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Original article

Synthesis and biological evaluation of 1β-methylcarbapenems having guanidino moieties

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Abstract

The synthesis of a new series of 1β-methylcarbapenems having the substituted guanidinocarbonyl pyrrolidine moieties is described. Their in vitro antibacterial activities against both Gram-positive including MRSA and Gram-negative bacteria were tested and the effect of substituents on the pyrrolidine ring was investigated. In particular, the compound **Ib** having piperazinylguanidine moiety showed the most potent antibacterial activity.

Keywords: 1β-Methylcarbapenems; Antibacterial activity; Substituent effects; Carbapenems

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 having 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 synthesized and investigated [7–13]. In our previous work [13] the introduction of guanidine moieties showed potent and well-balanced antibacterial activity including anti-MRSA.

In this paper, we described the synthesis and structure–activity relationships of the l β-methylcarbapenems having a 5′-substituted guanidinocarbonyl pyrrolidin-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

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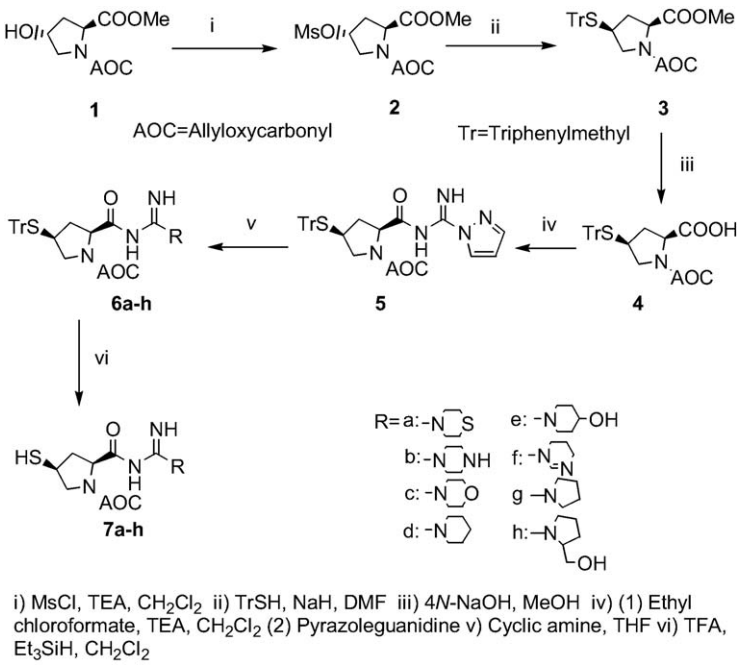


i) MsCl, TEA, CH_2Cl_2 ii) TrSH, NaH, DMF iii) 4*N*-NaOH, MeOH iv) (1) Ethyl chloroformate, TEA, CH_2Cl_2 (2) Pyrazoleguanidine v) Cyclic amine, THF vi) TFA, Et_3SiH, CH_2Cl_2

Scheme 1.

in a usual manner. 2-(*N*-Substituted guanidinocarbonyl)-pyrrolidine derivatives (**7a**–**h)** were prepared by the sequence shown in Scheme 1. *N*-Protected hydroxy-L-proline methyl ester (**1**) was converted to the *O*-mesylated compound **2** by treatment of mesyl chloride and subsequently treated with sodium triphenyl methylthioate, which was generated in situ from triphenylmethyl mercaptan and sodium hydride in DMF, to provide **3** with inversion of the C-4 configuration. The ester (**3**) was converted to the carboxylic acid **4** by treatment of 4*N*-NaOH and subsequently treated with ethyl chloroformate and 1*H*-pyrazole-1-carboxamidine to provide **5**. Preparation of the guanidine type compound (**6a**–**h**) was accomplished by treatment of compound **5** with corresponding cyclic amine. Deprotection of the trityl group to mercaptans (**7a**–**h**) was achieved by treatment of **6a**–**h** with trifluoroacetic acid in the presence of triethylsilane (Scheme 1).

Finally, the reaction of **8** [14] with thiols (**7a**–**h**) in the presence of diisopropylethylamine provided the corresponding 2-substituted carbapenems (**9a**–**h**), respectively. Deprotection of these compounds by treatment of tetrakis(triphenylphosphine)palladium(0) and tributyltin hydride gave the crude products, which were purified by HP-20 column to give the pure carbapenems (**Ia**–**h**) (Scheme 2).

