SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF NEW 3-PHENOXYMETHYLCEPHALOSPORINS

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The synthesis and biological properties of new 3-phenoxymethylcephalosporins (**1**) are described. These compounds exhibited good antibacterial activity against Gram-positive and Gram-negative bacteria.

Many new cephalosporin antibiotics with a broad spectrum of activity and increased activity against β-lactamase-producing bacteria have been developed[1]. Most of them have a 2-aminothiazole moiety as a C-7 substitutent of cephalosporin nucleus. In contrast, they have a variety of substituents at C-3.

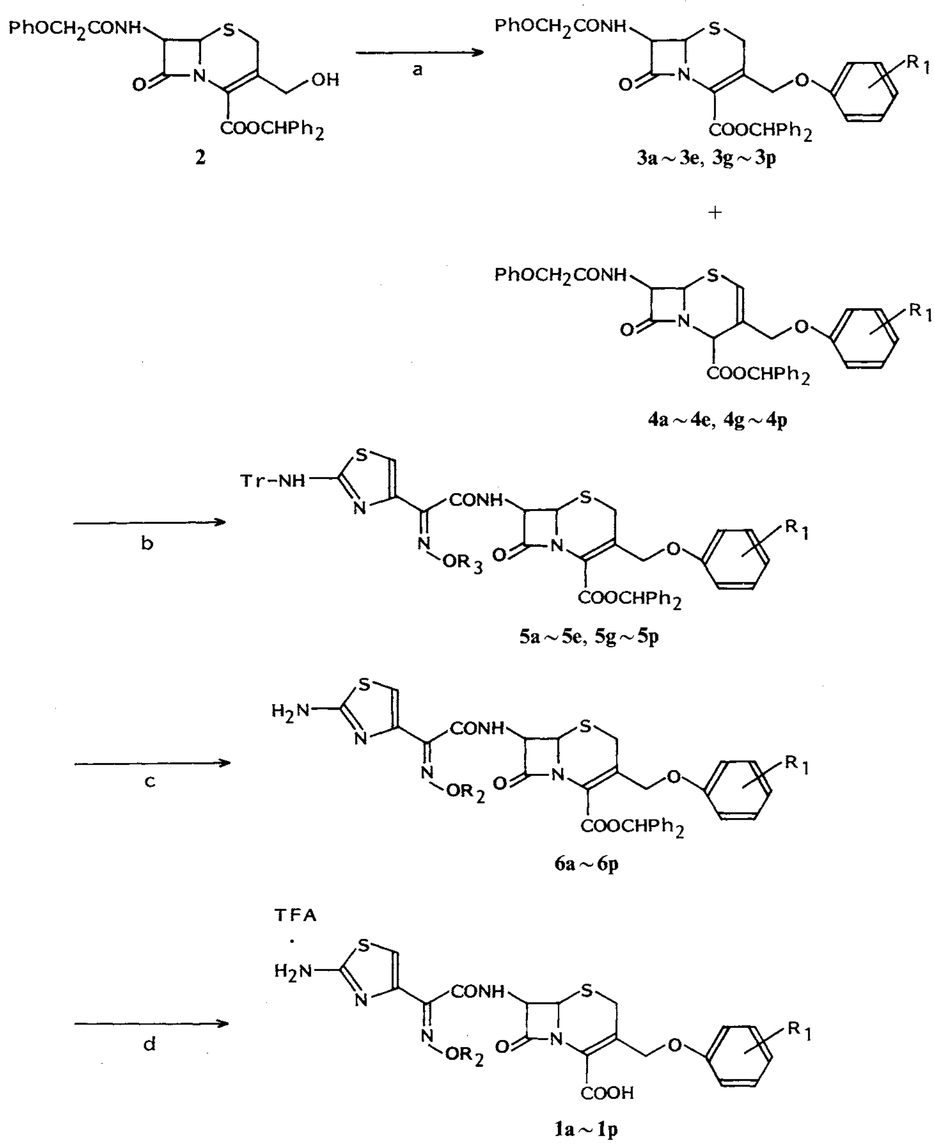
3-Alkoxymethylcephalosporins that have good antibacterial activity have already been synthesized. Among them, 3-methoxymethylcephalosporin, cefpodoxime proxetil (CS807)[2] is now in clinical use in Japan. However, there has been no report on 3-phenoxymethylcephalosporins although a few reports on 3-heterocyclic oxymethylcephalosporins have already been published[3,4]. 3-Phenoxymethylcephalosporins are of interest from both 1) antibacterial and 2) synthetic points of views; 1) it is well known that electron-withdrawing substituents at C-3 position of the cephalosporin increase antibacterial activity. A 3-phenoxymethylcephalosporin is expected to have enhanced activity to 3-methoxymethylcephalosporin because of the electron-withdrawing nature of phenyl group, 2) reaction of 7β-aminocephalosporanic acid (7-ACA) with phenol under acidic conditions has been reported to yield exclusively 7β-amino-3-(*o*- and *p*-hydroxyphenyl)methylcephalosporanic acid *via* *C*-alkylation of phenol[5]. Namely, 7β-amino-3-phenoxymethylcephalosporanic acid, which would be generated *via* *O*-alkylation process, could not be isolated. This indicates synthetic difficulty with 3-phenoxymethylcephalosporin.

