Synthesis and Oral Activity of Pivaloyloxymethyl 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*Z*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (ME1207) and Its Related Compound

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7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3(*Z*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylic acid (11, ME1206) and its 3-*trans* isomer (13) were prepared to test antibacterial activity. These compounds exhibited excellent antibacterial activity against both gram-positive and gram-negative bacteria, including β-lactamase producing strains.

The pivaloyloxymethyl esters (12 and 14) of the compounds (11 and 13) were prepared by esterification with pivaloyloxymethyl iodide. Among them, pivaloyloxymethyl 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*Z*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (12, ME1207) showed good urinary recovery after oral administration in mice.

Keywords cephalosporin; oral cephalosporin; *in vitro* antibacterial activity; structure–activity relationship; prodrug

Cephalosporins bearing 2-alkyloxyimino 2-(2-aminothiazol-4-yl) acetamido moieties as a C-7 side chain, which had broad and potent antibacterial activity against gram-positive and gram-negative bacteria, have been widely used for antibacterial chemotherapy. However, most of them are not suitable for oral administration because of their low absorption from the gastrointestinal tract, except for cefixime (CFIX)[1] and cefetram pivoxil (CFTM-PI).[2] Thus, the need still exists for development of a new orally active, semi-synthetic cephalosporin which exhibits potent and broad-spectrum antibacterial activity.

In a previous paper[3] relating to the antibacterial activity and oral absorption of 3-alkylthio-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(*O*-substituted oxyimino)acetamido]cephalosporins having various *O*-substituents of the oxime, we reported that the pivaloyloxymethyl ester of 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylic acid had good *in vivo* efficacy against mice infection caused by *Escherichia coli* No. 29 and showed high urinary recovery after oral administration in mice. Although the free acid, active form of this cephalosporin showed excellent activity against gram-negative bacteria, it did not show satisfactory activity against gram-positive bacteria. In due course, we investigated a modification of the 3-substituent in the hope of improving the antibacterial activity against gram-positive bacteria while retaining high antibacterial activity against gram-negative bacteria. As a result, the introduction of heterocyclic substituted vinyl groups to C-3 was fruitful.[4] In particular, pivaloyloxymethyl 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*Z*)-4-(methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (**12**, ME1207)[5] showed excellent oral activity and ME1206 (**11**),[5] an active form of ME1207, showed potent and broad antibacterial activity against both gram-positive and gram-negative bacteria. This paper deals with the synthesis and structure–activity relationships of a new orally active cephalosporin, ME1207, and a 3-trans isomer (**14**) of ME1207.

Results and Discussion

Chemistry The *p*-methoxybenzyl 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate (**1**)[6] was converted to the corresponding triphenylphosphonium iodide (**2**) by treatment with NaI and PPh_3 in acetone in 90% yield. A Wittig reaction of **2** with 5-formyl-4-methylthiazole (**3**)[7] was carried out in a heterogeneous system of dichloromethane–water at room temperature in the presence of sodium bicarbonate to give an 84% yield of a mixture of the vinyl derivative **4** (*Z*, *cis* isomer) and **5** (*E*, *trans* isomer) in a ratio of 4.7 : 1. Each isomer could be separated by fractional recrystallization followed by column chromatography. The olefin geometry was determined on the basis of proton nuclear magnetic resonance (^{1}H-NMR) spectra; the major product having a smaller vinyl coupling constant ($J = 11$ Hz) was assigned to be the *Z* isomer, whereas the minor one with a larger coupling constant ($J = 16$ Hz) was the *E* isomer.

The phenylacetyl side chains of **4** and **5** were cleaved by a known imino-chloride method, followed by silicagel column chromatography to afford amino ester (**6**) and **7** in good yields, respectively. Compounds **6** and **7** were coupled with 2-(2-tritylaminothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**8**)[8] using $POCl_3$ as a coupling reagent to give the protected cephalosporins **9** (*Z* isomer) and **10** (*E* isomer), respectively.

Removal of the protective groups of **9** and **10** with CF_3COOH–anisole, and purification by Diaion HP-20 column chromatography gave new cephalosporins **11** and **13**, respectively. Alternately, the sodium salts (**11** and **13**) were treated with iodomethyl pivalate in dimethylformamide (DMF) to give the pivaloyloxymethyl esters (**12** and **14**) in good yields.

