Studies on New Catechol Containing Cephalosporins

II. Synthesis and Structure-activity Relationships of Cephalosporins Having a Catechol Moiety at the C-7 Position

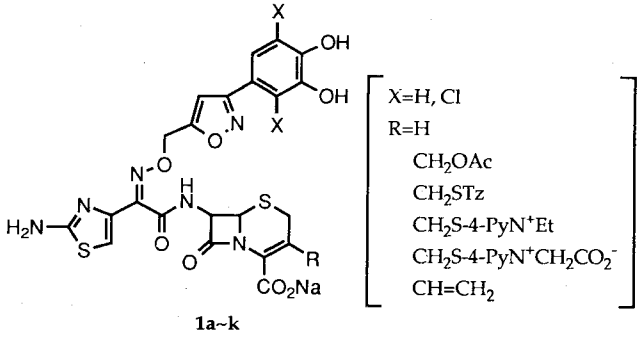
KYUNG IL CHOI, JOO HWAN CHA, AE NIM PAE, YONG SEO CHO, HAN-YOUNG KANG,† HUN YEONG KOH and MOON HO CHANG*

Division of Applied Science, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea

(Received for publication April 17, 1995)

In the preceding paper, we discussed the synthesis and structure-activity relationships of cephalosporins having a catecholylvinyl group with an isoxazole spacer at the C-3 position. At this stage, the possibility of utilizing the isoxazolylcatechol unit as an element of the C-7 aminothiazole substituent was investigated on the basis of iron-transport channel mechanism.[1] Although it has been known[2~4] that the catechol unit could be employed as a component of the C-7 substituent, no substituent containing isoxazolylcatechol has been reported. Thus the isoxazolylcatechol component was introduced at the alkoxy group of the C-7 2-(2-aminothiazol-4-yl)alkoxyiminoacetyl side chain, and the resulting cephalosporins with various C-3 side chain substituents were evaluated. Herein, we wish to report the synthesis and the structure-activity relationships of cephalosporins having a catechol moiety at the C-7 position.

Fig. 1

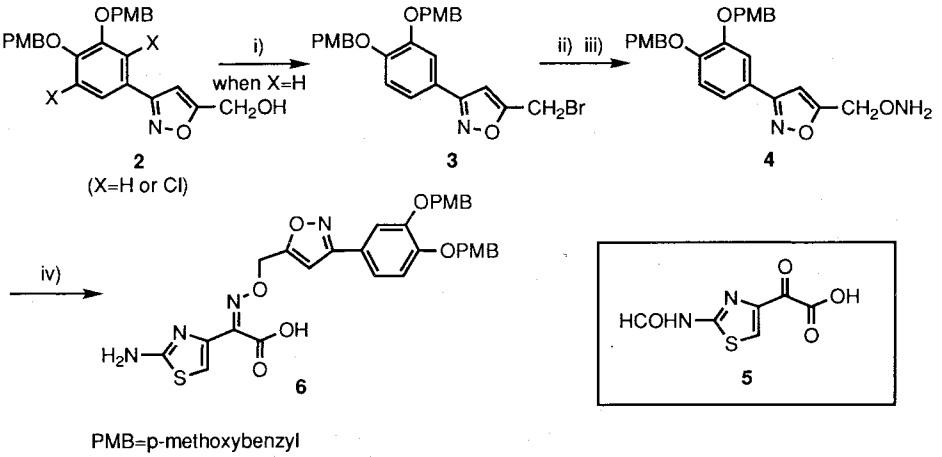


1a~k

Chemistry

Synthesis of cephalosporins bearing unsubstituted catechol and dichlorocatechol at the C-7 position was achieved by almost the same procedure as described in the case of the cephalosporins possessing a catechol group at the C-3 position (Schemes 1 and 2). The preparation of the C-7 substituent was accomplished starting from the alcohol **2**, the synthesis of which was described in the preceding paper. Bromination (CBr_4, PPh_3) followed by conversion to methoxylamine **4** *via* the Gabriel synthesis[5] was easily achieved. (**4**; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.79 (6H, s, $2OCH_3$), 4.81 (2H, s, $NOCH_2$), 5.16 (4H, s, $2CH_2$), 6.53 (1H, s, isoxazole-H), 6.85~7.60 (11H, m, 2Ph and catechol-H)) Condensation with 2-formylaminothiazol-4-ylglyoxylic acid (**5**) provided the desired compound **6** which is to be used as the C-7 substituent (Scheme 1). The synthetic route to the desired cephalosporins having a catechol group at the C-7 position is illustrated in Scheme 2. Thus, the acid **6** was coupled with 7-aminocephem **7** (p-TsCl, Et_3N) to yield the compound **8**. The reaction pathway diverged at this point depending on the C-3 substituent. When R_1 was hydrogen, acetoxymethyl, 1-methyltetrazol-5-ylthiomethyl, or vinyl, the protected cephalosporin **8** was subjected

