# Synthesis of 4-Oxo-4*H*-quino[2,3,4-*i,j*][1,4]-benoxazine-5-carboxylic Acid Derivatives



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The synthesis and antibacterial activity of 1-substituted amino-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic acid derivatives is described. Key steps in the synthesis include carbon homologation and two intramolecular nucleophilic displacement cyclization reactions to generate the 4-oxo-4*H*-quino[2,3,4-*i,j*]-[1,4]benoxazine-5-carboxylic acid nucleus.

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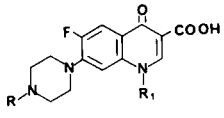
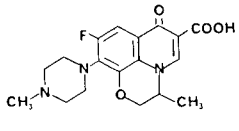
The recent discoveries of the potent clinically important antibacterials Norfloxacin **1** [1], Ciprofloxacin **2** [2] and Ofloxacin **3** [3], members of the quinolone-3-carboxylic acid group of antibacterial agents [4], have stimulated considerable interest in the synthesis of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives. During our research on the synthesis of novel quinolone derivatives as antibacterial agents, we discovered that 1 aryl substitution generated highly potent compounds as exemplified by Difloxacin **4** [4] and A-56620 **5** [5].



1 R=H, $R_1$=$C_2H_5$
2 R=H, $R_1$=$C_3H_5$
4 R=$CH_3$, $R_1$=p-$FC_6H_4$
5 R=H, $R_1$=p-$FC_6H_4$



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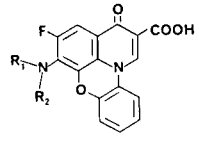

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Compound **3** has an oxazine moiety. The attractive antimicrobial features of **3-5** led us to speculate whether incorporation of both of these features in a single molecule would be consistent with antimicrobial activity. In this paper, we would like to report the synthesis and antibacterial activity of the hybrid quinolone antibacterials - 1-substituted amino-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]-benoxazine-5-carboxylic acid derivatives **6**.

Our synthetic pathway to the desired compounds was designed so as to generate a common intermediate having the basic ring skeleton with a leaving group at the 1 position. Displacement at 1 position with different amines would generate many derivatives. Fluorine atom was chosen as the leaving group since aromatic fluorine group is very susceptible for nucleophilic displacement. Hence, 1,2-difluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic acid (**14**) was synthesized by an intramolecular nucleophilic displacement cyclization reaction (Scheme I), a process that had been successfully applied to the syntheses Amifloxacin [6] and 1-arylquinolones [5].

Treatment of 2,3,4,5-tetrafluorobenzoic acid (**7**) with thionyl chloride gave the corresponding acid chloride which, without purification, was reacted with dilithiodianion of monoethyl malonate [7] to give the 2,3,4,5-tetrafluorobenzoylacetate (**8**) (mp 41-44°, 89%). It existed in both keto and enol forms. Treatment of this ester with triethylorthoformate in acetic anhydride gave the one carbon homolog enol ether intermediate which upon evaporation of solvent to dryness was allowed to react with a slight excess of 2-hydroxyaniline in methylene chloride at room temperature to give the ethyl 3-(2-hydroxyanilino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate (**9**) (mp 161-165°, 97%). This enaminoketo ester exists in both *trans* and *cis* forms in solution with one of the isomers being predominant (more than 90%).

The phenolic group of **9** was protected by a tetrahydropyran group upon reacting **9** with dihydropyran in the presence of hydrochloric acid to yield the tetrahydropyran derivative **10** (mp 130-131°, 71.2%). Regiospecific cyclization of compound **10** with one molar equivalent of sodium hydride in tetrahydrofuran (THF) yielded ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate **11** (mp 147-150°, 65.2%). Hydrolysis of **11** with dilute hydrochloric acid gave the deprotected derivative **12** (mp 197-199°, 92%). Cyclization of compound **11** was achieved by reacting it with sodium hydride at room temperature to give ethyl 1,2-difluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylate (**13**) (mp >250°, 88%). Saponification of compound **13** with aqueous sodium hydroxide yielded 1,2-difluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic acid (**14**) (mp >250°, 83%).

