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Orally Active Cephalosporins. Part 3: Synthesis, Structure–Activity Relationships and Oral Absorption of Novel C-3 Heteroarylmethylthio Cephalosporins

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Abstract—A series of 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(heteroarylmethylthio)cephalosporins was designed, synthesized and evaluated for antibacterial activity and oral absorption in rats. Antibacterial activity was markedly influenced by the structure of the heteroaromatic ring moiety. Oral absorption was influenced by the heteroaromatic ring moiety as well as by the arrangement of heteroatoms. Among these compounds, FK041 (**2o**), having a 4-pyrazolylmethylthio moiety, showed potent antibacterial activity against both Gram-positive and Gram-negative bacteria including *Haemophilus influenzae*. Further, it showed higher oral absorption than CFDN.

Introduction

Orally active cephalosporins such as cefixime (CFIX),[1] cefdinir (CFDN) (**1**)[2] and cefditoren pivoxil (CDTR-PI)[3] are of key clinical importance for the treatment of bacterial infections. After we discovered CFDN, further efforts have been made to find oral cephalosporins which have more potent and well balanced antibacterial activity, especially against *Haemophilus influenzae*, an important pathogen that is the cause of severe respiratory infections. In a previous paper,[4] we investigated a series of cephems having a pyridine moiety connected through various spacer moieties at the C-3 position and finally discovered FR86830 (**2a**) (Fig. 1), having a 4-pyridylmethylthio moiety, which demonstrated potent and well-balanced antibacterial activity, including *H. influenzae*, and moderate oral absorption in mice and rats. Therefore, we initiated optimization studies of the heteroaromatic moiety of this type of derivative and to maximize the effectiveness of this methylthio linkage at the C-3 position. We report herein the synthesis, structure–activity relationships and oral absorption of novel 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(heteroarylmethylthio)cephalosporins.

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Chemistry

Scheme 1 outlines the synthesis of the C-3 side chain fragments. The alcohols (**3**) were easily converted to mesylates (**4**) in good yield. Mesylates (**4**) and halides (**5**, **6**) were then treated with thiobenzoic acid in the presence of potassium *tert*-butoxide to afford thiobenzoates (**7**). These thiobenzoates could also be obtained directly from alcohols (**3**) by using the Mitsunobu reaction with thiobenzoic acid. Compound **7d** was then treated with sodium methoxide to afford thiol **8d**, whereas the other thiobenzoates were treated with sodium methoxide in a similar manner, but used in the next reaction without isolation. Other thiols (**8b**,**c**,**e**) were synthesized according to literature procedures.[5–7]

Scheme 2 shows the two methods used for synthesis of 3-(heteroarylmethylthio)cephalosporins (**2**). The preparation of compounds **2c** and **2e** was carried out by Method A and the other derivatives were obtained by Method B. Method A involves introduction of the C-3 side chain in the first step and the C-7 side chain is introduced afterwards. Thus, diphenylmethyl 7β-formamido-3-methanesulfonyloxy-3-cephem-4-carboxylate (**9**)[8] was reacted with the corresponding thiols (**8c**,**e**) in the presence of *N*,*N*-diisopropylethylamine in DMF at −20 °C to give **10c**,**e**. The C-7 formyl group of **10c**,**e** was

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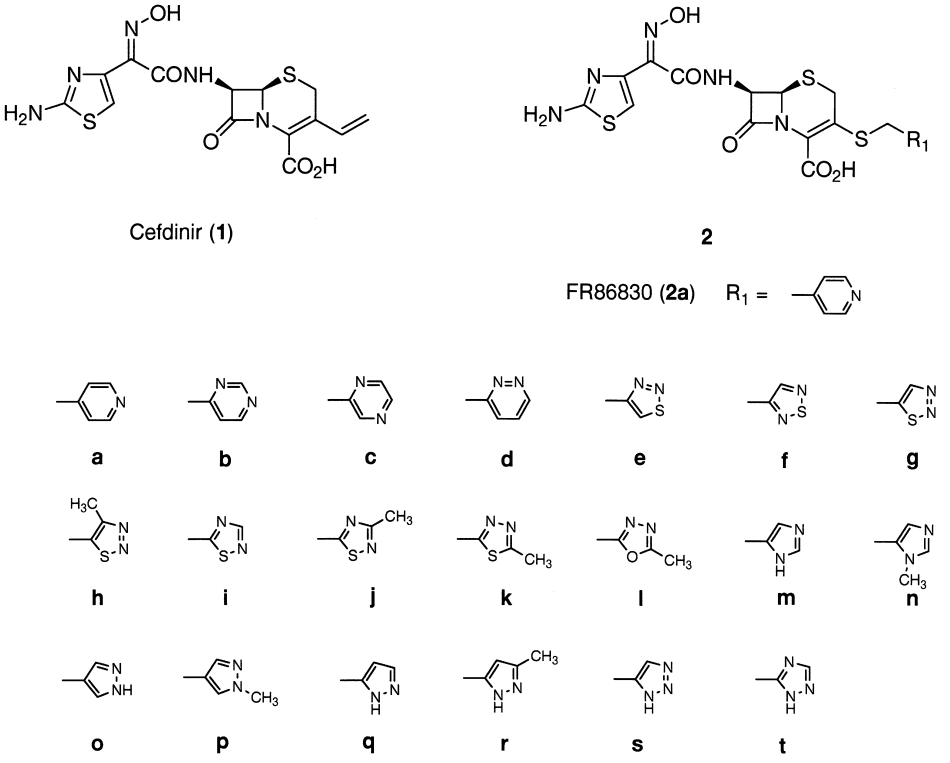
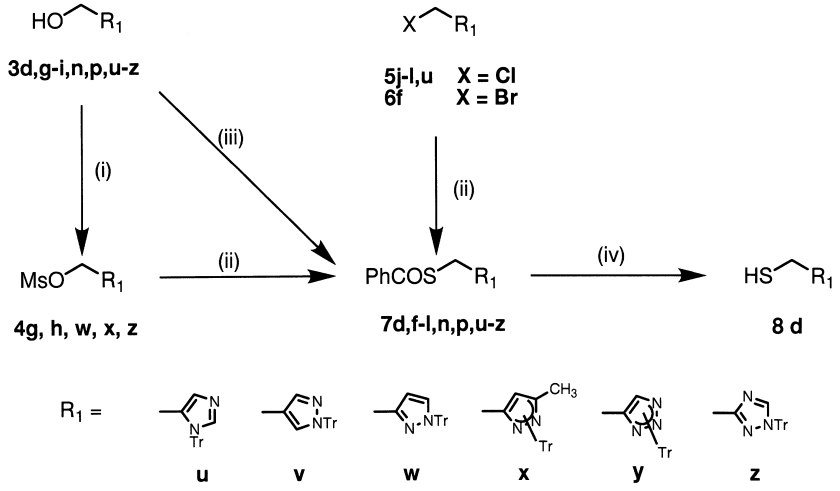


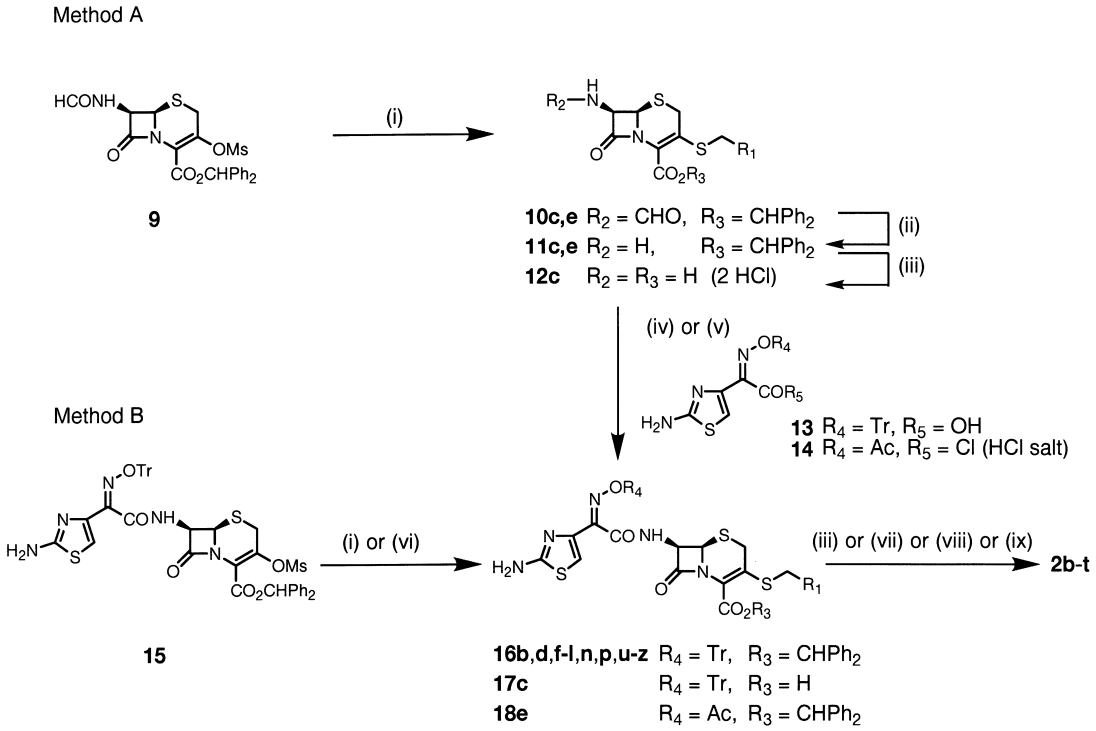
Figure 1. Structures of cefdinir (**1**) and cephalosporins (**2**).



