SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF QUATERNARY AMMONIUM CEPHALOSPORINS WITH HYDROXYLATED ALICYCLIC OR ALIPHATIC AMINES

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The opportunistic infections caused by various Gram-negative bacteria including *Pseudomonas aeruginosa*, have become a serious problem in chemotheraphy. Many efforts have been made to afford new injectable cephalosporins exhibiting stronger antibacterial activity against Gram-negative bacteria.[1~3] Recently, it was reported that aminothiazolylcephalosporins having the dihydroxy aromatic moiety like a catechol or its isosters at the C-3 position exhibited potent activity against *P. aeruginosa*.[4,5] We investigated the effect of the introduction of hydroxy groups to aliphatic or alicyclic amines at C-3 alicyclic heterocycles. In this paper, we wish to describe the synthesis and antimicrobial activities of quaternary hydroxylated alicyclic or aliphatic ammoniomethyl cephalosporins.

Preparation of new cephalosporins having a quaternary hydroxylated alicyclic ammonium group in the 3-side chain was performed according to the procedure illustrated in Scheme 1. The new cephalosporins (**5a**~**5r**) were prepared by quaternization of iodomethyl cephem (**1**) with hydroxylated heterocycle (**2a**~**2i**) followed by *in situ* acylation with aminothiazole hydroxybenzothiazole active ester (**3** or **4**) in a one-pot procedure. Although no Δ-2 isomer was detected in this procedure, the use of excessive amine (>10 equiv) or longer reaction time (>2 days) led to the formation of Δ-2 isomer. The general procedure is as follows; To a stirred solution of iodomethyl cephem (**1**, 100 mg, 0.29 mmol) in DMF (2 ml) was added heterocycle (**2a**~**2i**, 0.87 mmol) in one portion at room temperature. After 1 hour aminothiazole- or aminothiadiazole hydroxybenzothiazole ester (**3** or **4**, 0.29 mmol) was added to the reaction mixture. After 12 hours the reaction mixture was subjected to flash column chromatography on silica gel (CH_3CN-H_2O, 4:1) to afford new cephalosporins (Table 1).

The MICs of the new cephalosporins against Gram-positive and Gram-negative bacteria were determined by an *in vitro* agar dilution method. For comparisons, the MIC values of ceftazidime and cefpirome are listed in Table 2.

Table 2 shows *in vitro* activity of the aminothiazolyl and aminothiadiazolyl derivatives of hydroxylated aliphatic or alicyclic ammonium cephalosporins (**5a**~**5r**). The activities of the most of the compounds are similar to each other. Aminothiazolyl derivatives (**5a**~**5i**) showed somewhat better activities than ceftazidime and somewhat lesser activities than cefpirome against Gram-positive organisms. The anti-pseudomonal activities of them were comparable to ceftazidime and cefpirome. Especially, they exhibited higher activity against *Enterobacter cloacae* P99, which is resistant to ceftazidime.

The activities of aminothiadiazolyl derivatives (**5j**~**5r**) exhibited better activity than ceftazidime against Gram-positive and Gram-negative organisms. The replacement of aminothiazole moiety to aminothiadiazole moiety caused somewhat increase of anti-pseudomonal activities and somewhat decrease of anti-staphylococcal activity. Aminothiadiazolyl derivatives (**5j**~**5r**) also exhibited high activity against *E. cloacae* P99.

In order to examine the effect of the stereo-

Scheme 1.

