Synthesis and Antibacterial Activity of New 5-Substituted 1-Cyclopropyl-6-fluoro-7-piperazinyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids

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The 5-hydroxymethyl and the 5-formyl-1-cyclopropyl-6-fluoro-7-piperazinyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids have been prepared *via* a 5-trimethylsilyl group and were tested *in vitro* as potential antibacterials.

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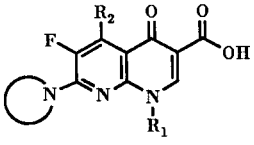
Recently, the introduction of a methyl group at the 5-position of the naphthyridines **1** (R_2 = Me) was found to lead to potent antibacterial agents especially when R_1 = cyclopropyl or 2,4-difluorophenyl (Figure 1) [1,2,9].



1 R_1 = *t*-Butyl, cyclopropyl, or 2,4-difluorophenyl

Figure 1

To extend the structure-activity relationship for the 5-substitution of the naphthyridines, we prepared the 5-hydroxymethyl and the 5-formyl analogues **1** (R_2 = CH_2OH and CHO, R_1 = cyclopropyl).

The first approach to introduce the 4-hydroxymethyl group *via* the 4-formyl **3** on the precursor **2**, was to follow the same methodology we used to obtain the 5-methyl derivative [1]. This was accomplished by deprotonation of the nicotinic acid **2**, followed by alkylation of the lithio intermediate with dimethylformamide (Scheme I).

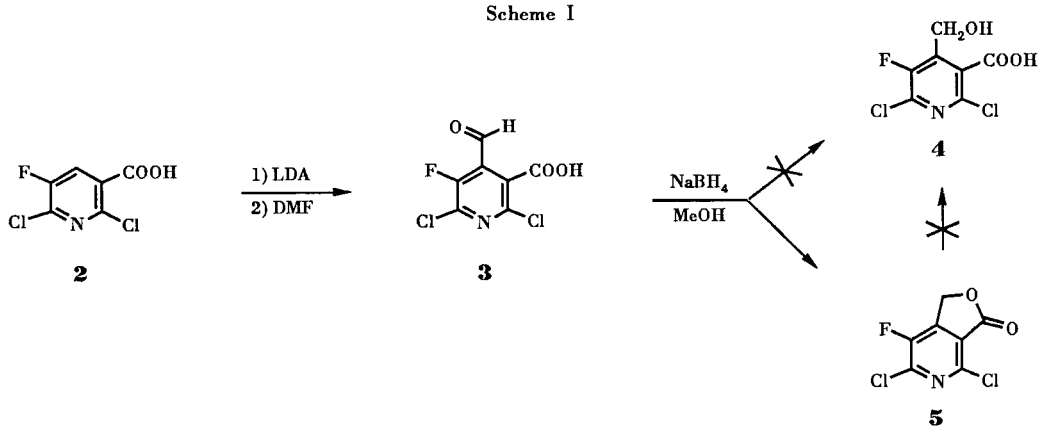
The resulting 4-formyl derivative **3** was then reduced with sodium borohydride. Unfortunately, after acidification of the reaction mixture, we obtained only the undesired lactone **5**. Any attempts to open this lactone either in acidic or basic media to give the derivative **4** were unsuccessful [3].

A second approach was based on the introduction of the formyl group at a later stage in the synthesis of the naphthyridine ring. This was achieved by introduction of a silyl group on **2** by deprotonation and alkylation with chlorotrimethylsilane which led to the 4-silylated nicotinic acid **6**.

