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CP6679, A New Injectable Cephalosporin. Part1: Synthesis and Structure–Activity Relationships

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Abstract—A series of cephalosporins bearing a 5,5-fused ring system, an (imidazo[5,1-*b*]thiazolium-6-yl)methyl group, at the C-3 position were synthesized and evaluated for in vitro antibacterial activities. CP6679 (**1s**) and its analogues showed potent antibacterial activities against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. They were also highly active against methicillin-resistant *Staphylococcus aureus* (MRSA). CP6679 (**1s**) showed more potent antibacterial activity than ceftazidime (CAZ) or cefpirome (CPR) against *Pseudomonas aeruginosa* and MRSA.

Introduction

Nosocomial and opportunistic infections, mainly involving *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), have become a serious clinical problem. To counter this, we have been searching for novel cephalosporins with potent activity against these organisms.[1,2] Several active derivatives have recently been reported by others.[3–6] Some effective cephalosporin agents[3,4,7–9] are already clinically available, but new agents are needed because of the problem of drug resistance.

Here we describe a novel cephalosporin, CP6679 (**1s**), which has strong activity against both *P. aeruginosa* and MRSA. In this paper, we present the synthesis and biological activities of CP6679 (**1s**) and related compounds.[10]

Chemistry

Compound **1s** (CP6679) was synthesized as shown in Scheme 1. Treatment of (*R*)-*N*-Boc-alanine **3** with 2-(aminomethyl)thiazole[11] in the presence of 1-hydroxybenzotriazole (HOBT) and dicyclohexylcarbodiimide (DCC) gave the acylated product **4**. After replacement of the protective group, **4** was cyclized in phosphorus oxychloride ($POCl_3$) to afford the imidazo[5,1-*b*]thiazole **5**. Removal of the protective group and formylation gave 5-[(*R*)-1-(formylamino)ethyl]imidazo[5,1-*b*]thiazole **6**. Next, the cephem nucleus **7**[12] was acylated with 2-(5-amino-1,2,4-thiadiazol-3-yl)-(*Z*)-2-fluoromethoxyiminoacetic acid[13] by a known procedure[2] to afford the amide compound **8**. The compound **8** was converted into the tetravalent amino compound **9** through the corresponding iodide intermediate by substitution with the heterocyclic compound **6**. The tetravalent amino compound **9** was subjected to deprotection using trifluoroacetic acid and anisole to afford **1s** (CP6679). Related compounds were prepared similarly. The synthesis of other heterocyclic compounds (3-substituted imidazo[5,1-*b*]thiazoles and 5-substituted imidazo[5,1-*b*]thiazoles) will be reported elsewhere.

Results and Discussion

We have synthesized a series of cephalosporins bearing a (substituted imidazo[5,1-*b*]thiazolium-6-yl)methyl group at the C-3 position (Fig. 1). We selected a 2-alkyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamide group for the C-7 position, because this group is known to be favorable for potent antibacterial activities against Gram-positive and Gram-negative bacteria including *P. aeruginosa*.[3,14–18] Then we introduced several 3-substituted imidazo[5,1-*b*]thiazole and 5-substituted imidazo[5,1-*b*]thiazole groups, and evaluated the resultant compounds. The results are shown in Tables 1 and 2. In Table 1, compounds **1a**–**1g** bearing a 3-substituted imidazo [5,1-*b*]thiazole group showed potent antibacterial activities against Gram-positive bacteria

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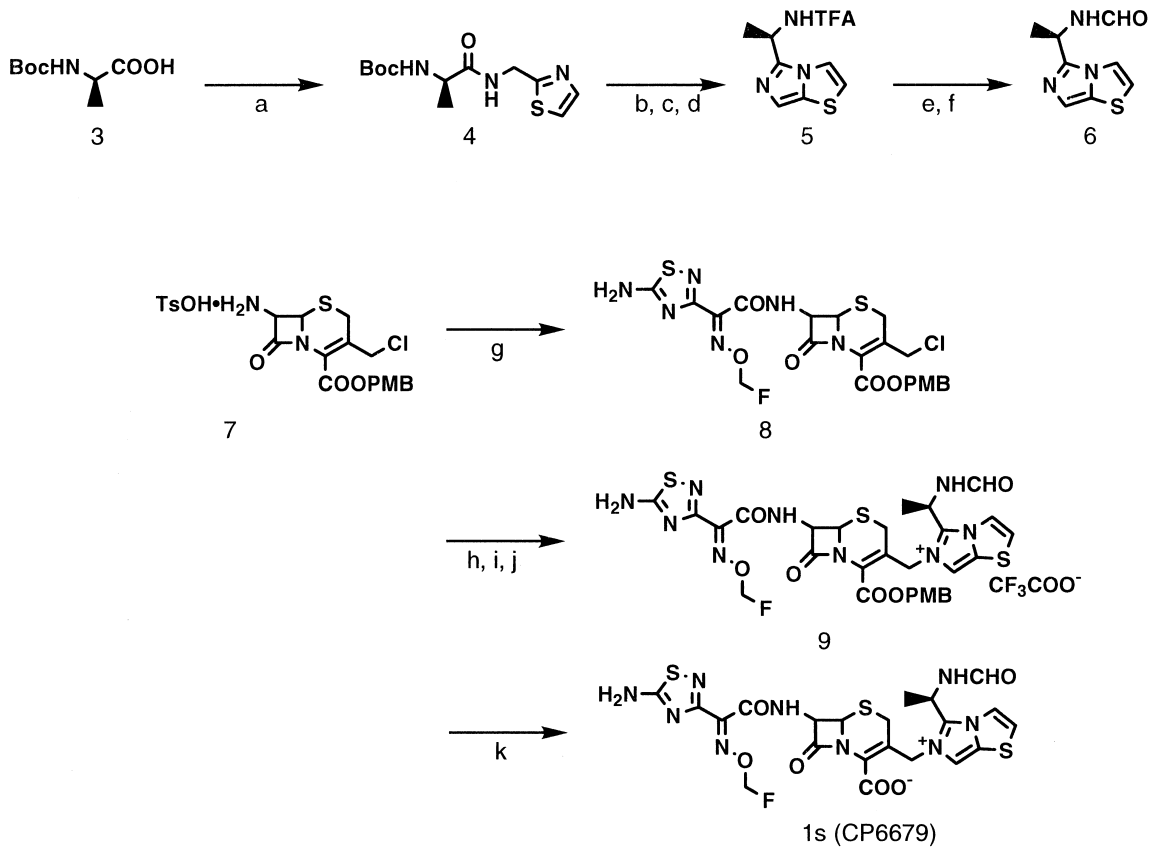


*PMB : p-methoxybenzyl

Conditions

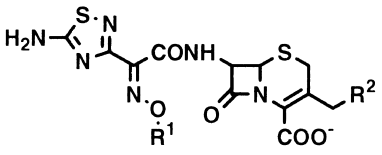
a : 2-(aminomethyl)thiazole, HOBT, DCC / CH_2Cl_2, r.t., 1 hr; b : HCl; r.t., 1 hr;
c : TFAOEt, TEA / CH_2Cl_2, r.t., 1 hr; d : $POCl_3$, reflux, 4 hr; e : KOH / H_2O, r.t., 1 hr;
f : HCOOH, Ac_2O, r.t., 1 hr; g : 2-(5-amino-1,2,4-thiadiazol-3-yl)-(*Z*)-2-fluoromethoxyiminoacetyl chloride, N,O-bis(trimethylsilyl)acetamide / CH_2Cl_2, -20°C, 1 hr; h : NaI / acetone, r.t., 1 hr; i : 4 / DMF, r.t., 3 hr;
j : CF_3COONa / H_2O, r.t., 1 hr; k : TFA, anisole, r.t., 1 hr

Scheme 1. Synthesis of **1s** (CP6679).

