STUDIES ON β-LACTAM ANTIBIOTICS. VI†

EFFECT ON ANTIBACTERIAL ACTIVITY OF α-SUBSTITUENTS IN THE 2-(2-AMINO-4-THIAZOLYL)ACETYL SIDE CHAIN OF A CEPHALOSPORIN NUCLEUS

HISASHI TAKASUGI, ZENZABURO TOZUKA and TAKAO TAKAYA*

Research Laboratories, Fujisawa Pharmaceutical Co., Ltd.
Kashima, Yodogawaku, Osaka, Japan

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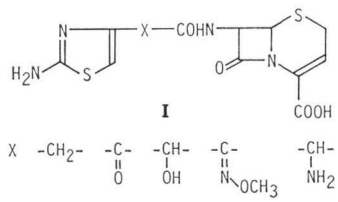
Synthesis and *in vitro* antibacterial activity of semisynthetic cephalosporins (**I**) having an α-substituted 2-(2-amino-4-thiazolyl)acetyl side chain at the 7-position were described.

In general, at least one hydrogen atom seems to be necessary on the α-carbon in a 7-acetyl side chain of a cephem nucleus in order to afford favorable compounds with respect to both potency and spectrum of antimicrobial activity.[1~7]

However, discovery of nocardicin A,[8,9] a novel monocyclic β-lactam antibiotic with a unique oxyiminoacetyl side chain on the amino radical attached to the β-lactam ring, led us to synthesize a new family of cephalosporins[10~16] having the 7-oxyiminoacetyl side chains. In the series of the oxyiminoacetylcephalosporins, ceftizoxime[11,15] has been selected as a clinical candidate, and was brought to the market in early 1982.

In this report, we examined the effect on antibacterial activity of the cephalosporins represented by the general structure **I** upon replacement of one or both hydrogen atoms of the α-methylene in the 2-(2-amino-4-thiazolyl)acetyl side chain by other functional groups such as hydroxyl, amino, carbonyl, and methoxyimino.



I

X	$-CH_2-$	$-\overset{\overset{O}{\|}}{C}-$	$-\underset{\underset{OH}{\|}}{CH}-$	$-\overset{\overset{N\!-\!OCH_3}{\|}}{C}-$	$-\underset{\underset{NH_2}{\|}}{CH}-$

Chemistry

The synthesis of the novel cephalosporins (**I**) is outlined in Scheme 1. Acylation of *p*-nitrobenzyl 7-aminocephalosporanate (**1a**) with 4-bromo-3-oxobutyryl bromide gave 4-bromo-3-oxobutyrylcephem (**2**), which afforded 2-(2-amino-4-thiazolyl)acetylcephem (**3a**) on treatment with thiourea. The (2-formamido-4-thiazolyl)glyoxalylcephem (**4a**) was obtained by acylation of **1a** with (2-formamido-4-thiazolyl)glyoxalic acid[16] which was activated by using a Vilsmeier reagent prepared from dimethylformamide (DMF) and phosphoryl chloride ($POCl_3$) or thionyl chloride ($SOCl_2$).

The protecting *p*-nitrobenzyl group of **3a** and **4a** was removed by hydrogenation in the presence of 10% palladium on carbon catalyst to give the corresponding cephalosporanic acids (**3b** and **4b**). De-

* To whom correspondence should be addressed.

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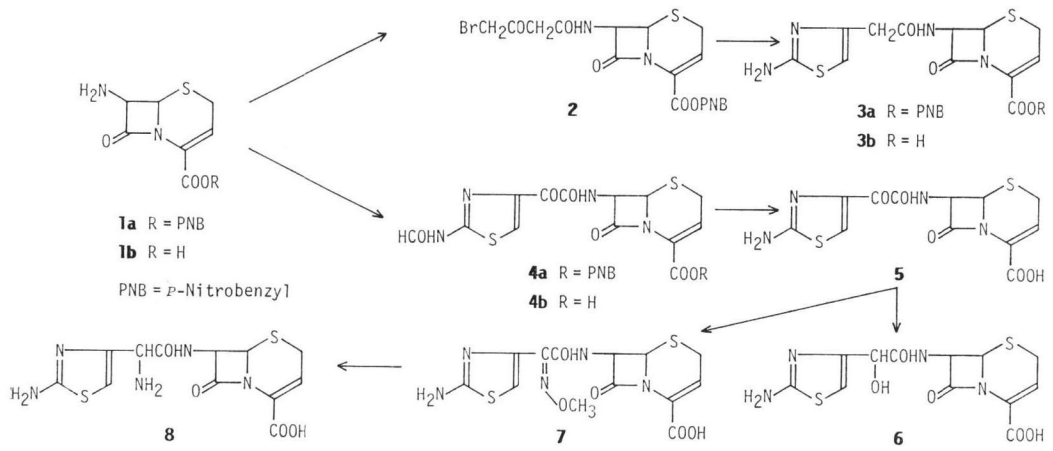
Scheme 1.



