SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL *N*-1-ARYL-6-FLUORO-5-METHYL1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACIDS

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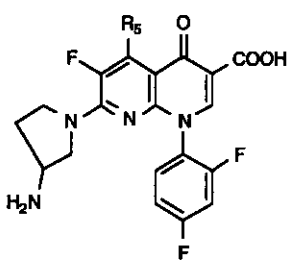
Abstract - A series of 5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acids was prepared in which the *N*-1 position was substituted by various aryl groups. Seven compounds showed excellent *in vitro* antibacterial activity against Gram-positive and Gram-negative strains.

During the last decade, a new class of 7-substituted amino-1-aryl-6-fluoro-1,4-dihydro-4-oxo-quinoline-



1 $R_5 = H$
2 $R_5 = Me$

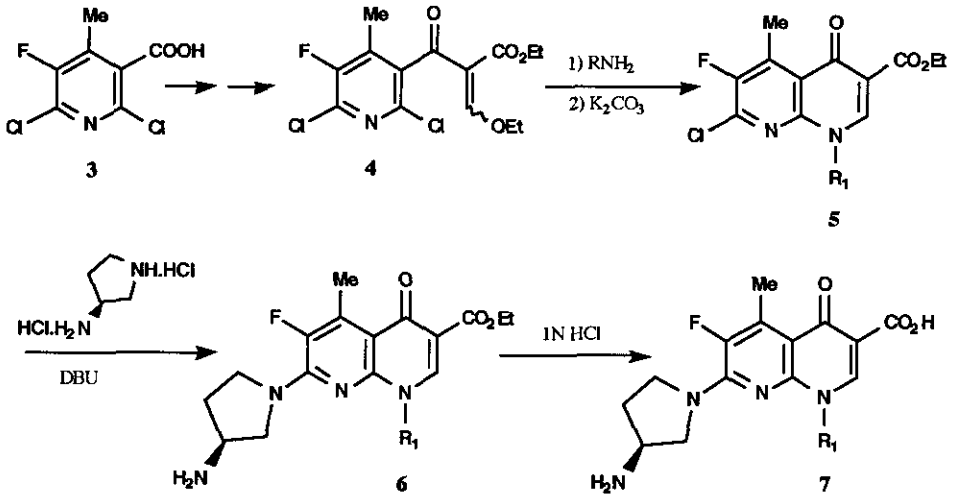
or 1,8-naphthyridine-3-carboxylic acid antibacterials has been developed.[1-20] Recently a par-

ticularly potent member of this class of compounds tosufloxacin, 7-(3-aminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**1**) has emerged as outstanding example.

In preparing new 5-methyl-1-aryl-1,8-naphthyridone candidates for biological evaluation, we have selected compound (**2**) with a (3*S*)-3-aminopyrrolidine appendage at C-7.[21] In the continuation of our search for more potent analogues, our interest was directed to other *N*-1-aryl substituents. In this paper, we report the synthesis and *in vitro* antibacterial activity of a series of novel 1-aryl-5-methyl-4-naphthyridones.

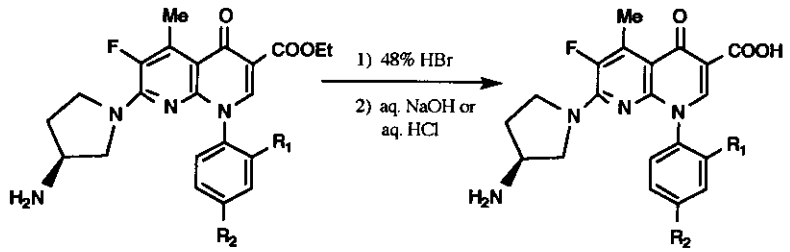
Chemistry

The general method used for the preparation of *N*-fluoroaryl naphthyridones, involving an



Scheme I

intramolecular nucleophilic cyclization, has been previously described, starting from 2,6-dichloro-5-fluoro-4-methylnicotinic acid (**3**).[21,22] The synthetic sequence of these naphthyridones is outlined in Scheme I. The anilines or aminopyridines were either commercial or prepared as reported in literature.[23,24] Some of the *N*-1-methoxyfluoroaniline were deprotected at the last step (Scheme II).