Scheme 1. Reagents: (i) MsCl, Et_3N, CH_2Cl_2; (ii) ^{t}BuOK, PhCOSH, DMF; (iii) PPh_3, diethyl azodicarboxylate (DEAD), PhCOSH, THF; (iv) NaOMe, MeOH.

removed using concentrated hydrochloric acid in MeOH to give **11c**,**e**. Deprotection of **11c** under acidic conditions gave fully deprotected cephem **12c**, which was coupled in the presence of *N*,*O*-bistrimethylsilylacetamide (BSA) with (*Z*)-2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetic acid (**13**),[9] which was activated with methanesulfonyl chloride in the presence of K_2CO_3, to give partially protected cephem **17c**. The trityl group was removed using 90% aqueous formic acid to give **2c**. Treatment of **11e** with BSA, followed by reaction with (*Z*)-2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetyl chloride hydrochloride (**14**),[10] gave **18e**, which was deprotected stepwise under acidic and then basic conditions to give **2e**.

Method B involved key intermediate **15**,[11] in which the C-7 side chain had already been introduced. Thus, compound **15** was reacted with the corresponding thiol or sodium thiolate, generated in situ by methanolysis of the corresponding heteroarylmethyl thiobenzoate, to give **16**. In the reaction of **15** with various sodium thiolates, a low temperature (below $-65\,^\circ C$) was necessary. If a higher temperature was employed, the amount of undesired Δ^2 isomer was significantly increased. In contrast, reaction of **15** with thiols (**b**,**d**) proceeded at $-20\,^\circ C$ and generation of the undesired Δ^2 isomer was not observed. Compounds **16** were deprotected under various conditions to give **2**. Overall, Method B is more expedient since **16** is produced in one step in reasonable yield.



Scheme 2. Reagents: (i) R_1CH_2SH, *N*,*N*-diisopropylethylamine, DMF; (ii) cHCl, MeOH; (iii) cHCl, HCO_2H; (iv) (a) **13**, MsCl, K_2CO_3, DMAc; (b) *N*,*O*-bistrimethylsilylacetamide (BSA), DMF; (v) **14**, BSA, CH_2Cl_2; (vi) **7**, NaOMe, MeOH, THF, DMF; (vii) 90% HCO_2H aq; (viii) (a) TFA, anisole, CH_2Cl_2; (b) $NaHCO_3$, NH_4Cl, MeOH, H_2O; (ix) $AlCl_3$, anisole, CH_3NO_2.

Biological results

The in vitro antibacterial activities of new cephalosporins against Gram-positive and Gram-negative bacteria are shown in Table 1. For comparison, CFDN (**1**) and FR86830 (**2a**) were employed as reference drugs. As can be deduced from these data, all of the synthesized compounds except for **2l** exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacteria and most compounds showed improved antibacterial activity against *H. influenzae* compared with CFDN. Thus, the effect of this methylthio linker moiety on activity towards *H. influenzae* was significant in this series of cephalosporins. Compounds with a six membered heteroaromatic ring (**2b–d**) showed moderate antibacterial activity against *Staphylococcus aureus*, although they were more active against *H. influenzae* than CFDN. Furthermore, antibacterial activity against *S. aureus* and *H. influenzae* was not influenced by the position of the ring nitrogen.

Among compounds having a thiadiazole (**2e–k**) in the side chain, **2e**,**g**,**h** with a 1,2,3-thiadiazole group showed the most potent antibacterial activity against *S. aureus* and potent antibacterial activity against Gram-negative bacteria including *H. influenzae*. In particular, 3-(4-methyl-1,2,3-thiadiazol-5-yl)methylthio cephem **2h** showed the most potent and well balanced antibacterial activity and a similar antibacterial profile to that of FR86830. Comparison of **2e** with **2g** indicated that antibacterial activity was influenced by the heteroatom positions. Comparison of **2e** with **2f**,**i** also indicated that antibacterial activity was influenced by the arrangement of heteroatoms. Introduction of a methyl substituent to thiadiazole resulted in an increase in antibacterial activity against *H. influenzae* (**2g** versus **2h**, **2i** versus **2j**), but slightly decreased antibacterial activity against *Escherichia coli*. Replacement of thiadiazole with oxadiazole dramatically decreased antibacterial activity, especially against *S. aureus* (**2k** versus **2l**). Thus, we abandoned further synthesis of compounds having an oxadiazole in the side chain since they were predicted to show relatively weak antibacterial activity. Compounds having an imidazole (**2m**,**n**) showed similar antibacterial activity to CFDN. Introduction of a methyl substituent at the C-1 position of imidazole had only a marginal effect on antibacterial activity. Among compounds having a pyrazole moiety (**2o–r**), **2o** showed the most potent and well balanced antibacterial activity, although it was slightly less active against *S. aureus* and *H. influenzae* compared with FR86830. Comparison of **2o** with **2q** indicated that antibacterial activity was influenced by the position of pyrazole nitrogen. Introduction of a methyl substituent (**2p**) to the C-1 position of the pyrazole in **2o** resulted in decreased antibacterial activity against all tested strains except for *Enterococcus faecalis*. In contrast, introduction of a methyl substituent (**2r**) to the C-3 position of pyrazole in **2q** resulted in increased antibacterial activity against Gram-positive bacteria and decreased antibacterial activity against *Morachisella catarrhalis*, *H. influenzae* and *E. coli*. Thus, introduction of a methyl substituent to the pyrazole moiety appears to be an unfavorable modification in terms of activity against Gram-negative bacteria. Among compounds having a triazole moiety (**2s** and **2t**), the antibacterial activity of **2s** is clearly superior to that of **2t**, except for *M. catarrhalis*. This result also indicates that the arrangement of the heteroatoms plays an important role in antibacterial activity.

Table 1. Antibacterial activity of cephaosporins[a]

Drugs	MIC[b] (μg/mL)					
	Staphylococcus aureus (MSSA) (9)	*Enterococcus faecalis* (9)	*Morachisella catarrhalis* (9)	*Haemophilus influenzae* (20)	*Escherichia coli* (4)	*Klebsiella pneunzoniae* (9)
2b	0.49	14.6	0.114	0.26	0.066	0.042
2c	0.57	10.7	0.113	0.27	0.195	0.117
2d	0.49	21	N.T.[d]	0.27	N.T.	N.T.
2e	0.155	5.8	0.061	0.146	0.061	0.045
2f	0.31	7.3	0.133	0.33	0.27	0.167
2g	0.195	3.6	0.123	0.124	0.053	0.036
2h	0.167	3.1	0.114	0.069	0.072	0.049
2i	0.31	6.8	0.144	0.23	0.084	N.T.
2j	0.422	7.3	0.181	0.112	0.211	0.167
2k	0.67	9.2	0.181	0.2	0.114	0.078
2l[c]	1.31	3.13	N.T.	N.T.	0.552	1.24
2m	0.31	17.0	0.072	0.34	0.049	N.T.
2n	0.422	6.25	0.090	0.419	0.062	N.T.
2o (FK041)	0.23	7.9	0.072	0.129	0.033	0.031
2p	0.72	6.3	0.21	0.25	0.25	0.181
2q	0.49	8.5	0.105	0.31	0.23	N.T.
2r	0.067	6.8	0.155	0.35	0.46	0.33
2s	0.33	10.7	0.106	0.188	0.049	N.T.
2t	0.98	14.6	0.105	0.36	0.090	N.T.
CFDN (1)[e]	0.33	13.5	0.072	0.41	0.133	0.062
FR86830 (2a)	0.14	5.8	0.11	0.067	0.061	0.041

[a]Müller–Hinton agar; 10^{-2}, stamp method; 37 °C, 20 h.
[b]Mean MIC.
[c]*S. aureus* (MSSA) (4); *E. faecalis* 115; *E. coli*; *K. pneumoniae* (3).
[d]N.T., not tested.
[e]CFDN, cefdinir.

Among all compounds prepared, **2e**,**g**,**h**,**o** exhibited potent and well balanced activity against both Gram-positive and Gram-negative bacteria. In particular, **2h** was 7-fold more active against *H. influenzae* than CFDN. Further, compared with FR86830 (**2a**), **2h** exhibited equal antibacterial activity against tested strains. Compound **2o**, with a pyrazole moiety, also showed improved antibacterial activity against most tested strains, including *H. influenzae*, compared to CFDN. Compared with FR86830, **2o** showed slightly less activity against *S. aureus*, *E. faecalis* and *H. influenzae*, but it exhibited superior antibacterial activity against the other tested strains. Thus, these compounds are highly attractive in terms of antibacterial activity.

