

Orally Active Cephalosporins. IV.¹⁾ Synthesis, Antibacterial Activity and Oral Absorption of 3-(1*H*-1,2,3-Triazol-4-yl)thiomethylthio-cephalosporins

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The synthesis, antibacterial activity and oral absorption of 3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic acids with various C-7 side chains (**2**) are described. The (1*H*-1,2,3-triazol-4-yl)thiomethylthio C-3 side chain was found to be an effective substituent for good oral absorption of cephalosporins with some C-7 side chains.

Keywords cephalosporin; (1,2,3-triazol-4-yl)thiomethylthio group; synthesis; antibacterial activity; oral absorption; cefatrizine

Inspection of the structural formulas of orally absorbable cephalosporins reveals that they have a relatively small substituent at the C-3 position of the cephem nucleus, except for cefatrizine.²⁾ Cefatrizine has a larger C-3 side chain including 1,2,3-triazole (Fig. 1). Replacement of 1,2,3-triazole of cefatrizine with other heteroaromatic rings such as imidazole and tetrazole decreased the oral absorbability.³⁾ These results suggested that a 1,2,3-triazole moiety plays an important role in good oral absorption. This suggestion prompted us to conduct extensive syntheses of cephalosporins possessing 1,2,3-triazole in the C-3 side chain. We finally obtained a new orally active cephalosporin, 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic

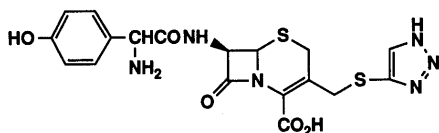


Fig. 1. Cefatrizine

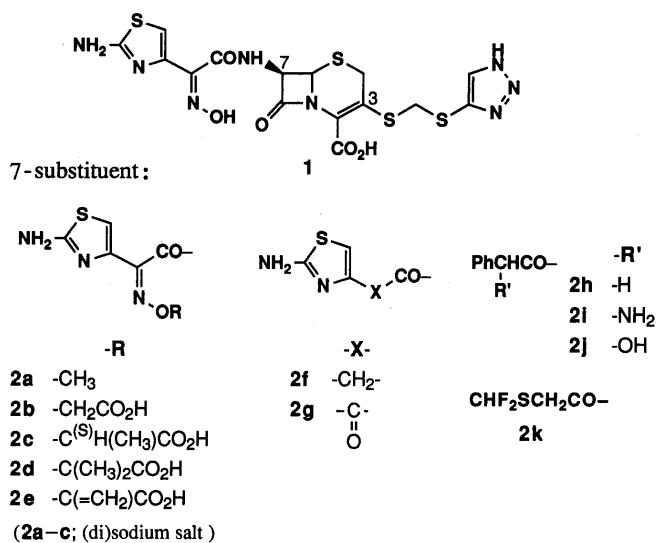
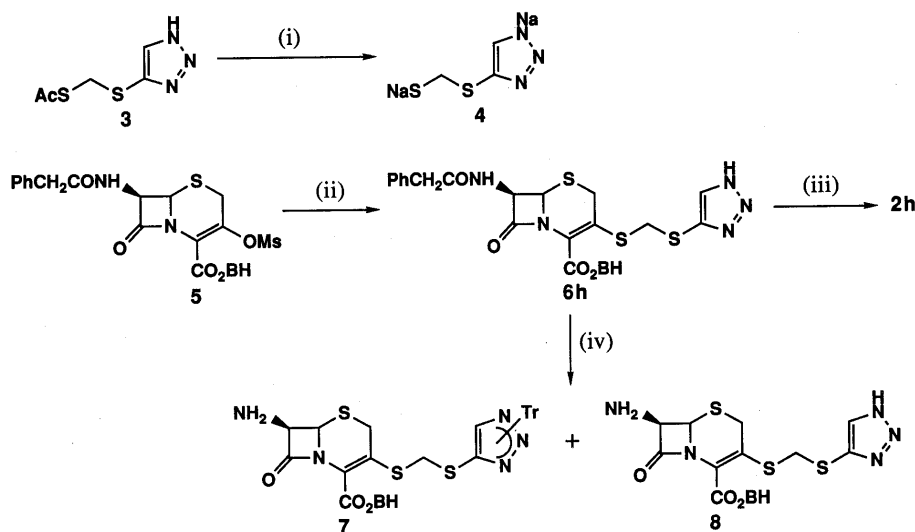