Displacement of **14** with an excess of piperazine or 4-methylpiperazine in pyridine at 80° yielded **15** (mp 243-245°, 91%) or **16** (mp >250°, 49%). Displacement of **13** with 3-acetamidopyrrolidine in pyridine at 70° gave the 3-acetamido derivative **17** (mp 208-209°, 70%). Hydrolysis of **17** with 6*N* hydrochloride acid yielded the 1-(3-aminopyrrolidin-1-yl)-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic acid hydrochloride (**18**) (mp >250°, 69%).

Scheme I

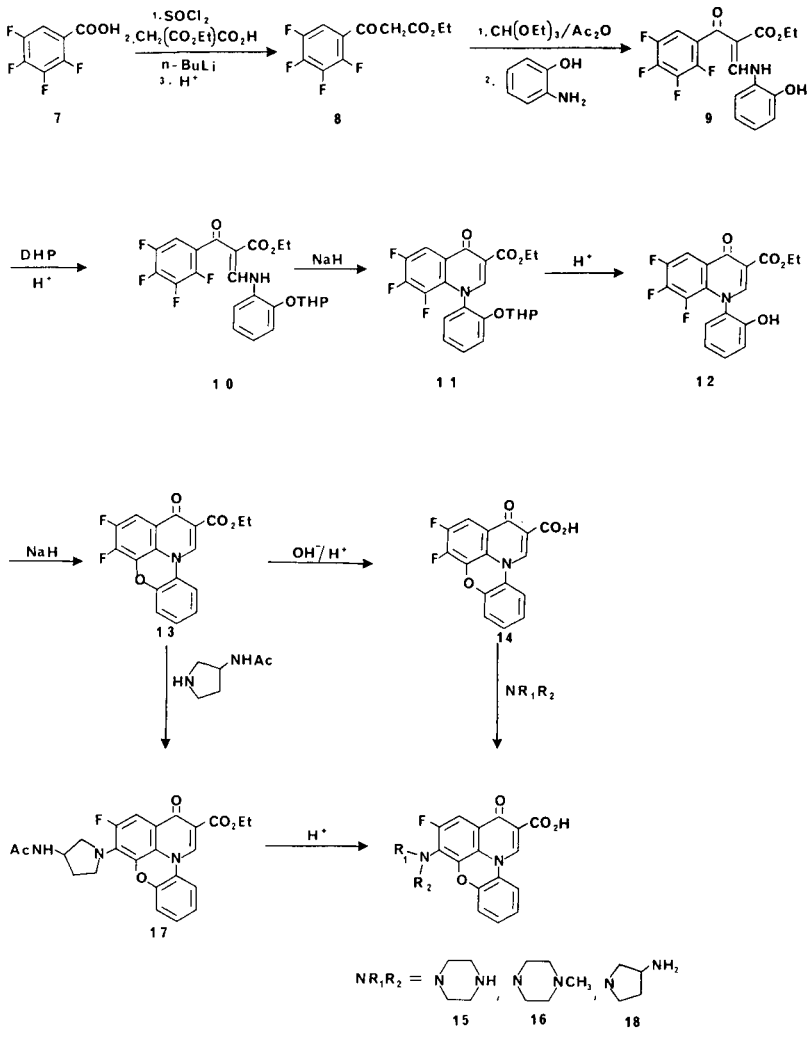

Table I

*In Vitro* Antibacterial Activity of 4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic Acids

Minimal Inhibitory Concentration (MIC), μg/ml [a]

| | Organism | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | Sa(A) | Sa | Se | Sf | Sp | Ec | Ea | Kp | Pa(5) | Pa(k) | A |
| **15** | 3.1 | 6.2 | 3.1 | 3.1 | 1.56 | 1.56 | 1.56 | .39 | 12.5 | 6.2 | 3.1 |
| **16** | 1.56 | 1.56 | 1.56 | 1.56 | 3.1 | 3.1 | 6.2 | 1.56 | 12.5 | 12.5 | 3.1 |
| **18** | .78 | .78 | .78 | 1.56 | 1.56 | .39 | 1.56 | .39 | 6.2 | 6.2 | 3.1 |
| **19** | .78 | .78 | .78 | 12.5 | 3.1 | .2 | .39 | .1 | .78 | 1.56 | .78 |

