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Short communication

# Synthesis and antibacterial activity of 1β-methyl-2-[5-(*N*-substituted-2-hydroxy iminoethyl)pyrrolidin-3-ylthio]carbapenem derivatives

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**Abstract**

The synthesis of a new series of 1-methylcarbapenems having the substituted thiazolopyrrolidine moiety is described. Their in vitro antibacterial activities against both gram-positive and gram-negative bacteria were tested and the effect of substituent on the pyrrolidine ring was investigated. In particular, compounds **12b** and **12k** showed the most potent antibacterial activity.


*Keywords:* 1β-Methylcarbapenem; β-Lactam antibiotics

## 1. Introduction

The carbapenem compounds which have a (3*S*)-pyrrolidin-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity [1], and a large number of derivatives have been synthesised and investigated with enthusiasm. Among those compounds, panipenem [2] and meropenem [3] were the first to be successfully launched in the market and clinical evaluations are in progress for S-4661 [4], BO-2727 [5] and DX-8739 [6], which have enhanced metabolic stability to renal dehydropeptidase-1 (DHP-1) due to the introduction of a 1β-methyl group into the carbapenem skeleton. We were also interested in this pyrroldin-3-ylthio group and 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 synthesised and investigated [7–13].

We conceived that introduction of an additional oxime moiety into the pyrrolidine side chain was responsible for the improvements, because the compounds having oxime moiety has shown to enhance drug activity in general.

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

## 2. Results and discussion

### 2.1. Chemistry

Our general synthetic route leading to new carbapenems involved the preparation of appropriately pro-

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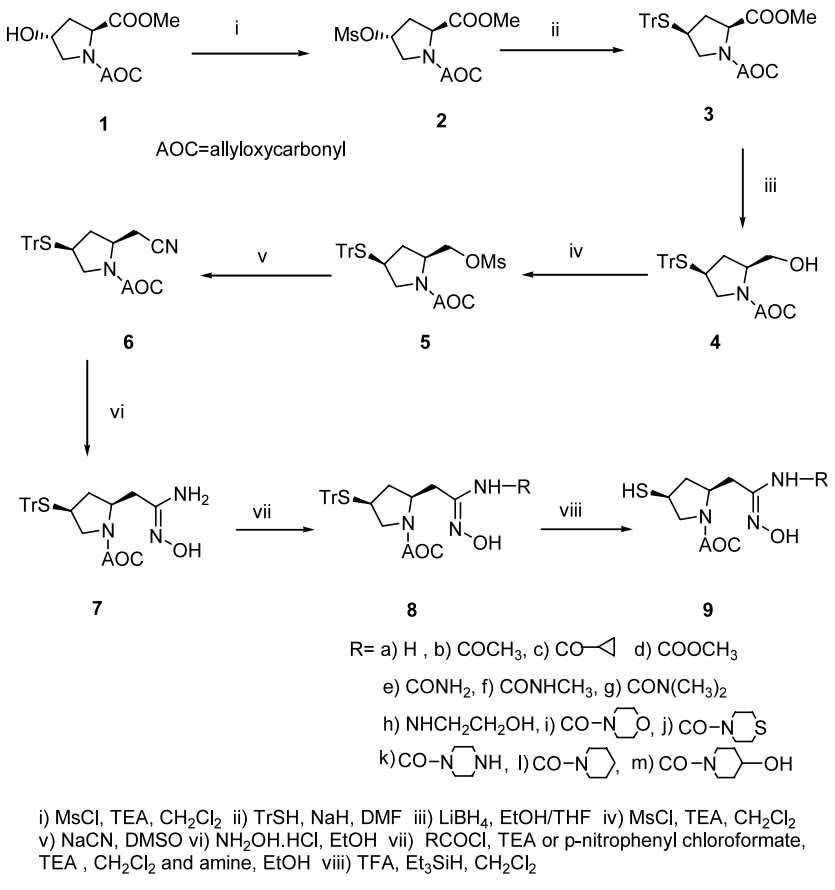
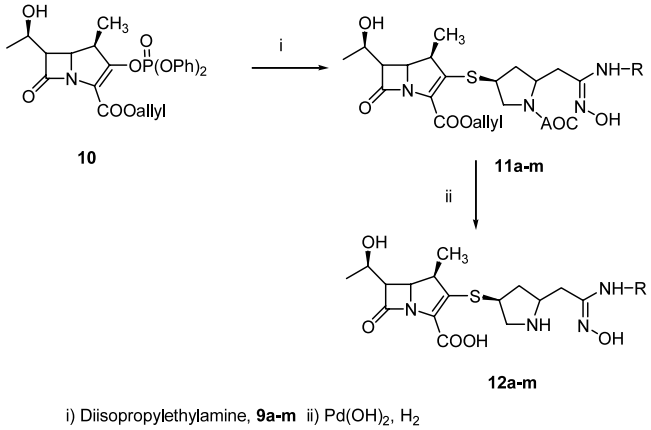



