STUDIES ON MONOCYCLIC β-LACTAM ANTIBIOTICS

V. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 3-[2-(2-AMINOTHIAZOL-4-YL)-(*Z*)-2-(*O*-SUBSTITUTED OXYIMINO)-ACETAMIDO]-1-(1*H*-TETRAZOL-5-YL)-2-AZETIDINONES HAVING VARIOUS FUNCTIONAL GROUPS AT C-4 POSITION OF β-LACTAM

CHOSAKU YOSHIDA*, KIYOSHI TANAKA, RIKIZO HATTORI, YOSHIKAZU FUKUOKA, MIWAKO KOMATSU, SUMIKO KISHIMOTO and ISAMU SAIKAWA

Research Laboratory, Toyama Chemical Co., Ltd.
2-4-1 Shimookui, Toyama 930, Japan

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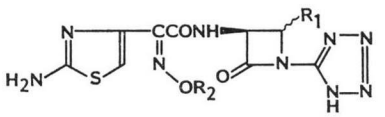
The synthesis and antibacterial activity of the 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido]-1-(1*H*-tetrazol-5-yl)-2-azetidinones having various functional groups at C-4 position of β-lactam are described. These compounds exhibited a strong activity against a variety of Gram-negative bacteria including β-lactamase-producing strains. Among various C-4 substituents explored, the fluoromethyl and carbamoyloxymethyl moiety were found to increase the activity.

In our previous paper,[1] the synthesis and antibacterial activity of (3*S*,4*R*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido]-4-methyl-1-(1*H*-tetrazol-5-yl)-2-azetidinones have been reported, and especially, the compound with the 2-(2-aminothiazol-4-yl)-(*Z*)-2-(2-fluoroethoxyimino)acetyl moiety as the 3-acyl side chain have been found to possess preferably broad antibacterial activities. With the view of further improvement of antibacterial activity, we synthesized *N*-(tetrazol-5-yl)azetidin-2-ones (**I**) (Fig. 1) having various functional moieties at C-4 position.

In this paper, the new derivatives represented by the general structure (**I**) are described.

Fig. 1.



I

R_1: Substituted methyl

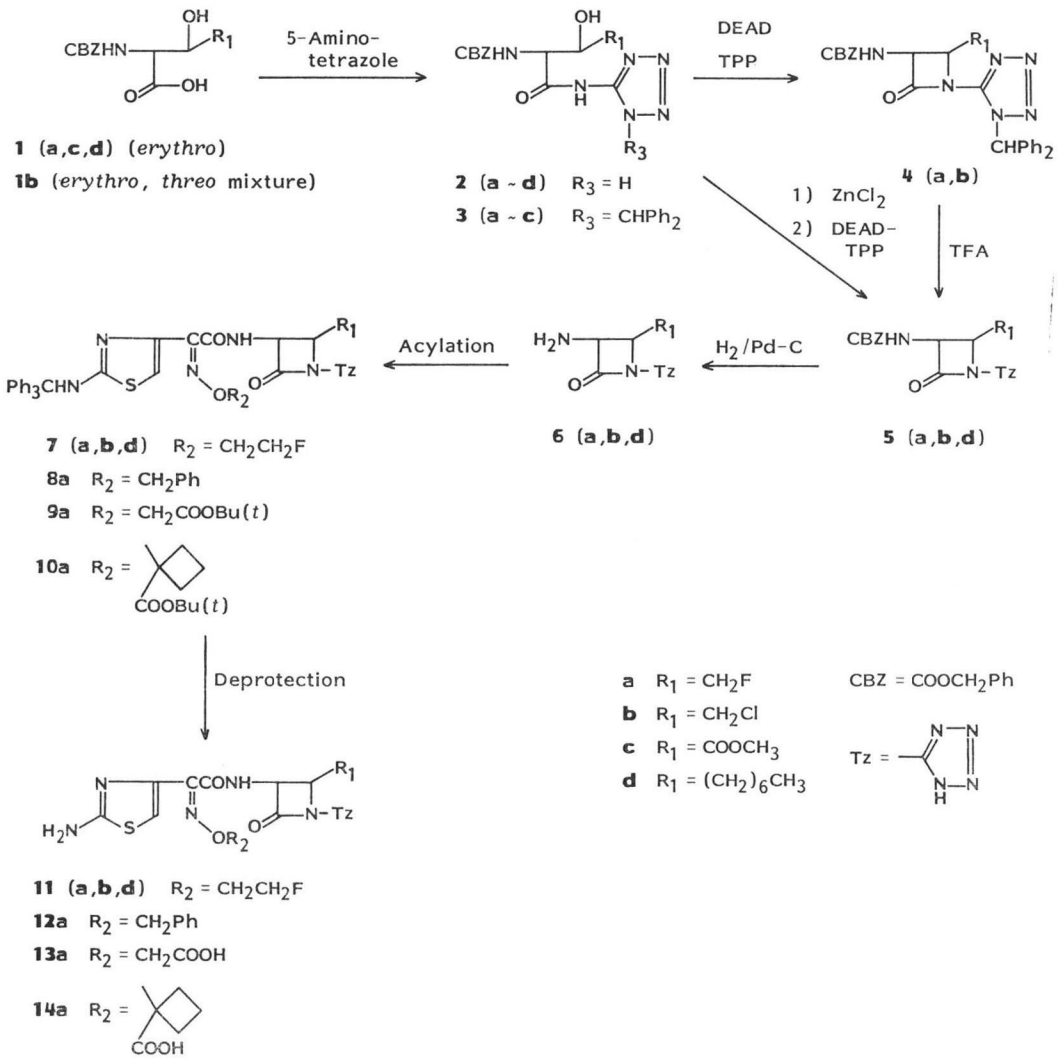
R_2: CH_2CH_2F, CH_2Ph, CH_2COOH, 

Chemistry

Various (3,4)-*cis* and *trans*-(4-substituted)azetidine-2-ones (**4** and **5**) were stereo selectively synthesized by using *erythro* and *threo* α-carbobenzoxy-β-hydroxyamino acids (**1**) as starting materials. The synthetic routes are described in Schemes 1～4.

β-Hydroxyamino acid of *erythro* forms (**1**) were condensed with 5-aminotetrazole mixed anhydride method[1] to afford β-hydroxybutyramides (**2**), and then N-1 position of tetrazole ring were protected with diphenyldiazomethane (DDM) to obtain *N*-protected amides (**3**). Compounds **3** were subjected to previously reported MITSUNOBU reaction,[2] *i.e.* intramolecular ring closure, to obtain *N*-(tetrazol-5-yl)azetidin-2-ones (**4**) without difficulty (36～65%). Subsequently, the diphenylmethyl and carbobenzoxy groups were removed with trifluoroacetic acid (TFA) and by hydrogenolysis, respectively, to

Scheme 1.

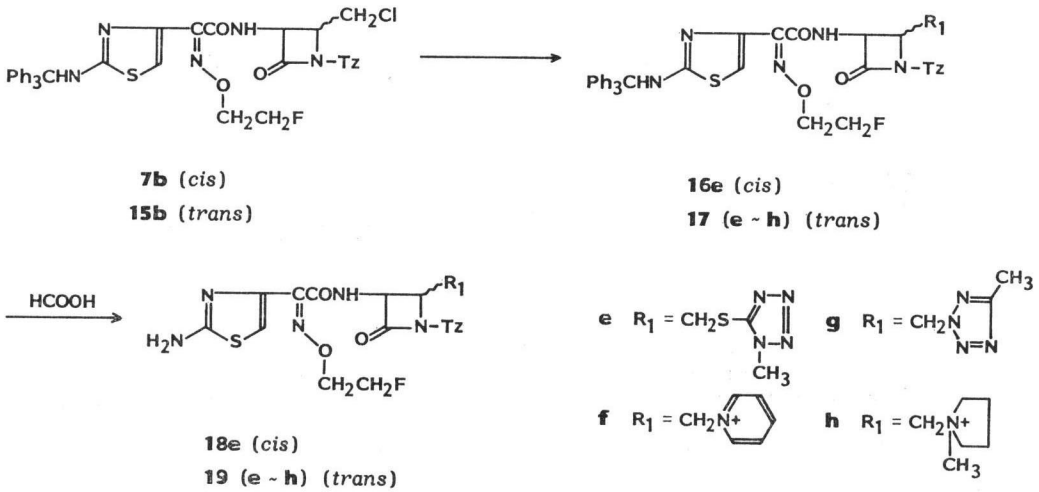


obtain 3-amino-β-lactams (**6**). Then, **6** were condensed with 2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetic acid in the presence of 1-hydroxybenzotriazole (HOBT) and *N*,*N'*-dicyclohexylcarbodiimide (DCC) to obtain 3-acylated derivatives (**7**~**10**). Subsequently, the triphenylmethyl group was removed with 50% formic acid (HCOOH) to obtain 4-substituted derivatives (**11**~**14**). The 3,4-*trans* isomers of **11a** and **11b** were similarly obtained from the corresponding *threo*-β-hydroxyamino acids.

