH_3CN$; (c) bromobenzene, reflux; (d) NaOH, $H_2O$.

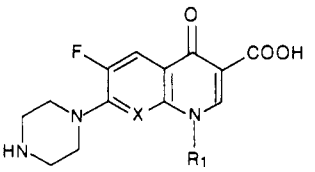
condensation with piperazine by heating in an appropriate solvent such as pyridine, *N*-methylpyrrolidine, or *N*-methylpyrrolidinone yields the quinolone **33**. Route B was used in the naphthyridine and 6,8-difluoroquinoline series; the ester **31b** or **31c** (X = N, X = CF) is condensed with piperazine in $CH_3CN$, with or without DBU as a base, to give ester **34**, which is hydrolyzed by heating with aqueous NaOH to afford the compounds **35** (Table I) (except **34** (X = CF), which is hydrolyzed with 1 equiv NaOH overnight at room temperature to give **8**).

Concerning the methylethenyl analogues **5** and **25**, the synthetic pathways are somewhat different (Schemes II and III). The (1-methylethenyl)quinolone **39** is prepared through the ammonium iodide **37** transformed into its quaternary salt, which is converted to the corresponding ethylenic compound. The naphthyridine analogue **43** is obtained by thermal decomposition of the sulfoxide **42** prepared by oxidation of the corresponding thio compound **40**.

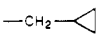
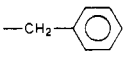
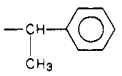
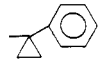
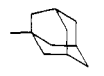
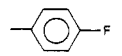
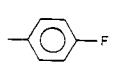
## Biological Results and Discussion

The in vitro antibacterial activity of 1-substituted quinolones and naphthyridines against Gram-positive

**Table I.** 1-Substituted Quinolones and Naphthyridines



1-28

| no. | $R_1$ | | X | mp, °C | method of prep | formula | yield, % | recryst solvent | ref |
|---|---|---|---|---|---|---|---|---|---|
| 1[a] | $C_2H_5$ | | CH | | | | | | 2 |
| 2 |  | | CH | 194 | A | $C_{18}H_{20}FN_3O_3$ | 34 | MeOH | |
| 3 |  | | CH | 252–3 | A | $C_{21}H_{20}FN_3O_3$ | 50 | DMF | 2 |
| 4 |  | | CH | 237–9 | A | $C_{17}H_{20}FN_3O_3$ | 37 | EtOH/$Et_2O$ | 10 |
| 5 |  | | CH | 242 | C | $C_{17}H_{18}FN_3O_3 \cdot H_2O$ | 58 | MeOH | |
| 6 |  | | CH | 232 | A | $C_{22}H_{22}FN_3O_3 \cdot H_2O$ | 20 | EtOH | |
| 7 |  | | CH | 202 | A | $C_{18}H_{22}FN_3O_3$ | 69 | $H_2O$ | |
| 8 |  | | CF | *e* | B | $C_{18}H_{21}F_2N_3O_3 \cdot H_2O$ | 78 | MeOH | |
| 9 |  | | CH | >270 | A | $C_{19}H_{24}FN_3O_3$ | 25 | EtOH/$Et_2O$ | |
| 10[b] |  | | CH | | | | | | 4 |
| 11 |  | | CF | | | | | | 11 |
| 12 |  | (trans) | CH | 238 | A | $C_{18}H_{20}FN_3O_3$ | 40 | MeOH | 12 |
| 13 |  | (cis) | CH | 254 | A | $C_{18}H_{20}FN_3O_3$ | 20 | *i*-PrOH | 12 |
| 14 |  | | CH | 216 | A | $C_{19}H_{22}FN_3O_3 \cdot 2H_2O$ | 30 | *i*-PrOH | |
| 15 |  | | CH | >270 | A | $C_{18}H_{20}FN_3O_3$ | 52 | *i*-PrOH | 12 |
| 16 |  | | CH | 241–3 | A | $C_{23}H_{22}FN_3O_3 \cdot H_2O$ | 37 | $H_2O$ | |
| 17 |  | | CH | 235–7 | A | $C_{18}H_{20}FN_3O_3$ | 45 | DMF | |
| 18 |  | | CH | 235–7 | A | $C_{19}H_{22}FN_3O_3$ | 72 | DMF | |
| 19 |  | | CH | 220–1 | A | $C_{19}H_{22}FN_3O_3 \cdot 2H_2O$ | 30 | $H_2O$ | |
| 20 |  | | CH | >270 | A | $C_{19}H_{20}FN_3O_3 \cdot HCl \cdot H_2O$ | 20 | EtOH/$H_2O$ | |
| 21 |  | | CH | >270 | A | $C_{24}H_{28}FN_3O_3 \cdot HCl \cdot H_2O$[e] | 5 | MeOH | |
| 22[c] |  | | CH | | | | | | 7 |
| 23[d] | $C_2H_5$ | | N | | | | | | 3 |
| 24 |  | | N | 250–1 | B | $C_{16}H_{19}FN_4O_3$ | 52 | DMF | 7 |
| 25 |  | | N | 243 | D | $C_{16}H_{17}FN_4O_3$ | 43 | DMF/$H_2O$ | 9 |
| 26 |  | | N | >270 | B | $C_{17}H_{21}FN_4O_3$ | 67 | $H_2O$ | |
| 27 |  | | N | | | | | | 13 |
| 28 |  | | N | | | | | | 14 |

