SYNTHESIS AND ACTIVITY OF POTENT 3-(ISOXAZOLIDIN-5-YL)- AND 3-(ISOXAZOLIDINIUM-5-YL)CEPHALOSPORINS†

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The syntheses and *in vitro* antibacterial activities of 3-(isoxazolidin-5-yl)- and 3-(isoxazolidinium-5-yl)cephalosporins are described. 1,3-Dipolar cycloaddition of 3-vinylcephalosporin with nitrone gave diastereomeric isomers of 3-(isoxazolidin-5-yl)cephalosporin. The antibacterial activities of 3′-(*S*)-isomers were superior to those of 3′-(*R*)-isomers. The quaternarization of isoxazolidine ring increased the antibacterial activity. Among them, compound **10b** with a hydroxyimino group in the C-7 side chain showed potent activities against staphylococci and compound **10f** with an *N*-hydroxypyridone exhibited an excellent antipseudomonal activity.

In the preceding paper, we prepared 3-(isoxazolin-5-yl)- and 3-(isoxazol-4-yl)cephalosporins *via* 1,3-dipolar cycloaddition of nitrile oxides with 3-vinylcephalosporin.[1] These isoxazoline- and isoxazole-cephalosporins exhibited moderate antibacterial activities. The antibacterial activity of cephalosporins is influenced by the substitution at the C-3 position. BOYD[2] described that the presence of a leaving group in the C-3 side chain could promote the antibacterial activity. Recently, NARISADA *et al.*[3] and NISHIKAWA *et al.*[4] reported that the chemical reactivity of the β-lactam ring was dependent on the electron-withdrawing character of the 3′-substituent on 7α-methoxy-1-oxacephems. These facts prompted us to introduce isoxazolidine and isoxazolidinio rings to cephem system in place of isoxazoline and isoxazole rings. In this report we describe the synthesis of 3-(isoxazolidin-5-yl)- and 3-(isoxazolidinium-5-yl)cephalosporins *via* 1,3-dipolar cycloaddition reaction of nitrone with 3-vinylcephalosporin and their potent antibacterial activities.

Chemistry

The isoxazolidine ring was constructed by 1,3-dipolar cycloaddition of nitrones with 3-vinylcephem (Fig. 1). The reaction of *p*-methoxybenzyl 7-phenylacetamido-3-vinyl-3-cephem-4-carboxylate[5] (**1**) with *N*-methylnitrone, generated from 38% formalin and *N*-methylhydroxylamine hydrochloride in the presence of sodium acetate *in situ*, at 90°C gave two diastereomeric 3-(2-methylisoxazolidin-5-yl)-3-cephems (**2** and **3**) in 82% yield. Each isomer was easily separable by the trituration of the mixture with ether. Compound **2** was more soluble in ether than **3**. The ethereal solution contained **2** and the insoluble solid was chromatographed on silica gel to isolate **2** and **3**. As expected, this 1,3-dipolar cycloaddition reaction proceeded regiospecifically, no isoxazolidin-4-yl isomer was detected. This fact was confirmed by ^{1}H NMR spectra according to the methine proton of isoxazolidine ring of **2** resonated at δ 5.24 and **3** at δ 5.55.

† Dedicated to the late Professor HAMAO UMEZAWA on the occasion of the 30th anniversary of the Institute of Microbial Chemistry.

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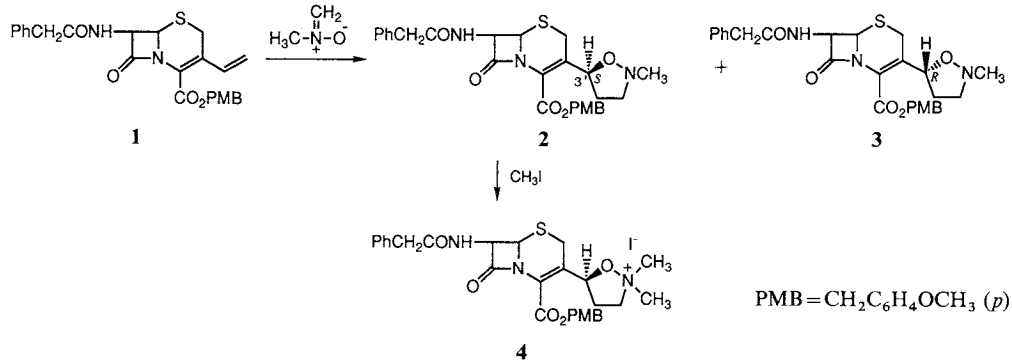
Fig. 1. Cycloaddition reaction with nitrone.



1 2 3 4

The alternative isoxazolidin-4-yl is not expected to show the signals at these chemical shifts. The reaction gave predominantly **2**, and the ratio of **2** and **3** was 2.7 : 1. ^{1}H NMR data such as chemical shifts, coupling constants and Δ values of coupling constants between C-4 methylene protons and C-5 methine proton of the isoxazolidine part failed to provide the clear evidence on the assignment of configuration of the isoxazolidine C-5 position. Compound **2** was treated with iodomethane to give isoxazolidinio derivative **4**. Compound **4** gave good crystals for X-ray crystallographic analysis.† Thus, the stereochemistry of the C-3′ position (C-5 position of the isoxazolidine ring) of **4** was determined to be *S*-configuration.

3′-(*S*)-Isomer **2** was treated with phosphorous pentachloride, pyridine and methanol to give 7-amino derivative **5** (Fig. 2). The amino group of **5** was acylated with a variety of aminothiazolyl-oximinoacetic acids **6** (**a**～**g** in Fig. 2) by *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBT) method to give protected compounds **7** in good yields. The treatment of **7** with trifluoroacetic acid (TFA) and anisole or with TFA-anisole and 50% formic acid gave final products **8**. Compounds **7** were methylated with iodomethane to give quaternary ammonium derivatives **9**. By the similar method used for **7**, the protecting groups of **9** were removed to give **10**. 3′-(*R*)-Isomer **3** was derivatized to **11** and **12** by the similar method. Protected aminothiazoleacetic acids (**6a**～**6f**)[6～10] were prepared by the known methods. Compound **6g** was derived from 3-hydroxy-4-hydroxymethylbenzoic acid (BF-127)[11] and 2-oxo-2-(2-tritylaminothiazol-4-yl)acetic acid.

