Survey of Carbon- and Proton-Fluorine Coupling Constants in Fluoro-quinolone Carboxylic Acid Derivatives

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Abstract : For fluoro-quinolone carboxylic acid derivatives, one bond carbon-fluorine coupling constants are ranged from 249 Hz to 257 Hz regardless of positions. But geminal and vicinal carbon-fluorine coupling constants vary according to positions, namely, geminal coupling constants are ranged from 6 Hz to 23 Hz, and vicinal coupling constants are ranged from 1.9 Hz to 7 Hz. In cases of proton-fluorine couplings, three bond coupling constants are ranged from 9 Hz to 10.3 Hz, and four bond coupling constants are ranged from 6 Hz to 8.3 Hz.(Received September 21, 1998; accepted November 19, 1998)

Introduction

Shielding effects caused by halogens on chemical shifts of ^{13}C NMR spectroscopy are known. While in cases of fluorine, chlorine and bromine, deshieldings occur, in case of iodine, a shielding does. Deshieldings depend on electronegativities, so that carbon-13 chemical shifts by fluorine substituents are shifted farthest to down field. In addition to chemical shifts, carbon-fluorine coupling constants have been studied. Like carbon-proton and carbon-carbon, one bond carbon-fluorine couplings depend on the s character of carbon-fluorine hybridization. In cases of vicinal couplings, the coupling constants are related to the dihedral angle, Φ, as following :[1]

$$^{3}J_{CF} = 5.5 \ cos2\Phi + 5.5 \tag{1}$$

For the survey of carbon- and proton-fluorine coupling constants such as $^{1}J_{CF}$, $^{2}J_{CF}$ and $^{3}J_{CF}$, fluoro-quinolone carboxylic acid derivatives are selected, because those compounds can be precursors of Y26611, ciprofloxacine or norfloxacine, which show a good effect of antimicrobial chemotherapy.[2] When fluoro-quinolone carboxylic acid derivatives are synthesized, the knowledge of carbon- and proton-fluorine coupling constants may help assignments of NMR data for the conformation of the synthetic process. Especially, fluorination of C6 position is required for antibacterial activities of quinolones, and that of C7 position makes a substitution with amines easy. Therefore, three common intermediate **1-3**, whose C6 position is fluorinated, are synthesized and studied for the

survey of carbon- and proton-fluorine coupling constants (Scheme 1).

Experimental Methods

NMR spectra were obtained on a Bruker DPX 400 (9.4 T) instrument in a 5 mm tube at 298 K. Samples were dissolved in 500 uL of deuterated solvents, CF_3COOD and DMSO-d_6 until saturation. Chemical shifts for all spectra were indirectly referenced to TMS. In case of the ^{1}H-NMR experiments, 16 transients were acquired with a 1 sec relaxation delay using
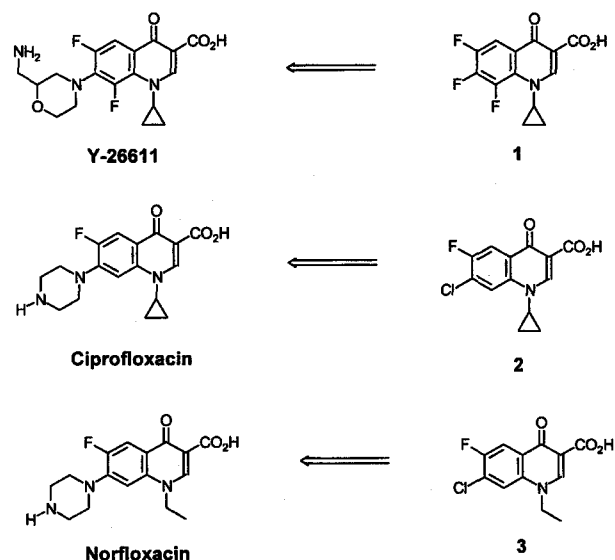
Scheme 1. Quinolone nuclei 1, 2, 3 and their corresponding clinical antibiotics.

