STUDIES ON CONDENSED-HETEROCYCLIC AZOLIUM CEPHALOSPORINS

III†. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7β-[2-(2-AMINO-5-SUBSTITUTED-THIAZOL-4-YL)-2(*Z*)-ALKOXYIMINOACETAMIDO]-3-(CONDENSED-HETEROCYCLIC AZOLIUM)METHYL-3-CEPHEM-4-CARBOXYLATES

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As a part of our research on the synthesis of cephalosporins bearing condensed-heterocyclic azolium groups at the 3 position in the cephalosporin nucleus, we describe herein the synthesis of 7β-[2-(2-amino-5-halogeno-, methylthio-, methylsulfinyl-, methylsulfonyl- and sulfothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]cephalosporins and their antibacterial activity. Among the compounds prepared, 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,5-*a*]-pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**14**) showed good antibacterial activity against both *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, whereas the antibacterial activity against other Gram-negative bacteria was a slightly lower than that of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium (**I-1**) and imidazo[1,5-*a*]pyridinium (**I-4**)-1-yl)methyl-3-cephem-4-carboxylates.

In our previous papers[1,2], we reported the synthesis and the antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]cephalosporins (**I**) bearing a condensed-heterocyclic azolium moiety such as imidazo[1,2-*a*]pyridinium, imidazo[1,2-*b*]pyridazinium, pyrazolo[1,5-*a*]pyridinium and imidazo[1,5-*a*]pyridinium at the 3 position of the cephalosporin nucleus. Although **I** showed potent antibacterial activity against both Gram-positive and Gram-negative bacteria, its activity against *Pseudomonas aeruginosa* and especially highly resistant *Pseudomonas aeruginosa* was not satisfactory.

It has been reported that some 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-cephalosporins show potent antibacterial activity against *Pseudomonas aeruginosa* and are stable against β-lactamase[3~5].

Thus, in an effort to expand the antibacterial spectrum of **I**, we examined the antibacterial activity of derivatives of **I** having various substituents at the 5 position in the thiazole ring.

In this paper, we describe the synthesis and the antibacterial activity of 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl cephalosporins.

Chemistry

Scheme 1 shows an outline for the preparation of 2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acids (**III**).

2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acids (**II-2**~**II-5**) were treated with *N*-chloro-

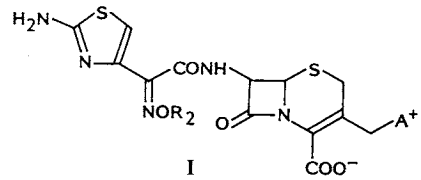
† See ref 1.

succinimide (NCS) in dimethylformamide or methanol to afford 2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyimino acetic acids (**III-2**～**III-5**). 2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**IV**) was also reacted with NCS to give 2-(5-chloro-2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**V**).

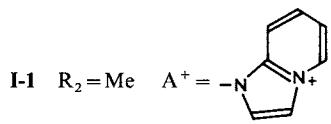
Methyl 2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**VI**) was treated with sodium thiocyanate and bromine in acetic acid or methanol to give methyl 2-(2-amino-5-thiocyanothiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**VII**), which was reacted with sodium borohydride in methanol containing an excess amount of methyl iodide to give methyl 2-(2-amino-5-methylthiothiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**VIII**).

The oxidation of **VIII** with 30% hydrogen peroxide in a mixture of acetic acid and dichloromethane at room temperature afforded methyl 2-(2-amino-5-methylsulfinylthiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**IX**). Further, methyl 2-(2-amino-5-methylsulfonylthiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**X**) was obtained by reacting **VIII** with an excess amount of 30% hydrogen peroxide at 55°C for 12 hours.

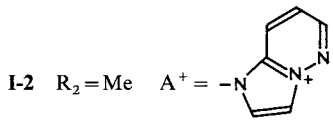
Fig. 1. 7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)-methyl-3-cephem-4-carboxylates.



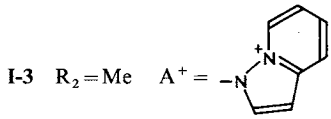
I



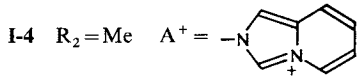
I-1 R_2=Me A^+=



I-2 R_2=Me A^+=



I-3 R_2=Me A^+=



I-4 R_2=Me A^+=

VIII, **IX**, and **X** were converted to the corresponding carboxylic acids (**III-6**～**III-8**, respectively) by hydrolysis.

Subsequently, the sulfonation of 2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**II-1**) with 30% oleum under ice-cooling for 10 minutes and then at room temperature for one hour afforded 2-(2-amino-5-sulfothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**III-9**).

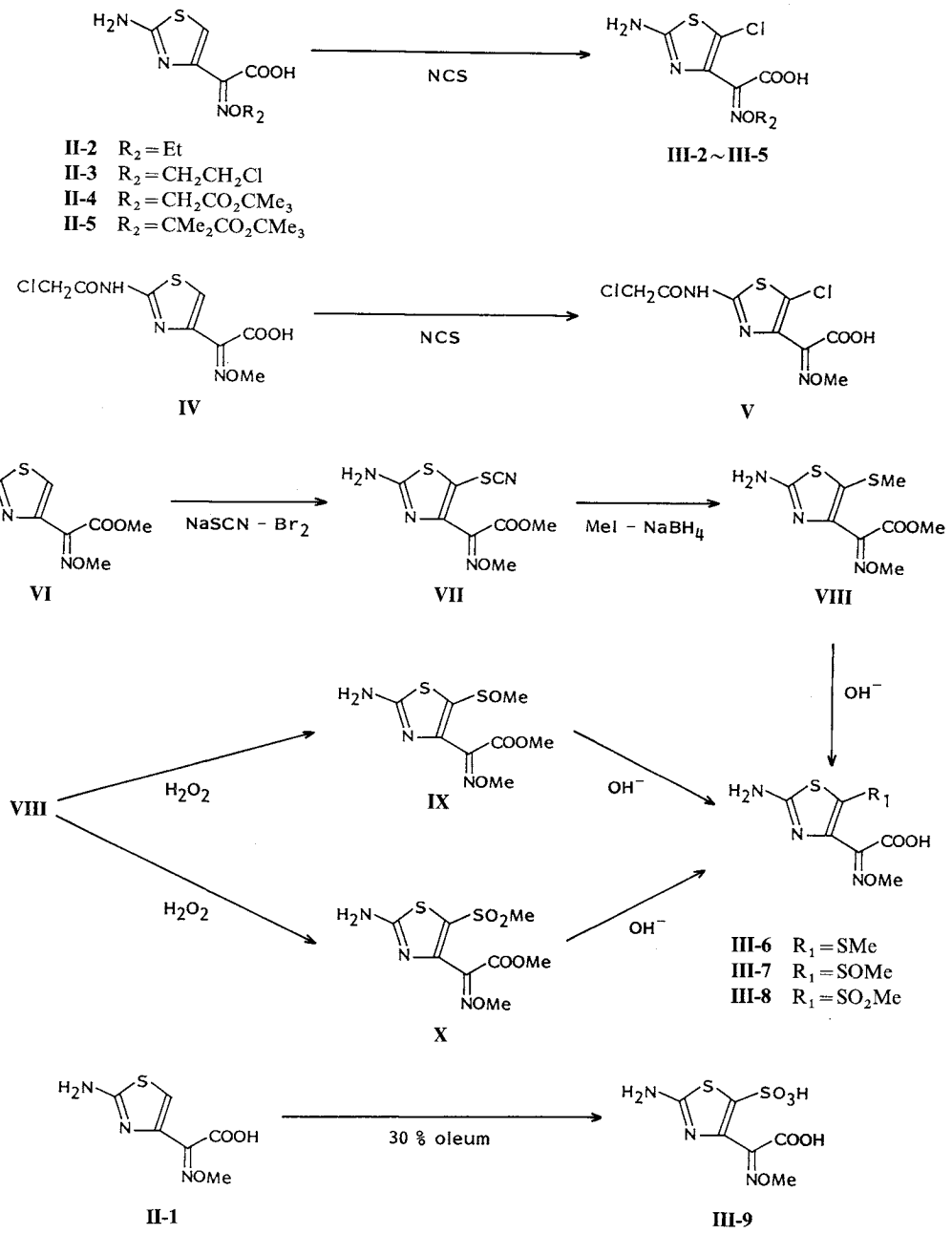
Scheme 2 shows an outline for the preparation of 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**XI**).

