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Short communication

Synthesis and biological activity of 1β-methyl-2-[5-(2-*N*-substituted aminoethylcarbamoyl)pyrrolidin-3-ylthio]carbapenem derivatives

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Abstract

The synthesis of a new series of 1β-methylcarbapenems having the substituted aminoethylcarbamoylpyrrolidine moiety is described. Their in vitro antibacterial activities against both Gram-positive including MRSA and Gram-negative bacteria were tested and the effect of substituent on the pyrrolidine ring was investigated. In particular, the compound **11g** having piperazinyl urea moiety showed the most potent antibacterial activity and **11k** exhibited excellent anti-MRSA.

Keywords: 1β-Methylcarbapenem; Antibacterial activity; Substituent effect

1. Introduction

A number of carbapenem antibiotics, for example imipenem, panipenem and meropenem, are currently in clinical use due to their broad antibacterial spectra and potent bactericidal effects [1]. However, a number of problems still remain with these agents, in particular, activity against resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and the Gram-negative pathogen *Pseudomonas aeruginosa*, is relatively weak. During the past decade, extensive synthetic efforts have been made to confer anti-MRSA activity on β-lactams such as a cephalosporin [2] or a carbapenem [3]. As a result, some cephalosporin and carbapenem derivatives with potent in vitro anti-MRSA activity were identified by introducing hydrophobic functional groups into the C-3 or C-7 side chain of the cephalosporin nucleus or the C-2 side chain of the carbapenem nucleus.

From the literature of carbapenem antibiotics, especially the SAR related to meropenem [4,5] and panipenem [6], the importance of a pyrrolidine ring for potent activity and high PBP affinity were noted. Thus we postulated that a combination of these two factors in a single side chain might lead to agents with a broader spectrum of activity and anti-MRSA activity.

Previously, we reported that the carbapenem compounds which have a pyrrolidine-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity, and a large number of derivatives have been synthesised and investigated [7–13].

In this paper, we described the synthesis and structure–activity relationships of the 1β-methylcarbapenems having a 5′-substituted aminoethylcarbamoyl pyrrolidine-3′-ylthio group as a C-2 side chain and our approach for improvement of anti-MRSA and antibacterial activity of the carbapenems is discussed.

2. Results and discussion

2.1. Chemistry

Our general synthetic route leading to new carbapenems involved the preparation of appropriately protected thiols containing pyrrolidine ring as a side chain and subsequent coupling reaction with the carbapenem diphenylphosphates, followed by deprotection of the resulting protected carbapenems in a usual manner. 2-

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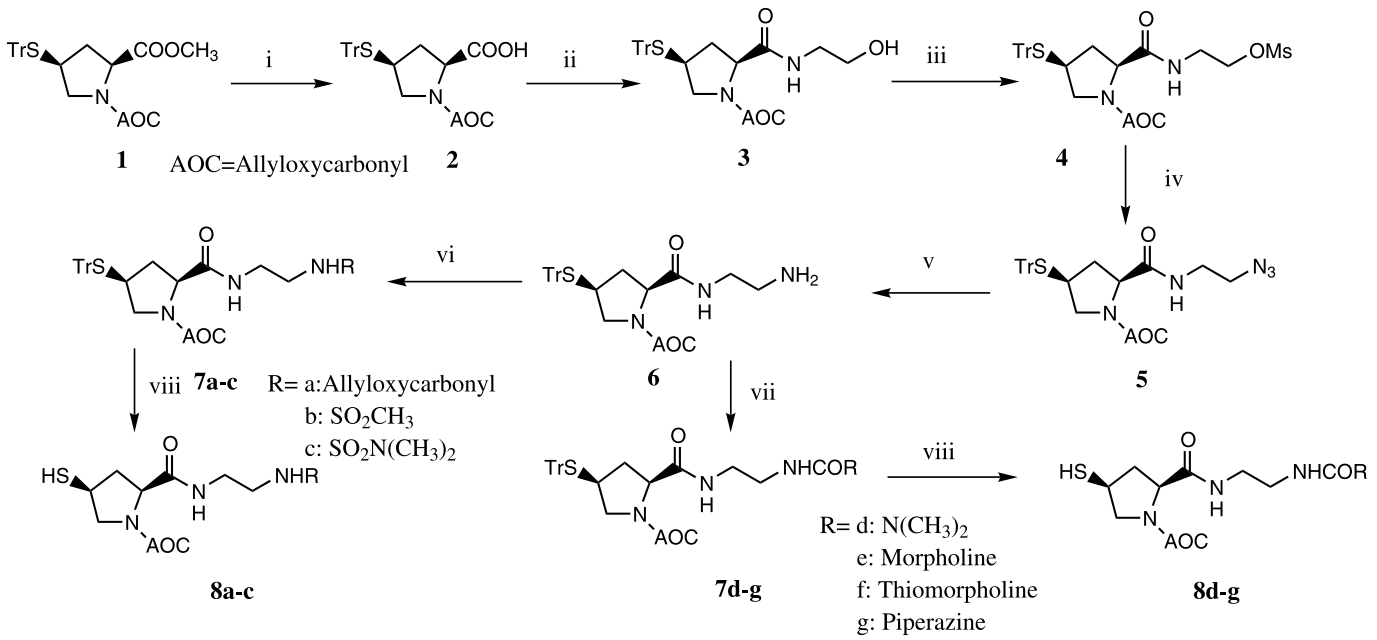
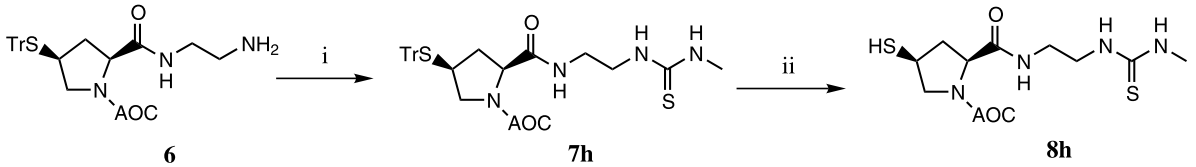


i) 4*N*-NaOH, MeOH, ii) 1) Ethyl chloroformate, TEA, CH_2Cl_2, 2) Ethanolamine, EtOH, iii) MsCl, TEA, CH_2Cl_2, iv) NaN_3, DMSO, v) PPh_3, H_2O, THF, vi) Corresponding chloride, TEA, CH_2Cl_2, vii) 1) *p*-Nitrophenyl chloroformate, TEA, CH_2Cl_2, 2) R_2NH, EtOH, viii) Trifluoroacetic acid, triethyl silane, CH_2Cl_2

Scheme 1. (i) 4 N NaOH–MeOH; (ii) (1) ethyl chloroformate, TEA, CH_2Cl_2, (2) ethanolamine, EtOH; (iii) MsCl, TEA, CH_2Cl_2; (iv) NaN_3, DMSO; (v) PPh_3, H_2O, THF; (vi) corresponding chloride, TEA, CH_2Cl_2; (vii) (1) *p*-Nitrophenyl chloroformate, TEA, CH_2Cl_2, (2) R_2NH, EtOH; (viii) trifluoroacetic acid, triethyl silane, CH_2Cl_2.

