STUDIES ON β-LACTAM ANTIBIOTICS

X.† SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 7β-[(Z)-2-(2-AMINO-4-THIAZOLYL)-2-(CARBOYMETHOXY-IMINO)ACETAMIDO]CEPHALOSPORIN DERIVATIVES

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The synthesis of 7β-[(Z)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)acetamido]-cephalosporins (**2a**~**h**) modified at the C-3 position of a cephem nucleus and the effect of the C-3 substituents on the antibacterial activity, oral absorptivity and therapeutic activity are discussed. The cephems (**2a** and **2b**) having a C-3 substituent such as hydrogen or vinyl were more potent than other cephalosporins against Gram-negative bacteria. However, the cephalosporin (**2f**) having methylthio group at the 3-position showed the highest absorption rate in rats. These three cephalosporins (**2a, b** and **f**) exhibited equally good protective activities in mice infected. Furthermore, the serum levels of these cephalosporins (**2a, b** and **f**) were examined in dogs, and **2b** and **2f** showed outstanding high and prolonged serum levels.

Recently, extensive studies have been undertaken on new β-lactam antibiotics possessing excellent activity against a variety of Gram-positive and Gram-negative bacteria including β-lactamase-producing strains.[1~6] But, all of them are for parenteral usage.

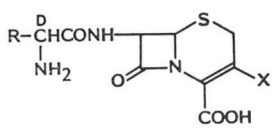
On the other hand, progress has been less evident among the oral cephalosporins. Cephalexin and its analogs (Fig. 1) are less active against Gram-negative bacteria and much less stable against β-lactamase-producing strains than the newer parenteral cephalosporins such as ceftizoxime (**1**, Fig. 2).[7~10]

In our preceding paper,[11] we described the process of finding a new orally active cephalosporin, 7β-[(Z)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)acetamido]-3-cephem-4-carboxylic acid (**2a**) (Fig. 2). **2a** completely differs in structure at the 7-side chain from the commercially available oral cephalosporins (Fig. 1), whereas the structures of cephalexin and its analogs are strikingly similar. They all have an amino substituent and a phenyl or analogous ring on the alpha carbon atom in the 7-acyl group. On the other hand, **2a** has (Z)-carboxymethoxyimino group and 2-amino-4-thiazol ring on the alpha carbon atom in the 7-acyl group. Structurally, **2a** is closely related to ceftizoxime (**1**), and similar to ceftizoxime, **2a** was far more potent than other orally active β-lactams in the antimicrobial activity against a wide range of Gram-negative bacteria, especially against β-lactamase-producing strain such as *Escherichia coli* 28.

In general, the 3-substituent of a cephem nucleus is very important for both antibacterial activity and pharmacokinetic properties. Therefore, we investigated the modification of the 3-substituent in **2** in order to find a new oral cephalosporin with even higher antibacterial potency and oral activity than **2a**.

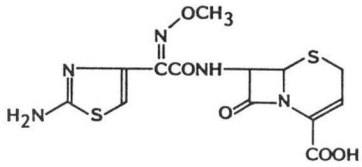
† Paper IX. See ref 13).

Fig. 1.

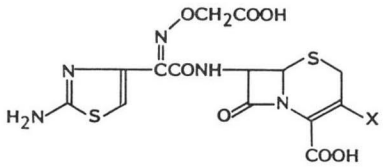


Cephalexin	X=CH_3	R=
Cefaclor	X=Cl	R=
Cephradine	X=CH_3	R=
Cefroxadine	X=OCH_3	R=
Cefadroxil	X=CH_3	R= HO-
Cefatrizine	X= CH_2S	R= HO-

Fig. 2.



Ceftizoxime (**1**)



2

2a	X=H
2b	X=CH=CH_2 (FK027)
2c	X=Cl
2d	X=CH_3
2e	X=OCH_3
2f	X=SCH_3
2g	X=CH_2OCH_3
2h	X=CH_2SCH_3

In this study, we mainly investigated sterically small 3-substituents because cephalexin-like analogs bear sterically small substituents at their 3-position except cefatrizine (Fig. 1).