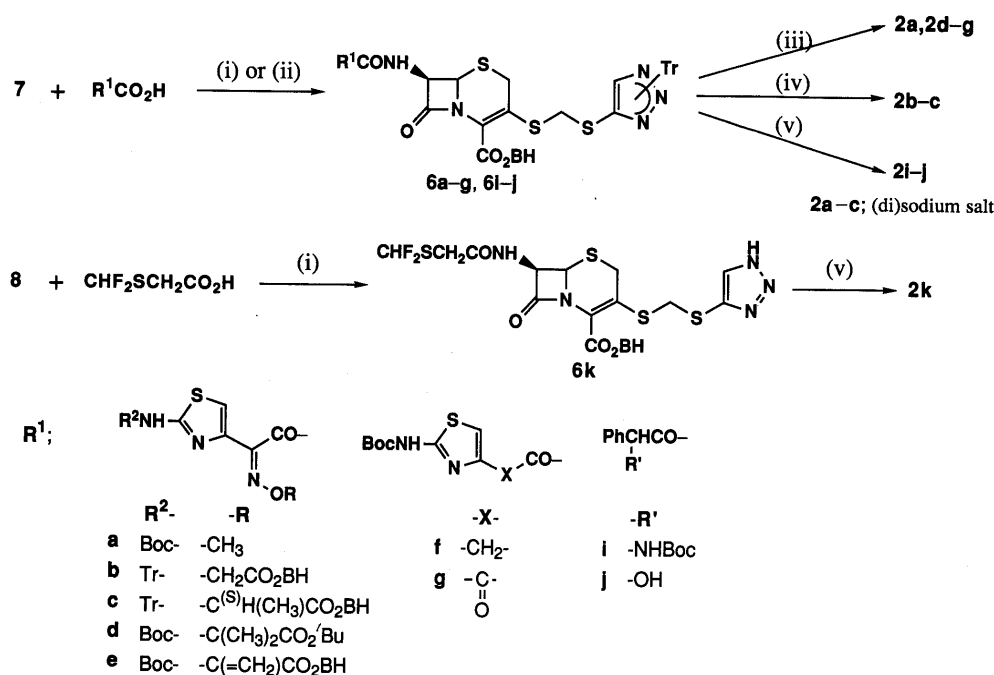
Fig. 2. 3-(1*H*-1,2,3-Triazol-4-yl)thiomethylthio-cephalosporins (**1** and **2a-k**)



(i) NaOMe / DMF-MeOH; (ii) **4** / DMF; (iii) CF₃CO₂H / anisole / CH₂Cl₂; (iv) 1) TrCl / pyridine, 2) PCl₅ / pyridine, 3) 1,3-butanediol.

Tr = triphenylmethyl, BH = diphenylmethyl

Chart 1



(i) *N*-methylmorpholine / Cl₂PO₂Ph / CH₂Cl₂; (ii) DCC / CH₂Cl₂; (iii) AlCl₃ / anisole / CH₃NO₂;
 (iv) 1) HCO₂H / H₂O, 2) AlCl₃ / anisole / CH₃NO₂; (v) CF₃CO₂H / anisole / CH₂Cl₂.
 DCC = *N,N'*-dicyclohexylcarbodiimide, Boc = *tert*-butoxycarbonyl

Chart 2

TABLE I. *In Vitro* Antibacterial Activity of Cephalosporins (2a–k and 1)

Organism	MIC (μg/ml)											
	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	1
<i>Staphylococcus aureus</i> FDA 209P JC-1	0.8	6.3	12.5	12.5	3.1	0.1	0.8	0.05	25	0.2	0.1	0.2
<i>S. aureus</i> SMITH	1.6	12.5	12.5	12.5	3.1	0.1	1.6	0.05	50	0.2	0.1	0.2
<i>S. aureus</i> SR3131	100	>100	>100	>100	100	50	50	25	100	25	25	12.5
<i>S. epidermidis</i> ATCC14990	1.6	6.3	6.3	6.3	3.1	0.1	0.8	0.1	12.5	0.4	0.1	0.2
<i>Streptococcus pyogenes</i> C-203	0.006	0.05	0.1	0.1	0.1	0.02	0.02	0.02	3.1	0.01	0.02	0.006
<i>S. pneumoniae</i> Type 1	0.01	0.2	0.2	0.2	0.1	0.05	0.1	0.02	6.3	0.05	0.02	0.02
<i>Escherichia coli</i> H	0.1	0.02	0.05	0.2	0.02	0.2	0.1	3.1	1.6	0.4	1.6	0.05
<i>E. coli</i> NIHJ JC-2	0.8	0.4	0.8	0.8	0.4	3.1	0.8	50	25	3.1	12.5	0.2
<i>E. coli</i> EC-14	0.4	0.1	0.2	0.4	0.1	0.8	0.4	12.5	12.5	1.6	3.1	0.1
<i>E. coli</i> SR377	1.6	3.1	3.1	3.1	0.8	>100	12.5	>100	>100	12.5	>100	1.6
<i>Klebsiella pneumoniae</i> SR1	0.1	0.02	0.05	0.1	0.02	0.4	0.2	6.3	6.3	0.8	1.6	0.1
<i>Proteus mirabilis</i> PR-4	0.05	0.006	0.01	0.01	<0.003	0.1	0.1	3.1	25	0.4	0.8	0.05
<i>P. vulgaris</i> CN-329	0.02	0.006	0.006	0.01	<0.003	0.8	0.4	12.5	>100	12.5	25	0.2
<i>Morganella morganii</i> SR9	0.1	0.02	0.1	0.2	0.01	12.5	3.1	>100	>100	25	>100	0.1
<i>Enterobacter cloacae</i> SR233	0.8	0.4	0.4	0.8	0.2	>100	12.5	>100	>100	50	>100	0.8
<i>Serratia marcescens</i> ATCC13880	0.8	0.4	0.8	0.8	0.2	>100	50	>100	>100	>100	>100	3.1
<i>Pseudomonas aeruginosa</i> ATCC25619	100	50	3.1	1.6	3.1	>100	>100	>100	>100	>100	>100	>100