Biological Evaluation The minimum inhibitory concentrations (MICs) of the new cephalosporins (**11** and **13**) were determined by the twofold agar dilution method. The MICs values of these compounds against several gram-positive and gram-negative bacteria are summarized in Table I and compared with the values of CFIX, CFTM[2] and cefaclor (CCL).[9] These compound showed potent and broad antibacterial activity against both gram-positive and gram-negative bacteria. Especially, the activity of these compounds (**11** and **13**) against gram-positive bacteria was more potent than either CFIX, CFTM or CCL. The activity of compounds **11** and **13** against gram-negative bacteria was more potent than CCL and comparable to CFIX and CFTM. The effect of the stereochemistry of **11** (*Z* isomer) and **13** (*E* isomer) on the anti-

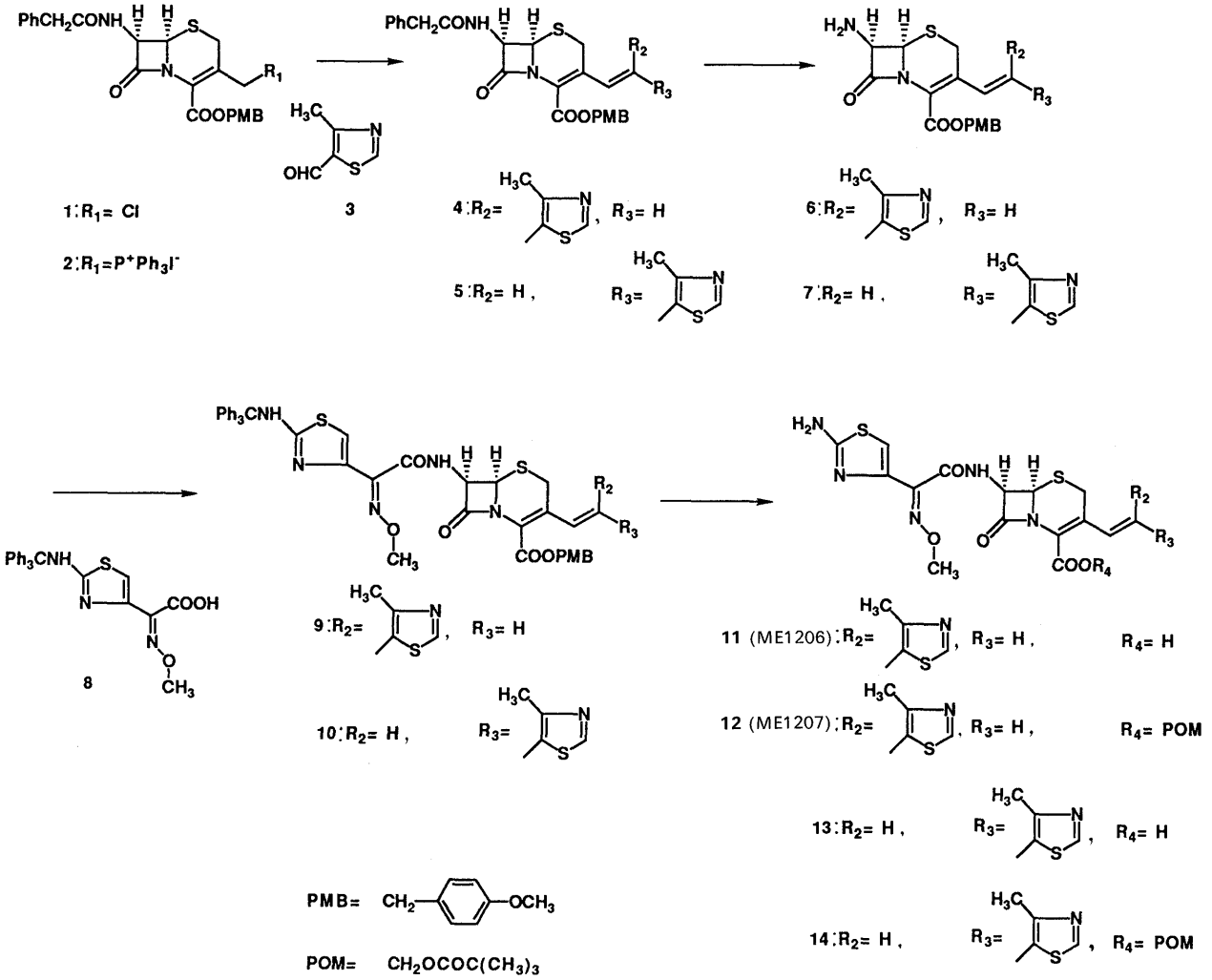

Chart 1

TABLE I. *In Vitro* Activity of ME1206 (**11**) and Related Cephalosporins

Test organism	MIC (μg/ml)				
	ME1206 (**11**)	**13**	CFTM	CFIX	CCL
Staphylococcus aureus 606[a]	0.78	0.78	6.25	6.25	3.13
S. aureus 606 E-25	0.78	0.78	3.13	6.25	3.13
Bacillus subtilis ATCC 6633	0.20	0.39	0.78	50	0.20
Escherichia coli W3630	0.39	0.20	0.39	0.78	25
RGN823[a]					
E. coli No. 29	0.39	0.39	0.39	0.20	1.56
Klebsiella pneumoniae GN69[a]	0.20	0.39	0.20	0.05	3.13
Salmonella typhi 0-901-W	0.05	0.10	0.05	<0.025	0.78
Proteus vulgaris GN76[b]	0.20	0.10	0.20	<0.025	>100
P. vulgaris GN76/C-1[b]	0.20	0.10	3.13	0.05	>100
Morganella morganii 1510/S-1	0.20	0.10	0.20	0.39	6.25
Shigella dysenteriae (shiga)	0.05	0.05	0.05	0.39	0.78
