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Synthesis and SAR study of novel 7-(pyridinium-3-yl)-carbonyl imidazo[5,1-*b*]thiazol-2-yl carbapenems

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Abstract—A new series of 1β-methyl carbapenems, possessing a 7-substituted imidazo[5,1-*b*]thiazol-2-yl group directly attached to the C-2 position of the carbapenem nucleus, was synthesized and evaluated for antibacterial activity. These compounds showed potent activities against Gram-positive bacteria, in particular methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP). They also exhibited potent activity against β-lactamase-negative ampicillin-resistant *Haemophilus influenzae* (BLNAR).

1. Introduction

Recently, the emergence of various types of resistant bacterial strains has become a serious clinical problem. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA)[1] is one of the most serious pathogens causing nosocomial infections. Only a few drugs such as arbekacin, vancomycin (VCM), teicoplanin, linezolid, and daptomycin are available for MRSA infections and many types of resistant strains have already been reported against these drugs.[2] To overcome this problem, new anti-MRSA agents are required.

β-Lactams have good bactericidal activity and safety profiles, but generally they are insufficient against MRSA due to their low affinity for PBP2a. Nevertheless, in the last decade, potent anti-MRSA β-lactams with improved affinity for PBP2a such as cephalosporins[3] and carbapenems[4] have been found. We have already reported various anti-MRSA β-lactams such as CP0467,[3a] CP6679,[5] CP0569,[6] and CP5068[7] (Fig. 1). Among them, CP5068 possesses a 6,7-disubstituted imidazo[5,1-*b*]thiazolium-2-yl group directly attached to the C-2 position of the carbapenem nucleus, and it shows potent activity against MRSA. In our search for more potent carbapenems against MRSA, we have synthesized various derivatives of CP5068 with a 7-heterocyclic carbonyl imidazo[5,1-*b*]thiazol-2-yl group. Among them, we found 7-(pyridinium-3-yl)carbonyl imidazo[5,1-*b*]thiazol-2-yl carbapenems with improved anti-MRSA activity. Furthermore, they exhibited potent activity against PRSP and BLNAR, which often cause serious respiratory tract infections. Herein, we report the synthesis and structure–activity relationships of these compounds (Fig. 2).

2. Chemistry

First, we introduced various heterocyclic carbonyl groups at the C-7 position of the imidazo[5,1-*b*]thiazole ring. The synthesis of **7g** possessing 3-pyridyl ketone is illustrated in Scheme 1 as an example. Selective iodination at the C-7 position of imidazo[5,1-*b*]thiazole **1** gave compound **2**. Grignard reaction of **2** with 3-pyridinecarboxyaldehyde followed by oxidation with manganese (IV) oxide afforded 7-(3-pyridylcarbonyl)imidazo[5,1-*b*]thiazole **3**. A tri-*n*-butyl stannyl group was introduced at the C-2 position of **3** by *n*-Bu_3SnCl and LHMDS. The Stille coupling reaction of **4** and a trifluoromethanesulfonate of **5** afforded the key intermediate **6**. After removal of the 4-nitrobenzyl group of **6**, compound **7g** was obtained as a lyophilized amorphous powder. Related compounds **7a**–**j** were prepared

Keywords: Carbapenem; Imidazo[5,1-*b*]thiazole; 7-Heterocyclic carbonyl imidazo[5,1-*b*]thiazol-2-yl group; Anti-MRSA activity; MRSA; PRSP; BLNAR.
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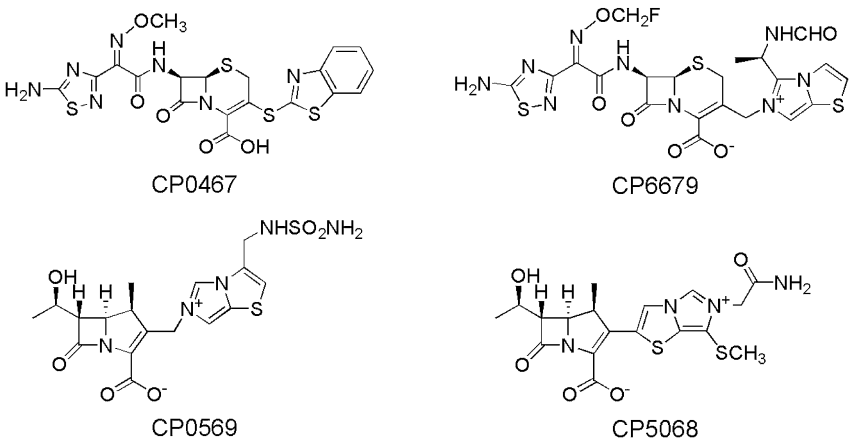


Figure 1. Our previous compounds.

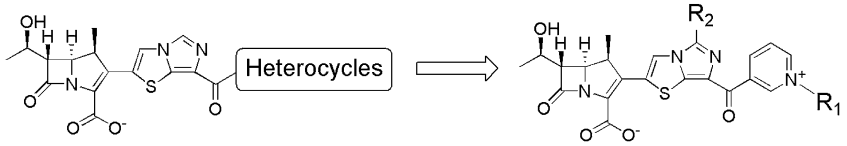
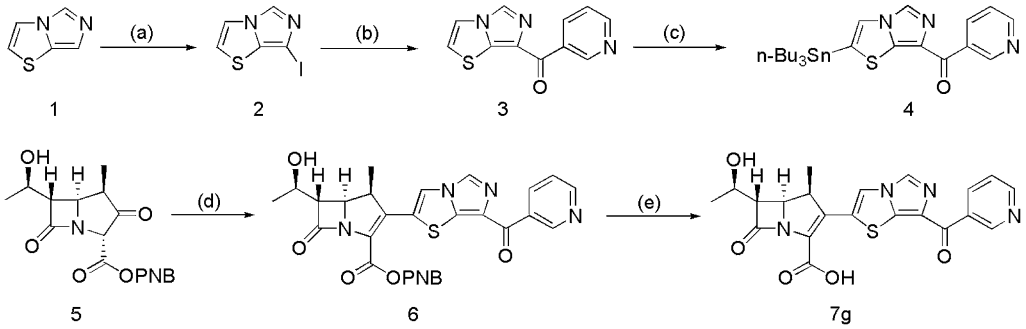


Figure 2. Our strategy for anti-MRSA carbapenems.



Scheme 1. Synthesis of **7g**. Reagents and conditions: (a) NIS, CH_2Cl_2, rt, 70%; (b) i—MeMgBr, 3-pyridinecarboxyaldehyde, THF, 0 °C; ii—MnO_2, CH_2Cl_2, rt, 74%; (c) *n*-Bu_3SnCl, LHMDS, THF, −40 °C, 65%; (d) i—DIPEA, Tf_2O, CH_3CN, −35 °C; ii—**4**, $Pd_2(dba)_3$, P(2-furyl)$_3$, $ZnCl_2$, NMP, 50 °C, 78%; (e) H_2, 10% Pd/C, THF–1/15 M phosphate buffer, rt, 40%.

similarly from **2** and the corresponding heterocyclic aldehydes (Fig. 3).

Synthesis of **9b** from the key intermediate **6** is shown in Scheme 2. Reaction with iodoacetamide converted **6** to a quaternary pyridinium salt **8** without quaternization at the C-6 position of imidazo[5,1-*b*]thiazole. Finally, deprotection of the 4-nitrobenzyl group of **8** afforded the desired compound **9b**. The other quaternary salts **9a** and **9c**–**j** were obtained similarly (Fig. 4).

