Synthesis and Antibacterial Activities of Novel C(7)-Catechol-substituted Cephalosporins (II)

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In the previous paper,[1] we described the synthesis and antibacterial activities of cephalosporins which possess both catechol moiety at the 7-position and pyrimidiniumthiomethyl, pyrimidinothiomethyl, or pyrimidiniummethyl group at the 3-position of cephem nucleus. Those compounds exhibited excellent activities against Gram-negative bacteria, but showed moderate activities against Gram-positive bacteria. They also showed poor activities against *E. faecalis*. When vinyl spacer was introduced in the C-3 position of cephem nucleus as in the case of E-1077,[2] the bioactivity was good against Gram-positive strains and also showed stability against β-lactamases. As a part of our research program on new injectable cephalosporins possessing improved activity against Gram-positive bacteria while maintaining potent antibacterial activities against Gram-negative strains including *P. aeruginosa*, we have synthesized a new series of cephalosporins with a 3-substituted pyrimidiniumyl-, pyrimidinylthio-, or pyrimidiniumylthio-1-(*E*)-propenyl group and 7-substituted catechol moiety (Fig. 1). We report herein the synthesis of these compounds and their antibacterial activities.

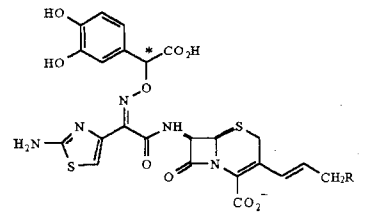
Chemistry

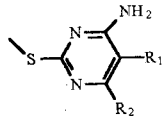
The compounds **1**~**9** from oxime **10** and bromide **11** were prepared as follows (Scheme 1). Coupling of oxime **10** and benzyl bromide **11** in the presence of potassium carbonate and potassium iodide in *N*,*N*-dimethylformamide (DMF) followed by treatment with catalytic amount of Pd(0) afforded the carboxylic acid **12**. The acid **12** was added to the methylene chloride solution containing *p*-methoxybenzyl-7-amino-3-chloromethyl-3-cephem-4-carboxylate (7-ACLE) and pyridine at $-20°C$, then phosphorous oxychloride ($POCl_3$) was added to the solution to afford the allyl chloride **13**. After preparation of Wittig reagent by treatment of triphenylphosphine and sodium iodide to the chloride **13**, ylid was made by using 1 N sodium hydroxide. Reaction of the ylid with the chloroacetaldehyde afforded (*Z*)-propenyl chloride **14**. Then the (*Z*)-propenyl-chloride in **14** was first replaced with iodide to produce (*E*)-propenyl iodide[3] and the (*E*)-iodide was displaced with nucleophiles (pyrimidine thiones, pyrimidine thiols, or pyrimidines) in DMF. Finally, deprotection of the corresponding coupling products in the presence of trifluoroacetic acid (TFA) and anisole afforded the cephalosporins **1***S*,*R*~**9***S*,*R*† (Most compounds have two diastereomers which contain *R* and *S* configuration on benzylic position of the catechol moiety. Thus, from now on, each diastereomers will be described as *R* and *S*). Spectra for **1***S*: IR (nujol) 1775 cm^{-1} (carbonyl on β-lactam ring); ^1H NMR (δ, D_2O) 3.33 (ABq, 2H, J=15.5 Hz), 4.71 (ABq, 2H, J=14.0 Hz), 5.02 (d, 1H, J=2.7 Hz), 5.37 (s, 1H), 5.63 (d, 1H, J=2.7 Hz), 5.77 (s, 1H), 5.72~5.95 (m, 1H), 6.55 (d, 1H, J=7.6 Hz), 6.77~7.02 (m, 4H), 8.16 (s, 1H).