Antibacterial Activity

Minimum inhibitory concentrations (MICs) of these compounds against various microorganisms are listed in Tables 1 and 2. All compounds are highly potent. The antibacterial activity of 3′-(*S*)-isomers (**8a**, **10a**) is 2 to 4 times that of 3′-(*R*)-isomers (**11**, **12**). The configuration at the C-3′ position of isoxazolidine derivatives much influenced the antibacterial activities in contrast to 3-(isoxazolin-5-yl)cephalosporins.[1] Quaternarization of isoxazolidine ring (**10**) markedly enhanced the activity against both of Gram-positive and Gram-negative bacteria. Among isoxazolidinio derivatives, **10b** having a hydroxyimino group in the C-7 side chain was the most active against staphylococci. Compounds **8f** and **10f** consisting with *N*-hydroxypyridone in the C-7 side chain showed high activity against Gram-negative bacteria, especially *Pseudomonas*. Antipseudomonal activities of **8f** and **10f** against clinical isolates (57 strains) were superior to those of ceftazidime (CAZ) as shown in Table 3.

† The X-ray crystallographic analysis was performed by Mr. YOSHIO KODAMA, Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd.

Fig. 2. Synthesis of 3-(isoxazolidin-5-yl)cephalosporins.

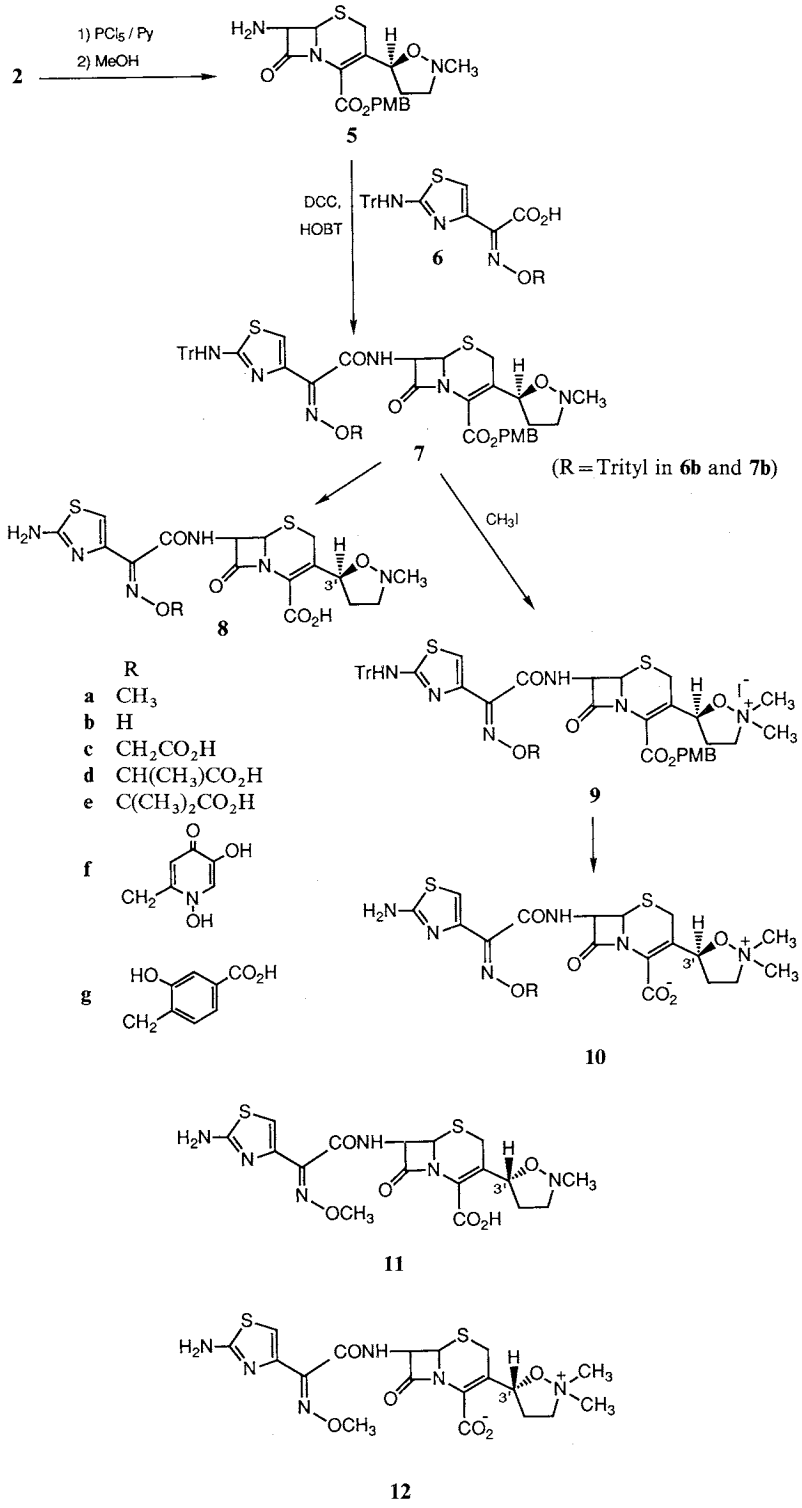


Table 1. Antibacterial activity of 3-(2-methylisoxazolidin-5-yl)cephalosporins and CAZ.