We also introduced various substituents at the C-5 position of the imidazo[5,1-*b*]thiazole ring of **9b**. Synthesis of **14a**–**g** is illustrated in Scheme 3. These substituents were introduced by acylation of aminomethylthiazole **10** with the corresponding acid anhydride or acyl chloride,

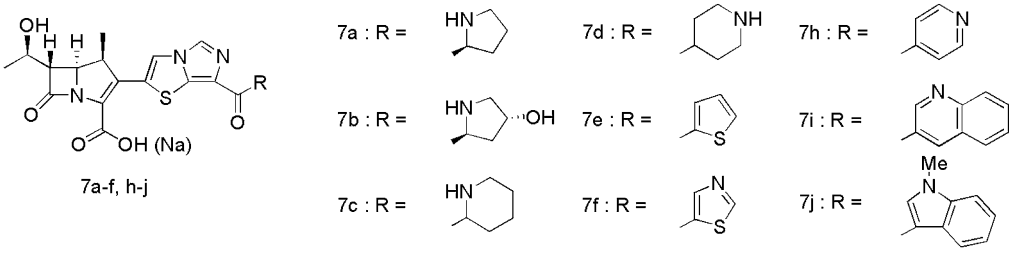
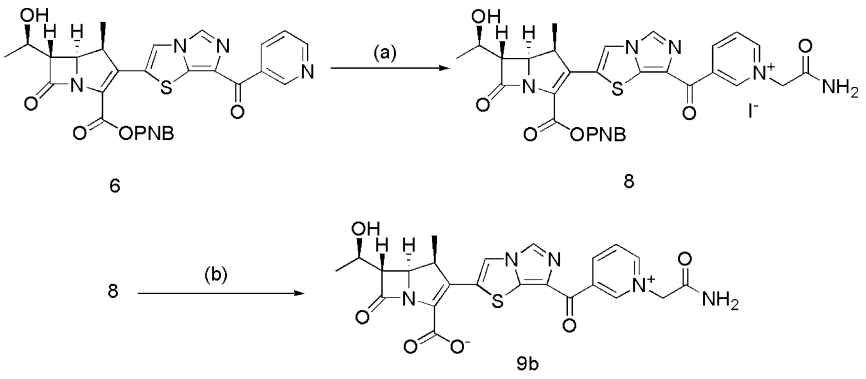


Figure 3. Structures of compounds **7a**–**f**, **7h**–**j**.



Scheme 2. Synthesis of **9b**. Reagents and conditions: (a) ICH_2CONH_2, acetone, 35 °C, 93%; (b) H_2, 10% Pd/C, THF–H_2O, rt, 43%.

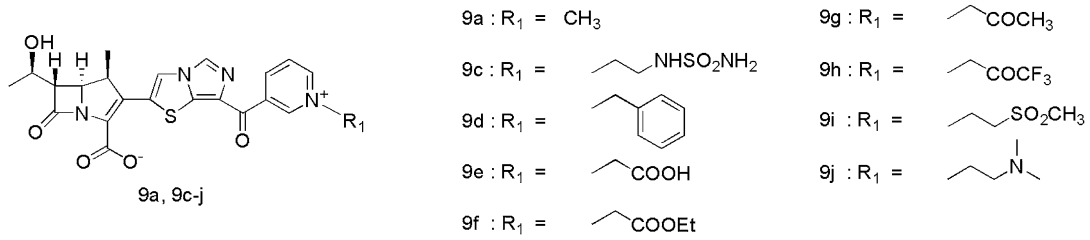
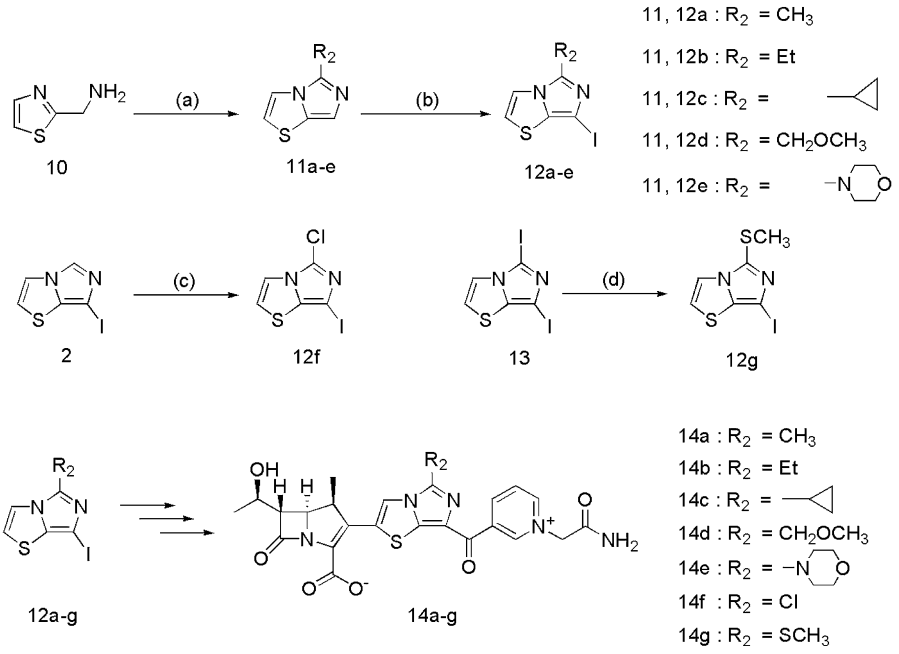


Figure 4. Structures of compound **9a**, **9c**–**j**.



Scheme 3. Synthesis of **14a**–**g**. Reagents and conditions: (a) i—$(R_2CO)_2O$ or R_2COCl, Et_3N, CH_2Cl_2, 0 °C; ii—$POCl_3$, toluene, 100 °C; (b) NIS, CH_2Cl_2, rt; (c) NCS, $ClCH_2CH_2Cl$, rt; (d) EtMgBr, $CH_3SSO_2CH_3$, THF, 0 °C.

followed by cyclization with $POCl_3$. Iodination of **11a**–**e** proceeded readily with *N*-iodosuccinimide. A chlorine atom (**12f**) was introduced by the reaction of 7-iodoimidazo[5,1-*b*]thiazole **2** and *N*-chlorosuccinimide. Grignard reaction of 5,7-diiodoimidazo[5,1-*b*]thiazole **13** and methyl methanethiosulfonate resulted in selective methylsulfanylation at the C-5 position (**12g**). 5-Substituted-7-iodoimidazo[5,1-*b*]thiazoles **12a**–**g** were converted to the desired compounds **14a**–**g**, respectively, by the same method as employed for **9b**.

3. Biological activity

Table 1 shows the antibacterial activities of the novel 7-heterocyclic carbonyl imidazo[5,1-*b*]thiazolyl carba-

Table 1. Antibacterial activities of **7a–j**, CP5068, and VCM (MIC; μg/mL)

Test organism	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**	**7j**	CP5068	VCM
S. aureus 209P JC-1	≦0.008	0.016	0.016	0.008	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008	0.008	0.008	0.5
S. aureus M-126[a]	1	1	1	1	0.031	0.031	1	0.063	0.016	0.031	1	1
S. aureus M-126HR[b]	4	4	4	4	4	4	4	4	2	8	4	2
S. pneumoniae KK133[c]	0.063	0.063	0.125	0.063	0.125	0.031	0.031	0.031	0.031	0.125	0.031	0.5
E. coli NIHJ JC-2	0.125	0.063	0.125	0.063	2	1	1	2	4	4	0.016	>128
K. pneumoniae GN69	0.125	0.125	0.25	0.125	4	2	2	2	8	8	0.031	>128
M. catarrhlis W-0500	0.031	0.031	0.063	0.031	0.016	0.016	0.016	0.031	0.031	0.016	0.031	64
H. influenzae 870[d]	0.125	0.125	0.25	0.063	0.125	0.063	0.031	0.031	0.125	0.125	0.5	>128

[a] MRSA.
[b] Carbapenem-resistant MRSA.
[c] PRSP.
[d] BLNAR.