Enterobacter cloacae G-0008[b]	0.78	0.78	1.56	0.78	>100
Pseudomonas aeruginosa	25	100	100	>100	>100
GN10362[b]					

a) Penicillinase producing strain. *b*) Cephalosporinase producing strain.

bacterial activity was not significant.

When the pivaloyloxymethyl esters **12** and **14** were orally administrated in mice, the urinary recovery of **11** and **13** was determined by bioassay using *Escherichia coli* K-12 HW 8236 as a test strain after oral administration of the test samples (25 mg/kg as a parental cephalosporin) in mice ($n=3$, 0—4 h). The results are shown in Table II. The olefin geometry of **12** (*Z* isomer) and **14** (*E* isomer) had a significant effect on the urinary recovery in oral administration in mice. Compound **12** showed higher urinary recovery (21%) than **14** (15%) and was comparable with CFTM-PI. Therefore, ME1207 (**12**) was chosen as a candidate for further biological evaluation.

TABLE II. Urinary Recovery of Cephalosporin after Oral Administration in Mice (%)

Compound	ME1207 (**12**)	**14**	CFTM-PI	CFIX	CCL
Urinary recovery (%) (25 mg/kg, $n=3$, 0—4 h)	21.0	15.0	28.0	10.5	53.5

Clinical evaluation studies of ME1207 have been in progress.

Experimental

Melting points were uncorrected. Infrared (IR) spectra were recorded on a JASCO-IR-1 spectrometer. ^{1}H-NMR spcetra were determined with tetramethylsilane as an internal standard on either a Hitachi R-90H or JAXC 400GX, with chemical shifts given in ppm units. Mass spectra (MS) measurements were taken on a Hitachi M-80B mass spectrometer.

