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A novel series of parenteral cephalosporins exhibiting potent activities against both *Pseudomonas aeruginosa* and other Gram-negative pathogens. Part 2: Synthesis and structure–activity relationships

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Abstract—A novel series of 7β-[2-(2-amino-5-chloro-thiazol-4-yl)-2(*Z*)-((*S*)-1-carboxyethoxyimino)acetamido]cephalosporins bearing various pyridinium groups at the C-3′ position were synthesized and their in vitro antibacterial activities against Gram-negative pathogens including *Pseudomonas aeruginosa* and several Gram-positive pathogens were evaluated. Among the cephalosporins prepared, we found that a cephalosporin bearing the 2-amino-1-(3-methylamino-propyl)-1*H*-imidazo[4,5-*b*]pyridinium group at the C-3′ position (**8a**) showed potent and well-balanced antibacterial activities against *P. aeruginosa* and other Gram-negative pathogens including the strains which produce class C β-lactamase and extended spectrum β-lactamase (ESBL). Compound **8a** also showed efficacious in vivo activity and high stability against AmpC β-lactamase. These findings indicate that 2-aminoimidazopyridinium having an aminoalkyl group at the 1-position as a C-3′ side chain is suitable for cephalosporins bearing an aminochlorothiazolyl moiety and a carboxyethoxyimino moiety on the C-7 side chain.

1. Introduction

Pseudomonas aeruginosa is one of the most important pathogens for nosocomial and opportunistic infections. The most widely used medicines to treat these infections are broad spectrum cephalosporins such as cefepime (CFPM),[1] cefozopran (CZOP),[2] and ceftazidime (CAZ)[3] (see Fig. 1) or quinolones such as ciprofloxacin.[4] Aminoglycosides[5] are also one of the important therapeutic agents in clinical practice, but in the case of refractory pathogens with those cephalosporins and quinolones, carbapenems[6] such as imipenem (IPM) and doripenem (DRPM) are used as last-resort agents.

In the field of treatment with cephalosporins, an increasing emergence of resistance caused by β-lactamase is becoming a serious matter.[7] Surveillance of resistant strains has shown a significant increase of CFPM-resistant, CAZ-resistant strains in recent years. Under these circumstances, we reported a novel cephalosporin **1** (Fig. 1),[8] which was derived from CAZ and S-3578[9] by chemical modification, that exhibits broad spectrum and potent antibacterial activities against both *P. aeruginosa* and other Gram-negative pathogens. The unique structural feature of **1** is the presence of 2-(2-amino-5-chloro-thiazol-4-yl)acetamide and (*S*)-1-carboxyethoxyimino moieties at the C-7 position, and a 1-(3-(methylamino)propyl)-1*H*-pyrrolo[3,2-*b*]pyridinium moiety at the C-3′ position. For further improvement of antibacterial activities against both Gram-negative pathogens including *P. aeruginosa* and Gram-positive pathogens, we synthesized a novel series of cephalosporins bearing various C-3′ pyridinium

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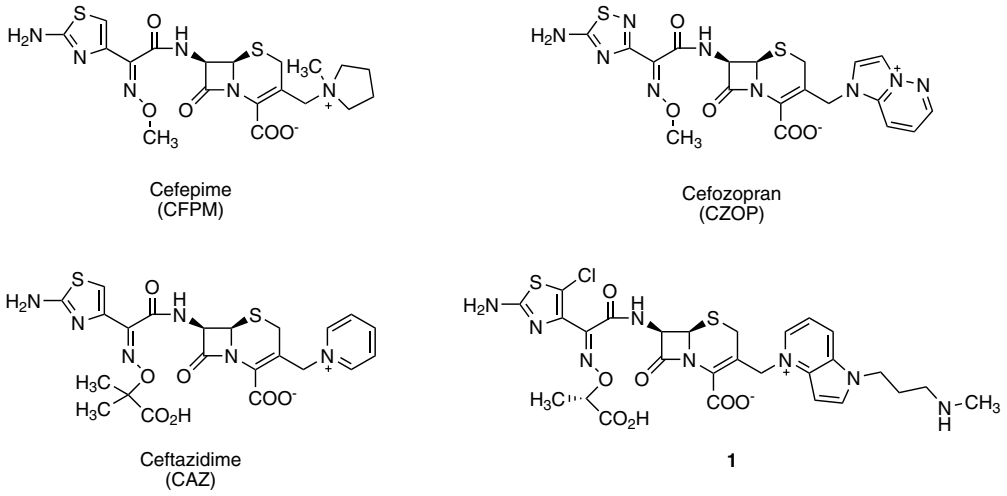


Figure 1. Structures of CFPM, CZOP, CAZ and **1**.

groups. Here we report the preparation of cephalosporins bearing various C-3′ pyridinium groups and their antibacterial activities, and the effect of various C-3′ pyridinium groups on the stability against β-lactamase.

2. Chemistry

Novel cephalosporins **3**–**10** having a chloroaminothiazolylacetamide and a carboxyethoxyimino moiety at C-7, and pyridinium derivatives at C-3′ were prepared by a method similar to one reported,[8] as shown in Scheme 1. The sulfoxide **2** bearing a chloromethyl group at C-3 was allowed to react with C-3′ side chains **3a**′–**k**′, **4**–**7**, **8a**′–**e**′, **9**′, and **10a**′–**c**′ (shown in Schemes 2–7 and Fig. 2), followed by reduction of sulfoxide using acetyl chloride and potassium iodide, which gave pyridinium salts. The salts were then treated with aluminum trichloride in the presence of anisole in dichloroethane/nitromethane to remove all protecting groups to afford **3**–**10**.

Pyrrolopyridine derivatives, which were used for the synthesis of **3a**–**k**, were derived from azaindole **11** as shown in Scheme 2. The protection of 1-N on **11** was easily achieved by treatment with di-*tert*-butyl dicarbonate (Boc_2O) to afford **3a**′. Alternatively, **11** was allowed to react with alkylating agents in the presence of sodium hydride to afford **3e**′ or **3d**′. The hydroxyl group of **3d**′ was deprotected to give **12**, which was an intermediate to prepare **3g**′–**k**′. Treatment of **12** with trichloroacetylisocyanate followed by deprotection gave **3g**′. **12** was subjected to the Mitsunobu reaction with *tert*-butyl sulfamoylcarbamate to afford **3k**′. Meanwhile, **12** was converted to amine derivatives **3h**–**3j** through phthalimide **13** by conventional methods.

2-Aminopyrrolopyridine derivative **7**′ was derived from pyridinylacetonitrile as shown in Scheme 3. **14**[10] was converted to **15** under the conditions of hydrogenation and the resultant amine **15** was subjected to reductive amination with aldehyde to give **16**. Cyclization of acetonitrile **16** was achieved under acidic conditions followed by protection of the amine on the azaindole by *tert*-butoxycarbonyl group, giving **7**′.

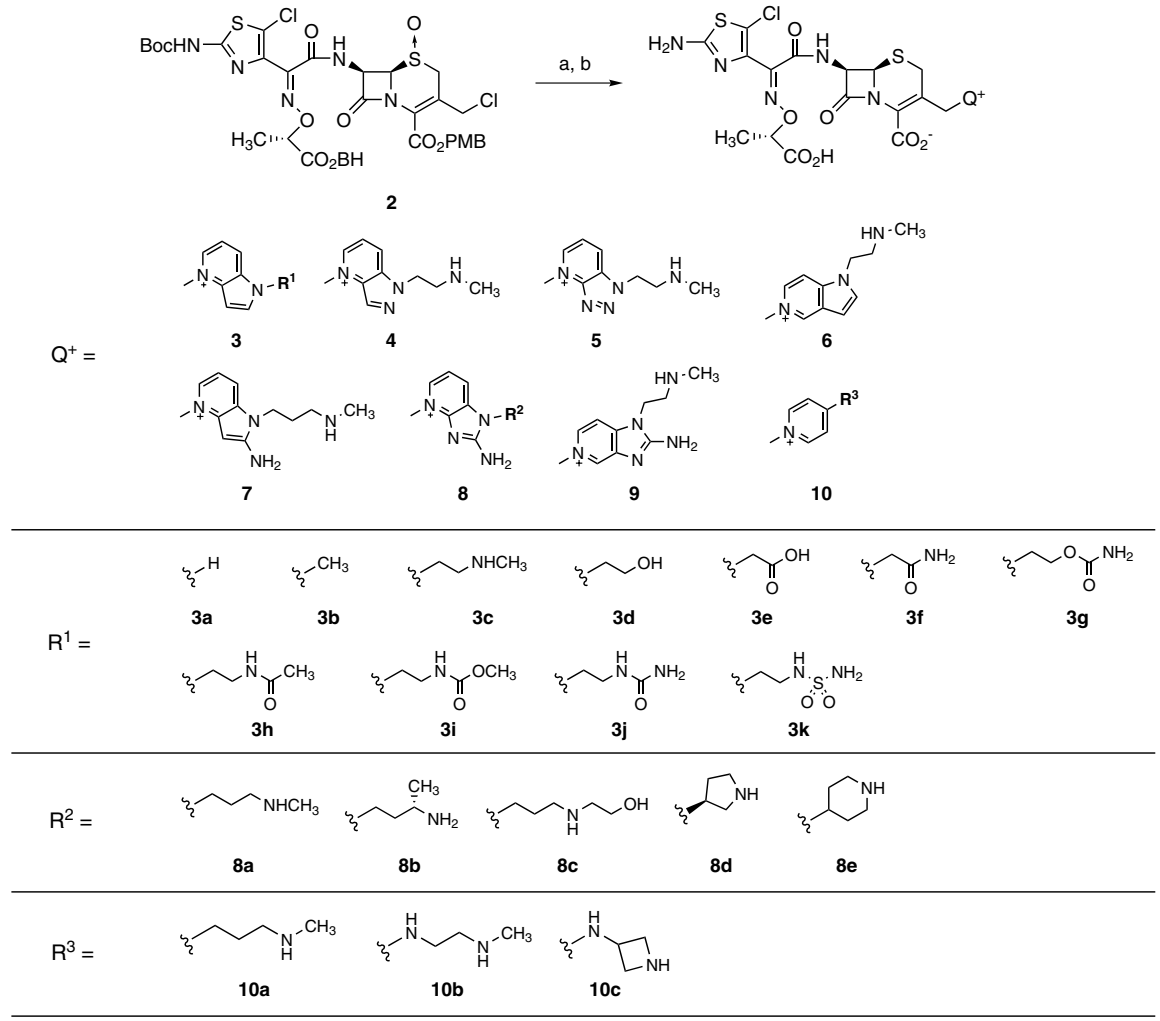
Scheme 4 outlines the synthesis of the aminoimidazopyridine derivatives **8**. Lithiation of known imidazopyridines **18**[9] using *sec*-buthyllithium followed by treatment with 4-dodecylbenzenesulfonyl azide gave **19**. Azides **19** were converted to aminoimidazopyridine derivatives **20** under the conditions of hydrogenation. The amino groups at C-2 position on the imidazopyridines were protected by the *tert*-butoxycarbonyl group to give **8** as a mixture of regioisomers of Boc group, which were used for the subsequent alkylation with **2** without purification.

Scheme 5 shows the synthesis of 2-aminoimidazo[4,5-*c*]pyridine derivative **9**′. Imidazopyridine **23** was prepared by a reported procedure with *N*-methylhydrazine.[11] **9**′ was synthesized from **23** by a procedure similar to that used for **8** in Scheme 4.

Scheme 6 shows the synthesis of **10a**′ having an aminoalkyl moiety at the C-4 position on the pyridine. Commercially available alcohol **25** was converted to mesylate followed by treatment with methylamine, and protection of the amino group gave **10a**′.

The synthesis of 4-aminopyridine derivatives **10b**′ and **c**′ is shown in Scheme 7. 4-Bromopyridine hydrochloride **26** was coupled with the corresponding amines under the conditions of Buchwald-Hartwig amination[12] to give **27b**′ or **10c**′. The amino group of **27b**′ was protected by the Boc group to give **10b**′, whereas it was found to be impossible to protect the amino group of **10c**′ due to its steric hindrance.

