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단 신

Quinolone(IV); 1-Alkyl-8-amino-6-fluoro-4-oxo-1,4-dihydro-pyrido [2,3-h]quinoline-3-carboxylic Acids의 합성 및 항균력 검사

李在瑾 · 崔基烈 · 張師禎† · 朴泰鎬‡
경북대학교 자연과학대학 화학과
†한국과학기술연구원
‡한국화학연구소 항생제연구팀
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Quinolone(IV); The Preparation of 1-Alkyl-8-amino-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylic Acids and the Test of Their Biological Activities

Jae Keun Lee, Ki Yeul Choi, Sha Joung Chang†, and Tae Ho Park‡
Department of Chemistry, Kyungpook National University, Taegu 702-701, Korea
†Division of Applied Science, Korea Institute of Science Technology, Seoul 130-650, Korea
‡Korean Research Institute of Chemical Technology, Daejeon 302-343, Korea
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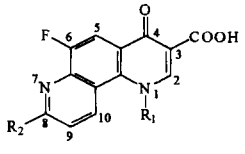
In previous paper[1], we have reported the synthesis of the 1-ethyl-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylic acid (**1a**).

Compound **1a** was extremely insoluble in organic solvents and water, so we could not evaluate properly its antibacterial activity. But considering its similiar structure to ciprofloxacin and norfloxacin, which has 6-fluoro and 7-*t*-amino groups respectively, in its basic ring system, we could imagine that it would have good antibacterial activity. Therefore, we are interested in increasing its solubility by putting chloro and amino groups at 8-position of 6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h] quinoline-3-carboxylic acid, such as 8-chloro (**1b**), 8-piperidinyl (**1c**) and 8-pyrrolidinyl (**1d**). Since we found that N_1-(*n*-propyl) derivatives had better activitives than N_1-ethyl in compound 2,[2] we are also interested in synthesizing the N_1-(*n*-propyl) derivatives **1e**, **1f** and **1g** and evaluating their biological activities.

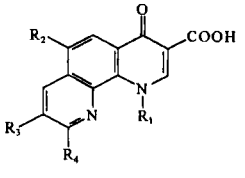
First, compound **10** was synthesized through *Scheme* 1. We started with 2-chloro-8-nitroquinoline[3] (**3**) since the chlorination of 8-fluoroquinoline to 2-chloro-8-fluoroquinoline through the N-oxidation[4] was not successful.

The nitro group was reduced with stannous chloride[5] to 8-amino-2-chloroquinoline and the amino group was replaced by fluorine[6] to give 2-chloro-8-fluoroquinoline (**4**).

The 2-chloro-8-fluoroquinoline (**4**) was nitrated,[7] and reduced to 5-amino-2-chloro-8-fluoroquinoline (**6**), which was successfully reacted with EMME,[8] and thermally cyclized to ethyl 8-chloro-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylate (**7**). Compound **7** was alkylated with ethyl



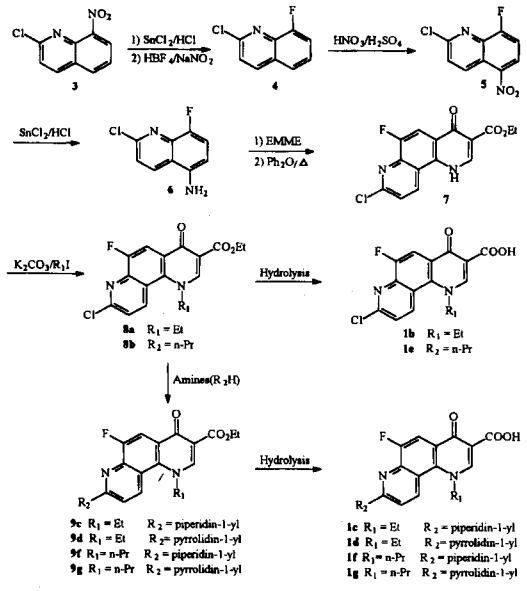
1a R_1 = Et, R_2 = H
1b R_1 = Et, R_2 = Cl
1c R_1 = Et, R_2 = piperidin-1-yl
1d R_1 = Et, R_2 = pyrrolidin-1-yl
1e R_1 = n-Pr, R_2 = Cl
1f R_1 = n-Pr, R_2 = piperidin-1-yl
1g R_1 = n-Pr, R_2 = pyrrolidin-1-yl