[a] The MICs were determined by the two-fold agar dilution on Brain-Heart Infusion agar. Organisms selected for inclusion in the table are: Sa(A), *Staphylococcus aureus* ATCC 6538P; Sa, *Staphylococcus aureus* CMX 686B; Se, *Staphylococcus epidermidis* 3519; Sf, *Streptococcus faecium* ATCC 8043; Sp, *Streptococcus pyogenes* 930; Ec, *Eschericia coli* Juhl; Ea, *Enterobacter aerogenes* ATCC 13048; Kp, *Klebsiella pneumoniae* 8045; Pa (5), *Pseudomonas aeruginosa* 5007; Pa(k), *Pseudomonas aeruginosa* K799/WT; A, *Acinetobacter sp.* CMX 669.

Biological Results.

Table I summarizes the *in vitro* antibacterial activity of the 4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic acids against five gram-positive bacteria (*Staphylococcus aureus* ATCC 6538P, *Staphylococcus aureus* CMX 686B, *Staphylococcus epidermidis* 3519, *Streptococcus faecium* ATCC 8043, and *Streptococcus pyogenes* 930) and six gram-negative organisms (*Escherichia coli* Juhl, *Enterobacter aerogenes* ATCC 13048, *Klebsiella pneumoniae* 8045, *Pseudomonas aeruginosa* 5007, *Pseudomonas aeruginosa* K799/WT, and *Acinetobacter sp.* (MX669). The data of 1-phenyl-6-fluoro-7-piperazin-1-yl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**19**), an arylquinolone, is included for comparison. Inspection of the table revealed that the three compounds have good broad spectrum antibacterial activities. However, they are slightly less potent than their uncyclized arylquinolone.

## EXPERIMENTAL

Melting points were taken in a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were obtained (unless otherwise specified) were with ± 0.4% of the theoretical values. Microanalyses were performed by the Abbott analytical department. The NMR spectra were obtained on a Varian T-60 and HA-100 spectrometers using tetramethylsilane as an internal standard. The NMR peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. The ir spectra were recorded on a Perkin-Elmer Model 710 A infrared spectrometer. The ir, nmr, and ms data of all compounds were consistent with the assigned structures. Solutions were dried over magnesium sulphate.

Ethyl 2,3,4,5-Tetrafluorobenzoylacetate (**8**).

One drop of dimethylformamide (DMF) was added to a solution of 2,3,4,5-tetrafluorobenzoic acid (1.94 g, 10 mmoles) in thionyl chloride (20 ml). After heating the mixture at 80° for 4 hours, the solvent was removed by evaporation under reduced pressure yielding a yellowish mobile oil, 2,3,4,5-tetrafluorobenzoyl chloride. Monoethyl malonate (2.64 g, 20 mmoles) and 3 mg of biquinoline were dissolved in 25 ml dry tetrahydrofuran (THF) and cooled to −30°. A solution of 2.2 *M* *n*-butyllithium in hexane was added until a pink color remained at −5°C (16.2 ml). The suspension was then cooled to −50°. The acid chloride obtained as described above, dissolved in 20 ml of THF, was added to the suspension dropwise. After 0.5 hours, the dry ice bath was removed and the reaction was allowed to warm up to room temperature. The reaction was acidified with 40 ml of 1 *N* hydrochloric acid and was extracted with ether. The ether fraction was washed with saturated aqueous sodium bicarbonate solution and then water. The ether solution was dried and evaporated to dryness yielding a yellowish oil. This was purified by use of Kugelrohr to give 2.36 g of **8** (89%), mp 41-44°; $^1$H nmr (deuteriochloroform): δ (two sets of signals), 1.27 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 1.37 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 3.82 (d, J = −13 Hz, 1, $CH_2$), 4.07 (d, J = −13 Hz, 1, $CH_2$), 4.23 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 4.27 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 5.84 (1H, s, vinyl H), 7.55 (two sets 1H, m, aromatic H), 12.57 (s, 1, enol OH).

*Anal.* Calcd. for $C_{11}H_8F_4O_3$: C, 50.01; H, 3.05. Found: C, 50.05; H, 3.26.

Ethyl 3-(2-Hydroxyanilino)-2-(2,3,4,5-tetrafluoro)benzoylacrylate (**9**).

