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Studies on 3′-Quaternary Ammonium Cephalosporins—IV. Synthesis and Antibacterial Activity of 3′-(2-Alkyl-3-aminopyrazolium)cephalosporins Related to FK037

Hidenori Ohki, Kohji Kawabata,* Yoshiko Inamoto, Shinya Okuda, Toshiaki Kamimura and Kazuo Sakane

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

Abstract—The synthesis and in vitro antibacterial activity of 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido] cephalosporins bearing various 2-alkyl-3-aminopyrazolium groups at the 3-position are described. Antibacterial activity against MRSA was affected by the nature of the substituent at the 2-position on the 3′-aminopyrazolium groups. Among the cephalosporins prepared in this study, 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-pyrazolio]methyl-3-cephem-4-carboxylate sulfate (**23e**, FK037) showed extremely potent broad-spectrum activity against both Gram-positive bacteria including MRSA, and Gram-negative bacteria including *Pseudomonas aeruginosa*. In particular, the in vivo activity against MRSA of FK037 was the highest of all the β-lactam antibiotics tested. © 1997 Elsevier Science Ltd.

Introduction

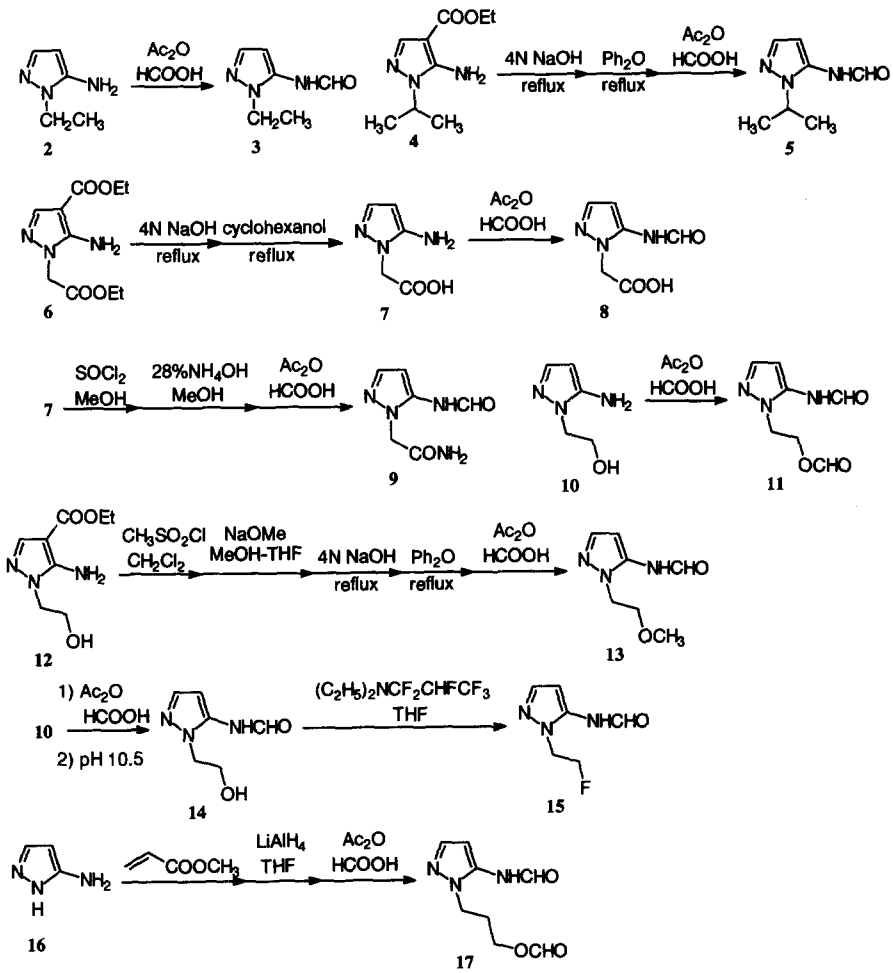
In previous papers[1–3] we reported the synthesis and antibacterial activity of novel 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporin derivatives having various pyrazolium methyl groups at the 3-position. As a result, we discovered that the introduction of an amino group to the pyrazolium ring imparts increased potency against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, leading to the discovery of FK037 as a potent new, parenteral cephalosporin.[1] Furthermore, 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporins having five- or six-membered ring fused aminopyrazolium methyl groups at the 3-position showed very potent activity against both Gram-positive bacteria, including *S. aureus*, and Gram-negative bacteria, including *P. aeruginosa*.[3] In particular, the introduction of a 3-imidazopyrazolium methyl group to the cephalosporin nucleus was found to be most effective in improving antibacterial activity against MRSA.

In order to find an aminopyrazolium cephalosporin with improved activity, especially against MRSA, we postulated that the difference of the in vitro activity against MRSA of 3-imidazopyrazolium and 3-[2,3-dihydro-5-(1*H*-imidazo[1,2-*b*]pyrazolium)]methyl-substituted cephalosporins,[3] (50 and 100 μg/mL, respectively) indicates that the steric and electronic environment around the nitrogen atom at the 2-position on the aminopyrazolium ring can significantly affect antibacterial activity. Therefore, we studied the antibacterial activity of novel 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporins having various substituents at the 2-position of the aminopyrazolium ring. Our design process necessitated the preparation of analogues of FK037, in which the steric and electronic nature of the 2-position substituent varied. We wish to describe the synthesis and antibacterial activity of this novel series of 3′-aminopyrazolium cephalosporins in this paper.

Results and Discussion

Synthesis

The preparation of the various 1-alkyl-5-aminopyrazoles employed as cephalosporin substituents described in this study was performed according to the procedures shown in Scheme 1. The 1-alkyl-5-formylaminopyrazoles (**3** and **11**) were obtained by formylation of the corresponding aminopyrazoles (**2** and **10**). Formylaminopyrazoles (**5** and **8**) were synthesized by hydrolysis, decarboxylation and formylation of 1-alkyl-5-amino-4-ethoxycarbonylpyrazoles (**4** and **6**). The 1-alkyl-5-amino-4-ethoxycarbonylpyrazoles (**4**, **6** and **12**) were obtained by reaction with the corresponding monoalkylhydrazine and ethyl 2-ethoxymethylene-2-cyanoacetate according to the procedure described in the literature.[4] 5-Amino-1-carboxymethylpyrazole (**7**) was esterified, treated with ammonium hydroxide, and then protected at nitrogen by formylation to give 1-carbamoylmethyl-5-formylaminopyrazole (**9**). 5-Formylamino-1-(2-methoxyethyl)pyrazole (**13**) was obtained by reacting **12** with methanesulfonylchloride, and subsequent treatment with sodium methoxide, and then treatment of the intermediate methyl ether in a similar manner to that of **5**. 5-Formylamino-1-(2-hydroxyethyl)-