Table 2. Antibacterial activities of **9a–j** (MIC; μg/mL)

Test organism	**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	**9i**	**9j**	**7g**
S. aureus 209P JC-1	≦0.008	≦0.008	≦0.008	≦0.008	0.031	0.016	0.016	0.016	≦0.008	≦0.008	≦0.008
S. aureus M-126[a]	1	0.5	1	0.5	2	2	1	1	1	1	1
S. aureus M-126HR[b]	4	2	2	4	8	8	4	4	4	4	4
S. pneumoniae KK133[c]	0.031	0.031	0.031	0.016	0.063	0.063	0.063	0.063	0.031	0.031	0.031
E. coli NIHJ JC-2	0.063	0.031	0.031	0.5	0.031	0.031	0.125	0.125	0.5	0.125	1
K. pneumoniae GN69	0.063	0.063	0.063	1	0.063	0.063	0.25	0.25	0.5	0.25	2
M. catarrhlis W-0500	0.031	0.016	0.016	0.063	0.031	0.031	0.031	0.031	0.016	0.031	0.016
H. influenzae 870[d]	0.063	0.063	0.063	0.063	0.063	0.063	0.063	0.063	0.063	0.063	0.031

[a] MRSA.
[b] Carbapenem-resistant MRSA.
[c] PRSP.
[d] BLNAR.

penems **7a–j**. All these compounds had strong anti-MRSA, and they could be divided into two groups according to their antibacterial activity spectra. Compounds **7a–d**, possessing a pyrrolidine or piperidine ring, showed potent antibacterial activities against both Gram-positive and Gram-negative bacteria. The other group, **7e–j** possessing an aromatic heterocycle, showed excellent anti-G(+) activities, but insufficient activities against G(−)-bacteria such as *Escherichia coli* and *K. pneumoniae*. The activities against G(−)-bacteria appeared to be dependent on the lipophilicity and the size of the heterocycle; compounds with larger substituents (**7i** and **7j**) showed weaker activities. Among them, **7i** showed the best anti-MRSA activity, however, we were not satisfied with its activities against G(−)-bacteria, especially BLNAR. Anti-MRSA and anti-PRSP activity of **7g** was as strong as CP5068 and its anti-BLNAR activity was clearly stronger than CP5068. Considering the balance of the activities against not only MRSA but also PRSP and BLNAR, we chose **7g** for further derivatization.

The antibacterial activities of the quaternary pyridinium salts **9a–j** are shown in Table 2. Introduction of carboxylic acid (**9e**) and its ethyl ester (**9f**) weakened the MRSA activity compared with **7g**. A carbonyl group (**9g**, **9h**), sulfonyl group (**9i**), and basic moiety (**9j**) also failed to improve anti-MRSA activity, however, amide moieties (**9b** and **9c**) strengthened the anti-MRSA activity. Furthermore, all quaternized derivatives showed improved

Table 3. Antibacterial activities of **14a–g** (MIC; μg/mL)

Test organism	**14a**	**14b**	**14c**	**14d**	**14e**	**14f**	**14g**	**9b**
S. aureus 209P JC-1	0.016	0.016	0.016	0.031	0.031	0.008	0.008	≦0.008
S. aureus M-126[a]	1	1	0.5	2	2	0.5	0.5	0.5
S. aureus M-126HR[b]	4	4	2	4	8	2	1	2
S. pneumoniae KK133[c]	0.031	0.031	0.031	0.063	0.063	0.031	0.016	0.031
E. coli NIHJ JC-2	0.25	2	4	8	16	1	4	0.031
K. pneumoniae GN69	0.5	4	4	4	16	2	4	0.063
M. catarrhlis W-0500	0.008	0.031	0.016	0.031	0.063	0.016	0.016	0.016
H. influenzae 870[d]	0.063	0.063	0.031	0.063	0.125	0.063	0.031	0.063

[a] MRSA.
[b] Carbapenem-resistant MRSA.
[c] PRSP.
[d] BLNAR.

activity against G(−)-bacteria such as *E. coli* and *K. pneumoniae* compared to **7g**. Among them, we focused on **9b** because it showed the strongest anti-MRSA activity.

In order to examine the SAR of **9b**, we further synthesized various derivatives. Table 3 shows the antibacterial activities of **14a**–**g**, which have various substituents at the C-5 position of the imidazo[5,1-*b*]thiazole ring. Substitution at this position weakened the antibacterial activities against G(−)-bacteria, especially *E. coli* and *K. pneumoniae*, possibly because of increased lipophilicity. A similar tendency was seen in **7e**–**7j**. Compounds **14a**–**f** did not exhibit improved anti-MRSA activity compared to **9b**, either. Introduction of a methylthio group (**14g**) decreased water solubility, however, increased anti-MRSA activity. It was interesting information for the SAR study of anti-MRSA carbapenems, because the anti-MRSA activity of our former compound CP5068 was also strengthened by the introduction of a methylthio group to the imidazo[5,1-*b*]thiazole ring.[7]

4. Conclusion

In order to find a novel β-lactam with potent anti-MRSA activity, we introduced various heterocycles at the C-7 position of the imidazo[5,1-*b*]thiazole ring directly attached to the C-2 position of the carbapenem nucleus. Among them, we focused on **7g** with the pyridine ring because of its balanced antibacterial activity and prepared various derivatives of **7g**. As a result, we successfully found several compounds such as **9b** and **14g**, which showed potent anti-MRSA activity superior to that of VCM, and also exhibited strong activities against PRSP and BLNAR.[8]

5. Experimental

5.1. General methods

^{1}H NMR spectra were measured with a JEOL JNM-LA400 NMR spectrometer at 400 MHz in $CDCl_3$, DMSO-d_6, or D_2O. TMS (0 ppm) in $CDCl_3$ and DMSO-d_6 or HDO (4.80 ppm) in D_2O were used as internal reference standards. Mass spectra were obtained on a JEOL JMS-700 mass spectrometer for FAB-MS and FABHRMS. Purity of final compounds was evaluated by HPLC analysis on a HITACHI L-7000 HPLC system (Column: Nacalai tesque Cosmosil 5C_{18}-PREP) 4.6 × 150 mm, detection UV: 315 nm, flow rate: 1.0 ml/min, eluent: 1/15 M phosphate buffer (pH 6.8)/methanol = 70:30 or 60:40. Silica gel flash column chromatography was performed on Wako-gel C-300 and reversed-phase column chromatography was performed on Nacalai tesque Cosmosil 40 C_{18}-PREP.

5.2. Antimicrobal activity in vitro

Minimum inhibitory concentration (MIC) was determined by the agar dilution method using Sensitivity Disk Agar-N (Nissui) supplemented with hemin (5 μg/ml), NAD (15 μg/ml), and horse blood (5%). The final inoculum was adjusted to approximately 10^4 CFU per spot. After incubation for 18 h at 35 °C, the MIC was defined as the lowest drug concentration that prevented viable growth.

