Pergamon

Tetrahedron 56 (2000) 5657–5665

TETRAHEDRON

Structural Modifications and Biological Evaluation of 3-Isoxazolylvinylcephalosporins

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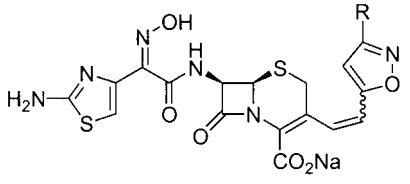
Received 4 October 1999; accepted 20 December 1999

Abstract—Structural modifications and biological evaluations of 3-isoxazolylvinylcephalosporins (**I**) were performed. The replacement of a hydrogen atom at the 7-aminothiazole group by a chlorine resulted in an improvement of the activity against resistant Gram-positive bacterial strains including the methicillin-resistant *Staphylococcus aureus* (MRSA) and the ciprofloxacin-resistant *Staphylococcus aureus* (CRSA). The introduction of other heterocycles such as an isothiazole or a thiadiazole in place of the isoxazole moiety gave slightly decreased in vitro activities.

Introduction

In recent years, the worldwide incidence of antibiotic resistance among Gram-positive bacteria, e.g. *Staphylococcus, Streptococcus* and *Enterococcus* species, has increased. Consequently, great concern has been focused on the development of novel cephalosporin antibiotics having improved antibacterial activities against resistant bacterial strains. During the last several years we have synthesized various 3-isoxazolylvinylcephalosporins **I**[1] and investigated their antibacterial activities. There we found that the introduction of an isoxazole moiety into the C-3 position of a cephem nucleus gave a remarkable enhancement in the activities against Gram-positive bacteria including *Streptococcus pyogenes* and *Staphylococcus aureus*. As the C-7 substituent, 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido group was a good match.



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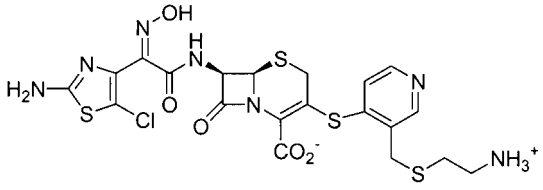

MC-02,479

In 1997, Microcide Pharmaceutical Inc. (MPI) reported that the chlorine-substituted aminothiazole moiety of the cephalosporin derivative MC-02479 was responsible for its excellent activity against resistant *Staphylococcus aureus*.[2] While working on optimizing in vitro activities and pharmacokinetic properties of 3-isoxazolylvinylcephalosporins **I** against Gram-positive bacteria, we became interested in the chlorine-substituted aminothiazole, i.e. 2-amino-5-chlorothiazole, and selected it as the major structural modification at the C-7 position. The replacement of isoxazole moiety by other heterocycles such as the isothiazole or the thiadiazole was also carried out. Herein we report the synthesis and biological evaluation of modified 3-isoxazolylvinylcephalosporins **1** and **3**–**6** focusing on Gram-positive bacteria (Fig. 1).

Synthesis

The cephalosporins **1** and **2** were synthesized following the reaction pathway depicted in Scheme 1. The cephalosporins **2** had been reported previously,[1d] and here they were freshly

Keywords: antibacterials; cephalosporins; isoxazoles; thiazoles.
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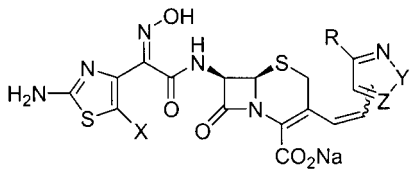
PII: S0040-4020(00)00415-4

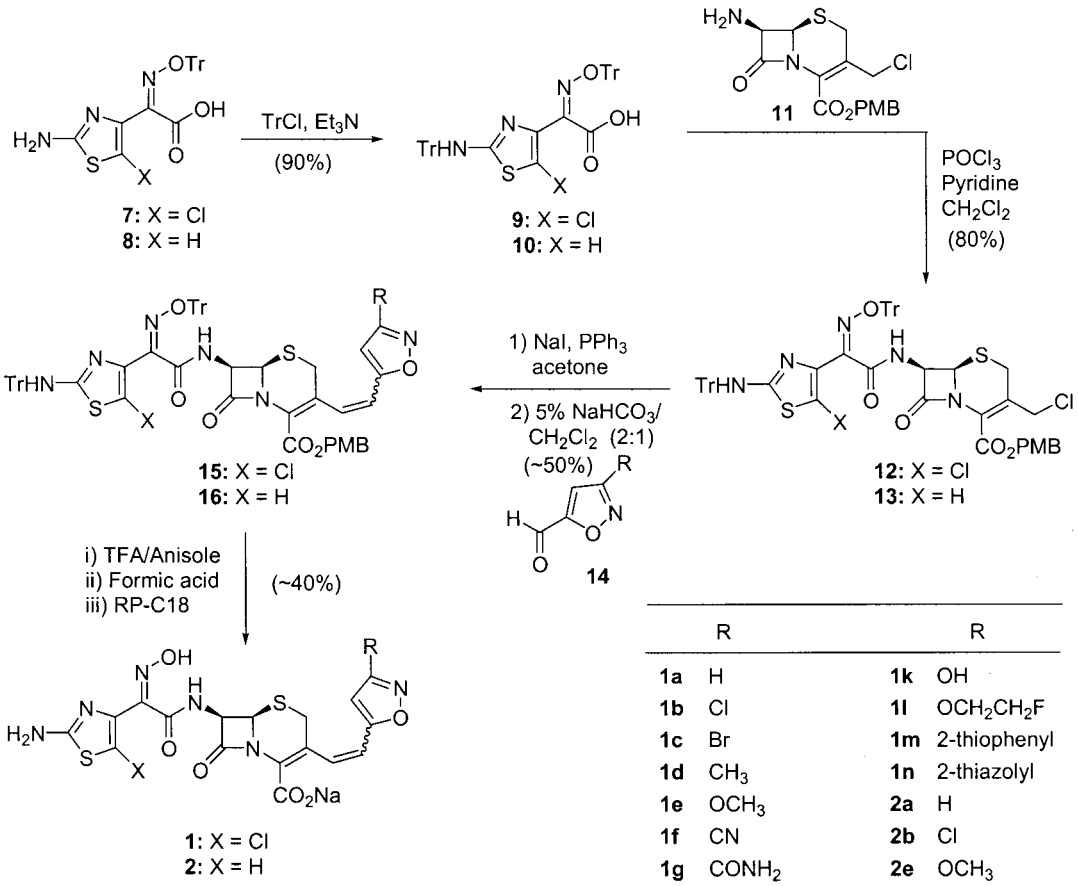


Compd	X	Y	Z
1	Cl	O	C
2	H	O	C
3	Cl	S	C
4	H	S	C
5	Cl	S	N or C
6	H	S	N or C

Figure 1.

