STUDIES ON CONDENSED-HETEROCYCLIC AZOLIUM CEPHALOSPORINS

V. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 3-(CONDENSED-TRIAZOLO-PYRIDINIUM, -PYRIMIDINIUM, AND -PYRIDAZINIUM)-METHYL CEPHALOSPORINS

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(Received for publication September 26, 1991)

As a part of our studies on cephalosporins bearing condensed-heterocyclic azolium methyl groups at the 3 position in the cephalosporin nucleus, we describe here the synthesis and antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido] cephalosporins (**1**~**16**), 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido] cephalosporins (**17**, **18**) and 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido] cephalosporins (**19**~**23**) containing a variety of condensed-heterocyclic triazolium methyl groups at the 3 position in the cephalosporin nucleus. These cephalosporins exhibited potent antibacterial activity, and it appears that condensed-heterocyclic triazolium as well as condensed-heterocyclic imidazolium rings are effective moieties for improving antibacterial activity and the spectrum of activity. Among the cephalosporins tested, 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(5-methyl[1,2,3]triazolo-[1,5-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**9**) and 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(6-methoxy[1,2,4]triazolo[1,5-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**11**) showed good antibacterial activity.

In our ongoing series of studies on cephalosporins with a broad antibacterial spectrum and potent activity, we have reported the synthesis and the antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido][1~3] (**IA**, **IB**) and 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido] cephalosporins[4] (**IC**) bearing condensed-heterocyclic azolium methyl groups at the 3 position in the cephalosporin nucleus (Fig. 1).

Among the condensed-heterocycles tested, we found that imidazo[1,2-*a*]pyridine, imidazo[1,5-*a*]-pyridine, imidazo[1,2-*b*]pyridazine and pyrazolo[1,5-*a*]pyridine are effective moieties for improving antibacterial activity and spectrum[2,3]. We revealed that delocalization of the positive charge of the condensed-heterocyclic azolium moiety leads to an expanded antibacterial spectrum and increased antibacterial activity.

Also, the quaternization of a condensed-heterocyclic triazole bearing the nitrogen on the bridged-head results in positive charge delocalization. Thus, we examined the antibacterial activity of cephalosporins bearing condensed-heterocyclic triazolium methyl moieties at the 3 position (Fig. 2).

In this report, we describe the synthesis of these cephalosporins and their antibacterial activity.

Chemistry

The preparation of condensed-triazolo heterocyclic compounds is shown in Scheme 1.

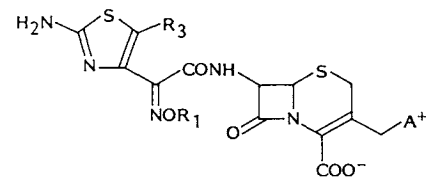
[1,2,4]Triazolo[1,5-*a*]pyridines (**II**) were prepared according to the procedure of POTT[5] or OKAMOTO[6].

[1,2,4]Triazolo[4,3-*a*]pyridines (**III**)[7] and [1,2,3]-triazolo[1,5-*a*]pyridines (**VIII**)[8] were prepared according to the procedures of BOWER *et al.* [1,2,4]-Triazolo[4,3-*b*]pyridazines (**V**)[9], [1,2,4]triazolo-[1,5-*a*]pyrimidines (**VI**)[10] and [1,2,4]triazolo[4,3-*a*]-pyrimidine (**VII**)[11] were prepared following the methods of TAKAHASHI[9], MAKISUMI[10] and SIRAKAWA[11], respectively.

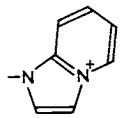
[1,2,4]Triazolo[1,5-*b*]pyridazines (**IV**) were prepared following POLANC's procedure[12]. 3-Amino-6-chloropyridazine (**IXa**) was reacted with dimethylformamide dimethylacetal to give 3-chloro-6-dimethylaminomethyleneaminopyridazine (**Xa**), which was converted to 3-chloro-6-hydroxyimino-methyleneaminopyridazine (**XIa**) with hydroxylamine hydrochloride. 6-Chloro[1,2,4]triazolo[1,5-*b*]-pyridazine (**IVa**) was obtained by cyclization of **XIa** with polyphosphoric acid. [1,2,4]Triazolo-[1,5-*b*]pyridazine (**IVc**) was obtained by the reduction of **IVa** with Pd-C/H_2. Also, 6-dimethylamino- (**IVd**), 6-methoxy- (**IVe**) and 6-methylthio[1,2,4]-triazolo[1,5-*b*]pyridazine (**IVf**) were prepared by the substitution of **IVa** with dimethylamine, sodium methoxide and sodium methylthiolate, respectively. 6-Methyl[1,2,4]triazolo[1,5-*b*]pyridazine (**IVb**) was prepared from 3-amino-6-methylpyridazine (**IXb**) following a procedure similar to that mentioned above.

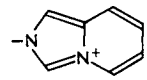
Schemes 2 and 3 show the synthetic steps for preparation of the desired cephalosporins (**1**～**23**).

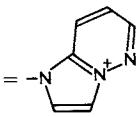
Fig. 1. 7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**IA** and **IB**) and 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**IC**).

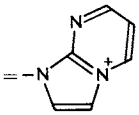


IA: R_3=H

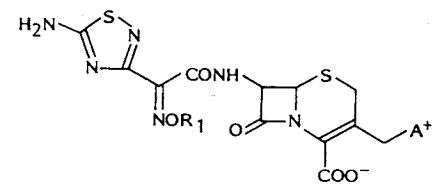
Ia: R_1=Me, R_3=H, A^+= 

Ib: R_1=Me, R_3=H, A^+= 

Ic: R_1=Me, R_3=H, A^+= 

Id: R_1=Me, R_3=H, A^+= 

IB: R_3=Cl, R_1 and A^+: same as A^+ of **Ia**～**Id**



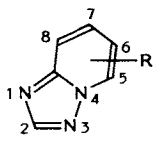
IC

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XIIa**)[2] or 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XIIb**)[4] was heated with equal amounts of condensed-triazole and sodium iodide in 50% aqueous acetonitrile for 1～3 hours. The reaction mixture was purified by column chromatography on silica gel and subsequently MCI gel CHP 20P to afford the condensed-triazolium cephalosporins (**1**～**9**, **17**, **18**) [Method A].