8 R_1 = OMe, R_2 = F

9 R_1 = F, R_2 = OMe

10 R_1 = H, R_2 = OMe

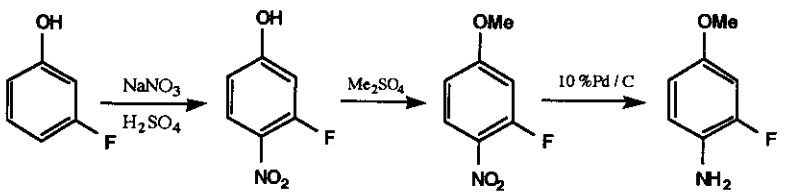
11 R_1 = OH, R_2 = F

12 R_1 = F, R_2 = OH

13 R_1 = H, R_2 = OH

Scheme II

The 2-fluoro-4-methoxyaniline (**17**) was prepared from 3-fluorophenol (**14**) *via* 3-fluoro-4-nitrophenol (**15**), followed by methylation with dimethyl sulfate and finally hydrogenation over 10 % Pd on C (Scheme III).[23] Using the same route, the 5-fluoro-2-nitrophenol gave the corresponding 4-fluoro-2-methoxyaniline.



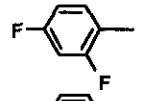
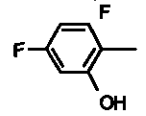
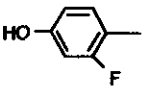
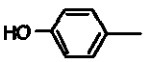
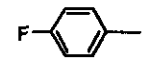
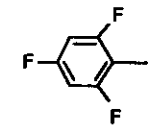
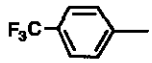
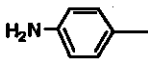
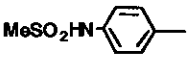
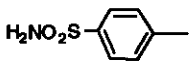
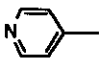
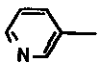
14 **15** **16** **17**

Scheme III

From 4-nitroaniline, the 4-methylsulfonylamidoaniline was obtained by sulfonation with methanesulfonyl chloride, followed by metallic reduction with iron in presence of ferric chloride.[24]

Physical properties of *N*-1-aryl substituted 1,8-naphthyridone-3-carboxylic acids (**2**), (**11**)-(**13**) and (**18**)-(**25**) are showed in Table I.

Table II. Physical properties of *N*-1-Aryl-6-fluoro-5-methyl-1,8-naphthyridine-3-carboxylic acids (7).

No	R_1	Yield[1] %	mp °C	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2[2]		68	> 260	$C_{20}H_{17}N_4O_3F_3$. HCl	52.81	3.99	12.32	52.75	4.02.	12.18
11[2]		40	245	$C_{20}H_{18}N_4O_4F_2$. p-$MeC_6H_4SO_3H$. H_2O	53.46	4.65	9.24	53.25	4.71	9.05
12[2]		23	260	$C_{20}H_{18}N_4O_3F_2$. HBr	48.30	3.85	11.26	48.02	3.86	10.95
13[2]		42	250	$C_{20}H_{19}N_4O_4F$. HCl. 2 H_2O	51.01	5.14	11.9	51.23	5.03	11.86
18[2]		54	228	$C_{20}H_{18}N_4O_3F_2$. HCl. H_2O	52.81	4.65	12.32	52.48	4.54	12.00
19[2]		56	> 260	$C_{20}H_{16}N_4O_3F_4$. p-$MeC_6H_4SO_3H$. H_2O	51.76	4.18	8.94	51.87	4.08	8.85
20[2]		67	230	$C_{21}H_{18}N_4O_3F_4$. HCl. 2,5 H_2O	47.42	4.55	10.53	47.25	4.52	10.22
21[3]		65	260	$C_{20}H_{20}N_5O_3F$. 2 HCl	51.07	4.71	14.89	50.87	4.55	14.53
22[4]		62	240	$C_{21}H_{22}N_5O_5FS$. HCl. 1,5 H_2O	46.80	4.86	12.99	46.48	4.68	12.66
23[2]		55	> 260	$C_{20}H_{20}N_5O_5FS$. HCl. 1,5 H_2O	45.76	4.60	13.34	45.40	4.56	13.05
24[2]		54	> 260	$C_{19}H_{18}N_5O_3F$. 2 HCl. H_2O	48.07	4.63	14.75	47.74	4.47	14.73
25[5]		65	> 260	$C_{19}H_{18}N_5O_3F$. 2 HCl	50.01	4.42	15.35	49.68	4.51	15.05

1) Yields are those obtained from the final step (hydrolysis), including the salt formation.
2) The starting anilines are commercially available.
3) Starting material was 4-acetylaminoaniline, which was deprotected at the final stage.
4) Starting material was 4-nitroaniline.[24]
5) 3-Aminopyridine was purified over silica gel prior use.