2 K data point, and 90° pulse was 9.7 μsec, spectral width, 200 Hz. For the ¹³C-NMR and DEPT experiments, 3,000 transients were acquired with a 2 sec relaxation delay using 4 K data points, and 90° pulse was 9.8 usec, spectral width, 20,000 Hz. The COSY spectrum was collected with the magnitude method. 128 blocks were collected with spectral width of 4,200 Hz, and 16 scans were accumulated for each block with free induction decays of 2048 data point. 16 dummy scans were used, and an acquisition time of 0.25 sec was employed. The time domain data were multiplied in the t1 and t2 dimension by a squared sine bell with phase shift of 0 and were zero-filled to obtain 2 K x 2 K real data points. The HMQC spectrum and the HMBC spectrum were collected with the methods as described by Bax[3] and Summers,[4] respectively. 256 blocks were collected with spectral width of 4,000 Hz of t2 dimension, and that of 22,000 Hz of t1 dimension. The number of scans for each block was 128 and data points of t2 dimension were 1024. Dummy scans were 16, and an acquisition time, 0.12 sec. The time domain data were multiplied in the t1 and t2 dimension by a sine bell, and were zero-filled to obtained 1 K x 1 K real data points. The delay for the long ranged coupling of HMBC was 70 msec.

All computational calculations were performed using msi software (San Diego, CA) on Silicon Graphics INDY R4400 workstation. The dihedral angle was calculated with Discover module of InsightII, where the consistent-valence forcefield (CVFF) was used for 500 psec. Analytical thin-layer chromatography was performed by using precoated silica gel 60 F₂₅₄ plates and the silica gel used for flash column chro-

matography was supplied from Merck (230~400 mesh, 60 Å).

General procedures for N-cyclopropyl quinolone nuclei 1 and 2. N-cyclopropyl quinolones 1 and 2 were prepared according to literature[5,6] methods as shown in scheme 2.

Ethyl 2,3,4,5-tetrafluoro-benzoyl acetate (6a)

16.2 g of diethyl malonate (102 mmol) and 10.7 g of magnesium ethoxide (96 mmol) was added to 100 mL of ether under ice-bath. The mixture was refluxed for 5 h and cooled to room temperature. To the cooled reaction mixture, was added (17.5 g, 90 mmol) of 2,3,4,5-tetrafluorobenzoyl chloride, prepared from 2,3,4,5-tetrafluorobenzoic acid 4a (17.5 g, 90 mmol) and SOCl₂ in 50 mL of ether, and was stirred overnight. The reaction mixture was poured into 50 mL of 10%-H₂SO₄ and was stirred. After 1 h, the mixture was extracted with ether (50 mL x 3). Combined organic layers were washed with saturated NaHCO₃ solution and dried under MgSO₄. After filtration, the filtrate was evaporated to give an oil-residue. To the residue 130 mL of 5%-H₂SO₄ was added, and mixture was refluxed for 7 h. After cooling, the acidic solution was extracted with ether (50 mL x 3). Organic layer was washed with saturated NaHCO₃ solution and dried under MgSO₄. Filtration and evaporation gave desired product 6a in 69% yield (16.4 g); m.p. 48~49°C. The same procedures were applied to prepare 6b, starting with 2,4-dichloro-5-fluorobenzoic acid 4b. yield 72%; m.p. 45~46°C.

Ethyl 3-(cyclopropylamino)-2-(2,3,4,5-tetrafluorobenzoyl) acrylate (7a)

A mixture of benzoyl ester 6a (15.4 g, 58.3 mmol), triethylorthoformate (18 mL) and acetic anhydride (22 mL) was refluxed for 2 h and evaporated to give a residue. The residue was dissolved into CH₂Cl₂ (70 mL). To a solution was added cyclopropylamine (6.6 g, 116 mmol) and stirred for 3 h. The solvent was evaporated to dryness and crystallized from 30% ether in n-hexane solution, yielding 17.4 g of 7a (91%); m.p. 65°C.

The same procedures were applied to prepare 7b, starting with 6b. yield 87%; m.p. 89~90°C.

1-Cyclopropyl-6,7,8,-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (1)