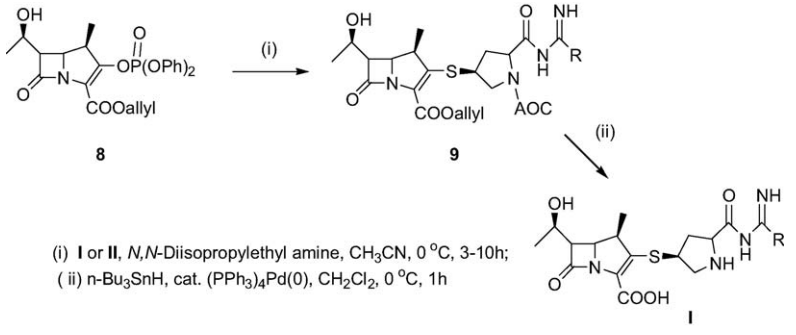
2.2. Biological assay

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 hours. The MICs of a compound were defined as the lowest concentration that visibly inhibited growth.

2.2.2. Antibacterial activity studies

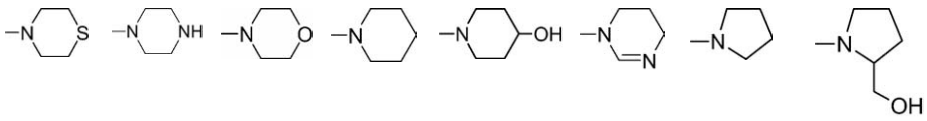
The in vitro antibacterial activities of the new carbapenems (**Ia**–**h**) prepared above against Gram-positive and negative bacteria including MRSA are listed in Tables 1 and 2. For comparison, the MIC values of imipenem, meropenem and vancomycin are also listed. Among these compounds, **Ia**,



(i) **I** or **II**, *N,N*-Diisopropylethyl amine, CH_3CN, 0 °C, 3-10h; (ii) n-Bu_3SnH, cat. $(PPh_3)_4Pd(0)$, CH_2Cl_2, 0 °C, 1h

Scheme 2.

Table 1
In vitro antibacterial activities of carbapenem derivatives (**Ia**–**h**)

R =									IPM[a]	MPM[b]
Organism	**Ia**	**Ib**	**Ic**	**Id**	**Ie**	**If**	**Ig**	**Ih**		
Streptococcus pyogenes 308A	0.01	<0.01	0.01	0.03	<0.01	0.01	0.01	<0.01	<0.01	0.01
S. pyogenes 77A	0.01	<0.01	0.01	0.01	<0.01	0.03	0.03	<0.01	<0.01	0.01
Streptococcus aureus SG 511	0.20	0.03	0.20	0.40	0.03	0.10	0.05	0.03	0.01	0.05
S. aureus 503	0.10	0.03	0.10	0.10	0.03	0.05	0.05	0.03	0.01	0.05
Escherichia coli DC O	0.05	0.05	0.05	0.10	0.05	0.05	0.05	0.05	0.40	0.03
E. coli 1507 E	0.03	0.05	0.05	0.05	0.05	0.05	0.05	0.03	0.10	0.03
P. aeruginosa 9027	3.10	0.80	6.20	6.20	1.50	6.20	6.20	1.50	0.80	0.40
Salmonella typhimurium	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.05	0.80	0.05
Enterobacter cloacae P 99	0.10	0.05	0.20	0.10	0.05	0.05	0.10	0.05	0.10	0.03
E. cloacae 1321 E	0.05	0.05	0.05	0.10	0.05	0.05	0.10	0.03	0.20	0.03
DHP-I	1.95	2.20	2.37	1.67	2.31	1.85	1.54	1.98	0.09	1.00

MIC (μg ml^{-1}) determined by agar dilution method.
[a] IPM = imipenem.
[b] MPM = meropenem.

Table 2
Anti-MRSA activities of **Ia**, **Ib** and **Ie**

Methicillin resistant strains	**Ia**	**Ib**	**Ie**	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

Ib, **Ie** and **Ih** 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 iminocarbamoyl side chain, the compounds **Ie** and **Ih** having hydroxyl group were generally more potent than the non-hydroxy compounds **Id** and **Ig**.