Biology

Table II contains a summary of the *in vitro* antibacterial data, for the compounds synthesized, against three Gram-positive and four Gram-negative organisms. For comparison, the activity of **1** (tosufloxacin) is shown.

Table II. *In vitro* antibacterial activity of *N*-1-aryl-5-methyl-6-fluoro-1,8-naphthyridine-3-carboxylic acids (7) (MIC, μg/ml).*

No	*S. pneumoniae*	*E. faecalis*	*S. aureus*	*E. coli*	*E. cloacae*	*P.aeruginosa*
1**	0.06	0.25	0.016	0.004	0.03	0.25
2	0.03	0.06	0.002	0.002	0.002	0.5
11	0.5	1	0.06	0.06	0.13	1
12	0.008	0.13	0.016	0.016	0.06	0.5
13	0.03	0.06	0.01	0.001	0.02	0.25
18	0.03	0.06	0.004	0.002	0.002	0.25
19	0.5	1	0.13	0.03	0.25	0.5
20	2	2	1	0.03	0.03	1
21	0.25	8	0.13	0.03	0.03	0.5
22	64	128	16	2	16	128
23	8	4	1	0.125	0.25	32
24	1	0.25	0.06	0.003	0.003	1
25	2	2	2	0.03	0.03	1

* Organisms selected for the table are as follows : *Streptococcus pneumoniae, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Enterobacter cloacae,* and *Pseudomonas aeruginosa.*
** tosufloxacin.

The effect of substituents on the *N*-1-aryl ring of the 7-aminopyrrodinyl-6-fluoro-5-methyl-4-naphthyridones on the *in vitro* antibacterial potency is displayed in Table II. The position of the aromatic nitrogen on *N*-1-pyridinyl derivatives seemed to be critical to keep interesting *in vitro* potency. The *N*-1-(4-pyridinyl) derivative (**24**) was twice to four times as active as the *N*-1-(3-pyridinyl) analogue (**25**). Methyl sulfonation of the *N*-1-(4-aminophenyl) appendage led to a dramatic loss of in vitro activity (**22** vs **21**).

Good Gram-positive activity was observed for the *N*-1-(4-hydroxyphenyl) derivatives (**12**) and (**13**). Compound (**13**) showed also very good Gram-negative antibacterial activity. The effect of the 4-hydroxy group was already observed by Chu *et al.*[1] Despite these good activities in *vitro*, the *N*-1-(4-hydroxyphenyl) derivatives were not selected for further studies because their bad in *vivo* activities (data not shown). The best overall antibacterial profile was seen with the *N*-1-(4-fluoro- and 2,4-difluorophenyl) compounds (**2**) and (**18**). Finally **2**, a 5-methyl analogue of tosufloxacin with a chiral (3*S*)-3-aminopyrrolidine appendage at C-7 was chosen as a promising candidate for preclinical studies.

EXPERIMENTAL SECTION

Unless otherwise noted, materials were obtained from commercial suppliers and were 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. ^{1}H nmr spectra were recorded on a Bruker AC 200 apparatus. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Flash column chromatography was performed with Merck silica gel 60F, 70-230 mesh ASTM. Elemental analysis was performed by the Bristol-Myers Squibb Analytical Department.

Microbiology. General procedures of *in vitro* studies:

The *in vitro* antibacterial activity was studied by a side-by-side comparison with tosufloxacin (**1**) 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 °C for 18 h.

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1-(4-hydroxyphenyl)-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (13):

To a solution of 4.5 g (12 mmol) of ethyl 3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxopropionate (**4**)[22] in 20 ml of absolute ethanol was added in one portion 1.5 g (12 mmol) of 4-methoxyaniline. The reaction mixture was stirred at room temperature for 2 h and evaporated to dryness *in vacuo* to yield 5.5 g of ethyl 2-[((4-methoxyphenyl)amino)- methylene]-3-(2,6-dichloro-3-fluoro-4-methyl-5-pyridinyl)-3-oxo-propionate as an oil which was used without further purification. A suspension of 5.5 g of the above oil and 1.8 g (13 mmol) of anhydrous K_2CO_3 in 40 ml of acetonitrile was refluxed for 2 h, evaporated to dryness *in vacuo* and the residue was crystallized from water, the precipitate was collected and washed with water to give 4.1 g (82%) of **5** (R_1= 4-methoxyphenyl); mp 234-235 °C. ^{1}H Nmr (DMSO-d_6) δ: 1.26 (t, J = 7.0 Hz, 3H, CH_3 ester); 2.83 (d, J_{H-F} = 3.2 Hz, 3H, Me-5); 3.85 (s, 3H, O-Me ar.); 4.21 (q, J = 7.0 Hz, 2H, CH_2 ester); 7.11 and 7.47 (2d, J = 9 Hz, 4H, Ar.); 8.46 (s, 1H, H-2).

