SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7β-[1-(2-AMINOTHIAZOL-4-YL)-1-CYCLOPROPANECARBOXYAMIDO]CEPHEM DERIVATIVES

SHINTARO NISHIMURA, NOBUYOSHI YASUDA, HIROSHI SASAKI, KAZUO SAKANE and TAKAO TAKAYA

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan

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The synthesis and antibacterial activity of several 7β-[1-(2-aminothiazol-4-yl)-1-cyclopropanecarboxyamido]cephem derivatives (**1**) are described. The structure-activity relationships of **1** are also presented.

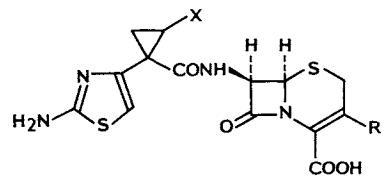
Since ceftizoxime (**2**)[1], cefmenoxime[2], and cefotaxime[3] were found to possess potent antibacterial activity, it has become very common for many institutes to do synthetic studies of alkyloxyiminocephem derivatives. Introduction of the alkyloxyimino moiety at the C-7 position confers potent and broad antibacterial spectrum to cephalosporins.

On the other hand, new type cephem derivatives, such as SG-164 (**3**)[4] and 7432-S (**4**)[5], have a vinyl moiety at the C-7 position instead of the alkyloxyimino moiety as shown in Fig. 1, and show good antibacterial activity. Since there is a common structural feature between the alkyloxyimino moiety and the vinyl moiety (both have sp^2 hybridization), we thought that introduction of similar moieties at the C-7 position might introduce good biological activity. Thus, we were interested in the cyclopropane structure, which has well documented "double-bond" character[6], and have synthesized a series of cyclopropane derivatives **1**.

Chemistry

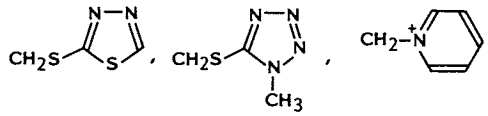
The new compounds **1** were prepared as described in Schemes 1 and 2. Initially, four cyclopropanecarboxylic acids, **10a**~**10d** were obtained from diketene (**5**) as shown in Scheme 1. Compound **6** was prepared by the treatment of *p*-methoxybenzyl alcohol with 4-chloroacetoacetyl chloride, which is

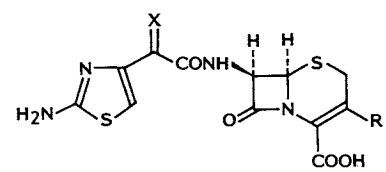
Fig. 1. Structures of compounds **1**~**4**.



1

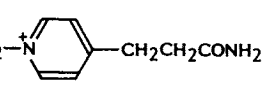
X=H, Cl, Br, OAc
R=$-CH_2OAc$,





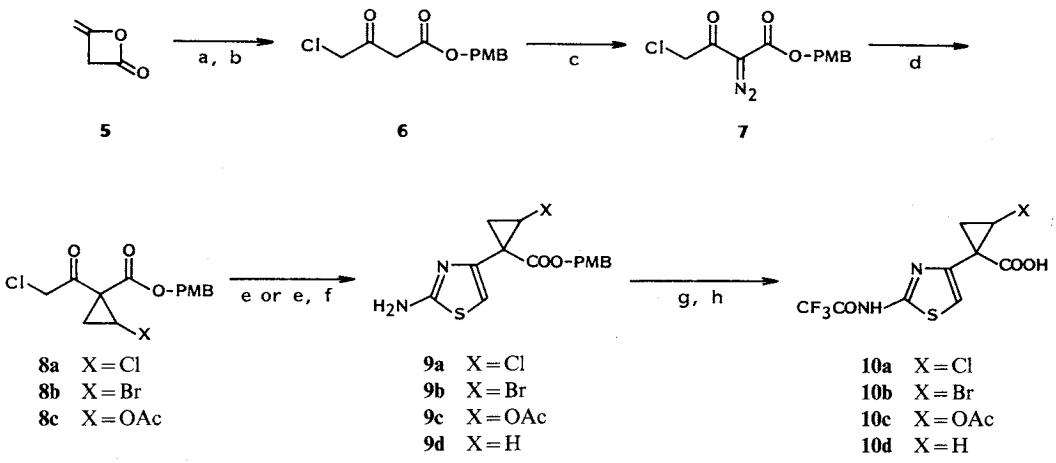
2 X=$=NOCH_3(Z)$, R=H
3 X=$=CHCl(Z)$,

R=



4 X=$=CHCH_2COOH(Z)$, R=H

Scheme 1. Synthesis of compounds **10a**~**10d**.