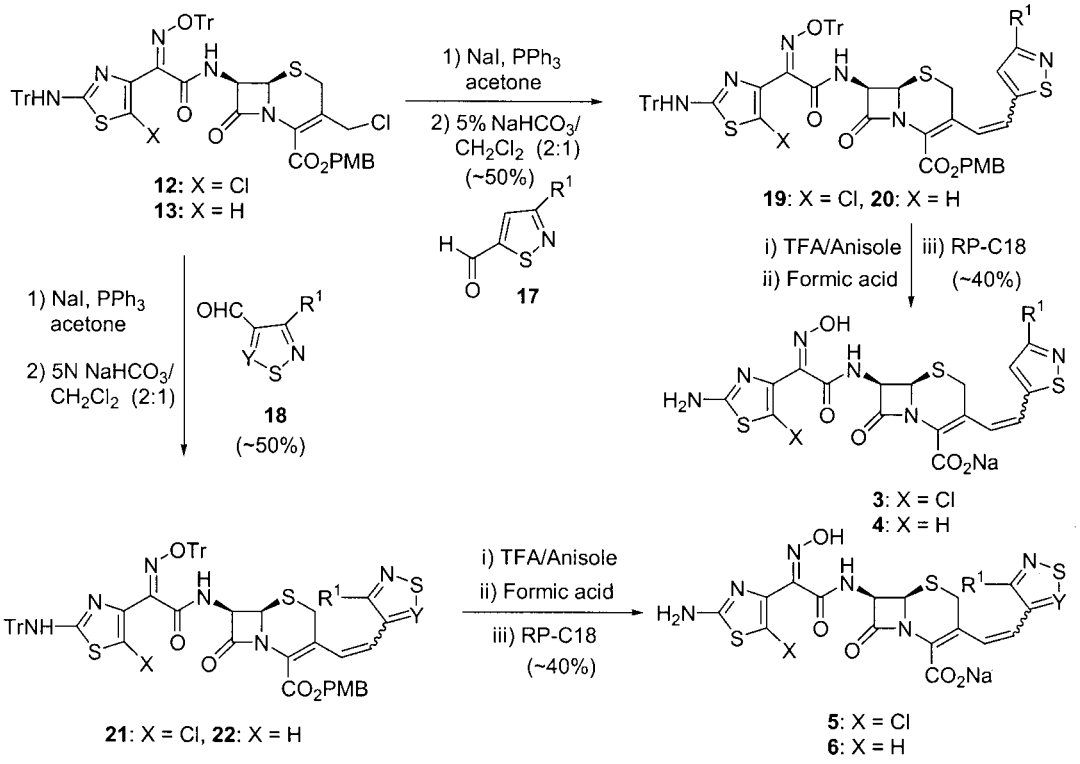
resynthesized for comparison. The amine function of 2-(2-amino-5-chlorothiazol-4-yl)-2-trityloxyiminoacetic acid (**7**), which was prepared by a known method,[2] and 2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetic acid (**8**) each was protected (Ph_3CCl/Et_3N). The completely protected carboxylic acids **9** and **10** each was reacted with *p*-methoxybenzyl 7-amino-3-chloromethylcephalosporanate **11** using phosphorus oxychloride ($POCl_3$) and pyridine at −40°C to afford the key intermediates **12** and **13**, respectively. Then they were coupled with the isoxazole aldehydes[3] **14** via phosphonium salts to produce the compounds **15** and **16**, respectively in ca. 50% yield as mixtures of geometrical isomers (*Z*/*E*~9:1). The major (*Z*)-isomer was separated from the mixture by column chromatography using a mixed solvent of hexane and ethyl acetate (3:2) as the eluent. Through the sequential deprotection by trifluoroacetic acid and formic acid, crude free acids of the final products **1** and **2** were obtained. Sodium salt formation by the treatment with aqueous sodium bicarbonate solution followed by purification by reverse phase column chromatography (Lichrosorb® RP-18, 20%, aq. MeOH) and lyophilization afforded the pure final products **1** and **2** in ca. 40% yield.

The synthesis of cephalosporin compounds **3**–**6** is outlined in Scheme 2. It utilized basically the same protocol adopted in the preparation of **1** and **2**. The intermediates **12** and **13** were each coupled with the isothiazole or the thiadiazole aldehyde[4] (**17** and **18**) via phosphonium salts to produce the compounds **19** and **20**, or **21** and **22**, respectively, in ca. 50% yield as mixtures of geometrical isomers (*Z*/*E*~2:1). The



	R		R
1a	H	**1k**	OH
1b	Cl	**1l**	OCH_2CH_2F
1c	Br	**1m**	2-thiophenyl
1d	CH_3	**1n**	2-thiazolyl
1e	OCH_3	**2a**	H
1f	CN	**2b**	Cl
1g	$CONH_2$	**2e**	OCH_3
1h	$CON(CH_3)_2$	**2m**	2-thiophenyl
1i	CH_2OCONH_2	**2n**	2-thiazolyl
1j	$CH_2OCON(CH_3)_2$		

Scheme 1. Synthesis of 3-isoxazolylvinylcephalosporins.



Compds.	R^1	Compds.	R^1	Compds.	Y	R^1	Compds.	Y	R^1
3a	H	**4a**	H	**5a**	N	H	**6a**	N	H
3e	OCH_3	**4e**	OCH_3	**5d**	C	CH_3	**6d**	C	CH_3
3k	OH	**4k**	OH						

Scheme 2. Synthesis of 3-isothiazolylvinyl- and 3-thiadiazolylvinylcephalosporins.

(*Z*)- and (*E*)-isomer were separated, if possible, by column chromatography using hexane and ethyl acetate (3:2) as the eluent. Following the same procedure described above for the preparation of compounds **1** and **2**, the compounds **3**–**6** could be obtained in ca. 40% yield.

Biological Activity

In vitro antibacterial activities (MIC) of all the compounds prepared and references were determined by the Mueller–Hinton agar dilution method.[5] The activities of the compounds synthesized were compared with cefdnir, cefpodoxime and vancomycin as references. In vitro activities of the compounds **1** and references against selected strains are summarized in Table 1. Most of the compounds **1** showed good antibacterial activity against Gram-positive bacterial strains including MRSA and CRSA. Comparing the activities of **1a** and **2a**, **1b** with **2b** and **1e** with **2e**, the introduction of a chlorine atom into the aminothiazole of the C-7 substituent enhanced the activity slightly against MRSA and considerably against CRSA. The activities of **1a**, **1b** and **1e** each was comparable or superior to the corresponding compound **2** by factors of 2 against MRSA, and 2–4 against CRSA. In our previous work, the compound **2b** showed the best activity of the series.[1d] The compounds **1m** and **1n** having a heterocyclic substitutent on the isoxazole also showed good activities against Gram-positive bacteria. The compound **1m** was superior to vancomycin in activity against all the strains tested. Regarding the effect of the substitutents of the isoxazole, halogen substituents conferred higher activity, and hydrophilic substituents such as carbamoyl or hydroxyl groups gave lower activity against Gram-positive bacteria.

In vitro activities of the compounds **3**–**6**, having an isothiazole or a thiadiazole moiety instead of the isoxazole, against selected strains are summarized in Table 2. Comparing the activities of **4a** with **2a** and **4e** with **2e**, the replacement of the isoxazole by an isothiazole resulted in reduced activities against Gram-positive bacteria (Tables 1 and 2). As was the case with cephalosporins **2**, the introduction of a chlorine atom into the aminothiazole of the C-7 substituent of 3-isothiazolylvinylcephalosporins **4** enhanced the activity against Gram-positive bacteria. Unlike other series of compounds, the cephalosporins **4** showed considerable difference in activity according to the geometry of the C-3 vinyl group. Comparing **4k**(*E*) with **4k**(*Z*), and **4e**(*E*) with **4e**(*Z*), respectively, (*E*)-vinyl isomer of 3-isothiazolylvinylcephalosporins exhibited better antibacterial activity than (*Z*)-isomer by factors of 2–8 against Gram-positive bacteria. Interestingly, in the case

Table 1. In vitro antibacterial activities of 3-isoxazolylvinylcephaloporins (MIC (agar dilution method, Mueller–Hinton agar, 10^4 CFU/Spot), μg/mL)

