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Synthesis of novel di- and tricationic carbapenems with potent anti-MRSA activity

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ABSTRACT

A new series of 1β-methyl carbapenems possessing a 6,7-disubstituted imidazo[5,1-*b*]thiazol-2-yl group directly attached to the C-2 position of the carbapenem nucleus was prepared, and their activities against methicillin-resistant *Staphylococcus aureus* (MRSA) were evaluated. First, a benzyl moiety was introduced at the C-6 position of imidazo[5,1-*b*]thiazole attached to the carbapenem. These benzylated molecules showed potent anti-MRSA activity, but poor water solubility. In order to overcome this drawback, we designed and synthesized di- and tricationic carbapenems and finally discovered a novel carbapenem (**15i**), which exhibited excellent anti-MRSA activity and good water solubility.

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA)[1] are one of the most serious clinical problems worldwide because only a few therapeutic agents such as Arbekacin, vancomycin (VCM), and teicoplanin are effective against MRSA. Moreover, glycopeptide-resistant strains have been emerging due to the increasing use of glycopeptide.[2] Recently, linezolid and daptomycin have also been available for MRSA infections. However, new resistant strains against many drugs including them have already been reported.[3] Therefore, new and potent anti-MRSA agents are urgently required.

During the past decade, a number of research groups have attempted to synthesize novel β-lactams with anti-MRSA activity. These efforts yielded cephalosporins[4] and carbapenems[5] with potent activity against MRSA. Recently, we have discovered a novel anti-MRSA β-lactam, CP5068[6], which had an imidazo[5,1-*b*]thiazolium side chain at the C-2 position of the carbapenem skeleton.

Most anti-MRSA β-lactams have a hydrophobic side chain, such as an aryl[7], a benzothiazolylthio[8], or a fluorenyl[9] group, at the C-2 position of carbapenem or the C-3 position of cephalosporin. It suggested that introduction of a hydrophobic side chain increases the binding affinity of the β-lactam to PBP2' protein of MRSA.[10]

Based on the above findings, we introduced a benzyl moiety as a hydrophobic side chain at the 6-position of imidazo[5,1-*b*]thiazole in place of the carbamoylmethyl moiety of CP5068 in an attempt to increase anti-MRSA activity (Fig. 1). Moreover, we designed and synthesized novel di- and tricationic carbapenems containing the benzyl moiety to increase water solubility.[5a] Herein we report the synthesis and SAR study of benzyl-substituted imidazo[5,1-*b*]thiazolium di- and tricationic carbapenems having excellent anti-MRSA activity and good water solubility.

Carbapenem derivatives having a benzyl moiety were prepared as shown in Scheme 1. 7-Iodoimidazo[5,1-*b*]thiazole **2**, which was derived from **1** by iodination with *N*-iodosuccinimide in 70% yield, was converted to **3** using Grignard reagent followed by sulfenylation. The stannane **4** was synthesized in order to introduce imidazothiazole into the carbapenem nucleus through Stille coupling. Then the key intermediate **6** was smoothly obtained in NMP at 50 °C via the Stille coupling reaction of **4** and **5**. This key intermediate **6** could be reacted with several benzyl bromides **7a–h** and led to the corresponding quaternary ammonium salts **8a–h**. Deprotection of **8a–h** was performed by hydrogenation with Pd/C and H_2. After purification of the crude products by reversed-phase column chromatography, the desired carbapenem derivatives **9a–h** were obtained, each as a lypophilized amorphous powder.

Introduction of a quaternary ammonium substituent into the benzyl moiety is illustrated in Scheme 2. We selected α,α′-dibromoxylenes as a building block to synthesize several dicationic carbapenems. Thus, the reaction of **6** with *o*-, *m*-, and *p*-α,α′-dibromoxylene provided **10a–c**, respectively. In these reactions, dicationic carbapenem dimers were obtained as by-products. However, these dimers were easily removed by resin purification.

