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CP0569, A New Broad-Spectrum Injectable Carbapenem. Part 1: Synthesis and Structure–Activity Relationships

Kazuhiro Aihara,* Yuko Kano, Sohjiro Shiokawa, Toshiro Sasaki, Fumihito Setsu, Yumiko Sambongi, Miyuki Ishii, Kazuyo Tohyama, Takashi Ida, Atsushi Tamura, Kunio Atsumi and Katsuyoshi Iwamatsu

Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan

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Abstract—A series of 1β-methylcarbapenems bearing an (imidazo[5,1-*b*]thiazolium-6-yl)methyl moiety, a 5,5-fused heterobicycle, at the C-2 position was synthesized and evaluated for in vitro antibacterial activities. CP0569 (**1r**) and its analogues showed potent antibacterial activities against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), and Gram-negative bacteria, including *Pseudomonas aeruginosa*. Moreover, CP0569 (**1r**) exhibited stronger antibacterial activity against MRSA and higher resistance to renal dehydropeptidase-1 (DHP-1) than any currently marketed carbapenems, that is, imipenem (IPM), panipenem (PAPM), and meropenem (MEPM).
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Introduction

With the increasing average age of the population, the incidence of infections in immunocompromised patients has been increasing. In addition, resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA)[1] and resistant *Pseudomonas aeruginosa* have appeared. Consequently, new agents are needed to treat serious infections. Our strategic approach to meet this need is to search for agents with very broad antibacterial spectra against resistant organisms and with potent short-time bactericidal activity. We chose the carbapenem skeleton as a basic structure, because carbapenems meet these criteria, having a broad spectrum from Gram-positive to Gram-negative bacteria including *P. aeruginosa*, and a intrinsic bactericidal activity.

Research and development of carbapenem derivatives have been energetically conducted by many pharmaceutical companies worldwide, and imipenem (IPM), panipenem (PAPM), and meropenem (MEPM) are already in clinical use. In order to enhance their resistance to renal dehydropeptidase-1 (DHP-1) and to reduce nephrotoxicity, IPM and PAPM are used as mixtures with cilastatin and betamipron, respectively. MEPM was the first derivative to be used as a single active agent in preparations, because its resistance to the enzyme was improved by the introduction of a 1β-methyl group into the carbapenem nucleus. Nonetheless, the biological stability of MEPM is still not ideal. Furthermore, the marketed carbapenems are insufficiently active against MRSA and drug-resistant *P. aeruginosa*. Thus, novel carbapenem antibiotics possessing superior antibacterial activity against these bacteria are needed.

We have previously reported CP6679,[2,3] a new injectable cephalosporin showing potent antibacterial activity against both Gram-positive and Gram-negative bacteria, including MRSA and *P. aeruginosa*. CP6679 has an (imidazo[5,1-*b*]thiazolium-6-yl)methyl moiety, a 5,5-fused heterobicyclic system,[4] at the C-3 position of the cephem skeleton.

We have now succeeded in synthesizing novel carbapenem derivatives bearing a substituted or unsubstituted (imidazo[5,1-*b*]thiazolium-6-yl)methyl group at the C-2 position of the mother nucleus. They showed potent antibacterial activity with a broad spectrum against bacteria including MRSA and drug-resistant

*Corresponding author. Tel.: +81-45-541-3160; fax: +81-45-543-9771; e-mail: kazuhiro_aihara@meiji.co.jp

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P. aeruginosa, in addition to having high resistance to renal DHP-1. Among them, CP0569 (**1r**), a 1β-methylcarbapenem having a (3-(aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazolium-6-yl)methyl group, had the best activity profile and exhibited superior antibacterial activity against MRSA and drug-resistant *P. aeruginosa* compared with the clinically used cephalosporins and carbapenems, as well as having better resistance to DHP-1. In this paper, we describe the synthesis and biological activities of CP0569 (**1r**) and related compounds.

Chemistry

Compound **1r** (CP0569) was synthesized as shown in Scheme 1. Treatment of *N*-Boc-aminoacetonitrile **10** with ammonia-hydrogen sulfide complex afforded the thioamide **11**, which was treated with ethyl bromopyruvate to give the thiazole **12**. After removal of the Boc group and formylation of the generated amino group, formylaminomethylthiazole was cyclized in phosphoryl chloride to provide ethyl imidazo[5,1-*b*]thiazole-3-carboxylate **13**. Reduction of the ethoxycarbonyl group and Mitsunobu reaction[5] with phthalimide, followed by removal of the protective group afforded the 3-aminomethyl compound **16**, which was transformed into 3-(aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazole **17**. Next, after phosphorylation of the 2-hydroxymethylcarbapenem nucleus **18**, the intermediate obtained was converted into a quaternary salt in the presence of sodium iodide and the heterocycle **17**, and finally removal of the two protective groups[6] yielded the desired **1r** (CP0569, y. 16% from **18**). Related compounds were prepared similarly.

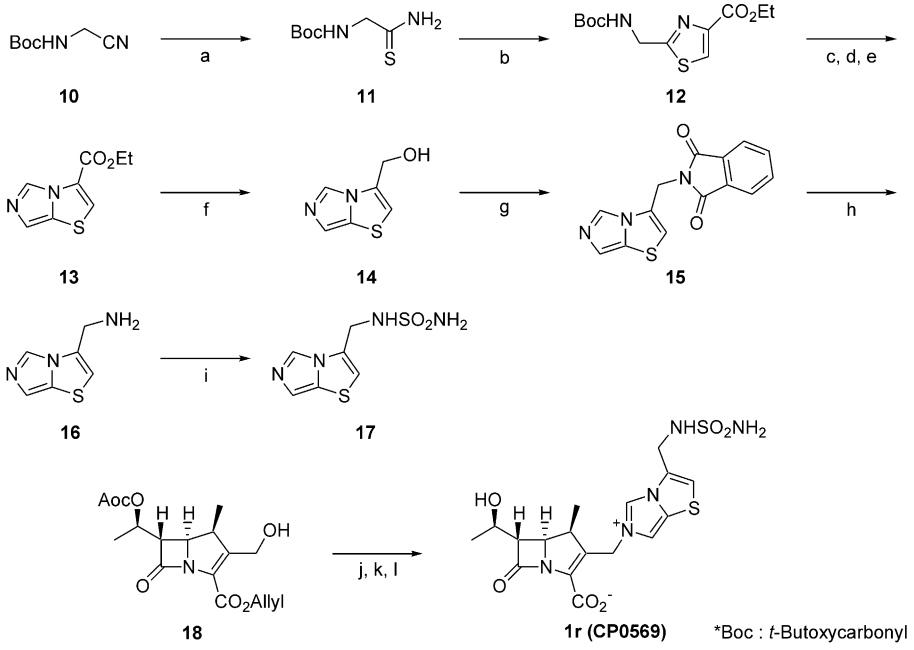
Results and Discussion

We have synthesized a series of 1β-methylcarbapenems having a tetravalent aminomethyl group at the C-2 position (Figs 1 and 2, **1a–z**, **2–7**). The Shionogi group has already reported the pyridinium compound **2** in 1993,[7] but the antibacterial activity of **2** was not superior to that of IPM.

Table 1 shows that the imidazo[5,1-*b*]thiazolium compound **1a** had more potent antibacterial activity against both high-MRSA (H-MRSA) and *P. aeruginosa* than other carbapenems **2–7** bearing various heterocycles. Pyridinium **2** and imidazolium **3** derivatives exhibited only weak activity against H-MRSA. Bicyclic imidazolium compounds **4–7** showed anti-MRSA activity, but none of them exhibited dual potent antibacterial activities against both MRSA and *P. aeruginosa*.

Next, we tried to evaluate the substituent effect by introduction of a hydroxymethyl moiety in order to establish the optimum position for substitution of the imidazo[5,1-*b*]thiazole ring (Table 2). Substitution at the C-3 position (**1c**) retained strong activities against MRSA and *P. aeruginosa* and increased the activity against Gram-negative bacteria. On the other hand, substitution at the C-2 position (**1b**) or the C-5 position (**1d**) weakened anti-MRSA activity and anti-pseudomonal activity, respectively. The antibacterial activity of the 7-substituted compound **1e** was clearly inferior to those of the others. Bi-substituted compounds **1f–g** were inferior to the mono-substituted compound **1c**.

Therefore, we focused on substitution at the C-3 position of the imidazo[5,1-*b*]thiazole ring (Tables 3 and 4).



