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단 신

7-(1,3-Dihydropyrrolo[3,4-*b*]pyridin-2-yl)quinolone-3-carboxylic Acid의 합성과 항균작용

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Synthesis and Antimicrobial Activity of 7-(1,3-Dihydropyrrolo[3,4-*b*] pyridin-2-yl)quinolone-3-carboxylic Acid

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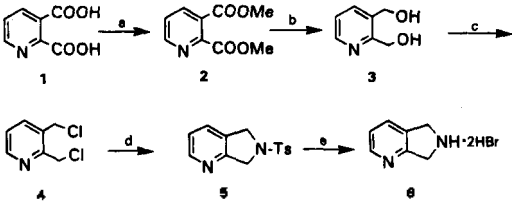
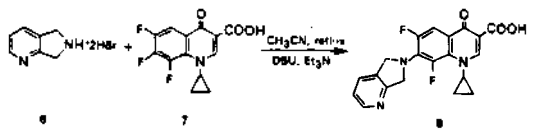
Quinolone antibacterial agents are a major class of antiinfectives with significant potential for continued development.[1] Most of modern examples of this antiinfectives class, which have broad spectrum activity, are substituted at the C-7 position of the quinolone or naphthyridine nucleus by cyclic aliphatic amines,[1,2] especially diamines such as piperazine derivatives. This moiety plays a significant role in determining antibacterial spectrum and potency, and represents a site amenable to significant modification. Recently, 3-aminomethylpyrrolidines and 3-aminopyrrolidines as C-7 substituent of quinolone carboxylic acid showed enhanced potency against Gram-positive strains and broad spectrum of antibacterial activity.[3]

In the course of our studies on the development of quinolone antibacterial agents,[4] we reported the synthesis and antibacterial activity of quinolone carboxylic acid derivatives containing 3-substitued pyrrolidinyl group at C-7 position. Herein we wish to report the synthesis and biological activity of 7-(1,3-dihydropyrrolo[3,4-*b*]pyridin-2-yl)quinolone-3-carboxylic acid (**8**).

1,3-Dihydropyrrolo [3,4-b]pyridine dihydrobromide (**6**) was prepared according to *Scheme* 1 from 2,3-pyridinedicarboxylic acid (**1**) as the starting material. In this sequence, the dihydropyrrolo group was introduced at the 2,3-positions of pyridine by the esterification of 2,3-pyridinedicarboxylic acid (**1**), reduction with LAH, displacement with thionyl chloride, and substitution with *p*-$TsNH_2$. Deprotection of compound **5** was accomplished with HBr/AcOH to afford 1,3-dihydropyrrolo [3,4-b]pyridine dihydrobromide (**6**). The coupling reaction between the quinolone nucleus **7** and compound **6** was performed according to the general procedure[5] (*Scheme* 2). New quinolone carboxylic acid **8** was tested against twenty organisms using



Scheme 1. *Reagents and conditions*: (a) CH_3COCl, CH_3OH, reflux, 12 h, (b) $LiAlH_4$, THF, 0 °C, 4 h, (c) $SOCl_2$, reflux, 1 h, (d) *p*-$TsNH_2$, NaH, DMF, 50 °C, 1 h, (e) HBr/AcOH, reflux, 4 h.



Scheme 2.

Table 1. *In vitro* antibacterial activities

Strains	MICs (μg/mL)	
	Compound **8**	Ciprofloxacin
Gram (+)		
Streptococcous pyogenes A308	0.781	1.563
Streptococcous pyogenes A77	0.781	0.195
Streptococcous feacium MD8*b*	1.195	0.781
Staphylococus aureus SG511	0.002	0.195
Staphylococus aureus 285	0.002	0.195
Staphylococus aureus 503	0.002	0.391
Gram (-)		
Escherichia coli 0 55	0.025	0.013
Escherichia coli DC 0	1.563	0.195
Escherichia coli DC 2	0.391	0.098
Escherichia coli TEM	0.391	0.098
Escherichia coli 1507E	0.049	0.049
Pseudomonas aureginosa 9027	0.391	0.098
Pseudomonas aureginosa 1592 E	0.391	0.195
Pseudomonas aureginosa 1771	0.391	0.195
Pseudomonas aureginosa 1771M	0.049	0.049
Salmonella typhimurium	0.025	0.013
Klebsiella oxytoca 1082E	0.049	0.002
K. aeruginosa 1522E	0.195	0.013
Enterobacter cloacae P99	0.049	0.013
Enterobacter cloacae 1321E	0.013	0.007

standard technique[6] and minimum inhibition concentrations (MICs in μg/mL) were determined (*Table* 1). The data for ciprofloxacin are included for comparison. Compound **8** showed broad spectrum antibacterial activity; it was slightly less potent than ciprofloxacin against Gram-negative but more potent against Gram-positive bacteria.