On the other hand, β-hydroxybutyramide (**2d**) was reacted with zinc chloride ($ZnCl_2$) to obtain zinc salt (R_3=1/2 Zn), which was transformed into β-lactam (**5d**) in a similar manner by MITSUNOBU reaction.

4-Chloromethyl derivatives (**7b** and **15b**) were reacted with various nucleophilic reagents (5-mercaptotetrazole, pyridine, 5-methyltetrazole and *N*-methylpyrolidine) to obtain 3,4-*cis* and *trans* compounds (**16e** and **17e**~**h**) having various heterocyclic groups at C-4 position. Then, triphenylmethyl group

Scheme 2.

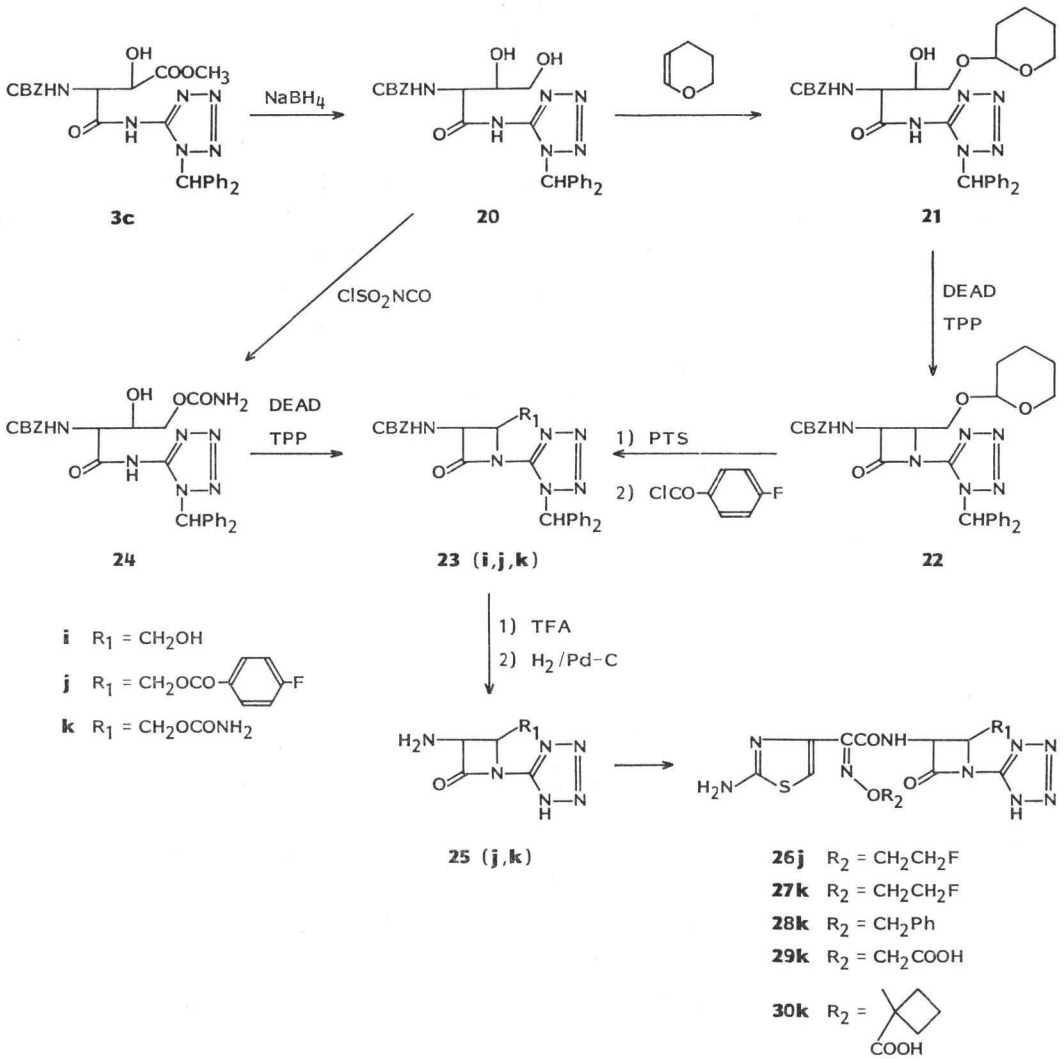


7b (*cis*)
15b (*trans*)

16e (*cis*)
17 (**e** ~ **h**) (*trans*)

18e (*cis*)
19 (**e** ~ **h**) (*trans*)

Scheme 3.



3c

20

21

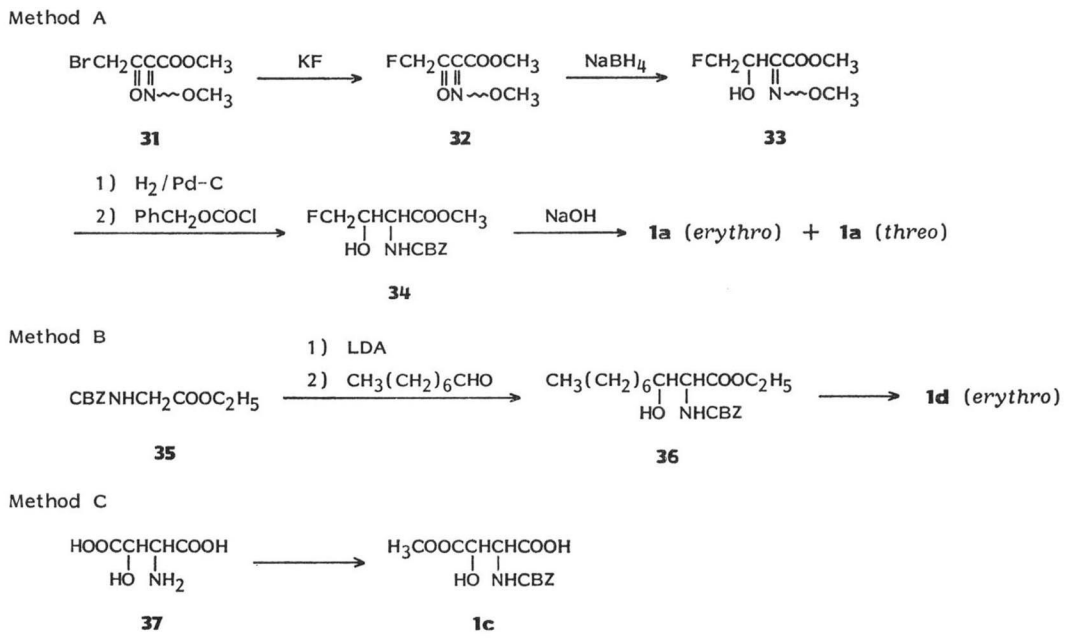
24

23 (**i**,**j**,**k**)

22

25 (**j**,**k**)

Scheme 4.



was removed with 50% formic acid to obtain 4-substituted derivatives (**18e** and **19e~h**).

On the other hand, (3,4-*cis*)-4-acyloxymethyl derivatives (**26j** and **30k**) were synthesized by the route shown in Scheme 3. Thus, hydroxymethyl derivative (**20**) was produced by reducing methoxycarbonyl group of **3c** with sodium borohydride ($NaBH_4$) (70%). The hydroxymethyl group of **20** was protected selectively with dihydropyran to obtain tetrahydropyranyl derivative (**21**), followed by cyclization in a similar manner as described in Scheme 1. Subsequently, pyranyl group was removed by *p*-toluenesulfonic acid (PTS) in aqueous methanol to obtain 4-hydroxymethyl-β-lactam (**23i**), and it was acylated with *p*-fluorobenzoyl chloride to obtain **23j**. On the other hand, carbamoyloxy derivative (**24**) was prepared by treating **20** with chlorosulfonyl isocyanate (65%). Compound **24** was converted into the 4-carbamoyloxymethyl-β-lactam (**23k**). After which, **26j~30k** were obtained in a similar manner to that described for the synthesis of 4-fluoromethyl derivatives (**11~14**). The structure of *N*-(tetrazol-5-yl)azetidin-2-ones were confirmed by IR and NMR.

β-Hydroxyamino acid derivatives (**1d~f**), being important starting materials in Scheme 1, were synthesized by three different routes shown in Scheme 4.

