Syntheses of New Pyridonecarboxylic Acid Derivatives Containing 3-, 5- or 6-Quinolyl Substituents at N-1 and their Anti-HIV-RT Activities

Yoon-Seok Oh*, Chi-Woo Lee, Yong-Ho Chung, and Sung-June Yoon

Research Laboratories, Dong Wha Pharmaceutical Industries Co., Ltd., 189, Anyang-Dong Anyang-City Kyunggi-Do, 430-010, Korea

Sung- Hye Cho*

Department of Chemistry, Chung-Ang University, Seoul, 156-756, Korea

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A series of new pyridonecarboxylic acid derivatives containing 3-, 5- or 6-quinolyl 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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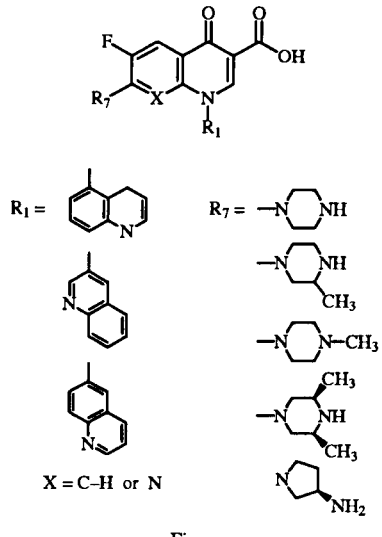
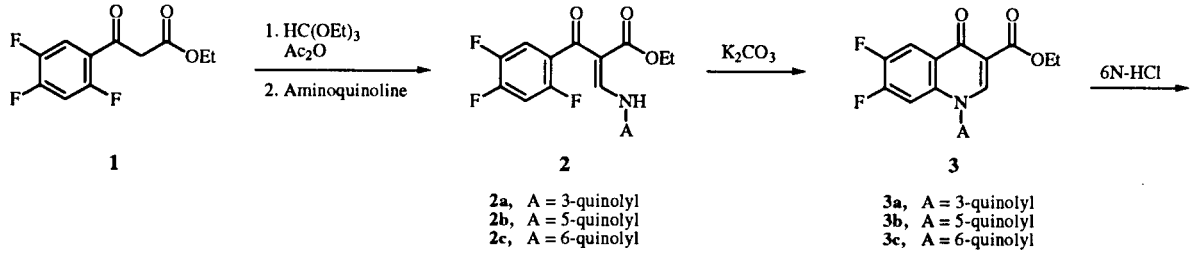
Acquired Immunodeficiency Syndrome (AIDS) epidemic was first reported in 1981 [1,2]. A large amount of information concerning this disease has been accumulated, since Human Immunodeficiency Virus (HIV) has been identified as the causative agent of the AIDS [3,4]. Unfortunately, despite a concerted worldwide 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].

Herein, we wish to report the syntheses of a series of pyridonecarboxylic acid derivatives containing 3-, 5- or 6-



Figure

Scheme 1



1

2

2a, A = 3-quinolyl
2b, A = 5-quinolyl
2c, A = 6-quinolyl

3

3a, A = 3-quinolyl
3b, A = 5-quinolyl
3c, A = 6-quinolyl

4

4a, A = 3-quinolyl
4b, A = 5-quinolyl
4c, A = 6-quinolyl

5

5aa, A = 3-quinolyl, R = 1-piperazinyl
5ab, A = 3-quinolyl, R = 3-methyl-1-piperazinyl
5ac, A = 3-quinolyl, R = 4-methyl-1-piperazinyl
5ad, A = 3-quinolyl, R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
5ae, A = 3-quinolyl, R = (3*S*)-3-amino-1-pyrrolidinyl
5ba, A = 5-quinolyl R = 1-piperazinyl
5bb, A = 5-quinolyl, R = 3-methyl-1-piperazinyl
5bc, A = 5-quinolyl, R = 4-methyl-1-piperazinyl
5bd, A = 5-quinolyl, R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
5be, A = 5-quinolyl, R = (3*S*)-3-amino-1-pyrrolidinyl
5ca, A = 6-quinolyl R = 1-piperazinyl
5cb, A = 6-quinolyl, R = 3-methyl-1-piperazinyl
5cc, A = 6-quinolyl, R = 4-methyl-1-piperazinyl
5cd, A = 6-quinolyl, R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
5ce, A = 6-quinolyl, R = (3*S*)-3-amino-1-pyrrolidinyl

quinolyl substituents at N-1 and their *in vitro* anti-HIV-RT activity (Figure).

Chemistry.

First, the synthetic procedure of new quinolone derivatives **5aa-5ce** was 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 the treatment with triethyl orthoformate and acetic anhydride. After removing of the solvent by evaporation, the crude residue, being not further purification, was treated with 3-, 5- or 6-aminoquinoline to afford acrylate derivatives **2**. Compound **2** was treated with potassium carbonate and 18-crown-6 in acetonitrile to afford cyclized product **3**. Compound **3** was hydrolyzed to compound 4 by 6*N*-hydrcchloric acid aqueous solution. The final products **5aa-5ce** could be obtained from **4a, 4b** or **4c** in reasonable yield by introducing several cyclic secondary amines into the C-7 position in acetonitrile.

As another part of our efforts, new naphthyridine derivatives **10aa-10ce** 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 by the reported procedure [12].

Biological Results.

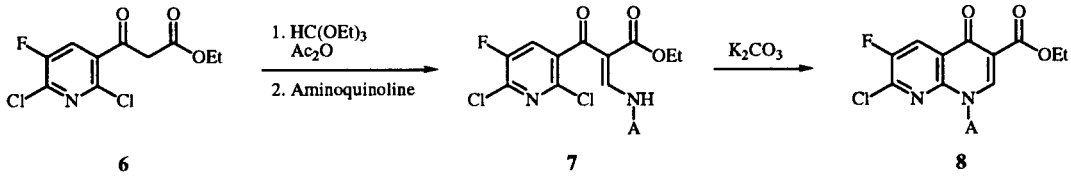
In vitro anti-HIV-RT activities of all the prepared compounds were tested by applied "Non-radioactive Reverse transcriptase assay Kit (Boehringer Mannheim)" method [13], and the thus obtained anti-HIV-RT activity values are summarized in Tables 1, 2 and 3. Anti-HIV-RT activities of these series were compared with that of Atevirdine [14].

In conclusion, most of the compounds prepared were found to have a characteristic that showed less reduced anti-HIV-RT activity in low tested concentration (0.1 μg/ml) compared with Atevirdine. Compounds **5ac, 10ad, 10ae** had better activities than that of Atevirdine. Especially, compound **10ae** had the most potent activity. These results obtained in this study show that a part of new series of pyridonecarboxylic acid derivatives containing 3-, 5- or 6-quinolyl substituents at N-1 can be promising candidates with the possibility to be developed as anti-HIV drug.