In this paper, we wish to report the synthesis of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)acetamido]cephalosporins (Fig. 2) modified at the C-3 position, and the effect of the C-3 substituents on antibacterial activity and on urinary and biliary excretion after oral administration of the cephalosporins to rats. In addition, this article presents some results for protective effect on mice infection and serum levels in dogs after oral administration.

Chemistry

As outlined in Scheme 1, the novel 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)-acetamido]cephalosporins were prepared by acylation of 7-aminocephalosporin derivatives (**3c**~**h**) with [(*Z*)-2-*tert*-butoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)]acetic acid (**7**) followed by subsequent removal of protecting groups. The synthesis of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)acetamido]-3-cephem-4-carboxylic acid (**2a**) was previously reported.[12] And the synthesis of **2b** (FK027) was reported in detail in the preceding paper.[13]

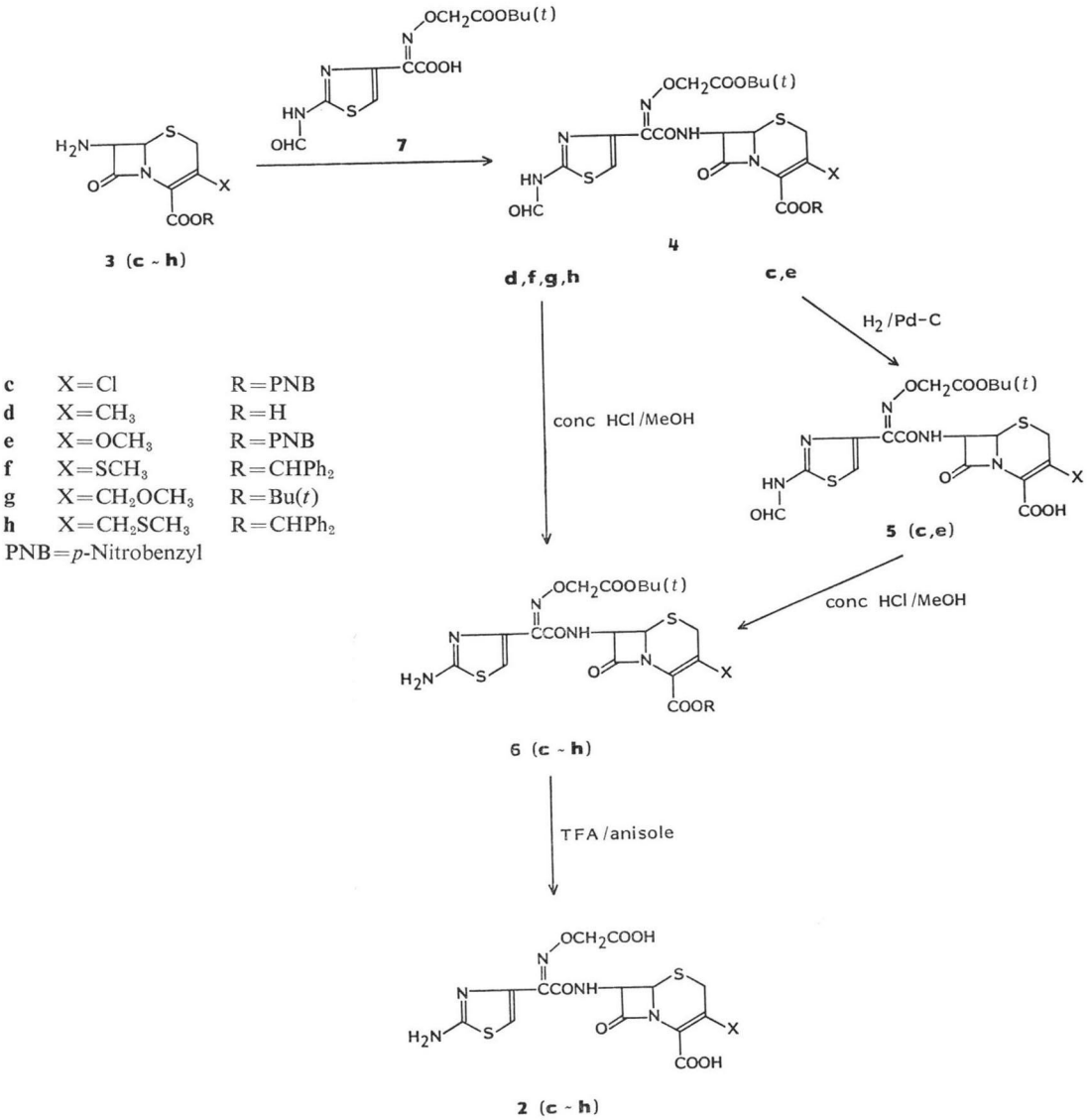
The acid (**7**) was activated with Vilsmeier reagent prepared from *N*,*N*-dimethylformamide (DMF) and phosphoryl chloride ($POCl_3$) for the above coupling reaction. The protecting *p*-nitrobenzyl group of **4c** and **4e** was removed by hydrogenation in the presence of 10% palladium on carbon catalyst. Diphenylmethyl and *tert*-butyl groups were removed by treatment with trifluoroacetic acid (TFA) and anisole. A *N*-formyl group was removed by treatment with concentrated hydrochloric acid and methanol (MeOH).

