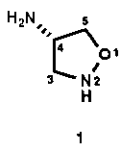
SYNTHESIS OF AN AMINOISOXAZOLIDINE SUBSTITUTED QUINOLONE ACID

Kyoung Soon Kim
The Upjohn Company, Cancer and Infectious Diseases Research,
Kalamazoo, Michigan 49001, USA

Abstract —— New heterocycle aminoisoxazolidine **7** and tetrafluorobenzoic acid are synthesized for the synthesis of a quinolone antibacterial agent. The synthesis of a chiral aminoisoxazolidine substituted quinolone acid, U-82662A, is described.

It has been demonstrated that a wide variety of C-7 heterocycle substituted quinolone acid compounds exhibit potent antibacterial activities.[1] In our search for alternative C-7 heterocyclic substituents, we elected to prepare the novel aminoisoxazolidine **1** and aminopyrazolidine **2** which ultimately led to quinolone antibacterial agents U-82662A and U-83140A, respectively.

The recent disclosure of isoxazolidine containing quinolone analogs by C. B. Ziegler, Jr. et al. prompted us to report our work.[2] In this paper, we describe syntheses of 4-(S)-*t*-butyloxylcarbonylaminoisoxazolidine (*t*-BOC) protected aminoisoxazolidine **1** and 2,3,4,5-tetra-



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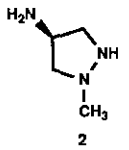

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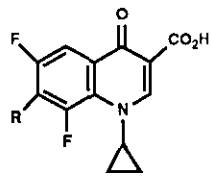
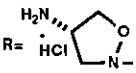
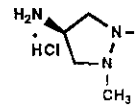


U-82662A: R=



U-83140A: R=

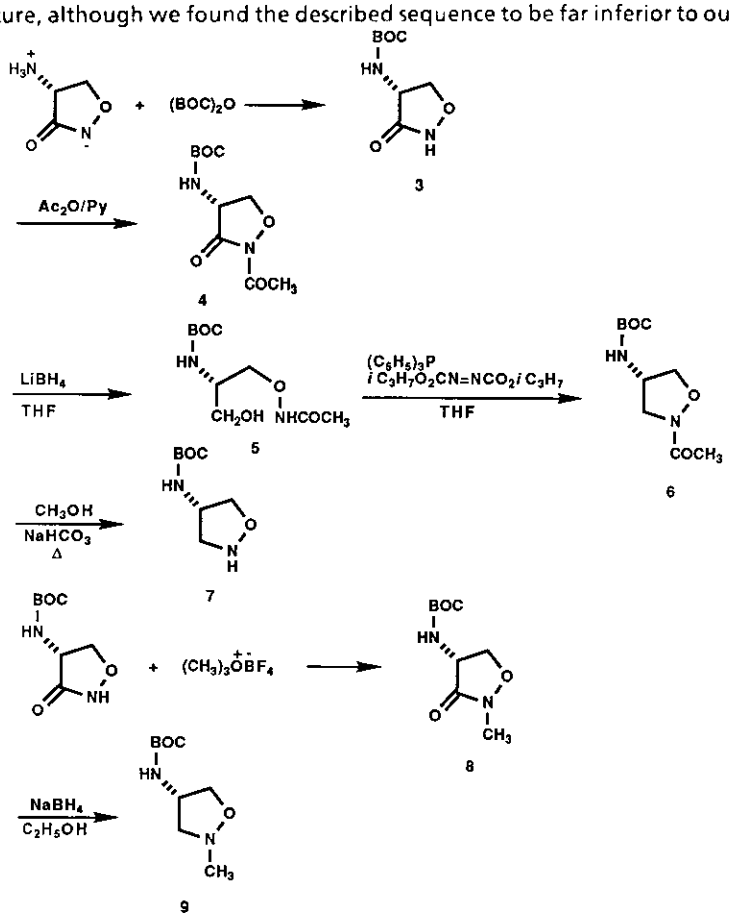


fluorobenzoic acid which led to the synthesis of aminoisoxazolidine containing quinolone acid, 1-cyclopropyl-6,8-difluoro-7-(4-(S)-aminoisoxazolidine-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (U-82662A). The synthesis of aminopyrazolidine analog **2** will be reported in the following paper of this journal.

