STUDIES ON β-LACTAM ANTIBIOTICS

XIX.† STRUCTURE-ACTIVITY RELATIONSHIPS OF CEPHALOSPORINS HAVING A THIADIAZOLYLTHIOMETHYL GROUP AT THE C-3 SIDE CHAIN

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The synthesis and antibacterial activity of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(hydroxy or alkoxy)iminoacetamido]cephalosporins with various thiadiazolylthiomethyl moieties at the 3-position are discussed.

Of the compounds (**1a**～**1e**, **7a**～**7d**), 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-[(1,2,4-thiadiazol-5-yl)thiomethyl]cephalosporin (**1d**: FK312) exhibited the highest activity against Gram-positive and Gram-negative bacteria, especially, against methicillin-resistant *Staphylococcus aureus*.

Furthermore, the pharmacokinetic profiles of the compound **1d** showed longer serum levels than that of ceftriaxone in rats.

In general, cephalosporin antibiotics of the so-called third generation possess very potent activity against Enterobacteriaceae, but weak or moderate activity against *Staphylococcus aureus*. Furthermore the activity of such a drug against methicillin-resistant *S. aureus* (MRSA) is very low. As a result of the spread of third generation cephalosporins, infectious disease due to *S. aureus* has progressively increased and become a serious problem, especially concerning MRSA in chemotherapy.[2] Some cephalosporins with enhanced activity against *S. aureus* have been recently developed or introduced into therapy.[3] However, a cephalosporin possessing sufficient activity against MRSA has not been reported so far. The goal of our research effort was the synthesis of an injectable cephalosporin having excellent activity against *S. aureus* including MRSA, as well as Gram-negative bacteria.

A recent report[1] from our laboratories has described the structure-activity relationships of 7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetyl]cephalosporins with sterically small substituents relating to cefdinir (FK482), a new orally active cephalosporin. Most of the hydroxyimino compounds exhibited highly potent activity against methicillin-sensitive *S. aureus* (MSSA). However the activity of these compounds against MRSA was not so high as that of cefdinir.[4]

3-Thiadiazolylthiomethyl cephalosporins such as cefazolin (CEZ), ceftezol (CTZ) and cefuzonam (CZON) show generally good anti-*S. aureus* activity. Consequently, we synthesized various 3-thiadiazolylthiomethyl derivatives of the hydroxyimino cephalosporin and studied the structure-activity relationships. In our study we have found that 3-(1,2,4-thiadiazol-5-yl)thiomethyl cephalosporin derivative (**1d**: FK312) shows the highest activity against MRSA as well as MSSA. Second, we directed our efforts towards the synthesis of 7β-amino-3-(1,2,4-thiadiazol-5-yl)thiomethyl cephalosporin derivatives with various alkoxyimino groups which seemed to be favorable for enhancement of activity against Gram-positive

† Paper XVIII: See ref 1.

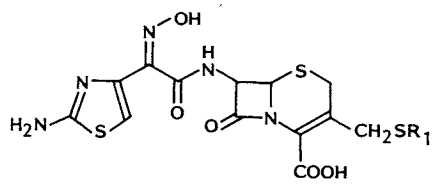
bacteria. Thus in this paper we report the preparation of 3-thiadiazolylthiomethyl cephalosporins (**1** and **7**), structure-activity relationships and further evaluation of FK312.

