Korean Journal of Life Science
Vol. 13. No. 6. 943~949, 2003

Syntheses and Antibacterial Activities of New Quinolones Containing *cis*- or *trans*-3-Amino-4-methylthiomethylpyrrolidine Moiety

Jae Wook Lee* and Gui Taek Lim

Department of Chemistry, Dong-A University, Hadan-2-dong, Busan 604-714, Korea

Abstract

New quinolone derivatives of 7-(*cis*- or *trans*-3-amino-4-methylthiomethylpyrrolidinyl) quinolone-3-carboxylic acids were synthesized by condensation of 7-halo substituted quinolone-3-carboxylic acids with *cis*- or *trans*-3-amino-4-methylthiomethylpyrrolidine. Some of these compounds showed broad spectra of antibacterial activities against Gram-positive and Gram-negative organisms except *Pseudomonas aeruginosa*, and exhibited much stronger activity against MRSA.

Key words – antibacterial agents, antibacterial activities, pyrrolidine, quinolone

Introduction

Since the discovery of norfloxacin, most of quinolone antibacterials research has been focused on the basic group at the C-7 position to produce more potent quinolones which contain piperazine derivatives at the C-7 position[2]. Also, this piperazine structure has been replaced with two appropriate mimics, 3-aminopyrrolidine and 3-(aminomethyl)pyrrolidine[2]. Our initial structure-activity relationship studies about C-7 derivatives were concentrated on the pyrrolidine mimics, methylthio-substituted pyrrolidines which sulfur atom has lone pair electrons that can participate in hydrogen bonding with drug target and increase the liphophilicity of the novel compounds. From our own research on C-7 amine modifications of the quinolone, we previously reported that 7-(3-methylthiomethyl)pyrrolidine substituted quinolones exhibited potent antibacterial activities against Gram-positive strains *in vitro*[4]. However, 7-(3-methylthiomethyl)pyrrolidine substituted quinolones showed severe solubility problem and also insufficient *in vivo* activities. Since our goal was the discovery of new quinolone antibacterial agents with strong activity to Gram-positive strains and improved physical properties, we had designed novel pyrrolidine groups, which possessed both a methylthiomethyl substitute and an amino-substitute [3]. This structural modification of the pyrrolidine ring was proved to allow modulation of the physical properties of the corresponding quinolones while retaining their strong biological activities, thereby improving their pharmacokinetics properties and *in vivo* potencies. In this paper, we describe the syntheses and antibacterial activities of new quinolone derivatives having *cis*- or *trans*-3-amino-4-methylthiomethylpyrrolidine at the C-7 position.

*To whom all correspondence should be addressed
Tel : 051-200-7251, Fax : 051-200-7259
E-mail : jlee@donga.ac.kr

Materials and Methods

Melting points were taken on a Gallenkemp melting

point apparatus and are uncorrected. Proton NMR spectra were recorded on Bruker FT-80 spectrometer. Column chromatography was performed with E. Merk silica gel, 70~230 mesh ASTM, and thin layer chromatography was performed with silica gel 60 F254 plates. The minimum inhibition concentrations (MICs in μg/ml) for new quinolone derivatives were determined by using standard technique and compared to ciprofloxacin.

***N*-Boc-(*cis* or *trans*-3-hydroxy-4-toluenesulfonyloxymethyl) pyrrolidine (2c or 2t).** A solution of TsCl (5 g, 26.6 mmol) in pyridine (10 mL) was added slowly to a solution of *N*-Boc-3-hydroxy-4-hydroxymethylpyrrolidine 1 (4.82 g, 22.2 mmol) in pyridine (15 mL) at 0℃ and was stirred for 12 h at 0℃. After the solvent was removed by evaporation and residue was dissolved with EtOAc (80 mL). The resulting solution was washed with 5% HCl solution, water, and aqueous $NaHCO_3$ solution, dried, and evaporated to give a crude product that was purified by column chromatography using EtOAc/n-hexane (1:1) as an eluent to provide *cis-trans* mixture. Further purification of this mixture by crystallization using ether afforded the solid *trans* isomer 2t (1.98 g, 24% yield) with oily *cis* isomer 2c (4.6 g, 56% yield). 2t: mp 136~140℃; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.46 (s, 3H), 2.36 ~2.72 (m, 1H), 2.93~3.19 (m, 1H), 3.40-3.63 (m, 3H), 3.98~4.45 (m, 2H), 4.37 (m, 1H). 2c: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.46 (s, 3H), 2.36~2.57 (m, 1H), 3.05~3.32 (m, 2H), 3.45~3.71 (m, 2H), 4.01 (d, J = 6.4 Hz, 2H), 4.20 (m, 1H).