In this paper, we describe a synthesis and *in vitro* antibacterial activities of new 3-phenoxymethylcephalosporins.

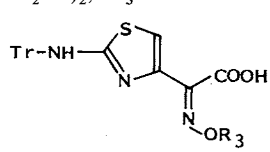
Chemistry

We investigated a new method for the synthesis of 3-phenoxymethylcephalosporin. First, we tried the ether synthesis first described by WILLIAMSON *et al.*[6]; however, the reaction of phenoxide anion with 7β-phenoxyacetyl-3-iodomethyl-3-cephem-4-carboxylate did not afford the desired product. Then we examined the MITSUNOBU reaction[7] and found that the reaction of 3-hydroxymethylcephalosporin derivative with phenol afforded the desired 3-phenoxymethylcephalosporin derivative. So we applied this method to the synthesis of 3-phenoxymethylcephalosporin (**1**). The general synthetic route is shown in Scheme 1. The MITSUNOBU reaction of diphenylmethyl 3-hydroxymethyl-7β-phenoxyacetamido-3-cephem-4-carboxylate (**2**)[2], which was readily available from 7-ACA, with *p*-bromophenol in the presence of triphenylphosphine and dimethyl azodicarboxylate in tetrahydrofuran successfully gave the desired 3-phenoxymethyl compound (**3a**), together with its Δ^2-isomer (**4a**) in 11% and 8% yields, respectively. The Δ^2-isomer (**4a**) can be converted to the desired Δ^3-compound (**3a**) by a usual manner (oxidation with

Scheme 1.



a; $(R_1)PhOH$, $(=NCO_2Me)_2$, Ph_3P

b; $POCl_3$, Et_2NPh, 

c; HCO_2H, MeOH

d; CF_3CO_2H, anisole, CH_2Cl_2

a	$R_1=p$-Br	$R_2=H$	$R_3=Tr$	**i**	$R_1=p$-OMe	$R_2=H$	$R_3=Tr$
b	$R_1=H$	$R_2=H$	$R_3=Tr$	**j**	$R_1=p$-SMe	$R_2=H$	$R_3=Tr$
c	$R_1=p$-F	$R_2=H$	$R_3=Tr$	**k**	$R_1=o$-F	$R_2=H$	$R_3=Tr$
d	$R_1=p$-CN	$R_2=H$	$R_3=Tr$	**l**	$R_1=m$-F	$R_2=H$	$R_3=Tr$
e	$R_1=p$-COMe	$R_2=H$	$R_3=Tr$	**m**	$R_1=o,p$-F_2	$R_2=H$	$R_3=Tr$
f	$R_1=p$-SOMe	$R_2=H$		**n**	$R_1=m,p$-F_2	$R_2=H$	$R_3=Tr$
g	$R_1=p$-COOMe	$R_2=H$	$R_3=Tr$	**o**	$R_1=m$-F	$R_2=Me$	$R_2=Me$
h	$R_1=p$-COOH	$R_2=H$	$R_3=Tr$	**p**	$R_1=m$-F	$R_2=CH_2F$	$R_3=CH_2F$