A 60% NaH in oil suspension (556 mg, 11.4 mmol) was slowly added to a cold solution of acrylate 7a (3.63 g, 10.5 mmol) in 30 mL of dimethoxyethane. The mixture was heated at 90°C for 2 h and cooled. 100 mL of H₂O was added, and resulting precipitate was filtered, washed with water. This quinolone ester 8a was suspended in 40 mL of THF. 25 mL of 1 N NaOH was added to the suspension, and the mixture was refluxed for 2 h. After cooling, 100
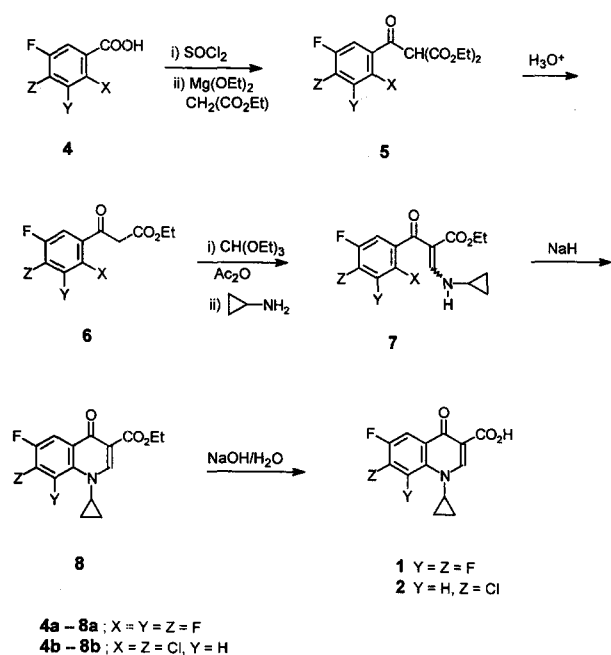
Scheme 2. Synthesis of N-cyclopropyl quinolone nuclei 1 and 2.

mL of water was added followed by the addition of 4 mL of acetic acid. Resulting precipitate filtered off, washed with H_2O, ether and dried to give desired quinolone 1 (2.5 g, 84%); m.p. 228~229°C.

The same procedures were applied to prepare 2, starting with 7b. yield 92%; m.p. 242~243°C.

General procedures for N-ethyl quinolone nucleus 3

N-cyclopropyl quinolone 3 was prepared according to literature[7] methods as shown in scheme 3.

Ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (11)

4.38 g (30 mmol) of 3-chloro-4-fluoroaniline (9) and 6.48 g of diethyl ethoxymethylenemalonate was added to 40 mL of ethanol and the mixture was heated at 120°C for 3 h. The solvent was evaporated to give a malonate 10 which was used in the next reaction without purification (m.p. 54~56°C). The crude malonate 10 was added to 60 mL of phenyl ether and refluxed for 2 h. After cooling the reaction mixture, resulting precipitate was filtered off and washed with benzene and n-haxene to give quinolone ester 11 (8.95 g, 65%); ^{1}H-NMR (CF_3COOD) δ 1.57 (3H, t, CH_3), 4.73 (2H, q, CH_2), 8.35 (1H, d), 8.37 (1H, d), 9.35 (2H, s).

### 7-Chloro-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (3)

4.05 g (15 mmol) of quinolone ester 11 and 6 mL of

ethyliodide (75 mmol) was added to 40 mL DMF. To the above solution, 5.18 g (37.5 mmol) of K_2CO_3 was added and resulting suspension was heated at 100°C for 10 h. After cooling, the mixture was evaporate to dryness and partitioned into 50 mL of CH_2Cl_2 and 50 mL of H_2O. The separated organic layer was dried ($MgSO_4$), filtered, and filtrate was evaporated to give an ester 12 (m.p. 141~143°C). The crude ester 12 was used in the next hydrolysis reaction without purification. A mixture of crude ester 12 (2.16 g, 7.3 mmol) and 2 N NaOH solution (30 mL, 60 mmol) was refluxed for 3 h. After cooling, the reaction mixture was acidified to pH = 3, and resulting precipitate filtered off, washed with H_2O, and dried to give desired quinolone 3 (3.52 g, 87%). m.p. 283~285°C; ^{1}H-NMR (CF_3COOD) δ 1.81 (3H, t, CH_3), 4.93 (2H, q, CH_2), 8.37 (1H, d), 8.41 (1H, d), 9.38 (2H, s).

Results and Discussion

For N-cyclopropyl derivatives 1 and 2, the requisite compound 5 was prepared by the condensation of ethyl ethoxy-magnesium malonate with corresponding acid chloride from acid 4. After hydrolysis, resulting ketoester 6 was treated with ethyl orthoformate in acetic anhydride and the product, without isolation, was allowed to react with cyclopropylamine to give the enamineketoester 7. Heating of 7 with sodium hydride gave desired quinolone ester 8 which was hydrolyzed with aqueous NaOH to give 1 and 2 respectively.