γ-Fluoro-β-hydroxyamino acids (**1a**) were prepared from methyl 4-bromo-2-methoxyimino-3-oxobutyrates (**31**)[3] in the following process. Compound **31** was treated with potassium fluoride in the presence of 18-crown-6 to obtain γ-fluoro derivatives (**32**). And then, the β-carbonyl group of **32** was reduced with sodium hydride to afford β-hydroxyl derivatives (**33**), and the α-methoxyimino group of compound **33** was subjected to hydrogenolysis to obtain α-amino compounds. Then, after the amino group was protected with carbobenzoxy chloride (CBZ-Cl), the ester group of **34** was hydrolyzed with sodium hydroxide to obtain an epimeric mixture of **1a**. The mixture was fractionally recrystallized to obtain **1a** (*erythro* form) (50.5%) and its *threo* form (33.3%), separately. γ-Chloro-β-hydroxyamino acids (**1b**) were prepared from 4-chloro-2-methoxyimino-3-oxobutyrate by the method described above. However, **1b** (*erythro* and *threo* mixture) could not be fractionated, so that, the

mixture was converted into **4b**, which were fractionally chromatographed on silica gel to obtain 3,4-*cis*-β-lactam (**4b**) and its *trans* isomer. (Method A)

N-Carbobenzoxyglycine ethyl ester (**35**) was reacted with lithium diisopropylamine and octyl aldehyde to obtain β-hydroxyamino acid (**36**), and it was treated in a similar way as that for **1b** to obtain **1d** (*erythro*, 78%).[4] (Method B)

4-Methoxycarbonyl derivative (**1c**) was prepared from (*erythro*)-*N*-carbobenzoxy-β-hydroxy-DL-aspartic acid (**37**) by the synthetic method elaborately established by IZUMIYA *et al.*[5~7] (Method C)

Antibacterial Activity and Conclusion

The minimum inhibitory concentration (MIC) of *N*-(tetrazol-5-yl)azetidin-2-ones (**I**) against several Gram-positive and Gram-negative bacteria are shown in Tables 1 and 2. Aztreonam[8] was used as reference compound. The previous report[1] has shown that the compound with 2-(2-aminothiazol-4-yl)-(*Z*)-2-(2-fluoroethoxyimino)acetamido group as an acyl moiety had broader activity than the corresponding compound with methoxyimino group in an acyl moiety. Hence, in this study, while the acyl moiety being fixed, the structure-activity relationships of β-lactams having various functional groups at C-4 position were studied, and the results are shown in Table 1.

11a and **27k** showed strong antibacterial activity against Gram-negative bacteria other than *Pseudomonas aeruginosa*. Among them, 4-fluoromethyl derivative (**11a**) showed the best result, followed by 4-carbamoyloxymethyl derivative (**27k**). As the lipophilicity and bulkiness of substituents at C-4 position increased, the compound showed less activity against Gram-negative bacteria. When **11a** and **11b** were compared in terms of configuration and antibacterial activity, there were no remarkable difference in activity. In case of derivatives having bulky substituents (**18e** and **19e**), *trans* form (**19e**) showed stronger activity. However, against Gram-positive bacteria, only **26j** showed relatively strong activity against *Staphylococcus epidermidis* (0.2 μg/ml) and against *S. aureus* (12.5 μg/ml), indicating insufficient activity. As described above, it was difficult to develop a compound

Table 1. Effect of 4-substituent on antibacterial activity (MIC μg/ml) of *N*-(tetrazol-5-yl)azetidin-2-ones.

Compound No.	3,4-Configuration	*S.e.*[a] IID 866	*S.a.** F-137	*E.c.* NIHJ JC-2	*K.p.* Y-50	*En.c.* IID 977	*S.m.* IID 620	*P.m.* T-111
**	3*S*,4*R* (methyl)	3.13	50	0.2	0.2	0.78	0.39	0.39
11a	*cis*	6.25	25	≤0.1	≤0.1	0.39	0.39	0.2
trans Isomer of **11a**		12.5	50	0.2	≤0.1	0.39	0.2	0.39
11b	*cis*	25	200	0.2	0.39	1.56	0.78	3.13
trans Isomer of **11b**		12.5	50	0.78	0.39	0.2	0.39	0.78
11d	*cis*	50	>200	6.25	12.5	25	100	12.5
26j	*cis*	0.2	12.5	0.78	0.78	3.13	3.13	1.56
27k	*cis*	200	>200	0.2	≤0.1	0.39	0.39	0.39
18e	*cis*	50	>200	6.25	6.25	3.13	12.5	12.5
19e	*trans*	6.25	50	0.39	0.2	0.2	0.39	0.78
19f	*trans*	6.25	100	0.78	0.78	0.78	1.56	0.78
19g	*trans*	12.5	200	1.56	0.39	0.39	1.56	3.13
19h	*trans*	25	>200	6.25	6.25	6.25	6.25	25
Aztreonam		>200	>200	0.2	≤0.1	3.13	≤0.1	≤0.1

[a] Organisms included in the Table are: *S.e.*, *Staphylococcus epidermidis*; *S.a.*, *Staphylococcus aureus*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *En.c.*, *Enterobacter cloacae*; *S.m.*, *Serratia marcescens*; *P.m.*, *Proteus mirabilis*.

*: Penicillinase producing strain. **: This compound was reported in our previous paper.[1]

Table 2. Effect of the oxime-substituent (R_2) on antibacterial activity (MIC μg/ml) of 3-(±)*cis* *N*-(tetrazol-5-yl)azetidin-2-ones.

Organisms[a]	**12a**	**28k**	**13a**	**29k**	**14a**	**30k**	Aztreonam
S.a. FDA 209P	3.13	50	>200	>200	200	>200	>200
S.e. IID 866	0.78	25	>200	>200	50	>200	>200
E.c. NIHJ JC-2	1.56	1.56	0.39	0.78	0.39	1.56	0.2
K.p. Y-50	3.13	3.13	0.39	0.2	0.39	0.78	≤0.1
En.c. IID 977	3.13	12.5	0.39	0.39	0.39	0.39	3.13
S.m. IID 620	12.5	25	0.2	≤0.1	≤0.1	≤0.1	≤0.1
P.m. T-111	12.5	6.25	0.1	≤0.1	≤0.1	≤0.1	≤0.1
P.a. IFO 3445	>200	>200	200	25	6.25	12.5	3.13
S.a. F-137*	3.13	100	200	>200	>200	>200	>200
E.c. TK-3*	3.13	6.25	≤0.1	0.2	≤0.1	0.39	≤0.1
E.c. GN 5482**	1.56	1.56	3.13	0.78	0.39	0.78	6.25
K.p. Y-4*	12.5	25	0.2	0.2	0.39	0.78	≤0.1
P.v. GN 76**	1.56	1.56	0.2	0.2	≤0.1	≤0.1	≤0.1
S.m. W-8**	1.56	3.13	0.78	0.78	0.39	0.39	6.25
P.a. GN 918**	50	50	100	12.5	0.78	1.56	12.5

[a] Organisms included in the Table are: *S.a.*, *Staphylococcus aureus*; *S.e.*, *Staphylococcus epidermidis*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *En.c.*, *Enterobacter cloacae*; *S.m.*, *Serratia marcescens*; *P.m.*, *Proteus mirabilis*; *P.a.*, *Pseudomonas aeruginosa*; *P.v.*, *Proteus vulgaris*.

*: Penicillinase producing strain. **: Cephalosporinase producing strain.

showing activity against not only Gram-negative bacteria but also against Gram-positive bacteria despite of the introduction of lipophilic and polar group at C-4 position.

The 4-fluoromethyl and 4-carbamoyloxymethyl derivatives showing excellent antibacterial activity against Gram-negative bacteria were selected for replacement of their oxyimino groups with various substituted oxyimino groups known in the cephem literature. The results are shown in Table 2.

12a showed well-balanced but insufficient activity against Gram-positive and Gram-negative bacteria. As expected, **14a** showed excellent activity against not only Gram-negative bacteria including *P. aeruginosa* but also β-lactamase-producting bacteria, which exceeded that of aztreonam.

Despite the effort to introduce various functional groups at the C-4 position, we failed to find a compound having sufficient activity against Gram-positive bacteria as well as Gram-negative bacteria.

As discussed above, however, this extensive study led us to find a compound exceeding aztreonam in activity. Therefore, further study remains for further *in vitro* and *in vivo* evaluation of the compound.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Hitachi model 260-30 spectrophotometer. NMR spectra were recorded on a Hitachi R-24 (60 MHz) spectrometer using TMS as an internal standard. Organic solvents were dried over anhydrous $MgSO_4$, and all concentration and evaporation of solvent were carried out under reduced pressure. Column chromatography was carried out on Wako silica gel (C-200).

In Vitro Antibacterial Activity

Minimum inhibition concentrations (MICs) were determined by the agar dilution method using heart infusion agar (Eiken) after incubation for 20 hours at 37°C and an inoculum size of about 10^4 cfu.

