STUDIES ON ORALLY ACTIVE CEPHALOSPORIN ESTERS

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The synthesis and the biological properties of orally active cephalosporin esters are described. 3-Methoxymethyl cephem derivatives having a 2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamide function at C-7 (**1**) showed good activity against a wide variety of bacteria including some β-lactamase producing species. The prodrug type esters of **1** exhibited a good urinary recovery after oral administration to mice and 1-(isopropoxycarbonyloxy)ethyl ester (**2a**, CS-807) has been pre-clinically tested as an orally active cephem prodrug.

Recently, remarkable developments have been achieved with respect to β-lactam antibiotics. The cephalosporins bearing an aminothiazole-oxime moiety at the C-7 position of the cephem nucleus, so-called third generation cephalosporins[1~4], have been developed clinically as parenteral antibiotics. They possess a wide antimicrobial spectrum against Gram-positive and Gram-negative bacteria and an increased resistance against bacterial β-lactamases. On the other hand, less significant developments have been achieved with orally active cephalosporins. Cephalexin (CEX) and its analogs bearing D-phenylglycine or closely related acyl side chains at the C-7 position are now in clinical use but are less active against Gram-negative bacteria than the third generation cephalosporins[5]. Therefore, many efforts have been made to afford new orally active cephalosporins exhibiting wider and stronger antibacterial activity than CEX and its analogs. Recently, orally active third generation cephalosporins, cefixime (FK027)[6] and T-2588[7] (**12d**), have been reported.

The current cephalosporins clinically used for injection are not suitable for oral administration because of their low absorption from the gastro-intestinal tract. According to our experiments, cefazolin (CEZ) and cefmetazole (CMZ) (Fig. 1), typical parenteral cephem antibiotics, each resulted in only 4% urinary recovery after oral administration to mice.

One of the reasons for such low absorption could be attributed to the relatively low *pKa* value of these compounds, *i.e.*, *pKa* 2.2 for CEZ and *pKa* 2.3 for CMZ, and so would almost completely exist as the unfavorable ionic form for passive absorption in the intestinal tract after oral administration. Therefore, we assumed that esterification of the carboxyl group at the C-4 position of the third generation cephem antibiotics may increase intestinal absorption of the drugs. The prodrug approach has been frequently utilized in penicillins to give a lipophilicity which is known to be one of the important factors in the passive absorption from the intestinal tract[8].

During the course of our research into orally active cephalosporins, we found that the combination of the substituent at C-3 and the ester at C-4 strongly influenced intestinal absorption. Some

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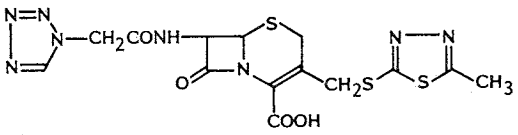
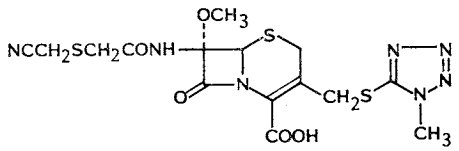
Fig. 1.

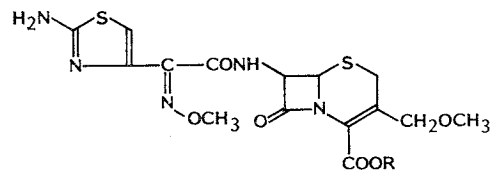


Cefazolin (CEZ)



Cefmetazole (CMZ)

Fig. 2.



1 R = H

2a (CS-807) R = $CHOCOOCH(CH_3)_2$ (CH_3)

esters of 3-alkoxymethyl and 3-methyl derivatives exhibited better urinary recovery than those of compounds possessing other substituents at the C-3 position. In particular, 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid (**1**, Fig. 2) showed a well-balanced antimicrobial activity against Gram-positive and Gram-negative bacteria and its esters exhibited excellent urinary recovery after oral administration to mice.

In this paper, we describe the synthesis and the biological properties of prodrug type cephalosporin esters, 1-(isopropoxycarbonyloxy)ethyl 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (**2a**, Fig. 2) and its related compounds.

Chemistry

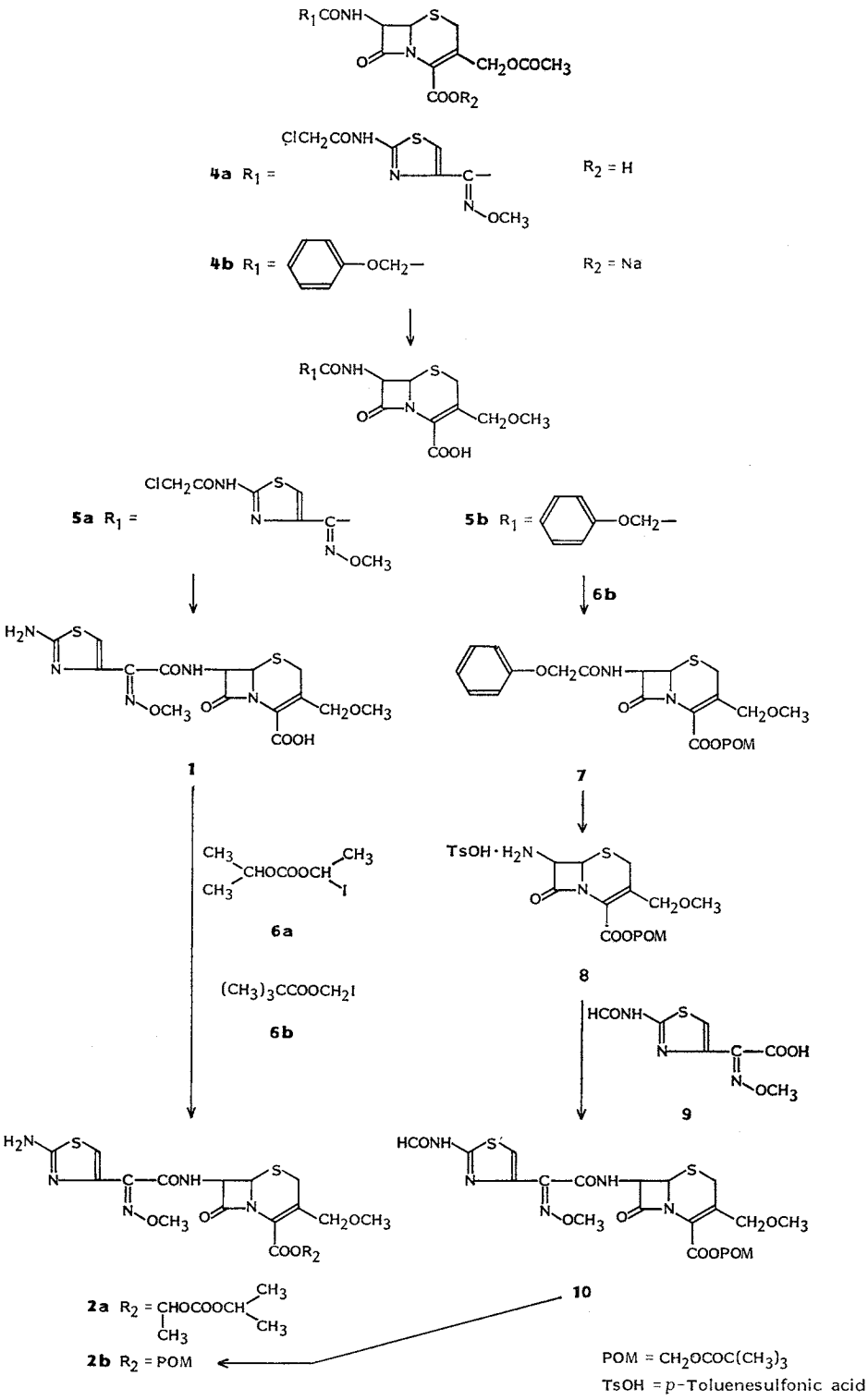
The synthetic routes of the esters (**2a** and **2b**) of 3-methoxymethyl cephem derivative (**1**) are shown in Scheme 1. The 3-acetoxymethyl cephem derivatives (**4a** and **4b**) prepared by acylation of 7-aminocephalosporanic acid (7ACA) were treated with aqueous methanol in the presence of $CaCl_2$ to give the corresponding 3-methoxymethyl cephem derivatives (**5a** and **5b**). The chloroacetyl group of **5a** was removed by treatment with thiourea in water to afford the compound **1** in 75.5% yield. Esterification of **1** with iodides (**6a** and **6b**) gave the corresponding esters (**2a** and **2b**).