Scheme 1. Synthesis of **1r** (CP0569). Conditions: (a) NH_3, H_2S/MeOH (yield 76%); (b) $BrCH_2C(O)CO_2Et$, $CaCO_3$/EtOH (yield 74%); (c) TFA; (d) $NaHCO_3$, HCO_2H, Ac_2O/H_2O–CH_2Cl_2; (e) $POCl_3/CH_2Cl_2$, then $POCl_3$, heat (yield 85%); (f) $NaBH_4$/MeOH (yield 98%); (g) phthalimide, PPh_3, DEAD/THF (yield 77%); (h) NH_2NH_2/EtOH (yield 85%); (i) $ClSO_2NH_2$, DIPEA/DMF (yield 66%); (j) $ClP(O)(OPh)_2$, DMAP/CH_2Cl_2; (k) NaI, **17**/DMF; (l) $Pd(PPh_3)_4$, PPh_3, 2-ethylhexanoic acid, potassium 2-ethylhexanoate/CH_2Cl_2 (yield 16%).

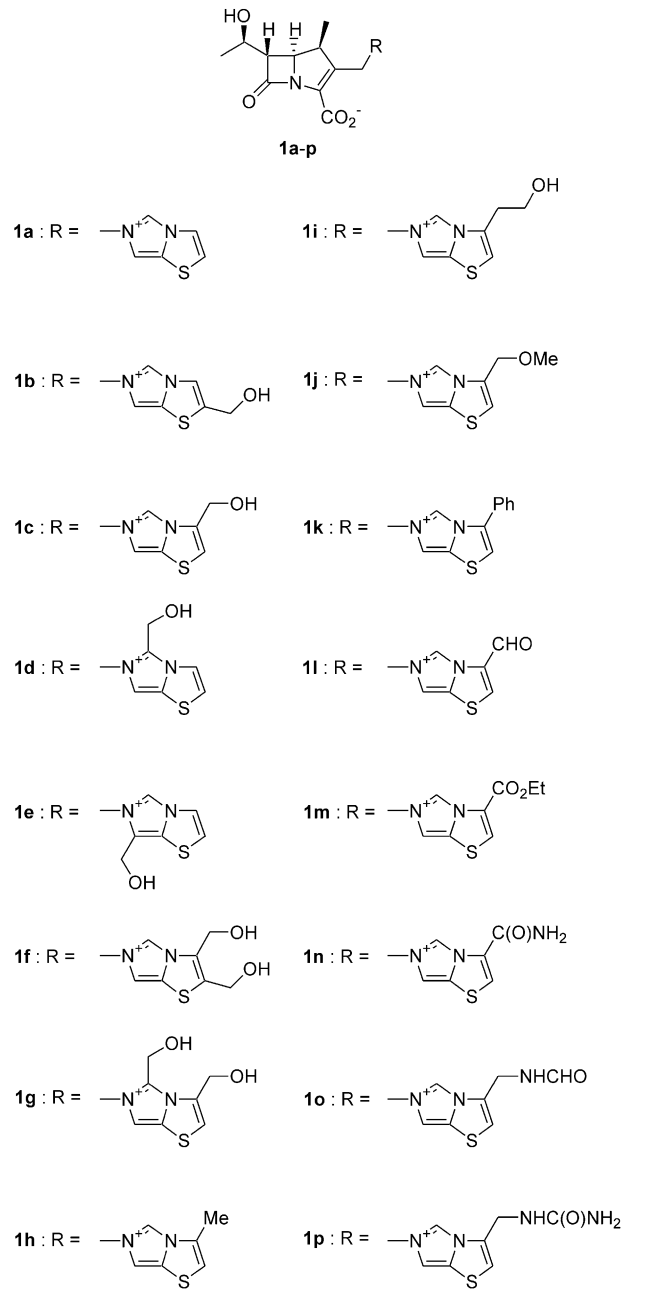


Figure 1.

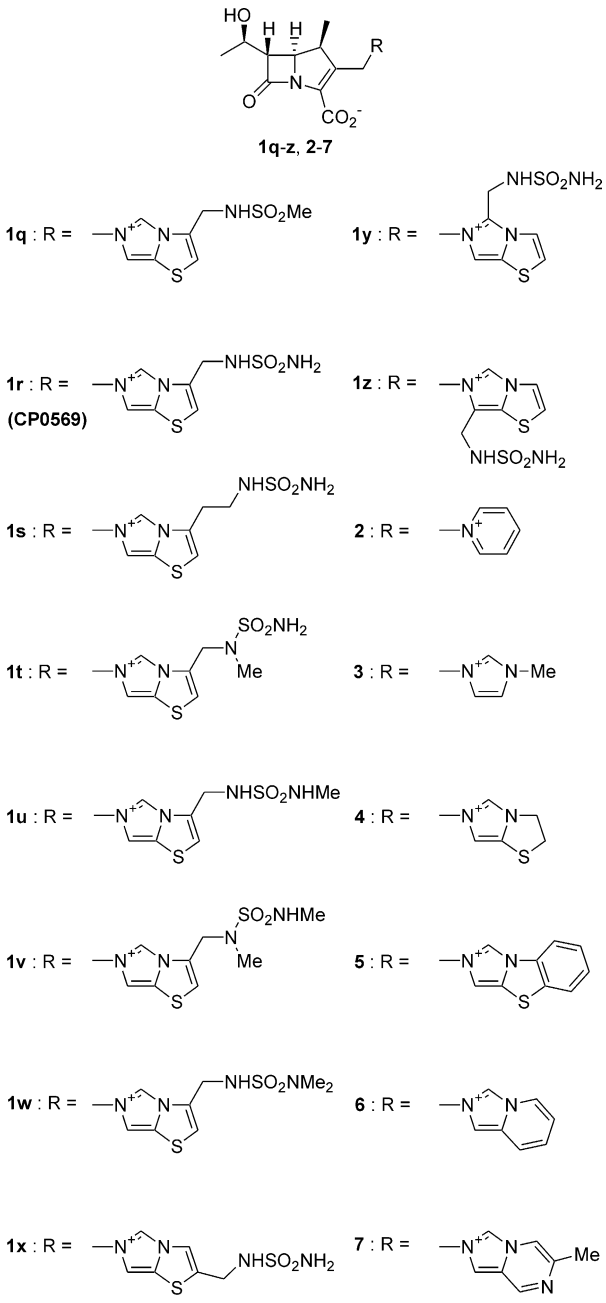


Figure 2.

Compounds **1h** (methyl), **1i** (2-hydroxyethyl) and **1k** (phenyl) showed stronger anti-MRSA activity, but weaker activity against *P. aeruginosa* in comparison with **1c**. Compounds **1j** (methoxymethyl), **1n** (carbamoyl), **1o** (formylaminomethyl), **1p** (ureidomethyl), **1r** ((aminosulfonyl)aminomethyl), and **1s** (2-(aminosulfonyl)aminoethyl) exhibited similar anti-MRSA activity to **1c**. Among them, only **1r** showed superior anti-pseudomonal activity to **1c**. Compounds **1l** (formyl), **1m** (ethoxycarbonyl), and **1q** (methanesulfonylaminomethyl) had weaker antibacterial activities against both MRSA and *P. aeruginosa* than **1c**. Therefore, we selected **1r** for further modification.

As shown in Table 5, introduction of a methyl group at the *N*- and/or *N*′-(aminosulfonyl)aminomethyl moiety decreased the activity against MRSA and/or *P. aeruginosa* (**1t**–**w**). Substitution of the (aminosulfonyl)aminomethyl group at other positions also decreased the activity against MRSA and/or *P. aeruginosa* (**1x**–**z**). The 2-substituted compound **1x** was twice as potent as the others against Gram-negative bacteria other than *P. aeruginosa*.

Finally, we synthesized and evaluated the 1β-nonsubstituted carbapenem **8r** bearing the same heterocycle as **1r** (Scheme 2, Table 6). Antibacterial activities of **8r** against MRSA and Gram-negative bacteria including *P. aeruginosa* were weakened. A study of the resistance of **1r** and **8r** to porcine and mouse renal DHP-1 indicated that **1r** was quite stable, but **8r** was not.

