SYNTHETIC CEPHALOSPORINS

VIII. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF CP6232, A NEW ANTI-PSEUDOMONAL CEPHALOSPORIN

Sir:

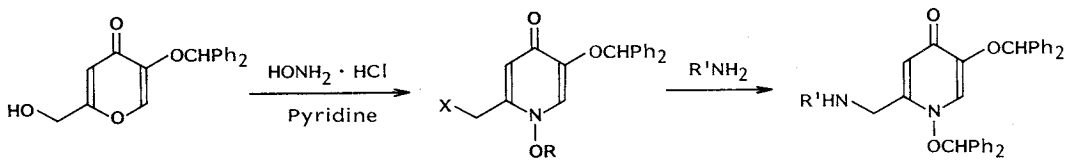
The opportunistic infections caused by various Gram-negative bacteria including *Pseudomonas aeruginosa*, have progressively increased and become a serious problem in chemotherapy. In recent years, it was reported that cephalosporins having a catechol and related aromatics at the C-3 position exhibited potent activity against *Pseudomonas aeruginosa*[1,2]. We also reported that cephalosporins having 3-hydroxy-4-pyridone groups at the C-3 or C-7 position of cephalosporins showed excellent antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*[3~5].

In particular, 7-[(*Z*)-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl)ethoxyiminoacetamido]-3(*Z*)-[2-(1,5-dihydroxy-4-pyridon-2-yl)ethenyl]-3-cephem-4-carboxylic acid (CP6162)[5] showed excellent antibacterial activity against *Pseudomonas aeruginosa*. In continuing our efforts to improve the antibacterial activity against Gram-negative bacteria, we examined other possibilities of 2-(1,5-dihydroxy-4-pyridon-2-yl)ethenyl group as substituent in the C-3 side chain of cephalosporins by modifying the linkage with the C-3 position. As a result, we found that 7-[(*Z*)-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl)ethoxyiminoacetamido]-3-[*N*-(1,5-dihydroxy-4-pyridon-2-yl)methyl-*N*-methyl]aminomethyl-3-cephem-4-carboxylic acid (CP6232), in which the 1,5-dihydroxy-4-pyridone entity was connected with the C-3 of the cephalosporin through CH_2–$N(CH_3)$–CH_2 bonds, showed an excellent antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*. This communication describes the synthesis and antibacterial activity of CP6232 and the related compounds.

N-(1,5-Diphenylmethoxy-4-pyridon-2-yl)methyl-*N*-alkylamines (**5a**~**5e**), required as new side chains of the C-3 position of the cephalosporins, were synthesized as shown in Scheme 1. Compound **3** was prepared from 2-hydroxymethyl-5-diphenylmethoxy-4-pyrone (**1**) in the manner described previously[5] and treated with thionyl chloride to give 2-chloromethyl derivative (**4**), which was, without purification, subjected to react with excess of alkylamines to give the corresponding amines (**5a**~**5e**) in good yields. On the other hand, *p*-methoxybenzyl 7-[(*Z*)-(2-aminothiazol-4-yl)-2-(1-diphenylmethoxycarbonyl-1-methyl)ethoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (**6**)[2,3] was converted by treatment with NaI in acetone into 3-iodomethyl derivative (**7**), which reacted with the amines (**5a**~**5e**) to give the corresponding protected cephalosporins (**8a**~**8e**). Removal of the protective groups of **8a**~**8e** with CF_3COOH afford the new cephalosporins (**9a**~**9e**), respectively.

The minimum inhibitory concentrations (MICs) of the new cephalosporins were determined by the standard, 2-fold, agar dilution method. In Table 1, the MIC values of these compounds against several Gram-positive and Gram-negative bacteria are summarized and compared with those of ceftazidime (CAZ), which is one of the most potent agents against *Pseudomonas aeruginosa* used in the current clinical chemotherapy[6]. The new cephalosporins showed an excellent antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*. Among them, the compound **9a** (CP6232) exhibited the most potent activity against Gram-negative bacteria and the anti-pseudomonal activity was 5~10-fold higher than those of CAZ. As observed in the case of the compounds (**9c** and **9d**), the increasing lipophilicity of the *N*-substituent

Scheme 1.



1

2 R=H X=OH
3 R=$CHPh_2$ X=OH
4 R=$CHPh_2$ X=Cl

5a R'=$-CH_3$
5b R'=$-CH_2CH_2OH$
5c R'=$-CH_2(CH_2)_3CH_3$
5d R'=$-CH(CH_3)_2$
5e R'=$-CH_2CH{=}CH_2$

Scheme 2.

