ORALLY ACTIVE CEPHALOSPORINS

III. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NEW 3-HETEROCYCLICTHIOMETHYLTHIO-7β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-3-CEPHEM-4-CARBOXYLIC ACIDS

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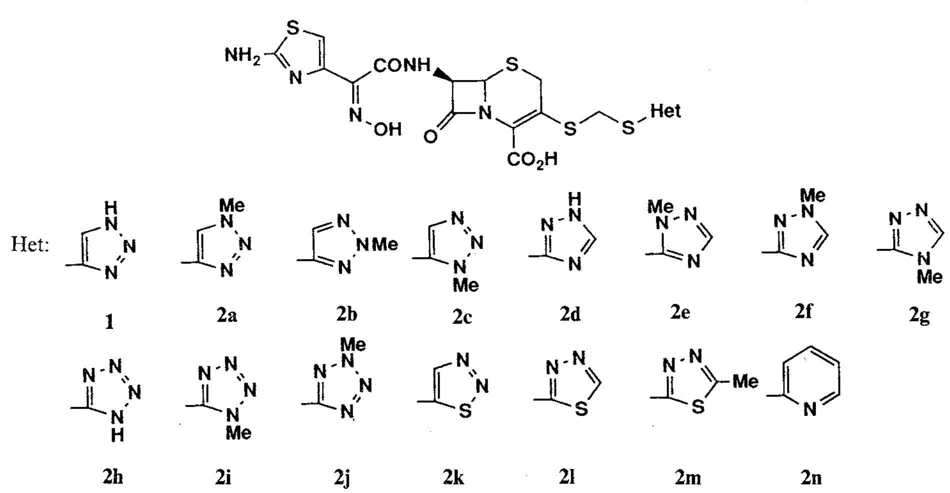
3-Heterocyclicthiomethylthio-7β-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cephem-4-carboxylic acids (**2**) were synthesized. Their antibacterial activity and oral absorbability were much influenced by the structure of heteroaromatic moiety in the side chain at the 3-position of a cephem nucleus. In this cephalosporin series, 3-thiadiazolylthiomethylthiocephalosporins (**2k**, **2l** and **2m**) exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacteria, whereas 3-(2-methyl-1,2,3-triazol-4-yl)thiomethylthiocephalosporin (**2b**) and 3-(pyridin-2-yl)thiomethylthiocephalosporin (**2n**) showed better oral absorption in mice than the other cephalosporins prepared. The structure-activity relationships of **2** are presented.

In our preceding paper,[1] we have reported on the synthesis, the antibacterial activity and the oral absorbability of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]cephalosporins with 1,2,3-triazole in the C-3 side chain. Among these compounds 3-(1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic acid (**1**) was selected for further evaluation, which showed well-balanced good antibacterial activity against Gram-positive and Gram-negative bacteria and attained high plasma level after oral administration in mice and monkeys. That study has also given us the finding that the spacer moiety between C-3 of the cephem nucleus and C-4′ of 1,2,3-triazole was a factor affecting the oral absorbability;

Fig. 1. 3-Heterocyclicthiomethylthiocephalosporins (**1** and **2a**～**2n**).



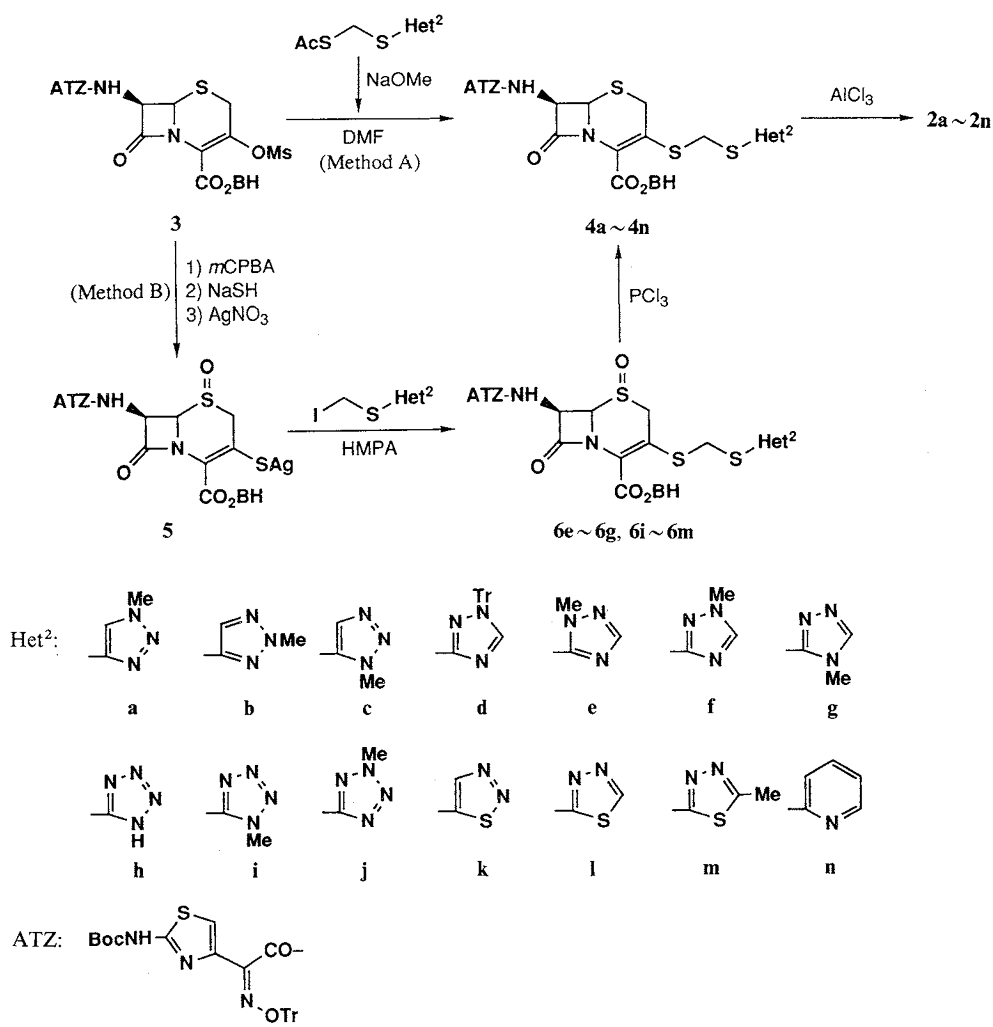
good oral absorbability was obtained when the spacer moiety was a three-atom chain, especially a thiomethylthio chain. In this paper, we wish to report the synthesis of **2** and the effects of the alteration of the heteroaromatic ring in the C-3 side chain of **1** on antibacterial activity and oral absorbability in mice.

Chemistry

Scheme 1 outlines two methods for the synthesis of the 3-heterocyclicthiomethylthiocephalosporins (**2**). The preparation of **2a**~**2d**, **2h** and **2n** was carried out by method A and that of **2e**~**2g** and **2i**~**2m** by method B.

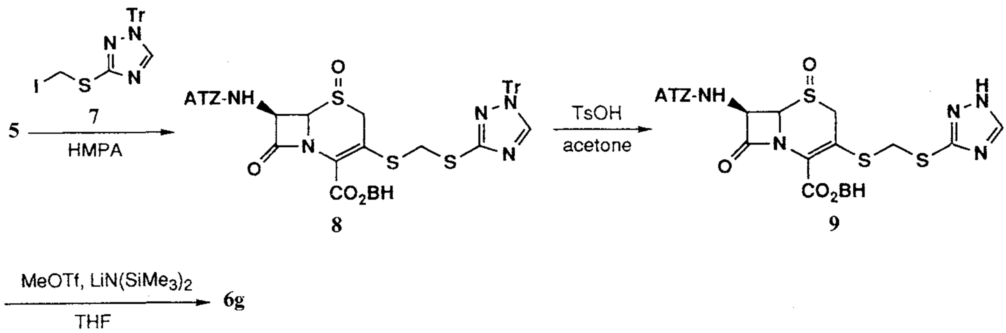
Method A, which had also been used for the synthesis of compound **1**, involves the coupling of 3-methanesulfonyloxycephalosporin[1] (**3**) with sodium thiolate, prepared *in situ* by methanolysis of the corresponding heterocyclicthiomethyl thioacetate, to give 3-substituted compound **4**. This method gave compound **4** in one step but in some cases could not give **4**, even in a poor yield, probably due to the

Scheme 1.



BH=diphenylmethyl, Tr=triphenylmethyl, *m*CPBA=*m*-chloroperbenzoic acid, HMPA=hexamethylphosphoric triamide.