Other condensed-heterocyclic pyridines, which were known or easily prepared by the reported method, are shown in Figure 2.[13] Compounds **5**′ and **6**′ were prepared from 1*H*-[1,2,3]triazolo[4,5-*b*]pyridine or 1*H*-pyrrolo[3,2-*c*]pyridine, respectively, by a procedure involving alkylation similar to that used for **4**′.[11]

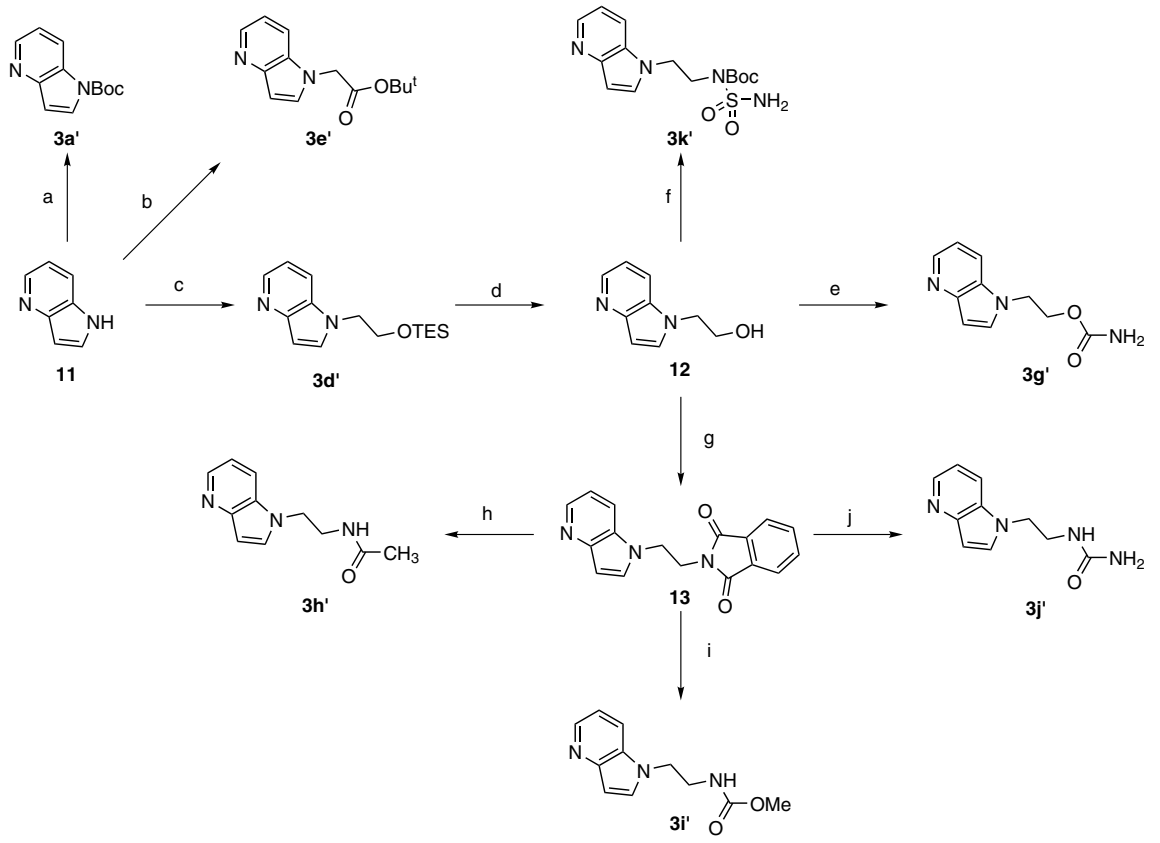


Scheme 1. Reagents and conditions: (a) (i) C-3′ side chains (see Schemes 2–7 and Fig. 2), NaBr, DMF, (ii) AcCl, KI, DMF; (b) $AlCl_3$, anisole, CH_2Cl_2, CH_3NO_2.

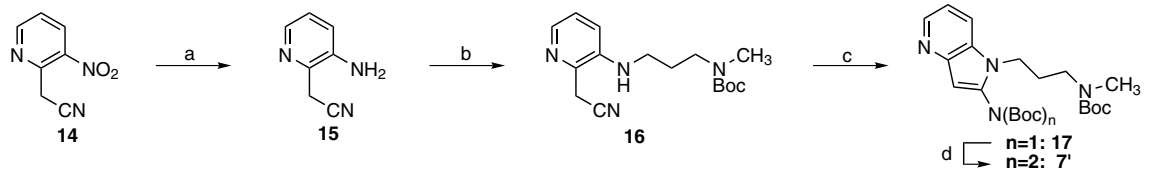
3. Results and discussion

The in vitro antibacterial activity (MICs) of the new cephalosporins, along with CAZ and CFPM as reference compounds, against various selected Gram-positive and Gram-negative bacteria are shown in Tables 1–3. MICs were determined by the standard serial agar dilution method using Mueller–Hilton agar. As can be deduced from the data, most of the compounds synthesized exhibited potent antibacterial activity against Gram-negative bacteria including *P. aeruginosa* and Gram-positive bacteria including penicillin-resistant *Streptococcus pneumoniae* (PRSP). In particular, the activities of several compounds against β-lactamase-producing or CAZ-resistant *P. aeruginosa* and *Enterobacter cloacae* were superior to the reference compounds and **1**.

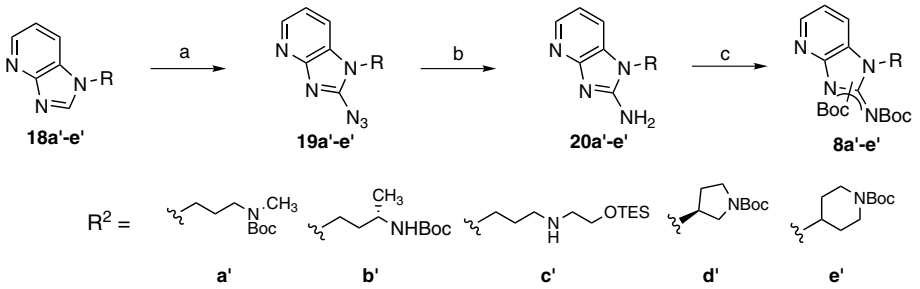
We first examined the effect of alkyl substituents on the 1-position of pyrrolopyridinium at C-3′. Table 1 shows the in vitro antibacterial activities (MICs) of several cephalosporins having pyrrolopyridinium derivatives as a C-3′ side chain. **3a** having no substituent at the 1-position on the pyrrolopyridinium moiety exhibited potent antibacterial activity which was slightly superior to **1** against several strains, but the antibacterial activity against *P. aeruginosa* was equal to that of **1**. The antibacterial activity against *P. aeruginosa* of **3b** bearing the methyl group was nearly equal to that of **3a**. The MICs of **3c** and **1** showed that the length of the carbon chain did not have a significant effect on the antibacterial activity. Replacement of the methylamino group at the end of carbon chain by hydroxyl (**3d**) resulted in a slight decrease of antibacterial activity against 3 strains of *P. aeruginosa*, while replacement by carboxyl (**3e**) led to even less activity against CAZ-resistant *P. aeruginosa* and *E. cloacae*. The antibacterial activity of amido derivative **3f** was somewhat inferior to **1**, but **3g** with carbamate moiety showed potent and well-balanced activity which was almost equal to **1**. **3h**–**3k** were prepared to examine the effect of a substituent on the amino group. **3h** with acetyl, **3i** with methoxycarbonyl, and urea derivative **3j** exhibited satisfactory antibacterial activity, but there still remained room for improvement. The sulfamoyl derivative **3k** showed potent antibacterial activity against the strains tested, whose activity was almost equal to that of **1**. In this examination we found many compounds (**3a**–**c**, **3g**, and **3k**) exhibiting comparable antibacterial activity to **1**. However, on closer



Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, THF; (b) *tert*-butyl bromoacetate, NaH, DMF; (c) (2-bromoethoxy)triethylsilane, NaH, DMF; (d) TBAF, THF; (e) (i) trichloroacetylisocyanate, THF, (ii) silica gel, MeOH; (f) *tert*-butyl sulfamoylcarbamate, DEAD, PPh_3, THF; (g) (i) MsCl, NEt_3, CH_2Cl_2, (ii) potassiumphthalimide, DMF; (h) (i) hydrazine hydrate, EtOH, (ii) acetylchloride, NEt_3, CH_2Cl_2; (i) (i) hydrazine hydrate, EtOH, (ii) methyl chloroformate, NEt_3, CH_2Cl_2; G) (i) hydrazine hydrate, EtOH, (ii) trichloroacetylisocyanate, THF, (iii) silica gel, MeOH.



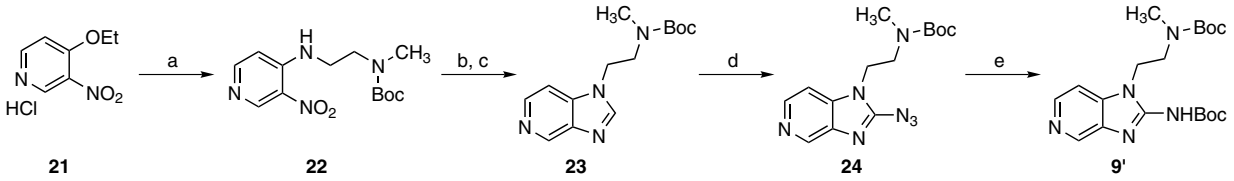
Scheme 3. Reagents and conditions: (a) H_2, Pd/C, EtOH, THF; (b) *tert*-butyl methyl(4-oxobutyl)carbamate, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (c) (i) HCl-1,4-dioxane, EtOH; (ii) $(Boc)_2O$, NEt_3, DMAP, CH_2Cl_2; (d) $(Boc)_2O$, DMAP, 1,4-dioxane.



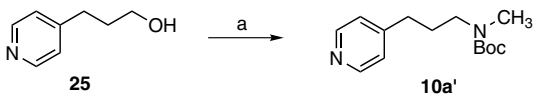
Scheme 4. Reagents and conditions: (a) (i) *sec*-BuLi, THF, (ii) 4-dodecylbenzenesulfonyl azide, THF; (b) H_2, Pd/C, EtOH; (c) $(Boc)_2O$, DMAP, CH_2Cl_2.

examination of the antibacterial activity against *P. aeruginosa*, it was unfortunately found that their activities against β-lactamase-producing or CAZ-resistant strains were inferior to that of **1**.

We next focused our attention on the scope and limitation of condensed-heterocyclic pyridinium as a C-3′ side chain. Table 2 presents the antibacterial activity of cephalosporins bearing condensed-heterocyclic pyridinium



Scheme 5. Reagents and conditions: (a) (i) *N*-methylhydrazine, EtOH, (ii) $(Boc)_2O$, THF, CH_3CN; (b) H_2, Pd/C, EtOH; (c) $(EtO)_2CHOAc$, EtOH; (d) (i) *sec*-BuLi, THF, (ii) 4-dodecylbenzenesulfonyl azide, THF; (e) (i) H_2, Pd/C, EtOH, (ii) $(Boc)_2O$, DMAP, CH_2C1_2.

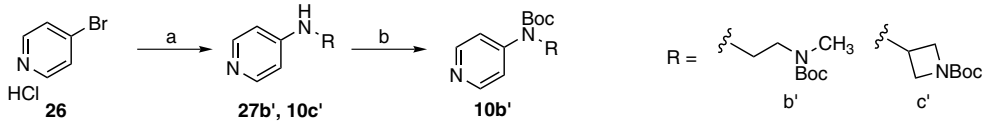


Scheme 6. Reagents and conditions: (a) (i) methanesulfonyl chloride, THF, (ii) methylamine, THF, (iii) $(Boc)_2O$, THF.

or monocyclic pyridinium substituted as a C-3′ side chain. The pyrazolo[4,3-*b*]pyridinium derivative **4** had somewhat lower antibacterial activity than **1** against most strains tested, whereas **5** having triazolo[4,5-*b*]pyridinium showed a considerable decrease of the activity against CAZ-resistant *P. aeruginosa*. The pyrrolo[3,2-*c*]pyridinium derivative **6** with a different type of condensed-heterocycle from **1** showed antibacterial activity against *P. aeruginosa* as potent as **1**, but the activity against AmpC producing *E. cloacae* decreased. Introduction of the amino group on the heterocycle had an effect on the MIC. The 2-aminopyrrolo[3,2-*b*]pyridinium derivative **7** exhibited more potent antibacterial activity against *P. aeruginosa* SR24 and SR24-12 than **1**. Unexpectedly, **8a** bearing 2-aminoimidazo[4,5-*b*]pyridinium as a C-3′ side chain showed the most potent and well-balanced antibacterial activity among the compounds prepared thus far, whereas the compound with imidazo[4,5-*b*]pyridinium at C-3′ was reported to be less active.[8] Although the imidazo[4,5-*c*]pyridinium derivative **9** maintained the antibacterial activity against Gram-negative strains, that against Gram-positive strains decreased. The antibacterial activity of the common pyridinium derivative **10a** having an aminoalkyl at C-4 on pyridine was somewhat lower than that of **1** or **8a**. However, the antibacterial activity of 4-aminopyridinium derivative **10b** was improved compared to that of **10a**, being comparable to that of **1**. **10c** bearing azetidine also showed potent and well-balanced antibacterial activity, which was superior to that of **10b** against several strains. These results imply that the amino group on the C-3′ pyridinium moiety is effective for improving activities against Gram-negative bacteria including *P. aeruginosa*, and suggest that a 2-aminoimidazo[4,5-*b*]pyridinium as a C-3′ side chain is suitable for our cephalosporins. Compound **8a** having this side chain had potent and well-balanced antibacterial activity against Gram-positive bacteria including penicillin-resistant *Streptococcus pneumoniae* (PRSP) and Gram-negative bacteria including AmpC or ESBL-producing strains. Additionally **8a** exhibited the high water solubility which is an important factor as a parenteral antibiotic.

The above results prompted us to prepare several cephalosporins having 2-aminoimidazopyridinum derivatives as a C-3′ side chain. Table 3 shows the antibacterial activities (MICs) of **8a** and its several analogues **8b–e**. The 2-aminoimidazo[4,5-*b*]pyridinium derivative bearing a primary amine on the alkyl chain such as **8b** exhibited antibacterial activity as potent as **8a** and well-balanced antibacterial activity. Introducing a hydroxyethyl group (**8c**) on the nitrogen atom at the end of the alkyl chain resulted in a slightly decreased activity. Replacement of alkylamine by cyclic amine (**8d–e**) on the aminoimidazopyridinium had some effect on the MIC. The antibacterial activity against AmpC producing *P. aeruginosa* SR24-12 and imipenem-resistant *P. aeruginosa* SR6554 was slightly superior to that of **8a**. However, subsequent evaluation of **8d** and **8e** revealed that their water solubility and acute toxicity were inferior to those of **8a**.

