STUDIES ON CONDENSED-HETEROCYCLIC AZOLIUM CEPHALOSPORINS

IV[†]. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7β-[2-(5-AMINO-1,2,4-THIADIAZOL-3-YL)-2(*Z*)-ALKOXYIMINOACETAMIDO]-3-(CONDENSED-HETEROCYCLIC AZOLIUM)METHYL CEPHALOSPORINS INCLUDING SCE-2787

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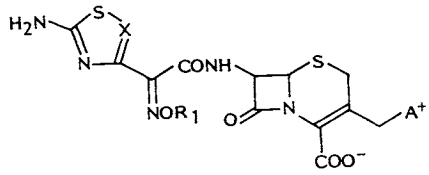
The synthesis and *in vitro* antibacterial activity of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido] cephalosporins bearing various condensed-heterocyclic azolium groups at the 3 position in the cephalosporin nucleus are described. The thiadiazolyl cephalosporins showed good antibacterial activity against both Gram-positive and Gram-negative bacteria and the MICs of the thiadiazolyl cephalosporins against *Pseudomonas aeruginosa* was more potent than that of the corresponding 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl cephalosporins. Also, the thiadiazolyl cephalosporins bearing (imidazo[1,2-*b*]-pyridazinium-1-yl)methyl groups at the 3 position showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Among the cephalosporins tested, 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylate (**4**, SCE-2787) which exhibited the most potent antibacterial activity and the broadest antibacterial spectrum was selected as a parenteral cephalosporin candidate for further biological evaluation.

In the preceding reports[2~4], we described the synthesis and antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido] cephalosporins (**I**, Fig. 1) bearing condensed-heterocyclic azolium methyl groups such as imidazo[1,2-*a*]pyridinium methyl, pyrazolo[1,5-*a*]pyridinium methyl, imidazo[1,5-*a*]pyridinium methyl and imidazo[1,2-*b*]pyridazinium methyl at the 3 position of cephalosporin nucleus. The antibacterial activity of **I** against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa* was superior to that of cefmenoxime (CMX) or ceftazidime (CAZ). Furthermore, we found that 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,5-*a*]pyridinium-2-yl)methyl-3-cephem-4-carboxylate (**IIa**) showed even better antibacterial activity against both cephalosporin-resistant *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA)[4], whereas the antibacterial activity of **IIa** against the other Gram-negative bacteria was weaker than that of **Ia**~**Id**. These differences in the antibacterial activity of **Ia**~**Id** and **IIa** appeared to be due to the decrease in the *pK*a value of the amino group caused by the substitution of the thiazole ring with a chlorine atom.

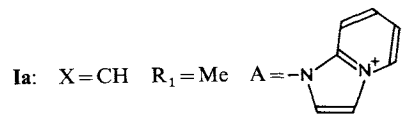
We speculated that cephalosporins having a 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetyl moiety as the 7-acyl group would show potent activity against both Gram-positive bacteria including MRSA and Gram-negative bacteria including *Pseudomonas aeruginosa* for the following reasons. The

[†] Part of this work has been presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy[1].

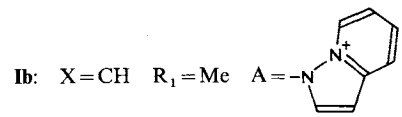
Fig. 1. 7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)-methyl-3-cephem-4-carboxylates (**I**) and 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**II**).



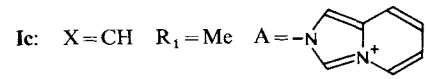
I, II



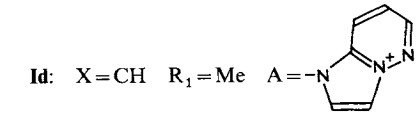
Ia: X=CH R_1=Me



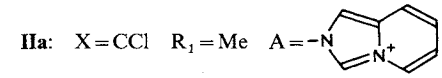
Ib: X=CH R_1=Me



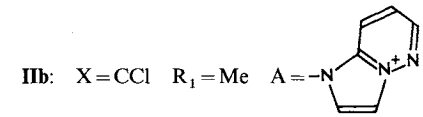
Ic: X=CH R_1=Me



Id: X=CH R_1=Me



IIa: X=CCl R_1=Me



IIb: X=CCl R_1=Me

amino group of the 5-amino-1,2,4-thiadiazole has low *pK*a value compared to that of the 2-aminothiazole[5] and the size of the thiadiazole ring is almost the same as that of a 2-aminothiazole ring. Therefore, we examined the antibacterial activity of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido] cephalosporins bearing a condensed-heterocyclic azolium methyl moiety at the 3-position. In this report, we describe the synthesis of these cephalosporins and their antibacterial activity.