Table 1. Antibacterial activities of **1a** and **2–7** (MIC[a]; μg/mL)

Test organism	1a	2	3	4	5	6	7
Staphylococcus aureus 209P JC-1	<0.025	<0.025	<0.025	<0.025	<0.025	<0.025	0.05
S. aureus M133[b]	0.20	0.39	0.78	0.10	0.20	0.78	0.39
S. aureus M126[c]	6.25	50	50	6.25	6.25	12.5	25
S. epidermidis ATCC14990	<0.025	0.05	<0.025	<0.025	<0.025	<0.025	0.05
Enterococcus hirae ATCC8043	1.56	6.25	3.13	3.13	0.78	1.56	6.25
E. faecalis W-73	6.25	12.5	3.13	12.5	3.13	12.5	12.5
Escherichia coli NIHJ JC-2	0.39	0.39	0.20	0.78	0.78	0.39	0.39
E. coli 255	0.39	0.39	0.20	0.78	0.78	0.39	0.78
Klebsiella pneumoniae PCI602	0.39	3.13	0.78	1.56	0.78	0.39	0.78
Proteus vulgaris GN76	1.56	12.5	6.25	6.25	3.13	1.56	6.25
Morganella morganii 1510	1.56	3.13	3.13	1.56	1.56	1.56	3.13
Citrobacter freundii GN346	0.20	0.39	0.20	0.39	0.78	0.20	0.39
Enterobacter cloacae GN7471	0.39	0.39	0.20	0.39	0.78	0.20	0.39
Serratia marcescens GN10857	1.56	3.13	0.78	3.13	12.5	0.78	1.56
Pseudomonas aeruginosa GN16362	6.25	6.25	6.25	12.5	50	6.25	6.25
P. aeruginosa M-0148	6.25	6.25	3.13	6.25	50	6.25	12.5
P. aeruginosa E-2	6.25	6.25	6.25	6.25	50	6.25	12.5

[a]Minimum inhibitory concentration.
[b]Low-MRSA.
[c]High-MRSA.

Table 2. Antibacterial activities of **1a–g** (MIC[a]; μg/mL)

Test organism	1a	1b	1c	1d	1e	1f	1g
S. aureus 209P JC-1	<0.025	<0.025	<0.025	<0.025	0.05	<0.025	<0.025
S. aureus M133[b]	0.20	0.39	0.39	0.20	0.39	0.20	0.39
S. aureus M126[c]	6.25	12.5	6.25	6.25	25	12.5	6.25
S. epidermidis ATCC14990	<0.025	<0.025	<0.025	<0.025	0.10	<0.025	<0.025
E. hirae ATCC8043	1.56	1.56	1.56	1.56	6.25	1.56	1.56
E. faecalis W-73	6.25	6.25	6.25	6.25	50	3.13	6.25
E. coli NIHJ JC-2	0.39	0.39	0.20	0.10	0.78	0.20	0.20
E. coli 255	0.39	0.39	0.20	0.20	0.78	0.39	0.39
K. pneumoniae PCI602	0.39	0.39	0.39	0.39	1.56	0.39	0.39
P. vulgaris GN76	1.56	1.56	1.56	3.13	12.5	1.56	3.13
M. morganii 1510	1.56	1.56	0.78	1.56	3.13	1.56	1.56
C. freundii GN346	0.20	0.20	0.20	0.20	0.78	0.20	0.39
E. cloacae GN7471	0.39	0.20	0.20	0.20	0.78	0.20	0.39
S. marcescens GN10857	1.56	0.78	0.78	0.78	3.13	1.56	1.56
P. aeruginosa GN16362	6.25	3.13	6.25	12.5	25	6.25	25
P. aeruginosa M-0148	6.25	6.25	6.25	6.25	25	6.25	12.5
P. aeruginosa E-2	6.25	6.25	6.25	12.5	25	6.25	12.5

[a]Minimum inhibitory concentration.
[b]Low-MRSA.
[c]High-MRSA.

Table 3. Antibacterial activities of **1a**, **1c**, and **1h–g** (MIC[a]; μg/mL)

Test organism	1a	1h	1c	1i	1j	1k	1l
S. aureus 209P JC-1	<0.025	<0.025	<0.025	<0.025	<0.025	<0.025	0.20
S. aureus M133[b]	0.20	0.10	0.39	0.10	0.39	0.10	12.5
S. aureus M126[c]	6.25	3.13	6.25	3.13	6.25	3.13	100
S. epidermidis ATCC14990	<0.025	<0.025	<0.025	<0.025	<0.025	<0.025	0.39
E. hirae ATCC8043	1.56	1.56	1.56	1.56	0.78	0.78	12.5
E. faecalis W-73	6.25	6.25	6.25	6.25	3.13	6.25	100
E. coli NIHJ JC-2	0.39	0.20	0.20	0.20	0.20	6.25	3.13
E. coli 255	0.39	0.20	0.20	0.39	0.20	6.25	3.13
K. pneumoniae PCI602	0.39	0.39	0.39	0.39	0.20	6.25	3.13
P. vulgaris GN76	1.56	0.78	1.56	1.56	1.56	12.5	6.25
M. morganii 1510	1.56	0.78	0.78	0.78	1.56	6.25	12.5
C. freundii GN346	0.20	0.39	0.20	0.39	0.20	3.13	3.13
E. cloacae GN7471	0.39	0.20	0.20	0.39	0.20	6.25	3.13
S. marcescens GN10857	1.56	1.56	0.78	1.56	1.56	50	12.5
P. aeruginosa GN16362	6.25	12.5	6.25	12.5	12.5	100	>100
P. aeruginosa M-0148	6.25	12.5	6.25	12.5	12.5	100	100
P. aeruginosa E-2	6.25	12.5	6.25	12.5	12.5	100	100

[a]Minimum inhibitory concentration.
[b]Low-MRSA.
[c]High-MRSA.

Table 4. Antibacterial activities of **1m–s** (MIC[a]; μg/mL)

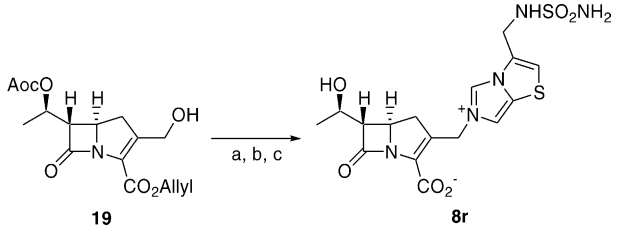
Test organism	1m	1n	1o	1p	1q	1r	1s
S. aureus 209P JC-1	0.05	<0.025	<0.025	<0.025	0.05	<0.025	0.05
S. aureus M133[b]	0.78	0.39	0.20	0.78	6.25	0.39	0.39
S. aureus M126[c]	25	6.25	6.25	6.25	12.5	6.25	6.25
S. epidermidis ATCC14990	0.05	<0.025	<0.025	<0.025	0.05	<0.025	0.05
E. hirae ATCC8043	3.13	1.56	1.56	1.56	6.25	1.56	1.56
E. faecalis W-73	12.5	3.13	6.25	6.25	12.5	6.25	12.5
E. coli NIHJ JC-2	0.39	0.20	0.20	0.20	0.78	0.20	0.20
E. coli 255	0.39	0.20	0.20	0.39	0.78	0.20	0.39
K. pneumoniae PCI602	0.39	0.39	0.39	0.39	0.78	0.20	0.39
P. vulgaris GN76	3.13	1.56	1.56	1.56	3.13	1.56	1.56
M. morganii 1510	n.t.[d]	0.78	0.78	1.56	3.13	1.56	n.t.[d]
C. freundii GN346	0.78	0.20	0.20	0.39	0.39	0.20	0.39
E. cloacae GN7471	0.78	0.39	0.20	0.20	0.39	0.20	0.20
S. marcescens GN10857	6.25	0.78	0.78	1.56	3.13	0.78	1.56
P. aeruginosa GN16362	>100	6.25	6.25	12.5	25	1.56	12.5
P. aeruginosa M-0148	>100	6.25	6.25	12.5	12.5	3.13	12.5
P. aeruginosa E-2	100	6.25	6.25	12.5	12.5	1.56	6.25

[a]Minimum inhibitory concentration.
[b]Low-MRSA.
[c]High-MRSA.
[d]Not tested.

Table 5. Antibacterial activities of **1r** and **1t–z** (MIC[a]; μg/mL)

Test organism	1r	1t	1u	1v	1w	1x	1y	1z
S. aureus 209P JC-1	<0.025	<0.025	<0.025	0.05	<0.025	<0.025	0.05	0.05
S. aureus M133[b]	0.39	0.39	0.78	0.78	3.13	0.78	0.39	1.56
S. aureus M126[c]	6.25	6.25	12.5	6.25	12.5	12.5	6.25	25
S. epidermidis ATCC14990	<0.025	0.05	<0.025	0.05	0.05	<0.025	0.05	0.05
E. hirae ATCC8043	1.56	1.56	3.13	3.13	6.25	1.56	3.13	6.25
E. faecalis W-73	6.25	12.5	12.5	12.5	6.25	3.13	25	>25
E. coli NIHJ JC-2	0.20	0.39	0.20	0.78	0.78	0.10	0.20	1.56
E. coli 255	0.20	0.39	0.39	0.78	0.39	0.10	0.20	1.56
K. pneumoniae PCI602	0.20	0.39	0.39	0.78	0.39	0.39	1.56	1.56
P. vulgaris GN76	1.56	1.56	1.56	3.13	3.13	1.56	12.5	6.25
M. morganii 1510	1.56	1.56	1.56	3.13	3.13	0.78	3.13	3.13
C. freundii GN346	0.20	0.39	0.39	0.78	0.78	0.10	0.39	0.78
E. cloacae GN7471	0.20	0.39	0.20	0.78	0.78	0.10	0.39	0.78
S. marcescens GN10857	0.78	3.13	1.56	6.25	6.25	0.78	3.13	3.13
P. aeruginosa GN16362	1.56	3.13	6.25	25	50	3.13	50	12.5
P. aeruginosa M-0148	3.13	6.25	6.25	25	50	3.13	50	25
P. aeruginosa E-2	1.56	3.13	6.25	25	25	3.13	50	12.5

[a]Minimum inhibitory concentration.
[b]Low-MRSA.
[c]High-MRSA.