Test organism	MIC (μg/ml)							
	8a	**11**	**8b**	**8c**	**8d**	**8e**	**8f**	CAZ
Staphylococcus aureus FDA209P	3.13	6.25	0.78	50	50	50	25	12.5
S. aureus Terajima	1.56	3.13	0.20	25	25	25	12.5	1.56
S. aureus MS353	3.13	6.25	0.78	50	50	50	25	12.5
Bacillus subtilis ATCC 6633	0.39	0.78	0.20	1.56	3.13	6.25	3.13	3.13
Micrococcus luteus ATCC 9341	0.10	1.56	0.20	6.25	1.56	12.5	3.13	3.13
Escherichia coli NIHJ JC-2	0.39	0.78	0.20	0.20	0.39	0.20	0.10	0.20
E. coli K-12 C600	0.025	0.10	0.20	0.20	0.39	0.39	0.012	0.20
E. coli K-12 W3630 Rms212[a]	0.39	1.56	1.56	0.39	0.78	0.78	0.006	0.39
E. coli K-12 W3630 Rms213[a]	0.20	0.39	0.20	1.56	0.05	0.05	0.006	0.10
E. coli K-12 W3630 Rms823[a]	0.78	3.13	12.5	0.20	0.78	0.78	0.025	0.78
E. coli K-12 W3630 Rte16[a]	6.25	3.13	0.78	25	25	25	25	6.25
E. coli GN5482[b]	1.56	6.25	3.13	1.56	1.56	1.56	0.78	3.13
Klebsiella pneumoniae PCI602	0.025	0.05	0.10	0.20	0.20	0.20	0.003	0.20
K. oxytoca GN10560[c]	6.25	25	25	3.13	1.56	0.78	0.05	0.39
Citrobacter freundii GN7391[b]	>100	>100	>100	100	>100	>100	>100	>100
Salmonella typhimurium IID971	0.39	1.56	0.39	0.20	0.78	0.78	<0.003	0.39
S. typhi 901	0.20	0.78	0.20	0.10	0.20	0.39	0.012	0.20
S. paratyphi 1015	0.05	0.10	0.20	0.20	0.20	0.39	0.012	0.05
S. schottmuelleri 8006	0.05	0.10	0.20	0.05	0.10	0.39	0.006	0.10
S. enteritidis G14	0.20	0.78	0.20	0.20	0.39	0.78	0.05	0.20
Serratia marcescens IAM1184	0.20	0.39	0.78	0.10	0.05	0.20	0.10	0.05
Enterobacter cloacae 963	0.39	1.56	0.78	0.39	0.39	1.56	0.05	0.20
E. cloacae GN5797	3.13	12.5	50	6.25	3.13	1.56	3.13	12.5
E. cloacae GN7471[b]	12.5	50	50	12.5	6.25	3.13	6.25	3.13
E. aerogenes ATCC 13048	0.39	0.78	0.78	0.39	1.56	0.78	0.05	0.39
Morganella morganii IFO3848	0.012	0.05	0.20	0.012	<0.003	0.006	0.025	0.025
M. morganii GN5407[b]	0.10	0.39	0.39	0.05	0.10	0.39	0.05	0.20
Providencia rettgeri IFO3850	0.012	0.025	0.025	0.006	0.012	0.05	<0.003	0.05
P. rettgeri GN4430[b]	0.05	0.10	0.025	0.012	0.05	0.10	0.025	0.10
Proteus vulgaris OX-19	0.39	0.78	6.25	0.05	0.025	0.025	0.39	0.05
P. vulgaris HX-19	0.025	0.10	0.39	0.025	0.012	0.025	0.05	0.05
P. vulgaris GN7919[c]	50	100	>100	0.78	0.78	0.78	12.5	3.13
P. mirabilis IFO3849	0.10	0.20	0.39	0.025	0.025	0.05	0.05	0.05
Pseudomonas aeruginosa IFO3445	50	>100	100	12.5	6.25	1.56	0.10	0.78
P. aeruginosa NCTC10490	12.5	100	100	3.13	1.56	0.78	0.012	0.78
P. aeruginosa PAO1	100	>100	>100	25	6.25	6.25	0.05	1.56
P. aeruginosa Rms139/M1[a]	50	>100	100	12.5	3.13	6.25	0.05	0.78
P. aeruginosa GN10362[b]	>100	>100	>100	50	12.5	12.5	0.10	3.13

[a] Penicillinase-producing strain.
[b] Cephalosporinase-producing strain.
[c] Cefuroximase-producing strain.
MICs were determined by two-fold agar dilution method at 37°C for 18 hours using Bacto Mueller-Hinton Medium (Difco).

The 1,3-dipolar cycloaddition reaction of nitrone with 3-vinylcephalosporin could introduce a new ring system to cephalosporin and provide highly potent cephalosporins, such as **8f**, **10b**, and **10f**.

Experimental

General

Mass spectra were measured on a JEOL JMX-SX102 mass spectrometer. ^{1}H NMR spectra were

Table 2. Antibacterial activity of 3-(2,2-dimethylisoxazolidinium-5-yl)cephalosporins.

