Syntheses of New Pyridonecarboxylic Acid Derivatives Containing 1- or 2-Naphthyl Substituents at N-1 and their Anti-HIV-RT Activities

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A series of new pyridonecarboxylic acid derivatives containing 1- or 2-naphthyl substituents at N-1 were synthesized and their *in vitro* anti-HIV-RT activities were evaluated. Several compounds in this series showed better activity than Atevirdine.

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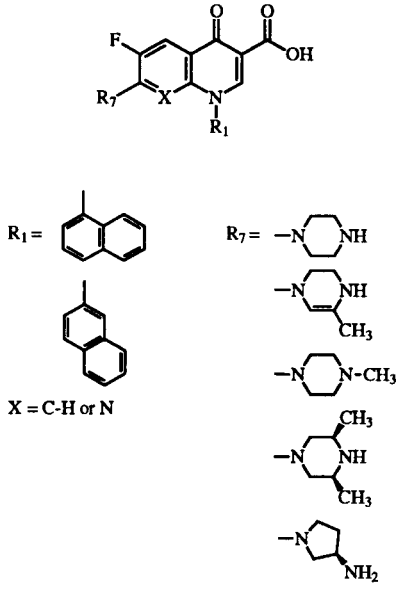
Acquired Immunodeficiency Syndrome (AIDS) epidemic was first reported in 1981 [1,2]. A large amount of information concerning this disease has been accumulated, since Human Immunodeficiency Virus (HIV) has been identified as the causative agent of the AIDS [3,4]. Unfortunately, despite a concerted worldwide research effort, effective options to treat this disease remain severely limited. A major limitation of such treatment is the emergence of resistant virus with specific mutations in the reverse transcriptase (RT) gene [5,6]. To date, while a number of agents for the suppression of HIV replication have been studied, none of these has been shown to be effective and safe in the long term therapy. Recently, it has been reported that some synthetic antibacterial agents, which have a pyridonecarboxylic acid skeleton as their common structure, show the anti-HIV-RT activity [7-9].

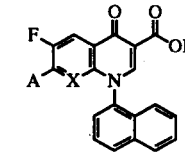


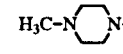
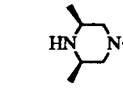
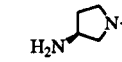
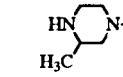
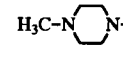
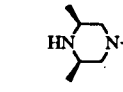
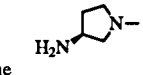
Figure

Herein, we wish to report the syntheses of a series of pyridonecarboxylic acid derivatives containing 1- or 2-naphtyl substituents at N-1 and their *in vitro* anti-HIV-RT activity (Figure).

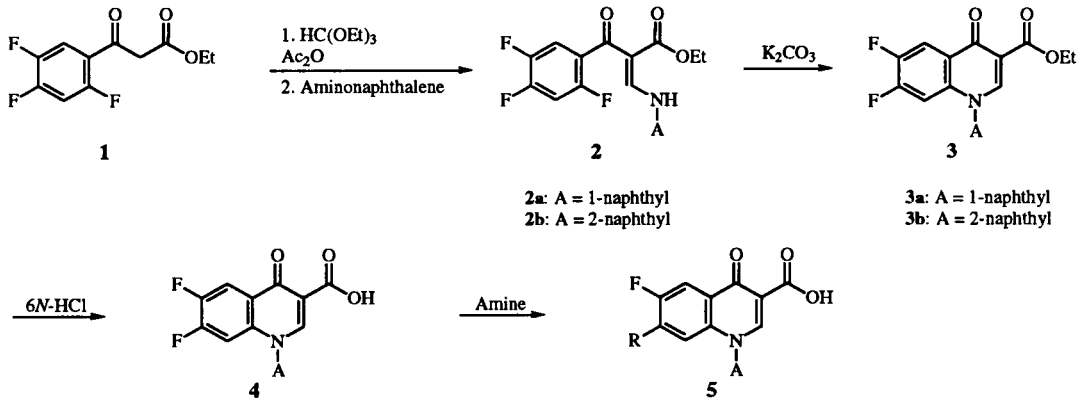
Table 1

Inhibitory Activities for HIV-RT of Several New Pyridonecarboxylic Acid Derivatives Containing a 1-Naphthyl Substituent at N-1



Compounds	X	A	Anti-HIV-RT activities (%) 1μg/ml	0.1 μg/ml
5aa	CH		40	31
5ab	CH		24	19
5ac	CH		60	35
5ad	CH		47	18
5ae	CH		39	36
10aa	N		45	29
10ab	N		49	34
10ac	N		27	1
10ad	N		39	20
10ae	N		31	16
	Atevirdine		64	25

Scheme 1



1

2: **2a**: A = 1-naphthyl; **2b**: A = 2-naphthyl

3: **3a**: A = 1-naphthyl; **3b**: A = 2-naphthyl

4: **4a**: A = 1-naphthyl; **4b**: A = 2-naphthyl

5:

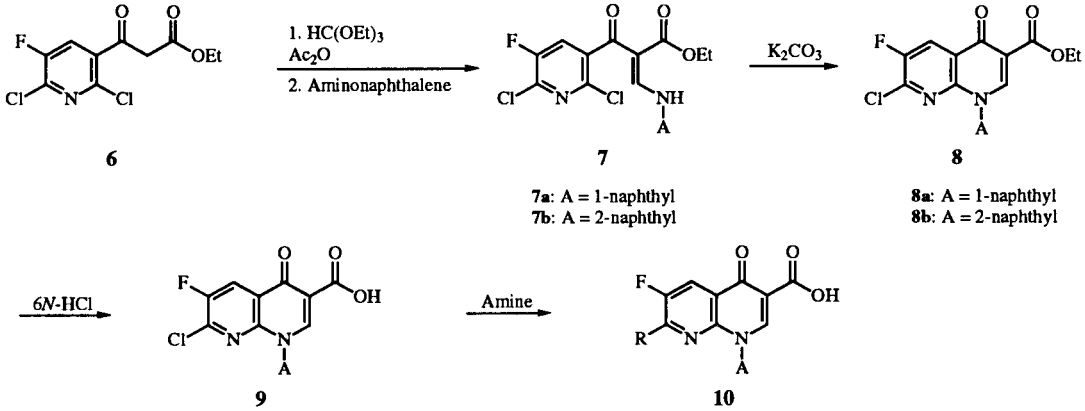
5aa:	A = 1-nathhthyl	R = 1-piperazinyl
5ab:	"	R = 3-methyl-1-piperazinyl
5ac:	"	R = 4-methyl-1-piperazinyl
5ad:	"	R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
5ae:	"	R = (3*S*)-3-amino-1-pyrrolidinyl
5ba:	A = 2-naphthyl	R = 1-piperazinyl
5bb:	"	R = 3-methyl-1-piperazinyl
5bc:	"	R = 4-methyl-1-piperazinyl
5bd:	"	R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
5be:	"	R = (3*S*)-3-amino-1-pyrrolidinyl

Chemistry.

The synthetic procedure of new quinolone derivatives **5aa-5be** is shown in Scheme 1. The starting material, ethyl 3-oxo-3-(2,4,5-trifluorophenyl)propanoate **1**, was prepared from the 2,4,5-trifluorobenzoic acid according to the reported procedure in reasonable yield [10].

According to the known procedure [11], compound **1** was converted to the ethyl 3-ethoxy-2-(2,4,5-trifluorobenzoyl)-2-propenoate by treatment with triethyl orthoformate and acetic anhydride. After removing of the solvent by evaporation, the crude residue, not further purification, was treated with 1- or 2- aminonaphthalene to afford acrylate derivatives **2**. Compounds **2** were treated with potassium carbonate and 18-crown-6 in acetonitrile to afford cyclized product **3**. Compounds **3** were hydrolyzed to compounds **4** by 6*N* aqueous hydrochloric acid solution. The final products **5aa-5be** could be obtained from **4a** or **4b** in reasonable yield by introducing several cyclic secondary amines into the C-7 position in acetonitrile.

Scheme 2



6

7: **7a**: A = 1-naphthyl; **7b**: A = 2-naphthyl

8: **8a**: A = 1-naphthyl; **8b**: A = 2-naphthyl

9: **9a**: A = 1-naphthyl; **9b**: A = 2-naphthyl

10:

10aa:	A = 1-nathhthyl	R = 1-piperazinyl
10ab:	"	R = 3-methyl-1-piperazinyl
10ac:	"	R = 4-methyl-1-piperazinyl
10ad:	"	R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
10ae:	"	R = (3*S*)-3-amino-1-pyrrolidinyl
10ba:	A = 2-naphthyl	R = 1-piperazinyl
10bb:	"	R = 3-methyl-1-piperazinyl
10bc:	"	R = 4-methyl-1-piperazinyl
10bd:	"	R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
10be:	"	R = (3*S*)-3-amino-1-pyrrolidinyl

As another part of our efforts, new naphthyridine derivatives **10aa-10be** were similarly prepared from **6** (Scheme 2) [11]. The starting material, ethyl 3-(2,6-dichloro-5-fluoro-3-pyridyl)-3-oxopropanoate **6**, was obtained from the ethyl fluoroacetate, ethyl formate, malonamide according to the reported procedure [12].

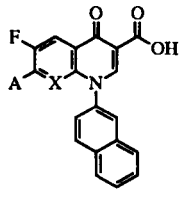
Biological Results.

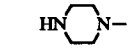
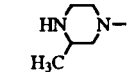
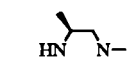
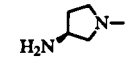
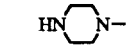
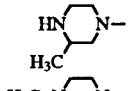
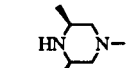
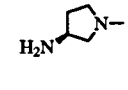
In vitro anti-HIV-RT activities of all the prepared compounds were tested by applied "Nonradioactive Reverse transcriptase assay Kit (Boehringer Mannheim)" method [13], and thus anti-HIV-RT activity values obtained are summarized in Tables 1 and 2. Anti-HIV-RT activities of this series were compared with that of Atevirdine [14].

In conclusion, several new pyridonecarboxylic acid derivatives containing 1- or 2-naphthyl substituents at N-1 (compounds **5ac, 5ba, 5bb, 5bd, 10be**) showed activity similar to that of Atevirdine at 1 μg/ml concentration. Especially, compounds **5ba, 5bb, 5bd** showed better activity than Atevirdine at 0.1 μg/ml concentration. The results obtained in this study show that a part of new series of pyridonecarboxylic acid derivatives containing 1- or 2-naphthyl substituents at N-1 may be promising candidates with the possibility to be developed as anti-HIV drugs.