***N*-Boc-(*cis* or *trans*-3-azido-4-methylthiomethyl) pyrrolidine (3c or 3t).** A solution of *N*-Boc-(*cis*-3-hydroxy-4-toluenesulfonyloxymethyl)pyrrolidine 2c (2.69 g, 7.25 mmol) and sodium thiomethoxide (0.7 g, 9.43 mmol) in acetonitrile (30 mL) was stirred for 2 h at rt before treating with ice-water. The resulting mixture was extracted with $CHCl_3$ twice. The combined organic solution was dried and concentrated to give a crude *N*-Boc-(*cis*-3-hydroxy-4-methylthiomethyl)pyrrolidine. The crude product was dissolved in CH_2Cl_2 (15 mL) followed by treating with MsCl (0.92 g, 8 mmol) and Et_3N (0.8 g, 8 mmol) at 0℃. The reaction mixture was stirred for 12 h at rt before the additional CH_2Cl_2 (35 mL) was added. The resulting solution was washed with water and aqueous $NaHCO_3$ solution, dried, and evaporated to give a crude product. Finally, the crude product was dissolved in DMF (15 mL) in the presence of sodium azide (0.52 g, 8 mmol). The resulting mixture was stirred for 14 h at 85℃ before adding EtOAc (50 mL). The organic phase was washed with brine, dried, and evaporated to give a crude product that was purified by column chromatography using EtOAc/n-hexane (1:4) as an eluent to provide *N*-Boc-(*trans*-3-azido-4-methylthiomethyl) pyrrolidine 3t (1.32 g, 67% yield). 3t: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.15 (s, 3H), 2.47~2.78 (m, 3H), 2.92~3.18 (m, 1H), 3.50~3.74 (m, 3H), 4.17 (m, 1H). *N*-Boc-(*cis*-3-azido-4-methylthiomethyl)pyrrolidine 3c was obtained in 51% yield from *N*-Boc-(*trans*-3-hydroxy-4-toluenesulfonyloxymethyl) pyrrolidine 2t applying the same method as described above. 3c: ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.14 (s, 3H), 2.25~2.70 (m, 3H), 3.11~3.43 (m, 2H), 3.54~3.65 (m, 2H), 3.79~3.96 (m, 1H).

(*cis* or *trans*-3-Amino-4-methylthiomethyl)pyrrolidine (4c or 4t). A solution of *N*-Boc-(*cis*-3-azido-4-methylthiomethyl) pyrrolidine 3c (0.3 g, 1.1 mmol) in MeOH (10 mL) in the presence of 5% Pd/C (0.1 g) at H_2 atmosphere was stirred for 12 h at rt. The resulting solution was filtered with Celite and concentrated to give the reduced crude product. The crude product was dissolved in EtOAc (5 mL) followed by treating with HCl (g). The reaction mixture was stirred for 2 h at rt. The precipitate was collected by the filteration and dried to give the desired (*cis*-3-amino-4-methylthiomethyl)pyrrolidine 4c as a dihydrochloride salt (0.19 g, 86% yield). 4c: ^{1}H NMR (D_2O) δ 2.18 (s, 3H), 2.65~2.95 (m, 3H), 3.16~3.57 (m,

2H), 3.71~3.90 (m, 3H). (*trans*-3-Amino-4-methylthiomethyl) pyrrolidine 4t as a dihydrochloride salt was obtained in 90% yield from *N*-Boc-(*trans*-3-azido-4-methylthiomethyl) pyrrolidine 3t applying the same method as described above. 4t: ^{1}H NMR (D_2O) δ 2.18 (s, 3H), 2.77~3.19 (m, 3H), 3.34~3.92 (m, 4H), 4.02~4.14 (m, 1H).