Compounds	Microorganisms[a]										
	S.*a*	MRSA1	MRSA2	MRSA3	CRSA	MSSA	S.*e*	E.*f*	S.*p*	E.*c*1	E.*c*2
1a(M)[b]	0.5	0.5	1	0.5	2	0.5	≤0.12	0.5	≤0.12	≤0.12	0.25
1b(*Z*)	0.25	0.5	1	0.25	2	0.5	≤0.12	0.5	≤0.12	0.5	0.5
1c(*Z*)	0.5	1	2	0.5	4	1	≤0.12	1	≤0.12	0.5	1
1d(*Z*)	0.5	0.5	2	0.5	2	0.5	≤0.12	0.5	≤0.12	≤0.12	0.25
1e(*Z*)	0.5	1	2	0.5	4	1	≤0.12	0.5	≤0.12	0.25	0.5
1f(*Z*)	0.5	0.5	1	0.5	2	0.5	≤0.12	0.5	≤0.12	0.25	0.5
1g(*Z*)	0.5	1	2	0.5	2	1	≤0.12	0.5	≤0.12	≤0.12	0.25
1h(*Z*)	1	1	4	1	4	1	0.5	0.5	≤0.12	0.5	0.5
1i(*Z*)	1	1	2	0.5	4	1	0.25	0.5	≤0.12	≤0.12	0.25
1j(*Z*)	0.5	1	2	1	4	0.5	0.25	0.5	≤0.12	1	2
1k(*Z*)	2	2	16	2	16	4	1	4	≤0.12	≤0.12	0.25
1l(*Z*)	1	1	2	1	4	1	0.25	0.5	≤0.12	0.25	0.5
1m(*Z*)	0.25	0.5	1	0.25	1	1	≤0.12	0.5	≤0.12	0.5	1
1n(*Z*)	0.5	0.5	1	0.5	2	1	0.25	1	≤0.12	1	1
2a(*Z*)	0.5	0.5	2	0.25	8	0.5	≤0.12	1	≤0.12	≤0.12	≤0.12
2b(*Z*)	0.25	0.25	2	0.25	4	0.25	≤0.12	1	≤0.12	≤0.12	≤0.12
2e(*Z*)	1	1	4	0.5	16	1	0.25	2	≤0.12	≤0.12	0.25
2m(*Z*)	0.25	0.5	2	0.25	4	0.25	≤0.12	1	≤0.12	0.25	0.5
2n(*Z*)	0.5	0.5	4	0.25	8	0.5	≤0.12	2	≤0.12	0.25	0.25
Cefdnir	0.5	0.5	8	0.25	>32	0.5	≤0.12	4	≤0.12	≤0.12	≤0.12
Cefpd.[c]	4	4	>32	2	>32	4	1	>32	≤0.12	≤0.12	0.25
VCM[d]	1	1	1	1	1	1	0.5	2	0.25	>32	>32

[a] S.*a*: *Staphylococcus aureus* ATCC 29213, MRSA1: Methicillin-resistant *Staphylococcus aureus* C2207, MRSA2: Methicillin-resistant *Staphylococcus aureus* C5100, MRSA3: Methicillin-resistant *Staphylococcus aureus* C6068, CRSA: ciprofloxacin-resistant *Staphylococcus aureus* C1062, MSSA: Methicillin-susceptible *Staphylococcus aureus* C7142, S.*e*: *Staphylococcus epidermis* ATCC 12228, E.*f*.: *Enterococcus faecalis* ATCC 29212, S.*p*: *Streptococcus pyogenes* ATCC 8668, E.*c*1: *Enterobacter cloacae* C4008, E.*c*2: *Escherichia coli* ATCC 10536.
[b] Mixture of geometrical isomers: the (*Z*)-isomer was partly isomerized during lyophilization.
[c] Cefpodoxime.
[d] Vancomycin.

Table 2. In vitro antibacterial activities of 3-isothiazolyl- and 3-thiadiazolylvinylcephaloporins (MIC (agar dilution method, Mueller–Hinton agar, 10^4 CFU/Spot) μg/mL)

Compounds	Microorganisms[a]										
	S.*a*	MRSA1	MRSA2	MRSA3	CRSA	MSSA	S.*e*	E.*f*	S.*p*	E.*c*1	E.*c*2
3a(M)[b]	0.5	0.5	1	0.5	2	0.5	0.25	1	≤0.12	0.5	0.5
3a(E)	0.5	1	1	0.5	2	0.5	0.25	1	≤0.12	0.5	0.5
3e(*Z*)	0.25	0.5	1	0.5	2	1	≤0.12	0.5	≤0.12	0.5	0.5
3e(*E*)	0.5	1	1	0.5	2	0.5	0.25	0.25	≤0.12	1	0.5
3k(*Z*)	0.5	0.5	2	0.5	4	0.5	0.25	2	≤0.12	≤0.12	≤0.12
4a(M)[b]	0.5	1	4	0.5	8	0.5	0.25	4	≤0.12	≤0.12	≤0.12
4e(*Z*)	1	1	8	0.5	32	1	0.25	4	≤0.12	0.5	1
4e(*E*)	0.5	1	2	0.5	4	0.5	0.5	0.25	≤0.12	≤0.12	≤0.12
4k(*Z*)	1	1	8	0.5	32	1	0.25	4	≤0.12	≤0.12	≤0.12
4k(*E*)	0.5	1	2	0.5	4	0.5	0.5	0.5	≤0.12	≤0.12	≤0.12
5a(*Z*)	2	2	8	2	16	2	0.5	4	≤0.12	1	1
5d(*E*,*Z*)[c]	0.25	0.5	2	0.5	4	0.5	≤0.12	1	≤0.12	≤0.12	≤0.12
6a(*Z*)	0.5	0.5	4	0.25	8	0.5	≤0.12	2	≤0.12	≤0.12	≤0.12
6a(*E*)	0.5	0.5	4	0.5	8	0.5	≤0.12	1	≤0.12	≤0.12	≤0.12
6d(*E*,*Z*)[c]	0.25	0.5	4	0.25	16	0.25	≤0.12	1	≤0.12	≤0.12	0.25
Cefdnir	0.5	0.5	8	0.25	>32	0.5	≤0.12	4	≤0.12	≤0.12	≤0.12
Cefpd.[d]	4	4	>32	2	>32	4	1	>32	≤0.12	≤0.12	0.25
VCM[e]	1	1	1	1	1	1	0.5	2	0.25	>32	>32

[a] S.*a*: *Staphylococcus aureus* ATCC 29213, MRSA1: Methicillin-resistant *Staphylococcus aureus* C2207, MRSA2: Methicillin-resistant *Staphylococcus aureus* C5100, MRSA3: Methicillin-resistant *Staphylococcus aureus* C6068, CRSA: ciprofloxacin-resistant *Staphylococcus aureus* C1062, MSSA: Methicillin-susceptible *Staphylococcus aureus* C7142, S.*e*: *Staphylococcus epidermis* ATCC 12228, E.*f*.: *Enterococcus faecalis* ATCC 29212, S.*p*: *Streptococcus pyogenes* ATCC 8668, E.*c*1: *Enterobacter cloacae* C4008, E.*c*2: *Escherichia coli* ATCC 10536.
[b] Mixture of geometrical isomers: the (*Z*)-isomer was partly isomerized during lyophilization.
[c] The isomers could not be separated by column chromatography.
[d] Cefpodoxime.
[e] Vancomycin.

of 3-thiadiazolyvinyl cephalosporins, the effect of introducing a chlorine atom into the aminothiazole was reversed. Comparing **5a**(*Z*) with **6a**(*Z*), chlorine substitution at the aminothiazole lowered the activity of the cephalosporin compound against almost all the strains tested.

Conclusion

For the 3-isoxazolylvinyl- and the 3-isothiazolylvinyl-cephalosporins, the introduction of a chlorine atom into the aminothiazole of the C-7 substitutent enhanced the activity slightly against MRSA and considerably against CRSA. But the tendency was reversed for the 3-thidiazolyl-vinylcephalosporins. Replacing the isoxazole of the 3-isoxazolylvinylcephalosporins by an isothiazole or a thiadiazole did not give better results. Up to this point, the series of cephalosporins **1** looks like the best combination. Of them, the compounds, **1a**, **1b**, **1f**, **1m** and **1n** showed promising in vitro activities. Their in vivo efficacy and pharmacokinetic properties are now under evaluation. The oral bioavailability of their C-4 esters is also being studied.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer and a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts of protons were recorded in ppm relative to tetramethylsilane as an internal standard unless stated otherwise. Infrared spectra were recorded on a Perkin Elmer 16F PC FT-IR using the potassium bromide pellet. HRMS spectra were obtained on a VG70-VSEQ (VG ANALYTICAL, UK) mass spectrometer. All the commerically available reagents were obtained from Aldrich, Fluka, and Tokyo Kasei chemical company and generally used without further purification. All the organic solvents were obtained from Orienta and Samchun. Methylene chloride was distilled from calcium hydride. Flash column chromatography was conducted with silica gel grad 230–400 mesh (Merck Kiesegel 60 Art 9385). Reverse phase column chromatography was conducted with LiChroprep® RP-18 (40–63 μm).