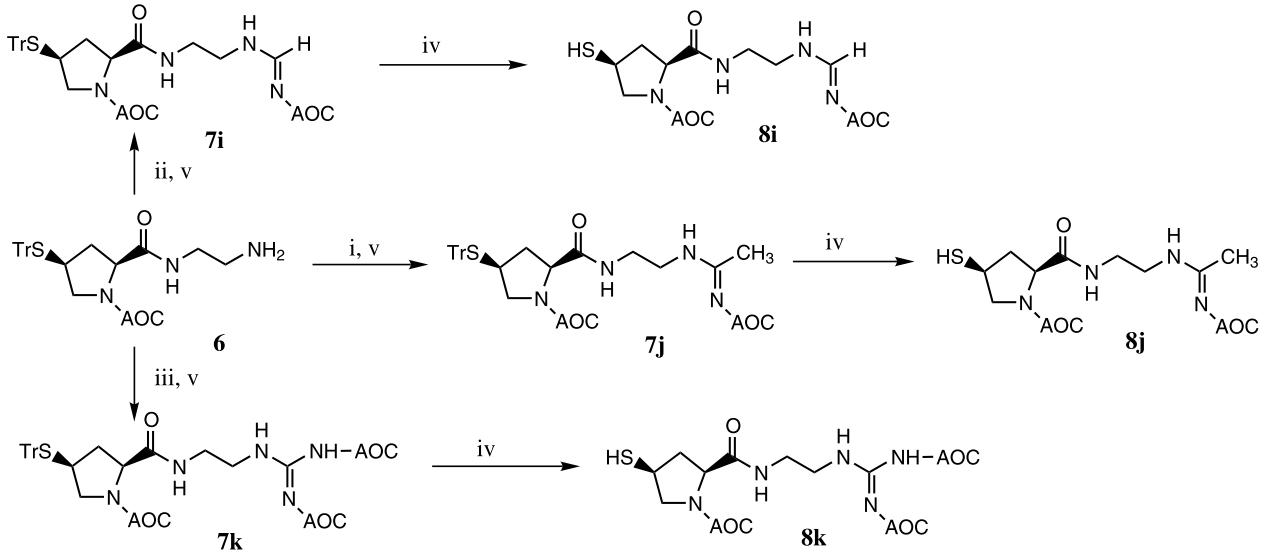
(*N*-substituted aminoethylcarbamoyl)-Pyrrolidine derivatives (**8a**–**m**) were prepared by the sequence shown in Schemes 1–4. N-Protected proline methyl ester [13] was converted to the carboxylic acid **2** by treatment of 4 N NaOH and subsequently treated with ethyl chloroformate and ethanolamine to provide **3**. Compound **3** was reacted with mesylchloride and subsequently treatment with sodium azide in DMSO gave the azide compound **5**, which was successfully converted into amine **6** using triphenylphosphine. Treatment of **6** with allyl chloroformate, mesyl chloride and dimethylsulfamoyl chloride afforded the corresponding *N*-acylated products, **7a**, **7b** and **7c**. Carbamoylation of amine was carried out by a conventional method using *p*-nitrophenyl chloroformate to give urea type compounds **7d**–**g** (Scheme 1). Preparation of the thiourea type compound (**7h**) was accomplished by treatment of compound **6** with methylisothiocyanate reagent (Scheme 2). The imine derivatives (**7i**–**k**) were prepared by reaction of **6** with ethyl formidiate, ethyl acetimidate and 1*H*-pyrazole-1-carboxamidine hydrochloride (Scheme 3). Compounds **7l**–**m** were obtained by reaction of mesylate **4** with thiomorpholine and piperazine (Scheme 4). Deprotection of the trityl group to mercaptans (**8a**–**m**) were achieved by treatment of **7a**–**m** with trifluoroacetic acid in the presence of triethylsilane.

Finally, the reaction of **9** [9] with thiols (**8a**–**m**) in the presence of diisopropylethylamine provided the corresponding 2-substituted carbapenems (**10a**–**m**), respectively. Derivatives **10l** and **10m** containing cyclic amine substituents were converted to quaternary salts by methyl iodide and deprotected to give **11lQ** and **11mQ**. Deprotection of these compounds by catalytic hydrogenation gave the crude products, which were purified by HP-20 column to give the pure carbapenems (**11a**–**mQ**) (Scheme 5).



i) Methyl isothiocyanate, TEA, CH_2Cl_2, ii) Trifluoroacetic acid, triethyl silane, CH_2Cl_2

Scheme 2. (i) Methyl isothiocyanate, TEA, CH_2Cl_2; (ii) trifluoroacetic acid, triethyl silane, CH_2Cl_2.



i) Ethyl acetimidate.HCl, EtOH, ii) Ethyl formidiate.HCl, EtOH, iii) 1H-pyrazole-1-carboxamidine .HCl, EtOH
iv) Trifluoroacetic acid, triethyl silane, CH_2Cl_2, v) Allyl chloroformate, TEA, CH_2Cl_2

Scheme 3. (i) Ethyl acetimidate·HCl, EtOH; (ii) ethyl formidiate·HCl, EtOH; (iii) 1*H*-pyrazole-1-carboxamidine·HCl, EtOH; (iv) trifluoroacetic acid, triethyl silane, CH_2Cl_2; (v) allyl chloroformate, TEA, CH_2Cl_2.

2.2. Biological assay

2.2.1. Measurement of in vitro antibacterial activity

The MICs were determined by the agar dilution method using test agar. An overnight culture of bacteria in tryptosoy broth was diluted to about 10^6 cells per mL with the same broth and inoculated with an inoculating device onto agar containing serial twofold dilutions of the test compounds. Organisms were incubated at 37 °C for 18–20 h. The MICs of a compound were defined as the lowest concentration that visibly inhibited growth.

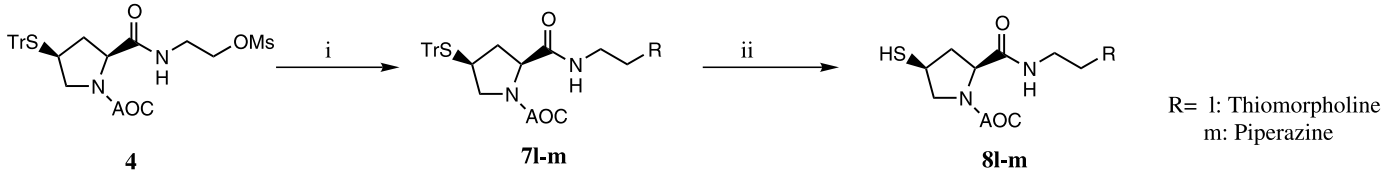
2.2.2. Determination of susceptibility to renal dehydropeptidase-I (DHP-I)

The relative hydrolysis rate of carbapenems by porcine renal DHP-I was determined, taking the initial hydrolysis rate of imipenem as 1.0. Partially purified porcine DHP-I (final concentration, 0.3 U mL^{-1}) was incubated with 50 μM carbapenem at 35 °C in 50 mM MOPS buffer, pH 7.0. The initial hydrolysis rate was monitored by the spectrophotometric method. One unit of activity was defined as the amount of enzyme hydrolysing 1 μM of glycyldehydrophenylalanine per min when the substrate, 50 μM, was incubated at 35 °C in 50 mM MOPS buffer, pH 7.0.