As expected, the piperazine compound **Ib** exhibited the most potent and well balanced activity including the anti-MRSA activity. Furthermore we observed that the thiomorpholine urea **Ia** is more potent than the morpholine urea **Ic**.

The stability [13] to DHP-I of most compounds was tested and all the compounds were more stable than meropenem.

3. Experimental part

Melting point (mp): Thomas Hoover apparatus, uncorrected. UV spectra: Hewlett–Packard 8451A UV–VIS spectrophotometer. IR spectra: Perkin–Elmer 16F-PC FT-IR. NMR spectra: Varian Gemini 300 spectrometer, tetramethylsilane (TMS), as an internal standard. The mass spectrometry system was based on a HP5989A MS Engine (Palo Alto, CA, USA) mass spectrometer with a HP Model 59987A.

*3.1. (2S,4R)-4-Mesyloxy-1-(allyloxycarbonyl)pyrrolidin-2-carboxylic acid methyl ester (**2**)*

A solution of **1** (92.5 g, 0.41 mol) and triethylamine (65.0 ml, 0.49 mol) in dry CH_2Cl_2 (600 ml) was cooled to 0 °C under nitrogen and treated with methanesulfonyl chloride (56.0 g, 0.49 mol). The mixture was stirred at 0 °C for 1 h, diluted with CH_2Cl_2 (500 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 (EtOAc/n-hexane = 1:2) to give **2** (23.2 g, 93.2%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 2.27 (m, 1H), 2.75 (m, 1H), 3.06 (s, 3H), 3.77 and 3.80 (2 s, 3H), 3.82–3.97 (m, 2H), 4.42 (m, 1H), 4.57 (d, 2H, *J*=5.8 Hz), 5.25 (m, 3H), 5.92 (m, 1H).

*3.2. (2S,4S)-4-Tritylthio-1-(allyloxycarbonyl)pyrrolidin-2-carboxylic acid methyl ester (**3**)*

To a stirred solution of triphenylmethyl mercaptan (80.0 g, 0.29 mol) in dry DMF (600 ml) was added dropwise sodium hydride (11.6 g, 0.29 mol, 60% oil suspension) at 0 °C and was stirred for 1 h at room temperature. To the resulting solution was added **2** (75.7 g, 0.25 mol) solution in dry DMF (150 ml) at 0 °C and was stirred for 3 h at room temperature. The reaction mixture was poured into cold dilute HCl and extracted with ethyl acetate. 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

(EtOAc/n-hexane = 1:7) to give **3** (100.6 g, 82.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 2.01 (m, 1H), 2.55 (m, 1H), 3.16 (bs, 1H), 3.54 (bs, 1H), 3.77 and 3.80 (2 s, 3H), 3.97 (m, 1H), 4.42 (m, 1H), 4.55 (d, 2H, J = 5.5 Hz), 5.26 (m, 2H), 5.98 (m, 1H) 7.23 (m, 9H), 7.48 (m, 6H).

*3.3. (2S,4S)-4-Tritylthio-1-(allyloxycarbonyl)pyrrolidin-2-carboxylic acid (**4**)*

To a solution of **3** (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. The mixture was neutralized 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 water, and dry in air to give **4** (39.4 g, 83.3%) as a white solid. M.p. 150–153 °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).

*3.4. (2S,4S)-2-[(Iminopyrazol-1-ylmethyl)carbamoyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidne (**5**)*

A solution of **4** (23.7 g, 0.05 mol) and triethylamine (7.4 ml, 0.055 mol) in dry CH_2Cl_2 (300 ml) was cooled 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 1*H*-pyrazole-1-carboxamidine hydrochloride (8.1 g, 0.055 mol) and strirred 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 (EtOAc/n-hexane = 1:4) to give **5** (25.3 g, 89.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.85 (m, 1H), 2.18–2.26 (m, 1H), 2.79–2.86 (bs, 1H), 3.06 (m, 1H), 3.15 (m, 1H), 4.05 (m, 1H), 4.50–4.62 (bs, 2H), 5.28 (m, 2H), 5.87 (m, 1H), 6.42 (s, 1H), 7.27 (m, 9H), 7.48 (m, 6H), 7.71 (d, 1H, J = 2.6 Hz), 8.37 (d, 1H, J = 2.6 Hz), 9.51 (bs, 1H).

