The Synthesis of a Series of 7-Amino-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acids as Potential Antibacterial Agents

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A series of 7-amino-1-cyclopropyl-1,4-dihydro-8-fluoro-4-oxo-1,6-naphthyridine-3-carboxylic acids has been prepared and evaluated for antibacterial activity. These compounds were prepared by the displacement of the chloro substituent from 7-chloro-1-cyclopropyl-1,4-dihydro-8-fluoro-4-oxo-1,6-naphthyridine-3-carboxylic acid employing the requisite nitrogen nucleophile to produce the title compounds. The naphthyridine acid was synthesized in ten steps from ethyl 2,4-dihydroxy-3-nitro-5-pyridinecarboxylate. The key step in the sequence was a Schiemann reaction carried out using the hexafluorophosphate salt of the diazonium ion derived from ethyl 3-amino-2,4-dichloro-5-pyridinecarboxylate.

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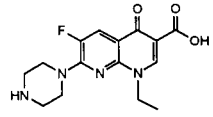
As part of our quinolone antibacterial program [1], we desired to make a series of naphthyridines related to the antiinfective agent, enoxacin (**1**), in which the 8-nitrogen and the 6-(C-F) functionalities are transposed to give an



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8-fluoro-1,6-naphthyridine. Literature reports [2] had already established 1,6-naphthyridines as antibacterial agents, but only one report [3] dealt with 1-cyclopropyl derivatives, and the reported compounds did not contain the 8-fluoro substituent which we believed would enhance activity.

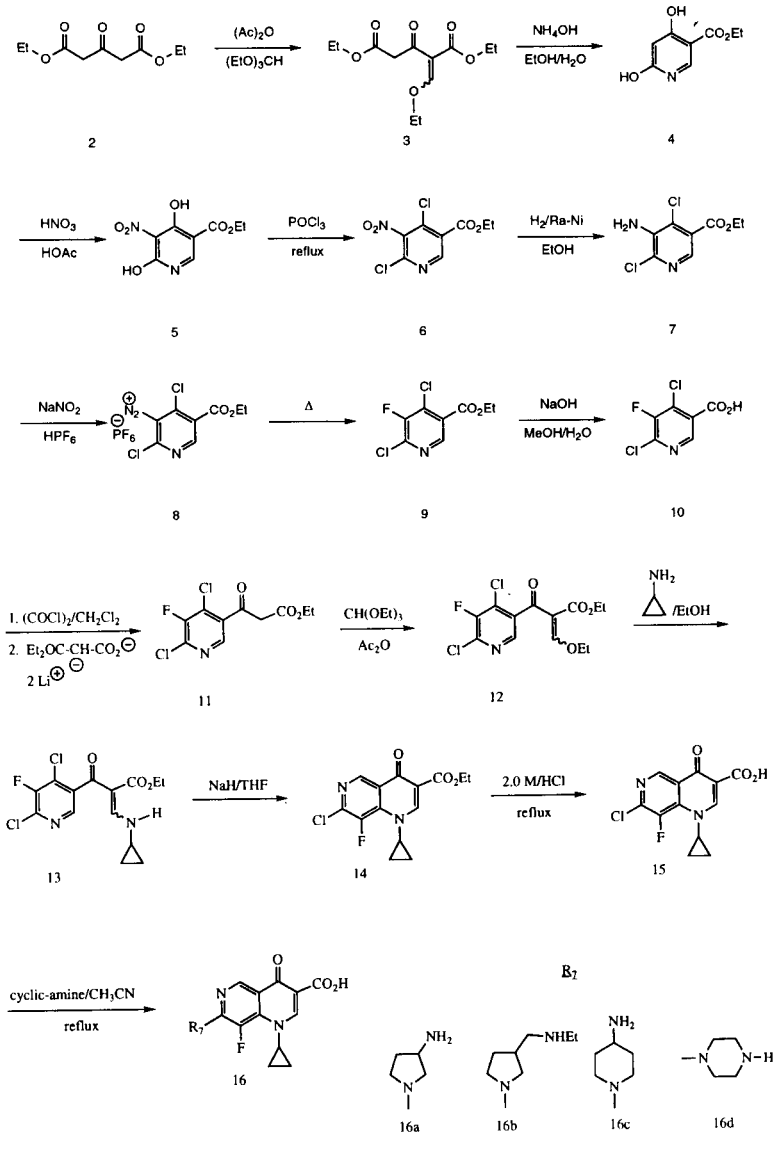
A perusal of the literature established ethyl 2,4-dihydroxy-5-pyridinecarboxylate (**4**) (Scheme I) prepared by a route originally described by Errera [4] and modified by den Hertog [5] as a potentially useful starting material. The above scheme employs the ethoxymethylene derivative **3** of diethyl acetonedicarboxylate **2** which was ring closed directly with ammonia in a one pot reaction, providing **4** in an over-all yield of 60%. Nitration of **4** using mild nitrating conditions (70% nitric acid in acetic acid) proceeded as reported by Kogl *et al.* [6]. This literature sequence proceeded smoothly to afford quantities of material from which we continued with our planned synthesis.