5 **6** **7**

8a X=Cl
8b X=Br
8c X=OAc

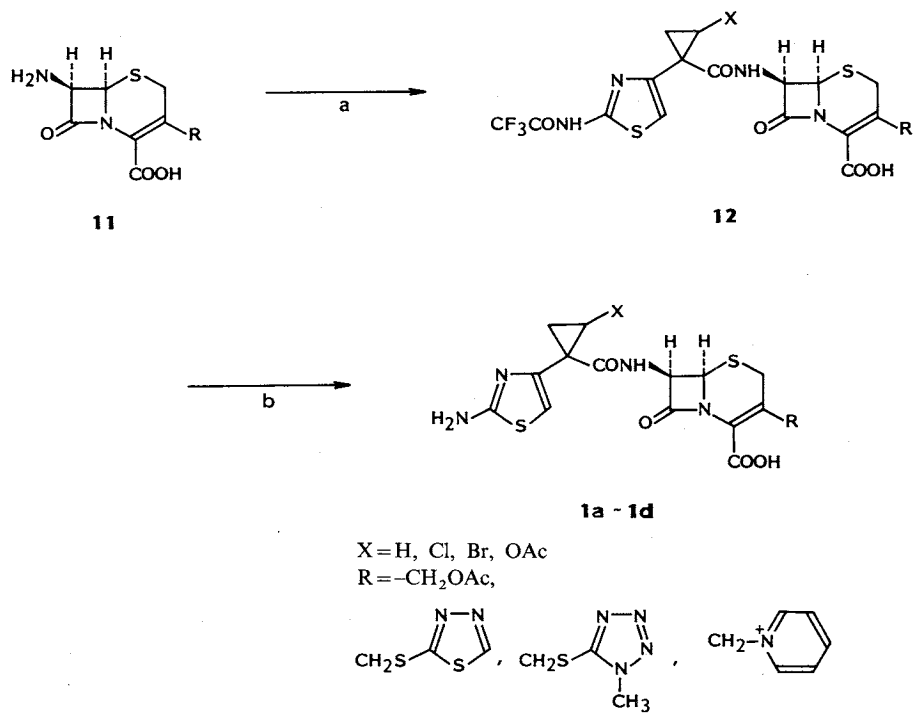
9a X=Cl
9b X=Br
9c X=OAc
9d X=H

10a X=Cl
10b X=Br
10c X=OAc
10d X=H

a) Cl_2, b) PMB alcohol, c) *p*-toluenesulfonyl azide, *N*,*N*-diisopropylethylamine, d) rhodium(II) acetate dimer, vinyl chloride (X=Cl), vinyl bromide (X=Br), vinyl acetate (X=OAc), e) thiourea, f) tributyltin hydride, g) trifluoroacetic anhydride, pyridine, h) TFA, anisole.

PMB: *p*-Methoxybenzyl.

Scheme 2. Synthesis of compounds **1a**~**1d**.



11 **12**

1a~**1d**

X=H, Cl, Br, OAc
R=$-CH_2OAc$,

a) **10a**~**10d**: Vilsmeier reagent, b) sodium acetate.

derived from diketene **5** and chlorine, in 93% yield. The treatment of **6** with *p*-toluenesulfonyl azide and *N*,*N*-diisopropylethylamine gave diazo compound **7** in 63% yield. The conversion of **7** to cyclopropane compounds, **8a**~**8c** was accomplished by carbene addition to vinyl halide or vinyl acetate in the presence

of rhodium catalyst. The configuration of the cyclopropane moieties of **8a**~**8c** could not be assigned by ^{1}H NMR. Compounds **8a**~**8c** were converted to the aminothiazole compounds, **9a**~**9c** by the reaction with thiourea, respectively. Compound **9d** was obtained by a radical reduction of **8b** using tributyltin hydride and azobisisobutyronitrile in 90% yield. Aminothiazole compounds, **9a**~**9d** were trifluoroacetylated, followed by deprotection of the *p*-methoxybenzyl group, to give carboxylic acids **10a**~**10d**, respectively.