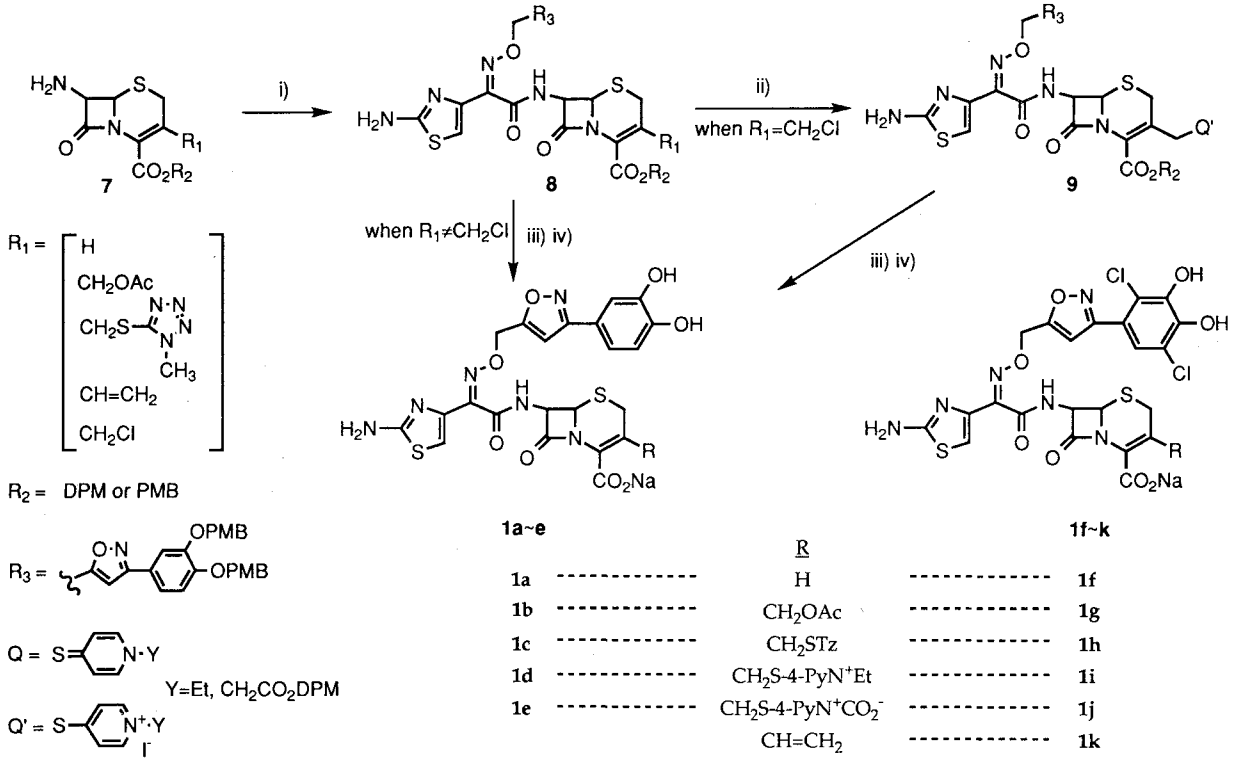
Scheme 1. Synthesis of C-7 aminothiazole substituent.



Conditions i)CBr_4, PPh_3, THF, 75% ii)N-hydroxyphthalimide, Et_3N, THF/DMF iii)hydrazine hydrate, CH_2Cl_2 iv)**5**, EtOH/H_2O, pH~5, 73%

† Present address: Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 360-763, Korea

Scheme 2. Synthesis of C-7 catechol containing cephalosporins.