To evaluate the clinical efficacy of **8a** more precisely, we next examined the sensitivities of CAZ-resistant clinical isolates (6 strains) of *P. aeruginosa* to **1** and **8a**, as shown



Scheme 7. Reagents and conditions: (a) amine, $Pd_2(dba)_3$, $NaOBu^t$, BINAP, toluene; (b) $(Boc)_2O$, THF.

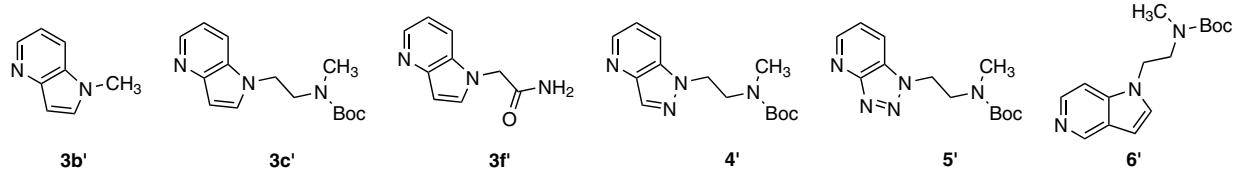
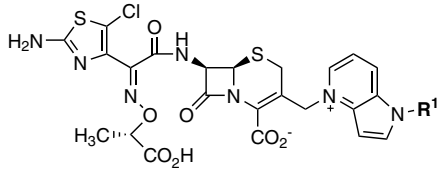
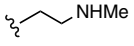
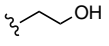
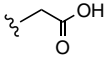
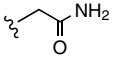
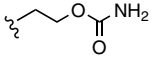
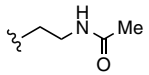
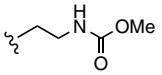
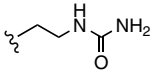
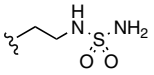
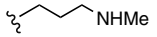


Figure 2. Structures of known or easily synthesized condensed-heterocyclic pyridines for C-3′ side chains.

Table 1. In vitro antibacterial activities (MIC, μg/mL) of compounds **3a–k**

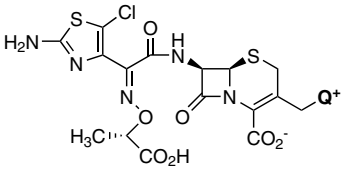


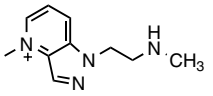
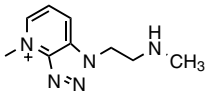
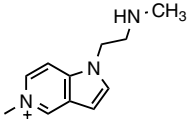
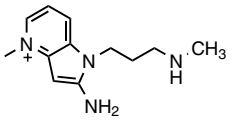
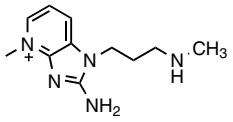
R^1	 **3a**	 **3b**	 **3c**	 **3d**	 **3e**	 **3f**	 **3g**
S. aureus Smith[a]	1	1	2	2	8	2	2
S. pneumoniae SR16675[b]	2	2	4	4	4	2	2
E. coli NIHJ JC-2	0.25	0.125	0.5	0.25	0.5	0.25	0.25
E. coli SR21003[c]	1	1	2	2	4	2	2
E. cloacae ATCC 13047	0.25	0.25	0.5	0.5	1	0.5	0.25
E. cloacae SR4321[d]	2	1	2	4	16	4	2
P. aeruginosa SR24	1	0.5	**1**	1	2	1	0.5
P. aeruginosa SR24-12[e]	4	4	4	8	32	4	4
P. aeruginosa SR5393	2	2	2	4	4	4	2
P. aeruginosa SR6554[f]	8	16	8	16	32	16	8
H. influenzae ATCC49766	0.016	0.016	0.032	0.032	0.016	0.032	0.032
H. influenzae SR11435[g]	0.032	0.032	0.125	0.063	0.063	0.063	0.063
M. catarrhalis ATCC43617[h]	0.016	0.016	0.032	0.016	0.032	0.016	0.032

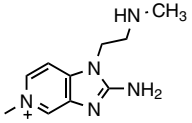
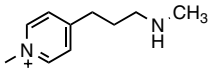
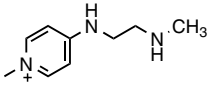
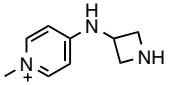
R^1	 **3h**	 **3i**	 **3j**	 **3k**	 **1**	CAZ	CFPM
S. aureus Smith[a]	4	4	4	2	2	8	2
S. pneumoniae SR1 6675[b]	4	4	4	2	4	8	2
E. coli NIHJ JC-2	0.25	0.5	0.25	0.25	0.5	0.25	0.063
E. coli SR21003[c]	2	4	2	2	2	1	4
E. cloacae ATCC 13047	0.5	1	0.5	0.5	0.5	8	0.125
E. cloacae SR4321[d]	4	4	4	4	2	64	4
P. aeruginosa SR24	2	2	1	1	1	0.5	0.5
P. aeruginosa SR24-12[e]	8	8	8	4	4	64	32
P. aeruginosa SR5393	4	8	4	4	2	2	4
P. aeruginosa SR6554[f]	16	16	16	8	8	32	64
H. influenzae ATCC49766	0.032	0.032	0.032	0.032	0.032	0.063	0.032
H. influenzae SR11435[g]	0.125	0.063	0.063	0.063	0.063	0.125	0.5
M. catarrhalis ATCC43617[h]	0.032	0.032	0.032	0.016	0.016	0.063	0.5

[a] *Staphylococcus aureus Smith*.
[b] Penicillin resistant *S. pneumoniae*.
[c] Toho 2 (ESBL) producing *Escherichia coli*.
[d] AmpC producing *E. cloacae*.
[e] AmpC hyperproducing *P. aeruginosa*.
[f] imipenem resistant *P. aeruginosa*.
[g] β-lactamase negative ampicillin resistant *Haemophilus influenzae* (BLNAR).
[h] *M. catarrhalis*, Moraxella subgenus *Branhamella catarrhalis*.

Table 2. In vitro antibacterial activities (MIC, μg/mL) of compounds **4**–**7**, **8a**, **9**, and **10a**–**c**

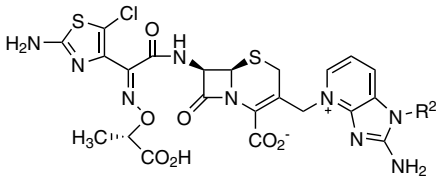


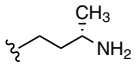
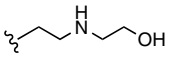
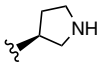
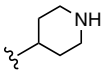
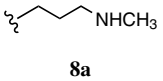
Q^+	 **4**	 **5**	 **6**	 **7**	 **8a**
S. aureus Smith	4	4	4	1	2
S. pneumoniae SR16675	4	2	4	4	2
E. coli NIHJ JC-2	1	0.25	0.25	0.25	0.25
E. coli SR21003	4	2	2	2	2
E. cloacae ATCC 13047	1	0.5	0.5	0.5	0.5
E. cloacae SR4321	4	8	8	2	2
P. aeruginosa SR24	1	2	1	0.5	0.5
P. aeruginosa SR24-12	8	64	4	2	4
P. aeruginosa SR5393	4	8	2	2	2
P. aeruginosa SR6554	16	64	8	16	8
H. influenzae ATCC49766	0.125	0.125	0.032	0.016	0.032
H. influenzae SR11435	0.125	0.5	0.125	0.063	0.063
M. catarrhalis ATCC43617	0.032	0.032	0.032	0.016	0.016

Q^+	 **9**	 **10a**	 **10b**	 **10c**	**1**
S. aureus Smith	16	8	4	2	2
S. pneumoniae SR16675	4	4	4	4	4
E. coli NIHJ JC-2	0.25	1	0.5	0.5	0.5
E. coli SR21003	1	4	4	4	2
E. cloacae ATCC 13047	0.5	1	0.5	0.5	0.5
E. cloacae SR4321	4	8	4	4	2
P. aeruginosa SR24	1	1	0.5	0.5	1
P. aeruginosa SR24-12	4	8	4	4	4
P. aeruginosa SR5393	2	4	2	2	2
P. aeruginosa SR6554	8	16	16	8	8
H. influenzae ATCC49766	0.032	0.125	0.125	0.063	0.032
H. influenzae SR11435	0.125	0.25	0.25	0.25	0.063
M. catarrhalis ATCC43617	0.032	0.032	0.032	0.016	0.016

Abbreviations: see footnote in Table 1.

Table 3. In vitro antibacterial activities (MIC, μg/mL) of compounds **8a–e**



R^2	 **8b**	 **8c**	 **8d**	 **8e**	 **8a**
S. aureus Smith	2	4	4	2	2
S. pneumoniae SR1 6675	2	2	2	2	2
E. coli NIHJJC-2	0.25	0.5	0.25	0.25	0.25
E. coli SR21003	2	4	2	2	2
E. cloacae ATCC 13047	0.5	0.5	0.5	0.25	0.5
E. cloacae SR4321	2	2	2	2	2
P. aeruginosa SR24	0.5	1	0.5	0.5	0.5
P. aeruginosa SR24-12	4	4	2	2	4
P. aeruginosa SR5393	2	4	2	2	2
P. aeruginosa SR6554	8	16	8	4	8
H. influenzae ATCC49766	0.016	0.032	0.032	0.016	0.032
H. influenzae SR1 1435	0.063	0.063	0.125	0.063	0.063
M. catarrhalis ATCC43617	0.008	0.016	0.016	0.016	0.016

Abbreviations: see footnote in Table 1.

Table 4. Antibacterial activity (MIC, μg/mL) of **1, 8a** against CAZ-resistant clinical isolates of *P. aeruginosa* (6 strains)

P. aeruginosa	MIC (μg/ml)		
	8a	**1**	CAZ
SR24722	4	8	64
SR24736	2	8	128
SR24765	4	8	128
SR24770	4	8	64
SR24797	4	8	64
SR24816	2	4	64

in Table 4. The MIC values of the two compounds against their strains were significantly lower than those of CAZ. Furthermore, it was clearly found that **8a** was superior to **1**. **8a** is expected to produce more efficacious treatment in clinical practice than CAZ.

The in vivo efficacy of **8a**, as well as that of CAZ, was evaluated and the results are shown in Table 5. The therapeutic effect was evaluated with the mouse systemic infection model using two strains, CAZ-susceptible *P. aeruginosa* SR24 and CAZ-resistant *P. aeruginosa* SR24-12. The efficacy of each compound was expressed as 50% effective dose values (ED_{50}) which were calculated by the prohibit method from the number of mice surviving seven days after infection. The in vivo antibacterial activity of **8a** against SR24 was twice that of CAZ in spite of the same MIC value. Furthermore, **8a** had activity twenty-five times more efficacious than CAZ against SR24-12 as predicted from its MIC value.

Some compounds with potent in vitro antibacterial activity were selected and characterized by studying their stability under hydrolysis by AmpC β-lactamase, as shown in Table 6. The relative rate of remaining compounds after reaction with AmpC for 30 min was evaluated. **1**, **8a**, and **10b** were highly stable against AmpC, whereas the amount of CAZ and CFPM markedly decreased under the same conditions. Among the compounds tested, **8a**, in particular, was found to be the most stable against AmpC. This result implies that the combination of C-7 moiety (2-amino-5-chloroaminothiazole moiety and carboxyethyloxyimino moiety) and C-3′ side chain (2-aminoimidazo[4,5-*b*]pyridinium-bearing aminoalkyl chain) plays an important part in the stability against AmpC. The potent activity of **8a** may be attributable to its stability.

Table 5. In vivo efficacy of **8a** in the mouse systemic infection model

Compound	*P. aeruginosa* SR24		*P. aeruginosa* SR24-12	
	MIC (μg/mL)	ED_{50} (mg/kg)	MIC (μg/mL)	ED_{50} (mg/kg)
8a	0.5	1.33	4	4.69
CAZ	1	2.83	64	>128

Table 6. Stability of **8a** under hydrolysis by AmpC

Compound	**8a**	**10b**	**1**	CAZ	CFPM
Relative %[a]	90.2	80.3	78.4	18.0	12.9

[a] Taking the resisted rate of the compounds as 100% against hydrolysis by AmpC.

4. Conclusion

Based on the parent 7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-((*S*)-1-carboxyethoxyimino)acetamido]cephalosporin **1**, novel analogues with modified and optimized aminoalkyl chains on the pyrropyridinium and condensed-heterocyclic pyridinium at the C-3′ side chain were synthesized. Among the prepared cephalosporins, we found **8a** bearing 1*H*-2-aminoimidazo[4,5-*b*]pyridinium to exhibit the most potent antibacterial and well-balanced activity against Gram-negative bacteria including β-lactamase producing or CAZ-resistant *P. aeruginosa* and *E. cloacae* and Gram-positive bacteria including *S. aureus* and penicillin-resistant *S. pneumoniae*. The activity of **8a** was superior to that of **1** previously reported. As reflected by this potent in vitro antibacterial activity, **8a** was found to show a strong in vivo efficacy. The attractive activities of **8a** were considered to be attributable to its high stability against AmpC.