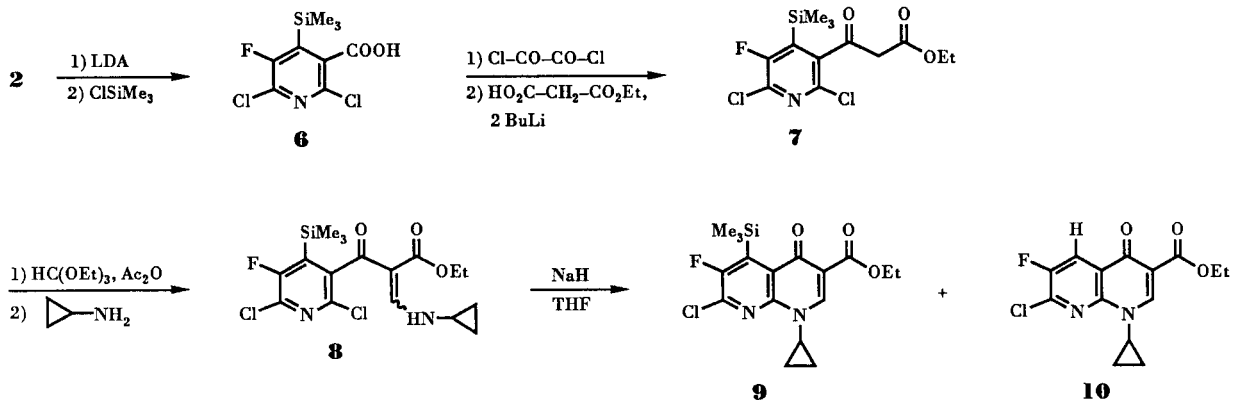
After acid chloride formation and alkylation with the mono-ethyl ester of malonic acid we obtained the keto-ester **7**, which was successively treated with triethyl orthoformate and cyclopropylamine. The resulting enamine **8** was cyclized [4] with sodium hydride to give the expected silyl derivative **9** (55% yield) and the known desilylated analogue **10** (20% yield) [5] (Scheme II).

Ipso-substitution on the 5-trimethylsilyl group of **9** [6] performed with the Vilsmeier reagent (phosphorus oxychloride/dimethyl formamide) gave the 5-formyl derivative **11** in 24% yield along with the desilylated derivative **10**. Reduction of **11** with sodium borohydride (100% mole) led