General Procedure (I) of DL-*erythro*-2-Benzyloxycarbonylamino-*N*-(1*H*-tetrazol-5-yl)butyramide (**2a**, **c** and **2d**) and *erythro-threo* Mixture (**2b**)

To a solution of 2-benzyloxycarbonylamino-4-substituted-3-hydroxybutyric acid (**1a**~**d**) (22 mmol) in CH_2Cl_2 (60 ml) was added *N*-methylmorpholine (23.5 mmol) under ice-cooling. A solution of ClCOOEt (23 mmol) in CH_2Cl_2 (5 ml) was added dropwise to the resulting solution at −30~−20°C over 10~15 minutes, and stirred at −20~−15°C for 1 hour. 5-Aminotetrazole monohydrate (26.6 mmol) in DMF (60 ml) was added dropwise to the resulting mixture at −25~−20°C over 10 minutes, and stirred at −10~0°C for 1 hour, 0~10°C for 1 hour and more over 20°C for 30 minutes. H_2O (30 ml) and EtOAc (60 ml) were added to the reaction mixture, and adjusted to pH 7.0 with saturated $NaHCO_3$ solution. The separated aqueous layer was washed with Et_2O (30 ml), and adjusted to pH 2.0 with 6 N HCl. The resulting crystals were collected by filtration and washed with H_2O to afford **2a**~**d** in 70~80%. The physical properties of **2a**~**d** are summarized in Table 3.

General Procedure (II) for the Protection of **2a**~**c**

To a solution of **2a**~**c** (16.3 mmol) in MeOH (50 ml) and THF (50 ml) was added DDM (25 ml, 28.7 mmol) (20% w/v in EtOAc solution) at room temp, and stirred for 24 hours. The reaction mixture was evaporated and the residue was dissolved in EtOAc (100 ml) and H_2O (50 ml), and adjusted to pH 7.0 with saturated $NaHCO_3$ solution. The organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography (toluene - EtOAc, 5: 1) to afford **3a**~**c** as an amorphous powder in 80~90% yield. The physical properties of **3a**~**c** are summarized in Table 3.

Table 3. Spectral and physical properties of compounds **2** and **3**.

Compound No.	Configuration	MP (°C)	^{1}H NMR (Solvent) δ (J=Hz)	IR $\nu_{C=O}^{KBr}$ (cm^{-1})
2a	*erythro*	196~198 (dec)	(DMSO-d_6); 3.67~4.80 (5H, m), 5.05 (2H, s), 6.97 (1H, d, 8), 7.34 (5H, s), 12.00 (1H, br s)	1720, 1685
threo Isomer of **2a**		208~211 (dec)	(DMSO-d_6); 3.80~4.95 (5H, m), 5.06 (2H, s), 5.60 (1H, br s), 7.35 (6H, m), 12.20 (1H, br s)	1720, 1690
2b	*erythro-threo* Mixture	195~197 (dec)	(DMSO-d_6); 3.70 (2H, d, 6), 4.12~4.47 (2H, m), 4.65 (1H, m), 5.14 (2H, s), 5.75 (1H, br s), 7.25~7.42 (6H, m), 12.20 (1H, br s)	1710, 1690, 1660
2c	*erythro*	190~194 (dec)	(DMSO-d_6); 3.62 (3H, s), 4.07~4.86 (3H, m), 4.03 (2H, s), 6.20 (1H, br s), 7.24 (5H, s), 7.72 (1H, d, 9), 12.22 (1H, br s)	1740, 1710, 1690
2d	*erythro*	185~190	(DMSO-d_6); 0.78~1.58 (15H, m), 3.70~4.49 (3H, m), 5.09 (2H, s), 7.00 (1H, br s), 7.36 (5H, s), 7.71 (1H, d, 8), 12.15 (1H, br s)	1720, 1685
3a	*erythro*	Amorphous	($CDCl_3$); 3.77~4.80 (5H, m), 4.91 (2H, s), 6.26 (1H, d, 9), 6.88 (1H, s), 7.18 (15H, m), 10.36 (1H, br s)	1720, 1700
threo Isomer of **3a**		Amorphous	($CDCl_3$); 3.76~4.86 (5H, m), 4.95 (2H, s), 6.26 (1H, d, 7), 6.94 (1H, s), 7.25 (15H, m), 10.25 (1H, br s)	1720, 1700
3b	*erythro-threo* Mixture	Amorphous	($CDCl_3$); 3.44 (2H, d, 6), 4.11~4.70 (3H, m), 4.92 (2H, s), 6.35 (1H, d, 8), 6.84 (1H, s), 7.12 (15H, m), 10.40 (1H, br s)	1720, 1700
3c	*erythro*	Amorphous	($CDCl_3$); 3.50 (3H, s), 4.42 (2H, m), 4.90 (3H, m), 6.40 (1H, d, 9), 6.82 (1H, s), 7.16 (15H, m), 10.29 (1H, br s)	1740, 1720, 1705

cis-3-Benzyloxycarbonylamino-1-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-4-fluoromethyl-2-azetidinone (**4a**)

To a solution of **3a** (5 g, 9.9 mmol) in THF (200 ml) was added diethyl azodicarboxylate (DEAD) (3.9 ml, 24.8 mmol) at −20°C. A solution of triphenylphosphine (TPP) (6.5 g, 24.8 mmol) in THF (50 ml) was added to the mixture over 10 minutes at 0~10°C, and stirred at the room temp for 3 hours. The reaction mixture was evaporated to give a residue, which was purified by column chromatography (benzene - EtOAc, 50: 1) to afford **4a** (2.6 g, 53.9%) as colorless crystals. MP 162~163°C; IR (KBr) $\nu_{C=O}$ 1790, 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.23 (1H, m), 4.65~4.90 (1H, m), 5.07 (2H, s), 5.48 (2H, m), 7.20 (16H, m), 7.60 (1H, s).

Anal Calcd for $C_{26}H_{23}FN_6O_3$: C 64.19, H 4.76, N 17.27.
Found: C 64.38, H 4.72, N 17.35.

Preparation of *trans* Isomer of **4a**

To a solution of *threo* isomer of **3a** (2 g, 3.96 mmol) and TPP (2.08 g, 7.9 mmol) in DMF (40 ml) was added dropwise a solution of DEAD (1.25 ml, 7.94 mmol) in DMF (10 ml) over 15 minutes at room temp, and stirred for 3 hours at the same temp. The resulting mixture was treated by a method similar to that described above. Yield 36.3%. An amorphous powder; IR (KBr) $\nu_{C=O}$ 1785, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.03~4.50 (2H, m), 4.61~5.20 (4H, m), 6.06 (1H, d, J=8.0 Hz), 7.26 (15H, m), 7.60 (1H, s).

Anal Calcd for $C_{26}H_{23}FN_6O_3$: C 64.19, H 4.76, N 17.27.
Found: C 64.34, H 4.82, N 17.08.

Preparation of **4b** and Its *trans* Isomer

To a solution of **3b** (16 g, 30.7 mmol) and triphenyl phosphite (28.6 g, 92 mmol) in DMF (150 ml) was added DEAD (6.3 ml, 40 mmol) at room temp, and stirred for 4 hours at 40~50°C. The reaction mixture was evaporated to give a residue, which was purified by column chromatography (benzene - EtOAc, 50: 1) to afford **4b** (1.0 g, 6.5%) and its *trans* isomer (9.0 g, 58.3%).

4b: MP 163~165°C; IR (KBr) $\nu_{C=O}$ 1790, 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.87 (2H, d, J=6.0 Hz), 4.63 (1H, m), 5.08 (2H, s), 5.34 (1H, m), 7.28 (15H, m), 7.52 (1H, s), 7.87 (1H, d, J=9.0 Hz).

Anal Calcd for $C_{26}H_{23}ClN_6O_3$: C 62.09, H 4.61, N 16.71.
Found: C 62.21, H 4.52, N 16.75.

trans Isomer of **4b**: An amorphous powder; IR (KBr) $\nu_{C=O}$ 1785, 1715 cm^{-1}; NMR ($CDCl_3$) δ 3.82 (2H, m), 4.50~4.79 (2H, m), 5.00 (2H, s), 6.02 (1H, d, J=8.0 Hz), 7.20 (15H, s), 7.55 (1H, s).

Anal Calcd for $C_{26}H_{23}ClN_6O_3$: C 62.09, H 4.61, N 16.71.
Found: C 61.82, H 4.65, N 16.65.

General Procedure (III) for Deprotection of *cis*-3-Benzyloxycarbonylamino-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**5a** and **5b**) and Its *trans* Isomers

To a solution of **4** (3.3 mmol) in anisole (15 ml) was added TFA (45 ml) under ice-cooling, and stirred at room temp for 30 minutes. The solvent was evaporated to afford a residue, which was suspended in a mixture of Et_2O (20 ml) and H_2O (20 ml), and adjusted to pH 7.0 with saturated $NaHCO_3$ solution. The separated aqueous layer was adjusted to pH 2.0 with 2 N HCl, extracted with EtOAc, washed successively with H_2O and brine, dried, and evaporated to give a residue, which was triturated with diisopropyl ether to afford **5** as a white powder in 85~90%.