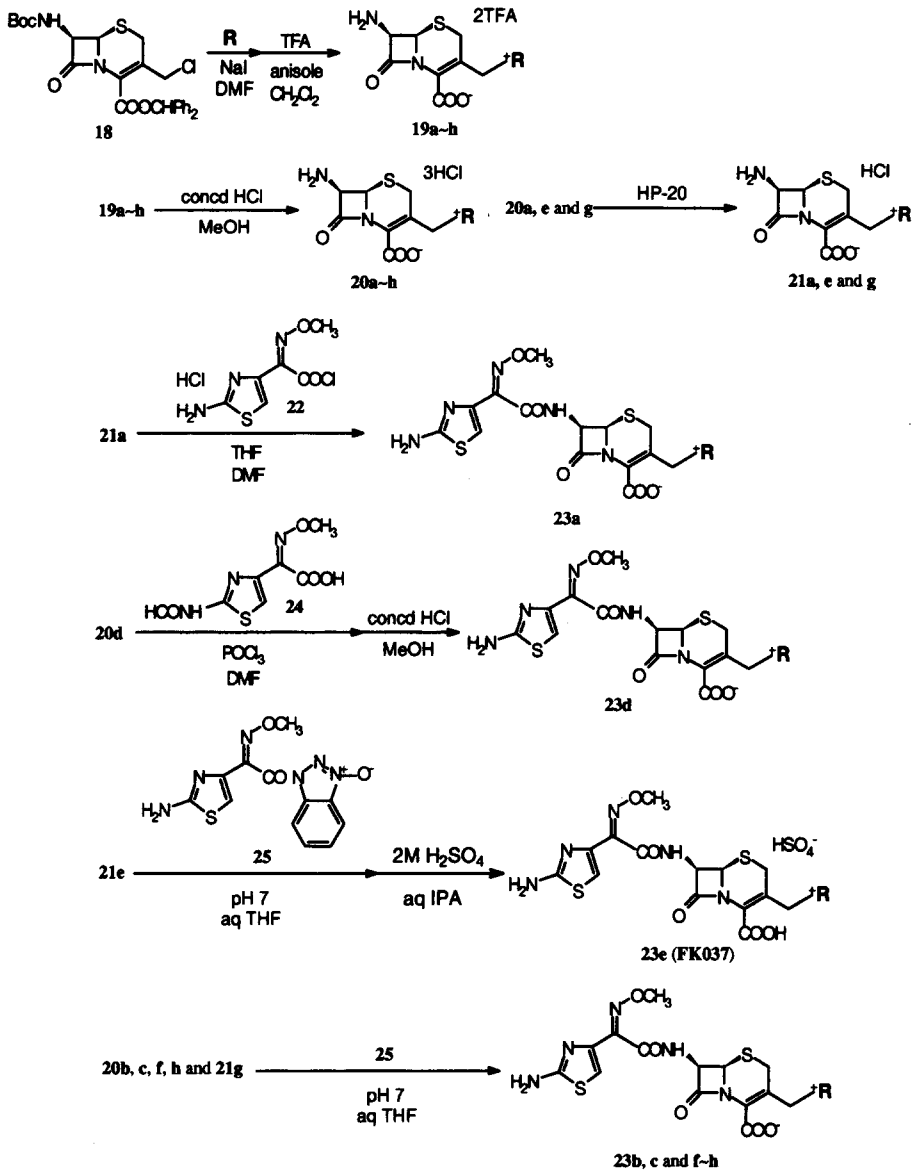
Scheme 1.

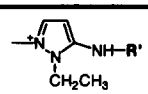
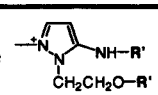
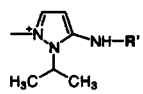
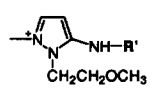
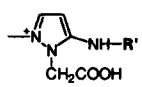
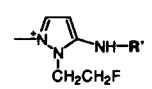
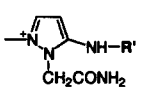
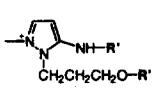
pyrazole (**14**), prepared by selective hydrolysis of **11** at pH 10.5, was treated with the Ishikawa reagent[5] to effect fluorination to give 1-(2-fluoroethyl)-5-formylaminopyrazole (**15**). 5-Aminopyrazole (**16**) was treated with methyl acrylate by an established procedure[6] to afford the 1,4-conjugate addition product that was then reduced with lithium aluminum hydride and formylated to give 5-formylamino-1-(3-formyloxypropyl)pyrazole (**17**).

Having obtained the various protected pyrazoles, the synthesis of 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-aminopyrazolio)methylcephalosporins (**23a–h**) was performed as outlined in Scheme 2. 7ACA derivatives (**20a–h**) were prepared by a similar procedure to that described previously,[2,3] involving coupling of the pyrazoles with chloromethyl cephalosporin (**18**) and subsequent removal of the protecting group. Cephems (**20a**, **e**, and **g**) were then purified by column chromatography with HP-20 to give the crystalline 7ACA derivatives (**21a**, **e** and **g**). The 7ACA derivative (**21a**) was then acylated with (*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetylchloride hydrochloride (**22**)[2,7] to give a good yield of 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporin (**23a**) with no Δ^2-isomer formation. The 7ACA derivative (**20d**) was acylated by Vilsmeier's method with (*Z*)-2-(2-formylaminothiazol-4-yl)-2-methoxyiminoacetic acid (**24**), followed by deformylation with concentrated HCl in methanol, to give **23d**. The 7ACA derivative (**21e**) was acylated with 1-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetyl]benzotriazol-3-oxide (**25**) to give the 3-pyrazoliomethyl cephalosporin derivative (**23e**: FK037) after HP-20 purification and crystallization with 2 M sulfuric acid in a mixture of isopropyl alcohol and water. The other 7ACA derivatives (**20b**, **c**, **f**, **h**, and **21g**) were acylated with **25** to give 3-pyrazoliomethyl cephalosporin derivatives (**23b**, **c**, **f–h**) in moderate to good yields after HP-20 purification and lyophilization.

Antibacterial activity

The in vitro antibacterial activity (MICs) of the prepared 3′-pyrazolium cephalosporins along with Cefpirome (CPR)[8], as a reference compound, against selected Gram-positive and Gram-negative bacteria are shown in Table 1. MICs were determined by the standard serial twofold agar dilution method using Müeller–Hinton agar.

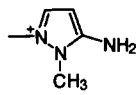
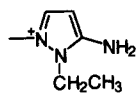
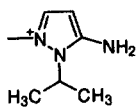
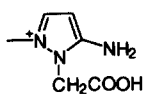
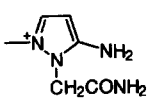
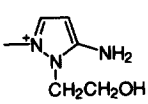
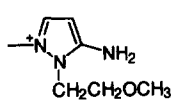
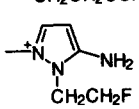


	+R	R' (19)	R' (20, 21 and 23)		+R	R' (19)	R' (20, 21 and 23)
a		CHO	H	e		CHO	H
b		CHO	H	f		CHO	H
c		CHO	H	g		CHO	H
d		CHO	H	h		CHO	H

Scheme 2.