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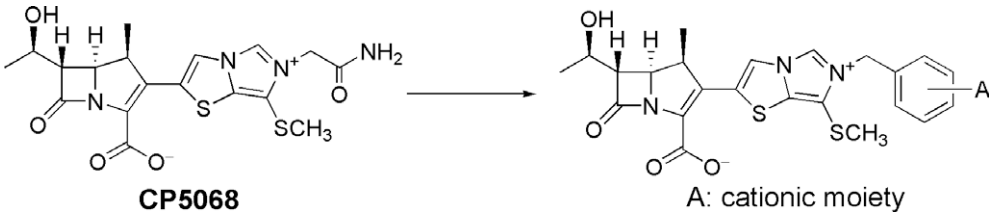


Figure 1. Strategy for synthesizing anti-MRSA carbapenems.

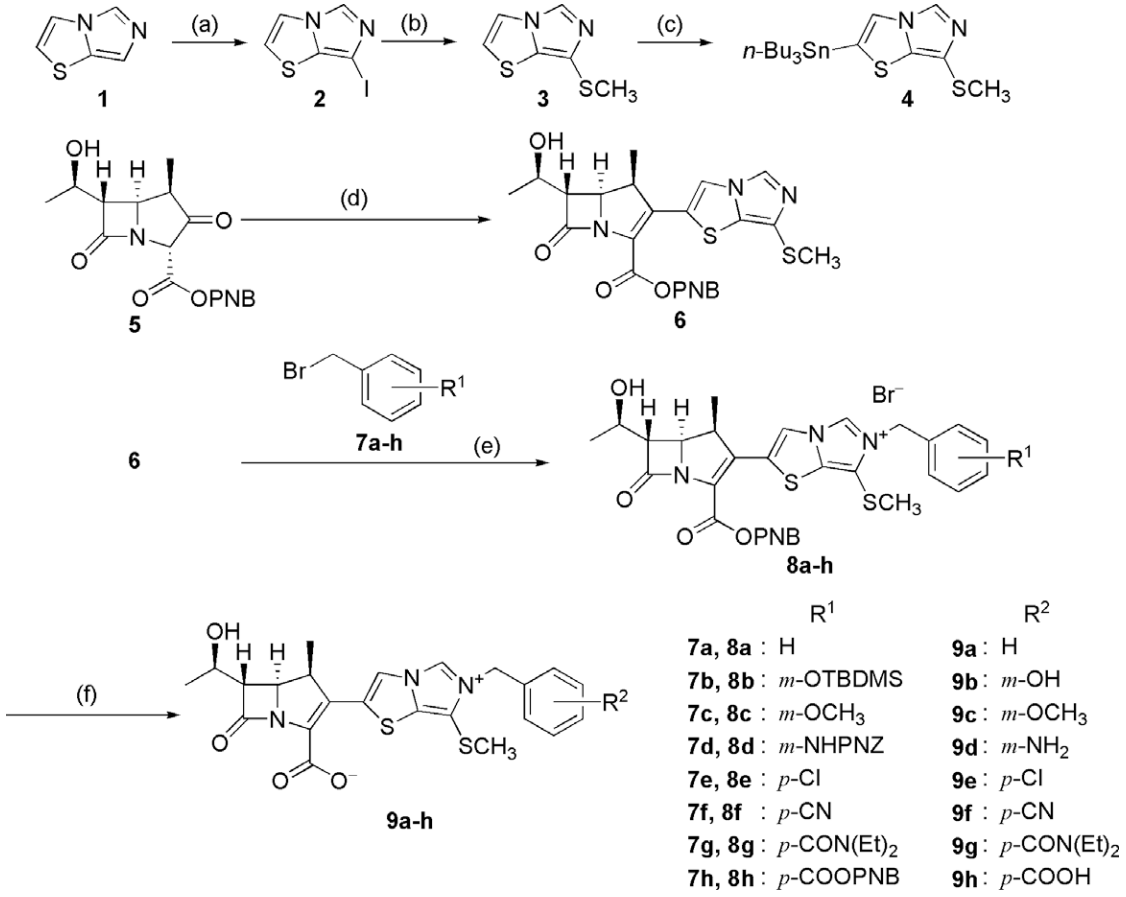
The intermediates **10a–c** were converted to **11a–f** by the reaction with pyridine or 4-methylmorpholine. Removal of the 4-nitrobenzyl group of **11a–f** afforded the desired dicationic carbapenems **12a–f**, which showed good water solubility.