2.2.3. Antibacterial activity studies

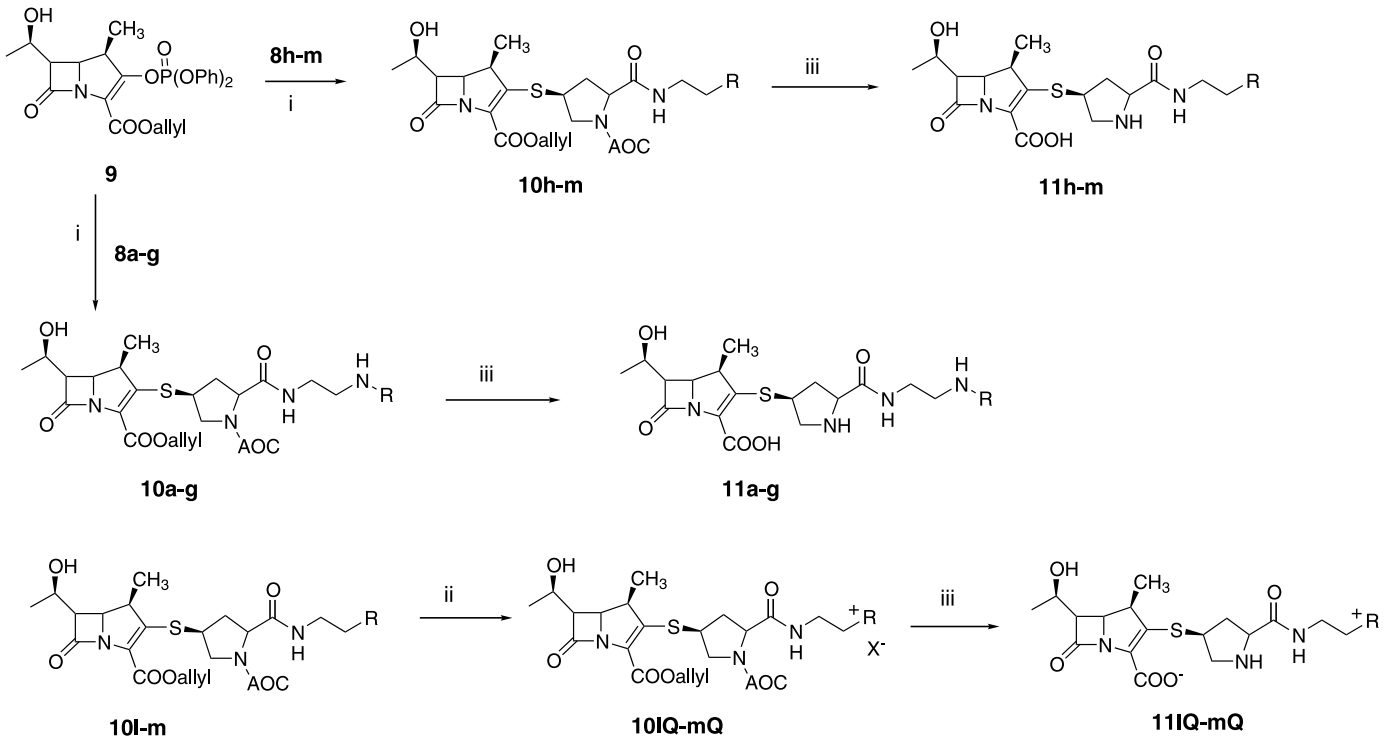
The in vitro antibacterial activities of the new carbapenems (**11a**–**mQ**) prepared above against Gram-positive and negative bacteria including strains of MRSA are listed in Tables 1 and 2. For comparison, the MIC values of imipenem, meropenem and vancomycin are also listed. Among these compounds, **11c**, **11g**, **11k** and **11i** showed superior or similar antibacterial activity against Gram-positive bacteria to Meropenem, and exhibited improved antibacterial activity against Gram-negative bacteria than Imipenem.

As to the substituent of the aminoethylcarbamoyl side chain, the compounds **11f** and **11g** having cyclic urea moieties were generally more potent than the non urea compounds **11l** and **11m**. Comparing the compounds **11e**–**g** having cyclic urea moieties showed slight differences in the antibacterial activities against Gram-positive and negative bacteria. As expected, the piperazine



i) Thiomorpholine or piperazine, CH_3CN, ii) Trifluoroacetic acid, triethyl silane, CH_2Cl_2

Scheme 4. (i) Thiomorpholine or piperazine, CH_3CN; (ii) trifluoroacetic acid, triethyl silane, CH_2Cl_2.



Scheme 5. (i) Diisopropylethyl amine, **8a**–**m**, CH_3CN; (ii) methyl iodide, acetone; (iii) $Pd(OH)_2$–C, H_2.

urea compound **11g** exhibited the most potent and well-balanced activity. Furthermore, we observed that the thiomorpholine urea **11f** is more potent than the morpholine urea **11e**. Introduction of sulphamoyl group (**11c**) led to significantly enhanced antibacterial activity against Gram-negative bacteria compared with carbamoyl group (**11d**). The quaternised compounds (**11lQ**, **11mQ**) showed more improved activity against *P. aeruginosa* than the unquaternised compounds (**11l**, **11m**).

The anti-MRSA activity was the best when the substituent is guanidine moiety (**11k**), whereas it possessed low activity against Gram-negative bacteria.

The stability to DHP-I of most compounds was tested and all the compounds were more stable than Meropenem. In particular, the quaternised compounds **11lQ** and **11mQ** exhibited the most stability.

3. Experimental part

Melting point (m.p.): Thomas Hoover apparatus, uncorrected. UV spectra: Hewlett-Packard 8451A UV–vis spectrophotometer. IR spectra: Perkin–Elmer 16F-PC FTIR. NMR spectra: Varian Gemini 300 spectrometer, tetramethylsilane (TMS), as an internal standard. The HRMS spectra were obtained with JEOL Model JMS-700 High Resolution Mass Spectrometer.

*3.1. (2S,4S)-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine-2-carboxylic acid (**2**)*

To a solution of **1** (48.7 g, 0.10 mol) in MeOH (500 mL) was added slowly 4 N NaOH (38 mL, 0.15 mol) at 0 °C and was stirred for 5 h at room temperature (r.t.). The mixture was neutralised with 4 N HCl (38 mL) and concentrated, and the resulting residue was diluted with water (300 mL) and ethyl acetate (200 mL). The resulting precipitates were filtered and the solid was washed with water, and dried in air to give **2** (39.4 g, 83.2%) as a white solid. M.p. 202–203 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ 1.98 (m, 1H), 2.75–2.82 (m, 1H), 3.01 (m, 1H), 3.55 (bs, 2H), 3.98 (m, 1H), 4.55 (d, 2H, $J = 5.9$ Hz), 5.25 (m, 2H), 5.90 (m, 1H), 7.27 (m, 9H), 7.47 (m, 6H), 12.7 (bs, 1H). ^{13}C-NMR ($CDCl_3$): 36.7, 41.2, 53.3, 58.8, 65.7, 67.6, 118.2, 127.3, 128.5, 129.9, 132.7, 144.9, 153.8, 174.4. IR (KBr): 3440, 3060, 1745, 1670 cm^{-1}.

*3.2. (2S,4S)-2-(2-hydroxyethylcarbamoyl)-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (**3**)*

A solution of **2** (23.7 g, 0.05 mol) and triethylamine (7.4 mL, 0.055 mol) in dry CH_2Cl_2 (300 mL) was cooled

Table 1
In vitro antibacterial activity (MIC, μg mL^{-1}) and DHP-I stability of the carbapenem derivatives

	Strains	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	11m	11lQ	11mQ	IMP [a]	MPM [b]
1	*Streptococcus pyogenes* 308A	0.05	0.01	0.03	0.01	0.03	0.03	0.01	0.05	0.10	0.10	0.01	0.03	0.01	0.01	0.01	<0.01	0.01
2	*S. pyogenes* 77A	0.10	0.01	0.05	0.01	0.03	0.05	0.03	0.10	0.20	0.10	0.03	0.05	0.03	0.03	0.03	<0.01	<0.01
3	*S. aureus* SG511	0.10	0.40	0.10	0.20	0.10	0.10	0.10	0.10	0.10	0.10	0.03	0.10	0.05	0.10	0.05	0.01	0.10
4	*S. aureus* 285	0.20	0.40	0.20	0.40	0.10	0.20	0.20	0.20	0.20	0.10	0.01	0.20	0.20	0.20	0.05	0.01	0.10
5	*Escherichia coli* DC2	0.05	0.05	0.01	0.03	0.05	0.03	0.03	0.03	0.01	0.10	0.03	0.03	0.05	0.10	0.10	0.40	0.03
6	*E. coli* TEM	0.03	0.05	0.01	0.03	0.05	0.03	0.03	0.01	0.01	0.10	0.03	0.05	0.05	0.05	0.05	0.20	0.03
7	*Pseudomonas aeruginosa* 9027	12.5	3.10	1.56	3.10	3.10	3.10	0.80	0.80	0.80	0.80	0.40	6.20	0.80	1.56	0.40	0.80	0.20
8	*Salmonella typhimurium*	0.05	0.10	0.03	0.10	0.10	0.05	0.05	0.05	0.05	0.20	0.10	0.10	0.10	0.10	0.20	0.80	0.03
9	*Klebsiella aerogenes* 1522E	0.05	0.10	0.03	0.05	0.10	0.05	0.05	0.05	0.05	0.20	0.10	0.10	0.10	0.10	0.10	0.10	0.05
10	*Enterobactor cloacae* 1321E	0.03	0.05	0.01	0.03	0.03	0.01	0.03	0.03	0.01	0.10	0.03	0.03	0.03	0.05	0.10	0.10	0.03
	DHP-I	1.44	1.56	1.12	1.24	1.26	1.25	1.25	1.57	1.08	0.94	0.99	1.12	1.27	1.42	1.65	0.18	1.00

[a] IMP, imipenem.
[b] MPM, meropenem.