Biological Results and Discussion

MIC values of cephalosporin derivatives **1a**~**1e** against several Gram-positive and Gram-negative bacteria are shown in Table 1 compared with CZON and flomoxef (FMOX). **1c** and **1d** showed better activity against *S. aureus* 2538 (MRSA) than other derivatives, and **1d** had excellent activity (3.13 μg/ml) against *S. aureus* 3004 (MRSA). Against Gram-negative bacteria, all of the compounds prepared here showed highly potent activities. This showed that (1,2,4-thiadiazol-5-yl)thiomethyl moiety might be the most suitable substituent at the 3-position for our purposes. Therefore, we tried to optimize the 7-acyl side chain of 3-(1,2,4-thiadiazol-5-yl)thiomethyl cephalosporin. The antibacterial activity of 3-(1,2,4-thiadiazol-5-yl)thiomethyl cephalosporin derivatives (**7** and **1d**) possessing various oxime moieties in the 7-acyl side chain are shown in Table 2. Hydroxyimino compound **1d** exhibited better Gram-positive and also Gram-negative antibacterial activity than alkoxyimino compounds **7a**~**7d**, although cyclopentenyloxyimino compound (**7c**) showed excellent activity against Gram-positive bacteria. Consequently, **1d** (FK312) was selected as a candidate for further evaluation.

Antibacterial activity of **1d** against resistant *S. aureus* are shown in Table 3 compared with CZON and FMOX. Strains of *S. aureus* resistant to methicillin were highly susceptible to **1d**. All strains of

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



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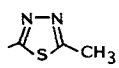
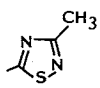
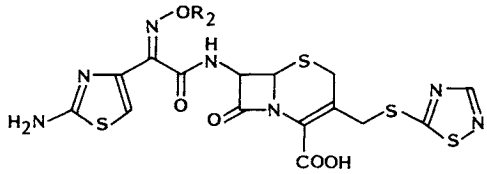
Compound No.	R_1	MIC[a] (μg/ml)							
		S.a. 209P JC-1	*S.a.* 32	*S.a.* 2538[b]	*S.a.* 3004[b]	*B.s.* ATCC 6633	*E.c.* NIHJ JC-2	*K.p.* 12	*P.m.* 1
1a		0.20	0.39	12.5	3.13	0.78	0.05	0.05	0.05
1b		0.39	1.56	100	100	1.56	0.10	0.78	0.10
1c		0.10	0.20	3.13	50	0.78	0.10	0.20	0.025
1d		0.10	0.20	3.13	3.13	0.78	0.10	0.20	0.025
1e		0.39	0.78	12.5	12.5	0.78	0.20	0.78	0.05
CZON		0.78	0.78	12.5	100	0.78	0.20	0.10	0.025
FMOX		0.39	0.78	12.5	50	0.39	0.10	0.10	0.20

Abbreviations: *S.a.*, *Staphylococcus aureus*; *B.s.*, *Bacillus subtilis*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *P.m.*, *Proteus mirabilis*; CZON, cefuzonam; FMOX, flomoxef.

[a] Heart Infusion agar (Difco) 10^6 cfu/ml; stamp method; 37°C, 18 hours.

[b] *S.a.* 2538: 25 μg/ml to methicillin , *S.a.* 3004: >100 μg/ml to methicillin.

Table 2. Antibacterial activity of cephalosporins (**1d** and **7a**~**7d**).



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Compound No.	R_2	MIC[a] (μg/ml)							
		S.a. 209P JC-1	*S.a.* 32	*S.a.* 2538[b]	*S.a.* 3004[b]	*B.s.* ATCC 6633	*E.c.* NIHJ JC-2	*K.p.* 12	*P.m.* 1
1d	$-H$	0.10	0.20	3.13	3.13	0.78	0.10	0.20	0.025
7a	$-CH_3$	0.78	1.56	100	100	3.13	0.10	0.20	0.025
7b	$-CH_2CH{=}CH_2$	0.39	0.78	25	100	0.20	0.20	0.78	0.025
7c		0.20	0.78	6.25	12.5	0.20	0.78	1.56	0.20
7d	$-CHF_2$	0.39	0.78	25	50	0.39	0.10	0.39	0.025

Abbreviations: *S.a.*, *Staphylococcus aureus*; *B.s.*, *Bacillus subtilis*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *P.m.*, *Proteus mirabilis*.

[a] Heart Infusion agar (Difco) 10^6 cfu/ml; stamp method; 37°C, 18 hours.

[b] *S.a.* 2538: 25 μg/ml to methicillin, *S.a.* 3004: >100 μg/ml to methicillin.

