

STUDIES ON CONDENSED-HETEROCYCLIC AZOLIUM CEPHALOSPORINS

II[†]. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7 β -[2-(2-AMINOTHIAZOL-4-YL)-2(Z)-ALKOXYIMINOACETAMIDO]-3-(CONDENSED-HETEROCYCLIC AZOLIUM)METHYL-3-CEPHEM-4-CARBOXYLATESYOSHINOBU YOSHIMURA, AKIO MIYAKE*, TATSUO NISHIMURA,
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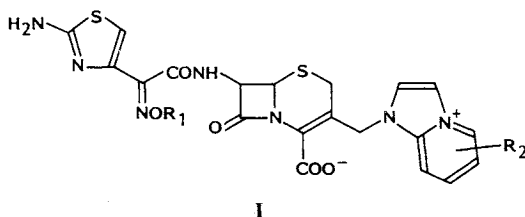
(Received for publication May 20, 1991)

From our series of 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 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]cephalosporins containing imidazo[1,5-a]pyridinium, imidazo[1,2-b]pyridazinium, imidazo[1,2-a]pyrimidinium, imidazo[1,2-c]pyrimidinium, and pyrazolo[1,5-a]pyridinium methyl groups at the 3 position. Among the cephalosporins tested, 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(imidazo[1,5-a]pyridinium-2-yl) (1), (imidazo[1,2-b]pyridazinium-1-yl) (2), and (pyrazolo[1,5-a]pyridinium-1-yl) (3)methyl-3-cephem-4-carboxylates showed potent antibacterial activity and broad antibacterial spectrum. The antibacterial activity of these cephalosporins (1~3) was superior to that of ceftazidime (CAZ). These results imply that the delocalization of the positive charge of the imidazo[1,5-a]pyridinium, pyrazolo[1,5-a]pyridinium and imidazo[1,2-b]pyridazinium groups leads to an expanded antibacterial spectrum and increased activity and that these condensed-heterocyclic compounds as well as imidazo[1,2-a]pyridine are effective moieties for improving antibacterial activity and spectrum.

In our previous paper²⁾, we reported that 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]-cephalosporins (I, Fig. 1) bearing (imidazo[1,2-a]pyridinium-1-yl)methyl at the 3 position in the cephalosporin nucleus showed potent antibacterial activity against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. Also, we found that putting an imidazo[1,2-a]pyridine (II) moiety at the 3 position was an effective way to improve the antibacterial activity of cephalosporins.

Imidazo[1,5-a]pyridine (III), imidazo[1,2-b]pyridazine (IV), imidazo[1,2-a]pyrimidine (V), imidazo[1,2-c]pyrimidine (VI), imidazo[1,2-a]pyrazine (VII), and pyrazolo[1,5-a]pyridine (VIII) are azole condensed-heterocyclic rings having a nitrogen atom at the bridge head as is imidazo[1,2-a]pyridine (Fig. 2). We noted that the quaternization of these condensed-heterocycles lead the positive charge to be delocalized as is the case with imidazo[1,2-a]pyridinium.

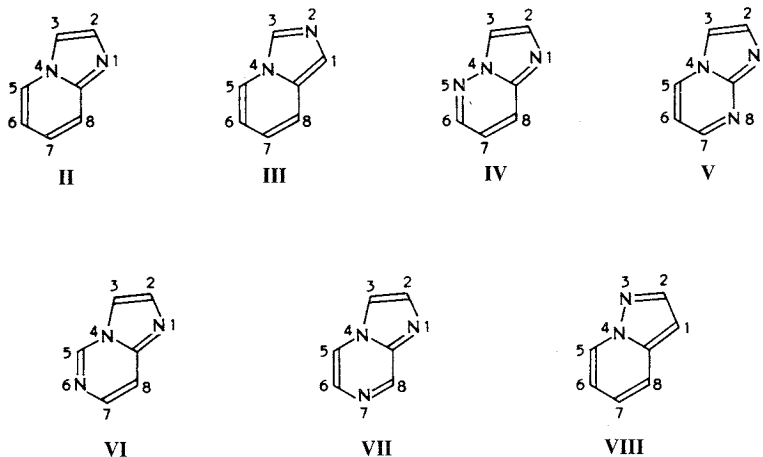
Fig. 1. Structure of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(substituted imidazo[1,2-a]pyridium-1-yl)methyl-3-cephem-4-carboxylate.



Ia $R_1 = \text{Me}$ $R_2 = \text{H}$

[†] Part of this paper was presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy¹⁾.

Fig. 2. Structures of condensed-heterocycles.



Thus, we are interested in the antibacterial activity of 7β -[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]cephalosporins bearing these condensed-heterocyclic azolium methyl groups at the 3 position. In this report, we describe the synthesis and antibacterial activity of these cephalosporins.

Chemistry

The condensed-heterocyclic compounds were prepared according to published procedures for known compounds and/or the procedures described in Scheme 1.

Imidazo[1,5-*a*]pyridine derivatives (**III**) were prepared according to the procedures of BOWER³), FENTES⁴) and PAUDLER⁵). Imidazo[1,2-*b*]pyridazine (**IVa**), 6-methyl-(**IVb**), 6-fluoro-(**IVc**) and 6-chloro-(**IVd**) imidazo[1,2-*b*]pyridazines were prepared according to the procedures of TISLER^{6,7}) and POLLAK⁸). 6-Methoxyimidazo[1,2-*b*]pyridazine (**IVf**) was prepared according to the procedure of LOMBARDINO⁹) and 6-hydroxy-(**IVe**) and 6-methylthioimidazo[1,2-*b*]pyridazines (**IVg**) were obtained by the reaction of **IVd** with sodium hydroxide or sodium mercaptane.

