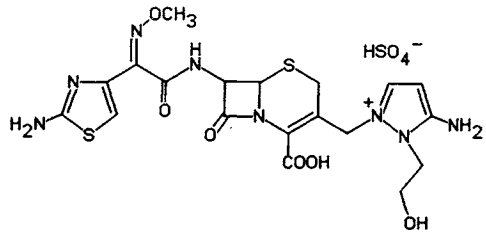
FK037, A NEW PARENTERAL CEPHALOSPORIN WITH A BROAD ANTIBACTERIAL SPECTRUM: SYNTHESIS AND ANTIBACTERIAL ACTIVITY

Sir:

In recent years, a number of new parenteral cephalosporins with a broad spectrum of antibacterial activity and a high stability against various β-lactamases have been reported[1]. Most of them have a 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetamido] side chain, such as ceftizoxime (CZX) and ceftazidime (CAZ). They show excellent activity against Gram-negative bacteria and moderate activity against Gram-positive bacteria, especially *Staphylococcus aureus*.

Recently, 3'-quaternary ammonium cephalosporins, such as cefpirome (CPR)[2] and cefepime (CFPM)[3] which show increased activity against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa* have been developed. Thus, our efforts have been focused on synthesizing novel 3'-quaternary ammonium cephalosporins with enhanced activity against Gram-positive and Gram-negative bacteria including *P. aeruginosa*. As a result, we have discovered a new parenteral cephalosporin, FK037 (**1**), 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)pyrazolio]methyl-3-cephem-4-carboxylate sulfate. In this paper we report the synthesis and antibacterial activity of FK037[4].

The synthesis of FK037 is outlined in Scheme 1. Diphenylmethyl 7β-*tert*-butoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (**2**) was treated with 5-formylamino-1-(2-formyloxyethyl)pyrazole in the presence of sodium iodide, followed by deprotection of all protecting groups with TFA and then concd hydrochloric acid to give 7β-amino-3-[3-amino-2-(2-hydroxyethyl)pyrazolio]methyl-3-cephem-4-carboxylate hydrochloride (**4**) in 37.5% yield from **2**. **4** was acylated with 1-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyminoacetyl)]benzotriazol-3-oxide (**5**), followed by treatment with



FK037 (**1**)

Scheme 1.

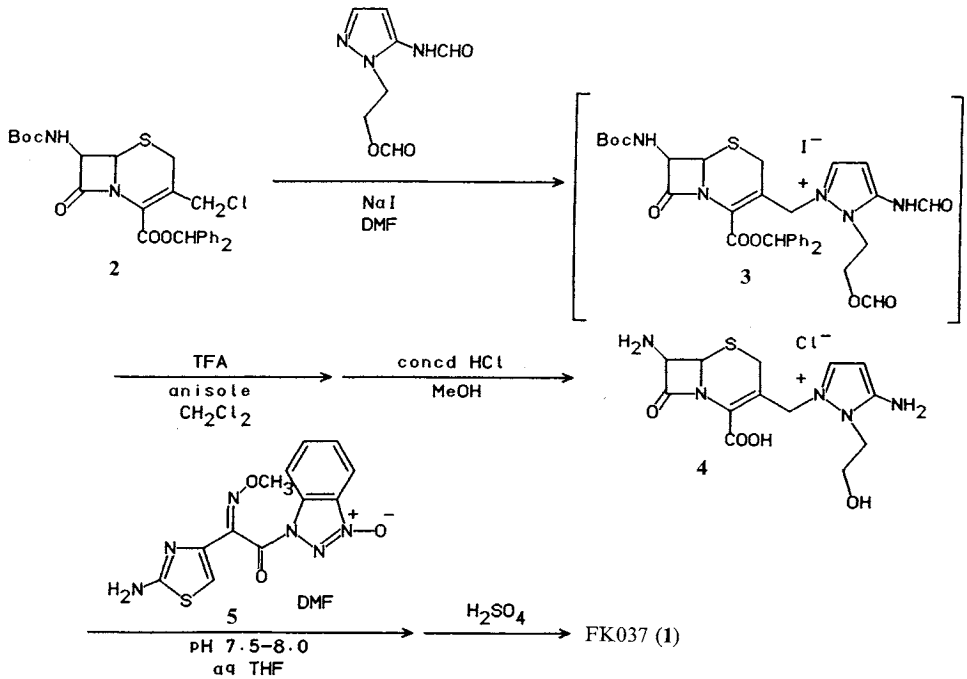


Table 1. Analytical, IR and ^{1}H NMR data of **1**.