General Coupling Procedure. A solution of quinolone nucleus 5 (0.5 mmol), *cis* or *trans*-3-amino-4-methylthiomethylpyrrolidine 4c or 4t (0.6 mmol), Et_3N (1.8 mmol), and DBU (0.5 mmol) in CH_3CN (4 mL) was refluxed for 6~24 h. After cooling to rt, the formed solids were filtered and washed with cold CH_3CN and Et_2O to give the desired product.

1-Cyclopropyl-6-fluoro-8-chloro-7-(*cis*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (6c). 61% yield; mp 216~222℃ (decomp.); ^{1}H NMR (DMSO- d_6) δ 0.97~1.27 (m, 4H), 2.14 (s, 3H), 2.57~2.95 (m, 3H), 3.00~3.26 (m, 1H), 3.35~3.94 (m, 4H), 4.26~4.44 (m, 1H), 7.84 (d, 1H), 8.81 (s, 1H).

1-Cyclopropyl-6-fluoro-8-chloro-7-(*trans*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (6t). 64% yield; mp 216~220℃ (decomp.); ^{1}H NMR (DMSO- d_6) δ 0.97~1.26 (m, 4H), 2.14 (s, 3H), 2.57~2.87 (m, 2H), 3.25~3.38 (m, 2H), 3.61~3.88 (m, 3H), 4.04~4.37 (m, 2H), 7.84 (d, 1H), 8.82 (s, 1H).

1-Cyclopropyl-6,8-fluoro-7-(*cis*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (7c). 63% yield; mp 156~160℃ (decomp.); ^{1}H NMR (DMSO- d_6) δ 1.19~1.29 (m, 4H), 2.15 (s, 3H), 2.58~2.95 (m, 3H), 3.23~3.80 (m, 3H), 3.88~4.00 (m, 3H), 7.84 (dd, 1H), 8.72 (s, 1H).

1-Cyclopropyl-6,8-fluoro-7-(*trans*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (7t). 61% yield; mp 182~186℃ (decomp.); ^{1}H NMR (DMSO- d_6) δ 1.21~1.33 (m, 4H), 2.15 (s, 3H), 2.58~2.85 (m, 3H), 3.81~4.04 (m, 6H), 7.80 (dd, 1H), 8.71 (s, 1H).

1-Cyclopropyl-6-fluoro-8-methoxy-7-(*cis*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (8c). 55% yield; mp 198~216℃ (decomp.); ^{1}H NMR (DMSO- d_6+CF_3COOD) δ 1.06~1.15 (m, 4H), 2.15 (s, 3H), 2.55~2.95 (m, 3H), 3.62 (s, 3H), 3.73-4.21 (m, 6H), 7.70 (d, 1H), 8.69 (s, 1H).

1-Cyclopropyl-6-fluoro-8-methoxy-7-(*trans*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (8t). 54% yield; mp 202~210℃ (decomp.); ^{1}H NMR (DMSO- d_6+CF_3COOD) δ 1.07~1.19 (m, 4H), 2.15 (s, 3H), 2.56~2.88 (m, 3H), 3.60 (s, 3H), 3.72~4.14 (m, 6H), 7.70 (d, 1H), 8.69 (s, 1H).

1-Cyclopropyl-6-fluoro-7-(*cis*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (9c). 81% yield; mp 204~210℃ (decomp.); ^{1}H NMR (DMSO- d_6+CF_3COOD) δ 1.08~1.23 (m, 4H), 2.14 (s, 3H), 2.73~2.88 (m, 3H), 3.66-4.09 (m, 6H), 7.95 (d, 1H), 8.56 (s, 1H).