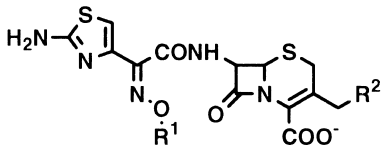
except MRSA and *Enterococcus hirae*, and against Gram-negative bacteria including *P. aeruginosa*. The introduction of a substituent at the 3-position in the heterocycle had little effect on the antibacterial activities. On the other hand, the compounds **1h**–**1o** bearing a 5-substituted imidazo[5,1-*b*]thiazole group also showed potent antibacterial activities, although they were inferior to those of the 3-substituted imidazo[5,1-*b*] thiazole derivatives, as shown in Table 2. Among these compounds, **1m** showed superior antibacterial activity against MRSA, so we selected **1m** for further modification and synthesized various derivatives.

Firstly, we replaced the C-7 side chain group. The results are shown in Table 3. For a given alkyloxyimino group in the C-7 side chain, the compounds **1m** and **1p**–**1r** bearing a 5-amino-1,2,4-thiadiazole group showed similar or superior antibacterial activities to those of the compounds **2m** and **2p**–**2r** bearing a 2-aminothiazole group against MRSA and Gram-negative bacteria, including *P. aeruginosa*. On the other hand, the compounds **1m** and **1p**–**1r** bearing a 5-amino-1,2,4-thiadiazole group showed inferior antibacterial activities to those of the compounds **2m** and **2p**–**2r** bearing a 2-aminothiazole group against Gram-positive bacteria except MRSA. Among the compounds in Table 3, **1m** had the highest potency against MRSA and *P. aeruginosa*. Furthermore, **1q** showed the strongest activity against *P. aeruginosa*, and therefore we synthesized derivatives with a 2-(5-amino-1,2,4-thiadiazole-3-yl)-2-fluoromethoxyiminoacetamide group at the C-7 position in an attempt to improve the antibacterial activities against Gram-positive bacteria, especially MRSA.

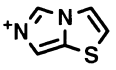
Next, we introduced a methyl or a hydroxymethyl group into the heterocycle at the C-3 position. The results are shown in Table 4. The introduction of an (*R*)-methyl or (*R*)-hydroxymethyl group (compounds **1s** and **1u**) increased the antibacterial activities against MRSA and *P. aeruginosa*. But the introduction of an (*S*)-methyl or (*S*)-hydroxymethyl group (compounds **1t** and **1v**) decreased the activity against *P. aeruginosa*. Furthermore, the introduction of a dimethyl group (compound **1w**) decreased the activities against MRSA and *P. aeruginosa*. The compounds **1s** and **1u** bearing (*R*)-configuration showed superior activities to those of the compounds **1t** and **1v** bearing (*S*)-configuration. No difference in antibacterial activities was found between

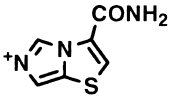


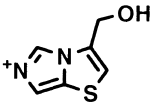
1a-1w

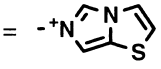


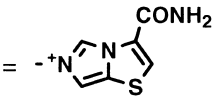
2m, 2p-2r

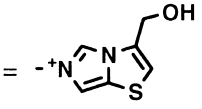
a : $R^1 = CH_2F$, R^2 = 

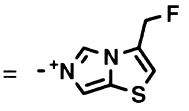
b : $R^1 = CH_2F$, R^2 = 

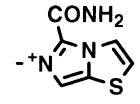
c : $R^1 = CH_2F$, R^2 = 

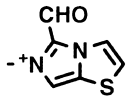
d : $R^1 = CH_2CH_2F$, R^2 = 

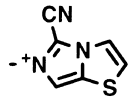
e : $R^1 = CH_2CH_2F$, R^2 = 

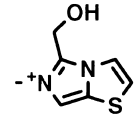
f : $R^1 = CH_2CH_2F$, R^2 = 

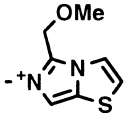
g : $R^1 = CH_2CH_2F$, R^2 = 

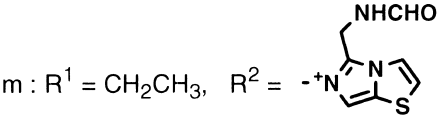
h : $R^1 = CH_2CH_3$, R^2 = 

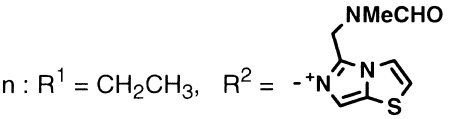
i : $R^1 = CH_2CH_3$, R^2 = 

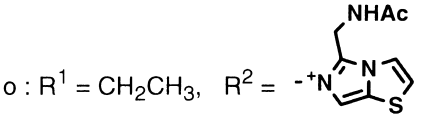
j : $R^1 = CH_2CH_3$, R^2 = 

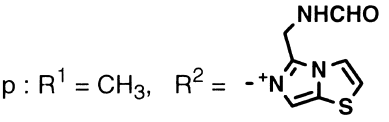
k : $R^1 = CH_2CH_3$, R^2 = 

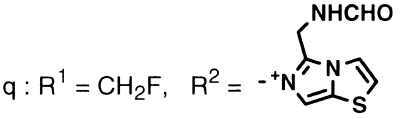
l : $R^1 = CH_2CH_3$, R^2 = 

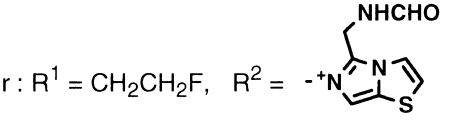
m : $R^1 = CH_2CH_3$, R^2 = 

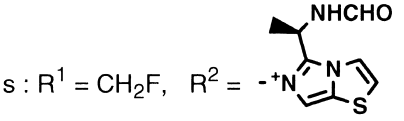
n : $R^1 = CH_2CH_3$, R^2 = 

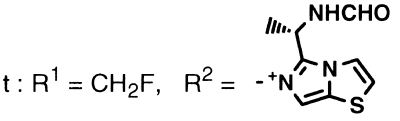
o : $R^1 = CH_2CH_3$, R^2 = 

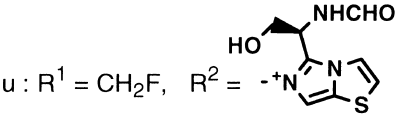
p : $R^1 = CH_3$, R^2 = 

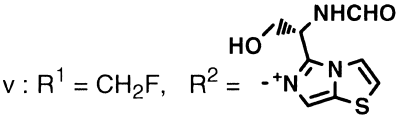
q : $R^1 = CH_2F$, R^2 = 

r : $R^1 = CH_2CH_2F$, R^2 = 

s : $R^1 = CH_2F$, R^2 = 

t : $R^1 = CH_2F$, R^2 = 

u : $R^1 = CH_2F$, R^2 = 

v : $R^1 = CH_2F$, R^2 = 

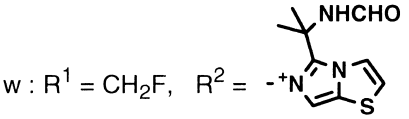
w : $R^1 = CH_2F$, R^2 = 

Figure 1. CP6679 (**1s**) and related compounds.