Representative procedures

***p*-Methoxybenzyl (6*R*,7*R*)-7-(*Z*)-[2-(5-chloro-2-trityl-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-chloro-methyl-3-cephem-4-carboxylate (12).** To a mixture of (*Z*)-2-(5-chloro-2-tritylaminothiazol-4-yl)-2-trityloxyimino-acetic acid (**9**, 2.00 g, 2.83 mmol) and *p*-methoxybenzyl (6*R*,7*R*)-7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (**11**, 1.15 g, 2.83 mmol) in CH_2Cl_2 (40 mL) were added pyridine (920 μL), 1.13 mmol) and $POCl_3$ (53 μL, 0.56 mmol) at −40°C. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, washed with brine, dried over $MgSO_4$ and evaporated to give the crude protected product. The crude product was purified on silica gel column chromatography (hexane/ethyl acetate/chloroform=2:1:1) to afford **12** (2.24 g, 75%). ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.48–7.16 (m, 32H, phenyl-H), 6.92 (d, 2H, phenyl-H), 6.06 (m, 1H, C7-H), 5.26 (s, 2H, $-CO_2CH_2Ph$), 5.04 (d, 1H, J=5.0 Hz, C6-H), 4.48 (dd, 2H, C3–CH_2Cl), 3.79 (s, 3H, $-OCH_3$), 3.41 (dd, 2H, C2-H).

***p*-Methoxybenzyl (6*R*,7*R*)-7-(*Z*)-[2-(5-chloro-2-trityl-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(3-chloroisoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (15b(*Z*)).** To the solution of *p*-methoxybenzyl (6*R*,7*R*)-7-(*Z*)-[2-(5-chloro-2-tritylaminothiazol-4-yl)-2-trityloxyimino-acetamido]-3-chloromethyl-3-cephem-4-carboxylate (**12**, 1.5 g, 1.42 mmol) in acetone (4 mL) were added sodium iodide (223 mg, 1.49 mmol) and triphenylphosphine (391 mg, 1.49 mmol) in acetone (4 mL) were added sodium iodide (223 mg, 1.49 mmol) and triphenylphosphine (391 mg, 1.49 mmol). The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (9 mL), and to the solution were added 3-chloro-5-formylisoxazole (255 mg, 1.94 mmol) and 5% aq $NaHCO_3$ (6 mL). After stirring at room temperature for 1 h, the reaction mixture was extracted with ethyl acetate (5 mL×2). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified on silica gel column chromatography (hexane/ethyl acetate=3:2) to afford the product **15b**(*Z*) (823 mg, 51%). IR (KBr) 3396, 3052, 1796, 1720, 1683, 1500, 1248, 979, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 32H, phenyl-H), 7.12 (d, 1H, –NH), 6.91 (d, 2H, phenyl-H), 6.78 (d, 1H, J=12.3 Hz, vinyl-H), 6.39 (d, 1H, J=12.3 Hz, vinyl-H), 6.18 (m, 1H, C7-H), 6.09 (s, 1H, isoxazole), 5.19 (s,2H,–OCH_2Ph), 5.17 (d, 1H, C6-H), 3.82 (s, 3H, $-OCH_3$), 3.51 (d, 1H, J=18.4 Hz, C2-H), 3.08 (d, 1H, J=18.4 Hz, C2-H).

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-chloroisoxazol-5-yl)-vinyl]-3-cephem-4-carboxylate (1b(*Z*)). The compound **15b**(*Z*) (720 mg, 0.63 mmol) was dissolved in anisole (2.1 mL, 19 mmol) and added trifluoroacetic acid (TFA 7.3 mL, 95 mmol) under ice cooling. The reaction mixture was stirred for 30 min at the same temperature followed by stirring for 1 h at room temperature, and triturated with isopropyl ether (15 mL). The resulting precipitate was dissolved in formic acid (500 μL). After stirring for 1 h at room temperature, the reaction mixture was triturated with isopropyl ether (15 mL) again. The crude free acid obtained by filtration was dissolved with aq. sodium bicarbonate solution. The sodium salt was purified by a reverse phase column chromatography (LiChrosorb® RP-18, 20% aq. MeOH) followed by the freeze drying to yield the pure product **1b**(*Z*) (68 mg, 19%). IR (KBr) 3363, 1769, 1651, 1618, 1543, 1366 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.52 (d, 1H, J=12.1 Hz, vinyl-H), 6.33 (s, 1H, isoxazole), 6.29 (d, 1H, J=12.1 Hz, vinyl-H), 5.77 (d, 1H, C7-H), 5.20 (d, 1H, C6-H), 3.52 (d, 1H, J=18.0 Hz, C2-H), 3.23 (d, 1H, J=18.0 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 169.6, 168.7, 167.2, 165.2, 164.7, 154.2, 147.2, 136.0, 135.2, 130.7, 119.6, 116.0, 115.3, 104.9, 59.0, 57.9, 26.8; HRMS (M+H), FAB): calcd for $C_{17}H_{13}Cl_2N_6O_6S_2$ 530.9715, found 530.9716.