1-Cyclopropyl-6-fluoro-7-(*trans*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (9t). 79% yield; mp 204~212℃ (decomp.); ^{1}H NMR (DMSO- d_6+CF_3COOD) δ 1.09~1.22 (m, 4H), 2.14 (s, 3H), 2.63~2.89 (m, 3H), 3.63~4.09 (m, 6H), 7.91 (d, 1H), 8.52 (s, 1H).

1-(2,4-Difluorophenyl)-6-fluoro-7-(*cis*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (10c). 76% yield; mp 186~192℃ (decomp.); ^{1}H NMR (DMSO- d_6) δ 2.13 (s, 3H), 2.53~2.61 (m, 3H), 3.37~4.15 (m, 5H), 7.35~7.67 (m, 3H), 8.12 (d, 1H), 8.84 (s, 1H).

1-(2,4-Difluorophenyl)-6-fluoro-7-(*trans*-3-amino-4-methylthiomethylpyrrolidinyl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (10t). 74% yield; mp 162~166℃ (decomp.); ^{1}H NMR (DMSO- d_6) δ 2.13 (s, 3H), 2.46~2.72 (m, 3H), 3.25~4.09 (m, 5H), 7.06~7.71 (m, 3H), 7.98 (d, 1H), 8.62 (s, 1H).

Results and Discussion

(*trans*-3-Amino-4-methylthiomethyl)pyrrolidine **4t** and its *cis* isomer **4c** were synthesized as shown in Fig. 1, starting with *N*-Boc-3-hydroxy-4-hydroxymethylpyrrolidine[5,10] **1**. Selective mono-tosylation of **1** by treatment of TsCl and triethylamine gave *cis-trans* mixture in 80% yield. *trans*-Isomer **2t** was separated from simple recrystallization of *cis-trans* mixture using Et_2O. The isolated *cis-trans* isomer ratio was about 2.3:1. The major *cis* isomer might be originated from the isomers of the

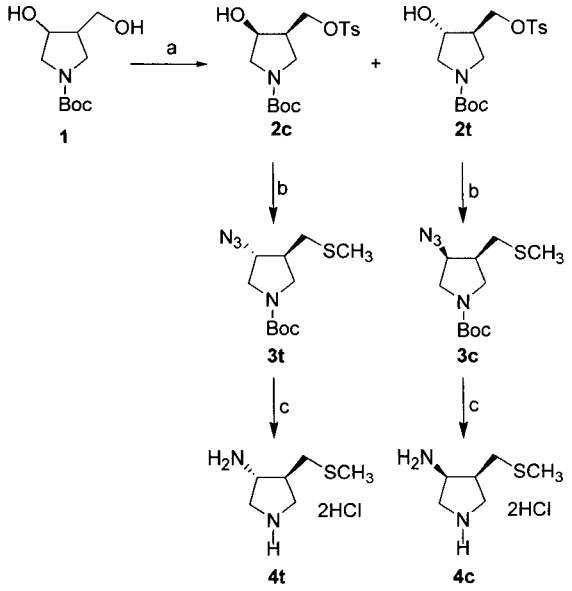

Fig. 1. Synthesis of (*trans*-3-amino-4-methylthiomethyl) pyrrolidine **4t** and its *cis* isomer **4c**. Reagents and conditions: (a) TsCl, pyridine, 12 h at 0℃; (b) (i) $NaSCH_3$, CH_3CN, 2h at rt; (ii) MsCl, Et_3N, CH_2Cl_2, 12h at rt; (iii) NaN_3, DMF, 14h at 85℃; (c) (i) Pd/C, H_2, MeOH, 12 at rt; (ii) HCl(g), EtOAc, 2h at rt.

starting material **1** that their isomer could not be separated. Conversion of *cis* isomer **2c** to *trans* isomer **3t** was accomplished easily through three reaction steps. The reaction of **2c** with sodium thiomethoxide in DMF gave methylthiolated alcohol, which was converted into mesyl derivative using MsCl and Et_3N. Next, the mesyl group in mesyl derivative underwent S_N2 displacement with sodium azide in DMF to furnish azide product **3t** that was in agreement with the *trans* configuration. Reduction of azide group of **3t** with Pd/C and H_2 and subsequent deprotection reaction of Boc group with HCl (g) afforded *trans*-3-amino-4-methylthiomethylpyrrolidine **4t** as a white solid. *cis*-3-Amino-4-methylthiomethylpyrrolidine **4c** was synthesized from *trans*-isomer **2t** applying the same procedures as the synthesis of **4t** from **2c**.