We chose (R)-(+)-cycloserine as a starting material for the synthesis of 4-(S)-*t*-BOC-aminoisoxazolidine with the hope of an easy reduction of the C-3-carbonyl to methylene at a later stage of the synthesis. We protected the C-4 and ring amino groups with *t*-BOC[3] and acetyl groups, respectively, to produce compound **4**. Without protection of the ring nitrogen reduction of the ring carbonyl under a variety of reaction conditions failed due to the very acidic amino hydrogen. When this hydrogen is replaced by a methyl group, sodium borohydride reduction produces N-methyl-isoxazolidine **9** smoothly.

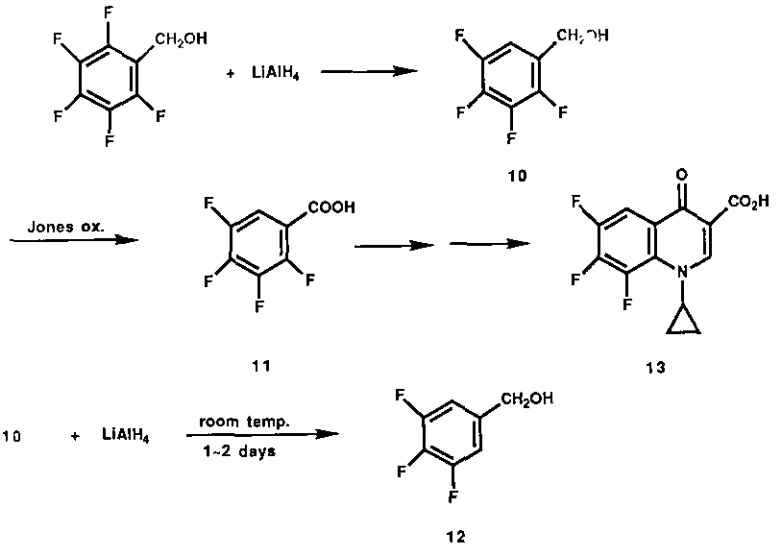
Reaction of **4** with lithium borohydride selectively reduces the ring carbonyl to yield the acyclic compound **5** which was recyclized under Mitsunobu reaction conditions to obtain N-acetylisoxazolidine **6**. Deprotection of the N-acetyl group with methanolic sodium bicarbonate afforded the final desired 4-(S)-*t*-BOC-aminoisoxazolidine (**7**).

Polyfluorinated benzoic acids are key intermediates for building quinolone nuclei, and yet their syntheses often require harsh reaction conditions. We felt pentafluorobenzyl alcohol could serve as a starting material *via* a regioselective intramolecular reductive defluorination. A similar study has been reported in the literature, although we found the described sequence to be far inferior to ours.[4]



Treatment of pentafluorobenzyl alcohol with lithium aluminum hydride reductively removes one fluorine atom at C-2 *via* intramolecular hydride transfer to give *2,3,4,5-tetrafluorobenzyl alcohol* (**10**).

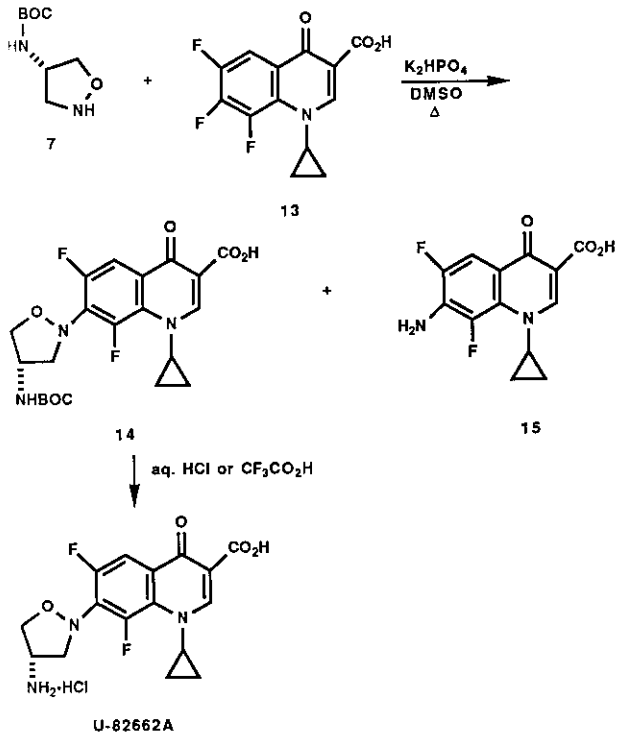
A second fluorine atom can be removed regioselectively *via* another reductive defluorination reaction of *10 to obtain 3,4,5-trifluorobenzyl alcohol* (**12**), although this requires a higher temperature. This temperature dependence allows us to easily limit the reduction at the stage of 2,3,4,5-tetrafluorobenzyl alcohol.[5] Jones oxidation of tetrafluorobenzyl alcohol (**10**) to tetrafluorobenzoic acid (**11**) proceeded smoothly. Conversion of this tetrafluorobenzoic acid to 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**13**) was achieved by following standard literature procedures.[6]