5. Experimental

Infrared (IR) spectra were recorded on a JASCO FT/IR-700 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard. HR-FAB/MS were recorded on a JEOL LMS-SX/SX 102A. Analytical thin layer chromatography (TLC) was carried out on Merck precoated TLC plates silica gel 60 F_{254} and visualized with UV light or 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. Column chromatography was performed with Merck silica gel 60 (230–400 mesh).

5.1. Synthesis of 7β-[2-(2-aminothiazol-4-yl) -2(*Z*)-(1-carboxyethoxyimino)acetamide]-3-pyridiniummethyl-3-cephem-4-carboxylate

5.1.1. Compound 8a. To a solution of **2** (556 mg, 0.60 mmol) in DMF (1.7 mL) was added **8a′** (410 mg, <0.70 mmol), which was prepared as described in the following section, and NaBr (123 mg, 1.20 mmol). The reaction mixture was stirred at room temperature for 12 h, and then KI (697 mg, 4.20 mmol) and DMF (6 mL) were added. The mixture was cooled to −40 °C and acetylchloride (0.21 mL, 3.00 mmol) was added. The mixture was allowed to warm to 0 °C and stirred for a further 1 h. The resulting mixture was poured into a cooled aqueous solution of NaCl (100 mL) containing $Na_2S_2O_5{\cdot}5H_2O$ (1.0 g). The mixture was stirred at 0 °C for 20 min and the insoluble material was collected by filtration and dried in vacuo to give an aminoimidazopyridinium salt (905 mg) which was used for the next step without further purification.

To a solution of the above aminoimidazopyridinium salt (905 mg), which was prepared in the previous step, in CH_2Cl_2 (9 mL) and CH_3NO_2 (9 mL) at −40 °C was added anisole (0.78 mL) and $AlCl_3$ (3.6 mL, 2.0 M in CH_3NO_2, 7.2 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 1 h before being poured into an ice-cooled mixture of 1 N HCl (20 mL), CH_3CN (20 mL), and Et_2O (50 mL) with stirring. The aqueous layer was concentrated by evaporation, chromatographed on HP-20ss column with aqueous CH_3CN. The fractions containing the desired compounds were collected and lyophilized to give **8a** (330 mg, 74%) as an amorphous powder: ^{1}H NMR (D_2O) δ: 1.44 (3H, d, J = 7.0 Hz), 2.20 (2H, m), 2.70 (3H, s), 3.12 (2H, m), 3.24 and 3.50 (2H, ABq, J = 17.9 Hz), 4.22 (2H, t, J = 7.1 Hz), 4.55 (1H, q, J = 7.0 Hz), 5.18 (1H, d, J = 4.8 Hz), 5.25 and 5.56 (2H, ABq, J = 14.7 Hz), 5.84 (1H, d, J = 4.8 Hz), 7.30 (1H, t-like), 7.89 (1H, d, J = 7.8 Hz), 8.12 (1H, d, J = 6.6 Hz). IR (KBr) cm^{-1}: 3363, 3181, 1772, 1651, 1600, 1565, 1494, 1394, 1364, 1315, 1288, 1223, 1163, 1091, 1034. MS (ESI): 693$^+$ $(M+H)^+$. Anal. Calcd for $C_{26}H_{29}ClN_{10}O_7S_2{\cdot}2.9H_2O$: C, 41.89; H, 4.71; N, 18.79; Cl, 4.76; S, 8.60. Found: C, 41.93; H, 4.73; N, 18.81; Cl, 4.51; S, 8.51.

The following compounds were prepared by a procedure similar to that used for **8a** with **3a′**–**k′**, **4**–**7**, **8a′**–**e′**, **9′**, and **10a′**–**c′**, respectively.

5.1.2. Compound 3a. Amorphous powder. 61% yield. ^{1}H NMR (DMSO-d_6) δ : 1.37 (3H, d, J = 7.1 Hz), 3.03 and 3.28 (2H, ABq, J = 17.4 Hz), 4.56 (1H, q, J = 7.1 Hz), 5.01 (1H, d, J = 4.8 Hz), 5.69 (3H, m), 7.32 (1H, d, J = 2.9 Hz), 7.41 (2H, s), 7.67 (1H, t-like), 8.27 (1H, d, J = 2.9 Hz), 8.60 (1H, d, J = 8.4 Hz), 9.06 (1H, d, J = 5.7 Hz), 9.68 (1H, brs), 13.45 (1H, brs). IR (KBr) cm^{-1}: 3410, 2938, 1777, 1673, 1613, 1537, 1457, 1385, 1361, 1225, 1185, 1156, 1114, 1033. MS (ESI): 606$^+$$(M+H)^+$. Anal. Calcd for $C_{23}H_{20}ClN_7O_7S_2{\cdot}2.5H_2O$: C, 42.43; H, 3.87; N, 15.06; Cl, 5.45; S, 9.85. Found: C, 42.44; H, 3.69; N, 14.90; Cl, 5.24; S, 9.94.

5.1.3. Compound 3b. Amorphous powder. 69% yield. ^{1}H NMR (DMSO-d_6) δ: 1.36 (3H, d, J = 7.1 Hz), 2.97 and 3.25 (2H, ABq, J = 17.3 Hz), 4.03 (3H, s), 4.55 (1H, q, J = 7.1 Hz), 4.97 (1H, d, J = 5.1 Hz), 5.61–5.72 (3H, m), 5.60 and 5.73 (2H, ABq, J = 15.2 Hz), 7.37 (1H, d, J = 3.3 Hz), 7.41 (1H, s), 7.78 (1H, dd, J = 6.3, 8.2 Hz), 8.28 (1H, d, J = 3.3 Hz), 8.74 (1H, d, J = 8.2), 9.16 (1H, d, J = 6.3 Hz), 9.61 (1H, brs). IR (KBr) cm^{-1}: 3423, 2986, 1778, 1674, 1618, 1538, 1500, 1469, 1416, 1368, 1324, 1281, 1222, 1187, 1154, 1094, 1062, 1032. MS (ESI): 620$^+$$(M+H)^+$. Anal. Calcd for $C_{24}H_{22}ClN_7O_7S_2{\cdot}2.6H_2O$: C, 43.22; H, 4.11; N, 14.70; Cl, 5.32; S, 9.62. Found: C, 43.16; H, 3.99; N, 14.88; Cl, 5.12; S, 9.61.

5.1.4. Compound 3c. Amorphous powder. 69% yield. ^{1}H NMR (D_2O) δ: 1.44 (3H, d, J = 7.2 Hz), 2.73 (3H, s), 3.17 and 3.38 (2H, ABq, J = 18.0 Hz), 3.63 (2H, t, J = 6.0 Hz), 4.65 (1H, q, J = 7.2 Hz), 4.80 (2H, t, J = 6.0 Hz), 5.17 (1H, d, J = 4.8 Hz), 5.56 and 5.69 (2H, ABq, J = 15.0 Hz), 5.85 (1H, d, J = 4.8 Hz), 7.09 (1H, d, J = 3.3 Hz), 7.73 (1H, dd, J = 6.3, 8.4 Hz), 8.15 (1H, d, J = 3.3 Hz), 8.62 (1H, d, J = 8.4 Hz), 8.68 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3407, 2452, 1773, 1603, 1539, 1500, 1467, 1392, 1364, 1287, 1184, 1120, 1089, 1063, 1032. MS (FAB): 663$^+$$(M+H)^+$. Anal. Calcd for $C_{26}H_{27}ClN_8O_7S_2{\cdot}5.2H_2O$: C, 41.26; H, 4.98; N, 14.81;

Cl, 4.68; S, 8.47. Found: C, 41.41; H, 4.90; N, 14.55; Cl, 4.54; S, 8.46.

5.1.5. Compound 3d. Amorphous powder. 18% yield. ^{1}H NMR (D_2O) δ: 1.43 (3H, d, J = 7.2 Hz), 3.18 and 3.34 (2H, ABq, J = 18.0 Hz), 3.97 (2H, t, J = 4.8 Hz), 4.54 (2H, t, J = 4.8 Hz), 4.64 (1H, q, J = 7.2 Hz), 5.16 (1H, d, J = 4.8 Hz), 5.53 and 5.71 (2H, ABq, J = 15.0 Hz), 5.87 (1H, d, J = 4.8 Hz), 7.00 (1H, d, J = 3.0 Hz), 7.67 (1H, dd, J = 6.3, 8.1 Hz), 8.12 (1H, d, J = 3.0 Hz), 8.59 (1H, d, J = 8.1 Hz), 8.62 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3408, 2938, 1776, 1670, 1615, 1539, 1496, 1466, 1447, 1362, 1322, 1240, 1187, 1159, 1130, 1072, 1034. MS (FAB): 650$^+$(M+H)$^+$. Anal. Calcd for $C_{25}H_{24}ClN_7O_8S_2{\cdot}4.1H_2O$: C, 41.48; H, 4.48; N, 13.54; Cl, 4.90; S, 8.86. Found: C, 41.48; H, 4.40; N, 13.59; Cl, 5.07; S, 8.88.

5.1.6. Compound 3e. Amorphous powder. 66% yield. ^{1}H NMR (D_2O) δ: 1.43 (3H, d, J = 7.2 Hz), 3.21 and 3.35 (2H, ABq, J = 18.0 Hz), 4.64 (1H, q, J = 7.2 Hz), 5.01 (2H, s), 5.17 (1H, d, J = 4.8 Hz), 5.53 and 5.74 (2H, ABq, J = 15.0 Hz), 5.89 (1H, d, J = 4.8 Hz), 6.98(1H, d, J = 3.3 Hz), 7.67 (1H, dd, J = 6.3, 8.1 Hz), 8.04 (1H, d, J = 3.3 Hz), 8.44 (1H, d, J = 8.1 Hz), 8.62 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3415, 2989, 2527, 1778, 1725, 1672, 1630, 1537, 1500, 1467, 1373, 1328, 1229, 1162, 1129, 1063, 1035. MS (ESI): 664$^+$(M+H)$^+$. Anal. Calcd for $C_{25}H_{22}ClN_7O_9S_2{\cdot}3.0H_2O$: C, 41.81; H, 3.93; N, 13.65; Cl, 4.94; S, 8.93. Found: C, 41.75; H, 3.89; N, 13.71; Cl, 5.08; S, 8.84.

5.1.7. Compound 3f. Amorphous powder. 69% yield. ^{1}H NMR (D_2O) δ: 1.43 (3H, d, J = 6.9 Hz), 3.20 and 3.37 (2H, ABq, J = 17.7 Hz), 4.64 (1H, q, J = 6.9 Hz), 5.17 (1H, d, J = 4.8 Hz), 5.27 (2H, s), 5.56 and 5.73 (2H, ABq, J = 15.0 Hz), 5.88 (1H, d, J = 4.8 Hz), 7.06 (1H, d, J = 3.3 Hz), 7.70 (1H, dd, J = 6.3, 8.1 Hz), 8.07 (1H, d, J = 3.3 Hz), 8.51 (1H, d, J = 8.1 Hz), 8.67 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3407, 3191, 2988, 1776, 1684, 1615, 1537, 1500, 1467, 1364, 1331, 1225, 1189, 1160, 1131, 1063, 1034. MS (ESI): 663$^+$(M+H)$^+$. Anal. Calcd for $C_{25}H_{23}ClN_8O_8S_2{\cdot}3.9H_2O$: C, 40.95; H, 4.23; N, 15.28; Cl, 4.83; S, 8.74. Found: C, 40.93; H, 4.06; N, 15.26; Cl, 4.82; S, 8.64.

5.1.8. Compound 3g. Amorphous powder. 24% yield. ^{1}H NMR (D_2O) δ: 1.44 (3H, d, J = 6.9 Hz), 3.16 and 3.31 (2H, ABq, J = 18.0 Hz), 4.43 (2H, t, J = 4.5 Hz), 4.65 (1H, q, J = 6.9 Hz), 4.68 (2H, t, J = 4.5 Hz), 5.17 (1H, d, J = 5.1 Hz), 5.54 and 5.71 (2H, ABq, J = 15.0 Hz), 5.87 (1H, d, J = 5.1 Hz), 7.01 (1H, d, J = 3.0 Hz), 7.69 (1H, dd, J = 6.3, 8.1 Hz), 8.12 (1H, d, J = 3.0 Hz), 8.61 (1H, d, J = 8.1 Hz), 8.63 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3415, 3193, 2987, 1777, 1718, 1673, 1614, 1537, 1497, 1466, 1447, 1364, 1328, 1225, 1188, 1135, 1080, 1034. MS (FAB): 693$^+$(M+H)$^+$. Anal. Calcd for $C_{26}H_{25}ClN_8O_9S_2{\cdot}3.0H_2O$: C, 41.80; H, 4.18; N, 15.00; Cl, 4.75; S, 8.58. Found: C, 41.68; H, 4.19; N, 14.79; Cl, 4.78; S, 8.91.