We next planned to synthesize various water-soluble dicationic carbapenems starting from **10b** (Scheme. 3). We chose *m*-substituted derivatives because of their strongest anti-MRSA activities compared to those of *o*- and *p*- substituted compounds (Table. 2). Reaction of **10b** with **13a–e**, followed by deprotection of the 4-nitrobenzyl groups afforded the corresponding dicationic carbapenems **15a–e**.

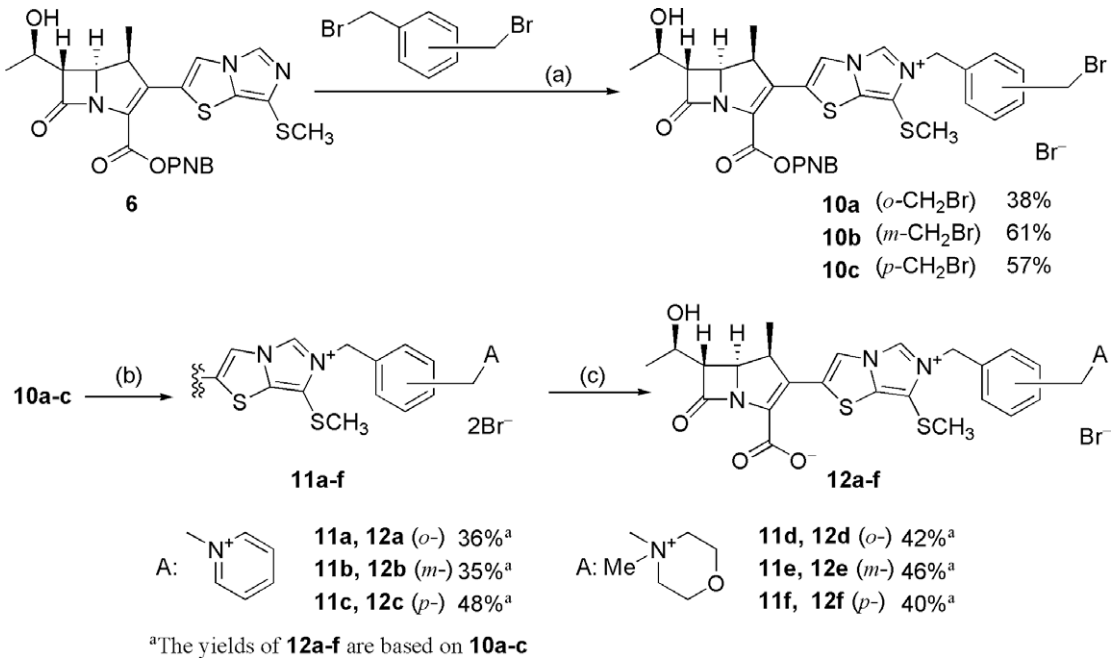
To study the influence of an additional cationic charge on anti-MRSA activity, we synthesized tricationic carbapenems. Reaction of **10b** with cationic analogs of DABCO (1,4-diaza-[2,2,2]-bicyclooctane), **13f–i**, resulted in tricationic ammonium salts **14f–i**. These ammonium salts were converted to the desired tricationic carbapenems **15f–i** by removal of the protecting groups.

Table 1 shows the antibacterial activities of the novel benzyl-substituted carbapenems **9a–h** together with those of CP5068, imipenem (IPM), and VCM. Compound **9a** showed potent anti-MRSA activity, like other carbapenems with a hydrophobic side chain.[7–9] It was more potent than CP5068 and IPM by 1-, 2- and 8-fold, respectively, and equipotent with VCM. Substituted benzyl compounds **9b–f** also exhibited potent anti-MRSA activity, but showed insufficient water solubility[11] because of their hydrophobic side chain. Compound **9g** with a diethylcarbamoyl group showed neither good anti-MRSA activity nor water solubility. Although **9h** had sufficient water solubility owing to the introduction of the carboxylic acid, it showed poor anti-MRSA activity. We considered that higher water solubility (>20 mg/mL) without decrease of activity (MIC value of MRSA M126 HR $\leqslant$1.56) was indispensable for the target profile of our compounds.