19 8r

Scheme 2.

Hence, we chose **1r** as the best compound and evaluated it in comparison with marketed β-lactams (Table 7). Compound **1r** has the strongest anti-MRSA activity and is equipotent to the others in antibacterial activity against Gram-negative bacteria including *P. aeruginosa*. Furthermore, **1r** is more resistant to renal DHP-1's than the clinically used injectable carbapenems. The results of further evaluation of **1r** will be reported elsewhere.

Experimental

General methods

All reagents and solvents were of the best grades commercially available.

^{1}H NMR spectra were recorded on 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 HOD (4.80 ppm) in D_2O were used as internal reference standards. Mass spectra were measured on a JEOL JMS-700 mass spectrometer.

Antibacterial activity in vitro

Minimum inhibitory concentration (MIC) was determined by the agar plate dilution method. Seed cultures

Table 6. Antibacterial activities (MIC[a]; μg/mL) and resistance to DHP-1[b] (%) of **1r** and **8r**

Test organism	1r	8r
S. aureus 209P JC-1	<0.025	<0.025
S. aureus M133[c]	0.39	0.10
S. aureus M126[d]	6.25	12.5
S. epidermidis ATCC14990	<0.025	<0.025
E. hirae ATCC8043	1.56	0.78
E. faecalis W-73	6.25	6.25
E. coli NIHJ JC-2	0.20	0.39
E. coli 255	0.20	0.39
K. pneumoniae PCI602	0.20	0.39
P. vulgaris GN76	1.56	1.56
M. morganii 1510	1.56	3.13
C. freundii GN346	0.20	0.78
E. cloacae GN7471	0.20	0.39
S. marcescens GN10857	0.78	1.56
P. aeruginosa GN16362	1.56	3.13
P. aeruginosa M-0148	3.13	6.25
P. aeruginosa E-2	1.56	3.13
Resistance to porcine DHP-1[e]	92	69
Resistance to mouse DHP-1[e]	98	81

[a]Minimum inhibitory concentration.
[b]Dehydropeptidase-1.
[c]Low-MRSA.
[d]High-MRSA.
[e]Residual percentage after 3 h.

of test strains were prepared 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.

Sensitivity to renal DHP-1

The susceptibility of carbapenems to renal DHP-1 was determined with purified porcine and mouse renal DHP-1 according to the following method. The activity of DHP-1 was spectrophotometrically determined by measuring the hydrolysis of glycyldehydrophenylalanine as a substrate.

Preparation of DHP-1 from kidney acetone powder of each animal. Acetone powder of kidney (1.5 g) (Sigma), porcine Type II (Lot 33H7225), was suspended in 100 mL of 50 mM Tris–HCl buffer (pH 7.0) containing 20% *n*-butane, and the suspension was stirred at 5 °C for 48 h. The suspension was then dialyzed against 50 mM Tris–HCl buffer (pH 7.0) in cellulose tubing (30/32, Viskase Sales Corp.) until the odor of *n*-butanol was no longer detectable, thereby removing *n*-butanol. The dialyzate was centrifuged at 10,000g (Kubota 6800) for 20 min, and the supernatant was obtained as partially purified DHP-1. This partially purified porcine DHP-1 was subdivided and stored at −80 °C. The above procedure was repeated, except that 1.5 g of acetone powder of kidney from mouse (Lot 23F8105) was used. The partially purified mouse DHP-1 thus prepared was stored.

Measurement of susceptibility to DHP-1. A solution of carbapenem substrate [2000 μg (potency)/mL] was prepared using sterilized, purified water, and this solution was added to the partially purified DHP-1 of each animal to give a final concentration at 100 μg (potency)/mL.

Table 7. Antibacterial activities (MIC[a]; μg/mL) and resistance to DHP-1[b] (%) of **1r** and clinically used injectable β-lactams

Test organism	1r	IPM[c]	PAPM[d]	MEPM[e]	CAZ[f]	CPR[g]	CFSL[h]
S. aureus 209P JC-1	<0.025	<0.025	<0.025	0.10	3.13	0.20	0.39
S. aureus M133[i]	0.39	0.39	0.20	6.25	25	6.25	6.25
S. aureus M126[j]	6.25	50	25	25	>100	100	50
S. epidermidis ATCC14990	<0.025	<0.025	<0.025	0.10	3.13	0.39	0.39
E. hirae ATCC8043	1.56	1.56	0.39	6.25	>100	1.56	6.25
E. faecalis W-73	6.25	1.56	0.39	6.25	>100	25	>100
E. coli NIHJ JC-2	0.20	0.10	0.10	<0.025	0.20	0.05	0.10
E. coli 255	0.20	0.20	0.10	<0.025	12.5	0.10	0.39
K. pneumoniae PCI602	0.20	0.39	0.20	0.05	0.10	0.05	0.10
P. vulgaris GN76	1.56	6.25	3.13	0.10	0.05	0.20	0.20
M. morganii 1510	1.56	3.13	0.39	0.10	12.5	0.39	0.39
C. freundii GN346	0.20	0.20	0.10	0.05	25	1.56	3.13
E. cloacae GN7471	0.20	0.20	0.20	<0.025	6.25	0.20	0.78
S. marcescens GN10857	0.78	0.78	0.78	0.10	0.39	0.78	1.56
P. aeruginosa GN16362	1.56	1.56	12.5	0.39	1.56	3.13	6.25
P. aeruginosa M-0148	3.13	3.13	6.25	1.56	1.56	6.25	12.5
P. aeruginosa E-2	1.56	1.56	6.25	1.56	1.56	3.13	6.25
Resistance to porcine DHP-1[k]	92	0.5	19	71	n.t.[l]	n.t.[l]	n.t.[l]
Resistance to mouse DHP-1[k]	98	24	28	17	n.t.[l]	n.t.[l]	n.t.[l]

[a]Minimum inhibitory concentration.
[b]Dehydropeptidase-1.
[c]Imipenem/cilastatin.
[d]Panipenem/betamipron.
[e]Meropenem.
[f]Ceftazidime.
[g]Cefpirome.
[h]Cefoselis.
[i]Low-MRSA.
[j]High-MRSA.
[k]Residual percentage after 3 h.
[l]Not tested.

For the blank, 50 mM Tris–HCl buffer (pH 7.0) was used instead of the partially purified DHP-1 of each animal. The reaction was allowed to proceed at 37 °C for 3 h, then a sample was taken. An equal amount of methanol was added to the sample under ice cooling to terminate the reaction. The mixture was filtered through a filter (Sanprep LCR 13-LH, manufactured by Millipore) and subjected to HPLC (column: Capcell Pack C18 SG120, manufactured by Shiseido Co., Ltd.; detection: UV; eluent: acetonitrile/10 mM aqueous acetic acid solution) to determined the residual amount of the carbapenem (%).

$$\text{Residual amount (\%)} = (\text{Sample Peak Area}/\text{Blank Peak Area}) \times 100$$

(*t*-Butoxycarbonylamino)acetothioamide (11). Into ice-cooled methanol (230 mL), ammonia gas (25 g, 1.56 mol) and hydrogen sulfide gas (50 g, 1.47 mol) were introduced successively, and then (*t*-butoxyamino)acetonitrile **10** (71.45 g, 0.457 mol) was added. The reaction mixture was stirred at room temperature overnight, then ice-cooled, mixed gradually with water (500 mL), and further stirred for 2 h under ice cooling. Precipitated crystals were collected by filtration, washed with ice-cooled water (300 mL), and dried under reduced pressure to give **11** (65.88 g, yield 76%) as colorless crystals: ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 4.16 (2H, d, J = 6.2 Hz), 5.2–5.3 (1H, br. s), 7.4–7.7 (1H, br. s), 7.7–8.0 (1H, br. s).

Ethyl 2-(*t*-butoxycarbonylamino)methylthiazole-4-carboxlate (12). To a solution of **11** (10 g, 52.6 mmol) in ethanol (150 mL), ethyl bromopyruvate (7.3 mL, 58.2 mmol) and calcium carbonate (2.7 g, 27.0 mmol) were added. The reaction mixture was stirred at room temperature for 6 h and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform, and this solution was washed with saturated $NaHCO_3$ aq and water successively, dried over $MgSO_4$, and filtered. Removal of the solvent afforded **12** (11.2 g, 74%): ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, J = 7 Hz), 1.47 (9H, s), 4.57 (2H, q, J = 7 Hz), 4.60 (2H, s), 7.12 (1H, s).