Scheme 1. (i) MsCl, TEA, $CH_2Cl_2$; (ii) TrSH, NaH, DMF; (iii) $LiBH_4$, EtOH/THF; (iv) MsCl, TEA, $CH_2Cl_2$; (v) NaCN, DMSO; (vi) $NH_2OH \cdot HCl$, EtOH; (vii) RCOCl, TEA or *p*-nitrophenyl chloroformate, TEA, $CH_2Cl_2$ and amine, ETOH; (viii) TFA, $Et_3SiH$, $CH_2Cl_2$.

tected 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-(3-Substituted-2-hydroxyiminoethyl)pyrrolidine derivatives (**9a**–**9m**) were prepared by the sequence shown in Scheme 1. *N*-Protected proline methyl ester was converted to the *O*-mesylate **2** by treatment of mesyl chloride and subsequently treated with sodium triphenylmethylthioate, which was generated in situ from triphenylmethylmercaptan and sodium hydride in DMF, to provide **3** with inversion of the C-4 configuration. **3** was reduced with lithium borohydride in THF–EtOH and subsequently mesylated to give **5**. The treatment of the mesylate **5** with sodium cyanide in DMSO gave the cyano compound **6**, which was successfully converted into *N*-hydroxyacetamidine **7** by reaction of hydroxylamine. Treatment of **7** with acetyl chloride, cyclopropyl chloride, allyl chloroformate and methyl chloroformate afforded the corresponding *N*-acetylated products, **8a**, **8b**, **8c** and **8d**. Carbamoylation of amine was carried out by a conventional method using *p*-nitrophenyl chloroformate to give urea type compounds **8e**–**8m**. Deprotection of the trityl group to mercaptans (**9a**–**9m**) were achieved by treatment of **8a**–**8m** with trifluoroacetic acid in the presence of triethylsilane.

Finally, the reaction of **10** [9] with thiols (**9a**–**9m**) in the presence of diisopropylethylamine provided the corresponding 2-substituted carbapenem (**11a**–**11m**). Deprotection of these compounds by catalytic hydrogenation gave the crude products, which were purified




Scheme 2. (i) Diisopropylethylamine, **9a**–**9m**; (ii) $Pd(OH)_2$, $H_2$.

by HP-20 column to give the pure carbapenems (**12a**–**12m**) (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 $mL^{-1}$ 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 was defined as the lowest concentration that visibly inhibited growth.

#### 2.2.2. Determination of susceptibility to renal DHP-1

The relative hydrolysis rate of carbapenems by porcine renal DHP-1 was determined, taking the initial hydrolysis rate of imipenem as 1.0. Partially purified porcine DHP-1 (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 (**12a**–**12m**) prepared above against gram-positive and -negative bacteria are listed in Table 1. For comparison, the MIC values of imipenem and meropenem are also listed. All the compounds (**12a**–**12m**) displayed superior or similar antibacterial activities against gram-positive to meropenem, and against gram-negative bacteria except *Pseudomonas aeruginosa* to imipenem.

The effects of substituent on the pyrrolidine ring were investigated. The cyclic urea substituted compounds (**12i**–**12m**) showed more improved activity against both gram-positive and -negative bacteria including *P. aeruginosa* than that of aliphatic ureas (**12e**–**12g**). Comparing the compounds **12i**–**12m** having cyclic urea moieties on the pyrrolidine ring showed slight differences in the antibacterial activities against gram-positive and -negative bacteria. As expected, the piperazine urea compound **12k** exhibited the most potent and well-balanced activity. Furthermore, we observed that the thiomorpholine urea **12j** is more potent than the morpholine urea **12i**.

The stability to DHP-1 of most compounds was tested and all the compounds were more stable than meropenem.