The dihydroxynitro compound **5** was refluxed with phosphorus oxychloride to produce the dichloronitro ester **6**. Catalytic hydrogenation using Raney-nickel produced the dichloroamino ester **7** in nearly quantitative yields (94%). Several methods of preparing diazonium tetrafluoroborates, including the use of sodium nitrite and organic nitrites in 48% tetrafluoboric acid either neat or in ethanol and/or ether failed, to provide material suitable for the introduction of the fluoro substituent by the Schiemann reaction. Even the anhydrous method developed by Doyle [7], failed to provide crystalline material. However, diazotization using sodium nitrite in aqueous hexafluorophophoric acid provided the diazonium hexafluorophosphate salt, **8**. Although this salt was relatively unstable, if used promptly, it proved to be suitable for thermal decomposition to the fluoro ester **9**, albeit in disappointing yields (27%). Careful base hydrolysis using a 10 mole % excess of sodium hydroxide in tetrahydrofuran at room temperature provided the dichlorofluoro acid **10** without any observable displacement of the 7-chloro substituent.

Elaboration of the acid **10** into the requisite 1,6-naphthyridine **15** proceeded in a manner analogous to the synthesis of the 1,8-naphthyridine analogue [8]. The acid **10** was converted to the acid chloride by reaction with oxalyl chloride in dichloromethane with a catalytic amount of *N,N*-dimethylformamide. The material was isolated and without purification, reacted with the dianion of monoethyl malonate to give the keto ester, **11**. Condensation of the keto ester with triethyl orthoformate in acetic anhydride provided the ethoxymethylene adduct **12** which was immediately reacted with cyclopropylamine to give the enamine **13**. Ring closure of the enamine using sodium hydride in tetrahydrofuran proceeded as smoothly as in the 1,8-naphthyridine synthesis to provide the 1,6-naphthyridine ester **14** in nearly quantitative yield (96%). Hydrolysis of the ester group under mildly acidic conditions gave the acid **15**. The 7-chloro substituent was readily displaced from the acid **15** with the requisite amines in refluxing acetonitrile using triethylamine as the co-base to provide the final naphthyridine antiinfective agents **16a-16d**.

An initial attempt to prepare the final compounds di-

Scheme I



rectly from the ester **14**, using triethylamine in refluxing acetonitrile (the conditions normally used for the acids) proved to be difficult because of the limited solubility of the esters. However, the addition of approximately 15% of dimethyl sulfoxide to the reaction mixture improved the solubility enough to allow displacement of the 7-chloro substituent by the 3-[(*N*-*tert*-butoxycarbonyl)amino]pyrrolidine side chain. Acid hydrolysis of the ester with simultaneous deprotection of the 3-amino functionality provided the quinolone **16a** which completed the series.