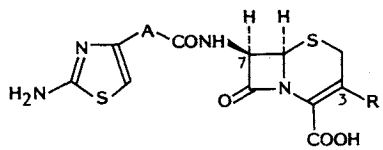
The general synthetic procedure to prepare compounds **1a**~**1d** is shown in Scheme 2. Carboxylic acids **10a**~**10d** were activated with Vilsmeier reagent followed by the treatment with silylated 7-aminocephalosporanic acids **11** to give 7-acylated cephem **12**, which were deprotected with excess amount of sodium acetate to give the target compounds **1a**~**1d**, respectively.

Antibacterial Activity

The *in vitro* antibacterial activities of a series of 7β-(1-cyclopropanecarboxyamido)cephem derivatives, **1a**~**1d** against selected Gram-positive and Gram-negative bacteria are shown in Table 1. As a whole, compounds **1a**~**1d** possess good activity against *Staphylococcus aureus* 209P JC-1 and *Proteus vulgaris* IAM 1025, moderate activity against *Escherichia coli* NIHJ JC-2 and *Klebsiella pneumoniae* 12, and no activity against *Pseudomonas aeruginosa* IAM 1095. The chloro derivatives **1a** generally more potent activity than the others and the 3-(1,3,4-thiadiazol-5-yl)thiomethyl derivative **1a-3** has the most potent activity.

C-7 cyclopropane cephems of type **1** have better antibacterial actvity than the corresponding methylene type **14**[7] which has no activity against *P. vulgaris* IAM 1025. The dimethylmethylene type **15**[8] has weak activity not only against *P. vulgaris* IAM 1025 but against *S. aureus* 209P JC-1 and *E. coli* NIHJ JC-2.

Table 1. MIC's of 7β-(1-cyclopropanecarboxyamido)cephem derivatives.



Compound	A	R	MIC[a] (μg/ml)				
			S.a.	*E.c.*	*K.p.*	*P.v.*	*P.a.*
1a-1		PY	0.39	0.78	3.13	0.78	>100
1a-2		TRZ	3.13	0.78	1.56	0.05	>100
1a-3		TDZ	0.39	0.39	1.56	≦0.025	>100
1b-1		PY	0.39	1.56	6.25	0.39	>100
1b-2		TDZ	0.78	1.56	3.13	≦0.025	>100
1b-3		$-CH_2OAc$	3.13	1.56	3.13	0.10	>100
1c		TRZ	6.25	3.13	12.5	0.20	>100
1d-1		PY	0.39	1.56	6.25	3.13	>100
1d-2		TDZ	3.13	6.25	12.5	0.10	>100
CMX	$>C=NOCH_3$	TRZ	1.56	≦0.025	0.20	≦0.025	50
13[9]	>C=CHCl	TRZ	0.39	0.05	0.39	≦0.025	3.13
14[7]	$-CH_2-$	TRZ	0.78	0.39	—	>100	>100
15[8]	$-C(CH_3)_2-$	TRZ	50[b]	>100[c]	—	>100[d]	—

Abbreviations: *S.a.*, *Staphylococcus aureus* 209P JC-1; *E.c.*, *Escherichia coli* NIHJ JC-2; *K.p.*, *Klebsiella pneumoniae* 12; *P.v.*, *Proteus vulgaris* IAM 1025; *P.a.*, *Pseudomonas aeruginosa* IAM 1095; [b] *Staphylococcus aureus* 1840, [c] *Escherichia coli* T-7, [d] *Proteus vulgaris* GN 4413; PY, (1-pyridinio)methyl; TRZ, (1-methyltetrazol-5-yl)thiomethyl; TDZ, (1,3,4-thiadiazol-5-yl)thiomethyl.

[a] Mueller-Hinton agar 10^{-2}; stamp method; 37°C, 18 hours.

It is not at all clear why the cyclopropane moiety produces better antibacterial activity than the dimethylmethylene moiety. However it may relate to a difference in molecular shape between **1** and **15** due to the increased strain of the cyclopropane ring.

These results suggest that the cyclopropane moiety of **1** may have an important role for enhancing antibacterial activity just as the vinyl and alkyloxyimino moieties as can be seen from the MICs of **13**[9] and cefmenoxime (CMX).

