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NMR Spectroscopic Study of Quinolone Carboxylic Acid Derivatives

Dongsoo Koh[1], Inwon Lee, Jongmin Park, Hyeseung Lee and Yoongho Lim*

Department of Applied Biology and Chemistry, Konkuk University and
[1]Department of Applied Chemistry, Dongduk Women's University
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Abstract: Authors synthesized common intermediates which are applicable for potential antibiotics. Their complete ^{13}C and ^{1}H NMR chemical shift data as well as carbon- and proton-fluorine coupling constants are reported. The knowledge of proton- and carbon-fluorine coupling constants may help one assign the NMR data of the fluorinated quinolone derivatives. These results agree with the data published previously.

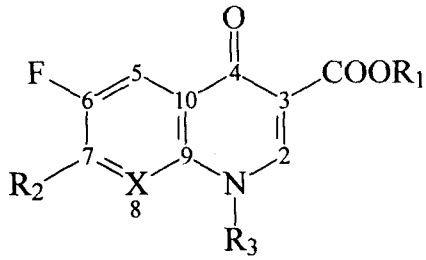
INTRODUCTION

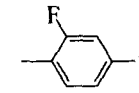
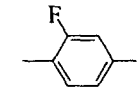
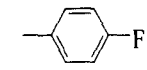
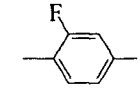
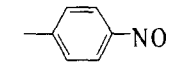
Since nalidixic acid, which shows a good antibacterial effect on Gram-negative bacteria, was introduced into theraphy in 1963, a large number of its analogues have been synthesized and evaluated as antibacterial agents. These agents share several common structural features among which are a fluorine atom at C6, a basic group such as piperazine at C7, and a cycloproply or ethyl group or fluorophenyl group at the quinolone ring nitrogen. Also C8 could be CH, CF or N as shown in Table 1. We synthesized common intermediates (Table 1) which are applicable for potential antibiotics such as Y-26611 (from **5**), Ciprofloxacin (from **1**), Norfloxacin (from **2**),[1] Enoxacin (from **7**), and Tosufloxacin (from **10**, see scheme 1).[2] Here complete ^{13}C and ^{1}H NMR chemical shift data as well as carbon- and proton-fluorine coupling constants for eleven derivatives are reported.

EXPERIMENTAL

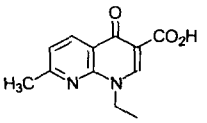
The synthetic scheme for the preparation of the several compounds in Table 1 (**1 - 5**, **10**) were reported previously (Ref. 1). The others which have naphthyrine nucleus (**6 - 9**, Nitrogen at C8) are shown in Schemes 2 and 3. All NMR experiments were carried out on Bruker Avance 400 (9.4 T). Samples were dissolved in 500μL of deuterated solvents, DMSO-d_6 until saturation and moved into the 5 mm NMR tube. The 90° pulse of the ^{1}H

Table 1. The Structures of Eleven Quinolone Carboxylic Acid Derivatives.

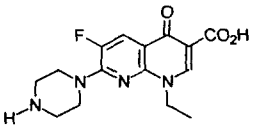


Compound	X	R_1	R_2	R_3
1	CH	H	Cl	
2	CH	H	Cl	$-CH_2CH_3$
3	CH	H	F	
4	CF	H	F	
5	CF	H	F	
6	N	H	Cl	$-CH_2CF_3$
7	N	H	Cl	$-CH_2CH_2F$
8	N	H	Cl	
9	N	H	Cl	
10	CH	$-CH_2CH_3$	Cl	
11	N	$-CH_2CH_3$	Cl	$-C(CH_3)_3$

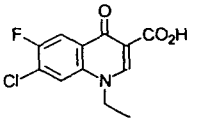
Scheme 1. Quinolone nuclei and their corresponding clinical antibiotics.



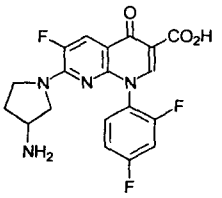
Nalidixic acid



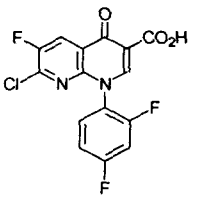
Enoxacin



A (6, 7 analogue)