meta-chloroperbenzoic acid in methylene chloride, then reduction of the 1-sulfoxide with acetyl chloride and potassium iodide in dimethyl formamide). The structure of **3a** was assigned by ^{1}H NMR spectrum. The signals at δ 4.77 and 4.92 (2H, ABq) in **3a** can reasonably be assigned to 3'-methylene protons.

The phenoxyacetyl side chain of **3a** was cleaved by an imino-chloride method[8] (phosphorus pentachloride, pyridine and propanol), to afford the amine hydrochloride. The coupling reaction of this amine hydrochloride with 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(trityloxyimino)acetic acid[9] afforded a good yield of compound (**5a**), in which amino and carboxylic groups are protected by trityl (Tr) and diphenylmethyl groups. The protecting groups of **5a** were removed by the reaction with formic acid in methanol at 40°C, and subsequently with trifluoroacetic acid and anisole in methylene chloride under ice-cooling to give the final compound (**1a**) as a salt with trifluoroacetic acid. The compounds **1b**~**1e** and **1g**~**1n** were prepared by the same procedure using corresponding phenols. In the synthesis of *p*-carboxy compound (**1h**), diphenylmethyl *p*-hydroxybenzoate was used as a phenol fragment. In the synthesis of **1o** and **1p**, 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(methoxyimino)acetic acid[9] and 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(monofluoromethoxyimino)acetic acid[10] were used respectively for the coupling reactions. The methylsulfinyl compound (**1f**) was synthesized from **5j** by oxidation with one molar equivalent of *meta*-chloroperbenzoic acid, followed by treatment with trifluoroacetic acid.

Antimicrobial Activity

The *in vitro* antibacterial activities of these compounds (trifluoroacetic acid salts) are shown in Table 1. All of these compounds exhibited potent activity against broad range of microorganisms. These compound have potent activity especially against Gram-positive bacteria. In comparison with the unsubstituted phenoxyl derivative (**1b**), the introduction of an electron-withdrawing moiety into the phenyl ring enhances the antibacterial activity. *p*-Methylsulfinyl derivative (**1f**) showed superior activity against both Gram-positive and Gram-negative bacteria to *p*-methyl sulfide compound (**1j**). Introduction of a carboxy function into the phenyl ring (**1h**) enhanced the activity against Gram-negative bacteria, although the activity against Gram-positive bacteria was very poor. A *p*-fluorine substituted compound (**1c**) showed strong activity against Gram-positive and Gram-negative bacteria, although a *p*-bromo compound (**1a**) showed inferior activity against Gram-negative bacteria.

Table 2 demonstrates the effect of the position of the substituents. The *meta*- or *para*-substituted

Table 1. Antibacterial activity (MIC, μg/ml) of **1a**~**1j**.

Compound	*S.a.*	*S.a.* (R)	*E.c.*	*E.c.* (R)	*K.p.*	*K.p.* (R)	*E.cl.*	*S.m.*	*P.v.*	*M.m.*
1a	≤0.01	0.02	3.1	3.1	3.1	1.5	3.1	1.5	≤0.01	6.2
1b	0.02	0.1	0.8	0.8	1.5	3.1	3.1	0.8	0.05	12.5
1c	≤0.01	0.05	0.8	0.8	1.5	1.5	3.1	1.5	0.02	6.2
1d	≤0.01	0.05	0.8	0.8	0.8	1.5	1.5	0.8	≤0.01	3.1
1e	≤0.01	0.05	0.4	0.8	0.4	1.5	1.5	0.4	≤0.01	3.1
1f	0.02	0.1	0.1	0.4	0.2	1.5	0.8	0.2	0.02	6.2
1g	≤0.01	0.1	0.8	0.8	1.5	1.5	3.1	1.5	≤0.01	6.2
1h	0.1	0.2	0.2	1.5	0.05	0.8	0.8	0.2	≤0.01	25
1i	≤0.01	0.05	0.4	0.8	0.8	1.5	1.5	0.4	≤0.01	6.2
1j	≤0.01	0.02	1.5	1.5	1.5	1.5	3.1	1.5	≤0.01	6.2