To a solution of ethyl 2,3,4,5-tetrafluorobenzoylacetate (**8**) (1.50 g, 5.68 mmoles) in triethylorthoformate (1.37 ml, 8.24 mmoles) and acetic anhydride (2.4 ml, 25.4 mmoles) was heated at 130° for 4 hours with the removal of ethyl acetate formed during the reaction. The solution was evaporated under reduced pressure to a mobile oil which was then dissolved in methylene chloride (50 ml). 2-Hydroxyaniline (0.90 g, 8.24 mmoles) was added to the solution. After 2 hours, the solution was evaporated to dryness and the product was purified through silica gel column yielding 2.1 g of **9** (97% yield), mp 161-165°; $^1$H nmr (deuteriochloroform): δ (2 sets of signals), 1.12 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 1.15 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 4.13 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 4.14 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 6.74 (m, 2, aromatic H), 7.08 (m, 2, aromatic H), 7.36 (m, 1, aromatic H), 8.66 (m, 2, vinyl H and NH).

*Anal.* Calcd. for $C_{18}H_{13}F_4NO_4$: C, 56.40; H, 3.42; N, 3.65. Found: C, 56.12; H, 3.45; N, 3.60.

Ethyl 3-(2-Tetrahydropyranoxyanilino)-2-(2,3,4,5-tetrahydrofluoro)benzoylacrylate (**10**).

To a solution of benzoylacrylate **9** (4.5 g, 11.8 mmoles) in methylene chloride (300 ml) and 12 *N* hydrochloric acid (20 ml) was added dihydropyran (5.36 ml 59 mmoles) dropwise. After standing overnight at room temperature, the solvent was removed under reduced pressure. The residue was washed with hexane yielding 3.75 g of **10** (71%), mp 130-131°; $^1$H nmr (deuteriochloroform): δ 1.17 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 1.85 (m, 6, $(CH_2)_3$), 3.66 (m, 1, $OCH_2$), 3.89 (m, 1, $OCH_2$), 4.14 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 5.57 (m, 1, OCH), 7.07 (m, 2, aromatic H), 7.18 (m, 1, aromatic H), 7.40 (m, 1, aromatic H), 8.68 (d, J = 13.5 Hz, 1, vinyl H), 12.8 (d, J = 13.5 Hz, 1, NH).

*Anal.* Calcd. for $C_{23}H_{21}F_4NO_5 \cdot 1/3\ H_2O$: C, 58.37; H, 4.60; N, 2.96. Found: C, 58.34; H, 4.49; H, 2.83.

Ethyl 1-(2-Tetrahydropyranoxyphenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**11**).

To a cold solution of benzoylacrylate **10** (2.0 g, 4.3 mmoles) in THF (25 ml) was slowly added a 60% sodium hydride-in-oil suspension (118 mg, 4.7 mmoles). The mixture was heated at 40° for 3.5 hours under nitrogen atmosphere and was cooled and evaporated under reduced pressure to approximately 2 ml solution. Water (100 ml) was added and the mixture was filtered. The yellowish solid was washed with water and dried yielding 1.25 g of **11** (65%), mp 147-150°; $^1$H nmr (deuteriochloroform): δ 1.37 (2 sets of t, J = 7.5 Hz, 3, ethyl $CH_3$), 1.46 (m, 6, $(CH_2)_3$), 3.58 (m, 2, $OCH_2$), 4.39 (2 sets of d, J = 7.5 Hz, 2, ethyl $CH_2$), 5.57 (m, 1, $OCH_2$), 7.30 (m, 4, aromatic H), 8.18 (m, 1, aromatic H), 8.37 (d, J = 16.5 Hz, 1, vinyl H).

*Anal.* Calcd. for $C_{23}H_{20}F_3NO_5 \cdot 1/4\ H_2O$: C, 61.14; H, 4.57; N, 3.07. Found: C, 61.06; H, 4.47; N, 2.96.

Ethyl 1-(2-Hydroxyphenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**12**).

To a solution of 4-oxoquinoline **11** (1 g, 2.24 mmoles) in methylene chloride (30 ml) was added in 10 ml of water followed by the addition of 3 drops of concentrated hydrochloric acid. The mixture was stirred for 1-5 hours. Ten ml of water was added and precipitate appeared. After 1 hour the mixture was filtered and washed with methylene chloride and dried yielding 0.8 g **12** (92%), mp 197-199°; $^1$H nmr (DMSO-$d_6$): δ 1.26 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 4.23 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 7.03 (m, 2, aromatic H), 7.41 (m, 1, aromatic H), 7.60 (m, 1, aromatic H), 8.04 (m, 1, aromatic H), 8.28 (s, 1, vinyl H), 10.44 (s, 1, phenolic OH).