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

Scheme 2



6

7

7a, A = 3-quinolyl
7b, A = 5-quinolyl
7c, A = 6-quinolyl

8

8a, A = 3-quinolyl
8b, A = 5-quinolyl
8c, A = 6-quinolyl

9

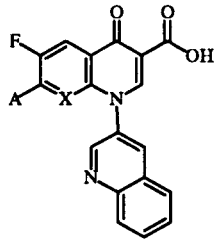
9a, A = 3-quinolyl
9b, A = 5-quinolyl
9c, A = 6-quinolyl

10

10aa, A = 3-quinolyl, R = 1-piperazinyl
10ab, A = 3-quinolyl, R = 3-methyl-1-piperazinyl
10ac, A = 3-quinolyl, R = 4-methyl-1-piperazinyl
10ad, A = 3-quinolyl, R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
10ae, A = 3-quinolyl, R = (3*S*)-3-amino-1-pyrrolidinyl
10ba, A = 5-quinolyl R = 1-piperazinyl
10bb, A = 5-quinolyl, R = 3-methyl-1-piperazinyl
10bc, A = 5-quinolyl, R = 4-methyl-1-piperazinyl
10bd, A = 5-quinolyl, R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
10be, A = 5-quinolyl, R = (3*S*)-3-amino-1-pyrrolidinyl
10ca, A = 6-quinolyl R = 1-piperazinyl
10cb, A = 6-quinolyl, R = 3-methyl-1-piperazinyl
10cc, A = 6-quinolyl, R = 4-methyl-1-piperazinyl
10cd, A = 6-quinolyl, R = (3*R*,5*S*)-3,5-dimethyl-1-piperazinyl
10ce, A = 6-quinolyl, R = (3*S*)-3-amino-1-pyrrolidinyl

Table 1

Inhibitory Activities for HIV-RT of Several New Pyridonecarboxylic Acid Derivatives Containing 3-Quinolyl Substituent at N-1



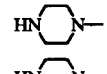
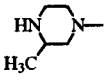
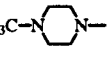
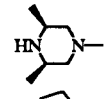
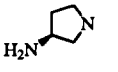
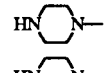
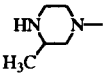
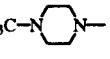
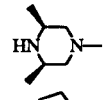
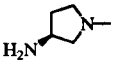
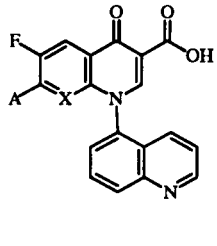
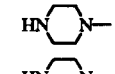
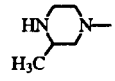
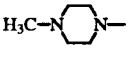
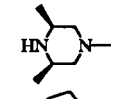
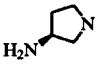
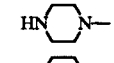
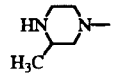
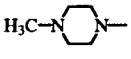
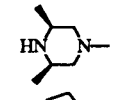
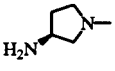
Compounds	X	A	Anti-HIV-RT activities(%) 1μg/ml	0.1 μg/ml
5aa	CH		42	36
5ab	CH		32	20
5ac	CH		63	32
5ad	CH		42	36
5ae	CH		39	37
10aa	N		39	35
10ab	N		52	48
10ac	N		47	28
10ad	N		68	51
10ae	N		70	58
	Atevirdine		64	25

Table 2

Inhibitory Activities for HIV-RT of Several New Pyridonecarboxylic Acid Derivatives Containing 5-Quinolyl Substituent at N-1



Compounds	X	A	Anti-HIV-RT activities(%) 1μg/ml	0.1 μg/ml
5ba	CH		48	24
5bb	CH		11	6
5bc	CH		38	27
5bd	CH		23	4
5be	CH		26	11
10ba	N		49	19
10bb	N		19	5
10bc	N		52	38
10bd	N		37	12
10be	N		48	33
	Atevirdine		64	25

Electrothermal IA9200 Digital Melting Point Apparatus and are uncorrected. Elemental analyses were performed by Korea Basic Science Institute. 2,4,5- Trifluorobenzoic acid, 3-, 5 or 6-aminoquinoline, several amines, *etc* were obtained 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 silicagel 60 F_{254}, supplied by Merck.

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

In a typical procedure to **2a, 2b, 2c, 7a, 7b,** and **7c,** 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 3-aminoquinoline (2.99 g, 20.7 mmoles) 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** (7.30 g, 90%) as a pale yellow solid, mp 153-155; ^{1}H nmr (deuteriochloroform): δ two sets of signals 1.01 and 1.13 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.14 (m, 2H, ethyl CH_2 signal overlap), 6.90 (m, 1H, aromatic CFCHCF), 7.40 (m, 1H, quinolyl CH), 7.65 (m, 1H, quinolyl CH), 7.74 (m, 1H, quinolyl CH), 7.87 (m, 1H, quinolyl CH), 8.06 (m, 1H, quinolyl CH), 8.21 (m, 1H, quinolyl CH), 8.58 (m, 1H, aromatic CCHCF), 8.89 (m, 1H, vinyl H).

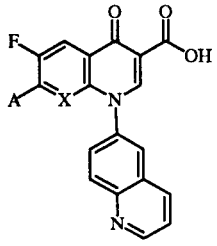
Anal. Calcd. for $C_{21}H_{15}N_2F_3O_3$: C, 63.00; H, 3.78; N, 7.00. Found: C, 63.06; H, 3.85; N, 6.98.

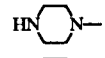
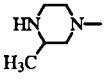
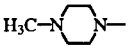
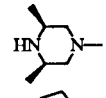
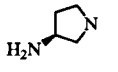
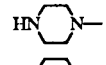
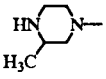
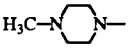
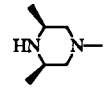
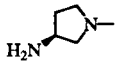
Ethyl 3-(5-Quinolylamino)-2-(2,4,5-trifluorobenzoyl)-2-propenoate (**2b**).

This compound was prepared from **1** in 92% yield as a pale yellow solid by following the above typical procedure used to prepare **2a**, mp 155-158; ^{1}H nmr (deuteriochloroform): δ two sets of

Table 3

Inhibitory Activities for HIV-RT of Several New Pyridonecarboxylic Acid Derivatives Containing 6-Quinolyl Substituent at N-1



Compounds	X	A	Anti-HIV-RT activities(%) 1μg/ml	0.1 μg/ml
5ca	CH		32	14
5cb	CH		40	29
5cc	CH		37	20
5cd	CH		47	28
5ce	CH		46	21
10ca	N		34	23
10cb	N		40	32
10cc	N		22	11
10cd	N		51	38
10ce	N		52	28
	Atevirdine		64	25

signals 1.03 and 1. 14 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.15 (m, 2H, ethyl CH_2 signal overlap), 6.92 (m, 1H, aromatic CFCHCF), 7.36 (m, 1H, quinolyl CH), 7.60 (m, 2H, quinolyl 2 CH), 7.83 (m, 1H, quinolyl CH), 8.16 (m, 1H, quinolyl CH), 8.58 (m, 1H, quinolyl CH), 8.70 (m, 1H, aromatic CCHCF), 9.05 (m, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{15}N_2F_3O_3$: C, 63.00; H, 3.78; N, 7.00. Found: C, 63.08; H, 3.81; N, 6.95.