5a: MP 157~158°C; IR (THF) $\nu_{C=O}$ 1790, 1725 cm^{-1}; NMR (DMSO-d_6) δ 4.42~4.72 (2H, m), 5.31~5.62 (4H, m), 7.38 (5H, s), 8.29 (1H, d, J=9.0 Hz), 12.00 (1H, br s).

Anal Calcd for $C_{13}H_{13}FN_6O_3$: C 48.75, H 4.09, N 26.24.
Found: C 48.61, H 4.13, N 26.31.

trans Isomer of **5a**: An amorphous powder; IR (KBr) $\nu_{C=O}$ 1790, 1725 cm^{-1}; NMR (DMSO-d_6) δ 4.35~4.66 (2H, m), 4.76~5.43 (4H, m), 7.33 (5H, s), 8.16 (1H, d, J=8.0 Hz), 10.23 (1H, br s).

Anal Calcd for $C_{13}H_{13}FN_6O_3$: C 48.75, H 4.09, N 26.24.
Found: C 48.69, H 4.21, N 26.40.

5b: MP 96~99°C; IR (KBr) $\nu_{C=O}$ 1780, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.95 (2H, d, J=6.0 Hz), 4.65 (1H, m), 5.05 (2H, s), 5.43 (1H, dd, J=5.0 Hz, 9.0 Hz), 6.35 (1H, d, J=9.0 Hz), 7.23 (5H, s), 11.97 (1H, br s).

Anal Calcd for $C_{13}H_{13}ClN_6O_3$: C 46.37, H 3.89, N 24.96.
Found: C 46.10, H 3.62, N 25.17.

trans Isomer of **5b**: An amorphous powder; IR (KBr) $\nu_{C=O}$ 1780, 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.03~4.22 (2H, m), 4.66 (1H, m), 4.90 (1H, m), 5.07 (2H, s), 7.26~7.47 (6H, m), 12.60 (1H, br s).

Anal Calcd for $C_{13}H_{13}ClN_6O_3$: C 46.37, H 3.89, N 24.96.
Found: C 46.22, H 3.86, N 24.91.

cis-3-Benzyloxycarbonylamino-4-heptyl-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**5d**)

To a solution of **2d** (9 g, 22.3 mmol) in H_2O (200 ml) and $NaHCO_3$ (1.87 g, 22.3 mmol) was added $ZnCl_2$ (1.8 g, 13.4 mmol), and then saturated with NaCl. The resulting mixture was extracted with THF (200 ml), washed with brine, dried, and evaporated to give a residue, which was dissolved in THF (300 ml) and added DEAD (4.5 ml, 29 mmol). A solution of TPP (7.6 g, 29 mmol) in THF (50 ml) was added to the mixture over 30 minutes at 10~15°C, and stirred for 30 minutes at 15~20°C. The resulting mixture was poured into H_2O (200 ml) and EtOAc (100 ml), and adjusted pH 2.5 with 6 N HCl. The separated organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography ($CHCl_3$ - acetone, 30: 1) to afford **5d** (2.0 g, 23.3%) as an amorphous powder. IR (KBr) $\nu_{C=O}$ 1780, 1715 cm^{-1}; NMR (DMSO-d_6) δ 0.75~2.17 (15H, m), 4.34 (1H, m), 5.13 (2H, s), 5.32 (1H, dd, J=6.0 Hz, 8.0 Hz), 6.99 (1H, br s), 7.37 (5H, s), 8.37 (1H, d, J=8.0 Hz).

Anal Calcd for $C_{19}H_{26}N_6O_3$: C 59.05, H 6.78, N 21.75.
Found: C 59.26, H 6.76, N 21.75.

General Procedure (IV) of 3-Amino-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**6**)

Compounds **5** (3.1 mmol) were hydrogenated in MeOH (190 ml) for 4 hours over 5% Pd-C (0.3 g) at room temp under a hydrogen atmosphere. The insolubles were filtrated and added to a solution of $NaHCO_3$ (0.27 g, 3.2 mmol) in H_2O (2 ml), and stirred for 30 minutes. The insolubles were filtered off and the filtrate adjusted to pH 3.0 with 6 N HCl. The resulting crystals were collected by filtration to afford **6** in 75~85%. The physical properties of **6** are summarized in Table 4.

trans-3-Amino-4-fluoromethyl-1-(1*H*-tetrazol-5-yl)-2-azetidinone (*trans* Isomer of **6a**)

The *trans* isomer of **5a** (0.5 g, 1.56 mmol) was hydrogenated in MeOH (10 ml) for 6 hours over 5% Pd-C (0.2 g) at room temp under a hydrogen atmosphere. The catalyst was filtered off. The filtrate was evaporated to give a residue, which was triturated with EtOH to afford the *trans* isomer of **6a** (0.25 g, 86%). The physical properties are summarized in Table 4.

Table 4. Spectral and physical properties of compounds **6** and **25**.

Compound No.	3,4-Configuration	MP (°C, dec)	^1H NMR (Solvent) δ (J=Hz)	IR $\nu_{C=O}^{KBr}$ (cm^{-1})
6a	*cis*	197~198	(DMSO-d_6+DCl); 4.58~5.07 (3H, m), 5.58 (3H, m)	1775
trans Isomer of **6a**		161~163	(DMSO-d_6); 4.11~4.93 (3H, m), 5.33 (1H, m), 8.50 (2H, br s)	1770
6b	*cis*	195~197	(DMSO-d_6); 4.15 (2H, d, 6), 4.51 (1H, m), 4.78 (1H, d, 5), 5.80 (3H, m)	1750
trans Isomer of **6b**		160~163	(DMSO-d_6); 3.93~4.35 (2H, m), 4.50 (2H, m), 6.00 (2H, br s)	1765
6d	*cis*	126~131	(DMSO-d_6); 0.75~2.25 (15H, m), 4.27 (1H, m), 4.73 (1H, d, 6), 6.67 (3H, br s)	1760
25j	*cis*	169~173	(DMSO-d_6); 4.45~4.93 (4H, m), 6.22 (3H, br s), 7.13~7.42 (2H, m), 7.83~8.11 (2H, m)	1770, 1725
25k	*cis*	196~201	(CF_3COOD); 4.59~5.50 (3H, m), 5.59 (1H, d, 5)	1780, 1710

General Procedure (V) of 3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted Oxyimino)acetamido]-4-substituted Methyl-1-(1*H*-tetrazol-5-yl)-2-azetidinones (**11**~**14**)

i) Acylation of 3-Amino-1-(1*H*-tetrazol-5-yl)-2-azetidinones: To a solution of **6** (1 mmol) in DMF (5 ml) and Et_3N (1 mmol) were added successively 1-hydroxybenzotriazole hydrate (1.1 mmol), Molecular Sieves 4A (1 g), DCC (1.2 mmol) and (*Z*)-2-(*O*-substituted oxyimino)-2-(2-triphenylmethylaminothiazol-4-yl)acetic acid (1 mmol) at room temp, and stirred for 5 hours. The insolubles were filtered off and the filtrate poured into EtOAc (20 ml) and H_2O (30 ml), and adjusted to pH 2.5 with 2 N HCl. The separated organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography (benzene - EtOAc, 8: 1) to afford **7**~**10** in 70~85%, which were used in subsequently steps.

ii) Removal of the Triphenylmethyl Group with Formic Acid: The above compounds (**7**~**10**) (0.7~0.8 mmol) were dissolved in THF (3 ml) and 50% aq HCOOH (15 ml) and kept at 40~50°C for 1 hour. The solvent was evaporated to give a residue, which was dissolved in EtOAc (10 ml) and H_2O (5 ml), and adjusted to pH 7.0 with saturated $NaHCO_3$ solution. The separated aqueous layer was adjusted to pH 2.5 with 2 N HCl, extracted twice with EtOAc (10 ml), washed with brine, dried, and evaporated to give a residue, which was triturated with a mixture of EtOAc (1 ml) and isopropyl ether (5 ml) to afford **11**, **12** and *tert*-butyl ester (**9a** and **10a**) in 85~90%.

iii) Removal of the *tert*-Butyl Ester Group with TFA: The above *tert*-butyl ester (**9a** and **10a**) (0.5~0.6 mmol) were dissolved in CH_2Cl_2 (14 ml), and added TFA (14 ml) under ice-cooling, and stirred at room temp for 1 hour. The solvent was evaporated to give a residue, which was dissolved in EtOAc (5 ml) and H_2O (5 ml), and adjusted to pH 7.0 with saturated $NaHCO_3$ solution. The separated aqueous layer was adjusted to pH 2.0 with 2 N HCl, saturated with NaCl, extracted five times with EtOAc (10 ml), washed with brine, dried, and evaporated to give a residue, which was triturated with a mixture of EtOAc (10 ml) and Et_2O (10 ml) to afford **13** and **14** in 70~75%. The physical properties of **11**~**14** are summarized in Table 5.

cis-3-[(*Z*)-2-(2-Fluoroethoxyimino)-2-(2-triphenylmethylaminothiazol-4-yl)acetamido]-4-(1-methyltetrazol-5-yl)thiomethyl-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**16e**) and *trans* Isomer of **17e**

To a solution of **7b** (0.4 g, 0.62 mmol) in DMF (5 ml) were added 5-mercapto-1-methyltetrazole sodium salt dihydrate (0.42 g, 2.4 mmol) and Molecular Sieves 4A (2 g), and stirred for 7 hours at 50~60°C. The resulting mixture was poured into EtOAc (30 ml) and H_2O (20 ml), and adjusted to pH 2.0 with 2 N HCl. The separated organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography (toluene - EtOAc, 1: 1) to afford **16e** (0.24 g, 54.8%) as a white powder. MP 160°C (dec); IR (KBr) $\nu_{C=O}$ 1785, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.58~4.29 (7H, m), 4.48~5.08 (3H, m), 5.49 (1H, dd, J=6.0 Hz, 8.0 Hz), 6.88 (1H, s), 7.24 (15H, s), 7.45~7.65 (2H, m), 8.59 (1H, br s). Compound **17e** was prepared from **15b** by a method similar to that above described.