Pivaloyloxymethyl (POM) ester (**2b**) was also prepared *via* another procedure. The dicyclohexylamine salt of **5b** was treated with iodomethyl pivalate (**6b**) to give an ester (**7**) in 82% yield. The phenoxyacetyl group of **7** was removed by CHAUVETTE's modification[9]. 7-Amino derivative (**8**) was acylated with 2-(2-formylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid (**9**) and $POCl_3$ followed by removal of the formyl group from the resulting compound to give the desired POM ester (**2b**) in 83% yield.

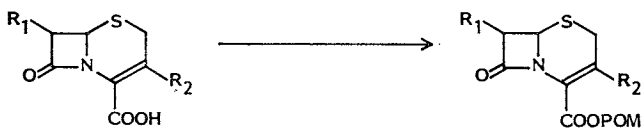
The other esters (**2c**~**2o**, **12a**~**12h**) were prepared by the esterification of the carboxylic acids (**1**, **11a**~**11h**) with the corresponding halides as shown in Scheme 2.

The parental cephem derivatives, **11a** and **11b**, were prepared as follows (Scheme 3). An acetyl group at C-3 of 7ACA was removed in methanol with NaOH and the successive acylation with phenoxyacetyl chloride gave 3-hydroxymethyl cephem derivative (**13**) in 50.6% yield. The esterification of **13** with diphenyldiazomethane followed by chlorination of the resulting 3-hydroxymethyl cephem ester (**14**) with $SOCl_2$ gave 3-chloromethyl derivative (**15**), which was treated with NaI in the usual manner; successive treatment of the resulting iodomethyl derivative with the corresponding alcohols

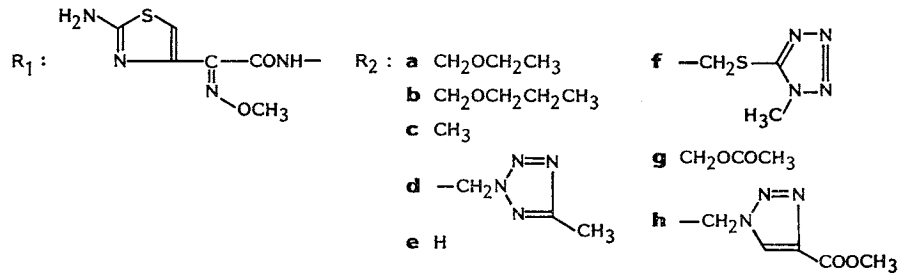
Scheme 1.


4a R1 = ClCH2CONH
R2 = H
4b R1 = OCH2
R2 = Na
5a R1 = ClCH2CONH
5b R1 = OCH2
6b
1
7
6a
8
6b
9
10
2a R2 = CHOCOOCH(CH3)2
2b R2 = POM
POM = CH2OCOC(CH3)3
TsOH = p-Toluenesulfonic acid

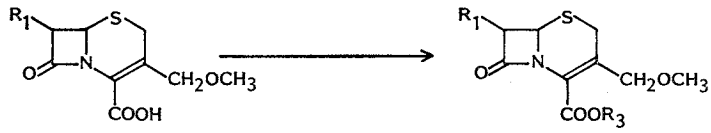
Scheme 2.



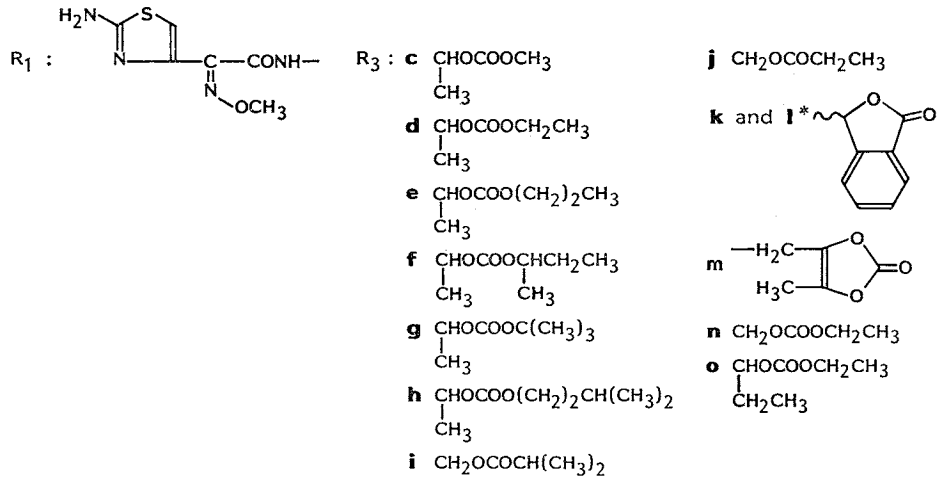
11a ~ 11h **12a ~ 12h**



POM = $CH_2OCOC(CH_3)_3$



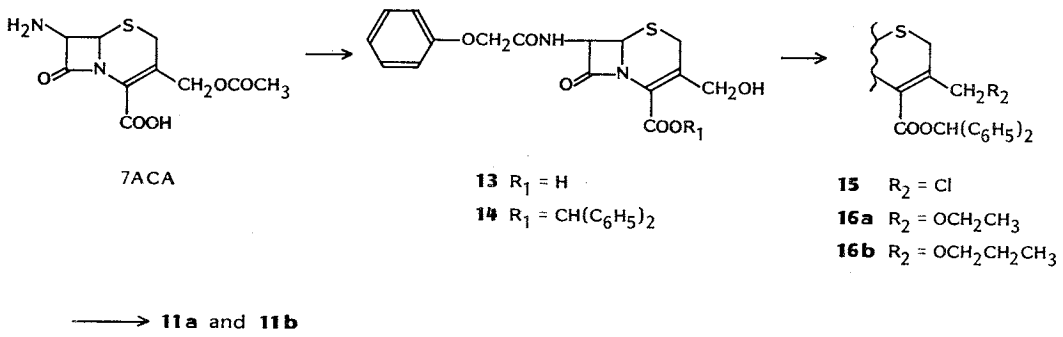
1 **2c ~ 2o**



* These esters (**2k**, **2l**) are diastereoisomers.

in the presence of $Hg(NO_3)_2 \cdot H_2O$ afforded 3-ethoxymethyl and 3-propoxymethyl derivatives (**16a** and **16b**). The desired cephems (**11a** and **11b**) were prepared from these compounds (**16a** and **16b**) by removal of the phenoxyacetyl group of **16a** and **16b**, the acylation of the resulting 7-amino cephem derivatives with 2-(chloroacetylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid and the removal of

Scheme 3.



the protective group of the resulting compounds successively.