Table 2
Anti-MRSA activities of **11g**, **11i** and **11k**

Methicillin resistant strains	11g	11i	11k	Vancomycin
S. aureus LG001	1.563	1.563	0.391	1.563
S. aureus LG002	0.391	0.195	0.098	0.781
S. aureus Y8012954	0.195	0.195	0.049	0.781
S. aureus QRS179	0.391	0.391	0.195	0.781
S. aureus QRS241	0.391	0.391	0.195	0.781
S. aureus Hoechst208E	0.195	0.195	0.098	0.781
S. aureus KIST2	6.25	6.25	1.56	0.781
S. aureus KIST5	0.781	0.781	0.195	0.781

to 0 °C under nitrogen and treated with ethyl chloroformate (5.25 mL, 0.055 mol). The mixture was stirred at 0 °C for 30 min, added with ethanolamine (3.3 mL, 0.055 mol) and stirred at 0 °C for 1 h. The mixture was washed with 10% $NaHCO_3$ and brine, and was dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography to give **3** (23.1 g, 89.5%) as a pale yellow oil. R_f 0.3 (ethyl acetate:*n*-Hex, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.95 (bs, 1H), 2.20 (bs, 1H), 2.75–2.86 (bs, 1H), 2.96 (bs, 1H), 3.55 (t, 2H, $J = 5.6$ Hz), 4.01 (m, 1H), 4.11 (t, 2H, $J = 5.6$ Hz), 4.50–4.62 (bs, 3H), 5.28 (m, 2H), 5.87 (m, 1H), 7.27 (m, 9H), 7.48 (m, 6H). ^{13}C-NMR ($CDCl_3$): 36.7, 41.9, 42.7, 53.3, 60.6, 61.8, 66.7, 67.9, 118.2, 127.3, 128.5, 129.9, 132.7, 144.9, 156.8, 172.4. IR (KBr): 3330, 2940, 1710, 1670 cm^{-1}.

3.3. (2S,4S)-2-(2-mesyloxyethylcarbamoyl)-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (4)

A solution of **3** (20.6 g, 0.04 mol) and triethylamine (5.9 mL, 0.044 mol) in dry CH_2Cl_2 (200 mL) was cooled to 0 °C under nitrogen and treated with methanesulfonyl chloride (5.01 g, 0.044 mol). The mixture was stirred at 0 °C for 1 h, diluted with CH_2Cl_2 (200 mL), and washed with 10% $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography to give **4** (21.8 g, 91.7%) as a pale yellow oil. R_f 0.4 (ethyl acetate:*n*-Hex, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.99 (bs, 1H), 2.21 (bs, 1H), 2.75–2.82 (bs, 1H), 2.96–3.08 (bs, 4H), 3.55 (t, 2H, $J = 5.6$ Hz), 4.01 (m, 1H), 4.25 (t, 2H, $J = 5.6$ Hz), 4.50–4.59 (bs, 3H), 5.28 (m, 2H), 5.88 (m, 1H), 7.27 (m, 9H), 7.48 (m, 6H). ^{13}C-NMR ($CDCl_3$): 30.7, 36.7, 39.7, 41.9, 52.5, 60.8, 61.6, 66.8, 67.8, 118.0, 127.3, 128.5, 129.9, 132.7, 144.9, 156.0, 171.8. IR (KBr): 3430, 2920, 1740, 1700, 1440 cm^{-1}.

3.4. (2S,4S)-2-(2-azidoethylcarbamoyl)-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (5)

A mixture of **4** (31.5 g, 0.053 mol) and sodium azide (13.8 g, 0.21 mol) in DMSO (300 mL) was heated at

70 °C for 5 h. The reaction mixture was poured into ice water and extracted with ethyl acetate (300 mL × 2). The organic layer was successively washed with water (200 mL × 2), brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography to give **5** (24.5 g, 85.4%) as a pale yellow oil. R_f 0.6 (ethyl acetate:*n*-Hex, 1:1). ^{1}H-NMR ($CDCl_3$) δ 2.13 (m, 1H), 2.82 (m, 1H), 2.95–3.08 (m, 1H), 3.39–3.48 (m, 5H), 4.05 (bs, 1H), 4.14 (m, 1H), 4.55 (m, 2H), 5.29 (m, 2H), 5.88 (m, 1H), 7.27 (m, 9H), 7.46 (m, 6H). ^{13}C-NMR ($CDCl_3$): 35.7, 39.3, 41.9, 51.1, 53.5, 60.4, 66.8, 67.9, 118.2, 127.3, 128.5, 129.9, 132.7, 144.9, 155.6, 171.7. IR (KBr): 3320, 2100, 1720, 1670 cm^{-1}.

3.5. (2S,4S)-2-(2-aminoethylcarbamoyl)-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (**6**)

A mixture of **5** (1.29 g, 2.4 mmol), triphenylphosphine (0.70 g, 2.6 mmol) and H_2O (0.44 mL, 24.0 mmol) in THF (10 mL) was heated at 40 °C for 4 h. After cooling, the reaction mixture was diluted with H_2O (20 mL) and ethyl acetate (30 mL). The organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography to give **6** (1.07 g, 86.4%) as a pale yellow oil. R_f 0.2 (ethyl acetate:MeOH, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.88 (m, 1H), 2.19 (m, 1H), 2.82–2.94 (bs, 2H), 2.95–3.08 (bs, 1H), 3.30–3.48 (bs, 4H), 4.02 (bs, 1H), 4.55 (bs, 2H), 5.22 (m, 2H), 5.84 (m, 1H), 7.27 (m, 9H), 7.46 (m, 6H). ^{13}C-NMR ($CDCl_3$): 37.2, 40.6, 41.7, 53.2, 53.8, 60.1, 66.6, 67.7, 117.7, 127.3, 128.5, 129.9, 132.7, 144.9, 155.7, 172.9. IR (KBr): 3430, 3060, 1720, 1670 cm^{-1}.

3.6. (2S,4S)-2-(2-allyloxycarbonylaminoethylcarbamoyl)-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (**7a**)

To a solution of **6** (1.3 g, 2.5 mmol) and triethylamine (0.37 mL, 2.75 mmol) in dry CH_2Cl_2 (20 mL) was added slowly allyl chloroformate (0.34 g, 2.75 mmol) at 0 °C and was stirred for 1 h at same temperature. The mixture was diluted with H_2O (100 mL), CH_2Cl_2 (100 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by silica gel column chromatography to give **7a** (1.30 g, 87.1%) as a pale yellow oil. R_f 0.7 (ethyl acetate:*n*-Hex, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.85 (bs, 1H), 2.22 (m, 1H), 2.63–2.80 (bs, 1H), 3.28–3.55 (bs, 5H), 3.59 (bs, 1H), 4.04 (m, 1H), 4.50–4.62 (bs, 4H), 5.20–5.44 (m, 4H), 5.80–5.98 (m, 2H), 6.24 (bs, 1H), 7.23 (m, 9H), 7.47 (m, 6H).

Compounds **7b** and **7c** were also prepared as described for the preparation of **7a** using the corresponding sulfonyl chlorides.