[a] Norfloxacin. [b] Ciprofloxacin. [c] A-56620. [d] Enoxacin. [e] See the Experimental Section.

(*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Morganella morganii*, and *Pseudomonas aeruginosa*) is shown in Table II. Data for norfloxacin, ciprofloxacin, enoxacin, and A-56620 are included for comparison. Considering N-1 alkyl or aralkyl (Figure 1a), when

**Table II.** In Vitro Antibacterial Activity (MIC, μg/mL)

| no. | *S. aureus* Smith A 9537 | *E. coli* A 15119 | *K. pneumoniae* A 9664 | *E. cloacae* A 9656 | *M. morganii* A 15153 | *P. aeruginosa* A 9843 |
|---|---|---|---|---|---|---|
| **1** | 0.25 | 0.13 | 0.03 | 0.06 | 0.015 | 0.5 |
| **2** | 1 | 0.5 | 2 | 4 | 1 | 4 |
| **3** | 0.5 | 0.25 | 0.5 | 0.5 | 4 | 0.5 |
| **4** | 1 | 0.5 | 1 | 2 | 0.25 | 1 |
| **5** | 0.5 | 0.13 | 0.25 | 0.06 | 0.13 | 0.5 |
| **6** | 4 | 2 | 4 | 4 | 16 | 32 |
| **7** | 0.06 | 0.06 | 0.13 | 0.13 | 0.25 | 0.5 |
| **8** | 0.25 | 0.06 | 0.25 | 0.25 | 0.5 | 4 |
| **9** | 0.25 | 0.5 | 1 | 1 | 4 | 4 |
| **10** | 0.13 | 0.03 | 0.03 | 0.008 | 0.015 | 0.13 |
| **11** | 0.13 | 0.03 | 0.06 | 0.06 | 0.008 | 0.25 |
| **12** | 1 | 0.06 | 2 | 0.13 | 1 | 2 |
| **13** | 0.13 | 0.13 | 1 | 0.5 | 0.25 | 1 |
| **14** | 1 | 1 | 2 | 4 | 8 | 32 |
| **15** | 0.25 | 0.06 | 0.25 | 0.5 | 0.25 | 0.5 |
| **16** | 0.13 | 0.13 | 0.25 | 0.25 | 0.25 | 4 |
| **17** | 0.5 | 0.13 | 0.13 | 1 | 0.5 | 1 |
| **18** | 4 | 2 | 4 | 32 | 16 | 32 |
| **19** | 0.5 | 0.25 | 2 | 1 | 0.5 | 8 |
| **20** | 2 | 1 | 1 | 8 | 8 | 8 |
| **21** | 8 | 2 | 8 | 4 | 32 | 63 |
| **22**[a] | 0.2 | 0.05 | 0.02 | | | 0.39 |
| **23** | 0.25 | 0.13 | 0.5 | 0.5 | 0.13 | 0.5 |
| **24** | 2 | 0.25 | 1 | 0.5 | 1 | 4 |
| **25** | 0.5 | 0.13 | 0.13 | 0.25 | 0.5 | 2 |
| **26** | 0.06 | 0.015 | 0.13 | 0.06 | 0.25 | 1 |
| **27** | 0.25 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 |
| **28**[b] | 0.39 | 0.05 | 0.1 | | | 0.39 |

[a] A-56620, ref 7. [b] Reference 14.