Scheme 2.



instability of the intermediate sodium thiolate.[2)] An alternative procedure (method B), which does not include the thiolate intermediate, was suited for the synthesis of **4** in such cases. Method B is more general than method A and also applicable to the compounds prepared by method A. In method B, **3** was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) and treated successively with sodium hydrosulfide and silver nitrate to yield silver salt (**5**), which was reacted with heterocyclicthiomethyl iodide in hexamethylphosphoric triamide (HMPA) to afford 3-substituted sulfoxide (**6**). 3-(4-Methyl-1,2,4-triazol-3-yl)thiomethylthiocephalosporin (**6g**) was prepared by modified method B. As shown in Scheme 2, **5** was reacted with [1-trityl-1,2,4-triazol-3-yl]thiomethyl iodide (**7**) to give 3-substituted compound (**8**). The trityl group was removed with *p*-toluenesulfonic acid to yield compound **9**, which was methylated with methyl triflate to give compound **6g**. The reduction of sulfoxide (**6**) with phosphorus trichloride (PCl_3) gave compound **4**.

The preparation of thioacetates and iodides used here was shown in Scheme 3. Each isomers (**12**~**14**; **18**, **19**; **28**, **29**) were assigned by means of NOE or ^{13}C NMR study,[3)] or by comparison with authentic samples.

Finally the deprotection of **4** by the conventional method using aluminum chloride ($AlCl_3$) produced the desired cephalosporin derivatives (**2a**~**2n**).

Antibacterial Activity and Oral Absorption

The *in vitro* antibacterial activity of the new cephalosporins (**2**) against selected Gram-positive and Gram-negative bacteria is shown in Table 1. Their plasma levels and urinary recovery after oral administration (40 mg/kg) to mice are summarized in Table 2. Also shown is their relative bioavailability which was calculated according to the following equation:

$$\text{relative bioavailability } (\%) = \frac{\text{urinary recovery after po dosage}}{\text{urinary recovery after sc dosage}} \times 100$$

and we used this bioavailability and plasma levels as measures of gastrointestinal absorption.

Most of the new cephalosporins exhibited potent activity against the Gram-positive and Gram-negative bacteria except *Pseudomonas aeruginosa* ATCC 25619, irrespective of the heteroaromatic ring. Derivatives with thiadiazole in the C-3 side chain (**2k**~**2m**) showed higher activity against a wide range of bacteria than the other cephalosporins prepared, including compound **1**. Compounds **2k** and **2l** showed the most potent activity against Gram-positive bacteria including *Staphylococcus aureus* SR3131 (MRSA) among all of the compounds tested.

Compounds (**2b** and **2n**) having 2-methyl-1,2,3-triazole or pyridine in the C-3 side chain, showed good

Scheme 3.

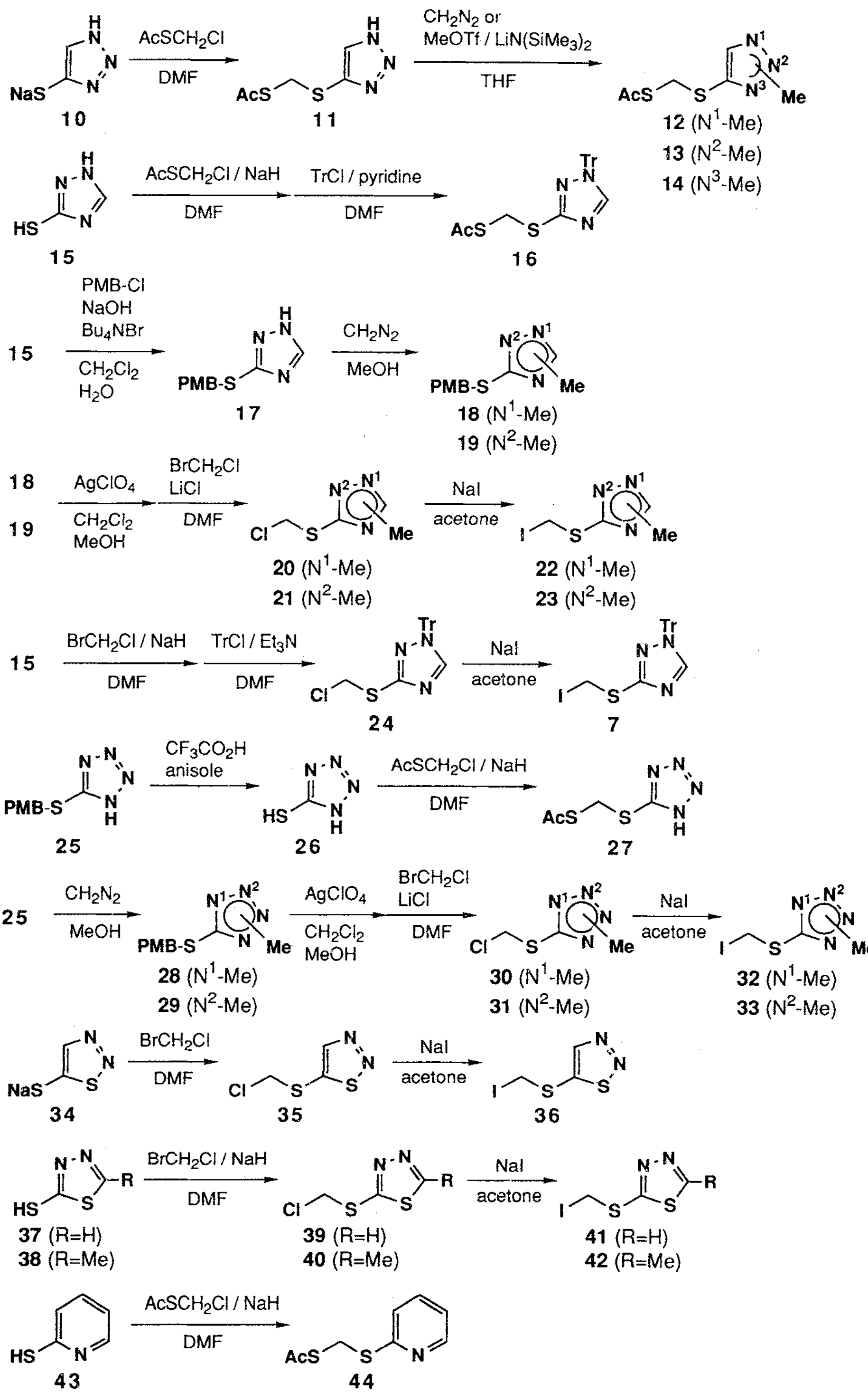

AcSCH2Cl
DMF
10
11
CH2N2 or
MeOTf / LiN(SiMe3)2
THF
12 (N1-Me)
13 (N2-Me)
14 (N3-Me)
AcSCH2Cl / NaH
DMF
TrCl / pyridine
DMF
15
16
PMB-Cl
NaOH
Bu4NBr
CH2Cl2
H2O
17
CH2N2
MeOH
18 (N1-Me)
19 (N2-Me)
AgClO4
CH2Cl2
MeOH
BrCH2Cl
LiCl
DMF
20 (N1-Me)
21 (N2-Me)
NaI
acetone
22 (N1-Me)
23 (N2-Me)
BrCH2Cl / NaH
DMF
TrCl / Et3N
DMF
24
7
CF3CO2H
anisole
25
26
27
28 (N1-Me)
29 (N2-Me)
30 (N1-Me)
31 (N2-Me)
32 (N1-Me)
33 (N2-Me)
BrCH2Cl
34
35
36
37 (R=H)
38 (R=Me)
39 (R=H)
40 (R=Me)
41 (R=H)
42 (R=Me)
43
44

Table 1. *In vitro* antibacterial activity of cephalosporins (**2a**~**2n** and **1**).

Organism	MIC (μg/ml)							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
Staphylococcus aureus FDA 209P JC-1	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.4
S. aureus Smith	0.2	0.2	0.1	0.4	0.2	0.4	0.4	0.8
S. aureus SR3131	6.3	12.5	3.1	3.1	3.1	12.5	12.5	12.5
S. epidermidis ATCC 14990	0.2	0.2	0.1	0.2	0.2	0.4	0.2	0.8
Streptococcus pyogenes C-203	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.05
S. pneumoniae Type 1	0.02	0.02	0.01	0.02	0.02	0.02	0.02	0.1
Escherichia coli H	0.1	0.2	0.05	0.05	0.1	0.1	0.05	0.05
E. coli NIHJ JC-2	0.4	3.1	0.2	0.2	0.8	0.8	0.1	0.4
E. coli EC-14	0.2	0.8	0.1	0.1	0.2	0.4	0.05	0.1
E. coli SR377	0.8	3.1	0.4	0.8	0.8	3.1	0.4	3.1
Klebsiella pneumoniae SR1	0.2	0.8	0.1	0.05	0.2	0.2	0.05	0.05
Proteus mirabilis PR-4	0.1	0.4	0.05	0.05	0.1	0.1	0.05	0.02
P. vulgalis CN-329	0.4	0.2	0.05	0.1	0.2	0.8	0.2	0.2
Morganella morganii SR9	0.2	0.8	0.1	0.2	0.4	0.8	0.1	0.4
Enterobacter cloacae SR233	0.8	3.1	0.4	0.8	0.8	1.6	0.4	12.5
Serratia marcescens ATCC 13880	3.1	12.5	1.6	3.1	6.3	12.5	3.1	12.5
Pseudomonas aeruginosa ATCC 25619	>100	>100	>100	>100	>100	>100	>100	>100