Table 2

Inhibitory Activities for HIV-RT of Several New Pyridonecarboxylic Acid Derivatives Containing a 2-Naphthyl Substituent at N-1



Compounds	X	A	Anti-HIV-RT activities (%) 1μg/ml	0.1 μg/ml
5ba	CH		58	45
5bb	CH		69	54
5bc	CH		38	35
5bd	CH		62	52
5be	CH		50	36
10ba	N		50	44
10bb	N		25	21
10bc	N		39	28
10bd	N		25	15
10be	N		63	20
	Atevirdine		64	25

EXPERIMENTAL

The nmr spectra were obtained on a JEOL Lambda 400 MHz spectrophotometer and chemical shift are reported in δ ppm relative to tetramethylsilane. Melting points were determined on an Electrothermal IA9200 Digital melting point apparatus and uncorrected. Elemental analyses were performed by Korea Basic Science Institute. 2,4,5-Trifluorobenzoic acid, 1- or 2-aminonaphthalene, several amines, *etc* were abtained from Aldrich or Janssen Chimica. All other commercially available reagents were obtained in high purity. Thin-layer chromatography was carried out using glass plates, precoated with silica gel 60 F_{254}, supplied by Merck.

Ethyl 3-(1-Naphthylamino)-2-(2,4,5-trifluorobenzoyl)-2-propenoate (**2a**).

In a typical procedure for **2a, 2b, 7a, 7b**, a mixture of ethyl 3-oxo-3-(2,4,5-trifluorophenyl)propanoate **1** (5 g, 20.3 mmoles), triethyl orthoformate (5.7 ml, 34.5 mmoles), and acetic anhydride (5.7 ml, 60.9 mmoles) was heated to reflux for 4 hours. The solvent was removed by evaporation and the residue was cooled to -10°. After dilution with ethanol (150 ml), the solution was treated with 1-aminonaphthalene (2.97 g, 0.7 mmole) below -10°. The reaction mixture was stirred at -10-25° for 3 hours and the resulting solid was filtered, washed with ethanol and dried to afford desired compound **2a**, (6.65 g, 82%) as a white-yellow solid, mp 139°; ^{1}H nmr (deuteriochloroform): δ two sets of signals 1.02 and 1.13 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.13 (m, 2H, ethyl CH_2 signal overlap), 6.90 (m, 1H, aromatic CFCHCF), 7.35-7.64 (m, 5H, naphthyl 5 CH), 7.78 (m, 1H, naphthyl CH), 7.90 (m, 1H, naphthyl CH), 8.11 (m, 1H, aromatic CCHCF), 8.72 (m, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{16}NF_3O_3$: C, 66.17; H, 4.04; N, 3.51. Found: C, 66.09; H, 3.98; N, 3.49.

Ethyl 3-(2-Naphthylamino)-2-(2,4,5-trifluorobenzoyl)-2-propenoate (**2b**).

This compound was prepared from **1** in 91% yield as a white yellow solid by following the typical procedure above used to prepare **2a**, mp 120°; ^{1}H nmr (deuteriochloroform): δ two sets of signals 0.99 and 1.12 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.12 (m, 2H, ethyl CH_2 signal overlap), 6.89 (m, 1H, aromatic CFCHCF), 7.24-7.65 (m, 5H, naphthyl 5 CH), 7.88 (m, 3H, naphthyl 2 CH and aromatic CCHCF), 8.69 (m, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{16}NF_3O_3$: C, 66.17; H, 4.04; N, 3.51. Found: C, 66.24; H, 4.09; N, 3.52.

Ethyl 2-[(2,6-Dichloro-5-fluoro-3-pyridyl)carbonyl]-3-(1-naphthylamino)-2-propenoate (**7a**).

This compound was prepared from **6** in 94% yield as a white-yellow solid by following the typical procedure above used to prepare **2a**, mp 133°; ^{1}H nmr (deuteriochloroform): δ two sets

of signals 0.95 and 1.10 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.10 (m, 2H, ethyl CH_2 signal overlap), 7.46-7.66 (m, 5H, naphthyl 5 CH), 7.80 (m, 1H, naphthyl CH), 7.92 (m, 1H, naphthyl CH), 8.09 (m, 1H, aromatic CCHCF), 8.80 (m, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{15}Cl_2FN_2O_3$: C, 58.22; H, 3.49; N, 6.47. Found: C, 58.45; H, 3.54; N, 6.47.

Ethyl 2-[(2,6-Dichloro-5-fluoro-3-pyridyl)carbonyl]-3-(2-naphthylamino)-2-propenoate (**7b**).

This compound was prepared from **6** in 82% yield as a white-yellow solid by following the typical procedure above used to prepare **2a**, mp 125°; ^{1}H nmr (deuteriochloroform): δ two sets of signals 0.93 and 1.10 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.09 (m, 2H, ethyl CH_2 signal overlap), 7.41-7.55 (m, 4H, naphthyl 4 CH), 7.70 (m, 1H, naphthyl CH), 7.84 (m, 2H, naphthyl 2 CH), 7.92 (m, 1H, aromatic CCHCF), 8.82 (m, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{15}Cl_2FN_2O_3$: C, 58.22; H, 3.49; N, 6.47. Found: C, 58.16; H, 3.50; N, 6.44.

Ethyl 6,7-Difluoro-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (**3a**).

In a typical procedure for **3a**, **3b**, **8a**, **8b**, a mixture of ethyl 3-(1-naphthylamino)-2-(2,4,5-trifluorobenzoyl)-2-propenoate **2a** (7.3 g, 18.3 mmoles), potassium carbonate (5.05 g, 36.6 mmoles), and 18-crown-6 (1.45 g, 5.5 mmoles) in acetonitrile (100 ml) was heated to reflux for 2.5 hours. After cooling to room temperature, water (150 ml) was added to the mixture. The resulting white solid was collected by filtration, washed with 25% aqueous ethanol and dried to afford **3a**, (6.81 g, 98%), mp 190°; ^{1}H nmr (deuteriochloroform): δ 1.36 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.36 (q, J = 7.07 Hz, 2H, ethyl CH_2), 6.47 (m, 1H, aromatic CFCHCF), 7.26 (m, 1H, naphthyl CH), 7.52 (m, 1H, naphthyl CH), 7.60-7.70 (m, 3H, naphthyl 3 CH), 8.04 (m, 1H, naphthyl CH), 8.13 (m, 1H, naphthyl CH), 8.34 (m, 1H, aromatic CCHCF), 8.53 (s, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{15}F_2NO_3$: C, 69.65; H, 3.99; N, 3.69. Found: C, 69.61; H, 3.92; N, 3.63.