The comparative *in vitro* activities of the 1,6-naphthyridines **16a-16d** showed them to be 4-fold less active *in vitro*, against both Gram-positive and Gram-negative organisms than their 1,8-naphthyridine isomers [1e]. A manuscript detailing the comparative biological activities of these compounds will be published at a later date.

EXPERIMENTAL

All melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. The infrared (ir) spectra were determined in potassium bromide on a Nicolet FTIR SX-20 instrument. Proton magnetic resonance (nmr) spectra were recorded on either a Varian XL-300 or a Bruker AM-250 spectrometer. Shifts are reported in δ units relative to internal tetramethylsilane. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. Karl Fischer water determinations were performed on an ABU 93 Triburet Radiometer with a SAM 90 Sample Station and a VIT 90 Videotitrator. All organic solutions were dried over magnesium sulfate, and all concentrations

were performed *in vacuo* at 10-30 mm Hg.

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

A suspension of 80.0 g (0.35 mole) of ethyl 2,4-dihydroxy-3-nitropyridine-5-carboxylate (**5**) [4] in 500 ml of phosphorus oxychloride was heated to 115°. The resulting solution was slowly treated with 29.4 g (0.35 mole) of solid sodium bicarbonate using a screw-type powder addition funnel (**Caution! vigorous gas evolution**). After the addition was complete, the reaction was stirred at 115° for 48 hours. The solvent was removed *in vacuo* and the residue was dissolved in 500 ml of toluene which was also removed *in vacuo*. The residue was cooled in an ice bath and 500 ml of ethanol was carefully added portionwise with stirring. After the addition was complete, the mixture was allowed to come to room temperature where it was stirred for 1 hour. The mixture was concentrated *in vacuo* and the residue was partitioned between chloroform-water (1000:500 ml) and made basic by the addition of solid sodium bicarbonate. The layers were separated and the organic layer was washed with water, dried, filtered and concentrated *in vacuo*. The residue was dissolved in 500 ml of hexane/chloroform (1:1) and filtered through a bed of silica gel on a sintered glass funnel. The filtrate was evaporated *in vacuo* and the solid residue was recrystallized from hexane with the aid of a small amount of ether to give 67.7 g (73%) of **6**, mp 151-152°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.35 (t, 3H), 4.40 (q, 2H), 9.09 (s, 1H); ms: m/z (relative intensity) 267 (21), 266 (20), 265 (35), 264 (28), 221 (64), 219 (100), 175 (41), 173 (61).

Anal. Calcd. for $C_8H_6Cl_2N_2O_4$: C, 36.25; H, 2.28; N, 10.57; Cl, 26.75. Found: C, 36.14; H, 2.17; N, 10.75; Cl, 26.65.

Ethyl 3-Amino-2,4-dichloropyridine-5-carboxylate (**7**).

A solution of 29.0 g (0.11 mole) of **6** in 400 ml of tetrahydrofuran was treated with 5.0 g of Raney-nickel and shaken in a hydrogen atmosphere at temperatures of 26-34° and pressures of 24-50 psi for 21 hours. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The residue was crystallized by the addition of hexane and the solid was removed by filtration, washed with hexane and dried *in vacuo* affording 24.4 g (94%) of **7**, mp 71-72°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.31 (t, 3H), 4.33 (q, 2H), 6.17 (s, 2H), 7.95 (s, 1H); ms: m/z (relative intensity) 237 (23), 236 (39), 235 (38), 234 (59), 208 (23), 206 (35), 191 (64), 189 (100).

Anal. Calcd. for $C_8H_8Cl_2N_2O_2$: C, 40.88; H, 3.43; N, 11.92; Cl, 30.16. Found: C, 40.81; H, 3.22; N, 11.83; Cl, 30.53.

2,4-Dichloro-5-(ethoxycarbonyl)-3-pyridinediazonium Salt with Hexafluorophosphate (−1) (1:1) (**8**).