*3.5. (2S,4S)-2-[(Iminothiomorpholin-1-ylmethyl)carbamoyl]-4-tritylthio-1-(allyloxycarbonyl) pyrrlidine (**6a**)*

To a solution of **5** (1.00 g, 1.8 mmol) in THF (30 ml) was added thiomorpholine (0.23 g, 2.2 mmol) at room temperature and was stirred for 3 h at the reflux. The mixture was concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (EtOAc/n-hexane = 1:1) to give **6a** (0.87 g, 80.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.78 (bs, 1H), 2.09–2.16 (m, 1H), 2.55–2.88 (bs, 6H), 3.08 (bs, 1H), 3.25–3.44 (bs, 4H), 3.95 (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), 8.01 (s, 1H).

Compounds **6b**–**h** from **5** were carried out by the same procedure as described for the preparation of **6a**.

6b: Yield 69.8%. ^{1}H-NMR ($CDCl_3$) δ 1.77 (bs, 1H), 2.28 (m, 1H), 2.76 (bs, 1H), 2.98 (bs, 1H), 3.45 (bs, 1H), 3.50–3.74 (bs, 8H), 3.98 (m, 1H), 4.43 (bs, 2H), 5.04–5.26 (m, 2H), 5.85 (m, 1H), 7.23 (m, 9H), 7.46 (m, 6H), 7.67 (bs, 1H).

6c: Yield 76.6%. ^{1}H-NMR ($CDCl_3$) δ 1.79 (bs, 1H), 2.28 (m, 1H), 2.79 (bs, 1H), 3.04 (bs, 1H), 3.30–3.45 (bs, 5H), 3.51–3.64 (bs, 4H), 4.02 (m, 1H), 4.43 (bs, 2H), 5.06–5.23 (m, 2H), 5.89 (m, 1H), 7.23 (m, 9H), 7.46 (m, 6H), 7.97 (bs, 1H).

6d: Yield 77.9%. ^{1}H-NMR ($CDCl_3$) δ 1.43–1.57 (bs, 4H), 1.60–1.98 (bs, 3H), 2.17 (bs, 1H), 2.77–2.89 (bs, 1H), 2.94–3.01 (m, 1H), 3.09–3.38 (bs, 2H), 3.65–3.89 (bs, 4H), 4.26–4.43 (bs, 2H), 5.04–5.26 (m, 2H), 5.70–5.85 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H), 8.07 (s, 1H).

6e: Yield 69.8%. ^{1}H-NMR ($CDCl_3$) δ 1.45–1.95 (bs, 5H), 2.17 (bs, 1H), 2.75–2.87 (bs, 1H), 2.94–3.01 (m, 1H), 3.09–3.33 (bs, 3H), 3.65–3.89 (bs, 4H), 4.26–4.43 (bs, 2H), 5.04–5.26 (m, 2H), 5.70–5.85 (m, 1H), 7.24 (m, 9H), 7.44 (m, 6H), 8.03 (s, 1H).

6f: Yield 58.7%. ^{1}H–NMR ($CDCl_3$) δ 1.77–1.90 (bs, 2H), 1.96 (bs, 1H), 2.28 (m, 1H), 2.77–3.01 (bs, 3H), 3.32–3.51 (bs, 4H), 4.05 (bs, 2H), 4.43 (bs, 2H), 5.04–5.26 (m, 2H), 5.80–5.89 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H), 8.06 (s, 1H).

6g: Yield 75.4%. ^{1}H–NMR ($CDCl_3$) δ 1.24–1.34 (bs, 2H), 1.74–1.95 (bs, 3H), 2.37 (m, 1H), 2.77–2.89 (bs, 1H), 2.94 (bs, 1H), 3.26–3.58 (bs, 5H), 3.99 (m, 1H), 4.43 (bs, 2H), 5.04–5.26 (m, 2H), 5.74–5.92 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H), 8.02 (bs, 1H).

6h: Yield 60.4%. ^{1}H-NMR ($CDCl_3$) δ 1.27–1.32 (bs, 2H), 1.74–2.01 (bs, 3H), 2.33 (m, 1H), 2.77–2.89 (bs, 1H), 2.94 (bs, 1H), 3.22–3.55 (bs, 4H), 3.96 (m, 1H), 4.21 (bs, 2H), 4.43 (bs, 2H), 5.04–5.26 (m, 2H), 5.70–5.90 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H), 8.01 (bs, 1H).