Chemistry

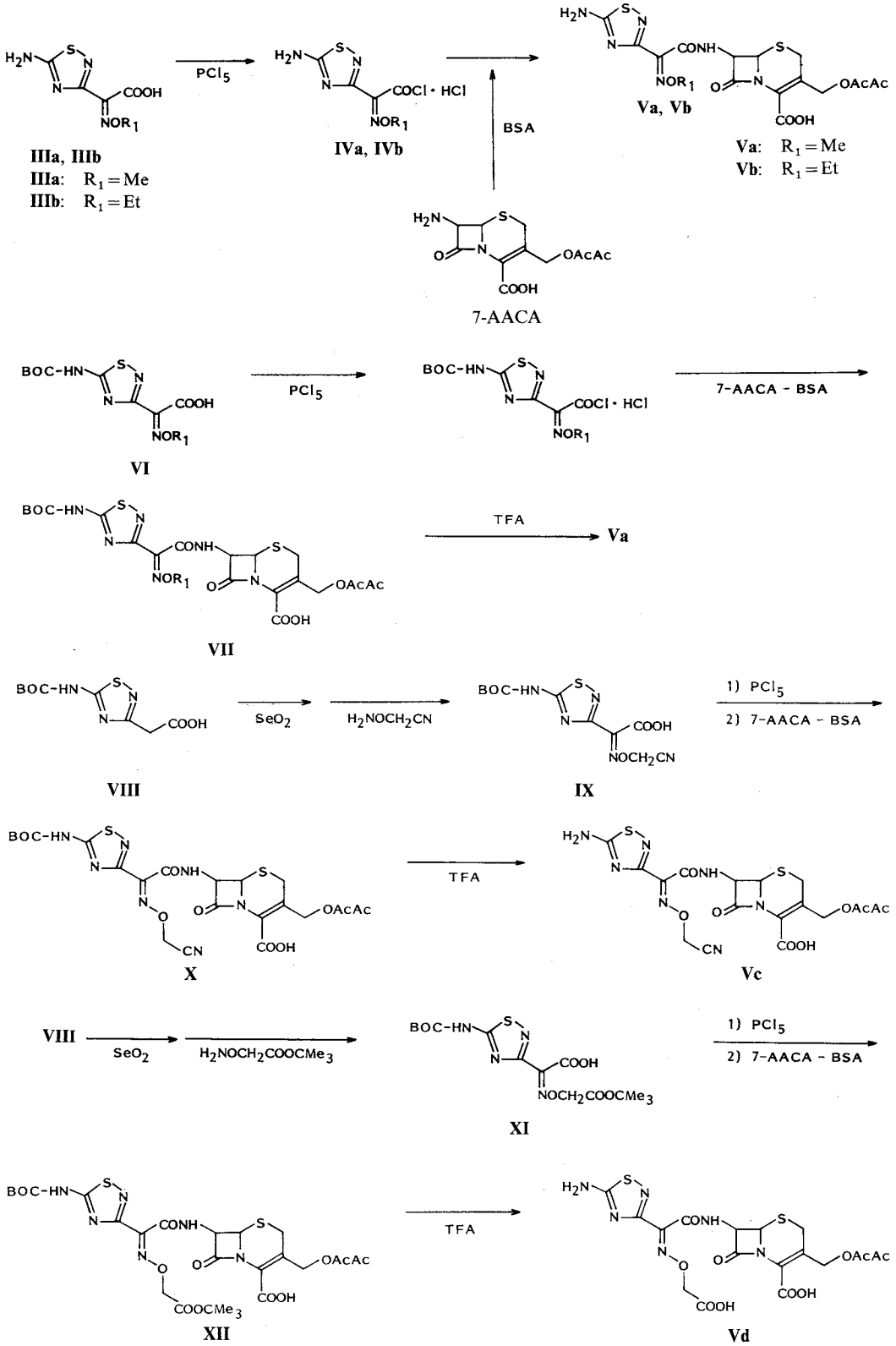
The preparation of the starting cephalosporins, 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**V**), is shown in Scheme 1.

2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetic acid (**III**)[6,7] was treated with phosphorous pentachloride to give the acid chloride (**IV**), which was condensed with 7β-amino-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (7-AACA) in the presence of bistrimethylsilylacetamide (BSA) to afford 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxy and ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**Va**, **Vb**).

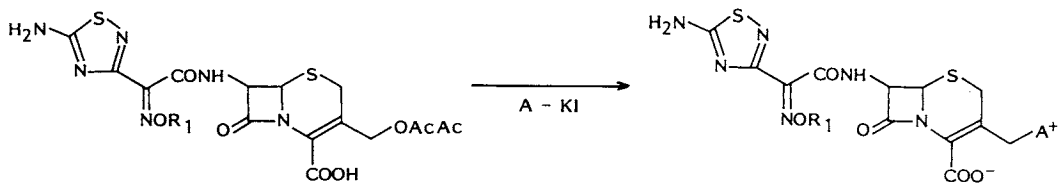
2-(5-*tert*-Butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetic acid (**VIa**) was converted by the treatment with phosphorous pentachloride to the corresponding acid chloride, which was reacted with 7-AACA in the presence of BSA to give 7β-[2-(5-*tert*-butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**VII**). **Va** was also obtained by the deprotection of the BOC group of **VII** with trifluoroacetic acid.

2-(5-*tert*-Butoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetic acid (**VIII**) was oxidized with selenium dioxide and then treated with *O*-cyanomethylhydroxylamine to give 2-(5-*tert*-butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-cyanomethoxyiminoacetic acid (**IX**). **IX** was reacted with phosphorous pentachloride to afford the corresponding acid chloride, which was condensed with 7-AACA in the presence of BSA to give 7β-[2-(5-*tert*-butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-cyanomethoxyiminoacetamido]-3-(3-

Scheme 1.


PCl5
BSA
IIIa, IIIb
IIIa: R1 = Me
IIIb: R1 = Et
IVa, IVb
Va, Vb
Va: R1 = Me
Vb: R1 = Et
7-AACA
VI
7-AACA - BSA
VII
TFA
Va
VIII
SeO2
H2NOCH2CN
IX
1) PCl5
2) 7-AACA - BSA
X
Vc
H2NOCH2COOCMe3
XI
XII
Vd

Scheme 2.



Va ~ Vd **1 ~ 24**

A: Azole

oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**X**). **X** was deprotected with trifluoroacetic acid to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-cyanomethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**Vc**).

VIII was converted to 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XII**) according to the similar procedure employed for the preparation of **Vc** mentioned above. 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-carboxymethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**Vd**) was obtained by the deprotection of *tert*-butyl ester of **XII** with trifluoroacetic acid.

The preparation of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates is outlined in Scheme 2.

V was heated with the condensed-heterocyclic azole (A) in the presence of potassium iodide in 50% aqueous acetonitrile at 60~70°C for 1~2 hours. The reaction mixture was purified by column chromatography on silica gel with aqueous acetone as the eluent followed by rechromatography on Amberlite XAD-2 or MCI gel to give the cephalosporins **1 ~ 24**, in 1~23% yield. Among the cephalosporins prepared, **7**, **11**, and **14** were isolated as the sodium salt. Also, **4** was converted to the hydrochloride salt.