The carboxymethyl and carbamoylmethyl derivatives **23c** and **23d**, having electron-withdrawing groups, respectively, showed substantially less activity than **1** against *S. aureus* 209P JC-1 (MSSA) and were inactive against *S. aureus* 3004 (MRSA). The antibacterial activity of ethyl, isopropyl or 2-methoxyethyl com-

Table 1. Antibacterial activity (MIC, μg/ml) of 3′-aminopyrazolium cephalosporins (**1** and **23a–h**); 10^6 cfu/mL

Compound No.	$^+$R	*S.a.* 1	*S.a.* 2	*E.c.*	*K.p.*	*P.a.**
1		0.78	>100	≤0.025	0.05	12.5
23a		0.78	50	≤0.025	0.1	25
23b		0.78	50	0.05	0.1	25
23c		3.13	>100	0.1	0.2	50
23d		3.13	>100	0.1	0.2	12.5
23e (FK037)		0.39	25	≤0.025	0.1	6.25
23f		0.78	>100	0.05	0.2	25
23g		0.39	50	≤0.025	0.05	12.5
23h		0.78	100	≤0.025	0.1	12.5
CPR		0.78	>100	0.05	0.1	6.25

**S.a.* 1, *Staphylococcus aureus* 209P JC-1; *S.a.* 2, *Staphylococcus aureus* 3004 (MRSA); *E.c.*, *Escherichia coli* NIHJ JC-2; *K.p.*, *Klebsiella pneumoniae* 12; *P.a.*, *Pseudomonas aeruginosa* IAM 1095.

pounds **23a**, **23b** and **23f** were similar against MSSA but less potent against *P. aeruginosa* compared to **1**. MICs against MRSA of **23a**, **23b**, **23e** and **23g** bearing a large substituent at the 2-position were more potent compared to **1**, but the MICs of **23f** and **23h** bearing larger substituents than **23e** were similar to that of **1**. In particular, **23e** (FK037) showed the most potent activity against MRSA. Thus, in order to improve the antibacterial activity against MRSA, a substituent with a suitable electronic nature and appropriate size at the 2-position of the 3′-aminopyrazolium group seems to be necessary. Among the cephalosporins tested, 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)pyrazolio]methyl-3-cephem-4-carboxylate sulfate (**23e**, FK037; Cefoselis) showed extremely potent broad-spectrum activity against both Gram-positive bacteria, including MRSA, and Gram-negative bacteria including *P. aeruginosa*.[1]

Table 2 shows the antibacterial activity of FK037 (**23e**) along with CPR, Flomoxef (FMOX), Ceftazidime (CAZ) and Imipenem (IPM) as reference compounds (Fig. 1) against some clinically isolated strains. FK037 displayed the same activity against MSSA as CPR. However, the antibacterial activity against MRSA of FK037 was fourfold superior compared to that of CPR. Compared to the standard compounds tested in this work, activity against MRSA was highest, with FK037 as indicated by the MIC_{80} values.[10]

The therapeutic effect in mice of FK037 and the reference drugs (CPR, FMOX and IPM) against MRSA (*S. aureus* 9087) are shown in Table 3. Efficacy of each compound was expressed as the 50% effective dose value (ED_{50}) calculated by the probit method. The ED_{50} value of FK037 against MRSA was the most effective of the reference drugs tested, including IPM.[10]

Thus, FK037 was selected as a clinical candidate for further development.[9]

Experimental

Melting points were determined using a Thomas–Hoover capillary melting apparatus and are uncorrected. IR spectra were taken on a Hitachi 260-10 spectrophotometer. NMR spectra were recorded at 90

Table 2. Antibacterial activity (MIC, μg/ml) of FK037 against clinical isolates

Organism (No. of strains)		MIC (μg/ml) 50%	80%	Range
S. aureus (48) (MSSA)	FK037	1.56	1.56	0.78–3.13
	CPR	0.78	1.56	0.39–6.25
	CAZ	12.5	12.5	6.25–50
	FMOX	0.78	1.56	0.2–6.25
S. aureus (57) (MRSA)	FK037	25	25	6.25–50
	CPR	100	100	25–>100
	FMOX	50	100	12.5–>100
	IMP	25	100	6.25–100
P. aeruginosa (110)	FK037	6.25	12.5	0.39–>100
	CPR	6.25	25	0.39–>100
	CAZ	3.13	6.25	0.39–>100

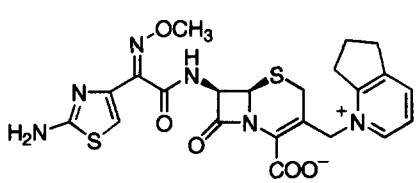
MHz on Varian EM-390 NMR spectrometer, a Hitachi R-90H NMR spectrometer or a Bruker AC200P at 200 MHz. Chemical shifts are reported in ppm from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS in D_2O) or TMS (in $CDCl_3$ and DMSO-d_6) as internal standard.

Synthesis of aminopyrazoles

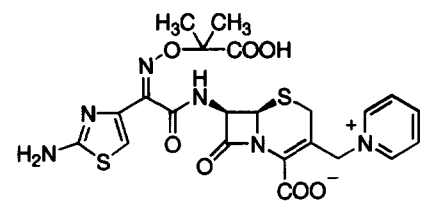
5-Formamido-1-(2-formyloxyethyl)pyrazole (11). A mixture of formic acid (5.93 mL, 0.16 mol) and acetic anhydride (11.1 mL, 0.12 mol) was stirred at room temperature for 30 min. To the reaction mixture was added 5-amino-1-(2-hydroxyethyl)pyrazole (**10**) (5.0 g, 39 mmol) in several portions at 4 °C, and the mixture was then stirred for 1 h at 30–40 °C. The mixture was then added to a mixture of tetrahydrofuran, ethyl acetate and water, and adjusted to pH 6 with sodium bicarbonate. The organic layer was separated, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure to give **11** (5.18 g, 72%). IR (Nujol) cm^{-1} 3180, 1705, 1660; ^1H NMR (DMSO-d_6) δ 4.21–4.61 (4H, m), 6.11 and 6.34 (1H, each d, J = 3 Hz), 7.47 (1H, d, J = 3 Hz), 8.00 (1H, s), 8.33 (1H, s).

1-Ethyl-5-formamidopyrazole (3). Preparation of **3** was carried out by a method similar to the formylation described for synthesis of **11**, using 5-amino-1-ethylpyrazole instead of **10**. IR (Nujol) cm^{-1} 3200, 1690, 1665; ^1H NMR (DMSO-d_6) δ 1.27 (3H, t, J = 7.2 Hz), 4.01 and 4.03 (2H, each q, J = 7.2 Hz), 6.15 and 6.27 (1H, each d, J = 3 Hz), 7.34 and 7.35 (1H, each d, J = 3 Hz), 7.29 (1H, d, J = 3 Hz), 8.26 and 8.34 (1H, each s), 10.34 (1H, s).