formylation of **4b** with hydrochloric acid in methanol gave (2-amino-4-thiazolyl)glyoxalylcephem (**5**). Reduction of **5** with sodium borohydride in methanol gave α-hydroxyl analog (**6**). Treatment of **5** with methoxyamine afforded the methoxyimino analog (**7**) which was identical with an authentic sample prepared by acylation of 7-amino-3-cephem-4-carboxylic acid (**1b**) with 2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetic acid.[18] The oxyimino group of **7** was assigned the *Z*-configuration on the basis of the NMR chemical shifts, retention times for high performance liquid chromatography, and Rf values for thin layer chromatography. Reduction of **7** with zinc powder in 90% formic acid gave α-amino analog (**8**).[17,18]

Biological Activity

The minimum inhibitory concentration (MIC) values for the cephalosporins (**3b**, **5**, **6**, **7** and **8**) against one Gram-positive and six Gram-negative bacteria are shown in Table 1. The effect of α-substituent variation on the *in vitro* activity can be seen in Table 1 by comparing vertically the MIC values with those of the α-unsubstituted cephem (**3b**). Against *Staphylococcus aureus* 6, the α-substituted cephems are 2~32 times less active than **3b**. Substitution of one of the α-hydrogen atoms by a hydroxyl or amino group shows little or no effect against Gram-negative bacteria, although antibacterial activity of both **6** and **8** tends to be slightly enhanced against resistant species of *Escherichia coli* 28. However, substitution of both of the α-hydrogens tends to enhance *in vitro* activity against Gram-negative bacteria. Activity of the oxocephem (**5**) is enhanced 2~4 times against *Klebsiella pneumoniae* 20, *Proteus mirabilis* 18 and *Proteus vulgaris* 1, but it is two times less active against *E. coli* 28. Interestingly, the methoxyimino cephem (**7**) is 8~2,000 times more active against all of the Gram-negative bacteria.

Experimental

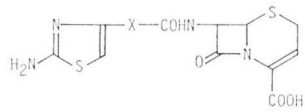
NMR spectra were recorded at 60 MHz on a JNM-PMX 60 NMR spectrometer and at 100 MHz on a JEOL-MH 100 NMR spectrometer using Me_4Si as an internal standard. IR spectra were taken on a Hitachi 260-10 spectrophotometer or on a Shimadzu IR-420 spectrophotometer.

Column chromatography was carried out on macroporous non-ionic adsorption resin "Diaion HP-20" (Trademark, manufactured by Mitsubishi Chemical Industries Ltd.).

Preparation of 7β-Amino-3-cephem-4-carboxylic Acid (**1b**)

p-Nitrobenzyl 7β-amino-3-cephem-4-carboxylate (**1a**) was obtained by a modification of the method

Table 1. Antimicrobial activity of cephalosporins (I).



Compounds	X	MIC (μg/ml)						
		S. aureus	*E. coli*		*K. pneumoniae*	*P. mirabilis*	*P. vulgaris*	*P. aeruginosa*
		6	32	28[a]	20	18	1	NCTC 10490
3b	$-CH_2-$	1.56	0.39	3.13	0.20	0.39	1.56	>800
6	$-CH-$ $\vert$ OH	3.13	0.39	0.78	0.39	0.78	1.56	>800
8	$-CH-$ $\vert$ NH_2	50	0.39	1.56	0.39	0.39	1.56	800
5	$-C-$ $\Vert$ O	12.5	0.78	6.25	0.10	0.10	0.39	>800
7	$-C-$ $\Vert$ $N-OCH_3$ (Ceftizoxime)	3.13	0.05	0.05	$\leqq$0.025	$\leqq$0.025	$\leqq$0.025	0.39

[a] Cephalosporinase producer.

of SCARTAZZINI and BICKEL[10] from *p*-nitrobenzyl 7β-phenylacetamido-3-hydroxy-3-cephem-4-carboxylate.