Ethyl 3-(6-Quinolylamino)-2-(2,4,5-trifluorobenzoyl)-2-propenoate (**2c**).

This compound was prepared from **1** in 91% yield as a pale yellow solid by following the above typical procedure used to prepare **2a**, mp 189-192; ^{1}H nmr (deuteriochloroform): δ two sets of signals 1.00 and 1.12 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.12 (m, 2H, ethyl CH_2 signal overlap), 6.90 (m, 1H, aromatic CFCHCF), 7.32 (m, 1H, quinolyl CH), 7.52 (m, 1H, quinolyl CH), 7.63 (m, 2H, quinolyl 2 CH), 8.24 (m, 2H, quinolyl 2 CH), 8.62 (m, 1H, aromatic CCHCF), 8.90 (m, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{15}N_2F_3O_3$: C, 63.00; K 3.78; N, 7.00. Found: C, 63.09; H, 3.81; N, 6.92.

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

This compound was prepared from **6** in 85% yield as a white yellow solid by following the above typical procedure used to prepare **2a**, mp 144-145; ^{1}H nmr (deuteriochloroform): δ two sets of signals 0.92 and 1.08 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.09 (m, 2H, ethyl CH_2 signal overlap), 7.41 (m, 1H, quinolyl CH), 7.62 (m, 1H, quinolyl CH), 7.72 (m, 1H, quinolyl CH), 7.84 (m, 1H, quinolyl CH), 8.03 (m, 1H, quinolyl CH), 8.12 (m, 1H, quinolyl CH), 8.77 (m, 1H, aromatic CCHCF), 8.90 (m, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{14}Cl_2FN_3O_3$: C, 55.32; H, 3.25; N, 9.68. Found: C, 55.28; H, 3.28; N, 9.71.

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

This compound was prepared from **6** in 95% yield as a white yellow solid by following the above typical procedure used to prepare **2a**, mp 158-161; ^{1}H nmr (deuteriochloroform): δ two sets of signals 0.95 and 1.10 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.11 (m, 2H, ethyl CH_2 signal overlap), 7.48 (m, 1H, quinolyl CH), 7.61 (m, 2H, quinolyl 2 CH), 7.81 (m, 1H, quinolyl CH), 8.13 (m, 1H, quinolyl CH), 8.50 (m, 1H, quinolyl CH), 8.80 (m, 1H, aromatic CCHCF), 9.03 (m, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{14}Cl_2FN_3O_3$: C, 55.32; H, 3.25; N, 9.68. Found: C, 55.29; H, 3.28; N, 9.62.

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

This compound was prepared from **6** in 82% yield as a white yellow solid by following the above typical procedure used to prepare **2a**, mp 163-165; ^{1}H nmr (deuteriochloroform): δ two sets of signals 0.94 and 1.10 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.12 (m, 2H, ethyl CH_2 signal overlap), 7.43 (m, 1H, quinolyl CH), 7.74-7.86 (m, 3H, quinolyl 3 CH), 8.56 (m, 2H, quinolyl 2 CH), 8.79 (m, 1H, aromatic CCHCF), 9.05 (m, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{14}Cl_2FN_3O_3$: C, 55.32; H, 3.25; N, 9.68. Found: C, 55.29; H, 3.29; N, 9.64.

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

In a typical procedure for **3a, 3b, 3c, 8a, 8b,** and **8c**, a mixture of ethyl 3-(3-quinolylamino)-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 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** (6.60 g, 95%) as a white yellow solid, mp 238; ^{1}H nmr (deuteriochloroform): δ 1.37 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.36 (q, J = 7.07 Hz, 2H, ethyl CH_2), 6.76 (m, 1H, aromatic CFCHCF), 7.79 (m, 1H, quinolyl CH), 7.97 (m, 2H, quinolyl 2 CH), 8.28-8.36 (m, 2H, quinolyl 2 CH), 8.41 (m, 1H, quinolyl CH), 8.53 (s, 1H, aromatic CCHCF), 8.97 (s, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{14}F_2N_2O_3$: C, 66.32; H, 3.71; N, 7.37. Found: C, 66.25; H, 3.75; N, 7.34.

Ethyl 6,7-Difluoro-1-(5-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (**3b**).

This compound was prepared from **2b** in 96% yield as a white yellow solid by following the above typical procedure used to prepare **3a**, mp 297-298; ^{1}H nmr (deuteriochloroform): δ 1.33 (t, J = 7.07 Hz, 3H, ethyl CH_3) 4.35 (q, J = 7.07 Hz, 2H, ethyl CH_2), 6.42 (m, 1H, aromatic CFCHCF), 7.48 (m, 1H, quinolyl CH), 7.67 (m, 1H, quinolyl CH), 7.73 (m, 1H, quinolyl CH), 7.95 (m, 1H, quinolyl CH), 8.31 (m, 1H, quinolyl CH), 8.43 (m, 1H, quinolyl CH), 8.49 (s, 1H, aromatic CCHCF), 9.06 (m, 1H, vinyl H).

Anal. Calcd. for $C_{21}H_{14}F_2N_2O_3$: C, 66.32; K 3.71; N, 7.37. Found: C, 66.23; H, 3.74; N, 7.43.

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

This compound was prepared from **2c** in 92% yield as a white yellow solid by following the above typical procedure used to prepare **3a**, mp 241-244; ^{1}H nmr (deuteriochloroform): δ 1.37 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.36 (q, J = 7.07 Hz, 2H, ethyl CH_2), 6.79 (m, 1H, aromatic CFCHCF), 7.61 (m, 1H, quinolyl CH), 7.73 (m, 1H, quinolyl CH), 8.00 (m, 1H, quinolyl CH), 8.30 (m, 2H, quinolyl 2 CH), 8.41 (m, 1H, quinolyl CH), 8.56 (s, 1H, aromatic CCHCF), 9.10 (m, 1H, vinyl H)

Anal. Calcd. for $C_{21}H_{14}F_2N_2O_3$: C, 66.32; H, 3.71; N, 7.37. Found: C, 66.24; H, 3.76; N, 7.34.

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

This compound was prepared from **7a** in 93% yield as a pale yellow solid by following the above typical procedure used to prepare **3a**, mp 271-273 ; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.39 (q, J = 7.07 Hz, 2H, ethyl CH_2), 7.72 (m, 1H, quinolyl CH), 7.88-7.97 (m, 2H, quinolyl 2 CH), 8.29 (m, 2H, quinolyl 2 CH), 8.50 (m, 1H, quinolyl CH), 8.72 (s, 1H, aromatic CCHCF), 8.99 (m, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{13}ClFN_3O_3$: C, 60.39; H, 3.29; N, 10.56. Found: C, 60.35; H, 3.32; N, 10.49.

Ethyl 7-Chloro-6-fluoro-l-(5-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**8b**).