*3.6. Allyl (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-{5-[(iminothiomorpholin-1-ylmethyl)carbamoyl]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio}-1-methylcarbapen-2-em-3-carboxylate (**9a**)*

To a solution of **6a** (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 room temperature, 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 (**7a**), 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 (**8**, 0.50 g, 1.0 mmol) in CH_3CN (10 ml) was cooled to 0 °C under N_2. To this solution was added diisopropylethyl amine (0.13 g, 1.0 mmol) and a solution of the mercapto compound **7a** in CH_3CN (5 ml). After stirring for 5 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 (EtOAc/n-hexane = 1:1) to

give **9a** (0.39 g, 61.5%) as a yellow amorphous solid. ^{1}H-NMR($CDCl_3$) δ 1.20 (d, 3H, J = 7.0 Hz), 1.27 (d, 3H, J = 6.2 Hz), 1.58 (bs, 1H), 1.96 (bs, 1H), 2.46–2.80 (bs, 5H), 3.10 (bs, 1H), 3.25–3.36 (m, 2H), 3.49–3.59 (bs, 1H), 3.71–3.88 (bs, 4H), 3.95 (m, 1H), 4.10–4.23 (bs, 2H), 4.40–4.52 (bs, 2H), 4.55 (dd, 1H, J = 5.2 and 5.6 Hz), 4.68 (dd, 1H, J = 5.2 and 5.6 Hz), 5.12–5.50 (m, 4H), 5.65–6.01 (bs, 2H), 7.60 (bs, 1H).

The synthesis of compounds **9b**–**h** were carried out by the same procedure as described for the preparation of **9a**.

9b: Yield 63.9%. ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, J = 7.0 Hz), 1.35 (d, 3H, J = 6.2 Hz), 1.68 (bs, 1H), 2.03 (bs, 1H), 2.80 (bs, 1H), 3.13 (bs, 1H), 3.35–3.46 (m, 3H), 3.59–3.79 (bs, 10H), 3.95 (m, 1H), 4.18–4.23 (bs, 2H), 4.40–4.52 (bs, 1H), 4.55 (bs, 2H), 4.59 (m, 1H), 4.78 (m, 2H), 5.12–5.50 (m, 4H), 5.65–6.01 (bs, 3H), 7.68 (bs, 1H).

9c: Yield 64.3%. ^{1}H-NMR($CDCl_3$) δ 1.22 (d, 3H, J = 7.0 Hz), 1.29 (d, 3H, J = 6.2 Hz), 1.61 (bs, 1H), 2.02 (bs, 1H), 2.46 (bs, 1H), 3.10 (bs, 1H), 3.25–3.39 (m, 6H), 3.49–3.59 (bs, 1H), 3.71–3.88 (bs, 4H), 3.95 (m, 1H), 4.10–4.23 (bs, 2H), 4.40–4.52 (bs, 2H), 4.55 (bs, 1H), 4.68 (bs, 1H), 5.13–5.45 (m, 4H), 5.69–6.00 (bs, 2H), 7.70 (bs, 1H).

9d: 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), 1.43–1.57 (bs, 4H), 1.60–1.98 (bs, 3H), 1.98 (m, 1H), 2.46 (bs, 1H), 3.10 (bs, 1H), 3.25–3.39 (m, 2H), 3.49–3.69 (bs, 5H), 3.95 (m, 1H), 4.10–4.23 (bs, 2H), 4.40–4.52 (bs, 2H), 4.55 (bs, 1H), 4.68 (bs, 1H), 5.13–5.45 (m, 4H), 5.69–6.00 (bs, 2H), 7.70 (bs, 1H).

9e: Yield 69.9%. ^{1}H-NMR($CDCl_3$) δ 1.25 (d, 3H, J = 7.0 Hz), 1.32 (d, 3H, J = 6.1 Hz), 1.43–1.57 (bs, 2H), 1.60–1.98 (bs, 3H), 1.98 (m, 1H), 2.46 (bs, 1H), 3.10 (bs, 1H), 3.25–3.39 (m, 2H), 3.49–3.69 (bs, 5H), 3.80 (bs, 1H), 3.95 (m, 1H), 4.10–4.20 (bs, 2H), 4.40–4.52 (bs, 2H), 4.55 (bs, 1H), 4.68 (bs, 1H), 5.10–5.49 (m, 4H), 5.69–6.00 (bs, 2H), 7.80 (bs, 1H).