Table 3. Antibacterial activity of **1d** against resistant *Staphylococcus aureus*.

Organism (No. of strains)	MIC[a] (μg/ml)		
	1d (FK312)	CZON	FMOX
DMPPC[b]-resistant *S. aureus* (MRSA) (32)	2.17	24.5	5.26
MCIPC[c]-resistant *S. aureus* (10)	5.84	100	14.4
CZON-resistant *S. aureus* (27)	2.55	37.8	6.10
FMOX-resistant *S. aureus* (9)	5.80	100	19.9

[a] Heart Infusion agar (Difco) 10^6 cfu/ml; stamp method; 37°C, 18 hours.

[b] DMPPC: Methicillin, MIC: ≧12.5 μg/ml to DMPPC.

[c] MCIPC: Cloxacillin, MIC: ≧6.25 μg/ml to MCIPC.

CZON: Cefuzonam, FMOX: flomoxef.

Table 4. Protective effect of **1d** and related compounds (CZON, FMOX) against infection with *Staphylococcus aureus* in mice.

Organisms (cells/mouse)	Compounds	ED_{50} (mg/kg)	MIC[a] (μg/ml)
S. aureus 47 (5.4×10^7; 1 MLD)	**1d** (FK312)	0.93	0.20
	CZON	5.94	0.78
	FMOX	2.50	0.39
S. aureus 2499 (1.5×10^8; 1 MLD)	**1d** (FK312)	3.06	0.78
	CZON	19.1	3.13
	FMOX	2.50	1.56

Mice: ICR strain, 4-week-old male (19~22 g), $n=10$.

Infection: Mucin suspension, 0.5 ml/mouse, intraperitoneally.

Therapy: 1 hour after challenge, subcutaneously, ED_{50} was determined by the probit method.

[a] Mueller-Hinton agar (Difco) 10^6 cfu/ml; stamp method; 37°C, 18 hours.

CZON: Cefuzonam, FMOX: flomoxef.

S. aureus resistant to CZON and FMOX were also highly susceptible to **1d**.

In the next step, the protective effects on mice infection and the pharmacokinetic profiles in rats after intravenous injection of compound **1d** were evaluated.

Protective activities of **1d** against two kinds of *S. aureus* infection in mice are indicated in Table 4, compared with CZON and FMOX. Against *S. aureus* 47 the effects of **1d** were superior to that of FMOX and CZON, and against *S. aureus* 2499 similar to that of FMOX.

Fig. 1. Plasma levels of compound **1d** and related compounds (ceftriaxone, cefuzonam) in rats after iv injection of 20 mg/kg.

○ Ceftriaxone, ● **1d** (FK312), △ cefuzonam.

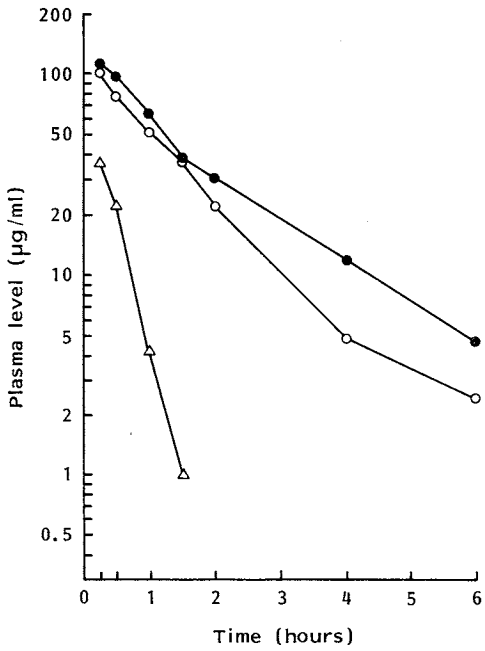


Table 5. Pharmacokinetic parameters of compound **1d** and related compounds (CTRX, CZON) in rats after iv administration of 20 mg/kg.