Ethyl imidazo[5,1-*b*]thiazole-3-carboxylate (13). A solution of **12** (1.50 g, 5.24 mmol) in trifluoroacetic acid (5 mL) was stirred at room temperature for 30 min. After evaporation, the residue was dissolved in saturated $NaHCO_3$ aq and adjusted to pH 8. To a vigorously stirred mixture of the above aqueous solution and dichloromethane (30 mL), a pre-mixed solution of formic acid (1 mL, 26.5 mmol) and acetic anhydride (1 mL, 10.5 mmol) at 50 °C for 30 min was added. The reaction mixture was stirred for 1 h. After separation of the organic layer, the water layer was extracted with dichloromethane twice. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure to provide crude ethyl 2-(formylamino)methylthiazole-4-carboxylate (1.15 g).

To a solution of the crude 2-(formylamino)methylthiazole-4-carboxylate (1.15 g) in dichloromethane (30 mL), phosphoryl chloride (1.2 mL, 12.9 mmol) was added at −20 °C. The reaction mixture was stirred at room temperature for 30 min, and then concentrated under vacuum. The residual material was dissolved in phosphoryl chloride (12 mL), and this solution was stirred at 100 °C for 30 min, then cooled to room temperature. After removal of phosphoryl chloride under reduced pressure, the residue was dissolved in water (30 mL), and the resulting solution was washed with dichloromethane (20 mL), adjusted to pH 8 with $NaHCO_3$ powder, and extracted with dichloromethane (30 mL×2). The combined extract was dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure to yield **13** (0.885 g, yield 85%) as slightly amber-colored crystals: ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, t, J = 7 Hz), 4.44 (2H, q, J = 7 Hz), 7.17 (1H, s), 7.77 (1H, s), 8.57 (1H, s).

3-Hydroxymethylimidazo[5,1-*b*]thiazole (14). To a solution of **13** (0.800 g, 4.08 mmol) in methanol (16 mL), sodium borohydride (0.400 g, 10.6 mmol) was added, and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched with acetone (3 mL), and after stirring for a further 0.5 h, the mixture was concentrated in vacuo to give a crude product, which was dissolved in dichloromethane (20 mL) and saturated brine (20 mL). This solution was stirred for 10 min. After separation of the organic layer, the water layer was extracted with dichloromethane (20 mL×2). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford **14** (0.615 g, yield 98%) as slightly amber-colored crystals: ^{1}H NMR ($CDCl_3$) δ 4.97 (2H, s), 6.71 (1H, s), 7.04 (1H, s), 8.06 (1H, s).

3-(Phthalimido)methylimidazo[5,1-*b*]thiazole (15). To a mixed solution of **14** (1.00 g, 6.48 mmol), phthalimide (1.91 g, 13.0 mmol), and triphenylphosphine (3.39 g, 12.9 mol) in anhydrous tetrahydrofuran (30 mL), diethyl azodicarboxylate (2.26 g, 13.0 mmol) was added dropwise at room temperature under an argon atmosphere. The mixture was stirred for 1 h. After removal of the solvent, the residue was purified by silica gel flash column chromatography (PhMe/AcOEt = 5:1) to give **15** (1.41 g, yield 77%): ^{1}H NMR ($CDCl_3$) δ 4.98 (2H, s), 6.98 (1H, s), 7.09 (1H, s), 7.7–7.8 (2H, m), 7.85–7.95 (2H, m), 8.29 (1H, s).

3-Aminomethylimidazo[5,1-*b*]thiazole (16). To a solution of **15** (4.400 g, 15.5 mmol) in ethanol (155 mL), anhydrous hydrazine (0.63 mL, 20.1 mmol) was added. The mixture was stirred under reflux overnight. After cooling, filtration, and evaporation in vacuo, 2 N HCl aq (40 mL) and ethyl acetate (60 mL) were added to the residual solution and shaken. The water layer was separated, adjusted to pH 12, and extracted with dichloromethane (100 mL×2). The organic solution was dried over K_2CO_3 and filtered. The filtrate was evaporated under reduced pressure to yield **16** (2.029 g, yield 85%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 4.47 (2H, s), 6.75 (1H, s), 7.11 (1H, s), 8.27 (1H, s).

3 - (Aminosulfonyl)aminomethylimidazo[5,1 - *b*]thiazole (17). To a mixed solution of **16** (0.857 g, 5.6 mmol) and *N*,*N*-diisopropylethylamine (4.39 mL, 25.2 mmol) in *N*,*N*-dimethylformamide (15 mL), aminosulfonyl chloride (0.972 g, 8.4 mmol) was added at −65 °C, and the whole was stirred with gradual warming to −30 °C for 2 h. After concentration under a vacuum and adjustment to pH 7.5 with $NaHCO_3$ aq, the neutralized solution was purified by Diaion HP-20 (Mitsubishi Chemical) column chromatography (20% acetone aq fraction) to afford **17** (0.854 g, yield 66%): ^{1}H NMR (DMSO-d_6) δ 4.24 (2H, d, J = 6.3 Hz), 6.85 (2H, s), 7.06 (1H, s), 7.09 (1H, s), 7.31 (1H, t, J = 6.3 Hz), 8.23 (1H, s).

(1*S*,5*R*,6*S*) - 2 - [3 - (Aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1r, CP0569). To a mixed solution of allyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-(allyloxycarbonyloxy)ethyl]-2-hydroxymethyl-1-methyl-1-carbapen-2-em-3-carboxylate[8] **18** (3.50 g, 9.58 mmol) and 4-*N*,*N*-dimethylaminopyridine (1.52 g, 12.4 mmol) in dichloromethane (17 mL), diphenylphosphorus chloride (2.39 mL, 11.5 mmol) was added drop by drop at −45 °C for 5 min under an argon atmosphere. Stirring was continued at the same temperature for 45 min. The reaction mixture was diluted with dichloromethane (400 mL), washed with semi-saturated $NaHCO_3$ aq (140 mL), 0.1 N HCl aq (140 mL×2), and semi-saturated brine in succession, dried over $MgSO_4$, filtered, and concentrated under vacuum to half the initial volume. To the remaining solution, 3-(aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazole 17 (2.78 g, 12.0 mmol), sodium iodide (2.88 g, 19.2 mmol), and *N*,*N*-dimethylformamide (35 mL) were added. After removal of dichloromethane, the resultant solution was stirred at room temperature for 4 h, then diluted with ethyl acetate (700 mL), washed with semi-saturated brine (250 mL×3), dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was washed with diethyl ether (100 mL×2) and dried in vacuo to give a crude intermediate (5.87 g).

To a solution of the crude intermediate obtained above (5.87 g) in dichloromethane (200 mL), triphenylphosphine (0.653 g, 2.49 mmol), potassium 2-ethylhexanoate (1.59 g, 8.70 mmol), 2-ethylhexanoic acid (1.39 mL, 8.70 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.83 g, 2.45 mmol) were added successively. The reaction mixture was stirred at room temperature under an argon atmosphere, diluted with dichloromethane (100 mL) and extracted with water (100 mL×2). After concentration of the aqueous layer under a vacuum, the residual solution was purified by reversed-phase flash column chromatography (Cosmosil 40C_{18} PREP, manufactured by Nacalai Tesque) (water/MeOH = 20:1 to 10:1 fraction) to obtain **1r** (683 mg, yield 16%): ^{1}H NMR (D_2O) δ 1.08 (3H, d, J = 7.4 Hz), 1.25 (3H, d, J = 6.3 Hz), 3.00–3.11 (1H, m), 3.48 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.18–4.27 (2H, m), 4.55 (2H, s), 5.24 (1H, d, J = 15.0 Hz), 5.74 (1H, d, J = 15.0 Hz), 7.51 (1H, s), 7.76 (1H, s); FABMS m/z 456 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{22}N_5O_6S_2$ [(M + H)$^+$]: 456.1012, found: 456.1019.