Conditions i)6, pTsCl, Et_3N, DMF, 50~90% ii)Q, NaI, THF, 70~83% iii)TFA/Anisole iv)$NaHCO_3$, 40~56%(2 steps)

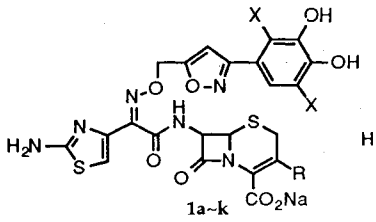
sequentially to deprotection (TFA, anisole), sodium salt formation ($NaHCO_3$), purification by reverse phase column chromatography (LiChrosorb RP-18, 20% aq methanol), and lyophilization to afford the final products **1a**~**1c**, **1f**~**1h** and **1k**. (**1b**; ^{1}H NMR (300 MHz, D_2O) δ 2.21 (3H, s, OAc), 2.87~3.42 (2H, ABq, J=17.3 Hz, 2-H), 4.47~4.89 (2H, ABq, J=15.5 Hz, 3'-H), 5.07 (1H, d, J=3.9 Hz, 6-H), 5.34 (2H, br s, $NOCH_2$), 5.72 (1H, d, J=3.9 Hz, 7-H), 6.79 (1H, s, isoxazole-H), 6.89 (1H, d, J=8.3 Hz, catechol-H), 7.00 (1H, s, thiazole-H), 7.17 (1H, d, J=8.3 Hz, catechol-H), 7.24 (1H, s, catechol-H)) When R_1 was chloromethyl, the compound **8** was further reacted with sulfur nucleophile Q (1-ethylpyrid-4-thione or 1-diphenylmethoxycarbonylmethylpyrid-4-thione) in the presence of sodium iodide to give compound **9**, which was also deprotected and purified as a sodium salt to yield cephalosporins **1d**, **1e**, **1i** and **1j**. (**1j**; ^{1}H NMR (300 MHz, D_2O) δ 3.02~3.51 (2H, ABq, J=17.3 Hz, 2-H), 4.11 (2H, br s, 3'-H), 5.00 (2H, br s, NCH_2), 5.10 (1H, d, J=3.9 Hz, 6-H), 5.37 (2H, br s, $NOCH_2$), 5.71 (1H, d, J=3.9 Hz, 7-H), 6.88 (1H, s, isoxazole-H), 6.96 (1H, s, thiazole-H), 7.02 (1H, s, catechol-H), 7.62 (2H, br s, pyridinium-H), 8.26 (2H, br s, pyridinium-H)). One exception was that having 1-ethylpyridinium-4-ylthiomethyl group as a C-3 substituent (**1d** and **1i**). They were subjected to the antibacterial activity test in the form of an internal salt.

Biological Study

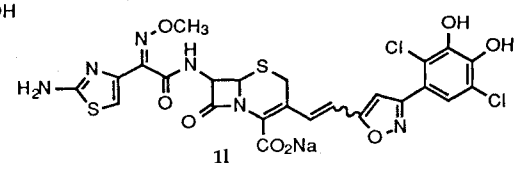
In vitro antibacterial activity of synthesized cephalosporins were determined by the Mueller-Hinton agar dilution method,[6] and thus obtained MIC values against selected strains are shown in Table 1. MICs of cefotaxime and cefpirome are also presented for references.

The overall profile of the antibacterial spectrum was similar to that of cephalosporins possessing a catechol group at the C-3 position described in the preceding paper. All the cephalosporins **1a**~**1k** exhibited excellent activity against Gram-negative bacteria and good activity against Gram-positive bacteria, except *S. faecium*. Against Gram-negative bacteria, compounds bearing the dichlorocatechol unit (**1f**~**1k**) showed more potent activity than those with the unsubstituted catechol unit (**1a**~**1e**). On the other hand, the activity trend against Gram-positive bacteria was reversed. For the group containing the unsubstituted catechol unit (**1a**~**1e**), antibacterial activity against both Gram-positive and Gram-negative strains was increased as the polarity of the C-3 substituent increased. The activities of the other group (**1f**~**1k**) were, however, almost independent on the polarity change of C-3 substituent. The effect of isoxazolylcatechols could be deduced by comparing activity of **1b** and **1g** with cefotaxime. Neither isoxazolylcatechol nor isoxazolyldichlorocatechol altered activity against Gram-positive bacteria. They, however, significantly affected activity against *P. aeruginosa*. Both

Table 1. *In vitro* antibacterial activity of new catechol type cephalosporins (MIC, μg/ml).