acid (**1**), the (1*H*-1,2,3-triazol-4-yl)thiomethylthio side chain of which was found to be the best substituent for oral absorption.⁴⁾ Our interest has now turned to the versatility of this C-3 side chain as a substituent of orally active cephalosporins. In this paper, we wish to report the synthesis, antibacterial activity and oral absorption of 3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic acids with various C-7 side chains (**2**).

Chemistry The desired 3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-cephalosporins (**2**) were synthesized by the route shown in Charts 1 and 2.

Diphenylmethyl 3-methanesulfonyloxy-7β-phenylacet-

amido-3-cephem-4-carboxylate (**5**)⁵⁾ was allowed to react with the disodium salt (**4**), prepared *in situ* by methanolysis of (1*H*-1,2,3-triazol-4-yl)thiomethyl thioacetate (**3**),¹⁾ to afford the protected 3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-cephalosporin (**6h**). The desired 7β-phenylacetamido-cephalosporin (**2h**) was obtained by the deprotection of **6h** with trifluoroacetic acid. For the preparation of the other desired cephalosporin derivatives (**2a–g**, **2i–k**), protection of the 1,2,3-triazole of **6h** with a triphenylmethyl (trityl) group followed by the cleavage of the C-7 phenylacetyl side chain was carried out to give 7β-amino-cephalosporin derivatives (**7** and **8**). Without tritylation, the cleavage of

TABLE II. Plasma Levels and Urinary Recovery of Cephalosporins (**2a–k**, **1**) in Mice after Oral Administration of 40 mg/kg

Compound	Plasma level ($\mu\text{g/ml}$)		Urinary recovery (%)
	15 min	120 min	
2a	15.3	13.0	2.1
2b	2.05	4.37	0.6
2c	0.41	0.73	<0.3
2d	<0.16	<0.16	<0.3
2e	0.77	0.62	0.7
2f	17.1	2.83	36.3
2g	19.0	9.80	14.0
2h	15.1	3.96	22.1
2i	60.0	15.4	7.8
2j	18.5	7.26	10.7
2k	28.4	2.53	44.6
1	29.6	51.3	5.5

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

the phenylacetyl group gave **8** only in a poor yield. Compounds **7** and **8** were separated by column chromatography on silica gel and acylated with the corresponding carboxylic acids to afford the protected cephalosporins (**6a–g** and **6i–k**). Successive treatment of **6b** and **6c** with aqueous formic acid and aluminum chloride (AlCl_3) gave the desired cephalosporins (**2b** and **2c**). Cephalosporins (**2a** and **2d–g**) were obtained by the deprotection of **6a** and **6d–g** with AlCl_3 and cephalosporins (**2i–k**) by that of **6i–k** with trifluoroacetic acid.

Biological Evaluation The minimum inhibitory concentration (MIC) values of the synthesized cephalosporins (**2**) against selected strains of gram-positive and gram-negative bacteria are shown in Table I. Their plasma levels and urinary recovery after oral administration (40 mg/kg) to mice are summarized in Table II.

7β -[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporin (**2a**) showed antibacterial activity comparable to that of the hydroxyimino derivative (**1**) against gram-positive and gram-negative bacteria except *Staphylococci*. 7β -[(*Z*)-2-(2-Aminothiazol-4-yl)-2-carboxyalkoxyiminoacetamido]cephalosporins (**2b–e**) were much less active against gram-positive bacteria than **1**. However, their activity against most gram-negative bacteria was much better than that of **1**. Other cephalosporins (**2f–h**, **2j** and **2k**) exhibited activity comparable to that of **1** against gram-positive bacteria but showed lower activity against gram-negative bacteria. The phenylglycyl cephalosporin (**2i**) showed only poor antibacterial activity, which seemed to be due to its instability under the conditions of measurement.