EXPERIMENTAL

Melting points were taken on a Gallenkemp melting point apparatus and are uncorrected. Proton NMR spectra were recorded on Bruker FT-80 spectrometer. Chemical shifts are reported in δ units relative to tetramethylsilane as an internal standard. Column chromatography was performed with E. Merck silica gel 60, 70-230 mesh ASTM, and thin layer chromatography was performed with silica gel 60 F_{254} plates. Compound **7** was prepared from 2,3,4,5-tetrafluorobenzoic acid as reported previously.[7]

Synthesis of dimethyl 2,3-pyridine dicarboxylate (2). To a stirred solution of acetyl chloride (28.4 mL, 0.4 mol) in methanol (500 mL) was added 2,3-pyridinedicarboxylic acid **1** (33.4 g, 0.2 mol) at room temperature. The reaction mixture was refluxed for 12 h, cooled to room temperature, evaporated the solvent in vacuo, and extracted with ethyl acetate (200 mL) and aqueous $NaHCO_3$ (10%, 200 mL). The organic layer was dried, and concentrated to give 31 g of dimethyl 2,3-pyridinedicarboxylate **2** (79%) as a white solid.

mp: 56-58 °C;

^{1}H NMR ($CDCl_3$) δ 3.88 (s, 6H), 7.51~8.81 (m, 3H)

Synthesis of 2,3-bis(hydroxymethyl)pyridine (3). To a stirred suspension of lithium aluminum hydride (3.8 g, 0.1 mol) in dry THF (400 mL) was added dropwise diester **2** (9.8 g, 0.05 mol) in THF (200 mL) for 1.5 h at − 78 °C. After being warmed to 0 °C, reaction mixture was stirred for 4 h. Saturated aqueous $MgSO_4$ (60 mL) and $MgSO_4$ (6 g) were added to the reaction mixture. The resulting mixture stirred for 1.5 h, filtered, and the filtrate was concentrated *in vacuo*. The residual oil was purified by column chromatography using chloroform/methanol (7/1) to give 4.5 g of diol **3** (65%).

^{1}H NMR ($CDCl_3$) δ 3.72-4.23(br, 2H), 4.68(d, 4H), 7.20-8.41(m, 3H)

Synthesis of 1,3-dihydro-2-(*p*-toluenesulfonyl) pyrrolo [3,4-b]pyridine (5). A solution of diol **3** (3.1 g, 0.023 mol) in thionyl chloride (27 mL, 0.37 mol) was refluxed for 1 h, and concentrated *in vacuo* to give crude 2,3-bis(chloromethyl)pyridine **4** as brown solid. Compound **4** used in next step without further purification. To a stirred suspension of 60% NaH (1.11 g, 0.77 mol) in DMF (30 mL) was added dropwise *p*-toluenesulfonamide (3.94 g, 0.023 mol) in DMF (20 mL) at room temperature for 0.5 h. To the suspension was added dropwise a solution of compound **4** in DMF (10

mL) at room temperature over 1 h. The reaction mixture was heated for 1 h at 50 °C, extracted with chloroform (40 mL) and saturated aqueous NH_4Cl solution (40 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give 4.5 g of compound **5** (76%) as pale brown solid.

^{1}H NMR($CDCl_3$) δ 4.62(s, 4H), 7.45~8.6z5(m, 3H), 9.70(br, 3H)

Synthesis of 1,3-dihydropyrrolo[3,4-*b*]pyridine dihydrobromide (6). A solution of compound **5** (1.0 g, 3.65 mmol) in 30%-HBr/AcOH (10 mL) was refluxed for 4 h and cooled to room temperature. The precipitate was collected by filtration, washed with diethyl ether, and dried *in vacuo* to yield 0.9 g of compound **6** (88%).

mp: 180-185 °C;

^{1}H NMR (DMSO-d_6) δ 4.62 (s, 4H), 7.45-7.60 (m, 1H), 7.97-8.13(m, 1H), 8.56-8.70(m, 1H), 9.70 (br, 3H)

Synthesis of 1-cyclopropyl-6,8-difluoro-7-(1,3-dihydropyrrolo[3,4-*b*]pyridin-2-yl)-1,4-dihydro-4-oxo-3-quinoline carboxylic acid (8). A mixture of compound **7** (0.2 g, 0.70 mmol), DBU (0.11 g, 0.72 mmol), triethylamine (0.15 g, 1.48 mmol), and compound **6** (0.2 g, 0.71 mmol) in acetonitrile (5 mL) was refluxed for 3 h and then stirred for 3 h at room temperature. The precipitate was collected by filtration, washed with acetone, and dried in vacuo to give 0.24 g of compound **8** (88%).

mp: 280 °C (decomp.);

^{1}H NMR ($NaOD/D_2O$) δ 0.80-1.23 (m, 4H), 3.31-3.74 (m, 1H), 4.51 (s, 4H), 6.81-7.22 (m, 3H), 7.80-8.03 (m, 1H), 8.13 (s, 1H)

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