8-Methyl-7-substituted-1,6-naphthyridine-3-carboxylic Acids as New 6-Desfluoroquinolone Antibacterials [1]

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1,6-Naphthyridine-8-methyl-7-substituted-3-carboxylic acids were synthesized as new 6-desfluoroquinolone antibacterials in which the usual fluorine atom at C-6 position was replaced by an endocyclic nitrogen atom. Comparing the antibacterial activity of these 6-azaquinolones with our previous 6-amino and 6-hydrogen counterparts, they resulted always less active. However, the presence of methyl group at C-8 position ensure good Gram-positive antibacterial activity, with minimum inhibitory concentrations values on the same order of ciprofloxacin for piperidinyl derivative **3d** and tetrahydroisoquinolinyl derivative **3c**.

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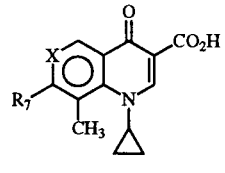
Introduction.

Quinolones are an important class of wide spectrum antibacterial agents resembling the 4-oxo-1,4-dihydroquinoline skeleton. Almost all the clinically useful quinolones bear a fluorine atom at C-6 position of the quinolone structure which, coupled with an appropiate base at C-7, confers broad and potent antimicrobial activity.

As a part of our program on antibacterial quinolone structure-activity relationships, we recently described some 6-desfluoroquinolones with potent antibacterial activity showing that an amino group [2,3], or a simple hydrogen atom [4], are good substitutes for the C-6 fluorine atom when coupled with a selected substituent set in the quinolone ring. In particular, those 6-desfluoroquinolones bearing a methyl group at C-8 position (structures **1** and **2**, Figure 1) displayed an antibacterial activity against Gram-positive bacteria, including methicillin- and ciprofloxacin-resistant strains [3-5], superior to that of ciprofloxacin. A study carried out using these 6-desfluoroquinolones, as well as their 6-fluoro counterparts, showed that the substituent at C-6 position could also play an important role in the quinolone/DNA/DNA-gyrase interaction [6].



1 X = C-NH_2
2 X = C-H
3 X = N

R_7 = heterocyclic side chain

Figure 1.

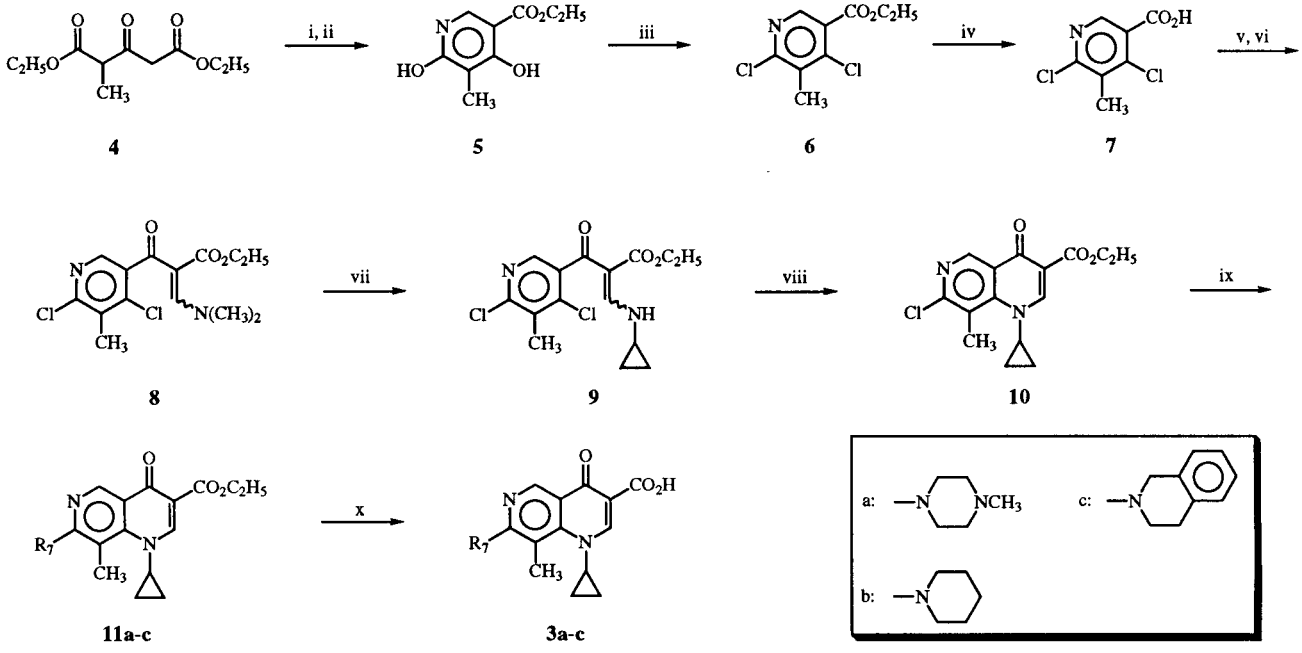
In an attempt to extend our knowledge about the C-6 substituent, we now report a new series of 6-desfluoroquinolones in which the substituent at the C-6 position was omitted by inserting an endocyclic nitrogen atom. In the resulting 1,6-naphthyridine derivatives (structure **3**, Figure 1) the arrangement of functional groups which a 6-desfluoroquinolone structure-activity relationship study indicated as optimun was mantained: cylopropyl group at N-1, methyl group at C-8, and piperidinyl or tetrahydroisoquinolinyl as C-7 side chain [7]. The piperazine was also considered as C-7 substituent since it represents the classical heterocyclic base in the antibacterial quinolones.