Table 1. Antibacterial activities of **1a**–**1g** (MIC; μg/mL)

Test organism	1a	1b	1c	1d	1e	1f	1g
Staphylococcus aureus 209P JC-1	0.39	0.39	0.39	0.39	0.39	0.78	0.78
S. aureus M133[a]	6.25	6.25	12.5	6.25	6.25	6.25	6.25
S. aureus M126[a]	12.5	12.5	25	12.5	12.5	25	12.5
S. epidermidis ATCC14990	0.39	0.39	0.39	0.39	0.39	0.39	0.78
Enterococcus hirae ATCC8043	25	12.5	25	12.5	6.25	25	12.5
Escherichia coli NIHJ JC-2	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
Klebsiella pneumoniae PCI602	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
E. coli 255	0.10	0.10	0.10	0.20	0.20	0.20	0.20
E. coli GN206	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Proteus vulgaris GN76	0.20	0.20	0.39	0.20	0.20	0.39	0.78
P. vulgaris GN76/C-1	3.13	3.13	12.5	3.13	3.13	12.5	12.5
Morganella morganii 1510	1.56	1.56	1.56	3.13	3.13	3.13	3.13
M. morganii 1510/S-1	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
Citrobacter freundii GN346	3.13	3.13	6.25	3.13	3.13	12.5	6.25
C. freundii GN346/16	0.10	0.10	0.10	0.10	0.10	0.20	0.10
Enterobacter cloacae G-0008	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	0.05	0.05
Serratia marcescens No.1	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	0.05	0.05
Pseudomonas aeruginosa GN10362	0.78	0.78	1.56	0.78	0.78	1.56	1.56
P. aeruginosa E-2	0.78	0.78	0.78	0.78	0.78	1.56	1.56

[a]These strains are MRSA.

Table 2. Antibacterial activities of **1h**–**1o** (MIC; μg/mL)

Test organism	1h	1i	1j	1k	1l	1m	1n	1o
S. aureus 209P JC-1	0.78	0.39	1.56	0.78	0.78	0.78	0.78	0.78
S. aureus M133[a]	6.25	6.25	12.5	6.25	3.13	3.13	6.25	12.5
S. aureus M126[a]	6.25	12.5	12.5	12.5	6.25	6.25	12.5	25
S. epidermidis ATCC14990	0.39	0.39	1.56	0.78	0.78	0.78	1.56	1.56
E. hirae ATCC8043	1.56	25	3.13	12.5	3.13	3.13	3.13	1.56
E. coli NIHJ JC-2	0.20	0.05	0.20	0.10	0.10	0.05	0.10	0.05
K. pneumoniae PCI602	0.20	0.05	0.39	0.10	0.10	0.05	0.10	0.10
E. coli 255	0.20	0.20	0.39	0.39	0.20	0.20	0.10	0.10
E. coli GN206	0.10	0.05	0.10	0.10	0.05	< 0.025	< 0.025	< 0.025
P. vulgaris GN76	0.78	0.39	1.56	0.78	1.56	0.78	1.56	0.78
P. vulgaris GN76/C-1	12.5	12.5	25	12.5	12.5	6.25	12.5	12.5
M. morganii 1510	3.13	6.25	6.25	3.13	1.56	0.39	0.39	0.39
M. morganii 1510/S-1	0.10	0.05	0.20	0.05	0.05	< 0.025	0.05	< 0.025
C. freundii GN346	6.25	12.5	6.25	6.25	3.13	1.56	0.78	1.56
C. freundii GN346/16	0.20	0.20	0.39	0.20	0.10	0.05	0.10	0.05
E. cloacae G-0008	0.20	0.05	0.39	0.10	0.20	0.10	0.20	0.10
S. marcescens No.1	0.10	0.05	0.20	0.10	0.20	0.10	0.10	0.05
P. aeruginosa GN10362	3.13	1.56	6.25	3.13	3.13	1.56	3.13	3.13
P. aeruginosa E-2	3.13	1.56	6.25	3.13	3.13	1.56	3.13	3.13

[a]These strains are MRSA.

the compounds bearing methyl and hydroxymethyl groups. Overall, **1s** had the highest potency against all the tested bacteria, including MRSA and *P. aeruginosa*.

Compound **1s** was compared with clinically used injectable cephalosporins (Table 5). It showed a similar or superior antibacterial activity to ceftazidime,[8] cefpirome,[7] cefozopran[3] and cefoselis,[4] and had the strongest activity among these cephalosporins against MRSA and *P. aeruginosa*. Further evaluation of compound **1s** as a candidate drug is in progress.

Experimental

General methods

^{1}H NMR spectra were measured with a JEOL JNM-GSX 400 NMR spectrometer for 400 MHz or a Varian Gemini 300 NMR spectrometer for 300 MHz in $CDCl_3$, DMSO-d_6, or D_2O. TMS (0 ppm) in $CDCl_3$ and DMSO-d_6 or HDO (4.8 ppm) in D_2O was used as internal reference standard. IR spectra were recorded on a Shimadzu FT-IR 8100 spectrometer as KBr pellets. Mass spectra were obtained on a JEOL JMS-700 mass spectrometer for FABMS and FABHRMS. Silica gel flash column chromatography was performed on Wakogel C-300 (Wako Chemical).

Antibacterial activity in vitro

Minimum inhibitory concentration (MIC) was determined by the agar plate dilution method. Test strains were subjected to seed culture using Sensitivity test broth (STB, Nissui Pharmaceutical). A 5 μL portion of cell suspension of test strains having about 10^6 cfu/mL was inoculated and incubated at 37 °C for 20 h. The MIC was then measured.