Biological Results and Discussion

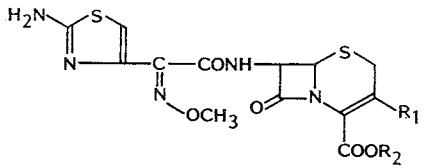
To start with preparation and biological estimation on POM esters of 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-substituted-3-cephem-4-carboxylic acid (**1**, **11a**~**11h**) were carried out as POM esters are generally regarded as useful prodrugs in oral administration of β-lactam antibiotics such as pivampicillin[10] and pivmecillinam[11]. The antimicrobial activity of parental cephalosporins (**1**, **11a**~**11h**) and their urinary recovery as a measure of intestinal absorption after oral administration of their POM esters (**2b**, **12a**~**12h**) are shown in Table 1. Among the POM esters, 3-alkoxymethyl derivatives (**2b**, **12a** and **12b**) and 3-methyl derivative[12] (**12c**) showed 62~83% dose recovery in urine. Although ceftizoxime[4] (**11e**), cefmenoxime[2] (**11f**) and cefotaxime[1] (**11g**) showed excellent antimicrobial activity, their esters (**12e**~**12g**)[13] showed less urinary recovery than **2b** and **12a**~**12c**. The low urinary recovery of **12g** and **12h** could be attributed to their instability *in vivo*. They would be converted into metabolites unable to be absorbed in the gastro-intestinal tract or biologically inactive metabolites. Among the 3-methyl and 3-alkoxymethyl derivatives (**1**, **11a**~**11c**) whose POM esters showed high intestinal absorption after oral administration, the 3-methoxymethyl derivative (**1**) showed the strongest antimicrobial activity against Gram-positive and Gram-negative bacteria.

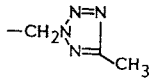
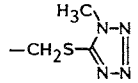
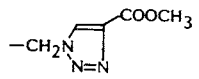
Therefore, the preparation and the biological evaluation of several kinds of esters of **1**, other than POM ester, were carried out (Table 2). The POM ester (**2b**) gave good recovery in urine among the acyloxyalkyl esters (**2b**, **2i** and **2j**). Of the other types of esters (**2d**, **2k**~**2m**), ethoxycarbonyloxyethyl ester (**2d**) showed relatively high urinary recovery. The phthalidyl[14] and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl[15] esters of **1** (**2k**, **2l** and **2m**) showed relatively low recovery.

Subsequently, alkoxycarbonyloxyalkyl (carbonate type) esters have been further elaborated in order to improve intestinal absorption (Table 3). Among a series of the compounds (**2d**, **2n** and **2o**) possessing a terminal ethyl group (R_2) in the ester function, the compounds having a methyl or an ethyl group as R_1, **2d** and **2o**, each gave 60% urinary recovery. Of the above, the ester **2d** having a methyl substituent as R_1 was better than **2o** with respect to practical preparation. From our experiments, a methyl substituent as R_1 resulted in superior urinary recovery when the drugs possessed the same terminal aklyl group (R_2). We then studied carbonate type esters possessing a methyl groups as R_1 in the ester function (**2a**, **2c**~**2h**).

According to these results, the combination of carbonate type ester and 3-methoxymethyl sub-

Table 1. Antibacterial activity (μg/ml)[a] of 7-aminothiazolyl cephalosporins and their urinary recovery (% of dose)[b] after oral administration of their pivaloyloxymethyl (POM) esters to mice.



R_1	Compound No. (R_2=H)	*S.a.*[c]	*S.a.*(R)	*E.c.*	*E.c.*(R)	*K.p.*	*K.p.*(R)	*P.v.*	Compound No. (R_2=POM)	Urinary recovery (%)
CH_2OCH_3	**1**	0.8	0.8	0.4	0.4	0.1	0.8	≦0.01	**2b**	76
$CH_2OC_2H_5$	**11a**	1.5	1.5	0.8	1.5	0.4	1.5	0.05	**12a**	83
$CH_2OC_3H_7$	**11b**	0.8	1.5	1.5	3.1	1.5	3.1	0.02	**12b**	68
CH_3	**11c**	12.5	12.5	0.4	0.8	≦0.1	1.5	≦0.1	**12c**	62
	**11d**	0.8	1.5	0.2	0.4	0.4	0.8	≦0.01	**12d**	39
H	**11e**	0.8	0.8	≦0.01	0.1	≦0.01	0.1	≦0.01	**12e**	27
	**11f**	0.2	0.4	0.05	0.1	0.05	0.2	≦0.01	**12f**	14
CH_2OCOCH_3	**11g**	0.2	0.4	0.05	0.05	0.02	0.2	≦0.01	**12g**	8
	**11h**	0.8	1.5	0.2	0.4	0.2	1.5	≦0.01	**12h**	2

[a] Determined with an inoculum of 10^7 cfu/ml.

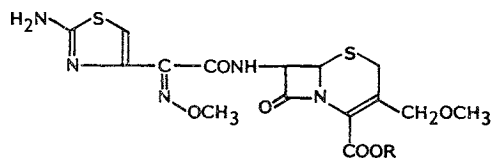
[b] Urinary recovery was determined by disk method on nutrient agar using *Bacillus subtilis* ATCC 6633 as a test strain after oral administration of POM esters (50 mg/kg as a parental cephalosporin) in slc *dd*Y (SPF) mice (n=5, 0~24 hours).

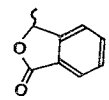
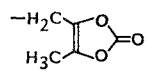
[c] *S.a.*; *Staphylococcus aureus* 209 P JC-1, *S.a.*(R); *S. aureus* 56, *E.c.*; *Escherichia coli* NIHJ JC-2, *E.c.*(R); *E. coli* 609, *K.p.*; *Klebsiella pneumoniae* 806, *K.p.* (R); *K. pneumoniae* 846, *P.v.*; *Proteus vulgalis* 1420. (R) means β-lactamase producing strains.

stituent exhibited a fairly good recovery of parental cephem compound (**1**) in urine when these esters were administered orally to mice. Some of the carbonate type esters having a branched methyl substituent in the terminal alkyl moiety of the ester function such as **2a** and **2f** showed a good intestinal absorption as well as CEX. These compounds showed similar biological properties in the further studies. 1-(Isopropoxycarbonyloxy)ethyl ester (**2a**) was more favorable than **2f** in an aspect of the practical preparation because two asymmetric centers in the ester function of **2f** gave a complex mixture of two pairs of diastereoisomers in comparison with a mixture of diastereoisomers derived from an asymmetric center in the case of **2a**. From the various chemical and biological properties, **2a** (CS-807) was chosen as a clinical candidate.

1-(Isopropoxycarbonyloxy)ethyl ester (**2a**) was hydrolyzed rapidly in a homogenate of the small intestine and in a serum of rats *in vitro*, and **1** was found in the blood of the portal vein after oral administration of **2a** to rats. The serum levels of **1** and CEX after oral administration of **2a** and CEX are shown in Table 4. 1-(Isopropoxycarbonyloxy)ethyl ester (**2a**), CS-807, exhibited high

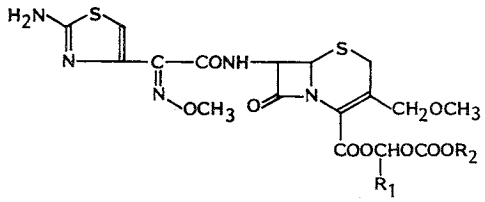
Table 2. Urinary recovery (% of dose)[a] of **1** after oral administration of 3-methoxymethyl cephem esters to mice.



Compound No.	R	Urinary recovery (%)
2b	$CH_2OCOC(CH_3)_3$	76
2i	$CH_2OCOCH(CH_3)_2$	56
2j	$CH_2OCOCH_2CH_3$	37
2d	$CH(OCOOCH_2CH_3)CH_3$	60
2k and **2l**[b]		19 and 21
2m		22

[a] Urinary recovery was determined by the same method as described in Table 1.
[b] These esters (**2k** and **2l**) are diastereoisomers.

Table 3. Urinary recovery (% of dose) of **1** after oral administration of carbonate type esters (**2a**, **2c**~**2h**, **2n** and **2o**) to mice.



Compound No.	R_1	R_2	Urinary recovery (%)
2a (CS-807)	CH_3	$CH(CH_3)_2$	67
2c	CH_3	CH_3	63
2d	CH_3	CH_2CH_3	60
2e	CH_3	$CH_2CH_2CH_3$	45
2f	CH_3	$CH(CH_3)CH_2CH_3$	76
2g	CH_3	$C(CH_3)_3$	56
2h	CH_3	$(CH_2)_2CH(CH_3)_2$	55
2n	H	CH_2CH_3	40
2o	CH_2CH_3	CH_2CH_3	60
Cephalexin			66

Urinary recovery was determined by the same method as described in Table 1.