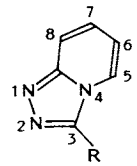
Scheme 3 shows the steps using 3-hydroxymethyl cephalosporin derivatives and the condensed-triazoles in the presence of ethyl *o*-phenylenephosphate or 2-phenyl-2-oxo-1,3,2-benzodioxaphosphole[13].

7β-Amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (**XIII**) was reacted with 2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetyl chloride hydrochloride to give 7β-[2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylic acid (**XIV**).

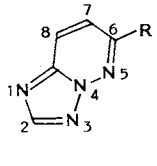
Fig. 2. Condensed-heterocyclic triazoles.



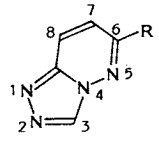
II
IIa R=H
IIb R=5-Me
IIc R=6-Me
IId R=7-Me
IIe R=8-Me



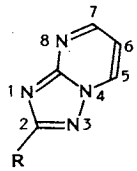
III
IIIa R=H
IIIb R=Me



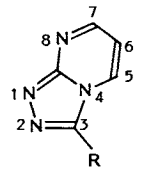
IV
IVa R=Cl
IVb R=Me
IVc R=H
IVd R=NMe_2
IVe R=OMe
IVf R=SMe



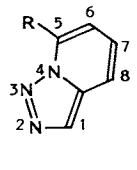
V
Va R=OMe



VI
VIa R=H
VIb R=Me

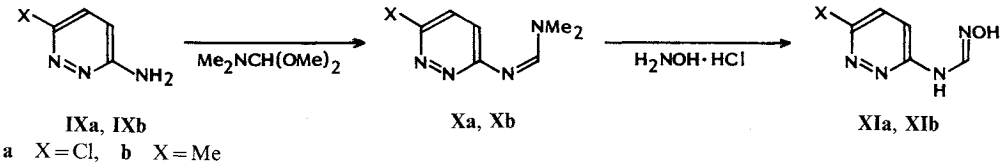


VII
VIIa R=Me



VIII
VIIIa R=H
VIIIb R=Me

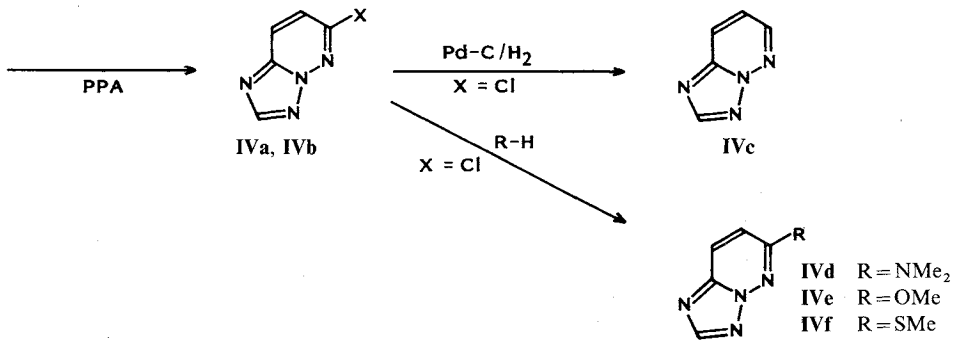
Scheme 1.



IXa, IXb
a X=Cl, **b** X=Me

Xa, Xb

XIa, XIb



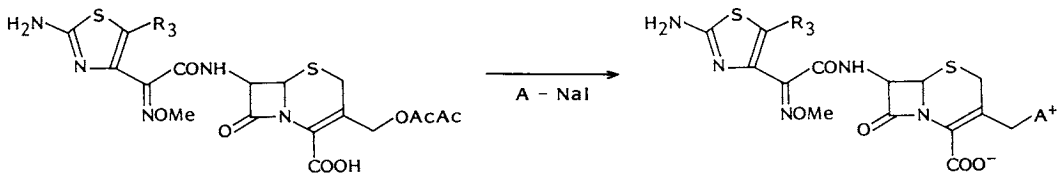
IVa, IVb

IVc

IVd R=NMe_2
IVe R=OMe
IVf R=SMe

XIV was deprotected with sodium *N*-methyldithiocarbamate to give 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylic acid (**XV**) which was then converted to the tributylammonium salt. The tributylammonium salt of **XV** was reacted with the condensed-triazole in the presence of ethyl *o*-phenylenephosphate, and the mixture was purified by column chromatography to

Scheme 2.



XII
XIIa R_3=H
XIIb R_3=Cl

1~**9**, **17**, **18**
1~**9** R_3=H
17, **18** R_3=Cl

AcAc: $-COCH_2COMe$
A: condensed-triazolo heterocycles

Method A

give the cephalosporins (**10**~**12**, **15**, **16**) [Method B].

7β-[2-(2-Tritylaminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylic acid (**XVI**) was reacted with the condensed-triazole according to Method B to afford 7β-[2-(2-tritylaminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(condensed-triazolium)methyl-3-cephem-4-carboxylate, which was deprotected with trifluoroacetic acid and purified by column chromatography to give the desired cephalosporins (**13** and **14**) [Method C].

Tributylammonium 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylate (**XVIII**) was reacted with the condensed-triazole in the presence of ethyl *o*-phenylenephosphate, and the mixture was purified by column chromatography on silica gel and subsequently MCI gel or Amberlite XAD-2 to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-(condensed-triazolium)methyl-3-cephem-4-carboxylates (**19**~**23**) [Method D].

Among the cephalosporins obtained, **6**, **7** and **13** were a mixture of the two (condensed-triazolium 1-yl and 2-yl)cephalosporin isomers. The ratio of the isomers in the mixture was determined by ^{1}H NMR, but the antibacterial activity was tested without separation of the isomers.

Biological Results and Discussion

The MICs of the prepared cephalosporins against strains of Gram-positive and Gram-negative bacteria were determined by the standard serial 2-fold dilution method.

Table 1 shows the MICs of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-triazolopyridinium)methyl cephalosporins (**1**~**9**) along with those of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido] cephalosporins bearing imidazo[1,2-*a*]pyridinium (**Ia**) and pyrazolo[1,5-*a*]pyridinium (**Ib**) and ceftazidime (CAZ) and cefmenoxime (CMX) as reference compounds.