A mixture of 3.52 g (9 mmol) of the above ester (**5**, R_1= 4-methoxyphenyl), 0.86 g (10 mmol) of 3-(3*S*)-aminopyrrolidine and 1.3 ml (9 mmol) of DBU in 40 ml of dry acetonitrile was stirred at room temperature overnight. The solvent was evaporated to dryness *in vacuo* and the residue was crystallized from water to provide 3.88 g (98 %) of the ester (**10**). ^{1}H Nmr (DMSO-d_6) δ: 1.24 (t, J= 7.0 Hz, 3H, CH_3 ester); 1.57-2.09 (m, 3H, CH_2 pyrrol.); 2.65 (d,J_{H-F} =3 Hz, 3H, Me-5); 3.31-3.45 (m, 4H, CH_2 pyrrol.); 3.83 (s, 3H, O-Me ar.); 4.17 (q, J = 7.0 Hz, 2H, CH_2 ester); 7.05 and 7.41 (2d, J = 9 Hz, 4H, Ar.); 8.23 (s, 1H, H-2).

The suspension of 3.45 g (7.8 mmol) of the ester (**10**) in 33 ml of 48 % HBr in acetic acid was refluxed for 4 h. The solvent was evaporated *in vacuo* and the residue was dissolved in 100 ml of water at 50 °C, the pH was adjusted to 7 with 2N NaOH. The resulting precipitate was collected, washed with water and dried *in vacuo* at 40 °C to give 2 g of the base which was transformed into its hydrochloride salt in a refluxing mixture of ethanol/ water/ hydrochloric acid (20/ 20/ 3). Finally the solution was cooled and the resulting precipitate was collected and recrystallized from ethanol/water to give 1.4 g (43 %) of the desired compound (**13**); mp 250 °C. Ir (KBr): 3406, 1702, 1627 cm^{-1}.^{1} H Nmr (DMSO-d_6) δ: 1.97-2.17 (2m, 2H, CH_2 pyrrol.); 2.73 (d, J_{H-F} =3 Hz, 3H, Me-

5); 3.36-3.78 (2m, 5H, CH_2 pyrrol.); 6.91 and 7.32 (2d, J = 8.6 Hz, 4H, Ar.); 8.47 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 16.3 ° (c = 0.5, MeOH, 0.1 N HCl 50: 50).

Using a similar methodology the following derivatives were prepared :

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1-(4-fluoro-2-hydroxyphenyl)-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, 4-toluenesulfonate salt (11): mp 245 °C. Ir (KBr): 3429, 3063, 1712, 1626, 1498 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ: 1.95-2.14 (2m, 2H, CH_2 pyrrol.); 2.26 (Me, tosylate); 2.69 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.41-3.78 (2m, 5H, CH_2 pyrrol.); 6.82 (m, 2H, Ar); 7.12 and 7.48 (2d, J = 8.Hz, 4H, tosylate) ; 7.42 (m, 1H, Ar.); 8.47 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 13.5 ° (c = 0.5, MeOH/ 0.1 N HCl 50: 50).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-1-(2-fluoro-4-hydroxyphenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrobromide salt (12): mp 260 °C (decomp.). Ir (KBr): 3359, 3172, 3057, 2948, 1694, 1625, 1466 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ:1 .98-2.19 (2m, 2H, CH_2 pyrrol.); 2.73 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.66-3.98 (2m, 5H, CH_2 pyrrol.); 6.76 (m, 2H, Ar.); 7.43 (m, 2H, Ar.); 8.62 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 23.5 ° (c = 0.25, MeOH).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (18): mp 228 °C (decomp.). Ir (KBr): 3434, 3059, 2948, 1715, 1627 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ: 2.02-2.21 (2m, 2H, CH_2 pyrrol.); 2.74 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.47-3.90 (2m, 5H, CH_2 pyrrol.); 7.39 and 7.62 (2d, J = 8.6 Hz, 4H, Ar.); 8.61 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 18.8 ° (c = 0.5, MeOH/ 0.1 N HCl 60: 40).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-1-(2,4,6-trifluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, 4-toluenesulfonate salt (19): mp > 260 °C (decomp.). Ir (KBr): 3349, 3057, 2948, 1710, 1625 cm^{-1}. ^{1}H Nmr (DMSO-d_6) d: 1.68-2.14 (2m, 2H, CH_2 pyrrol.); 2.72 (d, J_{H-F} =3 Hz, 3H, Me-5); 3.29-3.45 (2m, 5H, CH_2 pyrrol.); 7.52 (m, 2H, Ar.); 8.55 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 18.8 ° (c = 0.5, MeOH).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-1-(4-trifluoromethylphenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (20): mp 230 °C (decomp.). Ir (KBr): 3420, 2939, 2890, 1710, 1628, 1445, 1323 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ: 2.04-2.16 (2m, 2H,