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

| Strains | 12a | 12b | 12c | 12d | 12e | 12f | 12g | 12h | 12i | 12j | 12k | 12l | 12m | Imipenem | Meropenem |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Streptococcus pyogenes* 308A | 0.01 | <0.01 | 0.01 | <0.01 | <0.01 | 0.20 | 0.01 | <0.01 | <0.01 | <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 | 0.10 | 0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| *Staphylococcus aureus* SG511 | 0.05 | 0.03 | 0.10 | 0.03 | 0.05 | 0.80 | 0.10 | 0.05 | 0.03 | 0.05 | 0.02 | 0.05 | 0.05 | 0.1 | 0.10 |
| *S. aureus* 285 | 0.10 | 0.05 | 0.40 | 0.05 | 0.03 | 0.80 | 0.20 | 0.10 | 0.05 | 0.05 | 0.02 | 0.05 | 0.02 | 0.01 | 0.10 |
| *Escherichia coli* DC2 | 0.10 | 0.05 | 0.20 | 0.10 | 0.05 | 0.10 | 0.40 | 0.10 | 0.10 | 0.10 | 0.05 | 0.05 | 0.05 | 0.40 | 0.03 |
| *E. coli* TEM | 0.05 | 0.05 | 0.20 | 0.05 | 0.05 | 0.40 | 1.56 | 0.05 | 0.05 | 0.10 | 0.05 | 0.05 | 0.05 | 0.20 | 0.03 |
| *P. aeruginosa* 9027 | 1.56 | 0.40 | 1.56 | 0.80 | 0.80 | 3.10 | 3.10 | 3.10 | 0.40 | 0.80 | 0.40 | 0.80 | 0.80 | 0.80 | 0.20 |
| *Salmonella typhimurium* | 0.20 | 0.10 | 0.40 | 0.10 | 0.40 | 0.40 | 0.20 | 0.20 | 0.10 | 0.10 | 0.05 | 0.20 | 0.10 | 0.80 | 0.03 |
| *Klebsicella aerogenes* 1522E | 0.10 | 0.05 | 0.20 | 0.10 | 0.10 | 0.80 | 3.10 | 0.20 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.05 |
| *Enterobactor cloacae* 1321E | 0.05 | 0.05 | 0.20 | 0.05 | 0.05 | 0.20 | 0.80 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.03 |
| DHP-1 | 1.48 | 2.23 | 1.23 | 2.08 | 2.43 | 1.57 | 1.50 | 2.08 | 2.24 | 1.62 | 1.99 | 2.24 | 1.87 | 0.21 | 1.00 |

## 3. Experimental

Melting point (m.p.): 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 and tetramethylsilane (TMS), as an internal standard. The mass spectrometry system was based on an HP 5989A MS Engine (Palo Alto, CA) mass spectrometer with an HP Model 59987A.

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

A solution of **1** [14] (94.0 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 to give **2** (117.1 g, 93.2%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 2.27$ (m, 1H), 2.65 (m, 1H), 3.03 (s, 3H), 3.77 and 3.80 (2s, 3H), 3.82–3.97 (m, 2H), 4.42 (m, 1H), 4.57 (d, 2H, $J = 5.8$ Hz), 5.25–5.40 (m, 3H), 5.88 (m, 1H). $^{13}$C-NMR: 36.7, 37.8, 39.0, 52.9, 57.5, 66.6, 78.5, 117.9, 132.8, 154.5, 172.6. IR (KBr): 2970, 1745, 1666, 1358 $cm^{-1}$.

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

To a stirred solution of triphenylmethylmercaptan (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** (76.6 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 to give **3** (100.6 g, 82.5%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 2.01$ (m, 1H), 2.55 (m, 1H), 3.16 (bs, 1H), 3.54 (bs, 1H), 3.77 and 3.80 (2s, 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). $^{13}$C-NMR ($CDCl_3$): 37.1, 38.2, 42.0, 52.7, 58.5, 66.3, 67.8, 117.6, 127.3, 128.3, 129.9, 132.9, 144.9, 153.5, 172.6. IR (KBr): 2950, 1765, 1708 $cm^{-1}$.