Abbreviations: *S.a.*, *Staphylococcus aureus* 209P 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; *E.cl.*, *Enterobacter cloacae* 963; *S.m.*, *Serratia marcescens* 1184; *P.v.*, *Proteus vulgaris* 1420; *M.m.*, *Morganella morganii* 1510. (R): Means β-lactamase producing strains.

Table 2. Antibacterial activity (MIC, μg/ml) of **1k**~**1q**.

Compound	*S.a.*	*S.a.* (R)	*E.c.*	*E.c.* (R)	*K.p.*	*K.p.* (R)	*E.cl.*	*S.m.*	*P.v.*	*M.m.*
1k	≤0.01	0.05	1.5	1.5	1.5	1.5	3.1	1.5	≤0.01	6.2
1l	≤0.01	0.05	0.8	0.8	0.8	0.8	1.5	0.8	≤0.01	3.1
1m	≤0.01	0.01	1.5	3.1	1.5	1.5	3.1	1.5	≤0.01	6.2
1n	≤0.01	0.05	1.5	1.5	1.5	0.8	1.5	0.8	≤0.01	3.1
1o	0.05	0.2	0.4	0.4	0.8	0.2	0.8	0.2	≤0.01	1.5
1p	0.05	0.1	0.4	0.4	0.4	0.2	0.8	0.2	≤0.01	1.5
1q	0.8	0.8	0.4	0.4	0.2	0.8	1.5	0.2	0.02	50

1q: 7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid.
Abbreviations mean the same strains as in Table 1.

phenoxyl derivatives (**1c** and **1l**) were more active than the corresponding *ortho*-substituted derivative (**1k**) against Gram-negative bacteria. However, there was little difference against Gram-positive activity among *ortho*-, *meta*- and *para*-substituted derivatives. Substitution of both *meta*- and *para*-positions or *ortho*- and *para*-positions in the phenyl ring showed no significant improvement in the activity (**1m** and **1n**). Among these, a *m*-fluoro compound (**1l**) had the most potent activity.

Introduction of methyl or monofluoromethyl group to the hydroxyimino moiety of the C-7 side chain of *m*-fluorophenoxy compound (**1l**) enhanced the Gram-negative activity, but slightly diminished activity against Gram-positive bacteria (**1o** and **1p**).

In conclusion, we have synthesized cephalosporin derivatives having a new 3-phenoxymethyl substituent and found them to have good antibacterial activity especially against Gram-positive bacteria. The compounds (**1l**, **1o**, **1p**) showed the well-balanced activity against both Gram-positive and Gram-negative bacteria comparable to 3-methoxymethylcephalosporin (**1q**).

Experimental

IR spectra were recorded on a Jasco FT-IR 8300 spectrometer. ^{1}H NMR spectra were recorded on a Jeol-270GX (270 MHz) spectrometer using TMS as an internal standard. MICs were dererermined in nutrient agar medium (Eiken) by the 2-fold dilution method with 10^7 cfu/ml inoculum size after incubation at 37°C for 18 hours.

General Procedure for the Preparation of 3-Phenoxymethyl Compounds

Diphenylmethyl 3-(4-Bromophenoxy)methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate (**3a**) and Diphenylmethyl 3-(4-Bromophenoxy)methyl-7β-phenoxyacetamido-2-cephem-4-carboxylate (**4a**)

