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# Synthesis and Pharmacokinetic Profile of 3-Methoxymethyl Cephalosporin Prodrugs

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Preparation and biological activity of prodrug-type 3-methoxymethyl cephalosporins were described. From the mixtures, R- and S-prodrugs were separated and their absolute configurations were determined, and also their bioavailability was investigated.

**Key words :** 3-Methoxymethylcephalosporins, Prodrug, Cycloalkylcarbonateoxyethyl, Oral cephalosporin

## INTRODUCTION

3-Methoxymethyl cephalosporins have already been reported as the partial structure of cefodoxime and cefdaloxime. Cefodoxime proxetil (Fujimoto *et al.*, 1987) and cefdaloxime pentexil (Adam *et al.*, 1989) are the carrier-linked type prodrugs of cefodoxime and cefdaloxime, respectively (Fig. 1). The former is one of oral cephalosporins in the market and sold as a R/S mixture, while the latter is sold as pure S-isomer which is known to have higher enteral absorption than R-isomer. We have introduced different substituents from the above prodrugs at C-4 positions, namely, cycloalkylcarbonateoxyethyl derivatives. In the previous reports (Jung *et al.*, 1997) we also were able to separate both R and S isomer, and furthermore, to determine their absolute configurations (*vide infra*). The compound **2A** (p-TSA salt) and **2B** (HCl salt) are proven to have R- and S-configuration, respectively. Bioavailability of the compounds, **4aA-4bB, 4, 7aA-7bB,** and **7** was investigated.

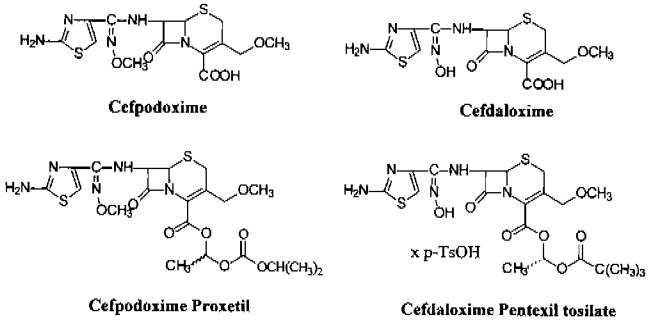


**Fig. 1.**

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## RESULTS AND DISCUSSION

### Chemistry

The starting material, 7-ACA was converted to the compound **1a, 1b** (Hirayama *et al.*, 1991). As in the previous works (Jung *et al.*, 1994), the two diastereomers were successfully separated using p-toluenesulfonic acid or dry HCl to give **2aA, 2bA, 2aB**, and **2bB** spectroscopically homogeneously. The isomers **2A** and **2B** were coupled with 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (FMS was used to activate the acid moiety (Lee *et al.*, 1987)) to afford compounds **3A** and **3B**. To enhance stability and purity, the resulting **3A** and **3B** were converted to their tosylate salts, **4A** and **4B** by the treatment of p-toluenesulfonic acid (Scheme 1).

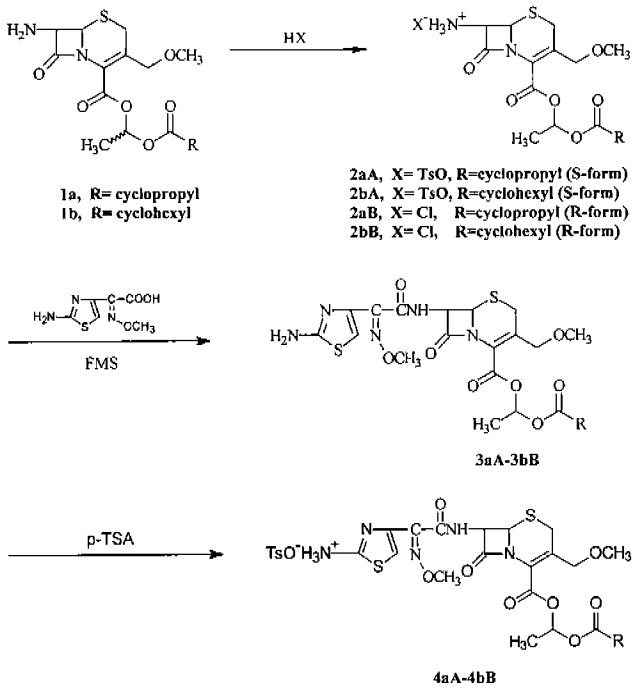
When the diastereomeric mixture **1** was converted directly to **4**, a diastereomeric mixture at a 1:1 ratio was obtained (Scheme 2).