The urinary and biliary recoveries of these compounds after oral administration to rats are shown in Table 2. Among these compounds, **2o** and **2q**–**s** showed high oral absorption although most of the other compounds only showed moderate oral absorption. In particular, **2o** (FK041) exhibited extraordinarily high and improved oral absorption compared with CFDN. Regarding the C-3 pyrazole derivatives, comparison of **2o** with **2q** indicated that oral absorption was influenced by the position of ring nitrogen. Further, decreased oral absorption for **2p** suggested the possibility that a hydrogen bond donor in the C-3 pyrazole moiety was required for high oral absorption. Results from comparison of six membered ring derivatives (**2b**–**d**), thiadiazole derivatives (**2e**–**g**,**i**) and triazole derivatives (**2s**,**t**) indicated that oral absorption is influenced by the arrangement of heteroatoms. Further, analogues having a methyl substituted heteroaromatic moiety such as **2h**,**j**,**n**,**p**,**r** showed decreased oral absorption without exception compared with the corresponding parent compounds (**2g**,**i**,**m**,**o**,**q**). Thus, introduction of a methyl substituent to the C-3 heteroaromatic ring appears to be unfavorable for oral absorption.

Table 2. 24-Hour urinary and biliary recovery of cephalosporins after oral administration (20 mg/kg) to rats

Drugs	Recovery (%)	
	Urine	Bile
2b	5.62	1.12
2c	12.0	5.12
2d	10.7	1.1
2e	10.4	2.05
2f[a]	7.94	7.08
2g	8.31	2.13
2h	4.43	3.02
2i	7.66	1.38
2j	4.40	1.60
2k	3.54	1.52
2l	5.79	0.92
2m	9.60	0.46
2n	3.45	1.90
2o (FK041)	42.9	6.81
2p	7.41	3.15
2q	28.7	6.43
2r	9.19	9.58
2s	15.3	1.62
2t	6.49	0.31
CFDN (1)	32.5	1.40
FR86830 (2a)	4.91	4.80

[a]Oral administration (20 mg/kg) to mice.

Although four compounds (**2e**,**g**,**h**,**o**) showed attractive antibacterial activity, only **2o** exhibited higher oral absorption than CFDN. Thus, we selected **2o** (FK041) as

an optimal compound with regards to both antibacterial activity and oral absorption.

FK041 was tested against a wide variety of clinical isolates of bacteria and exhibited broad spectrum activity.[11] FK041 also showed high in vivo efficacy, good oral absorption and pharmacokinetics in other animals.[12] Since further studies of antibacterial activity, pharmacokinetics and in vivo efficacy displayed good results, FK041 is now under clinical development.

Conclusions

Based on the parent 3-(4-pyridylmethylthio)cephalosporin (**2a**; FR86830), new analogues optimized and modified at the C-3 heteroaromatic ring were synthesized, and we thereby discovered FK041 (**2o**), having a 4-pyrazolylmethylthio moiety at the C-3 position, which exhibited potent and well balanced antibacterial activity against both Gram-positive and Gram-negative bacteria, including *H. influenzae*. Further, oral absorption of FK041 was distinctly higher than that of CFDN in rats. Our further studies to optimize the absorption and activity of compounds derived from FK041 will be presented in subsequent papers.

Experimental

IR spectra were recorded on a Hitachi 260-10 spectrophotometer. NMR spectra were recorded at 90 MHz on a Varian EM-390 NMR spectrometer, a Hitachi R-90H NMR spectrometer or a Bruker AC200P at 200 MHz. Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra were obtained on a Hitachi Model M-80 mass spectrometer (EIMS), a Finnigan MAT TSQ-70 (FABMS) and elemental analyses were carried out on a Perkin–Elmer 2400 CHN Elemental Analyzer.

5-Methanesulfonyloxymethyl-4-methyl-1,2,3-thiadiazole (4h). Under an N_2 atmosphere, Et_3N (10 mL, 72.6 mmol) and methanesulfonyl chloride (4.1 mL, 53 mmol) were added successively to a solution of 5-hydroxymethyl-4-methyl-1,2,3-thiadiazole (**3h**) (6.2 g, 48.2 mmol) in CH_2Cl_2 (60 mL) at −30 °C. After stirring for 30 min, the mixture was poured into a mixture of water and CH_2Cl_2. After the aqueous layer was separated, the organic layer was washed with saturated $NaHCO_3$, diluted HCl and brine and dried over $MgSO_4$. Evaporation of the solvent gave **4h**. Colorless oil. Yield: 9.8 g (98%). ^{1}H NMR ($CDCl_3$) δ 2.76 (3H, s), 3.06 (3H, s), 5.51 (2H, s).

The following compounds were obtained using a method similar to that used for **4h**.

5-Methanesulfonyloxymethyl-1,2,3-thiadiazole (4g). Colorless oil. Yield: 6.3 g (70%). ^{1}H NMR ($CDCl_3$) δ 3.09 (3H, s), 5.63 (2H, s), 8.76 (1H, s).

3 - Methanesulfonyloxymethyl - 1 - tritylpyrazde (4w). Amorphous solid. Yield: 1.9 g (91%). ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 5.27 (2H, s), 6.35 (1H, d, $J = 2.5$ Hz), 7.07–7.40 (15H, m), 7.37 (1H, d, $J = 2.5$ Hz).

3-Methanesulfonyloxymethyl-(1- and 2-trityl)-5-methylpyrazole (4x). Amorphous solid. Yield: 9.1 g (90%). IR (KBr) cm^{-1} 1550, 1492; ^{1}H NMR (DMSO-d_6) δ 1.98 and 2.28 (total 3H, s), 2.92 and 3.10 (total 3H, s), 5.75 (2H, s), 6.35–6.40 (1H, m), 7.00–7.36 (10H, m).

3-Methanesulfonyloxymethyl-1-trityl-1,2,4-triazole (4z). Amorphous solid. Yield: 2.8 g (55%). IR (KBr) cm^{-1} 1493, 1450; ^{1}H NMR ($CDCl_3$) δ 3.16 (3H, s), 5.29 (2H, s), 7.00–7.36 (15H, m), 8.27 (1H, s).

5 - Benzoylthiomethyl - 4 - methyl - 1,2,3 - thiadiazole (7h). Under an N_2 atmosphere, thiobenzoic acid (6.6 mL, 56.5 mmol) was added dropwise to a solution of *tert*-BuOK (6.1 g, 54.1 mmol) in DMF (80 mL) at 0 °C. After stirring for 10 min, a solution of **4h** (9.8 g, 47.0 mmol) in DMF (30 mL) was added slowly to the mixture at the same temperature. The whole mixture was stirred at 80 °C for 2 h and poured into a mixture of ethyl acetate and aqueous $NaHCO_3$. The aqueous layer was separated and the organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with *n*-hexane–ethyl acetate to give **7h**. Amorphous solid. Yield: 7.5 g (64%). IR (KBr) cm^{-1} 1670, 1587; ^{1}H NMR ($CDCl_3$) δ 2.73 (3H, s), 4.47 (2H, s), 7.42–7.65 (3H, m), 7.90–7.97 (2H, m). ESIMS *m*/*e* 273 [$(M + Na)^+$].

The following compounds were obtained using a method similar to that used for **7h**.

3-Benzoylthiomethyl-1,2,5-thiadiazole (7f). Amorphous solid. Yield: 46.5 g (20%). IR (KBr) cm^{-1} 1725, 1671, 1662, 1589; ^{1}H NMR ($CDCl_3$) δ 4.58 (2H, s), 7.40–7.70 (3H, m), 7.90–8.00 (2H, m), 8.61 (1H, s). ESIMS *m*/*e* 259 [$(M + Na)^+$].

5-Benzoylthioxymethyl-1,2,3-thiadiazole (7g). Amorphous solid. Yield: 3.1 g (87%). IR (KBr) cm^{-1} 1654, 1592; ^{1}H NMR ($CDCl_3$) δ 4.61 (2H, s), 7.44–7.67 (3H, m), 7.92–7.98 (2H, m), 8.68 (1H, s). EIMS *m*/*e* 236 [M^+].

3 - Methyl - 5 - benzoylthimethyl - 1,2,4 - thiadiazole (7j). Amorphous solid. Yield: 3.9 g (77%). IR (KBr) cm^{-1} 1673, 1583; ^{1}H NMR (DMSO-d_6) δ 2.56 (3H, s), 4.79 (2H, s), 7.55–7.80 (3H, m), 7.94–8.00 (2H, m). EIMS *m*/*e* 251 [$(M + H)^+$].

2 - Methyl - 5 - benzoylthiomethyl - 1,3,4 - thiadiazole (7k). Amorphous solid. Yield: 4.0 g (90%). IR (KBr) cm^{-1} 1655, 1585; ^{1}H NMR (DMSO-d_6) δ 2.67 (3H, s), 4.74 (2H, s), 7.40–7.65 (2H, m), 7.68–7.85 (1H, m), 7.90–8.00 (2H, m). EIMS *m*/*e* 250 [M^+].

2 - Methyl - 5 - benzoylthiomethyl - 1,3,4 - oxadiazole (7l). Amorphous solid. Yield: 4.2 g (90%). IR (KBr) cm^{-1} 1666, 1585; ^{1}H NMR (DMSO-d_6) δ 2.48 (3H, s), 4.59

(2H, s), 7.55–7.79 (3H, m), 7.94–8.00 (2H, m). EIMS *m/e* 234 [M^+].