A solution of 4.0 g (17.0 mmoles) of **7** in 20 ml of hexafluorophosphoric acid was diluted with 8 ml of water and treated portionwise with 1.53 g (22.2 mmoles) of solid sodium nitrite. A precipitate formed immediately and the mixture was stirred for 5 minutes after the final addition. The solid was removed by filtration, washed with ice water, hexane-ether (1:1) and air dried to give 6.1 g (91%) of **8**, mp 125-132°. This material was relatively unstable and was used immediately for the thermal decomposition without further purification.

Ethyl 2,4-Dichloro-3-fluoropyridine-5-carboxylate (**9**).

A 500 ml three-necked, round bottom flask was equipped with a gas inlet adapter, screw-type powder addition funnel and dry-ice condenser. After placing the flask in an oil bath preheated to 150°, a gentle flow of argon was started through the system followed by the slow addition (0.5 hour) of 13.6 g (34.7 mmoles) of **8** *via* the screw funnel. As the diazonium salt decomposed, the product was flushed through the system and solidified on the cold finger of the dry ice condensor. After cooling to room temperature, the system was rinsed with methanol and the solution was neutralized with triethylamine. After concentrating *in vacuo*, the residue was partitioned between chloroform and water. The layers were separated and the organic layer was washed with water, dried, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting first with 98:2 then 95:5 hexane/ethyl acetate to afford 2.3 g (27%) of **9**, mp 37-38°; ^{1}H nmr (deuteriochloroform): δ 1.43 (t, 3H), 4.45 (q, 2H), 8.68 (s, 1H); ms: m/z (relative intensity): 239 (19), 237 (28), 211 (63), 209 (96), 194 (66), 192 (100).

Anal. Calcd. for $C_8H_6Cl_2FNO_2$: C, 40.37; H, 2.54; N, 5.88; F, 7.98. Found: C, 40.34; H, 2.38; N, 5.80; F, 8.01.

2,4-Dichloro-3-fluoropyridine-5-carboxylic Acid (**10**).

A solution of 2.2 g (9.1 mmoles) of **9** in 70 ml of tetrahydrofuran was cooled to 5° and 28 ml of water was added followed by the dropwise addition of 10 ml (10 mmoles) of 1.0 *N* sodium hydroxide. The reaction mixture was allowed to come to room temperature over 0.5 hour, saturated with sodium chloride and extracted with ethyl acetate (2 x 200 ml). The combined organic layers were washed with brine, dried, filtered and evaporated *in vacuo* to give 1.9 g (97%) of **10**, mp 103-104°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.65 (s, 1H), 14.20 (bs, 1H); ms: m/z (relative intensity): 211 (68), 209 (100), 194 (50), 192 (76).

Anal. Calcd. for $C_6H_2Cl_2FNO_2 \cdot 1H_2O$: C, 31.60; H, 1.75; N, 6.14. Found: C, 31.86; H, 1.76; N, 6.05.

Ethyl 4,6-Dichloro-5-fluoro-β-oxo-3-pyridinepropanoate (**11**).

A suspension of 4.5 g (21.4 mmoles) of **10**, 3.3 g (2.3 ml, 26.0 mmoles) of oxalyl chloride and 90 ml of dichloromethane was treated with 0.5 ml of *N,N*-dimethylformamide and stirred at room temperature for 2 hours. The reulting solution was concentrated *in vacuo* and the residue was redissolved in 100 ml of dichloromethane, which was also evaporated *in vacuo* to remove any unreacted oxalyl chloride. The acid chloride was dissolved in 200 ml of dry tetrahydrofuran, cooled to −78° and added *via* a canula to a −78° suspension of the dilithio anion of monoethyl malonic acid, prepared as follows. A solution of 5.5 g (41.6 mmoles) of monoethyl malonate in 200 ml of dry tetrahydrofuran was treated with 0.1 g of 2,2'-bipyridyl indicator. After cooling to −20°, it was treated dropwise with a solution of 42.0 ml (84.0 mmoles) of 2.0 *M* *n*-butyllithium in hexane to give a light pink suspension with the temperature allowed to rise to −5° during the addition. The reaction mixture was recooled to −78° and treated, as previously described, with the acid chloride solution prepared above. The reaction mixture was stirred at −78° for 1 hour, warmed to −50° and quenched with 15.0 ml (90.0 mmoles) of 6.0 *M* hydrochloric acid. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed with 5% sodium bicarbonate, water, dried, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane/tetrahydrofuran (initially 95:5 then 9:1) to afford 3.7 g (63%) of **11**, as a 70:30 mixture of the enol and keto forms, mp 156-157°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.26 (t, 1H), 1.35 (t, 2H), 4.20 (q, 0.6H), 4.30 (q, 1.4H), 5.05 (s, 0.7H enol vinyl), 5.61 (s, 0.6H keto CH_2), 8.42 (s, 0.7H), 8.48 (s, 0.3H), 12.5 (s, 0.7H enol OH); ms: m/z (relative intensity): 280 (5), 210 (15), 208 (15), 194