5.3. 7-Iodoimidazo[5,1-*b*]thiazole (2)

To a solution of 31.0 g of imidazo[5,1-*b*]thiazole (**1**) in 550 ml of 1,2-dichloroethane, 56.3 g of *N*-iodosuccinimide was added at 5 °C, and the mixture was stirred at room temperature for 17 h. The solution was washed with aqueous $Na_2S_2O_3$ and water, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/hexane/AcOEt = 1:1:1) to give 39.9 g of the title compound.

NMR ($CDCl_3$) δ: 6.89 (1 H, d, J = 4.2 Hz), 7.50 (1H, d, J = 4.2 Hz), 7.96 (1H, s); FABHRMS calcd for $C_5H_4N_2SI$ [$(M+H)^+$]: 250.9140, found: 250.9138.

5.4. 7-[(Pyridin-3-yl)carbonyl]imidazo[5,1-*b*]thiazole (3)

A solution of 2.50 g of 7-iodoimidazo[5,1-*b*]thiazole (**2**) in 50 ml of dry THF was cooled in an ice bath, and 11.3 ml of a 0.93 M methylmagnesium bromide/THF solution was added to the cooled solution. Twenty min later, 3-pyridine-carboxaldehyde (1.04 ml) was added thereto, and the mixture was stirred at that temperature for 40 min and then at room temperature for 4 h. Water was added to the reaction solution, and the whole was extracted with CH_2Cl_2 five times. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20:1) to give 1.93 g of 7-[(pyridin-3-yl)hydroxymethyl]imidazo[5,1-*b*]thiazole. Manganese dioxide (1.0 g) was added to a solution of 1.02 g of 7-[(pyridin-3-yl)hydroxymethyl]imidazo[5,1-*b*]thiazole in 40 ml of CH_2Cl_2, and the mixture was stirred at room temperature for 5 h. The reaction solution was filtered and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 1.10 g of 7-[(pyridin-3-yl)carbonyl]imidazo[5,1-*b*]thiazole (**3**) as a yellow solid.

NMR ($CDCl_3$) δ: 7.20 (1 H, d, J = 4.2 Hz), 7.4–7.5 (1H, m), 7.63 (1H, d, J = 4.2 Hz), 8.10 (1H, s), 8.75–8.85 (2H, m), 9.7–9.75 (1H, m); FABHRMS calcd for $C_{11}H_8N_3OS$ [$(M+H)^+$]: 230.0388, found: 230.0387.

5.5. 7-(Pyridin-3-yl)carbonyl-2-(tri-*n*-butylstannyl)imidazo[5,1-*b*]thiazole (4)

Tri-*n*-butylstannyl chloride (0.841 ml) and 2.95 ml of a 1.0 N lithium bis(trimethylsilyl)amide/THF solution were added to a solution of 520 mg of **3** in 25 ml THF at −60 °C, and the mixture was stirred for 20 min. The temperature of the mixture was raised to −50 °C, and

1.0 ml of a 1.0 N lithium bis(trimethylsilyl)amide/THF solution was added thereto. The mixture was stirred for 30 min. The temperature of the mixture was raised to −40 °C, and 0.5 ml of a 1.0 N lithium bis(trimethylsilyl)amide/THF solution was added thereto. The mixture was stirred for 30 min. Aqueous NH_4Cl was added to the reaction solution, and the whole was extracted with AcOEt, followed by washing with brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was then removed by evaporation, and the residue was purified by short column chromatography on silica gel (hexane/AcOEt = 2:1 to AcOEt only) to give 712 mg of the title compound. Compound **4** was employed for the next Stille coupling reaction immediately due to its instability.

NMR ($CDCl_3$) δ: 0.92 (9H, t, J = 7.2 Hz), 1.2–1.3 (6H, m), 1.3–1.45 (6H, m), 1.55–1.65 (6H, m), 7.36 (1H, s), 7.4–7.45 (1H, m), 8.03 (1H, s), 8.75–8.85 (2H, m), 9.65–9.7 (1H, m).

5.6. 4-Nitrobenzyl (1*S*,5*R*,6*S*)-6-((1*R*)-1-hydroxyethyl)-1-methyl-2-[7-(pyridin-3-yl)carbonyl imidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (6)

Under an argon atmosphere at −30 °C, *N*,*N*-diisopropylethylamine (0.343 ml) was added dropwise to a solution of 474 mg of compound **5** in 13 ml of dry CH_3CN, and 0.218 ml of anhydrous trifluoromethanesulfonic acid was then added dropwise thereto. The mixture was stirred at the same temperature for 30 min. AcOEt (30 ml) was then added thereto, followed by washing with brine, a mixed solution composed of brine and 1 N HCl, a mixed solution composed of brine and saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous magnesium sulfate and removed by evaporation. The residue was dissolved in 6 ml of dry *N*-methylpyrrolidinone. Tri-2-furylphosphine (37 mg), 343 mg of zinc chloride, 37 mg of tris (dibenzylideneacetone) dipalladium (0), and 712 mg of **4** were added to the above solution, and the mixture was stirred at 5 °C for 2 h. AcOEt (30 ml) and 15 ml of aqueous $NaHCO_3$ were added to the reaction solution, and the mixture was stirred. Insolubles were removed by filtration. The organic layer was washed three times with 20 ml of semisaturated brine and dried over anhydrous magnesium sulfate. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20:1–10:1) to give 388 mg of the title compound **6**.

NMR (DMSO-d_6) δ: 1.19 (3 H, d, J = 6.0 Hz), 1.24 (3H, d, J = 7.5 Hz), 3.45 (1H, dd, J_1 = 6.3 Hz, J_2 = 3.0 Hz), 3.7–3.85 (1H, m), 4.0–4.1 (1H, m), 4.68 (1H, dd, J_1 = 9.9 Hz, J_2 = 3.0 Hz), 5.17 (1H, d, J = 5.4 Hz), 5.41 (1H, d, J = 13.8 Hz), 5.55 (1H, d, J = 13.7 Hz), 7.55–7.65 (1H, m), 7.74 (2H, d, J = 9.0 Hz), 8.22 (2H, d, J = 9.0 Hz), 8.47 (1H, s), 8.64 (1H, s), 8.65–8.75 (1H, m), 8.75–8.8 (1H, m), 9.55–9.6 (1H, m); FABHRMS calcd for $C_{28}H_{24}N_5O_7S$ [$(M+H)^+$]: 574.1396, found: 574.1395.

5.7. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-(pyridin-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylic acid (7g)

Compound **6** (129 mg) was dissolved in 6.7 ml THF and 6.7 ml of 1/15 M sodium phosphate buffer (pH 6.8), and 130 mg of 10% Pd–C was added to the solution. The air in the reaction vessel was replaced with hydrogen, and the mixture was stirred at room temperature for 2 h. The catalyst was removed by filtration, followed by washing with water. The filtrate was washed with AcOEt and then concentrated under reduced pressure to a volume of about 2 ml. The concentrate was purified by column chromatography on Cosmosil 40 C_{18}-PREP (5% aqueous MeOH solution) to give 41 mg of the title compound.

NMR (D_2O) δ: 1.15 (3H, d, J = 7.2 Hz), 1.33 (3H, d, J = 6.3 Hz), 3.45–3.6 (2H, m), 4.2–4.35 (2H, m), 7.35–7.45 (1H, m), 7.91 (1H, s), 8.07 (1H, s), 8.25–8.3 (1H, m), 8.5–8.55 (1H, m), 8.85–8.9 (1H, m); FABHRMS calcd for $C_{21}H_{19}N_4O_5S$ [$(M+H)^+$]: 439.1076, found: 439.1073; HPLC analysis: 96.8% (Area %).