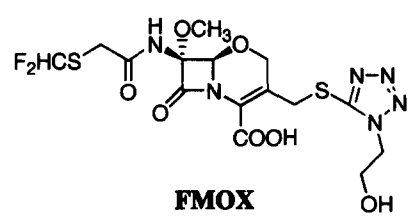
5-Formamido-1-isopropylpyrazole (5). A suspension of 5-amino-4-ethoxycarbonyl-1-isopropylpyrazole (**4**) (103.5 g, 520 mmol) in aqueous 4 N sodium hydroxide solution (260 mL) was refluxed for 2 h. The reaction mixture was then cooled and adjusted to pH 3.5 with concentrated HCl, and the precipitate was collected by filtration to give crude 5-amino-4-carboxy-1-isopropylpyrazole (80.5 g, 91%). IR (Nujol) cm^{-1} 3400, 3300, 1660, 1620, 1540; ^1H NMR (DMSO-d_6) δ 1.29 (6H, d,



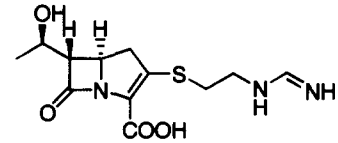
CPR



CAZ



FMOX



IPM

Figure 1.

Table 3. Therapeutic effect of FK037 and reference drugs in mice against MRSA

Organism		MIC (μg/ml)	ED_{50} (mg/kg)
S. aureus 9087 (MRSA)	FK037	12.5	11.8
	CPR	25	47.2
	FMOX	50	192
	IPM	12.5	30.3

J = 6.5 Hz), 4.36–4.50 (1H, m), 6.15 (2H, s), 7.44 (1H, s), 11.7 (1H, s). A suspension of crude 5-amino-4-carboxy-1-isopropylpyrazole (0.25 g, 1.48 mmol) in diphenyl ether (1 mL) was stirred for 2 h at 160–165 °C. The solution was cooled and chromatographed on a column of silica gel. The column was eluted with ethyl acetate. The fractions containing the desired product were collected and evaporated under reduced pressure give 5-amino-1-isopropylpyrazole (0.13 g, 68%). IR (Nujol) cm^{-1} 3300, 3150, 1640, 1540, 1500; ^1H NMR (DMSO-d_6) δ 1.30 (6H, d, J = 7 Hz), 4.35 (1H, m), 4.98 (2H, s), 5.23 (1H, d, J = 3 Hz), 7.00 (1H, d, J = 3 Hz). 5-Amino-1-isopropylpyrazole was formylated by a method similar to that described for **11** to give **5**. ^1H NMR ($CDCl_3$) δ 1.47 and 1.50 (6H, each d, J = 7 Hz), 4.2–4.7 (1H, m), 6.09 and 6.23 (6H, each d, J = 3 Hz), 7.43 (1H, d, J = 3 Hz), 8.28 (1H, s), 8.88 (1H, s).

1-Carboxymethyl-5-formamidopyrazole (8). A suspension of 5-amino-4-ethoxycarbonyl-1-ethoxycarbonylmethylpyrazole (**6**) (95.0 g, 0.39 mol) in aqueous 4 N sodium hydroxide solution (295 mL) was refluxed for 1 h. The reaction mixture was then cooled and adjusted to pH 2.5 with concentrated HCl, and the precipitate was collected by filtration to give 5-amino-4-carboxy-1-carboxymethylpyrazole (76.5 g, 100%). IR (Nujol) cm^{-1} 3450, 3325, 3200, 1650, 1600; ^1H NMR (DMSO-d_6) δ 4.69 (2H, s), 6.24 (2H, s), 7.39 (1H, s). A suspension of 5-amino-4-carboxy-1-carboxymethylpyrazole (75 g, 0.41 mol) in cyclohexanol (225 mL) was then refluxed for 30 min, the solution cooled and the resulting precipitate was collected by filtration to give 5-amino-1-carboxymethylpyrazole (**7**) (46.9 g, 82%). IR (Nujol) cm^{-1} 3320, 3170, 1640, 1590; ^1H NMR (DMSO-d_6) δ 4.61 (2H, s), 5.23 (1H, d, J = 3 Hz), 7.01 (1H, d, J = 3 Hz), 7.16 (2H, br s). 5-Amino-1-carboxymethylpyrazole was formylated by a method similar to that described for **11** to give **8**. IR (Nujol) cm^{-1} 1680, 1580, 1530; ^1H NMR (DMSO-d_6) δ 4.78 (2H, s), 6.25 (1H, s), 7.25 (1H, s), 8.11 (1H, s), 10.6 (1H, s).

1-Carbamoylmethyl-5-formamidopyrazole (9). To a solution of **7** (26 g, 0.18 mol) in methanol (260 mL) was added thionyl chloride (67.6 mL, 0.93 mol) at −10 °C and the solution stirred for 3 h at room temperature. The reaction mixture was evaporated under reduced pressure, and the residue was added to diisopropyl ether and the resulting precipitate was collected by filtration. The powder was added to a mixture of ethyl acetate and water and adjusted to pH 7 with saturated sodium bicarbonate aqueous solution. The organic layer was separated, and dried over anhydrous $MgSO_4$. The filtrate was then concentrated under reduced pressure to give 5-amino-1-methoxycarbonylmethylpyrazole (24.9 g, 87%). IR (Nujol) cm^{-1} 3395, 3180, 1740, 1638, 1555, 1510; ^1H NMR (DMSO-d_6) δ 3.65 (3H, s), 5.16 (2H, s), 5.65 (1H, d, J = 3 Hz), 7.89 (1H, d, J = 3 Hz), 7.56 (2H, br s). To a solution of 5-amino-1-methoxycarbonylmethylpyrazole (8.0 g, 51.6 mmol) in methanol (40 mL) was added 28% ammonium hydroxide (36 mL) and the solution stirred for 1 h at room temperature. The reaction mixture was then evaporated under reduced pressure to give 5-amino-1-carbamoylmethylpyrazole (6.72 g, 93%). IR (Nujol) cm^{-1} 3360, 3080, 1685, 1560; ^1H NMR (DMSO-d_6) δ 4.45 (2H, s), 5.08 (2H, s), 5.25 (1H, d, J = 2 Hz), 7.02 (1H, d, J = 2 Hz), 7.13 (2H, br s). 5-Amino-1-carbamoylmethylpyrazole was formylated by a method similar to that described for **11** to give **9**. IR (Nujol) cm^{-1} 3360, 3270, 3160, 1690, 1640, 1560; ^1H NMR (DMSO-d_6) δ 4.68 (2H, s), 6.31 (1H, s), 7.20 (1H, br s), 7.33 (2H, br s), 8.20 (1H, s), 10.33 (1H, br s).