Physicochemical properties of the final products

Sodium (6*R*,7*R*)-7-[2-(2-amino-5-chlorothiazol-4-yl)-2-

hydroxyiminoacetamido]-3-[(isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1a(*E*,*Z*). ^{1}H NMR (300 MHz, D_2O) δ (*E*): 8.39 (s, 1H, isoxazole), 7.43 (d, 1H, *J*=16.5 Hz, vinyl-H), 6.78 (d, 1H, *J*=16.5 Hz, vinyl-H), 6.51 (s, 1H, isoxazole), 5.93 (d, 1H, C7-H), 5.32 (d, 1H, C6-H), 3.84 (s, 1H, *J*=15.8 Hz, C2-H), 3.72 (d, 1H, *J*=15.8 Hz, C2-H), (*Z*): 8.39 (s, 1H, isoxazole), 6.28 (d, 1H, *J*=11.2 Hz, vinyl-H), 6.54 (d, 1H, *J*=11.2 Hz, vinyl-H), 6.41 (s, 1H, isoxazole), 5.93 (d, 1H, C7-H), 5.38 (d, 1H, C6-H), 3.68 (s, 1H, *J*=18.8 Hz, C2-H), 3.40 (d, 1H, *J*=18.8 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 168.9, 167.1, 166.8, 165.1, 164.7, 151.8, 147.1, 136.1, 133.5, 130.5, 120.4, 117.2, 116.3, 115.2, 104.2, 101.8; HRMS (M+H, FAB): calcd for $C_{17}H_{14}ClN_6O_6S_2$ 497.0105, found 497.0106.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-bromoisoxazol-5-yl)-vinyl]-3-cephem-4-carboxylate (1c(*Z*)). ^{1}H NMR (300 MHz, D_2O) δ 6.72 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.55 (s, 1H, isoxazole), 6.48 (d, 1H, *J*=11.8 Hz, vinyl-H), 5.94 (d, 1H, *J*=4.7 Hz, C7-H), 5.37 (d, 1H, *J*=4.6 Hz, C6-H), 3.68 (d, 1H, *J*=18.0 Hz, C2-H), 3.38 (d, 1H, *J*=18.1 Hz, C2-H); HRMS (M+H, FAB): calcd for $C_{17}H_{13}BrClN_6O_6S_2$ 574.9210, found 574.9207.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methylisoxazol-5-yl)-vinyl]-3-cephem-4-carboxylate (1d(*Z*)). IR (KBr) 3320, 1774, 1656, 1543, 1355 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.45 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.27 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.10 (s, 1H, isoxazole), 5.77 (d, 1H, C7-H), 5.19 (d, 1H, C6-H), 3.54 (d, 1H, *J*=17.8 Hz, C2-H), 3.20 (d, 1H, *J*=17.8 Hz, C2-H), 2.09 (s, 3H, isoxazole-CH_3); ^{13}C NMR (300 MHz, D_2O) δ 168.8, 167.1, 167.0, 165.0, 164.8, 161.9, 147.1, 136.2, 133.2, 130.6, 120.6, 116.4, 115.0, 105.6, 58.9, 58.0, 27.2, 10.9; HRMS (M+H, FAB): calcd for $C_{18}H_{16}ClN_6O_6S_2$ 511.0261, found 511.0265.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methoxyisoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1e(*Z*)). IR (KBr) 3342, 1774, 1656, 1559, 1511, 1409 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.70 (d, 1H, *J*=9.0 Hz, vinyl-H), 6.49 (d, 1H, *J*=9.0 Hz, vinyl-H), 6.18 (s, 1H, isoxazole), 5.96 (d, 1H, C7-H), 5.48 (d, 1H, C6-H), 3.97 (s, 3H, –OCH_3), 3.68 (d, 1H, *J*=18.0 Hz, C2-H), 3.40 (d, 1H, *J*=18.0 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 173.0, 168.7, 168.5, 167.1, 165.0, 164.8, 147.1, 136.2, 134.2, 134.1, 130.9, 120.2, 116.5, 116.1, 95.2, 58.9, 58.1, 57.9, 27.2; HRMS (M+H, FAB): calcd for $C_{18}H_{16}ClN_6O_7S_2$ 527.0210, found 527.0208.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-cyanoisoxazol-5-yl)-vinyl]-3-cephem-4-carboxylate (1f(*Z*)). IR (KBr) 3331, 3181, 1779, 1672, 1618, 1538, 1409, 1253, 1193, 1055, 1006 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.81 (s, 1H, isoxazole), 6.75 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.53 (d, 1H, *J*=12.1 Hz, vinyl-H), 5.92 (d, 1H, *J*-4.8 Hz, C7-H), 5.36 (d, 1H, *J*=4.8 Hz, C6-H), 3.19 (d, 1H, *J*=17.9 Hz, C2-H), 3.38 (d, 1H, *J*=17.9 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 170.2, 168.6, 167.1, 165.0, 164.7, 147.1, 140.0, 136.2, 130.9, 119.2, 115.1, 110.7, 106.8, 59.0, 26.9; HRMS (M+H, FAB): calcd for $C_{18}H_{13}ClN_7O_6S_2$ 522.0057, found 522.0055.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-carbamoylisoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1g(*Z*)). IR (KBr) 3299, 1774, 1677, 1565, 1538, 1355, 1259 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.60 (d, 1H, *J*=12./1 Hz, vinyl-H), 6.59 (s, 1H, isoxazole), 6.42 (d, 1H, *J*=12.1 Hz, vinyl-H), 5.83 (d, 1H, C7-H), 5.28 (d, 1H, C6-H), 3.57 (d, 1H, *J*=18.0 Hz, C2-H), 3.28 (d, 1H, *J*=18.0 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 169.5, 168.7, 167.0, 64.9, 164.8, 163.1, 158.5, 147.0, 136.2, 134.7, 130.7, 120.0, 115.8, 115.0, 103.6, 59.0, 58.1, 27.2; HRMS (M+H, FAB): calcd for $C_{18}H_{15}ClN_7O_7S_2$ 540.0163, found 540.0162.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-dimethylcarbamoyl-5-yl)vinyl]-3-cephem-4-carboxylate (1h(*Z*)). IR (KBr) 3342, 1774, 1629, 1543, 1377, 1253, 1001 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.74 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.57 (s, 1H, isoxazole), 6.55 (d, 1H, *J*=12.1 Hz, vinyl-H), 5.93 (d, 1H, C7-H), 5.37 (d, 1H, C6-H), 3.70 (d, 1H, *J*=17.9 Hz, C2-H), 3.39 (d, 1H, *J*=17.9 Hz, C2-H), 3.12 (s, 3H, –NCH_3–), 3.10 (s, 3H, –NCH_3–); ^{13}C NMR (300 MHz, D_2O) δ: 163.7, 163.5, 162.0, 160.0, 159.8, 157.8, 153.6, 142.4, 131.3, 130.0, 126.1, 114.9, 110.6, 110.0, 99.3, 54.0, 53.2, 34.4, 31.0, 22.3; HRMS (M+H, FAB): calcd for $C_{20}H_{19}ClN_7O_7S_2$ 568.0476, found 568.0482.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-carbamoyloxymethyl-isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1i(*Z*)). IR (KBr) 3310, 2365, 1769, 1715, 1656, 1543, 1393, 1334, 1098 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.72 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.50 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.43 (s, 1H, isoxazole), 5.95 (d, 1H, *J*=4.5 Hz, C7-H), 5.37 (d, 1H, *J*=4.5 Hz, C6-H), 5.15 (s, 2H, –CH_2OCO–), 3.66 (d, 1H, *J*=17.3 Hz, C2-H), 3.37 (d, 1H, *J*=17.3 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 168.7, 168.2, 167.1, 165.0, 162.8, 161.3, 158.8, 147.1, 136.2, 134.1, 130.8, 120.4, 116.1, 115.1, 103.7, 58.9, 58.7, 58.0, 27.1; HRMS (M+H, FAB): calcd for $C_{19}H_{17}ClN_7O_8S_2$ 570.0268, found 570.0268.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-(*N*,*N*-dimethylcarbamoyloxymethyl)isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1j(*Z*)). IR (KBr) 3046, 2934, 1774, 1688, 1629, 1543, 1404, 1194 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 6.69 (d, 1H, *J*=7.5 Hz, vinyl-H), 6.48 (d, 1H, *J*=7.5 Hz, vinyl-H), 6.40 (s, 1H, isoxazole), 5.93 (d, 1H, C7-H), 5.32 (d, 1H, C6-H), 5.15 (s, 2H, –CH_2OCON–), 3.60 (d, 1H, *J*=18.0 Hz, C2-H), 3.33 (d, 1H, *J*=18.0 Hz, C2-H), 2.87 (br d, 6H, –$OCON(CH_3)_2$); ^{13}C NMR (300 MHz, D_2O) δ 168.6, 168.1, 166.8, 164.8, 164.7, 164.4, 161.3, 157.2, 147.0, 136.4, 134.3, 131.2, 120.4, 115.9, 114.6, 103.8, 59.1, 58.9, 58.2 36.5, 36.1, 27.2; HRMS (M+H, FAB): calcd for $C_{21}H_{21}ClN_7O_8S_2$ 598.0581, found 598.0585.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-hydroxyisoxazol-5-