For the 7-hydroxyimino analog, each of the isomer **2aA** through **2bB** was reacted with 2-(2-triphenylmethylaminothiazol-4-yl)-2-triphenylmethyloxyiminoacetic acid in the presence of dimethylaniline(DMA) and $POCl_3$ to give compounds **5aA** through **5bB**, respectively. Deprotection of the trityl group and subsequent salt formation afforded **7aA-7bB** (Scheme 3).

Again, when the diastereomeric mixture **1** was converted directly to **7**, a diastereomeric mixture at a 1:1 ratio was obtained (Scheme 4).

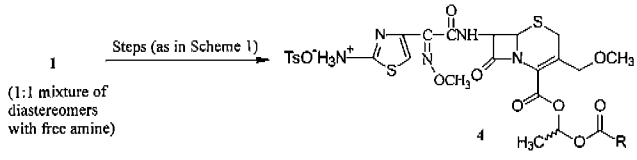
### Biological test

In order to determine whether the prodrug type compounds can be orally absorbed, they were sus-

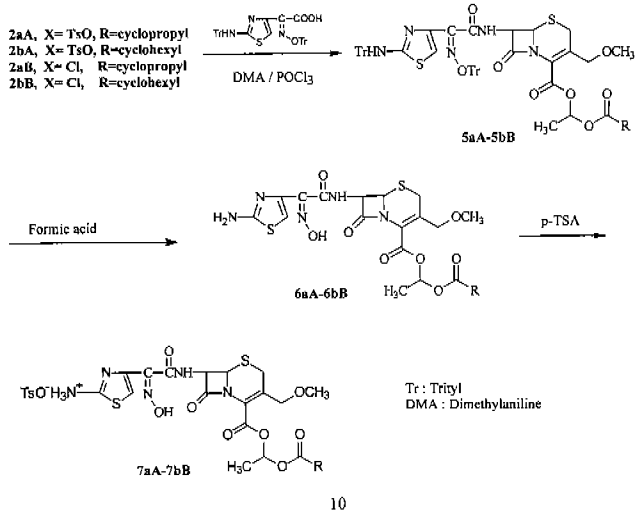



FMS :1-methanesulfonyloxy-6-trifluoromethylbenzotriazole
p-TSA : p-Toluenesulfonic acid

**Scheme 1.**

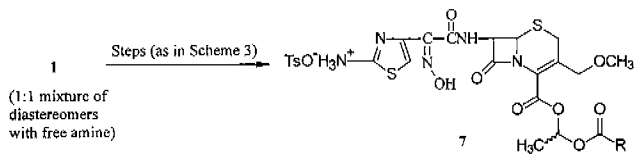



**Scheme 2.**




**Scheme 3.**

pended either in dimethylsulfoxide or 0.5% carboxymethyl cellulose and were administered orally at a dose of 40 mg potency per kg of body weight into mice. The drug concentration in the blood which with-




**Scheme 4.**

drawn from the tail veil after administration of the compounds was determined by microbiological assay with the most susceptible bacterial strains. The AUC (area under the curve) value from zero to four hours after administration was obtained from the plot of blood concentration versus times.

The extent of oral absorption of each diastereomer of prodrug was evaluated by comparing the AUCs of these ester forms given orally with those of the corresponding parent compounds injected subcutaneously. The results were summarized in Table I, showing that both types of esterifications conferred a fairly high oral absorbability compared to the parent compounds. Their relative AUCs were ranged from approximately 33% to 100% of the subcutaneously administered parent compounds. When the same ester forms of the different parent compounds were compared with each other, it was found that esters of the compounds having methoxy group (**4a, 4b, 4aA, 4aB, 4bA, 4bB**) were absorbed better than those having hydroxy group (**7a, 7b, 7aA, 7aB, 7bB, 7bB**). Furthermore, it was noticed that their bioavailability was increased when the both esters (**4a, 4b, 7a, 7b**) were in R/S mixture form.

## EXPERIMENTAL SECTION

**General:** Melting Points were determined on a Thomas-Hoover apparatus and uncorrected. IR spectra were taken on a Shimadzu IR-435 spectrophotometer. $^1$H NMR spectra were recorded at 300 MHz and 500 MHz on a Bruker AM-300 NMR and AMX-500 NMR spectrometer. The following abbreviations are used: s, singlet; d, doublet; dd, double doublet; q, quartet; m,

**Table I.** Oral absorptivity of C-4 esters of 3-methoxymethyl cephalosporins

| C-7 Methoxyimino compounds | | C-7 Hydroxyimino compounds | |
|---|---|---|---|
| Compounds | Relative AUC (%) | Compounds | Relative AUC (%) |
| cefpodoxime | | cefdaloxime | |
| **4a** | 87 | **7a** | 68 |
| **4b** | 100 | **7b** | 43 |
| **4aB** | 59 | **7aA** | 33 |
| **4aB** | 73 | **7aB** | 46 |
| **4bA** | 82 | **7bA** | 36 |
| **4bB** | 49 | **7bB** | 46 |

multiplet; brs, broad singlet; ABq, AB quartet.