For N-ethyl derivative 3, 3-chloro-4-fluoroaniline (9) was heated with diethyl ethoxymethylene malonate to give malonate 10 which, without purification, was cyclized to quinoline ester 11. Alkylation of 11 in K_2CO_3/DMF with ethyliodide gave 12 in good yield. The N-ethylester 12 was hydrolyzed with aqueous NaOH to produce the carboxylic acid 3, whose N-ethyl-4-quinolone structure was confirmed by ^{1}H-NMR, ^{13}C-NMR, DEPT, HMQC and HMBC. The numbering of 3 is shown in Fig. 1, and chemical shifts of ^{13}C, multiplicities obtained from DEPT, chemical shifts of ^{1}H attached to ^{13}C obtained from HMQC, and complete assignments are listed in Table 1. As shown in Fig. 2, the ^{13}C-NMR spectrum gives information of several carbon-fluorine couplings such as $^1J_{C6-F}$
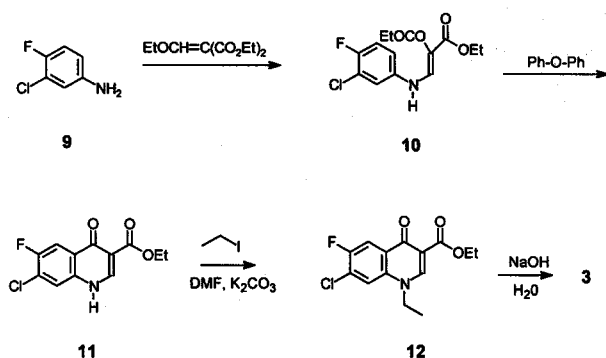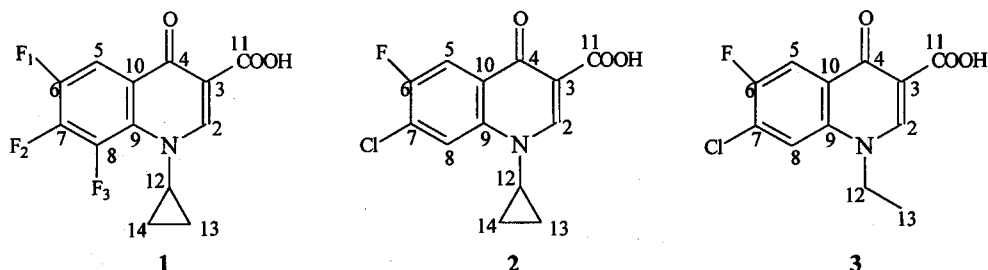
Scheme 3. Synthesis of N-ethyl quinolone nucleus 3.

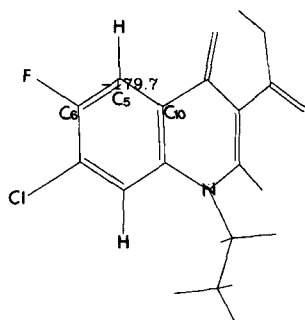Fig. 1. The structures and numberings of the compounds 1, 2 and 3.

Table 1. The NMR data and assignments of the compound 3.

δ_c (JCF/Hz)	CH$_n$ DEPT	δ_H of directly attached protons, HMQC	assignments
15.0	q	1.40(m, 7.1, 1.7)	C13
49.8	t	4.61(m)	C12
108.2	s	8.20(d, 9.1)	C3
112.4(d, 22.8)	d	8.44(d, 6.1)	C5
121.4	d		C8
126.4(d, 6.9)	s		C10
127.8(d, 20.2)	s		C7
136.6	s		C9
150.1	d	9.06	C2
155.3(d, 249.5)	s		C6
165.9	s		C11
176.9	s		C4

(d: doublet; m: multiplet)
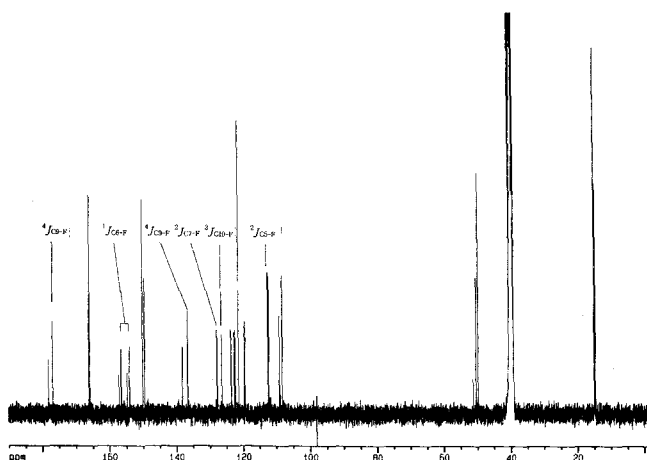
Fig. 2. The ^{13}C-NMR spectrum of the compound 3.