Table 3. Antibacterial activities of **1m**, **1p**–**1r**, **2m** and **2p**–**2r** (MIC; μg/mL)

Test organism	1p	1m	1q	1r	2p	2m	2q	2r
S. aureus 209P JC-1	0.78	0.78	0.78	1.56	0.39	0.78	0.78	0.78
S. aureus M133[a]	6.25	3.13	6.25	6.25	6.25	6.25	12.5	6.25
S. aureus M126[a]	12.5	6.25	12.5	12.5	25	25	25	25
S. epidermidis ATCC14990	0.78	0.78	0.39	1.56	0.39	0.78	0.39	0.78
E. hirae ATCC8043	3.13	3.13	3.13	6.25	3.13	12.5	6.25	12.5
E. coli NIHJ JC-2	0.05	0.05	< 0.025	0.05	0.05	0.20	0.05	0.10
K. pneumoniae PCI602	0.05	0.05	< 0.025	0.05	0.05	0.20	0.05	0.10
E. coli 255	0.05	0.20	0.05	0.20	0.10	0.39	0.10	0.20
E. coli GN206	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	0.05	< 0.025	0.05
P. vulgaris GN76	0.78	0.78	0.39	0.78	0.20	0.78	0.10	0.78
P. vulgaris GN76/C-1	25	6.25	6.25	12.5	3.13	3.13	1.56	3.13
M. morganii 1510	0.39	0.39	0.20	0.78	0.20	0.39	0.10	0.39
M. morganii 1510/S-1	< 0.025	< 0.025	< 0.025	0.05	< 0.025	0.05	< 0.025	< 0.025
C. freundii GN346	0.78	1.56	0.78	1.56	3.13	3.13	3.13	3.13
C. freundii GN346/16	0.05	0.05	< 0.025	0.10	0.10	0.39	0.10	0.20
E. cloacae G-0008	0.05	0.10	< 0.025	0.10	0.10	0.39	0.10	0.20
S. marcescens No.1	0.05	0.10	< 0.025	0.10	0.05	0.20	0.05	0.20
P. aeruginosa GN10362	1.56	1.56	0.78	3.13	6.25	6.25	6.25	6.25
P. aeruginosa E-2	1.56	1.56	1.56	3.13	6.25	6.25	6.25	6.25

[a]These strains are MRSA.

Table 4. Antibacterial activities of **1q** and **1s**–**1w** (MIC; μg/mL)

Test organism	1q	1s	1t	1u	1v	1w
S. aureus 209P JC-1	0.78	0.78	0.78	0.78	0.78	1.56
S. aureus M133[a]	6.25	6.25	6.25	6.25	6.25	12.5
S. aureus M126[a]	12.5	6.25	12.5	6.25	12.5	25
S. epidermidis ATCC14990	0.39	1.56	1.56	0.78	1.56	1.56
E. hirae ATCC8043	3.13	1.56	1.56	1.56	1.56	12.5
E. coli NIHJ JC-2	< 0.025	< 0.025	0.05	< 0.025	0.10	0.78
K. pneumoniae PCI602	< 0.025	0.05	0.10	< 0.025	0.10	0.78
E. coli 255	0.05	0.05	0.20	0.05	0.20	1.56
E. coli GN206	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	0.20
P. vulgaris GN76	0.39	0.39	0.78	0.39	1.56	6.25
P. vulgaris GN76/C-1	6.25	12.5	25	12.5	50	50
M. morganii 1510	0.20	0.20	0.20	0.20	0.20	3.13
M. morganii 1510/S-1	< 0.025	< 0.025	0.05	< 0.025	0.05	0.39
C. freundii GN346	0.78	0.39	0.78	0.78	6.25	12.5
C. freundii GN346/16	< 0.025	0.05	0.10	< 0.025	0.10	0.78
E. cloacae G-0008	< 0.025	0.05	0.20	0.05	0.20	1.56
S. marcescens No.1	< 0.025	0.05	0.10	< 0.025	0.10	0.39
P. aeruginosa GN10362	0.78	0.78	3.13	0.78	3.13	6.25
P. aeruginosa E-2	1.56	0.78	1.56	0.78	3.13	6.25

[a]These strains are MRSA.

2-[(*N*-*tert*-Butoxycarbonyl-D-alanyl)amino]methylthiazole (4). To a suspended solution of **3** (946 mg, 5.00 mmol) and 1-hydroxybenzotriazole (743 mg, 5.50 mmol) in dry CH_2Cl_2 (10 mL) was added 2-aminomethylthiazole[11] (628 mg, 5.50 mmol) at 0 °C. Then, to the reaction mixture was added dicyclohexylcarbodiimide (1.135 g, 5.50 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. After filtration of insoluble, the filtrate was washed with 5% aqueous $NaHCO_3$ (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to give **4** (1.425 g, 5.00 mmol, 100%) : ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, J = 7 Hz), 1.43 (9H, s), 4.15–4.30 (1H, m), 4.76 (1H, dd, J = 6 Hz, 12 Hz), 4.77 (1H, dd, J = 6 Hz, 12 Hz), 4.90–5.10 (1H, m), 6.95–7.15 (1H, m), 7.28 (1H, d, J = 3 Hz), 7.70 (1H, d, J = 3 Hz).

5-[(*R*)-1-(Trifluoroacetylamino)ethyl]imidazo[5,1-*b*]thiazole (5). To a solution of **4** (1.425 g, 5.00 mmol) in CH_2Cl_2 (20 mL) was added 4N aqueous HCl (10 mL) at 0 °C, and the mixture was stirred at room temperature for 19 h. After separation of the organic layer, the aqueous layer was adjusted at pH > 14 by the adding 40% aqueous KOH and extracted with CH_2Cl_2 (10 mL) twice. To the aqueous layer was added K_2CO_3 (8 g), and it was extracted with CH_2Cl_2 (10 mL) twice. The combined organic layer was dried over K_2CO_3 and concentrated under reduced pressure to give 2-(D-alanylaminomethyl)thiazole.

To a solution of 2-(D-alanylaminomethyl)thiazole in CH_2Cl_2 (1 mL) were added triethylamine (1.4 mL, 10.0 mmol) and ethyl trifluoroacetate (1.2 mL, 10.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. To the reaction mixture was added diisopropylether (2 mL), and then the reaction mixture was filtrated at 10 °C to collect 2-[(*N*-trifluoroacetyl-D-alanyl)amino]methylthiazole (1.405 g, 5.00 mmol, 100%): ^{1}H

Table 5. Antibacterial activities of **1s** and clinically used cephalosporins (MIC; μg/mL).

Test organism	**1s**	Ceftazidime	Cefpirome	Cefozopran	Cefoselis
S. aureus 209P JC-1	0.78	3.13	0.39	0.39	0.39
S. aureus M133[a]	6.25	100	25	12.5	12.5
S. aureus M126[a]	6.25	>100	100	50	25
S. epidermidis ATCC14990	1.56	3.13	0.39	0.39	0.39
E. hirae ATCC8043	1.56	>100	3.13	50	6.25
E. coli NIHJ JC-2	<0.025	0.20	0.05	0.05	0.10
K. pneumoniae PCI602	0.05	0.10	0.05	0.05	0.10
E. coli 255	0.05	12.5	0.20	0.20	0.39
E. coli GN206	<0.025	1.56	<0.025	0.05	0.05
P. vulgaris GN76	0.39	0.10	0.39	0.39	0.20
P. vulgaris GN76/C-1	12.5	0.10	3.13	6.25	0.78
M. morganii 1510	0.20	12.5	0.20	3.13	0.39
M. morganii 1510/S-1	<0.025	0.10	<0.025	0.10	<0.025
C. freundii GN346	0.39	25	0.78	1.56	3.13
C. freundii GN346/16	0.05	0.78	0.10	0.05	0.10
E. cloacae G-0008	0.05	0.20	0.05	0.10	0.10
S. marcescens No.1	0.05	0.05	0.05	0.10	0.05
P. aeruginosa GN10362	0.78	1.56	3.13	0.78	3.13
P. aeruginosa E-2	0.78	1.56	3.13	0.78	3.13

[a]These strains are MRSA.