Experimental

MP's were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer. NMR spectra were recorded with a Hitachi R-90H spectrometer. Chemical shifts (δ) are reported in ppm from sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS, in D_2O) or TMS (in $CDCl_3$ and DMSO-d_6) as internal standard.

p-Methoxybenzyl 4-Chloro-3-oxo-butyrate (**6**)

To a solution of diketene (**5**) (30 ml, 0.39 mol) in dichloromethane (100 ml) was added chlorine (286 g, 10 weight % solution in carbon tetrachloride) at $-40\sim-35$°C over 30 minutes. The mixture was stirred at $-35\sim-20$°C for 30 minutes. Excess chlorine was removed by bubbling nitrogen through the mixture. To the mixture was added *p*-methoxybenzyl alcohol (47.8 ml, 0.38 mol) and *N*,*N*-diisopropylethylamine (66.7 ml, 0.38 mol) at $-35\sim-25$°C over 25 minutes. The mixture was stirred at the same temperature for 20 minutes and poured into ice-water. The organic layer was separated, washed successively with water, saturated aqueous sodium hydrogen carbonate, water and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo* to give oily compound **6** (93.1 g, 93%): IR (Film) cm^{-1} 1740~1710, 1605, 1500, 1240, 1170; ^1H NMR ($CDCl_3$) δ 3.60 (2H, s), 3.75 (2H, s), 4.14 (2H, s), 5.06 (2H, s), 6.84 and 7.25 (4H, ABq, $J=9$ Hz).

p-Methoxybenzyl 4-Chloro-2-diazo-3-oxo-butyrate (**7**)

To a mixture of **6** (70 g, 0.27 mol) and *p*-toluenesulfonyl azide (51.1 g, 0.26 mol) in acetonitrile (350 ml) was added *N*,*N*-diisopropylethylamine (45.1 ml, 0.257 mol) at $-43\sim-40$°C over 30 minutes. The mixture was stirred at the same temperature for 20 minutes and evaporated *in vacuo*. The residue was extracted with diethyl ether. The extract was evaporated *in vacuo*. The oily residue was triturated with dichloromethane to give a precipitate. The precipitate was removed by filtration. The filtrate was evaporated *in vacuo* to give **7** (48.6 g, 63%) as solid: IR (Nujol) cm^{-1} 2130, 1695, 1655, 1500, 1330, 1280, 1240, 1210, 1145, 1025; ^1H NMR ($CDCl_3$) δ 3.80 (3H, s), 4.57 (2H, s), 5.30 (2H, s), 6.93 and 7.40 (4H, ABq, $J=9$ Hz).

p-Methoxybenzyl 2-Chloro-1-(2-chloroacetyl)-1-cyclopropanecarboxylate (**8a**)

A mixture of **7** (15 g, 53.1 mmol), vinyl chloride (91 g, 1.46 mol) and rhodium(II) acetate dimer (90 mg, 0.2 mmol) was stirred at 30°C in a sealed tube for 2.5 hours. The mixture was poured into diethyl ether (100 ml). The precipitate was filtered off. The filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (Wakogel C-200; 500 g, eluent; hexane-dichloromethane (3:2)) to give **8a** (12.2 g, 73%) as colorless oil: IR (Film) cm^{-1} 1710, 1600, 1560, 1500, 1455, 1370, 1310, 1295, 1240, 1165; ^1H NMR (DMSO-d_6) δ 1.87~2.20 (2H, m), 3.83 (3H, s), 4.07 (1H, t, $J=7$ Hz), 4.82 (2H, s), 5.23 (2H, s), 6.96 and 7.42 (4H, ABq, $J=8$ Hz).

p-Methoxybenzyl 2-Bromo-1-(2-chloroacetyl)-1-cyclopropanecarboxylate (**8b**)

This compound was prepared from **7** and vinyl bromide in 63% yield as described for **8a** from **7** and vinyl chloride.

IR (Film) cm^{-1} 1720, 1610, 1510, 1310, 1300, 1250, 1170, 1030; ^1H NMR (DMSO-d_6) δ 2.03 (1H, dd, $J=2$ and 7 Hz), 3.77 (3H, s), 3.90 (1H, t, $J=7$ Hz), 4.77 (2H, s), 5.30 (2H, s), 6.93 and 7.40 (4H, ABq, $J=9$ Hz).

p-Methoxybenzyl 2-Acetoxy-1-(2-chloroacetyl)-1-cyclopropanecarboxylate (**8c**)

This compound was prepared from **7** and vinyl acetate in 97% yield as a crude. Crude **8c** was used instantly in the next step because of its relative instability.

p-Methoxybenzyl 1-(2-Aminothiazol-4-yl)-2-chloro-1-cyclopropanecarboxylate (**9a**)