This compound was prepared from **7b** in 95% yield as a pale yellow solid by following the above typical procedure used to prepare **3a**, mp 265-268; ^{1}H nmr (deuteriochloroform): δ 1.36 (t, J = 7.07 Hz, 3H, ethyl CH_3), 4.37 (q, J = 7.07 Hz, 2H, ethyl CH_2), 7.45 (m, 1H, quinolyl CH), 7.64 (m, 2H, quinolyl 2 CH), 7.91 (m, 1H, quinolyl CH), 8.40 (m, 1H, quinolyl CH), 8.51 (m, 1H, quinolyl CH), 8.61 (s, 1H, aromatic CCHCF), 9.03 (s, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{13}ClFN_3O_3$: C, 60.39; H, 3.29; N, 10.56. Found: C, 60.35; H, 3.34; N, 10.48.

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

This compound was prepared from **7c** in 94% yield as a pale yellow solid by following the above typical procedure used to prepare **3a**, mp 222-225; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, J = 7.07 Hz, 3H, ethyl CH_3) 4.39 (q, J = 7.07 Hz, 2H, ethyl CH_2), 7.56 (m, 1H, quinolyl CH), 7.75 (m, 1H, quinolyl CH), 7.91 (m, 1H, quinolyl CH), 8.27-8.34 (m, 2H, quinolyl 2 CH), 8.5 1 (m, 1H, quinolyl CH), 8.75 (s, 1H, aromatic CCHCF), 9.07 (s, 1H, vinyl H).

Anal. Calcd. for $C_{20}H_{13}ClFN_3O_3$: C, 60.39; H, 3.29; N, 10.56. Found: C, 60.34; H, 3.37; N, 10.52.

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

In a typical procedure for **4a, 4b, 4c, 9a, 9b,** and **9c**, to a suspension of ethyl 6,7-difluoro-1-(3-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate **3a** (6.8 g, 17.9 mmoles) in ethanol (60 ml) was added aqueous 6*N* hydrochloric 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 >300; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.58 (m, 1H, aromatic C8-H), 8.24 (m, 1H, quinolyl CH), 8.44-8.56 (m, 2H, quinolyl 2 CH), 8.58 (m, 1H, quinolyl CH), 8.64 (m, 1H, quinolyl CH), 9.69 (m, 1H, quinolyl CH), 9.74 (s, 1H, aromatic C5-H), 9.95 (s, 1H, vinyl H).

Anal. Calcd. for $C_{19}H_{10}F_2N_2O_3$•HCl: C, 58.70; H, 2.85; N, 7.21. Found: C, 58.65; H, 2.83; N, 7.29.

6,7-Difluoro-1-(5-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Hydrochloride (**4b**).

This compound was prepared from **3b** in 97% yield as a white solid by following the above typical procedure used to prepare **4a**, mp >300; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.17 (m, 1H, aromatic C8-H), 8.23 (m, 1H, quinolyl CH), 8.47 (m, 1H, quinolyl CH), 8.55 (m, 1H, quinolyl CH), 8.62 (m, 1H, quinolyl CH), 8.71 (m, 1H, quinolyl CH), 8.93 (m, 1H, quinolyl CH), 9.46 (m, 1H, aromatic C5-H), 9.61 (s, 1H, vinyl H).

Anal. Calcd. for $C_{19}H_{10}F_2N_2O_3$•HCl: C, 58.70; H, 2.85; N, 7.21. Found: C, 58.63; H, 2.88; N, 7.23.

6,7-Difluoro-1-(6-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid Hydrochloride (**4c**).

This compound was prepared from **3c** in 98% yield as a white solid by following the above typical procedure used to prepare **4a**, mp >300; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 7.41 (m, 1H, aromatic C8-H), 8.37 (m, 1H, quinolyl CH), 8.46 (m, 1H, quinolyl CH), 8.61 (m, 1H, quinolyl CH), 8.91-8.94 (m, 2H, quinolyl 2 CH), 9.45-9.90 (m, 2H, quinolyl CH and aromatic C5-H), 9.61 (s, 1H, vinyl H).

Anal. Calcd. for $C_{19}H_{10}F_2N_2O_3$•HCl: C, 58.70; H, 2.85; N, 7.21. Found: C, 58.61; H, 2.89; N, 7.20.

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

This compound was prepared from **8a** in 96% yield as a white solid by following the above typical procedure used to prepare **4a**, mp 295-297; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 8.34 (m, 1H, quinolyl CH), 8.53-8.60 (m, 2H, quinolyl 2 CH), 8.66 (m, 1H, quinolyl CH), 8.81 (m, 1H, quinolyl CH), 9.63 (m, 1H, quinolyl CH), 9.75 (s, 1H, aromatic C5-H), 9.83 (s, 1H, vinyl H).

Anal. Calcd. for $C_{18}H_9ClFN_3O_3$•HCl: C, 53.22; H, 2.48; N, 10.34. Found: C, 53.17; H, 2.52; N, 10.28.

7-Chloro-6-fluoro-1-(5-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Hydrochloride (**9b**).

This compound was prepared from **8b** in 98% yield as a white solid by following the above typical procedure used to prepare **4a**, mp 295-296; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 8.27 (m, 1H, quinolyl CH), 8.39 (m, 1H, quinolyl CH), 8.58 (m, 1H, quinolyl CH), 8.83 (m, 2H, quinolyl 2 CH), 8.91 (m, 1H, quinolyl CH), 9.50 (s, 1H, aromatic C5-H), 9.67 (s, 1H, vinyl H).

Anal. Calcd. for $C_{18}H_9ClFN_3O_3$•HCl: C, 53.22; H, 2.48; N, 10.34. Found: C, 53.19; H, 2.49; N, 10.29.

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

This compound was prepared from **8c** in 97% yield as a white solid by following the above typical procedure used to prepare **4a**, mp >300; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 8.39 (m, 1H, quinolyl CH), 8.53 (m, 1H, quinolyl CH), 8.79-8.85 (in, 3H, quinolyl 3 CH), 9.44-9.50 (m, 2H, quinolyl CH and aromatic C5-H), 9.75 (s, 1H, vinyl H).

Anal. Calcd. for $C_{18}H_9ClFN_3O_3$•HCl: C, 53.22; H, 2.48; N, 10.34. Found: C, 53.16; H, 2.52; N, 10.31.

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

In a typical procedure for **5aa, 5ab, 5ad, 5bc, 5ca, 5cc, 5cd, 10ac, 10ad, 10ba, 10bc, 10bd, 10ca,** and **10cc,** a mixture of 6,7-difluoro-1-(3-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid hydrochloride **4a** (350 mg, 0.9 mmole), piperazine(271 mg, 3.2 mmoles) in acetonitrile (anhydrous; 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 (15ml), find the resulting solid was filtered and dried to afford **5aa** (341 mg, 78%) as a pale white solid, mp 232-235; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.76 (m, 4H, piperazine 2 CH_2), 3.93 (m, 4H, piperazine 2 CH_2), 7.04 (m, 1H, aromatic C8-H), 8.42 (m, 1H, quinolyl CH), 8.55 (m, 1H, quinolyl CH), 8.63-8.76 (m, 3H, quinolyl 3 CH), 9.59 (s, 1H, quinolyl CH), 9.90 (s, 1H, aromatic C5-H), 10.03 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3$: C, 66.02; H, 4.58; N, 13.39. Found: C, 65.98; H, 4.61; N, 13.33.