***p*-Methoxybenzyl 7-Phenylacetamido-3-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (4 and 5)** To the solution of *p*-methoxybenzyl 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate (10 g) in acetone (200 ml) were added PPh_3 (5.65 g) and NaI (3.2 g). The mixture was stirred at room temperature for 2 h and evaporated *in vacuo*. The residue was dissolved in dichloromethane (100 ml) and to the solution, 5-formyl-4-methylthiazole (**3**, 26.07 g) and 7% aq. sodium bicarbonate solution (100 ml) were added. After the mixture was stirred at room temperature for 17 h, the organic layer was washed with 10% aq. sodium hydrogen sulfite solution and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The remaining residue was triturated in methanol (200 ml) to give a yellow crystal (**5**, 1.20 g) of *E* isomer. The filtrate was evaporated *in vacuo* and the remaining residue was purified by column chromatography on silica gel using benzene–ethyl acetate (5 : 1) as an eluent to give a pale yellow powder (**4**, 7.8 g) of *Z* isomer. **4** (*Z* isomer). mp 78—82 °C (dec.). IR (Nujol): 3200—3350, 1790, 1730, 1670, 1620 cm^{-1}. NMR ($CDCl_3$) δ: 2.39 (3H, s, CH_3), 3.15, 3.45 (2H, ABq, J=16 Hz, 2-H), 3.62 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 5.00 (1H, d, J=5 Hz, 6-H), 5.08 (2H, s, CH_2), 5.82 (1H, dd, J=5, 8 Hz, 7-H), 6.15 (1H, d, J=8 Hz, CONH), 6.40 (2H, d, J=14 Hz, arom), 6.80 (1H, d, J=11 Hz, CH=), 7.1—7.3 (8H, m, CH=, arom), 8.52 (1H, s, thiazole 2-H). Field desorption–mass spectra (FD-MS) *m/z*: 561 (M^+). **5** (*E* isomer). mp 174—175 °C (CH_2Cl_2). IR (Nujol): 3280, 1780, 1710, 1650, 1620 cm^{-1}. NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.60 (2H, br s, 2-H), 3.62 (2H, s, CH_2), 3.78 (3H, s, OCH_3), 4.93 (1H, d, J=5 Hz, 6-H), 5.20 (2H, s, CH_2), 5.79 (1H, dd, J=5, 9 Hz, 7-H), 6.6—6.9 (4H, m, CH=, CONH, arom), 7.0—7.4 (8H, m, CH=, arom), 8.51 (1H, s, thiazole 2-H). FD-MS *m/z*: 562 $(M+H)^+$.

***p*-Methoxybenzyl 7-Amino-3(*Z*)-(4-methylthiazol-5-yl)-3-cephem-4-carboxylate (6)** To a solution of pyridine (1.04 ml) and phosphorus pentachloride (800 mg) in dichloromethane (20 ml), a solution of **4** (720 mg) in dichloromethane (3 ml) was added at −30 °C and the mixture was stirred at 0—5 °C for 2 h. The reaction mixture was poured into methanol (20 ml) at −20 °C and stirred for 1 h at 0—5 °C. The mixture was partitioned between dichloromethane (40 ml) and brine (20 ml) under ice-cooling, adjusted to pH 1.5—2.0 with 7% aq. sodium bicarbonate solution and stirred for 1 h at 0—5 °C. The separated organic layer was washed with brine and sat. $NaHCO_3$ dried over $MgSO_4$ and evaporated *in vacuo*. The remaining residue was purified by chromatography on silica gel using benzene–ethyl acetate (3 : 1) as an eluent and crystallized from ethyl acetate to give pale yellow crystals (443 mg) of **6**. mp 141—142 °C (ethyl acetate–dichloromethane). IR (Nujol): 1780, 1730, 1650, 1635, 1615 cm^{-1}. NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.20, 3.42 (2H, ABq, J=16 Hz, 2-H), 3.76 (3H, s, OCH_3), 4.75 (1H, d, J=5 Hz, 6-H), 5.00 (1H, d, J=5 Hz, 7-H), 5.08 (2H, s, CH_2), 6.25 (1H, d, J=11 Hz, CH=), 6.52 (1H, d, J=11 Hz, CH=), 6.76 (2H, d, J=8 Hz, arom), 7.18 (2H, d, J=8 Hz, arom), 8.52 (1H, s, thiazole 2-H). FD-MS *m/z*: 443 (M^+). *Anal.* Calcd for $C_{21}H_{21}N_3O_4S_2$: C, 56.87; H, 4.77; N, 9.47. Found: C, 56.81; H, 4.75; N, 9.31.

***p*-Methoxybenzyl 7-Amino-3(*E*)-(4-methylthiazol-5-yl)-3-cephem-4-carboxylate (7)** Using the procedure described for the preparation of **6**, this compound was prepared from **5**. Yellow crystals. mp 159—160 °C (ethyl acetate). IR (Nujol): 3420, 1780, 1720, 1610 cm^{-1}. NMR ($CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.63, 3.71 (2H, ABq, J=18 Hz, 2-H), 3.80 (3H, s, OCH_3), 4.75 (1H, d, J=5 Hz, 6-H), 4.96 (1H, d, J=5 Hz, 7-H), 5.24, 5.28 (2H, ABq, J=12 Hz, CH_2), 6.83 (1H, d, J=16 Hz, CH=), 6.90 (2H, d, J=8 Hz arom), 7.27 (1H, d, J=16 Hz, CH=), 7.38 (2H, d, J=8 Hz arom), 8.57 (1H, s, thiazole 2-H). FD-MS *m/z*: 443 (M^+). *Anal.* Calcd for $C_{21}H_{21}N_3O_4S_2$: C, 56.87, H, 4.77; N, 9.47. Found: C, 56.58; H, 4.77; N, 9.28.

