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COMMUNICATIONS TO THE EDITOR

FR192752, a Novel Orally Active Cephalosporin Synthesis and Biological Properties

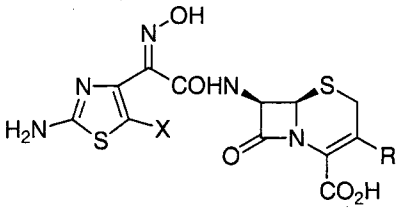
Sir:

New orally active cephalosporins such as cefdinir[1] (CFDN), cefditoren pivoxil[2] (CDTR-PI) are of key clinical importance for the treatment of bacterial infections. CFDN, which was discovered in our laboratories, has an excellent antibacterial activity against both Gram-positive and Gram-negative bacteria and high oral absorption.[3] However continuous efforts have been made to find a more well-balanced and more active compound especially against *Haemophilus influenzae*. Consequently, we discovered FK041 having a 4-pyrazolylmethylthio moiety at the C-3 position, exhibited potent and well balanced antibacterial activity against wide variety of clinical isolates of bacteria including *H. influenzae* and high oral absorption[4].

Recently, penicillin G-resistant *S. pneumoniae* (PRSP) have been encountered with increasing frequency. Penicillin G-resistant isolates show increased resistance to other β-lactam antibiotics[5,6]. Thus, PRSP causes serious problems these days. FK041 showed moderate activity against PRSP, however, in our research work derived from FK041 we have discovered FR192752, having 2-(2-amino-5-chlorothiazol-4-yl)-2-(hydroxyimino)acetamido moiety at the C-7 position, showed potent and well balanced antibacterial activity against both Gram-positive and Gram-negative bacteria including PRSP. Further, FR192752 showed higher oral absorption than FK041 in various animals. We report herein the synthesis and biological properties of FR192752.

The synthesis of FR192752 is outlined in Scheme 1. We used 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetic acid[7] (**3**) as starting material of 7β-side chain fragment. The acid (**3**) was treated with a mixture of acetic anhydride and formic acid to afford **4**. Protected acid (**4**) was chlorinated using *N*-chlorosuccimide (NCS) in THF to afford **5**, which was converted to acid chloride **6** using PCl_5 in CH_2Cl_2 in quantitative yield. The 3-mesyoxycephem[8] (**7**) was treated with sodium hydrosulfite in the presence of *N,N*-diisopropylethylamine (DIEA) in DMAc at 0°C, followed by addition of 4-chloromethyl pyrazole (**8**) to afford **9**. Under this reaction condition undesired Δ^2 isomer was not observed. Both the C-7 and the C-3 protecting group was removed successively to afford 7-ACA derivative **10**.