5-Formamido-1-(2-methoxyethyl)pyrazole (13). To a solution of 5-amino-4-ethoxycarbonyl-1-(2-hydroxyethyl)-pyrazole (**12**) (100 g, 0.50 mol) and triethylamine (105 mL, 0.75 mol) in CH_2Cl_2 (500 mL) was added dropwise methanesulfonyl chloride (42.7 mL, 0.55 mol) at 4 °C and the mixture then stirred for 3 h at room temperature. The reaction mixture was then added to water (250 mL) and adjusted to pH 7. The organic layer was separated, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure to give 5-amino-4-ethoxycarbonyl-1-(2-methylsulfonyloxyethyl)pyrazole (115 g, 83%). IR (Nujol) cm^{-1} 3320, 1650, 1540, 1300, 1160, 1000; ^1H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.0 Hz), 3.08 (3H, s), 4.16 (2H, q, J = 7.0 Hz), 4.26 (2H, t, J = 5.1 Hz), 4.48 (2H, t, J = 5.1 Hz), 6.37 (2H, s), 7.51 (1H, s). To a solution of 5-amino-4-ethoxycarbonyl-1-(2-methylsulfonyloxyethyl)pyrazole (50 g, 0.18 mol) in a mixture of methanol (250 mL) and tetrahydrofuran (300 mL) was added 28% sodium methoxide (42.4 g, 0.22 mol) in methanol at 4 °C and stirred for 2 h at 40 °C. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on a column of silica gel. The column was eluted with ethyl acetate. The fractions containing the desired product were collected and evaporated under reduced pressure to give a mixture of 5-amino-4-ethoxycarbonyl-1-(2-methoxyethyl)pyrazole and 5-amino-4-methoxycarbonyl-1-(2-methoxyethyl)pyrazole (20.3 g). IR (neat) cm^{-1} 3450, 3330, 1680, 1620, 1540, 1110. This mixture of 5-amino-4-ethoxycarbonyl-1-(2-methoxyethyl)pyrazole and 5-amino-4-methoxycarbonyl-1-(2-methoxyethyl)pyrazole was then treated by methods similar to those described for **5** to give **13**. IR (Nujol) cm^{-1} 3250, 1690, 1560, 1110; ^1H NMR (DMSO-d_6) δ 3.23 (3H, s), 3.63 (2H, t, J = 6 Hz), 4.17 (2H, t, J = 6 Hz), 6.23 and 6.28 (1H, each d, J = 3 Hz), 7.32 (1H, d, J = 3 Hz), 8.20 (1H, s).

1-(2-Fluoroethyl)-5-formamidopyrazole (15). A mixture of formic acid (22.3 mL, 0.59 mol) and acetic anhydride (44.5 mL, 0.47 mol) was stirred at room temperature for

1 h. To the reaction mixture was added **10** (30 g, 0.24 mol) in several portions at 4 °C, and the mixture was stirred for 30 min at 4 °C. The mixture was added to ice-cold water and adjusted to pH 10.5 with 40% potassium carbonate aqueous solution and stirred for 30 min at 4 °C. The mixture was then added to a mixture of tetrahydrofuran, ethyl acetate and water. The organic layer was separated, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure to give 5-formamido-1-(2-hydroxyethyl)pyrazole (**14**) (30.8 g, 84%). IR (Nujol) cm^{-1} 3230, 1695, 1570; ^1H NMR (DMSO-d_6) δ 3.62–3.95 (2H, m), 3.98–4.32 (2H, m), 6.22 and 6.36 (1H, each d, J = 3 Hz), 7.42 (1H, d, J = 3 Hz), 8.32 and 8.36 (1H, each s). To a solution of **14** (40 g, 0.26 mol) in tetrahydrofuran (200 mL) was added a solution of hexafluoropropene diethylamine (69 g, 0.31 mol) in tetrahydrofuran (280 mL) and stirred for 5 h at room temperature. The reaction mixture was added to a mixture of tetrahydrofuran and saturated sodium chloride aqueous solution and adjusted to pH 7 with saturated sodium bicarbonate aqueous solution. The organic layer was separated, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was chromatographed on a column of silica gel. The column was eluted with 20% dichloromethane in ethyl acetate. The fractions containing the desired product were collected and evaporated under reduced pressure to give **15** (13.83 g, 34%). IR (Nujol) cm^{-1} 3210, 1660, 1180; ^1H NMR (DMSO-d_6) δ 4.16 (1H, t, J = 7 Hz), 4.3–4.6 (2H, m), 4.95 (1H, t, J = 7 Hz), 6.16 and 6.30 (1H, each d, J = 3 Hz), 7.36 (1H, d, J = 3 Hz), 8.21 and 8.28 (1H, each s), 10.25 (1H, s).

5-Formamido-1-(3-formyloxypropyl)pyrazole (17). To 5-aminopyrazole (**16**) (30 g, 0.36 mol) was added methyl acrylate (43.3 mL, 0.40 mol) and the mixture refluxed for 1 h. The reaction mixture was cooled and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel. The column was eluted with ethyl acetate. The fractions containing the desired product were collected and evaporated under reduced pressure give 5-amino-1-(2-methoxycarbonylethyl)pyrazole (10.7 g, 18%). IR (Nujol) cm^{-1} 3340, 3200, 1720, 1560, 1440; ^1H NMR (DMSO-d_6) δ 2.75 (2H, t, J = 7 Hz), 3.60 (3H, s), 4.06 (2H, t, J = 7 Hz), 5.08 (2H, s), 5.25 (1H, d, J = 2 Hz), 7.00 (1H, d, J = 2 Hz). To a suspension of lithium aluminum hydride (7.20 g, 0.19 mol) in THF (120 mL) was added dropwise a solution of 5-amino-1-(2-methoxycarbonylethyl)pyrazole (10.7 g, 0.063 mol) in THF (80 mL) and stirred for 2 h. The reaction mixture was treated with sodium fluoride (31.9 g, 0.76 mol) and water (10.3 mL, 0.57 mol) and stirred for 1 h at 4 °C. After insoluble material was filtered off, the filtrate was evaporated under reduced pressure to give 5-amino-1-(3-hydroxypropyl)-pyrazole (5.3 g, 60%). IR (Nujol) cm^{-1} 3300, 3150, 1640, 1550, 1070; ^1H NMR (DMSO-d_6) δ 1.81 (2H, quintet, J = 6 Hz), 3.40 (2H, t, J = 6 Hz), 3.89 (2H, t, J = 6 Hz), 4.55 (1H, s), 5.01 (2H, s), 5.24 (1H, d, J = 2 Hz), 6.99 (1H, d, J = 2 Hz). 5-Amino-1-(3-hydroxypropyl)pyrazole was formylated by a method similar to that described for **11** to give **17**. IR (Nujol) cm^{-1} 3200, 1700, 1660, 1550, 1200, 1160; ^1H NMR (DMSO-d_6) δ 2.05 (2H, quintet, J = 6 Hz), 4.07 (4H, t, J = 6 Hz), 6.13 and 6.25 (1H, each d, J = 2 Hz), 7.33 (1H, d, J = 2 Hz), 8.14 (1H, s), 8.21 (1H, s).