Among the cephalosporins prepared, **9** showed the most potent antibacterial activity. The MICs of **1**~**3** against *Staphylococcus aureus* and Gram-negative bacteria except *Proteus vulgaris* were superior to that of CMX and similar to that of **Ia** and **Ib**. **7** showed an MIC similar to that of **Ib** and the antibacterial activity of **4**~**6** and **8** was inferior to that of **Ia**, **Ib**, CMX and CAZ.

Table 2 shows the MICs of triazolopyridazinium cephalosporins (**10**~**13**) along with that of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylate (**Ic**). The antibacterial activity of **11** was similar to that of **Ic**, whereas that of **10**, **12** and **13** was inferior to that of **Ic**.

Scheme 3.

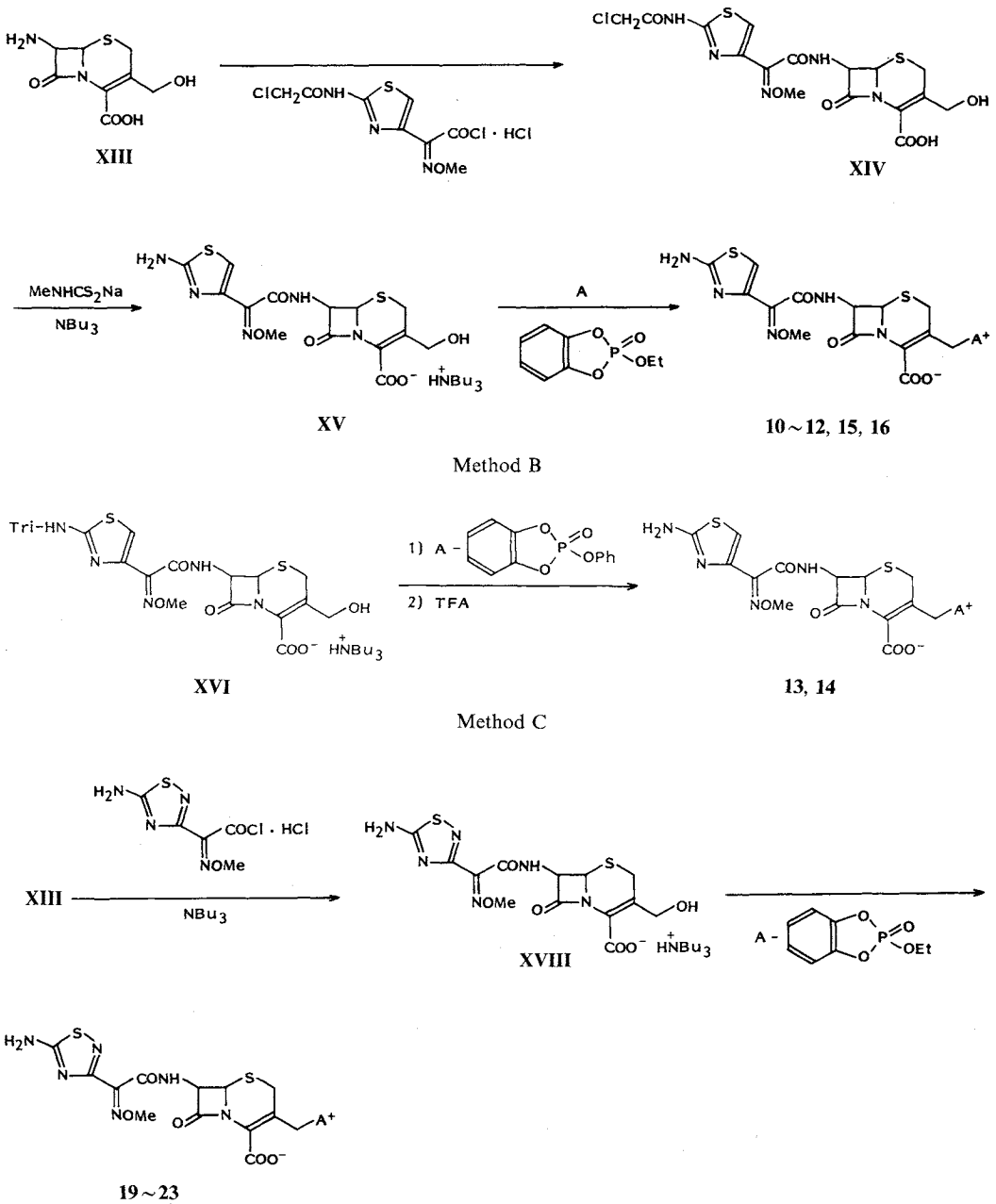
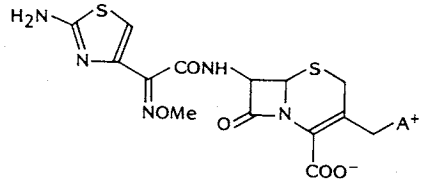


Table 3 shows the MICs of triazolopyrimidinium cephalosporins (**14**~**16**) and 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyrimidinium-1-yl)methyl-3-cephem-4-carboxylate (**Id**). The antibacterial activity of **15** against *Staphylococcus aureus* and Gram-negative bacteria except *Proteus vulgaris* was similar to that of CMX.

Previously, we reported[4] that substitution of the thiazole ring with a chlorine atom increased the

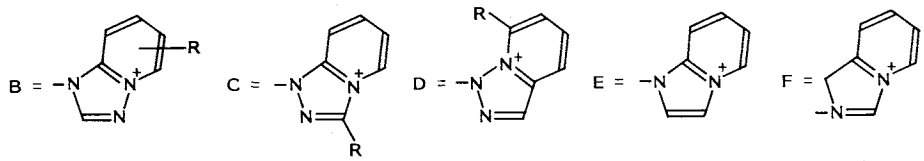
Table 1. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(triazolopyridinium)methyl-3-cephem-4-carboxylates (**1**~**9**), 7β-[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(imidazo[1,2-a]pyridinium-1-yl (**Ia**) and imidazo[1,5-a]pyridinium-2-yl (**Ib**))methyl-3-cephem-4-carboxylates, ceftazidime (CAZ) and cefmenoxime (CMX).