Antibacterial Activities and Discussion

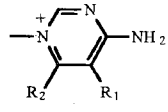
Agar dilution method was used to determine the minimal inhibitory concentration (MIC) of compounds **1**~**9** against selected organisms. The MIC values for ceftazidime against the same strains are shown for comparison. In general, most of the compounds in Table 1 showed better antibacterial activities than that of the reference (CAZ: ceftazidime). This series of new catechol substituted cephalosporins which possess vinyl spacer in C-3 substituents exhibited very good antibacterial activities against Gram-positive bacteria such as *S. aureus* and excellent activities against Gram-negative organisms

Fig. 1. Novel catechol-substituted cephalosporins **1**~**9** with various C-3 substituents.

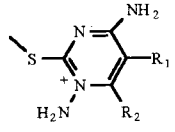




No.	R_1	R_2
4*R*,*S*	H	NH_2
5*R*,*S*	H	H
6*R*,*S*	$-CH_2CH_2CH_2-$	
7*S*	Me	NH_2



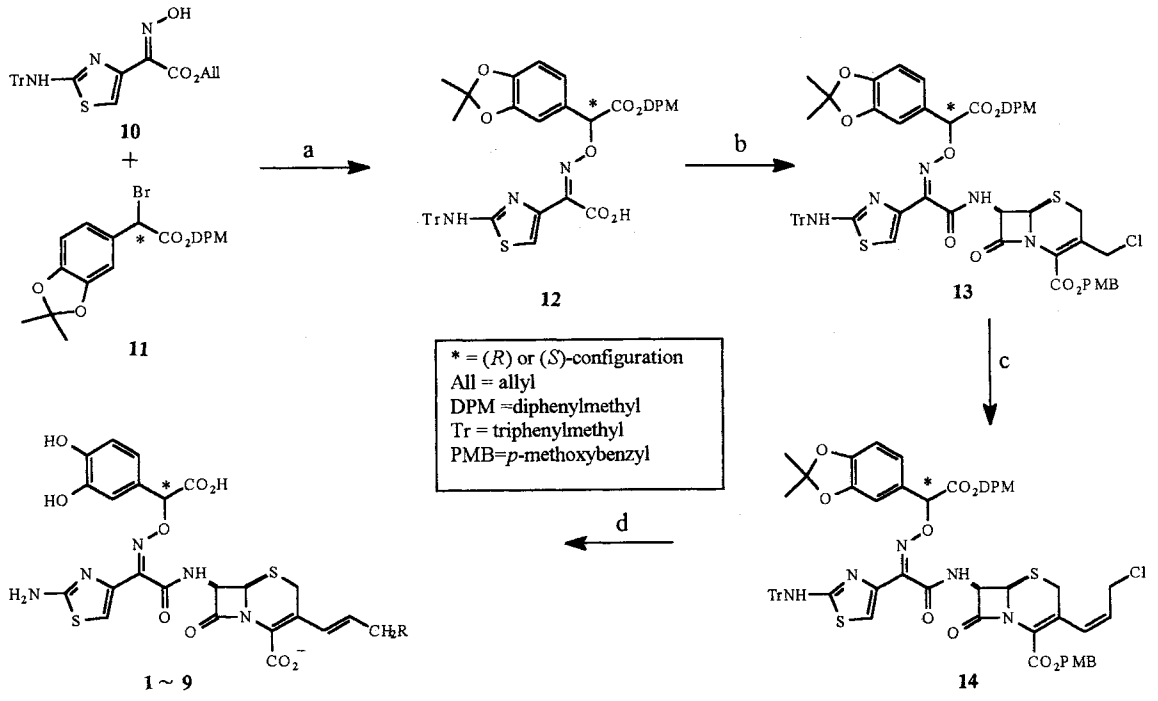
No.	R_1	R_2
1*R*,*S*	H	H
2*R*,*S*	H	NH_2
3*S*	Me	NH_2



No.	R_1	R_2
8*R*,*S*	H	H
9*R*,*S*	$-CH_2CH_2CH_2-$	

† *R* and *S* configurations were proved by the method shown in the ref. 4.