**[1-(Cyclopropanecarboxy)-1-methyl]methyl 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (3aA and 3aB)**

To a stirred solution of 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (0.50 g, 2.5 mmol) and 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS, 0.65 g, 2.3 mmol) in DMF (15 mL) at 0°C were added triethylamine (0.25 g, 2.5 mmol) and **2aA** (1.06 g, 2.0 mmol). After stirring at room temperature for 2 h, the reaction mixture was poured into a mixture of EtOAc (100 mL) and aq. $NaHCO_3$. The separated EtOAc layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with n-hexane to give 1.02 g (94%) of **3aA** as a powder. **3aB** was prepared in the same manner. Yield 91%.

**3aA:** mp 111~114°C; IR (KBr) $cm^{-1}$ 3400, 2900, 1780, 1740; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 1 H, NH), 6.98 (q, 1 H, $CO_2CH$), 6.74 (s, 1 H, 5-position aminothiazole-H), 6.04 (dd, 1 H, 7-H), 5.59 (brs, 2 H, $NH_2$), 5.06 (d, 1 H, 6-H), 4.29 (ABq, 2 H, $C\underline{H}_2OCH_3$), 4.02 (s, 3 H, $OCH_3$), 3.54 (brs, 2 H, 2-H), 3.30 (s, 3 H, $CH_2OC\underline{H}_3$), 1.60 (m, 1 H, cyclopropyl-H), 1.55 (d, 3 H, $CHC\underline{H}_3$), 1.04~0.85 (m, 4 H, cyclopropyl-H).

**3aB:** mp 106~108°C; IR (KBr) $cm^{-1}$ 3400, 2900, 1780, 1740; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 1 H, NH), 7.04 (q, 1 H, $CO_2CH$), 6.77 (s, 1 H, 5-position aminothiazole-H), 6.05 (dd, 1 H, 7-H), 5.57 (brs, 2 H, $NH_2$), 5.08 (d, 1 H, 6-H), 4.30 (ABq, 2 H, $C\underline{H}_2OCH_3$), 4.06 (s, 3 H, $OCH_3$), 3.56 (brs, 2 H, 2-H), 3.33 (s, 3 H, $CH_2OC\underline{H}_3$), 1.64 (m, 1 H, cyclopropyl-H), 1.56 (d, 3 H, $CHC\underline{H}_3$), 1.10-0.88 (m, 4 H, cyclopropyl-H).

**[1-(Cyclohexanecarboxy)-1-methyl]methyl 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (3bA and 3bB)**

The reaction between 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (0.50 g, 2.5 mmol) and **2bA** (1.08 g, 2.0 mmol) in the presence of 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole (0.65 g, 2.3 mmol) afforded 0.99 g of **3bA** (90%). **3bB** was prepared in the same manner in 79% yield.

**3bA:** mp 106~109°C; IR (KBr) $cm^{-1}$ 3400, 2910, 1780, 1750; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 1 H, NH), 6.96 (q, 1 H, $CO_2CH$), 6.74 (s, 1 H, 5-position aminothiazole-H), 6.03 (dd, 1 H, 7-H), 5.57 (brs, 2 H, $NH_2$), 5.05 (d, 1 H, 6-H), 4.31 (ABq, 2 H, $C\underline{H}_2OCH_3$), 4.02 (s, 3 H, $OCH_3$), 3.52 (brs, 2 H, 2-H), 3.30 (s, 3 H, $CH_2OC\underline{H}_3$), 2.28 (m, 1 H, cyclohexyl-H), 1.50 (d, 3 H, $CHC\underline{H}_3$), 1.89~1.16 (m, 10 H, cyclohexyl-H).

**3bB:** mp 101~104°C; IR (KBr) $cm^{-1}$ 3400, 2910, 1780, 1750; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 1 H, NH), 7.01 (q, 1 H, $CO_2CH$), 6.76 (s, 1 H, 5-position aminothiazole-H), 6.06 (dd, 1 H, 7-H), 5.57 (brs, 2 H, $NH_2$), 5.09 (d, 1 H, 6-H), 4.31 (ABq, 2 H, $C\underline{H}_2OCH_3$), 4.06 (s, 3 H, $OCH_3$), 3.54 (brs, 2 H, 2-H), 3.33 (s, 3 H, $CH_2OC\underline{H}_3$), 2.32 (m, 1 H, cyclohexyl-H), 1.54 (d, 3 H, $CHC\underline{H}_3$), 1.94-1.26 (m, 10 H, cyclohexyl-H).