Compound	AUC (μg·hour/ml)	$T_{1/2}$ (minutes)	Recovery (%)	
			Urine	Bile
1d (FK312)	181	54.3	81.6	21.0
CTRX	143	48.4	41.0	48.7
CZON	32.4	13.4	3.2	78.8

Rats: JCL SD strain, 6-week-old male, $n=6$.
CTRX: Ceftriaxone, CZON: cefuzonam.

Table 6. Serum protein binding of compound **1d** and CTRX, CZON.

Serum[a]	Protein binding (%)		
	1d (FK312)	CTRX	CZON
Human	99.0	98.3	91.8
Dog	72.0	84.0	33.7
Rabbit	99.2	93.6	95.7
Rat	97.5	92.8	84.4
Mouse	95.8	87.6	55.8

[a] At 90% serum and 30 μg/ml of compounds. Centrifuged ultrafiltration method.
CTRX: Ceftriaxone, CZON: cefuzonam.

The pharmacokinetic parameters and the plasma levels of **1d** in rats after intravenous injection are indicated in Table 5 and Fig. 1 and are compared with CTRX and CZON. The half-lives of **1d** was 54 minutes and the area under the curve (AUC) was 181 μg·hour/ml. These results indicate that compound **1d** exhibited a longer half-life than CTRX. Thus, serum protein binding of **1d** was examined to evaluate its long-acting effect. The serum protein binding of **1d** was considerably high as shown in Table 6. The binding value of **1d** was 97.5% for rat which was higher than that of CTRX. The high value seems to reflect the long acting property of **1d**.

Chemistry

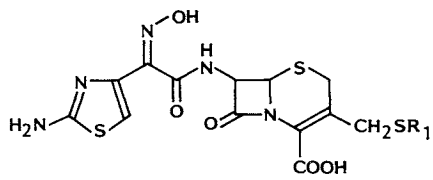
7β-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-hydroxyiminoacetamido]cephalosporins (**1b**～**1e**) were prepared as outlined in Scheme 1.

As the Method A, 7-aminocephalosporin derivatives (**2c** and **2d**) was treated with 4-chloroacetoacetyl chloride in the presence of 1,3-bis(trimethylsilyl)urea (BSU) to give the acylated compound **3**. Nitrosation of **3** with aqueous sodium nitrite gave the hydroxime compound **4**. **4** was reacted with thiourea in *N*,*N*-dimethylacetamide (DMAc) to give the thiazole derivatives (**1c** and **1d**).

As the Method B, the acid (**5**) was activated with the Vilsmeier reagent, prepared from DMF and phosphoryl chloride ($POCl_3$). The protecting trityl and tetrahydropyranyl groups of **6b** and **6e** were removed by treatment with concd hydrochloric acid in methanol to give **1b** and **1e**. The spectral data of compounds **1b**～**1e** are shown in Table 7.

The synthetic route of the C(3)-1,2,4-thiadiazolylthiomethyl cephalosporins (**7a**～**7d**) is outlined in Scheme 2. 7β-Amino-3-(1,2,4-thiadiazol-5-yl)thiomethyl cephalosporanic acid (**2d**) was acylated with

Scheme 1.



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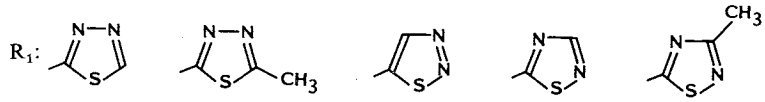
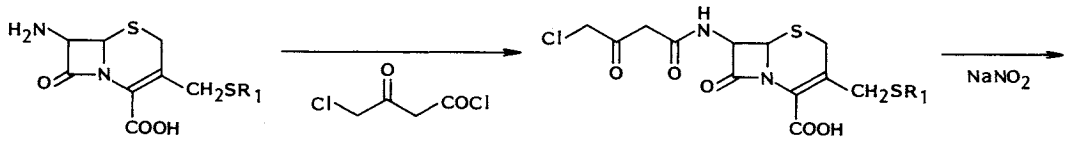
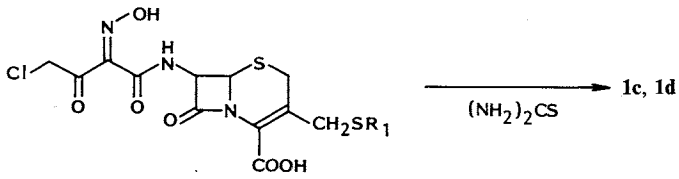