Coupling of isoxazolidine **7** with trifluoroquinolone acid **13** in the presence of potassium dibasic phosphate afforded C-7 aminoisoxazolidine substituted quinolone acid **14** in 81% yield along with C-7 aminoquinolone acid **15** in 18% yield based on quinolone acid **13**.

Interestingly, when the coupling reaction of **7** with the ethyl ester of quinolone acid **13** was attempted under the same reaction conditions, the reaction proceeded very sluggishly and afforded a complex mixture of products. We speculate that the C-3 carboxylic acid may activate the C-7 carbon more toward nucleophilic substitution *via* intramolecular hydrogen bonding with the C-4 carbonyl.[6]

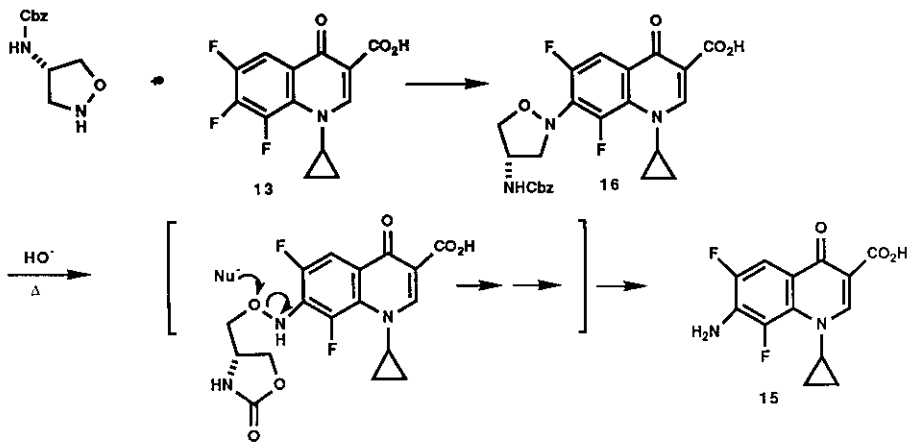
Deprotection of the *t*-BOC group of **14** by acid yielded the final quinolone acid U-82,662A.



U-82662A

The mechanism of the decomposition of **14** to C-7-aminoquinolone **15** is not clear. We have observed this kind of decomposition reaction frequently with C-7 alkoxyamino-containing quinolone compounds during our studies.

For instance, we originally prepared 4-(S)-N-benzyloxylcarbonyl (Cbz)-amino-isoxazolidine before 4-(S)-*t*-BOC-aminoisoxazolidine and coupled that with quinolone **13** to obtain Cbz-protected quinolone **16**.



However, we were unable to deprotect the Cbz group to obtain U-82662, which forced us to change the protecting group to *t*-BOC. Under acidic conditions, the hydrolysis reaction of the Cbz-group was very slow and produced a mixture of compounds.

On the other hand, under basic conditions, we obtained C-7-aminoquinolone **15** as a sole product.

We believe that the decomposition occurs *via* ring opening by the initially formed carbamate anion followed by the intra- or intermolecular nucleophilic attack on the oxygen atom.

Chiral aminoisoxazolidine containing quinolone U-82662A displays a very potent antibacterial activity.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on a Perkin Elmer 1750 FTIR or were obtained by the Physical and Analytical Chemistry department at The Upjohn Company as were all the mass spectra. Nmr spectra were recorded on a Bruker AM 300 operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C. Where DEPT editing of the carbon spectra was done, the multiplicities that would have been seen in the off-resonance spectra are indicated.

Tetrahydrofuran was distilled from sodium and benzophenone. Dimethylformamide and dimethyl sulfoxide were stored over molecular sieves. Other solvents and reagents were used as received from commercial sources. All reactions were run under a dry nitrogen atmosphere unless otherwise indicated. Column chromatography was performed using Kieselgel 60 silica gel (230-400 mesh).

4-(R)-t-BOC-Cycloserine (**3**).