The structures of the intermediates (**4c**~**h**, **5c**, **5e**, and **6b**~**g**) and **2c**~**h** were confirmed on the basis of IR and NMR spectral data as shown in Tables 4, 5 and 6.

Biological Results and Discussion

The antibacterial activity of the cephalosporins (**2a**~**h**) against selected Gram-positive and Gram-

Scheme 1. General synthetic route of **2c**~**h**.

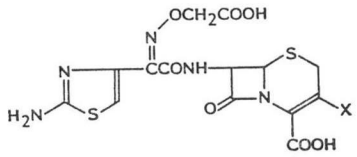


c X=Cl R=PNB
d X=CH_3 R=H
e X=OCH_3 R=PNB
f X=SCH_3 R=$CHPh_2$
g X=CH_2OCH_3 R=Bu(*t*)
h X=CH_2SCH_3 R=$CHPh_2$
PNB=*p*-Nitrobenzyl

negative bacteria are shown in Table 1. For comparison, the MIC values of ceftizoxime (**1**) and cephalexin are listed in Table 1. **2a** and **2b** were about 2 times superior to **2c** (X=Cl) and **2h** (X=CH_2SCH_3) in the antimicrobial activity against Gram-negative organisms. **2f** (X=SCH_3) and **2g** (X=CH_2OCH_3) were 2~8 times inferior to **2b** in the antimicrobial activity. The cephem (**2e**) with methoxy group at the C-3 position was less active than the others against Gram-negative bacteria. However, the activities of all of these cephalosporins (**2a**~**h**) against Gram-negative bacteria were much superior to that of cephalexin. These cephalosporins except for **2f** preserved excellent activity against *E. coli* 28 which is a cephalosporin-resistant strain.

In the next step, the effect of the substituent at the 3-position on excretion after oral administration to rats was studied. On the whole, as listed in Table 2, 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(car-

Table 1. Antibacterial activity of cephalosporins (**2**).



Inoculum size 10^6 cfu/ml

Compounds		MIC (μg/ml)					
No.	X	S.a.*	E.c.-2	E.c. 28	K.p.	P.m.	P.v.
2a	H	25	0.20	0.20	0.10	≦0.025	0.05
2b	$CH=CH_2$ (FK027)	25	0.20	0.39	0.10	≦0.025	≦0.025
2c	Cl	12.5	0.39	0.78	0.10	0.10	≦0.025
2d	CH_3	>100	0.39	0.39	0.20	0.10	0.20
2e	OCH_3	>100	0.78	0.78	0.39	0.39	0.78
2f	SCH_3	50	0.78	1.56	0.20	0.05	0.05
2g	CH_2OCH_3	50	0.78	0.78	0.20	0.10	0.10
2h	CH_2SCH_3	50	0.39	0.78	0.20	0.05	0.05
1 (Ceftizoxime)		6.25	≦0.025	0.05	0.05	≦0.025	≦0.025
Cephalexin		3.13	12.5	12.5	3.13	12.5	100