The coupling reactions of the new pyrrolidine derivatives **4t** or **4c** with various quinolone nuclei[1,6-9] **5** followed well-established literature procedures (Fig. 2), using DBU as a base in refluxing acetonitrile[1]. The yields are usually in the range of 55~81%.

The novel quinolones (**6c-10c** and **6t-10t**) were tested for *in vitro* antibacterial activities against 20 representative Gram-positive and Gram-negative strains. Data for selected strains are reported as minimum inhibitory concentrations (MIC) expressed in μg/mL (Table 1). For comparison, ciprofloxacin (CPFX) was employed as a reference. As can be deduced from these data, all of the synthesized compounds exhibited potent antibacterial

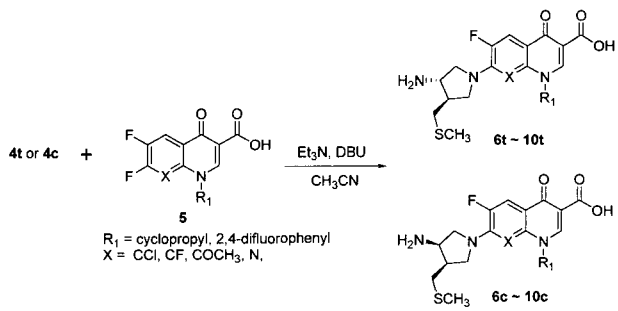

Fig. 2. Synthesis of quinolone derivatives **6c-10c** and **6t-10t**.

activities.

In the (*cis* or *trans*-3-amino-4-methylthiomethylpyrrolidinyl) quinolones series, those (**6t** and **7t**) with *trans* isomer are somewhat more potent than those (**6c** and **7c**) with *cis* isomer. On the other hand, those with *trans* isomer in **8**, **9**, and **10** show an activity similar to those with *cis* isomer. In the C-8 substituted (X) series, the order of antibacterial potency is CCl (**6**) > $COCH_3$ (**8**) > CF (**7**) > N (**9**,**10**).

Compounds **6c-8c** and **6t-8t** show strong activities against Gram-positive bacteria. In particular, they are highly potent against *Streptococcus pyogenes* (2 to 6 folds stronger than CPFX) and *Staphylococcus aureus* (4 to 7 folds stronger than to CPFX). Among them, **6t** displayed the most good activity profile against Gram-positive bacteria. On the other hand, the novel quinolones show comparable activities to CPFX against Gram-negative strains except *Pseudomonas aeruginosa*. Therefore, our novel quinolones displayed improved Gram-positive antibacterial activities, while retaining the good Gram-negative activities of ciprofloxacin.

The strong activities to Gram-positive strains are of importance since the emergence of resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) has become very serious clinical problems. Selected compounds were tested against clinical isolates of methicilin-resistant *S. aureus* (high-MRSA, 6 strains), ofloxacin-resistant strains (37 strains), *E. coli* (56 strains), and *P. aeruginosa* (24 strains). The MIC90% (MIC that inhibits $\geq$ 90% of all strains) for H-MRSA was 1.563, 0.781, and 50 mg/mL for **6t**, **8t**, and CPFX, respectively. For ofloxacin-resistant strains the MIC90% values were

Table 1. *In vitro* antibacterial activity of novel synthesized quinolones (MIC, $\mu g/m\ell$)