2a R_1 = Et, R_2 = F, R_3 = R_4 = H
2b R_1 = n-Pr, R_2 = F, R_3 = R_4 = H
2c R_1 = Et, R_2 = H, R_3 = F
R_4 = 4-methyl-1-piperazinyl

iodide, and *n*-propyl iodide under basic condition to compound **8a** and **8b** respectively.

8-Chloro of compound **8** was easily substituted with piperidine and pyrrolidine[9] to produce compound **9a** and **9b** and the hydrolysis of compound **8** and **9** in basic conditions[10,11] produced compound (**1**). These compounds showed the increased solubilities in DMSO and water as we expected, but no biological activities at all as shown in *Table* 3.



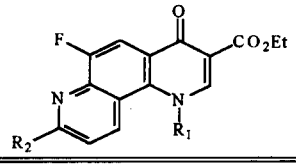
Scheme 1.

EXPERIMENTAL

Pmr and mass spectra were recorded on Varian EM-360, General Electric QE 300 and Shimazu GC MS-QP1000A, respectively. IR spectra were recorded on a JASCO-810. Melting points were determined on a Electrothermal melting point apparatus and are uncorrected.

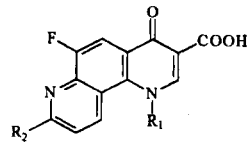
8-Amino-2-chloroquinoline. To a well-stirred solution of stannous chloride dihydrate (20 g) in 55 mL of conc. hydrochloric acid cooled to below 10 ℃ in an ice bath was added dropwise a solution of 2-chloro-8-nitroquinoline (**3**) (4 g, 19.1 mmol) in 26 mL of conc. hydrochloric acid. After the addition was completed, the solution was stirred for 1 hr at 10 ℃ and then allowed to reach to room tem-

Table 1. Physical and spectral properties of compound **8**, **9**



Compound	Substituent		Yield	mp	^{1}H NMR($CDCl_3$), δ(ppm)					M^+(m/z,
	R_1	R_2	(%)	(℃)	Ar-H	C_2-H	O-Et	N_1-R_1	R_2	rel. intensity)
8a	Et	Cl	61	137~138	9.5~7.7	9.2(s)	4.5(q)	4.3(q)		348(12)
							1.5(t)	1.6(t)		350(4)
8b	*n*-Pr	Cl	62	126~128	9.5~7.4	9.2(s)	4.5(q)	4.2(t)		362(8.6)
							1.5(t)	2.0(m)		364(2.7)
								1.1(t)		
9c	Et	piperidine	83	130~132	9.1~7.1	9.2(s)	4.5(q)	4.3(q)	3.9(br)	397(100)
							1.4(t)	1.5(t)	1.7(br)	
9d	Et	piperidine	82	152~154	9.1~6.9	9.2(s)	4.4(q)	4.3(q)	3.7(br)	383(55)
							1.4(t)	1.5(t)	1.6(br)	
9f	*n*-Pr	piperidine	83	132~134	9.1~7.1	9.17(s)	4.4(q)	4.2(t)	3.8(br)	411(100)
							1.4(t)	1.9(m)	1.7(br)	
								1.1(t)		
9g	*n*-Pr	piperidine	86	117~120	9.1~6.8	9.1(s)	4.4(q)	4.2(t)	3.7	397(43)
							1.4(t)	1.9(m)	2.1(br)	
								1.1(t)		

