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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF CEPHALOSPORINS HAVING HYDROXAMIC ACID AT C-7 POSITION

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Abstract: The synthesis and *in vitro* activity of cephalosporins with hydroxamic acid at the 7-position are described. Anti-pseudomonal activity of the compound **11a** was shown to be comparable to that of ceftazidime. Especially, the compound **11a** exhibited good activity against Gram-positive bacteria including *Streptococcus pneumoniae* and *Staphylococcus aureus*. Copyright © 1996 Elsevier Science Ltd

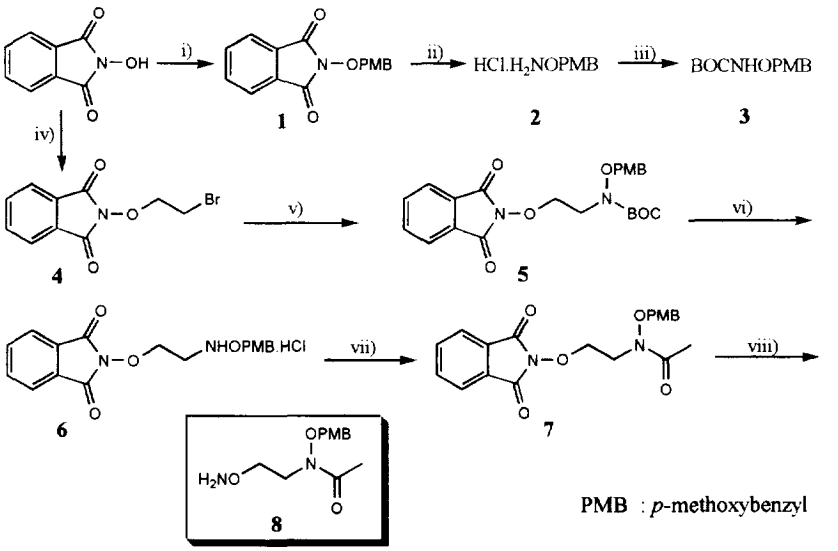
Cephalosporin antibiotics are still among the most effective drugs for the treatment of various infectious diseases. The opportunistic infectious diseases caused by Gram-negative bacteria such as *Pseudomonas aeruginosa* have become a serious problem in clinical use[1]. In the course of the investigation of anti-pseudomonal agents, we have recently developed cephalosporins bearing benzotriazolium methyl group at the 3-position[2].

On the other hand, it has been reported that the enhancement of anti-pseudomonal activity depends on the penetration of the outer membrane[3]. The catechol-substituted cephalosporins have potent antipseudomonal activity by utilizing a unique transport pathway[4]. These results have been based on the background that most microbes utilizing hydroxamic acids, catechols, and α-hydroxy acids as metal-binding components of siderophore[5]. However, most of the catecholic cephalosporins and related compounds were exhibited to be ineffective for Gram-positive bacteria such as *S. aureus* especially *in vitro* potency[6].

Thus, our studies have been concerned to synthesize non-catecholic cephalosporins through modification of the 7-position, which are expected to give the enhancement of broad spectrum and anti-pseudomonal activity. In this paper, we wish to describe the synthesis and antimicrobial activity of cephalosporins having hydroxamic acid at the 7-position.