a b c d e

Method A

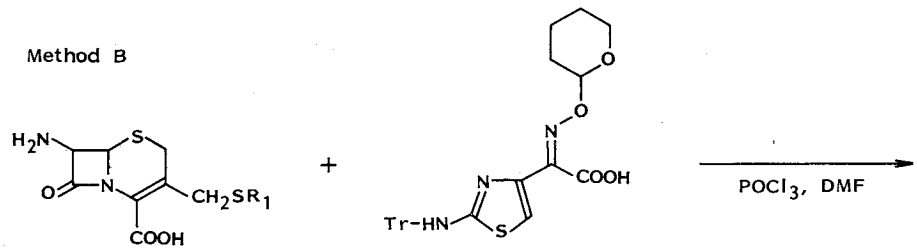


2c, 2d 3c, 3d

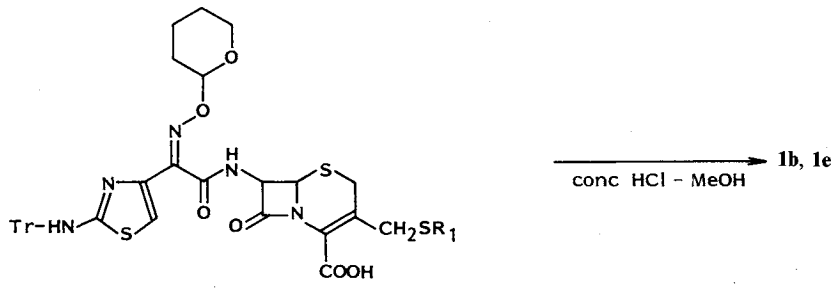


4c, 4d 1c, 1d

Method B



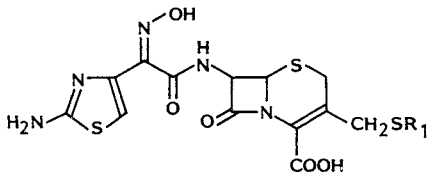
2b, 2e 5



6b, 6e 1b, 1e

Tr = $-CPh_3$

Table 7. NMR and IR spectral data of **1a**~**1e**.



