Studies on 3′-Quaternary Ammonium Cephalosporins† II[1]

Synthesis and Antibacterial Activity of 7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-cephalosporin Derivatives Bearing Various Quaternary Ammonium Methyl Groups at the 3 Position

HIDENORI OHKI, KOHJI KAWABATA*, SHINYA OKUDA, TOSHIAKI KAMIMURA and KAZUO SAKANE

New Drug Research Laboratories,
Fujisawa Pharmaceutical Co., Ltd.,
2-1-6 Kashima, Yodogawa-ku,
Osaka 532, Japan

(Received for publication April 27, 1995)

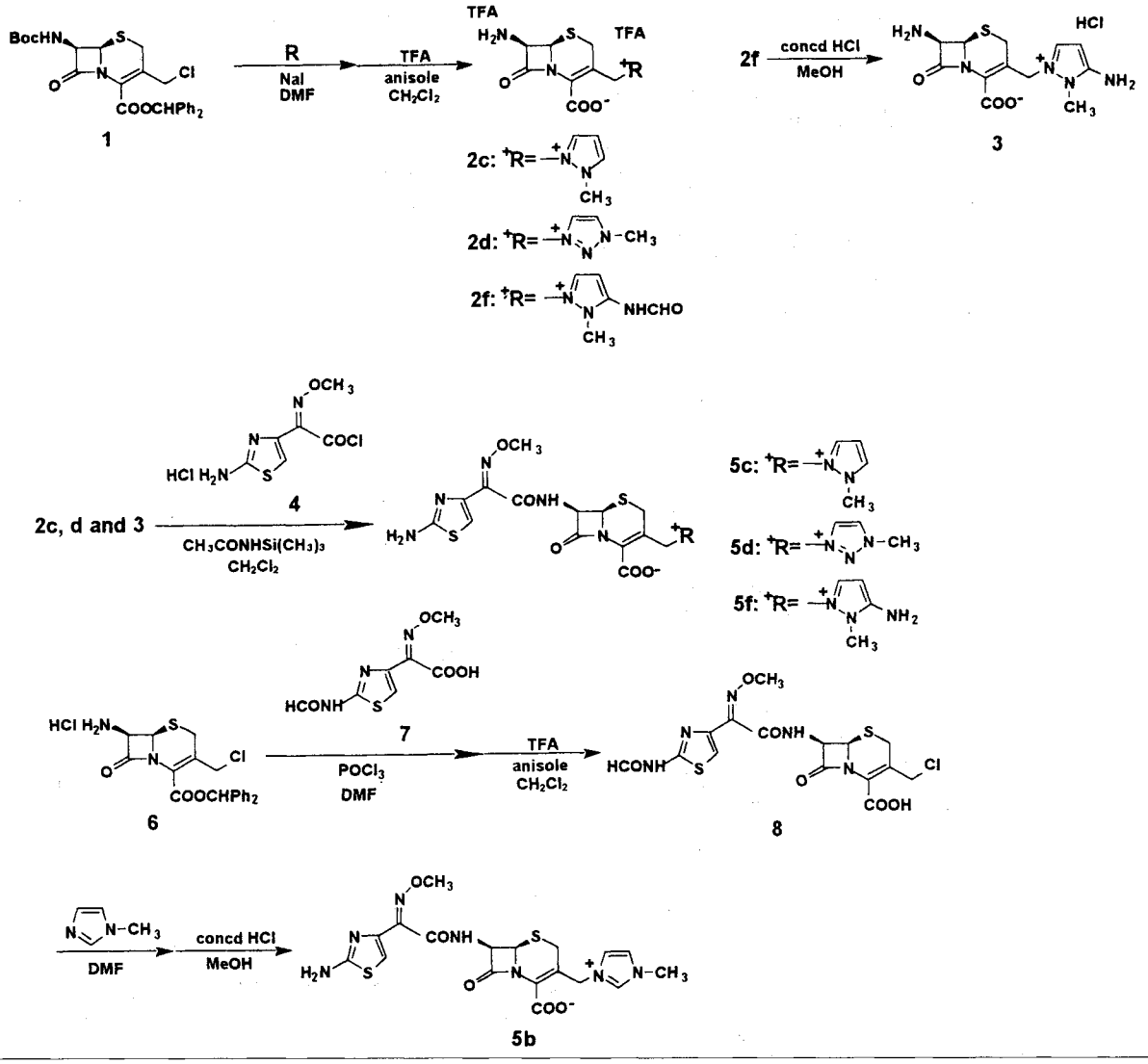
In the last decade, a number of new parenteral cephalosporins with a broad spectrum of antibacterial activity and high stability against various β-lactamases have been marketed[2]. Most of them have a 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetamido] side chain, such as ceftizoxime (CZX). They show excellent activity against Gram-negative bacteria except *Pseudomonas aeruginosa* and moderate activity against Gram-positive bacteria, especially *Staphylococcus aureus*.