2-(2-Amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acid (**III-2**～**III-9**) was converted with 1-hydroxybenzotriazole (HOBT) and dicyclohexylcarbodiimide to the HOBT ester, which was reacted with 7β-amino-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (7-AACA) to give **XI-2**～**XI-9**. 2-(5-Chloro-2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**V**) was converted with PCl_5 to the acid chloride, which was reacted with 7-AACA and gave **XI-1** after removal of the chloroacetyl group with sodium *N*-methyldithiocarbamate.

Scheme 3 shows an outline for the synthesis of 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**, **4**～**9**, **12**～**24**, **XII-10** and **XII-11**).

XI was heated with an excess amount of the condensed-heterocyclic azole and sodium iodide in 50% aqueous acetonitrile at 50～70°C for 1～3 hours. The reaction mixture was purified by column

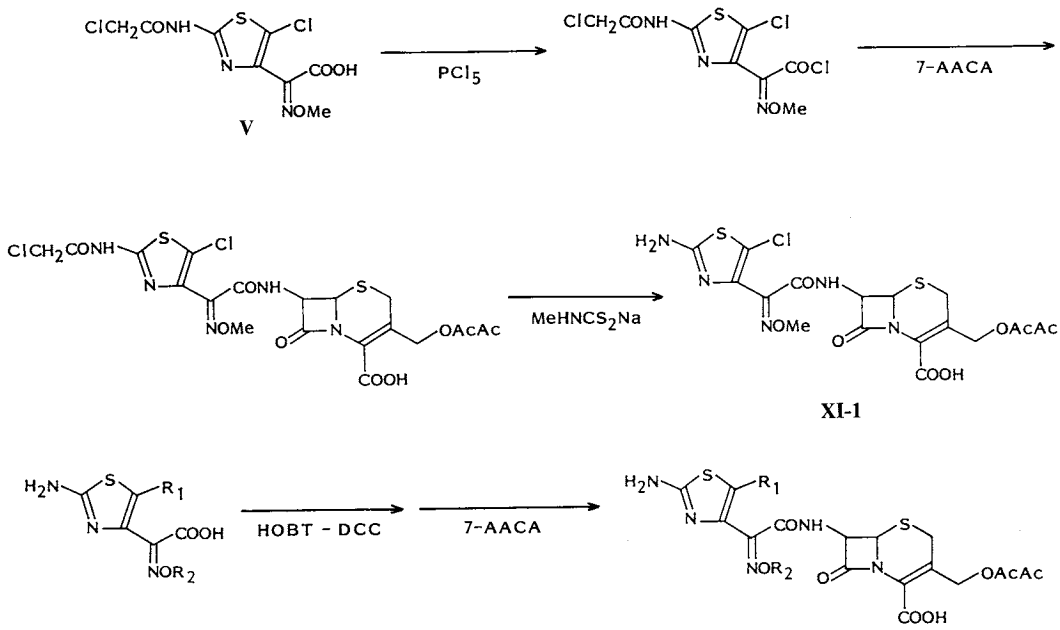
Scheme 1.



chromatography on silica gel with aqueous acetone as the eluent, followed by repurification by column chromatography on MCI gel CHP 20P or Amberlite XAD-2 to give the objective cephalosporins (**1**, **4**~**9**, **12**~**24**, **XII-10** and **XII-11**) in 1~26% yield.

In the case of the compounds **10** and **11**, **XII-10** and **XII-11** with an R_2 of *tert*-butoxycarbonyl group on the oxyimino moiety was deprotected with trifluoroacetic acid, and the desired cephalosporins were isolated as the sodium salt.

Scheme 2.



	R_1	R_2
XI-2	Cl	Et
XI-3	Cl	CH_2CH_2Cl
XI-4	Cl	$CH_2CO_2CMe_3$
XI-5	Cl	$CMe_2CO_2CMe_3$
XI-6	SMe	Me
XI-7	SOMe	Me
XI-8	SO_2Me	Me
XI-9	SO_3H	Me

Also, 7β-[2-(2-amino-5-bromo- (and 5-iodo)thiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo-[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**2**, **3**) were obtained by the direct halogenation of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**I-1**) with *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS), respectively (Scheme 4).

Antibacterial Activity

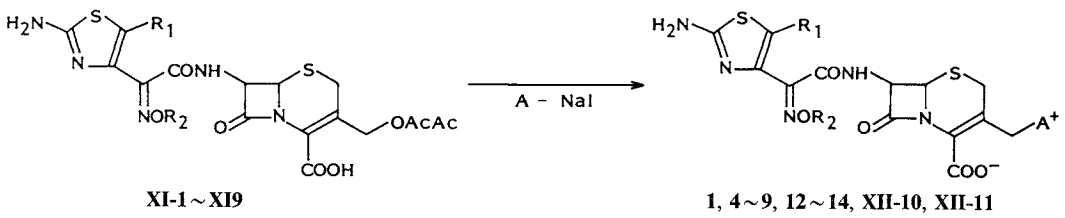
The MICs of the prepared cephalosporins against both Gram-positive and Gram-negative bacteria along with 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)-methyl-3-cephem-4-carboxylate (**I-1**), cefpirome (CPR) and cefmenoxime (CMX) as the reference compounds were determined by the standard serial two-fold agar dilution method[5].

Table 1 shows the MICs of 7β-[2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**～**7**).

The antibacterial activity of 5-halogenated derivatives (**1**～**3**) against *Staphylococcus aureus* was increased as compared to that of **I-1**, whereas the antibacterial activity of **1**～**3** against Gram-negative bacteria was decreased markedly. The substitution of the thiazole ring with sulfur derivatives led to reduced antibacterial activity against both Gram-positive and Gram-negative bacteria. Among the 5-halogeno-

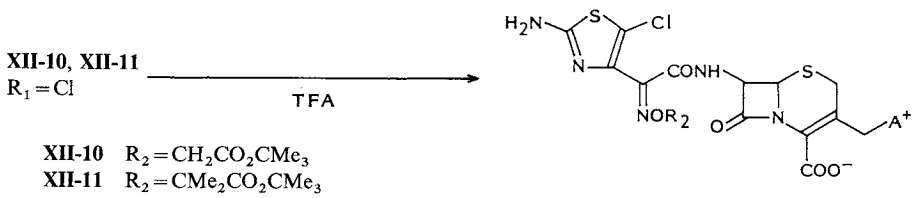
Scheme 3.