* S.a.; *Staphylococcus aureus* 209P JC-1, E.c.-2; *Escherichia coli* NIHJ JC-2, E.c. 28; *E. coli* 28 (cephalosporinase producer), K.p.; *Klebsiella pneumoniae* 12, P.m.; *Proteus mirabilis* 1, P.v.; *P. vulgaris* 1.

Table 2. 24 hours urinary and biliary recovery (%) of **2a**~**h** after oral administration in rats.

Compounds		Recovery (%)	
No.	X	Urine	Bile
2a	H	41.0	3.8
2b	$CH=CH_2$ (FK027)	34.0	18.2
2c	Cl	35.8	15.5
2d	CH_3	25.7	9.2
2e	OCH_3	41.6	18.0
2f	SCH_3	51.6	41.1
2g	CH_2OCH_3	31.2	13.6
2h	CH_2SCH_3	12.1	17.2

Dose: 100 mg/kg.

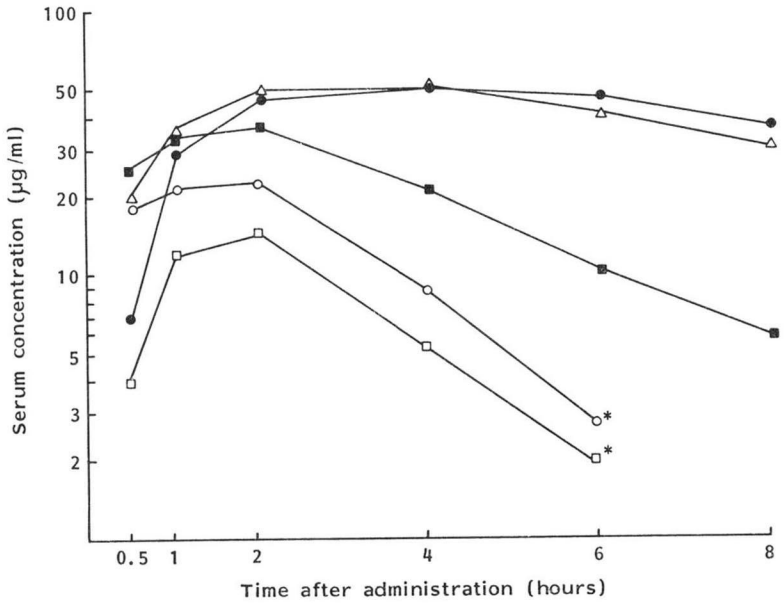
Table 3. Protective activities of **2a**, **b**, **c** and **f** and cephalexin against *E. coli* 29 infection in mice.

Compounds		MIC* (μg/ml)	ED_{50} (mg/kg)
No.	X		
2a	H	0.05	0.24
2b	$CH=CH_2$	0.05	0.33
2c	Cl	0.05	1.91
2f	SCH_3	0.05	0.37
Cephalexin		3.13	5.95

* Agar dilution method with Mueller-Hinton agar at 37°C for 18 hours.
Inoculum size 10^6 cfu/ml.

boxymethoxyimino)acetamido]cephalosporins (**2**) bearing a sterically small substituent at the C-3 position showed good recovery rate in rats. The oral absorptivity of the cephalosporins (**2a**, **b**, **c**, **e** and **g**) were found to be similar to one another. However, the oral absorptivity of **2d** and **2h** was significantly lower than that of the others. Remarkably, the cephalosporin (**2f**) bearing methylthio group at the 3-position showed the best oral absorptivity among these cephalosporins. Although **2f** showed less potency in its *in vitro* antibacterial activity than the analogs (**2a**, **b** and **c**), it was expected to have the same chemotherapeutic potency. Thus, the protective effects on mice infection and the serum concentrations attained in dogs after oral administration were examined to evaluate the potential utility of the cephalosporins (**2a**, **b**, **c** and **f**).