Ethyl 6,7-Difluoro-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (**3b**).

This compound was prepared from **2b** in 98% yield as a white-yellow solid by following the typical procedure above used to prepare **3a**, mp 200°; ^{1}H nmr (deuteriochloroform): δ 1.37 (t, J = 7.35 Hz, 3H, ethyl CH_3), 4.37 (q, J = 7.35 Hz, 2H, ethyl CH_2), 6.81 (m, 1H, aromatic CFCHCF), 7.45 (m, 1H, naphthyl CH), 7.66 (m, 2H, naphthyl 2 CH), 7.93 (m, 2H, naphthyl 2 CH), 8.00 (m, 1H, naphthyl CH), 8.09 (m, 1H, naphthyl CH), 8.31 (m, 1H, aromatic CCHCF), 8.57 (s, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{15}F_2NO_3$: C, 69.65; H, 3.99; N, 3.69. Found: C, 69.59; H, 3.91; N, 3.63.

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

This compound was prepared from **7a** in 97% yield as a white-yellow solid by following the typical procedure above used to prepare **3a**, mp 214°; ^{1}H nmr (deuteriochloroform): δ 1.37 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.38 (q, J = 7.07 Hz, 2H, ethyl CH_2), 7.24 (m, 1H, naphthyl CH), 7.48-7.68 (m, 4H, naphthyl 4 CH), 8.03 (m, 1H, naphthyl CH), 8.10 (m, 1H, naphthyl CH), 8.55 (m, 1H, aromatic CCHCF), 8.67 (s, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{14}ClFN_2O_3$: C, 63.57; H, 3.56; N, 7.06. Found: C, 63.53; H, 3.54; N, 7.03.

Ethyl 7-Chloro-6-fluoro-1-(2-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**8b**).

This compound was prepared from **7b** in 97% yield as a white-yellow solid by following the typical procedure above used to prepare **3a**, mp 219°; ^{1}H nmr (deuteriochloroform): δ 1.38 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.39 (q, J = 7.07 Hz, 2H, ethyl CH_2), 7.48 (m, 1H, naphthyl CH), 7.62 (m, 2H, naphthyl 2 CH), 7.88 (m, 1H, naphthyl CH), 7.91 (m, 1H, naphthyl CH), 7.96 (m, 1H, naphthyl CH), 8.02 (m, 1H, naphthyl CH), 8.50 (m, 1H, aromatic CCHCF), 8.76 (m, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{14}ClFN_2O_3$: C, 63.57; H, 3.56; N, 7.06. Found: C, 63.52; H, 3.55; N, 7.02.

6,7-Difluoro-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (**4a**).

In a typical procedure for **4a**, **4b**, **9a**, **9b**, to a suspension of ethyl 6,7-difluoro-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate **3a** (6.8 g, 17.9 mmoles) in ethanol (60 ml) was added a 6*N* aqueous hydrochloride acid solution (28 ml) and the mixture was refluxed for 18 hours. After cooling to -10°, the resulting solid was filtered, washed with 50% aqueous ethanol and dried to afford **4a** (6.04 g, 96%) as a white solid, mp 248°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.11 (m, 1H, aromatic C8-H), 7.30 (m, 1H, naphthyl CH), 7.69 (m, 1H, naphthyl CH), 7.85 (m, 1H, naphthyl CH), 7.89-7.94 (m, 2H, naphthyl 2 CH), 8.28 (m, 1H, naphthyl CH), 8.47 (m, 1H, naphthyl CH), 8.70 (m, 1H, aromatic C5-H), 9.58 (s, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{11}F_2NO_3$: C, 68.38; H, 3.16; N, 3.99. Found: C, 68.31; H, 3.10; N, 3.95.

6,7-Difluoro-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (**4b**).

This compound was prepared from **3b** in 99% yield as a white solid by following the typical procedure above used to prepare **4a**, mp 281°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.58 (m, 2H, aromatic C8-H and naphthyl CH), 7.85 (m, 2H, naphthyl 2 CH), 8.06 (m, 1H, naphthyl CH), 8.16 (m, 2H, naphthyl 2 CH), 8.32 (m, 1H, naphthyl CH), 8.63 (m, 1H, aromatic C5-H), 9.59 (s, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{11}F_2NO_3$: C, 68.38; H, 3.16; N, 3.99. Found: C, 68.37; H, 3.12; N, 3.97.

7-Chloro-6-fluoro-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**9a**).

This compound was prepared from **8a** in 98% yield as a white solid by following the typical procedure above used to prepare **4a**, mp 273°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.10 (m, 1H, naphthyl CH), 7.63 (m, 1H, naphthyl CH), 7.76-7.87 (m, 3H, naphthyl 3 CH), 8.22 (m, 1H, naphthyl CH), 8.38 (m, 1H, naphthyl CH), 8.87 (m, 1H, aromatic C5-H), 9.66 (s, 1H, vinyl H).

Anal. Calcd. for $C_{19}H_{10}ClFN_2O_3$: C, 61.89; H, 2.73; N, 7.60. Found: C, 61.80; H, 2.70; N, 7.58.

7-Chloro-6-fluoro-1-(2-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**9b**).