To a solution of R-cycloserine (25 g, 245 mmol) in 250 ml of 1N aq. NaOH at 0°C (t-BOC)$_2$O (55 g, 252 mmol) and 250 ml of 1N aq. NaOH were added simultaneously over 10 min with good stirring. The reaction mixture was stirred at 0°C for 4 days. After 4 days the mixture was washed with Et_2O (200 ml) and the aqueous layer was acidified with 6N aq. HCl to pH ~4. This acidified aqueous solution was washed with methylene chloride (6x300 ml). The methylene chloride solution was dried over $MgSO_4$, concentrated and the residue was triturated with Et_2O to obtain the white pure solid product (22 g). From the mother liquor, the second crop 4.5 g, and the third crop 3.2 g were obtained. Total 29.7 g, 60% yield, mp 141-143°C ; ^{1}H nmr ($CDCl_3$) δ:1.45 (s, 9H), 4.10 (dd, but looks like a triplet with J = 8.6 Hz, one of C-5-H), 4.60~4.75 (m, 2H), 5.50 (broad, 1H), 9.90 (very broad, 1H); ^{13}C nmr ($CDCl_3$) δ: 28.2 (q), 52.8 (d), 74.8 (t), 80.8 (s), 155.7 (s), 170.8 (s); ir (Nujol) cm^{-1}: 2925, 1711, 1689; ms (FAB): $C_8H_{15}N_2O_4$ [M + H] + : 203

4-(R)-*t*-BOC-Amino-2-N-acetylisoxazolidin -3-one (**4**).

Acetic anhydride (18.5 ml) was added to a solution of C-4-*t*-BOC-cycloserine (18.5 g, 91.6 mmol) in methylene chloride (130 ml) and pyridine (30 ml) at 0°C and the reaction mixture was allowed to stay overnight at 0°C. It was concentrated under reduced pressure and the residue was dissolved in EtOAc (250 ml), which was washed with H_2O (100 ml). The organic phase was dried over $MgSO_4$, concentrated and the product residue was triturated with Et_2O (60 ml) to obtain 18 g of white pure solid product after drying. Yield 80.5%, mp 94-96°C; ^1H nmr ($CDCl_3$) δ: 1.46 (s, 9H), 2.48 (s, 3H), 4.18 (dd, $J_1 = 9$ Hz, $J_2 = 6$ Hz, one of C-5-H), 4.70~4.80 (m, 2H), 5.20 (s, broad, 1H); ^{13}C nmr ($CDCl_3$): δ 23.1 (q), 28.2 (q), 53.6 (d) 72.1 (t), 81.0 (s), 155.0 (s), 164.0 (s), 167.0 (s); ir (Nujol) cm^{-1}: 2925, 1760, 1726, 1718, 1691; $[\alpha]_D = +66°C$ (C = 0.9 in CH_3OH); hrms (FAB) calcd for $C_{10}H_{17}N_2O_5$ [M + H] + : 245.1137; found: 245.1139.

2-(S)-*t*-BOC-Amino-3-N-acetylaminooxypropanol (**5**).

Lithium borohydride (3.19 g, 14.6 mmol) was added with stirring to a solution of **4** (18 g, 73.8 mmol) in anhydrous THF (180 ml) at 0°C. The reaction mixture was stirred for 2.5 h at 0°C and then acetone (25 ml) was added slowly followed by acetic acid (25 ml). It was concentrated under reduced pressure and the residue was passed through a column on silica gel eluting with 1:1/CH_2Cl_2:EtOAc followed by 450:450:100/CH_2Cl_2:

EtOAc:MeOH to obtain the desired product as a viscous material (11 g, 60% yield); ^1H nmr ($CDCl_3$) δ: 1.40 (s, 9H), 1.90 (s, 3H), 3.60~4.00 (m, 5H), 5.78 (d, J = 7.8 Hz), 10.40 (very broad, 1H); ^{13}C nmr ($CDCl_3$) δ: 19.3 (q), 28.0 (q), 49.8 (d), 60.1 (t), 74.9 (t), 79.6 (s), 156.2 (s), 168.4 (s); ir (Nujol) cm^{-1}: 2979, 1709, 1682 ; hrms (FAB) calcd for $C_{10}H_{21}N_2O_5$ [M + H] + : 249.1450; found: 249.1456.

4-(S)-*t*-BOC-Amino-2-N-acetylisoxazolidine (**6**).