### *3.3. (2S,4S)-2-Hydroxymethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**4**)*

To a solution of **3** (107.3 g, 0.22 mol) in THF (800 mL) was added slowly $LiBH_4$ (4.79 g, 0.22 mol) at 0 °C and was stirred for 25 h at room temperature. The mixture was diluted with $H_2O$ (200 mL), 1*N*-HCl (200 mL) and extracted with ethyl acetate (800 mL). The organic layer was dried over anhydrous $Na_2SO_4$, concentrated and the resulting residue was purified by silica gel column chromatography to give **4** (79.3 g, 78.5%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.98$ (m, 1H), 2.75–2.82 (m, 2H), 3.01 (m, 1H), 3.55 (bs, 2H), 3.78 (m, 1H), 4.55 (d, 3H, $J = 5.9$ Hz), 5.25 (m, 3H), 5.90 (m, 1H), 7.27 (m, 9H), 7.47 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.1, 41.0, 53.2, 53.9, 60.9, 66.6, 67.2, 67.6, 117.9, 127.3, 128.5, 129.9, 132.9, 145.0, 156.8. IR (KBr): 3450, 2950, 1735 $cm^{-1}$.

### *3.4. (2S,4S)-2-Mesyloxymethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**5**)*

A solution of **4** (68.9 g, 0.15 mol) and triethylamine (24.2 mL, 0.18 mol) in dry $CH_2Cl_2$ (400 mL) was cooled to 0 °C under nitrogen and treated with methanesulfonyl chloride (20.6 g, 0.18 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 **5** (76.3 g, 94.8%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.91$ (bs, 1H), 2.11 (bs, 1H), 2.75–2.82 (bs, 2H), 2.99 (s, 3H), 3.95 (bs, 1H), 4.01 (m, 1H), 4.22 (bs, 1H), 4.55 (bs, 3H), 5.31 (m, 2H), 5.91 (m, 1H), 7.27 (m, 9H), 7.48 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 31.9, 35.1, 37.5, 41.4, 52.9, 55.8, 66.2, 67.8, 69.4, 117.9, 127.3, 128.5, 129.6, 133.0, 144.9, 154.7. IR (KBr): 2940, 1682, 1380 $cm^{-1}$.

### *3.5. (2S,4S)-2-Cyanomethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**6**)*

A mixture of **5** (59.2 g, 0.11 mol) and sodium cyanide (10.8 g, 0.22 mol) in DMSO (300 mL) was heated at 75 °C for 5 h. The reaction mixture was poured into ice water and extracted with ethyl acetate ($2 \times 300$ mL). The organic layer was successively washed with water ($2 \times 200$ mL), 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** (45.9 g, 89.1%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.88$ (m, 1H), 2.19 (m, 1H), 2.82 (d, 2H), 2.85–3.01 (m, 2H), 3.88 (m, 1H), 4.15 (bs, 1H), 4.55 (d, 2H, $J = 5.9$ Hz), 5.29 (m, 2H), 5.88 (m, 1H), 7.27 (m, 9H), 7.47 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 22.7, 38.1, 39.2, 41.4, 53.0, 53.8, 66.3, 67.8, 117.6, 118.9,

127.4, 128.5, 129.9, 132.9, 144.9, 154.7. IR (KBr): 2940, 2248, 1700 $cm^{-1}$.

### 3.6. (2S,4S)-2-(N-Hydroxyacetamidine)-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (7)

To a solution of **6** (23.4 g, 0.05 mol) and hydroxylamine hydrochloride (10.4 g, 0.15 mol) in EtOH (250 mL) was added slowly a solution of $Na_2CO_3$ (15.9 g, 0.15 mol) in water (70 mL) at room temperature and stirred for 20 h at 60 °C. The mixture was diluted with $H_2O$ (200 mL) and then was neutralised with 6*N*-HCl, diluted with ethyl acetate (300 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 **7** (19.3 g, 77.1%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.81$ (bs, 1H), 2.19 (m, 2H), 2.73–2.82 (bs, 3H), 3.88 (bs, 1H), 4.55 (d, 2H, $J =$ 5.9 Hz), 4.71 (bs, 1H), 5.22 (m, 2H), 5.88 (m, 1H), 7.23 (m, 9H), 7.47 (m, 6H), 8.55 (br, 1H). $^{13}$C-NMR ($CDCl_3$): 36.6, 38.4, 41.7, 53.1, 53.9, 55.6, 66.1, 67.8, 117.7, 127.2, 128.5, 129.9, 133.1, 145.1, 152.1, 154.9. IR (KBr): 3476, 3360, 2940, 1694, 1592 $cm^{-1}$.