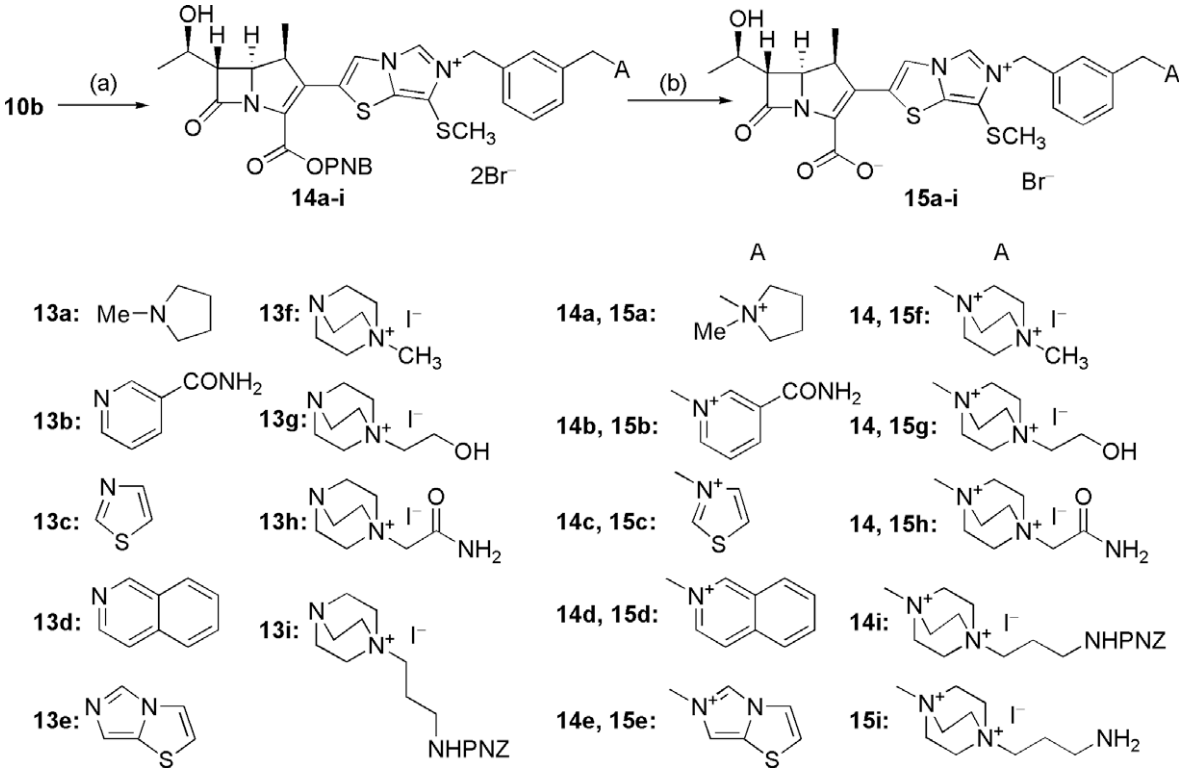
To increase water solubility, we designed and synthesized di- and tricationic derivatives (Scheme 2). Their anti-MRSA activities are



Scheme 1. Synthesis of carbapenem derivatives (1). Reagents and conditions: (a) NIS, CH_2C1_2, rt, 70%; (b) EtMgBr, $CH_3SO_2SCH_3$, THF, 0 °C, 84%; (c) i—*n*-BuLi; ii—*n*-Bu_3SnCl; iii—LHMDS, THF, −40 °C, 86%; (d) i—DIPEA, Tf_2O, CH_3CN, −35 °C; ii—**4**, $Pd_2(dba)_3$, P(2-furyl)$_3$, $ZnCl_2$, NMP, 50 °C, 71%; (e) $CHC1_3$–CH_3CN, rt; (f) Pd/C, H_2, THF–H_2O, rt, 4–57% (for **9b**, TBAF and AcOH were added before deprotection of the 4-nitrobenzyl group).