Compounds 1a–1p, 1q–1z, and 2–7. These compounds were prepared by a similar procedure to that described for the preparation of **1r**. The imidazo[5,1-*b*]thiazoles were prepared according to our patented method.[7,9] Pyridine and *N*-methylimidazole were commercial products. 2,3-Dihydroimidazo[5,1-*b*]thiazole,[10] benzo[*d*]imidazo[5,1-*b*]thiazole,[11,12] and imidazo[1,5-*a*]pyridine[13] were prepared as reported. 6-Methylimidazo[1,5-*a*]pyradine was synthesized from commercially available 2-aminomethylpyradine in two steps.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(imidazo[5,1-*b*]thiazolium-6-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1a). This was obtained in 25% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.14 (3H, d, J = 7.2 Hz), 1.31 (3H, d, J = 6.4 Hz), 3.10 (1H, m), 3.52 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.1 Hz), 4.20-4.30 (2H, m), 5.24 (1H, d, J = 15.0 Hz), 5.82 (1H, d, J = 15.0 Hz), 7.59 (1H, d, J = 4.2 Hz), 7.72 (1H, s), 7.97 (1H, d, J = 4.2 Hz), 9.41 (1H, s); FABMS m/z 348 [(M + H)$^+$]; FABHRMS calcd for $C_{16}H_{18}N_3O_4S$ [(M + H)$^+$]: 348.1018, found: 348.1015.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(2-hydroxymethylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1b). This was obtained in 3.1% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.2 Hz), 1.26 (3H, d, J = 6.5 Hz), 3.04 (1H, m), 3.48 (1H, m), 4.17–4.25 (2H, m), 4.80 (2H, s), 5.17 (1H, d, J = 14.6 Hz), 5.78 (1H, d, J = 14.6 Hz), 7.69 (1H, s), 7.90 (1H, s), 9.30 (1H, s); FABMS m/z 378 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{20}N_3O_5S$ [(M + H)$^+$]: 378.1124, found: 378.1124.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-hydroxymethylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1c). This was obtained in 19% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.2 Hz), 1.25 (3H, d, J = 6.3 Hz), 3.04 (1H, m), 3.47 (1H, m), 4.21 (2H, m), 4.87 (2H, s), 5.19 (1H, d, J = 15.0 Hz), 5.80 (1H, d, J = 15.0 Hz), 7.47 (1H, s), 7.75 (1H, s), 9.43 (1H, s); FABMS m/z 378 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{20}N_3O_5S$ [(M + H)$^+$]: 378.1124, found: 378.1124.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(5-hydroxymethylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1d). This was obtained in 2.8% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.13 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.5 Hz), 2.95 (1H, m), 3.47 (1H, m), 4.13–4.25 (2H, m), 5.15 (2H, s), 5.16 (1H, d, J = 15.5 Hz), 5.94 (1H, d, J = 15.5 Hz), 7.58 (1H, d, J = 4.1 Hz), 7.74 (1H, s), 8.06 (1H, d, J = 4.1 Hz); FABMS m/z 378 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{20}N_3O_5S$ [(M + H)$^+$]: 378.1124, found: 378.1124.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(7-hydroxymethylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1e). This was obtained in 0.9% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.14 (3H, d, J = 7.4 Hz), 1.28 (3H, d, J = 6.4 Hz), 2.95 (1H, m), 3.50 (1H, dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz), 4.16–4.28 (2H, m), 4.90 (2H, s), 5.18 (1H, d, J = 15.9 Hz), 5.88 (1H, d,

J = 15.9 Hz), 7.57 (1H, d, J = 4.3 Hz), 7.93 (1H, d, J = 4.3 Hz), 9.41 (1H, s); FABMS m/z 378 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{20}N_3O_5S$ [(M + H)$^+$]: 378.1124, found: 378.1124.

(1*S*,5*R*,6*S*)-2-[Di-2,3-(hydroxymethyl)imidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1f). This was obtained in 2.3% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.11 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.4 Hz), 3.02–3.08 (1H, m), 3.48 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.18–4.22 (2H, m), 4.85 (2H, s), 4.88 (2H,s), 5.18 (1H, d, J = 14.8 Hz), 5.79 (1H, d, J = 14.8 Hz), 7.74 (1H, s); FABMS m/z 408 [(M + H)$^+$]; FABHRMS calcd for $C_{18}H_{22}N_3O_6S$ [(M + H)$^+$]: 408.1229, found: 408.1229.

(1*S*,5*R*,6*S*)-2-[Di-3,5-(hydroxymethyl)imidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1g). This was obtained in 2.1% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.11 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.4 Hz), 3.02–3.08 (1H, m), 3.48 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.18–4.22 (2H, m), 4.87 (2H, s), 5.15 (2H, s), 5.18 (1H, d, J = 15.0 Hz), 5.79 (1H, d, J = 15.0 Hz), 7.47 (1H, s), 7.75 (1H, s); FABMS m/z 408 [(M + H)$^+$]; FABHRMS calcd for $C_{18}H_{22}N_3O_6S$ [(M + H)$^+$]: 408.1229, found: 408.1229.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(3-methylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-carbapen-2-em-3-carboxylate (1h). This was obtained in 12% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.4 Hz), 1.23 (3H, d, J = 6.3 Hz), 2.47 (3H, s), 3.01 (1H, m), 3.45 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz), 4.14–4.23 (2H, m), 5.15 (1H, d, J = 15.1 Hz), 5.81 (1H, d, J = 15.1 Hz), 7.11 (1H, s), 7.68 (1H, s), 9.35 (1H, s); FABMS m/z 362 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{20}N_3O_4S$ [(M + H)$^+$]: 362.1175, found: 362.1173.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-[3-(2-hydroxyethyl)imidazo[5,1-*b*]thiazolium-6-yl]methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1i). This was obtained in 27% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.10 (3H, d, J = 7.2 Hz), 1.26 (3H, d, J = 6.3 Hz), 3.02 (1H, m), 3.13 (2H, t, J = 6.0 Hz), 3.47 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz), 3.98 (2H, t, J = 6.0 Hz), 4.15–4.30 (2H, m), 5.18 (1H, d, J = 15.0 Hz), 5.80 (1H, d, J = 15.0 Hz), 7.26 (1H, s), 7.72 (1H, s), 9.43 (1H, s); FABMS m/z 392 [(M + H)$^+$]; FABHRMS calcd for $C_{18}H_{22}N_3O_5S$ [(M + H)$^+$]: 392.1280, found: 392.1280.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(3-methoxymethylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1j). This was obtained in 10% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.11 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.3 Hz), 3.06 (1H, m), 3.45 (3H, s), 3.50 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz), 4.18–4.31 (2H, m), 4.80 (2H, s), 5.24 (1H, d, J = 15.0 Hz), 5.83 (1H, d, J = 15.0 Hz), 7.61 (1H, s), 7.79 (1H, s), 9.41 (1H, s); FABMS m/z 392 [(M + H)$^+$]; FABHRMS calcd for $C_{18}H_{22}N_3O_5S$ [(M + H)$^+$]: 392.1280, found: 392.1280.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(3-phenylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-carbapen-2-em-3-carboxylate (1k). This was obtained in 13% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.2 Hz), 1.25 (3H, d, J = 6.3 Hz), 3.02 (1H, m), 3.46 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz), 4.15–4.22 (2H, m), 5.15 (1H, d, J = 15.0 Hz), 5.81 (1H, d, J = 15.0 Hz), 7.54 (1H, s), 7.60 (3H, m), 7.70 (2H, m), 7.78 (1H, s), 9.52 (1H, s); FABMS m/z 424 [(M + H)$^+$]; FABHRMS calcd for $C_{22}H_{22}N_3O_4S$ [(M + H)$^+$]: 424.1331, found: 424.1324.

(1*S*,5*R*,6*S*)-2-(3-Formylimidazo[5,1-*b*]thiazolium-6-yl)-methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1l). This was obtained in 3.3% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.10 (3H, d, J = 7.2 Hz), 1.27 (3H, d, J = 6.3 Hz), 3.02 (1H, m), 3.48 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz), 4.17–4.28 (2H, m), 5.25 (1H, d, J = 15.0 Hz), 5.86 (1H, d, J = 15.0 Hz), 7.90 (1H, s), 8.88 (1H, s), 9.86 (1H, s), 9.95 (1H, s); FABMS m/z 376 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{18}N_3O_5S$ [(M + H)$^+$]: 376.0967, found: 376.0967.

(1*S*,5*R*,6*S*)-2-(3-Ethoxycarbonylimidazo[5,1-*b*]thiazolium-6-yl)methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1m). This was obtained in 3.1% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.13 (3H, d, J = 7.4 Hz), 1.29 (3H, d, J = 5.0 Hz), 1.45 (3H, t, J = 7.1 Hz), 3.08 (1H, m), 3.51 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.20–4.30 (2H, m), 4.53 (2H, q, J = 7.1 Hz), 5.29 (1H, d, J = 14.8 Hz), 5.84 (1H, d, J = 14.8 Hz), 7.89 (1H, s), 8.56 (1H, s), 9.74 (1H, s); FABMS m/z 420 [(M + H)$^+$]; FABHRMS calcd for $C_{19}H_{22}N_3O_6S$ [(M + H)$^+$]: 420.1229, found: 420.1229.