Antibacterial Activity

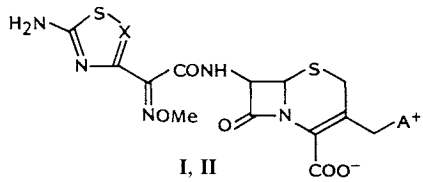
The MICs of the prepared cephalosporins against selected organisms, *i.e.*, *Staphylococcus aureus* 308A-1, *Staphylococcus aureus* N-241 (methicillin-resistant strain), *Escherichia coli* NIHJ JC-2, *Enterobacter cloacae* IFO 12937, *Serratia marcescens* IFO 12648, *Proteus vulgaris* IFO 3988, *Pseudomonas aeruginosa* IFO 3455 (β-lactam-sensitive strain, *P.a.*1) and *Pseudomonas aeruginosa* U-31 (β-lactam-resistant strain, *P.a.*2), were determined by the standard serial two-fold agar dilution method.

Table 1 shows a comparison of the antibacterial activity of the thiadiazolyl and the thiazolyl cephalosporins bearing imidazo[1,2-*a*]pyridinium methyl, pyrazolo[1,5-*a*]pyridinium methyl, imidazo-[1,5-*a*]pyridinium methyl and imidazo[1,2-*b*]pyridazinium methyl groups at the 3 position.

The antibacterial activity of thiadiazolyl cephalosporins (**1 ~ 4**) against *Staphylococcus aureus* was comparable to those of the thiazolyl cephalosporins (**Ia ~ Id**). The MICs of the thiadiazolyl cephalosporins (**1** and **2**) against *Serratia marcescens* and *Pseudomonas aeruginosa* were found to be more potent than those of the thiazolyl cephalosporins (**Ia** and **Ib**), whereas the MICs of **1** and **2** against *Escherichia coli* and *Proteus vulgaris* were inferior to those of **Ia** and **Ib**. The thiadiazolyl cephalosporins (**2**, **4**) bearing a pyrazolo[1,5-*a*]pyridinium and imidazo[1,2-*b*]pyridazinium groups showed more potent activity against *P. aeruginosa* (*P.a.*2) than the thiazolyl cephalosporins (**Ib**, **Id**).

Table 2 shows the MICs of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]

Table 1. Antibacterial activity (MIC, μg/ml) of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]- and 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(condensed-heterocyclic azolium)-methyl-3-cephem-4-carboxylates (**1**$\sim$**4** and **Ia**$\sim$**Id**), 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(condensed heterocyclic azolium)methyl-3-cephem-4-carboxylate (**IIa** and **IIb**) and ceftazidime (CAZ).



I, II

10^8 cfu/ml

Compound No.	X	A^+	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
1	N		0.39	0.2	0.78	0.39	0.78	1.56	>100
Ia	CH		0.39	<0.1	0.39	0.2	0.2	6.25	>100
2	N		1.56	0.2	0.78	0.2	1.56	0.78	12.5
Ib	CH		1.56	<0.1	0.78	0.39	0.2	1.56	100
3	N		0.78	<0.1	0.78	<0.1	0.2	6.25	50
Ic	CH		0.78	<0.1	1.56	<0.1	<0.1	1.56	>100
4	N		0.78	<0.1	0.39	0.2	0.39	0.78	12.5
Id	CH		0.78	<0.1	0.39	0.39	<0.1	1.56	100
IIa	CCl		0.78	0.78	1.56	0.78	0.78	3.13	6.25
IIb	CCl		0.78	1.56	6.25	3.13	1.56	3.13	6.25
CAZ			6.25	0.39	25	0.39	0.1	0.78	12.5

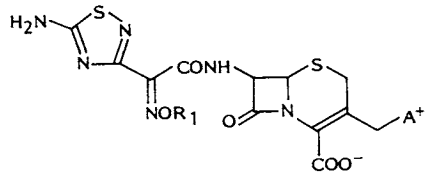
* *S.a.*; *Staphylococcus aureus* 308 A-1, *E.c.*; *Escherichia coli* NIHJ JC-2, *E.cl.*; *Enterobacter cloacae* IFO 12937, *S.m.*; *Serratia marsecens* IFO 12648, *P.v.*; *Proteus vulgaris* IFO 3988, *P.a.*1; *Pseudomonas aeruginosa* IFO 3455, *P.a.*2; *Pseudomonas aeruginosa* U31.

cephalosporins (**5**$\sim$**14**) bearing an imidazo[1,2-*a*]pyridinium, 6-cyanoimidazo[1,2-*a*]pyridinium, pyrazolo[1,5-*a*]pyridinium, or imidazo[1,2-*b*]pyridazinium methyl groups at the 3 position. In the case of imidazo[1,2-*a*]pyridinium cephalosporins, the antibacterial activity of the ethoxyimino cephalosporin (**5**) was superior to that of the methoxyimino cephalosporin (**1**). The MICs of the cyanomethoxy cephalosporins (**6**, **10**) were not improved as compared with those of **1** and **8**, respectively. The antibacterial activity of the carboxymethoxyimino cephalosporins (**7**, **11**, **14**) against *Staphylococcus aureus* was decreased.

Table 3 shows the MICs of the thiadiazolyl cephalosporins bearing substituted imidazo[1,2-*b*]-pyridazinium groups (**4**, **15**$\sim$**24**). The introduction of the substituents in the imidazo[1,2-*b*]pyridazine ring had no effect on the antibacterial activity.

The thiadiazolyl cephalosporins bearing condensed-heterocyclic azolium methyl at the 3 position in cephalosporin nucleus showed potent antibacterial activity and a broad antibacterial spectrum including

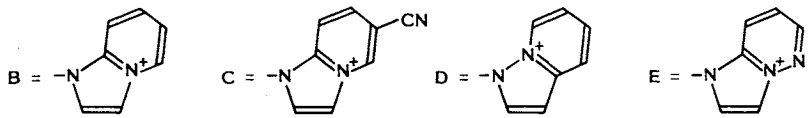
Table 2. Antibacterial activity (MIC, μg/ml) of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**, **2**, **4**~**14**).