Fig. 3. Serum levels in dogs after oral administration. (Beagle, 40 mg/kg, $n=3$)
* **2a** and amoxicillin were not detected at 8 hours after dosing.
□ **2a**, ● **2b**, △ **2f**, ○ amoxicillin, ■ cephalexin.



Protective activities of the four cephalosporins and cephalexin against *E. coli* 29 infection in mice are illustrated in Table 3. The effectiveness after the oral administration of the cephalosporins (**2a**, **b** and **f**) on mice infection were superior than that of cephalexin and approximately similar. **2c** showed low protective activity similar to cephalexin. The mean serum concentration time curves of the cephalosporins (**2a**, **b** and **f**), cephalexin and amoxicillin in dogs after oral dosing are illustrated in Fig. 3. **2b** and **2f** produced higher and more prolonged serum levels than cephalexin and amoxicillin, whereas the serum levels of **2a** was lower than that of amoxicillin and was not long-lasting.

As mentioned above, **2b** and **2f** showed the most unique chemotherapeutic and pharmacokinetic characteristics. However, **2b** showed even higher antibacterial potency against β-lactamase-producing strain, and further two-times higher serum levels (**2b**, 11 μg/ml) 24 hours after oral dosing in dogs compared with **2f**.

Consequently, **2b** (FK027, X=CH=CH_2) was chosen as a candidate for human trial. FK027 completely differs in structure from the commercially available oral cephalosporins. In addition, FK027 was observed to be very stable to both penicillinase- and cephalosporinase-type β-lactamases.[14] Moreover, FK027 has unique pharmacological properties of oral absorption and long-acting efficacy in comparison with cephalexin-type drugs.[15]

Experimental

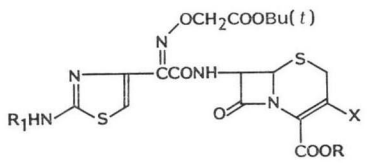
NMR spectra were recorded at 60 MHz on a JNM-PMX 60 NMR spectrometer and at 100 MHz on a Jeol-MH 100 NMR spectrometer using tetramethylsilane as an internal standard. IR specta were taken on a Hitachi 260-10 spectrophotometer or Shimadzu IR-420 spectrophotometer.

MICs were determined by the agar dilution method using heart infusion agar (Difco) after incubation at 37°C for 20 hours and with an inoculum size of about 10^6 cfu/ml. *E. coli* 28 is a cephalosporin-

Table 4. Yield, NMR and IR spectral data of **4c~h**.

No.	Compounds X	R	NMR (DMSO-d_6, δ) CHO (1H, s)	CONH (1H, d, J=8 Hz)	Thiazole 5-H (1H, s)	C7-H (1H, dd, J=5, 8 Hz)	C6-H (1H, d, J=5 Hz)	C2-H_2 (2H)	CH_2COO (2H, s)	X	IR (Nujol, cm^{-1}) β-Lactam	IR (Nujol, cm^{-1}) CONH	Yield (%)
4c	Cl	PNB	8.55	9.72	7.45	5.96	5.26	3.93 (q, J=16 Hz)	4.63	—	1785	1680	94.9
4d	CH_3	H	8.53	9.53	7.47	5.77	5.15	3.48 (m)	4.63	2.05 (3H, s)	1770	1680	87.0
4e	OCH_3	PNB	8.50	9.56	7.53	5.70	5.26	3.70 (br s)	4.66	3.86 (3H, s)	1770	1680	98.0
4f	SCH_3	$CHPh_2$	8.48	9.58	7.47	5.80	5.21	3.80 (m)	4.84	2.18 (3H, s)	1780	1690	68.4
4g	CH_2OCH_3	Bu(t)	8.53	9.58	7.43	5.86	5.26	3.53 (m)	4.62	3.23 (3H, s) 4.14 (2H, s)	1780	1680	90.3
4h	CH_2SCH_3	$CHPh_2$	8.54	9.63	7.48	5.92	5.32	3.60 (br s)	4.98	1.83 (3H, s) 3.66 (2H, s)	1783	1687	85.0

Table 5. Yield, NMR and IR spectral data of **5c**, **e** and **6c**~**h**.