	Compounds										
Stranis[a]	6c	6t	7c	7t	8c	8t	9c	9t	10c	10t	CPFX[b]
S.p. A 308	0.195	0.049	0.391	0.098	0.098	0.098	0.781	0.781	0.391	0.391	3.125
S.p. A 77	0.098	0.049	0.195	0.098	0.098	0.098	0.391	0.391	0.195	0.195	0.781
S.f. MD 8b	0.098	0.049	0.195	0.098	0.098	0.098	0.781	0.781	0.195	0.195	0.391
S.a. SG 511	0.025	0.004	0.025	0.013	0.013	0.013	0.049	0.049	0.025	0.025	0.195
S.a. 285	0.025	0.007	0.049	0.025	0.013	0.013	0.098	0.098	0.025	0.049	0.781
S.a. 503	0.013	0.004	0.025	0.013	0.013	0.013	0.049	0.049	0.025	0.025	0.391
E.c. O 55	0.004	<0.002	0.004	<0.002	0.007	0.007	0.007	0.007	0.025	0.049	0.004
E.c. DC 0	0.195	0.195	0.195	0.195	0.391	0.391	0.391	0.391	0.781	0.781	0.195
E.c. DC 2	0.025	0.025	0.025	0.025	0.025	0.049	0.049	0.098	0.098	0.098	0.098
E.c. TEM	0.025	0.013	0.013	0.013	0.025	0.025	0.025	0.025	0.049	0.098	0.013
E.c. 1507E	0.025	0.013	0.025	0.013	0.049	0.049	0.025	0.025	0.098	0.195	0.013
P.a. 9027	0.781	0.781	0.781	0.781	1.563	3.125	1.563	1.563	3.125	3.125	0.391
P.a. 1592E	0.781	0.781	0.781	0.781	1.563	1.563	0.781	1.563	3.125	3.125	0.195
P.a. 1771	0.781	0.781	0.781	0.781	1.563	1.563	0.781	1.563	3.125	3.125	0.195
P.a. 1771M	0.195	0.098	0.195	0.195	0.195	0.391	0.195	0.195	0.391	0.391	0.098
S.t.	0.013	0.004	0.007	0.007	0.025	0.025	0.013	0.013	0.025	0.049	0.007
K.o. 1082E	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	0.004	0.004	<0.002
K.o. 1522E	0.025	0.025	0.025	0.025	0.049	0.049	0.025	0.025	0.098	0.195	0.013
En.c. P 99	0.007	<0.002	0.004	0.004	0.007	0.007	0.007	0.007	0.025	0.049	0.013
En.c. 1321E	<0.002	<0.002	<0.002	<0.002	<0.002	0.004	0.004	0.004	0.007	0.013	<0.002

[a]S.P.: *Streptococcus pyogenes*, S.f.: *Streptococcus faecium*, E.a.: *Staphylococcus aureus*, E.c.: *Escherichia coli*, P.a.: *Pseudomonas aeruginosa*, S.t.: *Salmonella typhimurium*, K.o.: *Klebsiella oxytoca*, En.c.: *Enterobacter cloacae*.
[b]CPFX = ciprofloxacin.

50, 25, and 100 mg/mL respectively, for *E. coli* 3.125, 6.25, and 6.25 mg/mL respectively, and for *P. aeruginosa* 50, 100, and 25 mg/mL respectively. This data illustrates the superior activities of **6t** and **8t** against these multi-resistant organisms.

Summary

A series of quinolone antibacterial agents having *cis*- or *trans*-3-amino-4-methylthiomethylpyrrolidine at the C-7 position have been discovered. They showed strong activities against both Gram-positive and Gram-negative bacteria. In particular, the compound **6t** and **8t** exhibited an excellent broad-spectrum activities against Gram-positive and Gram-negative organisms as well as MRSA.

Acknowledgement

This paper was supported by the Dong-A University Research Fund in 2003.