10^8 cfu/ml

Compound No.	R_1	A^+	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
1	Me	B	0.39	0.2	0.78	0.39	0.78	6.25	>100
5	Et	B	0.2	<0.1	0.78	0.2	0.39	3.13	50
6	CH_2CN	B	0.39	0.2	1.56	0.39	0.78	3.13	>100
7	CH_2CO_2Na	B	1.56	0.2	3.13	0.2	0.78	3.13	50
8	Me	C	0.78	0.2	0.39	0.39	0.39	0.78	12.5
9	Et	C	0.78	<0.1	0.78	0.39	1.56	0.78	12.5
10	CH_2CN	C	0.78	0.2	1.56	0.39	0.78	0.78	25
11	CH_2CO_2Na	C	6.25	0.2	0.78	0.39	0.39	3.13	12.5
2	Me	D	1.56	0.2	0.78	0.2	0.78	0.78	12.5
12	Et	D	1.56	0.2	1.56	0.2	0.78	1.56	12.5
4	Me	E	0.78	<0.1	0.39	0.2	0.39	0.78	12.5
13	Et	E	0.78	<0.1	1.56	0.39	0.39	1.56	12.5
14	CH_2CO_2Na	E	6.25	<0.1	3.13	0.2	0.39	0.78	6.25

* See footnote in Table 1.



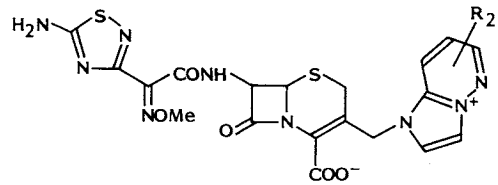
Pseudomonas aeruginosa and MRSA. In our previous report[4], we found that 5-chlorothiazolyl cephalosporin (**II**) showed good activity against *Pseudomonas aeruginosa* and MRSA, while the activity against the other Gram-negative bacteria was not satisfactory. However, the thiadiazolyl cephalosporins (**3**, **4**) bearing the same azolium moieties as **IIa** and **IIb** showed potent antibacterial activity against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa* (Tables 1 and 3). These results imply that the thiadiazolyl moiety is superior to the thiazolyl and the 5-chlorothiazolyl moieties for expanding antibacterial spectrum and improving activity.

Among the cephalosporins studied, 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylate (**4**, SCE-2787), which exhibited the most potent antibacterial activity and a broad antibacterial spectrum, has been selected as a candidate for further biological evaluation.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or HA-100A (100 MHz) spectrometer using tetramethylsilane as the internal or external standard. Organic solvents were dried over anhydr $MgSO_4$, and concentration by evaporation was carried out *in vacuo*. Column chromatography was carried out on Kieselgel 60 (Merck, Art 7734 or Art 9385), MCI gel CHP 20P (Mitsubishi Chemical), Amberlite XAD-2 (Rohm and Haas) and Sephadex LH-20 (Pharmacia Fine Chemical).

Table 3. Antibacterial activity (MIC, μg/ml) of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(substituted imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylates (**4**, **15**~**24**), 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,5-*a*]pyridinium-2-yl)methyl-3-cephem-4-carboxylate (**IIb**), cefmenoxime (CMX) and ceftazidime (CAZ).



10^8 cfu/ml

Compound No.	R_2	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2	MRSA*
4	H	0.78	<0.1	0.39	0.2	0.39	0.78	12.5	25
15	6-Me	1.56	<0.1	0.78	0.2	0.39	3.13	25	50
16	7-Me	0.78	0.2	0.78	0.39	0.78	1.56	12.5	50
17	8-Me	0.78	0.39	1.56	0.39	0.78	3.13	50	12.5
18	6-F	1.56	<0.1	0.78	0.2	0.39	1.56	12.5	50
19	6-Cl	1.56	<0.1	0.78	0.2	0.78	3.13	12.5	12.5
20	6-OMe	0.78	<0.1	0.78	<0.1	0.39	3.13	25	50
21	6-OEt	1.56	0.2	0.78	0.39	0.78	50	50	100
22	6-SMe	0.78	<0.1	0.2	0.2	0.78	6.25	25	25
23	6-NMe_2	0.78	<0.1	0.78	0.2	0.78	50	100	50
24	6-$SCH_2CH_2NMe_2$	3.13	0.2	1.56	0.78	1.56	50	25	50
IIb		0.78	1.56	6.25	3.13	1.56	3.13	6.25	6.25
CMX		1.56	0.2	6.25	0.39	<0.1	6.25	>100	>100
CAZ		6.25	0.39	25	0.39	0.1	0.78	12.5	>100

* See footnote in Table 1, MRSA; *Staphylococcus aureus* N-241.

Determination of *In Vitro* Antibacterial Activity

The MICs against selected strains of Gram-positive and Gram-negative bacteria were determined by the standard serial two-fold agar dilution method with Mueller-Hinton broth as the test medium, after incubation overnight at 37°C with an inoculum size of about 10^8 cfu/ml.

Preparation of Condensed-heterocycles

Condensed-heterocycles were prepared according to the procedure reported previously[2,3]. The other condensed-heterocycles were prepared according to the procedure mentioned below.

6-Ethoxyimidazo[1,2-*b*]pyridazine

6-Chloroimidazo[1,2-*b*]pyridazine (3 g) was refluxed in a solution of Na (0.55 g) and EtOH (30 ml) for 3 hours. The solvent was evaporated and the residue was dissolved in H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and satd aq NaCl, dried and evaporated to give 3.3 g (100%) of 6-ethoxyimidazo[1,2-*b*]pyridiazine as colorless crystals; MP 102~103°C; ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, J=7 Hz), 4.53 (2H, q, J=7 Hz), 6.63 (1H, d, J=10 Hz), 7.56 (1H, br), 7.68 (1H, br), 7.74 (1H, d, J=10 Hz).

Anal Calcd for $C_8H_9N_3O$: C 58.88, H 5.56, N 25.75.
Found: C 58.78, H 5.67, N 25.73.