Among compounds (**2a–e**) having the C-7 side chain frequently used in so-called third generation cephalosporins, compound **2a** showed high plasma levels after oral administration, but compounds **2c–e** were almost unabsorbable. Compound **2b** exhibited much lower oral absorbability than that of **1** although **2b** was expected to be readily absorbable because of having the same C-7 side chain as the known orally active cephalosporin, cefixime.⁶⁾ All of the other cephalosporins (**2f–k**) exhibited high plasma levels and better urinary recovery as compared with **1**.

It is noteworthy that most of these cephalosporins having

various C-7 side chains showed good oral absorption, considering that the C-7 side chains of orally active cephalosporins used in clinical medicine are limited to a few specific substituents, e.g., arylglycine,²⁾ (*Z*)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetic acid,⁶⁾ and (*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetic acid.⁷⁾ This (1*H*-1,2,3-triazol-4-yl)thiomethylthio side chain is potentially useful for the development of novel oral cephalosporins in combination with suitable C-7 side chains.

Experimental

General Procedures Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Jasco IR-700 spectrometer. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded at 200 MHz on a Varian VXR-200 NMR spectrometer using tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in D_2O) as an internal standard. Mass spectra (high-resolution secondary ion (SI) MS) were measured on a Hitachi M-90 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 under a nitrogen atmosphere.

Diphenylmethyl 7 β -Phenylacetamido-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylate (6h**)** A solution of (1*H*-1,2,3-triazol-4-yl)thiomethyl thioacetate (**3**)¹⁾ (6.79 g, 35.9 mmol) in *N,N*-dimethylformamide (DMF) (200 ml) at -70°C was treated with sodium methoxide in MeOH (1.26N, 56 ml). After being stirred at -60°C for 20 min, the reaction mixture was cooled to -78°C and a solution of diphenylmethyl 3-methanesulfonyloxy-7 β -phenylacetamido-3-cephem-4-carboxylate (**5**)⁵⁾ (17.0 g, 29.4 mmol) in DMF (50 ml) was added dropwise to the mixture. The mixture was stirred at the same temperature for 40 min, then 6 ml of acetic acid and 12 ml of 10% HCl were successively added. 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 EtOAc to give 10.3 g (56%) of **6h** as white crystals; mp $162\text{--}163^\circ\text{C}$. *Anal.* Calcd for $\text{C}_{31}\text{H}_{27}\text{N}_5\text{O}_4\text{S}_3$: C, 59.12; H, 4.32; N, 11.12; S, 15.27. Found: C, 58.84; H, 4.36; N, 11.04; S, 15.02. The spectral data of **6h** are listed in Table III.

Diphenylmethyl 7 β -Amino-3-[1(or 2)-triphenylmethyl-1(or 2)*H*-1,2,3-triazol-4-yl]thiomethylthio-3-cephem-4-carboxylate (7**), Diphenylmethyl 7 β -Amino-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylate (**8**)** A suspension of **6h** (10.0 g, 15.9 mmol) in CH_2Cl_2 (100 ml) was treated with pyridine (1.54 ml, 19.1 mmol) and trityl chloride (5.32 g, 19.1 mmol) under ice-cooling. After the mixture had been stirred at room temperature for 1 h, 2 ml of 10% HCl was added and the whole 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 dissolved in CH_2Cl_2 (50 ml) and treated with pyridine (2.57 ml, 31.8 mmol) and phosphorus pentachloride (5.96 g, 28.6 mmol) under ice-cooling. After being stirred at the same temperature for 30 min, the reaction mixture was added to a solution of 1,3-butanediol (8.6 ml, 95.9 mmol) in CH_2Cl_2 (25 ml) at -30°C . After being stirred at the same temperature for 10 min and at ice-bath temperature for 40 min, the reaction mixture was diluted with CH_2Cl_2 , washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was triturated with Et_2O . A solution of the above powder in CH_2Cl_2 was washed with 5% aqueous NaHCO_3 , dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent: toluene–EtOAc, 2:1) to yield 6.70 g (56%) of **7** as a yellow froth and 2.72 g (33%) of **8** as white crystals.