### 3.7. (2S,4S)-2-(3-Allyloxycarbonylamino-2-hydroxyimino)ethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**8a**)

To a solution of **7** (1.00 g, 2.0 mmol) 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 $H_2O$ (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 **8a** (1.03 g, 88.3%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.82$ (bs, 2H), 2.19 (m, 1H), 2.24 (m, 1H), 2.63–2.85 (bs, 3H), 3.88 (bs, 1H), 4.55 (bs, 2H), 4.72 (d, 2H, $J = 5.9$ Hz), 5.20–5.44 (m, 5H), 5.85–5.98 (m, 2H), 7.23 (m, 9H), 7.47 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.1, 38.4, 41.6, 53.1, 55.6, 66.1, 67.8, 68.1, 117.6, 127.3, 128.5, 129.7, 133.2, 145.0, 152.1, 154.9, 157.3. IR (KBr): 3450, 2940, 1700, 1644, 1592 $cm^{-1}$.

**8b**, **8c** and **8d** were also prepared as described for the preparation of **8a** using the corresponding carbonyl chlorides.

**8b**: Yield 82.5%. $^1$H-NMR ($CDCl_3$) $\delta = 1.82$ (bs, 1H), 2.03 (s, 3H), 2.19 (m, 1H), 2.54 (m, 1H), 2.63–2.85 (bs, 3H), 3.88 (bs, 1H), 4.55 (bs, 2H), 5.25 (m, 3H), 5.90 (m, 1H), 7.23 (m, 9H), 7.47 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 18.8, 36.3, 38.4, 41.6, 53.1, 55.6, 66.1, 67.8, 117.6, 127.3, 128.5, 129.7, 133.1, 145.0, 152.1, 154.9, 167.3. IR (KBr): 3430, 2920, 1740, 1674, 1512 $cm^{-1}$.

**8c**: Yield 87.8%. $^1$H-NMR ($CDCl_3$) $\delta = 0.82$ (bs, 3H), 1.12 (bs, 2H), 1.82 (bs, 1H), 2.29 (m, 1H), 2.54 (m, 1H), 2.63–2.89 (bs, 3H), 3.83 (bs, 1H), 4.55 (bs, 2H), 5.25–5.34 (m, 3H), 5.87 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 11.2, 14.1, 36.3, 38.5, 41.6, 53.1, 55.4, 66.2, 67.8, 117.8, 127.2, 128.5, 129.9, 132.1, 144.7, 154.9, 156.5, 179.8. IR (KBr): 3420, 2930, 1720, 1670, 1490 $cm^{-1}$.

**8d**: Yield 83.5%. $^1$H-NMR ($CDCl_3$) $\delta = 1.84$ (bs, 1H), 2.28 (bs, 1H), 2.54 (m, 1H), 2.60–2.72 (bs, 3H), 3.85 (bs, 1H), 3.90 (s, 3H), 4.50 (bs, 2H), 5.25 (m, 3H), 5.86 (m, 1H), 7.24 (m, 9H), 7.46 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.1, 38.4, 41.6, 50.8, 53.1, 55.6, 66.1, 67.8, 117.6, 127.3, 128.5, 129.7, 133.1, 145.2, 152.5, 154.5, 169.5. IR (KBr): 3430, 2930, 1720, 1690, 1510 $cm^{-1}$.

### 3.8. (2S,4S)-2-(3-Aminocarbonylamino-2-hydroxyimino)ethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**8e**)

To a solution of **7** (1.00 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 ammonia water (10 mL) and stirred for 1 h at room temperature. 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 **8e** (0.89 g, 81.5%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.82$ (bs, 1H), 2.19 (m, 1H), 2.27 (m, 1H), 2.63–2.99 (bs, 3H), 3.84 (bs, 1H), 4.55 (bs, 2H), 4.72 (bs, 2H), 5.26 (m, 3H), 5.85 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.1, 38.4, 41.6, 53.1, 55.6, 66.1, 67.8, 117.7, 127.3, 128.6, 129.5, 133.2, 145.0, 152.5, 154.9, 158.7. IR (KBr): 3430, 2920, 1710, 1660 $cm^{-1}$.

Compounds **8f**–**8m** were also prepared as described for the preparation of **8e** using the corresponding amines.