Scheme 1.



a) K_2CO_3, KI, DMF; $Pd(PPh_3)_4$, potassium 2-ethylhexanoate; b) $POCl_3$, 7-ACLE; c) (1) PPh_3, NaI; (2) 1 N NaOH, sat'd NaCl, $ClCH_2CHO$; d) NaI, acetone; nucleophile (R); TFA, anisole.

Table 1. Antibacterial activities of cephalosporins **1**~**9** (MIC, μg/ml).

Compound	*S.a.*	*E.f.*	*E.c.*1	*E.c.*2	*P.a.*	*A.c.*	*E.c.*	*K.a.*	*S.m.*
1*S*	2	16	0.016	0.063	1	2	128	0.25	1
2*S*	1	16	0.016	0.063	0.25	1	128	0.25	1
3*S*	1	4	<0.008	0.031	0.25	0.25	8	0.13	0.25
4*S*	0.5	4	0.016	0.063	0.5	0.5	8	0.5	0.5
5*S*	0.5	4	<0.008	0.031	0.5	1	32	0.13	0.25
6*S*	1	4	0.008	0.063	0.5	0.5	16	0.13	0.5
7*S*	1	16	<0.008	0.031	0.25	0.5	4	0.13	0.25
8*S*	1	8	0.016	0.063	0.5	0.5	16	0.25	0.5
9*S*	1	4	0.016	0.063	0.25	2	8	0.25	0.25
Ceftazidime	16	>128	0.13	0.25	1	2	64	0.25	0.25

S.a., *Staphylococcus aureus* ATCC-6538p; *E.f.*, *Enterococcus faecalis* 29212; *E.c.*1, *Escherichia coli* ATCC-10536; *E.c.*2, *Escherichia coli* TEM1 1193E; *P.a.*, *Pseudomonas aeruginosa* 1912E; *A.c.*, *Acinetobacter calcoaceticus* 15473; *E.c.*, *Enterobacter cloacae* P99; *K.a.*, *Klebsiella aerogenes* SHV-1 1976E; *S.m.*, *Serratia marcescens* 1826E.

Table 2. Pharmacokinetic data of the compounds **1***S*~**8***S* in rats.

Parameters	**1***S*	**2***S*	**3***S*	**4***S*	**5***S*	**6***S*	**7***S*	**8***S*	CAZ
$T_{1/2}$ (minute)	45	53	50	34	55	33	53	59	20
AUC (mg·minute/ml)	3824	4948	3927	1964	3215	2197	3187	2366	1863

including *Pseudomonas aeruginosa*. The cephalosporins **1**~**9** showed much better antibacterial activities against most of the Gram-positive strains than the other catechol-containing cephalosporins.[5~9] Interestingly, the compounds **1**~**9** exhibited good activity against *E. faecalis* while the compounds which have same structure except no C-3 vinyl spacer[1] showed poor activity. It is worthwhile to note that the compounds having (*S*)-configuration on the catechol side chain were significantly more active than the compounds which contain the corresponding (*R*)-side chain (The MIC's of (*R*)-isomers are not shown in this paper but in patents).[1] Among these series of compounds, cephalosporins with pyrimidiniumyl moiety showed the most balanced antibacterial activity profiles.

As expected by the *ton-B* dependent iron transport mechanism,[10,11] cephalosporins **1**~**9** had a good potency against *P. aeruginosa*, especially the (*S*)-configurated diastereomers showed excellent anti-pseudomonal activity. The compounds **1**~**9** were also very stable to the extended spectrum of TEM1 and SHV-1 β-lactamases. Thus, they possessed much better activity against resistant *E. coli* and *K. aerogenes* expressing above β-lactamases than that of the ceftazidime. Pharmacokinetic studies on the new cephalosporins **1***S*~**8***S* were shown in Table 2. In rats, they showed significantly higher AUC values and longer half life compared to ceftazidime after a dose of 20 mg/kg intravenously.

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