**Tosylate salts of [1-(cyclopropanecarboxy)-1-methyl]methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (4aA and 4aB)**

To a stirred solution of **3aA** (2.15 g, 3.98 mmol) in 10 mL EtOAc was added dropwise a solution of p-toluenesulfonic acid monohydrate (0.76 g, 3.98 mmol) in 30 mL EtOAc. After stirring at room temperature for 1 h, the precipitates were filtered and the filter cake was washed with EtOAc, then recrystallized from $CHCl_3$ to give 2.50 g (88%) of **4aA** as a white solid. **4aB** was prepared in the same manner in 95% yield.

**4aA:** mp 102~104°C; IR (KBr) $cm^{-1}$ 3100~3000, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 9.83 (d, 1 H, NH), 7.30 (ABq, 4 H, arom. H), 6.93 (s, 1 H, 5-position aminothiazole H), 6.88 (q, 1 H, $CO_2CH$), 5.84 (dd, 1 H, 7-H), 5.23 (d, 1 H, 6-H), 4.15 (ABq, 2 H, $C\underline{H}_2$-$OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.58 (ABq, 2 H, 2-H), 3.19 (s, 3 H, $CH_2$-$OC\underline{H}_3$), 2.28 (s, 3 H, Ph-$C\underline{H}_3$), 1.63 (m, 1 H, cyclopropyl-H), 1.46 (d, 3 H, $CHC\underline{H}_3$), 0.93 (m, 4 H, cyclopropyl-H).

**4aB:** mp 101~103°C; IR (KBr) $cm^{-1}$ 3100~3000, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 9.82 (d, 1 H, NH), 7.30 (ABq, 4 H, arom. H), 6.94 (s, 1 H, 5-position aminothiazole H), 6.93 (q, 1 H, $CO_2CH$), 5.81 (dd, 1 H, 7-H), 5.20 (d, 1 H, 6-H), 4.09 (ABq, 2 H, $C\underline{H}_2$-$OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.56 (ABq, 2 H, 2-H), 3.21 (s, 3 H, $CH_2$-$OC\underline{H}_3$), 2.28 (s, 3 H, Ph-$C\underline{H}_3$), 1.63 (m, 1 H, cyclopropyl-H), 1.47 (d, 3 H, $CHC\underline{H}_3$), 0.93 (m, 4 H, cyclopropyl-H).

**Tosylate salts of [1-(cyclohexanecarboxy)-1-methyl]methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (4bA and 4bB)**

To a stirred solution of **3bA** (2.30 g, 3.98 mmol) in 10 mL EtOAc was added dropwise a solution of p-toluenesulfonic acid monohydrate (0.76 g, 3.98 mmol) in 30 mL EtOAc. After stirring at room temperature for 1 h, the precipitates were filtered and the filter cake was washed with EtOAc, then recrystallized from $CHCl_3$ to give 2.73 g (92%) of **4bA** as a white solid. **4bB** was prepared in the same manner in 85% yield.

**4bA:** mp 104~106°C; IR (KBr) $cm^{-1}$ 3100, 2910, 1780, 1750; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 9.82 (d, 1 H, NH), 7.30 (ABq, 4 H, arom. H), 6.93 (s, 1 H, 5-position aminothiazole H), 6.88 (q, 1 H, $CO_2CH$), 5.83 (dd, 1 H, 7-H), 5.22 (d, 1 H, 6-H), 4.18 (ABq, 2 H, $C\underline{H}_2$-$OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.58 (ABq, 2 H, 2-

H), 3.19 (s, 3 H, $CH_2$-$OCH_3$), 2.28 (s, 3 H, Ph-$CH_3$), 2.30 (m, 1 H, cyclohexyl-H), 1.89-1.23 (m, 10 H, cyclohexyl-H), 1.45 (d, 3 H, $CHCH_3$).

**4bB:** mp 97~99°C; IR (KBr) $cm^{-1}$ 3100, 2910, 1790~1780, 1750; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 9.82 (d, 1 H, NH), 7.30 (ABq, 4 H, arom. H), 6.94 (s, 1 H, 5-position aminothiazole H), 6.93 (q, 1 H, $CO_2CH$), 5.80 (dd, 1 H, 7-H), 5.20 (d, 1 H, 6-H), 4.12 (ABq, 2 H, $CH_2$-$OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.57 (ABq, 2 H, 2-H), 3.19 (s, 3 H, $CH_2$-$OCH_3$), 2.28 (s, 3 H, Ph-$CH_3$), 2.30 (m, 1 H, cyclohexyl-H), 1.89-1.23 (m, 10 H, cyclohexyl-H), 1.46 (d, 3 H, $CHCH_3$).