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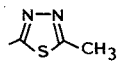
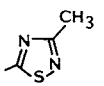
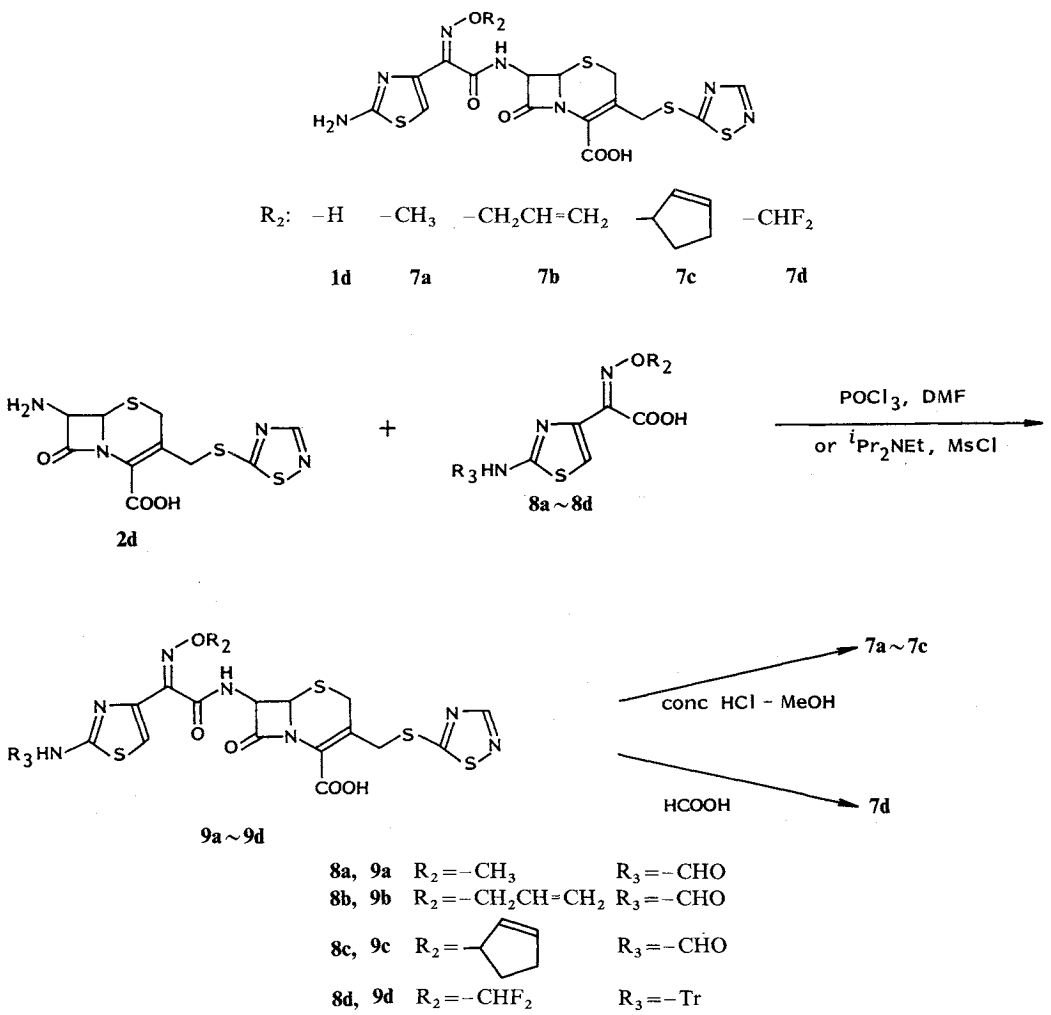
Compounds No.	R_1	NMR (DMSO-d_6, δ)								IR (Nujol) cm^{-1}	
		N-OH (1H, br s)	CONH (1H, d, J=8 Hz)	Thiazole 5-H (1H, s)	C7-H (1H, dd, J=5, 8 Hz)	C6-H (1H, d, J=5 Hz)	C3-H (2H)	C2-H (2H)	R_1	β-Lactam	CONH
1a		11.67	9.30	6.59	5.62	4.98	4.33, 4.58 (ABq, J=13 Hz)	3.47 (br s)	9.43 (1H, s)	1770	1660
1b		11.27	9.41	6.66	5.78	5.13	4.20, 4.53 (ABq, J=13 Hz)	3.53, 3.80 (ABq, J=18 Hz)	2.70 (3H, s)	1770	1670
1c		11.27	9.42	6.85	5.77	5.17	4.25 (br s)	3.53, 3.77 (ABq, J=18 Hz)	8.84 (1H, s)	1760	1665
1d		11.30	9.43	6.67	5.80	5.15	4.31, 4.63 (ABq, J=13 Hz)	3.53, 3.80 (ABq, J=18 Hz)	8.73 (1H, s)	1760	1670
1e		11.35	9.42	6.64	5.73	5.10	4.20, 4.60 (ABq, J=13 Hz)	2.70 (br s)	2.51 (3H, s)	1760	1660

Scheme 2.



various alkoxyimino acetic acids (**8a**~**8d**), activated with Vilsmeier reagent or methanesulfonyl chloride to give compounds **9a**~**9d**. Deprotection of the *N*-formyl group of the acylated compounds (**9a**~**9c**) proceeded at room temperature in MeOH containing concd hydrochloric acid. The trityl group of **9d** was cleaved at room temperature by treatment with formic acid. The spectral data of these final compounds (**7a**~**7d**) are shown in Table 8.