Recently, 3′-quaternary ammonium cephalosporins, such as ceftazidime (CAZ), cefpirome (CPR)[3] and cefepime (CFPM, **5e**)[4] which show increased activity against both Gram-positive bacteria including *S. aureus* and Gram-negative bacteria including *P. aeruginosa* have been marketed or developed. Thus, our efforts have been focused on synthesizing novel 3′-quaternary ammonium cephalosporins with enhanced activity against Gram-positive bacteria including *S. aureus* and Gram-negative bacteria including *P. aeruginosa*.

In this paper, we report the synthesis and antibacterial activity of new 3′-quaternary ammonium cephalosporins.

3′-Quaternary ammonium cephalosporins (**5a** and **5e**)

Scheme 1.



† This paper was presented in part at the 13th Symposium on Medicinal Chemistry., Tokyo, Dec. 2~4, 1992

with pyridinium and 1-methylpyrrolidinium were prepared according to the procedure in the literature[3,4]. 3'-Azolium cephalosporins (**5b**~**d** and **f**) were prepared by the two routes outlined in Scheme 1. Diphenylmethyl 7β-*tert*-butoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (**1**) was treated with the corresponding azole compounds (**R**) in the presence of sodium iodide, followed by deprotection of the *tert*-butoxycarbonyl and diphenylmethyl groups with trifluoroacetic acid to give 7β-amino-3-azoliomethyl-3-cephem-4-carboxylate (**2c**, **d** and **f**). The formyl group of **2f** was removed with concd hydrochloric acid to give 7β-amino-3-(3-amino-2-methylpyrazolio)methyl-3-cephem-4-carboxylate hydrochloride (**3**). The 7ACA derivatives (**2c**, **d** and **3**) were acylated with (*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetylchloride hydrochloride (**4**)[5] to give 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-azoliomethylcephalosporin derivatives (**5c**, **d** and **f**).

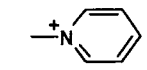
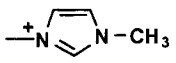
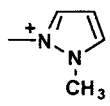
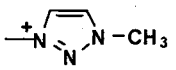
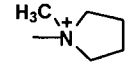
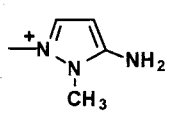
Alternatively, compound **5b** was prepared by substitution of 3-chloromethylcephalosporanic acid (**8**) with 1-methylimidazole. Diphenylmethyl 7β-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (**6**)[6] was acylated by the Vilsmeier method with (*Z*)-2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetic acid (**7**)[7], followed by deprotection with TFA to give 7β-[(*Z*)-2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylic acid (**8**). **8** was treated with 1-methylimidazole, followed by deprotection with concd hydrochloric acid to give 3-(3-methylimidazolio)methylcephalosporin (**5b**).

The antibacterial activity (MICs) of the prepared 3'-quaternary ammonium cephalosporins (**5a**~**f**) along with CZX and CPR as reference compounds against selected Gram-positive and Gram-negative bacteria are shown in Table 1. MICs were determined by the standard serial 2-fold agar dilution method using Müeller-Hinton agar.

The antibacterial activity of the synthesized cephalosporins (**5a**~**e**) against *S. aureus* were superior to that of CZX. Furthermore, the cephalosporins except **5b** showed better activity against *P. aeruginosa* than CZX. MICs of the heteroaromatic derivatives such as pyridinium (**5a**) and azolium (**5b**~**d**) cephalosporins against *S. aureus* were superior to that of the alicyclic ammonium derivative such as 1-methylpyrrolidinium cephalosporin (**5e**). However, the heterocyclic derivatives (**5a**, **c** and **d**) except **5b** have slightly less activity against *P. aeruginosa* than **5e**.