***p*-Methoxybenzyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*Z*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (9)** A solution of $POCl_3$ (214 mg) in dichloromethane (3 ml) was added dropwise to a solution of **6** (443 mg) and (*Z*)-2-(tritylaminothiazol-4-yl)-2-methoxyiminoacetic acid (**8**, 457 mg) in dichloromethane (30 ml) containing pyridine (0.32 ml) at −20 °C. After stirring for 2 h at −20 to −10 °C, the reaction mixture was poured into water (10 ml). The separated organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel using benzene–ethyl acetate (5 : 1) as an eluent to give pale yellow powder (632 mg) of **9**. mp 134—136 °C (dec.). IR (Nujol): 3350, 1790, 1730, 1680, 1630, 1620 cm^{-1}. NMR ($CDCl_3$) δ: 2.41 (3H, s, CH_3) 3.30, 3.48 (2H, ABq, J=18 Hz, 2-H), 3.78 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 5.08—5.15 (3H, m, 6-H, CH_2), 5.95 (1H, dd, J=5, 8.8 Hz, 7-H), 6.30 (1H, d, J=11.7 Hz, CH=), 6.58 (1H, d, J=11.7 Hz, CH=), 6.70 (1H, s, thiazole 5-H), 6.82 (2H, d, J=8 Hz, arom), 6.90 (1H, d, J=8.8 Hz, CONH), 7.03 (1H, br s, NH), 7.12—7.32 (17H, m, arom), 8.58 (1H, s, thiazole 2-H). FD-MS *m/z*: 869 $(M+H)^+$.

***p*-Methoxybenzyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*E*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (10)** Using the procedure described for the preparation of **9**, this compound was prepared from **7** and **8**. A white powder. mp 137—138 °C (dec.). IR (Nujol): 3350, 1790, 1730, 1680, 1630, 1610 cm^{-1}. NMR ($CDCl_3$) δ: 2.47 (3H, s, CH_3), 3.62, 3.75 (2H, ABq, J=18 Hz, 2-H), 3.80 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 5.06 (1H, d, J=5 Hz, 6-H), 5.24 (2H, s, CH_2), 5.90 (1H, dd, J=5, 9 Hz, 7-H), 6.72 (1H, s, thiazole 5-H), 6.85 (1H, d, J=16 Hz, CH=), 6.90 (2H, d, J=8 Hz, arom), 7.00 (1H, d, J=9 Hz, CONH), 7.02 (1H, s, NH), 7.25—7.38 (18H, m, CH=, arom), 8.57 (1H, s, thiazole 2-H). FD-MS *m/z*: 869 $(M+H)^+$.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*Z*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylic Acid (11, ME1206) Compound **9** (200 mg) was treated with anisole (0.5 ml) and CF_3COOH (2 ml) at 0 °C for 1 h. The solution was diluted with isopropyl ether and the precipitate was triturated in isopropyl ether (100 ml). The resulting powder was dissolved in a mixture of water (1 ml) and ethyl acetate (3 ml) and the mixture was adjusted to pH 7.2 with $NaHCO_3$. The aqueous layer was chromatographed on a column of Diaion HP-20 using water–acetone (4 : 1) as an eluent. The fractions were collected and lyophilized to give the sodium salt (95 mg) of **11** as pale yellow crystals, which were recrystallized from water. mp 195—200 °C (dec.). IR (Nujol): 3450, 1775, 1680, 1620, 1590 cm^{-1}. NMR (dimethylsulfoxide (DMSO)-d_6) δ: 2.30 (3H, s, CH_3), 3.00, 3.28 (2H, ABq, J=18 Hz, 2-H), 3.82 (3H, s, OCH_3), 5.10 (1H, d, J=5 Hz, 6-H), 5.62 (1H, dd, J=5, 8 Hz, 7-H), 6.34 (1H, d, J=11 Hz, CH=), 6.71 (1H, s, thiazole 5-H), 6.77 (1H, d, J=11 Hz, CH=), 7.22 (2H, br s, NH_2), 8.89 (1H, s, thiazole 2-H), 9.54 (1H, d, J=8 Hz, CONH). Secondary ion mass spectrometer (SI-MS) *m/z*: 529 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{17}O_5N_3NaS_2 \cdot 1.5\ H_2O$: C, 41.07; H, 3.63; N, 15.13. Found: C, 41.2; H, 3.6; N, 15.2.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*E*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylic Acid (13) Using the procedure described for the preparation of **11**, the sodium salt of **13** was prepared from **10**. A white powder. mp 184—185 °C (dec.). IR (Nujol): 3450, 1775, 1680 cm^{-1}. NMR (D_2O DOH at 4.82) δ: 2.50 (3H, s, CH_3), 3.86 (2H, br s, 2-H), 4.06 (3H, s, OCH_3), 5.34 (1H, d, J=5 Hz, 6-H), 5.87 (1H, d, J=5 Hz, 7-H), 6.97 (1H, d, J=16 Hz, CH=), 7.09 (1H, d, J=16 Hz, CH=), 7.08 (1H, s, thiazole 5-H), 8.77 (1H, s, thiazole 2-H). SI-MS *m/z*: 529 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{17}O_5N_3NaS_2 \cdot 2H_2O$: C, 40.42; H, 3.74; N, 14.89. Found: C, 40.99; H, 3.6; N, 14.62.