Organism	MIC (μg/ml)						
	2i	**2j**	**2k**	**2l**	**2m**	**2n**	**1**
Staphylococcus aureus FDA 209P JC-1	0.2	0.2	0.1	0.1	0.1	0.05	0.2
S. aureus Smith	0.2	0.4	0.1	0.1	0.2	0.2	0.2
S. aureus SR3131	6.3	6.3	1.6	1.6	3.1	3.1	12.5
S. epidermidis ATCC 14990	0.2	0.2	0.1	0.1	0.2	0.1	0.2
Streptococcus pyogenes C-203	0.006	0.006	<0.003	<0.003	0.006	0.006	0.006
S. pneumoniae Type 1	0.02	0.02	0.01	0.01	0.02	0.01	0.02
Escherichia coli H	0.05	0.2	0.05	0.02	0.1	0.2	0.05
E. coli NIHJ JC-2	0.4	1.6	0.4	0.2	0.8	1.6	0.2
E. coli EC-14	0.1	0.8	0.2	0.1	0.4	0.8	0.1
E. coli SR377	0.4	1.6	0.4	0.4	0.8	1.6	1.6
Klebsiella pneumoniae SR1	0.1	0.4	0.05	0.05	0.2	0.4	0.1
Proteus mirabilis PR-4	0.05	0.1	0.05	0.05	0.1	0.2	0.05
P. vulgalis CN-329	0.2	0.4	0.1	0.1	0.1	0.1	0.2
Morganella morganii SR9	0.1	0.4	0.05	0.1	0.1	0.8	0.1
Enterobacter cloacae SR233	0.8	1.6	0.4	0.4	0.8	1.6	0.8
Serratia marcescens ATCC 13880	1.6	12.5	1.6	1.6	3.1	6.3	3.1
Pseudomonas aeruginosa ATCC 25619	>100	>100	>100	>100	>100	>100	>100

oral absorbability in mice as well as **1** but their plasma levels did not reach the level of **1**. All of the other compounds exhibited only a limited absorption. The phenomenon that replacement of 1,2,3-triazole in the C-3 side chain with other heteroaromatics decreased oral absorbability, had also been observed in the case of cefatrizine and its congeners.[4,5] Furthermore, two of the compounds possessing *N*-methyl-1,2,3-triazole or *N*-methyl-1,2,4-triazole in the C-3 side chain (**2b** or **2e**) were found to exhibit as good oral absorbability as the compounds possessing *N*-unsubstituted 1,2,3-triazole or 1,2,4-triazole (**1**

Table 2. Plasma levels, urinary recovery and oral bioavailability of cephalosporins (**2a**~**2n**, **1**) in mice after oral administration of 40 mg/kg.

Compound	Plasma level (μg/ml) 15 minutes	Plasma level (μg/ml) 120 minutes	Urinary recovery (%)	Relative bioavailability (%)	Compound	Plasma level (μg/ml) 15 minutes	Plasma level (μg/ml) 120 minutes	Urinary recovery (%)	Relative bioavailability (%)
2a	3.73	2.83	5.9	17	**2i**	0.74	0.30	2.1	6.6
2b	17.2	6.10	8.0	46	**2j**	2.04	0.70	1.8	8.3
2c	1.82	0.73	1.5	4.0	**2k**	1.86	0.67	2.7	12
2d	4.78	2.81	5.4	17	**2l**	3.34	0.87	3.4	13
2e	3.36	1.28	9.4	24	**2m**	1.34	0.31	3.5	13
2f	0.90	0.76	1.5	6.9	**2n**	18.7	12.8	3.5	73
2g	0.78	0.38	1.2	3.8	**1**	29.6	51.3	5.5	36
2h	0.80	2.79	0.6	2.5					

Mice: ICR-strain, 6-week-old male, n = 5.

The urinary samples were collected over 2 hours and the relative bioavailability was calculated from the urinary recovery over 2 hours.

or **2d**), but other *N*-methylated derivatives (**2a**, **2c** or **2f**, **2g**) showed lower oral absorbability.

Experimental

MP was determined with a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were taken on a Jasco IR-700 spectrometer. ^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR-200 NMR spectrometer using TMS or sodium 2,2-dimethyl-2-silapentan-5-sulfonate (in D_2O) as an internal standard. Mass spectra (EI-MS) was measured on a Hitachi M-68 mass spectrometer. The following abbreviations are used: s, singlet; d, doublet; m, multiplet; br, broad; ABq, AB quartet. All reactions under anhydrous conditions were carried out using anhydrous solvents dried over Molecular Sieves type 4A in a nitrogen atmosphere.

Determination of Antibacterial Activity

All the *in vitro* antibacterial activities are given as MIC in μg/ml required to prevent growth of the bacterial culture. MICs were determined by the serial agar dilution method (Sensitivity Disk Agar-N) after incubation at 37°C for 18~20 hours with an inoculum size of about 10^6 cells/ml.

Oral Absorption Study

Male ICR-strain mice aged 6 weeks weighing 24~30 g were used in groups of 5. The antibiotics were given to mice orally in a single dose of 40 mg/kg or subcutaneously in 20 mg/kg as a solution in dilute aqueous sodium bicarbonate. Plasma samples were collected at 0.25 and 2 hours respectively after dosing and urine specimens were collected over a period of 2 hours after dosing. The concentrations of the test compounds were determined by the Band Culture method[6] using *Escherichia coli* 7437 as a test organism and Trypto-soy agar as the test medium.

Method A: Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-(1-methyl-1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylate (4a)

A solution of **12** (392 mg, 1.93 mmol) in THF (2 ml) and DMF (6 ml) was cooled to −78°C and treated with a solution of sodium methoxide in MeOH (1.28 N, 1.33 ml). After the mixture was stirred at −78°C for 15 minutes, a solution of **3** (1.50 g, 1.54 mmol) in DMF (5 ml) was added dropwise to the above mixture. After being stirred at the same temperature for 50 minutes, the mixture was neutralized with 10% HCl, diluted with water and extracted with EtOAc. The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 3 : 2) to yield 1.43 g (90%) of **4a** as colorless froth.

Compounds **4b**~**4d**, **4h** and **4n** were similarly prepared from **3** with corresponding thioacetates (**13**,

Table 3. ^{1}H NMR and IR spectral data of **4a**~**4n**.