Imidazo[1,2-*a*]pyrimidine (**Va**) and 5,7-dimethylimidazo[1,2-*c*]pyrimidine (**VIa**) were prepared according to the methods of PAUDLER and KUDER¹⁰).

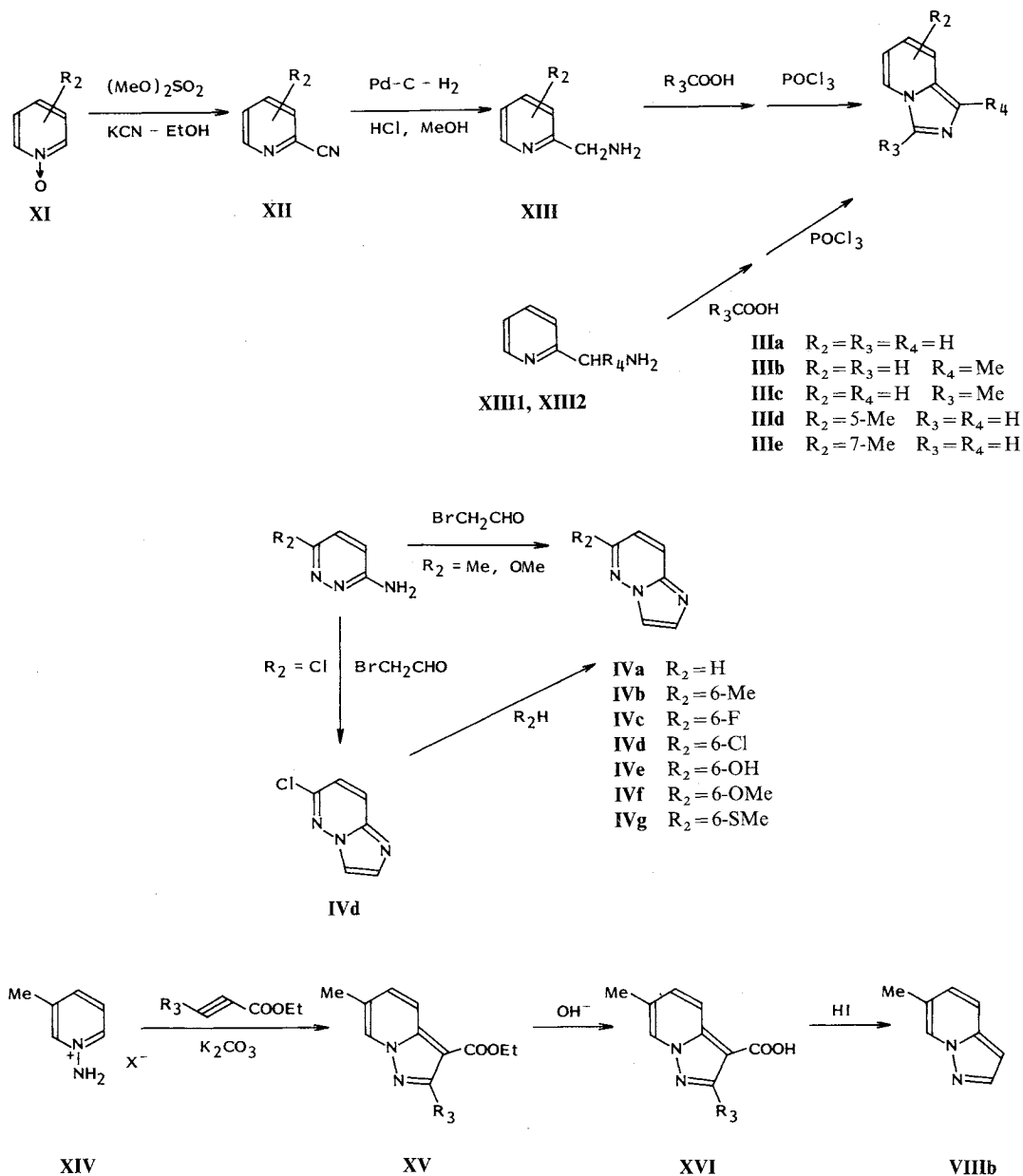
Pyrazolo[1,5-*a*]pyridine (**VIIIa**) was prepared following the procedures reported by BOWER and RAMAGE¹¹), and 6-methylpyrazolo[1,5-*a*]pyridine (**VIIIb**) was obtained by the dealkoxycarbonylation of 3-alkoxycarbonylimidazo[1,5-*a*]pyridine derivative (**XV**), which was prepared by 1,3-dipolar cycloaddition of pyridine *N*-imines with acetylenecarboxylic acid ester¹²).

The synthesis of 7β -[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl cephalosporins (**1**~**26**) is outlined in Scheme 2.

7β -[2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XVII**)²) was heated with an equal amount by weight of the condensed-heterocyclic compound and potassium iodide in 50% aqueous acetonitrile at 50~60°C for 2~3 hours. The mixture was chromatographed on silica gel with aqueous acetone as the eluent, and then the eluate was purified by chromatography on MCI gel CHP-20P. The desired cephalosporins (**1**~**19**, **21**~**25**) were isolated as amorphous powders in yields of 2~13%.

7β -[2-(2-Aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(3-

Scheme 1.

