Communications

Synthesis and Antibacterial Activity of Novel Cephalosporins Containing 2,3-Disubstituted-1,8-naphthyridiniummethyl Group at the C-3 Position

Hyun Ju, Sun-Kwon Im, Jae-Man Jeon, Jae-Seon Kang, Dong-Uk Kim, and Sung-Ki Cho*

*Department of Pharmaceutical Engineering, Inje University, Gimhae 621-749, Korea. *E-mail: peace@inje.ac.kr*

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Nowadays, researches for development of β-lactam antibiotics have been done extensively for a long time. Above all, cephalosporins, widely used antibiotics for the treatment of infections, have been studied actively and modified chemically because of the continuing need to produce more effective therapy.[1]

In recent years, a number of cephalosporins containing a quaternary ammoniummethyl group at the C-3 position and a 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-alkoxyiminoacetamido] group at the C-7 position such as cefpirome (CPR),[2] ceftazidime (CAZ) and cefepime (CEPM)[3] have been prepared. They have shown excellent activities against Gram-positive bacteria including *Staphylococcus aureus* and also Gram-negative bacteria including *Pseudomonas aeruginosa*.

In the previous paper,[4] we were interested in subsititution at the C-3 position by 2,3-disubsitituted-1,8-naphthyridine derivatives. So we have synthesized various new cephalosporins having the aminothiazoylmethoxyimino moiety at the C-7 position and 1,8-naphthyridinium moiety at the C-3 position of the cephem nucleus. Among them, the product **3a**, having a 2-amino-1,8-naphthyridine-3-carboxamide **1** at the C-3 position, has the best activity against most bacteria (Figure 1).

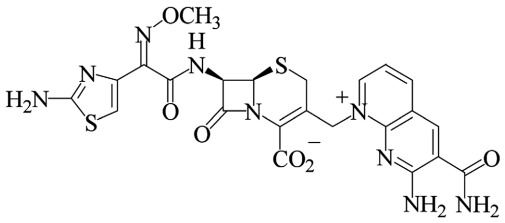
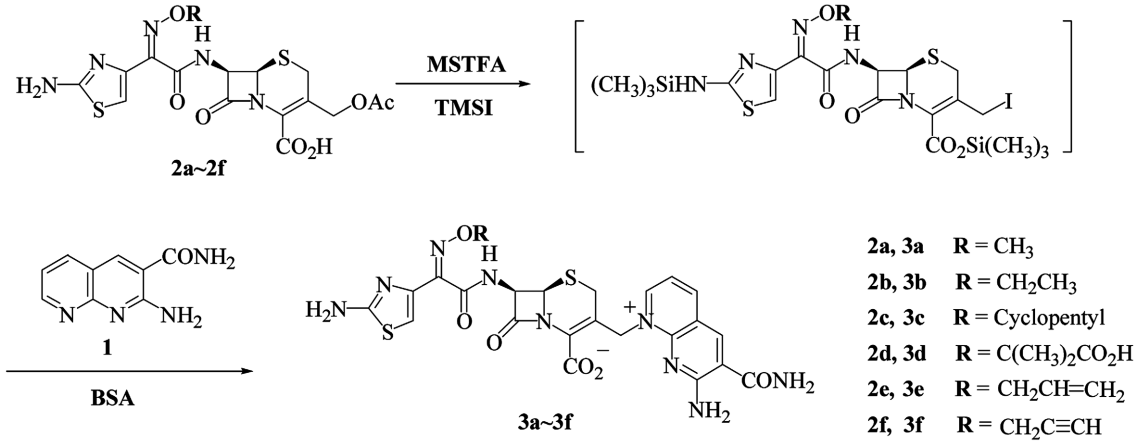


Figure 1. Structure of 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamido]-3-[8-(2-amino-3-carboxamide)-1,8-naphthyridiniummethyl]-3-cephem-4-carboxylic acid inner salt **3a**.

Therefore, our effort to expand the antibacterial potency has been made toward a chemical modification of product **3a** by various alkyl groups and carboxylic groups at the C-7 oxyimino moiety.

The C-3 substituent, 2-amino-1,8-naphthyridine-3-carboxamide **1**, was made from 2-aminonicotinaldehyde with cyanoacetamide using piperidine as catalyst by Friedländer reactions.[5,6]

The quaternary ammonium cephalosporins, **3a-3f**, were synthesized according to the general procedure as shown in Scheme 1. The silylation of 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-alkoxyiminoacetamido]-3-cephem-4-carboxylic acid, **2a-2f**, was carried out with *N*-methyl-*N*-(trimethylsilyl)-



Scheme 1. Synthesis of new cephalosporin derivatives.