6-(2-Dimethylaminoethyl)thioimidazo[1,2-*b*]pyridazine

NaOMe in MeOH soln (2 M, 20 ml) was added to a MeOH (20 ml) soln of 2-dimethylaminoethanethiol hydrochloride (2.8 g). 6-Chloroimidazo[1,2-*b*]pyridazine (3 g) was added to this solution, and the mixture was heated at 150°C in a sealed tube for 4 hours. After cooling, the solvent was evaporated and the residue was dissolved in H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with satd aq

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

Compound No.	Yield %	Formula	Elemental analysis %						IR (KBr) cm^{-1}
			Calcd			Found			
			C	H	N	C	H	N	
1	10	$C_{20}H_{18}N_8O_5S \cdot 4H_2O$	40.95	4.47	19.10	41.15	4.23	18.94	1770, 1620, 1530
2	1	$C_{20}H_{18}N_8O_5S_2 \cdot \frac{7}{2}H_2O$	41.59	4.36	19.40	41.80	4.61	19.48	1770, 1670, 1620, 1520
3	17	$C_{20}H_{18}N_8O_5S_2 \cdot 3H_2O$	42.25	4.25	19.71	42.17	4.01	19.56	1765, 1660, 1610, 1520
4	17	$C_{19}H_{17}N_9O_5S_2 \cdot 3H_2O$	40.07	4.07	22.13	39.78	3.81	21.89	1765, 1660, 1610, 1520
5	19	$C_{21}H_{20}N_8O_5S_2 \cdot 4H_2O$	41.99	4.70	18.66	42.25	4.52	18.44	1770, 1610, 1530
6	3	$C_{21}H_{17}N_9O_5S_2 \cdot 4H_2O$	42.49	3.91	21.24	42.31	3.69	20.93	1760, 1605, 1520
7	23	$C_{21}H_{17}N_8O_7S_2 \cdot Na \cdot 5H_2O$	37.61	4.06	16.71	37.38	3.79	16.48	1760, 1600, 1520
8	23	$C_{21}H_{17}N_9O_5S_2 \cdot 3H_2O$	42.49	3.91	21.24	42.56	3.67	21.01	2250, 1760, 1600, 1520
9	15	$C_{22}H_{19}N_9O_5S_2 \cdot 4H_2O$	42.24	4.35	20.15	42.12	3.98	19.97	2250, 1760, 1620, 1525
10	11	$C_{23}H_{17}N_9O_5S_2 \cdot \frac{9}{2}H_2O$	42.85	4.07	19.56	42.68	4.01	19.51	2250, 1760, 1670, 1650
11	14	$C_{22}H_{16}N_9O_7S_2 \cdot 5H_2O$	37.99	3.77	18.12	38.17	3.63	17.96	2240, 1760, 1600, 1520
12	1.5	$C_{21}H_{20}N_8O_5S_2 \cdot 4H_2O$	41.99	4.70	18.66	42.16	4.71	18.30	1770, 1670, 1610, 1510
13	5	$C_{20}H_{19}N_9O_5S_2 \cdot 4H_2O$	39.93	4.52	20.95	40.35	4.68	20.68	1770, 1670, 1610, 1520
14	7	$C_{20}H_{16}N_9O_7S_2 \cdot \frac{13}{2}H_2O$	34.38	4.18	18.04	34.48	3.64	17.54	1770, 1600, 1520
15	11	$C_{20}H_{19}N_9O_5S_2 \cdot 5H_2O$	38.77	4.72	20.35	38.94	4.69	20.32	1765, 1660, 1605, 1520
16	15	$C_{20}H_{19}N_9O_5S_2 \cdot 5H_2O$	38.77	4.72	20.35	38.82	4.75	20.32	1760, 1665, 1610, 1520
17	7	$C_{20}H_{19}N_9O_5S_2 \cdot \frac{9}{2}H_2O$	39.34	4.62	20.65	39.48	4.92	20.74	1765, 1670, 1610, 1520
18	12	$C_{19}H_{16}N_9O_5S_2 \cdot F \cdot 4H_2O$	37.68	3.99	20.82	38.03	3.89	20.55	1770, 1670, 1610, 1520
19	10	$C_{19}H_{16}N_9O_7S_2 \cdot Cl \cdot 4H_2O$	36.69	3.89	20.27	36.80	3.72	20.09	1775, 1670, 1610, 1520
20	8	$C_{20}H_{19}N_9O_6S_2 \cdot \frac{9}{2}H_2O$	38.34	4.50	20.12	38.39	4.54	20.02	1770, 1670, 1610, 1510
21	11	$C_{21}H_{21}N_9O_6S_2 \cdot 3H_2O$	41.11	4.44	20.54	40.95	4.56	20.32	1770, 1670, 1600, 1510
22	7	$C_{20}H_{19}N_9O_5S_3 \cdot \frac{7}{2}H_2O$	38.46	4.20	20.18	38.40	4.25	20.11	1770, 1670, 1600, 1520
23	12	$C_{21}H_{22}N_{10}O_5S_2 \cdot 4H_2O$	40.00	4.80	22.21	40.26	5.00	22.07	1775, 1670, 1610, 1590
24	16	$C_{23}H_{26}N_{10}O_5S_3 \cdot 2HCl \cdot \frac{11}{2}H_2O$	34.94	4.97	17.71	35.15	4.46	17.66	1770, 1675, 1625, 1510

NaCl, dried and evaporated to give 2.5 g (58%) of 6-(2-dimethylaminoethyl)thioimidazo[1,2-*b*]pyridazine as pale yellow crystals; MP 52～54°C; ^{1}H NMR ($CDCl_3$) δ 2.34 (6H, s), 2.70 (2H, t, J=7 Hz), 3.37 (2H, t, J=7 Hz), 6.83 (1H, d, J=10 Hz), 7.68 (1H, br), 7.74 (1H, d, J=10 Hz), 7.81 (1H, br).

Anal Calcd for $C_{10}H_{14}N_4S$: C 54.03, H 6.35, N 25.20.
Found: C 54.26, H 6.56, N 25.30.

6-Dimethylaminoimidazo[1,2-*b*]pyridazine

A mixture of 6-chloroimidazo[1,2-*b*]pyridazine (2.8 g) and 17% Me_2NH - EtOH soln (50 ml) was heated at 180°C in a sealed tube for 5 hours. After removal of the solvent, the residue was dissolved in H_2O, alkalized with 10% NaOH and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and satd aq NaCl, dried and evaporated to give 2.6 g (88%) of 6-dimethylaminoimidazo-[1,2-*b*]pyridazine as yellow crystals; MP 83～85°C; ^{1}H NMR ($CDCl_3$) δ 3.10 (6H, s), 6.72 (1H, d, J=10 Hz), 7.53 (1H, br), 7.68 (1H, br), 7.69 (1H, d, J=10 Hz).