This compound was prepared from **8b** in 97% yield as a white solid by following the typical procedure above used to prepare **4a**, mp 286°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.60 (m, 1H, naphthyl CH), 7.75 (m, 2H, naphthyl 2 CH), 7.99 (m, 1H, naphthyl CH), 8.07 (m, 2H, naphthyl 2 CH), 8.18 (m, 1H, naphthyl CH), 8.77 (m, 1H, aromatic C5-H), 9.67 (s, 1H, vinyl H).

Anal. Calcd. for $C_{19}H_{10}ClFN_2O_3$: C, 61.89; H, 2.73; N, 7.60. Found: C, 61.78; H, 2.75; N, 7.56.

6-Fluoro-7-(1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5aa**).

In a typical procedure to prepare compounds **5aa-5ad, 5ba-5bd, 10aa-10ad, 10ba-10bd,** a mixture of 6,7-difluoro-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid **4a** (300 mg, 0.85 mmole), piperazine (184 mg, 2.1 mmoles) in anhydrous acetonitrile (15 ml) was heated to reflux for 6 hours. When the reaction was completed, the reaction mixture was concentrated by evaporation. To the residue was added a small amount of water and isopropyl alcohol (15 ml) and resulting solid was filtered. To the filtered solid was added 5% aqueous ethanol (15 ml), 1*N* methanesulfonic acid in an ethanol solution (4.3 ml, 4.25 mmoles), then the reaction mixture was stirred for 4 hours at room temperature. After the solvent was removed by evaporation, then isopropyl alcohol (5 ml) and ethyl ether (20 ml) were added to the concentrated residue. The mixture was stirred for 1 hour at room temperature, the resulting solid was collected by filtration, washed and dried to afford **5aa** (350 mg, 80%) as a pale, white solid, mp 230°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.13 (s, 3H, CH_3SO_3H), 3.53 (m, 2H, piperazine CH_2), 3.67 (m, 6H, piperazine 3 CH_2), 6.70 (m, 1H, aromatic C8-H), 7.12 (m, 1H, naphthyl CH), 7.65 (m, 1H, naphthyl CH), 7.79-7.91 (m, 3H, naphthyl 3 CH), 8.24 (m, 1H, naphthyl CH), 8.41-8.48 (m, 2H, aromatic C5-H and naphthyl CH), 9.39 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{20}FN_3O_3 \cdot CH_3SO_3H$: C, 58.47; H, 4.71; N, 8.18. Found: C, 58.41; H, 4.65; N, 8.15.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5ab**).

This compound was prepared from **4a** in 68% yield as a white solid by following the typical procedure above used to prepare **5aa**, mp 286°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.59 (m, 3H, $CHCH_3$), 3.27 (s, 3H, CH_3SO_3H) 3.24-3.70 (m, 4H, piperazine 2 CH_2), 4.02 (m, 3H, piperazine CH_2 and $CHCH_3$), 6.78 (m, 1H, aromatic C8-H), 7.20 (m, 1H, naphthyl CH), 7.75 (m, 1H, naphthyl CH), 7.88-8.02 (m, 3H, naphthyl 3 CH), 8.33 (m, 1H, naphthyl CH), 8.50-8.54 (m, 2H, aromatic C5-H and naphthyl CH), 9.47 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{22}FN_3O_3 \cdot CH_3SO_3H$: C, 59.19; H, 4.97; N, 7.97. Found: C, 59.15; H, 5.01; N, 7.97.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5ac**).

This compound was prepared from **4a** in 73% yield as a white solid by following the typical procedure above used to prepare **5aa**, 286° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.18 (s, 3H, NCH_3), 3.20 (s, 3H, CH_3SO_3H), 3.43 (m, 4H, piperazine 2 CH_2), 3.75-4.00 (m, 4H, piperazine 2 CH_2), 6.77 (m, 1H, aromatic C8-H), 7.15 (m, 1H, naphthyl CH), 7.70 (m, 1H, naphthyl CH), 7.83-7.95 (m, 3H, naphthyl 3 CH), 8.28 (m, 1H, naphthyl CH), 8.45-8.53 (m, 2H, aromatic C5-H and naphthyl CH), 9.43 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{22}FN_3O_3 \cdot CH_3SO_3H$: C, 59.19; H, 4.97; N, 7.97. Found: C, 59.12; H, 4.99; N, 7.89.

6-Fluoro-7-[(3*R*,5*S*)-3,5-dimethyl-1-piperazinyl]-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5ad**).

This compound was prepared from **4a** in 74% yield as a white solid by following the typical procedure above used to prepare **5aa**, 271° dec; ^{1}H nmr (deuteriotrifluoroacetic acid and dimethyl-d_6 sulfoxide): δ 0.83 (m, 3H, piperazine $CHCH_3$), 0.91 (m, 3H, piperazine $CHCH_3$), 2.49-2.65 (m, 5H, CH_3SO_3H and piperazine CH_2), 3.10-3.34 (m, 4H, piperazine CH_2 and piperazine 2 $CHCH_3$), 6.10 (m, 1H, aromatic C8-H), 6.63 (m, 1H, naphthyl CH), 7.12 (m, 1H, naphthyl CH), 7.25-7.35 (m, 3H, naphthyl 3 CH), 7.72 (m, 1H, naphthyl CH), 7.88-7.91 (m, 2H, aromatic C5-H and naphthyl CH), 8.84 (m, 1H, vinyl H).

Anal. Calcd. for $C_{26}H_{24}FN_3O_3 \cdot CH_3SO_3H$: C, 59.88; H, 5.21; N, 7.76. Found: C, 59.82; H, 5.23; N, 7.74.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl]-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5ae**).