Preparation of 3-pyrazoliomethyl cephalosporin derivatives

7β-Amino-3-[3-formamido-2-(3-formyloxypropyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate bistrifluoroacetate (19h). To a suspension of diphenylmethyl 7β-*tert*-butoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (**18**) (5.87 g, 11.4 mmol) and sodium iodide (1.71 g, 11.4 mmol) in DMF (5.9 mL) was added 5-formamido-1-(3-formyloxypropyl)pyrazole (**17**) (6.74 g, 34.2 mmol) and the mixture stirred for 24 h at room temperature. The reaction mixture was added to a mixture of ethyl acetate and water. The organic layer was separated, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure to give diphenylmethyl 7β-*tert*-butoxycarbonylamino-3-[3-formamido-2-(3-formyloxypropyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide (6.60 g, 72%). ^1H NMR (DMSO-d_6) δ 1.43 (9H, s), 2.06 (2H, quintet, J = 6 Hz), 3.46 (2H, br s), 4.06 (2H, t, J = 6 Hz), 4.08 (2H, t, J = 6 Hz), 5.16 (1H, d, J = 5 Hz), 5.40 (2H, s), 5.60 (1H, dd, J = 5 Hz, 8 Hz), 6.89 (1H, s), 7.00 (1H, d, J = 3 Hz), 7.1–7.5 (10H, m), 7.95 (1H, d, J = 8 Hz), 7.97 (1H, s), 8.20 (1H, d, J = 3 Hz), 8.50 (1H, s). To a mixture of diphenylmethyl 7β-*tert*-butoxycarbonylamino-3-[3-formamido-2-(3-formyloxypropyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide (6.50 g, 8.09 mmol) and anisole (6.5 mL) in dichloromethane (19.5 mL) was added dropwise trifluoroacetic acid (13 mL) under ice cooling and the solution stirred for 3 h at the same temperature. The reaction mixture was added to a mixture of diisopropyl ether (100 mL) and ethyl acetate (100 mL) and the resulting precipitate collected by filtration to give **19h** (5.30 g, 100%). IR (Nujol) cm^{-1} 1780, 1700; ^1H NMR (DMSO-d_6) δ 2.06 (2H, quintet, J = 6 Hz), 3.50 (2H, br s), 4.06 (4H, t, J = 6 Hz), 5.23 (2H, m), 5.46 (2H, s), 7.04 (1H, d, J = 3 Hz), 8.12 (1H, s), 8.34 (1H, d, J = 3 Hz), 8.53 (1H, s).

Preparation of **19a–g** was carried out by a method similar to that described for **19h**.

7β-Amino-3-(3-formamido-2-ethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate bistrifluoroacetate (19a). IR (Nujol) cm^{-1} 1780, 1660, 1575; ^1H NMR (DMSO-d_6) δ 1.26 (3H, t, J = 7 Hz), 3.50 (2H, br s), 4.47 (2H, q, J = 7 Hz), 5.26 (2H, m), 5.50 (2H, s), 7.08 (1H, d, J = 3 Hz), 8.37 (1H, d, J = 3 Hz), 8.54 (1H, s).

7β-Amino-3-(3-formamido-2-isopropyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate bistrifluoroacetate (19b). IR (Nujol) cm^{-1} 1780, 1660, 1560; ^1H NMR (DMSO-d_6) δ 1.57 (6H, d, J = 7 Hz), 3.50 (2H, br s), 4.2–4.5 (1H, m), 5.05 (1H, m), 5.20 (2H, s), 5.50 (1H, m), 7.05 (1H, d, J = 3 Hz), 8.26 (1H, d, J = 3 Hz), 8.50 (1H, s).

7β-Amino-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate bistrifluoroacetate (19e). IR (Nujol) cm^{-1} 1780, 1715, 1660; ^1H NMR (DMSO-d_6) δ 3.53 (2H, br s), 4.28–4.56 (2H, m), 4.78–4.99 (2H, m), 5.29 (2H, br s), 5.53 (2H, br s), 7.14 (1H, d, J = 3 Hz), 8.22 (1H, s), 8.46 (1H, d, J = 3 Hz), 8.63 (1H, s).

7β-Amino-3-[3-formamido-2-(2-methoxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate bistrifluoroacetate (19f). IR (Nujol) cm^{-1} 1780, 1670, 1200; ^1H NMR (DMSO-d_6) δ 3.23 (3H, s), 3.56 (2H, br s), 3.65 (2H, t, J = 5.5 Hz), 4.20 (2H, t, J = 5.5 Hz), 5.30 (2H, m), 5.50 (2H, s), 7.10 (1H, d, J = 3 Hz), 8.34 (1H, d, J = 3 Hz), 8.54 (1H, s).

7β-Amino-3-[3-formamido-2-(2-fluoroethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate bistrifluoroacetate (19g). IR (Nujol) cm^{-1} 1790, 1680, 1200; ^1H NMR (DMSO-d_6) δ 3.50 (2H,br s), 4–4.6 (3H, m), 5.00 (1H, m), 5.23 (2H, m), 5.45 (2H, s), 7.10 (1H, d, J = 3 Hz), 8.37 (1H, d, J = 3 Hz), 8.56 (1H, s).

7β-Amino-3-[3-amino-2-(3-hydroxypropyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate trishydrochloride (20h). To a solution of **19h** (5.30 g, 8.31 mmol) in methanol (31.8 mL) was added concentrated HCl (2.65 mL) and then stirred for 3 h at room temperature. The reaction mixture was added dropwise to ethyl acetate (400 mL) and the produced precipitate collected by filtration to give **20h** (2.74 g, 71%). IR (Nujol) cm^{-1} 1780, 1630, 1580; ^1H NMR (DMSO-d_6) δ 1.60–2.00 (2H, m), 3.30–3.60 (4H, m), 3.65–3.83 (2H, m), 5.23 (2H, m), 5.30 (2H, br s), 5.92 (1H, d, J = 3 Hz), 8.14 (1H, d, J = 3 Hz).

Preparation of **20a–g** was carried out by a method similar to that described for **20h**.

7β-Amino-3-(3-amino-2-ethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trishydrochloride (20a). IR (Nujol) cm^{-1} 1780, 1630, 1580; ^1H NMR (DMSO-d_6) δ 1.15 (3H, t, J = 7.3 Hz) 3.30–3.60 (2H, m), 4.19 (2H, q, J = 7.3 Hz), 5.22 (1H, d, J = 5.1 Hz), 5.26 (1H, d, J = 5.1 Hz), 5.30 (2H, s), 5.90 (1H, d, J = 3.3 Hz), 7.72 (2H, s), 8.18 (1H, d, J = 3.3 Hz).

7β-Amino-3-(3-amino-2-isopropyl-1-pyrazolio)methyl-3-cephem-4-carboxylate trishydrochloride (20b). IR (Nujol) cm^{-1} 1780, 1640, 1200; ^1H NMR (DMSO-d_6) δ 1.46 (6H, d, J = 7 Hz), 3.2–3.5 (2H, m), 4.2–4.5 (1H, m), 5.20 (2H, br s), 5.33 (2H, m), 5.90 (1H, d, J = 3 Hz), 7.40 (2H, s), 8.12 (1H, d, J = 3 Hz).