10^8 cfu/ml

Compound No.	R	A^+	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
1	H	B	1.56	<0.1	0.78	0.2	0.2	3.13	>100
2	5-Me	B	1.56	<0.1	0.2	0.2	0.2	3.13	100
3	6-Me	B	1.56	<0.1	0.39	0.2	0.2	3.13	>100
4	7-Me	B	1.56	0.2	0.39	0.39	0.39	6.25	100
5	8-Me	B	3.13	0.39	0.78	0.78	0.39	25	>100
6	H	C	1.56	0.2	6.25	0.39	0.2	12.5	>100
7	Me	C	1.56	<0.1	0.78	0.2	0.2	3.13	>100
8	H	D	3.13	<0.1	1.56	0.2	0.78	6.25	>100
9	Me	D	0.78	<0.1	0.39	<0.1	<0.1	3.13	>100
Ia		E	0.39	<0.1	0.39	0.2	0.2	6.25	>100
Ib		F	1.56	<0.1	0.78	0.39	0.2	1.56	100
CAZ			6.25	0.39	25	0.39	0.1	0.78	12.5
CMX			1.56	0.2	6.25	0.39	<0.1	6.25	>100

* *S.a.*; *Staphylococcus aureus* 308A-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* U31.

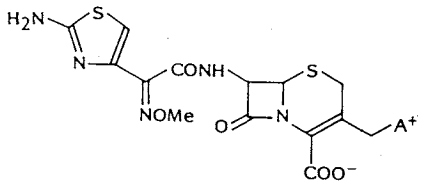


antibacterial activity against *Pseudomonas aeruginosa* but decreased the antibacterial activity against the other Gram-negative bacteria as compared with that of **IA**. In the case of [1,2,4]triazolopyridinium cephalosporins (**17** and **18**) bearing 2-(2-amino-5-chlorothiazol-4-yl)-2(Z)-methoxyiminoacetamido group as the acyl moiety, improved activity was observed against highly resistant *Pseudomonas aeruginosa* (*P.a.*2), whereas the activity against the other Gram-negative bacteria was decreased (Table 4).

Also, we reported[1] that the antibacterial activity of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoxyiminoacetamido]-3-azoliummethyl cephalosporins against *Pseudomonas aeruginosa* were improved compared with that of 7β-[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido] cephalosporins. The antibacterial activity of the condensed-triazolium cephalosporins (**19**~**23**) was no better than that of the thiazolyl cephalosporins bearing condensed-triazolium moieties.

Among the cephalosporins tested, **1**~**3**, **9** and **11** showed good antibacterial activity. These results imply that the condensed-triazolo heterocycles such as [1,2,4]triazolo[1,5-a]pyridine and [1,2,3]triazolo-[1,5-a]pyridine are effective moieties for improving antibacterial activity and spectrum of cephalosporins as are imidazo[1,2-a]pyridine and pyrazolo[1,5-a]pyridine.

Table 2. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(triazolopyridazinium)methyl-3-cephem-4-carboxylates (**10**～**13**), 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylate (**Ic**), ceftazidime (CAZ) and cefmenoxime (CMX).



10^8 cfu/ml

Compound No.	R	A^+	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
10	H	B	6.25	0.78	6.25	0.78	0.39	12.5	>100
11	OMe	B	0.78	<0.1	0.78	<0.1	<0.1	3.13	100
12	SMe	B	3.13	0.2	1.56	0.39	0.2	25	>100
13		C	1.56	<0.1	3.13	0.2	<0.1	6.25	>100
Ic		D	0.78	<0.1	0.39	0.2	<0.1	1.56	100
CAZ			6.25	0.39	25	0.39	0.1	0.78	12.5
CMX			1.56	0.2	6.25	0.39	<0.1	6.25	>100

* See footnote in Table 1.

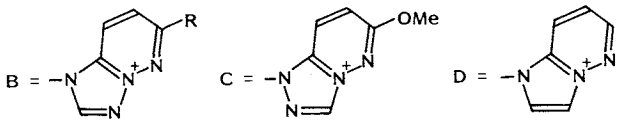
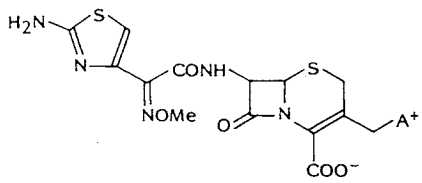


Table 3. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(triazolopyrimidinium)methyl-3-cephem-4-carboxylates (**14**～**16**), 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyrimidinium-1-yl)methyl-3-cephem-4-carboxylate (**Id**), ceftazidime (CAZ) and cefmenoxime (CMX).



10^8 cfu/ml

Compound No.	R	A^+	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
14	H	B	3.13	0.2	3.13	0.78	0.2	12.5	>100
15	Me	B	1.56	0.2	1.56	0.2	0.39	3.13	100
16		C	3.13	0.39	25	1.56	0.2	25	>100
Id		D	0.39	<0.1	0.39	0.2	0.2	6.25	>100
CAZ			6.25	0.39	25	0.39	0.1	0.78	12.5
CMX			1.56	0.2	6.25	0.39	<0.1	6.25	>100

* See footnote in Table 1.

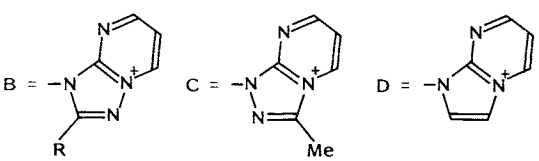
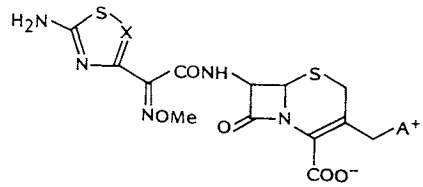


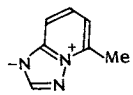
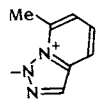
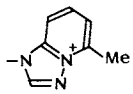
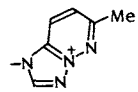
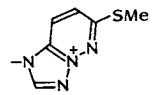
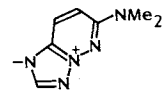
Table 4. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-amino-5-chlorothiazol-4-yl) (**17**, **18**) and 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)(**19**~**23**) -2(*Z*)-methoxyiminoacetamido]-3-(condensed-heterocyclic-azolium)methyl-3-cephem-4-carboxylates.