A mixture of **1a** (20.1 g, 0.06 mole) and 10% palladium on carbon (10.0 g) in MeOH (400 ml), THF (800 ml), AcOH (6 ml), and H_2O (60 ml) was subjected to catalytic hydrogenation at room temperature under atmospheric pressure for 4 hours. The insoluble material was filtered off, and the filtrate was evaporated. The residue and above insoluble substance were extracted with aqueous $NaHCO_3$ solution, and the separated aqueous layer was washed with AcOEt. The aqueous layer was acidified to pH 3.5 with 10% HCl under ice-cooling. The precipitate was filtered off, washed with H_2O and acetone, and dried (P_2O_5) to give 5.7 g (47.8%) of **1b**.

Preparation of *p*-Nitrobenzyl 7β-(4-Bromo-3-oxobutyramido)-3-cephem-4-carboxylate (**2**)

A mixture of **1a** (5 g, 15 mmole) and *O,N*-bis(trimethylsilyl)acetamide (BSA) (20 ml) in AcOEt (50 ml) was dissolved with stirring at 45°C for 1.5 hours, and the resultant solution was cooled at −15°C. To the solution was added dropwise a solution of 4-bromo-3-oxobutyryl bromide (4.39 g, 18 mmole) in methylene chloride (CH_2Cl_2) (14 ml). After stirring at the same temperature for 30 minutes, the reaction mixture was poured into H_2O and extracted with AcOEt. The extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness to give 6.15 g (82.3%) of **2**. IR (Nujol) 1780, 1740, 1630 cm^{-1}, NMR (DMSO-d_6) δ 3.62 (2H, broad s), 4.37 (2H, s), 5.08 (1H, d, J=5 Hz), 5.40 (2H, s), 5.77~6.05 (3H, m), 6.67 (1H, t, J=5 Hz), 7.68 (2H, d, J=9 Hz), 8.04 (2H, d, J=9 Hz), 9.07 (1H, d, J=8 Hz).

Preparation of *p*-Nitrobenzyl 7β-[2-(2-Amino-4-thiazolyl)acetamido]-3-cephem-4-carboxylate (**3a**)

To a solution of **2** (6.15g, 12.3 mmole) in THF (60ml) was added a solution of thiourea (1.13g, 14.8 mmole) and $NaHCO_3$ (1.24 g, 14.8 mmole) in H_2O (20 ml). After stirring at room temperature for one hour, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in H_2O and extracted with AcOEt. The extracts were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The oily residue was subjected to column chromatography on silica gel and eluted successively with benzene, a mixture of benzene and AcOEt (1 : 1), and AcOEt. The eluate with AcOEt was evaporated to dryness *in vacuo* to give 1.5 g (25.5%) of **3a**. IR (Nujol) 3350, 1780, 1740, 1680, 1610 cm^{-1}, NMR (DMSO-d_6) δ 3.40 (2H, broad s), 3.68 (2H, broad s), 5.12 (1H, d, J=5 Hz), 5.43 (2H, s), 5.84 (1H, dd, J=5 Hz, 8 Hz), 6.30 (1H, s), 6.70 (1H, broad s), 7.22 (2H, d, J=9 Hz), 8.27 (2H, d, J=9 Hz), 8.93 (1H, d, J=8 Hz).