*Anal.* Calcd. for $C_{18}H_{12}F_3NO_4$: C, 59.51; H, 3.33; N, 3.86. Found: C, 59.41; H, 3.28; N, 3.77.

Ethyl 1,2-Difluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylate (**13**).

To a cold solution of 4-oxoquinoline **12** (100 mg, 0.275 mmole) in THF (6 ml) was slowly added a 60% sodium hydride-in-oil suspension (12.2 mg, 0.3 mmole). The mixture was stirred at room temperature for 4.5 hours under nitrogen atmosphere and was evaporated to nearly dryness under reduced pressure. Water (20 ml) was added and the solid was filtered and washed with ether yielding 85 mg of **13** (88%) mp >250°; $^1$H nmr (deuteriochloroform): δ 1.44 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 4.43 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 7.27 (m, 1, aromatic H), 7.35 (m, 2, aromatic H), 7.73 (m, 2, aromatic H), 9.14 (s, 1, vinyl H).

*Anal.* Calcd. for $C_{18}H_{11}F_2NO_4 \cdot 1/3\ H_2O$: C, 61.89; H, 3.37; N, 4.01. Found: C, 61.53; H, 3.29; N, 3.90.

1,2-Difluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic Acid (**14**).

To a solution of benoxazine **13** (1.06 g, 3.09 mmoles) in THF (10 ml) was added in 1.4 ml of 0.2475 *N* sodium hydroxide solution (3.40 mmoles). The mixture was heated at 80° for 16 hours. The solution was cooled and the THF was removed by distillation under reduced pressure. Water (25 ml) was added and the *p*H of the solution was adjusted to 4 by the addition of acetic acid. The precipitate was filtered and washed with ether and dried yielding 846 mg of **14** (83%), mp >250°; $^1$H nmr (trifluoroacetic acid): δ 7.57 (m, 2, aromatic H), 7.73 (m, 1, aromatic H), 8.07 (m, 2, aromatic H), 9.77 (s, 1, vinyl-1).

*Anal.* Calcd. for $C_{16}H_7F_2NO_4 \cdot 5/6\ H_2O$: C, 58.19; H, 2.65; N, 4.24. Found: C, 57.84; H, 2.65; N, 3.99.

1-Piperazin-1-yl-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic Acid (**15**).

To a solutin of the fluoro acid **14** (0.5 g, 1.59 mmoles) in pyridine (30 ml) at 90° was added in piperazine (0.41 g, 4.76 mmoles). After heating at 90° under nitrogen atmosphere for 20 hours, the solution was evaporated to nearly dryness under reduced pressure. The orange solid was refluxed in ethanol for 30 minutes. The mixture was cooled and filtered and washed with water and dried yielding 551 mg of **15** (91%), mp 243-245°; $^1$H nmr (trifluoroacetic acid): δ 3.74 (m, 4, $N(CH_2)_2$), 3.95 (m, 4, $N(CH_2)_2$), 7.43 (m, 1, aromatic H), 7.53 (m, 1, aromatic H), 7.70 (m, 1, aromatic H), 7.98 (m, 2, aromatic H), 9.61 (s, 1, aromatic H).

*Anal.* Calcd. for $C_{20}H_{16}FN_3O_4 \cdot 5/6\ H_2O$: C, 60.06; H, 4.49; N, 10.60. Found: C, 60.42; H, 4.32; N, 10.49.

1-(4-Piperazin-1-yl)-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic Acid (**16**).

Compound **16** was prepared from **14** by using the same experimental procedure as the preparation of **15** reacting with *N*-methylpiperazine instead of piperazine, 49% yield, mp >250°; $^1$H nmr (DMSO-$d_6$): δ 2.27 (s, 3, $NCH_3$), 3.28 (m, 4, $N(CH_2)_2$), 3.35 (m, 4, $N(CH_2)_2$), 7.28 (m, 2, aromatic H), 7.39 (m, 1, aromatic H), 7.54 (m, 1, aromatic H), 8.58 (1, aromatic H), 9.19 (s, 1, vinyl H).