17e: Yield 28.6%. MP 145~150°C (dec); IR (KBr) $\nu_{C=O}$ 1780 1670 cm^{-1}; NMR (DMSO-d_6) δ 3.65~4.23 (7H, m), 4.36~4.86 (2H, m), 4.93~5.36 (4H, m), 6.64 (1H, s), 7.26 (15H, s), 9.33 (1H, d, J=8.0 Hz).

5-{*trans*-3-[(*Z*)-2-(2-Fluoroethoxyimino)-2-(2-triphenylmethylaminothiazol-4-yl)acetamido]-4-(1-pyridiniomethyl)-2-azetidinone}tetrazolide (**17f**)

To a solution of **15b** (1.15 g, 1.74 mmol) in pyridine (20 ml) was added sodium iodide (0.35 g, 2.33 mmol), and stirred for 20 hours at 70~80°C. The resulting mixture was evaporated to give a residue, which was dissolved in EtOAc (30 ml) and H_2O (20 ml). The organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography ($CHCl_3$ - MeOH, 5: 1) to afford **17f** (0.1 g, 8.2%) as a white powder. MP 165~170°C (dec); IR (KBr) $\nu_{C=O}$ 1775, 1665 cm^{-1}.

trans-3-[(*Z*)-2-(2-Fluoroethoxyimino)-2-(2-triphenylmethylaminothiazol-4-yl)acetamido]-4-(2*H*-5-methyltetrazol-2-yl)methyl-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**17g**)

To a solution of **15b** (1.0 g, 1.5 mmol) in DMF (10 ml) were added sodium iodide (260 mg, 1.5

Table 5. Spectral and physical properties of *N*-(tetrazol-5-yl)azetidin-2-ones.

Compound No.	3,4-Configuration	MP (°C, dec)	^{1}H NMR (DMSO-d_6) δ (J=Hz)	IR $\nu_{C=O}^{KBr}$ (cm^{-1})
11a	*cis*	>230	4.11 (2H, m), 4.36~5.22 (5H, m), 5.58 (1H, m), 6.72 (1H, s), 7.17 (2H, br s), 8.18 (2H, m), 9.38 (1H, d, 8)	1765, 1660
trans Isomer of **11a**		>230	4.14~5.56 (8H, m), 7.15 (1H, s), 9.69 (1H, d, 9), 14.90 (2H, br s)**	1765, 1660
11b	*cis*	>230	3.87~4.32 (4H, m), 4.47~4.78 (2H, m), 5.00 (1H, m), 5.65 (1H, dd, 5, 9), 6.11 (3H, br s), 6.79 (1H, s), 9.45 (1H, d, 9)	1765, 1660
trans Isomer of **11b**		159~162	4.02~4.40 (4H, m), 4.53~4.80 (2H, m), 5.00~5.20 (2H, m), 5.70 (2H, br s), 6.81 (1H, s), 7.00 (1H, br s), 9.40 (1H, d, 8)	1770, 1660
11d	*cis*	209~212	0.69~2.08 (15H, m), 4.15 (2H, m), 4.53 (1H, m), 4.80~5.25 (2H, m), 5.49 (1H, dd, 6, 9), 6.73 (1H, s), 7.21 (3H, br s), 9.42 (1H, d, 9)	1765, 1660
12a	*cis*	>230	4.14~5.10 (5H, m), 5.64 (1H, m), 6.74 (1H, s), 7.29 (5H, s), 8.64 (2H, br s), 9.50 (1H, d, 8)	1760, 1655
13a	*cis*	208~211	4.35~5.05 (4H, m), 5.25 (1H, m), 5.70 (1H, m), 6.83 (1H, s), 7.36 (2H, br s), 9.40 (2H, m)	1775, 1690 (sh), 1670
14a	*cis*	205~208	1.67~2.46 (6H, m), 4.41~5.13 (2H, m), 5.29 (1H, m), 5.70 (1H, m), 6.80 (1H, s), 9.42 (1H, d, 9), 10.03 (3H, m)	1770, 1720, 1660
18e	*cis*	170~173	3.59~4.36 (7H, m), 4.40~5.23 (3H, m), 5.53 (1H, dd, 6, 9), 6.81 (1H, s), 7.69 (3H, br s), 9.43 (1H, d, 9)	1780, 1670
19e	*trans* Isomer of **11e**	150~152	3.40~4.44 (11H, m), 4.66 (1H, m), 4.83~5.30 (2H, m), 6.64 (1H, s), 9.33 (1H, d, 8)	1770, 1660
19f	*trans*	187~190	3.79~4.68 (6H, m), 4.80~5.32 (2H, m), 6.67 (1H, s), 7.22 (3H, br s), 7.85~8.27 (2H, m), 8.51 (1H, m), 8.90~9.48 (3H, m)	1770, 1670
19g	*trans*	>230	2.50 (3H, s), 3.50~4.77 (6H, m), 4.82~5.23 (2H, m), 6.77 (1H, s), 7.17 (3H, br s), 9.30 (1H, d, 8)	1770, 1660
19h	*trans*	180~182	2.13 (4H, m), 3.15 (3H, s), 3.36~4.75 (11H, m), 5.03 (1H, dd, 3, 9), 6.83 (1H, s), 7.25 (2H, br s), 9.60 (1H, d, 9)	1770, 1660
26j	*cis*	206~209	3.83~5.15 (7H, m), 5.73 (1H, dd, 6, 8), 6.40~7.48 (6H, m), 7.82~8.17 (2H, m), 9.55 (1H, d, 8)	1785, 1720, 1650
27k	*cis*	195~199	4.01~4.86 (6H, m), 5.24 (3H, m), 5.66 (1H, m), 6.52 (2H, br s), 6.96 (1H, s), 7.29 (1H, br s), 9.33 (1H, d, 8)	1770, 1700, 1660
28k	*cis*	223~224	3.90~4.71 (3H, m), 5.18 (2H, s), 5.68 (1H, m), 6.51 (2H, br s), 6.80 (1H, s), 7.14 (2H, br s), 7.35 (5H, s), 9.37 (1H, d, 8)	1780, 1695, 1660
29k*	*cis*	186~190	3.90~4.77 (5H, m), 5.70 (1H, m), 6.53 (2H, br s), 6.82 (1H, s), 8.07~9.32 (5H, m)	1775, 1720, 1670, 1630
30k*	*cis*	193~196	1.64~2.48 (6H, m), 3.86~4.89 (3H, m), 5.77 (1H, m), 6.50 (2H, br s), 6.86 (1H, s), 7.88 (5H, m), 9.26 (1H, d, 9)	1775, 1715, 1665, 1630

*: TFA salt. **: Measured in a mixture of DMSO-d_6 and CF_3COOD.

mmol) and sodium 5-methyltetrazole (167 mg, 1.5 mmol), and stirred for 15 hours at 60°C. The resulting mixture was treated by a method similar to that described in preparation of **16e**. Yield 0.26 g (24.1%). MP 185~190°C (dec); IR (KBr) $\nu_{C=O}$ 1780, 1670 cm^{-1}; NMR (DMSO-d_6) δ 2.40 (3H, s), 4.10 (2H, m), 4.56~5.69 (6H, m), 6.71 (1H, s), 7.29 (15H, s), 8.70 (1H, br s), 9.32 (1H, d, J= 8.0 Hz).