Preparation of 7β-[2-(2-Amino-4-thiazolyl)acetamido]-3-cephem-4-carboxylic Acid (**3b**)

A mixture of **3a** (1.4 g, 2.94 mmole) and 10% palladium on carbon (0.7 g) in MeOH (45 ml), THF (60 ml) and AcOH (7 ml) was subjected to catalytic reduction at room temperature under atmospheric pressure for 8.5 hours. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in aqueous $NaHCO_3$ solution. After adjusted to pH 4.5 with dil. HCl, the solution was subjected to column chromatography on HP-20 resin and eluted with 20% aqueous isopropyl alcohol (*iso*-PrOH). The eluate was concentrated to remove the *iso*-PrOH, and the remaining solution was lyophilized to give 0.185 g (18.5%) of **3b**. IR (Nujol) 3550, 3330, 1750, 1670, 1620 cm^{-1}, NMR (DMSO-d_6) δ 3.42 (2H, s), 3.60 (2H, d, J=4 Hz), 4.80 (1H, d, J=4 Hz), 5.08 (1H, d, J=5 Hz), 5.77 (1H, dd, J=5 Hz, 8 Hz), 6.30 (1H, s), 6.52 (1H, t, J=4 Hz), 8.87 (1H, d, J=8 Hz).

Preparation of *p*-Nitrobenzyl 7β-[(2-Formamido-4-thiazolyl)glyoxarylamido]-3-cephem-4-carboxylate (**4a**)

To a solution of DMF (4.0 g, 54.8 mmole) in THF (200 ml) was dropwise added $POCl_3$ (8.4 g, 54.8 mmole) at $-5 \sim 5$°C under stirring, and the mixture was stirred at this temperature for 10 minutes to prepare Vilsmeier reagent. To the above mixture was added (2-formamido-4-thiazolyl)glyoxalic acid (5.35 g, 26.7 mmole) under ice-cooling, and the mixture was stirred at this temperature for 30 minutes to produce an activated acid solution. To the suspension of **1a** (9.0 g, 24.3 mmole) and BSA (20 ml) in AcOEt (100 ml) was added the above activated acid solution at -15°C, and the reaction mixture was stirred at $-15 \sim 0$°C for 30 minutes. To the reaction mixture was added H_2O (50 ml), and the resulting precipitate was collected by filtration, washed with H_2O, and dried over P_2O_5 to give 7.12 g (57.0%) of **4a**. The organic layer of the filtrate was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 1.03 g (8.2%) of **4a**. IR (Nujol) 1775, 1725, 1650 cm^{-1}, NMR (DMSO-d_6) δ 3.66 (2H, s), 5.17 (1H, d, J=5 Hz), 5.42 (2H, s), 5.90 (1H, dd, J=5 Hz, 8 Hz), 6.66 (1H, t, J=5 Hz), 7.67 (2H, d, J=9 Hz), 8.22 (2H, d, J=9 Hz), 8.39 (1H, s), 8.55 (1H, s), 9.87 (1H, d, J=8 Hz).

Preparation of 7β-[(2-Formamido-4-thiazolyl)glyoxarylamido]-3-cephem-4-carboxylic Acid (**4b**)

A mixture of **4a** (3.0 g, 5.82 mmole) and 10% palladium on carbon (1.5 g) in MeOH (70 ml), THF (30 ml), and AcOH (10 ml) was subjected to catalytic reduction at room temperature under atmospheric pressure for 4 hours. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in aqueous $NaHCO_3$ solution. The solution was washed once with AcOEt and then adjusted to pH 2.0 with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O, and dried over P_2O_5 to give 1.57 g (71.0%) of **4b**. IR (Nujol) 1780, 1670 cm^{-1}, NMR (DMSO-d_6) δ 3.63 (2H, m), 5.17 (1H, d, J=5 Hz), 5.87 (1H, dd, J=5 Hz, 8 Hz), 6.53 (1H, t, J=4 Hz), 8.42 (1H, s), 9.83 (1H, d, J=8 Hz).

Preparation of 7β-[(2-Amino-4-thiazolyl)glyoxarylamido]-3-cephem-4-carboxylic Acid (**5**)

To a mixture of **4b** (2.44 g, 6.41 mmole) in MeOH (20 ml) was added conc. HCl (5 ml) at room temperature, and the mixture was stirred at this temperature for 5 hours. The reaction mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in aqueous $NaHCO_3$ solution, and the resulting solution was washed with AcOEt. The aqueous solution was adjusted to pH 3.5 with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O and dried over P_2O_5 to give 0.49 g (21.7%) of **5**. The filtrate and the washings were combined and subjected to column chromatography on HP-20 resin. The eluate with 15% aqueous *iso*-PrOH was concentrated *in vacuo*. The remaining solution was lyophilized to give 1.56 g (69.0%) of **5**. IR (Nujol) 1780, 1668 cm^{-1}, NMR (D_2O) δ 3.57 (2H, m), 5.17 (1H, d, J=5 Hz), 5.78 (1H, d, J=5 Hz), 6.33 (1H, m), 8.26 (1H, s).