7β-Amino-3-(3-amino-2-carboxymethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate trishydrochloride (20c). ^1H NMR (D_2O+$NaHCO_3$) δ 3.23 and 3.54 (2H, ABq, J = 18 Hz), 4.8–5.6 (6H, m), 6.02 (1H, d, J = 3 Hz), 7.98 (1H, d, J = 3 Hz).

7β-Amino-3-(3-amino-2-carboxymethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate trishydrochloride (20d). IR (Nujol) cm^{-1} 1780, 1680, 1630, 1580; ^1H NMR (D_2O) δ 3.07–3.73 (2H, m), 4.83–5.63 (6H, m), 6.01 (1H, d, J = 3 Hz), 7.98 (1H, d, J = 3 Hz).

7β-Amino-3-[3-amino-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate trishydrochloride (20e). IR (Nujol) cm^{-1} 1770, 1700, 1625; ^1H NMR (DMSO-d_6) δ 3.43 (2H, br s), 3.52–3.88 (2H, m), 4.18–4.48 (2H, m), 5.28 (1H, br s), 5.37 (2H, br s), 5.97 (1H, d, J = 3 Hz), 7.56 (2H, br s), 8.18 (1H, d, J = 3 Hz).

7β-Amino-3-[3-amino-2-(2-methoxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate trishydrochloride (20f). IR (Nujol) cm^{-1} 1780, 1700, 1640; ^1H NMR (DMSO-d_6) δ 3.20 (3H, s), 3.56 (2H, br s), 3.60 (2H, t, J = 5.5 Hz), 4.16 (2H, t, J = 5.5 Hz), 5.23 (2H, s), 5.30 (2H, m), 5.92 (1H, d, J = 3 Hz), 8.10 (1H, d, J = 3 Hz).

7β-Amino-3-(3-amino-2-(2-fluoroethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate trishydrochloride (20g). IR (Nujol) cm^{-1} 1780, 1630, 1580; ^1H NMR (DMSO-d_6) δ 3.3–3.6 (2H, m), 4.0–4.6 (3H, m), 4.7–5.0 (1H, m), 5.0–5.3 (4H, m), 5.93 (1H, d, J = 3 Hz), 7.75 (2H, s), 8.12 (1H, d, J = 3 Hz).

7β-Amino-3-(3-amino-2-ethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate hydrochloride (21a). The crude powder of **20a** (3.88 g, 8.97 mmol) was dissolved in water (15.5 mL) and subjected to column chromatography on a Diaion HP-20. The column was eluted with water. The fractions containing the desired compound were collected; dropwise isopropyl alcohol was added (145 mL) and the solution stirred for 1.5 h at 4 °C. The white crystals which were formed were collected by filtration to give **21a** (1.58 g, 63%). IR (Nujol) cm^{-1} 1780, 1640, 1580; ^1H NMR (D_2O) δ 1.29 (3H, t, J = 7 Hz), 3.21 and 3.46 (2H, ABq, J = 18 Hz), 4.20 (2H, q, J = 7 Hz), 5.10 (1H, d, J = 5 Hz), 5.19 (2H, s), 5.29 (1H, d, J = 5 Hz), 5.95 (1H, d, J = 3 Hz), 7.86 (1H, d, J = 3 Hz).

Preparation of **21e** and **g** was carried out by a method similar to that described for **21a**.

7β-Amino-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate hydrochloride (21e). Anal. calcd for $C_{13}H_{18}ClN_5O_4S \cdot 2H_2O$: C, 37.90; H, 5.38; Cl, 8.60; N, 17.00; found: C, 37.82; H, 5.56; Cl, 8.60; N, 16.73. IR (Nujol) cm^{-1} 1790, 1635–1560; ^1H NMR (DMSO-d_6) δ 3.43–3.77 (2H, m), 4.47–5.07 (4H, m), 5.07 (1H, d, J = 5 Hz), 5.12 and 5.38 (2H, ABq, J = 16 Hz), 5.92 (1H, d, J = 3 Hz), 7.56 (2H, s), 8.11 (1H, d, J = 3 Hz).