Compound No.	^{1}H NMR (Solvent, δ)	IR ($CHCl_3$) cm^{-1} (C=O)
4a	($CDCl_3$); 8.83 (1H, br s), 7.66 (1H, d, *J*=8.6 Hz), 7.50~7.15 (26H, m), 6.99 (1H, s), 6.93 (1H, s), 5.91 (1H, dd, *J*=4.7 and 8.6 Hz), 5.06 (1H, d, *J*=4.7 Hz), 4.08 (2H, s), 3.92 (3H, s), 3.51 and 3.35 (2H, ABq, *J*=16.8 Hz), 1.49 (9H, s)	1781, 1714, 1684
4b	($CDCl_3$); 8.85 (1H, br s), 7.61 (1H, d, *J*=8.3 Hz), 7.49 (1H, s), 7.45~7.15 (25H, m), 6.99 (1H, s), 6.90 (1H, s), 5.86 (1H, dd, *J*=4.9 and 8.3 Hz), 5.07 (1H, d, *J*=4.9 Hz), 4.10 (3H, s), 3.98 (2H, s), 3.43 and 3.32 (2H, ABq, *J*=16.8 Hz), 1.50 (9H, s)	1785, 1717, 1686
4c	($CDCl_3$-CD_3OD); 7.73 (1H, s), 7.50~7.15 (25H, m), 7.06 (1H, s), 6.96 (1H, s), 5.99 (1H, d, *J*=4.8 Hz), 5.12 (1H, d, *J*=4.8 Hz), 3.95 (3H, s), 3.94 and 3.87 (2H, ABq, *J*=13.7 Hz), 3.55 and 3.43 (2H, ABq, *J*=17.3 Hz), 1.52 (9H, s)	1784, 1714, 1683
4d	($CDCl_3$); 8.6~8.4 (1H, br s), 7.89 (1H, s), 7.55~7.05 (41H, m), 7.02 (1H, s), 6.94 (1H, s), 5.90 (1H, dd, *J*=4.9 and 8.5 Hz), 4.95 (1H, d, *J*=4.9 Hz), 4.17 (2H, s), 3.41 and 3.30 (2H, ABq, *J*=17.4 Hz), 1.50 (9H, s)	1781, 1715, 1683
4e	($CDCl_3$); 9.3~9.15 (1H, br s), 7.84 (1H, s), 7.83 (1H, d, *J*=8.6 Hz), 7.5~7.2 (25H, m), 6.95 (1H, s), 6.93 (1H, s), 5.91 (1H, dd, *J*=4.6 and 8.6 Hz), 5.01 (1H, d, *J*=4.6 Hz), 4.48 and 4.29 (2H, ABq, *J*=13.4 Hz), 3.69 (3H, s), 3.46 and 3.37 (2H, ABq, *J*=17.9 Hz), 1.49 (9H, s)	1790, 1724, 1690
4f	($CDCl_3$); 9.3~9.0 (1H, br s), 7.89 (1H, s), 7.77 (1H, d, *J*=8.2 Hz), 7.5~7.2 (25H, m), 7.00 (1H, s), 6.89 (1H, s), 5.85 (1H, dd, *J*=4.6 and 8.2 Hz), 5.05 (1H, d, *J*=4.6 Hz), 4.25 (2H, s), 3.76 (3H, s), 3.49 and 3.41 (2H, ABq, *J*=17.8 Hz), 1.50 (9H, s)	1790, 1725, 1690
4g	($CDCl_3$); 10.1~9.7 (1H, br s), 8.27 (1H, d, *J*=8.5 Hz), 8.05 (1H, s), 7.5~7.2 (25H, m), 6.95 (1H, s), 6.91 (1H, s), 5.94 (1H, dd, *J*=5.0 and 8.5 Hz), 5.04 (1H, d, *J*=5.0 Hz), 4.67 and 4.34 (2H, ABq, *J*=14.2 Hz), 3.56 and 3.43 (2H, ABq, *J*=17.2 Hz), 3.31 (3H, s), 1.46 (9H, s)	1789, 1723, 1689
4h	($CDCl_3$-CD_3OD); 7.50~7.15 (25H, m), 7.06 (1H, s), 6.95 (1H, s), 5.99 (1H, d, *J*=4.8 Hz), 5.10 (1H, d, *J*=4.8 Hz), 4.46 (2H, s), 3.71 and 3.58 (2H, ABq, *J*=17.6 Hz), 1.52 (9H, s)	1786, 1717, 1672
4i	($CDCl_3$-CD_3OD); 7.50~7.15 (25H, m), 7.05 (1H, s), 6.94 (1H, s), 6.02 (1H, d, *J*=5.0 Hz), 5.09 (1H, d, *J*=5.0 Hz), 4.56 (2H, s), 3.81 (3H, s), 3.73 and 3.57 (2H, ABq, *J*=17.6 Hz), 1.52 (9H, s)	1788, 1717, 1686
4j	($CDCl_3$); 8.9~8.7 (1H, br s), 7.57 (1H, d, *J*=8.2 Hz), 7.5~7.2 (25H, m), 6.98 (1H, s), 6.89 (1H, s), 5.85 (1H, dd, *J*=4.8 and 8.2 Hz), 5.07 (1H, d, *J*=4.8 Hz), 4.28 (2H, s), 4.25 (3H, s), 3.40 (2H, br s), 1.50 (9H, s)	1792, 1725, 1690
4k	($CDCl_3$-CD_3OD); 8.51 (1H, s), 7.50~7.15 (25H, m), 7.05 (1H, s), 6.99 (1H, s), 6.02 (1H, d, *J*=5.0 Hz), 5.13 (1H, d, *J*=5.0 Hz), 4.16 and 4.00 (2H, ABq, *J*=13.7 Hz), 3.67 and 3.51 (2H, ABq, *J*=17.6 Hz), 1.52 (9H, s)	1789, 1718, 1686
4l	($CDCl_3$); 8.97 (1H, s), 8.8~8.6 (1H, br s), 7.58 (1H, d, *J*=8.8 Hz), 7.5~7.2 (25H, m), 7.03 (1H, s), 6.97 (1H, s), 5.98 (1H, dd, *J*=4.8 and 8.8 Hz), 5.07 (1H, d, *J*=4.8 Hz), 4.58 and 4.53 (2H, ABq, *J*=13.7 Hz), 3.67 and 3.51 (2H, ABq, *J*=17.5 Hz), 1.50 (9H, s)	1787, 1719, 1690
4m	($CDCl_3$); 8.9~8.6 (1H, br s), 7.69 (1H, d, *J*=8.8 Hz), 7.5~7.2 (25H, m), 7.03 (1H, s), 6.97 (1H, s), 6.00 (1H, dd, *J*=4.8 and 8.8 Hz), 5.07 (1H, d, *J*=4.8 Hz), 4.50 (2H, s), 3.68 and 3.53 (2H, ABq, *J*=17.5 Hz), 2.69 (3H, s), 1.50 (9H, s)	1787, 1720, 1690
4n	($CDCl_3$); 8.55 (1H, br s), 8.41 (1H, ddd, *J*=1.0, 1.8 and 4.9 Hz), 7.53~7.11 (28H, m), 7.03 (1H, s), 7.01 (1H, ddd, *J*=1.0, 4.9 and 7.4 Hz), 6.90 (1H, s), 5.87 (1H, dd, *J*=4.9 and 8.6 Hz), 5.04 (1H, d, *J*=4.9 Hz), 4.45 (2H, s), 3.56 and 3.42 (2H, ABq, *J*=17.2 Hz), 1.51 (9H, s)	1784, 1717, 1686

14, **16**, **27** and **44**) according to the procedure described for **4a**. The spectral data of **4a**~**4d**, **4h** and **4n** are listed in Table 3.

Method B: Diphenylmethyl 7*β*-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-mercapto-3-cephem-4-carboxylate 1-Oxide Silver Salt (**5**)

A solution of **3** (20.0 g, 20.6 mmol) in methylene chloride (200 ml) was cooled to −30°C. *m*CPBA

(80%) (4.89 g, 22.7 mmol) was added to this solution. After being stirred at $-20\sim-30°C$ for 30 minutes, the mixture was diluted with methylene chloride, washed successively with 5% aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 5:1→3:1) to yield 18.6 g (91%) of diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-methanesulfonyloxy-3-cephem-4-carboxylate 1-oxide as pale brown froth: ^1H NMR ($CDCl_3$) δ 8.33 (1H, br s), 7.88 (1H, d, *J*=10 Hz), 7.50~7.15 (25H, m), 7.00 (2H, s), 6.31 (1H, dd, *J*=5.0 and 10.1 Hz), 4.55 (1H, d, *J*=5.0 Hz), 3.89 and 3.35 (2H, ABq, *J*=18.6 Hz), 2.74 (3H, s), 1.50 (9H, s); IR ($CHCl_3$) cm^{-1} 3400, 1806, 1725, 1687, 1543, 1510, 1493, 1368, 1154, 1045.

A solution of this sulfoxide (18.6 g, 18.8 mmol) in DMF (150 ml) was cooled to $-30°C$ and treated with sodium hydrosulfide (70%) (3.77 g, 47.1 mmol). After the mixture was stirred at $-20\sim-30°C$ for 1.5 hours, 10% HCl (15 ml) was added to the mixture. This mixture was diluted with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was dissolved in toluene and concentrated to yield 17.6 g (93%) of diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-mercapto-3-cephem-4-carboxylate 1-oxide which contained 8% of toluene: ^1H NMR ($CDCl_3$) δ 8.41 (1H, br s), 7.84 (1H, d, *J*=10.0 Hz), 7.61~7.15 (25H, m), 7.01 (1H, s), 6.90 (1H, s), 6.25 (1H, dd, *J*=4.8 and 10.0 Hz), 5.12 (1H, br s), 4.50 (1H, d, *J*=4.8 Hz), 3.67 and 3.27 (2H, ABq, *J*=18.4 Hz), 1.49 (9H, s); IR ($CHCl_3$) cm^{-1} 3396, 1799, 1715, 1686, 1543, 1509, 1493, 1445, 1383, 1369, 1040.

A solution of this mercaptan (92%) (17.5 g, 17.5 mmol) in THF (120 ml) was treated with an aqueous solution of silver nitrate (3.26 g, 19.2 mmol in 16 ml of water) under ice-cooling. After being stirred at ice-bath temperature for 30 minutes, the mixture was diluted with methylene chloride and water. The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4 and evaporated to give 19.7 g of dark yellow froth: Calculated purity of **5** was 92%.

Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)thiomethylthio-3-cephem-4-carboxylate 1-Oxide (**6e**)

A solution of **23** (1.47 g) in HMPA (3 ml) was added to a solution of **5** (92%) (3.37 g, 3.00 mmol) in HMPA (20 ml). After the mixture was stirred at room temperature for 3 hours, brine and EtOAc were added to the mixture and the resulting precipitate was filtered off. The organic layer was separated, washed with brine six times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 1:1) to yield 1.76 g (56%) of **6e** as pale brown froth.