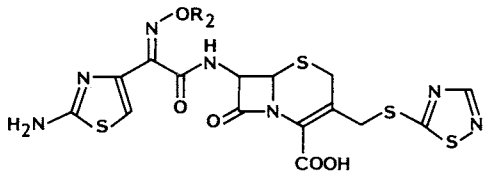
Experimental

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 TMS as an internal standard. IR spectra were taken on a Hitachi 260-10 spectrophotometer or Shimadzu IR-420 spectrophotometer.

Assay Procedure for Pharmacokinetics

Drug concentrations were measured by the disk-plate diffusion technique using *Bacillus subtilis* ATCC 6633 as the test organism and sodium citrate agar (sodium citrate 1.0%, agar 1.0%, Polypeptone 0.5%, and beef extract 0.3%) as the test medium. The plates were incubated at 37°C for 18 to 20 hours, and

Table 8. NMR and IR spectral data of **7a**~**7d**.



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Compounds No.	R_2	NMR (DMSO-d_6, δ) 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)	C3-H (2H)	C2-H (2H)	R_2	IR (Nujol) cm^{-1} β-Lactam	IR (Nujol) cm^{-1} CONH
7a	$-CH_3$	9.59	6.77	5.76	5.13	4.30, 4.66 (ABq, J=13 Hz)	3.53, 3.80 (ABq, J=18 Hz)	3.86 (1H, s)	1770	1670
7b	$-CH_2CH=CH_2$	9.62	6.75	5.83	5.17	4.30, 4.63 (ABq, J=13 Hz)	3.56, 3.82 (ABq, J=18 Hz)	4.47~4.77, 5.07~5.53, 5.70~6.17 (5H, m)	1770	1670
7c		9.48	6.69	5.77	5.13	4.31, 4.62 (ABq, J=13 Hz)	3.53, 3.79 (ABq, J=18 Hz)	5.45~6.2 (2H, m), 5.0~5.40 (1H, m), 1.6~2.5 (4H, m)	1770	1670
7d	$-CHF_2$	9.87	6.96	5.80	5.20	4.30, 4.62 (ABq, J=13 Hz)	3.53, 3.80 (ABq, J=18 Hz)	7.08 (1H, t, J=71 Hz)	1780	1670

zones of inhibition were measured and compared with similarly prepared standards.

Binding to Serum Protein

A 0.5 ml volume of an antibiotic soluotion (300 μg/ml) in 0.067 M phosphate buffer (pH 7.0) was added to 4.5 ml of fresh serum and incubated at 37°C for 1 hour. This mixture was placed in a Visking tube (size 8/32) and centrifuged at 1,000 × g for 30 to 40 minutes to obtain the ultrafiltrate. The drug concentration in the filtrate was bioassayed using standard solutions prepared with 0.067 M phosphate buffer (pH 7.0). The degree of binding of the antibiotics was calculated in a conventional manner.

Antibiotic Susceptibility

MICs were determined by the agar dilution method using Heart-Infusion agar (Difco). MICs were read after incubation at 37°C for 18 hours.

Compound **1a** was prepared according to the method of the literature.[5]

General Procedure for Acylation of **2c** and **2d**

To a solution of **2c** or **2d** (30 mmol) and BSU (90 mmol) in THF (200 ml) was added 4-chloroacetoacetyl chloride (36 mmol) at −20°C, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added EtOAc (200 ml) and H_2O (200 ml) and the mixture was adjusted to pH 6.5 with 5% $NaHCO_3$ soln.

The separated aq layer 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 diisopropyl ether (IPE) to give **3c** (79%), **3d** (81%).