Dimethyl azodicarboxylate (0.90 ml) in dry THF (60 ml) was added to a stirred solution of **2** (3.00 g), *p*-bromophenol (1.17 g) and triphenylphosphine (1.80 g) in dry THF (60 ml) during 15 minutes under ice-cooling. After stirring for another 15 minutes at the same temperature, reaction mixture was diluted with brine and extracted with EtOAc. The extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on a Lobar silica gel column (Merck, silica gel, benzene - MeCN (4 : 1) to give **3a** (420 mg) and **4a** (300 mg). **3a**: IR (KBr) cm^{-1} 1785, 1487, 1231. ^{1}H NMR ($CDCl_3$) δ 3.55 and 3.63 (2H, ABq, J=18.7 Hz, 2-CH_2), 4.57 (2H, s, PhOCH_2), 4.77, 4.92 (2H, ABq, J=13.6 Hz, 3'-CH_2), 5.03 (1H, d, J=5.1 Hz, 6-H), 5.96 (1H, dd, J=5.1 and 9.5 Hz, 7-H), 6.61 (2H, d, J=9.2 Hz, arom-H), 6.8~7.5 (19H, m, arom-H, CONH, CH). **4a**: IR (KBr) cm^{-1} 1775, 1486, 1234. ^{1}H NMR ($CDCl_3$) δ 4.35 and 4.48 (2H, ABq, J=11.4 Hz, 3'-CH_2), 4.56 (2H, s, PhOCH_2), 5.31 (1H, J=1.8 Hz, 4-H), 5.33 (1H, d, J=4.4 Hz, 6-H), 5.73 (1H, dd, J=9.2 and 4.4 Hz, 7-H), 6.42 (1H, d, J=1.8 Hz, 2-H), 6.62 (2H, d, J=8.8 Hz, arom-H), 6.8~7.5 (19H, m, $CHPh_2$, CONH and arom-H).

Diphenylmethyl 7β-[2-(2-Tritylaminothiazol-4-yl)-(*Z*)-2-(trityloxyimino)acetamido]-3-(4-bromophenoxy)methyl-3-cephem-4-carboxylate (**5a**)

Anhydrous pyridine (0.28 ml) was added to a stirred solution of PCl_5 (630 mg) in $CHCl_3$ (14 ml) and stirred for 15 minutes. **3a** (890 mg) in $CHCl_3$ (6 ml) was added to the above reaction mixture under ice-cooling. The mixture was stirred for 1 hour at room temperature and then cooled to −30°C. *n*-PrOH (1.70 ml) was added to the resulting solution, the mixture was gradually warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was triturated with isopropyl ether, and the resulting power was collected by filtration to give diphenylmethyl 7β-amino-3-(4-bromophenoxy)methyl-3-cephem-4-carboxylate hydrochloride (760 mg). $POCl_3$ (0.15 ml) was added to a stirred solution of above amine hydrochloride, 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(trityloxyimino)acetic acid (1.050 g) and diethylaniline (0.93 ml) in CH_2Cl_2 (15 ml) under ice-cooling. After stirring for 1 hour, the reaction mixture was poured into ice-water and extracted with EtOAc. The extracts were washed with dil HCl, brine, aq $NaHCO_3$, brine, then dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was chromatographed

Table 3. ^{1}H NMR (270 MHz) data of **1a**～**1p** (DMSO-d_6, δ ppm).