7: $^1\text{H-NMR}$ (CDCl_3) δ : 7.45 (1H, s), 7.5–7.05 (27H, m), 6.90 (1H, s), 4.87 (1H, d, $J=5.0\text{ Hz}$), 4.66 (1H, d, $J=5.0\text{ Hz}$), 4.16, 4.05 (2H, ABq, $J=13.4\text{ Hz}$), 3.82, 3.62 (2H, ABq, $J=17.6\text{ Hz}$). IR (CHCl_3): 3410, 1782, 1731, 1605, 1496, 1450, 1390, 1368 cm^{-1} .

8: mp $112\text{--}115^\circ\text{C}$. $^1\text{H-NMR}$ (CDCl_3) δ : 7.56 (1H, s), 7.5–7.25 (10H, m), 6.97 (1H, s), 4.94 (1H, d, $J=5.0\text{ Hz}$), 4.73 (1H, d, $J=5.0\text{ Hz}$), 4.14, 4.05 (2H, ABq, $J=13.7\text{ Hz}$), 3.73, 3.58 (2H, ABq, $J=17.5\text{ Hz}$). IR (CHCl_3): 3430, 1780, 1730, 1602, 1495, 1451, 1388, 1362 cm^{-1} . HRMS Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_5\text{O}_3\text{S}_3$ (MH^+): 512.0885. Found m/z : 512.0880 (MH^+).

Diphenylmethyl 7 β -[(*Z*)-2-(2-Triphenylmethylaminothiazol-4-yl)-2-diphenylmethoxycarbonylmethoxyiminoacetamido]-3-[1(or 2)-triphenylmethyl-1(or 2)*H*-1,2,3-triazol-4-yl]thiomethylthio-3-cephem-4-carboxylate (6b**)** A solution of **7** (800 mg, 1.06 mmol) and (*Z*)-2-(2-triphenylmethylaminothiazol-4-yl)-2-diphenylmethoxycarbonylmethoxyiminoacetic acid⁸⁾

(728 mg, 1.11 mmol) in CH_2Cl_2 (8 ml) was cooled to -30°C . *N*-Methylmorpholine (0.27 ml, 2.46 mmol) and phenylphosphoryl dichloride (0.19 ml, 1.27 mmol) were added to the mixture. After being stirred at -30°C for 30 min, the reaction mixture was neutralized with 10% HCl, diluted with water and extracted with EtOAc. The extract was washed with brine twice, dried over anhydrous Na_2SO_4 and evaporated. The

resulting residue was purified by column chromatography on silica gel (eluent: toluene–EtOAc, 10:1) to yield 1.07 g (73%) of **6b** as a pale yellow froth.

Compounds **6a**, **6c–g**, **6i** and **6k** were similarly prepared from **7** or **8** with the corresponding carboxylic acids according to the procedure described for the preparation of **6b**.