*Anal.* Calcd. for $C_{21}H_{12}FN_3O_4 \cdot 1\ 1/4\ H_2O$: C, 60.36; H, 4.94; N, 10.05. Found: C, 60.39; H, 5.32; N, 10.06.

Ethyl 1-(3-Acetamidopyrrolidin-1-yl)-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*]-[1,4]benoxazine-5-carboxylate (**17**).

To a solution of the benoxazine **13** (1 g, 2.91 mmoles) in pyridine (20 ml) at 70° was added in 3-acetamidopyrrolidine (1.12 g, 8.74 mmoles). After heating at 70° under nitrogen atmosphere for 20 hours, the solution was evaporated to nearly dryness under reduced pressure. The residue was treated with water (30 ml) and filtered and the gummy residue was purified on silica gel column to yield 0.92 g of **17** (70%), mp 208-209°; $^1$H nmr (DMSO-$d_6$): δ 1.32 (t, J = 7.5 Hz, 3, ethyl $CH_3$), 1.81 (m, 1, $CH_2$), 1.85 (s, 3, acetyl $CH_3$), 2.10 (m, 1, $CH_2$), 3.43 (m, 1, $NCH_2$), 3.66 (m, 1, $NCH_2$), 3.76 (m, 1, $NCH_2$), 3.85 (m, 1, $NCH_2$), 4.25 (q, J = 7.5 Hz, 2, ethyl $CH_2$), 4.28 (m, 1, NCH), 7.18 (m, 2, aromatic H), 7.27 (m, 1, aromatic), 7.32 (s, 1, NH), 7.63 (m, 1, aromatic H), 8.16 (m, 1, aromatic H), 8.79 (s, 1, vinyl H).

*Anal.* Calcd. for $C_{24}H_{22}FN_3O_5 \cdot 1/3\ H_2O$: C, 63.01; H, 4.99; N, 9.19. Found: C, 63.07; H, 4.60; N, 9.10.

1-(3-Aminopyrrolidin-1-yl)-2-fluoro-4-oxo-4*H*-quino[2,3,4-*i,j*][1,4]benoxazine-5-carboxylic Acid Hydrochloride (**18**).

A suspension of the carboxylate **17** (439 mg, 0.9 mmoles) in 20 ml 6 N HCl was heated at 120° for 20 hours. The solvent was removed under reduced pressure. The residues was refluxed in ethanol (20 ml) for 2 hours. It was cooled and the solid was collected by filtration and dried yielding 0.29 g of **18** (69%) mp >250°; $^1$H nmr (DMSO-$d_6$): δ 1.86 (m, 1, $CH_2$), 2.06 (m, 1, $CH_2$), 2.27 (m, 1, $NCH_2$), 3.52 (m, 1, $NCH_2$), 3.62 (m, 3, $NH_2 \cdot HCl$), 3.79 (m, 1, $NCH_2$), 3.89 (m, 1, $NCH_2$), 3.99 (m, 1, NCH), 7.25 (m, 1, aromatic H), 7.35 (m, 2, aromatic H), 7.50 (m, 1, aromatic H), 8.01 (m, 1, aromatic H), 9.11 (s, 1, vinyl H), 8.37 (sb, 1, COOH).

*Anal.* Calcd. for $C_{20}H_{16}FN_3O_4 \cdot HCl \cdot 2/3\ H_2O$: C, 55.89; H, 4.20; N, 9.78. Found: C, 55.97; H, 3.87; N, 9.65.

*In Vitro* Antibacterial Activity.

The *in vitro* antibacterial activity of the test compound was determined by conventional agar dilution procedures. The organisms were grown overnight in brain-heart infusion (BHI) broth (Difco0037-01-6) at 36°. Two-fold dilutions of the stock solution (2,000 μg/ml) of test compound were made in BHI agar to obtain a test concentration ranging from 200 μg/ml - 0.005 μg/ml. The plate was inoculated with approximately $10^4$ organisms. It was then incubated at 36° for 18 hours. The minimal inhibitory concentration (MIC) was the lowest concentration of the test compound that yielded no visible growth on the plate.

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