X=CCl
17, **18**

X=N
19~**23**

10^8 cfu/ml

Compound No.	A^+	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2*
2-(2-Amino-5-chlorothiazol-4-yl)								
17		0.78	1.56	3.13	3.13	1.56	3.13	12.5
18		1.56	1.56	3.13	3.13	1.56	6.25	25
2-(5-Amino-1,2,4-thiadiazol-3-yl)								
19		1.56	<0.1	0.78	0.2	0.78	1.56	25
20		6.25	0.39	3.13	1.56	1.56	3.13	100
21		6.25	0.39	1.56	1.56	1.56	12.5	50
22		3.13	<0.1	0.39	0.39	0.39	12.5	100
23		3.13	0.2	0.78	0.78	0.78	50	100

* See footnote in Table 1.

Experimental

Melting points were determined on 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) 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).

Determination of *In Vitro* Antibacterial Activity

The MICs were determined according to the procedure mentioned in the previous paper[4].

Preparation of Condensed-triazolo Heterocycles

[1,2,4]Triazolo[1,5-*a*]pyridines (II)

[1,2,4]Triazolo[1,5-*a*]pyridine (**IIa**) was prepared according to OKAMOTO's procedure[6]; MP 101~102°C (lit.[6] MP 102~103°C). Methyl derivatives (**IIb**~**IIe**) were obtained by treatment of the corresponding methyl-1,2-diaminopyridinium iodide with formic acid following POTTS's method[5].

5-Methyl[1,2,4]triazolo[1,5-*a*]pyridine (**IIb**); MP 52~53°C (lit.[5] MP 58~59°C); ^{1}H NMR ($CDCl_3$) δ 2.80 (3H, s), 6.85 (1H, d, J=7.5 Hz), 7.3~7.8 (2H, m), 8.38 (1H, s): 6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (**IIc**); semi-solid (lit.[5] MP 57~58°C); ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 7.37 (1H, d, J=9 Hz), 7.67 (1H, d, J=9 Hz), 8.31 (1H, s), 8.42 (1H, s): 7-methyl[1,2,4]triazolo[1,5-*a*]pyridine (**IId**); MP 74~75°C (lit.[5] MP 79°C); ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 6.76 (1H, d, J=7.5 Hz), 7.44 (1H, s), 8.23 (1H, s), 8.41 (1H, d, J=7.5 Hz) and 8-methyl[1,2,4]triazolo[1,5-*a*]pyridine (**IIe**); semi-solid (lit.[5] MP 51°C); ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 7.35 (1H, d, J=7.5 Hz), 7.67 (1H, d, J=7.5 Hz), 8.28 (1H, s), 8.40 (1H, s).

[1,2,4]Triazolo[4,3-*a*]pyridines (III)

[1,2,4]Triazolo[4,3-*a*]pyridine (**IIIa**); semi-solid and 3-methyl[1,2,4]triazolo[4,3-*a*]pyridine (**IIIb**); MP 132~134°C (lit.[7] MP 129~130°C) were prepared according to BOWER's method[7].

[1,2,4]Triazolo[1,5-*b*]pyridazines (IV)

6-Chloro[1,2,4]triazolo[1,5-*b*]pyridazine (**IVa**), [1,2,4]triazolo[1,5-*b*]pyridazine (**IVc**); MP 148~150°C (lit.[12] MP 138~140°C), 6-methoxy[1,2,4]triazolo[1,5-*b*]pyridazine (**IVe**); MP 173~175°C (lit.[12] MP 178~180°C) and 6-methylthio[1,2,4]triazolo[1,5-*b*]pyridazine (**IVf**); MP 129~130°C (lit.[12] MP 128~130°C) were obtained according to POLANC's method.

6-Methyl[1,2,4]triazolo[1,5-*b*]pyridazine (IVb)

3-Amino-6-methylpyridazine (**IXb**, 5 g) in a mixture of dimethylacetamide dimethylacetal (25 ml) and toluene (25 ml) was refluxed for 4 hours, and the solvent was evaporated to give a brown oil, which was dissolved in MeOH (30 ml) and stirred with hydroxylamine hydrochloride (3 g) at room temperature overnight. The solid was collected by filtration, washed with MeOH and dried. The solid was heated with polyphosphoric acid (10 g) at 80~100°C for 3 hours, and the mixture was poured into crushed ice. The solution was alkalinized with K_2CO_3 and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and satd aq NaCl, dried and evaporated to give 0.54 g (10%) of **IVb** as a yellow solid; MP 155~158°C; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 7.29 (1H, d, J=10 Hz), 8.05 (1H, d, J=10 Hz), 8.43 (1H, s).

6-Dimethylamino[1,2,4]triazolo[1,5-*b*]pyridazine (IVd)

A solution of **IVa** (0.9 g) and 7.2% dimethylamine-EtOH soln (10 ml) in EtOH (10 ml) was stirred at room temperature for 24 hours. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (100 ml). The solution was washed with H_2O and satd aq NaCl, dried, and evaporated to give 0.82 g (86%) of **IVd** as colorless crystals; MP 113°C; ^{1}H NMR ($CDCl_3$) δ 3.17 (6H, s), 7.04 (1H, d, J=10 Hz), 7.84 (1H, d, J=10 Hz), 8.20 (1H, s).

6-Methoxy[1,2,4]triazolo[4,3-*b*]pyridazine (**Va**)[9], [1,2,4]triazolo[1,5-*a*]pyrimidine (**VIa**)[10], 2-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine (**VIb**)[10] and 3-methyl[1,2,4]triazolo[4,3-*a*]pyrimidine (**VIIa**)[11] were prepared according to the procedures of TAKAHASHI[9], MAKISUMI[10] and SIRAKAWA[11].

[1,2,3]Triazolo[1,5-*a*]pyridines (VIII)

[1,2,3]Triazolo[1,5-*a*]pyridine (**VIIIa**); MP 37~38°C (lit.[8] MP 39~40°C): 5-methyl[1,2,3]-triazolo[1,5-*a*]pyridine (**VIIIb**); MP 40~42°C were prepared according to the procedure of BOWER and RANGE[8].