1a~k



1l

Compound	X	R	*S. p.*	*S. f.*	*S. a.*	*Es. c.*	*P. a.*	*S. t.*	*K. o.*	*En. c.*
1a	H	H	0.003	>100	1.56	0.012	0.049	0.012	0.098	0.20
1b	H	CH_2OAc	0.006	50	3.13	0.025	0.20	0.025	3.13	1.56
1c	H	CH_2STz	≤0.0015	50	0.78	0.003	0.049	0.003	0.78	0.20
1d	H	CH_2S-4-PyN^+Et	≤0.0015	25	0.20	0.003	0.39	0.012	1.56	0.39
1e	H	CH_2S-4-$PyN^+CH_2CO_2^-$	0.0115	12.5	0.78	≤0.0015	0.049	≤0.0015	1.56	0.20
1f	Cl	H	0.025	>100	3.13	≤0.0015	0.025	≤0.0015	0.049	0.049
1g	Cl	CH_2OAc	0.006	50	3.13	≤0.0015	0.025	≤0.0015	0.20	0.098
1h	Cl	CH_2STz	0.006	>100	1.56	≤0.0015	0.025	≤0.0015	0.39	0.049
1i	Cl	CH_2S-4-PyN^+Et	0.012	50	3.13	0.012	0.39	0.012	1.56	0.39
1j	Cl	CH_2S-4-$PyN^+CH_2CO_2^-$	0.049	100	3.13	≤0.0015	0.025	0.003	0.39	0.049
1k	Cl	$CH=CH_2$	0.007	>100	3.13	≤0.0015	0.39	≤0.0015	0.098	0.098
1l	-	-	0.025	100	6.25	0.003	0.39	0.003	50	0.39
cefotaxime	-	-	0.003	100	1.56	0.006	12.5	0.025	0.78	0.003
cefpirome	-	-	0.098	25	0.39	0.049	1.56	0.025	3.13	0.012

Abbreviations: *S.p.=Streptococcus pyogenes* 77A; *S. f.=Streptococcus faecium* MD8b; *S. a.=Staphylococcus aureus* SG511; *Es. c.=Escherichia coli* DC2; *P. a.=Pseudomonas aeruginosa* 1592E; *S. t.=Salomonella typhimurium*; *K. o.=Klebsiella oxytoca* 1082E; *En. c.=Enterobacter cloacae* 1321E; Tz=1-methyltetrazol-5-yl; PyN^+=pyridinium

increased antipseudomonal activity in factors of *ca.* 60 and 400, respectively compared to that of cefotaxime. Another comparison revealed roughly the effect of isoxazolylcatechol as a C-3 and a C-7 component in the structure containing the C-3 vinyl group and the C-7 2-(2-aminothiazol-4-yl)methoxyiminoacetamido group. Introduction of isoxazolyldichlorocatechol unit into the C-7 substituent was more effective in enhancing antimicrobial activity than that into the C-3 substituent, which was deduced by comparing the activity of **1k** with **1l**. Activity of **1k** was *ca.* four and five hundred times more potent than **1l** against *S. pyogens* and *K. oxytoca*, respectively. The activity of catecholylcephalosporin compounds against *K. oxytoca* seems to depend largely on the polarity of the C-7 substituent. Compound **1e** exhibited the best-balanced spectrum of antibacterial activity.

Acknowledgments

We are grateful to the Korea Ministry of Science and Technology for financial support.

References

1) Watanabe, N. A.; T. Nagasu, K. Katsu & K. Kitch: E-0702, a new cephalosporin, is incorporated into *Escherichia coli* cells *via* the ton B-dependent iron transport system. Antimicrob. Agents Chemother. 31: 497~504, 1987

2) Newall, C. E. & B. E. Looker (Glaxo group Limited): 7-(α-(2-amino-4-thiazolyl)-α-oximinoacetamido)cephem antibiotics. GB 2,197,649, Sep. 25, 1987

3) Angehrn, P.; A. Furlenmeier, P. Hebeisen, W. Hofheinz & H. Link (F. Hoffmann-La Roche AG): Cephalosporin derivative. Eur. Pat. 544,166, Nov. 14, 1992

4) Albrecht, H. A.; G. Beskid, J. G. Christenson, K. H. Deitcher, N. H. Georgopapadakou, D. D. Keith, F. M. Konzelmann, D. L. Pruess & C. C. Wei: Ro 25-0534: A tertiary amine-linked dual-action cephalosporin. 33rd Intersci. Conf. on Antimicrob. Agents Chemother., Abstract No. 1495, New Orleans, Oct. 17~20, 1993

5) Gibson, M. S. & R. W. Bradshaw: The Gabriel Synthesis of Primary Amines. Angew. Chem. Internat. Edit. 7: 919~930, 1968

6) Leitner, F.; M. Misiek, T. A. Pursiano, R. E. Buck, D. R. Chisholm, R. G. DeRegis, Y. H. Tsai & K. E. Price: Laboratory evaluation of BL-S 786, a cephalosporin with broad-spectrum antibacterial activity. Antimicrob. Agents Chemother. 10: 426~435, 1976