Table 4. Serum levels (μg/ml) after oral administration to mice of **2a** (CS-807)[a] and cephalexin (CEX).

Compound	Serum levels (μg/ml)						
	7.5 minutes	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes	180 minutes
2a (CS-807)	23.5	39.6	34.4	18.8	11.7	8.1	2.7
CEX	30.0	43.3	31.7	13.7	NT	9.2	2.6

Compound	T_{max} (hour)	C_{max} (μg/ml)	$T_{1/2}$ (hour)	AUC (μg·hours/ml)
2a (CS-807)	0.25	39.6	0.684	45.9
CEX	0.25	43.3	0.445	44.5

[a] Measured as **1**. Method and materials were the same as in the determination of urinary recovery as described in Table 1.

NT: Not tested.

Table 5. ^{1}H NMR data of pivaloyloxymethyl esters (**12a**, **12b** and **12h**).

	$CDCl_3$, δ ppm, J in Hz
12a	1.19 (3H, t, J=7, CH_2CH_3), 1.24 (9H, s, *tert*-butyl), 3.49 (2H, q, J=7, CH_2CH_3), 3.58 (2H, br s, 2-CH_2), 4.06 (3H, s, $NOCH_3$), 4.37 (2H, s, 3′-CH_2), 5.07 (1H, d, J=5, 6-CH), 5.57 (2H, br s, NH_2), 5.88 (2H, s, CH_2), 6.04 (1H, dd, J=5 and 9, 7-CH), 6.76 (1H, s, thiazole ring-H), 7.90 (1H, d, J=9, 7-NHCO).
12b	0.90 (3H, t, J=7, $(CH_2)_2CH_3$), 1.23 (9H, s, *tert*-butyl), 1.2~1.9 (2H, m, $CH_2CH_2CH_3$), 3.38 (2H, t, J=7, $CH_2CH_2CH_3$), 3.59 (2H, s, 2-CH_2), 4.04 (3H, s, $NOCH_3$), 4.37 (2H, s, 3′-CH_2), 5.07 (1H, d, J=5, 6-CH), 5.68 (2H, br, NH_2), 5.87 (2H, s, CH_2), 6.02 (1H, dd, J=5 and 9, 7-CH), 6.71 (1H, s, thiazole ring-H), 8.03 (1H, d, J=9, 7-NHCO).
12h	1.23 (9H, s, *tert*-butyl), 3.53 (2H, s, 2-CH_2), 3.92 (3H, s, CH_3), 3.95 (3H, s, CH_3), 5.07 (1H, d, J=5, 6-CH), 5.34 (2H, br s, 3′-CH_2), 5.77 (2H, br s, NH_2), 5.92 (2H, s, CH_2), 6.01 (1H, dd, J=5 and 9, 7-CH), 6.70 (1H, s, thiazole ring-H), 7.83 (1H, d, J=9, 7-NHCO), 8.46 (1H, s, triazole ring-H).

serum levels and good urinary recovery, which were on a par with CEX.

Experimental

IR spectra were recorded on a Japan Spectroscopic Co., Ltd., IRA-2 spectrometer. NMR spectra were determined on a Varian EM-360 (60 MHz) spectrometer using TMS as an internal standard.

The melting points were determined using Yanagimoto micro-melting point apparatus. The melting points and the boiling points are uncorrected.

7β-[2-(2-Chloroacetylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic Acid (**5a**)

To a solution of **4a** (26 g) and $NaHCO_3$ (4.1 g) in water (80 ml) were added methanol (170 ml) and $CaCl_2 \cdot 2H_2O$ (375 g) successively at room temp. After stirring for 75 minutes at 70°C, the mixture was poured into ice-water (500 ml). The mixture was acidified with conc HCl (10 ml) and extracted with EtOAc (2×500 ml). The extracts were combined and washed with brine. The organic layer was extracted with 10% aq K_2HPO_4 (350, 150 and 100 ml successively). The aqueous layers were combined and extracted with EtOAc (2×500 ml) after acidification with HCl. The organic layers were washed with brine and dried ($MgSO_4$), and concd to about 1/5 volume to yield a precipitate. The mixture was allowed to stand at room temp for 3 hours. The resulting precipitate was collected by filtration to give **5a** (15.97 g) in 64.8% yield. ^{1}H NMR (DMSO-d_6) δ 3.27 (3H, s, OCH_3), 3.60 (2H, br s, 2-CH_2), 3.97 (3H, s, $NOCH_3$), 4.26 (2H, s, 3′-CH_2), 4.43 (2H, s, $COCH_2Cl$), 5.25 (1H, d, J=5 Hz, 6-CH), 5.89 (1H, dd, J=5 and 9 Hz, 7-CH), 7.56 (1H, s, thiazole ring-H), 9.83 (1H, d, J=9 Hz, 7-NHCO).

Anal Calcd for $C_{17}H_{18}ClN_5O_7S_2$: C 40.52, H 3.60, Cl 7.04, N 13.90, S 12.72.
Found: C 40.27, H 3.53, Cl 6.98, N 13.83, S 12.70.

7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic Acid (**1**)

To a solution of **5a** (8 g) and $NaHCO_3$ (4 g) in water (20 ml) was added thiourea (1.82 g) at room temp. After stirring for 14 hours at the same temp, the resulting precipitate was filtered off and conc HCl (20 ml) was added to the solution on an ice bath with stirring. The resulting precipitate was filtered off again. The filtrate was adjusted to about pH 2~3 with aq NaOH to yield a precipitate which was collected by filtration to give **1** (5.12 g) in 75.5% yield. IR (KBr) cm^{-1} 1760 (β-lactam C=O), 1670 (amide C=O); ^1H NMR (DMSO-d_6) δ 3.13 (3H, s, OCH_3), 3.52 (2H, br s, 2-CH_2), 3.86 (3H, s, $NOCH_3$), 4.30 (2H, s, 3'-CH_2), 5.17 (1H, d, *J*=5 Hz, 6-CH), 5.80 (1H, dd, *J*=5 and 8.5 Hz, 7-CH), 6.78 (1H, s, thiazole ring-H), 6.8~7.6 (2H, br, NH_2), 9.60 (1H, d, *J*=8.5 Hz, 7-NHCO).

Anal Calcd for $C_{15}H_{17}N_5O_6S_2$: C 42.15, H 4.01, N 16.38, S 15.00.
Found: C 42.14, H 4.06, N 16.38, S 14.88.

1-Iodoethyl Isopropyl Carbonate (**6a**)

To a mixture of ethyl chloroformate (280 ml) and sulfuryl chloride (260 ml) was added benzoyl-peroxide (1 g) at room temp. After being refluxed for 7.5 hours, the mixture was distilled to give 1-chloroethyl chloroformate (217 g) (boiling range 119~140°C). To a solution of 1-chloroethyl chloroformate (317 g) in CH_2Cl_2 (2,000 ml) was added isopropyl alcohol (397 ml) under cooling with stirring. Pyridine (230 ml) was added dropwise to the solution over 20 minutes and the mixture was stirred for 30 minutes at the temp. The reaction mixture was washed successively with water (500 ml), brine (500 ml) and 5% aq $KHSO_4$, and dried ($MgSO_4$). The solvent was removed and the resulting liquid was distilled under reduced pressure to give 1-chloroethyl isopropyl carbonate (228 g). BP_{55} 92~94°C; ^1H NMR (CCl_4) δ 1.33 (6H, d, *J*=6 Hz, $CH(CH_3)_2$), 1.79 (3H, d, *J*=6 Hz, $CHClCH_3$), 4.84 (1H, septet, *J*=6 Hz, $CH(CH_3)_2$), 6.37 (1H, q, *J*=6 Hz, $CHClCH_3$).