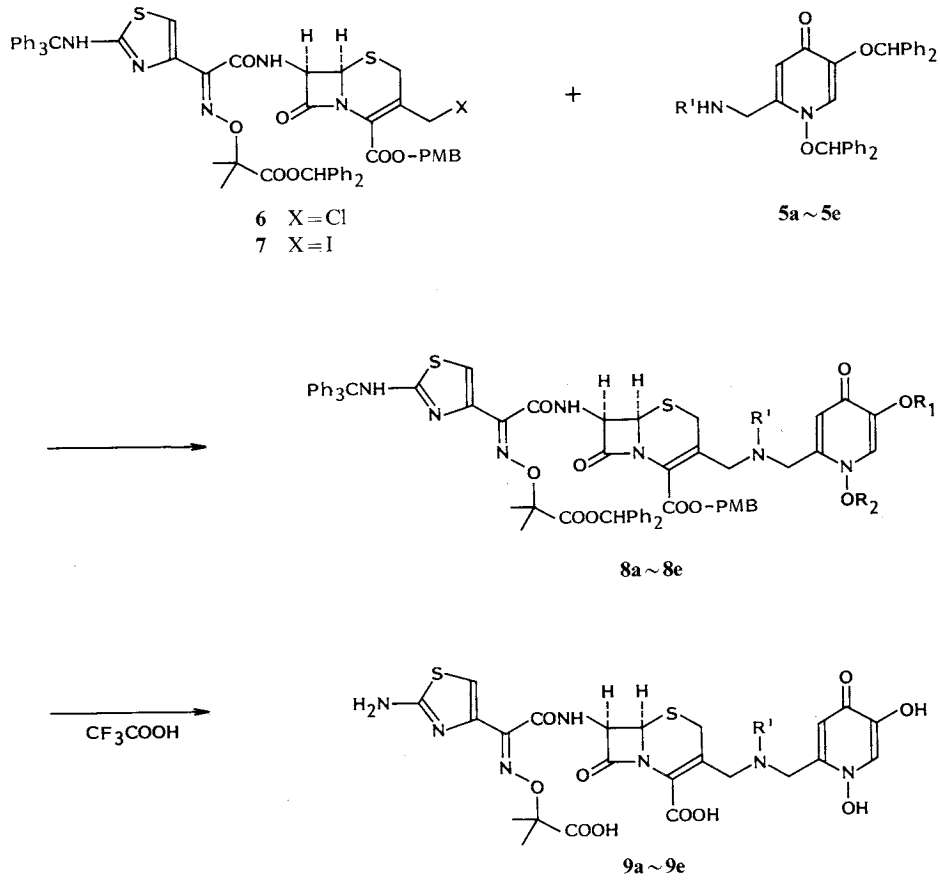
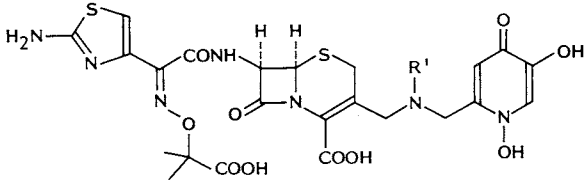


Table 1. ^{1}H NMR data of 2 Na salts of 3-[*N*-alkyl-*N*-(1,5-dihydroxy-4-pyridon-2-yl)methylamino]methylcephalosporins (**9a**~**9e**).