Scheme 2. Synthesis of carbapenem derivatives (2). Reagents and conditions: (a) $CHCl_3$–CH_3CN, rt; (b) pyridine or 4-methylmorpholine, $CHC1_3$–CH_3CN, rt; (c) Pd/C, H_2, THF–H_2O, rt.



Scheme 3. Synthesis of carbapenem derivatives (3). Reagents and conditions: (a) **13a–i**, $CHCl_3$–CH_3CN, rt; (b) Pd/C, H_2, THF–H_2O, rt, 20–63% (from **10b**).

shown in Table 2. All compounds showed good water solubility. Considering the anti-MRSA activity of **12a–f**, we decided to focus on the synthesis of *m*-substituted derivatives. Among the dicationic derivatives, aliphatic ammonium salts (**12d–f, 15a**) showed reduced activity, but aromatic ammonium salts (**15b–e**) were as potent as **9a**. All tricationic derivatives (**15f–i**) showed excellent anti-MRSA activity. Compound **15i**, possessing a primary amine, exhibited the most potent anti-MRSA activity, superior to VCM.

In order to clarify the anti-MRSA activity of **15i**, we evaluated the anti bacterial activity of **15i** and VCM against 54 MRSA strains isolated in the clinic (Table 3). MIC_{50} and MIC_{90} of **15i** were 0.39 and 0.78 μg/mL, respectively, being superior to those of VCM.

Table 1
Antibacterial activities of **9a–h** and reference compounds (MIC[a]; μg/mL)

Test organism	*S. aureus* 209P JC-1	*S. aureus* M-126[a]	*S. aureus* M-126HR[b]
9a	<0.006	0.39	1.56
9b	<0.006	0.39	1.56
9c	<0.006	0.78	1.56
9d	<0.006	0.78	3.13
9e	<0.006	0.78	1.56
9f	<0.006	0.78	3.13
9g	0.013	1.56	6.25
9h	0.025	3.13	12.5
CP5068	<0.006	1.56	3.13
IPM	0.013	25	100
VCM	0.78	1.56	1.56

[a] MRSA.
[b] Carbapenem-resistant MRSA.

Table 2
Antibacterial activities of **12a–f** and **15a–i** (MIC; μg/mL)

Test organism	*S. aureus* 209P JC-1	*S. aureus* M-126[a]	*S. aureus* M-126HR[b]
12a	<0.006	1.56	3.13
12b	<0.006	0.78	1.56
12c	<0.006	0.78	1.56
12d	<0.006	1.56	3.13
12e	<0.006	0.78	3.13
12f	<0.006	1.56	3.13
15a	<0.006	0.78	3.13
15b	<0.006	0.39	1.56
15c	<0.006	0.78	3.13
15d	<0.006	0.78	1.56
15e	<0.006	0.78	1.56
15f	<0.006	0.78	1.56
15g	<0.006	0.78	1.56
15h	<0.006	0.78	1.56
15i	<0.006	0.39	0.78

[a] MRSA.
[b] Carbapenem-resistant MRSA.

Table 3
Anti-MRSA (n = 54) activities of **15i** and VCM

Compounds	MIC		
	50%	90%	Range
15i	0.39	0.78	<0.05–1.56
VCM	1.56	1.56	0.78–3.13

The water solubility of **15i** was over 20 mg/mL, which is acceptable for parenteral injection.

In order to improve the anti-MRSA activity of CP5068, we introduced a benzyl moiety as a hydrophobic side chain at the 6-position of imidazo[5,1-*b*]thiazole in place of the carbamoylmethyl moiety of CP5068. The anti-MRSA activity was increased, but the water solubility was decreased. To improve water solubility, we designed and synthesized di- and tricationic derivatives, and obtained novel carbapenems with excellent anti-MRSA activity and sufficient water solubility. Among them, **15i**[12] showed very strong anti-MRSA activity, superior to VCM, with sufficient water solubility for use as an injectable antimicrobial.

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