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

This compound was prepared from **4a** in 82% yield as a white solid by following the above typical procedure used to prepare **5aa**, mp 252-254; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.58 (m, 3H, CHC*H*$_3$), 3.43 and 3.58 (m, 1H and 1H, piperazine CH_2), 3.60 and 3.75 (m, 1H and 1H, piperazine CH_2), 3.99 (m, 2H, piperazine CH_2), 4.14 (m, 1H, piperazine C*H*CH$_3$), 7.01 (m, 1H, aromatic C8-H), 8.40 (m, 1H, quinolyl CH), 8.54 (m, 1H, quinolyl CH), 8.61- 8.70 (m, 3H, quinolyl 3 CH), 9.54 (m, 1H, quinolyl CH), 9.83 (m, 1H, aromatic C5-H), 9.93 (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, 66.61; H, 4.94; N, 12.95.

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

In a typical procedure for **5ac, 5ba, 5bb, 5bd, 5cb, 10aa, 10ab, 10bb, 10cb,** and **10cd,** a mixture of 6,7- difluoro-1-(3-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid hydrochloride **4a** (350 mg, 0.9 mmole), *N*-methylpiperazine (316 mg, 3.2 mmoles) in acetonitrile (anhydrous, 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) was 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 **5ac** (562 mg, 71%) as a pale white solid, mp 234-237; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.62 (s, 6H, 2 CH_3SO_3H), 1.65 (s, 3H, NCH_3), 1.98 (m, 4H, piperazine 2 CH_2), 2.29 (m, 2H, piperazine CH_2), 2.55 (m, 2H, piperazine CH_2), 5.41 (m, 1H, aromatic C8-H), 6.84 (m, 1H, quinolyl CH), 6.93 (m, 1H, quinolyl CH), 7.07 (m, 2H, quinolyl 2 CH), 7.19 (m, 1H, quinolyl CH), 7.91 (m, 1H, quinolyl CH), 8.23 (m, 1H, aromatic C5-H), 8.42 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{21}FN_4O_3$•2CH_3SO_3H: C, 49.99; H, 4.68; N, 8.97. Found: C, 49.97; H, 4.70; N, 8.91.

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

This compound was prepared from **4a** in 75% yield as a white solid by following the above typical procedure used to prepare **5aa**, mp 292-296; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.46 (m, 6H, piperazine 2 CHC*H*$_3$), 3.27 (m, 2H, piperazine CH_2), 4.04 (m, 2H, piperazine CH_2), 4.12 (m, 2H, piperazine 2 C*H*CH$_3$), 7.04 (m, 1H, aromatic C8-H), 8.36 (m, 1H, quinolyl CH), 8.50 (m, 1H, quinolyl CH), 8.56-8.66 (m, 3H, quinolyl 3 CH), 9.49 (m, 1H, quinolyl CH), 9.79 (m, 1H, aromatic C5-H), 9.88 (m, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{23}FN_4O_3$: C, 67.25; H, 5.19; N, 12.55. Found: C, 67.21; H, 5.21; N, 12.50.

6-Fluoro-7-[(3S)-3-amino-1-piperazinyl]-l-(3-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (**5ae**).

In a typical procedure for **5ae, 5be, 5ce, 10be,** and **10ce,** a mixture of 6,7-difluoro-1-(3-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid hydrochloride **4a** (300 mg, 0.77 mmole), (3*S*)-3-amino-1-pyrrolidine dihydrochloride (307 mg, 1.93 mmoles), and 1,8-diazabicyclo[5.4.0]undec-7-ene (822 mg, 5.39 mmoles) in acetonitrile (anhydrous, 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, washed and dried to afford **5ae** (200 mg, 62%) as a pale yellow solid, dec 271; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.51 and 2.62 (m, 1H and 1H, pyrrolidine CH_2CH_2CH), 3.72 (m, 2H, pyrrolidine NCH_2), 4.18 and 4.35 (m, 1H and 1H, pyrrolidine NCH_2), 4.47 (m, 1H, pyrrolidine C*H*NH$_2$), 6.37 (m, 1H, aromatic C8-H), 8.37 (m, 2H, quinolyl 2 CH), 8.59-8.70 (m, 3H, quinolyl 3 CH), 9.37 (s, 1H, quinolyl CH), 9.77 (m, 1H, aromatic C5-H), 9.88 (m, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3$: C, 66.02; H, 4.58; N, 13.39. Found: C, 65.97; H, 4.63; N, 13.35.

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

This compound was prepared from **4b** in 67% yield as a white solid by following the above typical procedure used to prepare **5ac**, mp 196-199; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.21 (s, 6H, 2 CH_3SO_3H), 3.70-3.81 (m, 8H, piperazine 4 CH_2), 6.68 (m, 1H, aromatic C8-H), 8.31 (m, 1H, quinolyl CH), 8.53-8.60 (m, 2H, quinolyl 2 CH), 8.68 (m, 1H, quinolyl CH), 8.82 (m, 1H, quinolyl CH), 8.99 (m, 1H, quinolyl CH), 9.49 (s, 1H, aromatic C5-H), 9.60 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3 \cdot 2CH_3SO_3H$: C, 49.18; H, 4.46; N, 9.18. Found: C, 49.15; H, 4.48; N, 9.15.

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

This compound was prepared from **4b** in 72% yield as a pale white solid by following the above typical procedure used to prepare **5ac**, mp 274-277; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.57 (m, 3H, piperazine CHC*H*$_3$), 3.20 (s, 6H, 2 CH_3SO_3H), 3.36-3.77 (m, 3H, piperazine CH_2 and piperazine C*H*$_2$), 3.81-3.85 (m, 2H, piperazine CH_2), 3.92 (m, 1H, piperazine C*H*$_2$), 4.05 (m, 1H, piperazine C*H*CH$_3$), 6.70 (m, 1H, aromatic C8-H), 8.37 (m, 1H, quinolyl CH), 8.53 (m, 1H, quinolyl CH), 8.59 (m, 1H, quinolyl CH), 8.66 (m, 1H, quinolyl CH), 8.82 (m, 1H, quinolyl CH), 8.98 (m, 1H, quinolyl CH), 9.47 (s, 1H, aromatic C5-H), 9.59 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{21}FN_4O_3 \cdot 2CH_3SO_3H$: C, 49.99; H, 4.68; N, 8.97. Found: C, 49.95; H, 4.71; N, 8.92.

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

This compound was prepared from **4b** in 78% yield as a white solid by following the above typical procedure used to prepare **5aa**, mp 275-279; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.2 1 (s, 3H, NCH_3), 3.48 (m, 4H, piperazine 2 CH_2), 3.82 (m, 2H, piperazine CH_2), 3.97-4.06 (m, 2H, piperazine CH_2), 6.70 (m, 1H, aromatic C8-H), 8.36 (m, 1H, quinolyl CH), 8.53-8.61 (m, 2H, quinolyl 2 CH), 8.67 (m, 1H, quinolyl CH), 8.83 (m, 1H, quinolyl CH), 8.96 (m, 1H, quinolyl CH), 9.46 (m, 1H, aromatic C5-H), 9.53 (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, 66.63; H, 4.94; N, 12.92.