5.1.9. Compound 3h. Amorphous powder. 18% yield. ^{1}H NMR (D_2O) δ: 1.43 (3H, d, J = 6.9 Hz), 1.74 (3H, s), 3.18 and 3.33 (2H, ABq, J = 17.7 Hz), 3.62 (2H, t, J = 5.4 Hz), 4.53 (2H, t, J = 5.4 Hz), 4.65 (1H, q, J = 6.9 Hz), 5.18 (1H, d, J = 4.8 Hz), 5.53 and 5.71 (2H, ABq, J = 14.7 Hz), 5.87 (1H, d, J = 4.8 Hz), 6.99 (1H, d, J = 3.0 Hz), 7.69 (1H, dd, J = 6.3, 8.4 Hz), 8.07 (1H, d, J = 3.0 Hz), 8.57 (1H, d, J = 8.4 Hz), 8.62 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3400, 2938, 1777, 1629, 1540, 1497, 1467, 1450, 1368, 1323, 1288, 1240, 1189, 1159, 1134, 1095, 1035. MS (FAB): 691$^+$(M+H)$^+$. Anal. Calcd for $C_{27}H_{27}ClN_8O_8S_2{\cdot}4.1H_2O$: C, 41.51; H, 4.77; N, 14.34; Cl, 4.54; S, 8.21. Found: C, 41.33; H, 4.56; N, 14.36; Cl, 4.88; S, 8.39.

5.1.10. Compound 3i. Amorphous powder. 21% yield. ^{1}H NMR (D_2O) δ: 1.43 (3H, d, J = 7.5 Hz), 3.15 and 3.32 (2H, ABq, J = 17.7 Hz), 3.91(3H, s), 3.57 (2H, brs), 4.51(2H, m), 4.65 (1H, q, J = 7.5 Hz), 5.17 (1H, d, J = 4.8 Hz), 5.55 and 5.70 (2H, ABq, J = 14.7 Hz), 5.87 (1H, d, J = 4.8 Hz), 7.00 (1H, d, J = 3.3 Hz), 7.69 (1H, dd, J = 6.0, 8.1 Hz), 8.09 (1H, d, J = 3.3 Hz), 8.59 (1H, d, J = 8.1 Hz), 8.64 (1H, d, J = 6.0 Hz). IR (KBr) cm^{-1}: 3410, 2987, 2940, 1777, 1677, 1626, 1537, 1499, 1466, 1365, 1322, 1271, 1191, 1157, 1132, 1096, 1035. HR-MS (FAB): Calcd for $C_{27}H_{28}ClN_8O_9S_2$: 707.1109. Found: 707.1106.

5.1.11. Compound 3j. Amorphous powder. 24% yield. ^{1}H NMR (D_2O) δ: 1.44 (3H, d, J = 6.9 Hz), 3.18 and 3.33 (2H, ABq, J = 17.7 Hz), 3.54 (2H, t, J = 4.5 Hz), 4.49 (2H, t, J = 4.5 Hz), 4.65 (1H, q, J = 6.9 Hz), 5.17 (1H, d, J = 5.1 Hz), 5.52 and 5.70 (2H, ABq, J = 15.0 Hz), 5.87 (1H, d, J = 5.1 Hz), 6.98 (1H, d, J = 3.3 Hz), 7.67 (1H, dd, J = 6.3, 8.1 Hz), 8.07 (1H, d, J = 3.3 Hz), 8.55 (1H, d, J = 8.1 Hz), 8.60 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3375, 1773, 1660, 1609, 1543, 1497, 1466, 1451, 1362, 1288, 1240, 1188, 1159, 1133, 1098, 1035. MS (FAB): 692$^+$(M+H)$^+$. Anal. Calcd for $C_{26}H_{26}ClN_9O_8S_2{\cdot}4.3H_2O$: C, 40.58; H, 4.53; N, 16.38; Cl, 4.61; S, 8.33. Found: C, 40.46; H, 4.38; N, 16.84; Cl, 5.26; S, 7.73.

5.1.12. Compound 3k. Amorphous powder. 65% yield. ^{1}H NMR (D_2O) δ: 1.43 (3H, d, J = 7.2 Hz), 3.14 and 3.31 (2H, ABq, J = 17.7 Hz), 3.53 (2H, t-like), 4.57 (2H, t-like), 4.64 (1H, q, J = 7.2 Hz), 5.17 (1H, d, J = 4.8 Hz), 5.54 and 5.70 (2H, ABq, J = 15.0 Hz), 5.87 (1H, d, J = 4.8 Hz), 7.00 (1H, d, J = 3.3 Hz), 7.68 (1H, dd, J = 6.3, 8.4 Hz), 8.13 (1H, d, J = 3.3 Hz), 8.62 (1H, d, J = 8.4 Hz), 8.62 (1H, d, J = 6.3 Hz). IR (KBr) cm^{-1}: 3316, 1775, 1671, 1611, 1538, 1497, 1467, 1448, 1363, 1326, 1241, 1157, 1134, 1097, 1035. MS (FAB): 728$^+$(M+H$^+$). Anal. Calcd for $C_{25}H_{26}ClN_9O_9S_3{\cdot}3.6H_2O$: C, 37.86; H, 4.22; N, 15.90; Cl, 4.47; S, 12.13. Found: C, 37.88; H, 4.10; N, 15.92; Cl, 4.37; S, 12.00.

5.1.13. Compound 4. Amorphous powder. 68% yield. ^{1}H NMR (D_2O + DCl) δ: 1.44 (3H, d, J = 7.1 Hz), 2.80 (3H, s), 3.20 and 3.53 (2H, ABq, J = 17.9 Hz), 3.75 (2H, t, J = 5.5 Hz), 4.66 (1H, q, J = 7.1 Hz), 5.03 (2H, t, J = 5.5 Hz), 5.23 (1H, d, J = 5.0 Hz), 5.79 (2H, s), 5.88 (1H, d, J = 5.0 Hz), 8.07 (1H,dd, J = 8.7, 5.8 Hz), 8.82 (1H, s), 8.96 (1H, d, J = 8.7 Hz), 9.05 (1H, d, J = 5.8 Hz). IR (KBr) cm^{-1}: 3408, 1773, 1604, 1540,

1476, 1447, 1394, 1352, 1316, 1289, 1222, 1187, 1159, 1080, 1034. MS (FAB): $664^{+}(M+H)^{+}$. Anal. Calcd for $C_{25}26_{9}ClN_{9}O_{7}S_{2}\cdot 3.0H_{2}O$: C, 41.81; H, 4.49; N, 17.55; Cl, 4.94; S, 8.93. Found: C, 41.86; H, 4.45; N, 17.66; Cl, 4.81; S, 8.71.

5.1.14. Compound 5. Amorphous powder. 20% yield. ^{1}H NMR (D_2O + DCl) δ: 1.55 (3H, d, J = 7.2 Hz), 2.85 (3H, s), 3.53 and 3.80 (2H, ABq, J = 18.0 Hz), 3.91 (2H, t, J = 6.0 Hz), 5.34 (1H, d, J = 4.8 Hz), 5.40 (2H, t, J = 6.0 Hz), 5.96 (1H, d, J = 4.8 Hz), 6.07 and 6.29 (2H, ABq, J = 15.0 Hz), 8.28 (1H,dd, J = 5.4, 8.4 Hz), 9.25 (1H, d, J = 8.4 Hz), 9.34 (1H, d, J = 5.4 Hz). IR (KBr) cm^{-1}: 3408, 2448, 1774, 1606, 1539, 1465, 1393, 1348, 1283, 1188, 1155, 1093, 1065, 1034. MS (ESI): $655(M+H)^{+}$. Anal. Calcd for $C_{24}H_{25}ClN_{10}O_{7}S_{2}\cdot 3.6H_{2}O$: C, 39.49; H, 4.45; N, 19.19; Cl, 4.86; S, 8.79. Found: C, 39.50; H, 4.42; N, 19.21; Cl, 4.80; S, 8.67.

5.1.15. Compound 6. Amorphous powder. 70% yield. ^{1}H NMR (D_2O) δ: 1.42 (3H, d, J = 6.9 Hz), 2.74 (3H, s), 3.17 (1H, d, J = 18.0 Hz), 3.56–3.61 (3H, m), 4.61–4.76 (3H, m), 5.23–5.31 (2H, m), 5.54 (1H, d, J = 14.7 Hz), 5.56 (1H, d, J = 4.5 Hz), 7.12 (1H, d, J = 3.4 Hz), 7.80 (1H, d, J = 3.4 Hz), 7.99 (1H, d, J = 7.0 Hz), 8.52 (1H, d, J = 7.0 Hz), 9.086 (1H, s). IR (KBr) cm^{-1}: 3398, 2452, 1773, 1604, 1540, 1514, 1494, 1448, 1395, 1363, 1286, 1223, 1187, 1119, 1065, 1034. MS (FAB): $663^{+}(M+H)^{+}$. Anal. Calcd for $C_{26}H_{27}ClN_{8}O_{7}S_{2}\cdot 4.0H_{2}O$: C, 42.48; H, 4.80; N, 15.24; Cl, 4.82; S, 8.72. Found: C, 42.45; H, 4.57; N, 15.20; Cl, 4.86; S, 8.70.

5.1.16. Compound 7. Amorphous powder. 65% yield. ^{1}H NMR (D_2O + DCl) δ: 1.54 (3H, d, J = 6.9 Hz), 2.14–2.24 (2H, m), 2.71 (3H, s), 3.11 (2H, t, J = 8.4 Hz), 3.25 and 3.48 (2H, ABq, J = 18.3 Hz), 4.28 (2H, t, J = 7.5 Hz), 4.99 (1H, q, J = 6.9 Hz), 5.29 (1H, d, J = 4.8 Hz), 5.34 and 5.51 (2H, ABq, J = 15.6 Hz), 5.91 (1H, d, J = 4.8 Hz), 7.08 (1H, dd, J = 6.6, 7.5 Hz), 7.78 (1H, d, J = 7.5 Hz), 7.91 (1H, d, J = 6.6 Hz). IR (KBr) cm^{-1}: 3341, 3177, 1772, 1646, 1564, 1473, 1439, 1394, 1346, 1284, 1190, 1162, 1092, 1058, 1034. MS (FAB): $692^{+}(M+H)^{+}$. Anal. Calcd for $C_{27}H_{30}ClN_{9}O_{7}S_{2}\cdot 3.8H_{2}O$: C, 42.63; H, 4.98; N, 16.57; Cl, 4.66; S, 8.43. Found: C, 42.69; H, 4.81; N, 16.49; Cl, 4.67; S, 8.51.

5.1.17. Compound 8b. Amorphous powder. 53% yield. ^{1}H NMR (D_2O + DCl) δ: 1.43 (3H, d, J = 6.9 Hz), 1.55 (3H, d, J = 7.1 Hz), 2.17 (2H, m), 3.35 and 3.59 (2H, ABq, J = 18.6 Hz), 3.51 (1H, m), 4.28 (2H, t-like), 4.97 (1H, q, J = 7.1), 5.27 (1H, d, J = 4.8 Hz), 5.45 and 5.67 (2H, ABq, J = 15.0 Hz), 5.91 (1H, d, J = 4.8 Hz), 7.3 (1H, t-like), 7.97 (1H, d, J = 7.8 Hz), 8.13 (1H, d, J = 6.9 Hz). IR (KBr) cm^{-1}: 3408, 1773, 1650, 1601, 1565, 1495, 1395, 1363, 1317, 1287, 1224, 1165, 1090, 1034. MS (ESI): $693^{+}(M+H)^{+}$. Anal. Calcd for $C_{26}H_{29}ClN_{10}O_{7}S_{2}\cdot 3.7H_{2}O$: C, 41.10; H, 4.83; N, 18.43; Cl, 4.67; S, 8.44. Found: C, 41.15; H, 4.69; N, 18.33; Cl, 4.65; S, 8.17.

5.1.18. Compound 8c. Amorphous powder. 65% yield. ^{1}H NMR (D_2O + DCl) δ: 1.55 (3H, d, J = 7.0 Hz), 2.21–2.32 (2H, m), 3.20–3.25 (4H, m), 3.37 and 3.61 (2H, ABq, J = 18.5 Hz), 3.83 (2H, t, J = 5.0 Hz), 4.29 (2H, t, J = 7.1 Hz), 4.99 (1H, q, J = 7.0 Hz), 5.29 (1H, d, J = 4.5 Hz), 5.50 and 5.68 (2H, ABq, J = 15.2 Hz), 5.92 (1H, d, J = 4.5 Hz), 7.34 (2H, t-like), 7.66 (1H, d, J = 7.8 Hz), 8.13 (1H, d, J = 6.6 Hz). IR (KBr) cm^{-1}: 3368, 1773, 1627, 1556, 1455, 1395, 1349, 1321, 1287, 1090, 1158, 1093, 1065, 1034. MS (ESI): $723^{+}(M+H)^{+}$. Anal. Calcd for $C_{27}H_{31}ClN_{10}O_{8}S_{2}\cdot 2.8H_{2}O$: C, 41.92; H, 4.77; N, 18.11; Cl, 4.58; S, 8.29. Found: C, 41.93; H, 4.73; N, 18.06; Cl, 4.46; S, 8.17.