To a solution of 1-chloroethyl isopropyl carbonate (102 g) in benzene (1,000 ml) were added NaI (200 g) and 18-crown-6 (5 g) and the mixture was refluxed overnight. The mixture was washed with water and 5% aq $Na_2S_2O_3$. The organic layer was dried ($MgSO_4$) and concd *in vacuo* to give **6a** (144 g). ^1H NMR ($CDCl_3$) δ 1.32 (6H, d, *J*=6 Hz, $CH(CH_3)_2$), 2.18 (3H, d, *J*=6 Hz, $CHICH_3$), 4.82 (1H, septet, *J*=6 Hz, $CH(CH_3)_2$), 6.68 (1H, q, *J*=6 Hz, $CHICH_3$).

1-(Isopropoxycarbonyloxy)ethyl 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (**2a**)

To a solution of **1** (427 mg) in *N*,*N*-dimethylacetamide (20 ml) were added dicyclohexylamine (200 mg) and **6a** (310 mg) successively under cooling. After stirring for 30 minutes, EtOAc (100 ml) was added to the mixture. The resulting precipitate was filtered off and the filtrate was washed with dil HCl, aq $NaHCO_3$ and brine successively. The organic layer was dried ($MgSO_4$) and concd *in vacuo* to give a yellow solid. The solid was chromatographed on a silica gel column (EtOAc - cyclohexane, 3 : 1) to give **2a** (501 mg, 89.9% yield) as a mixture of a pair of diastereomers derived from an asymmetric center in the ester function. IR (KBr) cm^{-1} 1780 (β-lactam C=O), 1680 (amide C=O). ^1H NMR (Table 6).

Anal Calcd for $C_{21}H_{27}N_5O_9S_2$: C 45.24, H 4.88, N 12.56, S 11.50.
Found: C 45.27, H 5.07, N 12.30, S 11.44.

The esters (**2c~2j**, **2m~2o**) were prepared in a procedure similar to that described above. NMR data are listed in Table 6.

Phthalidyl 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (**2k** and **2l**)

Sodium salt of **1** (500 mg) was dissolved in DMSO (5 ml) and phthalidyl bromide (356 mg) was added to the solution at room temp. After stirring for 15 minutes, the mixture was diluted with EtOAc (100 ml) and washed with aq $NaHCO_3$ and brine.

The organic layer was dried ($MgSO_4$) and concd *in vacuo* to give a mixture of **2k** and **2l**. The

Table 6. ^{1}H NMR data of esters of 3-methoxymethyl cephem derivatives (**2a**~**2o**).

	$CDCl_3$, δ ppm, J in Hz
2a	1.31 (6H, d, J=6, $CH(CH_3)_2$), 1.56 (3H, d, J=5.5, $CHCH_3$), 3.30 (3H, s, OCH_3), 3.52 (2H, br s, 2-CH_2), 4.00 (3H, s, $NOCH_3$), 4.32 (2H, s, 3′-CH_2), 4.5~5.2 (1H, m, $CH(CH_3)_2$), 5.06 (1H, d, J=5, 6-CH), 6.02 (1H, dd, J=5 and 9, 7-CH), 6.72 (1H, s, thiazole ring-H), 7.88 and 7.96 (total 1H, q×2, J=5.5, $CHCH_3$), 8.06 and 8.10 (total 1H, d×2, J=9, 7-NHCO).
2b	1.23 (9H, s, *tert*-butyl), 3.31 (3H, s, OCH_3), 3.56 (2H, br s, 2-CH_2), 4.03 (3H, s, $NOCH_3$), 4.31 (2H, s, 3′-CH_2), 5.08 (1H, d, J=5, 6-CH), 5.79 (2H, br s, NH_2), 5.88 (2H, s, CH_2), 6.02 (1H, dd, J=5 and 9, 7-CH), 6.70 (1H, s, thiazole ring-H), 8.11 (1H, d, J=9, 7-NHCO).
2c	1.55 (3H, d, J=5.5, $CHCH_3$), 3.27 (3H, s, OCH_3), 3.51 (2H, br s, 2-CH_2), 3.76 (3H, s, OCH_3), 3.96 (3H, s, $NOCH_3$), 4.25 (2H, s, 3′-CH_2), 5.00 (1H, d, J=5, 6-CH), 5.4~6.1 (3H, m, 7-CH and NH_2), 6.59 (1H, s, thiazole ring-H), 6.77 and 6.87 (total 1H, q×2, J=5.5, $CHCH_3$), 8.02 (1H, d, J=9, 7-NHCO).
2d	1.32 (3H, t, J=7, CH_2CH_3), 1.58 (3H, d, J=5.5, $CHCH_3$), 3.33 (3H, s, OCH_3), 3.55 (2H, br s, 2-CH_2), 4.03 (3H, s, $NOCH_3$), 4.21 (2H, q, J=7, CH_2CH_3), 4.33 (2H, s, 3′-CH_2), 5.03 (1H, d, J=5, 6-CH), 5.4~6.2 (2H, br, NH_2), 5.8~6.2 (1H, m, 7-CH), 6.70 (1H, s, thiazole ring-H), 6.83 and 6.92 (total 1H, q×2, J=5.5, $CHCH_3$), 7.97 (1H, d, J=9, 7-NHCO).
2e	0.95 (3H, t, J=7.5, CH_3), 1.56 (3H, d, J=5.5, $CHCH_3$), 1.3~2.0 (2H, m, CH_2), 3.30 (3H, s, OCH_3), 3.52 (2H, br s, 2-CH_2), 4.00 (3H, s, $NOCH_3$), 4.11 (2H, t, J=7.5, CH_2), 4.31 (2H, br s, 3′-CH_2), 5.04 (1H, d, J=5, 6-CH), 5.7~6.1 (3H, m, 7-CH and NH_2), 6.64 (1H, s, thiazole ring-H), 6.80 and 6.88 (total 1H, q×2, J=5.5, $CHCH_3$), 8.14 (1H, d, J=9, 7-NHCO).
2f	0.91 (3H, t, J=7, CH_3), 1.2~1.9 (2H, m, CH_2), 1.27 (3H, d, J=6, CH_3), 1.55 (3H, d, J=5.5, $CHCH_3$), 3.28 (3H, s, OCH_3), 3.51 (2H, br s, 2-CH_2), 3.99 (3H, s, $NOCH_3$), 4.29 (2H, s, 3′-CH_2), 4.4~4.9 (1H, m, CH), 5.00 (1H, d, J=5, 6-CH), 5.1~6.0 (2H, br, NH_2), 5.7~6.1 (1H, m, 7-CH), 6.61 (1H, s, thiazole ring-H), 6.6~7.0 (1H, m, $CHCH_3$), 7.6~8.0 (1H, m, 7-NHCO).
2g	1.48 (9H, s, *tert*-butyl), 1.55 (3H, d, J=5.5, $CHCH_3$), 3.29 (3H, s, OCH_3), 3.51 (2H, br s, 2-CH_2), 3.99 (3H, s, $NOCH_3$), 4.29 (2H, s, 3′-CH_2), 5.00 (1H, d, J=5, 6-CH), 5.64 (2H, br s, NH_2), 5.8~6.2 (1H, m, 7-CH), 6.64 (1H, s, thiazole ring-H), 6.6~7.0 (1H, m, $CHCH_3$), 7.84 and 7.87 (total 1H, d×2, J=9, 7-NHCO).
2h	0.98 (6H, d, J=6, $CH(CH_3)_2$), 1.58 (3H, d, J=5.5, $CHCH_3$), 1.3~2.3 (3H, m, CH and CH_2), 3.32 (3H, s, OCH_3), 3.54 (2H, br s, 2-CH_2), 4.02 (3H, s, $NOCH_3$), 4.0~4.4 (2H, CH_2), 4.32 (2H, s, 3′-CH_2), 5.05 (1H, d, J=5, 6-CH), 5.2~6.2 (2H, br, NH_2), 5.8~6.2 (1H, m, 7-CH), 6.69 (1H, s, thiazole ring-H), 6.81 and 6.90 (total 1H, q×2, J=5.5, $CHCH_3$), 7.74 and 7.80 (total 1H, d×2, J=9, 7-NHCO).
2i	1.20 (6H, d, J=6.5, $COCH(CH_3)_2$), 2.66 (1H, septet, J=6.5, $COCH(CH_3)_2$), 3.21 (3H, s, OCH_3), 3.40 (2H, br s, 2-CH_2), 4.01 (3H, 3, $NOCH_3$), 4.16 (2H, s, 3′-CH_2), 5.05 (1H, d, J=5, 6-CH), 5.6~6.2 (5H, m, CH_2, NH_2 and 7-CH), 6.65 (1H, s, thiazole ring-H), 8.06 (1H, d, J=9, 7-NHCO).
2j	1.15 (3H, t, J=7, $COCH_2CH_3$), 2.40 (2H, q, J=7, $COCH_2CH_3$), 3.32 (3H, s, OCH_3), 3.54 (2H, br s, 2-CH_2), 4.02 (3H, s, $NOCH_3$), 4.30 (2H, s, 3′-CH_2), 5.03 (1H, d, J=4.5, 6-CH), 5.83 (2H, s, CH_2), 5.96 (1H, dd, J=4.5 and 9, 7-CH), 6.73 (1H, s, thiazole ring-H), 7.74 (1H, d, J=9, 7-NHCO).
2k	3.29 (3H, s, OCH_3), 3.53 (2H, br s, 2-CH_2), 4.00 (3H, s, $NOCH_3$), 4.26 (2H, s, 3′-CH_2), 5.01 (1H, d, J=4.5, 6-CH), 5.91 (1H, dd, J=4.5 and 9, 7-CH), 6.10 (2H, br, NH_2), 7.3~8.1 (6H, m, phenyl, CH and thiazole ring-H), 8.05 (1H, d, J=9, 7-NHCO).
2l	3.34 (3H, s, OCH_3), 3.69 (2H, s, 2-CH_2), 3.97 (3H, s, $NOCH_3$), 4.35 (2H, s, 3′-CH_2), 5.18 (1H, d, J=4.5, 6-CH), 5.96 (1H, dd, J=4.5 and 9, 7-CH), 6.70 (2H, br, NH_2), 7.5~8.2 (6H, m, phenyl, CH and thiazole ring-H), 8.44 (1H, d, J=9, 7-NHCO).
2m	2.16 (3H, s, CH_3), 3.29 (3H, s, OCH_3), 3.52 (2H, br, 2-CH_2), 3.97 (3H, s, $NOCH_3$), 4.25 (2H, br s, 3′-CH_2), 4.82 and 5.11 (2H, AB q, J=13.5, CH_2 in ester), 5.04 (1H, d, J=4.5, 6-CH), 5.7~6.3 (3H, m, NH_2 and 7-CH), 6.57 (1H, s, thiazole ring-H), 8.37 (1H, d, J=9, 7-NHCO).
2n	1.32 (3H, t, J=6.5 Hz, CH_2CH_3), 3.32 (3H, s, OCH_3), 3.54 (2H, br s, 2-CH_2), 3.98 (3H, s, $NOCH_3$), 4.23 (2H, q, J=6.5, CH_2CH_3), 4.31 (2H, s, 3′-CH_2), 5.04 (1H, d, J=4.5, 6-CH), 5.6~6.3 (5H, m, OCH_2O, NH_2 and 7-CH), 6.54 (1H, s, thiazole ring-H), 8.13 (1H, d, J=9, 7-NHCO).