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

This compound was prepared from **4b** in 71% yield as a white solid by following the above typical procedure used to prepare **5ac**, mp 247-250; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.52-1.56 (m, 6H, piperazine 2 CHC*H*$_3$), 3.24 (s, 6H, 2 CH_3SO_3H), 3.28 (m, 2H, piperazine CH_2), 3.91-4.0 1 (m, 4H, piperazine CH_2 and piperazine 2 C*H*CH$_2$), 6.79 (m, 1H, aromatic C8-H), 8.42 (m, 1H, quinolyl CH), 8.56-8.73 (m, 3H, quinolyl 3 CH), 8.86 (m, 1H, quinolyl CH), 9.01 (m, 1H, quinolyl CH), 9.49 (s, 1H, aromatic C5-H), 9.63 (s, 1H, vinyl H).

Anal. Calcd. for $C_{25}H_{23}FN_4O_3 \cdot 2CH_3SO_3H$: C, 50.78; H, 4.89; N, 8.77. Found: C, 50.73; H, 4.92; N, 8.79.

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

This compound was prepared from **4b** in 53% yield as a white solid by following the above typical procedure used to prepare **5ae**, mp 219-222; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.37-2.60 (m, 2H, pyrrolidine CH_2CH_2CH), 3.45-3.80 (m, 2H, pyrrolidine NCH_2), 4.20 (m, 2H, pyrrolidine NCH_2), 4.43 (m, 1H, pyrrolidine C*H*NH$_2$), 6.07 (m, 1H, aromatic C8-H), 8.39 (m, 2H, quinolyl 2 CH), 8.54 (m, 1H, quinolyl CH), 8.67 (m, 1H, quinolyl CH), 8.81 (m, 1H, quinolyl CH), 8.95 (m, 1H, quinolyl CH), 9.32 (s, 1H, aromatic C5-H), 9.53 (s, 1H, vinyl H)

Anal. Calcd. for $C_{23}H_{19}FN_4O_3$: C, 66.02; H, 4.58; N, 13.39. Found: C, 65.95; K 4.62; N, 13.33

6-Fluoro-7-(1-piperazinyl)-1-(6-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (**5ca**).

This compound was prepared from **4c** in 72% yield as a white solid by following the above typical procedure used to prepare **5aa**, mp > 300; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.76 (m, 4H, piperazine 2 CH_2), 3.88 (m, 4H, piperazine 2 CH_2), 6.93 (m, 1H, aromatic C8-H), 8.51 (m, 2H, quinolyl 2 CH), 8.59 (m, 1H, quinolyl CH), 9.00 (m, 2H, quinolyl 2 CH), 9.49 (s, 1H, quinolyl CH), 9.58 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3$: C, 66.02; H, 4.58; N, 13.39. Found: C, 65.96; H, 4.62; N, 13.38.

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

This compound was prepared from **4c** in 63% yield as a pale white solid by following the above typical procedure used to prepare **5ac**, dec 297; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.56 (m, 3H, piperazine CHC*H*$_3$), 3.17 (s, 6H, 2 CH_3SO_3H), 3.43 (m, 1H, piperazine C*H*$_2$), 3.60 (m, 2H, piperazine CH_2), 3.76 (m, 1H, piperazine C*H*$_2$), 3.91 (m, 2H, piperazine CH_2), 4.13 (m, 1H, piperazine C*H*CH$_3$), 6.90 (m, 1H, aromatic C8-H), 8.44 (m, 2H, quinolyl 2 CH), 8.54 (m, 1H, quinolyl CH), 8.95 (m, 2H, quinolyl 2 CH), 9.41 (s, 1H, quinolyl CH), 9.52 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{24}H_{21}FN_4O_3 \cdot 2CH_3SO_3H$: C, 49.99; H, 4.68; N, 8.97. Found: C, 49.95; H, 4.71; N, 8.92.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1-(6-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (**5cc**).

This compound was prepared from **4c** in 68% yield as a white solid by following the above typical procedure used to prepare **5aa**, dec 295; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.20 (s, 3H, NCH_3), 3.53 (m, 4H, piperazine 2 CH_2), 3.84 (m, 2H, piperazine CH_2), 4.11 (m, 2H, piperazine CH_2), 6.88 (m, 1H, aromatic C8-H), 8.46-8.55 (m, 3H, quinolyl 3 CH), 8.89 (m, 1H, quinolyl CH), 8.95 (s, 1H, quinolyl CH), 9.34 (s, 1H, quinolyl CH), 9.52 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{24}H_{21}FN_4O_3$: C, 66.66; H, 4.89; N, 12.96. Found: C, 66.63; H, 4.94; N, 12.90.

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

This compound was prepared from **4c** in 69% yield as a white solid by following the above typical procedure used to prepare **5aa**. dec 273; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.54 (m, 6H, piperazine 2 CHC*H*$_3$), 3.34 (m, 2H, piperazine CH_2), 3.91-4.20 (m, 4H, piperazine CH_2 and piperazine 2 C*H*CH$_3$), 6.98 (m, 1H, aromatic C8-H), 8.49-8.57 (m, 3H, quinolyl 3 CH), 8.93 (m, 1H, quinolyl CH), 9.00 (m, 1H, quinolyl CH), 9.43 (m, 1H, quinolyl CH), 9.55 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{25}H_{23}FN_4O_3$: C, 67.25; H, 5.19; N, 12.55. Found: C, 67.21; H, 5.21; N, 12.50.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl)-1-(6-quinolyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (**5ce**).

This compound was prepared from **4c** in 56% yield as a white yellow solid by following the above typical procedure used to prepare **5ae**, dec 260; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.34 and 2.50 (m, 1H and 1H, pyrrolidine CH_2CH_2CH), 3.74-3.97 (m, 2H, pyrrolidine NCH_2), 4.18 and 4.26 (m, 1H and 1H, pyrrolidine NCH_2), 4.46 (m, 1H, pyrrolidine C*H*NH$_2$), 6.33

(m, 1H, aromatic C8-H), 8.36 (m, 1H, quinolyl CH), 8.50 (m, 2H, quinolyl 2 CH), 8.92 (m, 2H, quinolyl 2 CH), 9.30 (s, 1H, quinolyl CH), 9.54 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{23}H_{19}FN_4O_3$: C, 66.02; H, 4.58; N, 13.39. Found: C, 65.95; H, 4.62; N, 13.33

6-Fluoro-7-(1-piperazinyl)-1-(3-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid 2 Methanesulfonate (**10aa**).

This compound was prepared from **9a** in 62% yield as a white solid by following the above typical procedure used to prepare **5ac**. dec 298; ^{1}H nmr (deuteriotrifluoroacetic acid and dimethyl-d_6 sulfoxide): δ 2.18 (s, 6H, 2 CH_3SO_3H), 2.65 (m, 4H, piperazine 2 CH_2), 3.28 (m, 4H, piperazine 2 CH_2), 7.33 (m, 1H, quinolyl CH), 7.47-7.64 (m, 4H, quinolyl 4 CH), 8.57 (m, 1H, quinolyl CH), 8.68 (s, 1H, aromatic C5-H), 8.90 (s, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{18}FN_5O_3 \cdot 2CH_3SO_3H$: C, 47.13; H, 4.28; N, 11.45. Found: C, 47.04; H, 4.31; N, 11.41.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(3-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3carboxylic Acid 2 Methanesulfonate (**10ab**).