1-Trityl-4-benzoylthiomethylimidazole (7u). Amorphous solid. Yield: 13.9 g (75%). IR (KBr) cm^{-1} 1655, 1594; ^1H NMR (DMSO-d_6) δ 4.20 (2H, s), 6.89 (1H, s), 7.04–7.72 (19H, m), 7.87–7.91 (2H, m). FABMS *m/e* 461 [$(M+H)^+$].

1-Trityl-3-(benzoylthiomethyl)pyrazole (7w). Amorphous solid. Yield: 7.6 g (67%). IR (KBr) cm^{-1} 1660, 1587, 1486; ^1H NMR (DMSO-d_6) δ 4.29 (2H, s), 6.27 (1H, d, J= 2.5 Hz), 7.00–7.95 (21H, m). ESIMS *m/e* 483 [$(M+Na)^+$].

4-Benzoylthiomethyl-(1- and 2-trityl)-3-methylpyrazole (7x). Amorphous solid. Yield: 9.1 g (92%). IR (KBr) cm^{-1} 1735, 1666; ^1H NMR (DMSO-d_6) δ 1.40 (3H, s), 4.19 (2H, s), 6.17 and 6.21 (total 1H, s), 7.0–7.95 (20H, m). FABMS *m/e* 475 [$(M+H)^+$].

3-Benzoylthiomethyl-1-trityl-1,2,4-triazole (7z). Amorphous solid. Yield: 2.6 g (85%). IR (KBr) cm^{-1} 1668, 1446; ^1H NMR (DMSO-d_6) δ 4.39 (2H, s), 7.02–7.07 (5H, m), 7.36–7.40 (10H, m), 7.52–8.05 (6H, m).

4-(Benzoylthiomethyl)-1-methyl-pyrazole (7p). Under an N_2 atmosphere, triphenylphosphine (78.7 g, 300 mmol) and diethyl azodicarboxylate (47.2 mL, 300 mmol) was added successively to a solution of **3p** (22.4 g, 200 mmol) in THF (250 mL) at 0 °C. After stirring for 1 h at the same temperature, thiobenzoic acid (42.3 mL, 360 mmol) was added dropwise to the mixture. Stirring was continued for 30 min and the mixture was poured into a mixture of water and ethyl acetate. The pH was adjusted to 9.5 with 30% aqueous K_2CO_3 and the aqueous layer was separated. The organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with *n*-hexane–ethyl acetate to afford **7p**. Amorphous solid. Yield: 18.3 g (39%). ^1H NMR (DMSO-d_6) δ 3.84 (3H, s), 4.14 (2H, s), 7.27–7.62 (5H, m), 7.92–7.98 (2H, m).

The following compounds were obtained using a method similar to that used for **7p**.

3-(Benzoylthiomethyl)pyridazine (7d). Amorphous solid. Yield: 10.6 g (45%). IR (KBr) cm^{-1} 1660, 1585; ^1H NMR (DMSO-d_6) δ 4.65 (2H, s), 7.5–7.9 (5H, m), 7.9–8.0 (2H, m), 9.1–9.2 (1H, m).

5-Benzoylthiomethyl-1,2,4-thiadiazole (7i). Amorphous solid. Yield: 3.3 g (68%). IR (KBr) cm^{-1} 1732, 1670; ^1H NMR ($CDCl_3$) δ 4.69 (2H, s), 7.40–7.80 (3H, m), 7.95–8.10 (2H, m), 8.60 (1H, s).

5-Benzoylthiomethyl-1-methyl-imidazole (7n). Amorphous solid. Yield: 1.0 g (19%). IR (KBr) cm^{-1} 1741, 1662, 1603; ^1H NMR (DMSO-d_6) δ 3.62 (3H, s), 4.40 (2H, s), 6.91 (1H, s), 7.52–7.74 (4H, m), 7.73–7.94 (2H, m).

4-Benzoylthiomethyl-1-(trityl)pyrazole (7v). Amorphous solid. Yield: 2.0 g (39%). IR (KBr) cm^{-1} 1708, 1654, 1596; ^1H NMR (DMSO-d_6) δ 4.15 (2H, s), 7.05–7.65 (20H, m), 7.90–8.00 (2H, m). FABMS *m/e* 461 [$(M+H)^+$].

4-Benzoylthiomethyl-1-trityl-1,2,3-triazole (7y). Amorphous solid. Yield: 0.64 g (48%). IR (KBr) cm^{-1} 1714, 1655; ^1H NMR (DMSO-d_6) δ 4.40 (2H, s), 6.99–7.03 (6H, m), 7.30–7.92 (15H, m). ESIMS *m/e* 484 [$(M+Na)^+$].

3-(Mercaptomethyl)pyridazine (8d). Under an N_2 atmosphere, 28% sodium methoxide in MeOH (9.6 mL, 46.0 mmol) was added to a solution of **7d** (1.06 g, 46.0 mmol) in CH_3CN (1 mL) at 5 °C. The mixture was stirred for 30 min at the same temperature and the solvent was evaporated in vacuo. The residue was diluted with a mixture of ice–water and ethyl acetate and neutralized by addition of 1N HCl. After the aqueous layer was separated, the organic layer was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave **8d**. Amorphous solid. Yield: 420 mg (34%). IR (KBr) cm^{-1} 3184, 2534, 1581; ^1H NMR (DMSO-d_6) δ 3.19 (1H, t, J=8 Hz), 4.00 (2H, d, J=8 Hz), 7.4–7.8 (2H, m), 9.1–9.2 (1H, m).

Method A: reaction of 9 with thiols

Diphenylmethyl 7β-formamido-3-[(pyrazin-2-yl)methylthio]-3-cephem-4-carboxylate (10c). To a solution of diphenylmethyl 7β-formamido-3-methanesulfonyloxy-3-cephem-4-carboxylate (**9**) (2.7 g, 5 mmol) in DMF (27 mL) was added 2-(mercaptomethyl)pyrazine (631 mg, 5 mmol) at −20 °C, followed by dropwise addition of *N*,*N*-diisopropylethylamine (0.9 mL, 5 mmol). The mixture was stirred for 45 min and poured into a mixture of ice–water (400 mL) and ethyl acetate (400 mL). The aqueous layer was separated and the organic layer was washed with water, brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with CH_2Cl_2–MeOH to give **10c**. Amorphous solid. Yield: 2.2 g (84%). IR (KBr) cm^{-1} 1782, 1692, 1680; ^1H NMR (DMSO-d_6) δ 3.96 (2H, s), 4.36 (2H, s), 5.19 (1H, d, J=5 Hz), 5.77 (1H, dd, J=9, 5 Hz), 6.83 (1H, s), 7.2–7.5 (10H, m), 8.18 (1H, s), 8.5-8.7 (3H, m), 9.14 (1H, d, J=9 Hz).

Compound **10e** was obtained using a method similar to that used for **10c**.

Diphenylmethyl 7β-formamido-3-[(1,2,3-thiadiazol-4-yl)-methylthio]-3-cephem-4-carboxylate (10e). Amorphous solid. Yield: 7.43 g (73%). IR (KBr) cm^{-1} 1760, 1680, 1645, 1555; ^1H NMR (DMSO-d_6) δ 3.99 (2H, s), 4.69 (2H, s), 5.20 (1H, d, J=4.7 Hz), 5.77 (1H, d, J=9.3, 4.7 Hz), 6.83 (1H, s), 7.2–7.5 (10H, m), 8.18 (1H, s), 9.02 (1H, s), 9.14 (1H, d, J=9.3 Hz).

Diphenylmethyl 7β-amino-3-[(pyrazin-2-yl)methylthio]-3-cephem-4-carboxylate (11c). To a solution of **10c** (28.5 g, 55.0 mmol) in MeOH (570 mL) was added dropwise concd HCl (45.8 mL) with ice cooling and the mixture was stirred at room temperature for 2 h. The mixture was poured into a mixture of ethyl acetate (1 L) and ice water (1 L) and adjusted to pH 6.5 by addition

of $NaHCO_3$. The aqueous layer was separated and the organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with CH_2Cl_2–MeOH to give **11c**. Amorphous solid. Yield: 21.0 g (78%). IR (KBr) cm^{-1} 1774, 1701; ^1H NMR (DMSO-d_6) δ 2.44 (2H, s), 3.92 (2H, s), 4.28 (2H, s), 4.80 (1H, d, $J=5$ Hz), 5.02 (1H, d, $J=5$ Hz), 6.80 (1H, s), 7.2–7.5 (10H, m), 8.5–8.6 (3H, m).

Compound **11e** was obtained using a method similar to that used for **11c**.

Diphenylmethyl 7β-amino-3-[(1,2,3-thiadiazol-4-yl)methylthio]-3-cephem-4-carboxylate (11e). Amorphous solid. Yield: 5.7 g (82%). IR (Nujol) cm^{-1} 2900, 2850, 1765; ^1H NMR (DMSO-d_6) δ 2.41 (2H, br s), 3.95 (2H, br s), 4.59 and 4.66 (2H, ABq, $J=14.3$ Hz), 4.81 (1H, d, $J=5.0$ Hz), 5.03 (1H, d, $J=5.0$ Hz), 6.81 (1H, s), 7.2–7.5 (10H, m), 8.99 (1H, s).