Anal Calcd for $C_8H_{10}N_4$: C 59.24, H 6.21, N 34.54.
Found: C 59.36, H 6.36, N 34.30.

Preparation of Starting Cephalosporins

Method A

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

Bistrimethylsilylacetamide (BSA, 28.9 g) was added to a suspension of 7β-amino-3-(3-oxobutyryloxy-methyl)-3-cephem-4-carboxylic acid (7-AACA, 9.6 g) in CH_2Cl_2 (240 ml). The mixture was stirred at room

Table 5. ^{1}H NMR data for 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**~**24**).

Compound No.	Solvent	Chemical shift δ							
		Cephem nuclei					7-Acyl		Azolium ring proton
		2-CH_2 ABq J=18 Hz	3-CH_2 ABq 14 Hz	6-H d 5 Hz	7-H dd 5 & 8 Hz	CONH d 8 Hz	NH_2 br	R_1	
1	A	2.96 3.42	5.26 5.48	4.98	5.62	9.43	—	3.86 (s)	7.40~7.60 (t, 6), 8.34~8.76 (m), 8.86~9.00 (d, 9)
2	B	3.06 3.48	5.60 (br)	—	5.85	—	—	—	7.72 (d, 4), 7.48~7.70 (m), 7.74~8.00 (m), 8.02~8.2 (m), 8.45 (d, 4), 9.15 (d, 7)
3	A	3.13 3.54	5.12 5.54	5.02	5.65	9.39	8.10	3.86 (s)	7.83 (d, 8), 8.50 (s), 8.65 (d, 6), 9.97 (br)
4	A	3.03 3.42	5.27 5.51	4.99	5.63	9.44	8.12	3.86 (s)	7.8~8.32 (m), 8.76 (s), 9.04 (d, 4), 9.31 (d, 9)
5	A	3.02 3.44	5.42 br	5.01	5.66	9.42	8.16	1.20 (t, 7) 4.12 (q, 7)	7.50 (t, 7), 8.00 (t, 7), 8.40~8.7 (m), 8.98 (d, 7)
6	A	3.16 3.53	5.31 br	5.15	5.82	—	—		7.4~7.8 (m), 7.9~8.3 (m), 8.6~8.8 (m)
7	B	3.16	5.32	5.22	5.86	—	—	—	7.4~8.80 (m)
8	A	2.98 3.46	5.28 5.54	5.00	5.64	9.44	8.11	3.86 (s)	8.2~9.0 (m), 9.78 (br)
9	A	2.98 3.44	5.1~ 5.6	5.00	5.66	9.42	8.10	1.19 (t, 7)	8.2~9.0 (m), 9.76 (br)
10	A	2.96 3.46	5.27 5.53	5.01	5.64	9.66	8.22	5.02 (s)	8.2~9.0 (m), 9.77 (br)
11	B	3.16 3.59	5.38	5.24	5.86	—	—	—	8.2~9.0 (m), 9.8 (br)
12	B	3.07 3.48	5.65 br	5.24	5.85	—	—	1.29 (t, 7) 4.31 (q, 7)	7.17 (d, 4), 7.48~7.72 (m), 7.74~8.2 (m), 8.44 (d, 4), 9.17 (d, 7)
13	A	3.03 3.44	5.28 5.52	4.99	5.65	9.43	—	1.20 (t, 7) 4.13 (q, 7)	7.8~8.2 (m), 8.75 (m), 9.05 (d, 4), 9.28 (s)
14	A	3.52 3.72	5.34 5.50	4.98	5.68	—	—	4.34 (s)	7.90 (dd, 5 & 10), 8.65 (d, 5), 9.08 (d, 10)
15	A	2.99 3.43	5.24 5.40	4.97	5.61	9.43	8.10	3.86 (s)	2.67 (s), 7.86 (d, 9), 8.58~8.74 (m), 9.20 (d, 9)
16	A	3.00	5.20 5.43	4.99	5.62	9.42	8.09	3.86 (s)	2.56 (s), 8.58~8.74 (m), 8.97 (br), 9.08 (br)
17	A	3.06 3.39	5.50 br	5.09	5.70	9.47	7.97	3.90 (s)	2.17 (s), 7.68 (d, 5), 8.32~8.52 (m), 8.56~8.66 (m), 8.84 (d, 5)
18	A	3.00 —	5.26 5.59	4.98	5.62	9.41	—	3.86 (s)	7.9~8.24 (m), 8.62~8.86 (m), 9.48~9.74 (m)
19	A	2.98	5.24 3.42	4.98 5.55	5.59	9.42	8.06	3.86 (s)	8.17 (d, 9), 8.73~8.9 (m), 9.48 (d, 9)
20	A	2.98 3.43	5.20 5.50	4.97	5.62	9.42	8.04	3.86 (s)	4.06 (s), 7.62 (d, 9), 8.38~8.68 (m), 9.22 (d, 9)
21	A	2.98 3.42	5.20 5.50	4.98	5.60	9.40	8.04	3.87 (s)	1.44 (t, 7), 4.46 (q, 7), 7.57 (d, 14), 8.46 (d, 2), 9.24 (d, 10)
22	A	3.01 —	5.22 5.50	4.98	5.63	9.44	8.10	3.86 (s)	2.66 (s), 7.91 (d, 10), 8.54~8.74 (m), 9.22 (d, 10)
23	A	3.04 br	5.15 5.43	4.96	5.57	9.40	8.07	3.86 (s)	3.14 (s), 7.68 (d, 10), 8.24 (br), 8.39 (br), 8.96 (d, 10)
24	B	—	5.46	5.18	5.82	—	—	4.08 (s)	2.90 (s), 3.3~3.85 (m), 7.97 (d, 10), 8.27 (br), 8.73 (d, 10), 8.79 (br)