yl)vinyl]-3-cephem-4-carboxylate (1k(*Z*)). IR (KBr) 3320, 2375, 1769, 1656, 1543, 1463, 1366, 1275 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 6.52 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.22 (d, 1H, *J*=12.1 Hz, vinyl-H), 5.82 (d, 1H, *J*=4.8 Hz, C7-H), 5.80 (s, 1H, isoxazole), 5.24 (d, 1H, *J*=4.9 Hz, C6-H), 3.55 (d, 1H, *J*=17.9 Hz, C2-H), 3.29 (d, 1H, *J*=17.9 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 172.5, 168.9, 168.2, 167.3, 165.3, 164.7, 147.2, 136.0, 133.6, 130.5, 120.4, 117.1, 115.3, 96.6, 59.0, 57.9, 26.9; HRMS (M+H, FAB): calcd for $C_{17}H_{14}ClN_6O_7S_2$ 513.0054, found 513.0050.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-(2-fluoroethoxy)isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1l(*Z*)). ^1H NMR (300 MHz, D_2O) δ 6.70 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.40 (d, 1H, *J*=12.1 Hz, vinyl-H), 6.12 (s, 1H, isoxazole), 5.96 (d, 1H, C7-H), 5.37 (d, 1H, C6-H), 4.90 (m, 1H, $-OCH_2CH_2F$), 4.75 (m 1H, $-OCH_2CH_2F$), 4.56 (m 1H, $-OCH_2CH_2F$), 4.46 (m 1H, $-OCH_2CH_2F$), 3.70 (d, 1H, *J*=18.0 Hz, C2-H), 3.40 (d, 1H, *J*=18.0 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 167.1, 163.7, 162.1, 160.0, 142.1, 131.2, 129.3, 126.2, 115.1, 111.3, 110.0, 90.4, 78.8, 76.6, 65.0, 64.8, 54.0, 53.2, 22.4.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-(thiophen-2-yl)isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1m(*Z*)). IR (KBr) 3353, 3170, 1779, 1661, 1618, 1565, 1425, 1393, 1259, 996 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.61 (dd, 1H, *J*=3.6 Hz, 1 Hz, thiophen), 7.56 (dd, 1H, *J*=5.0, 1 Hz, thiophen), 7.17 (dd, 1H, *J*=5.0 Hz, 3.6 Hz, thiophen), 6.91 (d, 1H, *J*=12.3 Hz, vinyl-H), 6.74 (s, 1H, isoxazole), 6.40 (d, 1H, *J*=12.3 Hz, vinyl-H), 5.91 (d, 1H, *J*=4.9 Hz, C7-H), 5.26 (d, 1H, *J*=4.9 Hz, C6-H), 3.68 (d, 1H, *J*=17.4 Hz, C2-H), 3.32 (d, 1H, *J*=17.4 Hz, C2-H); ^{13}C NMR (300 MHz, CD_3OD) δ 169.4, 169.1, 167.0, 165.5, 165.0, 159.3, 148.1, 138.7, 135.7, 134.9, 131.5, 129.5, 128.9, 128.9, 117.8, 115.0, 113.1, 103.0, 60.3, 59.9, 27.9; HRMS (M+H, FAB): calcd for $C_{12}H_{16}ClN_6O_6S_3$ 578.9982, found 578.9983.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-(thiazol-2-yl)isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (1n(*Z*)). IR (KBr) 3331, 3202, 2966, 1774, 1656, 1618, 1543, 1361, 1259, 1055, 818 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.86 (d, 1H, *J*=3.3 Hz, *J*=3.3 Hz, thiazole), 7.67 (d, 1H, *J*=12.0 Hz, thiazole), 6.77 (s, 1H, isoxazole), 6.66 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.45 (d, 1H, *J*=12.0 Hz, vinyl-H), 5.85 (d, 1H, *J*=4.8 Hz, C7-H), 4.29 (d, 1H, *J*=4.8 Hz, C6-H0, 3.59 (d, 1H, *J*=18.0 Hz, C2-H), 3.25 (d, 1H, *J*=18.0 Hz, C2-H); ^{13}C NMR (300 MHz, CD_3OD) δ 169.6, 168.1, 166.4, 164.6, 164.4, 158.4, 156.8, 147.1, 143.9, 137.2, 135.7, 132.9, 122.7, 117.9, 114.5, 113.3, 102.0, 59.1, 58.4, 27.0; HRMS (M+H, FAB): calcd for $C_{20}H_{15}ClN_7O_6S_3$ 579.9934, found 479.9936.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (2a(*Z*)). IR (KBr) (300 MHz, D_2O) δ 8.36 (s, 1H, isozazole), 7.00 (s, 1H, thiazole), 6.62 (d, 1H, vinyl-H), 6.50 (d, 1H, vinyl-H), 6.46 (s, 1H, isoxazole), 5.84 (d, 1H, C7-H), 5.34 (d, 1H, C6-H), 4.03 (s, 3H, $-NOCH_3$), 3.35 (ABq, 2H, C2-H); HRMS (M+H, FAB): calcd for $C_{17}H_{15}N_6O_6S_2$ 463.0494, found 463.0487.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-chloroisoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (2b(*Z*)). IR (KBr) 3365, 2947, 1666, 1638, 1446, 1381, 1267 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.04 (s, 1H, thiazole), 6.72 (d, 1H, vinyl-H), 6.52 (s, 1H, isoxazole), 6.51 (d, 1H, vinyl-H), 5.92 (d, 1H, C7-H), 5.40 (d, 1H, C6-H), 3.40 (2H, ABq, C2-H0; HRMS (M+H, FAB): calcd for $C_{17}H_{14}ClN_6O_6S_2$ 497.0105, found 497.0112.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methoxylisoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (2e(*Z*)). IR (KBr) 3045, 2957, 1666, 1636, 1576, 1526, 1466, 1411 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.02 (s, 1H, thiazole), 6.64 (d, 1H, vinyl-H), 6.36 (d, 1H, vinyl-H), 6.07 (s, 1H, isoxazole), 5.88 (d, 1H, C7-H), 5.36 (d, 1H, C6-H), 3.95 (s, 3H, isoxazole–OCH_3), 3.38 (ABq, 2H, C2-H); HRMS (M+H, FAB): calcd for $C_{18}H_{17}N_6O_7S_2$ 493.0600, found 493.0606.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-(thiazol-2-yl)isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (2m(*Z*)). IR (KBr) 3315, 1774, 1656, 1549, 1387, 936 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.67 (d, 1H, *J*=3.2 Hz, thiazole), 7.53 (d, 1H, *J*=3.2 Hz, thiazole), 6.75 (s, 1H, isoxazole), 6.64 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.58 (s, 1H, thiazole), 7.53 (d, 1H, *J*=3.2 Hz, thiazole), 6.75 (s, 1H, isoxazole), 6.64 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.58 (s, 1H, thiazole), 6.35 (d, 1H, *J*=12.1 Hz, vinyl-H), 5.76 (d, 1H, *J*=4.6 Hz, C7-H), 5.22 (d, 1H, *J*=4.7 Hz, C6-H), 3.49 (d, 1H, *J*=17.0 Hz, C2-H), 3.12 (d, 1H, *J*=17.6 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 165.9, 163.8, 163.5, 159.5, 152.8, 151.4, 143.2, 138.6, 136.0, 130.0, 126.2, 117.9, 115.6, 110.5, 107.4, 97.3, 54.2, 53.4, 22.6; HRMS (M+H, FAB): calcd for $C_{20}H_{16}N_7O_6S_3$ 546.0324, found 546.0329.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3(thiophen-2-yl)isoxazol-5-yl)vinyl]-3-cephem-4-carboxylate (2n(*Z*)). IR (KBr) 3375, 2871, 1740, 1651, 1636, 1571, 1406, 1272, 729 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.23 (dd, 1H, thiophen), 7.15 (dd, 1H, thiophen), 6.76 (s, 1H, thiophen), 6.68 (s, 1H, isoxazole), 6.58 (d, 1H, *J*=12.0 Hz, vinyl-H), 6.30 (s, 1H, thiazole), 6.23 (d, 1H, *J*=12.2 Hz, vinyl-H), 5.70 (d, 1H, *J*=4.6 Hz, C6-H), 3.31 (d, 1H, *J*=17.6 Hz, C2-H), 2.95 (d, 1H, *J*=17.5 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 170.8, 168.4, 167.7, 165.2, 164.3, 158.1, 148.4, 134.5, 131.7, 129.5, 129.1, 128.7, 128.4, 115.5, 112.5, 112.5, 102.6, 59.4, 58.6, 27.5; HRMS (M+H FAB): calcd for $C_{21}H_{17}N_6O_6S_3$ 545.0371, found 545.0373.