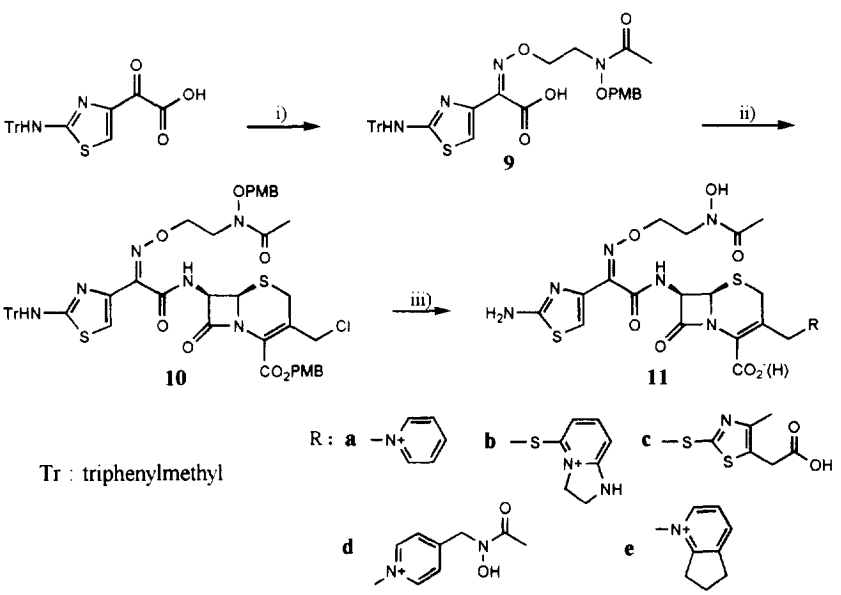
The protected hydroxylamine **8** was synthesized by the procedure as shown in Scheme I. First, the conversion of *N*-hydroxyphthalimide to the protected hydroxamate **3** was performed by protection of the alcohol followed by sequential deprotection of the phthaloyl group and protection of the resulting amine. Second, *N*-hydroxy phthalimide was treated with 2-bromoethanol in Mitsunobu condition to afford **4**, followed by introduction of **3** to give **5**. After deprotection of BOC group, the resulting amine **6** was acetylated and

Scheme I



Reagents: i) *p*-methoxybenzyl chloride / DMSO / K_2CO_3, rt, 3h (99 %), ii) $H_2NNH_2.H_2O$ / CH_3OH, rt, 10h and then 6N HCl / CH_3OH, rt, 1h (79 %), iii) Di-*tert*-butyl dicarbonate / THF / H_2O / Et_3N, rt, 1.5h (95 %), iv) 2-bromoethanol / Ph_3P / THF / diethyl azodicarboxylate, 0^0C - rt, 4h (70 %), v) **3** / DMF / NaH, 0 - 10^0C, 15h (52 %), vi) 4M HCl / ethyl acetate, 0^0C - rt, 10h (85 %), vii) Ac_2O / CH_2Cl_2 / Et_3N, 0^0C - rt, 1.5h (98 %), viii) $H_2NNH_2.H_2O$ / CH_3OH, rt, 14h (100 %).

Scheme II



Reagents: i) **8** / C_2H_5OH / $CHCl_3$, rt, 10h (78 %), ii) ACLE / CH_2Cl_2 / dimethylamine / 2,6-lutidine, -30^0C, 0.5h and then $POCl_3$ / CH_2Cl_2, -30 - -15^0C, 4h (55 %), iii) heterocycles / acetone / KI, rt, 3 - 5h and then TFA / anisole, 0^0C - rt, 5h.

subsequently deprotected the phthaloyl group with hydrazine monohydrate to furnish **8**.

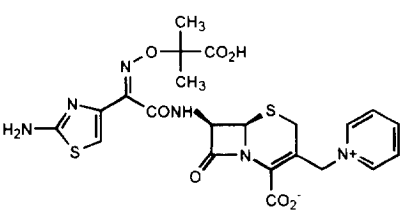
The cephalosporins synthesized were outlined as shown in Scheme II. The protected hydroxylamine **8** was introduced with glyoxylic acid[7] to give the iminoacetic acid **9**. The compound **9** was coupled with *p*-methoxy benzyl 7β-amino-3-chloromethyl-3-cephem-4-carboxylate (ACLE)[8] in the presence of $POCl_3$ to afford chloromethyl cephem **10**. The compound **10** was reacted with various heterocycles[9] and deprotection of the resulting products was performed by TFA in the presence of anisole to afford TFA salts. These TFA salts were neutralized by $NaHCO_3$ solution and purified by column chromatography on Diaion HP-20 to give **11a-e** (**11a**[10], 18 %; **11b**, 11 %; **11c**, 10 %; **11d**, 12 %; **11e**, 15 %, respectively).