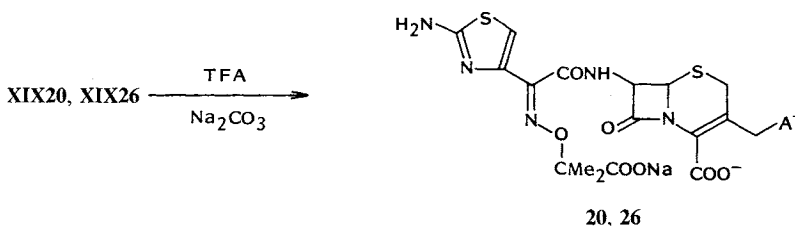
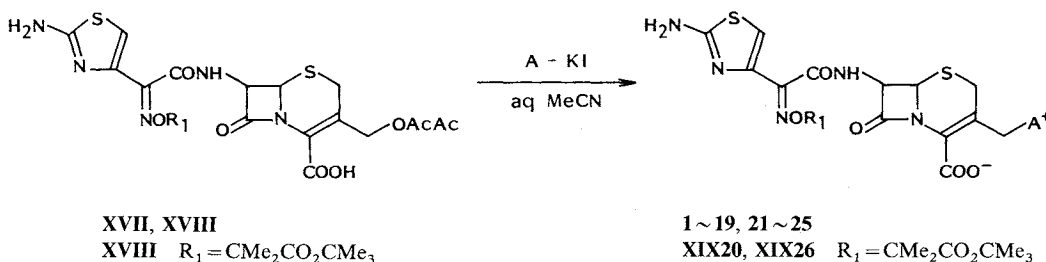


oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XVIII**)²⁾ was reacted with imidazo[1,5-*a*]pyridine (**IIIa**) or pyrazolo[1,5-*a*]pyridine (**VIIIa**), followed by purification by chromatography to give β -[2-(2-aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-azoliummethyl-3-cephem-4-carboxylate (**XIX**). Deprotection of **XIX** with trifluoroacetic acid followed by neutralization with sodium carbonate and purification by MCI gel column chromatography gave **20** or **26**.

Biological Results and Discussion

The MICs of this series of cephalosporins against strains of Gram-positive and Gram-negative

Scheme 2.



AcAc: $-\text{COCH}_2\text{COMe}$, A: Azole

bacteria were determined by the standard serial 2-fold agar dilution method.

Table 1 shows the MICs of 7β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]cephalosporins (1~5) bearing the various types of the condensed-heterocyclic azolium groups. The antibacterial activity of cephalosporins (1~5) against *Staphylococcus aureus* was reduced as compared to that of imidazo[1,2-a]pyridinium cephalosporin (**1a**). The cephalosporins having imidazo[1,5-a]pyridinium (**1**), imidazo[1,2-b]pyridazinium (**2**), pyrazolo[1,5-a]pyridinium (**3**) or imidazo[1,2-c]pyrimidinium (**4**) showed potent antibacterial activity against Gram-negative bacteria. The MIC of **2** against Gram-negative bacteria was superior to that of **1a**. Also the antibacterial activity of 1~3 against *Pseudomonas aeruginosa* was more potent than that of **1a**. In particular, the antibacterial activity of **2** was superior to that of ceftazidime.

Subsequently, the effect of adding various substituents to the imidazo[1,5-a]pyridinium, imidazo[1,2-b]pyridazinium, and pyrazolo[1,5-a]pyridinium moieties on the antibacterial activity was investigated.

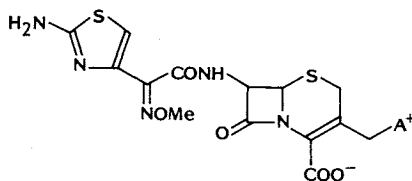
Table 2 shows the antibacterial activity of substituted imidazo[1,5-a]pyridinium cephalosporins (6~10). The MICs of 6~10 against *P. aeruginosa* were reduced as compared to that of **1** but were the same against other Gram-negative bacteria. The MIC of **7** against *S. aureus* and *Enterobacter cloacae* was higher than that of **1**.

Table 3 shows the MICs of a variety of substituted imidazo[1,2-b]pyridazinium cephalosporins (11~16). Among the cephalosporins tested, the 6-thiomethyl derivative (**16**) showed more potent activity against *S. aureus* and *E. cloacae* than **2**, whereas the activity of the others against those was similar or inferior to that of **2**. These results imply that these substituents have no effect on the antibacterial activity.

Table 4 shows the antibacterial activity of **3** and 6-methylpyrazolo[1,5-a]pyridinium cephalosporin (**17**). The activity of **17** against *E. cloacae* and *Serratia marcescens* was more potent than that of **3**.

Table 5 shows the antibacterial activity of several alkoxyimino cephalosporins (18~26) bearing imidazo[1,5-a]pyridine, imidazo[1,2-b]pyridazine and pyrazolo[1,5-a]pyridine moieties.

Table 1. Antibacterial activity (MIC, $\mu\text{g/ml}$) of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1a**, **1**~**5**), ceftazidime and cefmenoxime.



Compound No.	A ⁺	10 ⁸ cfu/ml						
		<i>S.a.</i>	<i>E.c.</i>	<i>E.cl.</i>	<i>S.m.</i>	<i>P.v.</i>	<i>P.a.1</i>	<i>P.a.2</i> ^a
1a		0.39	<0.1	0.39	0.2	0.2	6.25	>100
1		0.78	<0.1	1.56	<0.1	<0.1	1.56	>100
2		0.78	<0.1	0.39	0.2	<0.1	1.56	100
3		1.56	<0.1	0.78	0.39	0.2	1.56	100
4		0.78	<0.1	3.13	<0.1	<0.1	25	>100
5		3.13	<0.1	0.78	0.39	1.56	6.25	>100
Ceftazidime		6.25	0.39	25	0.39	0.1	0.78	12.5
Cefmenoxime		1.56	0.2	6.25	0.39	<0.1	6.25	>100

^a *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.