Chemistry.

The synthetic pathway (Scheme 1) chosen to derive the target acids **3a-c**, was based on the preparation of the suitable functionalized pyridine derivative, ethyl 2,4-dichloro-3-methylpyridine-5-carboxylate (**6**). Since all attempts to introduce the methyl group on known ethyl 2,4-dichloropyridine-5-carboxylate [8] failed, it was necessary to insert the methyl group in the first step of the synthesis, preparing the diethyl 2-methyl-3-oxopentanedioate derivative (**4**), and then building the pyridine ring following a classic route [8,9]. Thus, the methyl derivative **4**, prepared as reported in the literature [10], was converted to ethyl 2,4-dihydroxy-3-methylpyridine-5-carboxylate (**5**) in a one pot reaction by treatment with triethyl orthoformate in acetic anhydride and direct ring closure with 30% ammonia in an over-all yield of 43%. The dihydroxypyridine **5** was then heated in a sealed tube at 125° with phosphorus oxychloride until the starting suspension became a yellow solution. The dichloro ester derivative **6** so obtained was then hydrolized in 1 *N* sodium hydroxide solution affording the acid **7** in 95% yield. The latter was elaborated in the desired 1,6-naphthyridine nucleus **10**, by the usual cycloaracylation procedure. Thus, the reaction of the acid chloride of 2,4-dichloro-3-methylpyridine-5-carboxylic acid (**7**) with ethyl (dimethylamino)acrylate gave, after purification by column chromatography, adduct **8**. It was then

reacted at room temperature with cyclopropylamine to afford pure enamine **9** which was cyclized in the presence of sodium hydride at 0°. Nucleophilic substitution of C-7 chlorine atom of synthon **10** with the three selected heterocyclic side chains in acetonitrile or dimethyl sulfoxide and triethylamine as hydrochloric acid scavenger, gave esters **11a-c** in low yield. Finally, the target acids **3a,b** were obtained by acid hydrolysis, while tetrahydroisoquinolinyl derivative **3c** was derived using basic conditions because of its acid liability.

Scheme 1 [a]



[a] Reagents: (i) $(Ac)_2O$, $(EtO)_3CH$, 120°; (ii) 30% NH_4OH; (iii) $POCl_3$, 125°; (iv) 1 *N* NaOH, reflux; (v) $SOCl_2$, reflux; (vi) $(CH_3)_2NCH{=}CHCO_2Et$, Et_3N, toluene, 90°; (vii) cyclopropylamine, EtOH/Et_2O; (viii) 60% NaH, tetrahydrofuran, 0°; (ix) R_7H, dimethyl sulfoxide or CH_3CN, Et_3N; (x) 6 *N* HCl/EtOH or 1 *N* NaOH, reflux.

Results and Discussion.

The 1,6-naphthyridine derivatives **3a-c** were tested for their antibacterial activity against an assortment of eight Gram-negatives and eight Gram-positives including some clinical isolates, as well as a ciprofloxacin-resistant *Staphylococcus aureus* strain and methicillin-resistant *S. aureus*. In addition, 6-amino- (**1a-c**) and 6-hydrogen-quinolone (**2a-c**) counterparts, previously reported by us [1-3], as well as the control drug ciprofloxacin, are included for comparative purposes. The minimum inhibitory concentrations (MICs, μg/ml) were determined by microdilution technique using nutrient broth, according to National Committee for Clinical Laboratory Standards [11]; the data are presented in Table 1. The geometric means of the MICs were also calculated to facilitate the comparison of the activity.