References

1. Hagen, S. E., J. M. Domagala, C. L. Heifetz, J. P. Sanchez and M. Solomon. 1990. New quinolone antibacterial agents. Synthesis and biological activity of 7-(3,3- or 3,4-disubstituted-1-pyrrolidinyl)quinoline-3-carboxylic acids. *J. Med. Chem.* **33**, 849-854.
2. Hopper, D. C. and J. S. Wolfson. 1993. *Quinolones Antimicrobial Agents*. pp. 3-51, 2nd eds., Am. Soc. Microb, Washington, D. C.
3. Lee, J. W., H. J. Son, K. S. Lee, M. H. Park and B. O. Kim. 1994. Synthesis and antibacterial activities of quinolones containing 3-amino-4-methylthiomethyl-pyrrolidine at the 7-position. *Kor. J. Med. Chem.* **4**, 126-132.
4. Lee, J. W., H. J. Son, K. S. Lee, Y. H. Yu and D. Y. Kim. 1994. Synthesis and antimicrobial activity of 7-[(3-methylthio or 3-methylthiomethyl)pyrrolinyl] quinolone-3-carboxylic acids. *Yakhak Hoeji* **38**, 520-524.
5. Lee, J. W., H. J. Son, K. S. Lee, Y. H. Yu and G. J. Yoon. 1994. Synthesis and antimicrobial activity of 7-[3-hydroxy-(4-methylthio or 4-methylthiomethyl) pyrrolidinyl]quinolone-3-carboxylic Acids. *Yakhak Hoeji* **38**, 677-682.
6. Nishimura, Y. and J. Matsumoto. 1987. Pyridonecarboxylic acids as antibacterial agents. Synthesis and antibacterial activity of 1-substituted 6-fluoro-1,4-dihydro-4-oxo-7-(4-pyridyl)-1,8-naphthyridine-3-carbo xylic acids. *J. Med. Chem.* **30**, 1622-1626.
7. Rosen, T., D. T. W. Chu, I. M. Lico, P. B. Fernandes, L. Shen, S. Borodkin and A. G. Pernet. 1988. Asymmetric synthesis and properties of the enantiomers of the antibacterial agent 7-(3-aminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-1,4-dihydro-6-fluoro-4-oxo-1, 8-naphthyridine-3-carboxylic acid hydrochloride. *J. Med. Chem.* **31**, 1586-1590.
8. Sanchez, J. P., J. M. Domagala, S. E. Hagen, C. L. Heifetz, M. P. Hutt, J. B. Nichols and A. K. Trehan. 1988. Quinolone antibacterial agents. Synthesis and structure-activity relationships of 8-substituted quinoline-3-carboxylic acids and 1,8-naphthyridine- 3-carboxylic acids. *J. Med. Chem.* **31**, 983-991.
9. Uno, T., M. Takamatsu, Y. Inoue, Y. Kawahata, K. Iuchi and G. Tsukamoto. 1987. Synthesis of antimicrobial agents. 1. Syntheses and antibacterial activities of 7-(azole substituted)quinolones. *J. Med. Chem.* **30**, 2163-2169.
10. Wu, Y.-H. and R. F. Feldkamp. 1961. Pyrrolidinediols. 1-Substituted 3-hydroxymethyl-4-hydroxypyrrolidines and derivatives. *J. Org. Chem.* **26**, 1519-1524.

(Received August 7, 2003; Accepted December 4, 2003)

초록 : 시스 또는 트란스-3-아미노-4-메틸티오메틸피롤리디닐기를 포함하는 퀴놀론 항균물질의 합성과 효능검색

이재욱 · 임귀택
(동아대학교 화학과)

7번 위치에 할로겐이 치환된 여러종류의 퀴놀론 모핵과 시스 또는 트란스-3-아미노-4-메틸티오메틸피롤리딘을 반응시켜 7-(시스 또는 트란스-3-아미노-4-메틸티오메틸피롤리디닐)퀴롤론-3-카르복실산의 신규 항균제를 합성하였다. 새롭게 합성된 퀴놀론의 약효는 그람양성균에 대해 대조물질인 시프로플로삭신보다 매우 탁월하였고, 녹농균이외의 그람음성균에 대해서도 대조물질과 거의 유사하였다. 그리고 임상에서 문제가 되고 있는 메티실린 내성 포도상구균(MRSA)에 대한 신규 퀴놀론의 약효는 더욱더 향상되어진 것으로 나타났다.