7β-Amino-3-[3-amino-2-(2-fluoroethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate hydrochloride (21g). MP 178–183 °C, anal. calcd for $C_{13}H_{17}ClFN_5O_3S \cdot 1.5H_2O$: C, 38.57; H, 4.98; Cl, 8.76; N, 17.30; S, 7.92; found: C, 38.75; H, 4.89; Cl, 8.85; N, 17.10; S, 8.27. IR (Nujol) cm^{-1} 1780, 1635, 1580; ^1H NMR (DMSO-d_6) δ 3.14 and 3.32 (2H, ABq, J = 17.8 Hz), 4.16–4.95 (4H, m), 4.16–4.95 (4H, m), 4.87 (1H, d, J = 5.1 Hz), 5.03 (1H, d, J = 5.1 Hz), 5.15 (2H, br s), 5.91 (1H, d, J = 3.3 Hz), 7.74 (2H, s), 8.13 (1H, d, J = 3 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-ethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (23a). To a suspension of **21a** (0.50 g, 1.26 mmol, bishydrate) in a mixture of DMF (5 mL) and THF (5 mL) was added *N*-trimethylsilylacetamide (1.65 g, 12.6 mmol) and the mixture stirred until dissolution occurred. To this solution was added **22** (0.48 g, 1.52 mmol) and stirring continued for 2 h at 4 °C. The reaction mixture was poured into ethyl acetate (200 mL) and the resulting precipitate collected by filtration and dried under reduced pressure. The powder was dissolved in water and adjusted to pH 2 with satd sodium bicarbonate aq solution and then subjected to column chromatography on Diaion HP-20. The column was washed with water and eluted with 10% aqueous isopropanol. The fractions containing the desired compound were evaporated to remove isopropanol and then lyophilized to give **23a** (0.24 g, 38%). IR (Nujol) cm^{-1} 1760, 1660, 1530; ^1H NMR (D_2O) δ 1.49 (3H, t, J = 7 Hz), 3.13 and 3.36 (2H, ABq, J = 18 Hz), 3.99 (3H, s), 4.20 (2H, q, J = 7 Hz), 5.33 and 5.20 (2H, ABq, J = 15 Hz), 5.21 (1H, d, J = 5 Hz), 5.81 (1H, d, J = 5 Hz), 5.92 (1H, d, J = 3 Hz), 6.96 (1H, s), 7.85 (1H, d, J = 3 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-carbamoylmethyl-1-pyrazolio)-methyl-3-cephem-4-carboxylate (23d). A mixture of DMF (0.20 mL, 2.58 mmol) and phosphoryl chloride (0.24 mL, 2.64 mmol) in ethyl acetate (0.6 mL) was stirred for 20 min at 4 °C. To the mixture were added (*Z*)-2-(2-formylaminothiazol-4-yl)-2-methoxyiminoacetic acid (**24**) (0.50 g, 2.18 mmol) at 4 °C and the reaction mixture was stirred for 45 min at the same temperature. Meanwhile, a mixture of **20d** (1.0 g, 2.17 mmol) and *N*-trimethylsilylacetamide (2.84 g, 21.6 mmol) in CH_2Cl_2 (20 mL) was warmed to make a clear solution. The solution was then cooled to −20 °C and added to the activated acid solution obtained above. The reaction mixture was stirred for 2 h at −10 to 0 °C and then poured into ethyl acetate and the produced precipitate was collected by filtration, and dried under reduced pressure. To a solution of this powder in methanol (12.5 mL) was added concentrated HCl (1 mL) and the solution stirred for 2 h at room temperature and then poured into ethyl acetate (125 mL) and the resulting precipitate collected by filtration. The powder was dissolved in water and adjusted to pH 3 with saturated sodium bicarbonate aqueous solution and then subjected to column chromatography on Diaion HP-20. The column was washed with water and eluted with 5% aq isopropanol. The fractions containing the desired compound were pooled and evaporated to remove isopropanol and then lyophilized to give **23d** (0.21 g, 18%). IR (Nujol) cm^{-1} 1760, 1660–1580, 1520; ^1H NMR (D_2O) δ 3.00 and 3.41 (2H, ABq, J = 18 Hz), 3.98 (3H, s), 4.97 and 5.50 (2H, ABq, J = 18 Hz), 5.10 (2H, s), 5.16 (1H, d, J = 5 Hz), 5.80 (1H, d, J = 5 Hz), 5.97 (1H, d, J = 3 Hz), 6.99 (1H, s), 7.92 (1H, d, J = 3 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate sulfate (23e) (FK037). **21e** (1.53 g, 3.71 mmol) was dissolved in a mixture of water (15.3 mL) and THF (30.6 mL). The solution was adjusted to pH 7 with aq sodium bicarbonate and treated with 1-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminioacetyl]benzotriazol-3-oxide (**25**) (1.0 g, 2.47 mmol) and then maintained at pH 7 with aq sodium bicarbonate for 8 h at room temperature. The reaction mixture was washed with ethyl acetate and the aqueous solution was adjusted to pH 2 with 1 N HCl and washed with ethyl acetate. The aqueous solution was subjected to column chromatography on Diaion HP-20. The column was washed with water and eluted with 10% aqueous isopropanol. Fractions containing the desired compound were evaporated to 13 mL and then treated with 2 M sulfuric acid (1.29 mL) and isopropanol (18 mL) and stirred for 1 h at room temperature. The white crystals that were produced were collected by filtration to give **23e** (0.54 g, 35%). Anal. 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; ^1H NMR (DMSO-d_6) δ 3.21 and 3.33 (2H, ABq, J = 18.1 Hz), 3.50–3.70 (2H, m), 3.82 (3H, s), 4.00–4.20 (1H, m), 4.20–4.40 (1H, m), 5.12 and 5.30 (2H, ABq, J = 15.9 Hz), 5.17 (1H, d, J = 5 Hz), 5.85 (1H, dd, J = 8 and 5 Hz), 5.89 (1H, d, J = 2.8 Hz), 6.73 (1H, s), 7.22 (2H, s), 7.31 (2H, s), 7.97 (1H, d, J =2.8 Hz), 9.51 (1H, d, J = 8 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-isopropyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (23b). **20b** (2.50 g, 5.60 mmol) was dissolved in a mixture of water (25 mL) and THF (50 mL). The solution was adjusted to pH 7 with aq sodium bicarbonate and treated with 1-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetyl]benzotriazol-3-oxide (**25**) (3.29 g, 8.39 mmol) and then maintained at pH 7 with aq sodium bicarbonate for 6 h at 30 °C. The reaction mixture was washed with ethyl acetate and the aq solution was adjusted to pH 2 with 1 N HCl and washed with ethyl acetate. The aq solution was subjected to column chromatography on Diaion HP-20. The column was washed with water and eluted with 15% aq isopropanol. The fractions containing the desired compound were evaporated to remove isopropanol and then lyophilized to give **23b** (0.37 g, 13%). IR (Nujol) cm^{-1} 3300, 1770, 1600, 1040; ^1H NMR (D_2O) δ 1.50 (6H, d, J = 7 Hz), 3.00 and 3.20 (2H, ABq, J = 18 Hz), 4.00 (3H, s), 4.2–4.6 (1H, m), 5.10 (2H, br s), 5.20 (1H, d, J = 5 Hz), 5.77 (1H, d, J = 5 Hz), 5.90 (1H, d, J = 3 Hz), 6.96 (1H, s), 7.80 (1H, d, J = 3 Hz).

Preparation of **23c** and **23f–h** was carried out by a method similar to that described for **23b**.

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-carboxymethyl-1-pyrazolio)methyl-3-cephem-4-carboxylate (23c). 1H NMR (D_2O) δ 3.00 and 3.45 (2H, ABq, J = 18 Hz), 3.78 (3H, s), 4.70 (2H, s), 4.78–5.33 (3H, m), 5.77 (1H, d, J = 5 Hz), 5.99 (1H, d, J = 3 Hz), 7.07 (1H, s), 7.97 (1H, d, J = 3 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-(2-methoxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (23f). IR (Nujol) cm^{-1} 1770, 1610, 1030; ^1H NMR (D_2O) δ 3.10 and 3.46 (2H, ABq, J = 18 Hz), 3.36 (3H, s), 3.73 (2H,t, J =6 Hz), 4.36 (2H, d, J = 6 Hz), 5.12 (2H, br s), 5.22 (1H, d, J = 5 Hz), 5.80 (1H, d, J = 5 Hz), 5.96 (1H, d, J = 3 Hz), 6.97 (1H, s), 7.86 (1H, d, J = 3 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-fluoroethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (23g). IR (Nujol) cm^{-1} 3300, 1760, 1600, 1030; ^1H NMR (D_2O) δ 3.10 and 3.43 (2H, ABq, J = 18 Hz), 4.00 (3H, s), 4.46 (2H,m), 5.00 (2H, m), 5.10 (2H, s), 5.20 (1H, d, J = 5 Hz), 5.80 (1H, d, J = 5 Hz), 5.96 (1H, d, J = 3 Hz), 6.96 (1H, s), 7.89 (1H, d, J = 3 Hz).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-(3-hydroxypropyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (23h). IR (Nujol) cm^{-1} 3300, 1770, 1600, 1030; ^1H NMR (D_2O) δ 1.95 (2H, quintet, J = 6 Hz), 3.15 and 3.35 (2H, ABq, J = 18 Hz), 3.60 (2H, t, J = 6 Hz), 4.00 (3H, s), 4.26 (2H, t, J = 6 Hz), 5.12 (2H, m), 5.20 (1H, d, J = 5 Hz), 5.80 (1H, d, J = 5 Hz), 5.93 (1H, d, J = 3 Hz), 6.96 (1H, s), 7.83 (1H, d, J = 3 Hz).

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