Among the 1,6-naphthyridine quinolones, the 7-piperidinyl **3b** and 7-tetrahydroisoquinolinyl **3c** derivatives display good antibacterial activity against Gram-positive bacteria, on the same order of ciprofloxacin. While, the 1,6-naphthyridine derivatives show very low activity against Gram-negatives. Indeed, the piperazinyl derivative **3a** even though the most active, has a geometric mean of the MIC 30 times superior to that of ciprofloxacin. When compared with their 6-amino **1a-c** and 6-hydrogen **2a-c** counterparts, these 6-azaquinolones were always less active showing that the endocyclic nitrogen is not an equally valid substituent at the C-6 position.

The good activity displayed by **3b** and **3c** on Gram-positives is clearly due to the presence of a methyl group at C-8 position which was already shown to be an enhancer of Gram-positive antibacterial activity also in our previous 6-desfluoroquinolones.

A study, of the interaction of these new 6-desfluoroquinolones with DNA in the presence of magnesium ions, using fluorimetric technique, is in progress.

Table 1

Comparative *In Vitro* Antibacterial Activity for 1,6-Naphthyridines **3** Prepared in This Study, and 6-Amino (**1**) and 6-Hydrogen (**2**) Analogues

	Minimum Inhibitory Concentrations (MICs, μg/ml)									
Organism	**1a**	**2a**	**3a**	**1b**	**2b**	**3b**	**1c**	**2c**	**3c**	Ciprofloxacin
Gram-positives										
Staphylococcus aureus [a]	1	0.25	1	0.05	≤0.016	0.13	≤0.016	≤0.016	0.13	0.5
Staphylococcus aureus [b]	1	0.25	1	≤0.016	≤0.016	0.06	≤0.016	0.03	≤0.016	0.25
Staphylococcus aureus [c] methicillin-resistant	4	0.5	4	0.125	≤0.016	0.13	≤0.016	0.25	0.13	1
Staphylococcus aureus [d] ciprofloxacin-resistant	>16	8	8	8	1	4	2	2	16	>16
Streptococcus pyogenes [e]	4	2	8	0.5	0.03	2	≤0.016	0.25	2	0.5
Streptococcus pneumoniae [f]	8	2	2	2	≤0.016	2	0.25	1	4	1
Enterococcus faecalis [g]	2	2	4	0.5	1	2	0.25	1	4	1
Enterococcus faecalis [h]	4	1	2	1	0.03	0.5	0.125	0.5	2	0.5
Geometric means	3.364	1.090	2.828	0.376	0.052	0.597	0.075	0.272	0.852	0.917
Gram-negatives										
Escherichia coli [i]	0.03	0.06	0.25	0.125	0.03	0.25	0.125	1	2	≤0.016
Escherichia coli [j]	0.06	0.06	0.25	0.5	0.03	0.5	0.125	2	2	≤0.016
Enterobacter cloacae [k]	0.125	0.25	1	1	0.25	2	0.5	0.03	8	≤0.016
Proteus mirabilis [l]	1	2	2	4	4	8	>16	>16	16	0.06
Proteus vulgaris [m]	8	8	16	>16	8	>16	8	>16	>16	0.5
Klebsiella pneumoniae [n]	0.03	≤0.016	0.13	≤0.016	≤0.016	0.13	0.03	0.125	2	≤0.016
Pseudomonas aeruginosa [o]	2	2	8	4	4	16	8	>16	>16	0.06
Haemophilus influenzae	0.03	0.06	0.25	≤0.016	≤0.016	0.03	≤0.016	0.06	≤0.016	≤0.016
Geometric means	0.205	0.269	0.921	0.503	0.228	1.090	0.499	1.079	4.012	0.034

Gram-positive organism codes: [a] ATCC 29213; [b] MPR 5; [c] POMM 6214; [d] OBT 687; [e] OMNFI BI; [f] I 043; [g] LEP Br; [h] UCMC 39690.
Gram-negatives organism codes: [i] ATCC 25922; [j] 120; [k] OMNFI 174; [l] OBT 505; [m] CNUR 6; [n] ATCC 10031; [o] ATC1C 9027.