Sodium (6*R*,7*R*)-7-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(isothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (3a(*E*,*Z*)). IR (KBr) 3320, 2365, 1769, 1667, 1624, 1543, 1371, 1307, 1253, 1001 cm^{-1}; ^1H NMR (300MHz, D_2O) δ *E*; 8.28 (s, 1H, isothiazole), 7.50 (s, 1H, isothiazole), 7.22 (d, 1H, *J*=16.0 Hz, vinyl-H), 6.87 (d, 1H, *J*=16.0 Hz, vinyl-H), 5.80 (d, 1H, *J*=4.8 Hz, C7-H), 5.18 (d, 1H, *J*=4.8 Hz, C6-H), 3.68 (d, 1H, *J*=17.3 Hz, C2-H), 3.59 (d, 1H, *J*=17.3 Hz, C2-H) *Z*; 8.28 (s, 1H, isothiazole), 7.15 (s, 1H, isothiazole), 6.68 (d, 1H, *J*=4.8 Hz, C6-H), 3.53 (d, 1H, *J*=18.3 Hz, C2-H), 3.26 (d, 1H, *J*=18.3 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 168.6,

168.4, 166.8, 165.1, 164.6, 164.4, 159.2, 158.1, 146.9, 136.3, 132.9, 130.8, 122.1, 117.8, 114.9, 59.1, 58.0, 24.3; HRMS (M+H, FAB): calcd for $C_{17}H_{14}ClN_6O_5S_3$ 512.9876, found 512.9875.

Sodium (6*R*,7*R*)-7-(*E*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(isothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (3a(*E*)). IR (KBr) 3320, 3181, 1774, 1672, 1543, 1371, 1307, 1253, 1001 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 8.28 (s, 1H, isothiazole), 7.50 (s, 1H, isothiazole), 7.22 (d, 1H, *J*=16.0 Hz, vinyl-H), 6.87 (d, 1H, *J*=16.0 Hz, vinyl-H), 5.80 (d, 1H, *J*=4.8 Hz, C7-H), 5.18 (d, 1H, *J*=4.8 Hz, C6-H), 3.68 (d, 1H, *J*=18.3 Hz, C2-H), 3.59 (d, 1H, *J*=18.3 Hz, C2-H); HRMS (M+H, FAB): calcd for $C_{17}H_{14}ClN_6O_5S_3$ 512.9876, 512.9874.

Sodium (6*R*,7*R*)-7-(*E*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methoxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (3e(*E*)). IR (KBr) 3415, 2937, 1775, 1666, 1636, 1546, 1381 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.09 (d, 1H, 16.1 Hz, vinyl-H), 6.73 (d, 1H, *J*=16.0 Hz, vinyl-H), 6.59 (s, 1H, isothiazole), 5.78 (d, 1H, *J*=4.7 Hz, C7-H), 5.16 (d, 1H, *J*=4.74 Hz, C6-H), 3.84 (s, 3H, $-OCH_3$), 3.61 (ABq, 2H, *J*=29.6 Hz, *J*=17.4 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 171.2, 169.2, 166.9, 166.7, 165.7, 164.3, 148.0, 138.6, 132.3, 117.7, 116.2, 109.5, 60.2, 59.2, 56.0, 24.6; HRMS (M+H FAB): calcd for $C_{18}H_{16}ClN_6O_6S_3$ 542.9982, found 542.9987.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methoxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (3e(*Z*)). IR (KBr) 3315, 3106, 2937, 1760, 1735, 1621, 1506, 1451, 1362, 1237, 1177, 1053, 699 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 6.60 (d, 1H, *J*=11.4 Hz, vinyl-H), 6.56 (s, 1H, isothiazole) 6.43 (d, 1H, *J*=11.3 Hz, vinyl-H), 5.87 (d, 1H, *J*=4.8 Hz, C7-H), 5.35 (d, 1H, *J*=4.8 Hz, C6-H), 3.88 (s, 3H, $-OCH_3$), 3.61 (d, 1H, *J*=18.2 Hz, C2-H), 3.32 (d, 1H, *J*=18.3 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 169.3, 168.3, 166.9, 164.8, 161.9, 146.9, 136.3, 132.5, 131.1, 121.6, 120.69, 114.9, 112.5, 58.8, 57.3, 26.7, 20.9; HRMS (M+H, FAB): calcd for $C_{18}H_{16}ClN_6O_6S_3$ 542.9982, found 542.9987.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-hydroxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (3k(*Z*)). IR (KBr) 3375, 3226, 2927, 1785, 1656, 1606, 1546, 1347, 1267 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 6.87 (d, 1H, *J*=11.2 Hz, vinyl-H), 6.54 (d, 1H, *J*=11.5 Hz, vinyl-H), 6.33 (s, 1H, isothiazole), 5.97 (d, 1H, *J*=4.7 Hz, C7-H), 5.43 (d, 1H, *J*=4.7 Hz, C6-H), 3.69 (d, 1H, *J*=18.2 Hz, C2-H), 3.40 (d, 1H, *J*=18.1 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 172.3, 168.4, 167.2, 165.2, 164.7, 158.2, 147.1, 136.0, 133.4, 131.4, 122.1, 120.2, 115.3, 114.1, 58.9, 57.3, 26.4; HRMS (M+H FAB): calcd for $C_{17}H_{14}ClN_6O_6S_3$ 528.9825, found 528.9826.

Sodium (6*R*,7*R*)-7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(isothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (4a(*E*,*Z*)). IR (KBr) 3320, 2365, 1758, 1656, 1538, 1387, 1312, 1264, 1055, 1028 cm^{-1}; ^1H NMR (300 MHz, D_2O) *E*: δ 8.26 (s, 1H, isothiazole), 7.19 (s, 1H), 7.14 (d, 1H), 7.14 (d, 1H, *J*=4.9 Hz, vinyl-H), 6.88 (d, 1H, *J*=4.1 Hz, vinyl-H), 5.81 (d, 1H, *J*=4.7 Hz, C7-H), 5.32 (d, 1H, *J*=4.7 Hz, C6-H), 3.63 (s, 1H, C2-H), *Z*: δ 8.23 (s, 1H, isothiazole), 7.07 (s, 1H0, 6.67 (d, 1H, *J*=11.4 Hz, vinyl-H), 6.38 (d, 1H, *J*=11.1 Hz, vinyl-H), 5.76 (d, 1H, *J*=4.7 Hz, C7-H), 5.19 (d, 1H, *J*=4.7 Hz, C6-H), 3.51 (d, 1H, *J*=16.7 Hz, C2-H), 3.24 (d, 1H, *J*=18.0 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 171.1, 171.0, 168.8, 168.5, 165.5, 165.2, 164.2, 163.9, 161.4, 159.2, 158.1, 148.6, 148.5, 141.4, 132.7, 141.4, 132.7, 132.0, 131.1, 130.6, 125.4, 121.9, 121.7, 121.0, 117.9, 112.7, 59.3, 59.1, 57.5, 26.5, 24.0; HRMS (M+H, FAB): calcd for $C_{17}H_{15}N_6O_5S_3$ 479.0266, found 479.0269.

Sodium (6*R*,7*R*)-7-(*E*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methoxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (4e(*E*)). ^1H NMR (300 MHz, D_2O) δ 7.19 (d, 1H, *J*=15.9 Hz, vinyl-H),6.95 (s, 1H, thiazole), 6.80 (d, 1H, *J*=16.5 Hz, vinyl-H), 6.66 (s, 1H, isothiazole), 5.86 (d, 1H, 4.8 Hz, C7-H), 5.29 (s, 1H, *J*=4.4 Hz, C6-H), 3.95 (s, 3H, $-OCH_3$), 3.70 (ABq, 2h, C2-H); HRMS (M+H, FAB): calcd for $C_{18}H_{17}N_6O_6S_3$ 509.0371, found 509.0372.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methoxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (4e(*Z*)). ^1H NMR (300 MHz, D_2O) δ 7.00 (s, 1H, thiazole), 6.67 (d, 1H, *J*=11.5 Hz, vinyl-H), 6.62 (s, 1H, isothiazole), 6.53 (d, 1H, *J*=11.5 Hz, vinyl-H), 5.92 (d, 1H, *J*=4.8 Hz, C7-H), 5.43 (d, 1H, *J*=4.7 Hz, C6-H), 3.95 (s, 3H, $-OCH_3$), 3.65 (d, 1H, *J*=14.8 Hz, C2-H), 3.38 (d, 1H, *J*=14.8 Hz, C2-H); HRMS (M+H, FAB): calcd for $C_{18}H_{17}N_6O_6S_3$ 509.0371, found 509.0372.