5.8. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-((2*S*)-pyrrolidin-2-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylic acid (7a)

The title compound (**7a**) was obtained in 13% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and (*S*)-2-formyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (D_2O) δ: 1.24 (3H, d, J = 6.9 Hz), 1.35 (3H, d, J = 6.3 Hz), 2.5–2.2 (3H, m), 2.6–2.75 (1H, m), 3.4–3.65 (4H, m), 4.2–4.4 (2H, m), 5.05–5.2 (1H, m), 8.05 (1H, s), 8.17 (1H, s); FABHRMS calcd for $C_{20}H_{23}N_4O_5S$ [$(M+H)^+$]: 431.1389, found: 431.1385; HPLC analysis: 98.9% (Area %).

5.9. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-2-[7-((2*S*,4*R*)-4-hydroxypyrrolidin-2-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-methyl-1-carbapen-2-em-3-carboxylic acid (7b)

The title compound (**7b**) was obtained in 10% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and (2*S*,4*R*)-2-formyl-4-*t*-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (D_2O) δ: 1.24 (3H, d, J = 6.9 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.1–2.25 (1H, m), 2.65–2.75 (1H, m), 3.4–3.6 (4H, m), 4.2–4.35 (2H, m), 4.7–4.8 (1H, m), 5.2–5.3 (1H, m), 8.00 (1H, s), 8.08 (1H, s); FABHRMS calcd for $C_{20}H_{23}N_4O_6S$ [$(M+H)^+$]: 447.1338, found: 447.1335; HPLC analysis: 98.0% (Area %).

5.10. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-(piperidin-2-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylic acid (7c)

The title compound (**7c**) was obtained in 0.6% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and 1-(4-nitroben-

zyloxycarbonyl)piperidine-2-carboxaldehyde by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (DMSO-d_6) δ: 1.13 (3H, d, J = 6.9 Hz), 1.17 (3H, d, J = 6.3 Hz), 1.36–1.92 (6H, m), 2.3–2.45 (1H, m), 2.91–3.16 (2H, m), 3.32–3.48 (1H, m), 3.88–4.02 (1H, m), 4.02–4.16 (1H, m), 4.52–4.66 (1H, m), 5.03 (1H, m), 8.19 (1H, s), 8.23 (1H, s); FABHRMS calcd for $C_{21}H_{25}N_4O_5S$ [$(M+H)^+$]: 445.1546, found: 445.1548; HPLC analysis: 97.3% (Area %).

5.11. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-(piperidin-4-yl)carbonylimidazo[5,1-*b*] thiazol-2-yl]-1-carbapen-2-em-3-carboxylic acid (7d)

The title compound (**7d**) was obtained in 15% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and 1-(4-nitrobenzyloxycarbonyl)piperidine-4-carboxaldehyde by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (D_2O) δ: 1.21 (3H, d, J = 6.9 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.8–2.0 (2H, m), 2.05–2.2 (2H, m), 3.1–3.25 (2H, m), 3.25–3.6 (5H, m), 4.2–4.35 (2H, m), 7.92 (1H, s), 8.02 (1H, s); FABHRMS calcd for $C_{21}H_{25}N_4O_5S$ [$(M+H)^+$]: 445.1546, found: 445.1538; HPLC analysis: 99.6% (Area %).

5.12. Sodium (1*S*,5*R*,6*S*)-6-((1*R*)-1-hydroxyethyl)-1-methyl-2-[7-(thiophen-2-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (7e)

The title compound (**7e**) was obtained in 26% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and thiophene-2-carboxaldehyde by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (D_2O) δ: 1.16 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 3.42–3.51 (2H, m), 4.21–4.33 (2H, m), 7.08 (1H, m), 7.75 (1H, m), 7.83 (1H, s), 7.89 (1H, s), 8.02 (1H, m); FABHRMS calcd for $C_{20}H_{17}N_3NaO_5S_2$ [$(M+H)^+$]: 466.0507, found: 466.0510; HPLC analysis: 97.7% (Area %).

5.13. Sodium (1*S*,5*R*,6*S*)-6-((1*R*)-1-hydroxyethyl)-1-methyl-2-[7-(thiazol-5- yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (7f)

The title compound (**7f**) was obtained in 19% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and thiazole-5-carboxaldehyde by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (D_2O) δ: 1.21 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 3.52 (1H, dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz), 3.58 (1H, m), 4.29–4.37 (2H, m), 7.92 (1H, s), 8.05 (1H, s), 8.60 (1H, s), 9.03 (1H, s); FABHRMS calcd for $C_{19}H_{16}N_4NaO_5S_2$ [$(M+H)^+$]: 467.0460, found: 467.0541; HPLC analysis: 97.9% (Area %).

5.14. Sodium (1*S*,5*R*,6*S*)-6-((1*R*)-1-hydroxyethyl)-1-methyl-2-[7-(pyridin-4- yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (7h)

The title compound (**7h**) was obtained in 11% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and pyridine-4-carboxaldehyde by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (D_2O) δ: 1.16 (3H, d, J = 6.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 3.4–3.6 (2H, m), 4.2–4.35 (2H, m), 7.7–7.8 (2H, m), 7.96 (1H, s), 8.11 (1H, s), 8.5–8.6 (2H, m); FABHRMS calcd for $C_{21}H_{18}N_4NaO_5S$ [$(M+H)^+$]: 461.0896, found: 461.0893; HPLC analysis: 97.2% (Area %).

5.15. Sodium (1*S*,5*R*,6*S*)-6-((1*R*)-1-hydroxyethyl)-1-methyl-2-[7-(quinolin-3- yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (7i)

The title compound (**7i**) was obtained in 1.5% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and quinoline-3-aldehyde by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (DMSO-d_6) δ: 1.09 (3H, d, J = 7.3 Hz), 1.11 (3H, d, J = 6.4 Hz), 3.14 (1H, m), 3.47 (1H, m), 3.95 (1H, m), 4.09 (1H, dd, J_1 = 9.8 Hz, J_2 = 2.9 Hz), 5.02 (1 H, br s), 7.71 (1H, t, J = 6.8 Hz), 7.90 (1H, t, J = 8.5 Hz), 8.11 (1H, d, J = 9.0 Hz), 8.21 (1H, d, J = 7.8 Hz), 8.31 (1H, s), 8.37 (1H, s), 9.47 (1H, s), 9.73 (1H, s); FABHRMS calcd for $C_{25}H_{20}N_4NaO_5S$ [$(M+H)^+$]: 511.1052, found: 511.1047; HPLC analysis: 97.7% (Area %).

5.16. Sodium (1*S*,5*R*,6*S*)-6-((1*R*)-1-hydroxyethyl)-1-methyl-2-[7-(1-methylindol-3- yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (7j)

The title compound (**7j**) was obtained in 20% yield from 7-iodoimidazo[5,1-*b*]thiazole (**2**) and 1-methylindole-3-formyl by a procedure similar to that employed for the preparation of **3**–**7g**.

NMR (DMSO-d_6) δ: 1.09 (3H, d, J = 7.2 Hz), 1.12 (3H, d, J = 6.4 Hz), 3.03–3.08 (1H, m), 3.31–3.37 (1H, m), 3.79–3.94 (4H, m), 3.98–4.03 (1H, m), 4.94 (1H, d, J = 5.2 Hz), 7.14–7.24 (2H, m), 7.48 (1H, m), 8.20 (2H, s), 8.36 (1H, m), 9.05 (1H, s); FABHRMS calcd for $C_{25}H_{22}N_4NaO_5S$ [$(M+H)^+$]: 513.1209, found: 513.1205; HPLC analysis: 99.2% (Area %).