5-{*trans*-3-[(*Z*)-2-(2-Fluoroethoxyimino)-2-(2-triphenylmethylaminothiazol-4-yl)acetamido]-4-(1-methyl-1-pyrrolidinio)methyl-2-azetidinone}tetrazolide (**17h**)

To a solution of **15b** (1.0 g, 1.5 mmol) in DMF (10 ml) were added sodium iodide (260 mg, 1.5 mmol) and 1-methylpyrrolidine (0.78 ml, 7.55 mmol), and stirred for 20 hours at 60°C. The resulting mixture was treated by a method similar to that described in preparation of **16e**. Yield 0.15 g (14.5%). MP 185°C (dec); IR (KBr) $\nu_{C=O}$ 1775, 1660 cm^{-1}; NMR (DMSO-d_6) δ 1.80~2.24 (4H, m), 2.86~3.27 (4H, m), 3.34~4.29 (8H, m), 4.34~4.65 (2H, m), 4.95 (1H, m), 6.70 (1H, s), 7.24 (15H, s), 8.70 (1H, d, J=8.0 Hz).

cis-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(2-fluoroethoxyimino)acetamido]-4-substituted Methyl-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**18e** and **19e~h**)

According to the general procedure V-ii), the triphenylmethyl group of **16e** and **17e~h** was removed to give **18e** and **19e~h** as a white powder. The physical properties of **18e** and **19e~h** are summarized in Table 5.

DL-*erythro*-2-Benzyloxycarbonylamino-*N*-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-3,4-dihydroxybutyramide (**20**)

To a solution of **3c** (4 g, 7.54 mmol) in THF (45 ml) and H_2O (15 ml) was added in portions $NaBH_4$ (860 mg, 22.7 mmol) over 30 minutes at 0~5°C, and stirred for 5 hours at room temp. The resulting mixture was poured into EtOAc (50 ml) and ice water (50 ml) keeping pH at 2.0 with 2 N HCl. The organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was triturated with a mixture of EtOAc (3 ml) and Et_2O (9 ml) to afford **20** (2.7 g, 70%) as a white powder. MP 142~144°C; IR (KBr) $\nu_{C=O}$ 1770 cm^{-1}; NMR (DMSO-d_6) δ 3.37~4.01 (4H, m), 4.25~4.60 (2H, m), 4.89 (2H, s), 6.27 (1H, d, J=8.0 Hz), 6.89 (1H, s), 7.17 (15H, m), 10.05 (1H, br s).

DL-*erythro*-2-Benzyloxycarbonylamino-*N*-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-3-hydroxy-4-(tetrahydropyran-2-yl)oxybutyramide (**21**)

To a solution of **20** (3 g, 5.97 mmol) in CH_3CN (90 ml) were added *p*-toluenesulfonic acid monohydrate (0.15 g, 0.79 mmol), dihydropyran (0.55 ml, 6 mmol) and Molecular Sieves 4A (2 g) at room temp, and stirred for 24 hours at the same temp. The insolubles were filtered off and the filtrate evaporated to give a residue, which was dissolved in EtOAc (50 ml) and H_2O (50 ml). The organic layer was washed with brine, dried, and evaporated to give a residue, which was purified by column chromatography ($CHCl_3$ - acetone, 5: 1) to afford **21** (2.5 g, 71.4%) as an amorphous powder. IR (KBr) $\nu_{C=O}$ 1720, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.18~1.98 (6H, m), 3.18~4.22 (5H, m), 4.22~4.68 (3H, m), 5.06 (2H, s), 6.05 (1H, d, J=9.0 Hz), 6.90 (1H, s), 7.28 (15H, s), 10.22 (1H, br s).

cis-3-Benzyloxycarbonylamino-1-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-4-(tetrahydropyran-2-yl)-oxymethyl-2-azetidinone (**22**, Diastereomer Mixture)

Compound **22** was prepared from **21** by a method similar to that described for the synthesis of **4a**.

22A: MP 139~141°C; IR (KBr) $\nu_{C=O}$ 1780, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.02~1.67 (6H, m), 3.27~3.71 (2H, m), 3.92 (1H, m), 4.22~4.57 (3H, m), 5.14 (2H, s), 5.47 (1H, dd, J=6.0 Hz, 10.0 Hz), 6.49 (1H, d, J=10.0 Hz), 7.29 (15H, s), 7.76 (1H, s).

Anal Calcd for $C_{31}H_{32}N_6O_5$: C 65.48, H 5.67, N 14.78.
Found: C 65.47, H 5.88, N 14.71.

22B: MP 162~163°C; IR (KBr) $\nu_{C=O}$ 1780, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.04~1.61 (6H, m), 2.99~3.24 (2H, m), 3.69 (1H, m), 4.34~4.76 (3H, m), 5.16 (2H, s), 5.46 (1H, dd, J=6.0 Hz, 10.0 Hz), 5.59 (1H, d, J=9.0 Hz), 7.32 (15H, s), 7.89 (1H, s).

Anal Calcd for $C_{31}H_{32}N_6O_5$: C 65.48, H 5.67, N 14.78.
Found: C 65.71, H 5.62, N 14.88.

cis-3-Benzyloxycarbonylamino-1-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-4-hydroxymethyl-2-azetidinone (**23i**)

To a solution of **22** (1.4 g, 2.46 mmol) in 95% EtOH (20 ml) and THF (5 ml) was added PTS (80 mg, 0.42 mmol), and stirred for 2 hours at 50~60°C. The resulting mixture was evaporated to give a residue, which was dissolved in EtOAc (30 ml) and H_2O (30 ml). The organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was triturated with Et_2O to afford **23i** (1.1 g, 93%). MP 155~158°C; IR (KBr) $\nu_{C=O}$ 1780, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.83 (1H, br s), 3.80 (1H, m), 4.05~4.63 (2H, m), 5.10 (2H, s), 5.37 (1H, m), 6.05 (1H, d, J=9.0 Hz), 7.27 (15H, m), 7.59 (1H, s).

Anal Calcd for $C_{26}H_{24}N_6O_4$: C 64.44, H 5.00, N 17.35.
Found: C 64.22, H 5.02, N 17.51.

cis-3-Benzyloxycarbonylamino-4-(*p*-fluorobenzoyloxymethyl)-1-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-2-azetidinone (**23j**)

To a solution of **23i** (2 g, 4.13 mmol) in CH_2Cl_2 (20 ml) and pyridine (0.67 ml, 8.26 mmol) was added *p*-fluorobenzoyl chloride (0.98 ml, 8.26 mmol) under ice-cooling, and stirred for 3 hours at room temp. The resulting mixture was poured into H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated to give a residue, which was triturated with toluene to afford **23j** (2.2 g, 88%) as colorless crystals. MP 156~157°C; IR (KBr) $\nu_{C=O}$ 1810, 1725 cm^{-1}; NMR ($CDCl_3$) δ 4.37 (1H, m), 4.65 (2H, m), 5.07 (2H, s), 5.40 (1H, dd, J=6.0 Hz, 9.0 Hz), 5.63 (1H, d, J=9.0 Hz), 6.70~7.76 (20H, m).

Anal Calcd for $C_{33}H_{27}FN_6O_5$: C 65.34, H 4.49, N 13.85.
Found: C 65.22, H 4.52, N 13.99.

DL-*erythro*-2-Benzyloxycarbonylamino-4-carbamoyloxy-*N*-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-3-hydroxybutyramide (**24**)

To a solution of **20** (4.5 g, 8.95 mmol) in CH_3CN (225 ml) was added dropwise a solution of chlorosulfonyl isocyanate (1.02 ml, 11.7 mmol) in CH_3CN (12 ml) at −40~−35°C over 2 hours, and stirred for 30 minutes. A solution of sodium sulfite heptahydrate (4.5 g, 17.9 ml) in H_2O (120 ml) was added to the resulting mixture at −40°C, and allowed to come to room temp. The mixture was saturated with NaCl, and the organic layer was separated. The aqueous layer was extracted with CH_3CN (50 ml). The combined organic layer was washed twice with brine (50 ml). Anhydrous $MgSO_4$ (50 g) was added to the solution, and stirred for 1 hour at room temp. The insolubles were filtered off and the filtrate evaporated to give a residue, which was triturated with a mixture of EtOAc (10 ml) and Et_2O (10 ml) to afford **24** (3.2 g, 65.4%) as colorless crystals. MP 165~168°C; IR (KBr) $\nu_{C=O}$ 1705, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.52~4.64 (5H, m), 4.89 (2H, s), 5.42 (2H, br s), 6.42 (1H, d, J=8.0 Hz), 6.83 (1H, s), 6.92~7.39 (15H, m), 10.41 (1H, br s).

cis-3-Benzyloxycarbonylamino-1-(1-diphenylmethyl-1*H*-tetrazol-5-yl)-4-carbamoyloxymethyl-2-azetidinone (**23k**)

Compound **23k** was prepared from **24** by a method similar to that described for the synthesis of **4a**. MP 189~191°C (dec); IR (KBr) $\nu_{C=O}$ 1800, 1720, 1695 cm^{-1}; NMR (DMSO-d_6) δ 4.01~4.41 (2H, m), 4.68 (1H, m), 5.09 (2H, s), 5.44 (1H, m), 6.42 (2H, br s), 6.89 (1H, s), 7.30 (15H, m), 8.06 (1H, d, J=9.0 Hz).