(64), 192 (100).

Anal. Calcd. for $C_{10}H_8Cl_2FNO_3$: C, 42.88; H, 2.88; N, 5.00. Found: C, 42.93; H, 3.00; N, 5.01.

Ethyl 4,6-Dichloro-α-(ethoxymethylene)-5-fluoro-β-oxo-3-pyridinepropanoate (**12**).

A mixture of 4.6 g (16.4 mmoles) of **12**, 3.4 g (3.8 ml, 22.6 mmoles) of triethyl orthoformate and 60 ml of acetic anhydride was heated at reflux for 3.5 hours. The solvent was removed *in vacuo* and the residue was dissolved in 200 ml of toluene, which was also removed *in vacuo*. The residue was further dissolved in 100 ml of ethanol which was evaporated *in vacuo* to removed the last traces of acetic anhydride. The residue was dried at 0.1 mm for 24 hours to give 5.7 g (98%) of **12** which was used without purification in the next step.

Ethyl 4,6-Dichloro-α-[(cyclopropylamino)methylene]-5-fluoro-β-oxo-3-pyridinepropanoate (**13**).

A solution of 5.7 g (16.1 mmoles) of **12** in 17 ml of dry ethanol was cooled to 5° and treated dropwise with a solution of 1.0 g (1.2 ml, 17.6 mmoles) of cyclopropylamine in 5 ml of hexane and stirred for 4 hours. The resulting suspension was diluted with 10 ml of hexane and the precipitate was removed by filtration, washed with hexane and dried *in vacuo* to afford 4.0 g (72%) of **13**, mp 102-103°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 0.90 (m, 4H), 1.05 (t, 3H), 3.05 (m, 1H), 4.06 (q, 2H), 8.03 (s, 1H), 8.33 (d, 1H, vinyl-H), 11.56 (bd, 1H, NH); ms: m/z (relative intensity): 349 (3), 348 (4), 347 (5), 346 (5), 302 (32), 300 (49), 194 (60), 192 (98).

Anal. Calcd. for $C_{14}H_{13}Cl_2FN_2O_3$: C, 48.44; H, 3.77; N, 8.07; Cl, 20.42; F, 5.47. Found: C, 48.27; H, 3.56; N, 8.03; Cl, 20.13; F, 5.63.

Ethyl 7-Chloro-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylate (**14**).

A solution of 4.0 g (11.4 mmoles) of **13** in 40 ml of dry tetrahydrofuran was cooled to 5° and treated portionwise, over 5 minutes, with 1.1 g (12.0 mmoles) of 60% sodium hydride-mineral oil. The reaction mixture was stirred in the cold for 2 hours, diluted with 10 ml of hexane, filtered through a fiber glass pad to clarify and diluted with 300 ml of chloroform. After washing with water (2 x 100 ml), the organic layer was dried, filtered and evaporated *in vacuo* to give 3.4 g (96%) of **14**, mp 165-166°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.18 (m, 4H), 1.28 (t, 3H), 3.94 (m, 1H), 4.23 (q, 2H), 8.49 (s, 1H), 8.90 (s, 1H); ms: m/z (relative intensity): 311 (14), 238 (100), 237 (53), 229 (38).