**8f**: Yield 76.2%. $^1$H-NMR ($CDCl_3$) $\delta = 1.70$ (bs, 1H), 2.19 (bs, 1H), 2.27 (m, 1H), 2.63–2.90 (bs, 3H), 2.88 (d, 3H, $J = 4.7$ Hz), 3.83 (bs, 1H), 4.49 (bs, 2H), 5.26 (m, 3H), 5.88 (m, 1H), 6.44 (bs, 1H), 7.27 (m, 9H), 7.47 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 30.1, 36.3, 38.5, 41.6, 53.1, 55.4, 60.8, 66.2, 67.8, 117.8, 127.2, 128.5, 129.9, 132.1, 144.9, 154.2, 154.9, 157.5. IR (KBr): 3410, 2940, 1710, 1660, 1510 $cm^{-1}$.

**8g**: Yield 75.1%. $^1$H-NMR ($CDCl_3$) $\delta = 1.87$ (bs, 1H), 2.18 (m, 1H), 2.47 (m, 1H), 2.63–2.89 (bs, 3H), 3.01 (s, 6H), 3.84 (bs, 1H), 4.55 (bs, 2H), 5.04 (bs, 1H), 5.26 (m, 2H), 5.85 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 35.1, 36.3, 38.5, 41.6, 53.1, 55.4, 60.8,

66.2, 67.8, 117.8, 127.2, 128.5, 129.9, 132.1, 144.9, 154.1, 154.9, 157.5. IR (KBr): 3410, 2930, 1710, 1660, 1510 $cm^{-1}$.

**8h**: Yield 74.9%. $^1$H-NMR ($CDCl_3$) $\delta = 1.85$ (bs, 1H), 2.19 (m, 1H), 2.27 (m, 1H), 2.63–2.94 (bs, 3H), 2.99 (t, 2H, $J = 5.1$ Hz), 3.55 (t, 2H, $J = 5.1$ Hz), 3.84 (bs, 1H), 4.55 (bs, 2H), 5.16–5.33 (m, 3H), 5.85 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.1, 38.5, 41.6, 48.5, 53.1, 55.4, 62.8, 66.2, 67.8, 117.8, 127.2, 128.5, 129.9, 132.1, 144.9, 154.1, 154.9, 157.7. IR (KBr): 3550, 3410, 2930, 1710, 1670 $cm^{-1}$.

**8i**: Yield 71.3%. $^1$H-NMR ($CDCl_3$) $\delta = 1.84$ (bs, 1H), 2.26 (m, 1H), 2.45 (m, 1H), 2.63–2.72 (bs, 3H), 2.91(m, 1H), 3.51–3.57 (bs, 4H), 3.71–3.82 (bs, 4H), 4.56 (bs, 2H), 5.15–5.35 (m, 3H), 5.83 (m, 1H), 7.24 (m, 9H), 7.44 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.3, 38.8, 41.6, 47.1, 53.1, 55.5, 64.6, 66.2, 67.7, 117.8, 127.4, 128.5, 129.9, 133.2, 145.0, 154.1, 154.9, 156.6. IR (KBr): 3420, 2940, 1700, 1660, 1510 $cm^{-1}$.

**8j**: Yield 73.8%. $^1$H-NMR ($CDCl_3$) $\delta = 1.89$ (bs, 1H), 2.23 (m, 1H), 2.37 (m, 1H), 2.69–2.76 (bs, 6H), 2.96 (m, 2H), 3.74–3.84 (bs, 4H), 4.55 (bs, 2H), 5.16–5.33 (m, 3H), 5.85 (m, 1H), 7.24 (m, 9H), 7.44 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 27.6, 36.7, 38.8, 41.6, 47.1, 53.1, 55.5, 66.2, 67.7, 117.8, 127.4, 128.5, 129.9, 133.1, 144.9, 154.1, 154.9, 156.5. IR (KBr): 3420, 2940, 1700, 1660, 1510 $cm^{-1}$.

**8k**: Yield 72.9%. $^1$H-NMR ($CDCl_3$) $\delta = 1.90$ (bs, 1H), 2.25–2.37 (m, 1H), 2.63–2.74 (bs, 2H), 2.95 (m, 2H), 3.51–3.57 (bs, 8H), 3.84 (bs, 1H), 4.55 (bs, 2H), 5.14–5.35 (m, 3H), 5.85 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 36.7, 38.8, 41.6, 47.1, 49.9, 53.1, 55.5, 66.2, 67.7, 117.5, 127.4, 128.6, 129.9, 133.0, 144.9, 154.1, 154.9, 156.9. IR (KBr): 3440, 2920, 1710, 1670, 1510 $cm^{-1}$.