Compound	^{1}H NMR (400 MHz, δ in D_2O, ppm, DOH at 4.82)
9a (CP6232)	1.56 (6H, s, $(CH_3)_2$), 2.78 (3H, s, NCH_3), 3.4~4.25 (6H, m, 2-H, 3'-H, NH_2), 5.30 (1H, d, J=5 Hz, 6-H), 5.90 (1H, d, J=5 Hz, 7-H), 6.72 (1H, s, pyridone 3-H), 7.05 (1H, s, thiazole 5-H), 7.70 (1H, s, pyridone 6-H)
9b	1.50 (6H, br s, $(CH_3)_2$), 2.70 (2H, m, NCH_2), 3.3~3.8 (8H, m, 2-H, 3'-H, CH_2, NCH_2), 5.15 (1H, d, J=5 Hz, 6-H), 5.80 (1H, d, J=5 Hz, 7-H), 6.72 (1H, s, pyridone 3-H), 7.00 (1H, s, thiazole 5-H), 7.62 (1H, s, pyridone 6-H)
9c	0.85 (3H, m, CH_3), 1.2~1.7 (8H, m, $(CH_2)_4$), 1.50 (6H, br s, $(CH_3)_2$), 2.80 (2H, m, NCH_2), 3.4~4.1 (6H, m, 2-H, 3'-H, NCH_2), 5.20 (1H, d, J=5 Hz, 6-H), 5.82 (1H, d, J=5 Hz, 7-H), 6.70 (1H, s, pyridone 3-H), 7.00 (1H, s, thiazole 5-H), 7.55 (1H, s, pyridone 6-H)
9d	1.43 (6H, m, $(CH_3)_2$), 1.52 (3H, s, CH_3), 1.54 (3H, s, CH_3), 3.3~4.5 (7H, m, 2-H, 3'-H, NCH_2, CH), 5.15 (1H, d, J=5 Hz, 6-H), 5.85 (1H, d, J=5 Hz, 7-H), 6.65 (1H, s, pyridone 3-H), 7.00 (1H, s, thiazole 5-H), 7.65 (1H, s, pyridone 6-H)
9e	1.52 (3H, s, CH_3), 1.54 (3H, s, CH_3), 3.5 (2H, m, NCH_2), 3.7~4.3 (6H, m, 2-H, 3'-H, NCH_2), 5.25 (1H, d, J=5 Hz, 6-H), 5.55 (2H, m, $=CH_2$), 5.90 (1H, d, J=5 Hz, 6-H), 6.00 (1H, m, CH=), 6.75 (1H, s, pyridone 3-H), 7.05 (1H, s, thiazole 5-H), 7.65 (1H, s, pyridone 6-H)

Table 2. *In vitro* activity of 3-[*N*-alkyl-*N*-(1,5-dihydroxy-4-pyridon-2-yl)methylamino]methylcephalosporins (MIC: μg/ml).



Test organisms	R′ =	$-CH_3$					Ceftazidime
		Compound No.					
		CP6232 (**9a**)	**9b**	**9c**	**9d**	**9e**	
Staphylococcus aureus 606[a]		>100	>100	>100	>100	>100	6.25
S. aureus Smith (1)		>100	>100	>100	>100	>100	6.25
Escherichia coli W3630 RGN823[a]		0.78	0.78	6.25	3.13	0.78	0.39
E. coli No. 29		0.05	0.20	0.78	0.78	0.39	0.20
Klebsiella pneumoniae GN69[a]		0.05	0.05	0.20	0.39	0.10	0.20
K. pneumoniae PC1602		<0.025	<0.025	0.20	0.20	0.05	0.20
Salmonella typhi O-901-W		<0.025	<0.025	0.05	0.05	0.05	0.05
S. enteritidis No. 11		<0.025	<0.025	0.05	0.05	<0.025	0.05
Escherichia coli 255[b]		0.10	0.05	0.10	0.39	0.20	25
Proteus vulgaris GN76[b]		<0.025	0.05	0.39	0.20	0.05	0.05
P. vulgaris GN76/C-1/S-1		<0.025	0.05	0.20	0.20	0.05	0.05
Citrobacter freundii GN346[b]		12.5	25	25	25	25	100
Enterobacter cloacae GN7471[b]		0.78	6.25	12.5	12.5	6.25	6.25
E. cloacae G-0008		1.56	3.13	25	6.25	3.13	0.39
Serratia marcescens GN10857		1.56	3.13	12.5	6.25	6.25	1.56
S. marcescens No. 1		0.20	0.39	1.56	0.78	0.20	0.20
Pseudomonas aeruginosa GN10362[b]		0.39	0.20	0.78	0.78	0.20	1.56
P. aeruginosa E-2		0.05	0.05	0.39	0.10	0.05	1.56
P. aeruginosa IAM-1007		0.05	0.20	1.56	0.39	0.10	6.25
P. aeruginosa ML Rms139[a]		<0.025	0.05	0.39	0.10	0.10	1.56

[a] Penicillinase-producing strain.
[b] Cephalosporinase-producing strain.

of the C-3′ position of the cephalosporin tends to reduce activity especially against β-lactamase-producing strains, *Enterobacter cloacae* GN7471 and *Enterobacter cloacae* G-0008.

In conclusion, we found that 7-[(*Z*)-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl)ethoxyiminoacetamido]-3-[*N*-(1,5-dihydroxy-4-pyridon-2-yl)-methyl-*N*-methyl]aminomethyl-3-cephem-4-carboxylic acid (**9a**, CP6232), in which the 1,5-dihydroxy-4-pyridone entity was introduced *via* a unique linkage to the C-3 position of the cephalosporin, showed extremely potent antibacterial activity against Gram-negative bacteria. Although CP6232 showed weak activity against Gram-positive bacteria, present results also demonstrated that 1,5-dihydroxy-4-pyridone entity is a potent substituent in the 3-position of cephalosporin.

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