**Table III.** Efficacy on Systemic Infections and Acute Toxicity with Oral Administration in Mice

| | in vivo $PD_{50}$,[a] mg/kg po | | | | |
|---|---|---|---|---|---|
| no. | *S. aureus* Smith A 9537 | *P. aeruginosa* A 9843 | *E. coli* A 15119 | *K. pneumoniae* A 9664 | $LD_{50}$,[b] mg/kg po |
| **1** (NOR) | 10 (0.25) | 16 (0.5) | 3 (0.13) | 8 (0.03) | >2500 |
| **10** (CIP) | 4 (0.13) | 5 (0.13) | 0.7 (0.03) | 1.5 (0.03) | >2500 |
| **7** | 8 (0.06) | 18 (0.5) | NT[c] | NT | >2500 |
| **25** | 15 (0.5) | 20 (2.0) | NT | NT | NT |
| **26** | 1.1 (0.06) | 12 (1.0) | 2.4 (0.015) | 5.0 (0.13) | >2500 |
| **27** | 6.7 (0.25) | 3.6 (0.06) | 0.5 (0.06) | 2.2 (0.06) | NT |

[a] Dose to protect 50% of mice from lethal infection po. (Inoculum size: $3 \times 10^6$ cells per mouse). [b] See the Experimental Section. [c] Not tested.

the size of the N-1 group increases from ethyl (**1**, **23** ($R_1 = CH_3$, $R_2 = R_3 = H$)) to isopropyl (**4**, **24** ($R_1 = R_2 = CH_3$, $R_3 = H$)), the in vitro activity decreases, but **5** and **25** ($R_1 = R_2 = CH_2$, $R_3 = CH_3$) are more active than **4** and **24** and more or less as active as **1** and **23**. If one methyl group of the isopropyl group at N-1 is replaced by a phenyl group (**6** ($R_1 = Ph$, $R_2 = CH_3$, $R_3 = H$)), there is a dramatic loss of activity. If the carbon 2 of the ethyl group is replaced by a cyclopropyl ring (**2** ($R_1 = C_3H_5$, $R_2 = R_3 = H$)), one can note a decrease in the in vitro activity, which is partially restored with the phenyl analogue **3** ($R_1 = C_6H_5$, $R_2$, $R_3 = H$). If the two hydrogens of carbon 1 of the ethyl group are replaced by two methyl groups to yield N-1 *tert*-butyl derivatives ($R_1 = R_2 = R_3 = CH_3$), the in vitro activity of **7** and **26** is enhanced especially versus *S. aureus*. Against Gram-negative organisms, **7** and **26** have in vitro activity in the same range as the reference compounds but are less active against *K. pneumoniae* and *M. morganii*. The activity versus *P. Aeruginosa* is similar to that of norfloxacin (**1**) and A 56620 (**22**), ciprofloxacin (**10**) being the most active compound against this organism.

If the N-1 chain length of **7** is increased by one carbon ($R_1 = Et$, $R_2 = R_3 = CH_3$), the in vitro activity decreases, **9** being less active than **1** and **7** and almost as active as **4**. In the cycloalkyl series (Figure 1b), the cyclopropyl ring (**10**, $n = 1$) seems to be the optimum size: cyclobutyl ($n = 2$, **17**) and cyclopentenyl ($n = 3$, **20**) groups give less active compounds. The position of the substituent on the cycloalkyl ring is relevant for activity. Compounds substituted at carbon 2 ($R_5 \neq H$) are less active than compounds substituted at carbon 1 ($R_4 \neq H$): **15** ($R_4 = CH_3$, $n = 1$) and **19** ($R_4 = CH_3$, $n = 2$) are respectively more active than **12** and **13** ($R_5 = CH_3$, $n = 1$) and **18** ($R_5 = CH_3$, $n = 2$). The size of the substituent on carbon 1 of the ring is of less importance and the 1-phenylcyclopropyl derivative **16** ($R_4 = Ph$, $n = 1$) has similar activity to that of the corresponding 1-methyl analogue **15** ($R_4 = CH_3$, $n = 1$).