Preparation of 7β-[2-(2-Amino-4-thiazolyl)-2-hydroxyacetamido]-3-cephem-4-carboxylic Acid (**6**)

To a stirred solution of **5** (0.52 g, 1.34 mmole) in MeOH (15 ml) was added $NaBH_4$ (0.1 g) under ice-cooling. After stirring at the same temperature for 3 hours, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in H_2O (3 ml) and adjusted to pH 3.0 with 6 N HCl. The resulting precipitate was collected by filtration, washed with H_2O, and dried over P_2O_5 to give 0.29 g (61.1%) of **6**. IR (Nujol) 1775, 1630 cm^{-1}, NMR (D_2O+DMSO-d_6) δ 5.03 (1H, s), 5.07 (1H, d, J=5 Hz), 5.72 (1H, d, J=5Hz), 6.49 (1H, t, J=4 Hz), 6.67 (1H, s).

Preparation of 7β-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylic Acid (**7**)

A suspension of **6** (1.78 g, 4.58 mmole), methoxyamine hydrochloride (1.37 g, 16.4 mmole) and sodium acetate (0.38 g, 4.58 mmole) in H_2O (100 ml) was adjusted to pH 7.0 with aqueous $NaHCO_3$ solution, and the solution was stirred at 48°C for one hour, keeping the pH between 7.0~7.3 with aqueous $NaHCO_3$ solution. The reaction mixture was washed once with AcOEt and adjusted to pH 3.5 with 10% HCl under ice-cooling. The resulting precipitate was collected by filtration, washed with H_2O, and dried over P_2O_5 to give 0.12 g (6.8%) of **7**. The filtrate was subjected to column chromatography on HP-20 resin and eluted with 40% aqueous acetone. The eluate was concentrated *in vacuo* to remove the acetone and the remaining solution was lyophilized to give 0.95 g (54.0%) of **7**. IR (Nujol) 3460, 3290, 3150, 1780, 1655, 1623 cm^{-1}, NMR (DMSO-d_6) δ 3.63 (2H, broad s), 3.84 (3H, s), 5.12 (1H, d, J=5 Hz), 5.84 (1H, dd, J=5 Hz, 8 Hz), 6.52 (1H, t, J=5 Hz), 6.70 (1H, s), 7.26 (2H, broad s), 9.65 (1H, d, J=8 Hz).

Preparation of 7β-[2-(2-Amino-4-thiazolyl)-2-aminoacetamido]-3-cephem-4-carboxylic Acid (**8**)

Zinc powder (4.5 g) was added to a stirred solution of **7** (3.0 g, 7.82 mmole) in 90% formic acid (150 ml) under ice-cooling over 5 minutes, and stirred at the same temperature for 15 minutes. The reaction mixture was filtered and the residue washed with 90% formic acid. The filtrate and the washings were combined and concentrated *in vacuo* to a volume of about 20 ml. The concentrate was dissolved in H_2O (150 ml), and into the solution was bubbled hydrogen sulfide gas for 20 minutes under ice-cooling to form zinc sulfide, which was filtered off. The filtrate was treated with activated charcoal and then lyophilized to give 2.9 g (86.1%) of **8** as its formate. IR (Nujol) 3330, 3200, 3100, 1770, 1690 cm^{-1}, NMR (D_2O) δ 3.42~3.61 (2H, m), 5.06~5.12 (1H, m), 5.19 (1H, s), 5.60 (1/2H, d, J=5 Hz), 5.79 (1/2H, d, J=5 Hz), 6.39~6.50 (1H, m), 8.32 (1H, s).

Antibiotic Susceptibility

The *in vitro* antibacterial activity is given as the minimum inhibitory concentration (MIC) in μg/ml. MIC's were determined by the known agar dilution method using heart infusion agar (Difco) after incubation at 37°C for 20 hours, the inoculum being about 10^8 C.F.U./ml. *E. coli* 28 is a cephalosporin-resistant strain.

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