No.	Compounds X	R	R_1	NMR (DMSO-d_6, δ) CONH (1H, d, J=8 Hz)	CHO (1H, s)	Thiazole 5-H (1H, s)	C7-H (1H, dd, J=5, 8 Hz)	C6-H (1H, d, J=5 Hz)	$C2\text{-}H_2$ (2H)	CH_2COO (2H, s)	X	IR (Nujol, cm^{-1}) β-Lactam	IR (Nujol, cm^{-1}) CONH	Yield (%)
5c	Cl	H	CHO	9.54	8.50	7.55	5.78	5.23	3.80 (q, J=18 Hz)	4.60	—	1770	1667	65.5
5e	OCH_3	H	CHO	9.56	8.53	7.53	5.62	5.18	3.63 (s)	4.65	3.78 (3H, s)	1770	1680	70.2
6c	Cl	H	H	9.57	—	6.80	5.85	5.29	3.84 (q, J=18 Hz)	4.58	—	1770	1660	82.3
6d	CH_3	H	H	9.42	—	6.80	5.72	5.12	3.47 (m)	4.57	2.05 (3H, s)	1780	1680	94.0
6e	OCH_3	H	H	9.43	—	6.90	5.57	5.15	3.60 (s)	4.58	3.78 (3H, s)	1760	1670	79.8
6f	SCH_3	$CHPh_2$	H	9.47	—	6.83	5.77	5.21	3.80 (m)	4.57	2.35 (3H, s)	1778	1685	76.8
6g	CH_2OCH_3	Bu(t)	H	9.42	—	6.76	5.80	5.17	3.53 (m)	4.54	3.20 (3H, s) 4.13 (2H, s)	1785	1680	87.5
6h	CH_2SCH_3	$CHPh_2$	H	9.52	—	6.83	5.87	5.29	3.63 (br s)	4.60	1.83 (3H, s) 3.63 (2H, s)	1780	1680	90.9

Table 6. Yield, NMR and IR data of **2c**~**h**.

Compounds		NMR (DMSO-d_6, δ)							IR (Nujol, cm^{-1})		Yield (%)
No.	X	CONH (1H, d)	Thiazole 5-H (1H, s)	C7-H (1H, dd)	C6-H (1H, d)	C2-H_2 (2H)	CH_2COO (2H, s)	X	β-Lactam	CONH	
2c	Cl	9.59	6.83	5.86	5.29	3.86 (q, J=18 Hz)	4.63	—	1770	1660	92.3
2d	CH_3	9.43	6.83	5.73	5.12	3.47 (m)	4.63	2.05 (3H, s)	1750	1660	51.6
2e	OCH_3	9.60	7.05	5.62	5.20	3.67 (m)	4.73	3.83 (3H, s)	1760	1670	45.8
2f	SCH_3	9.41	6.83	5.67	5.13	3.73 (br s)	4.63	2.33 (3H, s)	1760	1665	68.4
2g	CH_2OCH_3	9.56	6.87	5.80	5.18	3.54 (m)	4.65	3.23 (3H, s) 4.20 (2H, s)	1770	1660	67.1
2h	CH_2SCH_3	9.45	6.77	5.73	5.17	3.57 (m)	4.60	2.00 (3H, s) 3.57 (2H, s)	1772	1670	87.0

resistant strain.