**Table IV.** Pharmacokinetic Parameters of **7**, **10**, and **26** after Oral Administration in Dog[a] (25 mg/kg)

| no. | $C_{max}$, μg/mL | $t_{1/2}$, h | AUC,[b] μg/mL per h | UR,[c] % |
|---|---|---|---|---|
| **10** (CIP) | 3 | 3.5 | 20 | 17 |
| **7** | 6.4 | 4.4 | 50 | 17 |
| **26** | 5.8 | 4.8 | 50 | 12 |

[a] See the Experimental Section. [b] Areas under the concentration/time, μg/mL per hour. [c] Urinary recovery after 24 h, percent of administered dose.

Efficacy in systemic infections, due to *S. aureus* Smith A 9537, *P. aeruginosa* A 9843, *E. coli* A 15119, and *K. pneumoniae* A 9664 in mice, of several selected compounds, is shown in Table III. The oral absorption in dog

is given in Table IV. It can be seen that against *S. aureus* infections compound **7** is at least equal to norfloxacin (**1**); compound **26** is 3 times more active than ciprofloxacin (**10**) and 6 times more active than ciprofloxacin analogue **27** in the naphthyridine series. Against Gram-negative organisms **7** and **26** appear similar to norfloxacin **1** but less efficacious than ciprofloxacin (**10**). As recorded in Table III, oral $LD_{50}$ for compounds **7** and **26** and for reference compounds **1** and **10** are in excess of 2500 mg/kg, suggesting that the *tert*-butyl group does not increase acute toxicity.

Oral bioavailability of compounds **7**, **26**, and ciprofloxacin (**10**) was evaluated in dogs at 25 mg/kg (Table IV). The *tert*-butyl compounds **7** and **26** show peak plasma levels and areas under the curve about twice that of the reference compound **10**. Water solubility is an important physicochemical property with potential influence on oral absorption and on toxicity. Compound **7** showed slightly higher (0.13 mg/mL) solubility than **10** (0.07 mg/mL), and the naphthyridine analogue **26** was considerably more soluble (0.82 mg/mL).

As mentioned by other authors in earlier studies,[1,8,9] structure–activity relationships in the quinolone and naphthyridine series leave room for innovation. We have shown that N-1 substituents with a quaternary carbon directly bound to the nitrogen atom give quinolone and naphthyridine derivatives with better antibacterial activity than expected from previous SAR data. This observation is emphasized by the pronounced in vitro and in vivo activity of the new *tert*-butyl derivatives described in this work. This new class of pyridonecarboxylic acid derivatives with a *tert*-butyl group at N-1 deserves further investigation. Synthesis and evaluation of further series of derivatives with varied substituents at the 7-position will be reported in a following paper.

## Experimental Section

**In Vitro Antibacterial Activity.** The in vitro antibacterial activity was studied by a side-by-side comparison with norfloxacin and ciprofloxacin and determined by the serial 2-fold dilution technique using nutrient broth. The inoculum size was adjusted to $10^6$ cfu/mL, and the concentration of the compounds range from 0.0005 to 250 μg/mL. Minimum inhibitory concentrations (MIC) were defined as the lowest concentration of the compound that prevents visible growth of bacteria after incubation at 37 °C for 18 h.

**Acute Toxicity on Oral Administration to Mice.** A solution of each test compound in sterile water was administered orally to OF1-strain female Swiss mice (18–25 g body weight, five per group). Seven days later, $LD_{50}$ values were determined by using the Karber and Behrens method.[19]

**Oral Absorption in Dogs.** Plasma and urine levels in dogs were determined by microbiological assay. Two 7–10-kg beagle dogs were fasted overnight prior to dosing; all animals were permitted free access to water. Compounds were administered in solution by oral gavage. Blood samples were obtained at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after dosing. Plasma was separated by centrifugation and frozen until tested. Urine was collected 0–4, 4–8, and 8–24 h after dosing and frozen until analysis. Plasma levels and urinary excretion of test compounds were determined by using the agar plates system. Test organism was *Bacillus subtilis* ATCC 6633 and the used standard was the test compound itself.