3.6.1. Compound *7b*

Yield 82.5%. R_f 0.6 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.91 (bs, 1H), 2.13 (m, 1H), 2.83–3.12 (bs, 6H), 3.25–3.48 (bs, 4H), 3.93 (m, 1H), 4.55 (bs, 2H), 5.25 (m, 2H), 5.88 (m, 1H), 6.44 (bs, 1H), 7.23 (m, 9H), 7.47 (m, 6H).

3.6.2. Compound *7c*

Yield 81.8%. R_f 0.7 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.94 (bs, 1H), 2.22 (m, 1H), 2.78 (s, 6H), 2.90–3.22 (bs, 2H), 3.20–3.32 (bs, 3H), 3.36–3.51 (bs, 2H), 3.93 (m, 1H), 4.55 (bs, 2H), 5.25 (m, 2H), 5.88 (m, 1H), 6.74 (bs, 1H), 7.23 (m, 9H), 7.47 (m, 6H).

3.7. (2S,4S)-2-[2-(3,3-dimethylureido)ethylcarbamoyl]-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (*7d*)

To a solution of **6** (1.03 g, 2.0 mmol) and triethylamine (0.30 mL, 2.2 mmol) in dry CH_2Cl_2 (30 mL) was added slowly *p*-nitrophenyl chloroformate (0.44 g, 2.2 mmol) at 0 °C and was stirred for 1 h at same temperature. The mixture was diluted with H_2O (30 mL), CH_2Cl_2 (50 mL) and washed with brine. The organic layer was concentrated in vacuo to give a residue, which was used without further purification. To the solution of residue in ethanol (20 mL) was added *N*,*N*-dimethylamine (2 mL) and stirred for 1 h at r.t. The reaction mixture was neutralised with 6 N HCl, diluted with ethyl acetate (100 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, which was purified by silica gel column chromatography to give **7d** (0.99 g, 81.6%) as a pale yellow oil. R_f 0.8 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.92 (bs, 1H), 2.19 (m, 1H), 2.83–2.89 (bs, 1H), 2.96 (2s, 6H), 3.04 (bs, 1H), 3.29–3.56 (bs, 5H), 4.01 (m, 1H), 4.55 (bs, 2H), 5.26 (bs, 2H), 5.85 (m, 1H), 6.86 (bs, 1H), 7.24 (m, 9H), 7.45 (m, 6H).

The compounds **7e**–**g** were also prepared as described for the preparation of **7d** using the corresponding amines.

3.7.1. Compound *7e*

Yield 76.2%. R_f 0.3 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.90 (bs, 1H), 2.22 (m, 1H), 2.73–2.80 (m, 1H), 2.93–3.03 (bs, 2H), 3.21–3.52 (bs, 8H), 3.65 (bs, 4H), 3.96 (m, 1H), 4.49 (bs, 2H), 5.26 (m, 2H), 5.88 (m, 1H), 6.84 (bs, 1H), 7.27 (m, 9H), 7.47 (m, 6H).

3.7.2. Compound *7f*

Yield 75.1%. R_f 0.2 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.92 (bs, 1H), 2.20 (m, 1H), 2.52 (bs, 4H), 2.73–2.82 (m, 1H), 2.95–3.05 (bs, 2H), 3.29–3.50 (bs, 4H), 3.62

(bs, 4H), 3.95 (m, 1H), 4.49 (bs, 2H), 5.26 (m, 2H), 5.67 (bs, 1H), 5.88 (m, 1H), 6.80 (bs, 1H), 7.27 (m, 9H), 7.47 (m, 6H).

*3.7.3. Compound **7g***

Yield 74.9%. R_f 0.5 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.92 (bs, 1H), 2.23 (m, 1H), 2.73–2.82 (bs, 1H), 2.93–3.05 (bs, 2H), 3.21–3.65 (bs, 12H), 3.96 (m, 1H), 4.49 (bs, 2H), 5.26 (m, 2H), 5.70 (bs, 1H), 5.84 (m, 1H), 6.77 (bs, 1H), 7.27 (m, 9H), 7.47 (m, 6H).

*3.8. (2S,4S)-2-[2-(3-methylthioureido)ethylcarbamoyl]-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (**7h**)*

A mixture of **6** (0.80 g, 1.60 mmol), triethylamine (0.43 mL, 3.20 mmol), methyl isothiocyanate (0.23 mL, 3.20 mmol) in CH_2Cl_2 (20 mL) was stirred at r.t. for 5 h. The reaction mixture was diluted with H_2O (20 mL) and CH_2Cl_2 (30 mL). The organic layer was successively washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography to give **7h** (0.81 g, 88.1%) as a pale yellow oil. R_f 0.6 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.92 (bs, 1H), 2.15 (m, 1H), 2.71–3.06 (5H), 3.16–3.30 (bs, 3H), 3.74 (bs, 2H), 3.97 (m, 1H), 4.42 (m, 1H), 5.26 (m, 2H), 5.98 (m, 1H), 6.79 (bs, 1H), 7.23 (m, 9H), 7.48 (m, 6H).

*3.9. (2S,4S)-2-[(2-allyloxycarbonylformimidoyl)aminoethylcarbamoyl]-4-tritylthio-1-(allyloxy-carbonyl)Pyrrolidine (**7i**)*

To a solution of **6** (1.03 g, 2.0 mmol) in EtOH was added dropwise ethyl formidiate hydrochloride (0.24 g, 2.2 mmol) and was heated at reflux for 3 h. Evaporation of the solvent in vacuo gave a crude residue, which was used without further purification. To the above solution and triethylamine (0.30 mL, 2.2 mmol) in dry CH_2Cl_2 (20 mL) was added slowly allyl chloroformate (0.27 g, 2.2 mmol) at 0 °C and was stirred for 1 h at same temperature. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with 10% $NaHCO_3$, brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by silica gel column chromatography to give **7i** (1.00 g, 79.8%) as a pale yellow oil. R_f 0.7 (ethyl acetate:*n*-Hex, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.82 (bs, 1H), 2.19 (m, 1H), 2.80–2.92 (bs, 1H), 3.02–3.17 (bs, 1H), 3.33–3.56 (bs, 3H), 3.78 (bs, 2H), 3.96 (m, 1H), 4.55 (bs, 2H), 4.72 (d, 2H, $J = 5.9$ Hz), 5.20–5.44 (m, 4H), 5.85–5.98 (m, 2H), 7.23 (m, 9H), 7.47 (m, 6H), 8.92 (s, 1H).

Compound **7j** was also prepared as described for the preparation of **7i** using the ethyl acetimidate hydrochloride.

*3.9.1. Compound **7j***

Yield 70.2%. R_f 0.5 (ethyl acetate:*n*-Hex, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.85 (bs, 1H), 2.19 (m, 1H), 2.24 (s, 3H), 2.80–2.92 (bs, 1H), 3.02–3.17 (bs, 2H), 3.30–3.56 (bs, 4H), 3.96 (m, 1H), 4.45 (bs, 2H), 4.70 (d, 2H, $J = 5.9$ Hz), 5.20–5.44 (m, 4H), 5.85–6.04 (m, 2H), 6.66 (bs, 1H), 7.23 (m, 9H), 7.47 (m, 6H).

Compound **7k** was also prepared as described for the preparation of **7i** using the 1*H*-pyrazole-1-carboxamidine hydrochloride.

*3.9.2. Compound **7k***

Yield 75.1%. R_f 0.7 (ethyl acetate:*n*-Hex, 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.89 (bs, 1H), 2.19 (m, 1H), 2.80–2.92 (bs, 1H), 2.95–3.07 (bs, 2H), 3.30–3.59 (bs, 4H), 3.96 (m, 1H), 4.25–4.58 (bs, 4H), 4.72 (d, 2H, $J = 5.9$ Hz), 5.20–5.57 (m, 6H), 5.75–5.98 (m, 3H), 7.23 (m, 9H), 7.47 (m, 6H), 8.92 (bs, 1H), 8.96 (bs, 1H).