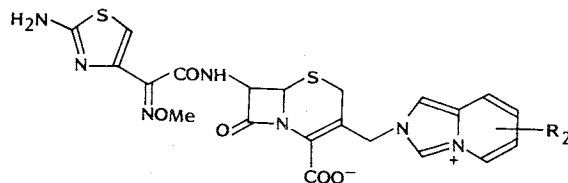
The antibacterial activity of **18**~**26** was not improved as compared to that of the corresponding methoxyimino cephalosporins (**1**~**3**). Also, introducing a carboxylic group into the alkoxyimino group reduced markedly the activity against Gram-positive bacteria.

Among the cephalosporins tested, **1**, **2** and **3** show highly potent antibacterial activity against both Gram-positive and Gram-negative bacteria including *P. aeruginosa* as does **1a**. It appears that 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 of cephalosporins as is imidazo[1,2-*a*]pyridine.

Experimental

MP's were determined on a Yanagimoto micro melting point apparatus and are uncorrected; boiling points are also uncorrected. IR spectra were taken on a Hitachi 215 spectrophotometer. ¹H NMR

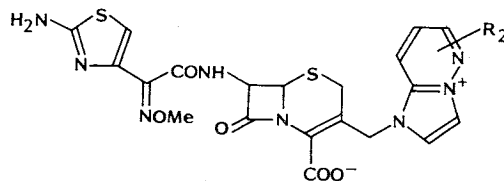
Table 2. Antibacterial activity (MIC, $\mu\text{g/ml}$) of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(substituted imidazo[1,5-*a*]pyridinium-2-yl)methyl-3-cephem-4-carboxylates (**1**, **6** ~ **10**).

10⁸ cfu/ml

Compound No.	R ₂	<i>S.a</i>	<i>E.c.</i>	<i>E.cl.</i>	<i>S.m.</i>	<i>P.v.</i>	<i>P.a.1</i>	<i>P.a.2</i> ^a
1	H	0.78	<0.1	1.56	<0.1	<0.1	1.56	>100
6	1-Me	0.78	<0.1	0.78	0.2	0.2	6.25	>100
7	3-Me	0.39	<0.1	0.39	<0.1	<0.1	3.13	>100
8	5-Me	0.78	<0.1	0.78	<0.1	0.2	3.13	>100
9	7-Me	3.13	<0.1	1.56	0.39	0.2	3.13	100
10	3,5-di-Me	0.39	<0.1	0.78	0.2	0.2	3.13	>100

^a Abbreviations: See footnote in Table 1.

Table 3. Antibacterial activity (MIC, $\mu\text{g/ml}$) of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(substituted imidazo[1,2-*b*]pyridazinium-1-yl)methyl-3-cephem-4-carboxylates (**2**, **11** ~ **16**).

10⁸ cfu/ml

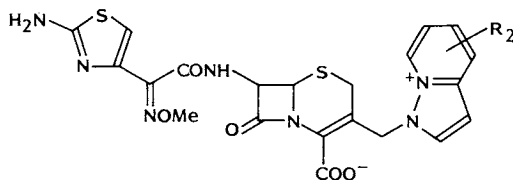
Compound No.	R ₂	<i>S.a</i>	<i>E.c.</i>	<i>E.cl.</i>	<i>S.m.</i>	<i>P.v.</i>	<i>P.a.1</i>	<i>P.a.2</i> ^a
2	H	0.78	<0.1	0.39	0.2	<0.1	1.56	100
11	6-Me	0.78	<0.1	0.78	0.2	0.2	3.13	>100
12	6-F	1.56	<0.1	1.56	0.39	0.2	6.25	>100
13	6-Cl	0.78	<0.1	0.78	0.2	0.39	3.13	100
14	6-OH	3.13	<0.1	12.5	0.78	<0.1	100	>100
15	6-OMe	0.78	<0.1	0.78	0.2	0.2	3.13	>100
16	6-SMe	0.39	<0.1	0.2	0.2	<0.1	6.25	50

^a Abbreviations: See footnote in Table 1.

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 anhydrous MgSO₄ and concentration by evaporation was carried out *in vacuo*. Column chromatography was carried out on Merck Kieselgel 60 (Art. No. 7734 or Art. No. 9385), Mitsubishi Chemical MCI gel CHP-20P, Rohm and Haas Amberlite XAD-2, and Pharmacia Fine Chemical Sephadex LH-20.

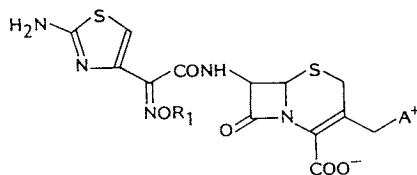
Determination of *In Vitro* Antibacterial Activity

The MICs against selected strains of Gram-positive and Gram-negative bacteria were determined by the standard serial 2-fold agar dilution method with Mueller-Hinton broth as the test medium, after incubation overnight at 37°C with an inoculum size of about 10⁸ cfu/ml.

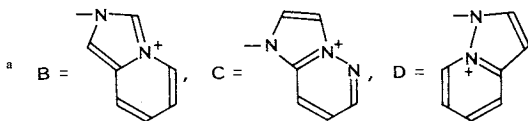
Table 4. Antibacterial activity (MIC, $\mu\text{g/ml}$) of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(substituted pyrazolo[1,5-a]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**3** and **17**).

Compound No.	R ₂	10 ⁸ cfu/ml							
		S.a.	E.c.	E.cl.	S.m.	P.v.	P.a.1	P.a.2 ^a	
3	H	1.56	<0.1	0.78	0.39	0.2	1.56	100	
17	6-Me	1.56	<0.1	0.39	<0.1	0.2	3.13	100	

^a Abbreviations: See footnote in Table 1.