### Tosylate salt of [1-(cyclopropanecarboxy)-1-methyl]-methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino-acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (4a)

1:1 diastereomeric mixture **4a** was prepared from diastereomeric mixture **1a** in the same manner described for compounds **3aA~4aA**. mp 90~91°C; IR (KBr) $cm^{-1}$ 3300, 3100, 2900, 1780, 1740; $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 9.83 (d, 2 H, NH), 7.30 (ABq, 8 H, arom. H), 6.94, 6.93 (2xs, 2 H, 5-position aminothiazole H), 6.94, 6.88 (2xq, 2 H, $CO_2CH$), 5.83 (m, 2 H, 7-H), 5.23, 5.20 (2xd, 2 H, 6-H), 4,15, 4.09 (2xABq, 4 H, $CH_2$-$OCH_3$), 3.93 (s, 6 H, $OCH_3$), 3.57 (ABq, 4 H, 2-H), 3.21 (s, 6H, $CH_2$-$OCH_3$), 2.28 (s, 6 H, Ph-$CH_3$), 1.64 (m, 2 H, cyclopropyl-H), 1.47, 1.46 (2xd, 6 H, $CHCH_3$), 0.94 (m, 8 H, cyclopropyl-H).

### Tosylate salt of [1-(cyclohexanecarboxy)-1-methyl]methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (4b)

The title compound (1:1 diastereomeric mixture) was prepared in the same manner described above using the diastereomeric mixture **1b**. mp 101~103°C; IR (KBr) $cm^{-1}$ 3100, 2910, 1790, 1750; $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 9.82 (d, 2 H, NH), 7.30 (ABq, 8 H, arom. H), 6.94, 6.93 (2xs, 2 H, 5-position aminothiazole H), 6.93, 6.88 (2xq, 2 H, $CO_2CH$), 5.83, 5.80 (2xdd, 2 H, 7-H), 5.22, 5.20 (2xd, 2 H, 6-H), 4.14 (2xABq, 4 H, $CH_2$-$OCH_3$), 3.93 (s, 6 H, $OCH_3$), 3.58, 3.57 (2xABq, 4 H, 2-H), 3.19 (s, 6 H, $CH_2$-$OCH_3$), 2.28 (s, 6 H, Ph-$CH_3$), 2.31 (m, 2 H, cyclohexyl-H), 1.88~1.28 (m, 20 H, cyclohexyl-H), 1.46, 1.45 (2xd, 3 H, $CHCH_3$).

### [1-(Cyclopropanecarboxy)-1-methyl]methyl 7-[2-(2-tritylaminothiazol-4-yl)-2-(Z)-trityloximinoacetamido]-3-methyl-3-cephem-4-carboxylates (5aA and 5aB)

To a stirred solution of 2-(2-tritylamino-4-thiazol-4-yl)-2-trityloxyiminoacetic acid (0.79 g, 1.18 mmol) and **2aA** (0.56 g, 1.07 mmol) in $CH_2Cl_2$ at 0°C was added dimethylaniline (0.30 mL, 2.36 mmol). After stirring for 30 min, 0.11 mL of $POCl_3$ was added at the same temperature then stirred for additional 1 h at room temperature. The reaction mixture was poured into a mixture of EtOAc and aq. $NaHCO_3$. The layers were separated, the organic layer was washed with brine, then dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was triturated with n-hexane to give 0.99 g (92%) of **5aA, 5aB** was prepared in the same manner. Yield 97%.

**5aA:** mp 102~103°C; IR (KBr) $cm^{-1}$ 3400, 2900, 1780, 1740; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.36~7.20 (m, 30 H, arom. H), 7.02 (q, 1 H, $CO_2CH$), 6.85 (brs, 1 H, NH), 6.72 (d, 1 H, NH, C-7), 6.43 (s, 1 H, 5-position aminothiazole-H), 6.06 (dd, 1 H, 7-H), 5.03 (d, 1 H, 6-H), 4.30 (brs, 2 H, $CH_2OCH_3$), 3.40 (ABq, 2 H, 2-H), 3.31 (s, 3 H, $OCH_3$), 1.62 (m, 1 H, cyclopropyl-H), 1.57 (d, 3 H, CH-$CH_3$), 1.10~0.75 (m, 4 H, cyclopropyl-H).