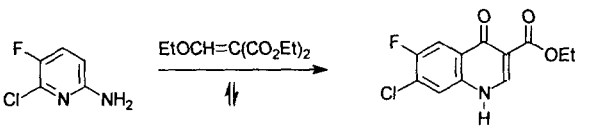


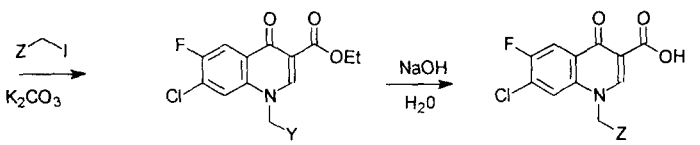
Tosufloxacin



9

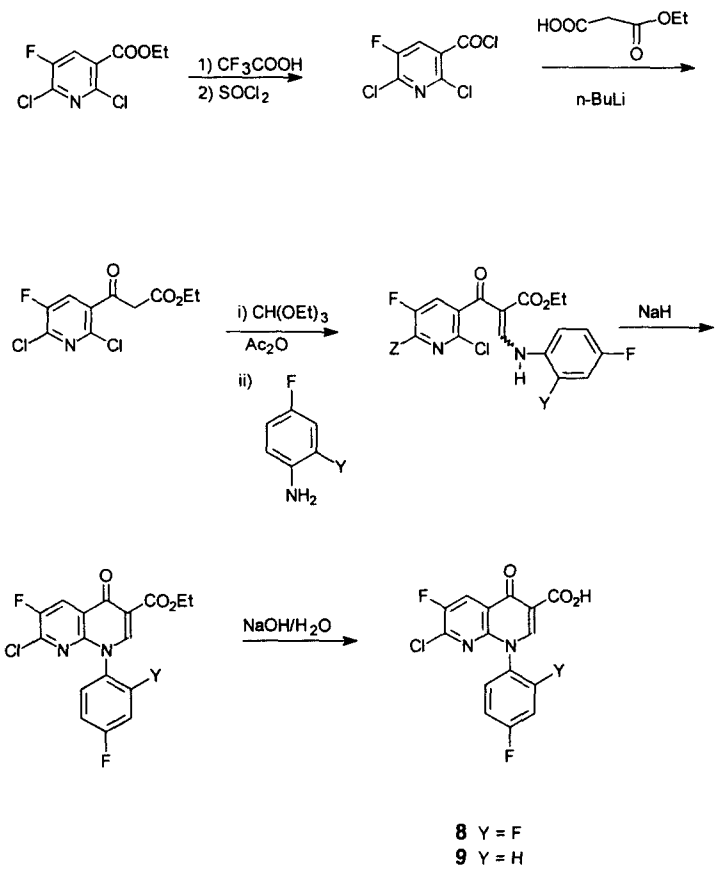
Scheme 2. Synthetic procedure for preparation of **6** and **7**.





6 Z = CF_3
7 Z = CH_2F

Scheme 3. Synthetic procedure for preparation of **8** and **9**.



NMR experiments was 9.7 μsec and that of ^{13}C NMR, 9.8 μsec. 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. The HMQC spectrum and the HMBC spectrum were collected as described by Bax[3] and Summers,[4] respectively. Two hundred and fifty-six blocks were collected with spectral width of 4,000 Hz in *t*2 dimension and 22,000 Hz in *t*1 dimension. The number of scans for each block was 128 and data points of *t*2 dimension were 1024. The delay for the long ranged coupling of HMBC was 70 msec. All 2D NMR data were post-processed using Felix.

Table 2. The ^{1}H Chemical Shifts of Quinolone Carboxylic Acid Derivatives.

Compound	H-2	H-5	H-8	H-11
1	8.75	8.19	8.52	14.60
2	9.06	8.20	8.44	14.92
3	8.98	8.35	7.45	14.44
4	8.75	8.15	-	14.30
5	8.84	8.25	-	14.03
6	9.27	8.68	-	13.83
7	9.18	8.72	-	14.24
8	8.90	8.77	-	14.09
9	9.08	8.77	-	13.91
10	8.55	8.08	7.30	-
11	8.84	8.46	-	-

(unit : ppm)

Table 3. The ^{13}C Chemical Shifts of Quinolone Carboxylic Acid Derivatives.

Com-pound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
1	154.85	113.07	182.00	117.43	160.68	132.66	126.83	143.77	130.01	170.86
2	150.14	108.24	176.87	112.37	155.28	127.84	121.42	136.62	126.38	165.94
3	151.12	109.20	177.27	113.98	148.89	154.00	108.24	122.74	138.75	165.29
4	156.60	112.98	181.21	113.48	153.73	149.17	150.00	127.91	134.43	170.47
5	152.72	109.46	175.93	108.84	148.73	143.88	141.69	122.51	128.23	164.84
6	151.39	111.00	177.59	123.58	152.73	142.95	-	144.69	122.07	164.79
7	151.29	109.60	177.76	123.29	153.84	143.10	-	144.86	122.13	165.25
8	151.53	110.62	178.49	123.71	153.11	143.41	-	146.57	122.45	165.63
9	151.34	110.89	177.75	123.51	152.74	143.19	-	145.32	121.77	164.78
10	154.26	116.41	177.32	118.07	160.21	130.06	125.99	142.72	133.25	167.32
11	147.45	110.70	172.16	123.56	151.64	138.66	-	145.23	125.64	164.77

(unit : ppm)

Table 4. Long Ranged Proton-carbon Correlations Observed in the HMBC Spectra of the Compounds.