Sodium (6*R*,7*R*)-7-(*E*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-hydroxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (4k(*E*)). ^1H NMR (300 MHz, D_2O) δ 7.07 (d, 1H, *J*=15.5 Hz, vinyl-H), 6.90 (s, 1H, isothiazole), 6.75 (d, 1H, *J*=15.9 Hz, vinyl-H), 6.30 (s, 1H, thiazole), 5.80 (d, 1H, *J*=3.6 Hz, C7-H), 5.22 (d, 1H, *J*=3.4 Hz, C6-H), 3.65 (ABq, 2H, *J*=24.8 Hz, *J*=17.7 Hz, C2-H); HRMS (M+H, FAB): calcd for $C_{17}H_{15}N_6O_6S_3$ 495.0215, found 495.0219.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-hydroxyisothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (4k(*Z*)). ^1H NMR (300 MHz, D_2O) δ 6.94 (s, 1H, isothiazole), 6.58 (d, 1H, *J*=11.4 Hz, vinyl-H), 6.41 (d, 1H, *J*=11.3 Hz, vinyl-H), 6.23 (s, 1H, thiazole), 5.85 (d, 1H, *J*=4.7 Hz, C7-H), 5.36 (d, 1H, *J*=4.8 Hz, C6-H), 3.63 (d, 1H, *J*=18.2 Hz, C2-H), 3.33 (d, 1H, *J*=18.2 Hz, C2-H); HRMS (M+H, FAB): calcd for $C_{17}H_{15}N_6O_6S_3$ 495.0215, found 495.0219.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(1,2,5-thiadiazol-5-yl)-vinyl]-3-cephem-4-carboxylate (5a(*Z*)). ^1H NMR (300 MHz, D_2O) δ 8.54 (s, 1H, thiadiazole), 6.65 (d, 1H, *J*=12.9 Hz, vinyl-H), 6.57 (d, 1H, *J*=12.0 Hz, vinyl-H) 5.78 (d, 1H, *J*=4.8 Hz, C7-H), 5.24 (d, 1H, *J*=4.8 Hz, C6-H), 3.60 (d, 1H, *J*=17.9 Hz, C2-H), 3.28 (d, 1H, 17.8 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 168.9, 163.1, 161.1, 159.2, 151.2, 149.0, 133.5, 130.6, 122.1, 119.6, 115.2, 59.8, 58.9, 57.9, 27.2, 23.2.

Sodium (6*R*,7*R*)-7-[2-(2-amino-5-chlorothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methylisothiazol-4-yl)-vinyl]-3-cephem-4-carboxylate (5d(*E*,*Z*)). IR (KBr) 3385, 3315, 3196, 2847, 1735, 1641, 1621, 1491, 1367, 1272, 1013, 918 cm^{-1}; ^1H NMR (300 MHz, D_2O) *E*; δ 8.85 (s, 1H, isothiazole), 7.18 (d, 1H, *J*=15.4 Hz, vinyl-H), 6.68 (d, 1H, *J*=16.6 Hz, vinyl-H), 6.47 (s, 1H), 5.86 (d, 1H, *J*=4.53 Hz, C7-H), 5.29 (d, 1H, *J*=4.6 Hz, C6-H), 3.86 (d, 1H, *J*=17.6 Hz, C2-H), 3.72 (d, 1H, *J*=17.6 Hz, C2-H) *Z*; δ 8.62 (s, 1H, isothiazole), 6.95 (d, 2H, *J*=15.3 Hz, vinyl-H), 6.47 (s, 1H), 6.47 (s, 1H), 5.81 (d, 1H, *J*=4.6 Hz, C7-H), 5.26 (d, 1H, *J*=4.7 Hz, C6-H), 3.46 (d, 1H, *J*=17.6 Hz, C2-H), 3.23 (d, 1H, *J*=17.6 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 169.1, 167.4, 167.1, 164.4, 146.9, 133.7, 130.6, 129.7, 123.1, 120.7, 120.3, 59.1, 58.9, 58.2, 58.0, 26.9, 17.1; HRMS (M+H, FAB): calcd for $C_{18}H_{16}ClN_6O_5S_3$ 527.0033, found 527.0037.

Sodium (6*R*,7*R*)-7-(*E*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(1,2,5-thiadiazol-5-yl)vinyl]-3-cephem-4-carboxylate (6a(*E*)). IR (KBr) 3395, 2971, 1745, 1666, 1606, 1536, 1381, 1207 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 8.76 (s, 1H, thiadiazole), 7.60 (d, 1H, *J*=11.3 Hz, vinyl-H), 6.98 (d, 1H, *J*=11.3 Hz, vinyl-H), 6.92 (s, 1H, thiazole). 5.81 (m, 1H, C7-H), 5.28 (m, 1H, C6-H), 3.74 (q, 1H, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 163.9, 163.0, 161.1, 149.7, 149.0, 136.5, 133.2, 132.6, 119.4, 117.3, 113.3, 110.9, 103.3, 59.3, 59.2, 23.7; HRMS (M+H, FAB): calcd for $C_{16}H_{14}N_7O_5S_3$ 480.0218, found 480.0221.

Sodium (6*R*,7*R*)-7-(*Z*)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(1,2,5-thiadiazol-5-yl)vinyl]-3-cephem-4-carboxylate (6a(*Z*)). ^1H NMR (300 MHz, D_2O) δ 8.55 (s, 1H, thiadiazole), 6.90 (s, 1H, thiazole), 6.66 (d, 1H, *J*=11.9 Hz, vinyl-H), 6.58 (d, 1H, *J*=11.9 Hz, vinyl-H), 5.79 (d, 1H, *J*=4.7 Hz, C7-H), 5.28 (d, 1H, *J*=4.7 Hz, C6-H), 3.63 (d, 1H, *J*=17.7 Hz, C2-H), 3.29 (d, 1H, *J*=17.8 Hz, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 171.2, 168.8, 165.7, 164.2, 159.2, 151.2, 148.7, 141.3, 133.5, 130.6, 122.1, 119.8, 112.8, 59.0, 58.0, 27.2; HRMS (M+H, FAB): calcd for $C_{16}H_{14}N_7O_5S_3$ 480.0218, found 480.0221.

Sodium (6*R*,7*R*)-7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(3-methylisothiazol-4-yl)vinyl]-3-cephem-4-carboxylate (6d(*E*,*Z*)). IR (KBr) 3465, 3226, 2897, 1775, 1666, 1586, 1391 cm^{-1}; ^1H NMR (300 MHz, D_2O) *Z*: δ 8.55 (s, 1H, isothiazole), 6.41 (s, 2H, vinyl-H), 5.79 (d, 1H, *J*=4.72 Hz, C7-H), 5.18 (d, 1H, *J*=4.7 Hz, C6-H), 3.40 (d, 1H, *J*=17.7 Hz, C2-H), 3.15 (d, 1H, *J*=17.8 Hz, C2-H), 2.34 (s, 3H), *E*: δ 8.85 (s, 1H, isothiazole), 7.18 (d, 1H, *J*=16.3 Hz, vinyl-H), 6.67 (d, 1H, *J*=16.5 Hz, vinyl-H), 6.47 (s, 1H, thiazole), 5.86 (d, 1H, C7-H), 5.29 (d, 1H, C6-H), 3.77 (ABq, 2H, C2-H); ^{13}C NMR (300 MHz, D_2O) δ 171.0, 169.0, 167.3, 165.5, 164.3, 148.5, 146.8, 141.4, 133.7, 130.9, 129.7, 123.0, 121.7, 112.6, 59.2, 58.4, 27.2, 17.6, 17.2; HRMS (M+H, FAB): calcd for $C_{18}H_{17}N_6O_5S_3$ 493.0422, found 493.0425.

Acknowledgements

We are grateful to the Korean Ministry of Science and Technology for financial support.

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