Among the 3'-quaternary ammonium cephalosporins

Table 1. Antibacterial activity (MIC, μg/ml) of 3'-quaternary ammonium cephalosporins (**5a**~**f**).

Compound No.	$^{+}$R	*S.a.*	*E.c.*	*K.p.*	*P.a.* 1	*P.a.* 2*
		10^6 cfu/ml				
5a		0.78	≦0.025	0.05	25	3.13
5b		1.56	0.05	0.05	200	200
5c		1.56	0.05	0.1	12.5	6.25
5d		0.78	≦0.025	0.05	25	3.13
5e (CFPM)		3.13	0.05	0.1	6.25	6.25
5f		0.78	≦0.025	0.05	12.5	3.13
CZX		12.5	≦0.025	≦0.025	50	25
CPR		0.78	0.05	0.1	6.25	6.25

* *S. a.*; *Staphylococcus aureus* 209P JC-1, *E. c.*; *Escherichia coli* NIHJ JC-2, *K. p.*; *Klebsiella pneumoniae* 12, *P. a.* 1; *Pseudomonas aeruginosa* IAM 1095, *P. a.* 2; *Pseudomonas aeruginosa* 2.

tested, pyrazolium cephalosporin (**5c**) showed well-balanced activity against Gram-positive bacteria including *S. aureus* and Gram-negative bacteria including *P. aeruginosa*. Thus, in order to find a pyrazolium cephalosporin with ever better activity, we introduced substituents on to the pyrazolium ring of 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporin (**5c**). As shown in Table 1, we discovered that the introduction of an amino group to the pyrazolium ring imparts increased potency against *S. aureus* and *P. aeruginosa* compared to CPR.

In summary, 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methylpyrazolio)-methyl-3-cephem-4-carboxylate (**5f**) showed extremely potent broad-spectrum activity against both Gram-positive bacteria, including *S. aureus*, and Gram-negative bacteria, including *P. aeruginosa*. Our further studies will be presented in subsequent papers.

References

1) OHKI, H.; K. KAWABATA, S. OKUDA, T. KAMIMURA & K. SAKANE: FK037, A new parenteral cephalosporin with a broad antibacterial spectrum: Synthesis and antibacterial activity. J. Antibiotics 46: 359~361, 1993
2) For a review, see: DUERCKHEIMER, W; J. BLUMBACH, R. LATTRELL & K. H. SCHEUNEMAN: Recent developments in the field of β-lactam antibiotics. Angew. Chem. Int. Ed. Engl. 24: 180~202, 1985
3) LATTRELL, R.; J. BLUMBACH, W. DUERCKHEIMER, H.-W. FEHLHABER, K. FLEISCHMANN, R. KIRRSTETTER, B. MENCKE, K.-H. SCHEUNEMANN, E. SCHRINNER, W. SCHWAB, K. SEEGER, G. SEIBERT & M. WIEDUWILT: Synthesis and structure-activity relationships in the cefpirome series. I. 7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-oxyiminoacetamido]-3-[(substituted-1-pyridinio)-methyl]ceph-3-em-4-carboxylates. J. Antibiotics 41: 1374~1394, 1988
4) NAITO, T.; S. ABURAKI, H. KAMACHI, Y. NARITA, J. OKUMURA & H. KAWAGUCHI: Synthesis and structure-activity relationships of a new series of cephalosporins, BAY-28142 and related compounds. J. Antibiotics 39: 1092~1107, 1986
5) DALOIA, E.; G. LIM, J. MELTON & J. ROUBIE: A convenient method for the preparation of (Z)-(2-aminothiazol-4-yl)-2-methoxyiminoacetylchloride hydrochloride. Synth. Commun. 23: 2617~2622, 1993
6) YAMANAKA, H.; T. CHIBA, K. KAWABATA, H. TAKASUGI, T. MASUGI & T. TAKAYA: Studies on β-lactam antibiotics. IX: Synthesis and biological activity of a new orally active cephalosporin, cefixime (FK027). J. Antibiotics 38: 1738~1751, 1985
7) TAKAYA, T.; H. TAKASUGI, T. MASUGI, T. CHIBA, H. KOCHI, T. TAKANO & H. NAKANO: Structure-activity relationships of sodium 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate (ceftizoxime) and its related compounds. Nippon Kagaku Kaishi 5: 785~804, 1981