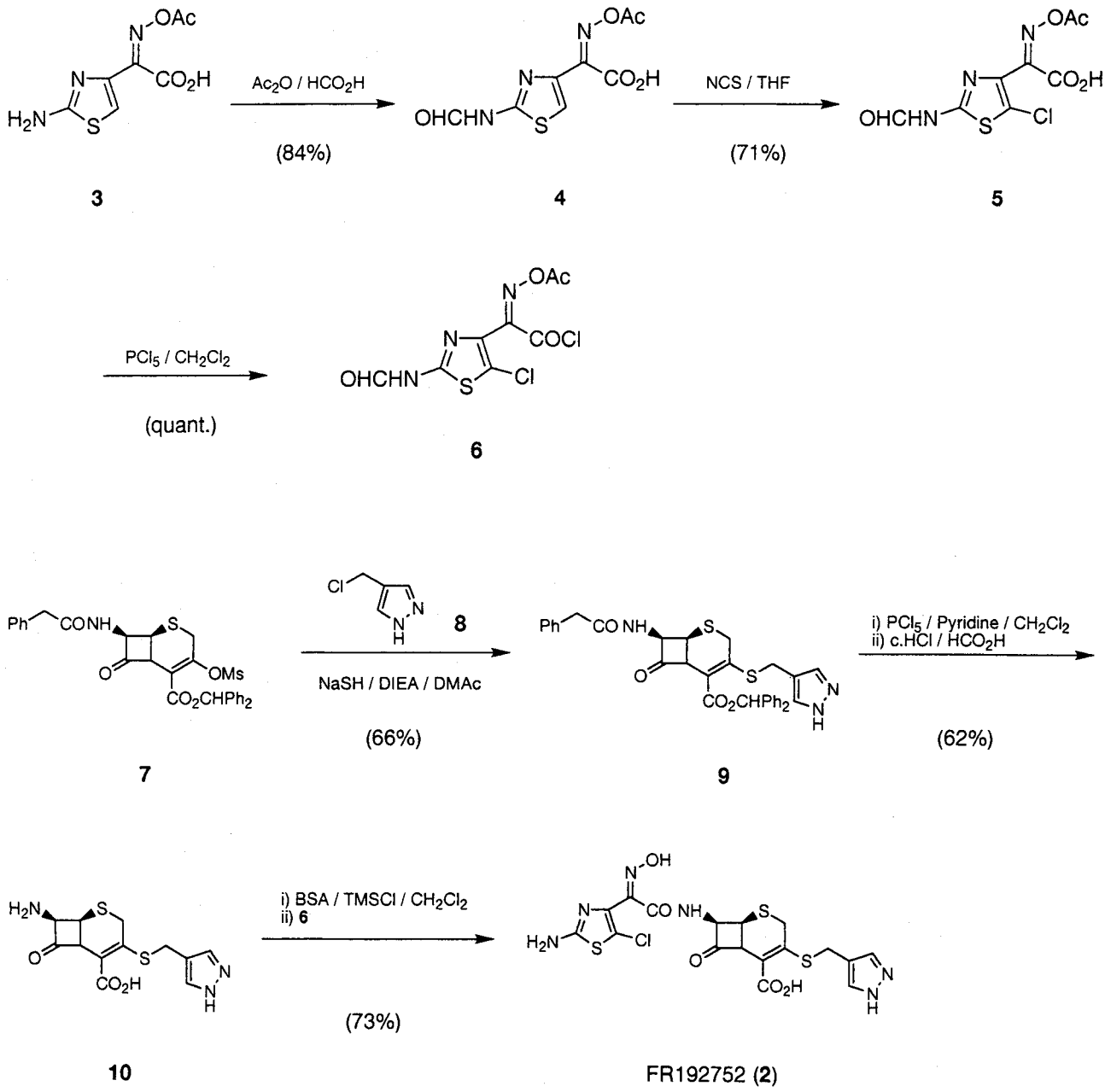
Fig. 1. Structures of CFDN, FK041 and FR192752.



	X	R
CFDN	—H	—CH=CH$_2$
FK041(1)	—H	—SCH$_2$—
FR192752 (2)	—Cl	—SCH$_2$—

Dedicated to the memory of Sir EDWARD ABRAHAM.

Scheme 1. Synthesis of FR192752 (**2**).



Condensation of **10** with **6** in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and trimethylsilyl chloride (TMSCl) in CH_2Cl_2 followed by acidic work-up gave desired compound **2**.

The antibacterial activity (MIC_{80}) of FR192752 is shown in Table 1. For comparison, the MIC values for FK041, CFDN and cefditoren (CDTR) are also listed. As can be seen from these data, FR192752 showed well balanced antibacterial activity. In particular, FR192752 showed most potent antibacterial activity against PRSP and *Moraxella catarrhalis* compared to reference drugs. Against Gram-positive bacteria except for PRSP FR192752 showed slightly less active than FK041 but showed improved antibacterial activity compared to CFDN and CDTR. Against *H. influenzae* FR192752 was more active than CFDN. Although FR192752 was less active against *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* compared to reference drugs, it maintains enough

Table 1. Antibacterial activity of FR192752 and reference antibiotics.[a)]

Drugs	MIC_{80} (μg/ml)								
	S.a	*S.e*	*S.p.*1	*S.p.*2	*M.c.*	*H.i.*	*E.c.*	*K.p.*	*P.m.*
FR192752	0.39	0.78	0.1	0.78	≦0.025	0.39	0.78	0.39	0.39
FK041	0.20	0.39	0.05	1.56	0.39	0.2	0.05	0.05	≦0.025
CFDN	0.39	1.56	0.1	6.25	0.2	0.78	0.39	0.1	0.1
CDTR	0.78	1.56	0.05	0.78	0.2	≦0.025	0.2	0.2	0.05

Agar dilution method (stamp method): Müller-Hinton agar; 10^3 cfu/spot, 37°C, 18 or 48 hours.

a) *S.a.,Staphylococcus aureus* (MSSA)(21); *S.e.,Staphylococcus epidermilis* (21); *S.p.*1, *Streptococcus pneumoniae* (PC-susceptible)(23); *S.p.*2, *Streptococcus pneumoniae* (PC-resistant)(17); *M.c.*, *Moraxella catarrhalis* (19); *H.i.,Haemophilus influenzae* (42); *E.c.,Escherichia coli* (20); *K.p.,Klebsiella pneumoniae* (21); *P.m.,Proteus mirabilis* (21).
CFDN: cefdinir, CDTR: cefditoren.