Test organism	MIC (μg/ml)							
	10a	**12**	**10b**	**10c**	**10d**	**10e**	**10f**	**10g**
Staphylococcus aureus FDA209P	0.78	1.56	0.20	12.5	12.5	6.25	12.5	1.56
S. aureus Terajima	0.39	0.78	0.10	0.78	1.56	1.56	3.13	0.78
S. aureus MS353	0.78	1.56	0.20	12.5	12.5	6.25	12.5	3.13
Bacillus subtilis ATCC 6633	0.20	0.39	0.20	0.78	1.56	3.13	3.13	0.20
Micrococcus luteus ATCC 9341	0.39	0.20	0.39	1.56	12.5	6.25	3.13	0.20
Escherichia coli NIHJ JC-2	0.20	0.39	0.39	0.05	0.05	0.20	0.20	1.56
E. coli K-12 C600	0.05	0.10	0.39	0.05	0.05	0.20	0.012	0.20
E. coli K-12 W3630 Rms212[a]	0.39	1.56	1.56	0.10	0.20	0.78	0.05	3.13
E. coli K-12 W3630 Rms213[a]	0.39	0.39	0.39	0.20	0.05	0.05	0.025	0.20
E. coli K-12 W3630 Rms823[a]	3.13	6.25	25	0.39	1.56	1.56	0.39	25
E. coli K-12 W3630 Rte16[a]	0.78	1.56	0.39	6.25	6.25	12.5	12.5	1.56
E. coli GN5482[b]	0.39	0.78	0.39	0.39	0.39	0.78	0.78	1.56
Klebsiella pneumoniae PCI602	0.05	0.10	0.39	0.10	0.10	0.10	0.025	0.39
K. oxytoca GN10560[c]	25	50	100	3.13	1.56	0.39	0.78	>100
Citrobacter freundii GN7391[b]	25	100	25	50	25	12.5	50	100
Salmonella typhimurium IID971	0.39	0.78	0.39	0.05	0.20	0.39	0.012	1.56
S. typhi 901	0.20	0.39	0.39	0.10	0.05	0.20	0.012	1.56
S. paratyphi 1015	0.05	0.05	0.39	0.025	0.025	0.05	0.025	0.39
S. schottmuelleri 8006	0.05	0.10	0.39	0.05	0.05	0.10	0.025	0.78
S. enteritidis G14	0.10	0.78	0.39	0.05	0.10	0.39	0.39	1.56
Serratia marcescens IAM1184	0.025	0.20	0.20	0.012	0.025	0.05	0.10	0.39
Enterobacter cloacae 963	0.20	0.20	0.39	0.05	0.10	0.39	0.05	0.78
E. cloacae GN5795	0.78	1.56	3.13	0.39	0.20	0.39	1.56	3.13
E. cloacae GN7471[b]	1.56	3.13	1.56	0.39	0.39	0.78	6.25	6.25
E. aerogenes ATCC 13048	0.20	0.39	0.78	0.10	0.10	0.39	0.05	1.56
Morganella morganii IFO3848	0.05	0.10	0.39	0.025	0.012	0.78	0.10	0.025
M. morganii GN5407[b]	0.39	0.20	0.39	0.05	0.05	0.10	0.10	3.13
Providencia rettgeri IFO3850	0.025	0.05	0.10	0.012	0.025	0.05	0.012	0.10
P. rettgeri GN4430[b]	12.5	0.05	0.05	0.012	0.10	0.10	0.10	0.39
Proteus vulgaris OX-19	0.78	1.56	6.25	0.10	0.05	0.10	6.25	12.5
P. vulgaris HX-19	0.10	0.10	0.78	0.005	0.025	0.05	0.20	0.10
P. vulgaris GN7919[c]	>100	>100	>100	12.5	6.25	6.25	12.5	>100
P. mirabilis IFO3849	0.20	0.20	0.39	0.05	0.05	0.10	0.20	0.39
Pseudomonas aeruginosa IFO3445	6.25	12.5	12.5	0.78	0.78	1.56	0.20	6.25
P. aeruginosa NCTC10490	3.13	6.25	25	0.78	0.78	0.78	0.012	6.25
P. aeruginosa PAO1	50	25	>100	1.56	1.56	1.56	0.10	12.5
P. aeruginosa Rms139/M1[a]	1.56	3.13	6.25	0.78	0.78	0.78	0.05	3.13
P. aeruginosa GN10362[b]	12.5	50	50	3.13	1.56	3.13	0.05	25

[a,b,c] See Table 1.

recorded on a JEOL JNM-GX400 or a Varian EM-360 spectrometers. IR spectra were measured on a Hitachi I-5020 FT-IR spectrometer.

p-Methoxybenzyl 7-Phenylacetamido-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylate (**2**) and *p*-Methoxybenzyl 7-Phenylacetamido-3-[(*R*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylate (**3**)

To a solution of **1** (3.72 g), sodium acetate (984 mg) and 38% formalin (1.27 ml) in a mixture of dioxane (75 ml) and ethanol (50 ml) was dropwise added a solution of *N*-methylhydroxylamine hydrochloride (1.0 g) in 83% aq ethanol (30 ml) at room temperature. After stirring at 90°C for 3 hours, the solution was concentrated. The residue was triturated with dichloromethane and the organic layer was washed with aq $NaHCO_3$ solution and satd NaCl solution, dried over anhydr Na_2SO_4 and evaporated to give a solid. The obtained solid was treated with ether. The ether solution was concentrated to give **2** (1.70 g). The ether-insoluble solid material was chromatographed on silica gel with chloroform-methanol

Table 3. Antibacterial activities of **8f**, **10f** and CAZ against 57 clinical isolates of *Pseudomonas aeruginosa*.

	MIC (μg/ml)		
	Range	50%	90%
8f	0.006~1.56	0.20	0.78
10f	0.024~1.56	0.20	0.78
CAZ	1.56~50	6.25	25

MICs were determined by two-fold agar dilution method at 37°C for 18 hours using Bacto Mueller-Hinton Medium (Difco). Clinical isolates (1986~1987) were purchased from Takeda Analytical Research Laboratories Ltd.

(96:4) to give **2** (0.8 g) and **3** (0.9 g). **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (1H, m, 4-Hb of isoxazolidine), 2.51 (1H, m, 3-Hb of isoxazolidine), 2.65 (3H, s, NCH_3), 2.75 (1H, m, 4-Ha of isoxazolidine), 3.24 (1H, m, 3-Ha of isoxazolidine), 3.59 (1H, d, J=19 Hz, 2-Hb), 3.60 and 3.66 (each 1H, d, J=16 Hz, $COCH_2Ph$), 3.73 (1H, d, J=19 Hz, 2-Ha), 3.80 (3H, s, OCH_3), 4.89 (1H, d, J=5 Hz, 6-H), 5.15 (2H, br s, CO_2CH_2Ar), 5.24 (1H, br t, J=8 Hz, 3'-H), 5.79 (1H, dd, J=5 and 9 Hz, 7-H) and 6.08 (1H, d, J=9 Hz, CONH). IR (KBr) cm^{-1} 1781, 1721, 1680, 1520, 1243, 1220 and 1180. **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (1H, m, 4-Hb of isoxazolidine), 2.44 (1H, m, 3-Hb of isoxazolidine), 2.56 (1H, m, 4-Ha of isoxazolidine), 2.66 (3H, s, NCH_3), 3.19 (1H, m, 3-Ha of isoxazolidine), 3.52 (1H, d, J=18 Hz, 2-Hb), 3.61 (1H, d, J=16 Hz, Hb of $COCH_2Ph$), 3.65 (1H, d, J=18 Hz, 2-Ha), 3.67 (1H, d, J=16 Hz, Ha of $COCH_2Ph$), 3.80 (3H, s, OCH_3), 4.89 (1H, d, J=5 Hz, 6-H), 5.18 (2H, br s, CO_2CH_2Ar), 5.55 (1H, br t, J=7 Hz, 3'-H), 5.73 (1H, dd, J=5 and 9 Hz, 7-H) and 6.09 (1H, d, J=9 Hz, CONH). IR (KBr) cm^{-1} 1781, 1721, 1679, 1518, 1240, 1203 and 1178.