9f: Yield 65.9%. ^{1}H-NMR($CDCl_3$) δ 1.15 (d, 3H, J = 7.0 Hz), 1.26 (d, 3H, J = 6.1 Hz), 1.37–1.57 (bs, 2H), 1.66 (bs, 1H), 1.98 (m, 1H), 2.40 (bs, 1H), 3.10 (bs, 1H), 3.25–3.39 (m, 3H), 3.49–3.61 (bs, 4H), 3.80 (bs, 1H), 3.95 (m, 1H), 4.10–4.20 (bs, 2H), 4.26–4.72 (bs, 4H), 4.95 (bs, 1H), 5.10–5.49 (m, 4H), 5.69–6.00 (bs, 2H), 7.80 (bs, 1H).

9 g: Yield 65.5%. ^{1}H-NMR($CDCl_3$) δ 1.28 (d, 3H, J = 7.0 Hz), 1.37 (d, 3H, J = 6.1 Hz), 1.43–1.57 (bs, 2H), 1.60–1.88 (bs, 3H), 1.98 (m, 1H), 2.46 (bs, 1H), 3.10 (bs, 1H), 3.20–3.44 (m, 4H), 3.49–3.69 (bs, 4H), 3.95 (m, 1H), 4.10–4.23 (bs, 1H), 4.26–4.68 (bs, 4H), 5.13–5.47 (m, 4H), 5.70–5.98 (bs, 2H), 7.70 (bs, 1H).

9h: Yield 68.4%. ^{1}H-NMR($CDCl_3$) δ 1.22 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.2 Hz), 1.36 (bs, 2H), 1.74–2.01 (bs, 3H), 2.35 (bs, 1H), 3.11 (bs, 1H), 3.23–3.38 (m, 3H), 3.42–3.51 (bs, 3H), 3.80 (bs, 1H), 3.90–4.03 (m, 3H), 4.09–4.21 (bs, 2H), 4.26–4.76 (bs, 4H), 5.10–5.51 (m, 4H), 5.69–6.00 (bs, 2H), 7.80 (bs, 1H).

*3.7. (1R,5S,6S)-6-[(1R)-Hydroxyethyl]-2-{5-[(iminothiomorpholin-1-ylmethyl)carbamoyl]pyrro lidin-3-ylthio}-1-methylcarbapen-2-em-3-carboxylic acid (**Ia**)*

To a stirred solution of **9a** (0.20 g, 0.33 mol) and $Pd(PPh_3)_4$ (30 mg) in CH_2Cl_2 (5 ml) was added dropwise *n*-tributytin hydride (0.18 ml, 0.66 mmol) at 0 °C and was stirred for 1 h at same temperature. To the resulting solution was diluted with water (10 ml) and the organic layers was washed with water (2 × 10 ml). The combined aqueous layers were washed with ethyl ether (2 × 10 ml) and lyophilized 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 lyophilized again to give the title compound **Ia** as a amorphorus solid. Yield 18.8%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 0.97 (d, 3H, J = 5.3 Hz), 1.06 (d, 3H, J = 6.3 Hz), 1.98 (bs, 1H), 2.48–2.57 (bs, 2H), 2.65–2.74 (m, 2H), 3.11–3.28 (bs, 4H), 3.53–3.65 (bs, 2H), 3.70–3.88 (bs, 3H), 3.96 (t, 2H, J = 9.1 Hz), 4.11 (m, 1H), 4.42 (m. 1H). IR (KBr): 3480, 1745, 1710, 1660, 1610 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{20}H_{29}N_5O_5S_2$ 483.1610, Found 483.1612.

The synthesis of compounds **Ib**–**h** were carried out by the same procedure as described for the preparation of **Ia**.

Ib: Yield 14.7%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.05 (d, 3H, J = 7.1 Hz), 1.18 (d, 3H, J = 6.5 Hz), 1.80 (m, 1H), 2.47 (m,2H), 2.97 (bs, 4H), 3.23 (bs, 2H), 3.28–3.30 (m, 1H), 3.54 (dd, 1H, J = 5.2 and 5.6 Hz), 3.59 (bs, 1H), 3.65–3.88 (bs, 3H), 4.10 (m, 2H), 4.19 (dd, 1H, J = 4.5 and 2.2 Hz). IR (KBr): 3460, 1740, 1710, 1670, 1610 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{20}H_{30}N_6O_5S$ 466.1998, Found 466.1998.