A: DMSO-d_6, B: D_2O.

temperature until it became a clear solution and was then cooled with an ice bath. 2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetyl chloride hydrochloride (**IVa**), which was prepared from 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetic acid (**IIIa**, 5.88 g) and PCl_5 (6.02 g) in CH_2Cl_2 (90 ml) according to the procedure of GOTO[7], was added to the mixture and the resultant mixture was stirred for one hour with ice-cooling. After evaporating the solvent, the residue was dissolved in methyl ethyl ketone. The solution was washed with H_2O, dried and evaporated. Et_2O was added to the residue and the resultant powder was collected by filtration and dried to give 11.8 g (82%) of **Va**; IR (KBr) cm^{-1} 1770, 1710, 1620, 1520, 1400, 1260, 1150, 1040; ^1H NMR (DMSO-d_6) δ 2.19 (3H, s), 3.40 and 3.65 (2H, ABq, J=18 Hz), 3.63 (2H, s), 3.95 (3H, s), 4.78 and 5.09 (2H, ABq, J=14 Hz), 5.14 (1H, d, J=4.8 Hz), 5.84 (1H, dd, J=8 and 4.8 Hz), 8.11 (2H, br), 9.59 (1H, d, J=8 Hz).

Method B

7β-[2-(5-*tert*-Butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**VII**)

A suspension of 2-(5-*tert*-butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetic acid[6] (**VI**, 302 mg) in CH_2Cl_2 (4 ml) was stirred with PCl_5 (208 mg) under ice-cooling for 15 minutes and then evaporated. *n*-Hexane was added to the residue and the solvent again removed by evaporation. The residue was dissolved in the CH_2Cl_2 (4 ml). This solution was added to a solution of 7-AACA (300 mg) and triethylamine (0.6 ml) in dimethylacetamide (5 ml) with stirring and ice-cooling. After stirring for 30 minutes, H_3PO_4 (10%, 10 ml) was added to the reaction mixture, and the resultant mixture was extracted with methyl ethyl ketone. The organic layer was washed with H_2O, dried and evaporated. EtOAc (50 ml) was added to the residue and evaporated to give 390 mg (65%) of **VII**; IR (KBr) cm^{-1} 2940, 2890, 1780, 1715, 1540, 1370, 1245, 1150, 1040, 835; ^1H NMR (DMSO-d_6) δ 1.55 (9H, s), 2.20 (3H, s), 3.43 and 3.70 (2H, ABq, J=18 Hz), 3.65 (2H, s), 4.00 (3H, s), 4.80 and 5.12 (2H, ABq, J=12 Hz), 5.18 (1H, d, J=4.5 Hz), 5.88 (1H, dd, J=9 and 4.5 Hz), 9.63 (1H, d, J=9 Hz).

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

VII (13 g) was added to TFA (50 ml) with ice-cooling and stirring. The mixture was stirred at room temperature for 30 minutes and then evaporated. EtOAc was added to the residue, and the resultant solution was evaporated. Et_2O (100 ml) was added to the residue. The resultant powder was collected by filtration and dried to give 10 g (92%) of **Va**. The IR and NMR spectra of this compound were identical to those of the **Va** obtained by method A.

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**Vb**)

A suspension of 7-AACA (11 g) in CH_2Cl_2 (200 ml) was stirred with BSA (14 g) at room temperature until the mixture became a clear solution and was then cooled with an ice bath. 2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-ethoxyiminoacetyl chloride hydrochloride (**IVb**, 14 g) was added to this cooled solution. The mixture was stirred for one hour and then evaporated. The residue was dissolved in methyl ethyl ketone, washed with H_2O, dried and evaporated to give 12.5 g (70%) of **Vb**; IR (KBr) cm^{-1} 1780, 1720, 1620, 1520, 1410, 1260, 1150, 1040; ^1H NMR (DMSO-d_6) δ 1.25 (3H, t, J=7 Hz), 2.18 (3H, s), 3.41 and 3.63 (2H, ABq, J=18 Hz), 3.62 (2H, s), 4.18 (2H, q, J=7 Hz), 4.76 and 5.06 (2H, ABq, J=13 Hz), 5.14 (1H, d, J=4.8 Hz), 5.82 (1H, dd, J=8 and 4.8 Hz), 8.00 (2H, br), 9.48 (1H, d, J=8 Hz).

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-cyanomethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**Vc**)

A mixture of 2-(5-*tert*-butoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetic acid (**VIII**, 13 g) and SeO_2 (10.7 g) in dioxane (100 ml) was heated at 90°C with stirring for 40 minutes and then evaporated. EtOAc (150 ml) was added to the residue and the solid was filtered off. The filtrate was evaporated and the residue was dissolved in EtOH (100 ml). *O*-Cyanomethylhydroxylamine (3.6 g) was added to the solution and the mixture was stirred for 30 minutes. After removal of the solvent, the residue was dissolved in EtOAc

(150 ml). The solution was washed with H_2O, extracted with 5% aq $NaHCO_3$ and the aqueous layer was separated. EtOAc was added to the aqueous solution and the aqueous layer was acidified with H_3PO_4. The organic layer was separated, dried and evaporated to give 2-(5-*tert*-butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-cyanomethoxyiminoacetic acid (**IX**). **IX** was dissolved in CH_2Cl_2 (30 ml) and the solution was stirred with PCl_5 (2.2 g) under ice-cooling. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (5 ml). This solution was added to a solution prepared from 7-AACA (3.1 g) and BSA (6 ml) in CH_2Cl_2 (60 ml) under ice-cooling, and the mixture was stirred for 30 minutes. After removal of the solvent, the residue was dissolved in EtOAc (100 ml). The solution was washed with H_2O, dried and evaporated. TFA (10 ml) was added to the residue with stirring and ice-cooling, and the mixture was stirred at room temperature for 30 minutes. EtOAc (50 ml) was added to the reaction mixture and the resultant solid was collected by filtration to give 2 g (4.7%) of **Vc**. The filtrate was evaporated and Et_2O was added to the residue. The resultant solid was collected by filtration to give 1.4 g (3.3%) of **Vc**; IR (KBr) cm^{-1} 1780, 1700, 1620, 1520, 1400; ^1H NMR (DMSO-d_6) δ 2.21 (3H, s), 3.44 and 3.68 (2H, ABq, J=18 Hz), 3.65 (2H, s), 4.79 and 5.10 (2H, ABq, J=14 Hz), 5.11 (2H, s), 5.17 (1H, d, J=4.8 Hz), 5.85 (1H, dd, J=4.8 and 8 Hz), 8.26 (2H, br), 9.74 (1H, d, J=8 Hz).