Table 2. Physical and spectral properties of compound **1**



Compound	Substituent		Yield	mp	^{1}H NMR(DMSO-d_6), δ(ppm)					M^+(m/z, rel. intensity)	IR (cm^{-1})
	R_1	R_2	(%)	(℃)	Ar-H	C_2-H	O-H	N_1-R_1	R_2		
1b	Et	Cl	85	302~304	9.4~7.9	9.1(s)		4.3(q)		348(12)	3421
								1.4(t)		350(4)	1703
											1628
1c	Et	piperidine	90	264~266	9.0~7.4	9.0(s)		4.3(q)	3.8(br)	369(100)	3421
								1.4(t)	1.6(br)		1691
											1601
1d	Et	piperidine	84	268~270	9.0~7.0	9.0(s)	13.4(s)	4.3(q)	3.6(br)	355(55)	3421
								1.4(t)	2.0(br)		1695
											1604
1e	*n*-Pr	Cl	91	296~298	9.5~7.9	9.1(s)		4.2(t)		334(6.0)	3421
								1.8(m)		346(1.9)	1700
								1.0(t)	3.8(br)		1620
1f	*n*-Pr	piperidine	90	260~262	9.0~7.4	8.9(s)	13.4(s)	4.2(t)	1.6(br)	383(100)	3421
								1.8(m)			1695
								1.0(t)	3.6(br)		1602
1g	*n*-Pr	piperidine	87	263~265	9.0~7.0	9.0(s)	13.4(s)	4.2(t)	2.0(br)	369(59)	3421
								1.8(m)			1695
								1.0(t)			1604

Table 3. MICs(mg/mL) of 1-alkyl-8-amino-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylic acid derivatives

Strains	Control.		Comp.
	(NAL)	(CIP)	**1a~f**
Gram (+)			
Bacillus subtilis (6633)	16	<0.25	>100,000
Staphylococcus aureus (6538P)	128	<0.25	>100,000
Gram (−)			
Salmonella typhimurium (14028)	16	<0.25	>100,000
Proteus mirabilis (25933)	8	<0.25	>100,000
Escherichia coli (25922)	8	<0.25	>100,000
Pseudomonas aeruginosa (25619)	32	<0.25	>100,000

perature and stirred for additional two hours. The canary yellow tin complex was completely dissolved in warm water. The orange red solution was made strongly alkaline by careful addition of concentrated sodium hydroxide solution while cooling in ice-bath. The tin salt was precipitated first, then redissolved in the excess alkali addition. After a couple miniutes later, the product was precipitated, collected on a filter and washed with water. The product was purified by silica gel column chromatography using ethyl acetate and *n*-hexane (1 : 1) as an eluent. Yield: 87.6%; mp 69 ℃; ^{1}H NMR ($CDCl_3$) δ 8.1~6.9 (m, 5H, Ar-H), 3.8 (broad, 2H, NH_2); MS: m/z (relative intensity) 178 (M^+, 100), 180 (34).

2-Chloro-8-fluoroquinoline (4). To a solution of 8-amino-2-chloroquinoline (3 g, 16.8 mmol) in 40% hydrofluoroboric acid (42 mL) was added at 0 ℃ a solution of sodium nitrite (1.5 g, 22 mmol) in 27 mL of water. After stirring for 3 hrs, the reaction mixture was treated with 30 mL of ethyl ether, and the diazonium salt was filtered. This diazonium salt was heated to 150 ℃ for 15 min without solvent under N_2. The decomposed tar was dissolved in $CHCl_3$ and washed twice with H_2O. The organic layer was dried with anhydrous $MgSO_4$, concentrated under reduced pressure after

filtering the $MgSO_4$. The product was purifide by silica gel column chromatography using ethyl acetate, *n*-hexane and pet. ether (1 : 2 : 2) as an eluent. Yield: 37.7%; mp 76~78 ℃; ^1H NMR ($CDCl_3$) δ 8.7~7.8(m, 5H, Ar-H); MS: m/z(relative intensity) 181(M^+, 94), 183(M+2, 30).