*3.10. (2S,4S)-2-[2-(thiomorpholin-4-yl)ethylcarbamoyl]-4-tritylthio-1-(allyloxycarbonyl)Pyrrolidine (**7l**)*

A mixture of **4** (1.2 g, 2.0 mmol) and thiomorpholine (0.41 g, 4.0 mmol) in CH_3CN (20 mL) was stirred at r.t. for 20 h. The mixture was diluted with 1 N HCl (30 mL), ethyl acetate (50 mL) and washed with brine. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography to give **7l** (1.03 g, 85.9%) as a pale yellow oil. R_f 0.2 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.88 (m, 1H), 2.19 (m, 1H), 2.52 (bs, 1H), 2.55–2.98 (bs, 7H), 3.08 (bs, 2H), 3.25–3.44 (bs, 4H), 3.95 (m, 1H), 4.15 (m, 1H), 4.45 (m, 2H), 5.29 (m, 2H), 5.88 (m, 1H), 6.74 (bs, 1H), 7.27 (m, 9H), 7.47 (m, 6H).

Compound **7m** was also prepared as described for the preparation of **7l** using the piperazine.

*3.10.1. Compound **7m***

Yield 72.4%. R_f 0.2 (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 1.87 (bs, 1H), 2.18 (m, 1H), 2.37–2.55 (bs, 6H), 2.77–2.89 (bs, 1H), 2.94–3.01 (bs, 2H), 3.22 (bs, 2H), 3.55 (bs, 4H), 4.01 (bs, 1H), 4.43 (bs, 2H), 5.04, 5.26 (m, 2H), 5.85 (m, 1H), 6.68 (bs, 1H), 7.24 (m, 9H), 7.45 (m, 6H).

*3.11. Allyl(1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[5-(2-allyloxycarbonylaminoethylcarbamoyl)]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (**10a**)*

To a solution of **7a** (0.60 g, 1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise triethylsilane (0.13 g, 1.1 mmol) at 5 °C, and then TFA (2 mL). After stirring for 30 min at r.t., the mixture was evaporated under reduced pressure. The residue was dissolved with ethyl acetate and washed with 10% $NaHCO_3$, brine. The

organic layer was concentrated in vacuo to give a residue (**8a**), which was used without further purification. A solution of allyl (1*R*,5*S*,6*S*)-2-(diphenylphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**9**, 0.50 g, 1.0 mmol) in CH_3CN (10 mL) was cooled to 0 °C under N_2. To this solution was added diisopropylethylamine (0.13 g, 1.0 mmol) and a solution of the mercapto compound **8a** in CH_3CN (5 mL). After stirring for 2 h, the mixture was diluted with ethyl acetate, washed with 10% $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. Evaporation in vacuo gave a foam, which was purified by silica gel chromatography to give **10a** (0.45 g, 71.1%) as a yellow amorphous solid. R_f 0.3 (ethyl acetate:acetone, 4:1). ^{1}H-NMR ($CDCl_3$) δ 1.25 (d, 3H, $J = 7.1$ Hz), 1.36 (d, 3H, $J = 6.4$ Hz), 2.21 (bs, 1H), 2.46 (bs, 1H), 2.95 (dd, 1H, $J = 3.3$ and 3.3 Hz), 3.06–3.55 (bs, 7H), 3.90 (bs, 2H), 4.15 (bs, 1H), 4.19 (bs, 1H), 4.45–4.69 (bs, 6H), 5.26–5.55 (m, 6H), 5.75–6.01 (bs, 3H).

The synthesis of compounds **10b**–**m** were carried out by the same procedure as described for the preparation of **10a**.

*3.11.1. Compound **10b***

Yield 63.9%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 7.1$ Hz), 1.37 (d, 3H, $J = 6.2$ Hz), 1.91 (m, 1H), 2.39 (bs, 1H), 2.86 (m, 1H), 2.99 (s, 3H), 3.21–3.42 (bs, 4H), 3.54 (m, 2H), 3.82 (bs, 1H), 3.99 (bs, 1H), 4.18 (m, 2H), 4.42 (m, 1H) 4.49–4.68 (bs, 4H), 5.25–5.53 (m, 4H), 5.75–6.01 (bs, 2H).

*3.11.2. Compound **10c***

Yield 64.3%. ^{1}H-NMR($CDCl_3$) δ 1.25 (d, 3H, $J = 7.1$ Hz), 1.35 (d, 3H, $J = 6.2$ Hz), 2.06 (m, 1H), 2.39 (bs, 1H), 2.80 (m, 1H), 2.89 (s, 6H), 3.21–3.33 (bs, 2H), 3.38–3.54 (bs, 3H), 3.58 (m, 1H), 3.82 (bs, 1H), 3.99 (bs, 1H), 4.18 (m, 2H), 4.40 (m, 1H), 4.49–4.68 (bs, 4H), 5.25–5.53 (m, 4H), 5.70–5.99 (bs, 2H).

*3.11.3. Compound **10d***

Yield 72.5%. ^{1}H-NMR($CDCl_3$) δ 1.28 (d, 3H, $J = 7.0$ Hz), 1.37 (d, 3H, $J = 6.1$ Hz), 1.98 (m, 1H), 2.30 (bs, 1H), 2.86 (m, 1H), 2.87 (s, 6H), 3.21–3.36 (bs, 2H), 3.40–3.55 (m, 3H), 3.60 (m, 1H), 3.82 (bs, 1H), 3.99 (bs, 1H), 4.18 (m, 2H), 4.42 (m, 1H), 4.49–4.68 (bs, 4H), 5.25–5.53 (m, 4H), 5.70–5.96 (bs, 2H).

*3.11.4. Compound **10e***

Yield 69.9%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 7.0$ Hz), 1.38 (d, 3H, $J = 6.0$ Hz), 1.91 (m, 1H), 2.39 (bs, 1H), 3.21–3.52 (bs, 9H), 3.54–3.62 (bs, 6H), 3.82 (bs, 1H), 4.03 (bs, 1H), 4.18 (m, 2H), 4.42 (m, 1H), 4.49–4.68 (bs, 4H), 5.25–5.53 (m, 4H), 5.75–5.97 (bs, 2H).

*3.11.5. Compound **10f***

Yield 65.9%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 7.0$ Hz), 1.38 (d, 3H, $J = 6.0$ Hz), 2.46 (m, 1H), 2.51 (bs, 4H), 2.79–2.85 (m, 1H), 3.03–3.16 (bs, 4H), 3.28–3.44 (bs, 3H), 3.54–3.65 (bs, 4H), 3.69 (m, 1H), 3.85 (bs, 1H), 3.99 (bs, 1H), 4.16 (bs, 1H), 4.45 (m, 1H), 4.45–4.67 (bs, 4H), 5.29–5.53 (m, 4H), 5.75–6.01 (bs, 2H).

*3.11.6. Compound **10g***

Yield 68.4%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 6.7$ Hz), 1.35 (d, 3H, $J = 6.2$ Hz), 1.97 (m, 1H), 2.34 (m, 1H), 2.70 (m, 1H), 3.10 (bs, 1H), 3.15–3.26 (bs, 5H), 3.30–3.49 (bs, 6H), 3.59 (bs, 2H), 3.94 (m, 1H), 4.12 (bs, 2H), 4.19 (m, 1H), 4.29 (m, 1H), 4.45–4.69 (bs, 6H), 5.26–5.55 (m, 6H), 5.75–6.01 (bs, 3H).

*3.11.7. Compound **10h***

Yield 65.5%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 6.9$ Hz), 1.35 (d, 3H, $J = 6.3$ Hz), 1.99 (m, 1H), 2.45 (m, 1H), 2.89 (bs, 3H), 3.11–3.39 (bs, 4H), 3.44–3.69 (bs, 3H), 3.80 (m, 1H), 3.91 (m, 1H), 4.06 (m, 1H), 4.16 (m, 1H), 4.33 (m, 1H), 4.47–4.69 (bs, 4H), 5.26–5.55 (m, 4H), 5.71–5.98 (bs, 2H).