(1*S*,5*R*,6*S*)-2-(3-Carbamoylimidazo[5,1-*b*]thiazolium-6-yl)methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1n). This was obtained in 8.0% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.12 (3H, d, J = 7.4 Hz), 1.28 (3H, d, J = 5.0 Hz), 3.05 (1H, m), 3.50 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.15–4.30 (2H, m), 5.25 (1H, d, J = 14.8 Hz), 5.83 (1H, d, J = 14.8 Hz), 7.82 (1H, s), 8.40 (1H, s), 9.77 (1H, s); FABMS m/z 391 [(M + H)$^+$]; FABHRMS calcd for $C_{17}H_{19}N_4O_5S$ [(M + H)$^+$]: 391.1076, found: 391.1076.

(1*S*,5*R*,6*S*)-2-[3-(Formylamino)methylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1o). This was obtained in 1.2% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.12 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 3.07 (1H, m), 3.51 (1H, dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz), 4.20–4.30 (2H, m), 4.72 (2H, s), 5.23 (1H, d, J = 15.2 Hz), 5.81 (1H, d, J = 15.2 Hz), 7.48 (1H, s), 7.78 (1H, s), 8.25 (1H, s), 9.37 (1H, s); FABMS m/z 405 [(M + H)$^+$]; FABHRMS calcd for $C_{18}H_{21}N_4O_5S$ [(M + H)$^+$]: 405.1233, found: 405.1233.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(3-ureidomethylimidazo[5,1-*b*]thiazolium-6-yl)methyl-1-carbapen-2-em-3-carboxylate (1p). This was obtained in 3.9% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.0 Hz), 1.26 (3H, d, J = 6.4 Hz), 3.05 (1H, m), 3.47

(1H, m), 4.21 (2H, m), 4.80 (2H, s), 5.21 (1H, d, $J=15.1$ Hz), 5.75 (1H, d, $J=15.1$ Hz), 7.38 (1H, s), 7.75 (1H, s), 9.37 (1H, s); FABMS m/z 420 $[(M+H)^+]$; FABHRMS calcd for $C_{18}H_{22}N_5O_5S$ $[(M+H)^+]$: 420.1342, found: 420.1336.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-[3-(methanesulfonylamino)methylimidazo[5,1-*b*]thiazolium-6-yl]methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1q). This was obtained in 1.2% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.11 (3H, d, $J=7.4$ Hz), 1.29 (3H, d, $J=5.0$ Hz), 3.10 (1H, m), 3.20 (3H, s), 3.52 (1H, dd, $J_1=6.0$ Hz, $J_2=2.9$ Hz), 4.21–4.29 (2H, m), 4.66 (2H, s), 5.30 (1H, d, $J=14.9$ Hz), 5.76 (1H, d, $J=14.9$ Hz), 7.58 (1H, s), 7.82 (1H, s), 9.44 (1H, s); FABMS m/z 455 $[(M+H)^+]$; FABHRMS calcd for $C_{18}H_{23}N_4O_6S_2$ $[(M+H)^+]$: 455.1059, found: 455.1059.

(1*S*,5*R*,6*S*) - 2 - [3 - [2 - (Aminosulfonyl)aminoethyl]imidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1s). This was obtained in 11% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.11 (3H, d, $J=7.4$ Hz), 1.27 (3H, d, $J=6.4$ Hz), 2.99–3.10 (1H, m), 3.18 (2H, t, $J=6.3$ Hz), 3.47–3.52 (3H, m), 4.18–4.28 (2H, m), 4.66 (2H, s), 5.20 (1H, d, $J=15.1$ Hz), 5.80 (1H, d, $J=15.1$ Hz), 7.32 (1H, s), 7.74 (1H, s); FABMS m/z 470 $[(M+H)^+]$; FABHRMS calcd for $C_{18}H_{24}N_5O_6S_2$ $[(M+H)^+]$: 470.1168, found: 470.1174.

(1*S*,5*R*,6*S*)-2-[3-(*N*-Aminosulfonyl-*N*-methylamino)methylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1t). This was obtained in 6.5% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.08 (3H, d, $J=7.2$ Hz), 1.26 (3H, d, $J=6.3$ Hz), 2.78 (3H, s), 3.07 (1H, m), 3.49 (1H, dd, $J_1=5.4$ Hz, $J_2=2.5$ Hz), 4.19–4.29 (2H, m), 4.53 (1H, d, $J=15.8$ Hz), 4.59 (1H, d, $J=15.8$ Hz), 5.27 (1H, d, $J=15.0$ Hz), 5.70 (1H, d, $J=15.0$ Hz), 7.60 (1H, s), 7.77 (1H, s); FABMS m/z 470 $[(M+H)^+]$; FABHRMS calcd for $C_{18}H_{24}N_5O_6S_2$ $[(M+H)^+]$: 470.1168, found: 470.1168.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-[3-[(*N*-methylamino)sulfonylamino]methylimidazo[5,1-*b*]thiazolium-6-yl]-methyl-1-methyl-1-carbapen-2-em-3-carboxylate (1u). This was obtained in 19% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.08 (3H, d, $J=7.4$ Hz), 1.26 (3H, d, $J=6.4$ Hz), 2.61 (3H, s), 3.00–3.11 (1H, m), 3.48 (1H, q, $J=3.0$ Hz), 4.18–4.28 (2H, m), 4.50 (2H, s), 5.26 (1H, d, $J=14.8$ Hz), 5.75 (1H, d, $J=14.8$ Hz), 7.53 (1H, s), 7.79 (1H, s), 9.42 (0.5H, s, partially exchanged with D); FABMS m/z 470 $[(M+H)^+]$; FABHRMS calcd for $C_{18}H_{24}N_5O_6S_2$ $[(M+H)^+]$: 470.1168, found: 470.1164.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-[3-[*N*-methyl-*N*-(*N*-methylaminosulfonyl)amino]methylimidazo[5,1-*b*]thiazolium-6-yl]methyl-1-carbapen-2-em-3-carboxylate (1v). This was obtained in 10% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.08 (3H, d, $J=7.1$ Hz), 1.27 (3H, d, $J=6.3$ Hz), 2.70 (3H, s), 2.82 (3H, s), 3.04–3.07 (1H, m), 3.49 (1H, q, $J=3.0$ Hz), 3.52–3.68 (1H, m), 4.19–4.27 (2H, m), 4.66 (1H, d, $J=15.9$ Hz), 4.74 (1H, d, $J=15.9$ Hz), 5.28 (1H, d, $J=14.8$ Hz), 5.72 (1H, d, $J=14.8$ Hz), 7.62 (1H, s), 7.79 (1H, s), 9.28 (0.5H, s, partially exchanged with D); FABMS m/z 484 $[(M+H)^+]$; FABHRMS calcd for $C_{19}H_{26}N_5O_6S_2$ $[(M+H)^+]$: 484.1325, found: 484.1321.

(1*S*,5*R*,6*S*)-2-[3-(*N*,*N*-Dimethylaminosulfonyl)aminomethylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1w). This was obtained in 3.3% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.08 (3H, d, $J=7.1$ Hz), 1.25 (3H, d, $J=6.3$ Hz), 2.75 (6H, m), 3.06 (1H, m), 3.48 (1H, dd, $J_1=5.8$ Hz, $J_2=2.8$ Hz), 4.56 (2H, s), 5.27 (1H, d, $J=14.7$ Hz), 5.74 (1H, d, $J=14.7$ Hz), 7.54 (1H, s), 7.80 (1H, s), 9.41 (1H, s); FABMS m/z 484 $[(M+H)^+]$; FABHRMS calcd for $C_{19}H_{26}N_5O_6S_2$ $[(M+H)^+]$: 484.1325, found: 484.1325.

(1*S*,5*R*,6*S*) - 2 - [2 - (Aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1x). This was obtained in 6.8% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, $J=6.5$ Hz), 1.26 (3H, d, $J=5.8$ Hz), 3.00–3.06 (1H, m), 3.46–3.49 (1H, m), 4.16–4.25 (2H, m), 4.47 (2H, s), 5.17 (1H, d, $J=14.8$ Hz), 5.75 (1H, d, $J=14.8$ Hz), 7.68 (1H, s), 7.93 (1H, s); FABMS m/z 456 $[(M+H)^+]$; FABHRMS calcd for $C_{17}H_{22}N_5O_6S_2$ $[(M+H)^+]$: 456.1012, found: 456.1012.

(1*S*,5*R*,6*S*) - 2 - [5 - (Aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1y). This was obtained in 2.9% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.14 (3H, d, $J=7.4$ Hz), 1.25 (3H, d, $J=6.3$ Hz), 2.95 (1H, m), 3.47 (1H, dd, $J_1=6.0$ Hz, $J_2=3.1$ Hz), 4.10–4.27 (2H, m), 4.85 (2H, s), 5.16 (1H, d, $J=15.7$ Hz), 6.01 (1H, d, $J=15.7$ Hz), 7.60 (1H, d, $J=4.3$ Hz), 8.06 (1H, d, $J=4.3$ Hz); FABMS m/z 456 $[(M+H)^+]$; FABHRMS calcd for $C_{17}H_{22}N_5O_6S_2$ $[(M+H)^+]$: 456.1012, found: 456.1012.