In a typical procedure to prepare compounds **5ae, 5be, 10ae, 10be,** a mixture of 6,7-difluoro-1-(1-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid **4a** (300 mg, 0.85 mmole), (3*S*)-3-amino-1-pyrrolidine dihydrochloride (340 mg, 2.1 mmoles), and 1,8-diazabicyclo[5.4.0]undec-7-ene (910 mg, 5.95 mmoles) in anhydrous acetonitrile (15 ml) was heated to reflux for 6 hours. When the reaction was completed, the reaction mixture was concentrated by evaporation. To the residue was added a small amount of water and isopropyl alcohol (15 ml), and the resulting solid was filtered. To the filtered solid was added 5% aqueous ethanol (15 ml), 1*N* methanesulfonic acid in an ethanol solution (4.3 ml, 4.25 mmoles), then the reaction mixture was stirred for 4 hours at room temperature. After the solvent was removed by evaporation, then isopropyl alcohol (5 ml) and ethyl ether (20 ml) were added to the concentrated residue. The mixture was stirred for 1 hour at room temperature, the resulting solid was filtered, washed and dried to afford **5ae** (268 mg, 61%) as a pale, yellow solid, mp 212°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.56 (m, 2H, pyrrolidine CH_2CH_2CH), 3.19 (s, 3H, CH_3SO_3H), 3.38-3.72 (m, 2H, pyrrolidine NCH_2), 3.90-4.20 (m, 2H, pyrrolidine NCH_2), 4.42 (m, 1H, pyrrolidine $CHNH_2$), 6.24 (m, 1H, aromatic C8-H), 7.20 (m, 1H, naphthyl CH), 7.70 (m, 1H, naphthyl CH), 7.84 (m, 2H, naphthyl 2 CH), 7.91 (m, 1H, naphthyl CH), 8.27 (m, 1H, naphthyl CH), 8.36 (m, 1H, naphthyl CH), 8.43 (m, 1H, aromatic C5-H), 9.27 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{20}FN_3O_3 \cdot CH_3SO_3H$: C, 58.47; H, 4.71; N, 8.18. Found: C, 58.43; H, 4.73; N, 8.17.

6-Fluoro-7-(1-piperazinyl)-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5ba**).

This compound was prepared from **4b** in 78% yield as a white solid by following the typical procedure above used to prepare **5aa**, 297° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.17 (s, 3H, CH_3SO_3H), 3.72 (m, 4H, piperazine 2 CH_2), 3.76 (m, 4H, piperazine 2 CH_2), 7.04 (m, 1H, aromatic C8-H), 7.63 (m, 1H, naphthyl CH), 7.87 (m, 2H, naphthyl 2 CH), 8.09 (m, 1H, naphthyl CH), 8.18 (m, 2H, naphthyl 2 CH), 8.33 (m, 1H, naphthyl CH), 8.45 (m, 1H, aromatic C5-H), 9.43 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{20}FN_3O_3 \cdot CH_3SO_3H$: C, 58.47; H, 4.71; N, 8.18. Found: C, 58.43; H, 4.68; N, 8.13.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5bb**).

This compound was prepared from **4b** in 68% yield as a pale, white solid by following the typical procedure above used to prepare **5aa**, 294° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.57 (m, 3H, piperazine $CHCH_3$), 3.19 (s, 3H, CH_3SO_3H), 3.40 and 3.53 (m, 1H and 1H, piperazine CH_2), 3.60 and 3.79 (m, 1H

and 1H, piperazine CH_2), 3.83-3.92 (m, 2H, piperazine CH_2), 4.04 (m, 1H, piperazine C*H*CH_3), 7.06 (m, 1H, aromatic C8-H), 7.65 (m, 1H, napthyl CH), 7.85-7.92 (m, 2H, naphthyl 2 CH), 8.10 (m, 1H, naphthyl CH), 8.19 (m, 2H, naphthyl 2 CH), 8.34 (m, 1H, naphthyl CH), 8.45 (m, 1H, aromatic C5-H), 9.43 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{22}FN_3O_3$•CH_3SO_3H: C, 59.19; H, 4.97; N, 7.97. Found: C, 59.15; H, 4.95; N, 7.89.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5bc**).

This compound was prepared from **4b** in 68% yield as a white solid by following the typical procedure above used to prepare **5aa**, mp 185°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.16 (s, 3H, NCH_3), 3.22 (s, 3H, CH_3SO_3H), 3.46-3.59 (m, 4H, piperazine 2 CH_2), 3.88 (m, 2H, piperazine CH_2), 4.05 (m, 2H, piperazine CH_2), 7.09 (m, 1H, aromatic C8-H), 7.66 (m, 1H, naphthyl CH), 7.86-7.94 (m, 2H, naphthyl 2 CH), 8.12 (m, 1H, naphthyl CH), 8.20 (m, 2H, naphthyl 2 CH), 8.35 (m, 1H, naphthyl CH), 8.48 (m, 1H, aromatic C5-H), 9.45 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{22}FN_3O_3$•CH_3SO_3H: C, 59.19; H, 4.97; N, 7.97. Found: C, 59.10; H, 5.00; N, 7.90.

6-Fluoro-7-[(3*R*,5*S*)-3,5-dimethyl-1-piperazinyl]-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5bd**).

This compound was prepared from **4b** in 72% yield as a white solid by following the typical procedure above used to prepare **5aa**, mp 198°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.49-1.54 (m, 6H, piperazine 2 CHC*H*$_3$), 3.22 (s, 3H, CH_3SO_3H), 3.27-3.33 (m, 2H, piperazine CH_2), 3.89 (m, 2H, piperazine CH_2), 4.02 (m, 2H, piperazine 2 C*H*CH_2), 7.10 (m, 1H, aromatic C8-H), 7.69 (m, 1H, naphthyl CH), 7.91 (m, 2H, naphthyl 2 CH), 8.13 (m, 1H, naphthyl CH), 8.22 (m, 2H, naphthyl 2 CH), 8.36 (m, 1H, naphthyl CH), 8.48 (m, 1H, aromatic C5-H), 9.44 (s, 1H, vinyl H).