Ic: Yield 17.3%. UV λ_{max} : 298 nm. ^{1}H-NMR (D_2O) δ 1.01 (d, 3H, J = 5.5 Hz), 1.06 (d, 3H, J = 6.7 Hz), 1.88 (bs, 1H), 2.48–2.59 (bs, 2H), 3.09–3.38 (bs, 5H), 3.53–3.65 (bs, 2H), 3.66–3.96 (m, 6H), 4.11 (m, 1H), 4.42 (m. 1H). IR (KBr): 3430, 1720, 1710, 1660, 1610 (C=NH) cm^{-1}. HRMS (FAB) Calc. for $C_{20}H_{29}N_5O_6S$ 467.1839, Found 467.1837.

Id: Yield 20.2%. UV λ_{max} : 298 nm. ^{1}H-NMR (D_2O) δ 1.01 (d, 3H, J = 7.0 Hz), 1.10 (d, 3H, J = 6.2 Hz), 1.40–1.57 (bs, 4H), 1.62–1.99 (bs, 3H), 2.45–2.56 (bs, 2H), 2.96–3.18 (bs. 2H), 3.21–3.44 (bs, 2H), 3.60–3.83 (bs, 5H), 4.14 (bs, 1H), 4.49 (m. 1H). IR (KBr): 3400, 1755, 1700, 1670, 1620 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{21}H_{31}N_5O_5S$ 465.2046, Found 465.2041.

Ie: Yield 13.6%. UV λ_{max} : 298 nm. ^{1}H-NMR (D_2O) δ 0.96 (d, 3H, J = 6.9 Hz), 1.06 (d, 3H, J = 6.2 Hz), 1.29–1.37 (bs, 2H), 1.50–1.69 (bs, 2H), 1.77–1.96 (bs, 2H), 2.44 (m, 2H), 3.03–3.10 (bs, 2H), 3.34–3.50 (bs, 2H), 3.64–3.79 (bs, 4H), 3.95 (bs, 1H), 4.16 (bs, 1H), 4.45 (m. 1H). IR (KBr): 3390, 1720, 1700, 1680, 1625 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{21}H_{31}N_5O_6S$ 481.1995, Found 481.1994.

If: Yield 11.9%. 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), 1.37–1.53 (bs, 2H), 1.98 (m, 1H), 2.46 (m, 1H), 2.79–2.85 (m,

1H), 3.01–3.16 (bs, 2H), 3.28–3.44 (bs, 3H), 3.54–3.65 (bs, 2H), 3.69 (m, 1H), 3.99 (bs, 1H), 4.13 (bs, 1H), 4.40 (m. 1H), 7.90 (s, 1H). IR (KBr): 3390, 1720, 1690, 1680, 1610 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{20}H_{28}N_6O_5S$ 464.1842, Found 464.1840.

Ig Yield 19.2%. 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), 1.43–1.57 (bs, 2H), 1.60–1.88 (bs, 3H), 2.45–2.53 (m, 1H), 2.88 (bs, 1H), 3.15–3.38 (bs, 4H), 3.49–3.73 (bs, 3H), 3.91 (m,1H), 4.06–4.12 (bs, 2H), 4.40 (m. 1H). IR (KBr): 3400, 1730, 1710, 1680, 1625 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{20}H_{29}N_5O_5S$ 451.1889, Found 451.1890.

Ih Yield 14.0%. 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), 1.36–1.44 (bs, 2H), 1.68–1.96 (bs, 3H), 2.46 (m, 1H), 2.85 (m, 1H), 3.05–3.19 (bs, 2H), 3.45–3.54 (bs, 2H), 3.60–3.78 (bs, 4H), 3.95–4.08 (bs, 2H), 4.18 (m, 1H), 4.39 (m. 1H). IR (KBr): 3390, 1740, 1715, 1680, 1620 (C=NH) cm^{-1}. HRMS(FAB) Calc. for $C_{21}H_{31}N_5O_6S$ 481.1995, Found 481.1991.

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