EXPERIMENTAL

Thin layer chromatography (tlc) was performed on precoated sheets of silica gel $60F_{254}$ (Merck) and visualized by using uv. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70-230) and flash chromatography on Merck silica gel 60 (mesh 230-400). Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. Elemental analyses were performed for C, H and N on a Carlo Erba elemental analyzer, Model 1106. The ^{1}H nmr spectra were recorded at 200 MHz (Broker AC-200) with tetramethylsilane as internal standard and chemical shifts are given in ppm (δ). The spectral data are consistent with the assigned structures. Reagents and solvents were purchased from common commercial suppliers and were used as received. Organic solutions were dried over anhydrous sodium sulfate and concentrated with a Büchi rotary evaporator at low pressure. Yields were of purified product and were not optimized. All starting materials were commercially available unless otherwise indicated.

Ethyl 2,4-Dihydroxy-3-methylpyridine-5-carboxylate (**5**).

A mixture of compound **4** [10] (5.5 g, 25.7 mmoles), triethyl orthoformate (4.7 ml, 28.3 mmoles), and acetic anhydride (4.85 ml, 51.4 mmoles), was heated at 120° for 1.5 hours with vigorous stirring. The dark yellow solution was then distilled *in vacuo* in an oil-bath at a temperature that did not go above 95-100°. The residue was cooled in ice, and mixed with 30% ammonia (2 ml). The mixture was then allowed to react for 1 hour giving a yellow solid which, after acidification with 2 *N* hydrochloric acid to *p*H = 5, became a white solid. This was filtered, dried, to give 2.20 g (43%) of **5**, mp 242-244°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 3H, J = 7 Hz, CH_2CH_3), 2.00 (s, 3H, CH_3), 4.35 (q, 2H, J = 7 Hz, CH_2CH_3), 8.20 (s, 1H, CH), 11.20 and 13.50 (each br s, 1H, OH).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 55.05; H, 5.50; N, 7.25.

Ethyl 2,4-Dichloro-3-methylpyridine-5-carboxylate (**6**).

A suspension of dihydroxypyridine **5** (1.2 g, 6.09 mmoles) and phosphorus oxychloride (7 ml), was heated in a sealed tube at 125° for 3 hours. After cooling, the solution was poured into ice-water, neutralized with sodium carbonate, and extracted with ethyl acetate . The combined organic layers were washed with water, dried and evaporated to dryness to give 1.15 g (81%) of **6** as yellow oil which was used in the next step without further purification; ^{1}H nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7 Hz, CH_2CH_3), 2.50 (s, 3H, CH_3), 4.35 (q, 2H, J = 7 Hz, CH_2CH_3), 8.50 (s, 1H, CH).

2,4-Dichloro-3-methylpyridine-5-carboxylic Acid (**7**).

The suspension of ester **6** (1.2 g, 5.13 mmoles) in 1 *N* sodium hydroxide (10 ml) was refluxed for 1 hour. After cooling, the solution was acidified with 2 *N* hydrochloric acid and the resulting precipitate was filtered to give 1.0 g, (95%) of **7** as a white solid which was used in the next step without further purification, mp 153-154°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.40 (s, 3H, CH_3), 8.60 (s, 1H, H-6).

Ethyl 2-(2,4-Dichloro-3-methyl-5-pyridinoyl)-3-(dimethylamino)acrylate (**8**).

A mixture of acid **7** (0.8 g, 3.9 mmoles) and thionyl chloride (5 ml) was refluxed for 2 hours. The excess thionyl chloride was removed by distillation under reduced pressure to give a mobile oil residue which was dissolved in dry toluene (10 ml) and added to ethyl 3-(dimethylamino)acrylate [12] (0.84 g, 5.85 mmoles) and dry triethyl amine (0.6 g, 5.85 mmoles). The resulting solution was heated at 90° for 4 hours. After cooling and filtering the insoluble material, the solvent was evaporated to dryness and the residue was purified by flash chromatography eluting with a gradient of cyclohexane/ethyl acetate (60:40) to cyclohexane/ethyl acetate (30:70) to give 0.7 g (54%) of **8** as a white solid, mp 152-155°; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, 3H, J = 7 Hz, CH_2CH_3), 2.50 (s, 3H, CH_3), 3.05 and 3.40 (each br s, 3H, NCH_3), 3.95 (q, 2H, J = 7 Hz, CH_2CH_3), 7.90 (s, 1H, vinyl H), 8.20 (s, 1H, aromatic H).

Anal. Calcd. for $C_{14}H_{16}Cl_2N_2O_3$: C, 50.77; H, 4.87; N, 8.46. Found: C, 50.75; H, 4.92; N, 8.30.