Method A



XI-1～XI9

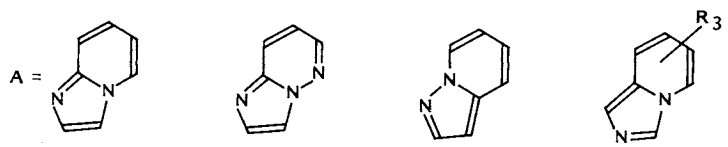
1, 4～9, 12～14, XII-10, XII-11



XII-10, XII-11
R_1=Cl

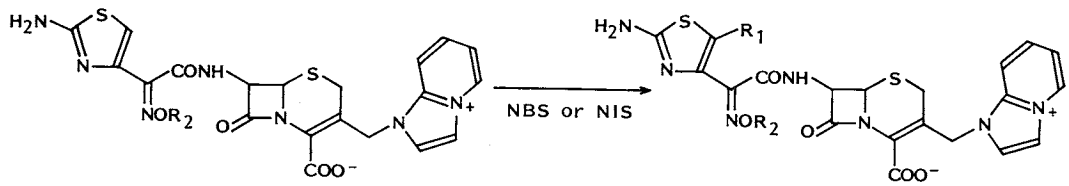
XII-10 $R_2=CH_2CO_2CMe_3$
XII-11 $R_2=CMe_2CO_2CMe_3$

10 $R_2=CH_2CO_2Na$
11 $R_2=CMe_2CO_2Na$



Scheme 4.

Method B



I-1

2 R_1=Br
3 R_1=I

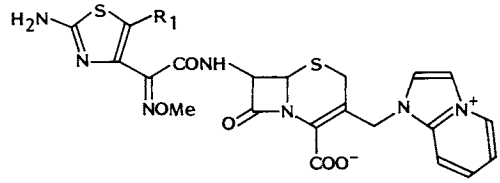
thiazolyl cephalosporins, the chlorine derivative (**1**) showed the most potent activity against both Gram-positive and *Pseudomonas aeruginosa* including cephalosporin-resistant strains.

Table 2 shows the effect of various oxime substituents (R_2) on the MIC of 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**8**～**11**).

The antibacterial activity of the ethyl derivative (**8**) and the 2-chloroethyl derivative (**9**) against *Staphylococcus aureus* and some strains of *Pseudomonas aeruginosa* was improved as compared to that of **1**, whereas the activity against the other Gram-negative bacteria was decreased.

Table 3 shows the effect of the various condensed-heterocyclic azolium rings (**A**), imidazo[1,2-

Table 1. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**～**7**), 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**I-1**), cefpirome (CPR) and cefmenoxime (CMX).

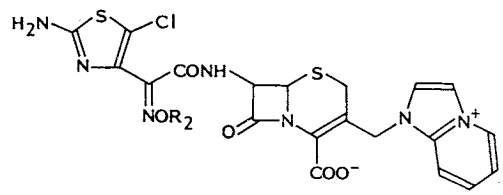


(10^8 cfu/ml)

Compound No.	R_1	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
I-1	H	0.39	<0.1	0.39	0.2	0.2	6.25	>100
1	Cl	0.2	3.13	3.13	1.56	0.78	12.5	25
2	Br	0.2	12.5	12.5	25	6.25	25	100
3	I	0.2	1.56	6.25	3.13	3.13	50	>100
4	SMe	0.78	>100	>100	>100	>100	>100	>100
5	SOMe	6.25	6.25	>100	12.5	12.5	>100	>100
6	SO_2Me	3.13	50	>100	>100	>100	>100	>100
7	SO_3Na	100	>100	>100	>100	>100	>100	>100
CPR		0.78	0.1	0.39	0.1	0.1	1.56	100
CMX		1.56	0.2	6.25	0.39	<0.1	6.25	>100

* *S.a.*; *Staphylococcus aureus* 308 A-1, *E.c.*; *Escherichia coli* NIHJ JC-2, *E.cl.*; *Enterobacter cloacae* IFO 12937, *S.m.*; *Serratia marcescens* IFO 12648, *P.v.*; *Proteus vulgaris* IFO 3988, *P.a.*1; *Pseudomonas aeruginosa* IFO 3455, *P.a.*2; *Pseudomonas aeruginosa* U-31.

Table 2. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**, **8**～**11**).



(10^8 cfu/ml)

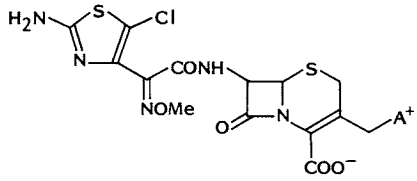
Compound No.	R_2	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
1	Me	0.2	3.13	3.13	1.56	0.78	12.5	25
8	Et	<0.1	3.13	6.25	6.25	3.13	6.25	25
9	CH_2CH_2Cl	<0.1	6.25	12.5	12.5	6.25	6.25	25
10	CH_2CO_2Na	1.56	0.39	1.56	0.39	0.2	6.25	25
11	CMe_2CO_2Na	1.56	1.56	3.13	3.13	0.78	3.13	12.5
CPR		0.78	0.1	0.39	0.1	0.1	1.56	100
CMX		1.56	0.2	6.25	0.39	<0.1	6.25	>100

* See footnote in Table 1.

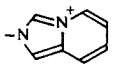
b]pyridazinium (**12**), pyrazolo[1,5-*a*]pyridinium (**13**) and imidazo[1,5-*a*]pyridinium (**14**) on the MIC of the 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]cephalosporins.

The imidazo[1,5-*a*]pyridinium derivative (**14**) showed good antibacterial activity against both

Table 3. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyimino-acetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**, **12**～**14**).



(10^8 cfu/ml)

Compound No.	A	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*	*S.a.*2**
1		0.2	3.13	3.13	1.56	0.78	12.5	25	NT[a]
12		0.78	1.56	6.25	3.13	1.56	3.13	6.25	6.25
13		0.78	1.56	3.13	3.13	3.13	1.56	12.5	NT
14		0.78	0.78	1.56	0.78	0.78	3.13	6.25	6.25
CPR		0.78	0.1	0.39	0.1	0.1	1.56	100	100
CMX		1.56	0.2	6.25	0.39	<0.1	6.25	>100	>100

* See footnote in Table 1.
** *S.a.*2; *Staphylococcus aureus* N-241 (MRSA).
[a] Not tested.

Gram-negative bacteria including *Pseudomonas aeruginosa* and Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA, *Staphylococcus aureus* N-241).

Table 4 shows the MICs of the 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(substituted imidazo[1,5-*a*]pyridinium-2-yl)methyl-3-cephem-4-carboxylates (**14**～**24**).

Among the alkyl derivatives, the 5-methyl derivative (**17**) showed slightly higher antibacterial activity than **14** against both Gram-positive bacteria and Gram-negative bacteria including *Pseudomonas aeruginosa*.

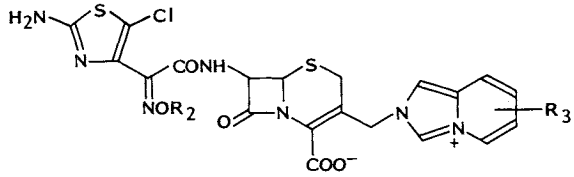
The MICs of the cephalosporins having an electron withdrawing group (**19**, **20** and **21**) were lower than those of the 5-chloro derivative (**14**).

In conclusion, we found that substitution of the thiazole ring with a chlorine atom increased the antibacterial activity against *Pseudomonas aeruginosa* and MRSA, whereas the activity against the other Gram-negative bacteria was decreased.