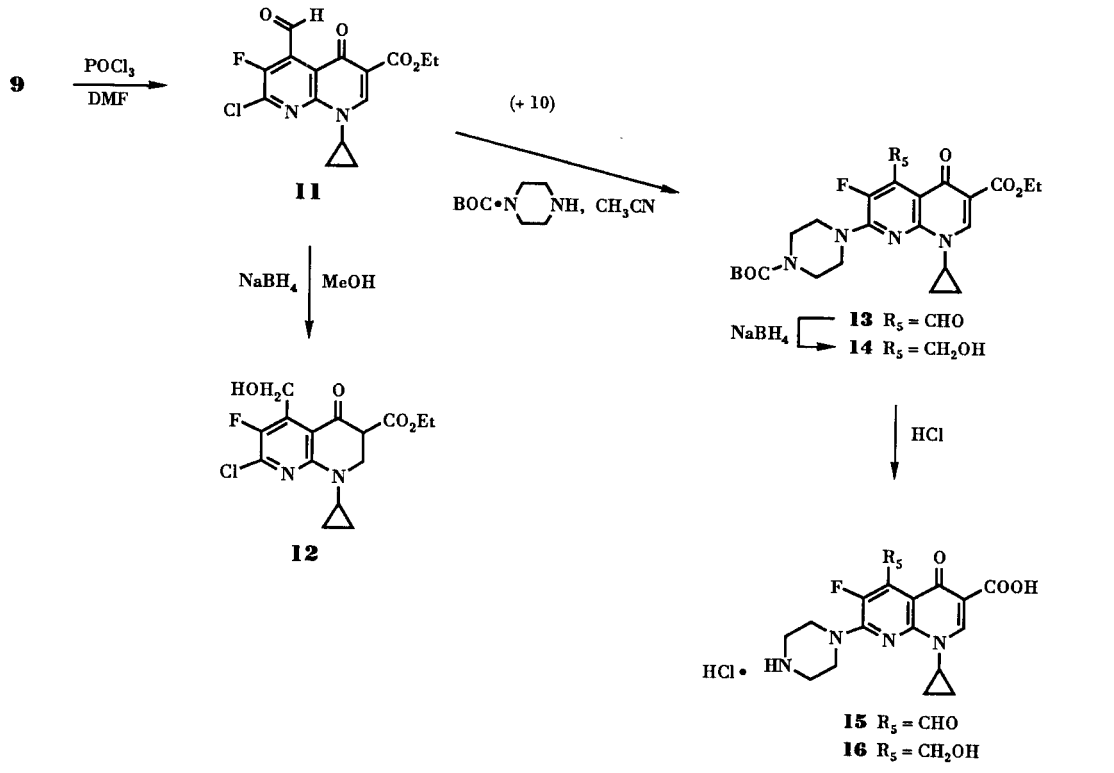
Scheme I



Scheme II



Scheme III

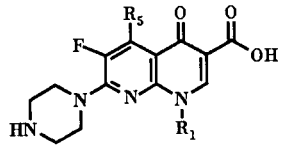


to the 2,3-dihydro-5-hydroxymethyl compound **12**. Condensation of *tert*-butyl-1-piperazinecarboxylate on the naphthyridine nuclei **11** gave the naphthyridine derivative **13**, which was reduced with sodium borohydride (25% mole) to **14**. Acidic hydrolysis of **13** and **14** gave respectively the amino-acids **15** and **16**. Potentially new derivatives resulting from the 5-silyl and 5-hydroxymethyl derivatives **9** and **14** like 5-nitro, 5-amino, 5-bromo and 5-fluoromethylnaphthyridines are under investigation.

A comparison of the *in vitro* antibacterial activity of **15** and **16** was made with previous synthesized derivatives **17-21** (Table 1) [7]. It clearly demonstrated that oxygenation of the 5-methyl group dramatically decrease the *in vitro* antibacterial activity especially on Gram-positive strains. On Gram-negative bacteria the 5-hydroxymethyl derivative **16** was better than the 5-ethyl analogue **21** but showed a poorer activity than the 5-hydrogen derivative **19**.

Table 1

In vitro Antibacterial Activity (Minimum Inhibitory Concentration, μg/ml [a])



Compound	R_1	R_5	*S. pn.* A 9585	S. *au.* A 9537	*E. co.* A 15119	*P. ae.* A 9843	Ref
17		H	1	0.06	0.02	0.5	[2]
18		CH_3	1	0.03	0.06	4	[2]
19		H	–	0.25	0.03	0.5	
20		CH_3	1	1	0.008	0.5	[2,7]
21		CH_2-CH_3	1	1	0.25	4	[2]
15		CHO	64	32	1	16	
16		CH_2OH	8	4	0.125	2	

[a] Organisms selected for the table are as follows: *Streptococcus pneumoniae* A9585; *Staphylococcus aureus* A9537; *Escherichia coli* A15119; *Pseudomonas aeruginosa* A9843.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken with a Büchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR 20 SXC spectrophotometer. All nmr spectra were observed with a Bruker AC 200 spectrometer. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane for ^1H and fluorotrichloromethane for ^{19}F. Flash column chromatography was performed with Merck silica gel 60F, 70-230 mesh ASTM. Elemental analysis were performed by the Bristol-Myers Squibb Analytical Department and the results analyzed for C, H and N were within ±0.4% of theoretical values.

Microbiology. General Procedures of *in vitro* Studies.

The *in vitro* antibacterial activity was studied by a side-by-side comparison with ciprofloxacin and determined by a serial 2-fold dilution technique using nutrient broth. The inoculum size was adjusted to 10^6 CFU-ml and the concentration of the compounds ranged from 0.0005 to 250 μg/ml. Minimum inhibitory concentrations (MICs) were defined as the lowest concentration of the compound that prevented visible growth of bacteria after incubation at 37° for 18 hours.

2,6-Dichloro-4-formyl-5-fluoronicotinic Acid (**3**).