Table 6. (Continued)

	$CDCl_3$, δ ppm, J in Hz
2o	0.99 (3H, t, J=7, CH_3), 1.30 (3H, t, J=7, CH_2CH_3), 1.6~2.2 (2H, m, CH_2), 3.28 (3H, s, OCH_3), 3.51 (2H, br s, 2-CH_2), 3.96 (3H, s, $NOCH_3$), 4.16 (2H, q, J=7, CH_2CH_3), 4.27 (2H, s, 3'-CH_2), 5.00 (1H, d, J=5, 6-CH), 5.6~6.2 (3H, m, NH_2 and 7-CH), 6.58 (1H, s, thiazole ring-H), 6.64 and 6.71 (total 1H, t×2, J=5, CH), 8.04 (1H, d, J=9, 7-NHCO).

The esters (**2a**, **2c**~**2e**, **2g**, **2h** and **2o**) were mixtures of diastereoisomers derived from the asymmetric carbon in the ester function. The ester **2f** was a mixture of two pairs of diastereoisomers derived from the two asymmetric centers in the ester group. The esters, **2k** and **2l**, are diastereoisomers with regard to the asymmetric carbon in the ester function.

mixture was separated on a silica gel column (EtOAc - cyclohexane, 4 : 1) to give **2k** (236 mg) and **2l** (188 mg), respectively. ^{1}H NMR (Table 6).

7β-Phenoxyacetamido-3-methoxymethyl-3-cephem-4-carboxylic Acid (**5b**)

To a solution of **4b** (10 g) in water (33 ml) were added methanol (67 ml) and $CaCl_2$ (100 g) at room temp. After stirring for 45 minutes at 70°C, the mixture was poured into ice-water (100 ml) and treated in a manner similar to that mentioned in the preparation of **5a**. The final extracts were concd *in vacuo* to give a yellow solid (**5b**) (7.15 g). The solid (**5b**) was dissolved in EtOAc (50 ml) and dicyclohexylamine (3.4 ml) was added to the solution. The resulting precipitate was collected by filtration to give dicyclohexylamine salt of **5b** (8.43 g) in 64.5% yield. IR (Nujol) cm^{-1} 1770 (β-lactam C=O), 1680 (amide C=O); ^{1}H NMR (DMSO-d_6) δ 0.8~2.3 (20H, m), 2.7~3.4 (2H, m, NCH of dicyclohexylamine ×2), 3.18 (3H, s, OCH_3), 3.38 (2H, br s, 2-CH_2), 4.19 (2H, s, 3'-CH_2), 4.60 (2H, s, CH_2), 4.99 (1H, d, J=5 Hz, 6-CH), 5.56 (1H, dd, J=5 and 9 Hz, 7-CH), 6.7~7.5 (5H, m, phenyl), 8.98 (1H, d, J=9 Hz, 7-NHCO).

Further purification was carried out as follows. The dicyclohexylamine salt of **5b** (2 g) was suspended in a mixture of water (50 ml) and EtOAc (50 ml), and the mixture was acidified with HCl. An insoluble material was filtered off and the EtOAc layer was separated. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed and the resulting solid was chromatographed on a silica gel column (EtOAc - EtOH - H_2O, 5 : 2 : 1) to give **5b** (1.28 g) in 94.7% yield. IR (Nujol) cm^{-1} 1790 (β-lactam C=O); ^{1}H NMR ($CDCl_3$) δ 3.38 (3H, s, OCH_3), 3.58 (2H, br s, 2-CH_2), 4.41 (2H, s, 3'-CH_2), 4.62 (2H, s, CH_2), 5.04 (1H, d, J=4.5 Hz, 6-CH), 5.89 (1H, dd, J=4.5 and 9 Hz, 7-CH), 6.8~7.6 (5H, m, phenyl), 7.59 (1H, d, J=9 Hz, 7-NHCO).

Anal Calcd for $C_{17}H_{18}N_2O_6S$: C 53.96, H 4.79, N 7.40.
Found: C 53.63, H 4.68, N 7.34.