Experimental

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi 215 spectrophotometer, and ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) and HL-100A (100 MHz) spectrometer using tetramethylsilane as the internal or external standard. Organic solvents were dried over anhydro $MgSO_4$, and concentration by evaporation was carried out *in vacuo*. Column chromatography was carried out on Kieselgel 60 (Merck Art. No. 7734 or 9385), Sephadex LH-20 (Pharmacia Fine Chemicals), MCI gel CHP 20P (Mitsubishi Chemical) and Amberlite XAD-2 (Rohm and Haas). The MIC values were determined by the standard

Table 4. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,5-*a*]pyridinium-2-yl)methyl-3-cephem-4-carboxylates (**14**~**24**) and 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,5-*a*]pyridinium-2-yl)methyl-3-cephem-4-carboxylates (**I-4**).



(10^8 cfu/ml)

Compound No.	R_2	R_3	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*	*S.a.*2**
14	Me	H	0.78	0.78	1.56	0.78	0.78	3.13	6.25	6.25
15	Me	1-Me	0.39	1.56	6.25	6.25	3.13	6.25	25	12.5
16	Me	3-Me	0.39	1.56	3.13	3.13	0.78	3.13	25	6.25
17	Me	5-Me	0.39	0.39	1.56	0.78	0.78	1.56	6.25	6.25
18	Me	7-Me	0.78	0.78	3.13	1.56	0.78	6.25	12.5	6.25
19	Me	7-Cl	0.78	0.78	3.13	0.78	0.78	3.13	12.5	6.25
20	Me	7-CO_2Me	1.56	1.56	3.13	3.13	0.78	3.13	12.5	6.25
21	Me	7-CN	0.78	0.78	1.56	1.56	0.78	3.13	12.5	6.25
22	Me	3,5-di-Me	0.39	0.78	3.13	1.56	0.78	3.13	12.5	6.25
23	Et	H	0.39	1.56	1.56	1.56	1.56	6.25	12.5	6.25
24	Et	7-CO_2Me	1.56	3.13	6.25	6.25	3.13	12.5	25	6.25
I-4	Me	H	0.78	<0.1	1.56	<0.1	<0.1	1.56	>100	NT[a]
CPR			0.78	0.1	0.39	0.1	0.1	1.56	100	100
CMX			1.56	0.2	6.25	0.39	<0.1	6.25	>100	>100

* See footnote in Table 1.
** See footnote in Table 3.
[a] Not tested.

serial 2-fold agar dilution method with Mueller-Hinton agar[6]. Cefpirome (CPR) was prepared according to the procedure described in the literature[5].

Preparation of 2-(2-Amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetic Acid (**III**)

2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyiminoacetic Acid (**III-4**)

A solution of 2-(2-aminothiazol-4-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyiminoacetic acid (**II-4**, 6.0 g) and *N*-chlorosuccinimide (NCS, 3.2 g) in MeOH (100 ml) was kept at 60°C for 2 hours with stirring. The reaction mixture was evaporated, and brine and 5% aq sodium thiosulfate soln were added to the residue. The mixture was extracted with THF and the extract was dried. The solvent was evaporated, and the residue was triturated with *n*-hexane to give 6.5 g (89%) of **III-4** as a colorless amorphous solid; IR (KBr) cm^{-1} 1735, 1630, 1540; ^1H NMR (DMSO-d_6) δ 1.41 (9H, s), 4.57 (2H, s), 6.8 (2H, br).

Anal Calcd for $C_{11}H_{14}ClN_3O_5S$: C 37.10, H 14.11, N 35.45.
Found: C 36.90, H 14.33, N 35.19.

2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetic Acid (**III-5**)

A solution of 2-(2-aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetic acid (**II-5**, 6.0 g) and NCS (2.4 g) in MeOH (50 ml) was stirred at room temperature for 6 hours. The reaction mixture was evaporated and the residue was dissolved in EtOAc. The organic layer was washed with aq satd NaCl, dried and evaporated to give 5.5 g (82%) of **III-5** as pale yellow crystals; IR (KBr) cm^{-1} 1720, 1635, 1540; ^1H NMR (DMSO-d_6 - $CDCl_3$) δ 1.42 (9H, s), 1.46 (6H, s), 6.80~7.80 (3H, m).

The other 2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acids (**III**) were prepared according

to the method mentioned above.

2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-ethoxyiminoacetic Acid (**III-2**)
Yield 85%; IR (KBr) cm^{-1} 1720, 1670, 1640.

2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(2-chloroethoxyimino)acetic Acid (**III-3**)
Yield 82%; IR (KBr) cm^{-1} 1725, 1670, 1640.

2-(5-Chloro-2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetic Acid (**V**)
A solution of 2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**IV**, 55.4 g) and NCS (32 g) in DMF (100 ml) was stirred at 60°C for one hour. To the reaction mixture was added H_2O (1200 ml), EtOAc (400 ml), methyl ethyl ketone (1200 ml) and 5% aq sodium thiosulfate soln (200 ml), and the resultant mixture was shaken. The organic layer was separated, washed with aq satd NaCl, dried and evaporated. The residue was crystallized from MeOH to give 32 g (64%) of **V**; MP 160~162°C (dec) (literature[5] MP 159~160°C); IR (KBr) cm^{-1} 1710, 1670, 1520; ^1H NMR (CD_3OD) δ 4.40 (3H, s), 4.27 (2H, s).

Anal Calcd for $C_8H_7Cl_2N_3O_4S$: C 30.78, H 2.26, N 13.46.
Found: C 30.70, H 2.41, N 13.30.

Methyl 2-(2-Amino-5-thiocyanothiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**VII**)
Bromine (176 g) was added dropwise to a solution of methyl 2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**VI**, 215 g) and NaSCN (97.3 g) in MeOH (1 liter) at such a rate as to maintain the reaction temperature between 25 and 30°C. After stirring at room temperature for one hour, the solvent was evaporated and the residue was dissolved in H_2O (2 liters). The solution was adjusted to pH 7.5 with $NaHCO_3$ and cooled to 0°C. The crystalline precipitate was collected by filtration, washed with H_2O and MeOH, and dried to give 218.6 g (80%) of **VII**; MP 146~147°C; IR (KBr) cm^{-1} 2160, 1725, 1620, 1535, 1430, 1365, 1275; ^1H NMR (DMSO-d_6) δ 3.80 (3H, s), 4.00 (3H, s), 7.86 (2H, s).

Anal Calcd for $C_8H_8N_4O_3S_2$: C 35.29, H 2.96, N 20.58.
Found: C 35.30, H 3.22, N 20.44.

Methyl 2-(2-Amino-5-methylthiothiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**VIII**)
MeI (28.4 g) was added to a solution of **VII** (27.2 g) in a mixture of MeOH (300 ml) and THF (300 ml) with ice-cooling and stirring. After the addition was complete, $NaBH_4$ (7.6 g) was added portionwise to the reaction mixture which was stirred at room temperature for 30 minutes. The reaction mixture was evaporated and the residue was crystallized from H_2O to give 24.1 g (92%) of **VIII**; MP 174~175°C; IR (KBr) cm^{-1} 1725, 1620, 1535, 1435, 1370, 1270; ^1H NMR (DMSO-d_6) δ 2.35 (3H, s), 3.77 (3H, s), 3.90 (3H, s), 7.28 (2H, br).

Anal Calcd for $C_8H_{11}N_3O_3S_2$: C 36.77, H 4.24, N 16.08.
Found: C 36.55, H 4.40, N 15.79.