7β-Amino-3-[(pyrazin-2-yl)methylthio]-3-cephem-4-carboxylic acid dihydrochloride (12c). To a solution of diphenylmethyl 7β-amino-3-[(pyrazin-2-yl)methylthio]-3-cephem-4-carboxylate (4.91 g, 10 mmol) in formic acid (19.6 mL) was added concd HCl (2.5 mL, 30 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into a mixture of ethyl acetate (140 mL) and acetone (70 mL). The resulting precipitate was collected by filtration and dried in vacuo to give **12c**. Amorphous solid. Yield: 3.5 g (87%). IR (Nujol) cm^{-1} 1774, 1701; ^1H NMR (DMSO-d_6) δ 2.44 (2H, s), 3.92 (2H, s), 4.28 (2H, s), 4.80 (1H, d, $J=5$ Hz), 5.02 (1H, d, $J=5$ Hz), 6.80 (1H, s), 7.2–7.5 (10H, m), 8.5–8.6 (3H, m).

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(pyrazin-2-yl)methylthio]-3-cephem-4-carboxylic acid (17c). To a mixture of (*Z*)-2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetic acid (**13**) (3.70 g, 8.61 mmol) in DMAc (37 mL) were added K_2CO_3 (1.19 g, 8.61 mmol) and methanesulfonyl chloride (1.33 mL, 17.2 mmol) at 5 °C. The mixture was stirred for 30 min at the same temperature. In another flask, to a solution of **12c** (3.42 g, 8.61 mmol) in DMF (19.3 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (14.9 mL, 60.3 mmol) at 5 °C and stirred for 20 min. To this solution was added the above mentioned solution of the activated acid. The mixture was stirred at 5 °C for 1 h and poured into 20% aqueous NaCl (350 mL). The resulting precipitate was collected by filtration, washed with water and dried in vacuo to give **17c**. Amorphous solid. Yield: 6.98 g (quant). IR (KBr) cm^{-1} 3488, 1778, 1665, 1626; ^1H NMR (DMSO-d_6) δ 3.25 and 3.87 (2H, ABq, $J=18$ Hz), 4.25 (2H, s), 5.18 (1H, d, $J=5$ Hz), 5.80 (1H, dd, $J=8$, 5 Hz), 6.65 (1H, s), 6.88 (1H, s), 7.1–7.4 (17H, m), 8.4–8.6 (3H, m), 9.88 (1H, d, $J=8$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(acetoxyimino)acetamido]-3-[(1,2,3-thiadiazol-4-yl)methylthio]-3-cephem-4-carboxylate (18e). 11e (2.0 g, 4.03 mmol) was dissolved in CH_2Cl_2 (40 mL) by addition of BSA (1.64 g, 8.06 mmol). To the resulting solution was added **14** (1.4 g, 4.84 mmol) at 5 °C and the mixture was stirred at the same temperature for 2 h and at room temperature for 1 h. The mixture was diluted with water and adjusted to pH 7 by addition of 1N aqueous NaOH. The aqueous layer was separated and the organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated in vacuo to give **18e**. Amorphous solid. Yield: 2.3 g (81%). ^1H NMR (DMSO-d_6) δ 2.19 (3H, s), 3.3–3.4 (2H, m), 4.71 (2H, s), 5.28 (1H, d, $J=4.7$ Hz), 5.86 (1H, dd, $J=8.2$, 4.7 Hz), 6.83 (1H, s), 6.88 (1H, s), 7.2–7.5 (12H, m), 9.03 (1H, s), 9.94 (1H, d, $J=8.2$ Hz).

Method B: reaction of 15 with thiol

Compounds **16b**,**d** were obtained using a method similar to that used for **10c** except for using **15** instead of **9**.

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(pyrimidin-4-yl)methylthio]-3-cephem-4-carboxylate (16b). Amorphous solid. Yield: 1.6 g (74%). IR (KBr) cm^{-1} 1786, 1686; ^1H NMR (DMSO-d_6) δ 3.90 (2H, s), 4.31 (2H, s), 5.30 (1H, d, $J=5$ Hz), 5.94 (1H, dd, $J=8$, 5 Hz), 6.68 (1H, s), 6.88 (1H, s), 7.2–7.6 (18H, m), 8.73 (1H, d, $J=5$ Hz), 9.09 (1H, s), 9.88 (1H, d, $J=8$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(pyridazin-3-yl)methylthio]-3-cephem-4-carboxylate (16d). Amorphous solid. Yield: 1.6 g (61%). IR (KBr) cm^{-1} 1784, 1728, 1684; ^1H NMR (DMSO-d_6) δ 3.96 (2H, s), 4.51 (2H, s), 5.29 (1H, d, $J=5$ Hz), 5.95 (1H, dd, $J=8$, 5 Hz), 6.68 (1H, s), 6.87 (1H, s), 7.1–7.7 (29H, m), 7.66 (2H, d, $J=3$ Hz), 9.13 (1H, t, $J=3$ Hz), 9.92 (1H, d, $J=8$ Hz).

Method B: reaction of 15 with sodium thiolate

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1-methylpyrazol-4-yl)methylthio]-3-cephem-4-carboxylate (16p). Under an N_2 atmosphere, 4.8N sodium methoxide in MeOH (1.35 mL, 6.5 mmol) was added slowly to a solution of 1-methyl-4-benzoylthiomethylpyrazole (1.50 g, 6.5 mmol) in a mixture of THF (6 mL) and DMF (18 mL) at 0 °C. The mixture was stirred for 1 h and cooled to −78 °C with a dry ice–acetone bath. In another flask, **15** (4.4 g, 5 mmol) was dissolved in a mixture of THF (15 mL) and DMF (25 mL) and cooled with a dry ice–acetone bath. To this solution, the above sodium thiolate generated in situ was added dropwise while the temperature was maintained under −65 °C. After stirring for 1 h, the reaction was quenched with 10% aqueous HCl. The mixture was poured into a mixture of water and ethyl acetate and the aqueous layer was separated. The organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with CH_2Cl_2–acetone to afford **16p**. Amorphous solid. Yield: 2.2 g (48%). IR (KBr) cm^{-1} 1785, 1729, 1685; ^1H NMR (DMSO-d_6) δ 3.71 (3H, s), 3.87 (2H, s), 4.05 (2H, d, $J=4.3$ Hz), 5.31 (1H, d, $J=4.6$ Hz), 5.93 (1H, dd, $J=8.6$, 4.6 Hz), 6.70 (1H,s), 6.83 (1H, d, $J=2.4$ Hz), 6.86 (1H, s), 7.19–7.59 (26H, m), 9.88 (1H, d, $J=8.6$ Hz).

The following compounds were obtained using a method similar to that used for **16p**.