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylic Acid (XV)

2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetyl chloride hydrochloride (29.4 g) was added portionwise to a solution of 7β-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (**XIII**, 16.97 g)

and $NaHCO_3$ (27.72 g) in 50% aq THF (800 ml) with ice-cooling and stirring. The resulting mixture was stirred for 30 minutes, and then a mixture of H_2O (150 ml) and EtOAc (200 ml) was added. The aqueous layer was removed and adjusted to pH 7.0 with 1 N HCl under ice-cooling and stirring, and then sodium *N*-methyldithiocarbamate (18.9 g) was added. After stirring at room temperature for 3 hours, the reaction mixture was washed with EtOAc. The aqueous layer was concentrated to 70 ml and purified by column chromatography on Amberlite XAD-2 with H_2O as the eluent. The eluate was concentrated to 100 ml and adjusted to pH 4 with 4 N HCl with ice-cooling. The crystalline precipitate was collected by filtration, washed successively with H_2O (100 ml), EtOAc (50 ml) and THF (50 ml), and dried to give 19.3 g (50%) of the acid form of **XV**; MP 200~210°C (dec); ^{1}H NMR (DMSO-d_6) δ 3.55 (2H, s), 3.84 (3H, s), 4.25 (2H, s), 5.08 (1H, d, J=5 Hz), 5.75 (1H, dd, J=5 and 8 Hz), 6.73 (1H, s), 7.16 (2H, s), 9.55 (1H, d, J=8 Hz).

Anal Calcd for $C_{14}H_{15}N_6O_6S_2 \cdot \frac{1}{2}H_2O$: C 39.81, H 3.82, N 16.58.
Found: C 39.73, H 3.74, N 16.39.

The acid form of **XV** (422 mg) was added to a solution of tributylamine (185 mg) in MeOH at −20°C and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and the solvent was evaporated to give the tributylammonium salt of **XV**.

Tributylammonium 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylate (**XVIII**)

1) 7β-Amino-3-acetoxymethyl-3-cephem-4-carboxylic acid (5.44 g) was dissolved in 1 N NaOH (40 ml) with stirring and ice-cooling, and the mixture was stirred at 0~5°C for one hour. The reaction mixture was diluted with Me_2CO (40 ml), and the 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetyl chloride hydrochloride (5.2 g) was added portionwise to the reaction mixture. After stirring for one hour, the mixture was evaporated. The residual solution was purified by column chromatography on MCI gel CHP 20P with H_2O as the eluent. The fractions containing the desired compound were combined, concentrated and lyophilized to afford 4.3 g of sodium 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylate; ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s), 3.83 and 4.21 (2H, ABq, J=13 Hz), 4.90 (1H, d, J=4.5 Hz), 5.59 (1H, dd, J=4.5 and 9 Hz), 8.11 (2H, br), 9.42 (1H, d, J=9 Hz).

2) An aqueous solution (20 ml) of the obtained sodium salt (3.1 g) was acidified with conc HCl under ice-cooling and stirring and extracted with a mixture of THF-methyl ethyl ketone (1 : 1). The combined organic layer was washed with satd aq NaCl, dried and filtered. Tributylamine (2.0 ml) was added to the filtrate and the mixture was concentrated. The residue was solidified with Et_2O to give 4.5 g (50%) of **XVIII** as a yellow powder; ^{1}H NMR (DMSO-d_6) δ 0.91 (9H, t, J=7 Hz), 1.1~1.9 (12H, m), 2.8~3.1 (6H, m), 3.47 (2H, br), 3.92 (3H, s), 4.18 (2H, br), 5.02 (1H, d, J=4.5 Hz), 5.71 (1H, dd, J=4.5 and 9 Hz), 8.13 (2H, br), 9.48 (1H, d, J=9 Hz).

General Method A

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

A solution of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XIIa**, 1.8 g), **IIb** (1.34 g) and NaI (1.34 g) in 50% aq MeCN (40 ml) was stirred at 50~60°C for 2 hours. After cooling, the mixture was chromatographed on silica gel with Me_2CO and aq Me_2CO as the eluents. The fractions containing the desired compound were combined and concentrated. The residual solution was purified by column chromatography on MCI gel CHP 20P with H_2O and aq EtOH as the eluents. The fractions containing **2** were combined, concentrated and lyophilized to give 100 mg (5%) of **2**. The analytical results are shown in Tables 5 and 6.

General Method B

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(2-methyl[1,2,4]triazolo[1,5-*a*]pyrimidinium-1-yl)methyl-3-cephem-4-carboxylate (**15**)

A solution of **XV** (0.9 g) and **VIb** (0.6 g) in dry CH_2Cl_2 (30 ml) was stirred with ethyl *o*-phenylenephosphate (0.9 g) at −35°C for 30 minutes; and at −15°C for 1.5 hours and then below 4°C

Table 5. IR and analytical data for 7β-[2-(2-aminothiazol-4-yl) (**1**～**16**), 2-(2-amino-5-chlorothiazol-4-yl) (**17**, **18**) and 2-(5-amino-1,2,4-thiadiazol-3-yl)(**19**～**23**) -2(*Z*)-methoxyiminoacetamido]-3-(condensed-heterocyclic triazolium)methyl-3-cephem-4-carboxylates.