Pivaloyloxymethyl 7β-Phenoxyacetamido-3-methoxymethyl-3-cephem-4-carboxylate (**7**)

To a solution of the dicyclohexylamine salt of **5b** (15 g) in *N*,*N*-dimethylacetamide (70 ml) was added iodomethyl pivalate (**6b**) (7.9 g) at room temp. After stirring for 15 minutes, EtOAc (200 ml) was added and the resulting precipitate was filtered off. The filtrate was washed with water, aq $NaHCO_3$ and brine successively. The organic layer was dried ($MgSO_4$) and concd *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane - EtOAc, 1 : 1) to give **7** (10.9 g) in 82.6% yield. ^{1}H NMR ($CDCl_3$) δ 1.21 (9H, s, *tert*-butyl), 3.26 (3H, s, OCH_3), 3.43 (2H, br s, 2-CH_2), 4.22 (2H, s, 3'-CH_2), 4.42 (2H, s, CH_2), 4.87 (1H, d, J=5 Hz, 6-CH), 4.5~6.0 (3H, m, 7-CH and OCH_2O), 6.4~7.2 (5H, m, phenyl), 7.40 (1H, d, J=8.5 Hz, 7-NHCO).

p-Toluenesulfonic Acid Salt of Pivaloyloxymethyl 7β-Amino-3-methoxymethyl-3-cephem-4-carboxylate (**8**)

To a solution of **7** (20 g) were added pyridine (6.6 ml) and PCl_5 (12.7 g) at −50°C with stirring. The cooling bath was removed and the mixture was stirred at room temp for 1 hour. After cooling the reaction mixture to −20°C, methanol (20 ml) was added. The mixture was then stirred for 1 hour at room temp again and concd *in vacuo*. The residue was dissolved in EtOAc (300 ml) and the solution was washed with ice-cooled aq $NaHCO_3$ twice and then brine. The organic layer was dried

($MgSO_4$) and concd. The residue was dissolved in EtOAc (100 ml) and a solution of *p*-toluenesulfonic acid mono hydrate (7.7 g) in EtOAc (50 ml) was added to the solution. The resulting precipitate was collected by filtration to give **8** (11.2 g) in 52% yield. MP 160~170°C (dec); IR (Nujol) cm^{-1} 1790 (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 1.20 (9H, s, *tert*-butyl), 2.30 (3H, s, CH_3), 3.26 (3H, s, OCH_3), 3.69 (2H, br s, 2-CH_2), 4.28 (2H, s, 3'-CH_2), 5.1~5.6 (2H, m, 6-H and 7-H), 5.83 and 5.93 (2H, AB q, J=6 Hz, OCH_2O), 7.14 (2H, d, J=8 Hz, phenyl), 7.59 (2H, d, J=8 Hz, phenyl).

Anal Calcd for $C_{15}H_{27}N_2O_6S \cdot C_7H_8O_3S$: C 49.80, H 5.70, N 5.28, S 12.08.
Found: C 49.76, H 5.60, N 5.00, S 12.06.

Pivaloyloxymethyl 7β-[2-(2-Formylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (**10**)

To a solution of **8** (3.93 g), **9** (1.88 g) and diethylaniline (3.65 g) in CH_2Cl_2 (60 ml) was added $POCl_3$ (1.27 g) under cooling with stirring. After 30 minutes the solvent was removed and displaced with EtOAc (200 ml). The solution was washed with 5% HCl twice, ice-cooled aq $NaHCO_3$ and brine successively. The organic layer was dried ($MgSO_4$) and concd *in vacuo*. The crude product was chromatographed on a silica gel column (EtOAc - $CHCl_3$, 3 : 1) to give **10** (3.95 g) as a colorless solid. ^1H NMR (DMSO-d_6) δ 1.19 (9H, s, *tert*-butyl), 3.22 (3H, s, OCH_3), 3.50 (2H, s, 2-CH_2), 3.90 (3H, s, $NOCH_3$), 4.18 (2H, s, 3'-CH_2), 5.22 (1H, d, J=5 Hz, 6-CH), 5.8~6.1 (3H, m, CH_2 and 7-CH), 7.42 (1H, s, thiazole ring-H), 8.52 (1H, s, HCO), 9.68 (1H, d, J=9 Hz, 7-NHCO).

Pivaloyloxymethyl 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (**2b**)

A): The esterification of **1** (3.1 g) was carried out with dicyclohexylamine (1.45 g) and **6b** (2 g) in *N*,*N*-dimethylacetamide (30 ml) by the method mentioned in the preparation of **2a**.

Purification by silica gel column chromatography (EtOAc - $CHCl_3$, 4 : 1) gave **2b** (2.99 g) in 76% yield. IR (Nujol) cm^{-1} 1785 (β-lactam C=O), 1680 (amide C=O). ^1H NMR (Table 6).

Anal Calcd for $C_{21}H_{27}N_5O_9S_2$: C 46.57, H 5.03, N 12.93, S 11.84.
Found: C 46.35, H 5.00, N 12.76, S 11.62.

B): To a suspension of **10** (3 g) in methanol (30 ml) was added conc HCl (0.9 ml) at room temp and the mixture was stirred for 30 minutes at 40°C to give a solution. The solution was diluted with EtOAc (150 ml) and washed with ice-cooled aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concd *in vacuo*. The residue was chromatographed on a silica gel column (EtOAc) to give **2b** (2.53 g) in 88.7% yield.

7β-Phenoxyacetamido-3-hydroxymethyl-3-cephem-4-carboxylic Acid (**13**)

To a suspension of 7ACA (200 g) in methanol (368 ml) was slowly added 1 N NaOH (735 ml) at −5°C with stirring. An additional portion of 1 N NaOH (735 ml) was added to the resulting solution and stirred for 30 minutes at 0~5°C. Acetone (500 ml) was added to the mixture and then phenoxyacetyl chloride (17 g) was added dropwise to the mixture over a period of 30 minutes at 0~5°C.

After washing the mixture with EtOAc (1,000 ml), the aqueous layer was acidified with conc HCl (83 ml) and extracted twice with EtOAc (1,000 ml). The extract was combined and concd to a small volume without drying to give precipitate. The precipitate was collected by filtration to give **13** (135.3 g) in 50.6% yield. MP 141~142°C; IR (KBr) cm^{-1} 1760 (β-lactam C=O), 1655 (amide C=O); ^1H NMR (DMSO-d_6) δ 3.55 (2H, br s, 2-CH_2), 4.28 (2H, s, 3'-CH_2), 4.58 (2H, s, CH_2), 4.99 (1H, d, J=4.5 Hz, 6-CH), 5.60 (1H, dd, J=4.5 and 8 Hz, 7-CH), 6.6~7.5 (5H, m, phenyl), 8.87 (1H, d, J=8 Hz, 7-NHCO).

Anal Calcd for $C_{16}H_{16}N_2O_6S$: C 52.74, H 4.43, N 7.69, S 8.80.
Found: C 52.60, H 4.36, N 7.67, S 8.77.

Diphenylmethyl 7β-Phenoxyacetamido-3-hydroxymethyl-3-cephem-4-carboxylate (**14**)

To a solution of **13** (64.88 g) was added a solution of diphenyldiazomethane (38 g) in EtOAc (100 ml) at 5°C. The mixture was stirred for 4 hours at the same temp and the solvent was removed. THF (500 ml) was added to the residue and insoluble material was filtered off. The filtrate was concd

to a small volume to give crystals. EtOAc (500 ml) was added to the mixture which was then allowed to stand on an ice bath for 1 hour. The resulting crystals were collected by filtration to give **14** (90.52 g) in 95.8% yield. MP 161~162°C; IR (KBr) cm^{-1} 1780 (β-lactam C=O), 1680 (amide C=O); ^1H NMR (DMSO-d_6) δ 3.59 (2H, br s, 2-CH_2), 4.20 (2H, d, J=5 Hz, 3'-CH_2), 4.57 (2H, s, CH_2), 5.03 (1H, t, J=5 Hz, OH), 5.06 (1H, d, J=4.5 Hz, 6-H), 5.68 (1H, dd, J=4.5 and 8 Hz, 7-CH), 6.6~7.6 (16H, m, phenyl and CH), 8.98 (1H, d, J=8 Hz, 7-NHCO).