**Chemistry.** All melting points were determined in capillary tubes on a Büchi 510 melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer 783 spectrophotometer. $^1H$ and $^{19}F$ spectra were taken at 200 MHz on a Bruker AC 200 apparatus with tetramethylsilane as internal standard, and chemical shifts are given in ppm (δ). IR and NMR spectra were obtained on all compounds and were consistent with assigned structure. All compounds were analyzed for C, H, N, and the analytical results were within ±0.4% of theoretical values (except compound **21**; C: calcd 60.05, found 59.41).

General methods to prepare intermediate **31a** (X = CH) were used with established literature conditions.[7,11,15,16]

As a typical example, the preparation of **7** is described.

**Method A. 6-Fluoro-7-chloro-1-(1,1-dimethylethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (32; $R_1$ = *t*-Bu, X = CH, Y = Cl).** To a solution of 7.24 g (20 mmol) of 3-(2,4-dichloro-5-fluorophenyl)-3-oxo-2-(((1,1-dimethylethyl)amino)-methylene)propanoic acid ethyl ester (**30**: $R_1$ = *t*-Bu, X = CH, Y = Cl) in 60 mL of dioxane at 7 °C was added portionwise 1.04 g (26 mmol) of 60% sodium hydride. After the addition, the suspension was stirred for 30 min at room temperature and then heated under reflux for 2.5 h. After filtration of insoluble material and concentration to dryness, 6.5 g of crude ester **31** was obtained. This ester was hydrolyzed with 1.84 g (28 mmol) of KOH in 32 mL of water under reflux for 1.5 h. The solution was brought to pH 1.5 and filtered. The collected solid was recrystallized from dioxane/water (5:1) to yield 4.97 g of quinoline **32** (Y = Cl, $R_1$ = *t*-Bu): yield 83.5%; mp 274 °C.

**7-Piperazinyl-6-fluoro-1-(1,1-dimethylethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (7, 33 ($R_1$ = *t*-Bu)).** A mixture of 0.3 g (1.01 mmol) of **32** and 0.3 g (3.48 mmol) of piperazine in 1 mL of pyridine was heated under reflux for 18 h. After concentration of the reaction was heated under reflux for 18 h. After concentration of the reaction mixture under reduced pressure, the residue was poured into 10 mL of 10% aqueous acetic acid. After filtration of insoluble material, the pH of the solution was adjusted to 7.5 and the water layer was extracted with $CH_2Cl_2$. After evaporation of the solvent, the resulting solid was purified by washing with water to give 0.24 g of **7**: yield 69%; mp 202 °C; $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.87 (9 H, s, *t*-butyl), 3.21–3.33 (8 H, 2 m, piperazine $CH_2$), 7.44 (1 H, d, $J_{H-F}$ = 10 Hz, H-5), 7.97 (1 H, d, $J_{H-F}$ = 6 Hz, H-8), 8.93 (1 H, s, H-2). Compounds **2–4**, **6**, **7**, **9**, and **12–21** were prepared according to method A.

**Method B. 6-Fluoro-7-chloro-1-(1,1-dimethylethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (31b; X = N, Y = Cl, $R_1$ = *t*-Bu). Cyclization Step. First Procedure.** There was gradually added 1.3 g (32.4 mmol) of 60% sodium hydride under nitrogen at room temperature to a solution of 10 g (27.5 mmol) of 3-(2,6-dichloro-3-fluoro-5-pyridinyl)-3-oxo-2-(((1,1-dimethylethyl)amino)methylene)-propanoic acid ethyl ester (**30**: X = N, Y = Cl, $R_1$ = *t*-Bu) in 34 mL of dry dioxane. After the mixture was stirred at 60 °C for 15 min, the solvent was evaporated. The resulting solid was extracted with $CH_2Cl_2$ and washed with water, dried, and concentrated to give 8.2 g of **31b** (X = N): yield 91%; mp 158–60 °C.