Sprague-Dawley rats ($n=3$) were fasted overnight and orally dosed with 100 mg/kg of the test drugs. Urinary samples were collected for 24 hours after dosing. For bile collection, another group of rats ($n=3$) were canulated with polystyrene tube into the bile duct and the test drugs were given orally at doses of 100 mg/kg. The samples were assayed by a disc-agar difusion method using *E. coli* NIHJ JC-2 or *E. coli* ATCC 33546 as test organism and nutrient agar (Difco) as the test medium.

Protective activities of the test agents were studied in four-week-old male ICR strain mice infected with *E. coli* 29. The challenge inoculum (8.1×10^4 cfu/mouse) was injected intraperitoneally. Ten mice were allocated to each of the various dosage levels. Appropriate doses in 0.5 ml of the diluent were administrated orally 1 hour after challenge. The 50% effective dose was calculated from the number of mice surviving 4 days after challenge.

The serum concentrations of male beagle dogs ($n=3$) were measured by the disc-plate diffusion method using *E. coli* ATCC 39188 as the test organism and nutrient agar (Difco) as the test medium. The reference drugs were assayed in the same way using *Bacillus subtilis* ATCC 6633 as the test organism and sodium citrate agar as the test medium.

Materials

The following compounds were prepared according to the methods of the literature: **3c**,[16] **3e**,[16] **3f**,[17] **3g**[18] and **3h**.[19]

General Procedure for Acylation of **3c~h**

To a mixture of DMF (8.8 mmol) in THF (25~30 ml) was dropwise added $POCl_3$ (8.8 mmol) at $-10\sim0$°C under stirring, and the mixture was stirred at this temp for further 30 minutes to prepare Vilsmeier reagent. To the above mixture was added the acid (**7**) (8 mmol) under ice-cooling. The reaction mixture was stirred at the same temp for 1 hour to produce an activated acid soln of **7**. To a soln of **3** (8 mmol) and *N*-trimethylsilylacetamide (MSA) (42 mmol) in EtOAc (30 ml) was added the above activated acid soln at -20°C, and the mixture was stirred at this temp for 30~60 minutes. To the reaction mixture were added EtOAc (30 ml) and H_2O (30 ml). The separated organic layer was washed with brine three times, and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue was triturated with diisopropyl ether (iPE) to afford an acylated cephalosporin derivative (**4**).

General Preparation of **5c, e**

A mixture of **4c, e** (6.8 g, 10 mmol) and 10% palladium on carbon (3.5 g) in a soln of MeOH (60 ml), THF (60 ml), AcOH (6 ml) and H_2O (10 ml) was subjected to catalytic reduction at room temp under atmospheric pressure for 2.5 hours. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in 5% $NaHCO_3$ soln. After being washed with EtOAc, the aq soln was adjusted to pH 3.0 with 10% HCl, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was triturated with Et_2O to give **5c, e**.

General Procedure for Deformylation of **4d, f, g, h** and **5c, e**

To a mixture of a *N*-formyl derivative (3.0 mmol), MeOH (25 ml) and THF (5 ml) was added concd HCl (9~12 mmol) at room temp, and the mixture was stirred at the same temp for 2~4 hours. The resultant mixture was neutralized with 5% $NaHCO_3$ soln and concentrated under reduced pressure. The residue was dissolved in a mixture of H_2O and EtOAc. The mixture was acidified to pH 2.0 with 10% HCl. The separated EtOAc layer was washed with brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was triturated with iPE to afford a deformylated derivative (**6c~h**).

General Procedure for Deesterification of **6c~h** with Trifluoroacetic Acid (TFA) and Anisole

To a mixture of an ester (**6**) (2 mmol), anisole (3 ml) and CH_2Cl_2 (3~6 ml) was added TFA (12 ml) under ice-cooling, and the mixture was stirred at room temp for 1 hour. The resultant mixture was dropwise added to iPE (100 ml) under stirring to form a precipitate. The collected precipitate was dissolved in 5% $NaHCO_3$ soln and the soln was washed with EtOAc. The separated aq soln

was acidified to pH 2.0 with 10% HCl under ice-cooling. The resultant precipitate was collected by filtration and dried to afford **2c~h.**

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