To a solution of **8a** (9.9 g, 31 mmol) in *N*,*N*-dimethylacetamide (49.5 ml) was added thiourea (2.38 g, 31 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour and poured into a mixture of 0.5% aqueous sodium hydrogen carbonate (500 ml) and diethyl ether (500 ml). The organic layer was separated, washed successively with water (300 ml × 3) and saturated aqueous sodium chloride (300 ml), dried over magnesium sulfate, and evaporated *in vacuo*. The residue was triturated with cold diisopropyl ether followed by filtration to give **9a** (6.97 g, 66%) as a powder: IR (Nujol) cm^{-1} 3410, 3290, 3130, 1715, 1635, 1610, 1585, 1520, 1345, 1300, 1250, 1210, 1180, 1165; ^1H NMR (DMSO-d_6) δ 1.57~1.97 (2H, s), 3.80 (3H, s), 3.90 (1H, dd, J=5 and 7 Hz), 5.15 (2H, s), 6.47 (1H, s), 6.88 and 7.32 (4H, ABq, J=8 Hz), 6.93 (2H, br s).

p-Methoxybenzyl 1-(2-Aminothiazol-4-yl)-2-bromo-1-cyclopropanecarboxylate (**9b**)

This compound was prepared from **8b** in 76% yield as described for **9a** from **8a**.

IR (Nujol) cm^{-1} 3380, 3300, 3170, 1700, 1630, 1610, 1530, 1510, 1350, 1300, 1200; ^1H NMR (DMSO-d_6) δ 1.57~2.00 (2H, m), 3.57~3.90 (1H, m), 5.13 (2H, s), 6.45 (1H, s), 6.90 and 7.33 (4H, ABq, J=9 Hz), 6.93 (2H, br s).

p-Methoxybenzyl 2-Acetoxy-1-(2-aminothiazol-4-yl)-1-cyclopropanecarboxylate (**9c**)

This compound was prepared from **8c** as described for **9a** from **8a**, however, the yield was only 8% owing to the instability of **8c**.

IR (Film) cm^{-1} 3430, 3350, 3120, 2960, 1750~1710, 1610, 1510, 1470~1430, 1370, 1340, 1300, 1250~1230, 1170; ^1H NMR (DMSO-d_6) δ 1.53 (1H, t, J=7 Hz), 1.82 (3H, s), 1.88 (1H, t, J=5 Hz), 3.74 (3H, s), 4.55 (1H, dd, J=5 and 7 Hz), 5.08 (2H, s), 6.42 (1H, s), 6.88 (2H, br s), 6.90 and 7.28 (4H, ABq, J=9 Hz).

p-Methoxybenzyl 1-(2-Aminothiazol-4-yl)-1-cyclopropanecarboxylate (**9d**)

A mixture of **9b** (5.25 g, 13.7 mmol), tributyltin hydride (7.38 ml, 27.4 mmol), and azobisisobutyronitrile (62 mg, 0.46 mmol) in benzene (50 ml) was refluxed for 3 hours in nitrogen atmosphere and evaporated *in vacuo*. The residue was triturated with hexane. The precipitate was prepared by filtration and dried *in vacuo* to give **9d** (3.77 g, 90%) as a powder: IR (Nujol) cm^{-1} 3410, 1705, 1695, 1630, 1530, 1305, 1250, 1170; ^1H NMR (DMSO-d_6) δ 1.12~1.50 (4H, m), 3.74 (3H, m), 5.02 (2H, s), 6.49 (1H, s), 6.78 (2H, br s), 5.87 and 7.25 (4H, ABq, t, J=1.5 and 9 Hz).

2-Choloro-1-[2-(trifluoroacetamido)thiazol-4-yl]-1-cyclopropanecarboxylic Acid (**10a**)