**5aB:** mp 104~106°C; IR (KBr) $cm^{-1}$ 3400, 3050, 2900, 1780, 1740; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.36~7.15 (m, 30 H, arom. H), 7.06 (q, 1 H, $CO_2CH$), 6.85 (brs, 1 H, NH), 6.73 (d, 1 H, NH, C-7), 6.43 (s, 1 H, 5-position aminothiazole-H), 6.03 (dd, 1 H, 7-H), 5.02 (d, 1 H, 6-H), 4.28 (brs, 2 H, $CH_2OCH_3$), 3.39 (ABq, 2 H, 2-H), 3.29 (s, 3 H, $OCH_3$), 1.60 (m, 1 H, cyclopropyl-H), 1.55 (d, 3 H, CH-$CH_3$), 1.12-0.80 (m, 4 H, cyclopropyl-H).

### [1-(Cyclohexanecarboxy)-1-methyl]methyl 7-[2-(2-tritylaminothiazol-4-yl)-2-(Z)-trityloximinoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (5bA and 5bB)

The reaction between 2-(2-tritylamino-4-thiazol-4-yl)-2-trityloxyimino acetic acid (0.82 g, 1.22 mmol) and **2bA** (0.61 g, 1.07 mmol) in the presence of dimethylaniline (0.31 mL, 2.44 mmol) and 0.11 mL $POCl_3$ under the same conditions to the synthesis of **5aA** afforded 0.96 g (85%) of **5bA. 5bB** was prepared in the same manner in 88% yield.

**5bA:** mp 112~113°C; IR (KBr) $cm^{-1}$ 3400, 2910, 1785, 1750; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.36~7.21 (m, 31 H, arom. H, NH, C-7), 6.99 (q, 1 H, $CO_2CH$), 6.84 (brs, 1 H, NH), 6.42 (s, 1 H, 5-position aminothiazole-H), 6.05 (dd, 1 H, 7-H), 5.02 (d, 1 H, 6-H), 4.30 (brs, 2 H, $CH_2OCH_3$), 3.47 (ABq, 2 H, 2-H), 3.31 (s, 3H, $OCH_3$), 2.31 (m, 1 H, cyclohexyl-H), 1.60 (d, 3 H, CH-$CH_3$), 1.92~1.15 (m, 10 H, cyclohexyl-H).

**5bB:** mp 116~118°C; IR (KBr) $cm^{-1}$ 3400, 2910, 1785, 1750; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.36~7.15 (m, 31 H, arom. H, NH, C-7), 7.05 (q, 1 H, $CO_2CH$), 6.86 (brs, 1 H, NH), 6.43 (s, 1 H, 5-position aminothiazole-H), 6.01 (dd, 1 H, 7-H), 5.02 (d, 1 H, 6-H), 4.27 (ABq, 2 H, $CH_2OCH_3$), 3.38 (ABq, 2 H, 2-H), 3.29 (s, 3 H, $OCH_3$), 2.32 (m, 1 H, cyclohexyl-H), 1.58 (d, 3 H, CH-$CH_3$), 2.05~1.15 (m, 10 H, cyclohexyl-H).

**[1-(Cyclopropanecarboxy)-1-methyl]methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (6aA and 6aB)**

A solution of **5aA** (0.86 g, 0.85 mmol) in 98% formic acid : water=4 : 1 was stirred at room temperature for 2 h. The insoluble materials were filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc then washed with aq. $NaHCO_3$, brine, and then with water. The organic layer was dried over anhydrous magnesium sulfate, then concentrated. The residue was recrystallized from n-hexane to give 0.32 g (73%) of **6aA. 6aB** was prepared in the same manner in 75% yield.

**6aA:** mp 112~114°C; IR (KBr) $cm^{-1}$ 3300, 2900, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.31 (s, 1 H, OH), 9.49 (d, 1 H, NH), 7.13 (brs, 2 H, $NH_2$), 6.89 (q, 1 H, $CO_2CH$), 6.65 (s, 1 H, 5-position aminothiazole H), 5.85 (dd, 1 H, 7-H), 5.20 (d, 1 H, 6-H), 4.13 (brs, 2 H, $CH_2OCH_3$), 3.56 (ABq, 2 H, 2-H), 3.20 (s, 3 H, $OCH_3$), 1.68 (m, 1 H, cyclopropyl-H), 1.47 (d, 3 H, CH-$CH_3$), 0.90 (m, 4 H, cyclopropyl-H).

**6aB:** mp 147~150°C; IR (KBr) $cm^{-1}$ 3300, 2910, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.32 (s, 1 H, OH), 9.48 (d, 1 H, NH), 7.14 (brs, 2H, $NH_2$), 6.95 (q, 1 H, $CO_2CH$), 6.66 (s, 1 H, 5-position aminothiazole H), 5.82 (dd, 1 H, 7-H), 5.18 (d, 1 H, 6-H), 4.09 (brs, 2 H, $CH_2OCH_3$), 3.54 (ABq, 2 H, 2-H), 3.20 (s, 3 H, $OCH_3$), 1.67 (m, 1 H, cyclopropyl-H), 1.48 (d, 3 H, CH-$CH_3$), 0.90 (m, 4 H, cyclopropyl-H).