5.17. 4-Nitrobenzyl (1*S*,5*R*,6*S*)-2-[7-(1-carbamoylmethylpyridinium-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate iodide (8)

Compound **6** (105.5 mg) was suspended in 2 ml of acetonitrile to prepare a suspension. 2-Iodoacetamide (340 mg) was added to the suspension, and the mixture was stirred at 50 °C for 6 h. The reaction solution was concentrated under reduced pressure, and 5 ml of ethyl acetate was added to the concentrate. Insolubles were

collected by filtration to give 157 mg of the title compound **8**.

NMR (DMSO-d_6) δ: 1.20 (3H, d, J = 6.3 Hz), 1.25 (3H, d, J = 7.2 Hz), 3.47 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.3 Hz), 3.75–3.85 (1H, m), 4.0–4.1 (1H, m), 4.38 (1H, dd, J_1 = 10.2 Hz, J_2 = 3.3 Hz), 5.42 (1H, d, J = 13.8 Hz), 5.5–5.6 (3H, m), 7.7–7.8 (3H, m), 8.08 (1H, br s), 8.22 (2H, d, J = 8.7 Hz), 8.3–8.4 (1H, m), 8.57 (1H, s), 8.69 (1H, s), 9.15–9.2 (1H, m), 9.55–9.6 (1H, m), 9.76 (1H, s); FABHRMS calcd for $C_{38}H_{27}N_6O_8S$ [$(M-I)^+$]: 631.1611, found: 631.1600.

5.18. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)-carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9b)

The title compound (**9b**) (1.62 g) was obtained from 4.43 g of compound **8** by a procedure similar to that employed for the preparation of **7g**.

NMR (D_2O) δ: 1.16 (3H, d, J = 7.5 Hz), 1.33 (3H, d, J = 6.0 Hz), 3.4–3.55 (2H, m), 4.15–4.35 (2H, m), 5.65 (2H, s), 7.89 (1H, s), 8.03 (1H, s), 8.1–8.2 (1H, m), 8.85–8.95 (1H, m), 9.15–9.2 (1H, m), 9.58 (1H, s); FABHRMS calcd for $C_{23}H_{22}N_5O_6S$ [$(M+H)^+$]: 496.1285, found: 496.1277; HPLC analysis: 97.6% (Area %).

5.19. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-(1-methylpyridinium-3-yl)carbonylimidazo[5,1-*b*]-thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9a)

The title compound (**9a**) was obtained in 19% yield from compound **6** and methyl trifluoromethanesulfonate by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (D_2O) δ: 1.13 (3H, d, J = 7.1 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.48–3.56 (2H, m), 4.23 (1H, dd, J_1 = 9.3 Hz, J_2 = 2.7 Hz), 4.29 (1H, m), 4.55 (3H, s), 8.02 (1H, s), 8.15 (1H, s), 8.18 (1H, s), 8.98 (1H, s), 9.17 (1H, s), 9.66 (1H, s); FABHRMS calcd for $C_{22}H_{21}N_4O_5S$ [$(M+H)^+$]: 453.1227, found: 453.1232; HPLC analysis: 95.4% (Area %).

5.20. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-[1-(2- sulfamoylaminoethyl)pyridinium-3-yl]carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9c)

The title compound (**9c**) was obtained in 28% yield from compound **6** and 2-(4-nitrobenzyloxycarbonyl-aminosulfonyl)aminoethyl trifluoromethanesulfonate by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (DMSO-d_6) δ: 1.14–1.21 (6H, m), 3.16 (1H, dd, J_1 = 6.0 Hz, J_2 = 2.6 Hz), 3.42–3.57 (3H, m), 3.95 (1H, m), 4.09 (1H, dd, J_1 = 9.5 Hz, J_2 = 2.7 Hz), 4.84 (2H, m), 5.07 (1H, d, J = 4.2 Hz), 6.80 (2H, s), 7.29 (1H, br s), 8.27 (1H, s), 8.32 (1H, m), 8.35 (1H, s), 9.14 (1H, m), 9.52 (1H, s), 9.78 (1H, s); FABHRMS calcd for $C_{23}H_{25}N_6O_7S_2$ [$(M+H)^+$]: 561.1221, found: 561.1223; HPLC analysis: 96.0% (Area %).

5.21. (1*S*,5*R*,6*S*)-2-[7-(1-Benzylpyridinium-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9d)

The title compound (**9d**) was obtained in 7.8% yield from compound **6** and benzyl bromide by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (D_2O) δ: 1.0–1.15 (3H, m), 1.30 (3H, d, J = 6.0 Hz), 3.35–3.5 (2H, m), 4.1–4.3 (2H, m), 5.86 (2H, s), 7.4–7.6 (5H, m), 7.85–8.1 (3H, m), 8.8–9.0 (2H, m), 9.6–9.7 (1H, m); FABHRMS calcd for $C_{28}H_{25}N_4O_5S$ [$(M+H)^+$]: 529.1540, found: 529.1544; HPLC analysis: 94.3% (Area %).

5.22. (1*S*,5*R*,6*S*)-2-[7-(1-Carboxymethyl-pyridinium-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9e)

The title compound (**9e**) was obtained in 16% yield from compound **6** and 4-nitrobenzyloxycarbonylmethyl trifluoromethanesulfonate by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (D_2O) δ: 1.18 (3H, d, J = 7.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.55 (1H, m), 3.64 (1H, m), 4.27–4.37 (2H, m), 5.39 (2H, s), 8.15 (1H, s), 8.24 (1H, m), 8.29 (1H, s), 8.97 (1H, m), 9.25 (1H, m), 9.67 (1H, s); FABHRMS calcd for $C_{23}H_{21}N_4O_7S$ [$(M+H)^+$]: 497.1125, found: 497.1129; HPLC analysis: 97.3% (Area %).

5.23. (1*S*,5*R*,6*S*)-2-[7-(1-Ethoxycarbonylmethyl-pyridinium-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9f)

The title compound (**9f**) was obtained in 13% yield from compound **6** and ethoxycarbonylmethyl bromide by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (DMSO-d_6) δ: 1.03–1.25 (9H, m), 3.02–3.10 (1H, m), 3.33–3.48 (1H, m), 3.82–3.94 (1H, m), 3.95–4.05 (1H, m), 4.19 (2H, t, J = 7.6 Hz), 4.95 (1H, m), 5.71 (2H, s), 8.22 (1H, s), 8.30–8.36 (2H, m), 9.11 (1H, m), 9.59 (1H, m), 9.75 (1H, s); FABHRMS calcd for $C_{25}H_{25}N_4O_7S$ [$(M+H)^+$]: 525.1438, found: 525.1439; HPLC analysis: 97.6% (Area %).

5.24. (1*S*,5*R*,6*S*)-2-[7-(1-Acetoxymethyl-pyridinium-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9g)

The title compound (**9g**) was obtained in 30% yield from compound **6** and dichloroacetone by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (D_2O) δ: 1.05–1.38 (6H, m), 2.44 (3H, s), 3.31–3.50 (1H, m), 4.02–4.28 (2H, m), 5.83 (2H, m), 7.87 (1H, s), 7.95–8.05 (2H, m), 8.90 (1H, m), 9.14 (1H, m), 9.58 (1H, s); FABHRMS calcd for $C_{24}H_{23}N_4O_6S$ [$(M+H)^+$]: 495.1333, found: 495.1339; HPLC analysis: 96.1% (Area %).