(1*S*,5*R*,6*S*)-2-[7-(Aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1z). This was obtained in 1.3% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.13 (3H, d, $J=7.2$ Hz), 1.26 (3H, d, $J=6.5$ Hz), 2.93 (1H, m), 3.49 (1H, dd, $J_1=5.9$ Hz, $J_2=2.8$ Hz), 4.16–4.28 (2H, m), 4.51 (2H, s), 5.19 (1H, d, $J=15.6$ Hz), 5.91 (1H, d, $J=15.6$ Hz), 7.56 (1H, d, $J=4.2$ Hz), 7.92 (1H, d, $J=4.2$ Hz); FABMS m/z 456 $[(M+H)^+]$; FABHRMS calcd for $C_{17}H_{22}N_5O_6S_2$ $[(M+H)^+]$: 456.1012, found: 456.1012.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(pyridinium-1-yl)methyl-1-carbapen-2-em-3-carboxylate (2). This was obtained in 28% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, $J=7.4$ Hz), 1.26 (3H, d, $J=6.4$ Hz), 3.03 (1H, m), 3.49 (1H, dd, $J_1=5.9$ Hz, $J_2=3.1$ Hz), 4.17–4.25 (2H, m), 5.37 (1H, d, $J=14.6$ Hz), 6.08 (1H, d, $J=14.6$ Hz), 8.09 (2H, m), 8.58 (1H, m), 8.91 (2H, m); FABMS m/z 303 $[(M+H)^+]$; FABHRMS calcd for $C_{16}H_{19}N_2O_4$ $[(M+H)^+]$: 303.1345, found: 303.1345.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(3-methylimidazolium-1-yl)methyl-1-carbapen-2-em-3-carboxylate (3). This was obtained in 8.0% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 5.8 Hz), 2.97–3.10 (1H, m), 3.47 (1H, dd, J_1 = 4.9 Hz, J_2 = 1.9 Hz), 3.90 (3H, s), 4.15–4.28 (2H, m), 5.00 (1H, d, J = 15.1 Hz), 5.56 (1H, d, J = 15.1 Hz), 7.44 (1H, s), 7.50 (1H, s), 8.80 (1H, s); FABMS m/z 306 [$(M+H)^+$]; FABHRMS calcd for $C_{15}H_{20}N_3O_4$ [$(M+H)^+$]: 306.1454, found: 306.1454.

(1*S*,5*R*,6*S*)-2-(2,3-Dihydroimidazo[5,1-*b*]thiazolium-6-yl)-methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (4). This was obtained in 8.2% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.2 Hz), 1.26 (3H, d, J = 6.4 Hz), 3.05 (1H, m), 3.47 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 3.93 (2H, t, J = 7.2 Hz), 4.17–4.25 (2H, m), 4.54 (2H, t, J = 7.2 Hz), 4.96 (1H, d, J = 15.0 Hz), 5.53 (1H, d, J = 15.0 Hz), 7.18 (1H, s), 8.87 (1H, s); FABMS m/z 350 [$(M+H)^+$]; FABHRMS calcd for $C_{16}H_{20}N_3O_4S$ [$(M+H)^+$]: 350.1175, found: 350.1175.

(1*S*,5*R*,6*S*)-2-(Benzo[*d*]imidazo[5,1-*b*]thiazolium-2-yl)methyl-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (5). This was obtained in 2.0% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.13 (3H, d, J = 5.8 Hz), 1.36 (3H, d, J = 6.2 Hz), 3.05–3.15 (1H, m), 3.45–3.55 (1H, m), 4.20–4.30 (2H, m), 5.24 (1H, d, J = 15.4 Hz), 5.84 (1H, d, J = 15.4 Hz), 7.60–7.70 (2H, m), 7.77 (1H, s), 7.85–7.95 (1H, m), 8.05–8.15 (1H, m), 9.83 (1H, s); FABMS m/z 398 [$(M+H)^+$]; FABHRMS calcd for $C_{20}H_{20}N_3O_4S$ [$(M+H)^+$]: 398.1175, found: 398.1175.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(imidazo[1,5-*a*]-pyridinium-2-yl)methyl-1-methyl-1-carbapen-2-em-3-carboxylate (6). This was obtained in 18% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.09 (3H, d, J = 7.1 Hz), 1.25 (3H, d, J = 4.9 Hz), 3.02 (1H, m), 3.47 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.16–4.25 (2H, m), 5.29 (1H, d, J = 14.8 Hz), 5.88 (1H, d, J = 14.8 Hz), 7.13 (1H, m), 7.23 (1H, m), 7.72 (1H, d, J = 9.4 Hz), 7.97 (1H, s), 8.33 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.0 Hz), 9.43 (1H, s); FABMS m/z 342 [$(M+H)^+$]; FABHRMS calcd for $C_{18}H_{20}N_3O_4$ [$(M+H)^+$]: 342.1454, found: 342.1449.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(6-methylimidazo[1,5-*a*]pyradinium-2-yl)methyl-1-carbapen-2-em-3-carboxylate (7). To a solution of 2-aminomethyl-5-methylpyradine (4.579 g, 37 mmol) in dichloromethane (90 mL), a pre-mixed solution of formic acid (7.60 mL, 200 mmol) and acetic anhydride (3.8 mL, 40 mmol), which had been held at 50 °C for 10 min, was added. The reaction mixture was stirred at room temperature for 1 h, adjusted to pH 11.5 with K_2CO_3 aq, extracted with dichloromethane and dried over $MgSO_4$. Filtration and removal of the solvent afforded the a crude product that was purified by silica gel column chromatography to provide 2-formylaminomethyl-5-methylpyradine (3.85 g, yield 69%): ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s), 4.63 (2H, d, J = 7.5 Hz), 6.78 (1H, br s), 8.32 (1H, s), 8.40 (1H, s), 8.50 (1H, s).

2-Formylaminomethyl-5-methylpyradine (3.35 g, 22.2 mmol) was dissolved in phosphoryl chloride (50 mL) and the solution was stirred at 60 °C for 1 h. After evaporation, the residue was dissolved and adjusted to pH 10.5 with K_2CO_3 aq, and then extracted with dichloromethane. After removal of the solvent, the residual oil was purified by silica gel column chromatography to obtain 6-methylimidazo[1,5-*a*]pyradine (2.26 g, yield 67%): ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 7.65 (1H, s), 7.75 (1H, s), 8.11 (1H, s), 8.93 (1H, s).

Compound **7** was obtained in the same manner as **1r** by the use of 6-methylimidazo[1,5-*a*]pyradine instead of 3-(aminosulfonyl)aminomethylimidazo[5,1-*b*]thiazole in 1.6% yield from compound **18**: ^{1}H NMR (D_2O) δ 1.08 (3H, d, J = 7.4 Hz), 1.24 (3H, d, J = 6.3 Hz), 2.47 (3H, s), 3.04 (1H, m), 3.48 (1H, m), 4.17–4.24 (2H, m), 5.34 (1H, d, J = 14.9 Hz), 5.88 (1H, d, J = 14.9 Hz), 8.16 (1H, s), 8.46 (1H, s), 9.21 (1H, s); FABMS m/z 357 [$(M+H)^+$]; FABHRMS calcd for $C_{18}H_{21}N_4O_4$ [$(M+H)^+$]: 357.1563, found: 357.1563.

(5*R*,6*S*)-2-[3-(Aminosulfonyl)aminomethylimidazo[5,1-*b*]-thiazolium-6-yl]methyl-6-[(1*R*)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylate (8r). This was prepared by a similar procedure to that described for the preparation of **1r**, except that allyl (5*R*,6*S*)-6-[(1*R*)-1-allyloxycarbonyloxyethyl]-2-hydroxymethyl-1-carbapen-2-em-3-carboxylate[8,14] **19** was used instead of **18**, thereby affording **8r** in 13% yield: ^{1}H NMR (D_2O) δ 1.25 (3H, d, J = 6.3 Hz), 2.86 (2H, m), 3.41 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.15–4.30 (2H, m), 4.57 (2H, s), 5.43 (1H, d, J = 15.0 Hz), 5.64 (1H, d, J = 15.0 Hz), 7.54 (1H, s), 7.77 (1H, s), 9.40 (1H, s); FABMS m/z 442 [$(M+H)^+$]; FABHRMS calcd for $C_{16}H_{20}N_5O_6S_2$ [$(M+H)^+$]: 442.0855, found: 442.0855.

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