Under nitrogen was added 6.25 ml (10 mmoles) of 1.6 *M* butyllithium in hexane to 5.5 ml dry tetrahydrofuran. The solution was cooled to −25° and a solution of 1.4 ml (10 mmoles) of diisopropylamine in 5 ml tetrahydrofuran was added dropwise and the solution was warmed at +5° in 50 minutes. The solution was cooled to −75° and a solution of 1 g (4.76 mmoles) of 2,6-dichloro-5-fluoronicotinic acid in 8 ml tetrahydrofuran was added dropwise under −65°. The solution was stirred 3 hours at −75° and a solution of 1.5 ml (19.3 mmoles) of dimethylformamide in 2 ml tetrahydrofuran was added dropwise. The suspension was stirred 1 hour at −70° and allowed to reach −20° in 45 minutes. The solution was poured in 4 ml of a saturated aqueous solution of ammonium chloride and was extracted with three portions of ether. The organic layers were collected and dried to yield 1.5 g of crude material which was chromatographed over silica gel (dichloromethane/methanol: 98/2) to give 0.93 g of a solid which was extracted in 15 ml of a solution of 10% aqueous sodium hydrogen carbonate. The aqueous layer was washed with ethyl acetate, and acidified with concentrated hydrochloric acid. The oily product was extracted with ethyl acetate, dried over magnesium sulfate to give 0.58 g of **3** (yield 51%), mp 169°, 2,4-dinitrophenylhydrazone, mp 232-235°. An analytical sample was obtained by recrystallization from toluene, mp 172°; ir (potassium bromide): 3227, 1786, 1414, 1101 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.86 (br s, C*H*O); ^{19}F nmr (dimethyl sulfoxide-d_6): δ −120 (s).

Anal. Calcd. for $C_7H_2Cl_2FNO_3$: C, 35.33; H, 0.85; N, 5.89. Found: C, 35.44; H, 0.96; N, 5.71.

2,6-Dichloro-5-fluorofuro[3,4-*c*]pyridin-3(1*H*)-one (**5**).

To a solution of 1.6 g (6.7 mmoles) of the aldehyde **3** in 48 ml methanol cooled at 0°, was carefully added 0.25 g (6.7 mmoles) of sodium borohydride. The mixture was stirred 1 hour at 0° and 1 hour at room temperature. It was added 0.12 g (3.3 mmoles) more sodium borohydride and the reaction mixture stirred 30 minutes longer. After evaporation of the mixture under reduced pressure the residue was taken up in water and the *p*H was brought to 0.5 with concentrated hydrochloric acid and extracted with ether to give 1.4 g of the lactone **5** (yield 87%). An analytical sample was recrystallized from water, mp 110°; ^1H nmr (dimethyl sulfoxide-d_6): δ 5.57 (s, CH_2 lactone).

Anal. Calcd. for $C_7H_2Cl_2FNO_2$: C, 37.87; H, 0.91; N, 6.31. Found: C, 37.49; H, 1.00; N, 6.18.

2,6-Dichloro-4-trimethylsilyl-5-fluoronicotinic Acid (**6**).

Under nitrogen was added 83.8 ml (0.21 mole) of 2.5 *M* of *n*-butyllithium in hexane to 84 ml dry tetrahydrofuran cooled to −30°, followed, dropwise, by a solution of 33.4 ml (0.24 mole) of diisopropylamine in 50 ml of dry tetrahydrofuran. The solution was kept at 0° for 45 minutes. Then the solution was cooled at −73° and a solution of 20 g (0.095 mole) of 2,6-dichloro-5-fluoronicotinic acid in 370 ml of tetrahydrofuran was added, keeping the temperature below −68°. The reaction mixture was stirred at −73° for 3 hours and it was added 36.2 ml (0.285 mole) of chlorotrimethylsilane in 37 ml of tetrahydrofuran below −66°, the solution was stirred 1 hour while the temperature was allowed to reach −15°. A solution of 200 ml of saturated ammonium chloride was rapidly added below 0°, followed by 250 ml of 2*N* hydrochloric acid. The reaction mixture was extracted with three portions of 250 ml of ether to give 34.5 g of an oil which was extracted from boiling petroleum ether to yield 18.4 g of **6** (yield 69%), mp 158-160°; ^{19}F nmr (dimethyl sulfoxide-d_6): δ −101.14 (s).