This compound was prepared from **9a** in 63% yield as a white solid by following the above typical procedure used to prepare **5ac**, mp 271-274; ^{1}H nmr (deuteriotrifluoroacetic acid and dimethyl-d_6 sulfoxide): δ 0.93 (m, 3H, piperazine CHC*H*$_3$), 2.61 (s, 6H, 2 CH_3SO_3H), 2.93-3.04 (m, 2H, piperazine CH_2), 3.12-3.28 (m, 3H, piperazine CH_2 and piperazine C*H*CH$_3$), 3.97-4.07 (m, 2H, piperazine CH_2), 7.84 (m, 1H, quinolyl CH), 7.99-8.06 (m, 2H, quinolyl 2 CH), 8.16 (m, 1H, quinolyl CH), 8.22 (m, 1H, quinolyl CH), 8.95 (m, 1H, quinolyl CH), 9.16 (s, 1H, aromatic C5-H), 9.39 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{20}FN_5O_3 \cdot 2CH_3SO_3H$: C, 47.99; H, 4.51; N, 11.19. Found: C, 47.93; H, 4.54; N, 11.15.

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

This compound was prepared from **9a** in 61% yield as a white yellow solid by following the above typical procedure used to prepare **5aa**, dec 270; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.19 (s, 3H, piperazine NCH_3), 3.49 (m, 2H, piperazine CH_2), 3.88 (m, 4H, piperazine 2 CH_2), 4.86 (m, 2H, piperazine CH_2), 8.36 (m, 1H, quinolyl CH), 8.56 (m, 2H, quinolyl 2 CH), 8.67 (m, 2H, quinolyl 2 CH), 9.70 (s, 1H, quinolyl CH), 9.82 (s, 1H, aromatic C5-H), 10.07 (s, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{20}FN_5O_3$: C, 63.73; H, 4.65; N, 16.16. Found: C, 63.69; H, 4.67; N, 16.10.

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

This compound was prepared from **9a** in 74% yield as a yellow white solid by following the above typical procedure used to prepare **5aa**, mp >300; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.43 (m, 6H, piperazine 2 CHC*H*$_3$), 3.47 (m, 2H, piperazine CH_2), 3.79 (m, 2H, piperazine CH_2), 4.77 (m, 2H, piperazine 2 C*H*CH$_3$), 8.38 (m, 1H, quinolyl CH), 8.52 (m, 1H, quinolyl CH), 8.60 (m, 1H, quinolyl CH), 8.67 (m, 2H, quinolyl 2 CH), 9.68 (s, 1H, quinolyl CH), 9.79 (s, 1H, aromatic C5-H), 9.95 (s, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{22}FN_5O_3$: C, 64.42; H, 4.96; N, 15.65. Found: C, 64.36; H, 4.95; N, 15.59.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl]-1-(3-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid 2 Methanesulfonate (**10ae**).

A mixture of 7-chloro-6-fluoro-1-(3-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrochloride **9a** (313 mg, 0.77 mmole), (3*S*)-3-amino-1-pyrrolidine dihydrochloride (307 mg, 1.93 mmoles), and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.06 g, 6.93 mmoles) in acetonitrile(anhydrous, 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) was 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 **10ae** (264 mg, 56%) as a pale yellow solid, mp 292-295; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.50 and 2.73 (m, 1H and 1H, pyrrolidine CH_2CH_2CH), 3.23 (s, 6H, 2 CH_3SO_3H), 3.85 and 4.08 (m, 1H and 1H, pyrrolidine NCH_2), 4.41-4.68 (m, 3H, pyrrolidine NCH_2 and pyrrolidine C*H*NH_2), 8.36 (m, 2H, quinolyl 2 CH), 8.57 (m, 1H, quinolyl CH), 8.64 (m, 2H, quinolyl 2 CH), 9.62 (s, 1H, quinolyl CH), 9.70 (s, 1H, aromatic C5-H), 10.04 (s, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{18}FN_5O_3 \cdot 2CH_3SO_3H$: C, 47.13; H, 4.28; N, 11.45. Found: C, 47.09; H, 4.33; N, 11.39.

6-Fluoro-7-(1-piperazinyl)-1-(5-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**10ba**).

This compound was prepared from **9b** in 71% yield as a white solid by following the above typical procedure used to prepare **5aa**, mp 281-282; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.57 (m, 4H, piperazine 2 CH_2), 4.14 (m, 4H, piperazine 2 CH_2), 8.34 (m, 1H, quinolyl CH), 8.45 (m, 1H, quinolyl CH), 8.52 (m, 1H, quinolyl CH), 8.61 (m, 1H, quinolyl CH), 8.89 (m, 2H, quinolyl 2 CH), 9.52 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{22}H_{18}FN_5O_3$: C, 63.00; H, 4.33; N, 16.70. Found: C, 62.97; H, 4.35; N, 16.65.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(5-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid 2 Methanesulfonate (**10bb**).

This compound was prepared from **9b** in 71% yield as a pale white solid by following the above typical procedure used to prepare **5ac**, mp 286-287; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.38 (m, 3H, piperazine CHC*H*$_3$), 3.16 (s, 6H, 2 CH_3SO_3H), 3.40 (m, 2H, piperazine CH_2), 3.42-3.59 (m, 3H, piperazine CH_2 and piperazine C*H*CH$_3$), 4.30 (m, 2H, piperazine CH_2), 8.32 (m, 1H, quinolyl CH), 8.41 (m, 1H, quinolyl CH), 8.47 (m, 1H, quinolyl CH), 8.57 (m, 1H, quinolyl CH), 8.85 (m, 2H, quinolyl 2 CH), 9.50 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{23}H_{20}FN_5O_3 \cdot 2CH_3SO_3H$: C, 47.99; H, 4.51; N, 11.19. Found: C, 47.92; H, 4.55; N, 11.15.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1-(5-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**10bc**).

This compound was prepared from **9b** in 69% yield as a pale white solid by following the above typical procedure used to prepare **5aa**, mp 274-276; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.14 (s, 3H, piperazine NCH_3), 3.32 (m, 2H, piperazine CH_2), 3.48 (m, 1H, piperazine CH_2), 3.71-3.79 (m, 3H, piperazine CH_2

and piperazine CH_2), 4.48 and 4.63 (m, 1H and 1H, piperazine CH_2), 8.30 (m, H, quinolyl CH), 8.44 (m, 1H, quinolyl CH), 8.58 (m, 1H, quinolyl CH), 8.62 (m, 1H, quinolyl CH), 8.86 (m, 2H, quinolyl 2 CH), 9.49 (m, 2H, aromatic C5-H and vinyl H)

Anal. Calcd. for $C_{23}H_{20}FN_5O_3$: C, 63.73; H, 4.65; N, 16.16. Found: C, 63.70; H, 4.68; N, 16.11.