**8l**: Yield 75.2%. $^1$H-NMR ($CDCl_3$) $\delta = 1.56$–$1.74$ (bs, 6H), 1.92 (m, 1H), 2.27 (m, 1H), 2.63–2.94 (bs, 3H), 2.95 (m, 2H), 3.50–3.59 (bs, 4H), 3.86 (bs, 1H), 4.52 (bs, 2H), 5.14–5.35 (m, 3H), 5.83 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 24.6, 27.9, 36.7, 38.8, 41.6, 41.9, 53.1, 55.5, 66.2, 67.7, 117.8, 127.4, 128.5, 129.9, 133.1, 144.9, 154.1, 154.9, 156.5. IR (KBr): 3430, 2930, 1710, 1670, 1510 $cm^{-1}$.

**8m**: Yield 79.5%. $^1$H-NMR ($CDCl_3$) $\delta = 1.60$–$1.71$ (bs, 2H), 1.80–1.1.99 (bs, 3H), 2.27 (m, 1H), 2.63–2.94 (bs, 2H), 2.95 (m, 2H), 3.21 (bs, 1H), 3.70–3.89 (bs, 4H), 3.96 (bs, 1H), 4.42 (bs, 2H), 5.14–5.35 (m, 3H), 5.83 (m, 1H), 7.24 (m, 9H), 7.45 (m, 6H). $^{13}$C-NMR ($CDCl_3$): 28.5, 36.7, 38.8, 41.6, 41.9, 53.1, 55.5, 61.8, 66.2, 67.7, 117.8, 127.4, 128.6, 129.8, 133.0, 144.9, 154.1, 154.9, 156.9. IR (KBr): 3540, 3430, 2930, 1710, 1670, 1500 $cm^{-1}$.

### *3.9. (2S,4S)-2-(3-Allyloxycarbonylamino-2-hydroxyimino)ethyl-4-mercaptan-1-(allyloxycarbonyl)pyrrolidine (**9a**)*

To a solution of **8a** (0.59 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, which was purified by silica gel column chromatography to give **9a** (0.21 g, 61.2%) as a pale yellow oil. $^1$H-NMR ($CDCl_3$) $\delta = 1.89$ (bs, 2H), 2.40–2.55 (bs, 3H), 2.84 (bs, 1H), 3.05–3.18 (bs, 1H), 4.01 (bs, 1H), 4.55 (bs, 2H), 4.72 (bs, 2H), 5.26–5.55 (m, 4H), 5.85–5.93 (m, 2H). $^{13}$C-NMR ($CDCl_3$): 33.3, 38.9, 41.9, 53.7, 55.6, 67.8, 68.2, 117.6, 133.2, 152.1, 159.3, 159.9. IR (KBr): 3450, 2920, 1700, 1660, 1410 $cm^{-1}$.

The synthesis of compounds **9b**–**9m** were carried out by the same procedure as described for the preparation of **9a** and was used without the further purification.

### *3.10. Allyl(1R,5S,6S)-6-[(1R)-hydroxyethyl]-3-[5-(3-allyloxycarbonylamino-2-hydroxyimino) ethyl-1-yl]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio-1-methylcarbapen-2-em-3-carboxylate (**11a**)*

A solution of allyl(1*R*,5*S*,6*S*)-3-(diphenylphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (10, 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 **9a** (0.35 g, 1.0 mmol) 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 **11a** (0.43 g, 68.6%) as a yellow amorphous solid. $^1$H-NMR ($CDCl_3$) $\delta = 1.25$ (d, 3H, $J = 7.2$ Hz), 1.35 (d, 3H, $J = 6.3$ Hz), 1.98 (bs, 1H), 2.46 (m, 2H), 2.95 (dd, 1H, $J = 3.3$ and 3.3 Hz), 3.31 (dd, 1H, $J = 2.5$ and 2.6 Hz), 3.40 (m, 2H), 3.61 (bs, 1H), 4.11–4.19 (m, 3H), 4.55 (d, 2H, $J = 5.4$ Hz), 4.72–4.79 (m, 4H), 5.26–5.55 (m, 7H), 5.85 (m, 3H). IR (KBr): 3410, 3230, 1720, 1705, 1660 $cm^{-1}$.