Table 1. *In vitro* antibacterial activity (MIC, μg/mL) of the cephalosporins (**3a-3f**)

Compound	MIC (μg/mL)								
	S.a.1	*S.a.2*	*M. l.*	*S. t.*	*E.c.1*	*E.c.2*	*P.a.*	*K. o.*	*E. cl.*
3a	0.625	0.019	0.156	0.039	0.075	0.075	0.075	0.019	0.156
3b	5	0.039	5	0.019	0.156	0.313	2.5	0.156	1.25
3c	2.5	0.019	10	0.075	0.156	0.625	1.25	0.075	2.5
3d	2.5	0.019	5	0.075	0.156	0.313	0.625	0.156	10
3e	1.25	0.625	0.039	5	2.5	0.156	1.25	1.25	20
3f	1.25	0.625	0.039	10	2.5	0.156	0.625	0.313	20
CAZ	5	2.5	1.25	0.313	0.156	0.313	0.039	0.039	5
CTX	1.25	0.019	0.625	0.039	0.039	0.075	0.075	0.019	2.5

trifluoroacetamide (MSTFA) in methylene chloride followed by *in situ* formation of the C-3 iodide with trimethylsilyl iodide (TMSI). The silylated iodo compounds were quaternized with 2-amino-1,8-naphthyridine-3-carboxamide **1**, to give the silylated cephalosporins which were deprotected with acetonitrile and acidified with HCl to afford the final products, **3a-3f**.[7-9]

Minimum inhibitory concentrations (MICs) of products, **3a-3f**, for an array of Gram-positive and Gram-negative bacterial species were determined by the Mueller-Hinton agar dilution method.[10,11] The results of MIC test were summarized in Table 1 and it included those of ceftazidime (CAZ) and cefotaxime (CTX) for comparison, as well.

Most of the products, **3a-3f**, were superior to ceftazidime and comparable to cefotaxime in antibacterial activity against *Staphylococcus aurues subsp. aurues* ATCC 6538P and *Salmonella typhimurium* KCTC 1925.

Especially the product **3a**, possessing methoxyimino group at C-7 position, showed more potent activity than cefotaxime (CTX) against *Staphylococcus aureus* KCTC 1928, *Micrococcus luteus* ATCC 9341 and *Enterbacter cloacae* ATCC 13047.

The products **3e** and **3f**, having allyl and propargyl moiety, uniquely showed sixteen times better activity than cefotaxime against *Micrococcus luteus* ATCC 9341. The product **3d**, possessing carboxyl group at the C-7 position, enhanced the anti-pseudomonal activity as expected. However, the result against *Pseudomonas aeruginosa* ATCC 15692 was unsatisfactory.

In conclusion, 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-alkoxyiminoacetamido]-3-[8-(2-amino-3-carboxamide)-1,8-naphthyridiniummethyl]-3-cephem-4-carboxylic acid inner salt, **3a-3f**, showed well-balanced activities against Gram-positive and Gram-negative bacteria, and these cephalosporins will be selected as candidates for further biological evaluation.

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9. General procedure for **3f**. 7β-[(Z)-2-(2-aminothiazole-4-yl-2-(2-propyn-3-oxyimino)acetamido]-3-cephem-4-carboxylic acid **2f** (500 mg, 1.1 mmol) was suspended in methylene chloride (10 mL) under nitrogen atmosphere. *N*-Methyl-*N*-(trimethylsilyl) trifluoroacetamide (0.8 mL, 4 mmol) was added and the mixture was stirred for 1 hour. The resulting homogeneous solution of cephem trimethylsilyl ester was cooled to 0°C and trimethylsilyliodide (0.75 mL, 4.4 mmol) was added. The solution was stirred for 30 minutes and then evaporated *in vacuo* to afford the 3-iodomethyl cephem as a viscous oil. The oily residue was dissolved in acetonitrile (10 mL) and tetrahydrofuran (2 mL). The stirred solution was added, in one portion, to a solution of 2-amino-1,8-naphthyridine-3-carboxamide **1** (197 mg, 1.1 mmol) silylated with *N,O*-bis-(trimethylsilyl)acetamide (1.05 mL, 3.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred for 3 hours at room temperature and then added to a mixture of methanol (1 mL) and acetonitrile (2 mL) at 0°C. The mixture was stirred at 0°C for 30 minutes. The precipitated solids were collected by filteration to provide a solid product. Water (10 mL) was added to the solid, and the mixture was neutralized with saturated sodium bicarbonate solution and then concentrated. The residue was purified by column chromatography over silica gel eluting with acetonitrile : water (4 : 1) and concentrated to give **3f** in 38% yield.
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 9.71 (1H, d, J = 8.1 Hz), 9.05-8.76 (4H, m), 7.67 (2H, s), 6.76 (1H, s), 6.05 (1H, d), 5.82 (1H, d), 5.40-5.11 (2H, ABq), 4.66 (2H, s), 3.41 (2H, d); ^{13}C-NMR (300 MHz, DMSO-d_6) δ = 164.2, 162.8, 159.4, 159.2, 158.3, 155.8, 145.4, 145.1, 143.1, 142.5, 137.9, 135.4, 123.9, 116.5, 115.4, 114.2, 112.8, 105.7, 75.7, 57.5, 54.6, 53.4, 49.3, 21.4; IR (KBr) 3392, 2123, 1772, 1676, 1635 cm^{-1}; HRMS (FAB) Calcd for $C_{25}H_{22}N_9O_6S_2$ $(M+H)^+$: 608.1134, Found 608.1129.
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