Anal. Calcd. for $C_{26}H_{24}FN_3O_3$•CH_3SO_3H: C, 59.88; H, 5.21; N, 7.76. Found: C, 59.80; H, 5.20; N, 7.72.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl)-1-(2-naphthyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Methanesulfonate (**5be**).

This compound was prepared from **4b** in 52% yield as a white solid by following the typical procedure above used to prepare **5ae**, 200° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.49-2.60 (m, 2H, pyrrolidine CH_2CH_2CH), 3.17 (s, 3H, CH_3SO_3H), 3.71-3.86 (m, 2H, pyrrolidine NCH_2), 4.18 (m, 2H, pyrrolidine NCH_2), 4.46 (m, 1H, pyrrolidine C*H*NH_2), 6.55 (m, 1H, aromatic C8-H), 7.63 (m, 1H, naphthyl CH), 7.84-7.91 (m, 2H, naphthyl 2 CH), 8.10 (m, 1H, naphthyl CH), 8.16-8.20 (m, 2H, naphthyl 2 CH), 8.31-8.35 (m, 2H, aromatic C5-H and naphthyl CH), 9.29 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{20}FN_3O_3$•CH_3SO_3H: C, 58.47; H, 4.71; N, 8.18. Found: C, 58.40; H, 4.68; N, 8.17.

6-Fluoro-7-(1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (**10aa**).

This compound was prepared from **9a** in 73% yield as a white solid by following the typical procedure above used to prepare **5aa**, 280° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.21 (s, 3H, CH_3SO_3H), 3.22-3.61 (m, 4H, piperazine 2 CH_2), 4.04-4.19 (m, 4H, piperazine 2 CH_2), 7.21 (m, 1H, naphthyl CH), 7.67 (m, 1H, naphthyl CH), 7.76-7.82 (m, 2H, naphthyl 2 CH), 7.86 (m, 1H, naphthyl CH), 8.23 (m, 1H, napthyl CH), 8.36 (m, 1H, naphthyl CH), 8.50 (m, 1H, aromatic C5-H), 9.51 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3$•CH_3SO_3H: C, 56.03; H, 4.51; N, 10.89. Found: C, 55.98; H, 4.53, N, 10.85.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (**10ab**).

This compound was prepared from **9a** in 71% yield as a white solid by following the typical procedure above used to prepare **5aa**, mp 226°; ^{1}H nmr (deuteriotrifluoroacetic acid and dimethyl-d_6 sulfoxide, ppm): δ 0.46-0.70 (m, 3H, piperazine CHC*H*$_3$), 2.49 (s, 3H, CH_3SO_3H), 2.65 and 2.77 (m, 1H and 1H, piperazine CH_2), 2.80 and 3.05 (m, 1H and 1H, piperazine CH_2), 3.28 and 3.52 (m, 1H and 1H, piperazine CH_2), 4.10 (m, 1H, piperazine C*H*CH_3), 6.86 (m, 1H, naphthyl CH), 7.19 (m, 1H, naphthyl CH), 7.25-7.48 (m, 3H, naphthyl 3 CH), 7.79 (m, 1H, naphthyl CH), 7.80-8.01 (m, 2H, aromatic C5-H and naphthyl CH), 9.03 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{21}FN_4O_3$•CH_3SO_3H: C, 56.81; H, 4.77; N, 10.60. Found: C, 56.77; H, 4.75; N, 10.58.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**10ac**).

This compound was prepared from **9a** in 86% yield as a white solid by following the typical procedure above used to prepare **5aa**, mp 255°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.16 (s, 3H, piperazine NCH_3), 3.00-3.42 (m, 2H, piperazine CH_2), 3.68-3.80 (m, 4H, piperazine 2 CH_2), 4.50-4.87 (m, 2H, piperazine CH_2), 7.31 (m, 1H, naphthyl CH), 7.77-7.98 (m, 4H, naphthyl 4 CH), 8.33 (m, 1H, naphthyl CH), 8.46 (m, 1H, naphthyl CH), 8.60 (m, 1H, aromatic C5-H), 9.61 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{21}FN_4O_3$: C, 66.66; H, 4.89; N, 12.96. Found: C, 66.57; H, 4.87; N, 12.95.

6-Fluoro-7-[(3*R*,5*S*)-dimethyl-1-piperazinyl]-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**10ad**).

This compound was prepared from **9a** in 71% yield as a white solid by following the typical procedure above used to prepare **5aa**, 272° dec; ^{1}H nmr (deuteriotrifluoroacetic acid and dimethyl-d_6 sulfoxide, ppm): δ 0.54 (m, 3H, piperazine CHC*H*$_3$), 0.84 (m, 3H, piperazine CHC*H*$_3$), 2.40-2.90 (m, 4H, piperazine 2 CH_2), 3.63-3.88 (m, 2H, piperazine 2 C*H*CH_3), 6.92 (m, 1H naphthyl CH), 7.21 (m, 1H, naphthyl CH), 7.35-7.45 (m, 3H, napthyl 3 CH), 7.81 (m, 1H, naphthyl CH), 7.93 (m, 1H, naphthyl CH), 8.00 (m, 1H, aromatic C5-H), 9.04 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{23}FN_4O_3$: C, 67.25; H, 5.19; N, 12.55. Found: C, 67.18; H, 5.17; N, 12.53.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl]-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (**10ae**).