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1,2,5-thiadiazol-3-yl)methylthio]-3-cephem-4-carboxylate (16f). Amorphous solid. Yield: 2.3 g (50%). IR (KBr) cm^{-1} 1783, 1722; ^1H NMR (DMSO-d_6) δ 4.19 and 4.42 (2H, ABq, $J=14.4$ Hz), 4.56 (2H, s), 5.31 (1H, d, $J=4.7$ Hz), 5.95 (1H, dd, $J=8.5$, 4.7 Hz), 6.68 (1H, s), 6.88 (1H, s), 7.15–7.60 (25H, m), 8.74 (1H, s), 9.94 (1H, d, $J=8.5$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1,2,3-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylate (16g). Amorphous solid. Yield: 4.2 g (92%). IR (KBr) cm^{-1} 1785, 1724; ^1H NMR (DMSO-d_6) δ 3.84 (2H, d, $J=4.6$ Hz), 4.68 (2H, s), 5.33 (1H, d, $J=4.8$ Hz), 5.98 (1H, dd, $J=8.5$, 4.8 Hz), 6.65 (1H, s), 6.89 (1H, s), 7.26–7.52 (25H, m), 8.83 (1H, s), 9.91 (1H, d, $J=8.5$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(4-methyl-1,2,3-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylate (16h). Amorphous solid. Yield: 6.8 g (71%). IR (KBr) cm^{-1} 1785, 1712; ^1H NMR (DMSO-d_6) δ 2.56 (3H, s), 3.76 and 3.91 (2H, ABq, $J=17$ Hz), 4.57 (2H, s), 5.32 (1H, d, $J=4.8$ Hz), 5.99 (1H, dd, $J=8.5$, 4.8 Hz), 6.65 (1H,s), 6.89 (1H, s), 7.2–7.6 (25H, m), 9.92 (1H, d, $J=8.5$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1,2,4-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylate (16i). Amorphous solid. Yield: 2.9 g (53%). IR (KBr) cm^{-1} 1792, 1734, 1686, 1617; ^1H NMR (DMSO-d_6) δ 3.83 and 3.92 (2H, ABq, $J=17$ Hz), 4.79 (2H, s), 5.31 (1H, d, $J=4.8$ Hz), 5.97 (1H, dd, $J=8.6$, 4.8 Hz), 6.65 (1H, s), 6.91 (1H, s), 7.2-7.6 (27H, m), 8.82 (1H, s), 9.88 (1H, d, $J=8.6$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(3-methyl-1,2,4-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylate (16j). Amorphous solid. Yield: 2.3 g (63%). IR (KBr) cm^{-1} 1785, 1765, 1618; ^1H NMR (DMSO-d_6) δ 2.53 (3H, s), 3.82 and 3.90 (2H, ABq, $J=16.9$ Hz), 4.72 (2H, s), 5.31 (1H, d, $J=4.7$ Hz), 5.97 (1H, dd, $J=8.6$, 4.7 Hz), 6.66 (1H, s), 6.91 (1H, s), 7.20–7.60 (28H, m), 9.89 (1H, d, $J=$ 8.6 Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(2-methyl-1,3,4-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylate (16k). Amorphous solid. Yield: 3.3 g (88%). IR (KBr) cm^{-1} 1788, 1686, 1616; ^1H NMR (DMSO-d_6) δ 2.62 (3H, s), 3.85 and 3.92 (2H, ABq, $J=15.1$ Hz), 4.67 (2H, s), 5.29 (1H, d, $J=4.8$ Hz), 5.96 (1H, d, $J=8.6$, 4.8 Hz), 6.67 (1H, s), 6.89 (1H, s), 7.26–7.58 (25H, m), 9.91 (1H, d, $J=8.6$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido-3-[(2-methyl-1,3,4-oxadiazol-5-yl)methylthio]-3-cephem-4-carboxylate (16l). Amorphous solid. Yield: 2.9 g (80%). IR (KBr) cm^{-1} 3442, 1795, 1687, 1616; ^1H NMR (DMSO-d_6) δ 2.42 (3H, s), 3.92 (2H, s), 4.49 (2H, s), 5.31 (1H, d, $J=4.7$ Hz), 5.98 (1H, dd, $J=8.5$, 4.7 Hz), 6.67 (1H, s), 6.89 (1H, s), 7.20–7.57 (27H, m), 9.53 (1H, d, $J=8.5$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido-3-[(1-methylimidazol-5-yl)methylthio]-3-cephem-4-carboxylate (16n). Amorphous solid. Yield: 1.6 g (45%). IR (KBr) cm^{-1} 3440, 3060, 1786, 1682, 1616; ^1H NMR (DMSO-d_6) δ 3.51 (3H, s), 3.89 (2H, s), 4.23 (2H, s), 5.31 (1H, d, $J=4.7$ Hz), 5.96 (1H, dd, $J=8.5$, 4.7 Hz), 6.68 (1H, s), 6.79 (1H, s), 6.89 (1H, s), 7.25–7.60 (28H, m), 9.91 (1H, d, $J=8.5$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido-3-[(3-tritylimidazol-4-yl)methylthio]-3-cephem-4-carboxylate (16u). Amorphous solid. Yield: 2.1 g (93%). IR (KBr) cm^{-1} 1785, 1689; ^1H NMR (DMSO-d_6) δ 3.68 (2H, s), 4.08 (2H, s), 5.24 (1H, d, $J=4.6$ Hz), 5.90 (1H, dd, $J=8.2$, 4.6 Hz), 6.72 (1H, s), 6.81–7.58 (33H, m), 9.88 (1H, d, $J=8.2$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1-tritylpyrazol-4-yl)methylthio]-3-cephem-4-carboxylate (16v). Amorphous solid. Yield: 5.3 g (93%). IR (KBr) cm^{-1} 1785, 1693; ^1H NMR (DMSO-d_6) δ 3.81 (2H, s), 4.07 (2H, s), 5.25 (1H, d, $J=4.6$ Hz), 5.91 (1H, dd, $J=8.6$, 4.6 Hz), 6.71 (1H, s), 6.86 (1H, s), 6.99–7.03 (6H, m), 7.20–7.57 (36H, m), 9.87 (1H, d, $J=8.6$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido-3-{[1-tritylpyrazol-3(or 5)-yl]methylthio}-3-cephem-4-carboxylate (16w). Amorphous solid. Yield: 6.0 g (quant.). IR (KBr) cm^{-1} 1781, 1683; ^1H NMR (DMSO-d_6) δ 3.87 (2H, s), 4,15 (2H, d, $J=6.1$ Hz), 4.98 (1H, d, $J=4.7$ Hz), 5.90 (1H, dd, $J=8.5$, 4.7 Hz), 6.22 (1H, d, $J=2.4$ Hz), 6.68 (1H, s), 6.89–7.60 (27H, m), 9.89 (1H, d, $J=8.5$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1- and 2-trityl-3-methylpyrazol-5-yl)methylthio]-3-cephem-4-carboxylate (16x). Amorphous solid. Yield: 5.0 g (87%). IR (KBr) cm^{-1} 1789, 1691, 1616; ^1H NMR (DMSO-d_6) δ 1.40 (3H, s), 3.88 (2H, s), 4.02 (2H, s), 5.04 (1H, d, $J=4.7$ Hz), 5.89 (1H, dd, $J=8.4$, 4.7 Hz), 6.13 (1H, s), 6.86 (1H, s), 6.9–7.6 (43H, m), 9.88 (1H, d, $J=8.4$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-{[1(or 2)-trityl-1,2,3-triazol-4-yl]-methylthio}-3-cephem-4-carboxylate (16y). Amorphous solid. Yield: 2.2 g (71%). IR (KBr) cm^{-1} 1786, 1732, 1684, 1616; ^1H NMR (DMSO-d_6) δ 3.92 (2H, s), 4.29 (2H, s), 5.25 (1H, d, $J=4.6$ Hz), 5.93 (1H, dd, $J=8.6$, 4.6 Hz), 6.71 (1H, s), 6.86 (1H, s), 6.99–7.65 (43H, m), 9.89 (1H, d, $J=8.6$ Hz).

Diphenylmethyl 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetamido]-3-[(1-trityl-1,2,4-triazol-3-yl)methylthio]-3-cephem-4-carboxylate (16z). Amorphous solid. Yield: 4.5 g (93%). IR (KBr) cm^{-1} 1786, 1690, 1616; ^1H NMR (DMSO-d_6) δ 3.90–4.02 (2H, m), 4.26 (2H, ABq, $J=15.2$ Hz), 5.05 (1H, d, $J=4.9$ Hz), 5.94 (1H, dd,

$J=8.4$, 4.9 Hz), 6.68 (1H, s), 7.02–7.75 (42H, m), 8.09 (1H, s), 9.91 (1H, d, $J=8.4$ Hz).

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(pyrazin-2-yl)methylthio]-3-cephem-4-carboxylic acid (2c). A solution of **17c** (1.50 g) in 90% aqueous formic acid (5.6 mL) was stirred at room temperature for 2 h. The insoluble material was filtered off and the filtrate was adjusted to pH 7 with $NaHCO_3$. The aqueous solution was washed with ethyl acetate and the aqueous layer was separated. The aqueous layer was adjusted to pH 5 and chromatographed with HP-20 eluting with aqueous IPA. The fractions containing the object compound were collected and lyophilized to give crude product, which was purified by preparative HPLC utilizing a C18 μ Bondapak resin to afford **2c.** Amorphous solid. Yield: 131 mg (13%). IR (KBr) cm^{-1} 3233, 1768, 1686, 1633; ^1H NMR (DMSO-d_6) δ 3.74 and 3.87 (2H, ABq, $J=17$ Hz), 4.21 (2H, s), 5.13 (1H, d, $J=5$ Hz), 5.71 (1H, dd, $J=8$, 5 Hz), 6.67 (1H, s), 7.13 (2H, s), 7.52 (1H, d, $J=5$ Hz), 8.75 (1H, d, $J=5$ Hz), 9.10 (1H, s), 9.47 (1H, d, $J=8$ Hz), 11.3 (1H, s). FABMS *m/e* 493 [M^+]. Anal. calcd for $C_{17}H_{15}N_7O_5S_3\cdot2.5H_2O$: C, 37.91; H, 3.74; N, 18.21; found: C, 38.02; H, 3.43; N, 18.11.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1,2,3-thiadiazol-4-yl)methylthio]-3-cephem-4-carboxylic acid (2e). To a solution of **18e** (2.29 g, 3.24 mmol) in CH_2Cl_2 (11 mL) and anisole (2.3 mL) was added trifluoroacetic acid (4.6 mL) at 5 °C. The mixture was stirred for 1.5 h at the same temperature and poured into IPE (200 mL). The resulting precipitate was collected by filtration, washed with IPE and dried in vacuo. The crude product was dissolved in a mixture of water (150 mL) and MeOH (7.5 mL), and thereto NH_4Cl (520 mg, 9.72 mmol) was added and the mixture was adjusted to pH 8 with aq $NaHCO_3$ solution. The solution was stirred for 2 h maintaining pH 8 with aq $NaHCO_3$ solution. The reaction mixture was adjusted to pH 6 by addition of 1N HCl. The mixture was concentrated in vacuo and adjusted to pH 5 with 1N HCl and chromatographed on HP-20 (100 mL) eluting with 5–10% aqueous IPA. The fractions containing the object compound were collected and lyophilized to give crude product, which was purified by preparative HPLC utilizing a C18 μ Bondapak resin to afford **2e.** Amorphous solid. Yield: 85 mg (5%). IR (Nujol) cm^{-1} 1750, 1630, 1520; ^1H NMR (DMSO-d_6) δ 3.80 and 3.91 (2H, ABq, $J=17.2$ Hz), 4.63 (2H, s), 5.15 (1H, d, $J=4.7$ Hz), 5.72 (1H, dd, $J=8.2$, 4.7 Hz), 6.68 (1H, s), 7.14 (2H, br s), 9.04 (1H, s), 9.48 (1H, d, $J=8.2$ Hz). FABMS *m/e* 500 [$(M+H)^+$]. Anal. calcd for $C_{15}H_{13}N_7O_5S_4\cdot1.7H_2O$: C, 33.98; H, 3.12; N, 18.49; found: C, 33.79; H, 2.86; N, 18.39.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1,2,4-triazol-3-yl)methylthio]-3-cephem-4-carboxylic acid (2t). To a solution of **16z** (4.5 g, 3.97 mmol) in formic acid (18 mL) was added concd HCl (1.65 mL, 19.9 mmol) at 5 °C. The mixture was stirred for 1.5 h at room temperature and then poured into a mixture of ethyl acetate (20 mL) and acetone (10 mL). The resulting precipitate was collected by filtration, washed with ethyl acetate–acetone and dried in vacuo. The crude product was dissolved in water (120 mL) at pH 6.5 using aq $NaHCO_3$ solution. The reaction mixture was adjusted to pH 4 by addition of 1N HCl and chromatographed on HP-20 (130 mL) eluting with 5% aqueous IPA. The fractions containing the object compound were collected and lyophilized to give crude product, which was further purified by using preparative HPLC described above to give **2t**. Yield: 361 mg (19%). IR (KBr) cm^{-1} 3317, 1744, 1663, 1616; ^1H NMR (DMSO-d_6) δ 3.88 (2H, m), 4.19 (2H, s), 5.12 (1H, d, $J=5.2$ Hz), 5.71 (1H, dd, $J=8.2$, 5.2 Hz), 6.68 (1H, s), 7.14 (2H, s), 8.37 (1H, br s), 9.48 (1H, d, $J=8.2$ Hz), 11.31 (1H, s), 13.8 (1H, br s). FABMS *m/e* 482 [M^+]. Anal. calcd for $C_{15}H_{14}N_8O_5S_3\cdot0.2H_2O$: C, 37.06; H, 2.99; N, 23.05; found: C, 37.09; H, 2.87; N, 22.81.