*3.11.8. Compound **10i***

Yield 66.4%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 6.9$ Hz), 1.35 (d, 3H, $J = 6.1$ Hz), 1.90 (m, 1H), 2.50–2.69 (m, 2H), 3.05–3.33 (bs, 5H), 3.42 (m, 1H), 3.55–3.66 (bs, 2H), 3.70 (bs, 1H), 4.01 (m, 1H), 4.31 (m, 1H), 4.45–4.69 (bs, 4H), 5.26–5.55 (m, 4H), 5.75–5.99 (bs, 2H), 7.88 (d, 1H, $J = 6.2$ Hz).

*3.11.9. Compound **10j***

Yield 62.4%. ^{1}H-NMR($CDCl_3$) δ 1.27 (d, 3H, $J = 6.9$ Hz), 1.36 (d, 3H, $J = 6.1$ Hz), 1.99 (m, 1H), 2.15 (s, 3H), 2.59–2.67 (m, 1H), 3.03 (m, 1H), 3.08–3.39 (bs, 5H), 3.53 (m, 1H), 3.69 (bs, 1H), 3.80 (m, 1H), 4.01–4.15 (bs, 2H), 4.35 (m, 1H), 4.45–4.69 (bs, 6H), 5.16–5.55 (m, 6H), 5.70–5.99 (bs, 3H).

*3.11.10. Compound **10k***

Yield 66.0%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 6.9$ Hz), 1.35 (d, 3H, $J = 6.1$ Hz), 1.98 (m, 1H), 2.59–2.69 (m, 1H), 3.03 (m, 1H), 3.08–3.62 (bs, 7H), 4.01–4.31 (bs, 3H), 4.35 (m, 1H), 4.45–4.89 (bs, 8H), 5.08–5.55 (m, 8H), 5.75–6.03 (bs, 4H).

*3.11.11. Compound **10l***

Yield 65.1%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 7.0$ Hz), 1.38 (d, 3H, $J = 6.0$ Hz), 2.36 (m, 1H), 2.51–2.85 (m, 10H), 3.18–3.24 (bs, 2H), 3.30–3.44 (bs, 4H), 3.69 (m, 1H), 3.85 (bs, 1H), 3.99 (bs, 1H), 4.19 (bs, 1H), 4.40 (m, 1H), 4.45–4.67 (bs, 4H), 5.25–5.53 (m, 4H), 5.75–6.00 (bs, 2H).

*3.11.12. Compound **10m***

Yield 68.0%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, $J = 6.9$ Hz), 1.35 (d, 3H, $J = 6.2$ Hz), 1.97 (m, 1H), 2.54–2.80 (bs, 5H), 3.11 (m, 1H), 3.15–3.26 (bs, 4H), 3.30–3.46 (bs, 5H), 3.59 (bs, 1H), 3.94 (m, 1H), 4.12 (bs, 2H), 4.19 (m, 1H), 4.29 (m, 1H), 4.45–4.69 (bs, 6H), 5.26–5.55 (m, 6H), 5.75–6.01 (bs, 3H).

*3.12. (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[5-(2-aminoethylcarbamoyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-Carboxylic acid (**11a**)*

Compound **10a** (0.31 g, 0.50 mmol) and 0.1 g of $Pd(OH)_2$ (10%) were dissolved in THF–phosphate buffer (pH 7) (1:1, 10 mL each). The mixture was hydrogenated at 50 psi for 1 h. The solution was filtered through celite and washed with water (2 × 10 mL). The combined filtrates were washed with ethyl ether (2 × 20 mL) and lyophilised to give a yellow powder which was purified on a Diaion HP-20 column, eluting with 2% THF in water. Fractions having UV absorption at 298 nm were collected and lyophilised again to give the title compound **11a** as an amorphous solid. Yield 21.8%. M.p. 150–165 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.11 (d, 3H, $J = 6.8$ Hz), 1.17 (d, 3H, $J = 5.9$ Hz), 1.78 (bs, 1H), 2.63 (m, 1H), 2.94 (m, 1H), 3.01–3.48 (bs, 5H), 3.53–3.65 (bs, 2H), 3.70 (bs, 2H), 4.01 (m, 1H), 4.51 (bs, 1H). IR (KBr): 3480, 1745, 1666 cm^{-1}. HRMS(FAB) Calc. for $C_{17}H_{27}N_4O_5S$: 399.1702. Found: 399.1705 $[M+H]^+$.

The synthesis of compounds **11b**–**m** were carried out by the same procedure as described for the preparation of **11a**.

*3.12.1. Compound **11b***

Yield 24.4%. M.p. 163–175 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.10 (d, 3H, $J = 7.1$ Hz), 1.16 (d, 3H, $J = 6.2$ Hz), 1.90 (m, 1H), 2.13 (bs, 1H), 2.86 (m, 1H), 2.97 (s, 3H), 3.03 (bs, 2H), 3.18–3.40 (bs, 4H), 3.54 (dd, 1H, $J = 5.2$ and 5.6 Hz), 3.89 (bs, 1H), 4.04 (bs, 2H), 4.42 (m, 1H). IR (KBr): 3390 (NH), 1710, 1680, 1410, 1166 cm^{-1}. HRMS(FAB) Calc. for $C_{18}H_{29}N_4O_7S_2$: 477.1478. Found: 477.1488 $[M+H]^+$.

*3.12.2. Compound **11c***

Yield 29.4%. M.p. 145–168 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.10 (d, 3H, $J = 7.0$ Hz), 1.16 (d, 3H, $J = 6.3$ Hz), 1.93 (m, 1H), 2.13 (bs, 1H), 2.65 (s, 6H), 2.86 (m, 1H), 3.02 (bs, 2H), 3.21–3.44 (bs, 4H), 3.59 (dd, 1H, $J = 5.4$ and 5.8 Hz), 3.87 (bs, 1H), 4.11 (bs, 2H), 4.42 (m, 1H). IR (KBr): 3390 (NH), 1715, 1690, 1400, 1166 cm^{-1}. HRMS(FAB) Calc. for $C_{19}H_{32}N_5O_7S_2$: 506.1743. Found: 506.1738 $[M+H]^+$.

*3.12.3. Compound **11d***

Yield 25.2%. M.p. 155–171 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.14 (d, 3H, $J = 7.0$ Hz), 1.25 (d, 3H, $J = 6.2$ Hz), 1.73 (m, 1H), 2.57 (bs, 1H), 2.68 (s, 6H), 2.96–3.18 (bs. 4H), 3.21–3.44 (bs, 3H), 3.60 (bs, 1H), 3.83 (bs, 1H), 4.14 (bs, 2H), 4.49 (m, 1H). IR (KBr): 3400, 1755, 1700, 1670, 1415 cm^{-1}. HRMS(FAB) Calc. for $C_{20}H_{32}N_5O_6S$: 470.2073. Found: 470.2079 $[M+H]^+$.

*3.12.4. Compound **11e***

Yield 20.2%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.06 (d, 3H, $J = 6.9$ Hz), 1.13 (d, 3H, $J = 6.2$ Hz), 1.93 (m, 1H), 2.46 (m, 1H), 3.03–3.30 (bs, 8H), 3.34–3.50 (bs, 2H), 3.54–3.69 (bs, 5H), 3.85 (bs, 2H), 3.99 (bs, 1H), 4.16 (bs, 1H), 4.45 (m, 1H). IR (KBr): 3390, 1720, 1700, 1680, 1591, 1400 cm^{-1}. HRMS(FAB) Calc. for $C_{22}H_{34}N_5O_7S$: 512.2179. Found: 512.2185 $[M+H]^+$.