Analysis	Calcd for $C_{19}H_{22}N_8O_6S_2 \cdot H_2SO_4$: C 36.77, H 3.90, N 18.05, S 15.50 Found: C 36.60, H 3.71, N 17.91, S 15.36
IR (Nujol) cm^{-1}	3212, 1770, 1658, 1035
^{1}H NMR (200 MHz, DMSO-d_6) δ	3.21 and 3.33 (2H, ABq, J=18.1 Hz, 2-H_2), 3.50~3.70 (2H, m, NCH_2CH_2OH), 3.82 (3H, s, OCH_3), 4.00~4.20 (1H, m, *H*CHOH), 4.20~4.40 (1H, m, HC*H*OH), 5.12 and 5.30 (2H, ABq, J=15.9 Hz, 3'-H_2), 5.17 (1H, d, J=5 Hz, 6-H), 5.85 (1H, dd, J=8 and 5 Hz, 7-H), 5.89 (1H, d, J=2.8 Hz, pyrazole 4-H), 6.73 (1H, s, thiazole 5-H), 7.22 (2H, s, thiazole NH_2), 7.31 (2H, s, pyrazole NH_2), 7.97 (1H, d, J=2.8 Hz, pyrazole 5-H), 9.51 (1H, d, J=8 Hz, CONH)

Table 2. Antibacterial activity of FK037.

Organism (No. of strains)		MIC (μg/ml) 50%	90%	Organism (No. of strains)		MIC (μg/ml) 50%	90%
Staphylococcus aureus	FK037	0.39	3.13	*Klebsiella pneumoniae*	FK037	0.05	6.25
(25) (MSSA)	CPR	0.39	3.13	(30)	CPR	0.05	6.25
S. aureus (41) (MRSA)	FK037	25	25	*Proteus mirabilis* (20)	FK037	0.1	0.1
	CPR	100	100		CPR	0.1	0.1
S. epidermidis (20)	FK037	1.56	6.25	*Serratia marcescens* (18)	FK037	0.78	3.13
	CPR	1.56	25		CPR	0.78	1.56
Streptococcus pyogenes[a]	FK037	≦0.025	≦0.025	*Pseudomonas aeruginosa*	FK037	3.13	6.25
(21)	CPR	≦0.025	≦0.025	(21)	CPR	6.25	6.25
S. pneumoniae[a] (21)	FK037	≦0.025	0.05	*P. cepacia* (11)	FK037	3.13	3.13
	CPR	≦0.025	0.1		CPR	3.13	6.25
Haemophilus influenzae[a]	FK037	0.1	0.2	*P. putida* (10)	FK037	0.39	3.13
(18)	CPR	0.1	0.1		CPR	0.78	3.13
Escherichia coli (30)	FK037	0.05	0.1				
	CPR	0.05	0.1				

Müller-Hinton agar; 10^{-2}, stamp method; 37°C, 20 hours.
[a] Supplemented with 5% horse blood.
CPR: Cefpirome.

sulfuric acid to give FK037 (**1**) in 46.0% yield. The structure of **1** was confirmed by elemental analysis, IR and ^{1}H NMR spectrum (Table 1).

Table 2 shows the antibacterial activity of FK037 along with CPR as a reference compound. FK037 displayed more potent activity than CPR against Gram-positive bacteria. In particular, antibacterial activity against methicillin-resistant *S. aureus* (MRSA) of FK037 was 4-fold superior to that of CPR (FK037, MIC_{90}: 25 μg/ml and CPR, MIC_{90}: 100 μg/ml). FK037 was the most active of all the cephalosporins tested and more active than imipenem against MRSA[5]. Moreover, FK037 was more active than CPR against *P. aeruginosa*, *P. cepacia* and *P. putida*. In summary FK037 showed extremely potent broad-spectrum against both Gram-positive including MRSA, and Gram-negative bacteria including *P. aeruginosa*.

Further evaluation of FK037 as a clinical candidate is now in progress.

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