(249.5 Hz), $^2J_{C5-F}$ (22.8 Hz), $^2J_{C7-F}$ (20.2 Hz) and $^3J_{C10-F}$ (6.9 Hz), and proton-fluorine couplings such as $^3J_{H5-F}$ (9.1 Hz) and $^4J_{H8-F}$ (6.1 Hz). According to the equation [1], the dihedral angle of F-C6-C5-C10 is calculated to be 37.6°, and the value of the dihedral angle obtained from molecular modeling is -179.7° as shown in Fig. 3. The fact that there is a resonance character in this compound is supposed to be the reason why the value of molecular modeling does not meet that of the equation [1].

Fig. 3. The dihedral angle of F-C6-C5-C10 of 3 obtained from molecular modeling.

Table 2. The NMR data and assignments of the compound 1.

δ_c (JCF/Hz)	CH$_n$ DEPT	δ_H of directly attached protons HMQC	assignments
13.92	t	1.20(m)	C13 or C14
13.99	t	1.20(m)	C13 or C14
39.5	d	4.15(m)	C12
113.0	s	8.15(ddd, 10.2, 8.2, 2.2)	C3
113.5(dd, 19.1, 3.81)	d		C5
127.9(dd, 6.4, 1.9)	s		C9
134.4(t)	s		C10
148.0(ddd, 257.0, 14.0, 2.5)	s		C8
149.0(dt, 254.1, 17.2, 15.6)	s		C7
153.5(dd, 249.3, 12.2)	s		C6
156.6	d	8.75(s)	C2
170.5	s		C11
181.2	s		C4

(s: singlet; d: doublet; t: triplet; m: multiplet)

Table 3. The NMR data and assignments of the compound 2.

δ_c (JCF/Hz)	CH$_n$ DEPT	δ_H of directly attached protons HMQC	assignments
13.3	t	1.27(m)	C13, C14
41.9	d	3.86(m)	C12
113.1	s	8.18(d, 9.0)	C3
117.4(d, 22.6)	d	8.52(d, 6.2)	C5
126.8	d		C8
130.5(d, 6.6)	s		C10
132.6(d, 20.3)	s		C7
143.8	s		C9
154.8	d	8.75	C2
160.0(d, 249.4)	s		C6
170.9	s		C11
182.0	s		C4

(d: doublet; m: multiplet)

Tables 2 and 3 list the data obtained from the same experiments carried out for the compounds 1 and 2, respectively, and Fig. 1 shows the numberings of the compounds 1 and 2. The ^{13}C-NMR spectrum of the compound 1 shown in Fig. 4 gives information of several carbon-fluorine couplings such as $^1J_{C6-F1}$ (249.3 Hz), $^1J_{C7-F2}$ (254.1 Hz), $^1J_{C8-F3}$ (257.0 Hz), $^2J_{C6-F2}$ (12.2 Hz), $^2J_{C7-F1}$ (17.2 Hz), $^2J_{C7-F3}$ (15.6 Hz), $^2J_{C8-F2}$ (14.0 Hz), $^2J_{C5-F1}$ (19.1 Hz), $^2J_{C9-F3}$ (6.4 Hz), $^3J_{C8-F1}$ (2.5 Hz), $^3J_{C5-F2}$(3.8 Hz) and $^3J_{C9-F2}$(1.9 Hz), and proton-fluorine couplings such as $^3J_{H5-F1}$ (10.2 Hz), $^4J_{H5-F2}$ (8.2 Hz) and $^5J_{H5-F3}$ (2.2 Hz). Likewise, the ^{13}C-NMR spectrum of the compound 2 shown in Fig. 5 gives information of several carbon-fluorine couplings such as $^1J_{C6-F}$ (249.4 Hz), $^2J_{C5-F}$ (22.6 Hz), $^2J_{C7-F}$ (20.3 Hz) and $^3J_{C10-F}$ (6.6 Hz), and proton-fluorine couplings such as $^3J_{H5-F}$ (9.0 Hz) and $^4J_{H8-F}$ (6.2 Hz). While C13 and C14 in ^{13}C-NMR data of 2 have the same chemical shift at 13.3 ppm, those of 1 show two separated peaks at 13.92 and 13.99 ppm. It may be caused from the steric hindrance by fluorination at C8 of 1.