Methyl 2-(2-Amino-5-methylsulfinylthiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**IX**)
H_2O_2 (30%, 3.0 ml) was added to a solution of **VIII** (7.84 g) in a mixture of AcOH (15 ml) and CH_2Cl_2 (15 ml). After stirring at 50°C for 4 hours, 5% aq sodium hydrogen sulfate soln was added to the reaction mixture to decompose the excess H_2O_2. The mixture was evaporated and the residue was diluted with H_2O. The crystalline precipitate was collected by filtration and dried to give 7.88 g (95%) of **IX**: MP 178~180°C; IR (KBr) cm^{-1} 1740, 1620, 1525, 1280; ^1H NMR (DMSO-d_6) δ 2.84 (3H, s), 3.80 (3H, s), 3.96 (3H, s), 7.75 (2H, br).

Anal Calcd for $C_8H_{11}N_3O_4S_2$: C 34.65, H 4.00, N 15.15.
Found: C 34.52, H 4.20, N 15.13.

Methyl 2-(2-Amino-5-methylsulfonylthiazol-4-yl)-2(*Z*)-methoxyiminoacetate (**X**)
H_2O_2 (30%, 7.0 ml) was added to a solution of **VIII** (7.84 g) in a mixture of CH_2Cl_2 (30 ml) and AcOH (60 ml). After the mixture was stirred at room temperature for 10 minutes, at 50°C for one hour and at 55°C for 12 hours. 10% Sodium hydrogen sulfate soln was added to the mixture. The solvent was evaporated

and the residue was suspended in cold H_2O. The crystalline precipitate was collected by filtration and dried to give 5.5 g (63%) of **X** as colorless crystals; MP 180~182°C; IR (KBr) cm^{-1} 1720, 1630, 1510, 1315, 1290; ^1H NMR (DMSO-d_6) δ 3.37 (3H, s), 3.79 (3H, s), 3.99 (3H, s), 8.01 (2H, br d).

Anal Calcd for $C_8H_{11}N_3O_5S_2$: C 32.76, H 3.78, N 14.33.
Found: C 32.70, H 3.90, N 14.09.

2-(2-Amino-5-methylthiothiazol-4-yl)-2(*Z*)-methoxyiminoacetic Acid (**III-6**)

A solution of **VIII** (7.84 g) in a mixture of MeOH (30 ml) and 4 N NaOH (30 ml) was stirred at room temperature for 30 minutes and then at 50°C for 15 minutes. 4 N HCl (30 ml) was added to the reaction mixture with ice-cooling and the MeOH was removed by evaporation. The residue was cooled and the precipitate was collected by filtration to give 7.09 g (96%) of **III-6** as colorless crystals; MP 126~130°C (dec); IR (KBr) cm^{-1} 1650, 1620, 1585, 1570, 1380, 1310; ^1H NMR (DMSO-d_6) δ 2.38 (3H, s), 3.89 (3H, s), 7.0 (2H, br).

Anal Calcd for $C_7H_9N_3O_3S_2$: C 34.00, H 3.67, N 16.99.
Found: C 34.21, H 3.90, N 16.99.

2-(2-Amino-5-methylsulfinylthiazol-4-yl)-2(*Z*)-methoxyiminoacetic Acid (**III-7**)

A solution of **IX** (7.88 g) in a mixture of MeOH (60 ml) and 4 N NaOH (30 ml) was stirred at room temperature for 10 minutes. 4 N HCl (30 ml) was added to the reaction mixture with ice-cooling. The solvent was evaporated and the residue was extracted with MeOH. The extract was evaporated and the residue was triturated with Et_2O. The solid was collected by filtration and dried to give 7.48 g (100%) of **III-7** as an amorphous solid; IR (KBr) cm^{-1} 1640, 1530, 1350, 1290, 1160; ^1H NMR (DMSO-d_6) δ 2.86 (3H, s), 3.91 (3H, s), 7.78 (2H, br).

Anal Calcd for $C_7H_9N_3O_4S_2$: C 31.93, H 3.45, N 15.96.
Found: C 31.83, H 3.75, N 15.69.

2-(2-Amino-5-methylsulfonylthiazol-4-yl)-2(*Z*)-methoxyiminoacetic Acid (**III-8**)

A solution of **X** (5.4 g) in a mixture of MeOH (60 ml) and 4 N NaOH (20 ml) was stirred at room temperature for 30 minutes. 4 N HCl (20 ml) was added to the reaction mixture which was then lyophilized. The residue was extracted with MeOH and the extract was evaporated. The residue was triturated with Et_2O to give 3.56 g (69%) of **III-8** as an amorphous solid; IR (KBr) cm^{-1} 1620, 1510, 1310, 1135, 1050; ^1H NMR (DMSO-d_6) δ 3.36 (3H, s), 3.92 (3H, s), 8.06 (2H, br).

Anal Calcd for $C_7H_9N_3O_5S_2$: C 30.10, H 3.25, N 15.05.
Found: C 30.01, H 3.55, N 14.79.

2-(2-Amino-5-sulfothiazol-4-yl)-2(*Z*)-methoxyiminoacetic Acid (**III-9**)

2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**II-1**, 6.0 g) was added portionwise to 30% oleum (20 ml) over 10 minutes with stirring at 5°C. The mixture was stirred with ice-cooling for 10 minutes and then at room temperature for one hour to give a clear solution. The reaction mixture was poured into a mixture of $NaHCO_3$ (80 g), cold H_2O (400 ml) and EtOAc (100 ml) with stirring and cooling. After removal of the solvent, the residue was extracted with MeOH and the extract was evaporated. The residue was crystallized from H_2O to give 4.2 g (58%) of **III-9** as colorless crystals; MP 190~193°C; IR (KBr) cm^{-1} 1635, 1440, 1235, 1210, 1060, 1040; ^1H NMR (DMSO-d_6) δ 3.99 (3H, s), 7.14 (3H, br).

Anal Calcd for $C_6H_7N_3O_6S_2 \cdot H_2O$: C 24.06, H 3.03, N 14.04.
Found: C 24.26, H 3.12, N 14.05.

Preparation of 7β-[2-(2-Amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acids (**XI**)

A) Acid Chloride Method

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-1**)

A solution of **V** (15.6 g) in CH_2Cl_2 (100 ml) was stirred with PCl_5 (12.5 g) at -10 to -5°C for 30 minutes. *n*-Hexane (150 ml) was added to the reaction mixture and the resulting mixture was stirred for

20 minutes with ice-cooling. The crystalline precipitate was collected by filtration and washed with a mixture (400 ml) of hexane and CH_2Cl_2 (3:1) to give 2-(5-chloro-2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetyl chloride as colorless crystals. The entire amount of the acid chloride was added portionwise to a solution of 7β-amino-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (7-AACA, 12.6 g) and $NaHCO_3$ (25.2 g) in 50% aq THF (200 ml) with stirring and ice-cooling. The mixture was stirred vigorously with ice-cooling for 30 minutes to give a solution containing 7β-[2-(5-chloro-2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid. Sodium *N*-methyldithiocarbamate (10.3 g) was added to the reaction mixture and then stirred at 40°C for one hour. EtOAc (200 ml) was added to the reaction mixture and the mixture was neutralized with conc HCl. The aqueous layer was separated and washed with EtOAc. The insoluble precipitate was filtered off and the filtrate was acidified to pH 2.0 with conc HCl with ice-cooling. After removal of the upper layer of the mixture by decantation, H_2O (30 ml) was added to the gummy residue and the mixture was allowed to stand in a refrigerator. The resulting solid was crushed, collected by filtration and dried to give 16.6 g (76%) of **XI-1** as an amorphous solid; ^{1}H NMR (DMSO-d_6) δ 2.20 (3H, s), 3.42 and 3.63 (2H, ABq, J=18 Hz), 3.64 (2H, s), 3.85 (3H, s), 4.76 and 5.88 (2H, ABq, J=14 Hz), 5.12 (1H, d, J=5 Hz), 5.79 (1H, dd, J=5 and 8 Hz), 9.50 (1H, d, J=8 Hz).