5.25. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-1-methyl-2-[7-(1- trifluoroacetoxymethyl-pyridinium-3-yl)carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9h)

The title compound (**9h**) was obtained in 17% yield from compound **6** and 3-bromo-1,1,1-trifluoroacetone by a procedure similar to that employed for the preparation of **8**–**9b**; HPLC analysis: 97.4% (Area %).

NMR (DMSO-d_6) δ: 1.10–1.28 (6H, m), 3.35–3.50 (1H, m), 3.60–3.76 (1H, m), 3.90–4.08 (1H, m), 4.20–4.30 (1H, m), 5.04–5.11 (2H, m), 6.89 (1H, s), 7.97 (1H, m), 8.48 (1H, s), 8.81 (1H, m), 9.72 (1H, m), 10.61 (1H, s); FABHRMS calcd for $C_{24}H_{20}F_3N_4O_6S$ [$(M+H)^+$]: 549.1050, found: 549.1043.

5.26. (1*S*,5*R*,6*S*)-6-((1*R*)-1-Hydroxyethyl)-2-[7-[1-[2-(methanesulfonyl)ethyl]pyridinium-3-yl]carbonylimidazo[5,1-*b*]thiazol-2-yl]-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9i)

The title compound (**9i**) was obtained in 32% yield from compound **6** and 2-(methanesulfonyl)ethyl trifluoromethanesulfonate by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (D_2O) δ (HOD = 4.65 ppm): 1.19 (3H, d, J = 7.3 Hz), 1.32 (3H, d, J = 6.4 Hz), 3.29 (3H, s), 3.43–3.54 (2H, m), 4.16–4.31 (4H, m), 5.34 (2H, t, J = 6.1 Hz), 7.98 (1H, s), 8.02 (1H, s), 8.17–8.24 (1H, m), 9.12–9.17 (1H, m), 9.21–9.27 (1H, m), 9.80 (1H, s); FABHRMS calcd for $C_{24}H_{25}N_4O_7S_2$ [$(M+H)^+$]: 545.1159, found: 545.1155; HPLC analysis: 95.2% (Area %).

5.27. (1*S*,5*R*,6*S*)-2-[7-[1-[2-(*N*,*N*-Dimethylamino)ethyl]pyridinium-3-yl]carbonylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (9j)

The title compound (**9j**) was obtained in 17% yield from compound **6** and 2-(*N*,*N*-dimethylamino)ethyl trifluoromethanesulfonate by a procedure similar to that employed for the preparation of **8**–**9b**.

NMR (DMSO-d_6) δ: 1.10–1.25 (6H, m), 2.21 (6H, s), 2.77–2.84 (2H, m), 3.10–3.22 (1H, m), 3.42–3.53 (1H, m), 3.88–4.01 (1H, m), 4.05–4.16 (1H, m), 4.76–4.88 (2H, m), 5.02 (1H, m), 8.25–8.35 (2H, m), 8.39 (1H, s), 9.12 (1H, m), 9.48 (1H, m), 9.80 (1H, s); FABHRMS calcd for $C_{25}H_{28}N_5O_5S$ [$(M+H)^+$]: 510.1806, found: 510.1810; HPLC analysis: 71.7% (Area %).

5.28. 5-Methylimidazo[5,1-*b*]thiazole (11a)

To a solution of 5.70 g of 2-aminomethylthiazole (**10**) in 60 ml CH_2Cl_2, 7.10 ml of acetic anhydride was added at room temperature. The mixture was stirred for 1 h, then washed with aqueous $NaHCO_3$, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the residue, 50 ml of toluene and 23.0 ml $POCl_3$ were added and the mixture was stirred at 100 °C for 1 h. After having been quenched with aqueous K_2CO_3, the mixture was extracted with CH_2Cl_2 three times. The organic layer was washed with aqueous NaCl, dried over anhydrous magnesium sulfate, and evaporated to give 6.00 g of the title compound.

NMR ($CDCl_3$) δ: 2.57 (3 H, s), 6.77 (1H, d, J = 4.2 Hz), 6.94 (1H, s), 7.20 (1H, d, J = 4.2 Hz), MS (EI) m/z :138 (M^+).

5.29. 7-Iodo-5-methylimidazo[5,1-*b*]thiazole (12a)

To a solution of 1.41 g of 5-methylimidazo[5,1-*b*]thiazole (**11a**) in 40 ml of 1,2-dichloroethane, 2.30 g of *N*-iodosuccinimide was added, and the mixture was stirred at room temperature for 3.5 h. The solution was washed with aqueous $Na_2S_2O_3$ and water, dried over anhydrous magnesium sulfate, and then concentrated under the reduced pressure. The obtained residue was employed for the next step without further purification.

NMR ($CDCl_3$) δ: 2.59 (3H, s), 6.92 (1H, d, J = 4.2 Hz), 7.30 (1H, d, J = 4.2 Hz).

The other 5-substituted-7-iodoimidazo[5,1-*b*]thiazoles (**12b**–**e**) were prepared by a procedure similar to that employed for the synthesis of **11a** and **12a**.

5.30. 5-Ethyl-7-iodoimidazo[5,1-*b*]thiazole (12b)

The title compound (**12b**) was obtained in 41% yield from compound **10**.

NMR ($CDCl_3$) δ: 1.36 (3H, t, J = 7.7 Hz), 2.91 (2H, q, J = 7.7 Hz), 6.83 (1H, d, J = 4.1 Hz), 7.32 (1H, d, J = 4.1 Hz).

5.31. 5-Cyclopropyl-7-iodoimidazo[5,1-*b*]thiazole (12c)

The title compound (**12c**) was obtained in 28% yield from compound **10**.

NMR ($CDCl_3$) δ: 1.09–1.25 (4H, m), 2.05–2.12 (4H, m), 6.82 (1H, d, J = 4.2 Hz), 7.35 (1H, d, J = 4.2 Hz).

5.32. 7-Iodo-5-methoxymethylimidazo[5,1-*b*]thiazole (12d)

The title compound (**12d**) was obtained in 12% yield from compound **10**.

NMR ($CDCl_3$) δ: 3.35 (3H, s), 4.71 (2H, s), 6.87 (1H, d, J = 4.1 Hz), 7.59 (1H, d, J = 4.1 Hz).

5.33. 7-Iodo-5-(morpholin-1-yl)imidazo[5,1-*b*]thiazole (12e)

The title compound (**12e**) was obtained in 15% yield from compound **10**.

NMR ($CDCl_3$) δ: 3.18 (4H, m), 3.84 (4H, m), 6.74 (1H, d, J = 4.2 Hz), 7.25 (1H, d, J = 4.2 Hz).

5.34. 5-Chloro-7-iodoimidazo[5,1-*b*]thiazole (12f)

To a solution of 1.49 g of 7-iodoimidazo[5,1-*b*]thiazole (**2**) in 30 ml of 1,2-dichloroethane, 801 mg of *N*-chlorosuccinimide was added at room temperature, and the mixture was stirred at room temperature for 18 h. Further *N*-chlorosuccinimide (795 mg) was added and the mixture was stirred for another 3 days. The solution was washed with aqueous NaCl twice, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel short chromatography (AcOEt) to give 1.53 g of the title compound. The obtained title compound was employed for the next step without further purification.

NMR ($CDCl_3$) δ: 6.93 (1H, d, J = 4.2 Hz), 7.38 (1H, d, J = 4.2 Hz).