Anal. Calcd. for $C_9H_{10}Cl_2FNO_2Si$: C, 38.31; H, 3.57; N, 4.96. Found: C, 38.56; H, 3.72; N, 5.03.

3-(2,6-Dichloro-4-trimethylsilyl-3-fluoro-5-pyridinyl)-3-oxopropanoic Acid Ethyl Ester (**7**).

To a suspension of 18 g (0.064 mole) of **6** in 120 ml of dichloromethane was added 15 drops of dimethylformamide. After completion of the solubilization, the solution was cooled to −20° and a solution of 11 ml (0.126 mole) of oxalyl dichloride in 40 ml dichloromethane was added. The reaction mixture was allowed to reach 25° for 5 hours. The solvent was evaporated under reduced pressure to give 19.7 g of the corresponding acid chloride which was used without further purification. To a solution of 16.8 g (0.128 mole) of propanedioic acid momoethyl ester in 265 ml of dry tetrahydrofuran cooled at −55° was added 160 ml (0.255 mole) of 1.6 *M* butyllithium in hexane keeping the temperature below −45°. After 30 minutes at −25°, the suspension was cooled at −73° and 19.7 g (0.064 mole) of the above nicotinic acid chloride was added. The suspension was kept at −70° for 1.5 hour. The temperature was raised to −30° and 100 ml of a solution of saturated ammonium chloride was poured into the reaction mixture. The *p*H was brought to 7.5 with hydrochloric acid and after extraction with two portions of 100 ml ether it was obtained 23.8 g of **7** as an oil which was used without purification (yield 100%).

3-(2,6-Dichloro-4-trimethylsilyl-3-fluoro-5-pyridinyl)-3-oxo-2-[((cyclopropyl)amino)methylene]propanoic Acid Ethyl Ester (**8**).

A mixture of 22.5 g (0.064 mole) of the propanoic acid ethyl ester **7** and 15.7 ml (0.166 mole) of acetic anhydride in 23.3 ml (0.14 mole) of triethylorthoformate was heated at 120° with distillation of ethyl acetate formed during the reaction. Excess of reactives were distilled off *in vacuo* to give 30.6 g of the corresponding 2-ethyloxymethylene derivative which was used without further purification. To a solution of 25.6 g (0.63 mole) of the above 2-ethyloxymethylene derivative in 45 ml of ethanol cooled to −40° was added dropwise 3.6 g (0.63 mole) of cyclopropylamine in 15 ml ethanol. After 2 hours at room temperature, the precipitate was filtered and dried to give 10.8 g of **8** (yield 41%), mp 125°.

7-Chloro-6-fluoro-5-trimethylsilyl-1-cyclopropyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**9**).

There was suspended 0.302 g (6.3 mmoles) of 50% sodium hydride in oil in 25 ml of dry dioxane. After stirring 10 minutes at room temperature, 2.51 g (6 mmoles) of **8** was poured into the suspension. After 1.5 hours at 45°, the reaction mixture was evaporated *in vacuo* and the residue was poured into ice-cooled water, the *p*H was made neutral with 1*N* aqueous hydrochloric acid. The precipitate was filtered and chromatographed over silica gel (dichloromethane/ethyl acetate: 95/5) to give 1.26 g of **9** (yield 55%), mp 185-189° (and 0.37 g (yield 20%) of **10**); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 0.38 (d, J = 2.8 Hz, 9H, $(CH_3)_3Si$), 1.08 and 1.16 (2m, 4H, CH_2 cyclopropyl), 1.28 (t, J = 6 Hz, 3H, CH_2-CH_3), 3.66 (m, 1H, CH cyclopropyl), 4.24 (q, J = 6 Hz, 2H, CH_2-CH_3), 8.55 (s, 1H, *H*-2 naphthyridine).