Anal. Calcd. for $C_{14}H_{12}ClFN_2O_3$: C, 54.12; H, 3.89; N, 9.02; F, 6.11. Found: C, 54.24; H, 3.90; N, 8.92; F, 6.26.

7-Chloro-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acid (**15**).

A solution of 3.4 g (11.0 mmoles) of **14** in 200 ml of 2.0 *M* hydrochloric acid and 200 ml of ethanol was heated at reflux for 9 hours. The reaction was cooled to 5° and the resulting precipitate was removed by filtration, washed with water and dried *in vacuo* affording 2.5 g (81%) of **15**, mp 131-132°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.12 (m, 4H), 4.09 (m, 1H), 8.76 (s, 1H), 9.12 (s, 1H), 13.81 (s, 1H); ms: m/z (relative intensity): 283 (100), 265 (43).

Anal. Calcd. for $C_{12}H_8ClFN_2O_3$: C, 50.99; H, 2.85; N, 9.91; Cl, 12.54. Found: C, 51.25; H, 2.78; N, 9.93; Cl, 12.74.

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acid (**16a**).

A suspension of 0.7 g (2.2 mmoles) of **14**, 0.6 g (3.1 mmoles) of 3-[*N*-(*tert*-butoxycarbonyl)amino]pyrrolidine [9], 1.4 g (1.4 mmoles) of triethylamine and 35 ml of acetonitrile was heated at reflux for 36 hours. After thin-layer chromatography (acetonitrile-water-triethylamine/18:2:1) indicated incomplete reaction, 0.2 g (1.0 mmole) of 3-[*N*-(*tert*-butoxycarbonyl)amino]pyrrolidine and 5 ml of dimethyl sulfoxide was added and reflux was continued for an additional 24 hours. The reaction mixture was cooled to room temperature and the precipitate was removed by filtration, washed with acetonitrile, ether and dried *in vacuo* to give 0.96 g. This solid was suspended in a mixture of 75 ml of 1.0 *M* hydrochloric acid and 75 ml of ethanol and refluxed for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water to *p*H 11.5 with 1.0 *N* sodium hydroxide. The resulting solution was filtered through a fiber glass pad to clarify and the *p*H was adjusted to 7.0 with 1.0 *M* hydrochloric acid. The resulting precipitate, was removed by filtration, washed with water, acetonitrile, ether and dried *in vacuo* to give 0.51 g (70%) of **16a**, mp 286-287°; ^{1}H nmr (deuteriodimethyl sulfoxide + trifluoroacetic acid): δ 1.21 (m, 4H), 2.13 (m, 1H), 2.34 (m, 1H), 3.85 (m, 5H), 4.01 (m, 1H), 8.24 (bs, 2H), 8.61 (s, 1H), 8.89 (s, 1H).

Anal. Calcd. for $C_{16}H_{17}FN_4O_3 \cdot 1.25\ H_2O$: C, 54.15; H, 5.53; N, 15.79. Found: C, 53.83; H, 5.49; N, 15.68.

1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-8-fluoro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acid (**16b**).

A suspension of 0.6 g (2.1 mmoles) of **15**, 0.4 g (3.2 mmoles) of *N*-ethyl-3-pyrrolidinemethanamine [10], 1.3 g (13.0 mmoles) of triethylamine and 30 ml of acetonitrile was heated at reflux for 15 hours. The precipitate was removed by filtration, washed with acetonitrile and dried *in vacuo*. The dry cake was suspended in 50 ml of water and dissolved by the addition of 1.0 *N* sodium hydroxide to *p*H 11.5. After filtering through a fiber glass pad to clarify, the *p*H was adjusted to 6.0 with 1.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, acetonitrile, ether and dried *in vacuo* to give 0.41 g (53%) of **16b**, mp 234-235°; ^{1}H nmr (deuteriodimethyl sulfoxide + trifluoroacetic acid): δ 1.14 (m, 4H), 1.20 (t, 3H), 1.78 (m, 1H), 2.08 (m, 1H), 2.60 (m, 1H), 3.01 (q, 2H), 3.11 (m, 2H), 3.48 (m, 1H), 3.70 (m, 1H), 3.82 (m, 1H), 3.93 (m, 2H), 8.55 (s, 1H), 8.82 (s, 1H).