Compound No.	Method	Yield %	Formula	Elemental analysis % Calcd C	H	N	Found C	H	N	IR (KBr) cm^{-1}
1	A	6	$C_{20}H_{18}N_8O_5S_2 \cdot 5H_2O$	39.73	4.67	18.53	39.81	4.49	18.57	1770, 1670, 1650, 1610
2	A	5	$C_{21}H_{20}N_8O_5S_2 \cdot \frac{9}{2}H_2O$	41.37	4.80	18.38	41.45	4.93	18.77	1770, 1670, 1610, 1530
3	A	5	$C_{21}H_{20}N_8O_5S_2 \cdot \frac{9}{2}H_2O$	41.37	4.80	18.38	40.92	4.75	18.55	1770, 1670, 1610, 1535
4	A	5	$C_{21}H_{20}N_8O_5S_2 \cdot 5H_2O$	40.77	4.89	18.11	40.98	4.94	18.30	1770, 1670, 1620, 1530
5	A	1	$C_{21}H_{20}N_8O_5S_2 \cdot 5H_2O$	40.77	4.89	18.11	40.87	5.11	18.09	1770, 1670, 1620, 1535
6	A	10	$C_{20}H_{18}N_8O_5S_2 \cdot \frac{7}{2}H_2O$	41.59	4.36	19.40	41.74	4.46	19.10	1770, 1670, 1625, 1525
7	A	14	$C_{21}H_{20}N_8O_5S_2 \cdot 3H_2O$	43.29	4.50	19.23	43.48	4.33	19.30	1770, 1665, 1610, 1520
8	A	5	$C_{20}H_{18}N_8O_5S_2 \cdot \frac{9}{2}H_2O$	40.33	4.57	18.81	40.45	4.14	18.68	1770, 1760, 1670, 1600
9	A	4	$C_{21}H_{20}N_8O_5S_2 \cdot 4H_2O$	41.99	4.70	18.66	41.72	4.90	18.44	1765, 1660, 1605, 1520
10	B	8	$C_{19}H_{17}N_9O_5S_2 \cdot 5H_2O$	37.68	4.49	20.82	37.86	4.38	20.98	1760, 1660, 1610, 1515
11	B	6	$C_{20}H_{19}N_9O_6S_2 \cdot \frac{5}{2}H_2O$	40.67	4.10	21.34	40.77	3.99	21.51	1770, 1665, 1615, 1520
12	B	20	$C_{19}H_{18}N_{10}O_5S_3 \cdot 3H_2O$	37.01	3.92	22.71	37.21	3.76	22.58	1770, 1660, 1610, 1530
13	C	7	$C_{20}H_{19}N_9O_6S_2 \cdot 4H_2O$	38.89	4.41	20.41	38.78	4.29	20.20	1765, 1660, 1630, 1610
14	C	3	$C_{19}H_{17}N_9O_5S_2 \cdot 5H_2O$	37.68	4.49	20.82	37.72	3.90	20.56	1765, 1660, 1630, 1610
15	B	10	$C_{20}H_{19}N_9O_5S_2 \cdot 4H_2O$	39.93	4.52	20.95	39.88	4.65	20.79	1764, 1660, 1610
16	B	2	$C_{20}H_{19}N_9O_5S_2 \cdot 4H_2O$	39.93	4.52	20.95	39.77	4.60	20.40	1762, 1610
17	A	8	$C_{21}H_{19}N_8O_5S_2Cl \cdot 4H_2O$	39.72	4.29	17.64	39.77	4.32	17.86	1770, 1660, 1610, 1530
18	A	4	$C_{21}H_{19}N_8O_5S_2Cl \cdot \frac{9}{2}H_2O$	39.16	4.36	17.23	39.03	4.36	17.23	1775, 1670, 1610, 1530
19	D	11	$C_{20}H_{19}N_9O_5S_2 \cdot 5H_2O$	38.77	4.72	20.34	39.03	4.78	20.29	1765, 1670, 1610, 1520
20	D	22	$C_{18}H_{16}N_{10}O_5S_2 \cdot \frac{5}{2}H_2O$	38.50	4.49	24.95	38.30	3.75	24.82	1770, 1670, 1605, 1515
21	D	7	$C_{19}H_{18}N_{10}O_5S_2 \cdot \frac{3}{2}H_2O$	35.24	4.82	21.63	35.01	4.79	21.48	1770, 1660, 1610, 1510
22	D	9	$C_{19}H_{18}N_{10}O_5S_3 \cdot 3H_2O$	37.01	3.92	22.71	37.18	3.94	22.82	1770, 1660, 1610, 1530
23	D	17	$C_{20}H_{21}N_{11}O_5S_2 \cdot 4H_2O$	38.03	4.63	24.39	37.74	4.63	24.21	1775, 1670, 1610, 1525

for 8 hours and at room temperature for 15 hours. The solvent was evaporated and the residue was suspended in a mixture of MeCN and H_2O (6:1, v/v). The solid was filtered off and the filtrate was chromatographed on silica gel with MeCN and aq MeCN as the eluents. The fractions containing the objective compound were combined and concentrated. The residual solution was purified by column chromatography on XAD-2 with H_2O and aq EtOH as the eluents. The fractions containing the cephalosporin were combined, concentrated and lyophilized to give 91 mg of **15** as a yellow powder. The analytical results are shown in Tables 5 and 6.

General Method C

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-([1,2,4]triazolo[1,5-*a*]pyrimidinium-1-yl)methyl-3-cephem-4-carboxylate (**14**)

A solution of 7β-[2-(2-tritylaminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-hydroxymethyl-3-cephem-4-carboxylic acid (**XVI**, 0.98 g) and **VIa** (0.54 g) in dry CH_2Cl_2 (20 ml) was stirred with 2-phenyl-2-oxo-1,3,2-benzodioxyphosphole (1.045 g) at −30°C for one hour followed by at 0～5°C for 6 hours. The solvent was evaporated and the residue was dissolved in a small amount of CH_2Cl_2. The solution was chromatographed on silica gel with MeCN and aq MeCN as the eluents to give 0.42 g of 7β-[2-(2-tritylaminothiazol-5-yl)-2(*Z*)-methoxyiminoacetamido]-3-([1,2,4]triazolo[1,5-*a*]pyrimidinium-1-yl)methyl-3-cephem-4-carboxylate (**XVII**). TFA (10 ml) was added to a suspension of **XVII** (0.40 g) in CH_2Cl_2 (10 ml) with ice-cooling, and the reaction mixture was then stirred for one hour. The solvent was evaporated, H_2O (20 ml) was added to the residue, and the mixture was adjusted to pH 5.8 with aq $NaHCO_3$. The solution was chromatographed on Amberlite XAD-2 with H_2O and aq EtOH as the eluents. The fractions containing the desired compound were combined and concentrated. The residual solution was purified by column chromatography on silica gel to give 29 mg of **14** as a yellow powder. The analytical

Table 6. ^{1}H NMR data for 7β-[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(condensed-heterocyclic triazolium)methyl-3-cephem-4-carboxylates (**1**~**16**), 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(condensed-heterocyclic triazolium)methyl-3-cephem-4-carboxylates (**17**, **18**) and 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoxyiminoacetamido]-3-(condensed-heterocyclic triazolium)methyl-3-cephem-4-carboxylates (**19**~**23**).