Anal. Calcd. for $C_{17}H_{20}ClFN_2O_3Si$: C, 53.33; H, 5.27; N, 7.32. Found: C, 53.15; H, 5.18; N, 7.23.

5-Formyl-6-fluoro-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**11**).

To 1.51 g (3.95 mmoles) of **9** in 4 ml of *o*-dichlorobenzene was added 0.74 g (10.25 mmoles) of anhydrous dimethylformamide and 1.05 g (6.91 mmoles) of phosphorus oxychloride [8]. The suspension was heated at 90-100° for 2 hours, cooled and neutralized with an aqueous solution of sodium acetate. The mixture was evaporated *in vacuo*. The residue was partitioned between dichloromethane and water, dried (magnesium sulfate) and chromatographed over silica gel (dichloromethane/acetone: 92/8) to give 0.32 g of **11** (yield 24%), mp 158-163°; ^{1}H nmr deuteriochloroform): δ 0.86 (m, 2H, CH_2 cyclopropyl), 1.13-1.20 (m + t, 5H, CH_2-CH_3 ester + CH_2 cyclopropyl), 3.45 (m, 1H, CH cyclopropyl), 4.16 (q, J = 6 Hz, 2H, CH_2 ethyl ester), 8.45 (s, 1H, *H*-2 naphthyridine), 10.32 (s, 1H, CHO).

Anal. Calcd. for $C_{15}H_{12}ClFN_2O_4$: C, 53.19; H, 3.57; N, 8.27. Found: C, 53.47; H, 3.72; N, 8.01.

5-Hydroxymethyl-6-fluoro-7-chloro-1-cyclopropyl-1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**12**).

To a suspension of 0.1 g (0.29 mmole) of the formyl derivative **11** in 3 ml of methanol cooled at 0° was added 11 mg (0.29 mmole) of sodium borohydride. The reaction mixture was stirred for 30 minutes at +5° and 30 minutes at room temperature, evaporated under reduced pressure and taken up with water. The *p*H was brought to 7 with 6*N* hydrochloric acid and the mixture was extracted with dichloromethane, dried (magnesium sulfate) to yield 68 mg of raw material. After chromatography over silica gel (dichloromethane/acetone: 95/5), there obtained 47 mg (yield 47%) of **12** as an amorphous solid; ^{1}H nmr (deuteriochloroform): δ 0.5-1 (m, 4H, CH_2 cyclopropyl), 1.32 (t, J = 6 Hz, 3H, CH_2-CH_3), 2.7 (m, 1H, CH cyclopropyl), 3.55 (m, 2H, 2-CH_2), 4.25 (q, J = 6 Hz, 2H, CH_2-CH_3), 4.67 (dd, 2H, CH_2OH), 5.24 (m, 1H, 3-*H*).

7-(*N*-*tert*-Butyloxycarbonylpiperazin-1-yl)-6-fluoro-5-formyl-1-cyclopropyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**13**).

A solution of 0.30 g (0.88 mmole) of the naphthyridine-3-carboxylic acid ethyl ester **11** and 0.47 g (2.5 mmoles) of *N*-*tert*-butyloxycarbonylpiperazine in 15 ml of acetonitrile was heated at 40° for 2 hours. The solvent was evaporated *in vacuo* and the residue was crystallized from water, extracted with dichloromethane,

washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to give 0.39 g of raw material which was purified over silica gel (dichloromethane/methanol: 98/2) to provide 0.25 g (yield 58%) of **13** as an amorphous solid; ^{1}H nmr (deuteriochloroform): δ 1.02 (m, 2H, CH_2 cyclopropyl), 1.21 (m, 2H, CH_2 cyclopropyl), 1.31 (t, 3H, CH$_2$-CH_3), 1.42 (s, 9H, *tert*-butyl), 3.42 (m, 1H, C*H* cyclopropyl), 3.47 (m, 4H, CH_2 piperazine), 3.77 (m, 4H, CH_2 piperazine), 4.29 (q, J = 6 Hz, 2H, CH_2 ethyl ester), 8.44 (s, 1H, *H*-2 naphthyridine), 10.36 (s, 1H, C*H*O).