NMR ($CDCl_3$) δ 1.51 (3H, d, $J=7$ Hz), 4.57 (1H, quintet, $J=7$ Hz), 4.77 (1H, dd, $J=6$ Hz, 16 Hz), 4.78 (1H, dd, $J=6$ Hz, 16 Hz), 6.90–7.10 (1H, m), 7.33 (1H, d, $J=3$ Hz), 7.35–7.55 (1H, m), 7.73 (1H, d, $J=3$ Hz).

To a suspended solution of 2-[(*N*-trifluoroacetyl-D-alanyl)amino]methylthiazole (1.405 g, 5.00 mmol) in toluene (5.1 mL) was added phosphorus oxychloride (5.1 mL), and the mixture was stirred at 120 °C for 3 h. After being cooled, the reaction mixture was concentrated under reduced pressure, and was added with CH_2Cl_2 (5 mL) and water (10 mL). The organic layer was separated and extracted with water (5 mL). The combined aqueous layer was adjusted to pH 7 with 30% aqueous K_2CO_3, and extracted with CH_2Cl_2 (10 mL) twice. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to give **5** (1.165 g, 4.43 mmol, 89% from **4**): ^{1}H NMR ($CDCl_3$) δ 1.63 (0.3H, d, $J=7$ Hz), 1.74 (2.7H, d, $J=7$ Hz), 5.43–5.75 (1H, m), 6.87 (1H, d, $J=4$ Hz), 6.98 (0.9H, s), 7.01 (0.1H, s), 7.51 (0.9H, d, $J=4$ Hz), 7.64 (0.1H, d, $J=4$ Hz), 7.55–7.75 (1H, m).

5-[(*R*)-1-(Formylamino)ethyl]imidazo[5,1-*b*]thiazole (6). To a solution of **5** (1.165 g, 4.43 mmol) in MeOH (20 mL) was added 12.7% aqueous KOH (20 mL) at 5 °C, and the mixture was stirred at room temperature for 1 h. After MeOH was removed from the reaction mixture under reduced pressure, the aqueous layer was extracted with CH_2Cl_2 (20 mL). To the aqueous layer was added K_2CO_3 (10 g), and the aqueous layer was extracted again with CH_2Cl_2 (10 mL) twice. The combined organic layer was dried over K_2CO_3 and concentrated under reduced pressure to give 5-[(*R*)-1-aminoethyl]imidazo[5,1-*b*]thiazole.

To a solution of 5-[(*R*)-1-aminoethyl]imidazo[5,1-*b*]thiazole in CH_2Cl_2 (20 mL) was added a mixture of formic acid (0.9 mL) and acetic anhydride (1.8 mL) stirred at 50 °C for 15 min, then at room temperature for 1 h. The reaction mixture was extracted with water (10 mL) twice, and the combined aqueous layer was adjusted to pH 10 with K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (20 mL) three times, and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give **6** (839 mg, 4.30 mmol, 97%): ^{1}H NMR ($CDCl_3$) δ 1.70 (3H, d, $J=7$ Hz), 5.61 (1H, q, $J=7$ Hz), 6.40–6.55 (1H, m), 6.81 (1H, d, $J=4$ Hz), 6.97 (1H, s), 7.59 (1H, d, $J=4$ Hz), 8.19 (1H, s).

(6*R*,7*R*)-7-[(*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(fluoromethoxyimino)acetamido]-3-[5-[(*R*)-1-(formylamino)ethyl]imidazo[5,1-*b*]thiazolium-6-yl]methyl-3-cephem-4-carboxylate (1s, CP6679). To a suspended solution of 2-(5-amino-1,2,4-thiadiazol-3-yl)-(*Z*)-2-fluoromethoxyiminoacetic acid (511 mg, 2.32 mmol) in dry CH_2Cl_2 (5 mL) was added phosphorous pentachloride (569 mg, 2.73 mmol) at −20 °C, and the mixture was stirred at −15 °C for 2.5 h to afford the acid chloride solution. To a suspended solution of **7** (1.23 g, 2.27 mmol) in dry CH_2Cl_2 (17.5 mL) were added *N*,*O*-bis(trimethy-lsilyl)acetamide (5 mL, 20 mmol) at room temperature, then above acid chloride solution at −20 °C, and the mixture was stirred at −20 °C for 1 h. After addition of water (50 mL), the mixture was stirred at room temperature for 30 min, and extracted with ethyl acetate (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to give **8** (1.10 g, 1.93 mmol, 85%): ^{1}H NMR ($CDCl_3$) δ 3.47 (1H, d, $J=18$ Hz), 3.67 (1H, d, $J=18$ Hz), 3.81 (3H, s), 4.34 (1H, d, $J=12$ Hz), 4.62 (1H, d, $J=12$ Hz), 5.09 (1H, d, $J=5$ Hz), 5.22 (2H, s), 5.73 (1H, dd, $J=54$ Hz, 3 Hz), 5.86 (1H, dd, $J=54$ Hz, 3 Hz), 6.11 (1H, dd, $J=5$ Hz, 9 Hz), 6.55 (2H, s), 6.89 (2H, d, $J=9$ Hz), 7.32 (2H, d, $J=9$ Hz), 8.28 (1H, d, $J=9$ Hz).

To a solution of **8** (651 mg, 0.800 mmol) in acetone (7 mL) was added sodium iodide (150 mg, 1.00 mmol), and the

mixture was stirred at room temperature for 1.5 h. After addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (10 mL×2). The combined organic layer was washed with 5% aqueous $Na_2S_2O_3$ (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 3-iodomethylcephem compound.

To a solution of 3-iodomethylcephem compound in DMF (7 mL) was added **6** (195 mg, 1.00 mmol), and the mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NaCl (50 mL), the mixture was extracted with ethyl acetate (20 mL×2). The combined organic layer was washed with saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. To the solution of the residue in DMF (2 mL) was added 2N aqueous CF_3COONa (20 mL), and the mixture was stirred at room temperature for 30 min. The mixture was filtrated to collect the precipitate **9**: ^{1}H NMR (DMSO-d_6) δ 1.55 (3H, d, J=7 Hz), 3.44 (1H, d, J=18 Hz), 3.52 (1H, d, J=18 Hz), 3.74 (3H, s), 5.10–5.55 (6H, m), 5.75 (2H, d, J=54 Hz), 5.93 (1H, dd, J=5 Hz, 9 Hz), 6.89 (2H, d, J=9 Hz), 7.33 (2H, d, J=9 Hz), 7.65 (1H, s), 7.86 (1H, d, J=4 Hz), 7.94 (1H, s), 8.08 (1H, s), 8.20 (2H, s), 8.26 (1H, d, J=4 Hz), 9.31 (1H, d, J=9 Hz).

To a solution of **9** in anisole (3.5 mL) was added trifluoroacetic acid (7 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was poured into diisopropyl ether (35 mL) under ice cooling. The precipitate were collected by filtration. The suspension of the precipitate in water (3 mL) was adjusted to pH 8.0 with saturated aqueous $NaHCO_3$ and purified by Diaion HP-20 (Mitsubishi Chemical) column chromatography (50 mL) to afford **1s** (118 mg, 0.193 mmol, 24%): ^{1}H NMR (D_2O) δ 1.69 (3H, d, J=7 Hz), 3.23 (1H, d, J=18 Hz), 3.49 (1H, d, J=18 Hz), 5.25 (1H, d, J=5 Hz), 5.32 (1H, d, J=15 Hz), 5.49 (1H, d, J=15 Hz), 5.58 (1H, q, J=7 Hz), 5.82 (2H, d, J=54 Hz), 5.88 (1H, d, J=5 Hz), 7.58 (1H, d, J=4 Hz), 7.69 (1H, s), 7.97 (1H, d, J=4 Hz), 8.11 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 610 [(M+H)$^+$]; FABHRMS calcd for $C_{21}H_{21}FN_9O_6S_3$ [(M+H)$^+$]: 610.0761, found: 610.0753.