2-Chloro-8-fluoro-5-nitroquinoline (5). 2-Chloro-8-fluoroquinoline (1.27 g, 7.0 mmol) was added gradually to a mixture of fuming nitric acid (12.7 mL) and sulfuric acid (2.6 mL) at 0 ℃. The solution became hot and was heated on steam-bath for five hours. The reaction mixture was poured into water, and the mixture was made alkaline with sodium hydroxide solution. The precipitate was filtered and washed with water and recrystallized from ethyl acetate to give compound **5**. Yield: 70.4%; mp 128~130 ℃; ^1H NMR ($CDCl_3$) δ 9.1~7.5(m, 4H, Ar-H); MS: m/z(relative intensity) 226(M^+, 29), 228(M+2, 9).

5-Amino-2-chloro-8-fluoroquinoline (6). The title compound was prepared by the method of compound **4**. The product was purified by silica gel column chromatography using ethyl acetate and *n*-hexane(1 : 2) as an eluent. Yield: 86.4%; mp 74~75 ℃; ^1H NMR ($CDCl_3$) δ 8.1~6.7(m, 4H, Ar-H), 3.9(broad, 2H, NH_2); MS: m/z(relative intensity) 196(M^+, 100), 198(M+2, 34).

Ethyl 8-chloro-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylate (7). A mixture of 5-amino-2-chloro-8-fluoroquinoline (**6**) (0.9 g, 4.58 mmole) and diethyl ethoxymethylene malonate (EMME) (0.99 mL, 4.58 mmol) in 5 mL of ethanol was refluxed for two hours. After evaporating ethanol under reduced pressure, the residue was suspended in 8.4 mL of diphenyl ether and refluxed for 10 min. at 255-258 ℃. Then, the reaction mixture was cooled to room temperature. The resulting precipitate was filtered and washed with *n*-hexane and recrystallized from DMF to give compound **7**. Yield: 83%; mp 284~286 ℃; ^1H NMR (TFA-D+$CDCl_3$) δ 11.6(s, 1H, NH), 9.5(s, 1H, C_2-H), 9.4~8.1(m, 3H, Ar-H), 4.7(q, *J*=7 Hz, 2H, CH_2), 1.5(t, *J*=7 Hz, 3H, CH_3); MS: m/z (relative intensity) 320(M^+, 20.8), 322(M+2, 7.1).

Ethyl 1-ethyl-8-chloro-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylate (8a) <general process>. The mixture of ethyl 8-chloro-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylate (**7**) (0.2 g, 0.62 mmol), ethyl iodide (0.4 g, 2.6 mmol) and anhydrous K_2CO_3 (0.24 g) in DMF (6 mL) was heated to 75 ℃ for 3.5 hr. After finishing the reaction, DMF was removed under reduced pressure. The residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ solution was dried with anhydrous $MgSO_4$ and the solvent was evaporated to dryness under rotary evaporator after filtering the $MgSO_4$. The product was purified by silica gel column chromatography using ethyl acetate and *n*-hexane (1 : 3) as an eluent.

1-Ethyl-8-chloro-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylic acid (1b) <general process>. A solution of compound **8a** (30 mg, 0.086 mmol), 0.2 mL of 1.0 N NaOH, and 4 mL of EtOH was stirred at room temperature for 18 hr. The solvent was removed under rotary evaporator and the residue was redissolved in 2 mL of water and filtered through a fiber glass pad to clarify it. The filterate was acidified to pH 2.2 with 6.0 M HCl and cooled to 5 ℃ and the precipitate was filtered, washed with water, and dried to give compound **1a**.

Ethyl 1-ethyl-6-fluoro-8-(piperidin-1-yl)-4-oxo-1,4-dihydro-pyrido[2,3-h]quinoline-3-carboxylate (9c) <general process>. The mixture of compound **8a** (0.1 g, 0.29 mmol), piperidine (0.043 g, 0.5 mmol) and ethanol (5 mL) was heated to 120 ℃ for 10 hours. The solvent was removed under rotary evaporator. The product was purified by silica gel column chromatography using benzene, ethyl acetate and *n*-hexane (6 : 1 : 10) as an eluent.

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