*3.12.5. Compound **11f***

Yield 21.5%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.06 (d, 3H, $J = 6.6$ Hz), 1.13 (d, 3H, $J = 6.1$ Hz), 1.87 (m, 1H), 2.46 (m, 1H), 2.51 (bs, 4H), 2.79–2.85 (m, 1H), 3.03–3.16 (bs, 4H), 3.28–3.44 (bs, 3H), 3.54–3.65 (bs, 4H), 3.69 (m, 1H), 3.85 (bs, 1H), 3.99 (bs, 1H), 4.16 (bs, 1H), 4.45 (m, 1H). IR (KBr): 3390, 1720, 1690, 1680, 1591, 1390 cm^{-1}. HRMS(FAB) Calc. for $C_{22}H_{34}N_5O_6S_2$: 528.1951. Found: 528.1950 $[M+H]^+$.

*3.12.6. Compound **11g***

Yield 21.9%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.03 (d, 3H, $J = 6.7$ Hz), 1.10 (d, 3H, $J = 6.2$ Hz), 1.87 (m, 1H), 2.46 (m, 1H), 2.85 (m, 1H), 3.05–3.46 (bs, 10H), 3.54 (bs, 2H), 3.69 (m, 2H), 3.85 (bs, 1H), 4.02 (bs, 2H), 4.18 (m, 1H), 4.45 (m, 1H). IR (KBr): 3390, 1740, 1715, 1680, 1411 cm^{-1}. HRMS(FAB) Calc. for $C_{22}H_{35}N_6O_6S$: 511.2339. Found: 511.2347 $[M+H]^+$.

*3.12.7. Compound **11h***

Yield 23.8%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.07 (d, 3H, $J = 7.0$ Hz), 1.17 (d, 3H, $J = 6.2$ Hz), 1.87 (m, 1H), 2.45–2.59 (m, 1H), 2.88 (bs, 3H), 3.15–3.39 (bs, 4H), 3.44–3.69 (bs, 3H), 3.80 (m, 1H), 3.91 (m, 1H), 4.06–4.12 (bs, 2H), 4.45 (m, 1H). IR (KBr): 3400, 1730, 1680, 1586, 1400 cm^{-1}. HRMS(FAB) Calc. for $C_{19}H_{30}N_5O_5S_2$: 472.1688. Found: 472.1692 $[M+H]^+$.

*3.12.8. Compound **11i***

Yield 24.3%. M.p. 148–162 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.03 (d, 3H, $J = 6.8$ Hz), 1.11 (d, 3H, $J = 6.2$ Hz), 1.56 (m, 1H), 2.50–2.59 (m, 1H), 2.95–3.10 (bs, 2H), 3.12–3.24 (bs, 2H), 3.27–3.40 (bs, 2H), 3.55–3.66 (bs, 2H), 3.70 (bs, 1H), 4.16 (m, 2H), 4.41 (m, 1H), 7.68 (d, 1H $J = 6.2$ Hz). IR (KBr): 3397, 1756, 1685, 1655, 1401 cm^{-1}. HRMS(FAB) Calc. for $C_{18}H_{28}N_5O_5S$: 426.1811. Found: 426.1815 $[M+H]^+$.

*3.12.9. Compound **11j***

Yield 22.2%. M.p. 196–205 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.10 (d, 3H, $J = 7.0$ Hz), 1.18 (d, 3H, $J = 6.3$ Hz), 1.60 (m, 1H), 2.05 (s, 3H), 2.59–2.67 (m, 1H), 2.99 (m, 1H), 3.08–3.39 (bs, 4H), 3.41–3.53 (m, 2H), 3.59 (bs, 1H), 3.73–3.89 (bs, 1H), 4.01–4.15 (bs, 2H), 4.45 (m, 1H). IR (KBr): 3490, 1740, 1700, 1650, 1400 cm^{-1}. HRMS(FAB) Calc. for $C_{19}H_{30}N_5O_5S$: 440.1968. Found: 440.1967 $[M+H]^+$.

*3.12.10. Compound **11k***

Yield 20.0%. M.p. 193–205 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.02 (d, 3H, $J = 7.3$ Hz), 1.10 (d, 3H, $J = 6.4$ Hz), 1.88 (m, 1H), 2.55–2.61 (m, 1H), 3.10–3.45 (bs, 6H), 3.55 (m, 1H), 3.88 (bs, 2H), 4.03 (bs, 2H), 4.45 (m, 1H). IR (KBr): 3980, 1710, 1640, 1580, 1405 cm^{-1}. HRMS(FAB) Calc. for $C_{18}H_{29}N_6O_5S$: 441.1920. Found: 441.1920 $[M+H]^+$.

*3.12.11. Compound **11l***

Yield 20.1%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 0.98 (d, 3H, $J = 7.1$ Hz), 1.06 (d, 3H, $J = 6.4$ Hz), 1.78 (m, 1H), 2.65–2.79 (bs, 5H), 2.90–3.01 (bs, 2H), 3.05–3.38 (bs, 5H), 3.55–3.60 (bs, 3H), 3.65 (bs, 1H), 3.80–3.88 (bs, 2H), 4.03 (bs, 2H), 4.45 (m, 1H). IR (KBr): 3470, 1730, 1685, 1580, 1425 cm^{-1}. HRMS(FAB) Calc. for $C_{21}H_{33}N_4O_5S_2$: 485.1892. Found: 485.1894 $[M+H]^+$.

*3.12.12. Compound **11m***

Yield 16.9%. M.p. 166–175 °C (dec.). UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.02 (d, 3H, $J = 7.1$ Hz), 1.08 (d, 3H, $J = 6.4$ Hz), 1.88 (m, 1H), 2.45–2.49 (m, 1H), 2.60–2.69 (bs, 4H), 3.07–3.15 (bs, 4H), 3.25–3.39 (bs, 4H), 3.66–3.78 (m, 2H), 3.89 (m, 2H), 4.03 (m, 2H), 4.26 (m, 1H), 4.45 (m, 1H). IR (KBr): 3370, 1755, 1690, 1580, 1430 cm^{-1}. HRMS(FAB) Calc. for $C_{21}H_{34}N_5O_5S$: 468.2281. Found: 468.2280 $[M+H]^+$.

*3.13. (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[5-(2-(1-methylthiomorpholin-1yl)ethylcarbamoyl)]pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-Carboxylic acid (**11lQ**)*

A mixture of **10l** (1.2 g, 2.0 mmol) and methyl iodide (4.1 g, 40.0 mmol) in acetone (20 mL) was stirred at r.t. for 20 h. Evaporation of the solvent in vacuo gave a crude residue, which was used without further purification. The **11lQ** was prepared by the deprotection procedure described for **11a**. Yield 20.1%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.02 (d, 3H, $J = 7.0$ Hz), 1.07 (d, 3H, $J = 6.3$ Hz), 1.85 (m, 1H), 2.61–2.70 (m, 2H), 2.88–3.00 (bs, 3H), 3.01 (s, 3H), 3.10–3.28 (bs, 3H), 3.35–3.44 (bs, 3H), 3.55–3.68 (bs, 5H), 3.73 (m, 1H), 3.83–3.88 (bs, 2H), 4.03 (bs, 1H), 4.45 (m, 1H). IR (KBr): 3470, 1730, 1685, 1580, 1425 cm^{-1}.

Compound **11mQ** was also prepared as described for the preparation of **11lQ**.

Yield 24.7%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.04 (d, 3H, $J = 7.1$ Hz), 1.09 (d, 3H, $J = 6.4$ Hz), 1.88 (m, 1H), 2.65–2.69 (bs, 1H), 3.01 (s, 3H), 3.05–3.19 (bs, 4H), 3.25–3.39 (bs, 4H), 3.63–3.78 (m, 2H), 3.85 (m, 2H), 4.01 (m, 2H), 4.26 (m, 1H), 4.45 (m, 1H). IR (KBr): 3370, 1755, 1690, 1580, 1430 cm^{-1}.

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