Ethyl 2-(2,4-Dichloro-3-methyl-5-pyridinoyl)-3-(cyclopropylamino)acrylate (**9**).

A stirred solution of **8** (0.6 g, 1.81 mmoles) in ethanol (2 ml) and diethyl ether (8 ml) was treated dropwise with cyclopropylamine (0.165 g, 2.9 mmoles). After 1 hour at room temperature the obtained precipitate was filtered, washed with ethanol to give 0.5 g (81%) of **9** as a white powdery solid, mp 130-132°; ^{1}H nmr (deuteriochloroform): δ 0.80-1.10 (m, 7H, cyclopropyl CH_2 and CH_2CH_3), 2.55 (s, 3H, CH_3), 2.95-3.10 (m, 1H, cyclopropyl CH), 4.00 (q, 2H, J = 7 Hz, CH_2CH_3), 8.00 (s, 1H, aromatic H), 8.30 (d, 1H, J = 12 Hz, vinyl H), 11.15 (br d, 1H, NH).

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O_3$: C, 52.49; H, 4.70; N, 8.16. Found: C, 52.70; H, 4.82; N, 8.05.

Ethyl 1-Cyclopropyl-7-chloro-8-methyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate (**10**).

Sodium hydride (60% in an oil suspension) (0.031 g, 1.28 mmoles) was added portionwise to a solution of **9** (0.40 g, 1.17 mmoles) in tetrahydrofuran (15 ml), maintained at 0°. The mixture was then stirred for 1 hour at the same temperature under a nitrogen atmosphere. The mixture was then evaporated to dryness and the residue was treated with water to give a solid which was filtered and dried, yielding 0.22 g (61%) of **10** as white solid, mp 200-202° dec; ^{1}H nmr (deuteriochloroform): δ 1.20-1.45 (m, 7H, cyclopropyl CH_2 and CH_2CH_3), 2.85 (s, 3H, CH_3), 3.90-4.05 (m, 1H, cyclopropyl CH), 4.40 (q, 2H, J = 7 Hz, CH_2CH_3), 8.65 (s, 1H, H-5), 9.20 (s, 1H, vinyl H).

Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 59.01; H, 4.85; N, 9.25.

Ethyl 1-Cyclopropyl-8-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate (**11a**).

A mixture of ester **10** (0.22 g, 0.72 mmole), *N*-methylpiperazine (0.288 g, 2.88 mmoles), and triethylamine (0.742 g, 7.20 mmoles) in dry acetonitrile (20 ml) was refluxed for 24 hours. After cooling, the reaction mixture was evaporated to dryness and the residue was purified by column chromatography eluting with methanol/chloroform (3:97) to give 0.08 g (36%) of **11a**, mp 204-206°; ^{1}H nmr (deuteriochloroform): δ 0.90-1.05 and 1.15-1.30 (each m, 2H, cyclopropyl CH_2), 1.40 (t, 3H, J = 7 Hz, CH_2CH_3), 2.45 (s, 3H, CH_3), 2.55-2.75 (m, 7H, piperazine CH_2 and CH_3), 3.40-3.55 (m, 4H, piperazine CH_2), 3.80-3.95 (m, 1H, cyclopropyl CH), 4.40 (q, 2H, J = 7 Hz, CH_2CH_3), 8.60 (s, 1H, H-5), 9.10 (s, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{26}N_4O_3$: C, 64.85; H, 7.07; N, 15.12. Found: C, 65.05; H, 7.30; N, 14.98.

Ethyl 1-Cyclopropyl-8-methyl-7-(1-piperidinyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate (**11b**).

This compound was prepared starting from **10** using piperidine as the nucleophile, by the same procedure as for **11a**, except that dimethyl sulfoxide was used instead of acetonitrile and the temperature was 100°. The yield was 40%, as a pale yellow solid, mp 170-172°; ^{1}H nmr (deuteriochloroform): δ 0.85-1.0 (m, 2H, cyclopropyl CH_2), 1.25-1.45 (m, 5H, cyclopropyl CH_2 and CH_2CH_3), 1.90-2.20 (m, 6H, piperidine CH_2), 2.55 (s, 3H, CH_3), 3.30-3.45 (m, 4H, piperidine CH_2), 3.80-4.00 (m, 1H, cyclopropyl CH), 4.40 (q, 2H, J = 7 Hz, CH_2CH_3), 8.60 (s, 1H, H-5), 9.15 (s, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.69; H, 7.12; N, 11.88.