To a mixture of **9a** (6.85 g, 20.2 mmol) and pyridine (3.27 ml, 40.4 mmol) in ethyl acetate (68 ml) was added trifluoroacetic anhydride (4.27 ml, 30.3 mmol) at −20~−10°C. The mixture was stirred at the same temperature for 15 minutes, poured into a mixture of ice-water (300 ml) and ethyl acetate (500 ml), and adjusted to pH 2 with 6 N hydrochloric acid. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo* to give *p*-methoxybenzyl 2-chloro-1-[2-(trifluoroacetamido)thiazol-4-yl]-1-cyclopropanecarboxylate (11.8 g) as crude. This crude was dissolved in anisole (25 ml). To the solution was added TFA (50 ml) at 0°C over 10 minutes. The mixture was stirred at the same temperature for 30 minutes and evaporated *in vacuo*. The residue was added to a mixture of ice-water (300 ml) and diisopropyl ether (500 ml). The mixture was neutralized with sodium hydrogen carbonate. The aqueous layer was separated, adjusted to pH 2 with 6 N hydrochloric acid, and extracted with diethyl ether. The extract was washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was triturated with hexane. The precipitate was prepared by filtration followed by drying *in vacuo* to give **10a** (5.47 g, 86%) as powder: IR (Nujol) cm^{-1} 1710, 1640, 1585, 1310, 1270, 1205, 1165; ^1H NMR (DMSO-d_6) δ 1.70~2.17 (2H, m), 4.07 (1H, dd, J=6 and 8 Hz), 7.40 (1H, s).

2-Bromo-1-[2-(trifluoroacetamido)thiazol-4-yl]-1-cyclopropanecarboxylic Acid (**10b**)

This compound was prepared from **9b** in 99% as described for **10a** from **9a**.

IR (Nujol) cm^{-1} 1705, 1575, 1300, 1265, 1200, 1160; ^1H NMR (DMSO-d_6) δ 1.73~2.10 (2H, m), 3.70~4.10 (1H, m), 7.30 (1H, s).

2-Acetoxy-1-[2-(trifluoroacetamido)thiazol-4-yl]-1-cyclopropanecarboxylic Acid (**10c**)

This compound was prepared from **9c** in 52% as described for **10a** from **9a**.

IR (Nujol) cm^{-1} 1730, 1590, 1270, 1220, 1210, 1155; ^1H NMR (DMSO-d_6) δ 1.67 (1H, t, J=7 Hz), 1.96 (1H, t, J=5 Hz), 2.03 (3H, s), 4.54 (1H, dd, J=5 and 7 Hz), 7.22 (1H, s).

1-[2-(Trifluoroacetamido)thiazol-4-yl]-1-cyclopropanecarboxylic Acid (**10d**)

This compound was prepared from **9d** in 75% as described for **10a** from **9a**.

IR (Nujol) cm^{-1} 1710, 1640, 1600, 1525, 1420, 1310, 1270, 1215, 1195, 1170, 1145; ^1H NMR (DMSO-d_6) δ 1.20~1.51 (4H, m), 7.12 (1H, s), 13.4 (1H, br).

7β-[1-(2-Aminothiazol-4-yl)-2-chloro-1-cyclopropanecarboxyamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (**1a-1**)

To a solution of Vilsmeier reagent prepared from phosphoryl chloride (0.296 ml, 3.18 mmol) and DMF (0.246 ml, 3.18 mmol) in THF (13 ml), was added **10a** (834 mg, 2.65 mmol) at 0°C. After being stirred at the same temperature for 20 minutes, the activated acid solution was added to a mixture of 7β-amino-3-(1-pyridinio)methyl-3-cephem-4-carboxylate dihydrochloride dihydrate (1.27 g, 3.29 mmol), *N,O*-bis(trimethylsilyl)acetamide (3.9 ml, 15.9 mmol), and *N*-trimethylsilylacetamide (2.08 g, 15.9 mmol) in THF (13 ml) at -20°C all at once. The mixture was stirred at -20~-15°C for 30 minutes, poured into a mixture of ice-water (15 ml), neutralized with sodium hydrogen carbonate, and washed with ethyl acetate (50 ml). To aqueous layer was added sodium acetate trihydrate (7.2 g, 52.9 mmol) at room temperature. The mixture was stirred at the same temperature for 15 minutes and further stirred at 30~40°C for 2 hours. The resulting mixture was adjusted to pH 2.0, and chromatographed over resin column (non-ionic adsorption resin Diaion HP-20; 30 ml). After washing with water, the column was eluted with isopropyl alcohol-water (1:9). The elution of product was lyophilized to give **1a-1** (293 mg, 23%) as powder: MP 148°C (dec); IR (Nujol) cm^{-1} 1765, 1630, 1605, 1520, 1345; ^1H NMR (D_2O) δ 1.55~2.00 (2H, m), 3.13 (0.5H, d, J=18 Hz), 3.16 (0.5H, d, J=18 Hz), 3.60~3.85 (1H, m), 3.62 (1H, d, J=18 Hz), 5.14 (1H, d, J=5 Hz), 5.31 and 5.56 (2H, ABq, J=14 Hz), 5.71 (0.5H, d, J=5 Hz), 5.77 (0.5H, d, J=5 Hz), 6.57 (1H, s), 7.95~8.22 (2H, m), 8.47~8.72 (1H, m), 8.84~9.05 (2H, m).