The following compounds were obtained using a method similar to that used for **2t**.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(pyrimidin-4-yl)methylthio]-3-cephem-4-carboxylic acid (2b). Amorphous solid. Yield: 366.0 mg (44%). IR (KBr) cm^{-1} 1767, 1664, 1635; ^1H NMR (DMSO-d_6) δ 3.75 and 3.85 (2H, ABq, $J=17$ Hz), 4.21 (2H, s), 5.13 (1H, d, $J=5$ Hz), 5.71 (1H, dd, $J=8$, 5 Hz), 6.67 (1H, s), 7.13 (2H, s), 7.52 (1H, d, $J=5$ Hz), 8.75 (1H, d, $J=5$ Hz), 9.10 (1H, s), 9.47 (1H, d, $J=8$ Hz), 11.3 (1H, s). FABMS *m/e* 494[$(M+H)^+$]. Anal. calcd for $C_{17}H_{15}N_7O_5S_3\cdot2.1H_2O$: C, 38.43; H, 3.64; N, 18.45; found: C, 38.17; H, 3.28; N, 18.16.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(pyridazin-3-yl)methylthio]-3-cephem-4-carboxylic acid (2d). Amorphous solid. Yield: 248 mg (24%). IR (KBr) cm^{-1} 1767, 1660, 1603, 1585; ^1H NMR (DMSO-d_6) δ 3.78 and 3.88 (2H, ABq, $J=17$ Hz), 4.41 (2H, s), 5.11 (1H, d, $J=5$ Hz), 5.71 (1H, dd, $J=8$, 5 Hz), 6.68 (1H, s), 7.14 (2H, s), 7.4–7.5 (2H, m), 9.1–9.2 (1H, m), 9.48 (1H, d, $J=8$ Hz), 11.30 (1H, s). FABMS *m/e* 494 [$(M+H)^+$]. Anal. calcd for $C_{17}H_{15}N_7O_5S_3\cdot2.5H_2O$: C, 37.91; H, 3.74; N, 18.21; found: C, 38.02; H, 3.43; N, 18.11.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(imidazol-4-yl)methylthio]-3-cephem-4-carboxylic acid (2m). Amorphous solid. Yield: 178 mg (20%). IR (KBr) cm^{-1} 3147, 1759, 1668; ^1H NMR (DMSO-d_6) δ 3.70 and 3.78 (2H, ABq, $J=17.3$ Hz), 3.98 and 4.12 (2H, ABq, $J=14.5$ Hz), 5.11 (1H, d, $J=4.7$ Hz), 5.68 (1H, dd, $J=8.2$, 4.7 Hz), 6.65 (1H, s), 7.06 (1H, s), 7.12 (1H, s), 7.84 (1H, s), 9.45 (1H, d, $J=8.2$ Hz), 11.28 (1H, s). FABMS *m/e* 482 [$(M+H)^+$]. Anal. calcd for $C_{16}H_{15}N_7O_5S_3\cdot3.4H_2O$: C, 35.41; H, 4.05; N, 18.06; found: C, 35.25; H, 3.60; N, 17.90.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1-methylimidazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2n). Amorphous solid. Yield: 532 mg (60%). IR (KBr) cm^{-1} 3334, 1767, 1666, 1608; ^1H NMR (DMSO-d_6) δ 3.62 (3H, s), 3.67 and 3.75 (2H, ABq, $J=17.3$ Hz), 4.16 (2H, s), 5.13 (1H, d, $J=4.7$ Hz), 5.71 (1H, dd, $J=8.2$, 4.7 Hz), 6.67 (1H, s), 6.85 (1H, s),

7.11 (2H, s), 7.63 (1H, s), 9.47 (1H, d, $J=8.2$ Hz). FABMS m/e 496 [$(M+H)^+$]. Anal. calcd for $C_{17}H_{17}N_7O_5S_3\cdot 2.8H_2O$: C, 37.40; H, 4.17; N, 17.96; found: C, 37.76; H, 3.98; N, 17.50.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1-methylpyrazol-4-yl)methylthio]-3-cephem-4-carboxylic acid (2p). Amorphous solid. Yield: 216 mg (16%). IR (KBr) cm^{-1} 3332, 1770, 1666, 1612, 1535; ^1H NMR (DMSO-d_6) δ 3.47 and 3.61 (2H, ABq, $J=16.9$ Hz), 3.87 (3H, s), 5.03 (1H, d, $J=4.7$ Hz), 5.62 (1H, dd, $J=8.2$, 4.7 Hz), 6.66 (1H, s), 7.12 (1H, s), 7.32 (1H, s), 7.60 (1H, s), 9.42 (1H, d, $J=8.2$ Hz). Anal. calcd for $C_{17}H_{17}N_7O_5S_3\cdot 2.5H_2O$: C, 37.77; H, 4.10; N, 18.14; found: C, 37.84; H, 4.08; N, 18.01.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(4-methyl-1,2,3-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2h). Under an N_2 atmosphere, a solution of $AlCl_3$ (1.88 g, 14.05 mmol) in anisole (4 mL) was added slowly to a solution of **16h** (2.60 g, 2.81 mmol) in a mixture of anisole (4.5 mL) and CH_3NO_2 (18 mL) at −20 to −30 °C. The mixture was stirred for 1 h at the same temperature and the reaction was quenched with 1N HCl (18 mL). The mixture was poured into a mixture of ethyl acetate and water, and the aqueous layer was separated. The organic layer was reextracted with water several times and the combined aqueous layer was concentrated in vacuo, chromatographed on an HP-20 (120 mL) column eluting with aqueous MeOH. The fractions containing the object compound were collected and lyophilized to give crude product, which was purified by preparative HPLC described above to afford **2h**. Amorphous solid. Yield: 151 mg (11%). IR (KBr) cm^{-1} 3321, 1768, 1662, 1647, 1603, 1556; ^1H NMR (DMSO-d_6) δ 2.58 (3H, s), 3.71 (2H, br s), 4.50 (2H, s), 5.15 (1H, d, $J=4.8$ Hz), 5.75 (1H, dd, $J=8.2$, 4.8 Hz), 6.66 (1H, s), 7.13 (2H, s), 9.49 (1H, d, $J=8.2$ Hz), 11.31 (1H, s).