Table 5. Antibacterial activity (MIC, $\mu\text{g/ml}$) of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**~**3**, **18**~**26**).

Compound No.	R ₁	10 ⁸ cfu/ml								
		A ^a	S.a	E.c.	E.cl.	S.m.	P.v.	P.a.1	P.a.2 ^b	
1	Me	B	0.78	<0.1	0.39	0.2	0.2	6.25	>100	
18	Et	B	0.78	<0.1	3.13	<0.1	0.2	1.56	>100	
19	CH ₂ CH ₂ F	B	0.78	<0.1	1.56	<0.1	0.2	1.56	100	
20	CMe ₂ CO ₂ Na	B	12.5	0.2	6.25	0.39	0.39	1.56	25	
2	Me	C	0.78	<0.1	0.39	0.2	<0.1	1.56	100	
21	Et	C	0.78	0.2	1.56	0.39	0.39	1.56	25	
22	CH ₂ CH ₂ F	C	1.56	<0.1	1.56	0.2	0.39	12.5	50	
23	CH ₂ CH ₂ Cl	C	0.39	0.78	3.13	1.56	1.56	3.13	50	
3	Me	D	1.56	<0.1	0.78	0.39	0.2	1.56	100	
24	Et	D	1.56	0.78	1.56	1.56	0.78	6.25	50	
25	CH ₂ CH=CH ₂	D	1.56	1.56	6.25	1.56	1.56	6.25	50	
26	CMe ₂ CO ₂ Na	D	12.5	0.78	12.5	1.56	0.2	3.13	50	



^b Abbreviations: See footnote in Table 1.

Preparation of Condensed-Heterocyclic Compounds

Preparation of Imidazo[1,5-a]pyridines (**III**)

Imidazo[1,5-a]pyridine (**IIIa**): MP 49~51°C (literature³) MP 54~55°C), 1-methylimidazo[1,5-a]pyridine (**IIIb**): MP 62~64°C (literature³) MP 64~65°C), 3-methylimidazo[1,5-a]pyridine (**IIIc**): MP 52~54°C (literature³) MP 55°C), 5-methylimidazo[1,5-a]pyridine (**IIId**): Oil (literature⁴) BP 95~98°C/0.1 mmHg), 7-methylimidazo[1,5-a]pyridine (**IIIe**): Oil,⁴) and 3,5-dimethylimidazo[1,5-a]pyridine (**IIIf**): MP 62~63°C⁵) were prepared according to the procedures described in the literatures.

Preparation of Imidazo[1,2-*b*]pyridazines (IV)

Imidazo[1,2-*b*]pyridazine (IVa): MP 47~49°C (literature⁶) MP 53~55°C) was prepared according to the procedure of KOBE. 6-Chloroimidazo[1,2-*b*]pyridazine (IVd): MP 112~114°C (literature⁷) MP 115°C) and 6-methylimidazo[1,2-*b*]pyridazine (IVb): MP 115~116°C (literature⁸) MP 125°C), 6-fluoroimidazo[1,2-*b*]pyridazine (IVc): Semi solid were prepared according to the procedures of TISLER and POLLAK, respectively. 6-Methoxyiminoimidazo[1,2-*b*]pyridazine (IVf): MP 105~108°C (literature⁹) MP 106~108°C) was prepared following the method of LOMBARDINO.

6-Hydroxyimidazo[1,2-*b*]pyridazine (IVe)

A mixture of IVd (3.3 g) and KOH (3.3 g) in 90% EtOH (50 ml) was heated at 170°C in a sealed tube for 4 hours. After cooling, the solid was filtered off and the filtrate was evaporated. The residue was dissolved in H₂O, neutralized with HCl and then evaporated. The residual solid was extracted with MeOH and the solvent was evaporated. The residue was recrystallized from EtOH-Et₂O to give 2.7 g (93%) of IVe: MP >280°C; ¹H NMR (DMSO-*d*₆) δ 6.34 (1H, d, *J*=10 Hz), 7.15 (1H, s), 7.33 (1H, d, *J*=10 Hz), 7.37 (1H, s).

6-Methylthioimidazo[1,2-*b*]pyridazine (IVg)

A mixture of IVd (3.1 g) in DMF (5 ml) and 15% aq NaSMe soln (13 ml) was heated with stirring at 100~105°C for 3 hours. After cooling, H₂O was added and the mixture was extracted with Et₂O. The combined organic layer was washed with H₂O and satd aq NaCl, dried and evaporated to give 2.8 g (84%) of IVg as colorless crystals: MP 66~68°C; ¹H NMR (CDCl₃) δ 2.59 (3H, s), 6.83 (1H, d, *J*=10 Hz), 7.63 (1H, s), 7.70 (1H, d, *J*=10 Hz), 7.85 (1H, br).

Anal Calcd for C₇H₇N₃S: C 50.89, H 4.27, N 25.43.

Found: C 50.72, H 4.22, N 25.42.

Imidazo[1,2-*a*]pyrimidine (Va) and 5,7-dimethylimidazo[1,2-*c*]pyrimidine (VIa) were prepared from 2-aminopyrimidine derivatives according to the procedure of PAUDLER and KUDER¹⁰.

Preparation of Pyrazolo[1,5-*a*]pyridine (VIII)

Pyrazolo[1,5-*a*]pyridine (VIIIa): Oil (literature¹¹) BP 108°C/25 mmHg) was prepared according to the procedure described in the literature.