TABLE III. ^1H -NMR and IR Spectral Data for **6a–k**

Compd. No.	^1H -NMR (Solvent, δ)	IR (CHCl_3) cm^{-1} (C=O)
6a	(CDCl_3); 8.9–8.7 (1H, brs), 7.46 (1H, s), 7.4–7.25 (20H, m), 7.15–7.05 (6H, m), 7.05 (1H, s), 6.87 (1H, s), 5.90 (1H, dd, $J=4.8, 8.8$ Hz), 5.02 (1H, d, $J=4.8$ Hz), 4.19, 4.10 (2H, ABq, $J=13.5$ Hz), 4.09 (3H, s), 3.82, 3.64 (2H, ABq, $J=17.4$ Hz), 1.52 (9H, s)	1780, 1720, 1680
6b	(CDCl_3); 8.11 (1H, d, $J=9.1$ Hz), 7.45 (1H, s), 7.4–7.0 (51H, m), 6.93 (1H, s), 6.87 (1H, s), 6.81 (1H, s), 5.80 (1H, dd, $J=5.0, 9.1$ Hz), 5.03, 4.93 (2H, ABq, $J=17.0$ Hz), 4.90 (1H, d, $J=5.0$ Hz), 4.12, 4.07 (2H, ABq, $J=13.2$ Hz), 3.62, 3.32 (2H, ABq, $J=17.1$ Hz)	1790, 1740, 1688
6c	(CDCl_3); 8.22 (1H, d, $J=8.7$ Hz), 7.45 (1H, s), 7.4–7.0 (51H, m), 6.87 (1H, s), 6.85 (1H, s), 6.77 (1H, s), 5.82 (1H, dd, $J=4.6, 8.7$ Hz), 5.20 (1H, q, $J=7.2$ Hz), 4.91 (1H, d, $J=4.6$ Hz), 4.16, 4.12 (2H, ABq, $J=13.4$ Hz), 3.66, 3.41 (2H, ABq, $J=16.8$ Hz), 1.65 (3H, d, $J=7.2$ Hz)	1787, 1730, 1685
6d	(CDCl_3); 8.4–8.1 (1H, brs), 8.19 (1H, d, $J=9.0$ Hz), 7.46 (1H, s), 7.4–7.05 (26H, m), 6.88 (1H, s), 5.94 (1H, dd, $J=4.9, 9.0$ Hz), 5.01 (1H, d, $J=4.9$ Hz), 4.20, 4.09 (2H, ABq, $J=13.4$ Hz), 3.84, 3.63 (2H, ABq, $J=17.3$ Hz), 1.63 (3H, s), 1.61 (3H, s), 1.53 (9H, s), 1.39 (9H, s)	1788, 1725, 1687
6e	(CDCl_3); 9.1–8.7 (1H, brs), 7.68 (1H, d, $J=9.0$ Hz), 7.45 (1H, s), 7.4–7.0 (36H, m), 6.93 (1H, s), 6.84 (1H, s), 5.89 (1H, s), 5.73 (1H, dd, $J=4.8, 9.0$ Hz), 5.66 (1H, s), 4.80 (1H, d, $J=4.8$ Hz), 4.07 (2H, s), 3.51, 3.33 (2H, ABq, $J=18.0$ Hz), 1.53 (9H, s)	1786, 1724, 1695
6f	(CDCl_3); 7.76 (1H, d, $J=8.0$ Hz), 7.44 (1H, s), 7.5–7.25 (19H, m), 7.15–7.05 (6H, m), 6.76 (1H, s), 6.57 (1H, s), 5.54 (1H, dd, $J=4.6, 8.0$ Hz), 4.79 (1H, d, $J=4.6$ Hz), 4.06, 4.02 (2H, ABq, $J=13.6$ Hz), 3.75, 3.72 (2H, ABq, $J=17.8$ Hz), 3.41 (2H, s), 1.57 (9H, s)	1780, 1718, 1672
6g	(CDCl_3); 8.86 (1H, s), 8.6–8.5 (1H, brs), 8.19 (1H, d, $J=9.2$ Hz), 7.47 (1H, s), 7.45–7.2 (19H, m), 7.15–7.05 (6H, m), 6.91 (1H, s), 5.70 (1H, dd, $J=4.7, 9.2$ Hz), 5.00 (1H, d, $J=4.7$ Hz), 4.21, 4.10 (2H, ABq, $J=13.3$ Hz), 3.85, 3.67 (2H, ABq, $J=17.1$ Hz), 1.55 (9H, s)	1788, 1725, 1672
6h	($\text{CDCl}_3 + \text{CD}_3\text{OD}$); 7.62 (1H, s), 7.5–7.25 (15H, m), 6.92 (1H, s), 5.72 (1H, d, $J=4.8$ Hz), 5.00 (1H, d, $J=4.8$ Hz), 4.14, 4.09 (2H, ABq, $J=13.6$ Hz), 3.69, 3.60 (2H, ABq, $J=17.2$ Hz), 3.63 (2H, s)	1784, 1698 ^a
6i	(CDCl_3); 7.59 (1H, s), 7.45–7.25 (24H, m), 7.15–7.05 (6H, m), 6.91 (1H, s), 6.50 (1H, d, $J=9.1$ Hz), 5.76 (1H, dd, $J=4.8, 9.1$ Hz), 5.62 (1H, d, $J=6.0$ Hz), 5.20 (1H, d, $J=6.0$ Hz), 4.81 (1H, d, $J=4.8$ Hz), 3.98, 3.93 (2H, ABq, $J=13.3$ Hz), 3.44, 3.32 (2H, ABq, $J=17.5$ Hz), 1.42 (9H, s)	1788, 1710, 1697
6j	(CDCl_3); 7.45 (1H, s), 7.4–7.25 (24H, m), 7.15–7.05 (6H, m), 6.98 (1H, d, $J=9.2$ Hz), 6.88 (1H, s), 5.69 (1H, dd, $J=4.8, 9.2$ Hz), 5.15 (1H, d, $J=3.3$ Hz), 4.91 (1H, d, $J=4.8$ Hz), 4.16, 4.06 (2H, ABq, $J=13.4$ Hz), 3.78, 3.57 (2H, ABq, $J=17.4$ Hz), 3.41 (1H, d, $J=3.3$ Hz)	1788, 1725, 1692
6k	(CDCl_3); 7.68 (1H, d, $J=8.7$ Hz), 7.59 (1H, s), 7.5–7.1 (10H, m), 6.91 (1H, t, $J_{\text{HF}}=56.2$ Hz), 6.90 (1H, s), 5.79 (1H, dd, $J=4.8, 8.7$ Hz), 4.99 (1H, d, $J=4.8$ Hz), 4.05 (2H, s), 3.59 (2H, s), 3.56 (2H, s)	1785, 1690

^a) KBr.