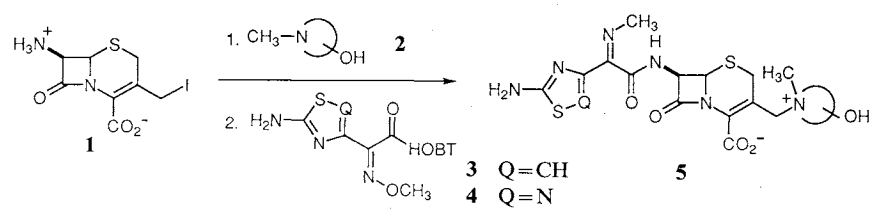
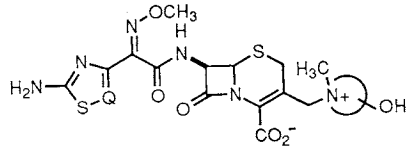
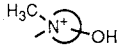
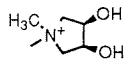
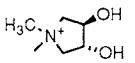
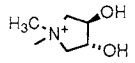
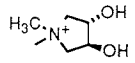
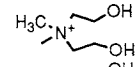
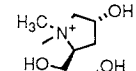
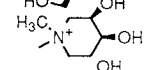
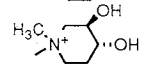
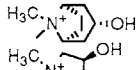
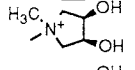
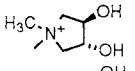
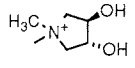
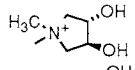
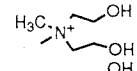
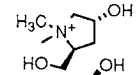
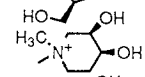
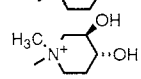
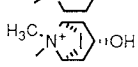


Table 1. Yield, IR and ^{1}H NMR data of the cephalosporins **5**.



Compound			Q	Yield from **1** (%)	IR (KBr) β-lactam (cm^{-1})	^{1}H NMR (300 MHz, δ in D_2O, ppm)				
						Thiazole-H (s)	6-H, 7-H (d, J=4~5 Hz)		OCH_3 (s)	N^+CH_3 (s)
5a		(meso)	CH	20	1769	7.04	5.90	5.39	4.02	3.12
5b		(rac-)[a]	CH	18	1775	7.02	5.88	5.37	4.00	3.22
5c		(L-)[b]	CH	17	1775	7.01	5.89	5.38	4.02	3.24
5d		(D-)[c]	CH	18	1775	7.01	5.89	5.38	4.02	3.24
5e			CH	15	1769	7.07	5.92	5.41	4.04	3.19
5f			CH	16	1771	7.02	5.87	5.38	4.00	3.12
5g		(rac-)[d]	CH	21	1771	7.04	5.91	5.40	4.07	3.19, 3.06
5h		(rac-)[d]	CH	14	1771	7.01	5.87	5.37	3.99	3.19, 3.06
5i			CH	14	1765	7.02	5.87	5.35	4.00	3.00
5j		(meso)	N	7	1771	—	5.90	5.38	4.10	3.27
5k		(rac-)[a]	N	17	1771	—	5.91	5.36	4.10	3.23
5l		(L-)[b]	N	17	1771	—	5.93	5.39	4.12	3.25
5m		(D-)[c]	N	16	1771	—	5.89	5.36	4.09	3.24
5n			N	10	1767	—	5.92	5.41	4.11	3.16
5o			N	10	1769	—	5.92	5.40	4.11	3.19
5p		(rac-)[d]	N	19	1772	—	5.94	5.41	4.10	3.18, 3.06
5q		(rac-)[d]	N	21	1771	—	5.91	5.40	4.07	3.19, 3.06
5r			N	18	1773	—	5.89	5.36	4.09	3.00

Starting heterocycles were prepared from [a]; racemic tartaric acid[6], [b]; L-tartaric acid, [c]; D-tartaric acid, [d]; cephalosporin was prepared from racemic mixture of heterocycle.

chemistry of the hydroxy group, the antibacterial activities of cephalosporins (**5b**~**5d** and **5k**~**5m**) quaternised with three optical isomers of 1-methyl-3,4-*trans*-dihydroxypyrrolidines were investigated. The necessary heterocycles were obtained from L-, D- and racemic tartaric acid, respectively.[6] The

Table 2. *In vitro* antimicrobial activity of the cephalosporins **5** (MIC: μg/ml).