B) HOBT-DCC Method

7β-[2-(2-Amino-5-methylthiothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-6**)

N,*N*-Dicyclohexylcarbodiimide (DCC, 4.95 g) was added to a solution of **III-6** (4.95 g) and 1-hydroxybenzotriazole hydrate (HOBT, 3.68 g) in DMF (25 ml) with ice-cooling. The mixture was stirred at 5°C for 10 minutes and then at room temperature for one hour. A solution of 7-AACA (6.28 g) and triethylamine (4.44 g) in DMF (25 ml) was added dropwise to the reaction mixture which was stirred at room temperature for 5 hours. The solid was filtered off and Et_2O was added to the filtrate. The mixture was cooled and the upper layer was discarded. The residue was dissolved in 5% aq triethylamine (100 ml) and concentrated to half volume. The residual solution was acidified to pH 3.0 with 4 N HCl with ice-cooling, and the precipitate was collected by filtration and then dried to give 7.7 g (71%) of **XI-6** as an amorphous solid; ^{1}H NMR (DMSO-d_6) δ 2.20 (3H, s), 2.39 (3H, s), 3.41 and 3.62 (2H, ABq, J=18 Hz), 3.62 (2H, s), 3.86 (3H, s), 4.76 and 5.06 (2H, ABq, J=14 Hz), 5.10 (1H, d, J=5 Hz), 5.76 (1H, dd, J=5 and 8 Hz), 7.18 (2H, br s), 9.40 (2H, br), 9.40 (1H, d, J=8 Hz).

The other 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**XI**) were prepared by a procedure similar to that mentioned above.

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-2**)

Yield 72%; IR (KBr) cm^{-1} 1770, 1700, 1620, 1530; ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, J=7 Hz), 2.20 (3H, s), 3.3~3.8 (2H, m), 3.62 (2H, s), 4.17 (2H, q, J=7 Hz), 4.83 and 5.09 (2H, ABq, J=12 Hz), 5.13 (1H, d, J=5 Hz), 5.81 (1H, dd, J=5 and 8 Hz), 6.63 (1H, br s), 7.24 (2H, br s), 9.50 (1H, d, J=8 Hz).

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(2-chloroethoxyimino)acetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-3**)

Yield 65%; IR (KBr) cm^{-1} 1780, 1735, 1620.

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-5**)

Yield 89%; IR (KBr) cm^{-1} 1780, 1720, 1660.

7β-[2-(2-Amino-5-methylsulfinylthiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-7**)

Yield 84%; ^{1}H NMR (DMSO-d_6) δ 2.17 (3H, s), 2.86 (3H, s), 3.40 and 3.73 (2H, ABq, J=18 Hz), 3.60 (2H, s), 3.89 (3H, s), 4.76 and 5.07 (2H, ABq, J=14 Hz), 5.10 (1H, d, J=5 Hz), 5.74 (1H, dd, J=5 and 8 Hz), 7.65 (2H, br), 9.52 (1H, d, J=8 Hz).

7β-[2-(2-Amino-5-methylsulfonylthiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-8**)

Yield 90%; ^{1}H NMR (DMSO-d_6) δ 2.20 (3H, s), 3.44 and 3.67 (2H, ABq, J=18 Hz), 3.39 (3H, s), 3.64 (2H, s), 3.98 (3H, s), 4.80 and 5.10 (2H, ABq, J=14 Hz), 5.15 (1H, d, J=5 Hz), 5.74 (1H, dd, J=5 and 8 Hz), 7.92 (2H, br), 9.40 (1H, d, J=8 Hz).

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylmethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-4**)

DCC (4.4 g) was added to a solution of **III-4** (6.0 g) and HOBT (3.8 g) in DMF (25 ml) and the reaction mixture was stirred with ice-cooling for 5 minutes and then at room temperature for 30 minutes. A solution of 7-AACA (5.61 g) and triethylamine (7.5 ml) in DMF (20 ml) was added to the mixture and the resulting solution was stirred at room temperature for 16 hours. The solid was filtered off and Et_2O (500 ml) was added to the filtrate. The upper layer was decantated off, and H_2O (100 ml), EtOAc (200 ml) and methyl ethyl ketone (200 ml) were added to the residue. The mixture was adjusted to pH 2.5 with conc HCl and the solid was filtered off. The organic layer was separated, washed with aq satd NaCl, dried and evaporated to give 10.1 g (89%) of **XI-4** as an amorphous solid; IR (KBr) cm^{-1} 1780, 1740, 1620; ^{1}H NMR (DMSO-d_6) δ 1.44 (9H, s), 2.10 (3H, s), 3.42 and 3.64 (2H, ABq, J=18 Hz), 3.64 (2H, s), 4.57 (2H, s), 4.79 and 5.08 (2H, ABq, J=13 Hz), 5.14 (1H, d, J=5 Hz), 5.84 (1H, dd, J=5 and 8 Hz), 7.8 (2H, br), 9.41 (1H, d, J=8 Hz).

7β-[2-(2-Amino-5-sulfothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XI-9**)

DCC (4.95 g) was added to a solution of **III-9** (2.99 g) and HOBT (3.68 g) in DMF (25 ml) with ice-cooling, and the resulting mixture was stirred at room temperature for 2 hours. A solution of 7-AACA (6.28 g) and triethylamine (4.4 g) in DMF (25 ml) was added to the mixture, and the resulting solution was then stirred at room temperature for 5 hours. The solid was filtered off and Et_2O (300 ml) was added to the filtrate. The upper layer was decantated off and the residue was triturated with Et_2O. The solid was collected by filtration and dissolved in H_2O (10 ml). The solution was adjusted to pH 1 with 4 N HCl and chromatographed on MCI gel CHP 20P with 0.01 N HCl as the eluent. The fraction eluted with 30% aq EtOH was lyophilized to afford 4.0 g (69%) of **XI-9**; ^{1}H NMR (DMSO-d_6) δ 2.20 (3H, s), 3.42 and 3.65 (2H, ABq, J=18 Hz), 3.64 (2H, s), 3.95 (3H, s), 4.89 and 5.07 (2H, ABq, J=14 Hz), 5.11 (1H, d, J=5 Hz), 5.71 (1H, dd, J=5 and 8 Hz), 7.76 (2H, br), 8.94 (1H, d, J=8 Hz).

Preparation of 7β-[2-(2-Amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates

7β-[2-(2-Amino-5-methylthiothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**4**) [Method A]

A mixture of **XI-6** (2.0 g), imidazo[1,2-*a*]pyridine (2.0 g) and NaI (4.0 g) in 50% aq MeCN (20 ml) was kept at 70°C for 1.5 hours with stirring. After cooling, the mixture was chromatographed on silica gel with Me_2CO and aq Me_2CO as the eluents. The fractions containing the objective compound were combined and concentrated, and the residual solution was purified by MCI gel CHP 20P column chromatography with H_2O and aq EtOH as the eluents. The fractions containing the objective compound were combined, concentrated and lyophilized to give 210 mg (11%) of **4**. The analytical results are shown in Tables 5 and 6.