7-(*N*-*tert*-Butyloxycarbonylpiperazin-1-yl)-6-fluoro-5-hydroxymethyl-1-cyclopropyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**14**).

To a solution of 0.2 g (0.41 mmole) of 5-formyl-1,8-naphthyridine-3-carboxylic acid ethyl ester **13** in 20 ml of methanol cooled to 0° was added 0.04 g (0.099 mmole) of sodium borohydride. The reaction mixture was stirred 1.5 hours at 0°, the solvent was evaporated *in vacuo*. The residue was partitioned between a *p*H 7 buffer and dichloromethane, extracted and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to give 0.16 g of raw material which was purified over silica gel (dichloromethane/methanol: 98/2). It was obtained 0.06 g (yield 30%) of **14**; ^{1}H nmr (deuteriochloroform): δ 0.94 and 1.15 (2m, 8H, CH_2 cyclopropyl), 1.33 (t, 3H, CH$_2$CH_3), 1.43 (s, 9H, *tert*-butyl), 3.48 and 3.76 (2m, 9H, C*H* cyclopropyl + CH_2 piperazine), 4.89 (d, 2H, CH_2OH), 8.49 (s, 1H, *H*-2 naphthyridine).

7-(Piperazin-1-yl)-6-fluoro-5-formyl-1-cyclopropyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid, Hydrochloride (**15**).

A solution of 0.25 g (0.51 mmole) of 7-(*N*-*tert*-butyloxycarbonylpiperazin-1-yl)-naphthyridine-3-carboxylic acid ethyl ester **13** and 8 ml (48 mmoles) of 6*N* hydrochloric acid in 20 ml of ethanol was heated under reflux for 3 hours. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol to give 0.14 g (yield 70%) of **15**, mp >260°; ir (potassium bromide): 2929, 2700, 1735, 1712, 1620, 1457 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.05-1.27 (2m, 4H, CH_2 cyclopropyl), 3.76 (m, 1H, C*H* cyclopropyl), 4.12 (m, 8H, CH_2 piperazine), 8.71 (s, 1H, *H*-2 naphthyridine), 10.5 (s, 1H, C*H*O).

Anal. Calcd. for $C_{17}H_{17}FN_4O_4$·HCl: C, 51.46; H, 4.57; N, 14.12. Found: C, 51.26; H, 4.71; N, 13.93.

7-(Piperazin-1-yl)-6-fluoro-5-hydroxymethyl-1-cyclopropyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (**16**).

A mixture of 0.31 g (0.63 mmole) of the ester **14** in a mixture of 25 ml of ethanol and 9.9 ml of 6*N* hydrochloric acid was heated under reflux for 3 hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was crystallized from ethanol, filtered and dried to give 0.22 g (yield 88%) of **16**, mp >260°; ir (potassium bromide): 3344, 2941, 2730, 1725, 1620, 1466 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.10-1.28 (2m, 4H, CH_2 cyclopropyl), 3.34 (m, 4H, CH_2 piperazine), 3.78 (m, 1H, C*H* cyclopropyl), 4.15 (m, 4H, CH_2 piperazine), 5.06 (s, 2H, 5-CH_2OH), 8.75 (s, 1H, *H*-2, naphthyridine), 9.50 (m, 1H, CH$_2$O*H*).

Anal. Calcd. for $C_{17}H_{19}FN_4O_4$·HCl: C, 51.20; H, 5.05; N, 14.05. Found: C, 50.97; H, 4.99; N, 13.96.

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[3] Experimental data not shown.

[4] Attempts to cyclize the enamine **8** with potassium carbonate in acetonitrile gave exclusively the desilylated derivative **10**.

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