Compounds **6f**, **6i~6m** and **8** were similarly prepared from **5** with corresponding iodides (**7**, **22**, **32**, **33**, **36**, **41** and **42**) according to the procedure described for **6e**. The spectral data of **6e**, **6f**, **6i~6m** and **8** are listed in Table 4.

Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-(1*H*-1,2,4-triazol-3-yl)thiomethylthio-3-cephem-4-carboxylate 1-Oxide (**9**)

A solution of **8** (11.3 g, 8.83 mmol) in acetone (60 ml) was treated with *p*-toluenesulfonic acid monohydrate (1.68 g, 8.83 mmol) under ice-cooling. After the mixture was stirred at room temperature for 4 hours, 5% aq $NaHCO_3$ and EtOAc were added to the mixture. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 1:1→1:2) to yield 2.84 g (31%) of **9** as brown froth: ^1H NMR ($CDCl_3$ - CD_3OD) δ 8.01 (1H, s), 7.4~7.15 (25H, m), 7.03 (1H, s), 6.89 (1H, s), 6.22 (1H, d, *J*=4.7 Hz), 4.62 (1H, d, *J*=4.7 Hz), 4.30 (2H, s), 4.06 and 3.58 (2H, ABq, *J*=17.8 Hz), 1.51 (9H, s); IR ($CHCl_3$) cm^{-1} 3380, 3200 (br), 1803, 1720, 1690, 1547, 1510, 1497, 1450, 1372, 1040.

Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-(4-methyl-4*H*-1,2,4-triazol-3-yl)thiomethylthio-3-cephem-4-carboxylate 1-Oxide (**6g**)

A solution of **9** (2.71 g, 2.61 mmol) in THF (50 ml) was treated with 1.0 M THF solution of lithium hexamethyldisilazane (2.9 ml) at $-78°C$. After the mixture was stirred at the same temperature for a few minutes, methyl triflate (0.33 ml, 2.92 mmol) was added to the mixture, which was stirred at $-78°C$ for

Table 4. ^{1}H NMR and IR spectral data of **6e**~**6g**, **6i**~**6m** and **8**.

Compound No.	^{1}H NMR (Solvent, δ)	IR ($CHCl_3$) cm^{-1} (C=O)
6e	($CDCl_3$); 8.59 (1H, br s), 8.02 (1H, d, J=10.0 Hz), 7.79 (1H, s), 7.5~7.2 (25H, m), 6.97 (1H, s), 6.96 (1H, s), 6.25 (1H, dd, J=4.8 and 10.0 Hz), 4.48 and 4.22 (2H, ABq, J=13.7 Hz), 4.38 (1H, d, J=4.8 Hz), 3.97 and 3.47 (2H, ABq, J=18.8 Hz), 3.66 (3H, s), 1.47 (9H, s)	1805, 1722, 1688
6f	($CDCl_3$); 8.66 (1H, br s), 8.02 (1H, d, J=9.8 Hz), 7.91 (1H, s), 7.55~7.20 (25H, m), 6.98 (1H, s), 6.93 (1H, s), 6.24 (1H, dd, J=4.8 and 9.8 Hz), 4.46 (1H, d, J=4.8 Hz), 4.28 (2H, s), 4.12 and 3.49 (2H, ABq, J=18.4 Hz), 3.76 (3H, s), 1.46 (9H, s)	1803, 1724, 1689
6g	($CDCl_3$-CD_3OD); 8.11 (1H, br s), 7.5~7.2 (25H, m), 7.01 (1H, s), 6.96 (1H, s), 6.26 (1H, d, J=4.8 Hz), 4.74 (1H, d, J=4.8 Hz), 4.70 and 4.12 (2H, ABq, J=14.6 Hz), 3.85 (2H, s), 3.31 (3H, s), 1.51 (9H, s)	1805, 1722, 1690
6i	($CDCl_3$); 8.48 (1H, br s), 7.73 (1H, d, J=10.2 Hz), 7.50~7.10 (25H, m), 7.00 (1H, s), 6.97 (1H, s), 6.27 (1H, dd, J=4.6 and 10.2 Hz), 4.50 (1H, d, J=4.6 Hz), 4.76 and 4.22 (2H, ABq, J=14.2 Hz), 3.89 and 3.73 (2H, ABq, J=17.6 Hz), 3.75 (3H, s), 1.48 (9H, s)	1802, 1718, 1686
6j	($CDCl_3$); 8.45 (1H, br s), 7.91 (1H, d, J=10.0 Hz), 7.5~7.2 (25H, m), 6.99 (1H, s), 6.95 (1H, s), 6.27 (1H, dd, J=4.8 and 10.0 Hz), 4.49 (1H, d, J=4.8 Hz), 4.41 and 4.24 (2H, ABq, J=13.9 Hz), 4.22 (3H, s), 4.02 and 3.50 (2H, ABq, J=17.9 Hz), 1.47 (9H, s)	1806, 1725, 1690
6k	($CDCl_3$); 8.47 (1H, s), 8.45 (1H, br s), 7.96 (1H, d, J=10.0 Hz), 7.50~7.15 (25H, m), 7.00 (1H, s), 6.98 (1H, s), 6.31 (1H, dd, J=4.8 and 10.0 Hz), 4.49 (1H, d, J=4.8 Hz), 4.09 and 3.91 (2H, ABq, J=14.1 Hz), 3.91 and 3.23 (2H, ABq, J=17.6 Hz), 1.48 (9H, s)	1804, 1718, 1690
6l	($CDCl_3$); 9.00 (1H, s), 8.7~8.45 (1H, br s), 7.86 (1H, d, J=10.1 Hz), 7.5~7.2 (25H, m), 7.00 (1H, s), 6.98 (1H, s), 6.27 (1H, dd, J=4.8 and 10.1 Hz), 4.84 and 4.29 (2H, ABq, J=14.2 Hz), 4.55 (1H, d, J=4.8 Hz), 3.98 and 3.74 (2H, ABq, J=17.9 Hz), 1.49 (9H, s)	1802, 1718, 1688
6m	($CDCl_3$); 8.6~8.4 (1H, br s), 7.89 (1H, d, J=10.2 Hz), 7.5~7.2 (25H, m), 7.00 (1H, s), 6.97 (1H, s), 6.28 (1H, dd, J=4.6 and 10.2 Hz), 4.75 and 4.23 (2H, ABq, J=14.2 Hz), 4.60 (1H, d, J=4.6 Hz), 3.97 and 3.76 (2H, ABq, J=18.2 Hz), 2.68 (3H, s), 1.49 (9H, s)	1802, 1718, 1686
8	($CDCl_3$); 8.30 (1H, br s), 8.04 (1H, d, J=10.1 Hz), 7.90 (1H, s), 7.5~7.05 (41H, m), 6.97 (1H, s), 6.19 (1H, dd, J=4.6 and 10.1 Hz), 4.22 and 4.16 (2H, ABq, J=13.7 Hz), 4.19 (1H, d, J=4.6 Hz), 3.82 and 3.19 (2H, ABq, J=18.5 Hz), 1.49 (9H, s)	1804, 1725, 1689

30 minutes. The reaction was quenched by 10% HCl (2.1 ml). The mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; EtOAc) to yield 730 mg (27%) of **6g** as pale brown froth. The spectral data of **6g** are listed in Table 4.

Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)thiomethylthio-3-cephem-4-carboxylate (**4e**)

A solution of **6e** (1.73 g, 1.64 mmol) in DMF (15 ml) was treated with phosphorus trichloride (0.41 ml, 4.08 mmol) at −20°C. After being stirred at the same temperature for 20 minutes, the mixture was poured into a cold mixture of 5% aq $NaHCO_3$ (*ca.* 42 ml) and EtOAc. The organic layer was separated, washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent: toluene - EtOAc, 2 : 1) to yield 1.60 g (94%) of **4e** as brown froth.

Compounds **4f**, **4g** and **4i**~**4m** were similarly prepared according to the procedure described for **4e**. The spectral data of **4e**~**4g** and **4i**~**4m** are listed in Table 3.

Table 5. ^{1}H NMR and IR spectral data of **2a**~**2n**.