1a	4.82, 4.86 (2H, ABq, J=13 Hz, 3′-CH_2), 5.19 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.76 (1H, s, thiazole-H), 6.94 (2H, d, J=9 Hz, arom-H), 7.46 (2H, d, J=9 Hz, arom-H), 9.59 (1H, d, J=8 Hz, CONH), 11.81 (1H, br s, NOH)
1b	4.85 (2H, s, 3′-CH_2), 5.19 (1H, d, J=5 Hz, 6-H), 5.80 (1H, dd, J=5, 8 Hz, 7-H), 6.74 (1H, s, thiazole-H), 6.95 (3H, m, arom-H), 7.32 (2H, m, arom-H), 9.58 (1H, d, J=8 Hz, CONH), 11.67 (1H, br s, NOH)
1c	4.80, 4.84 (2H, ABq, J=12 Hz, 3′-CH_2), 5.18 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.71 (1H, s, thiazole-H), 6.78 (2H, m, arom-H), 7.12 (2H, m, arom-H), 9.53 (1H, d, J=8 Hz, CONH), 11.55 (1H, br s, NOH)
1d	4.90, 4.97 (2H, ABq, J=12 Hz, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 6.72 (1H, s, thiazole-H), 7.14 (2H, d, J=9 Hz, arom-H), 7.78 (2H, d, J=9 Hz, arom-H), 9.54 (1H, d, J=8 Hz, CONH), 11.57 (1H, br s, NOH)
1e	2.52 (3H, s, CH_3), 4.92, 4.97 (2H, ABq, J=12 Hz, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 6.73 (1H, s, thiazole-H), 7.06 (2H, d, J=9 Hz, arom-H), 7.93 (2H, d, J=9 Hz, arom-H), 9.55 (1H, d, J=8 Hz, CONH), 11.06 (1H, br s, NOH)
1f	2.69 (3H, s, CH_3), 4.88, 4.94 (2H, ABq, J=12 Hz, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.73 (1H, s, thiazole-H), 7.18 (2H, d, J=9 Hz, arom-H), 7.68 (2H, d, J=9 Hz, arom-H), 9.56 (1H, d, J=8 Hz, CONH), 11.56 (1H, s, NOH)
1g	3.81 (3H, s, CH_3), 4.92 (2H, s, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.74 (1H, s, thiazole-H), 7.05 (2H, d, J=9 Hz, arom-H), 7.95 (2H, d, J=9 Hz, arom-H), 9.57 (1H, d, J=8 Hz, CONH), 11.70 (1H, s, NOH)
1h	4.92 (2H, s, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 7.04 (2H, d, J=9 Hz, arom-H), 7.89 (2H, d, J=9 Hz, arom-H), 9.55 (1H, d, J=8 Hz, CONH), 11.63 (1H, br s, NOH)
1i	3.69 (3H, s, CH_3), 4.79 (2H, s, 3′-CH_2), 5.18 (1H, d, J=5 Hz, 6-H), 5.80 (1H, dd, J=5, 8 Hz, 7-H), 6.72 (1H, s, thiazole-H), 6.86 (4H, s, arom-H), 9.57 (1H, d, J=8 Hz, CONH), 11.57 (1H, br s, NOH)
1j	2.41 (3H, s, CH_3), 4.83 (2H, s, 3′-CH_2), 5.18 (1H, d, J=5 Hz, 6-H), 5.80 (1H, dd, J=5, 8 Hz, 7-H), 6.73 (1H, s, thiazole-H), 6.95 (2H, d, J=9 Hz, arom-H), 7.30 (2H, d, J=9 Hz, arom-H), 9.54 (1H, d, J=8 Hz, CONH), 11.62 (1H, s, NOH)
1k	4.93 (2H, s, 3′-CH_2), 5.21 (1H, d, J=5 Hz, 6-H), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 6.74 (1H, s, thiazole-H), 6.9～7.3 (4H, m, arom-H), 9.58 (1H, d, J=8 Hz, CONH), 11.67 (1H, br s, NOH)
1l	4.82, 4.89 (2H, ABq, J=12 Hz, 3′-CH_2), 5.19 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.70 (1H, s, thiazole-H), 6.8～7.4 (4H, m, arom-H), 9.52 (1H, d, J=8 Hz, CONH), 11.50 (1H, br s, NOH)
1m	4.90 (2H, s, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 6.73 (1H, s, thiazole-H), 6.8～7.4 (3H, m, arom-H), 9.57 (1H, d, J=8 Hz, CONH), 11.66 (1H, br s, NOH)
1n	4.79, 4.87 (2H, ABq, J=12 Hz, 3′-CH_2), 5.19 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.72 (1H, s, thiazole-H), 6.8～7.5 (3H, m, arom-H), 9.54 (1H, d, J=8 Hz, CONH), 11.57 (1H, br s, NOH)
1o	3.58, 3.70 (2H, ABq, J=18 Hz, 2-CH_2), 3.87 (3H, s, CH_3), 4.82, 4.91 (2H, ABq, J=12 Hz, 3′-CH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.81 (1H, dd, J=5, 8 Hz, 7-H), 6.80 (1H, s, thiazole-H), 6.7～7.4 (4H, m, arom-H), 9.68 (1H, d, J=8 Hz, CONH)
1p	4.82, 4.90 (2H, ABq, J=12 Hz, 3′-CH_2), 5.22 (1H, d, J=5 Hz, 6-H), 5.75 (2H, d, J=55 Hz, CH_2F), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 6.95 (1H, s, thiazole-H), 6.7～7.4 (4H, m, arom-H), 9.86 (1H, d, J=8 Hz, CONH)