Table I. Antibacterial Activity of the Cephalosporin Analogues **11** (MICs : μg/ml, Inoculum size : 10^7 cfu/ml).

Organisms	**11a**	**11b**	**11c**	**11d**	**11e**	CAZ
S. pyogenes A77	0.007	0.025	0.013	0.007	0.004	0.098
S. pneumoniae type I	0.049	0.025	0.049	0.049	0.025	0.195
S. aureus Smith	3.125	1.563	12.5	12.5	0.781	6.25
S. aureus C2379 (MRSA)	12.5	12.5	100	50	6.25	50
E. coli DC 0	0.781	1.563	0.781	12.5	0.391	0.195
E. coli DC 2	0.195	1.563	0.098	0.391	0.195	0.098
K. pneumoniae NCTC 9632	0.098	0.025	0.098	0.781	0.195	0.049
S. marcescens IFO 12648	0.391	3.125	1.563	12.5	0.781	0.098
P. aeruginosa 9027	6.25	12.5	12.5	50	6.25	3.125
P. aeruginosa 1771	0.781	3.125	3.125	25	1.563	0.781
P. aeruginosa 1771M	0.391	3.125	0.391	6.25	0.781	0.391
P. aeruginosa C-1198	25	50	50	>100	50	>100
E. cloacae P99	25	50	50	50	25	>100
P. vulgaris GN76	0.781	3.125	0.049	6.25	1.563	0.049

Abbreviation: MRSA, Methicillin resistant *Staphylococcus aureus*

Ceftazidime (CAZ)



In vitro activity of cephalosporins **11a-e**[11] along with comparative data for the ceftazidime (CAZ) are listed in Table I. Antibacterial activity of **11a-e** was generally better than that of CAZ against Gram-positive

bacteria including *S. pneumoniae* and *S. aureus*. Although the compound **11e** showed the most potent activity against Gram-positive bacteria compared to **11a-d** and CAZ, it showed less active than that of CAZ in anti-pseudomonal activity. The compound **11a** exhibited better activity than CAZ against Gram-positive bacteria and its anti-pseudomonal activity was shown to be as good as that of CAZ. However, most of the analogues **11** except for **11a** were less active than CAZ against *P. aeruginosa*.

In conclusion, we have found that the compound **11a** with hydroxamic acid at C-7 showed anti-pseudomonal activity and contributed to the enhancement of the activity against Gram-positive bacteria. The further functional optimization of C-3 substituents including the introduction of hydroxamic acid at the C-3 position are under research.

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7. Bormann, D.; Knabe, B.; Schrinner, E.; Worm, M. *Ger. Offen DE 2,710,902*, **1978**.
8. ACLE is available from Otsuka Chemical Co. Ltd., Japan.
9. The heterocycles of **11a**, **11c** and **11e** were purchased from Aldrich Chemical Company. The heterocycle of **11b** was prepared from 2,6-dichloropyridine by 3 steps in 65% yield and that of **11d** was synthesized in 60% yield by condensing 4-pyridylcarbinol with **3** possessing acetyl group instead of BOC in Mitsunobu condition.
10. **11a** : ^{1}H-NMR (200 MHz, DMSO-d_6 + D_2O) δ : 2.05(s, 3H), 3.45(d, 1H, *J*=18.8Hz) 3.72(d, 1H, *J*=18.8Hz), 3.95(t, 2H, *J*=6.1Hz), 4.48(t, 2H, *J*=5.5Hz), 5.31(m, 2H), 5.80(d, 1H, *J*=4.8Hz), 7.18(s, 1H), 8.15(t, 2H, *J*=7.7Hz), 8.65(t, 1H, *J*=9.2Hz), 9.01(d, 2H, *J*=5.8Hz).
11. All the new compounds gave satisfactory spectroscopic data consistent with the proposed structures.

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