5.1.19. Compound 8d. Amorphous powder. 59% yield. ^{1}H NMR (D_2O + DCl) δ: 1.55 (3H, d, J = 7.2 Hz), 2.68 (2H, m), 3.36 and 3.60 (2H, ABq, J = 18.6 Hz), 3.57 and 3.97 (4H, m), 4.99 (1H, m), 5.29 (1H, d, J = 5.0 Hz), 5.50 and 5.69 (2H, ABq, J = 15.2 Hz), 5.92 (1H, d, J = 5.0 Hz), 7.34 (1H, t-like), 8.06 (1H, d, J = 7.5 Hz), 8.16 (1H, d, J = 6.6 Hz). IR (KBr) cm^{-1}: 3410, 1771, 1606, 1556, 1491, 1440, 1396, 1363, 1319, 1224, 1167, 1092, 1034. MS (FAB): $691^{+}(M+H)^{+}$. Anal. Calcd for $C_{26}H_{27}ClN_{10}O_{7}S_{2}\cdot 4.6H_{2}O$: C, 40.35; H, 4.71; N, 18.10; Cl, 4.58; S, 8.29. Found: C, 40.39; H, 4.17; N, 17.79; Cl, 4.49; S, 8.47.

5.1.20. Compound 8e. Amorphous powder. 43% yield. ^{1}H NMR (D_2O + DCl) δ: 1.55 (3H, d, J = 7.2 Hz), 2.33 (2H, d-like), 2.61 (2H, q-like), 3.25–3.39 (3H, m), 3.60 (1H, d, J = 18.3 Hz), 3.72 (2H, d-like), 4.99 (1H, q, J = 7.2 Hz), 5.29 (1H, d, J = 4.9 Hz), 5.50 and 5.69 (2H, ABq, J = 15.0 Hz), 5.92 (1H, d, J = 4.9 Hz), 7.33 (1H, t-like), 8.14 (2H, m). IR (KBr) cm^{-1}: 3380, 3182, 1772, 1601, 1555, 1491, 1440, 1395, 1362, 1317, 1287, 1225, 1169, 1092, 1033. MS (ESI): $705^{+}(M+H)^{+}$. Anal. Calcd for $C_{27}H_{29}ClN_{10}O_{7}S_{2}\cdot 4.5H_{2}O$: C, 41.25; H, 4.87; N, 17.81; Cl, 4.51; S, 8.16. Found: C, 41.38; H, 4.79; N, 17.71; Cl, 4.19; S, 7.50.

5.1.21. Compound 9. Amorphous powder. 72% yield. ^{1}H NMR (D_2O + DCl) δ: 1.55 (3H, d, J = 7.1 Hz), 2.82 (3H, s), 3.36 and 3.75 (2H, ABq, J = 18.5 Hz), 4.72 (2H, t, J = 6.5 Hz), 4.99 (1H, q, J = 7.1 Hz), 5.36 (1H, d, J = 4.8 Hz), 5.40 and 5.86 (2H, ABq, J = 14.9 Hz), 5.94 (1H, d, J = 4.8 Hz), 8.09 (1H, d, J = 6.8 Hz), 8.83 (1H, d, J = 6.8 Hz), 9.06 (1H, s). IR (KBr) cm^{-1}: 3370, 3174, 1771, 1667, 1606, 1541, 1504, 1449, 1399, 1360, 1312, 1281, 1184, 1113, 1067, 1035. MS (FAB): $679^{+}(M+H)^{+}$. Anal. Calcd for $C_{25}H_{27}ClN_{10}O_{7}S_{2}\cdot 4.0H_{2}O$: C, 39.97; H, 4.70; N, 18.65; Cl, 4.72; S, 8.54. Found: C, 40.02; H, 4.64; N, 18.79; Cl, 4.60; S, 8.31.

5.1.22. Compound 10a. Amorphous powder. 88% yield. ^{1}H NMR (D_2O) δ: 1.36 (3H, d, J = 6.9), 2.04 (2H, m), 2.64 (3H, s), 2.95 (2H, t, J = 7.8 Hz), 3.03 (2H, t, J = 7.8 Hz), 3.11 (1H, d, J = 17.7 Hz), 3.55 (1H, d, J = 17.7 Hz), 4.58 (1H, q, J = 6.9 Hz), 5. 17 (1H, d, J = 14.7 Hz), 5.19 (1H, d, J = 4.8 Hz), 5.45 (1H, d, J = 14.7 Hz), 5.81 (1H, d, J = 4.8 Hz), 7.86 (2H, d, J = 6.9 Hz), 8.76 (2H, d, J = 6.9 Hz). IR (KBr) cm^{-1}: 3397, 2821, 1776, 1606, 1538, 1467, 1394, 1350, 1287, 1231, 1187, 1152, 1094, 1066, 1033. MS (ESI): $638^{+}(M+H)^{+}$. Anal. Calcd for $C_{25}H_{28}ClN_{7}O_{7}S_{2}\cdot 3.8H_{2}O$: C, 42.50; H, 5.08; N, 13.88; Cl, 5.02; S, 9.08. Found: C, 42.34; H, 5.10; N, 13.97; Cl, 5.07; S, 9.29.

5.1.23. Compound 10b. Amorphous powder. 76% yield. ^{1}H NMR (D_2O) δ: 1.45 (3H, d, J = 6.9 Hz), 2.76 (3H, s), 3.17 (1H, d, J = 18.0 Hz), 3.33 (2H, t, J = 6.0 Hz), 3.58 (1H, d, J = 18.0 Hz), 3.75 (2H, t, J = 6.0 Hz), 4.66 (1H, q, J = 6.9 Hz), 4.89 (1H, d, J = 14.7 Hz), 5.09 (1H, d, J = 14.7 Hz), 5.24 (1H, d, J = 4.8 Hz), 5.86 (1H, d, J = 4.8 Hz), 6.94 (2H, d, J = 6.3 Hz), 8.04–8.35 (2H, m). IR (KBr) cm^{-1}: 3398, 3066, 1773, 1650, 1601, 1556, 1450, 1394, 1357, 1288, 1218, 1168, 1094, 1065, 1035. MS (FAB): 639$^+$(M+H)$^+$. Anal. Calcd for $C_{24}H_{27}ClN_8O_7S_2{\cdot}3.4H_2O$: C, 41.16; H, 4.86; N, 16.00; Cl, 5.06; S, 9.16. Found: C, 41.14; H, 4.69; N, 16.00; Cl, 4.97; S, 9.36.

5.1.24. Compound 10c. Amorphous powder. 62% yield. ^{1}H NMR (D_2O) δ: 1.44 (3H, d, J = 6.9 Hz), 3.16 (1H, d, J = 17.7 Hz), 3.57 (1H, d, J = 17.7 Hz), 4.21 (2H, m), 4.52 (2H, m), 5.11 (1H, d, J = 14.4 Hz), 5.24 (1H, d, J = 4.8 Hz), 5.86 (1H, d, J = 4.8 Hz), 6.89 (2H, m), 8.23 (2H, m). IR (KBr) cm^{-1}: 3399, 3059, 1772, 1649, 1601, 1551, 1445, 1361, 1288, 1217, 1167, 1095, 1065, 1035. MS (FAB): 637$^+$ (M+H)$^+$. Anal. Calcd for $C_{24}H_{25}ClN_8O_7S_2{\cdot}2.2H_2O$: C, 42.60; H, 4.38; N, 16.56; Cl, 5.24; S, 9.48. Found: C, 42.67; H, 4.31; N, 16.71; Cl, 5.16; S, 9.08.

5.2. Synthesis of C-3′ side chains

5.2.1. *tert*-Butyl 1*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (3a′). To a solution of **11** (590 mg, 5.0 mmol) in THF (4.7 mL) was added di-*tert*-butyl dicarbonate (1.15 mL, 5.25 mmol), and the mixture was stirred at room temperature for 48 h. After concentration, the residual oil was purified by column chromatography on silica gel to give **3a′** (1.08 g, 99%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.69 (9H, s), 6.79 (1H, d, J = 3.6 Hz), 7.23 (1H, dd, J = 4.5, 8.1 Hz), 7.84 (1H, d, J = 3.6 Hz), 8.37 (1H, d, J = 8.1 Hz), 8.52 (1H, dd, J = 0.9, 4.5 Hz). IR (KBr) cm^{-1}: 2975, 2932, 1687, 1602, 1393, 1365, 1307, 1161, 1133.

5.2.2. 1-(2-(Triethylsilyloxy)ethyl)-1*H*-pyrrolo[3,2-*b*]pyridine (3d′). To a solution of **11** (2.50 g, 21.0 mmol) in DMF (52 mL) was added (2-bromoethoxy)triethylsilane (10.0 g, 42 mmol), and then the reaction mixture was stirred at room temperature for 1 h before being poured into ice water. The whole mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentration. The residual oil was purified by the column chromatography on silica gel to give **3d′** (5.85 g, quant.) as an oil. ^{1}H NMR ($CDCl_3$) δ: 0.46 (6H, q, J = 7.8 Hz), 0.82 (9H, t, J = 7.8 Hz), 3.91 (2H, t, J = 5.7 Hz), 4.24 (2H, t, J = 5.7 Hz), 6.69 (1H, dd, J = 1.2, 3.3 Hz), 7.09 (1H, dd, J = 4.5, 8.1 Hz), 7.37 (1H, d, J = 3.3 Hz), 7.66 (1H, m), 8.44 (1H, dd, J = 1.2, 4.5 Hz). IR (KBr) cm^{-1}: 2945, 2911, 2875, 1676, 1605, 1556, 1508, 1459, 1420, 1385, 1359, 1324, 1294.

5.2.3. *tert*-Butyl 2-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)acetate (3e′). To an ice-cooled solution of **11** (238 mg, 2.0 mmol) in DMF (6 mL) was added sodium hydride (120 mg, 60% w/w, 3.0 mmol) and then the mixture was stirred for 30 min in an ice bath. To the mixture was added *tert*-butyl bromoacetate (0.35 mL, 2.4 mmol), and the whole mixture was stirred for 30 min in an ice bath. Saturated aqueous $NaHCO_3$ and AcOEt were added and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel to give **3e′** (468 mg, quant.) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.43 (9H, s), 4.74 (2H, s), 6.76 (1H, dd, J = 0.9, 3.6 Hz), 7.13 (1H, dd, J = 4.5, 8.4 Hz), 7.32 (1H, d, J = 3.6 Hz), 7.56 (1H, d, J = 8.4 Hz), 8.48 (1H, dd, J = 0.9, 4.5 Hz). IR (KBr) cm^{-1}: 3458, 3103, 3059, 3004, 2978, 2930, 2874, 1737, 1698, 1651, 1607, 1556, 1510, 1479, 1457, 1429, 1366, 1330, 1294, 1231.

5.2.4. 2-(1*H*-Pyrrolo[3,2-*b*]pyridin-1-yl)ethyl carbamate (3g′). To an ice-cooled solution of **3d′** (5.83 g, 21 mmol) in THF (60 mL) was added dropwise tetrabutylammonium fluoride (23.1 mL, 1.0 M soln. in THF), and then the mixture was stirred for 30 min in an ice bath. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel to give **12** (2.63 g, 77%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 3.98 (2H, t, J = 5.4 Hz), 4.26 (2H, t, J = 5.4 Hz), 6.43 (1H, d, J = 3.3 Hz), 7.05 (1H, dd, J = 4.8, 8.1 Hz), 7.33 (1H, d, J = 3.3 Hz), 7.68 (1H, m), 8.32 (1H, m). IR (KBr) cm^{-1}: 3128, 2923, 2889, 2840, 1501, 1408, 1371, 1358, 1331, 1294, 1266, 1070.

To a suspension of **12** (640 mg, 3.95 mmol) in THF (7 mL) was added trichloroacetyl isocyanate (0.51 mL, 4.34 mmol) at −30 °C, and then the reaction mixture was stirred for 30 min before being evaporated to remove THF. To the residue was added DMF (40 mL) and silica gel (20 g) and then the mixture was stirred overnight. The silica gel was removed by filtration and the filtrate was concentrated. The precipitated material was collected with AcOEt/Et_2O to give **3g′** (541 mg, 67%) as a solid. ^{1}H NMR (DMSO-d_6) δ: 4.22 (2H, t, J = 5.4 Hz), 4.41 (2H, t, J = 5.4 Hz), 6.50 (2H, brs), 6.56 (1H, d, J = 3.3 Hz), 7.12 (1H, dd, J = 4.5, 8.1 Hz), 7.64 (1H, d, J = 3.3 Hz), 7.90 (1H, d, J = 8.1 Hz), 8.32 (1H, dd, J = 0.9, 4.5 Hz). IR (KBr) cm^{-1}: 3290, 2954, 1712, 1416, 1401, 1323, 1298, 1140, 1069.

5.2.5. *N*-(2-(1*H*-Pyrrolo[3,2-*b*]pyridin-1-yl)ethyl)acetamide (3h′). To a solution of **12** (5.14 g, 31.6 mmol) in CH_2Cl_2 (120 mL) was added triethylamine (5.72 mL, 41.1 mmol) and methanesulfonyl chloride (2.93 mL, 37.9 mmol) at −50 °C, and then the reaction mixture was stirred at the same temperature for 1.5 h. AcOEt and saturated aqueous $NaHCO_3$ were added and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, dried *in vacuo* to give a mesylate as an oil, which was used for the next step without further purification. To the above mesylate in DMF (120 mL) was added potassium phthalimide (7.61 g, 41.1 g) and the mixture was stirred at 75 °C for 1.5 h. The resulting mixture was poured into ice in

saturated aqueous $NaHCO_3$. The precipitated material was collected by filtration and dried *in vacuo* to give **13** (5.90 g, 64%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 4.11 (2H, t, J = 6.9 Hz), 4.52 (2H, t, J = 6.9 Hz), 7.05 (1H, d, J = 3.3 Hz), 7.21 (1H, dd, J = 5.1, 8.1 Hz), 7.48 (1H, d, J = 3.3 Hz), 7.72–7.76 (2H, m), 7.79–7.83 (2H, m), 7.96 (1H, d, J = 8.1 Hz), 8.45 (1H, d, J = 5.1 Hz). IR (KBr) cm^{-1}: 2363, 1772, 1712, 1618, 1502, 1443, 1435, 1401, 1382, 1329, 1307.