To a solution of acyclic hydroxy compound **5** (7.6 g, 30.6 mmol) and triphenylphosphine (8.84 g, 33.6 mmol) in anhydrous THF (100 ml) at 0°C diisopropyl azodicarboxylate (6.3 ml, 32.1 mmol) was added with stirring. It was stirred at 0°C overnight and concentrated under reduced pressure. The residue was passed through a column on silica gel eluting with 400:200:200/C_6H_{12}:CH_2Cl_2:EtOAc followed by 400:200:200:20/C_6H_{12}:CH_2Cl_2:EtOAc:EtOH to obtain 5.1 g of the white solid product (72% yield), mp 72-75°C; ^1H nmr ($CDCl_3$) δ: 1.45 (s, 9H), 2.10 (s, 3H), 3.52 (dd, $J_1 = 12$ Hz, J_2 = very small, one of C-3-H), 3.87~4.06 (m, 3H), 4.64 (m, 1H of C-4), 5.10 (broad, -NH); ^{13}C nmr (DMSO-d_6) δ: 19.9 (q), 28.0 (q), 49.6 (t), 52.8 (d), 78.2 (s), 73.5 (t), 155.2 (s), 171.7 (s); ir (neat) cm^{-1}: 3300, 1710, 1688, 1528; ms (FAB): calcd for $C_{10}H_{19}N_2O_4$ [M + H] + : 231.1345; found: 231.1350.

4-(S)-t-BOC-Aminoisoxazolidine (7).

A mixture of N-acetylisoxazolidine **6** (3 g, 13 mmol) and $NaHCO_3$ (1 g, 12 mmol) in methanol (15 ml) was heated at reflux temperature for 4h.The mixture was concentrated under reduced pressure and purified by silica gel column chromatography eluting with 1:1/CH_2Cl_2:EtOAc followed by 450:450:100/CH_2Cl_2: EtOAc:MeOH to obtain the desired product as a white solid (1.9 g, 77% yield), mp 95-97°C; ^1H nmr ($CDCl_3$) δ: 1.40 (s, 9H), 3.05 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1H), 3.30 (m, 1H), 3.70 (m, 1H), 4.00 (m, 1H), 4.50 (m, 1H), 5.67 (broad, 1H), 6.10 (d, J = 7 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ: 28.3 (q), 55.6 (t), 55.8 (d), 76.0 (t), 80.0 (s), 155.0 (s); ir (neat) cm^{-1} 3331, 2975, 1688; hrms (FAB): calcd for $C_8H_{17}N_2O_3$ [M + H]+: 189.1239; found: 189.1240.

2,3,4,5-Tetrafluorobenzyl alcohol (10).

To a stirred solution of pentafluorobenzyl alcohol (19.8 g, 100 mmol) in anhydrous THF (100 ml) at -78°C, a slurry of $LiAlH_4$ in THF (3.8 g, 100 mmol in 200 ml THF) was added slowly over 15 min *via* a cannula. After a couple of minutes, the reaction mixture was put in an ice bath and it was stirred for 30 min at an ice bath temperature. Acetone (15 ml) was added slowly to the reaction mixture and it was stirred for 10 min at 0°C and then 200 ml of 3N aq. HCl was added slowly. After the addition of aq. HCl it was stirred at room temperature until the mixture becomes a clear solution. Here were added a small amount of NaCl and EtOAc (300 ml). The organic layer was taken and the aqueous layer was washed with EtOAc (200 ml). The combined organic layer was washed with aq. $NaHCO_3$ (150 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Distillation of the residue afforded an oily product (15.45 g, distilled at 107~109°/22 mm Hg) in 86% yield; ^1H nmr ($CDCl_3$) δ: 2.78 (s, 1H), 4.71 (s, 2H), 7.05 (m, 1H); ^{13}C nmr ($CDCl_3$) δ: 57.9 (t), 110 (C-6, m), 124 (C-1, m) 145 (C-2, m, $J_{C2\text{-}C2F}$ = 253 Hz), 140 (C-3 and C-4, m), 148 (C-5, m, $J_{C5\text{-}C5F}$ = 247 Hz); ir (neat) cm^{-1}: 3317, 1527, 1490; hrms (m/z): calcd for $C_7H_4OF_4$ [m/z]+: 180.0198; found: 180.0197.

2,3,4,5-Tetrafluorobenzoic acid (11).