**Second Procedure.** A mixture of 5 g (13.7 mmol) of **30** (X = N, Y = Cl, $R_1$ = *t*-Bu) and 1.89 g (13.7 mmol) of $K_2CO_3$ in 30 mL of anhydrous $CH_3CN$ was heated under reflux for 6 h. After workup as in the first procedure 4.0 g of **31b** (X = N) was obtained: yield 89%; mp 160 °C.

**Third Procedure.**[17] To a solution of 0.5 g (1.37 mmol) of **30** (X = N, Y = Cl, $R_1$ = *t*-Bu) in 2 mL of THF was added 2.74 mL of 1 M tetrabutylammonium fluoride in THF. After 1 h, the solvent was evaporated and the residue was subjected to flash chromatography over silica gel (AcOEt/hexane 1:1) to yield 0.26 g of **31b** (X = N) as a mixture of 7-fluoro- and 7-chloronaphthyridine (Y = Cl and F): yield 59%.

**7-Piperazinyl-6-fluoro-1-(1,1-dimethylethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (26).** To a solution of 0.487 g (5.65 mmol) of piperazine in 30 mL of $CH_3CN$, heated under reflux, was gradually added 0.612 g (1.87 mmol) of **31b** (X = N, Y = Cl, $R_1$ = *t*-Bu) over a 10-min period. The reflux was continued for 30 min and the solvent was removed with a rotary evaporator. The residue was taken up in water and filtered to give 0.435 g of **34** (X = N, $R_1$ = *t*-Bu), mp 169 °C. This ester 0.4 g (1.06 mmol) was suspended in 1 mL of water to which was added 1.9 mL of 1 N aqueous sodium hydroxide. This suspension was heated under reflux for 30 min. The solution was cooled and the

(18) Uno, T.; Takamatsu, M.; Inoue, Y.; Kawahata, Y.; Iuchi, K.; Tsukamato, G. *J. Med. Chem.* **1987**, *30*, 2163.
(19) Behrens, B.; Karber, G. *Arch. Exp. Pathol. Pharm.* **1935**, *177*, 379.

pH was adjusted to 7.5. The precipitate was filtered and washed with water to give 0.248 g of **26**: yield 67%; mp 270 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.85 (9 H, s, *t*-Bu), 2.86–3.73 (8 H, 2 m, piperazine, $CH_2$), 8.05 (1 H, d, $J_{H-F}$ = 12 Hz, H-5), 8.85 (1 H, s, H-2).

Concerning compound **8**, the procedure was essentially similar to method B. Compound **8**: $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.75 (9 H, s, *t*-Bu), 2.84–3.24 (8 H, 2 m, piperazine $CH_2$), 7.87 (1 H, dd, $J_{H-F}$ = 10 Hz, H-5), 9.02 (1 H, s, H-2); mp: this compound was thermally instable (it began to decompose at 60 °C, as shown by the thermogravimetric analysis). Compounds **24** and **27** were prepared according to method B.

**Method C. *N,N,N*-Trimethyl-2-(3-(ethoxycarbonyl)-7-chloro-6-fluoro-4-oxo-1,4-dihydro-1-quinolinyl)propanaminium Iodide (37).** The condensation of *N,N*-dimethyl-2-aminopropylamine with **29** gave **30** (X = CH, Y = Cl, $R_1$ = $CH(CH_3)(CH_2NMe_2)$), which was cyclized with NaH in dioxane to give the quinolone **36**. To a solution of 1.2 g (3.35 mmol) of **36** in 10 mL of acetone was added 2.1 mL (33.5 mmol) of methyl iodide. The mixture was stirred for 5 h at room temperature, and 5 mL of $Et_2O$ was added to precipitate the propanaminium iodide **37** in quantitative yield; mp 210 °C.