The following compounds were obtained using a method similar to that used for **2h**.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1,2,5-thiadiazol-3-yl)methylthio]-3-cephem-4-carboxylic acid (2f). Amorphous solid. Yield: 55 mg (4.4%). IR (KBr) cm^{-1} 3331, 1766, 1662, 1641; ^1H NMR (DMSO-d_6) δ 3.73 (1H, d, $J=19.2$ Hz), 4.46 (2H, s), 5.13 (1H, d, $J=4.7$ Hz), 5.71 (1H, dd, $J=8.2$, 4.7 Hz), 6.66 (1H, s), 7.13 (1H, s), 8.78 (1H, s), 9.48 (1H, d, $J=8.2$ Hz), 11.31 (1H, s). FABMS m/e 499 [M^+]. Anal. calcd for $C_{15}H_{13}N_7O_5S_4\cdot 3.2H_2O$: C, 32.33; H, 3.51; N, 17.60; found: C, 32.48; H, 3.06; N, 17.19.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1,2,3-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2g). Amorphous solid. Yield: 1.50 g (66%). IR (KBr) cm^{-1} 3332, 1768, 1666, 1635; ^1H NMR (DMSO-d_6) δ 3.73 (2H, s), 4.61 (2H, s), 5.16 (1H, d, $J=4.7$ Hz), 5.74 (1H, dd, $J=8.2$, 4.7 Hz), 6.66 (1H, s), 7.14 (2H, s), 8.84 (1H, s), 9.50 (1H, d, $J=8.2$ Hz), 11.32 (1H, s). FABMS m/e 500 [$(M+H)^+$]. Anal. calcd for $C_{15}H_{13}N_7O_5S_4\cdot 1.2H_2O$: C, 34.57; H, 2.98; N, 18.81; found: C, 34.38; H, 2.68; N, 18.66.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1,2,4-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2i). Amorphous solid. Yield: 746 mg (34%). IR (KBr) cm^{-1} 3330, 1770, 1668, 1647; ^1H NMR (DMSO-d_6) δ 3.77 (2H, s), 4.70 (2H, s), 5.13 (1H, d, $J=4.7$ Hz), 5.73 (1H, dd, $J=8.2$, 4.7 Hz), 6.66 (1H, s), 7.12 (2H, s), 8.82 (1H, s), 9.46 (1H, d, $J=8.2$ Hz), 11.30 (1H, s). Anal. calcd for $C_{15}H_{13}N_7O_5S_4\cdot 2.0H_2O$: C, 33.64; H, 3.20; N, 18.31; found: C, 33.63; H, 3.04; N, 18.15.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(3-methyl-1,2,4-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2j). Amorphous solid. Yield: 694 mg (58%). IR (KBr) cm^{-1} 3303, 1764, 1668, 1606; ^1H NMR (DMSO-d_6) δ 2.54 (3H, s), 3.49 and 3.59 (2H, ABq, $J=16.9$ Hz), 4.45 and 4.52 (2H, ABq, $J=15.7$ Hz), 5.01 (1H, d, $J=4.7$ Hz), 5.65 (1H, dd, $J=8.2$, 4.7 Hz), 6.64 (1H, s), 7.15 (2H, s), 9.43 (1H, d, $J=8.2$ Hz), 11.50 (1H, s). FABMS m/e 514 [$(M+H)^+$]. Anal. calcd for $C_{16}H_{15}N_7O_5S_4\cdot 1.8H_2O$: C, 35.20; H, 3.43; N, 17.96; found: C, 34.88; H, 3.34; N, 18.41.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(2-methyl-1,3,4-thiadiazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2k). Amorphous solid. Yield: 874 mg (48%). IR (KBr) cm^{-1} 3193, 1770, 1668, 1602; ^1H NMR (DMSO-d_6) δ .68 (3H, s), 3.35 (2H, s), 4.55 and 4.61 (2H, ABq, $J=15.2$ Hz), 5.12 (1H, d, $J=4.7$ Hz), 5.72 (1H, dd, $J=8.2$, 4.7 Hz), 6.67 (1H, s), 7.13 (2H, s), 9.47 (1H, d, $J=8.2$ Hz), 11.30 (1H, s). FABMS m/e 514 [$(M+H)^+$]. Anal. calcd for $C_{16}H_{15}N_7O_5S_4\cdot 2.3H_2O$: C, 34.63; H, 3.56; N, 17.67; found: C, 34.85; H, 3.33; N, 17.62.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(2-methyl-1,3,4-oxadiazol-5-yl)methylthio]-3-cephem-4-carboxylic acid (2l). Amorphous solid. Yield: 577 mg (37%). IR (KBr) cm^{-1} 3317, 1767, 1668; ^1H NMR (DMSO-d_6) δ 2.46 (3H, s), 3.51 and 3.74 (2H, ABq, $J=16.9$ Hz), 4.20 and 4.28 (2H, ABq, $J=15.0$ Hz), 5.03 (1H, d, $J=4.8$ Hz), 5.67 (1H, dd, $J=8.1$, 4.8 Hz), 6.65 (1H, s), 7.13 (2H, s), 9.45 (1H, d, $J=8.1$ Hz), 11.44 (1H, s). FABMS m/e 497 [M^+].

7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(pyrazol-4-yl)methylthio]-3-cephem-4-carboxylic acid (2o). Amorphous solid. Yield: 238 mg (17%). IR (KBr) cm^{-1} 3315, 1763, 1647, 1603, 1541; ^1H NMR (DMSO-d_6) δ 3.69 and 3.74 (2H, ABq, $J=14.2$ Hz), 3.99 and 4.06 (2H, ABq, $J=13.4$ Hz), 5.15 (1H, d, $J=4.6$ Hz), 5.69 (1H, dd, $J=8.2$, 4.6 Hz), 6.71 (1H, s), 7.30 (2H, s), 7.56 (2H, s), 9.48 (1H, d, $J=8.2$ Hz), 11.41 (1H, s). FABMS m/e 481 [M^+]. Anal. calcd for $C_{16}H_{15}N_7O_5S_3\cdot 3.75H_2O$: C, 35.00; H, 4.13; N, 17.52; found: C, 34.71; H, 3.84; N, 17.30.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(pyrazol-3-yl)methylthio]-3-cephem-4-carboxylic acid (2q). Amorphous solid. Yield: 133 mg (5.2%). IR (KBr) cm^{-1} 3315, 1765, 1664, 1605; ^1H NMR (DMSO-d_6) δ 3.80 (2H, d, $J=3.9$ Hz), 4.11 (2H, s), 5.12 (1H, d, $J=4.7$ Hz), 5.69 (1H, dd, $J=8.2$, 4.7 Hz),

6.19 (1H, d, $J=2.2$ Hz), 6.68 (1H, s), 7.12 (2H, s), 7.61 (1H, d, $J=2.2$ Hz), 9.44 (1H, d, $J=8.2$ Hz), 11.29 (1H, s), 12.99 (1H, br s). FABMS m/e 482 [$(M+H)^+$]. Anal. calcd for $C_{16}H_{15}N_7O_5S_3 \cdot 2.5H_2O$: C, 36.50; H, 3.83; N, 18.62; found: C, 36.45; H, 3.59; N, 18.51.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(5-methylpyrazol-3-yl)methylthio]-3-cephem-4-carboxylic acid (2r). Amorphous solid. Yield: 1.1 g (49%). IR (KBr) cm^{-1} 3317, 1764, 1662; ^1H NMR (DMSO-d_6) δ 2.17 (3H, s), 3.76 and 3.82 (2H, ABq, $J=17.1$ Hz), 4.02 (2H, s), 5.12 (1H, d, $J=4.6$ Hz), 5.68 (1H,dd, $J=8.2$, 4.6 Hz), 5.92 (1H, s), 6.68 (1H, s), 7.09 (2H, s), 9.42 (1H, d, $J=8.2$ Hz), 11.28 (1H, s). FABMS m/e 495 [M^+]. Anal. calcd for $C_{17}H_{17}N_7O_5S_3 \cdot 2.5H_2O$: C, 37.33; H, 4.10; N, 18.14; found: C, 37.44; H, 3.71; N, 17.83.

7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(1*H*-1,2,3-triazol-4-yl)methylthio]-3-cephem-4-carboxylic acid (2s). Amorphous solid. Yield: 195 mg (21%). IR (Nujol) cm^{-1} 3307, 1765, 1666, 1620, 1539; ^1H NMR (DMSO-d_6) δ 3.77 (2H, s), 4.20 (2H, s), 5.12 (1H, d, $J=4.7$ Hz), 5.70 (1H, dd, $J=8.2$, 4.7 Hz), 6.67 (1H, s), 7.13 (2H, s), 7.74 (1H, s), 9.47 (1H, d, $J=8.2$ Hz), 11.29 (1H, s). FABMS m/e 483 [$(M+H)^+$]. Anal. calcd for $C_{15}H_{14}N_8O_5S_3 \cdot 0.3H_2O$: C, 36.93; H, 3.02; N, 22.97; found: C, 36.93; H, 2.89; N, 23.11.

Measurement of in vitro antibacterial activity

According to the method of the Japan Society of Chemotherapy, the MICs of compounds were determined by the 2-fold agar dilution method using heart infusion agar (Eiken). The inoculum size was adjusted to 10^6 cfu/mL, and incubation was carried out at 37 °C for 20 h.

Urinary and biliary recovery

ICR mice and Sprague–Dawley rats were fasted overnight and orally dosed with 20 mg/kg of the test drugs. Urine samples were collected for 24 h after dosing. For bile collection another group of mice and rats was cannulated with a polystyrene tube into the bile duct and test drugs were given orally at doses of 20 mg/kg. The samples were assayed by a disc-agar diffusion method using *E. coli* NIHJ JC-2 or *E. coli* ATCC 33546 as test organism and nutrient agar (Difco) as the test medium.

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