6-Methylpyrazolo[1,5-*a*]pyridine (VIIIb)

A mixture of 1-amino-4-methylpyridinium iodide (XIV, 12 g) and anhydrous K₂CO₃ (9.8 g) in Me₂CO (100 ml) was stirred at room temperature for 10 minutes. Ethyl propiolate (6.2 g) was added dropwise to the mixture followed by stirring at room temperature for 6 hours. The solid was filtered off and the filtrate was evaporated. The residue was dissolved in a mixture of H₂O and EtOAc, and the organic layer was separated. The organic layer was washed with satd aq NaCl, dried and evaporated to give 10 g (ca. 100%) of 3-ethoxycarbonylpyrazolo[1,5-*a*]pyridine (XV) as an orange oil which was then solidified at room temperature: MP 61~63°C; ¹H NMR (CDCl₃) δ 1.41 (3H, t, *J*=7.5 Hz), 2.47 (3H, s), 4.39 (2H, q, *J*=7.5 Hz), 6.77 (1H, dd, *J*=1.5 and 7.5 Hz), 7.95 (1H, s), 8.37 (1H, d, *J*=1.5 Hz), 8.49 (1H, d, *J*=1.5 Hz).

A mixture of XV (9.0 g) and NaOH (3 g) in a mixture of MeOH (60 ml) and H₂O (13 ml) was heated at 60~70°C for 6 hours. The mixture was concentrated to remove MeOH, and the residual aqueous solution was acidified with conc HCl. The solid precipitate was collected by filtration, washed with H₂O and dried to give 4.6 g of 6-methylpyrazolo[1,5-*a*]pyridine-3-carboxylic acid (XVI) as yellow crystals: MP 213~215°C; ¹H NMR (DMSO-*d*₆) δ 2.45 (3H, s), 6.97 (1H, dd, *J*=1.5 and 7.5 Hz), 7.88 (1H, br), 8.34 (1H, s), 8.73 (1H, d, *J*=7.5 Hz).

XVI (9 g) was refluxed with 57% HI (50 ml) for 6 hours. After cooling, the reaction mixture was alkalized with aq K₂CO₃ and extracted with Et₂O. The combined ethereal solution was washed with 5% aq sodium thiosulfate soln and satd aq NaCl, dried and evaporated to give 4.3 g (64%) of VIIIb as a yellow oil; ¹H NMR (CDCl₃) δ 2.31 (3H, s), 6.34 (1H, d, *J*=1.5 Hz), 6.54 (1H, dd, *J*=1.5 and 7.5 Hz), 7.25 (1H, br), 7.88 (1H, d, *J*=1.5 Hz), 8.35 (1H, d, *J*=7.5 Hz).

Table 6. IR and analytical data for 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (**1**~**26**).

Compound No.	Yield (%)	Formula	Elemental analysis (%)						IR (KBr) cm ⁻¹
			Calcd			Found			
			C	H	N	C	H	N	
1	9	C ₂₁ H ₁₉ N ₇ O ₅ S ₂ ·3.5H ₂ O	43.74	4.55	17.00	43.79	4.30	16.79	1770, 1660, 1615, 1515
2	10	C ₂₀ H ₁₈ N ₈ O ₅ S ₂ ·4H ₂ O	40.95	4.47	19.10	40.96	4.55	18.84	1765, 1670, 1610, 1530
3	5	C ₂₁ H ₁₉ N ₇ O ₅ S ₂ ·5.5H ₂ O	41.17	4.94	16.00	41.23	4.25	16.38	1775, 1675, 1620, 1530
4	10	C ₂₀ H ₁₈ N ₈ O ₅ S ₂ ·3.5H ₂ O	41.59	4.36	19.40	41.63	4.26	19.13	1775, 1670, 1630, 1610
5	9	C ₂₂ H ₂₂ N ₈ O ₅ S ₂ ·5H ₂ O	41.77	5.10	17.71	41.87	4.69	17.24	1775, 1670, 1615, 1535
6	6	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·4H ₂ O	44.07	4.87	16.35	44.14	4.69	16.08	1760, 1660, 1610, 1530
7	7	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·2.5H ₂ O	46.15	4.58	17.12	46.17	4.28	16.85	1770, 1650, 1610, 1530
8	13	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·3.5H ₂ O	44.74	4.78	16.60	44.60	4.53	16.42	1770, 1660, 1610, 1530
9	11	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·6H ₂ O	41.57	5.23	15.42	41.72	4.83	15.15	1765, 1660, 1610, 1530
10	4	C ₂₃ H ₂₃ N ₇ O ₅ S ₂ ·3H ₂ O	46.38	4.91	16.46	46.64	4.87	16.52	1765, 1660, 1610, 1530
11	8	C ₂₁ H ₂₀ N ₈ O ₅ S ₂ ·4.5H ₂ O	41.37	4.80	18.38	41.50	4.86	17.91	1770, 1670, 1630, 1550
12	4	C ₂₀ H ₁₇ FN ₈ O ₅ S ₂ ·5.5H ₂ O	38.03	4.47	17.74	37.81	4.25	17.49	1765, 1660, 1610, 1525
13	7	C ₂₀ H ₁₇ ClN ₈ O ₅ S ₂ ·3H ₂ O	39.84	3.84	18.58	39.62	3.69	18.42	1780, 1670, 1610, 1530
14	4	C ₂₀ H ₁₈ N ₈ O ₆ S ₂ ·7.5H ₂ O	36.09	5.00	16.83	36.09	5.26	16.27	1760, 1660, 1605, 1575
15	7	C ₂₁ H ₂₀ N ₈ O ₆ S ₂ ·4.5H ₂ O	40.32	4.67	17.91	40.34	4.71	17.42	1775, 1670, 1620, 1510
16	8	C ₂₁ H ₂₀ N ₈ O ₅ S ₂ ·2.5H ₂ O	41.65	4.16	18.50	41.58	4.51	18.35	1770, 1670, 1610, 1530
17	4	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·3H ₂ O	45.43	4.68	16.86	45.10	3.93	16.43	1770, 1680, 1610, 1530
18	9	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·4.5H ₂ O	43.42	4.97	16.11	43.72	4.47	16.00	1760, 1600, 1520
19	12	C ₂₂ H ₂₀ FN ₇ O ₅ S ₂ ·3.5H ₂ O	43.42	4.42	16.11	43.58	4.29	15.85	1770, 1660, 1610, 1535
20	3	C ₂₄ H ₂₂ N ₇ O ₇ S ₂ Na·4.5H ₂ O	41.86	4.54	14.24	42.08	4.26	13.89	1780, 1660, 1610, 1520
21	7	C ₂₁ H ₂₀ N ₈ O ₅ S ₂ ·4H ₂ O	41.99	4.70	18.66	41.83	4.56	17.92	1770, 1670, 1610, 1530
22	10	C ₂₁ H ₁₉ FN ₈ O ₅ S ₂ ·3H ₂ O	42.00	4.20	18.66	42.22	3.98	18.99	1765, 1670, 1615, 1535
23	10	C ₂₁ H ₁₉ ClN ₈ O ₅ S ₂ ·3.5H ₂ O	40.29	4.19	17.90	40.59	4.36	17.64	1770, 1660, 1610, 1525
24	2	C ₂₂ H ₂₁ N ₇ O ₅ S ₂ ·4.5H ₂ O	43.42	4.97	16.11	43.21	5.26	16.09	1765, 1670, 1615, 1525
25	5	C ₂₃ H ₂₁ N ₇ O ₅ S ₂ ·6.5H ₂ O	42.07	5.22	14.93	42.29	5.24	14.51	1770, 1670, 1630, 1615
26	3	C ₂₄ H ₂₂ N ₇ O ₇ S ₂ Na·6H ₂ O	40.28	4.79	13.70	40.43	4.81	13.46	1775, 1665, 1610, 1540