Anal Calcd for $C_{27}H_{25}N_7O_5 \cdot H_2O$: C 59.44, H 4.99, N 17.97.
Found: C 59.21, H 5.03, N 18.20.

cis-3-Amino-4-substituted Methyl-1-(1*H*-tetrazol-5-yl)-2-azetidinone (**25j** and **25k**)

Compounds (**25j**, **25k**) were prepared from **23j** and **23k** by a method similar to that described for the synthesis of **6**. The physical properties of **25j** and **25k** are summarized in Table 4.

cis-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted Oxyimino)acetamido]-4-substituted Methyl-1-(1*H*-tetrazol-5-yl)-2-azetidinones (**26j**~**30k**)

Compounds (**26j**~**30k**) were prepared from **25j** and **25k** by according to the general procedure V. The physical properties of **26j**~**30k** are summarized in Table 5.

Methyl 4-Fluoro-2-methoxyimino-3-oxobutyrate (**32**)

A mixture of methyl 4-bromo-2-methoxyimino-3-oxobutyrate (**31**) (50 g, 0.21 mmol), 18-crown-6 (5 g, 18.9 mmol) and freshly dried potassium fluoride (25 g, 0.43 mol) in anhydrous CH_3CN (750 ml) was heated at reflux for 10 hours. The insolubles were filtered off and the filtrate evaporated to give a residue, which was dissolved in toluene (300 ml) and H_2O (300 ml). The organic layer was washed with H_2O, dried, and evaporated to give a residue, which was purified by column chromatography (*n*-hexane - EtOAc, 20: 1) to afford **32** (10 g, 26.9%) as a colorless oil. IR (neat) $\nu_{C=O}$ 1740, 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.84 (3H, s), 4.10 (3H, s), 4.96 (1H, s), 5.73 (1H, s).

Methyl 4-Fluoro-3-hydroxy-2-methoxyiminobutyrate (**33**)

To a solution of **32** (20 g, 0.17 mol) in MeOH (200 ml) was added portionwise $NaBH_4$ (1.18 g, 31.2 mmol) over 30 minutes at 0~5°C, and stirred for 1 hour at the same temp. The resulting mixture was concentrated to one third volume under reduced pressure, the concentrate was extracted with EtOAc. The extract was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography (toluene - EtOAc, 20: 1) to afford **33** (18.5 g, 91.6%) as a colorless oil. IR (neat) $\nu_{C=O}$ 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.63 (1H, m), 3.83 (3H, s), 3.91 (3H, s), 4.03~5.01 (3H, m).

Methyl 2-Benzyloxycarbonylamino-4-fluoro-3-hydroxybutyrate (**34**)

Compound **33** (18 g, 0.1 mol) was hydrogenated in MeOH (200 ml) for 8 hours over 5% Pd-C (6 g) at room temp under a hydrogen atmosphere. The catalyst was filtered off and the filtrate evaporated to give a residue, which was dissolved in CH_2Cl_2 (200 ml) and cooled to −20°C. After addition of benzyl chloroformate (15.8 ml, 0.11 mol), pyridine (8.9 ml, 0.11 mol) was added dropwise to the solution over 10 minutes at −20~−10°C, and stirred for 1 hour at 0~5°C, in addition, 1 hour at room temp. The reaction mixture was poured into H_2O. The organic layer was washed successively with H_2O and brine, dried, and evaporated to give a residue, which was purified by column chromatography (toluene - EtOAc, 20: 1) to afford **34** (14 g, 49%) as colorless crystals. MP 90~95°C; IR (KBr) $\nu_{C=O}$ 1770, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.28 (1H, m), 3.76 (3H, s), 4.08 (1H, m), 4.36~4.65 (2H, m), 4.80 (1H, m), 5.10 (2H, s), 5.72 (1H, d, J=8.0 Hz), 7.32 (5H, s).

Anal Calcd $C_{13}H_{16}FNO_5$: C 54.72, H 5.66, N 4.91.
Found: C 54.89, H 5.65, N 4.80.

Methyl 2-Benzyloxycarbonylamino-4-chloro-3-hydroxybutyrate

The title compound was prepared from methyl 4-chloro-3-hydroxy-2-methoxyiminobutyrate by a method similar to that described above. Yield 93%. MP 110~112°C; IR (KBr) $\nu_{C=O}$ 1745, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.59 (2H, d, J=6.0 Hz), 3.61 (3H, s), 4.10~4.40 (2H, m), 4.56 (1H, m), 4.84~5.07 (3H, m), 6.14 (1H, d, J=9.0 Hz), 7.24 (5H, s).

Anal Calcd $C_{13}H_{16}ClNO_5$: C 51.74, H 5.36, N 4.64.
Found: C 51.59, H 5.21, N 4.87.

DL-*erythro*-2-Benzyloxycarbonylamino-4-fluoro-3-hydroxybutyric Acid (**1a**) and Its *threo* Isomer

To a solution of **34** (9.8 g, 34.4 mmol) in acetone (50 ml) and H_2O (15 ml) was added dropwise a solution of 1 N NaOH (34.5 ml) over 30 minutes at 10~15°C, and stirred for 30 minutes at the same temp. The resulting mixture was concentrated to a half volume, and diluted with H_2O (50 ml) and washed with Et_2O. The solution was adjusted to pH 2.0 with 6 N HCl, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give a residue, which was triturated with benzene (50 ml) to afford **1a** (4.7 g, 50.5%) as colorless crystals. On the other hand, the filtrate was evaporated to give a residue, which was triturated with toluene (30 ml) to afford *threo* isomer of **1a** (3.1 g, 33.3%).

1a: MP 109~111°C; IR (KBr) $\nu_{C=O}$ 1720 (sh), 1690 cm^{-1}; NMR (DMSO-d_6) δ 4.32~4.82 (4H, m), 4.80 (1H, m), 5.07 (2H, s), 6.99 (1H, d, J=8.0 Hz), 7.34 (5H, s). The *threo* isomer of **1a**: MP 80~82°C; IR (KBr) $\nu_{C=O}$ 1720, 1690 cm^{-1}; NMR (DMSO-d_6) δ 3.85~4.90 (5H, m), 5.07 (2H, s), 7.00 (1H, d, J=8.0 Hz), 7.35 (5H, s).

DL-2-Benzyloxycarbonylamino-4-chloro-3-hyroxybutyric Acid

The title compound was prepared from methyl 2-benzyloxycarbonylamino-4-chloro-3-hydroxybutyrate by a method similar to that described above. Yield 50%. An amorphous powder; IR (KBr) $\nu_{C=O}$ 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.45 (2H, d, J=6.0 Hz), 4.12~4.65 (3H, m), 5.06 (2H, s), 6.05 (1H, d, J=8.0 Hz), 7.00 (1H, br s), 7.25 (5H, s).

DL-Ethyl 2-Benzyloxycarbonylamino-3-hydroxydecanoate (**36**)

To a solution of diisopropylamine (35 ml, 0.25 mol) and absolute THF (600 ml) was added dropwise *n*-butyllithium (124 ml, 1.5 N hexane solution) at −70°C, and stirred for 30 minutes at the same temp. A solution of ethyl *N*-carboxybenzylglycinate (**35**) (20 g, 84 mmol) and THF (50 ml) was added dropwise to the resulting mixture at −78°C. After being stirred for 1 hour at −70~ −60°C, octyl aldehyde (14.5 ml, 93 mmol) was added dropwise to the solution at −78°C, and stirred for 30 minutes at the same temp. After addition of AcOH (11 ml, 0.19 mol), the reaction mixture was poured into EtOAc (200 ml) and H_2O (300 ml). The organic layer was washed with brine, dried, and evaporated to give a residue, which was purified by column chromatography (toluene - EtOAc, 20: 1) to afford **36** (24 g, 78%) as a colorless oil. IR (neat) $\nu_{C=O}$ 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.73~1.56 (15H, m), 3.83~4.47 (5H, m), 5.09 (2H, s), 5.79 (1H, d, J=8.0 Hz), 7.30 (5H, s).

DL-*erythro*-Benzyloxycarbonylamino-3-hydroxydecanoic Acid (**1d**)

The title compound was prepared from **36** by a method similar to that described for the synthesis of **1a**. Yield 84%. An amorphous powder. IR (KBr) $\nu_{C=O}$ 1730, 1690 cm^{-1}; NMR (DMSO-d_6) δ 0.75~1.52 (15H, m), 3.63~4.20 (3H, m), 5.08 (2H, s), 6.85 (1H, d, J=9.0 Hz), 7.35 (5H, s).

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