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단 신

7-(5-Methylthio-2,7-diazabicyclo[3.3.0]oct-7-yl)quinolone-3-carboxylic Acids의 합성과 항균작용

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Syntheses and Antibacterial Activities of 7-(5-Methylthio-2,7-diazabicyclo[3.3.0]oct-7-yl)quinolone-3-carboxylic Acids

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INTRODUCTION

Over a few decades, medicinal chemists have devoted significant efforts to develop structure-activity relationships (SAR) for the quinolone class of antibacterial agents. This effort has rendered several of the most potent, orally active anti-infective agents available today, filling the need for structurally novel therapeutic agents for use against increasingly resistant pathogens.[1]

The new fluoroquinolones are structurally characterized by a five- or six-membered nitrogen-linked heterocycle at C-7. Particularly notable in this regard are the 1-piperazinyl and the 3-amino-1-pyrrolidinyl substituents, present in several of clinically relevant quinolones.[1,2] Our initial SAR studies about C-7 amino-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.[3] Also, we have designed novel pyrrolidines, which possessed both a methylthio substitute and an amine substitute.[4] While almost all of the nitrogen heterocycles are linked to the quinolone ring through the heterocyclic nitrogen, less attention has been paid to the application of bicyclic amine. From strictly chemical considerations, sulfur-substituted diazabicyclooctane derivative (**2**) can be envisioned (*Chart* 1), depending on the cyclization of 3-amino-4-methylthio-pyrrolidine (**1**). In this paper, we report the syntheses and antibacterial activities of new quinolone derivatives having sulfur-substituted bicyclic amine at the C-7 position.

RESULTS AND DISCUSSION

Alkaloids that contain saturated five- and six-membered nitrogen heterocycles[5] and diazabicyclic compounds[6] play an important role in many natural or unnatural products since they are important components in many biologically active compounds and show potent biological activities. To demonstrate the biological activity of quinolone having diazabi-

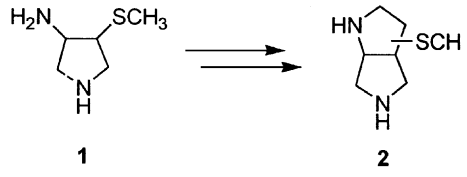
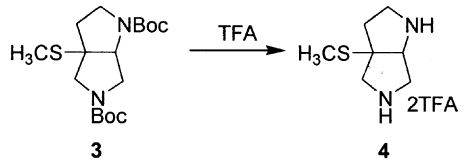


Chart 1.



Scheme 1.

cyclic derivative at C-7 position, we have designed and synthesized the protected 5-methylthio-2,7-azabicyclo[3.3.0]octane **3**.[7] First of all, for applying this derivative in the synthesis of quinolone antibacterial agents, the Boc protection group of **3** was deprotected by TFA to afford 5-methylthio-2,7-azabicyclo[3.3.0]octane **4** as shown in Scheme 1.[7] Next, the coupling reaction between compound **4** and the quinolone nucleus **5**[8-10] was performed according to the general procedures,[9] using DBU as a base in refluxing acetonitrile, to generate the new quinolone derivatives **6** in the range of 61-69% yield (*Scheme* 2).

The novel quinolones (**6**) were tested for *in vitro* antibacterial activity 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. In the C-8 substituted (X) series, the order of antibacterial potency is CCl (**6a**)>CF (**6b**) >N (**6c**) as can be deduced from *Table* 1.

Compounds **6a-6c** show strong activity against

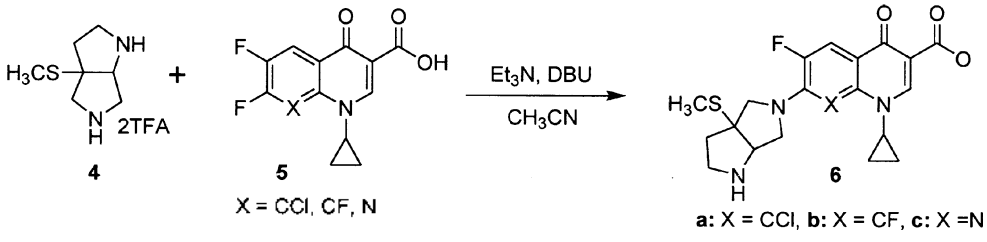
Table 1. *In vitro* antibacterial activity (MIC, μg/ml)

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

Gram-positive bacteria. In particular, they are highly potent against *Streptococcus pyogenes* (1 to 3 folds more potent than CPFX) and *Staphylococcus aureus* (1 to 4 folds more potent than CPFX). Among them, **6a** displayed the most strong activity profile against Gram-positive bacteria. On the other hand, the novel quinolones show somewhat less potent than CPFX against Gram-negative strains.