Compounds 1a–1r, 1t–1w, 2m and 2p–2r. These compounds were prepared by a similar procedure as described for the preparation of **1s**.

Compound **1a** was obtained in 34% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.24 (1H, d, J=18 Hz), 3.64 (1H, d, J=18 Hz), 5.15 (1H, d, J=14 Hz), 5.28 (1H, d, J=5 Hz), 5.30 (1H, d, J=14 Hz), 5.84 (2H, d, J=54 Hz), 5.90 (1H, d, J=5 Hz), 7.54 (1H, d, J=4 Hz), 7.77 (1H, s), 7.93 (1H, d, J=4 Hz), 9.37 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 539 [(M+H)$^+$]; FABHRMS calcd for $C_{18}H_{16}FN_8O_5S_3$ [(M+H)$^+$]: 539.0390, found: 539.0411.

Compound **1b** was obtained in 28% yield from compound **7**: ^{1}H NMR (D_2O, pD=1) δ 3.23 (1H, d, J=18 Hz), 3.64 (1H, d, J=18 Hz), 5.15 (1H, d, J=15 Hz), 5.27 (1H, d, J=5 Hz), 5.33 (1H, d, J=15 Hz), 5.81 (2H, d, J=55 Hz), 5.87 (1H, d, J=5 Hz), 7.88 (1H, s), 8.36 (1H, s), 8.97 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 582 [(M+H)$^+$]; FABHRMS calcd for $C_{19}H_{17}FN_9O_6S_3$ [(M+H)$^+$]: 582.0448, found: 582.0436.

Compound **1c** was obtained in 28% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.24 (1H, d, J=18 Hz), 3.65 (1H, d, J=18 Hz), 4.86 (2H, s), 5.15 (1H, d, J=15 Hz), 5.27 (1H, d, J=5 Hz), 5.31 (1H, d, J=15 Hz), 5.82 (2H, d, J=55 Hz), 5.88 (1H, d, J=5 Hz), 7.46 (1H, s), 7.80 (1H, s), 9.42 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 569 [(M+H)$^+$]; FABHRMS calcd for $C_{19}H_{18}FN_8O_6S_3$ [(M+H)$^+$]: 569.0495, found: 569.0510.

Compound **1d** was obtained in 39% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.26 (1H, d, J=18 Hz), 3.66 (1H, d, J=18 Hz), 4.50–4.72 (3H, m), 4.84–4.88 (1H, m), 5.16 (1H, d, J=15 Hz), 5.29 (1H, d, J=5 Hz), 5.32 (1H, d, J=15 Hz), 5.89 (1H, d, J=5 Hz), 7.56 (1H, d, J=4 Hz), 7.79 (1H, s), 7.95 (1H, d, J=4 Hz), 9.38 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 553 [(M+H)$^+$]; FABHRMS calcd for $C_{19}H_{18}FN_8O_5S_3$ [(M+H)$^+$]: 553.0546, found: 553.0551.

Compound **1e** was obtained in 20% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.24 (1H, d, J=18 Hz), 3.63 (1H, d, J=18 Hz), 4.49 (1H, m), 4.59 (1H, m), 4.68 (1H, m), 4.84 (1H, m), 5.18 (1H, d, J=14 Hz), 5.27 (1H, d, J=5 Hz), 5.33 (1H, d, J=14 Hz), 5.87 (1H, d, J=5 Hz), 7.88 (1H, s), 8.37 (1H, s), 9.78 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 596 [(M+H)$^+$]; FABHRMS calcd for $C_{20}H_{19}FN_9O_6S_3$ [(M+H)$^+$]: 596.0604, found: 596.0608.

Compound **1f** was obtained in 34% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.23 (1H, d, J=18 Hz), 3.63 (1H, d, J=18 Hz), 4.49 (1H, m), 4.58 (1H, m), 4.61 (1H, m), 4.79 (1H, m), 4.88 (2H, s), 5.16 (1H, d, J=15 Hz), 5.27 (1H, d, J=5 Hz), 5.30 (1H, d, J=15 Hz), 5.87 (1H, d, J=5 Hz), 7.47 (1H, s), 7.79 (1H, s), 9.42 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 583 [(M+H)$^+$]; FABHRMS calcd for $C_{20}H_{20}FN_8O_6S_3$ [(M+H)$^+$]: 583.0652, found: 583.0652.

Compound **1g** was obtained in 31% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.24 (1H, d, J=18 Hz), 3.64 (1H, d, J=18 Hz), 4.50 (1H, m), 4.59 (1H, m), 4.69 (1H, m), 4.84 (1H, m), 5.18 (1H, d, J=15 Hz), 5.27 (1H, d, J=5 Hz), 5.33 (1H, d, J=15 Hz), 5.69 (2H, d, J=48 Hz), 5.88 (1H, d, J=5 Hz), 7.77 (1H, s), 7.84 (1H, s), 9.55 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 585 [(M+H)$^+$]; FABHRMS calcd for $C_{20}H_{19}F_2N_8O_5S_3$ [(M+H)$^+$]: 585.0609, found: 585.0595.

Compound **1h** was obtained in 1.8% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.29 (3H, t, J=7 Hz), 3.27 (1H, d, J=18 Hz), 3.55 (1H, d, J=18 Hz), 4.31 (2H, q, J=7 Hz), 5.24 (1H, d, J=5 Hz), 5.42 (1H, d, J=15 Hz), 5.59 (1H, d, J=15 Hz), 5.86 (1H, d, J=5 Hz), 7.73 (1H, d, J=4 Hz), 8.02 (1H, s), 8.18 (1H, d, J=4 Hz); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 578 [(M+H)$^+$]; FABHRMS calcd for $C_{20}H_{20}N_9O_6S_3$ [(M+H)$^+$]: 570.0699, found: 578.0710.

Compound **1i** was obtained in 19% yield from compound **7**: ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, t, J = 7 Hz), 3.11 (1H, d, J = 18 Hz), 3.64 (1H, d, J = 18 Hz), 4.12 (2H, q, J = 7 Hz), 4.88 (1H, d, J = 15 Hz), 5.00 (1H, d, J = 5 Hz), 5.36 (1H, d, J = 15 Hz), 5.64 (1H, dd, J = 8 Hz, 5 Hz), 7.67 (1H, d, J = 4 Hz), 8.11 (2H, s), 8.21 (2H, m), 9.42 (1H, d, J = 8 Hz), 9.79 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 563 [(M + H)$^+$]; FABHRMS calcd for $C_{20}H_{19}N_8O_6S_3$ [(M + H)$^+$]: 563.0590, found: 563.0594.