General Preparation of **4c** and **4d**

To a solution of **3c** or **3d** (13.5 mmol) in AcOH (50 ml) was added a soln of $NaNO_2$ (17.6 mmol) in H_2O (7.7 ml) at 5~10°C under stirring. The mixture was stirred at the same temperature for 1.5 hours. The reaction mixture was poured into a mixture of EtOAc (200 ml) and H_2O (200 ml). The separated organic layer was washed with H_2O and brine, and dried ($MgSO_4$). The organic solvent was evaporated *in vacuo*, and to the residue was added IPE. The resultant precipitate was collected by filtration to give **4c** (81%), **4d** (93%).

General Procedure for Cyclization of **4c** and **4d** with Thiourea

To a solution of **4c** or **4d** (9.42 mmol) in DMAc (35 ml) was added thiourea (9.42 mmol) at room temperature. The mixture was stirred at the same temperature for 3 hours. The reaction mixture was poured into H_2O (200 ml), and adjusted to pH 3.0 with 10% HCl to form a precipitate. The collected precipitate was dissolved in 5% $NaHCO_3$ soln and was washed with EtOAc. The separated aq soln was acidified to pH 3.0 with 10% HCl under ice-cooling. The resultant precipitate was collected by filtration and dried to afford **1c** (80%), **1d** (83%).

General Procedure for Acylation of **2b**, **2d** and **2e**

To a mixture of DMF (32 mmol) and THF (150 ml) was added dropwise $POCl_3$ (32 mmol) at −10~0°C under stirring, and the mixture was stirred at this temperature for a further 30 minutes to prepare the Vilsmeier reagent. To the above mixture was added the acid (**5**[6] or **8a**~**8c**) (29 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 1 hour to produce an activated acid soln of **5** or **8a**~**8c**. To a mixture of **8d** (29 mmol) in DMF (250 ml) was added diisopropylethylamine (58 mmol) and the methanesulfonyl chloride (58 mmol), and the mixture was stirred at −30°C for 30 minutes to prepare an activated acid soln of **8d**.

To a soln of **2** (29 mmol) and *N*-trimethylsilylacetamide (MSA) (200 mmol) in THF (200 ml) was added the above activated acid soln at −20°C, and the mixture was stirred at the same temperature for 30~60 minutes. To the reaction mixture were added EtOAc (200 ml) and H_2O (200 ml). The separated organic layer was washed with brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue was triturated with IPE to afford **6b** (82%), **6e** (85%), **9a** (90%), **9b** (87%), **9c** (59%) and **9d** (51%).

General Procedure for Deprotection of **6b** and **6e**

To a mixture of **6b** or **6e** (23.8 mmol) in MeOH (200 ml) was added concd HCl (20 ml) at room temperature, and the mixture was stirred at 30~35°C for 2 hours. The reaction mixture was neutralized with 5% $NaHCO_3$ soln under ice-cooling and concentrated under reduced pressure. The residue was dissolved in mixture of EtOAc and H_2O. The separated aq layer was adjusted to pH 3.0 with 10% HCl under stirring. The resultant precipitate was collected by filtration to give **1b** (15%), **1e** (10%).

General Procedure for Deformylation of **9a~9c**

To a mixture of a *N*-formyl derivative (6.9 mmol), MeOH (70 ml) and THF (20 ml) was added concd HCl (2.5 ml) at room temperature, and the mixture was stirred at the same temperature for 1 hour. The resultant mixture was neutralized with 5% $NaHCO_3$ soln and concentrated under reduced pressure. The residue was dissolved in a mixture of EtOAc and H_2O. The mixture was acidified to pH 3.0 with 10% HCl. The separated organic layer was washed with brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was triturated with IPE to give **7a** (61%), **7b** (67%), **7c** (56%).

Procedure for Detritylation of **9d**

To a mixture of **9d** (8.6 mmol) in HCOOH (65 ml) was added H_2O (20 ml) under ice-cooling, and the mixture was stirred at the same temperature for 3 hours. The resultant mixture was poured into H_2O (100 ml), adjusted to pH 7.0 with 5% $NaHCO_3$ soln. After being washed with EtOAc, the aq soln was adjusted to pH 3.5 with 10% HCl, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was triturated with IPE to give **7d** (85%).

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