CH_2 pyrrol.); 2.76 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.57-3.83 (2m, 5H, CH_2 pyrrol.); 7.64 and 7.96 (2m, 4H, Ar.); 8.67 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 26.5 ° (c = 0.5, MeOH).

1-(4-Aminophenyl)-7- [(3*S*)-3-amino-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-5- methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (21): mp 260 °C (decomp.). Ir (KBr): 3421, 2889, 1720, 1631, 1443 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ: 2.09-2.16 (2m, 2H, CH_2 pyrrol.); 2.75 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.45-3.81 (2m, 5H, CH_2 pyrrol.); 7.21 and 7.46 (2d, J = 8.6 Hz, 4H, Ar.); 8.57 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 12.4° (c = 0.5, 0.1N HCl).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-1-(4-methylsulfonylaminophenyl)--5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (22): mp 240 °C (decomp.). Ir (KBr): 3418, 2921, 1706, 1635, 1439, 1326, 1150 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ : 2.09-2.16 (2m, 2H, CH_2 pyrrol.); 2.75 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.07 (s, 3H, Me sulfonylam.); 3.45-3.81 (2m, 5H, CH_2 pyrrol.); 7.37 and 7.52 (2d, J= 8.4 Hz, 4H, Ar.); 8.57 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 13.4° (c = 0.25, MeOH/ 0.1N HCl 50: 50).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-1-(4-aminosulfonylphenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (23): mp >260 °C (decomp.). Ir (KBr): 3379, 3161, 3055,1710, 1624 cm^{-1}. ^{1}H Nmr (DMSO-d_6) δ: 2.08-2.14 (2m, 2H, CH_2 pyrrol.); 2.75 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.62-3.80 (2m, 5H, CH_2 pyrrol.); 7.92 and 8.93 (2d, J = 5.0 Hz, 4H, Ar.); 8.73 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 8.4° (c = 0.12, MeOH/ 0.1N HCl 50: 50).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-5-methyl-1-(4-pyridinyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (24): mp >260 °C (decomp.). Ir (KBr): 3510, 3429, 1705, 1635 cm-1. ^{1}H Nmr (DMSO-d_6) δ: 2.09-2.16 (2m, 2H, CH2 pyrrol.); 2.74 (d, J_{H-F} = 3 Hz, 3H, Me-5); 3.45-3.81 (2m, 5H, CH_2 pyrrol.); 7.62 and 8.75 (2d, J = 6 Hz, 4H, Ar.); 8.71 (s, 1H, H-2). $[\alpha]_D^{25}$ = + 13.2 ° (c = 0.25, 0.1N HCl).

7- [(3*S*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-5-methyl-1-(3-pyridinyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid, hydrochloride salt (25): mp >260 °C (decomp.). Ir (KBr): 3570, 3428, 2880,1702, 1626, 1458, 1421 cm-1. ^{1}H Nmr (DMSO-d_6) δ: 2.07-2.15 (2m, 2H, CH_2 pyrrol.); 2.75 (d, J_{H-F} =3 Hz, 3H, Me-5); 3.60-3.96 (2m, 5H, CH_2 pyrrol.); 7.72 (m, 1H, Ar.); 8.14 (m, 1H, Ar.); 8.70 (s, 1H, H-2); 8.76 (m, 2H, Ar.). $[\alpha]_D^{25}$ = + 26.4 ° (c = 0.45, MeOH).