General Preparation of Cephalosporins

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

A mixture of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XVIIa**, 2 g), imidazo[1,5-a]pyridine (**IIIa**, 2 g) and KI (2.4 g) in 50% aq MeCN (40 ml) was heated with stirring at 50~60°C for 2 hours. After cooling, the reaction mixture was chromatographed on silica gel with Me₂CO and 80% aq Me₂CO as the eluents. The fractions containing the desired compound were combined and evaporated, and the residual solution was purified by MCI gel chromatography successively with H₂O and aq EtOH as the eluents. The fraction eluted with 10% aq EtOH was evaporated, and the residual solution was lyophilized to give 0.25 g (9%) of as amorphous **1**. The analytical results are shown in Tables 6 and 7.

7 β -[2-(2-Aminothiazol-4-yl)-2(Z)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(imidazo[1,5-a]pyridinium-2-yl)methyl-3-cephem-4-carboxylate Mono Sodium Salt (**20**)

A mixture of 7 β -[2-(2-aminothiazol-4-yl)-2(Z)-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**XVIII**, 2.1 g), **IIIa** (2 g) and KI (2 g) in 50% aq MeCN (30 ml) was heated with stirring at 60~70°C for 2 hours. After cooling, the reaction mixture was chromatographed on silica gel successively with 90% aq Me₂CO and 80% aq Me₂CO as the eluents. The fraction eluted with 80% aq Me₂CO was evaporated to dryness and the residual solution was purified by MCI gel chromatography successively with H₂O and aq EtOH as the eluents. The fraction eluted with

Table 7. ¹H NMR data for 7β-[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates (1~26).

Compound No.	Solvent ^a	Chemical shift δ (J=Hz)								
		Cephem nuclei				7-Acyl		R ₁	3-Azolium ring proton	
		2-CH ₂ Abq (18)	3-CH ₂ ABq (14)	6-CH d (5)	7-CH dd (5,8)	CONH d (8)	5-CH (s)			NH ₂ (br)
1	a	3.15, 3.56	5.11, 5.54	5.03	5.64	9.43	6.68	—	3.80 (s)	6.9~7.4 (m), 8.2~8.5 (m), 8.53 (s), 8.68 (d, 6), 10.03 (s)
2	a	3.35	5.28, 5.52	5.00	5.61	9.47	6.68	7.13	3.79 (s)	7.84~8.12 (m), 8.75 (s), 9.04 (d, 5), 9.32 (d, 9)
3	a	—	5.07	5.05	5.68	9.47	6.67	7.14	3.80 (s)	7.5~8.2 (m), 8.12~8.34 (m), 8.58~8.71 (m), 8.88~8.95 (m)
4	a	3.12, 3.54	5.15, 5.31	5.00	5.62	9.43	6.68	7.14	3.79 (s)	7.6~7.8 (m), 8.36 (d, 2.5), 9.0~9.18 (m), 9.3~9.55 (m)
5	c	—	5.48	5.27	5.88	—	7.05	—	4.06 (s)	8.02 (dd, 5, 7), 9.43 (dd, 2.5), 9.6 (s), 9.60 (dd, 2, 7)
6	a	3.14, 3.48	5.37, (br)	5.02	5.63	9.44	6.70	7.16	3.80 (s)	2.64 (s), 7.0~7.5 (m), 7.7~8.3 (m), 7.6~8.1 (m), 8.4~8.7 (m), 9.84 (s)
7	a	3.12, 3.47	5.26, 5.42	5.02	5.64	9.49	6.71	7.16	3.81 (s)	2.94 (s), 6.9~7.5 (m), 8.41 (s), 8.2~8.5 (m)
8	a	3.19, 3.52	5.07, 5.54	5.02	5.62	9.43	6.68	7.02	3.78 (s)	2.64 (s), 6.9~7.5 (m), 7.78 (d, 8), 8.64 (s), 9.95 (s)
9	a	3.00, 3.46	5.34, (br)	5.05	5.64	9.49	6.68	—	3.82 (s)	2.32 (s), 6.95~7.35, 7.7~8.1 (m), 8.30 (d, 6), 9.40 (d, 6)
10	a	3.09, 3.45	5.28, 5.48	5.01	5.63	9.46	6.70	7.16	3.81 (s)	2.90 (s), 3.20 (s), 6.7~7.5 (m), 7.64 (d, 9), 8.42 (s)
11	a	3.03, 3.46	5.25, 5.50	5.00	5.61	9.47	6.68	7.15	3.79 (s)	2.67 (s), 7.87 (d, 10), 8.55~8.74 (m), 9.19 (d, 10)
12	Not measured									
13	a	2.97, 3.43	5.21, 5.54	4.97	5.60	—	6.66	7.09	3.77 (s)	8.17 (d, 10), 8.71~8.84 (m), 9.34~9.54 (m)
14	a	2.93, —	5.00, 5.24	4.99	5.58	9.46	6.68	7.11	3.82 (s)	6.50 (d, 10), 7.67 (d, 2), 7.97 (d, 2), 8.19 (d, 2)