7β-[1-(2-Aminothiazol-4-yl)-2-chloro-1-cyclopropanecarboxyamido]-3-(1-methyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (**1a-2**)

Carboxylic acid **10a** (843 mg, 2.65 mmol) was activated with Vilsmeier reagent, which was derived from phosphoryl chloride (0.296 ml, 3.18 mmol) and DMF (0.246 ml, 3.18 mmol) as described for **1a-1**. On the other hand, 7β-amino-3-(1-methyl-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (1.05 g, 3.22 mmol) was dissolved in a mixture of sodium hydrogen carbonate (252 mg, 3.0 mmol), THF (10 ml), and water (10 ml) at 0~5°C. To the mixture was added the above activated acid solution with maintaining pH 7.5~8.0 by addition of aqueous sodium hydrogen carbonate at 0~5°C. The mixture was stirred for 30 minutes at 0~5°C, washed with diethyl ether (50 ml), adjusted to pH 3.0 with 6 N hydrochloric acid, and extracted with ethyl acetate (70 ml). The extract was evaporated *in vacuo*. The residue was triturated with diisopropyl ether the afford an acylated cephem derivative **12** (1.15 g, 69%, X=Cl, R=(1-methyltetrazol-5-yl)thiomethyl) as a powder. The powder was dissolved in a mixture of sodium acetate trihydrate (2.5 g, 18.4 mmol) and water (25 ml). The mixture was stirred for 16 hours at room temperature, diluted with water (30 ml), washed with ethyl acetate (30 ml), adjusted to pH 3.0 with 6 N hydrochloric acid, and extracted with ethyl acetate (50 ml). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was triturated with diethyl ether to afford **1a-2** as a powder (515 mg, 37% from **10a**): MP 135°C (dec); IR (Nujol) cm^{-1} 3280, 1770, 1630, 1520, 1225; ^1H NMR (DMSO-d_6) δ 1.65~2.05 (2H, m), 3.38~3.63 (1H, m), 3.69 (2H, br s), 3.95 (3H, s), 4.20 and 4.43 (2H, ABq, J=14 Hz), 5.10 (0.5H, d, J=5 Hz), 5.13 (0.5H, d, J=5 Hz), 5.74

(0.5H, dd, $J=5$ and 8 Hz), 5.83 (0.5H, dd, $J=5$ and 8 Hz), 6.40 (0.5H, s), 6.42 (0.5H, s), 7.15 (2H, br), 9.15 (0.5H, d, $J=6$ Hz), 9.17 (0.5H, d, $J=6$ Hz).

7β-[1-(2-Aminothiazol-4-yl)-2-chloro-1-cyclopropanecarboxyamido]-3-(1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem-4-carboxylic Acid (**1a-3**)

This compound was prepared from **10a** and 7β-amino-3-(1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem-4-carboxylic acid in 42% yield as described for **1a-2**.

MP 144°C (dec); IR (Nujol) cm^{-1} 3270, 1770, 1660~1630, 1520; ^1H NMR (DMSO-d_6) δ 1.62~2.04 (2H, m), 3.37~3.60 (1H, m), 3.55 and 3.83 (2H, ABq, $J=18$ Hz), 4.26 and 4.61 (2H, ABq, $J=14$ Hz), 5.10 (0.5H, d, $J=5$ Hz), 5.12 (0.5H, d, $J=5$ Hz), 5.63~5.95 (1H, m), 6.41 (0.5H, s), 6.43 (0.5H, s), 7.18 (2H, br), 9.15 (0.5H, d, $J=8$ Hz), 9.18 (0.5H, d, $J=8$ Hz), 9.56 (1H, s).

7β-[1-(2-Aminothiazol-4-yl)-2-bromo-1-cyclopropanecarboxyamido]-3-(1-pyridino)methyl-3-cephem-4-carboxylate (**1b-1**)

This compound was prepared from **10b** and 7β-amino-3-(1-pyridino)methyl-3-cephem-4-carboxylate in 46% yield as described for **1a-1**.