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

This compound was prepared from **9b** in 82% yield as a white solid by following the above typical procedure used to prepare **5aa**, mp 241-244; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.33 (m, 6H, piperazine 2 CHC*H*$_3$), 3.14 and 3.43 (m, 1H and 1H, piperazine CH_2), 3.62 (m, 2H, piperazine CH_2), 4.24 and 4.66 (m, 1H and 1H, piperazine 2 C*H*CH$_3$), 8.32 (m, 1H, quinolyl CH), 8.44-8.52 (m, 2H, quinolyl 2 CH), 8.62 (m, 1H, quinolyl CH), 8.87 (m, 2H, quinolyl 2 CH), 9.50 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{24}H_{22}FN_5O_3$: C, 64.42; H, 4.96; N, 15.65. Found: C, 64.38; H, 4.99; N, 15.61.

6-Fluoro-7-[(3*S*)-3-amino-1-pyrrolidinyl]-1-(5-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (**10be**).

This compound was prepared from **9b** in 51% yield as a pale yellow solid by following the above typical procedure used to prepare **5ae**, dec 296; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.35 and 2.64 (m, 1H and 1H, pyrrolidine CH_2CH_2CH), 3.36-3.60 (m, 2H, pyrrolidine NCH_2), 4.19-4.65 (m, 3H, pyrrolidine NCH_2 and pyrrolidine C*H*NH_2), 8.33-8.40 (m, 3H, quinolyl 3 CH), 8.60 (m, 1H, quinolyl CH), 8.88 (m, 2H, quinolyl 2 CH), 9.48 (m, 2H, aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{22}H_{18}FN_5O_3$: C, 63.00; H, 4.33; N, 16.70. Found: C, 62.95; H, 4.37; N, 16.62.

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

This compound was prepared from **9c** in 69% yield as a yellow white solid by following the above typical procedure used to prepare **5aa**, mp 275-278; ^{1}H nmr (deuteriotrifluoroacetic acid + dimethyl-d_6 sulfoxide): δ 3.00 (m, 4H, piperazine 2 CH_2), 3.63 (m, 4H, piperazine 2 CH_2), 8.03-8.13 (m, 2H, quinolyl 2 CH), 8.26 (m, 1H, quinolyl CH), 8.35 (m, 1H, quinolyl CH), 8.54 (m, 1H, quinolyl CH), 8.82 (m, 1H, quinolyl CH), 9.16 (m, 1H, aromatic C5-H), 9.33 (s, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{18}FN_5O_3$: C, 63.00; H, 4.33; N, 16.70. Found: C, 62.95; H, 4.37; N, 16.63.

6-Fluoro-7-(3-methyl-1-piperazinyl)-1-(6-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid 2 Methanesulfonate (**10cb**).

This compound was prepared from **9c** in 68% yield as a pale white solid by following the above typical procedure used to prepare **5ac**, mp >300; ^{1}H nmr (deuteriotrifluoroacetic acid + dimethyl-d_6 sulfoxide): δ 0.93 (m, 3H, piperazine CHC*H*$_3$), 2.49 (s, 6H, 2 CH_3SO_3H), 2.95 (m, 2H, piperazine CH_2), 3.07-3.30 (m, 3H, piperazine CH_2 and piperazine C*H*CH$_3$), 3.95-4.07 (m, 2H, piperazine CH_2), 8.06-8.16 (m, 2H, quinolyl 2 CH), 8.27 (m, 1H, quinolyl CH), 8.39 (m, 1H, quinolyl CH), 8.58 (m, 1H, quinolyl CH), 8.86 (m, 1H, quinolyl CH), 9.18 (m, 1H, aromatic C5-H), 9.34 (m, 1H, vinyl H).

Anal. Calcd. for $C_{23}H_{20}FN_5O_3 \cdot 2CH_3SO_3H$: C, 47.99; H, 4.51; N, 11.19. Found: C, 47.94; H, 4.53; N, 11.13.

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

This compound was prepared from **9c** in 71% yield as a pale white solid by following the above typical procedure used to prepare **5aa**, dec 296; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.17 (s, 3H, piperazine NCH_3), 3.45 (m, 2H, piperazine CH_2), 3.85 (m, 4H, piperazine 2 CH_2), 4.83 (m, 2H, piperazine CH_2), 8.43 (m, 1H, quinolyl CH), 8.50 (m, 1H, quinolyl CH), 8.63 (m, 1H, quinolyl CH), 8.89 (m, 2H, quinolyl 2 CH), 9.49-9.53 (m, 3H, quinolyl CH and aromatic C5-H and vinyl H).

Anal. Calcd. for $C_{23}H_{20}FN_5O_3$: C, 63.73; H, 4.65; N, 16.16. Found: C, 63.69; K 4.69; N, 16.10.

6-Fluoro-7-[(3*R*,5*S*)-3,5-dimethyl-1-piperazinyl)-1-(6-quinolyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid 2 Methanesulfonate (**10cd**).

This compound was prepared from **9c** in 66% yield as a white solid by following the above typical procedure used to prepare **5ac**, mp 220-222; ^{1}H nmr (deuteriotrifluoroacetic acid + dimethyl-d_6 sulfoxide): δ 0.91 and 0.98 (m, 3H and 3H, piperazine 2 CHC*H*$_3$), 2.49 (s, 6H, 2 CH_3SO_3H), 2.88 (m, 2H, piperazine CH_2), 3.13 (m, 2H, piperazine CH_2), 4.05 (m, 2H, piperazine 2 C*H*CH$_3$), 8.02-8.12 (m, 2H, quinolyl 2 CH), 8.24 (m, 1H, quinolyl CH), 8.36 (m, 1H, quinolyl CH), 8.51 (m, 1H, quinolyl CH), 8.84 (m, 1H, quinolyl CH), 9.16 (m, 1H, aromatic C5-H), 9.27 (m, 1H, vinyl H).

Anal. Calcd. for $C_{24}H_{22}FN_5O_3 \cdot 2CH_3SO_3H$: C, 48.82; H, 4.73; N, 10.95. Found: C, 48.80; H, 4.75; N, 10.90.

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

This compound was prepared from **9c** in 55% yield as a pale yellow solid by following the above typical procedure used to prepare **5ae**, dec 246; ^{1}H nmr (deuteriotrifluoroacetic acid + dimethyl-d_6 sulfoxide): δ 1.90-2.12 (m, 2H, pyrrolidine CH_2CH_2CH), 3.05-4.01 (m, 5H, pyrrolidine 2 NCH_2 and pyrrolidine C*H*NH_2), 8.00-8.17 (m, 2H, quinolyl 2 CH), 8.28-8.44 (m, 2H, quinolyl 2 CH), 8.60 (m, 1H, quinolyl CH), 8.83 (m, 1H, quinolyl CH), 9.22 (m, 1H, aromatic C5-H), 9.40 (m, 1H, vinyl H).

Anal. Calcd. for $C_{22}H_{18}FN_5O_3$: C, 63.00; H, 4.33; N, 16.70. Found: C, 62.95; H, 4.36; N, 16.61.

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