TABLE IV. ^1H -NMR and IR Spectral Data for **2a–k**

Compd. No.	^1H -NMR (Solvent, δ)	IR (KBr) cm^{-1} (C=O)
2a	(D_2O); 7.96 (1H, s), 7.01 (1H, s), 5.79 (1H, d, $J=4.7$ Hz), 5.16 (1H, d, $J=4.7$ Hz), 4.22, 4.10 (2H, ABq, $J=13.8$ Hz), 3.98 (3H, s), 3.66, 3.47 (2H, ABq, $J=17.3$ Hz)	1753, 1659
2b	(D_2O); 8.02 (1H, s), 7.04 (1H, s), 5.82 (1H, d, $J=4.8$ Hz), 5.18 (1H, d, $J=4.8$ Hz), 4.57 (2H, s), 4.24, 4.12 (2H, ABq, $J=13.8$ Hz), 3.70, 3.49 (2H, ABq, $J=17.4$ Hz)	1760, 1655
2c	(D_2O); 7.98 (1H, s), 7.02 (1H, s), 5.84 (1H, d, $J=4.8$ Hz), 5.18 (1H, d, $J=4.8$ Hz), 4.65 (1H, q, $J=7.0$ Hz), 4.23, 4.11 (2H, ABq, $J=13.8$ Hz), 3.67, 3.48 (2H, ABq, $J=17.2$ Hz), 1.46 (3H, d, $J=7.0$ Hz)	1760, 1655
2d	($\text{D}_2\text{O} + \text{NaHCO}_3$); 8.01 (1H, s), 6.99 (1H, s), 5.82 (1H, d, $J=4.9$ Hz), 5.19 (1H, d, $J=4.9$ Hz), 4.24, 4.12 (2H, ABq, $J=13.9$ Hz), 3.69, 3.50 (2H, ABq, $J=17.4$ Hz), 1.50 (3H, s), 1.48 (3H, s)	1768, 1670
2e	($\text{D}_2\text{O} + \text{NaHCO}_3$); 8.00 (1H, s), 7.21 (1H, s), 5.87 (1H, d, $J=4.8$ Hz), 5.32 (1H, d, $J=1.7$ Hz), 5.173 (1H, d, $J=4.8$ Hz), 5.168 (1H, d, $J=1.7$ Hz), 4.23, 4.11 (2H, ABq, $J=13.9$ Hz), 3.68, 3.48 (2H, ABq, $J=17.4$ Hz)	1766, 1660
2f	($\text{D}_2\text{O} + \text{CD}_3\text{OD} + \text{NaHCO}_3$); 7.92 (1H, s), 6.49 (1H, s), 5.65 (1H, d, $J=4.7$ Hz), 5.06 (1H, d, $J=4.7$ Hz), 4.20, 4.08 (2H, ABq, $J=13.8$ Hz), 3.60, 3.43 (2H, ABq, $J=17.4$ Hz), 3.57 (2H, s)	1759, 1664
2g	($\text{DMSO}-d_6$); 9.81 (1H, d, $J=8.2$ Hz), 8.1–7.9 (1H, brs), 7.87 (1H, s), 7.40 (2H, s), 5.68 (1H, dd, $J=4.6, 8.2$ Hz), 5.19 (1H, d, $J=4.6$ Hz), 4.44 (2H, s), 3.83 (2H, s)	1764, 1660
2h	($\text{D}_2\text{O} + \text{NaHCO}_3$); 7.89 (1H, s), 7.45–7.3 (5H, m), 5.60 (1H, d, $J=4.7$ Hz), 5.02 (1H, d, $J=4.7$ Hz), 4.19, 4.06 (2H, ABq, $J=13.8$ Hz), 3.69, 3.65 (2H, ABq, $J=14.8$ Hz), 3.55, 3.39 (2H, ABq, $J=17.2$ Hz)	1775, 1661
2i	(D_2O); 8.07 (1H, s), 7.54 (5H, s), 5.66 (1H, d, $J=4.4$ Hz), 5.27 (1H, s), 5.13 (1H, d, $J=4.4$ Hz), 4.31, 4.25 (2H, ABq, $J=14.2$ Hz), 3.67, 3.46 (2H, ABq, $J=17.1$ Hz)	1763, 1690
2j	($\text{D}_2\text{O} + \text{NaHCO}_3$); 8.02 (1H, s), 7.46 (5H, s), 5.62 (1H, d, $J=4.8$ Hz), 5.27 (1H, s), 5.07 (1H, d, $J=4.8$ Hz), 4.21, 4.10 (2H, ABq, $J=13.8$ Hz), 3.62, 3.39 (2H, ABq, $J=17.4$ Hz)	1770, 1673
2k	($\text{D}_2\text{O} + \text{NaHCO}_3$); 8.01 (1H, s), 7.09 (1H, t, $J_{\text{HF}}=55.4$ Hz), 5.66 (1H, d, $J=4.6$ Hz), 5.11 (1H, d, $J=4.6$ Hz), 4.24, 4.12 (2H, ABq, $J=13.4$ Hz), 3.68 (2H, s), 3.67, 3.47 (2H, ABq, $J=17.4$ Hz)	1765, 1662