REFERENCES AND NOTES

1. D. T. W. Chu, P. B. Fernandes, A. K. Clairbone, E. Pihuleac, C. W. Nordeen, R. E. Maleczka, Jr., and A. G. Pernet, J. Med. Chem. , 1985, **28**, 1558.
2. H. Narita, Y. Konishi, J. Nitta, H. Nagaki, I. Kitayama, Y. Kobayashi, M. Shinagawa, Y. Watanabe, and A. Yotsuji, German patent No 3, 514, 076 (Chem. Abstr., 1986, **104**, 129 888r).
3. H. Tone, H. Miyamoto, H. Ueda, and K. Nakagawa, European patent No 181, 521 Chem. Abstr., 1986, **105**, 114 931w).
4. D. T. W. Chu, P. B. Fernandes, and A. G. Pernet, J. Med. Chem. , 1986, **29**, 1531.
5. D. T. W. Chu, P. B. Fernandes, A. K. Clairbone, E. H. Gracey, and A. G. Pernet, J. Med. Chem. , 1986, **29**, 2363.
6. D. T. W. Chu, P. B. Fernandes, A. K. Clairbone, E. Pihuleac, R. E. Maleczka, C. W. Nordeen, and A. G. Pernet, J. Med. Chem. , 1987, **30**, 504.
7. T. Teraji, H. Matsushima, and A. Yamamura, European patent No 247, 464 (Chem. Abstr., 1988, **109**, 92 822q).
8. H. Narita, Y. Konishi, J. Nitta, H. Takagi, F. Iino, J. Kobayashi, and I. Saikawa, Japanese patent No 62, 033, 176 (Chem. Abstr., 1987, **106**, 213 923x).
9. H. Narita, Y. Konishi, J. Nitta, H. Nagaki, Y. Kobayashi, Y. Watanabe, S. Minami, and I. Saikawa, Yakugaku Zasshi, 1986, **106**, 795.
10. J. M. Domagala, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. B. Nichols, M. Solomon, and D. F. Worth, J. Med. Chem. , 1988, **31**, 991.
11. K. Grohe, and J. Hans, German patent No 3, 517, 535 (Chem. Abstr., 1987, **106**, 84 650e).
12. K. Grohe and H. Heltzer, Liebigs Ann. Chem., 1986, 29.
13. Fujisawa Pharm. Japanese patent No 61, 112, 27 (Chem. Abstr., 1987,**106**, 32 843 a).
14. S. Radl and V. Zikan, Coll. Czech. Chem. Comm., 1989, **54**, 2181.
15. W. Xiao, R. Krishnan, Y.-I. Lin, E. F. D. Santos, N. A. Kuck, R. E. Babine, and S. A. Lang Jr., J. Pharm. Sci., 1989, **78**, 585.
16. F. Sauter, U. Jordis, M. Rudolf, J. Wieser, and K. Baumann, German patent No 3, 721, 745 (Chem. Abstr., 1988, **108**, 186 594y).

17. T. Yatsunami, A. Yazaki, S. Inoue, H. Yamamoto, M. Yokomoto, J. Nomiyama, and S. Noda, European patent No 343, 560 (Chem. Abstr., 1990, **112**, 235 326f).

18. D. T. W. Chu and R. Hallas, European patent No 360, 258 (Chem. Abstr., 1990, **113**, 153 051u).

19. O. Masatera and H. Koga, J. Med. Chem. , 1991, **34**, 131.

20. S. Radl and L. Bruna, Ceskoslovenska Farmacie, 1990, **39**, 177.

21. P. Remuzon, A. Aulombard, D. Bouzard, P. Di Cesare, C. Demosthene, C. Dussy, P. Hoffmann, J. P. Jacquet, and J. R. Kiechel, 7th European Symposium in Organic Chemistry (ESOC-7), Namur, Belgium, July 15-19, 1991.

22. D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, B. Ledoussal, P. Remuzon, R. E. Kessler, and J. Fung-Tomc, J. Med. Chem., 1992, **35**, 518.

23. R. K. Noris, Austr. J. Chem., 1972, **25**, 262.

24. G. J. Atwell and B. F. Cain, J. Med. Chem., 1968, **11**, 295.

25. D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, P. Remuzon, A. Weber, T. Oki, and M. Masuyoshi , J. Med. Chem., 1989, **32**, 537 .

Received, 9th June, 1992