5.35. 7-Iodo-5-methylthioimidazo[5,1-*b*]thiazole (12g)

A solution of 2.05 g of 5,7-diiodoimidazo[5,1-*b*]thiazole (**13**) in 30 ml of dry THF was cooled in ice bath, and 6.43 ml of a 0.89 M ethylmagnesium bromide/THF solution was added. Fifteen min later, methylthiomethanesulfonate (0.617 ml) was added thereto, and the mixture was stirred at room temperature for 30 min. Further methylthiomethanesulfonate (0.150 ml) was added and the mixture was stirred for 1 h. Aqueous NH_4Cl and AcOEt were added to the reaction solution. The organic layer was washed with aqueous NaCl, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. Recrystallization of the residue (CH_2Cl_2/hexane) gave 1.54 g of the title compound (**12g**).

NMR ($CDCl_3$) δ: 2.55 (3H, s), 6.89 (1H, d, J = 4.2 Hz), 7.50 (1H, d, J = 4.2 Hz), MS (EI) m/z: 296 (M^+).

Compounds **14a**–**g** were obtained from the corresponding 5-substituted-7-iodoimidazo[5,1-*b*]thiazoles **12a**–**g** by a similar procedure to that adopted in the preparation of **3**–**6** and **8**–**9b**.

5.36. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)carbonyl-5-methylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14a)

The title compound (**14a**) was obtained in 25% yield from compound **12a**.

NMR (D_2O) δ: 1.17 (3H, d, J = 7.1 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.53 (3H, s), 3.42–3.52 (2H, m), 4.19–4.32 (2H, m), 5.65 (2H, s), 7.83 (1H, s), 8.14–8.20 (1H, m), 8.91-8.96 (1H, m), 9.19–9.25 (1H, m), 9.54 (1H, s); FABHRMS calcd for $C_{24}H_{24}N_5O_6S$ [$(M+H)^+$]: 510.1442, found: 510.1443; HPLC analysis: 96.4% (Area %).

5.37. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)carbonyl-5-ethylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14b)

The title compound (**14b**) was obtained in 7.5% yield from compound **12b**.

NMR (D_2O) δ: 1.10 (3H, d, J = 6.9 Hz), 1.24 (3H, t, J = 7.7 Hz), 1.32 (3H, d, J = 6.3 Hz), 2.71–2.77 (2H, m), 3.40–3.45 (2H, m), 4.14–4.30 (2H, m), 5.62 (2H, s), 7.74 (1H, s), 8.06–8.13 (1H, m), 8.88 (1H, d, J = 6.0 Hz), 9.23 (1H, d, J = 8.2 Hz), 9.53 (1H, s); FABHRMS calcd for $C_{25}H_{26}N_5O_6S$ [$(M+H)^+$]: 524.1598, found: 524.1593; HPLC analysis: 87.4% (Area %).

5.38. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)carbonyl-5-cyclopropylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14c)

The title compound (**14c**) was obtained in 28% yield from compound **12c**.

NMR (DMSO-d_6) δ: 0.95–1.18 (10H, m), 3.05–3.12 (1H, m), 3.42–3.58 (1H, m), 3.82–3.94 (1H, m), 3.98–4.08 (1H, m), 4.98 (1H, m), 5.47 (2H, s), 7.69 (1H, br s), 8.06 (1H, br s), 8.21–8.26 (1H, m), 8.33 (1H, s), 9.01 (1H, m), 9.44 (1H, m), 9.63 (1H, s); FABHRMS calcd for $C_{26}H_{26}N_5O_6S$ [$(M+H)^+$]: 536.1598, found:536.1602; HPLC analysis: 98.0% (Area %).

5.39. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)carbonyl-5-methoxymethylimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14d)

The title compound (**14d**) was obtained in 6.5% yield from compound **12d**.

NMR (D_2O) δ: 1.23 (3H, d, J = 7.1 Hz), 1.34 (3H, d, J = 6.3 Hz), 3.47 (3H, s), 3.50–3.62 (2H, m), 4.26–4.32 (2H, m), 4.76 (2H, s), 5.67 (2H, s), 8.01 (1H, s), 8.20–8.25 (1H, m), 8.97 (1H, d, J = 5.8 Hz), 9.32 (1H, d, J = 8.0 Hz), 9.66 (1 H, s); FABHRMS calcd for $C_{25}H_{26}N_5O_7S$ [$(M+H)^+$]: 540.1547, found: 540.1545; HPLC analysis: 97.1% (Area %).

5.40. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)carbonyl-5-(morpholin-1-yl)imidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14e)

The title compound (**14e**) was obtained in 10% yield from compound **12e**.

NMR (DMSO-d_6) δ: 1.09 (3H, d, J = 7.2 Hz), 1.16 (3H, d, J = 6.4 Hz), 3.09–3.18 (1H, m), 3.18–3.31 (4H, m), 3.62–3.88 (5H, m), 3.90–4.01 (1H, m), 4.03–4.12 (1H, m), 5.03 (1H, d, J = 5.2 Hz), 5.55 (1H, d, J = 15.8 Hz), 5.71 (1H, d, J = 15.8 Hz), 7.72 (1H, s), 8.07 (1H, s), 8.26–8.34 (2H, m), 9.08 (1H, m), 9.44 (1H, m), 9.82 (1H, s); FABHRMS calcd for $C_{27}H_{29}N_6O_7S$

[(M+H)$^+$]: 581.1813, found: 581.1816; HPLC analysis: 97.1% (Area %).

5.41. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)carbonyl-5-chloroimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14f)

The title compound (**14f**) was obtained in 10% yield from compound **12f**.

NMR (D_2O) δ: 1.04 (3H, d, J = 6.5 Hz), 1.28 (3H, d, J = 6.1 Hz), 3.20–3.38 (2H, m), 4.06 (1H, m), 4.20 (1H, m), 5.54 (2H, s), 7.57 (1H, s), 7.97 (1H, m), 8.81 (1H, m), 9.06 (1H, m), 9.29 (1H, s); FABHRMS calcd for $C_{23}H_{21}ClN_5O_6S$ [(M+H)$^+$]: 530.0896, found: 530.0905; HPLC analysis: 97.5% (Area %).

5.42. (1*S*,5*R*,6*S*)-2-[7-(1-Carbamoylmethylpyridinium-3-yl)-carbonyl-5-methylthioimidazo[5,1-*b*]thiazol-2-yl]-6-((1*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate (intramolecular salt) (14g)

The title compound (**14g**) was obtained in 3.7% yield from compound **12g**.

NMR (DMSO-d_6) δ: 1.13 (3H, d, J = 6.8 Hz), 1.19 (3H, d, J = 6.1 Hz), 2.67 (3H, s), 3.15 (1H, dd, J_1 = 6.8 Hz, J_2 = 2.7 Hz), 3.66 (1H, m), 3.97 (1H, m), 4.10 (1H, dd, J_1 = 9.3 Hz, J_2 = 2.7 Hz), 5.07 (1H, d, J = 5.1 Hz), 5.60 (1H, d, J = 15.7 Hz), 5.83 (1H, d, J = 15.7 Hz), 7.20 (1H, s), 7.74 (1H, s), 8.34 (1H, m), 8.45 (1H, s), 9.14 (1H, m), 9.50 (1H, m), 9.87 (1H, s); FABHRMS calcd for $C_{24}H_{24}N_5O_6S_2$ [(M+H)$^+$]: 542.1163, found: 542.1159; HPLC analysis: 95.6% (Area %).

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