Table 2. Comparative pharmacokinetics of FR192752 and reference antibiotics after single oral administration (20 mg/kg) to various animals.

Animal	Drugs	Cmax (μg/ml)	$T_{1/2}$ (h)	AUC (μg·h/ml)	Recovery(%)	
					Urine	Bile
Mouse	FR192752	36.7	0.81	56.2	51.7	21.6
	FK041	3.6	0.82	10.8	17.1	11.1
	CFDN	2.1	1.6	6.2	35.5	1.49
	CDTR-PI	8.7	1.2	14.8	1.94	12.2
Rat	FR192752	21.8	0.99	52.9	41.9	28.7
	FK041	6.3	1.09	23	42.9	6.81
	CFDN	2.0	1.68	6.8	32.4	1.4
	CDTR-PI	13.9	1.72	36.5	5.74	16.8
Rabbit	FR192752	11.7	1.49	27.9	78.6	nd
	FK041	13.2	1.40	40.5	48.8	nd
	CFDN	5.28	1.11	14.5	45.8	nd
	CDTR-PI	nd	nd	nd	nd	nd
Dog	FR192752	19.9	0.98	64.6	27.4	nd
	FK041	10.4	1.1	28.6	27.8	nd
	CFDN	40.9	3.75	403	41.3	0.013
	CDTR-PI*	0.9	0.9	2.7	nd	nd

* T.Matsumoto et al. 1992. Chemotherapy(Tokyo). 40(S-2): 120-130.
nd: not determined.

potency against these bacteria.

Table 2 shows the comparative pharmacokinetics and urinary and biliary recovery after oral administration (20 mg/kg) of FR192752, FK041, CFDN and CDTR-PI to various animals. FR192752 showed little variability in pharmacokinetics and recovery among tested animals and the plasma half-life of FR192752 was similar to that of FK041 among these animals. In mouse and rat, FR192752 showed the most superior data in terms of both pharmacokinetics and recovery. In particular, plasma

Table 3. Protective effect of FR192752, FK041 and CFDN on systemic infection in mice.

Organism	Challenge dose (CFU/mouse,i.p.)	Drugs	ED_{50} (mg/kg)	MIC (μg/ml)
S.aureus FP1469	$9.9x10^6$	FR192752	0.248	0.2
		FK041	0.293	0.2
		CFDN	1.47	0.39
S.aureus 47	$1.2x10^8$	FR192752	1.67	0.39
		FK041	2.18	0.2
		CFDN	4.31	0.39

Treatment : p.o., 1h after challenge.

concentration of FR192752 was extraordinary high compared to reference drugs. In rabbit, pharmacokinetics of FR192752 was similar to that of FK041 but FR192752 showed the best urinary recovery. In dog, pharmacokinetics and recovery of FR192752 was inferior to those of CFDN, however, CFDN shows exceptionally good data in dog. As a result, the pharmacokinetics and recovery of FR192752 were judged to be good in all animals.

We further tested *in vivo* activity of FR192752 against systemic infections with *S. aureus* FP1469 and *S. aureus* 47 in mice and results are shown in Table 3. The *in vivo* efficacy of FR192752 in an experimental infection due to *S. aureus* FP1469 was superior to that of CFDN and similar to that of FK041. In experimental infections caused by *S. aureus* 47, FR192752 showed greater *in vivo* efficacy than FK041 and CFDN, and this *in vivo* efficacy reflected the MIC values and pharmacokinetics.

In conclusion, introduction of a chloro substituent to the 5-position of the C-7 thiazole moiety of FK041 improved antibacterial activity against PRSP. This modification also improved the Cmax and the AUC values in various animals except for rabbit as well as the recovery in various animals except for dog. FR192752 showed potent and well balanced antibacterial activity against both Gram-positive and Gram-negative bacteria including PRSP. Further, FR192752 showed high oral absorption as well as good pharmacokinetics in various animals and high *in vivo* efficacy.

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