Compound No.	^{1}H NMR (D_2O+$NaHCO_3$, δ)	IR (KBr) cm^{-1} (C=O)
2a	8.09 (1H, s), 6.99 (1H, s), 5.83 (1H, d, J=4.6 Hz), 5.24 (1H, d, J=4.6 Hz), 4.22 and 4.12 (2H, ABq, J=14.0 Hz), 4.11 (3H, s), 3.81 and 3.50 (2H, ABq, J=17.4 Hz)	1770, 1650
2b	7.84 (1H, s), 6.99 (1H, s), 5.82 (1H, d, J=4.8 Hz), 5.23 (1H, d, J=4.8 Hz), 4.25 and 4.18 (2H, ABq, J=13.7 Hz), 4.17 (3H, s), 3.80 and 3.52 (2H, ABq, J=17.3 Hz)	1765, 1660
2c	7.95 (1H, s), 6.98 (1H, s), 5.84 (1H, d, J=4.5 Hz), 5.23 (1H, d, J=4.5 Hz), 4.27 and 4.14 (2H, ABq, J=14.1 Hz), 4.08 (3H, s), 3.78 and 3.53 (2H, ABq, J=17.4 Hz)	1765, 1660
2d	8.40 (1H, s), 6.98 (1H, s), 5.83 (1H, d, J=4.3 Hz), 5.21 (1H, d, J=4.3 Hz), 4.42 (2H, s), 3.79 and 3.54 (2H, ABq, J=17.4 Hz)	1765, 1655
2e	8.03 (1H, s), 6.98 (1H, s), 5.83 (1H, d, J=4.8 Hz), 5.21 (1H, d, J=4.8 Hz), 4.50 and 4.44 (2H, ABq, J=14.1 Hz), 3.85 (3H, s), 3.81 and 3.54 (2H, ABq, J=17.4 Hz)	1765, 1655
2f	8.36 (1H, s), 6.99 (1H, s), 5.82 (1H, d, J=4.7 Hz), 5.24 (1H, d, J=4.7 Hz), 4.40 (2H, s), 3.89 (3H, s), 3.83 and 3.55 (2H, ABq, J=17.2 Hz)	1765, 1660
2g	8.50 (1H, s), 7.00 (1H, s), 5.83 (1H, d, J=4.9 Hz), 5.19 (1H, d, J=4.9 Hz), 4.50 and 4.35 (2H, ABq, J=13.4 Hz), 3.80 and 3.53 (2H, ABq, J=17.5 Hz), 3.69 (3H, s)	1767, 1655
2h	6.99 (1H, s), 5.83 (1H, d, J=4.6 Hz), 5.18 (1H, d, J=4.6 Hz), 4.43 and 4.38 (2H, ABq, J=13.7 Hz), 3.65 and 3.47 (2H, ABq, J=17.4 Hz)	1765, 1650
2i	6.98 (1H, s), 5.83 (1H, d, J=4.9 Hz), 5.24 (1H, d, J=4.9 Hz), 4.63 and 4.58 (2H, ABq, J=13.8 Hz), 4.00 (3H, s), 3.90 and 3.59 (2H, ABq, J=17.4 Hz)	1765, 1660
2j	6.98 (1H, s), 5.82 (1H, d, J=4.7 Hz), 5.26 (1H, d, J=4.7 Hz), 4.50 (2H, s), 4.36 (3H, s), 3.88 and 3.58 (2H, ABq, J=17.3 Hz)	1767, 1660
2k	8.76 (1H, s), 6.97 (1H, s), 5.83 (1H, d, J=4.7 Hz), 5.25 (1H, d, J=4.7 Hz), 4.48 and 4.37 (2H, ABq, J=14.1 Hz), 3.88 and 3.58 (2H, ABq, J=17.4 Hz)	1760, 1655
2l	9.41 (1H, s), 6.98 (1H, s), 5.83 (1H, d, J=4.7 Hz), 5.24 (1H, d, J=4.7 Hz), 4.64 and 4.57 (2H, ABq, J=14.1 Hz), 3.89 and 3.60 (2H, ABq, J=17.4 Hz)	1765, 1665
2m	6.97 (1H, s), 5.83 (1H, d, J=4.8 Hz), 5.23 (1H, d, J=4.8 Hz), 4.57 and 4.51 (2H, ABq, J=14.0 Hz), 3.87 and 3.58 (2H, ABq, J=17.4 Hz), 2.72 (3H, s)	1772, 1668
2n	8.39 (1H, br d, J=4.9 Hz), 7.74 (1H, ddd, J=1.6, 7.5 and 8.0 Hz), 7.46 (1H, br d, J=8.0 Hz), 7.23 (1H, ddd, J=0.8, 4.9 and 7.5 Hz), 6.96 (1H, s), 5.80 (1H, d, J=4.6 Hz), 5.16 (1H, d, J=4.6 Hz), 4.49 and 4.43 (2H, ABq, J=14.0 Hz), 3.78 and 3.55 (2H, ABq, J=17.2 Hz)	1760, 1665

Deprotection of **4**: General Procedure Illustrated with the Preparation of 7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic Acid (**2b**)

A solution of $AlCl_3$ (1.43 g, 10.8 mmol) in anisole (5 ml) was added dropwise to a solution of **4b** (1.39 g, 1.34 mmol) in anisole (5 ml) and nitromethane (20 ml) at $-30\sim-40$°C. After the mixture was stirred at the same temperature for an hour, 11 ml of 1 N HCl, water and EtOAc were added to the mixture. The aqueous layer was separated and the organic layer was re-extracted with water. The combined aqueous layer was chromatographed on an Diaion HP-20 column (eluent; methanol-water, 4:1). After the concentration, the resulting precipitate was collected by filtration, washed with EtOAc and dried *in vacuo* to give 534 mg (75%) of **2b** as pale yellow powder.

The spectral data of various derivatives **2a**~**2n** are listed in Table 5.

1*H*-1,2,3-Triazol-4-ylthiomethyl Thioacetate (**11**)

A suspension of **10** (purchased from Dynamit Nobel Aktiengesellschaft) (38.0 g, 0.31 mol) in DMF (150 ml) was treated with chloromethyl thioacetate[7] (37.4 g, 0.30 mol) at −20°C. After being stirred at room temperature for 2 hours, the mixture was poured into water, extracted with EtOAc. The organic layer was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting crystalline residue was washed with hexane and dried *in vacuo*. Recrystallization from ether gave 38.9 g (69%) of **11** as white crystals: MP 88~89°C; ^{1}H NMR ($CDCl_3$) δ 7.73 (1H, s), 6.3 (1H, br s), 4.37 (2H, s), 2.36 (3H, s); IR ($CHCl_3$) cm^{-1} 3430, 3152, 1693; MS *m/z* 189 (M^+).

Anal Calcd for $C_5H_7N_3OS_2$: C 31.73, H 3.73, N 22.20, S 33.88.

Found: C 31.65, H 3.69, N 22.44, S 33.62.

1-Methyl-1*H*-1,2,3-triazol-4-ylthiomethyl Thioacetate (**12**), 2-Methyl-2*H*-1,2,3-triazol-4-ylthiomethyl Thioacetate (**13**) and 1-Methyl-1*H*-1,2,3-triazol-5-ylthiomethyl Thioacetate (**14**)

Methylation of **11** with Diazomethane

A solution of **11** (5.80 g, 30.7 mmol) in THF (50 ml) was treated with an ether solution of diazomethane under ice-cooling. After being stirred at the same temperature for an hour, the mixture was concentrated. The resulting residue was purified by Lobar column chromatography (eluent; toluene - EtOAc, 10 : 1→1 : 1→1 : 2) to afford 306 mg (5%) of **12** as white crystals, 3.77 g (61%) of **13** as a colorless oil and 429 mg (7%) of **14** as white crystals.

Methylation of **11** with Methyl Triflate

A solution of **11** (6.00 g, 31.8 mmol) in THF (30 ml) was treated with 1.0 M THF solution of lithium hexamethyldisilazane (35 ml) at −78°C. A few minutes later, methyl triflate (4.0 ml, 35.3 mmol) was added to the mixture. After the mixture was stirred at −78°C for 2 hours, 26 ml of 10% HCl was added to the mixture, which was diluted with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by Lobar column chromatography (eluent; toluene - EtOAc, 1 : 2) to afford 884 mg (14%) of **12**, 175 mg (3%) of **13** and 2.22 g (34%) of **14**.

12: MP 71∼72°C; ^{1}H NMR ($CDCl_3$) δ 7.59 (1H, s), 4.33 (2H, s), 4.11 (3H, s), 2.35 (3H, s); IR ($CHCl_3$) cm^{-1} 1691, 1434, 1354; MS *m/z* 203 (M^+).

Anal Calcd for $C_6H_9N_3OS_2$: C 35.45, H 4.46, N 20.67, S 31.55.
Found: C 35.50, H 4.46, N 20.79, S 31.37.

13: ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, s), 4.30 (2H, s), 4.20 (3H, s), 2.35 (3H, s); IR ($CHCl_3$) cm^{-1} 1691, 1446, 1369; MS *m/z* 203 (M^+).

Anal Calcd for $C_6H_9N_3OS_2$: C 35.45, H 4.46, N 20.67, S 31.55.
Found: C 35.29, H 4.55, N 20.66, S 31.25.

14: MP 37∼38°C; ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, s), 4.13 (5H, s), 2.32 (3H, s); IR ($CHCl_3$) cm^{-1} 1698, 1429, 1355; MS *m/z* 203 (M^+).

Anal Calcd for $C_6H_9N_3OS_2$: C 35.45, H 4.46, N 20.67, S 31.55.
Found: C 35.42, H 4.51, N 20.81, S 31.37.