MP 140°C (dec); IR (Nujol) cm^{-1} 1765, 1620, 1600, 1510, 1370, 1330; ^1H NMR (DMSO-d_6) δ 1.70~2.05 (2H, m), 3.03 and 3.56 (2H, ABq, $J=18$ Hz), 3.20~3.60 (1H, m), 5.04 (1H, d, $J=5$ Hz), 5.15 and 5.65 (2H, ABq, $J=14$ Hz), 5.66~5.82 (1H, m), 6.36 (1H, s), 7.09 (2H, br s), 7.95~8.27 (2H, m), 8.42~8.70 (1H, m), 8.86~9.14 (1H, m), 9.27~9.53 (2H, m).

7β-[1-(2-Aminothiazol-4-yl)-2-bromo-1-cyclopropanecarboxyamido]cephalosporanic Acid (**1b-3**)

This compound was prepared from **10b** and 7β-amino-cephalosporanic acid in 23% yield as described for **1a-2**.

MP 95°C (dec); IR (Nujol) cm^{-1} 1770, 1640, 1520, 1230; ^1H NMR (DMSO-d_6) δ 1.70~2.10 (2H, m), 2.03 (3H, s), 3.30~3.90 (3H, m), 4.66 and 4.97 (2H, ABq, $J=14$ Hz), 5.09 (0.5H, d, $J=5$ Hz), 5.13 (0.5H, d, $J=5$ Hz), 5.65~5.93 (1H, m), 6.37 (0.5H, s), 6.39 (0.5H, s), 7.11 (2H, br s), 9.10 (0.5H, d, $J=8$ Hz), 9.12 (0.5H, d, $J=8$ Hz).

7β-[2-Acetoxy-1-(2-aminothiazol-4-yl)-2-bromo-1-cyclopropanecarboxyamido]-3-(1-methyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (**1c**)

This compound was prepared from **10c** and 7β-amino-3-(1-methyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid in 65% yield as described for **1a-2**.

MP 130°C (dec); IR (Nujol) cm^{-1} 1780~1750, 1670~1630, 1510, 1215; ^1H NMR (DMSO-d_6) δ 1.48~1.72 (1H, m), 1.80~2.14 (1H, m), 1.95 (3H, s), 3.67 (2H, br s), 3.93 (3H, s), 4.17 and 4.42 (2H, ABq, $J=14$ Hz), 4.35~4.62 (1H, m), 5.08 (1H, d, $J=5$ Hz), 5.57~5.85 (1H, m), 6.32 (1H, s), 6.90~7.35 (2H, br), 8.82~9.07 (1H, m).

7β-[1-(2-Aminothiazol-4-yl)-1-cyclopropanecarboxyamido]-3-(1-pyridinio)methyl-3-cephem-4-carboxylate (**1d-1**)

This compound was prepared from **10d** and 7β-amino-3-(1-pyridinio)methyl-3-cephem-4-carboxylate in 31% yield as described for **1a-1**.

MP 115°C (dec); IR (Nujol) cm^{-1} 1760, 1630, 1610, 1515, 1340; ^1H NMR (DMSO-d_6) δ 1.06 (2H, br s), 1.24 (2H, br s), 3.05 and 3.53 (2H, ABq, $J=18$ Hz), 5.01 (1H, d, $J=5$ Hz), 5.16 and 5.67 (2H, ABq, $J=14$ Hz), 5.66 (1H, dd, $J=5$ and 8 Hz), 6.32 (1H, s), 7.01 (2H, br s), 8.00~8.25 (2H, m), 8.40~8.70 (2H, m), 9.40 (2H, d, $J=8$ Hz).

7β-[1-(2-Aminothiazol-4-yl)-1-cyclopropanecarboxyamido]-3-(1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem-4-carboxylae (**1d-2**)

This compound was prepared for **10d** and 7β-amino-3-(1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem-4-carboxylic acid in 57% yield as described for **1a-2**.

MP 145~155°C (dec); IR (Nujol) cm^{-1} 3300, 1760, 1630, 1510; ^1H NMR (DMSO-d_6) δ 1.05 (2H, br s), 1.24 (2H, br s), 3.55 and 3.82 (2H, ABq, $J=18$ Hz), 4.24 and 4.60 (2H, ABq, $J=14$ Hz), 5.08 (1H,

d, J=5 Hz), 5.72 (1H, dd, J=5 and 8 Hz), 6.35 (1H, s), 7.06 (2H, br s), 8.81 (1H, d, J=8 Hz), 9.53 (1H, s).

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