2-(5-*tert*-Butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyimino-acetic Acid (**XI**)

A mixture of **VIII** (13 g) and SeO_2 (10.9 g) in dioxane (200 ml) was heated at 80°C with stirring for 40 minutes and then evaporated. EtOAc (200 ml) was added to the residue, the solid was filtered off and then the filtrate was evaporated. The residue was dissolved into EtOH (100 ml) and cooled. *O*-(*tert*-Butoxycarbonylmethyl)hydroxylamine (6.2 g) was added to this solution with stirring and cooling. After stirring for 4 hours, the mixture was evaporated. A mixture of EtOAc (100 ml) and H_2O (200 ml) was added to the residue and the solid was filtered off. The organic layer was separated and shaken vigorously with 1.7% aq $NaHCO_3$ (300 ml). The organic layer was discarded and EtOAc (100 ml) was added to the aqueous layer. The mixture was acidified with 1 N HCl and shaken. The organic layer was separated, dried, and evaporated to give 11 g (55%) of **XI**, MP 128°C (decomp); ^1H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.55 (9H, s), 4.73 (2H, s).

7β-[2-(5-*tert*-Butoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyimino-acetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XII**)

A mixture of **XI** (13 g) and PCl_5 (7 g) in CH_2Cl_2 (100 ml) was stirred for 30 minutes with ice-cooling and then evaporated. The residue was dissolved in CH_2Cl_2, and this solution was added to an ice-cooled solution prepared from 7-AACA (10 g) and BSA (16 g) in CH_2Cl_2 (100 ml). After stirring for one hour, the mixture was evaporated. The residue was dissolved in EtOAc, washed with H_2O, and dried. The solvent was evaporated and *n*-hexane was added to the residue. The resultant powder was collected by filtration and dried to give 23 g (100%) of **XII**; IR (KBr) cm^{-1} 3250, 2960, 1780, 1715, 1540, 1370, 1205, 1150, 1060; ^1H NMR (DMSO-d_6) δ 1.43 (9H, s), 1.50 (9H, s), 2.18 (3H, s), 3.41 and 3.65 (2H, ABq, J=18 Hz), 3.62 (2H, s), 4.66 (2H, s), 4.78 and 5.06 (2H, ABq, J=12 Hz), 5.15 (1H, d, J=4.8 Hz), 5.86 (1H, dd, J=4.8 and 8 Hz), 9.56 (1H, d, J=8 Hz).

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-carboxymethoxyiminoacetamido]-3-(3-oxobutyryloxy-methyl)-3-cephem-4-carboxylic Acid (**Vd**)

XII (23 g) was added to TFA (50 ml) with stirring and ice-cooling, and the mixture was stirred at room temperature for 1.5 hours and then evaporated. EtOAc (50 ml) was added to the residue, and again evaporated. EtOAc (50 ml) was added to the residue and the solid was collected by filtration and dried to give 17 g (95%) of **Vd**; IR (KBr) cm^{-1} 1760, 1720, 1630, 1520, 1400, 1310,1180,1145; ^1H NMR (DMSO-d_6) δ 2.20 (3H, s), 3.41 and 3.65 (2H, ABq, J=18 Hz), 3.63 (2H, s), 4.65 (2H, s), 4.78 and 5.07 (2H, ABq, J=12 Hz), 5.15 (1H, d, J=4.8 Hz), 5.85 (1H, dd, J=4.8 and 8 Hz), 8.10 (2H, br), 9.48 (1H, d, J=8 Hz).

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*b*]pyridazi-nium-1-yl)methyl-3-cephem-4-carboxylate (**4**, SCE-2787)

A mixture of **Va** (1.1 g), imidazo[1,2-*b*]pyridazine (1.0 g) and KI (1.1 g) in 50% aq MeCN was stirred

at 60~70°C for 2 hours and then cooled. The mixture was chromatographed on silica gel with Me_2CO and 80% aq Me_2CO as the eluents. The fraction containing the product was evaporated and the residue was purified by column chromatography on MCI gel CHP 20P with H_2O and 2% aq EtOH as the eluents. The fractions containing the product were combined, evaporated and lyophilized to give 0.2 g (17%) of **4** (SCE-2787). The analytical results are shown in Tables 4 and 5.

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylate Hydrochloride (**4**·HCl, SCE-2787·HCl)

A solution of **4** (0.4 g) in 0.01 N HCl (1.0 ml) was chromatographed on Amberlite XAD-2 with 0.01 N HCl-MeCN (1:9, v/v) as the eluents. The fraction eluted with 0.01 N HCl-MeCN (1:9, v/v) was concentrated, and Me_2CO was added to the residue. The resultant powder was collected by filtration, washed with a small amount of Me_2CO and dried to give 0.25 g of **4**·hydrochloride; ^1H NMR (D_2O) δ 3.30 and 3.75 (2H, ABq, J=18 Hz), 4.09 (3H, s), 5.34 (1H, d, J=5 Hz), 5.44 (2H, d, J=14 Hz), 5.93 (1H, d, J=5 Hz), 7.97 (1H, dd, J=4 and 10 Hz), 8.28 (1H, d, J=2 Hz), 8.69 (1H, d, J=10 Hz), 9.02 (1H, d, J=4 Hz).

Anal Calcd for $C_{19}H_{17}N_9O_5S_2 \cdot 3H_2O \cdot HCl$: C 37.66, H 3.99, N 20.80.
Found: C 37.79, H 3.75, N 20.63.

The other cephalosporins (**1**~**3**, **5**~**24**) were prepared following the procedure mentioned above and the analytical results are shown in Tables 4 and 5.

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