1-Triphenylmethyl-1*H*-1,2,4-triazol-3-ylthiomethyl Thioacetate (**16**)

A solution of **15** (2.23 g, 22.1 mmol) in DMF (30 ml) was treated with sodium hydride (60% in oil) (840 mg, 21.0 mmol) and stirred at room temperature for 10 minutes. After the mixture was cooled to −60°C, a solution of chloromethyl thioacetate[7] (2.50 g, 20.1 mmol) in DMF (5 ml) was added to the reaction mixture. After the mixture was stirred at −50∼−60°C for 20 minutes, trityl chloride (6.70 g, 24.0 mmol) and pyridine (1.94 ml, 24.0 mmol) were added to the mixture, which was stirred at ice-bath temperature for 28 hours. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 20 : 1) and crystallized from ether to yield 3.37 g (39%) of **16** as white crystals: MP 124∼125°C; ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, s), 7.4∼7.3 (9H, m), 7.2∼7.1 (6H, m), 4.50 (2H, s), 2.32 (3H, s); IR ($CHCl_3$) cm^{-1} 1690, 1490, 1472, 1444, 1383, 1352.

HRMS Calcd for $C_{24}H_{21}N_3OS_2$ (M^+): 431.1126.
Found: *m/z* 431.1108 (M^+).

3-*p*-Methoxybenzylthio-1*H*-1,2,4-triazole (**17**)

To a solution of **15** (10.1 g 0.10 mol) and *p*-methoxybenzyl chloride (17.2 g, 0.11 mol) in methylene chloride (50 ml), 1 N aq NaOH (105 ml) and tetra-*n*-butylammonium bromide (750 mg, 2.33 mmol) were added. After the mixture was stirred at room temperature for 16 hours, the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was crystallized from toluene to afford 16.7 g (76%) of **17** as white crystals: MP 100~101°C; ^{1}H NMR ($CDCl_3$) δ 8.13 (1H, s), 7.8~7.0 (1H, br s), 7.27~7.23 and 6.83~6.79 (4H, AA'BB'), 4.32 (2H, s), 3.77 (3H, s); IR ($CHCl_3$) cm^{-1} 3440, 3120 (br), 1611, 1512, 1485, 1465, 1441, 1302; MS *m/z* 221 (M^+).

Anal Calcd for $C_{10}H_{11}N_3OS$: C 54.28, H 5.01, N 18.99, S 14.49.
Found: C 54.26, H 5.09, N 18.86, S 14.49.

3-*p*-Methoxybenzylthio-1-methyl-1*H*-1,2,4-triazole(**18**) and 5-*p*-Methoxybenzylthio-1-methyl-1*H*-1,2,4-striazole (**19**)

Compound **17** was treated with diazomethane as described for the preparation of **12**~**14** to yield **18** and **19** as colorless oils.

18: ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.34~7.30 and 6.85~6.80 (4H, AA'BB'), 4.31 (2H, s), 3.87 (3H, s), 3.78 (3H, s); IR ($CHCl_3$) cm^{-1} 1612, 1512, 1465, 1440, 1421, 1356, 1302.

HRMS Calcd for $C_{11}H_{13}N_3OS$ (M^+): 235.0779.
Found: *m/z* 235.0791 (M^+).

19: ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, s), 7.24~7.19 and 6.84~6.80 (4H, AA'BB'), 4.34 (2H, s), 3.79 (3H, s), 3.63 (3H, s); IR ($CHCl_3$) cm^{-1} 1611, 1511, 1476, 1464, 1440, 1360, 1302.

HRMS Calcd for $C_{11}H_{13}N_3OS$ (M^+): 235.0779.
Found: *m/z* 235.0782 (M^+).

3-Chloromethylthio-1-methyl-1*H*-1,2,4-triazole (**20**)

A solution of **18** (3.55 g, 15.1 mmol) in methylene chloride (30 ml) and methanol (30 ml) was treated with silver perchlorate (90%) (4.17 g, 18.1 mmol). After being stirred at room temperature for 1.5 hours, the mixture was diluted with methanol. The precipitate was collected by filtration and dried *in vacuo*. This white solid was suspended in DMF (30 ml), and bromochloromethane (30 ml) and lithium chloride (98%) (1.96 g, 45.3 mmol) were added to the suspension, which was stirred at room temperature for 20 hours. Brine and EtOAc were added to the reaction mixture and filtered. The organic layer was separated, washed with brine three times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 2:1) to yield 1.05 g (43%) of **20** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.06 (1H, s), 5.21 (2H, s), 3.93 (3H, s); IR ($CHCl_3$) cm^{-1} 1509, 1471, 1424, 1392, 1359.

HRMS Calcd for $C_4H_6ClN_3S$ (M^+): 162.9971.
Found: *m/z* 162.9984 (M^+).

5-Chloromethylthio-1-methyl-1*H*-1,2,4-triazole (**21**)

Compound **21** was prepared from **19** as described for the preparation of **20**: ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, s), 5.19 (2H, s), 3.87 (3H, s); IR ($CHCl_3$) cm^{-1} 1479, 1395, 1360.

HRMS Calcd for $C_4H_6ClN_3S$ (M^+): 162.9971.
Found: *m/z* 162.9972 (M^+).

3-Iodomethylthio-1-methyl-1*H*-1,2,4-triazole (**22**)

A solution of **20** (981 mg, 6.00 mmol) in acetone (10 ml) was treated with sodium iodide (1.78 g, 12.0 mmol) and stirred at 50°C for 3 hours. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to afford 1.50 g of crude **22** as a yellow oil. This oil was employed for the reaction with silver salt **5** without purification: ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, s), 4.75 (2H, s), 3.94 (3H, s).

5-Iodomethylthio-1-methyl-1*H*-1,2,4-triazole (**23**)

Compound **23** was prepared from **21** as described for the preparation of **22**: ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, s), 4.71 (2H, s), 3.84 (3H, s).

3-Chloromethythio-1-triphenylmethyl-1*H*-1,2,4-triazole (**24**)

A solution of **15** (10.0 g, 99.0 mmol) in DMF (100 ml) was treated with sodium hydride (60% in oil) (3.96 g, 99.0 mmol) under ice-cooling. After the mixture was stirred at the same temperature for 10 minutes, bromochloromethane (100 ml) was added to the mixture, which was stirred at room temperature for 15 hours. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was dissolved in DMF (100 ml) and cooled to ice-bath temperature. Trityl chloride (27.6 g, 99.0 mmol) and triethylamine (13.8 ml, 99.0 mmol) were added to the solution, which was stirred at the same temperature for 30 minutes. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was crystallized from ether to give 20.2 g (52%) of **24** as white crystals: MP 121～122°C; ^{1}H NMR ($CDCl_3$) δ 7.95 (1H, s), 7.4～7.3 (9H, m), 7.2～7.1 (6H, m), 5.18 (2H, s); IR ($CHCl_3$) cm^{-1} 1599, 1492, 1472, 1445, 1389, 1365, 1353, 1325.

HRMS Calcd for $C_{22}H_{18}ClN_3S$ (M^+): 391.0910.
Found: *m/z* 391.0885 (M^+).

3-Iodomethylthio-1-triphenylmethyl-1*H*-1,2,4-triazole (**7**)

Compound **7** was prepared from **24** as described for the preparation of **22**: ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, s), 7.4～7.3 (9H, m), 7.2～7.1 (6H, m), 4.70 (2H, s).

5-Mercapto-1*H*-tetrazole (**26**)

A solution of **25** (10.0 g, 45.0 mmol), which was similarly prepared as described in the literature,[8] in trifluoroacetic acid (100 ml) and anisole (20 ml) was heated at 80°C for 2 hours. The reaction mixture was concentrated and the crystalline residue was washed with toluene to obtain 4.33 g (94%) of **26** as white crystals: MP 198～200°C (dec); ^{13}C NMR (CD_3OD) δ 167.1; IR (KBr) cm^{-1} 3430 (br), 3040 (br), 2840, 1513, 1346; MS *m/z* 102 (M^+).

Anal Calcd for CH_2N_4S: C 11.76, H 1.97, N 54.86, S 31.40.
Found: C 11.84, H 2.05, N 54.60, S 31.33.

1*H*-Tetrazol-5-ylthiomethyl Thioacetate (**27**)

Compound **27** was similarly prepared from **26** as described for the preparation of **16**: MP 90°C; ^{1}H NMR ($CDCl_3$) δ 9.0～8.0 (1H, br s), 4.68 (2H, s), 2.42 (3H, s); IR ($CHCl_3$) cm^{-1} 3072 (br), 1692, 1500, 1356.

HRMS Calcd for $C_4H_6N_4OS_2$ (M^+): 189.9983.
Found: *m/z* 189.9971 (M^+).

5-*p*-Methoxybenzylthio-1-methyl-1*H*-tetrazole(**28**), 5-*p*-Methoxybenzylthio-2-methyl-2*H*-tetrazole (**29**)

Compound **25** was treated with diazomethane as described for the preparation of **12～14** to yield **28** as white crystals and **29** as a colorless oil.