The cephalosporins **1**, **5**, **6**, **8**, **9**, **12**~**24** were prepared by a procedure similar to that mentioned above, and the analytical results are shown in Tables 5 and 6.

7β-[2-(2-Amino-5-sulfothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**7**)

7β-[2-(2-Amino-5-sulfothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XI-9**) was reacted with imidazo[1,2-*a*]pyridine by a procedure similar to that of **4**. The reaction mixture was chromatographed on a silica gel column with Me_2CO and aq Me_2CO as the eluents. The fractions eluted with 30% aq Me_2CO were combined and concentrated, and the residual

Table 5. IR and analytical data for 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**～**24**).

Compound No.	Method*	Yield (%)	Formula	Elemental analysis (%)						IR (KBr) (cm^{-1})
				Calcd			Found			
				C	H	N	C	H	N	
1	A	6	$C_{21}H_{18}ClN_7O_5S_2 \cdot H_2O$	43.19	3.80	16.79	43.11	3.59	16.50	1765 1665 1605
2	B	40	$C_{21}H_{18}BrN_7O_5S_2 \cdot H_2O$	41.32	3.30	16.06	41.32	3.45	15.79	1765 1610 1530
3	B	27	$C_{21}H_{18}IN_7O_5S_2 \cdot H_2O$	38.36	3.07	14.91	38.18	3.31	14.70	1760 1670 1610
4	A	11	$C_{22}H_{21}N_7O_5S_3 \cdot \frac{3}{2}H_2O$	43.99	4.03	18.66	43.72	4.28	18.41	1770 1670 1610
5	A	7	$C_{22}H_{21}N_7O_6S_3 \cdot \frac{7}{2}H_2O$	41.37	4.42	15.35	41.20	4.70	15.18	1765 1670 1610
6	A	6	$C_{22}H_{21}N_7O_7S_3 \cdot \frac{5}{2}H_2O$	41.50	4.12	15.40	41.36	4.41	15.10	1765 1670 1610
7	A	13	$C_{21}H_{18}N_7NaO_8S_3 \cdot \frac{9}{2}H_2O$	36.21	3.91	14.07	35.90	4.18	13.88	1765 1665 1610
8	A	16	$C_{22}H_{20}ClN_7O_5S_2 \cdot 2H_2O$	44.18	4.05	16.39	44.04	3.87	16.13	1765 1605 1520
9	A	1	$C_{22}H_{19}Cl_2N_7O_5S_2 \cdot 3H_2O$	40.62	3.87	15.07	40.51	3.61	14.78	1760 1610 1520
10	A	4	$C_{22}H_{17}ClN_7NaO_7S_2 \cdot 3H_2O$	39.56	3.47	14.68	39.26	3.70	14.39	1760 1610 1530
11	A	3	$C_{24}H_{21}ClN_7NaO_7S_2 \cdot 4H_2O$	40.37	4.09	13.73	40.52	3.76	13.55	1765 1600 1520
12	A	10	$C_{20}H_{17}ClN_8O_5S_2 \cdot 3H_2O$	39.84	3.84	18.58	39.63	3.15	18.33	1770 1660 1610
13	A	3	$C_{21}H_{18}ClN_7O_5S_2 \cdot 3H_2O$	41.90	4.02	16.29	41.45	3.31	15.79	1763 1665 1610
14	A	4	$C_{21}H_{18}ClN_7O_5S_2 \cdot \frac{5}{2}H_2O$	42.53	3.91	16.53	42.33	3.96	16.82	1768 1665 1610
15	A	7	$C_{22}H_{20}ClN_7O_5S_2 \cdot 3H_2O$	42.89	4.25	15.92	42.93	3.99	15.91	1770 1670 1610
16	A	5	$C_{22}H_{20}ClN_7O_5S_2 \cdot \frac{3}{2}H_2O$	44.86	3.94	16.65	44.84	3.79	16.46	1770 1650 1610
17	A	9	$C_{22}H_{20}ClN_7O_5S_2 \cdot 3H_2O$	42.89	4.25	15.92	42.90	3.96	15.79	1770 1660 1610
18	A	5	$C_{22}H_{20}ClN_7O_5S_2 \cdot 5H_2O$	40.52	4.64	15.04	40.59	4.38	14.81	1760 1660 1605
19	A	3	$C_{21}H_{17}Cl_2N_7O_5S_2 \cdot 2H_2O$	40.78	3.42	15.85	41.02	3.38	15.70	1765 1660 1610
20	A	10	$C_{23}H_{20}ClN_7O_7S_2 \cdot 3H_2O$	41.85	3.97	14.85	41.80	3.78	15.09	1760 1710 1670
21	A	2	$C_{22}H_{17}ClN_8O_5S_2 \cdot \frac{7}{2}H_2O$	41.54	3.80	17.62	41.48	3.70	17.41	2240 1765 1660
22	A	3	$C_{23}H_{22}ClN_7O_5S_2 \cdot 2H_2O$	45.13	4.28	16.02	45.01	4.63	15.79	1770 1660 1610
23	A	10	$C_{22}H_{20}ClN_7O_5S_2 \cdot \frac{5}{2}H_2O$	43.53	4.15	16.15	43.45	4.01	15.92	1770 1660 1610
24	A	8	$C_{24}H_{22}ClN_7O_7S_2 \cdot 4H_2O$	41.65	4.37	14.17	41.73	4.10	14.06	1760 1720 1670

* See Experimental section.

solution was acidified to pH 1 with conc HCl. The resulting solution was chromatographed on MCI gel CHP 20P with 0.01 N HCl and 10% EtOH - 0.01 N HCl as the eluents. The fractions containing the objective compound were combined and concentrated, and the residual solution was adjusted to pH 7.5 with $NaHCO_3$. The resulting solution was chromatographed on Sephadex LH-20 with H_2O. The fractions containing the objective compound were combined, concentrated and lyophilized to give **7** (13%) as an amorphous solid. The analytical data are shown in Tables 5 and 6.

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(*Z*)-carboxymethoxyiminoacetamido]-3-(imidazo[1,2-*a*]-pyridinium-1-yl)methyl-3-cephem-4-carboxylate Monosodium Salt (**10**)

a) A mixture of 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XI-4**, 3.0 g), imiadzo[1,2-*a*]pyridine (3.0 g) and NaI (3.0 g) in 50% aq MeCN (20 ml) was heated at 70°C for 1.5 hours with stirring. After cooling, the reaction mixture was chromatographed on silica gel with aq MeCN as the eluent. The fractions containing the objective compound were combined and concentrated, and the residual solution was chromatographed on Sephadex LH-20 with H_2O as the eluent. The fractions containing the objective cephalosporin were combined, concentrated and lyophilized to give 0.3 g (9%) of 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**XII-10**) as an amorphous solid; IR (KBr) cm^{-1} 1760, 1670, 1610; ^1H NMR (DMSO-d_6) δ 1.38 (9H, s), 2.90 (2H, ABq, $J=18$ Hz), 4.48 (2H, s), 4.97 (1H, d, $J=5$ Hz), 5.25 and 5.49 (2H, ABq, $J=14$ Hz), 5.58 (1H, dd, $J=5$ and 8 Hz), 7.34 (2H, br s), 7.52 (1H, t, $J=8$ Hz), 8.00 (1H, t, $J=8$ Hz), 8.40 (1H, br), 8.52 (1H, br), 8.70 (1H, d, $J=9$ Hz), 8.94 (1H, d, $J=6$ Hz), 9.27 (1H, d, $J=8$ Hz).

b) **XII-10** (0.28 g) was stirred with TFA (10 ml) at room temperature for one hour. After evaporation,

Table 6. ^{1}H NMR spectral data for 7β-[2-(2-amino-5-substituted-thiazol-4-yl)-2(Z)-2-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates.