In summary, a series of quinolone antibacterial agents



Scheme 2. Synthesis of quinolone derivatives **6**.

having a 5-methylthio-2,7-diazabicyclo[3.3.0]oct-7-yl moiety at the C-7 position has been synthesized and the activities were tested. They showed strong activity against Gram-positive organisms but weak activity against Gram-negative organisms comparing to ciprofloxacin.

EXPERIMENTAL SECTION

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[11] and compared to ciprofloxacin.

General Coupling Procedure. A solution of quinolone nucleus **5** (0.5 mmol), 5-methylthio-2,7-azabicyclo[3.3.0]octane **4** (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-(5-methylthio-2,7-diazabicyclo[3.3.0]oct-7-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (6a): 61% yield; mp 214-218 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 0.95-1.23 (m, 4H), 2.19 (s, 3H), 2.11-2.33 (m, 2H), 3.27-3.58 (m, 5H), 3.93-4.12 (m, 2H), 4.38 (m, 1H), 7.91 (d, J=12.9Hz, 1H), 8.80 (s, 1H).

1-Cyclopropyl-6,8-difluoro-7-(5-methylthio-2,7-diazabicyclo[3.3.0]oct-7-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (6b): 65% yield; mp 186-188 °C (decomp.); ^{1}H NMR (DMSO-d_6+DCl) δ 1.08-1.27 (m, 4H), 2.18 (s, 3H), 2.06-2.27 (m, 2H), 3.21-3.82 (m, 5H), 3.92-4.21 (m, 2H), 4.54 (m, 1H), 7.74 (d, J=13.6Hz, 1H), 8.62 (s, 1H).

1-Cyclopropyl-6-fluoro-7-(5-methylthio-2,7-diazabicyclo[3.3.0]oct-7-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (6c): 69% yield; mp 140-146 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 0.95-1.25 (m, 4H), 2.22 (s, 3H), 2.08-2.36 (m, 2H), 3.34-3.82 (m, 5H), 4.02-4.25 (m, 2H), 4.67 (m, 1H), 8.09 (d, J = 12.6Hz, 1H), 8.61 (s, 1H).

REFERENCES

1. Appelbaum, P. C.; Hunter, P. A. *International Journal of Antimicrobial Agents* **2000**, *16*, 5.
2. Hopper, D. C.; Wolfson, J. S. *Quinolones Antimicrobial Agents*; Am. Soc. Microb.: Washington, D. C. 1993.
3. (a) Lee, J. W.; Son, H. J.; Lee, K. S.; Yu, Y. H.; Kim, D. Y. *Yakhak Hoeji* **1994**, *38*, 520. (b) Lee, J. W.; Kang, T. C.; Lee, K. S.; Son, H. J.; Yoon, G. J.; Yu, Y. H.; Kim, D. Y. *Yakhak Hoeji* **1994**, *38*, 197.
4. Lee, J. W.; Son, H. J.; Lee, K. S.; Park, M. H.; Kim, B. O. *Korean. J. Med. Chem.* **1994**, *4*, 126.
5. (a) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4081. (b) Wang, C. J.; Wuonola, M. A. *Org. Prep. Rep.* **1990**, 447.
6. Jorids, U.; Sauter, I.; Siddiqi, S. M.; Kuenburg, B.; Bhattacharya, K. Synthesis **1990**, 925.
7. Lee, J. W.; Son, H. J.; Lee, J. H.; Yoon, G. J.; Park, M. H. *Synth. Commun.* **1996**, *26*, 89.
8. Sanchez, J. P.; Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Nichols, J. B.; Trehan, A. K. *J. Med. Chem.* **1988**, *31*, 983.
9. Hagen, S. E.; Domagala, J. M.; Heifetz, C. L.; Sanchez J. P.; Solomon, M. *J. Med. Chem.* **1990**, *33*, 849.
10. Nishimura, Y.; Matsumoto, J. *J. Med. Chem.* **1987**, *30*, 1622.
11. Goto, S.; Jo, K.; Kawakita, T.; Kosakai, N.; Misuhashi, S.; Nishino, T.; Ohsawa, N.; Tanami, H. *Chemotherapy* **1982**, *29*, 76.