Compound **1j** was obtained in 2.5% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.33 (3H, t, J = 7 Hz), 3.34 (1H, d, J = 18 Hz), 3.69 (1H, d, J = 18 Hz), 4.36 (2H, q, J = 7 Hz), 5.31 (1H, d, J = 5 Hz), 5.45 (1H, d, J = 15 Hz), 5.56 (1H, d, J = 15 Hz), 5.91 (1H, d, J = 5 Hz), 8.04 (1H, d, J = 4 Hz), 8.30 (1H, s), 8.37 (1H, d, J = 4 Hz); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 560 [(M + H)$^+$]; FABHRMS calcd for $C_{20}H_{18}N_9O_5S_3$ [(M + H)$^+$]: 560.0593, found: 560.0591.

Compound **1k** was obtained in 14% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.34 (3H, t, J = 7 Hz), 3.25 (1H, d, J = 18 Hz), 3.57 (1H, d, J = 18 Hz), 4.36 (2H, q, J = 7 Hz), 5.22 (2H, s), 5.28 (1H, d, J = 15 Hz), 5.28 (1H, d, J = 5 Hz), 5.36 (1H, d, J = 15 Hz), 5.89 (1H, d, J = 5 Hz), 7.60 (1H, d, J = 4 Hz), 7.78 (1H, s), 8.07 (1H, d, J = 4 Hz); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 565 [(M + H)$^+$]; FABHRMS calcd for $C_{20}H_{21}N_8O_6S_3$ [(M + H)$^+$]: 565.0746, found: 565.0743.

Compound **1l** was obtained in 27% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.33 (3H, t, J = 7 Hz), 3.23 (1H, d, J = 18 Hz), 3.50 (3H, s), 3.53 (1H, d, J = 18 Hz), 4.36 (2H, q, J = 7 Hz), 5.11 (2H, s), 5.29 (1H, d, J = 15 Hz), 5.26 (1H, d, J = 5 Hz), 5.31 (1H, d, J = 15 Hz), 5.89 (1H, d, J = 5 Hz), 7.63 (1H, d, J = 6 Hz), 7.84 (1H, s), 8.06 (1H, d, J = 6 Hz); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 579 [(M + H)$^+$]; FABHRMS calcd for $C_{21}H_{23}N_8O_6S_3$ [(M + H)$^+$]: 579.0903, found: 579.0903.

Compound **1m** was obtained in 29% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.31 (3H, t, J = 7 Hz), 3.16 (1H, d, J = 18 Hz), 3.58 (1H, d, J = 18 Hz), 4.34 (2H, q, J = 7 Hz), 5.03 (2H, s), 5.28 (1H, d, J = 5 Hz), 5.29 (1H, d, J = 15 Hz), 5.34 (1H, d, J = 15 Hz), 5.87 (1H, d, J = 5 Hz), 7.59 (1H, d, J = 4 Hz), 7.73 (1H, s), 8.04 (1H, d, J = 4 Hz), 8.20 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 592 [(M + H)$^+$]; FABHRMS calcd for $C_{21}H_{22}N_9O_6S_3$ [(M + H)$^+$]: 592.0855, found: 592.0853.

Compound **1n** was obtained in 15% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.32 (3H, t, J = 7 Hz), 2.81 (0.75H, s), 3.08 (2.25H, s), 3.14 (0.25H, d, J = 18 Hz), 3.16 (0.75H, d, J = 18 Hz), 3.57 (0.25H, d, J = 18 Hz), 3.60 (0.75H, d, J = 18 Hz), 4.34 (2H, q, J = 7 Hz), 5.15 (1H, d, J = 15 Hz), 5.25 (1H, d, J = 15 Hz), 5.28 (1H, d, J = 5 Hz), 5.31 (1H, d, J = 17 Hz), 5.38 (1H, d, J = 17 Hz), 5.89 (1H, d, J = 5 Hz), 7.61 (0.25H, d, J = 4 Hz), 7.69 (0.75H, d, J = 4 Hz), 7.78 (0.75H, s), 7.86 (0.25H, s), 7.96 (0.75H, d, J = 4 Hz), 7.98 (0.25H, d, J = 4 Hz), 8.14 (0.75H, s), 8.41 (0.25H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 606 [(M + H)$^+$]; FABHRMS calcd for $C_{22}H_{34}N_9O_6S_3$ [(M + H)$^+$]: 606.1012, found: 606.1014.

Compound **1o** was obtained in 23% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.33 (3H, t, J = 7 Hz), 2.02 (3H, s), 3.15 (1H, d, J = 18 Hz), 3.59 (1H, d, J = 18 Hz), 4.35 (2H, q, J = 7 Hz), 4.94 (1H, s), 4.95 (1H, s), 5.28 (1H, d, J = 15 Hz), 5.29 (1H, d, J = 5 Hz), 5.36 (1H, d, J = 15 Hz), 5.88 (1H, d, J = 5 Hz), 7.59 (1H, d, J = 4 Hz), 7.74 (1H, s), 8.04 (1H, d, J = 4 Hz); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 606 [(M + H)$^+$]; FABHRMS calcd for $C_{22}H_{24}N_9O_6S_3$ [(M + H)$^+$]: 606.1012, found: 606.0999.

Compound **1p** was obtained in 13% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.15 (1H, d, J = 18 Hz), 3.58 (1H, d, J = 18 Hz), 4.05 (3H, s), 5.02 (2H, s), 5.27 (1H, d, J = 5 Hz), 5.28 (1H, d, J = 15 Hz), 5.33 (1H, d, J = 15 Hz), 5.86 (1H, d, J = 5 Hz), 7.58 (1H, d, J = 4 Hz), 7.73 (1H, s), 8.03 (1H, d, J = 4 Hz), 8.20 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 578 [(M + H)$^+$]; FABHRMS calcd for $C_{20}H_{20}N_9O_6S_3$ [(M + H)$^+$]: 578.0699, found: 578.0695.

Compound **1q** was obtained in 15% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.16 (1H, d, J = 18 Hz), 3.60 (1H, d, J = 18 Hz), 5.03 (2H, s), 5.20 (1H, d, J = 15 Hz), 5.32 (1H, d, J = 5 Hz), 5.36 (1H, d, J = 15 Hz), 5.90 (2H, d, J = 57 Hz), 5.84 (1H, d, J = 5 Hz), 7.60 (1H, d, J = 4 Hz), 7.73 (1H, s), 8.05 (1H, d, J = 4 Hz), 8.21 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 596 [(M + H)$^+$]; FABHRMS calcd for $C_{20}H_{19}FN_9O_6S_3$ [(M + H)$^+$]: 596.0604, found: 596.0608.

Compound **1r** was obtained in 17% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.17 (1H, d, J = 18 Hz), 3.60 (1H, d, J = 18 Hz), 4.50–4.75 (3H, m), 4.85–4.90 (1H, m), 5.04 (2H, s), 5.30 (1H, d, J = 5 Hz), 5.30 (1H, d, J = 15 Hz), 5.38 (1H, d, J = 15 Hz), 5.89 (1H, d, J = 5 Hz), 7.61 (1H, d, J = 4 Hz), 7.75 (1H, s), 8.06 (1H, d, J = 4 Hz), 8.22 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 610 [(M + H)$^+$]; FABHRMS calcd for $C_{21}H_{21}FN_9O_6S_3$ [(M + H)$^+$]: 610.0761, found: 610.0753.