Compound No.	Solvent[a]	Chemical shift (J=Hz)								
		Cephem nuclei					7-Acyl		R_2	3-Condensed-heterocyclic azolium residue and R_3
		2-CH_2 ABq (18)	3-CH_2 ABq (14)	6-H d (5)	7-H dd (5, 8)	CONH d (8)	5-R_1 s	NH_2 s		
1	a	2.96 3.44	5.20 5.50	4.97	5.61	9.44	—	7.32	3.80	7.5~9.0 (m)
2	a	2.98 3.43	5.27 5.48	4.98	5.60	9.42	—	7.36	3.80	7.51 (t, 7), 8.00 (t, 8), 8.40 (br s), 8.49 (br), 8.66 (d, 9), 8.94 (d, 6)
3	a	2.96 3.36	5.26 5.47	4.96	5.58	9.36	—	7.32	3.82	7.50 (t, 7), 8.01 (t, 8), 8.39 (br), 8.00 (t, br s), 8.67 (d, 9), 8.93
4	a	2.94 —	5.24 5.46	4.94	5.57	9.26	2.35	7.16	3.78	7.48 (t, 6), 7.97 (t, 8), 8.38 (br), 8.50 (br), 8.66 (d, 8), 8.92 (d, 6)
5	a	2.94 —	5.26 5.47	4.95	5.56	—	2.80	7.46	3.82	7.47 (t, 6), 7.97 (t, 8), 8.38 (br), 8.47 (br), 8.65 (d, 8), 8.92 (d, 6)
6	a	2.99 —	5.26 5.47	4.97	5.60	9.28	3.36	7.97	3.88	7.49 (t, 6), 8.38 (br), 8.48 (br), 8.65 (d, 8), 8.93 (d, 6)
7	b	3.20 3.55	5.34 (br)	5.22	5.82 (d, 5)	—	—	—	4.12	7.3~8.3 (m), 8.40 (d, 6), 8.70 (d, 6)
8	b	3.30 3.60	5.31 5.67	5.22	5.85	—	—	—	4.00	7.32~8.68 (m)
9	a	3.00 3.46	5.12 5.27	5.00	5.60	9.38	—	7.25	3.6~3.9 (m), 4.1~4.4 (m)	7.4~7.6 (m), 7.9~8.1 (m), 8.3~8.7 (m), 8.8~9.0 (m)
10	a	3.02 —	5.38 (br)	4.97	5.64	11.85	—	7.35	4.22 (br)	7.49 (t, 7), 7.98 (t, 8), 8.3~8.7 (m), 8.96 (d, 8)
11	a	3.05 3.45	5.42 (br)	4.98	5.68	—	—	7.30	1.12 (br)	7.49 (t, 7), 7.96 (t, 8), 7.3~8.7 (m), 8.95 (d, 8)
12	a	3.04 —	5.27 5.51	4.97	5.61	9.43	—	7.32	3.81	7.8~8.1 (m), 8.76 (s), 9.0~9.1 (m), 9.28 (s)
13	a	3.23 3.64	5.81 (br)	5.00	5.37	9.31	—	7.34	4.12	7.63~8.39 (d, 3)
14	a	3.21 —	5.10 5.53	5.00	5.62	9.42	—	7.35	3.79	7.00~8.77 (m), 10.00 (br)
15	a	3.13 —	5.37 (br)	5.00	5.64	9.40	—	7.30	3.82	2.63 (s), 7.0~7.5 (m), 7.7~8.3 (m), 8.4~8.7 (m)
16	a	3.10 3.45	5.24 5.42	4.98	5.62	9.42	—	7.43	3.82	2.95 (s), 7.0~7.5 (m), 7.6~8.1 (m), 8.44 (s), 8.2~8.5 (m)
17	a	3.16 3.52	5.05 5.53	5.00	5.62	9.38	—	7.31	3.80	2.65 (s), 6.9~7.4 (m), 7.79 (d, 9), 8.64 (s), 9.93 (s)
18	a	3.11 —	5.36 5.64	4.99	5.64	9.36	—	7.32	3.81	2.32 (s), 6.86~7.12 (m), 7.58 (br), 8.33 (s), 8.58~8.66 (m), 9.88 (s)
19	a	3.14 3.54	5.10 5.56	5.02	5.65	9.38	—	7.32	3.81	7.7~8.0 (m), 8.4~8.8 (m), 9.13 (br)
20	a	3.14 3.57	5.14 5.52	5.00	5.62	9.37	—	7.32	3.81	3.92 (s), 7.3~7.5 (m), 8.5~8.9 (m), 10.16 (br)
21	a	3.11 3.53	5.10 5.54	5.00	5.62	9.38	—	7.32	3.81	7.3~7.5 (m), 8.6~9.0 (m), 10.15 (br)
22	a	— —	5.27 —	4.98 5.46	5.62	9.42	—	7.34	3.82	2.90 (s), 3.21 (s), 6.7~7.2 (m), 7.66 (d, 8), 8.45 (s)
23	a	3.15 3.57	5.18 5.56	—	5.66	9.34	—	—	1.21 (t, 7), 4.08 (q, 7)	7.0~7.6 (m), 7.7~7.9 (m), 8.4~8.8 (m), 10.02 (br)
24	a	3.18 3.70	5.17 5.59	5.02	5.66	9.36	—	7.32	1.20 (t, 7), 4.07 (q, 7)	3.92 (s), 7.32 (br), 7.4~7.6 (m), 8.5~8.9 (m), 10.14 (br)

[a] a; DMSO-d_6, b; D_2O.

the residue was dissolved in a solution of $NaHCO_3$ (2.0 g) in H_2O (10 ml). The resulting solution was chromatographed on MCI gel CHP 20P successively with H_2O and aq EtOH as the eluents. The fractions containing the objective compound were combined, concentrated and lyophilized to give 12 mg (4%) of **10** as an amorphous solid. The analytical results are shown in Tables 5 and 6.

Direct Halogenation of 2-Aminothiazolyl Cephalosporin [Method B]

7β-[2-(2-Amino-5-bromothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**2**)

N-Bromosuccinimide (0.28 g) was added to a solution of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**I-1**, 0.40 g) in DMA (4 ml) with ice-cooling, and the mixture was stirred at room temperature for 2 hours. Et_2O (100 ml) was added to the reaction mixture, and the upper layer was decanted off. The residue was triturated with Et_2O and the solid was collected by filtration. The solid was dissolved in 50% aq MeCN and chromatographed on silica gel with aq Me_2CO as the eluent. The fraction eluted with 75% aq Me_2CO was concentrated and the residual solution was chromatographed on Sephadex LH-20 with H_2O as the eluent. The fractions containing the objective compound were combined, concentrated and lyophilized to give 0.19 g (40%) of **2** as an amorphous solid. The analytical results are shown in Tables 5 and 6.

7β-[2-(2-Amino-5-iodothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**3**)

3 was prepared from **I-1** and *N*-iodosuccinimide (NIS) following a procedure similar to that of **2**. The analytical results are shown in Tables 5 and 6.

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