Diphenylmethyl 7 β -[2-(*R*)-Hydroxy-2-phenylacetamido]-3-[1(or 2)-phenylmethyl-1(or 2)-*H*-1,2,3-triazol-4-yl]thiomethylthio-3-cephem-4-carboxylate (6j) A mixture of **7** (800 mg, 1.06 mmol), (*R*)-mandelic acid (242 mg, 1.59 mmol) and *N,N'*-dicyclohexylcarbodiimide (328 mg, 1.59 mmol) was stirred at ice-bath temperature for 1 h and concentrated. EtOAc was added to the concentrate and the precipitate was filtered off. The filtrate was evaporated and purified by column chromatography on silica gel (eluent: toluene-EtOAc, 2:1) to yield 466 mg (50%) of **6j** as a yellow froth.

The spectral data of **6a—g** and **6i—k** are listed in Table III.

7 β -[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)-acetamido]-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic Acid (2d) A solution of AlCl₃ (0.75 g, 5.64 mmol) in anisole (3 ml) was added dropwise to a solution of **6d** (822 mg, 0.706 mmol) in anisole (3 ml) and nitromethane (12 ml) at -30 — -40 °C. The mixture was stirred at the same temperature for 1 h, then 5.7 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 a Diaion HP-20 column (eluent: methanol-water, 4:1). After concentration, the resulting precipitate was collected by filtration, washed with EtOAc and dried *in vacuo* to give 299 mg (71%) of **2d** as a pale yellow powder.

Compounds **2a** and **2e—g** were similarly prepared from **6a** and **6e—g** according to the procedure described for the preparation of **2d**.

Disodium 7 β -[(*Z*)-2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylate (2b) A solution of **6b** (1.04 g, 0.749 mmol) in 98% formic acid (16 ml) and water (0.8 ml) was stirred at room temperature for 3 h and evaporated. The resulting residue was triturated and rinsed with ether to give 572 mg of a yellowish white powder. A solution of AlCl₃ (0.50 g, 3.76 mmol) in anisole (2 ml) was added dropwise to a suspension of the above powder in anisole (2 ml) and nitromethane (8 ml) at -30 — -40 °C. The mixture was stirred at the same temperature for 1 h, then 3.8 ml of 1*N* HCl, water and EtOAc were added. The aqueous layer was separated and the organic layer was re-extracted with water. The combined aqueous layer was chromatographed on a Diaion HP-20 column (eluent: methanol-water, 4:1). After concentration, the resulting precipitate was collected by filtration and washed with EtOAc to give 170 mg of a pale yellow powder. This powder was dissolved in diluted aqueous NaHCO₃, re-purified by column chromatography on a Diaion CHP-20P resin (eluent: water) and freeze-dried to give 121 mg (26%) of **2b** as a white powder.

Compound **2c** was prepared from **6c** as described for the preparation of **2b**.

7 β -Difluoromethylthioacetamido-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic Acid (2k) A suspension of **6k** (451 mg, 0.710 mmol) in CH₂Cl₂ (3 ml) was treated with anisole (1.2 ml) and trifluoroacetic acid (3.0 ml) under ice-cooling. After being stirred at ice-bath temperature for 1 h, the reaction mixture was evaporated. The resulting residue was triturated with Et₂O to give 257 mg (77%) of **2k** as a white powder.

Compounds **2h—j** were similarly prepared from **6h—j** according to the procedure described for the preparation of **2k**.

The spectral data of **2a—k** are listed in Table IV.

Determination of Antibacterial Activity All the *in vitro* antibacterial activities are given as MIC in μ g/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 h with an inoculum size of about 10⁶ 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 at a single dose of 40 mg/kg or subcutaneously at 20 mg/kg as an aqueous solution, or if necessary, as a solution in dilute aqueous sodium bicarbonate. Plasma samples were collected at 0.25 and 2 h after dosing and urine specimens were collected over a period of 2 h after dosing. The concentrations of the test compounds were determined by the band culture method using *Micrococcus luteus* ATCC 9341 or *Escherichia coli* 7437 as a test organism and Trypto-soy agar as the test medium.

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