Pivaloyloxymethyl 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*Z*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (12, ME1207) A solution of **11** (30 mg) in DMF (3 ml) was treated with iodomethyl pivalate (95 mg) in DMF (1 ml) at −20 °C, and the mixture was stirred for 1 h at −20 °C. The reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (20 ml). The organic layer was washed water (10 ml) and brine (10 ml), dried, and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel using ethyl acetate as an eluent to give a pale yellow powder (25 mg) of **12**. mp 127—129 °C. IR (Nujol): 3450, 1790, 1760, 1680, 1620 cm^{-1}. NMR ($CDCl_3$) δ: 1.15 (9H, s, $C(CH_3)_3$), 2.44 (3H, s, CH_3), 3.30, 3.53 (2H, ABq, J=18.7 Hz, 2-H), 4.03 (3H, s, OCH_3), 5.21 (1H, d, J=5 Hz, 6-H), 5.52 (2H, br s, NH_2), 5.79, 5.85 (2H, ABq, J=5.5 Hz, CH_2), 6.11 (1H, dd, J=5, 8 Hz, 7-H), 6.37 (1H, d, J=11.7 Hz, CH=), 6.67 (1H, d, J=11.7 Hz, CH=), 6.80 (1H, s, thiazole 5-H), 7.93 (1H, d, J=8 Hz, CONH), 8.58 (1H, s, thiazole 2-H). SI-MS *m/z*: 621 $(M+H)^+$.

Pivaloyloxymethyl 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3(*E*)-(4-methylthiazol-5-yl)vinyl-3-cephem-4-carboxylate (14) Using the procedure described for the preparation of **12**, this compound was prepared from **13**. A pale yellow powder. mp 128—130 °C. IR (Nujol): 3450, 1790, 1760, 1680, 1620 cm^{-1}. NMR ($CDCl_3$) δ: 1.21 (9H, s, $C(CH_3)_3$), 2.48 (3H, s, CH_3), 3.68, 3.78 (2H, ABq, J=18 Hz, 2-H), 4.05 (3H, s, OCH_3), 5.12 (1H, d, J=5 Hz, 6-H), 5.89 (2H, s, CH_2), 5.97 (1H, dd, J=5, 9 Hz, 7-H), 6.86 (1H, s, thiazole 5-H), 6.98 (1H, d, J=16 Hz, CH=), 7.33 (1H, d, J=16 Hz, CH=), 7.52 (1H, d, J=9 Hz, CONH), 8.57 (1H, s, thiazole 2-H). SI-MS *m/z*: 621 $(M+H)^+$.

Biological Evaluation MICs (μg/ml) were determined by the twofold agar dilution method using Sensitivity disk agar (Nissui Seiyaku, Co., Ltd.) after incubation at 37 °C for 20 h at inoculum sizes of 10^6 cfu/ml.

Urinary excretion was tested using male mice (Jcl : ICR, 4 weeks old). The test compounds were administered orally to three mice at a dose 25 mg/kg as a parental cephalosporin. Urinary recover rates (%) were calculated from the drug concentrations in urine at 0 to 4 h after

administration. Concentrations were determined by bioassay using *Escherichia coli* K-12 HW8236 as a test organism.

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