**[1-(Cyclohexanecarboxy)-1-methyl]methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (6bA and 6bB)**

From 0.92 g (0.87 mmol) of **5bA,** 0.32 g (64%) of **6bA** was obtained under the similar conditions to the synthesis of **6aA. 6bB** was prepared in 75% yield in the same manner.

**6bA:** mp 111~113°C; IR (KBr) $cm^{-1}$ 3400, 2900, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.30 (s, 1 H, OH), 9.49 (d, 1 H, NH), 7.13 (brs, 2 H, $NH_2$), 6.88 (q, 1 H, $CO_2CH$), 6.64 (s, 1 H, 5-position aminothiazole H), 5.83 (dd, 1 H, 7-H), 5.19 (d, 1 H, 6-H), 4.12 (brs, 2 H, $CH_2OCH_3$), 3.55 (ABq, 2 H, 2-H), 3.19 (s, 3 H, $OCH_3$), 2.33 (m, 1 H, cyclohexyl-H), 1.81~1.14 (m, 10 H, cyclohexyl-H), 1.45 (d, 3 H, CH-$CH_3$).

**6bB:** mp 110~112°C; IR (KBr) $cm^{-1}$ 3300, 2900, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.31 (s, 1 H, OH), 9.48 (d, 1 H, NH), 7.13 (brs, 2 H, $NH_2$), 6.94 (q, 1 H, $CO_2CH$), 6.64 (s, 1 H, 5-position aminothiazole H), 5.81 (dd, 1 H, 7-H), 5.17 (d, 1 H, 6-H), 4.10 (brs, 2 H, $CH_2OCH_3$), 3.57 (ABq, 2 H, 2-H), 3.19 (s, 3 H, $OCH_3$), 2.33 (m, 1 H, cyclohexyl-H), 1.82~1.14 (m, 10 H, cyclohexyl-H), 1.46 (d, 3 H, CH-$CH_3$).

**Tosylate salts of [1-(cyclopropanecarboxy)-1-methyl] methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (7aA and 7aB)**

To a stirred solution **6aA** (0.29 g, 0.56 mmol) in 5 mL EtOAc was added dropwise a solution of p-toluenesulfonic acid monohydrate (0.11 g, 0.56 mmol) in 10 mL EtOAc. After stirring at room temperature for 1 h, the precipitates were filtered and the filter cake was washed with EtOAc to give 0.31 g (81%) of **7aA. 7aB** was prepared in the same manner. Yield 75%.

**7aA:** mp 187~190°C; IR (KBr) $cm^{-1}$ 3300, 3100, 2900, 1770, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 12.25 (brs, 1 H, OH), 9.72 (d, 1 H, NH), 8.85 (brs, $NH_3^+$), 7.31 (ABq, 4 H, arom. H), 6.88 (q, 1 H, $CO_2CH$), 6.87 (s, 1 H, 5-position aminothiazole H), 5.79 (dd, 1 H, 7-H), 5.19 (d, 1 H, 6-H), 4.13 (brs, 2 H, $CH_2OCH_3$), 3.54 (ABq, 2 H, 2-H), 2.29 (s, 3 H, Ph-$CH_3$), 2.03 (s, 3 H, $CH_3$), 1.64 (m, 1 H, cyclopropyl-H), 1.46 (d, 3 H, CH-$CH_3$), 0.96 (m, 4 H, cyclopropyl-H).

**7aB:** mp 179~181°C; IR (KBr) $cm^{-1}$ 3300, 3150, 2900, 1780, 1740; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 12.25 (brs, 1 H, OH), 9.70 (d, 1 H, NH), 7.30 (ABq, 4 H, arom. H), 6.92 (q, 1 H, $CO_2CH$), 6.85 (s, 1 H, 5-position aminothiazole H), 5.73 (dd, 1 H, 7-H), 5.14 (d, 1 H, 6-H), 4.10 (brs, 2 H, $CH_2OCH_3$), 3.50 (ABq, 2 H, 2-H), 2.28 (s, 3 H, Ph-$CH_3$), 2.00 (s, 3 H, $CH_3$), 1.63 (m, 1 H, cyclopropyl-H), 1.46 (d, 3 H, CH-$CH_3$), 0.90 (m, 4 H, cyclopropyl-H).