This compound was prepared from **9a** in 70% yield as a pale, yellow solid by following the typical procedure above used to prepare **5ae**, mp 194°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.40-2.66 (m, 2H, pyrrolidine CH_2CH_2CH), 3.24 (s, 3H, CH_3SO_3H), 3.20 and 3.55 (m, 1H and 1H, pyrrolidine NCH_2), 4.21-4.73 (m, 3H, pyrrolidine NCH_2 and pyrrolidine C*H*NH_2), 7.23 (m, 1H, naphthyl CH), 7.70-7.90 (m, 4H, naphthyl 4 CH),

8.27 (m, 1H, naphthyl CH), 8.38-8.43 (m, 2H, aromatic C5-H and naphthyl CH), 9.44 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3 \cdot CH_3SO_3H$: C, 56.03; H, 4.51; N, 10.89. Found: C, 55.96; H, 4.50; N, 10.83.

6-Fluoro-7-(1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (**10ba**).

This compound was prepared from **9b** in 65% yield as a white solid by following tbe typical procedure above used to prepare **5aa**, mp 137°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.77 (s, 3H, CH_3SO_3H), 3.18 (m, 4H, piperazine 2 CH_2), 3.87 (m, 4H, piperazine 2 CH_2), 7.21 (m, 1H, naphthyl CH), 7.35-7.43 (m, 2H, naphthyl 2 CH), 7.62-7.71 (m, 3H, napthyl 3 CH), 7.80 (m, 1H, naphthyl CH), 8.04 (m, 1H, aromatic C5-H), 9.05 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3 \cdot CH_3SO_3H$: C, 56.03; H, 4.51; N, 10.89. Found: C, 56.00; H, 4.52; N, 10.89.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-napthyridine-3-carboxylic Acid Methanesulfonate (**10bb**).

This compound was prepared from **9b** in 82% yield as a pale, white solid by following the typical procedure above used to prepare **5aa**, mp 263°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.18 (m, 3H, piperazine CHC*H*$_3$), 3.13 (s, 3H, CH_3SO_3H), 3.46 (m, 2H, piperazine CH_2), 3.63 (m, 2H, piperazine CH_2), 3.83 and 4.55 (m, 1H and 1H, piperazine CH_2), 4.72 (m, 1H, piperazine C*H*CH$_3$), 7.58 (m, 1H, naphthyl CH), 7.73-7.80 (m, 2H, naphthyl 2 CH), 8.00-8.09 (m, 3H, naphthyl 3 CH), 8.18 (m, 1H, naphthyl CH), 8.38 (m, 1H, aromatic C5-H), 9.44 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3 \cdot CH_3SO_3H$: C, 56.03; H, 4.51; N, 10.89. Found: C, 55.95; H, 4.48; N, 10.81.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Methanesulfonate (**10bc**).

This compound was prepared from **9b** in 81% yield as a pale, white solid by following the typical procedure above used to prepare **5aa**, mp 267°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.08 (s, 3H, piperazine NCH_3), 3.14 (s, 3H, CH_3SO_3H), 3.27 (m, 2H, piperazine CH_2), 3.72 (m, 4H, piperazine 2 CH_2), 4.76 (m, 2H, piperazine CH_2), 7.59 (m, 1H, naphthyl CH), 7.76 (m, 2H, naphthyl 2 CH), 8.00 (m, 1H, naphthyl CH), 8.05 (m, 2H, naphthyl 2 CH), 8.18 (m, 1H, naphthyl CH), 8.42 (m, 1H, aromatic C5-H), 9.44 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3 \cdot CH_3SO_3H$: C, 56.03; H, 4.51; N, 10.89. Found: C, 55.97; H, 4.49; N, 10.83.

6-Fluoro-7-[(3*R*,5*S*)-3,5-dimethyl-1-piperazinyl)-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**10bd**).

This compound was prepared from **9b** in 78% yield as a white solid by following the typical procedure above used to prepare **5aa**, 288° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.33 (m, 6H, piperazine 2 CHC*H*$_3$), 3.65 (m, 4H, piperazine 2 CH_2), 4.73 (m, 2H, piperazine 2 C*H*CH$_3$), 7.65 (m, 1H, naphthyl CH), 7.85 (m, 2H, naphthyl 2 CH), 8.09-8.18 (m, 3H, naphthyl 3 CH), 8.28 (m, 1H, naphthyl CH), 8.46 (m, 1H, aromatic C5-H), 9.53 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{23}FN_4O_3$: C, 67.25; H, 5.19; N, 12.55. Found: C, 67.19; H, 5.17; N, 12.51.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl]-1-(1-naphthyl)-4-oxo-1,4-dihydro-1,8-Naphthyridine-3-carboxylic Acid Methanesulfonate (**10be**).

This compound was prepared from **9b** in 63% yield as a pale yellow solid by following the typical procedure above used to prepare **5ae**, mp 232°; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.32-2.59 (m, 2H, pyrrolidine CH_2CH_2CH), 3.06 (s, 3H, CH_3SO_3H), 3.61 and 3.77 (m, 1H and 1H, pyrrolidine NCH_2), 4.22-4.52 (m, 3H, pyrrolidine NCH_2 and pyrrolidine C*H*NH_2), 7.55 (m, 1H, naphthyl CH), 7.71 (m, 2H, naphthyl 2 CH), 7.96 (m, 2H, naphthyl 2 CH), 8.03 (m, 1H, naphthyl CH), 8.12 (m, 1H, naphthyl CH), 8.24 (m, 1H, aromatic C5-H), 9.31 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3 \cdot CH_3SO_3H$: C, 56.03; H, 4.51; N, 10.89. Found: C, 56.04; H, 4.53; N, 10.87.

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