Ethyl 1-Cyclopropyl-8-methyl-7-(1,2,3,4-tetrahydro-2-isoquinolinyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate (**11c**).

A mixture of ester **10** (0.20 g, 0.65 mmole), triethylamine (0.66 g, 6.51 mmoles), and 1,2,3,4-tetrahydroisoquinoline (0.348 g, 2.61 mmoles) in dimethyl sulfoxide, was heated at 120° for 10 hours. After cooling, the reaction mixture was poured into acidified ice-water and extracted with dichloromethane. The organic solvent was evaporated to dryness and the residue was treated with a mixture of diethyl ether and methanol to give a precipitate which was filtered and dried yielding 0.060 g (23%) of **11c** as yellow solid, mp 181-183°; ^{1}H nmr (deuteriochloroform): δ 0.90-1.05 and 1.15-1.30 (each m, 2H, cyclopropyl CH_2), 1.40 (t, 3H, J = 7 Hz, CH_2CH_3), 2.60 (s, 3H, CH_3), 3.05-3.20 and 3.60-3.75 (each m, 2H, isoquinoline CH_2), 3.80-4.00 (m, 1H, cyclopropyl CH), 4.40 (q, 2H, J = 7 Hz, CH_2CH_3), 4.60-4.70 (m, 2H, isoquinoline CH_2), 7.20-7.35 (m, 4H, isoquinoline aromatic H), 8.60 (s, 1H, H-5), 9.15 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.53; H, 6.10; N, 10.35.

1-Cyclopropyl-8-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic Acid Hydrochloride (**3a**).

A solution of ester **11a** (0.06 g, 0.162 mmole), in ethanol (0.5 ml) and 6 *N* hydrochloric acid (0.5 ml) was refluxed for 3 hours. After cooling, the solution was evaporated to dryness and the residue was treated with ethanol to give a yellow precipitate which was filtered, washed with ethanol and dried, to give 0.052 g (85%) of **3a**, mp 307-309°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 0.95-1.10 and 1.20-1.30 (each m, 2H, cyclopropyl CH_2), 2.65 (s, 3H, CH_3), 2.85 (d, 3H, J = 4.5 Hz, NCH_3), 3.10-4.00 (m, 8H, piperazine CH_2), 4.20-4.35 (m, 1H, cyclopropyl CH), 8.80 (s, 1H, H-5), 9.05 (s, 1H, vinyl H).

Anal. Calcd. for $C_{18}H_{22}N_4O_3$ HCl: C, 57.07; H, 6.12; N, 14.79. Found: C, 57.10; H, 6.00; N, 14.65.

1-Cyclopropyl-8-methyl-7-(1-piperidinyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic Acid (**3b**).

This compound was prepared starting from **11b** by the same procedure as for **3a**. It was obtained in 31%, as a yellow solid,

mp 182-184°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 0.85-1.10 and 1.20-1.35 (each m, 2H, cyclopropyl CH_2), 1.55-1.80 (m, 6H, piperidine CH_2), 2.50 (s, 3H, CH_3), 3.10-3.50 (m, 4H, piperidine CH_2), 4.15-4.35 (m, 1H, cyclopropyl CH), 8.80 (s, 1H, H-5), 9.00 (s, 1H, vinyl H), 14.80 (br s, 1H, CO_2H).

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.20; H, 6.58; N, 12.80.

1-Cyclopropyl-8-methyl-7-(1,2,3,4-tetrahydro-2-isoquinolinyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic Acid (**3c**).

The suspension of ester **11c** (0.04 g, 0.1 mmole) in 1 *N* sodium hydroxide (1.5 ml) was refluxed for 2 hours (until the suspension became a solution). After cooling, the solution was acidified with 2 *N* hydrochloric acid and the obtained precipitate was filtered, washed with diethyl ether and dried to give 0.020 g (54%) of **3c** as a pale yellow solid, mp 217-220; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 0.90-1.05 and 1.20-1.35 (each m, 2H, cyclopropyl CH_2), 2.65 (s, 3H, CH_3), 3.00-3.15 and 3.65-3.80 (each m, 2H, isoquinoline CH_2), 4.20-4.35 (m, 1H, cyclopropyl CH), 4.65-4.75 (m, 2H, isoquinoline CH_2), 7.15-7.35 (m, 4H, isoquinoline aromatic H), 8.80 (s, 1H, H-5), 9.05 (s, 1H, vinyl H), 14.70 (br s, 1H, CO_2H).

Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.43; H, 5.78; N, 11.15.

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