Table 7. (Continued)

Compound No.	Solvent ^a	Chemical shift δ (J =Hz)								
		Cephem nuclei					7-Acyl		R_1	3-Azoliium ring proton
		2-CH ₂ Abq (18)	3-CH ₂ ABq (14)	6-CH d (5)	7-CH dd (5,8)	CONH d (8)	5-CH (s)	NH ₂ (br)		
15	a	2.99, 3.44	5.21, 5.49	5.01	5.61	9.48	6.70	7.15	3.80 (s)	4.06 (s), 7.62 (d, 10), 8.48~8.66 (m), 9.21 (d, 10)
16	a	3.01, 3.43	5.20, 5.50	5.00	5.61	9.47	6.69	7.15	3.80 (s)	2.66 (s), 7.92 (d, 10), 8.55~8.72 (m), 9.1 (d, 10)
17	b	3.01, 3.47	5.62 (br)	5.24	5.81	—	6.81	—	3.96 (s)	2.52 (s), 6.99 (d, 3.5), 7.3~7.54 (m), 7.82 (br), 8.40 (d, 3.5), 9.05 (d, 8)
18	a	3.12, 3.55	5.07, 5.53	5.02	5.63	9.37	6.67	—	1.18 (t, 7), 4.05 (q, 7)	7.0~7.2 (m), 7.8~7.9 (m), 8.5~8.8 (m)
19	a	3.12, 3.57	5.53, 5.51	5.04	5.64	9.45	6.71	—	4.0~4.2 (m), 4.2~4.5 (m), 4.7~4.9 (m)	6.9~7.2 (m), 7.7~8.0 (m), 8.4~8.8 (m)
20	b	3.16, 3.56	5.11, 5.60	5.05	5.75	11.92	6.69	7.13	1.39 (s), 1.42 (s)	7.8~7.9 (m), 8.2~8.5 (m), 8.55~8.81 (m), 10.04 (br s)
21	a	3.03, 3.46	5.27, 5.52	5.01	5.63	9.43	6.66	7.14	1.18 (t, 7), 4.06 (q, 7)	7.8~8.1 (m), 8.68~8.84 (m), 8.95~9.14 (m), 9.34 (d, 9)
22	b	3.05, 3.46	5.30, 5.54	5.02	5.64	9.50	6.71	7.17	4.14 (t, 7), 4.86 (t, 7)	7.82~8.08 (m), 8.76 (br s), 8.96~9.10 (m), 9.35 (d, 19)
23	b	3.04, 3.47	5.28, 5.23	5.01	5.63	9.46	6.73	7.17	3.75 (t, 6), 4.23 (t, 6)	7.8~8.1 (m), 8.75 (br s), 9.04 (d, 4), 9.34 (d, 9)
24	a	—	4.90, 5.12	5.05	5.64	9.40	6.72	7.14	1.24 (t, 7), 4.11 (q, 7)	7.58~8.4 (m), 8.12~8.3 (m), 8.54~8.73 (m), 8.8~8.98 (m)
25	a	—	5.38 (br s)	5.02	5.63	9.48	6.84	7.14	4.46~4.68 (m), 5.24 (br s), 5.76~6.20 (m)	7.5~7.8 (m), 8.1~8.88 (m), 8.58~8.7 (m)
26	b	3.06, 3.52	5.66 (br s)	5.25	5.84	—	—	—	1.47 (s)	7.16~7.28 (m), 7.54~7.76 (m) 7.8~8.2 (m), 8.4~8.68 (m), 9.08~9.26 (m)

^a a: DMSO-*d*₆, b: D₂O, c: DMSO-*d*₆+D₂O.

40% aq EtOH was concentrated, and the residual solution was lyophilized. The powder obtained was dissolved in TFA (1 ml) and the mixture was stirred at room temperature for 1 hour. After evaporation, the residue was dissolved in H₂O (10 ml), and neutralized with Na₂CO₃ and then chromatographed on MCI gel with H₂O and aq EtOH as the eluents. The fraction eluted with 5% aq EtOH was concentrated, and the residual solution was lyophilized to give 75 mg (3%) of **20**. The analytical results are shown in Tables 6 and 7.

The other cephalosporins (**2**~**19** and **21**~**26**) were prepared following the procedures mentioned above, and the analytical results are shown in Tables 6 and 7.

Acknowledgment

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

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