p-Methoxybenzyl 3-[(*S*)-2,2-Dimethylisoxazolidinium-5-yl]-7-phenylacetamido-3-cephem-4-carboxylate Iodide (**4**)

To a solution of **2** (30 mg) in methanol (2 ml) was added iodomethane (82 mg). The solution was allowed to stand overnight at room temperature and concentrated to give a solid. The solid was crystallized from methanol to give needles **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.70 (2H, m, 4-H of isoxazolidine), 3.46 (1H, d, J=13.5 Hz, Hb of $COCH_2Ph$), 3.47 (1H, d, J=18 Hz, 2-Hb), 3.55 (1H, d, J=13.5 Hz, Ha of $COCH_2Ph$), 3.57 and 3.60 (each 3H, s, $N^+(CH_3)_2$), 3.75 (3H, s, OCH_3), 3.79 (1H, d, J=18 Hz, 2-Ha), 4.10 and 4.18 (each 1H, m, 3-H of isoxazolidine), 5.15 (1H, d, J=5 Hz, 6-H), 5.17 and 5.22 (each 1H, d, J=11 Hz, CO_2CH_2Ar), 5.67 (1H, t, J=8 Hz, 3'-H), 5.75 (1H, dd, J=5 and 8 Hz, 7-H) and 9.11 (1H, d, J=8 Hz, CONH).

p-Methoxybenzyl 7-Amino-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylate (**5**)

Anhydr pyridine (544 mg) was added to a mixture of PCl_5 (1.43 g) in dichloromethane (20 ml) at 0°C. After stirring at the same temperature for 1 hour, compound **2** (1.20 g) was added to above solution at 8°C. The stirring was continued for 1.5 hours at 8°C. The mixture was cooled to −30°C and methanol (9.2 ml) was added. After 1.5 hours below −15°C, it was diluted with dichloromethane (40 ml) and extracted with satd NaCl solution (40 ml). The aq layer was adjusted to pH 9 with aq $NaHCO_3$ solution and extracted with chloroform. After evaporation, **5** (811 mg, 87%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (1H, m, 4-Hb of isoxazolidine), 2.55 (1H, m, 3-Hb of isoxazolidine), 2.67 (3H, s, NCH_3), 2.77 (1H, m, 4-Ha of isoxazolidine), 3.28 (1H, m, 3-Ha of isoxazolidine), 3.61 (1H, d, J=19 Hz, 2-Hb), 3.75 (1H, d, J=19 Hz, 2-Ha), 3.80 (3H, s, $ArOCH_3$), 4.71 (1H, d, J=5 Hz, 7-H), 4.89 (1H, d, J=5 Hz, 6-H), 5.18 (2H, br s, CO_2CH_2Ar) and 5.25 (1H, m, 3'-H).

(*Z*)-2-[(3-Hydroxy-1-(*p*-methoxybenzyloxy)carbonylphen-4-yl)methoxyimino]-2-(2-tritylaminothiazol-4-yl)acetic Acid (**6g**)

A mixture of BF-127[11] (840 mg), 4-methoxybenzyl chloride (860 mg), NaBr (1.70 g) and K_2CO_3 (690 mg) in DMSO (10 ml) was stirred at room temperature for 24 hours. The reaction mixture was poured into a mixture of ethyl acetate and water, acidified with 10% HCl and extracted with ethyl acetate. The organic layer was washed with brine and water, dried over anhydr Na_2SO_4. After evaporation, the residue was chromatographed on silica gel with chloroform-MeOH (98.5:1.5) to afford *p*-methoxybenzyl 3-hydroxy-4-hydroxymethylbenzoate (585 mg). ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.80 (3H, s, OCH_3), 4.82 (2H, s, CH_2) and 5.23 (2H, s, CH_2). To a solution of above ester (1.15 g), *N*-hydroxyphthalimide (715 mg) and triphenylphosphine (990 mg) in THF (20 ml) was added a solution of diethyl azodicarboxylate (770 mg)

in THF (5 ml) at room temperature over 30 minutes. After stirring for 5 hours, the solution was evaporated. The residue was chromatographed on silica gel with chloroform to give *N*-[3-hydroxy-1-((*p*-methoxybenzyl)oxy)carbonylphen-4-yl]methoxyphthalimide (804 mg). ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.82 (3H, s, OCH_3), 5.28 (4H, s, $CH_2 \times 2$). To a solution of this phthalimide (394 mg) in THF (1.5 ml) was added a solution of hydrazine hydrate (45 mg) in MeOH (0.2 ml) at room temperature. After stirring for 30 minutes, 15% HCl (0.22 ml) was added to the solution under ice-cooling and the resulting mixture was stirred at the same temperature for 20 minutes. After adjusting to pH 7 with 10% NaOH solution, the insoluble material was filtered. To the neutral filtrate 2-oxo-2-(2-tritylaminothiazol-4-yl)acetic acid (331 mg) was added and the mixture was stirred for 1.5 hours at room temperature. The solvent was evaporated to give a residue, which was dissolved in a mixture of ethyl acetate and water. The resulting mixture was adjusted to pH 8 with satd $NaHCO_3$ solution. The separated aq layer was acidified to pH 2 with 10% HCl and extracted with ethyl acetate. After evaporation, **6g** (350 mg) was obtained. SI-MS *m/z* 700 (MH^+). ^{1}H NMR (90 MHz, $CDCl_3 + CD_3OD$) δ 3.82 (3H, s, OCH_3), 5.28 (2H, s, CH_2), 5.31 (2H, s, CH_2), 6.70 (1H, s, 5-H of thiazole).