To a suspension of **13** (874 mg, 3.0 mmol) in ethanol (18 mL) was added hydrazine hydrate (0.29 mL, 6.0 mmol) and the mixture was refluxed for 1 h. The precipitated material was removed by filtration, and the filtrate was concentrated. Ethanol was completely removed by codistillation with chloroform. To the residual oil in CH_2Cl_2 (20 mL) at −50 °C was added triethylamine (0.42 mL, 3.0 mmol) and acetyl chloride (0.21 mL, 3.0 mmol). The mixture was stirred at same temperature for 1 h before being poured into saturated aqueous $NaHCO_3$. The whole mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The precipitated material was collected by filtration and washed with ether to give **3h′** (303 mg, 50%) as a solid. ^{1}H NMR (DMSO-d_6) δ: 1.92 (3H, s), 3.59 (2H, q, J = 6.0 Hz), 4.40 (2H, t, J = 6.0 Hz), 5.58 (1H, brs), 7.07 (1H, d, J = 3.3 Hz), 7.24 (1H, dd, J = 5.4, 8.4 Hz), 7.47 (1H, d, J = 3.3 Hz), 7.93 (1H, d, J = 8.4 Hz), 8.48 (1H, d, J = 5.4 Hz). IR (KBr) cm^{-1}: 3311, 1653, 1617, 1560, 1504, 1445, 1375, 1366, 1336, 1305, 1227.

5.2.6. Methyl 2-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)ethylcarbamate (3i′). To a suspension of **13** (874 mg, 3.0 mmol) in ethanol (18 mL) was added hydrazine hydrate (0.29 mL, 6.0 mmol) and the mixture was refluxed for 1 h. The precipitated material was removed by filtration and the filtrate was concentrated. Ethanol was completely removed by codistillation with chloroform. To the residual oil in CH_2Cl_2 (18 mL) at −50 °C was added triethylamine (0.42 mL, 3.0 mmol) and methyl chloroformate (0.23 mL, 3.0 mmol). The mixture was stirred at the same temperature for 1 h before being poured into saturated aqueous $NaHCO_3$. The whole mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel to give **3i′** (229 mg, 35%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 3.54 (2H, q, J = 6.3 Hz), 3.68 (3H, s), 4.38 (2H, t, 6.3 Hz), 4.77 (1H, brs), 7.08 (1H, dd, J = 0.9, 3.3 Hz), 7.24 (1H, dd, J = 5.7, 8.1 Hz), 7.47 (1H, d, J = 3.3 Hz), 7.92 (1H, d, J = 8.1 Hz), 8.48 (1H, d, J = 5.7 Hz). IR (KBr) cm^{-1}: 3354, 2359, 1687, 1617, 1557, 1505, 1446, 1338, 1305, 1280.

5.2.7. 1-(2-(1*H*-Pyrrolo[3,2-*b*]pyridin-1-yl)ethyl)urea (3j′). To a suspension of **13** (874 mg, 3.0 mmol) in ethanol (18 mL) was added hydrazine hydrate (0.29 mL, 6.0 mmol), and the mixture was refluxed for 1 h. The precipitated material was removed by filtration and the filtrate was concentrated. Ethanol was completely removed by codistillation with chloroform. To the residual oil in THF (10 mL) at −50 °C was added trichloroacetyl isocyanate (0.43 mL, 3.6 mmol). The mixture was stirred at the same temperature for 1 h, and then allowed to warm to 0 °C. Methanol (4 mL) and silica gel (1 g) were added, and the reaction mixture was stirred for 3 days before being filtered to remove silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography on silica gel to give **3j′** (376 mg, 61%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 3.48 (2H, t, J = 6.0 Hz), 4.32 (2H, t, J = 6.0 Hz), 6.60 (1H, dd, 0.6, 3.3 Hz), 7.19 (1H, dd, J = 4.5, 8.1 Hz), 7.56 (1H, d, J = 3.3 Hz), 7.94 (1H, m), 8.29 (1H, dd, J = 0.9, 4.5 Hz). IR (KBr) cm^{-1}: 3335, 1658, 1607, 1558, 1506, 1421, 1327, 1294.

5.2.8. *tert*-Butyl 2-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)ethyl(sulfamoyl)carbamate (3k′). To a solution of **12** (649 mg, 4.0 mmol) and *tert*-butyl sulfamoylcarbamate (1.18 g, 6.0 mmol) in THF (20 mL) was added triphenylphosphine (1.57 g, 6.0 mmol) and the mixture was cooled to 0 °C. To this mixture was added diethyl azodicarboxylate (0.95 mL, 6.0 mmol) and then the reaction mixture was stirred at the same temperature for 1.5 h. To the resulting solution was added toluene, followed by evaporation to remove THF. The precipitated material was removed by filtration and the filtrate was concentrated. The residual oil was purified by column chromatography on silica gel to give **3k′** (972 mg, 71%) as a solid. ^{1}H NMR (DMSO-d_6) δ: 0.94 (9H, s), 3.91 (2H, t, J = 5.4 Hz), 4.40 (2H, t, J = 5.4 Hz), 6.55 (1H, d, J = 3.0 Hz), 7.13 (1H, dd, J = 4.5, 8.1 Hz), 7.60 (1H, d, J = 3.0 Hz), 7.70 (2H, brs), 7.91 (1H, m), 8.33 (1H, dd, J = 1.2, 4.5 Hz). IR (KBr) cm^{-1}: 3317, 2983, 1701, 1608, 1573, 1557, 1505, 1426, 1371, 1335, 1324, 1272.

The following compounds were prepared by a procedure similar to that used for **4′** which was referred to Ref. 11.

5.2.9. *tert*-Butyl 2-(1*H*-[1,2,3]triazolo[4,5-*b*]pyridin-1-yl)ethyl(methyl)carbamate (5′). This compound was obtained from 1*H*-[1,2,3]triazolo[4,5-*b*]pyridine as an oil. 7% yield. ^{1}H NMR ($CDCl_3$) δ: 1.19 and 1.40 (9H, s), 2.54 and 2.79 (3H, s), 3.78 (2H, t, J = 6.0 Hz), 4.85 (2H, m), 7.46 (1H, m), 7.84 and 8.00 (1H, m), 8.78 (1H, dd, J = 1.2, 4.2 Hz) (two rotational isomers were observed). IR (KBr) cm^{-1}: 3008, 1684, 1480, 1457, 1423, 1411, 1391, 1364, 1273, 1246, 1143.

5.2.10. *tert*-Butyl 2-(1*H*-pyrrolo[3,2-*c*]pyridin-1-yl)ethyl(methyl)carbamate (6′). This compound was obtained from 1*H*-[1,2,3]triazolo[4,5-*b*]pyridine as an oil. 56% yield. ^{1}H NMR ($CDCl_3$) δ: 1.24 and 1.44 (9H, s), 2.39 and 2.74 (3H, s), 3.56 (2H, m), 4.30–4.34 (2H, m), 6.62 (1H, brs), 7.04 and 7.11 (1H, m), 7.25 (1H, brs), 8.32 (1H, d, J = 6.0 Hz), 8.92 (1H, s) (two rotational isomers were observed). IR (KBr) cm^{-1}: 2978, 2935, 1686, 1606, 1479, 1454, 1394, 1367, 1167.

5.2.11. *tert*-Butyl 3-(2-bis-*tert*-butoxycarbonylamino-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)propyl(methyl)carbamate (7′). To a solution of **14** (27.5 g, 169 mmol) in ethanol (200 mL) and THF (200 mL) was added 10% palla-

dium-carbon (2.8 g), and then the mixture was stirred at room temperature under hydrogen atmosphere for 26 h. The resulting mixture was filtered through celite and the filtrate was concentrated to give **15** (23.2 g) which was used for the next step without further purification.

To a solution of **15** (666 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) was added *tert*-butyl methyl(3-oxopropyl)carbamate (1.12 g, 6.0 mmol) and acetic acid (0.63 mL, 11.0 mmol). To this stirred mixture at 0 °C was added sodium triacetoxyborohydride (1.34 g, 6.0 mmol, 95% w/w) and then the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The resulting mixture at 0 °C was basified with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered, and concentrated to give **16** (1.83 g) which was used for the next step without further purification.

To a solution of **16** (1.83 g), which was synthesized as described above, in ethanol (10 mL) was added 4 N hydrogen chloride in 1,4-dioxane (6.25 mL) and the mixture was stirred at 80 °C for 45 min. The resulting mixture was concentrated and then CH_2Cl_2 (10 mL), triethylamine (2.09 mL, 15.0 mmol), di-*tert*-butyl dicarbonate (4.02 mL, 17.5 mmol), and dimethylaminopyridine (61 mg, 0.5 mmol) were added. After stirring at room temperature for 1 h, the mixture was poured into water and $CHCl_3$ and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel to give **17** (1.83 g, 90%) as a foam. ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.54 (9H, s), 2.02 (2H, m), 2.85 (3H, s), 3.24 (2H, t, J = 6.3 Hz), 4.07 (2H, t, J = 6.3 Hz), 6.66 (1H, s), 7.01 (1H, dd, J = 4.8, 8.1 Hz), 7.46 (1H, dd, J = 1.2, 8.1 Hz), 8.39 (1H, dd, J = 1.2, 4.8 Hz).

To a solution of **17** (809 mg, 2.0 mmol) in 1,4-dioxane (5.0 mL) was added di-*tert*-butyl dicarbonate (0.51 mL, 2.2 mmol) and dimethylaminopyridine (24 mg, 0.2 mmol) and then the mixture was stirred at 100 °C for 5 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel to give **7′** (713 mg, 71%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.42 (27H, s), 2.00 (2H, m), 2.85 (3H, s), 3.31 (2H, m), 3.97 (2H, t, J = 7.8 Hz), 6.57 (1H, s), 7.14 (1H, dd, J = 4.5, 8.4 Hz), 7.59 (1H, dd, J = 1.2, 8.4 Hz), 8.46 (1H, dd, J = 1.2, 4.5 Hz). IR (KBr) cm^{-1}: 1750, 1715, 1685, 1423, 1398, 1371, 1349, 1320, 1234, 1148, 1117.

5.2.12. *tert*-Butyl 3-(2-azido-1*H*-imidazo[4,5-*b*]pyridin-1-yl)propyl(methyl)carbamate (19a′). To a solution of **18a′** (2.90 g, 10 mmol) in THF (58 mL) at −70 °C was added dropwise *sec*-BuLi (11.2 mL, 0.98 M in *n*-hexane) and the mixture was stirred at the same temperature for 50 min. To the mixture was added dropwise a solution of dodecylbenzenesulfonyl azide (4.22 g, 12.0 mmol) in THF (10 mL), and then the reaction mixture was stirred at −70 °C for 1 h before being quenched with saturated aqueous ammonium chloride. The whole mixture was poured into water and AcOEt and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The solution was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel to give **19a′** (2.88 g, 87%) as a solid, which was unstable under light, and so was immediately used for the next step. ^{1}H NMR ($CDCl_3$) δ: 1.43 (9H, s), 2.00 (2H, m), 2.86 (3H, s), 3.29 (2H, m), 4.01 (2H, t, J = 7.5 Hz), 7.14 (1H, dd, J = 5.1, 8.1 Hz), 7.53 (1H, d, J = 8.1 Hz), 8.45 (1H, dd, J = 1.2, 5.1 Hz).

The following compounds were prepared from the corresponding imidazo[4,5-*b*]pyridines by a procedure similar to that used for **19a′**.

19b′: *sec*-BuLi of two equivalents was used. Foam. 57% yield. ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, d, J = 6.9 Hz), 1.45 (9H, s), 1.91 (2H, m), 3.75 (1H, m), 4.06 (2H, m), 4.41 (1H, m), 7.12 (1H, dd, J = 4.8, 8.1 Hz), 7.54 (1H, dd, J = 1.5, 8.1 Hz), 8.44 (1H, dd, J = 1.5, 4.8 Hz).

19c′: Amorphous solid. 32% yield. ^{1}H NMR ($CDCl_3$) δ: 0.57 (6H, q, J = 8.1 Hz), 0.92 (9H, t, J = 8.1 Hz), 1.45 (9H, brs), 2.04 (2H, m), 3.29 (2H, brs), 3.34 (2H, brs), 3.69 (2H, brs), 4.01 (2H, t, J = 7.5 Hz), 7.16 (1H, dd, J = 5.1, 7.8 Hz), 7.60 (1H, m), 8.45 (1H, dd, J = 1.2, 5.1 Hz).

19d′: Foam. 44% yield. ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.33–2.49 (2H, m), 3.53 (1H, m), 3.61–3.93 (3H, m), 5.01 (1H, m), 7.13 (1H, dd, J = 5.1, 8.4 Hz), 7.58 (1H, d, J = 8.4 Hz), 8.46 (1H, dd, J = 1.5, 5.1 Hz).