**7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-(1-methylethenyl)-3-quinolinecarboxylic Acid (39).** A hot solution of 2.4 g (4.9 mmol) of ammonium **37** in 75 mL of methanol was treated twice with DOWEX 1 (OH form) (prepared from 9.6 g of DOWEX 1 (Cl form)). The resin was washed with 30 mL of methanol. The methanol was evaporated in vacuo and the residue was heated at 190 °C for 1 h under vacuum. After purification by chromatography over silica gel, 0.3 g of **38** (as methyl ester) was obtained; yield 21.1%. This ester was hydrolyzed in a mixture of 1 mL of methanol and 3.2 mL of 1 N NaOH under reflux for 2 h to provide 0.25 g of **39**; yield 87%; mp 229 °C.

**7-Piperazinyl-6-fluoro-1,4-dihydro-4-oxo-1-(1-methylethenyl)-3-quinolinecarboxylic Acid (5).** A mixture of 0.25 g (0.89 mmol) of **39** and 0.38 g (4.45 mmol) of piperazine in 2.1 mL of *N*-methylpyrrolidine was heated at 100 °C for 3 h 30 min. After cooling and precipitation with $Et_2O$, a product was obtained, which was recrystallized from methanol to yield 0.17 g of **5** (as monohydrate): yield 57.8%; mp 242 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 2.13 (3 H, s, $CH_3$), 3.0–3.30 (8 H, 2 m, piperazine $CH_2$), 5.39–565 (2 H, 2 s, = $CH_2$), 6.67 (1 H, d, $J_{H-F}$ = 6 Hz, H-8), 7.83 (1 H, d, $J_{H-F}$ = 12 Hz, H-5), 8.42 (1 H, s, H-2).

**Method D. 6-Fluoro-7-chloro-1-(2-(phenylsulfinyl)-1-methylethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (41).** *m*-Chloroperbenzoic acid (1.03 g, 6 mmol) was gradually added to a solution of 2.88 g (5.25 mmol) of **40** (prepared from **29** (X = N, Y = Cl) and 1-(phenylthio)-2-aminopropane) in 20 mL of $CH_2Cl_2$ at 5 °C. After the mixture was stirred at room temperature for 30 min, 25 mL of 10% $NaHCO_3$ solution was added to the reaction mixture. The organic layer was dried, evaporated, and purified by chromatography over silica gel to yield 1.5 g of **41**: yield 65%; mp 212 °C.

**7-Piperazinyl-6-fluoro-1-(2-(phenylsulfinyl)-1-methylethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (42).** To a suspension of 2.47 g (5.65 mmol) of naphthyridine **41** in 70 mL of $CH_3CN$ was added 1.95 g (22.6 mmol) of piperazine. The mixture was stirred 1 h at room temperature, the solvent was evaporated, and the residue was partitioned between $CH_2Cl_2$ and water, and the organic layer was separated, dried, and concentrated to provide 2.46 g of **42**: yield 90%.

**7-Piperazinyl-6-fluoro-1-(1-methylethenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester Hydrochloride (43).** A suspension of 2.3 g (4.7 mmol) of naphthyridine **42** in 80 mL of bromobenzene was heated under reflux for 2 h 15 min. After evaporation of bromobenzene under reduced pressure, the residue was crystallized from hexane to give 1.74 g of the base, which was transformed into its hydrochloride in acetone. After recrystallization from 95% aqueous ethanol, there was obtained 0.81 g of **43**; yield 43.5%.

**7-Piperazinyl-6-fluoro-1-(1-methylethenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (25).** A mixture of 0.63 g (1.58 mmol) of ester **43** and 4 mL of 2 N aqueous NaOH was heated under reflux for 1 h 40 min. After the mixture was cooled with ice, the pH was adjusted to 7.3. The solid was filtered and recrystallized from a mixture $DMF/H_2O$/2:1 to give 0.18 g of **25**: yield 35%; mp 243 °C (lit.[9] mp 244–47 °C); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 2.23 (3 H, s, $CH_3$), 2.82–3.72 (8 H, 2 m, piperazine $CH_2$), 5.36–5.49 (2 H, 2 s, = $CH_2$), 8.04 (1 H, d, $J_{H-F}$ = 12 Hz, H-5), 8.59 (1 H, s, H-2).

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