28: MP 68～69°C; ^{1}H NMR ($CDCl_3$) δ 7.31～7.27 and 6.86～6.82 (4H, AA'BB'), 4.49 (2H, s), 3.80 (3H, s), 3.79 (3H, s); IR ($CHCl_3$) cm^{-1} 1613, 1513, 1465, 1305; MS *m/z* 236 (M^+).

Anal Calcd for $C_{10}H_{12}N_4OS$: C 50.83, H 5.12, N 23.71, S 13.57.
Found: C 50.84, H 5.16, N 23.55, S 13.36.

29: ^{1}H NMR ($CDCl_3$) δ 7.34～7.30 and 6.85～6.81 (4H, AA'BB'), 4.38 (2H, s), 4.29 (3H, s), 3.78 (3H, s); IR ($CHCl_3$) cm^{-1} 1611, 1512, 1390, 1324, 1303; MS *m/z* 236 (M^+).

Anal Calcd for $C_{10}H_{12}N_4OS$: C 50.83, H 5.12, N 23.71, S 13.57.
Found: C 51.01, H 5.24, N 23.69, S 13.31.

5-Chloromethylthio-1-methyl-1*H*-tetrazole (**30**) and 5-Chloromethylthio-2-methyl-2*H*-tetrazole (**31**)

Compound **30** and **31** were prepared from **28** and **29** as described for the preparation of **20**.

30: MP 55～56°C; ^{1}H NMR ($CDCl_3$) δ 5.29 (2H, s), 4.03 (3H, s); IR ($CHCl_3$) cm^{-1} 1467, 1408, 1384.

HRMS Calcd for $C_3H_5ClN_4S$ (M^+): 163.9923.
Found: *m/z* 163.9926 (M^+).

31: ^{1}H NMR ($CDCl_3$) δ 5.23 (2H, s), 4.37 (3H, s); IR ($CHCl_3$) cm^{-1} 1440, 1422, 1410, 1395, 1325.

HRMS Calcd for $C_3H_5ClN_4S$ (M^+): 163.9923.
Found: *m/z* 163.9939 (M^+).

5-Iodomethylthio-1-methyl-1*H*-tetrazole (**32**) and 5-Iodomethylthio-2-methyl-2*H*-tetrazole (**33**)

Compound **32** and **33** were prepared from **30** and **31** as described for the preparation of **22**.

32: ^{1}H NMR ($CDCl_3$) δ 4.76 (2H, s), 3.98 (3H, s).

33: ^{1}H NMR ($CDCl_3$) δ 4.74 (2H, s), 4.38 (3H, s).

5-Chloromethylthio-1,2,3-thiadiazole (**35**), 2-Chloromethylthio-1,3,4-thiadiazole (**39**) and 2-Chloromethylthio-5-methyl-1,3,4-thiadiazole (**40**)

Compound **35**, **39** and **40** were similarly prepared from **34**,[9] **37** and **38** (**37**, **38**; purchased from Toyo Kasei Kogyo Co., Ltd.) as described for the preparation of **24**.

35: ^{1}H NMR ($CDCl_3$) δ 8.69 (1H, s), 4.93 (2H, s); IR ($CHCl_3$) cm^{-1} 1419, 1395; MS *m/z* 166 (M^+).

Anal Calcd for $C_3H_3ClN_2S_2$: C 21.62, H 1.81, Cl 21.27, N 16.81, S 38.48.
Found: C 21.49, H 2.02, Cl 21.54, N 16.98, S 38.25.

39: ^{1}H NMR ($CDCl_3$) δ 9.16 (1H, s), 5.32 (2H, s); IR ($CHCl_3$) cm^{-1} 1389, 1373; MS *m/z* 166 (M^+).

Anal Calcd for $C_3H_3ClN_2S_2$: C 21.62, H 1.81, Cl 21.27, N 16.81, S 38.48.
Found: C 21.58, H 2.01, Cl 21.31, N 16.84, S 38.59.

40: ^{1}H NMR ($CDCl_3$) δ 5.24 (2H, s), 2.79 (3H, s); IR ($CHCl_3$) cm^{-1} 1430, 1392, 1380.

HRMS Calcd for $C_4H_5ClN_2S_2$ (M^+): 179.9583.
Found: *m/z* 179.9591 (M^+).

5-Iodomethylthio-1,2,3-thiadiazole (**36**), 2-Iodomethylthio-1,3,4-thiadiazole (**41**) and 2-Iodomethylthio-5-methyl-1,3,4-thiadiazole (**42**)

Compound **36**, **41** and **42** were prepared from **35**, **39** and **40** as described for the preparation of **22**.

36: ^{1}H NMR ($CDCl_3$) δ 8.62 (1H, s), 4.53 (2H, s).

41: ^{1}H NMR ($CDCl_3$) δ 9.14 (1H, s), 4.85 (2H, s).

42: ^{1}H NMR ($CDCl_3$) δ 4.78 (1H, s), 2.79 (3H, s).

Pyridin-2-ylthiomethyl Thioacetate (**44**)

Compound **44** was similarly prepared from **43** as described for the preparation of **16**: ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, ddd, $J_{5,6}$=4.9 Hz, $J_{4,6}$=1.8 Hz, $J_{3,6}$=1.0 Hz), 7.51 (1H, ddd, $J_{4,5}$=7.4 Hz, $J_{3,4}$=8.0 Hz, $J_{4,6}$=1.8 Hz), 7.18 (1H, ddd, $J_{3,4}$=8.0 Hz, $J_{3,5}$=$J_{3,6}$=1.0 Hz), 7.03 (1H, ddd, $J_{4,5}$=7.4 Hz, $J_{5,6}$=4.9 Hz, $J_{3,5}$=1.0 Hz), 4.65 (2H, s), 2.35 (3H, s); IR ($CHCl_3$) cm^{-1} 1686, 1576, 1556, 1452, 1414, 1353; MS *m/z* 199 (M^+).

Anal Calcd for $C_8H_9NOS_2$: C 48.21, H 4.55, N 7.03, S 32.18.
Found: C 48.25, H 4.61, N 7.03, S 32.04.

References

1) KUME, M.; T. KUBOTA, Y. KIMURA, H. NAKASHIMIZU, K. MOTOKAWA & M. NAKANO: Orally active cephalosporins. II. Synthesis and structure-activity relationships of new 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]cephalosporins with 1,2,3-triazole in C-3 side chain. J. Antibiotics 46: 177~192, 1993

2) REID, E. E.: Chapter 4. Substituted mercaptans. *In* Organic Chemistry of Bivalent Sulfur. Volume 1. *Ed*., E. E. REID, pp. 376~435, Chemical Publishing Co., Inc., New York, 1958

3) ELGUERO, J.; C. MARZIN & J. D. ROBERTS: Carbon-13 magnetic resonance studies of azoles. Tautomerism, shift reagent effects, and solvent effects. J. Org. Chem. 39: 357~363, 1974

4) DUNN, G. L.; J. R. E. HOOVER, D. A. BERGES, J. J. TAGGART, L. D. DAVIS, E. M. DIETZ, D. R. JAKAS, N. YIM, P. ACTOR, J. V. URI & J. A. WEISBACH: Orally active 7-phenylglycyl cephalosporins. Structure-activity studies related to cefatrizine (SK&F 60771). J. Antibiotics 29: 65~80, 1976

5) KUME, M.; T. KUBOTA, Y. KIMURA, H. NAKASHIMIZU & K. MOTOKAWA: Orally active cephalosporins. I. Synthesis and structure-activity relationships of 7β-[2-(*R*)-amino-2-phenylacetamido]-3-(1*H*-1,2,3-triazol-4-yl)alkylthiomethyl-3-cephem-4-carboxylic acid and related compounds. Yakugaku Zasshi (Japanese) 112: 622~637, 1992

6) KIMURA, Y.; M. NAKANO & T. YOSHIDA: Microbiological assay methods for 6315-S (flomoxef) concentrations in body fluid. Chemotherapy (Tokyo) 35 (Suppl. 1): 129~136, 1987

7) VON BÖHME, H.; H. BEZZENBERGER, M. CLEMENT, A. DICK, E. NÜRNBERG & W. SCHLEPHACK: Über α-Hydroxyalkyl-acyl-sulfide und α-Halogenalkyl-acyl-sulfide. Liebigs Ann. Chem. 623: 92~102, 1959
8) TANAKA, K. (Fujisawa Pharmaceutical): The preparation of 1-substituted-1*H*-tetrazol-5-thiols. Jpn. Kokai 82067 ('75), July 3, 1975
9) CURRAN, W. V. & M. L. SASSIVER (American Cyanamid): 5-Mercapto-1,2,3-thiadiazole. Jpn. Kokai 78175 ('84), May 4, 1984