p-Methoxybenzyl 7-[(*Z*)-2-(Methoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylate (**7a**)

To a solution of **5** (811 mg) in DMF (10 ml) were added **6a** (870 mg), DCC (445 mg) and HOBT (292 mg). After stirring for 2 hours at room temperature, the solution was concentrated. The residue was dissolved in EtOAc and the solution was washed with satd NaCl, dried over anhydr Na_2SO_4 and concentrated. The solid was chromatographed on silica gel with chloroform to give **7a** (1.43 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (1H, m, 4-Hb of isoxazolidine), 2.53 (1H, m, 3-Hb of isoxazolidine), 2.67 (3H, s, NCH_3), 2.82 (1H, m, 4-Ha of isoxazolidine), 3.27 (1H, m, 3-Ha of isoxazolidine), 3.64 (1H, d, J=19 Hz, 2-Hb), 3.81 (3H, s, $ArOCH_3$), 3.82 (1H, d, J=19 Hz, 2-Ha), 4.08 (3H, s, $NOCH_3$), 5.00 (1H, d, J=5 Hz, 6-H), 5.17 (2H, s, CO_2CH_2Ar), 5.28 (1H, br t, 3'-H), 5.89 (1H, dd, J=5 and 9 Hz, 7-H) and 6.74 (1H, s, 5-H of thiazole).

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylic Acid (**8a**)

To a solution of **7a** (150 mg) in anisole (0.15 ml) was added TFA (1.5 ml) under ice-cooling. After stirring for 1 hour at 5°C, isopropyl ether (20 ml) was added to the reaction solution. The solvent was removed *in vacuo* and the residue was triturated with isopropyl ether. The insoluble solid was dissolved in 50% aq formic acid (3 ml). The solution was warmed at 50°C for 1 hour. After concentration, the residue was washed with EtOAc and dissolved in water (1.5 ml). The pH of aq solution was adjusted to 7.5 with aq $NaHCO_3$ solution. The resulting aq solution was chromatographed on Amberlite XAD-2 with elution of water and active fractions were collected and lyophilized to give **8a** sodium salt (55 mg). FAB-MS *m/z* 491 (MH^+). ^{1}H NMR (400 MHz, D_2O, 40°C) δ 2.74 (1.8H, s, NCH_3), 2.84 (1.2H, s, NCH_3), 3.38 (0.6H, d, J=18 Hz, 2-Hb), 3.47 (0.4H, d, J=18 Hz, 2-Hb), 3.58 (0.6H, d, J=18 Hz, 2-Ha), 3.61 (0.4H, d, J=18 Hz, 2-Ha), 4.01 (3H, s, OCH_3), 5.03 (0.4H, t, J=8 Hz, 3'-H), 5.26 (1H, d, J=5 Hz, 6-H), 5.30 (0.6H, t, J=8 Hz, 3'-H), 5.82 (0.6H, d, J=5 Hz, 7-H), 5.83 (0.4H, d, J=5 Hz, 7-H), 7.04 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3314, 1767, 1669, 1607, 1534, 1387 and 1038.

p-Methoxybenzyl 7-[(*Z*)-2-(Methoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylate Iodide (**9a**)

To a solution of **7a** (83 mg) in methanol (2 ml) was added iodomethane (60 mg). The solution was allowed to stand for 12 hours at room temperature and concentrated to give iodide **9a** (96 mg). FD-MS *m/z* 845 ($(M-I)^+$).

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic Acid (**10a**)

Deblocking of **9a** gave **10a** (29 mg) by a similar procedure used for **8a**. FAB-MS *m/z* 483 (MH^+). ^{1}H NMR (400 MHz, D_2O) δ 2.77 and 2.91 (each 1H, m, 4-H of isoxazolidine), 3.49 (1H, d, J=18 Hz, 2-Hb), 3.61 and 3.62 (each 3H, s, $N^+(CH_3)_2$), 3.64 (1H, d, J=18 Hz, 2-Ha), 4.01 (3H, s, OCH_3), 4.23 (2H, m,

3-H of isoxazolidine), 5.28 (1H, d, $J=5$ Hz, 6-H), 5.69 (1H, dd, $J=6.5$ and 9.5 Hz, 3'-H), 5.85 (1H, d, $J=5$ Hz, 7-H) and 7.03 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3210, 2938, 1773, 1665, 1617, 1534, 1464, 1379, 1341 and 1036.