on silica gel column to give **5a** (940 mg). IR (KBr) cm^{-1} 1790, 1487, 1228. ^1H NMR ($CDCl_3$) δ 3.40 and 3.55 (2H, ABq, $J=18.7$ Hz, 2-CH_2), 4.80 and 5.00 (2H, ABq, d, $J=13.6$ Hz, 3'-CH_2), 5.05 (1H, d, $J=5.1$ Hz, 6-H), 6.10 (1H, dd, $J=9.2$ and 5.1 Hz, 7-H), 6.42 (1H, s, thiazole-H), 6.62 (2H, d, $J=9.1$ Hz, arom-H), 6.74 (1H, br s, NH), 6.97 (1H, s, $CHPh_2$), 7.1~7.5 (33H, m, CONH and arom-H).

Diphenylmethyl 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-hydroxyiminoacetamido]-3-(4-bromophenoxy)-methyl-3-cephem-4-carboxylate (**6a**)

Formic acid (5.0 ml) was added to a stirred solution of **5a** (1.16 g) in methanol (5.0 ml) at room temperature. After stirring for 1 hour at 40°C, the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and the solution was washed with aq $NaHCO_3$. The organic phase was washed with brine and then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column to give **6a** (350 mg). IR (KBr) cm^{-1} 1764, 1723, 1487. ^1H NMR (DMSO-d_6) δ 3.66 (2H, s, 2-CH_2), 4.72 (2H, s, 3'-CH_2), 5.23 (1H, d, $J=4.9$ Hz, 6-H), 5.91 (1H, dd, $J=8.3$ and 4.9 Hz, 7-H), 6.67 (1H, s, thiazole-H), 6.75 (2H, d, $J=9.3$ Hz, arom-H), 6.94 (1H, s, $CHPh_2$), 7.0~7.5 (14H, m, NH_2 and arom-H), 9.50 (1H, d, $J=8.3$ Hz, CONH), 11.30 (1H, br s, NOH).

7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-hydroxyiminoacetamido]-3-(4-bromophenoxy)methyl-3-cephem-4-carboxylic Acid Trifluoroacetic Acid Salt (**1a**)

Trifluoroacetic acid (1.5 ml) was added to a stirred solution of **6a** (340 mg) and anisole (0.5 ml) in CH_2Cl_2 (1.0 ml) under ice-cooling. After stirring for 1 hour at the same temperature, isopropyl ether was added to the reaction mixture. The resulting powder was collected by filtration to afford **1a** (213 mg) as a powder. IR (KBr) cm^{-1} 1776, 1675, 1192. ^1H NMR (Table 3).

7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-hydroxyiminoacetamido]-3-(4-methylsulfinylphenoxy)methyl-3-cephem-4-carboxylic Acid Trifluoroacetic Acid Salt (**1f**)

Meta-chloroperbenzoic acid (196 mg) was added to a solution of **1j** (662 mg) in a mixture of methylene chloride (66.2 ml) and methanol (5 ml) at 35~40°C and stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-$NaHCO_3$ solution and extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4 and evaporated to give 660 mg crude oil. This oil was chromatographed on silica gel column to afford **6f** (198 mg). The obtained **6f** was treated in the same way as that described for the synthesis of **1a** to give 135 mg of **1f**. IR (KBr) cm^{-1} 1782, 1673, 1200. ^1H NMR (Table 3).

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