Comparing carbon-fluorine couplings of the compound 2 with those of the compound 3, errors ranged from 0.04% to
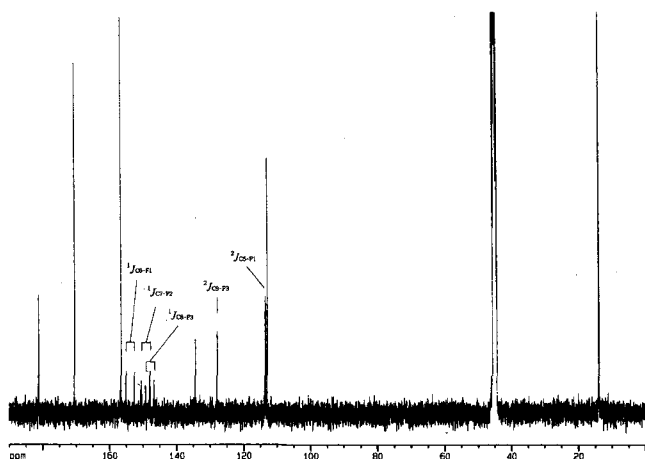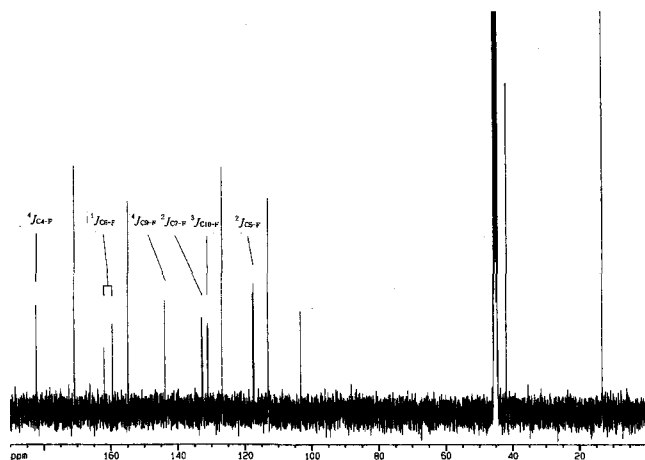
Fig. 4. The ¹³C-NMR spectrum of the compound 1.

Fig. 5. The ¹³C-NMR spectrum of the compound 2.

4% are observed. A comparison of proton-fluorine couplings of **2** to those of **3** gives the same result. In the case of **1**, however, while one bond couplings show similar results, geminal and vicinal couplings show different results. It can be explained because the compound **1** includes three fluorines and **2** and **3**, chlorine.

As a result, for fluoro-quinolone carboxylic acid derivatives, one bond carbon-fluorine coupling constants are ranged from 249 Hz to 257 Hz regardless of the number of bonds. But

geminal and vicinal carbon-fluorine coupling constants varie according to the number of bonds, namely, geminal coupling constants are ranged from 6 Hz to 23 Hz, and vicinal coupling constants are ranged from 1.9 Hz to 7 Hz. In cases of proton-fluorine couplings, three bond coupling constants are ranged from 9 Hz to 10.3 Hz, and four bond coupling constants are ranged from 6 Hz to 8.3 Hz.

Acknowledgement

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Fluoro-quinolone Carboxylic Acid 유도체로부터 탄소-불소 및 수소-불소간 Coupling Constants의 조사

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초 록 : Fluoro-quinolone carboxilic acid 유도체에서, 탄소-불소간 one bond coupling constants는 위치와 무관하게 249 Hz에서 257 Hz 사이의 값을 갖는데, geminal 및 vicinal coupling constants는 위치에 따라 그 값의 차이가 많이 생긴다. 즉, geminal coupling constants는 6 Hz에서 23 Hz의 값을 보이고 vicinal coupling constants는 1.9 Hz에서 7 Hz의 값을 보인다. 또한 수소-불소간 three bond coupling constants는 9 Hz에서 10.3 Hz의 값을 보이고, four bond coupling constants는 6 Hz에서 8.3 Hz의 값을 보인다.

찾는말 : carbon-fluorine coupling constants, proton-fluorine coupling constants, fluoro-quinolone carboxylic acid derivatives
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