Com Pound	Protons showing HMBC correlations for ^2J or ^3J									
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
1	-	-	H-2	-	H-5; H-8	H-5; H-8	-	H-2; H-5	H-8	H-2
2	-	H-2	H-2; H-5	-	H-5; H-8	H-5; H-8	-	H-2; H-5; H-8	H-8	H-2
3	-	H-2	H-2; H-5	-	H-5; H-8	H-5; H-8	-	H-2; H-8	H-2; H-5; H-8	H-2
4	-	-	H-2; H-5	-	H-5	H-5	-	-	H-2; H-5	H-2
5	-	H-2	H-2; H-5	-	H-5	H-5	-	-	H-2; H-5	H-2
6	-	-	H-2; H-5	-	H-5	H-5	-	H-2; H-5	-	H-2
7	-	-	H-2; H-5	-	H-5	H-5	-	H-2; H-5	-	H-2
8	-	-	H-2; H-5	-	H-5	H-5	-	H-2; H-5	-	H-2
9	-	H-2	H-2; H-5	-	H-5	H-5	-	H-2; H-5	-	H-2
10	-	-	H-2; H-5	-	H-5; H-8	H-5; H-8	-	H-2; H-5; H-8	-	H-2
11	-	-	H-2; H-5	-	H-5	H-5	-	H-2; H-5	H-5	H-2

RESULTS AND DISCUSSION

The ^{1}H NMR and ^{13}C NMR chemical shifts of the compounds are listed in Tables 2 and 3, respectively. Since only 1D experiments and HMQC cannot give complete information about chemical shifts, proton-carbon long ranged coupling experiments should be carried out and their results are listed in Table 4.

The knowledge of proton- and carbon-fluorine coupling constants may help one assign the NMR data of the fluorinated quinolone derivatives. Here authors report the results obtained from eleven quinolone derivatives. The ranges of $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$, $^3J_{C\text{-}F}$ and $^4J_{C\text{-}F}$ are 166.9~280.4 Hz, 6.4~40.0 Hz, 1.9~13.9 Hz and 1.6~4.0 Hz, respectively. In case of proton-fluorine coupling, the ranges of $^2J_{H\text{-}F}$, $^3J_{H\text{-}F}$, $^4J_{H\text{-}F}$ and $^5J_{H\text{-}F}$ are 46.4 Hz, 7.5~26.0 Hz, 6.0~8.9 Hz and 1.4~2.2 Hz, respectively. Complete data of carbon- and proton-fluorine coupling constants are listed in Tables 5 and 6. These results agree with the data published previously.[5-7]

Table 5. Carbon-fluorine Coupling Constants for Quinolone Carboxilic Acid Derivatives.

Compound	$^{1}J_{C\text{-}F}$	$^{2}J_{C\text{-}F}$	$^{3}J_{C\text{-}F}$	$^{4}J_{C\text{-}F}$
1	249.4	20.3~22.6	6.6	1.9~2.3
2	249.5	6.9~22.8	6.9	1.6~2.5
3	250.2~256.3	13.1~27.7	10.7~13.9	2.5~3.9
4	249.3~257.0	6.4~19.1	1.9~3.8	
5	250.3~258.6	6.5~27.7	2.9~13.3	3.6~3.8
6	259.5~280.4	20.9~40.0	3.7	1.9
7	166.9~258.8	19.6~22.8	3.8	2.1
8	246.9~259.5	20.9~22.7	3.6~9.3	1.7~2.9
9	249.7~259.5	13.2~27.5	3.7~13.6	3.6~4.0
10	247.8	20.2~22.7	5.8	1.9
11	258.3	19.9~22.3	2.3	1.7~2.1

(unit : Hz)

Table 6. Proton-fluorine Coupling Constants for Quinolone Carboxilic Acid Derivatives.

Compound	$^{2}J_{H\text{-}F}$	$^{3}J_{H\text{-}F}$	$^{4}J_{H\text{-}F}$	$^{5}J_{H\text{-}F}$
1	-	9.0	6.2	-
2	-	9.1	6.1	-
3	-	9.1~10.5	8.5~8.9	-
4	-	10.2	8.2	2.2
5	-	8.6~10.6	-	1.4
6	-	7.5~8.7	-	-
7	46.4	7.6~26.0	-	-
8	-	7.5~8.9	8.9	-
9	-	7.4~10.4	8.7	-
10	-	9.2	6.0	-
11	-	7.9	-	-

(unit : Hz)

Acknowledgements

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