Compound No.	Solvent	Chemical shift δ								
		Cephem nuclei					7-Acyl		Me	3-Triazolium ring proton
		2-CH_2 ABq J=18 Hz	3-CH_2 ABq 14 Hz	6-CH d 5 Hz	7-CH dd 5 & 8 Hz	CONH d 8 Hz	5-H br	NH_2 s	s	
1	B	3.00 3.34	5.5~ 5.25	5.00	5.63	—	6.69	—	3.83	7.6~7.9 (m), 8.20~8.5 (m), 8.7~8.9 (m), 9.29 (d, 7), 9.67 (s)
2	A	3.11 —	5.30 5.52	4.95	5.60	9.45	6.68	7.13	3.80	2.86 (s), 7.52~7.8 (m), 8.12~8.42 (m), 8.62~8.88 (m), 9.80 (s)
3	A	3.09 —	5.25 5.48	4.99	5.61	9.46	6.68	7.14	3.80	2.38 (s), 8.21 (d, 9), 8.82 (d, 9), 9.21 (s), 9.72 (s)
4	A	3.17 —	5.1~ 5.5	5.01	5.61	9.48	6.70	7.16	3.81	2.63 (s), 7.52~7.72 (m), 8.6~8.78 (m), 9.01 (s), 9.72 (s)
5	Not measured									
6[a]	A	3.17 3.45	5.45 5.86	4.96	5.60	9.45	6.67	7.13	3.80	7.5~7.7 (m), 8.0~8.35 (m), 8.85~9.14 (m), 9.83 (s)
7[b]	A	3.13 3.48	5.43 5.61	4.98	5.43	9.45 9.49	6.69 6.72	7.16	3.83 3.80	2.68 & 2.83 (two s), 7.8~8.4 (m), 8.64~9.14 (m)
8	B	3.15 3.46	5.3 5.72	5.02	5.90	—	6.74	—	3.86	7.06~7.27 (m), 7.3~ 7.5, 7.84~8.06 (m), 8.19 (s), 8.94~9.08 (m)
9	A	—	5.3~ 6.0	5.03	5.3~ 6.0	9.43	6.70	7.14	3.81	2.84 (s), 7.57~7.95 (m), 8.2~8.4 (m), 9.82 (s)

10	A	—	5.32	4.91	5.32	9.49	6.72	7.16	3.83	7.65 (dd, 4 & 9), 8.43 (dd, 1.5 & 9),
		—	5.58							8.62 (s), 8.70 (dd, 4.5 & 1.5)
11	D	3.25	5.35	5.29	5.86	—	6.97	—	4.00	4.23 (s), 7.88 (d, 10), 8.82 (d, 10), 9.41 (s)
		3.75	5.55							
12	B	—	5.43	5.06	5.82	—	6.83	—	3.93	3.31 (s), 7.62 (d, 9), 8.23 (s), 8.48 (d, 9),
		—	br							9.72 (s)
13[c]	B	3.54	5.61	5.32	5.85	—	6.96	—	4.06	4.19 & 4.22 (two s), 7.45 & 7.74 (two d,
		3.86	br	5.34	5.88		6.97			10), 8.28 & 8.71 (two d, 10), 9.51 (m)
14	C	3.50	5.35	5.27	5.88	—	7.05	—	4.06	8.02 (dd, 5 & 7), 9.43 (dd, 2 & 5), 9.6 (s),
		3.86	5.61							9.60 (dd, 2 & 7)
15	A	3.23	5.59	5.02	5.66	9.53	6.72	7.17	3.83	2.89 (s), 7.97 (dd, 5 & 7), 9.34 (dd,
		—	br							2 & 5), 9.81 (dd, 2 & 7)
16	B	3.71	5.56	5.32	5.90	—	7.05	—	4.07	3.21 (s), 7.63 (dd, 4 & 7), 9.00～9.24 (m)
		br	5.82							
17	A	3.09	5.30	4.97	5.61	9.41	7.31	3.80		2.86 (s), 7.55～7.8 (m), 8.1～8.4 (m),
		3.46	5.53							8.78 (d, 7), 9.78 (s)
18	B	—	5.03	5.15	5.90	—	—	3.88		6.9～7.12 (m), 7.25～7.48 (m), 7.71～7.94
			br							(m), 8.23 (s)
19	A	3.13	5.39	5.01	5.67	9.50	—			2.88 (s), 7.58～7.74 (m), 8.05～8.35 (m),
		3.31								8.4～8.6 (m), 9.57 (s)
20	A	3.36	5.53	5.17	5.84	9.48	8.02	3.88		7.5～7.7 (m), 8.3～8.5 (m), 8.62 (s),
		3.58	br							8.72 (d, 4.5)
21	B	—	5.4～	5.02	5.4～	9.44	8.06	3.91		2.63 (s), 7.55 (d, 9), 8.30 (d, 9), 8.53 (s)
22	A	3.26	5.70	5.14	5.97	9.46	8.04	3.86		3.18 (s), 7.54 (d, 9), 8.24 (s), 8.72 (d, 9)
		3.56	br							
23	A	3.0	5.37	5.03	5.71	9.44	8.00	3.92		3.20 (s), 7.34 (d, 9), 8.19 (s), 8.73 (d, 9)
		—	br				br			

A; d_6-DMSO, B; D_2O, C; d_6-DMSO-D_2O.

a) 1-yl : 2-yl = 17 : 3.

b) 1-yl : 2-yl = 2 : 1.

c) 1-yl : 2-yl = 4 : 3.

results are shown in Tables 5 and 6.

General Method D

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-([1,2,4]triazolo[1,5-*a*]-pyridazinium-1-yl)methyl-3-cephem-4-carboxylate (**20**)

A solution of **XVIII** (0.6 g) and **IVc** (0.24 g) in dry CH_2Cl_2 (15 ml) was stirred with ethyl *o*-phenylenephosphate (0.41 g) at −30°C for 30 minutes and then stirred at −30 to 0°C for 3 hours. Et_2O (5 ml) was added to the reaction mixture and the precipitate was collected by filtration. The solid was dissolved in 5% aq Na_2CO_3 soln (10 ml). The solution was chromatographed on MCI gel CHP 20P with H_2O and aq EtOH as the eluents. The fractions containing the desired cephalosporin were combined and concentrated, and the residual solution was lyophilized to give 0.12 g of **20** as a yellow powder. The analytical results are shown in Tables 5 and 6.

The other cephalosporins were prepared following methods A ~ D, and the analytical results are shown in Tables 5 and 6.

Acknowledgment

The authors wish to thank Drs. K. MORITA, Y. SUGINO, M. NISHIKAWA, M. FUJINO, S. TERAO, A. IMADA and S. KISHIMOTO for their encouragement throughout this work and Drs. M. KONDO and T. IWAHI and their coworkers for determining the antibacterial activity.

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