Analogs

Following compounds were prepared by the similar procedure as described above. 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylic acid (**8b**): FAB-MS *m/z* 477 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.79 (1.8H, s, NCH_3), 2.89 (1.2H, s, NCH_3), 3.38 (0.6H, d, $J=18$ Hz, 2-Hb), 3.47 (0.4H, d, $J=18$ Hz, 2-Hb), 3.59 (0.6H, d, $J=18$ Hz, 2-Ha), 3.62 (0.4H, d, $J=18$ Hz, 2-Ha), 5.08 (0.4H, t, $J=8$ Hz, 3'-H), 5.27 (1H, d, $J=5$ Hz, 6-H), 5.33 (0.6H, t, $J=8$ Hz, 3'-H), 5.85 (0.6H, d, $J=5$ Hz, 7-H), 5.86 (0.4H, d, $J=5$ Hz, 7-H), 7.02 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3310, 1767, 1607, 1534, 1456, 1389, 1339, 1289, 1186, 1046 and 995.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-((carboxymethoxy)imino)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carbocylic acid (**8c**): FAB-MS *m/z* 557 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.67 (1.8H, s, NCH_3), 2.74 (1.2H, s, NCH_3), 3.36 (0.6H, d, $J=18$ Hz, 2-Hb), 3.45 (0.4H, d, $J=18$ Hz, 2-Hb), 3.55 (0.6H, d, $J=18$ Hz, 2-Ha), 3.58 (0.4H, d, $J=18$ Hz, 2-Ha), 4.58 (2H, s, OCH_2CO_2), 4.96 (0.4H, t, $J=8$ Hz, 3'-H), 5.25 (1H, d, $J=5$ Hz, 6-H), 5.26 (0.6H, t, $J=8$ Hz, 3'-H), 5.84 (0.6H, d, $J=5$ Hz, 7-H), 5.85 (0.4H, d, $J=5$ Hz, 7-H) and 7.07 (1H, s, 5-H of thiazole). IR (KBr, cm^{-1}) 3411, 1767, 1601, 1534, 1395, 1319 and 1040.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(((*S*)-1-carboxyethoxy)imino)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylic acid (**8d**): FAB-MS *m/z* 571 (MH^+). ^1H NMR (400 MHz, D_2O) δ 1.47 (1.8H, d, $J=7$ Hz, $CHCH_3$), 1.48 (1.2H, d, $J=7$ Hz, $CHCH_3$), 2.66 (1.8H, s, NCH_3), 2.73 (1.2H, s, NCH_3), 3.36 (0.6H, d, $J=18$ Hz, 2-Hb), 3.46 (0.4H, d, $J=18$ Hz, 2-Hb), 3.56 (0.6H, d, $J=18$ Hz, 2-Ha), 3.59 (0.4H, d, $J=18$ Hz, 2-Ha), 4.66 (1H, q, $J=7$ Hz, $CHCH_3$), 4.96 (0.4H, t, $J=8$ Hz, 3'-H), 5.26 (1H, d, $J=5$ Hz, 6-H), 5.27 (0.6H, t, $J=8$ Hz, 3'-H), 5.84 (0.6H, d, $J=5$ Hz, 7-H), 5.85 (0.4H, d, $J=5$ Hz, 7-H) and 7.04 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3420, 1767, 1601, 1534, 1397, 1202 and 1032.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-((2-carboxy-2-propoxy)imino)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylic acid (**8e**): FAB-MS *m/z* 585 (MH^+). ^1H NMR (270 MHz, D_2O) δ 1.49 and 1.51 (each 3H, s, $OC(CH_3)_2$), 2.65 (1.8H, s, NCH_3), 2.72 (1.2H, s, NCH_3), 3.35 (0.6H, d, $J=18$ Hz, 2-Hb), 3.44 (0.4H, d, $J=18$ Hz, 2-Hb), 3.55 (0.6H, d, $J=18$ Hz, 2-Ha), 3.58 (0.4H, d, $J=18$ Hz, 2-Ha), 4.95 (0.4H, t, $J=8$ Hz, 3'-H), 5.24 (1H, d, $J=5$ Hz, 6-H), 5.25 (0.6H, t, $J=8$ Hz, 3'-H), 5.82 (0.6H, d, $J=5$ Hz, 7-H), 5.83 (0.4H, d, $J=5$ Hz, 7-H) and 7.00 (1H, s, 5-H of thiazole).

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(((1,3-dihydroxy-4-pyridon-6-yl)methoxy)imino)acetamido]-3-[(*S*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylic acid (**8f**): FAB-MS *m/z* 616 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.66 (1.8H, s, NCH_3), 2.74 (1.2H, s, NCH_3), 3.10 (0.6H, d, $J=18$ Hz, 2-Hb), 3.18 (0.4H, d, $J=18$ Hz, 2-Hb), 3.44 (0.6H, d, $J=18$ Hz, 2-Ha), 3.47 (0.4H, d, $J=18$ Hz, 2-Ha), 4.92 (0.4H, t, $J=8$ Hz, 3'-H), 5.15 (1H, d, $J=5$ Hz, 6-H), 5.22 (1H, dd, $J=1.5$ and 12 Hz, Hb of OCH_2Ar), 5.23 (0.6H, t, $J=8$ Hz, 3'-H), 5.36 (1H, d, $J=12$ Hz, Ha of OCH_2Ar), 5.77 (0.6H, d, $J=5$ Hz, 7-H), 5.78 (0.4H, d, $J=5$ Hz, 7-H), 6.73 (1H, s, 2-H of pyridone), 7.06 (1H, s, 5-H of thiazole) and 7.66 (1H, d, $J=1.5$ Hz, 5-H of pyridone).

7-[(*Z*)-2-((2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**10b**): FAB-MS *m/z* 469 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.76 and 2.91 (each 1H, m, 4-H of isoxazolidine), 3.49 (1H, d, $J=18$ Hz, 2-Hb), 3.61 and 3.62 (each 3H, s, $N^+(CH_3)_2$), 3.64 (1H, d, $J=18$ Hz, 2-Ha), 4.23 (2H, m, 3-H of isoxazolidine), 5.28 (1H, d, $J=5$ Hz, 6-H), 5.68 (1H, dd, $J=6.5$ and 10 Hz, 5-H of isoxazolidine), 5.87 (1H, d, $J=5$ Hz, 7-H) and 7.00 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3316, 1773, 1617, 1534, 1458, 1381, 1341, 1180, 1041 and 988.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-((carboxymethoxy)imino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**10c**): FAB-MS *m/z* 549 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.78 and 2.91 (each 1H, m, 4-H of isoxazolidine), 3.48 (1H, d, $J=18$ Hz, 2-Hb), 3.61 and 3.62 (each 3H, s, $N^+(CH_3)_2$), 3.63 (1H, d, $J=18$ Hz, 2-Ha), 4.23 (2H, m, 3-H of isoxazolidine), 4.59 (2H, s, OCH_2CO_2), 5.27 (1H, d, $J=5$ Hz, 6-H), 5.69 (1H, dd, $J=6$ and 9.5 Hz, 3'-H), 5.88 (1H, d, $J=5$ Hz, 7-H) and 7.06 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3418, 1775, 1609, 1532, 1387, 1318 and 1034.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(((*S*)-1-carboxyethoxy)imino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**10d**): FAB-MS *m/z* 563 (MH^+). ^1H NMR (400 MHz,