Compound **1t** was obtained in 34% yield from compound **7**: ^{1}H NMR (D_2O) δ 1.68 (3H, d, J = 7 Hz), 3.23 (1H, d, J = 18 Hz), 3.59 (1H, d, J = 18 Hz), 5.27 (1H, d, J = 5 Hz), 5.30 (1H, d, J = 15 Hz), 5.34 (1H, br-s), 5.64 (1H, q, J = 7 Hz), 5.83 (2H, d, J = 54 Hz), 5.87 (1H, d, J = 5 Hz), 7.59 (1H, d, J = 4 Hz), 7.72 (1H, s), 7.97 (1H, d, J = 4 Hz), 8.14 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 610 [(M + H)$^+$]; FABHRMS calcd for $C_{21}H_{21}FN_9O_6S_3$ [(M + H)$^+$]: 610.0767, found: 610.0753.

Compound **1u** was obtained in 26% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.13 (1H, d, J = 18 Hz), 3.48 (1H, d, J = 18 Hz), 3.98–4.00 (2H, m), 5.17 (1H, d, J = 5 Hz), 5.24 (1H, d, J = 15 Hz), 5.30 (1H, d, J = 15 Hz), 5.59 (1H, t, J = 5 Hz), 5.63 (1H, s), 5.77 (1H, d, J = 5 Hz), 5.81 (1H, s), 7.47 (1H, d, J = 4 Hz), 7.71 (1H, s), 7.90 (1H, d, J = 4 Hz), 8.11 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 626 [(M + H)$^+$]; FABHRMS calcd for $C_{21}H_{21}FN_9O_7S_3$ [(M + H)$^+$]: 626.0710, found: 626.0709.

Compound **1v** was obtained in 25% yield from compound **7**: ^{1}H NMR (D_2O) δ 3.24 (1H, d, J = 18 Hz), 3.49

(1H, d, $J=18$ Hz), 4.10 (1H, dd, $J=12$ Hz, 4.7 Hz), 4.14 (1H, dd, $J=12$ Hz, 5.1 Hz), 5.24 (1H, d, $J=15$ Hz), 5.25 (1H, d, $J=5$ Hz), 5.30 (1H, d, $J=15$ Hz), 5.69 (1H, dd, $J=5.1$ Hz, 4.7 Hz), 5.82 (2H, d, $J=54$ Hz), 5.88 (1H, d, $J=5$ Hz), 7.57 (1H, d, $J=4$ Hz), 7.75 (1H, s), 8.02 (1H, d, $J=4$ Hz), 8.19 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 626 $[(M+H)^+]$; FABHRMS calcd for $C_{21}H_{21}FN_9O_7S_3$ $[(M+H)^+]$: 626.0710, found: 626.0698.

Compound **1w** was obtained in 7% yield from compound **7**: ^1H NMR (D_2O) δ 1.97 (6H, s), 3.15 (1H, d, $J=18$ Hz), 3.57 (1H, d, $J=18$ Hz), 5.28 (1H, d, $J=4$ Hz), 5.30 (1H, d, $J=15$ Hz), 5.38 (1H, d, $J=15$ Hz), 5.83 (2H, d, $J=54$ Hz), 5.89 (1H, d, $J=4$ Hz), 7.57 (1H, d, $J=5$ Hz), 7.67 (1H, s), 8.09 (1H, s), 8.11 (1H, d, $J=5$ Hz); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 624 $[(M+H)^+]$; FABHRMS calcd for $C_{22}H_{23}FN_9O_6S_3$ $[(M+H)^+]$: 624.0917, found: 624.0909.

Compound **2m** was obtained in 10% yield from compound **7**: ^1H NMR (D_2O) δ 1.31 (3H, t, $J=7$ Hz), 3.19 (1H, d, $J=18$ Hz), 3.61 (1H, d, $J=18$ Hz), 4.28 (2H, q, $J=7$ Hz), 5.05 (2H, s), 5.31 (1H, d, $J=5$ Hz), 5.31 (1H, d, $J=15$ Hz), 5.38 (1H, d, $J=15$ Hz), 5.87 (1H, d, $J=5$ Hz), 7.02 (1H, s), 7.62 (1H, d, $J=4$ Hz), 7.75 (1H, s), 8.07 (1H, d, $J=4$ Hz), 8.22 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 591 $[(M+H)^+]$; FABHRMS calcd for $C_{22}H_{23}N_8O_6S_3$ $[(M+H)^+]$: 591.0903, found: 591.0912.

Compound **2p** was obtained in 32% yield from compound **7**: ^1H NMR (D_2O) δ 3.16 (1H, d, $J=18$ Hz), 3.59 (1H, d, $J=18$ Hz), 3.98 (3H, s), 5.03 (2H, s), 5.28 (1H, d, $J=5$ Hz), 5.29 (1H, d, $J=15$ Hz), 5.34 (1H, d, $J=15$ Hz), 5.83 (1H, d, $J=5$ Hz), 6.99 (1H, s), 7.59 (1H, d, $J=4$ Hz), 7.73 (1H, s), 8.04 (1H, d, $J=4$ Hz), 8.22 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 577 $[(M+H)^+]$; FABHRMS calcd for $C_{21}H_{21}N_8O_6S_3$ $[(M+H)^+]$: 577.0746, found: 577.0746.

Compound **2q** was obtained in 12% yield from compound **7**: ^1H NMR (D_2O) δ 3.19 (1H, d, $J=18$ Hz), 3.62 (1H, d, $J=18$ Hz), 5.05 (2H, s), 5.31 (1H, d, $J=15$ Hz), 5.32 (1H, d, $J=5$ Hz), 5.38 (1H, d, $J=15$ Hz), 5.80 (2H, d, $J=55$ Hz), 5.88 (1H, d, $J=5$ Hz), 7.19 (1H, s), 7.61 (1H, d, $J=4$ Hz), 7.75 (1H, s), 8.07 (1H, d, $J=4$ Hz), 8.22 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 595 $[(M+H)^+]$; FABHRMS calcd for $C_{21}H_{20}FN_8O_6S_3$ $[(M+H)^+]$: 595.0652, found: 595.0655.

Compound **2r** was obtained in 14% yield from compound **7**: ^1H NMR (D_2O) δ 3.18 (1H, d, $J=18$ Hz), 3.61 (1H, d, $J=18$ Hz), 4.40–4.70 (3H, m), 4.85 (1H, m), 5.05 (2H, s), 5.31 (1H, d, $J=5$ Hz), 5.31 (1H, d, $J=16$ Hz), 5.37 (1H, d, $J=16$ Hz), 5.87 (1H, d, $J=5$ Hz), 7.05 (1H, s), 7.61 (1H, d, $J=4$ Hz), 7.75 (1H, s), 8.07 (1H, d, $J=4$ Hz), 8.22 (1H, s); IR (KBr) cm^{-1} 1770 (C=O); FABMS m/z 609 $[(M+H)^+]$; FABHRMS calcd for $C_{22}H_{22}FN_8O_6S_3$ $[(M+H)^+]$: 609.0808, found: 609.0824.

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