**Tosylate salts of [1-(cyclohexanecarboxy)-1-methyl]-methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylates (7bA and 7bB)**

**7bA** and **7bB** were prepared under the similar conditions to the synthesis of **7aA** and **7aB** in 83% and 88% yield, respectively.

**7bA:** mp 185~187°C; IR (KBr) $cm^{-1}$ 3300, 3100, 2910, 1770, 1750; $^1H$ NMR (300 MHz, $CDCl_3$) δ 12.23 (brs, 1 H, OH), 9.69 (d, 1 H, NH), 8.85 (brs, $NH_3^+$), 7.30 (ABq, 4 H, arom. H), 6.87 (q, 1 H, $CO_2CH$), 6.86 (s, 1 H, 5-position aminothiazole H), 5.76 (dd, 1 H, 7-H), 5.17 (d, 1 H, 6-H), 4.15 (ABq, 2 H, $CH_2OCH_3$), 3.52 (ABq, 2 H, 2-H), 2.32 (m, 1 H, cyclohexyl-H), 2.28 (s, 3 H, Ph-$CH_3$), 2.02 (s, 3 H, $CH_3$), 1.80~1.20 (m, 10 H, cyclohexyl-H), 1.41 (d, 3 H, CH-$CH_3$).

**7bB:** mp 172~175°C; IR (KBr) $cm^{-1}$ 3300, 3150, 2910, 1780, 1750; $^1H$ NMR (300 MHz, $CDCl_3$) δ 12.27 (brs, 1 H, OH), 9.72 (d, 1 H, NH), 8.85 (brs, $NH_3^+$), 7.31 (ABq, 4 H, arom. H), 6.94 (q, 1 H, $CO_2CH$), 6.87 (s, 1 H, 5-position aminothiazole H), 5.74 (dd, 1 H, 7-H), 5.16 (d, 1 H, 6-H), 4.13 (ABq, 2 H, $CH_2OCH_3$), 3.52 (ABq, 2 H, 2-H), 2.33 (m, 1 H, cyclohexyl-H), 2.29 (s, 3 H, Ph-$CH_3$), 2.02 (s, 3 H, $CH_3$), 1.81~1.14 (m, 10

H, cyclohexyl-H), 1.46 (d, 3 H, CH-C$\underline{H}_3$).

**Tosylate salts of [1-(cyclopropanecarboxy)-1-methyl]-methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyimino-acetamido]-3-methoxymethyl-3-cephem-4-carboxy-late (7a)**

A 1:1 diastereomeric mixture **7a**, was prepared from diastereomeric mixture **1a** in the same manner described for the compounds **5aA~7aA**. mp 189~191°C; IR (KBr) $cm^{-1}$ 3300, 3100, 2900, 1780, 1740; $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 12.25 (brs, 2 H, OH), 9.07 (d, 2 H, NH), 9.47 (brs, 6 H, $NH_3^+$), 7.30 (ABq, 8 H, arom. H), 6.93, 6.89 (2xq, 2 H, $CO_2CH$), 6.87, 6.86 (2xs, 2 H, 5-position aminothiazole H), 5.77 (m, 2 H, 7-H), 5.17 (2xd, 2 H, 6-H), 3.50 (2xABq, 4 H, 2-H), 2.29 (s, 6 H, Ph-C$\underline{H}^3$), 2.03, 1.02 (2xs, 6 H, $CH_3$), 1.64 (m, 2 H, cyclopropyl-H), 1.47 (2xd, 6 H, CH-C$\underline{H}_3$), 0.95~0.89 (m, 8 H, cyclopropyl-H).

**Tosylate salt of [1-(cyclohexanecarboxy)-1-methyl]-methyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyimino-acetamido]-3-methoxymethyl-3-cephem-4-car-boxylate (7b)**

The title compound was prepared in the same manner described above using the diastereomeric mixture **1b**. mp 183~185°C; IR (KBr) $cm^{-1}$ 3300, 3100, 2900, 1780, 1750; $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 12.24 (brs, 2 H, OH), 9.70 (2xd, 2 H, NH), 9.50 (brs, 6 H, $NH_3^+$), 7.31 (ABq, 8 H, arom. H), 6.95, 6.90 (2xq, 2 H, $CO_2CH$), 6.86, 6,85 (2xs, 2 H, 5-position aminothiazole H), 5.75 (m, 2 H, 7-H), 5.17 (2xd, 2 H, 6-H), 3.52 (2xABq, 4 H, 2-H), 2.33 (m, 2 H, cyclohexyl-H), 2.29 (2, 6 H, Ph-C$\underline{H}_3$), 1.82-1.21 (m, 20 H, cyclohexyl-H), 1.46 (2xd, 6 H, CH-C$\underline{H}_3$).

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