19e′: Foam. 53% yield. ^{1}H NMR ($CDCl_3$) δ: 1.51 (9H, s), 1.89 (2H, d, J = 12.9 Hz), 2.26 (2H, m), 2.85 (2H, t, J = 12.9 Hz), 4.34 (3H, m), 7.11 (1H, dd, J = 5.1, 8.1 Hz), 7.65 (1H, dd, J = 1.5, 8.1 Hz), 8.44 (1H, dd, J = 1.5, 5.1 Hz).

5.2.13. *tert*-Butyl 3-(2-amino-1*H*-imidazo[4,5-*b*]pyridin-1-yl)propyl(methyl)carbamate (20a′). To above **19a′** (2.77 g, 8.36 mL) in EtOH (50 mL) was added 10% palladium-carbon (300 mg), and then the mixture was stirred at room temperature under hydrogen atmosphere for 4 h. The resulting mixture was filtered through celite and concentrated to give **20a′** (2.55 g, quant.) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.04 (2H, m), 2.87 (3H, s), 3.33 (2H, t, J = 6.0 Hz), 3.99 (2H, t, J = 6.3 Hz), 6.37 (2H, brs), 6.91 (1H, dd, J = 4.8, 7.5 Hz), 7.25 (1H, dd, J = 1.2, 7.5 Hz), 8.23 (1H, dd, J = 1.2, 4.8 Hz). IR (KBr) cm^{-1}: 1691, 1651, 1620, 1538, 1472, 1447, 1414, 1396, 1365, 1157.

The following compounds were prepared by a procedure similar to that used for **20a′** from **19b′**–**e′**, respectively.

5.2.14. (*S*)-*tert*-Butyl 4-(2-amino-1*H*-imidazo[4,5-*b*]pyridin-1-yl)butan-2-ylcarbamate (20b′). This compound was obtained as an oil after purification by column chromatography on silica gel. 79% yield. ^{1}H NMR ($CDCl_3$) δ: 1.17 (3H, d, J = 6.6 Hz), 1.47 (9H, s), 1.91 (2H, m), 3.78 (1H, m), 4.03 (2H, m), 4.94 (1H, m), 6.93 (1H, dd, J = 5.4, 7.8 Hz), 7.27 (1H, dd, J = 1.2, 7.8 Hz), 8.18 (1H, dd, J = 1.2, 5.4 Hz). IR (KBr) cm^{-1}: 3368,

3055, 1680, 1547, 1520, 1470, 1453, 1427, 1372, 1269, 1165.

5.2.15. *tert*-Butyl 3-(2-amino-1*H*-imidazo[4,5-*b*]pyridin-1-yl)propyl(2-(triethylsilyloxy)ethyl)carbamate (20c′). Amorphous solid. 79% yield. ^{1}H NMR ($CDCl_3$) δ: 0.58 (6H, q, J = 7.5 Hz), 0.93 (9H, t, J = 7.5 Hz), 1.46 (9H, s), 2.06 (2H, m), 3.31 (2H, t, J = 5.7 Hz), 3.40 (2H, t, J = 6.3 Hz), 3.71 (2H, t, J = 5.7 Hz), 4.05 (2H, t, J = 6.3 Hz), 6.84 (2H, brs), 6.94 (1H, dd, J = 5.0, 7.5 Hz), 7.27 (1H, dd, J = 1.2, 7.5 Hz), 8.22 (1H, dd, J = 1.2, 5.0 Hz). IR (KBr) cm^{-1}: 1691, 1623, 1542, 1469, 1416, 1365, 1267, 1242, 1157.

5.2.16. (*R*)-*tert*-Butyl 3-(2-amino-1*H*-imidazo[4,5-*b*]pyridin-1-yl)pyrrolidine-1-carboxylate (20d′). This compound was obtained as an amorphous solid after purification by column chromatography on silica gel. 80% yield. ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.34 (2H, m), 3.51 (1H, m), 3.62 (1H, m), 3.83 (2H, m), 5.14 (1H, m), 6.87 (1H, dd, J = 5.1, 7.8 Hz), 7.32 (1H, m), 8.14 (1H, dd, J = 1.2, 5.1 Hz). IR (KBr) cm^{-1}: 1656, 1613, 1537, 1412, 1365, 1269, 1164, 1130.

5.2.17. *tert*-Butyl 3-(2-amino-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (20e′). This compound was obtained as an amorphous solid after purification by column chromatography on silica gel. 98% yield. ^{1}H NMR ($CDCl_3$) δ: 1.51 (9H, s), 1.91 (2H, m), 2.22 (2H, m), 2.87 (2H, m), 2.30 (3H, m), 6.79 (2H, brs), 6.90 (1H, dd, J = 5.1, 7.8 Hz), 7.45 (1H, dd, J = 1.2, 7.8 Hz), 8.18 (1H, dd, J = 1.2, 5.1 Hz). IR (KBr) cm^{-1}: 1692, 1648, 1538, 1416, 1366, 1274, 1240, 1167, 1135.

5.2.18. Compound 8a′. To a solution of **20a′** (214 mg, 0.70 mmol) in CH_2Cl_2 (2.0 mL) was added di-*tert*-butyl dicarbonate (0.34 mL, 1.47 mmol) and dimethylamino pyridine (8.6 mg, 0.07 mmol), and then the reaction mixture was stirred for 45 min. The resulting mixture was diluted with AcOEt and washed with water and brine. This organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford **8a′** (410 mg) which was used for the next step without further purification, where it was allowed to react with **2** (0.60 mmol).

Compounds **8b′**–**e′** were prepared from **20b′**–**e′**, respectively, by a procedure similar to that used for **8a′** and used for the next step without further purification.

5.2.19. *tert*-Butyl 3-(2-*tert*-butoxycarbonylamino-1*H*-imidazo[4,5-c]pyridin-1- yl)propyl(methyl)carbamate (9′). To a solution of **21** (3.81 g, 20 mmol) in EtOH (30 mL) was added *N*-methylhydrazine (2.62 mL, 30 mmol), and the mixture was stirred under reflux for 8 h before being evaporated to remove the solvent. To a solution of the residue in THF (20 mL) and CH_3CN (10 mL) was added di-*tert*-butyl dicarbonate (11.5 mL, 50 mmol) and water (5 mL), and then the reaction mixture was stirred at room temperature for 5 h. The resulting mixture was diluted with AcOEt, then washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel to give **22** (4.88 g, 82%) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.92 (3H, s), 3.48–3.60 (4H, m), 6.80 (1H, m), 8.31 (1H, d, J = 6.3 Hz), 9.22 (1H, s).

To a solution of **22** (7.22 g, 24.3 mmol) in EtOH (180 mL) was added 10% palladium-carbon (800 mg) and the reaction mixture was stirred under hydrogen atmosphere for 6 h. The resulting mixture was filtered and the filtrate was concentrated to give an oil. To a solution of the above oil in EtOH (5.2 mL) was added diethoxymethyl acetate (10.4 mL, 63.7 mmol) and the mixture was stirred at 80 °C for 2 h. The resulting solution was diluted with AcOEt and the whole mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel to give **23** (4.12 g, 70%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.17 and 1.43 (9H, s), 2.51 and 2.83 (3H, s), 3.61 (2H, m), 4.29–4.42 (2H, m), 7.38 (1H, m), 7.92 (1H, m), 8.47 (1H, d, J = 5.7 Hz), 9.13 (1H, s) (two rotational isomers were observed).

Compound **24** was prepared by a procedure similar to that used for **19a′** and gave a solid. 95% yield. ^{1}H NMR ($CDCl_3$) δ: 1.18 and 1.36 (9H, s), 2.59 and 2.85 (3H, s), 3.55 (2H, m), 4.09–4.21 (2H, m), 7.15–7.24 (1H, m), 8.39 (1H, d, J = 4.5 Hz), 8.92 (1H, brs) (two rotational isomers were observed).

Compound **9′** was prepared by procedures similar to those used for **20a′** and **8a′**. **9′** was isolated as a solid via purification by column chromatography on silica gel. 37% yield. ^{1}H NMR ($CDCl_3$) δ: 1.31 and 1.41 (9H, s), 1.70 (9H, s), 2.78 and 2.89 (3H, s), 3.57 (2H, t, J = 5.7 Hz), 3.96–4.06 (2H, m), 6.76 and 6.92 (1H, d, J = 5.1 Hz), 7.64 (1H, brs), 8.30 (1H, d, J = 5.1 Hz), 8.68 (1H, brs) (two rotational isomers were observed). IR (KBr) cm^{-1}: 1736, 1681, 1595, 1555, 1479, 1390, 1366, 1156.

5.2.20. *tert*-Butyl methyl(3-(pyridin-4-yl)propyl)carbamate (10a′). To a solution of 3-(pyridin-4-yl)propan-1-ol **25** (1.37 g, 10.0 mmol) in THF (20 mL) was added triethylamine (1.67 mL, 12.0 mmol) and methanesulfonyl chloride (0.85 mL, 11.0 mL) at 0 °C, and then the reaction mixture was stirred at the same temperature for 0.5 h before being poured into water and AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. To a solution of the residual oil in THF (15 mL) was added methylamine (4.3 mL, 40% soln. in water) and the mixture was stirred at room temperature for 14 h and at 50 °C for 2 h. The resulting solution was evaporated to remove organic solvent and the residual solution was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. To a solution of the residue in THF (15 mL) was added di-*tert*-butyl dicarbonate (2.52 mL, 11.0 mmol) at 0 °C and the mixture was stirred at the same temperature for 1 h. The resulting solution was concentrated and the residual oil was purified by column chromatography on silica gel to give **10a′** (1.75 g, 70%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.83 (2H, m), 2.61 (2H, t, J = 7.5 Hz), 2.85

(3H, s), 3.26 (2H, brs), 7.13 (2H, d, $J = 6.0$ Hz), 8.50 (2H, d, $J = 6.0$ Hz). IR (KBr) cm^{-1}: 1725, 1406, 1369, 1343, 1319, 1290, 1157, 1133, 1074.

5.2.21. *tert*-Butyl methyl(2-(*N*-(*tert*-butoxycarbonyl)-*N*-pyridin-4-ylamino)ethyl)carbamate (10b′). To a suspension of 4-bromopyridine hydrochloride (1.94 g, 10.0 mmol) and *tert*-butyl 2-aminoethyl(methyl)carbamate (1.74 g, 10.0 mmol) in toluene (30 mL) was added 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (187 mg, 0.30 mmol) and sodium *tert*-butoxide (2.02 g, 21.0 mmol), and then the flask was evacuated and backfilled with nitrogen for degassing. To the mixture was added $Pd_2(dba)_3$ (183 mg, 0.20 mmol) and the whole mixture was stirred at 80 °C for 16 h. The resulting mixture was diluted with AcOEt (50 mL) and filtered through celite. The filtrate was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oil containing **27b′**. To a solution of this oil in THF (20 mL) was added di-*tert*-butyl dicarbonate (2.52 mL, 11.0 mmol) and the mixture was stirred at room temperature for 1 h. The resulting solution was concentrated and the residual oil was purified by column chromatography on silica gel to give **10b′** (2.51 g, 71%) as a solid. Analytical data were referred to Ref. 14.

5.2.22. *tert*-Butyl 3-(pyridin-4-ylamino)azetidine-1-carboxylate (10c′). This compound was prepared by a procedure similar to that used for **26b′** and obtained as a solid after purification by column chromatography on silica gel. 55% yield. ^1H NMR ($CDCl_3$) δ: 1.45 (9H, s), 3.77 (2H, dd, $J = 4.2$, 9.0 Hz), 4.20–4.35 (3H, m), 4.69 (1H, brs), 6.37 (2H, m), 8.23 (2H, m). IR (KBr) cm^{-1}: 3310, 1666, 1600, 1518, 1400, 1365, 1346, 1163, 1122.

5.3. Measurement of in vitro antibacterial activity

MICs were determined using a serial twofold dilution method using Sensitivity Disk Agar-N (Nissui Pharmaceutical, Tokyo, Japan). The overnight cultures of antibacterial strains in Mueller Hinton broth (Becton Dickinson) were diluted to about 10^6 CFU/mL. Bacterial suspensions of 1 μL were spotted onto agar plates containing various concentrations of the antibiotic and incubated for 20 h at 37 °C before the MICs were scored.

5.4. Measurement of in vivo antibacterial activity

Animals: Five-week-old female ICR mice (body weight, 20–25 g) were obtained from Japan SLC, Inc. (Shizuoka, Japan). Five mice per group were used in all experimental infection models. All studies with animals were approved by the Experimental Animal Committee of Shionogi Co., Ltd.

Systemic infection models: The in vivo potency of **8a** was determined using a mouse model of septicemia. The mice were injected intraperitoneally with 0.5 or 1.0 mL of a bacterial suspension. *P. aeruginosa* SR24 and SR24-12 (β-lactamase-producing strain) were injected as a suspension with 5% mucin (ICN, Cleveland, Ohio). **8a** and CAZ were administered subcutaneously 1 and 5 h after infection.[15] Mortality was recorded over 7 days to estimate the 50% effective dose (ED_{50}) and 95% confidence limits, which were determined by the logit method.

5.5. Measurement of stability against AmpC

Compound **8a** was reacted with AmpC protein, which was obtained as a crude enzyme by simplified purification, in potassium phosphate buffer (pH7.0) at 37 °C for 30 min. After the reaction mixture was heated at 70 °C for 5 min for quenching, the concentration of the compounds which resisted hydrolysis was determined by the bioassay method with *P. aeruginosa* PAO4141 (AmpC-deficient mutant) as the indicator organism.

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