D_2O) δ 1.49 (3H, d, J=7 Hz, $CHCH_3$), 2.79 and 2.93 (each 1H, m, 4-H of isoxazolidine), 3.49 (1H, d, J=18 Hz, 2-Hb), 3.61 and 3.62 (each 3H, s, $N^+(CH_3)_2$), 3.63 (1H, d, J=18 Hz, 2-Ha), 4.23 (2H, m, 3-H of isoxazolidine), 4.68 (1H, q, J=7 Hz, $CHCH_3$), 5.29 (1H, d, J=5 Hz, 6-H), 5.70 (1H, dd, J=6 and 9.5 Hz, 3'-H), 5.89 (1H, d, J=5 Hz, 7-H) and 7.04 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3374, 1775, 1601, 1534, 1459, 1387 and 1032.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-((2-carboxy-2-propoxy)imino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**10e**): FAB-MS m/z 577 (MH^+). ^1H NMR (400 MHz, D_2O) δ 1.51 and 1.53 (each 3H, s, $C(CH_3)_2$), 2.78 and 2.92 (each 1H, m, 4-H isoxazolidine), 3.49 (1H, d, J=18 Hz, 2-Hb), 3.61 and 3.62 (each 3H, s, $N^+(CH_3)_2$), 3.63 (1H, d, J=18 Hz, 2-Ha), 4.23 (2H, m, 3-H of isoxazolidine), 5.28 (1H, d, J=5 Hz, 6-H), 5.69 (1H, dd, J=6 and 9.5 Hz, 3'-H), 5.87 (1H, d, J=5 Hz, 7-H) and 7.00 (1H, s, 5-H of thiazole).

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(((1,3-dihydroxy-4-pyridon-6-yl)methoxy)imino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**10f**): FAB-MS m/z 608 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.73 and 2.91 (each 1H, m, 4-H of isoxazolidine), 3.14 (1H, d, J=18 Hz, 2-Hb), 3.51 (1H, d, J=18 Hz, 2-Ha), 3.61 and 3.63 (each 3H, s, $N^+(CH_3)_2$), 4.15~4.33 (2H, m, 3-H of isoxazolidine), 5.16 (1H, d, J=5 Hz, 6-H), 5.24 and 5.36 (each 1H, d, J=12 Hz, OCH_2Ar), 5.66 (1H, dd, J=5 and 9 Hz, 3'-H), 5.80 (1H, d, J=5 Hz, 7-H), 6.79 (1H, s, 2-H of pyridone), 7.06 (1H, s, 5-H of thiazole) and 7.70 (1H, s, 5-H of pyridone). IR (KBr) cm^{-1} 3393, 1769, 1618, 1534, 1387, 1177 and 1127.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(((1-carboxy-3-hydroxyphen-4-yl)methoxy)imino)acetamido]-3-[(*S*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**10g**): FAB-MS m/z 641 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.63 and 2.91 (each 1H, m, 4-H of isoxazolidine), 2.88 (1H, d, J=18 Hz, 2-Hb), 3.36 (1H, d, J=18 Hz, 2-Ha), 3.60 and 3.64 (each 3H, s, $N^+(CH_3)_2$), 4.22 and 4.28 (each 1H, m, 3-H of isoxazolidine), 5.07 (1H, d, J=5 Hz, 6-H), 5.28 and 5.37 (each 1H, d, J=10.5 Hz, CH_2Ar), 5.62 (1H, dd, J=6 and 9.5 Hz, 3'-H), 5.73 (1H, d, J=5 Hz, 7-H) and 7.03 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3318, 1767, 1613, 1539, 1385, 1291, 1183, 1265 and 1015.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(*R*)-2-methylisoxazolidin-5-yl]-3-cephem-4-carboxylic acid (**11**): FAB-MS m/z 491 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.73 (1.8H, s, NCH_3), 2.80 (1.2H, s, NCH_3), 3.46 (0.6H, d, J=18 Hz, 2-Hb), 3.53 (0.4H, d, J=18 Hz, 2-Hb), 3.66 (0.6H, d, J=18 Hz, 2-Ha), 3.72 (0.4H, d, J=18 Hz, 2-Ha), 4.01 (3H, s, OCH_3), 5.00 (0.4H, t, J=8 Hz, 3'-H), 5.24 (0.6H, d, J=5 Hz, 6-H), 5.25 (0.4H, d, J=5 Hz, 6-H), 5.31 (0.6H, t, J=8 Hz, 3'-H), 5.81 (1H, d, J=5 Hz, 7-H) and 7.04 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3314, 2942, 1765, 1671, 1607, 1534, 1389, 1339, 1291, 1119 and 1038.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(*R*)-2,2-dimethylisoxazolidinium-5-yl]-3-cephem-4-carboxylic acid (**12**): FAB-MS m/z 483 (MH^+). ^1H NMR (400 MHz, D_2O) δ 2.76 and 2.85 (each 1H, m, 4-H of isoxazolidine), 3.46 (1H, d, J=17 Hz, 2-Hb), 3.62 and 3.64 (each 3H, s, $N^+(CH_3)_2$), 3.75 (1H, d, J=17 Hz, 2-Ha), 4.01 (3H, s, OCH_3), 4.23 (2H, m, 3-H of isoxazolidine), 5.28 (1H, d, J=5 Hz, 6-H), 5.63 (1H, dd, J=6 and 10 Hz, 3'-H), 5.88 (1H, d, J=5 Hz, 7-H) and 7.04 (1H, s, 5-H of thiazole). IR (KBr) cm^{-1} 3306, 1775, 1617, 1534, 1381, 1208, 1179 and 1036.

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