Compound	*S.p.* 308A	*S.f.* MD	*S.a.* SG511	*S.a.* 503	*E.c.* TEM	*E.c.* 1507E	*P.a.* 9027	*P.a.* 1592E	*S.t.*	*K.a.* 1552E	*E.c.* P99	*E.c.* 1321E
5a	0.025	100	3.13	3.13	0.098	0.049	3.13	3.13	0.098	0.049	6.25	0.025
5b	0.025	50	3.13	1.56	0.049	0.025	1.56	1.56	0.049	0.049	6.25	0.013
5c	0.025	50	3.13	1.56	0.049	0.049	3.13	1.56	0.049	0.025	3.13	0.013
5d	0.025	100	3.13	1.56	0.049	0.025	3.13	1.56	0.049	0.049	6.25	0.013
5e	0.025	100	3.13	3.12	0.049	0.049	3.13	1.56	0.049	0.025	1.56	0.025
5f	0.025	50	3.13	1.56	0.049	0.049	3.13	3.13	0.025	0.025	3.13	0.013
5g	0.049	100	3.13	3.13	0.049	0.025	3.13	3.13	0.098	0.049	3.13	0.025
5h	0.049	100	3.13	3.13	0.025	0.013	3.13	3.13	0.098	0.049	1.56	0.025
5i	0.049	100	1.56	1.56	0.049	0.025	3.13	3.13	0.098	0.098	3.13	0.025
5j	0.098	100	6.25	3.13	0.39	0.20	1.56	0.78	0.20	0.20	3.13	0.049
5k	0.049	100	6.25	6.25	0.20	0.098	1.56	1.56	0.20	0.098	3.13	0.049
5l	0.049	100	6.25	3.13	0.20	0.098	1.56	0.78	0.098	0.098	3.13	0.025
5m	0.098	100	6.25	6.25	0.20	0.098	1.56	0.78	0.098	0.049	1.56	0.025
5n	0.098	100	12.5	6.25	0.098	0.098	1.56	1.56	0.098	0.049	1.56	0.049
5o	0.049	100	6.25	3.13	0.20	0.098	1.56	1.56	0.098	0.049	1.56	0.025
5p	0.098	100	6.25	3.13	0.20	0.20	1.56	0.78	0.20	0.098	1.56	0.098
5q	0.049	100	6.25	3.13	0.20	0.049	1.56	1.56	0.20	0.098	1.56	0.049
5r	0.049	100	3.13	1.56	0.39	0.20	1.56	1.56	0.39	0.098	3.13	0.098
Ceftazidime	0.098	>100	12.5	3.13	0.20	0.20	3.13	0.78	0.098	0.098	100	0.025
Cefpirome	0.013	6.25	0.39	0.20	0.025	0.049	3.13	1.56	0.013	0.013	3.13	0.025

Abbreviations: *S.p.* 308A, *Streptococcus pyogenes* 308A; *S.f.* MD, *Streptococcus faecium* MD; *S.a.* SG511, *Streptococcus aureus* SG511; *S.a.* 503, *Streptococcus aureus* 503; *E.c.* TEM, *Escherichia coli* TEM; *E.c.* 1507E, *Escherichia coli* 1507E; *P.a.* 9027, *Pseudomonas aeruginosa* 9027; *P.a.* 1592E, *Pseudomonas aeruginosa* 1592E; *S.t.*, *Salmonella typhimurium*; *K.a.* 1552E, *Klebsiella aerogenes* 1552E; *E.c.* P 99, *Enterobacter cloacae* P99; *E.c.* 1321E, *Enterobacter cloacae* 1321E.

activities of them were nearly the same as each other, there being no relationship of activity with the stereochemistry of the hydroxy group.

According to these results, hydroxylated aliphatic and alicyclic ammonium cephalosporins (**5a**~**5r**) were found to be more active than ceftazidime. The activities of aminothiadiazolyl derivatives (**5j**~**5r**) were comparable to cefpirome against Gram-negative strains, but none of them exceeded the activity of cefpirome against Gram-positive strains.

Acknowledgments

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