Anal. Calcd. for $C_{19}H_{23}FN_4O_3 \cdot 0.5\ H_2O$: C, 59.51; H, 6.31; N, 14.61. Found: C, 59.76; H, 6.07; N, 14.68.

7-(4-Amino-1-piperidinyl)-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acid (**16c**).

A suspension of 0.6 g (2.1 mmoles) of **15**, 0.6 g (3.0 mmoles) of 4-aminopiperidine dihydrochloride [11], 1.3 g (13.0 mmoles) of triethylamine and 35 ml of acetonitrile was heated at reflux for 18 hours. After thin-layer chromatography (acetonitrile-water-triethylamine/18:2:1) showed incomplete reaction, 0.5 ml of water, 10 ml of acetonitrile and 0.6 g (3.0 mmoles) of 4-aminopiperidine dihydrochloride was added and reflux was continued for an additional 20 hours. The reaction mixture was cooled to 5°, the precipitate was removed by filtration, dissolved in 5 ml of concentrated hydrochloric and filtered to remove unreacted 4-aminopiperidine. The filtrate was diluted with water and the resulting precipitate was removed by filtration, dissolved in water by adjusting to *p*H 11.5 with 1.0 *N* sodium hydroxide, filtered through

a fiber glass pad to clarify and readjusted the *p*H to 7.0 with 1.0 *M* hydrochloric acid. The precipitate was filtered, washed with water, acetonitrile, ether and dried *in vacuo* to give 0.52 g (65%) of **16c**, mp 253-255°; ^{1}H nmr (deuteriodimethyl sulfoxide + trifluoroacetic acid): δ 1.20 (m, 4H), 1.65 (m, 2H), 2.04 (m, 2H), 3.18 (m, 2H), 3.39 (m, 1H), 4.03 (m, 1H), 4.28 (m, 2H), 8.65 (s, 1H), 8.93 (s, 1H); ms: m/z (relative intensity): 347 (86), 346 (32), 329 (100).

Anal. Calcd. for $C_{17}H_{19}FN_4O_3 \cdot 2.25\ H_2O$: C, 52.77; H, 6.12; N, 14.48. Found: C, 52.75; H, 5.97; N, 14.27.

1-Cyclopropyl-8-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acid (**16d**).

A suspension of 0.5 g (1.8 mmoles) of **15**, 1.8 g (2.5 ml, 18.0 mmoles) of triethylamine and 50 ml of acetonitrile was heated at reflux for 0.5 hour and the resulting solution was treated with 0.6 g (7.0 mmoles) of piperazine. Reflux was continued for 6 hours during which a precipitate formed. The reaction mixture was cooled in an ice bath and the precipitate was removed by filtration, washed with acetonitrile and dried *in vacuo*. The dry powder was suspended in 25 ml of water and the *p*H was adjusted to 11.4 with 10% sodium hydroxide. The resulting solution was filtered through a fiber glass pad to clarify and the *p*H was readjusted to 6.8 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, acetonitrile, ether and dried *in vacuo* to give 0.45 g (73%) of **16d**, mp 265-267°; ^{1}H nmr (deuteriodimethylsulfoxide + trifluoroacetic acid): δ 1.26 (m, 4H), 3.33 (m, 4H), 3.87 (m, 4H), 4.06 (m, 1H), 8.68 (s, 1H), 8.98 (s, 1H); ms: m/z (relative intensity): 332 (16), 264 (100), 246 (59), 232 (40).

Anal. Calcd. for $C_{16}H_{17}FN_4O_3$: C, 57.83; H, 5.16; N, 16.86. Found: C, 57.74; H, 5.47; N, 16.58.

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