Anal Calcd for $C_{29}H_{26}N_2O_6S$: C 65.65, H 4.94, N 5.28, S 6.04.
Found: C 65.67, H 5.06, N 5.28, S 6.04.

Diphenylmethyl 7β-Phenoxyacetamido-3-chloromethyl-3-cephem-4-carboxylate (**15**)

To a solution of **14** (95 g) in THF (950 ml) was slowly added $SOCl_2$ (15.5 ml) at −20°C with stirring. After stirring for 4.5 hours at 0°C, the solvent was removed. The residue was dissolved in EtOAc (250 ml) and allowed to stand at room temp overnight. The resulting crystals were collected by filtration to give **15** (83.21 g) in 84.6% yield. MP 151~151.5°C (dec); IR (KBr) cm^{-1} 1780 (β-lactam C=O), 1690 (amide C=O); ^1H NMR (DMSO-d_6) δ 3.60 (2H, br s, 2-CH_2), 4.37 (2H, s, 3'-CH_2), 4.55 (2H, s, CH_2), 5.13 (1H, d, J=4.5 Hz, 6-CH), 5.74 (1H, dd, J=4.5 and 8 Hz, 7-CH), 6.5~7.6 (16H, m, phenyl and CH), 9.04 (1H, d, J=8 Hz, 7-NHCO).

Anal Calcd for $C_{29}H_{25}ClN_2O_5S$: C 63.44, H 4.59, N 5.10, Cl 6.46, S 5.84.
Found: C 63.45, H 4.72, N 5.08, Cl 6.34, S 6.13.

Diphenylmethyl 7β-Phenoxyacetamido-3-ethoxymethyl-3-cephem-4-carboxylate (**16a**)

To a solution of **15** (4.48 g) in acetone (120 ml) was added NaI (1.31 g) at room temp with stirring. The mixture was allowed to stand at the same temp for 1 hour. After removing the solvent, EtOAc was added to the residue and washed with water and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the corresponding iodomethyl derivative (5.17 g). To a suspension of the iodomethyl derivative (5 g) in ethanol was added a suspension of $Hg(NO_3)_2 \cdot H_2O$ (2.67 g) in CH_3CN (120 ml) and stirred for 20 minutes at room temp. An insoluble material was filtered off and the filtrate was poured into water. The aqueous layer was extracted with EtOAc and washed with water, and dried ($MgSO_4$). The solvent was removed and the residue was purified on a silica gel column (EtOAc-cyclohexane, 1:2) to give **16a** (3.12 g) in 71.5% yield. ^1H NMR ($CDCl_3$) δ 1.11 (3H, t, J=7 Hz, CH_2CH_3), 3.37 (2H, q, J=7 Hz, CH_2CH_3), 3.53 (2H, s, 2-CH_2), 4.28 (2H, s, 3'-CH_2), 4.54 (2H, s, CH_2), 4.99 (1H, d, J=5 Hz, 6-CH), 5.91 (1H, dd, J=5 and 9 Hz, 7-CH), 6.8~7.6 (17H, m, phenyl, CH and 7-NHCO).

Diphenylmethyl 7β-Phenoxyacetamido-3-propoxymethyl-3-cephem-4-carboxylate (**16b**)

The preparation of **16b** was carried out by a method similar to that described above. ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, J=7 Hz, $(CH_2)_2CH_3$), 1.1~1.8 (2H, m, $CH_2CH_2CH_3$), 3.21 (2H, t, J=7 Hz, $CH_2CH_2CH_3$), 3.45 (2H, br s, 2-CH_2), 4.25 (2H, s, 3'-CH_2), 4.50 (2H, s, CH_2), 4.90 (1H, d, J=5 Hz, 6-CH), 5.85 (1H, dd, J=5 and 9 Hz, 7-CH), 6.7~7.7 (17H, m, phenyl, CH and 7-NHCO).

Trifluoroacetic Acid Salt of 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-ethoxymethyl-3-cephem-4-carboxylic Acid (**11a**)

The removal of the phenoxyacetyl group of **16a** (1.117 g) was carried out by a method similar to that described in the preparation of **8** to give diphenylmethyl 7β-amino-3-ethoxymethyl-3-cephem-4-carboxylate (345 mg) in 40.6% yield. The 7-amino derivative (345 mg) in CH_2Cl_2 (4 ml) was acylated by the usual manner using 2-(chloroacetylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetyl chloride, which was prepared from the corresponding acid (271 mg), $(COCl)_2$ (124 mg) and triethylamine (99 mg) in CH_2Cl_2 by ENGEL's modification[16], in the presence of diethylaniline (0.35 ml) to give the acylated compound, diphenylmethyl 7β-[2-(2-chloroacetylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-ethoxymethyl-3-cephem-4-carboxylate (147 mg). To a solution of the acylated compound (147 mg) in *N*,*N*-dimethylacetamide (1.5 ml) was added thiourea (32 mg) and stirred for 3 hours at room temp. The reaction mixture was neutralized with aq $NaHCO_3$ and stirred for additional 2 hours. The reaction mixture was diluted with EtOAc and the mixture was washed with 5% aq $NaHCO_3$, water (×3) and brine, and dried ($MgSO_4$). The solvent was removed and chromatographed on a silica gel

column (EtOAc - cyclohexane, 3 : 2) to give a solid (73 mg). The solid was dissolved in anisole (0.7 ml) and trifluoroacetic acid (0.7 ml) was added to the solution at −15°C with stirring. After stirring for 20 minutes at room temp the solvent was removed and the residue was triturated with diisopropyl ether to give trifluoroacetic acid salt of **11a** (55 mg). ^{1}H NMR (acetone-d_6) δ 1.14 (3H, t, J=7 Hz, CH_2CH_3), 3.49 (2H, q, J=7 Hz, CH_2CH_3), 3.62 (2H, s, 2-CH_2), 4.03 (3H, s, $NOCH_3$), 4.35 (2H, s, 3′-CH_2), 5.19 (1H, d, J=5 Hz, 6-CH), 5.88 (1H, dd, J=5 and 8 Hz, 7-CH), 7.05 (1H, s, thiazole ring-H), 8.62 (1H, d, J=8 Hz, 7-NHCO).

Trifluoroacetic Acid Salt of 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-propoxymethyl-3-cephem-4-carboxylic Acid (**11b**)

The preparation of **11b** was carried out by a method similar to that mentioned above. ^{1}H NMR (acetone-d_6) δ 0.89 (3H, t, J=7 Hz, $(CH_2)_2CH_3$), 1.2∼1.8 (2H, m, $CH_2CH_2CH_3$), 3.38 (2H, t, J=7 Hz, $CH_2CH_2CH_3$), 3.63 (2H, s, 2-CH_2), 4.04 (3H, s, $NOCH_3$), 4.37 (2H, s, 3′-CH_2), 5.21 (1H, d, J=5 Hz, 6-CH), 5.90 (1H, dd, J=5 and 9 Hz, 7-CH), 7.10 (1H, s, thiazole ring-H), 8.65 (1H, d, J=9 Hz, 7-NHCO).

Sodium 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)methyl-3-cephem-4-carboxylate (**11h**)

3-Triazolylmethyl derivative was prepared by WILLNER's method[17]. ^{1}H NMR (DMSO-d_6) δ 3.10 and 3.48 (2H, AB q, J=18 Hz, 2-CH_2), 3.81 (6H, s, OCH_3 and $COOCH_3$), 5.00 (1H, d, J=5 Hz, 6-CH), 5.09 and 5.39 (2H, AB q, J=15 Hz, 3′-CH_2), 5.60 (1H, dd, J=5 and 8 Hz, 7-CH), 6.66 (1H, s, thiazole ring-H), 7.17 (2H, br, NH_2), 8.89 (1H, s, triazole ring-H), 9.53 (1H, d, J=8 Hz, 7-NHCO).

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