To a solution of tetrafluorobenzyl alcohol (18.0 g, 100 mmol) in 250 ml of acetone at 0°C, Jones reagent (75 ml of 2.4 M CrO_3 solution) was added dropwise with good stirring. After an hour at 0°C, the reaction mixture was warmed to room temperature and it was stirred for 2 h. The reaction mixture was quenched by adding 25 ml of isopropanol slowly and it was stirred at room temperature for 30 min. The green colored solid was filtered through a celite, washed with acetone and the filtrate solution was concentrated under reduced pressure. The residue was washed with CH_2Cl_2 (500 ml)/H_2O (350 ml) and the organic layer was taken. The aqueous layer was washed one more time with CH_2Cl_2 (200 ml), washed with brine (300 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The slightly greenish colored residue was distilled to obtain the desired product (17.5 g, 135~137°C/23 mmHg) in 90% yield.

Upon standing at room temperature, it was solidified, mp 81-83°C; ^{1}H nmr ($CDCl_3$) δ: 7.70 (m, 1H), 11.90 (s, COOH); cmr ($CDCl_3$) δ: 113 (m, C-6), 140-150 (5 carbons, m), 167 (s); ir (neat) cm^{-1}: 2870 (broad), 1686, 1489; hrms (m/z): calcd for $C_7H_2F_4O_2$ [m/z] + : 193.9991; found: 193.9981.

1-Cyclopropyl-6,8-difluoro-7-[4-(S)-*t*-BOC-aminoisoxazolidin-2-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**14**).

A mixture of *t*-BOC-aminoisoxazolidine **7** (1.57 g, 8.35 mmol) quinolone acid **10** (1.57 g, 5.5 mmol) and sodium dibasic phosphate (3 g) in 10 ml of DMSO was heated at 110~120°C for 4 h. It was cooled to room temperature and here was added water (10 ml) followed by MeOH (10 ml). It was stirred for 10 min and the solid was filtered, washed with a small amount of H_2O and CH_3OH and dried to obtain 1.82 g of the pure desired product. The filtrate solution was concentrated and water (20 ml) was added to the residue and it was stirred for one hour. The solid was filtered and this solid was again digested in 20 ml of Me OH which provided the second crop of pure product (200 mg) after filtering and drying. The filtrate aqueous solution was acidified with 2N aq. HCl which caused the precipitation of the pure solid product. This solid was filtered and dried to obtain 280 mg of C-7-amino compound **12**. Total 2.025 g of **11**. Yield 81% based on quinolone **10**, mp 214-217°C decomposed;^{1}H nmr (DMSO-d_6) δ:1.20 (m, 4H), 1.38 (s, 9H), 3.50~4.60 (4 sets of multiplet peaks for total 6H), 7.48 (d, 1H), 7.85 (dd, J_1 = 12 Hz, J_2 = 1.5 Hz, 1H), 8.70 (s, 1H), 14.60 (broad, 1H); ir (Nujol) cm^{-1}: 2953, 2922, 2854, 1728, 1681; ms (FAB): calcd for $C_{21}H_{24}N_3O_6F_2$ [M + H] + : 452.1633; found: 452.1632.

1-Cyclopropyl-6,8-difluoro-7-(4-(S)-aminoisoxazolidin-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (U-82662A).

A heterogeneous mixture of *t*-BOC-protected quinolone **11** (160 mg) in CH_3OH (10 ml), THF (4 ml) and 6N aq HCl (3 ml) was briefly heated to make it a homogeneous solution. The clear homogeneous solution was stirred for 4 h at 50~60° C. It was mostly concentrated and ethyl acetate (15 ml) was added to the residue which resulted in a desired pure product precipitation to obtain 89 mg of U-82662A after drying, mp 210~214°C decomp.; pmr (DMSO-d_6) δ: 1.20 (m, 4H), 3.80~4.50 (m, 6H), 7.91 (d, J = 12 Hz, 1H), 8.70 (s, 1H), 14.50 (s, 1H); ir (Nujol) cm^{-1}: 2885, 1728, 1685; hrms (FAB): calcd for $C_{16}H_{16}N_3O_4F_2$ [M + H]$^+$: 352.1109; found: 352.1116.

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5. The effect of the number of fluorine atoms of the aromatic ring toward a nucleophile is very large. In fact, we observed that the reduction of pentafluorobenzene is faster than the reduction of tetrafluorobenzyl alcohol under the same reaction conditions despite the latter is an intramolecular reaction.
6. Chemical shift of the carboxylic acid proton (δ = 14.3 ppm in DMSO-d_6) of compound **13** indicates that it is strongly hydrogen bonded to C-4 carbonyl.
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