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

### *3.11. (1R,5S,6S)-6-[(1R)-Hydroxyethyl]-3-[5-(3-amino-2-hydroxyiminoethyl-1-yl)pyrrolidin-3-yl-thio]-1-methylcarbapen-2-em-3-carboxylic acid (**12a**)*

Compound **11a** (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 **12a** as an amorphorus solid. Yield 17.9%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.11$ (d, 3H, $J = 6.9$ Hz), 1.19 (d, 3H, $J = 5.9$ Hz), 1.79 (bs, 2H), 2.65 (m, 1H), 2.86 (m, 2H), 3.21–3.43 (bs, 2H), 3.53 (bs, 1H), 3.70 (bs, 1H), 4.10 (m, 2H), 4.51 (bs, 1H). IR (KBr): 3378, 2970, 1745, 1666, 1592, 1392 cm$^{-1}$. HRMS (FAB) Calc. for $C_{16}H_{24}N_4O_5S$: 384.4517, Found: $[M+H]^+$ 384.4557.

The synthesis of compounds **12b**–**12m** were carried out by the same procedure as described for the preparation of **12a**.

**12b**: Yield 29.2%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.10$ (d, 3H, $J = 7.1$ Hz), 1.18 (d, 3H, $J = 6.3$ Hz), 1.67 (m, 1H), 1.90 (s, 3H), 2.74 (m, 1H), 2.86–2.96 (m, 2H), 3.21–3.44 (bs, 3H), 3.58 (dd, 1H, $J = 5.4$ and 5.8 Hz), 3.87 (bs, 2H), 4.11 (bs, 2H), 4.43 (m. 1H). IR (KBr): 3410, 1725, 1686, 1594, 1392 cm$^{-1}$. HRMS (FAB) Calc. for $C_{18}H_{26}N_4O_6S$: 426.4884, Found: $[M+H]^+$ 426.4869.

**12c**: Yield 23.8%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 0.79$ (m, 2H), 0.98 (m, 2H), 1.18 (d, 3H, $J = 7.1$ Hz), 1.31 (d, 3H, $J = 6.5$ Hz), 1.67 (m, 1H), 1.90–1.99 (bs, 2H), 2.63–2.74 (bs, 3H), 2.96 (m, 1H), 3.21–3.44 (bs, 2H), 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), 1745, 1680, 1650, 1410, 1166 cm$^{-1}$. HRMS (FAB) Calc. for $C_{20}H_{28}N_4O_6S$: 452.5257, Found: $[M+H]^+$ 452.5219.

**12d**: Yield 29.2%. UV $\lambda_{max}$: 298nm. $^1$H-NMR ($D_2O$) $\delta = 1.14$ (d, 3H, $J = 7.2$ Hz), 1.25 (d, 3H, $J = 6.6$ Hz), 1.77 (m, 1H), 2.44–2.57 (m, 2H), 2.96 (m, 1H), 3.21–3.44 (bs, 2H), 3.54 (bs, 1H), 3.83 (bs, 1H), 3.90 (s, 3H), 3.98 (bs, 1H), 4.14 (bs, 2H), 4.43 (m, 1H). IR (KBr): 3400, 1755, 1690, 1639, 1415 cm$^{-1}$. HRMS (FAB) Calc. for $C_{18}H_{26}N_4O_7S$: 442.4878, Found: $[M+H]^+$ 442.4899.

**12e**: Yield 20.6%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.12$ (d, 3H, $J = 7.2$ Hz), 1.25 (d, 3H, $J = 6.6$ Hz), 1.79 (m, 1H), 2.45–2.59 (m, 2H), 2.96 (m, 1H), 3.28–3.44 (bs, 2H), 3.54 (bs, 1H), 3.88 (bs, 1H), 3.99 (bs, 1H), 4.14 (bs, 2H), 4.45 (m. 1H). IR (KBr): 3388, 1757, 1689, 1591, 1409 cm$^{-1}$. HRMS (FAB) Calc. for $C_{17}H_{25}N_5O_6S$: 427.4765, Found: $[M+H]^+$ 427.4755.

**12f**: Yield 21.5%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.13$ (d, 3H, $J = 7.3$ Hz), 1.20 (d, 3H, $J = 6.6$ Hz), 1.77 (m, 1H), 2.55 (s, 3H), 2.59–2.75 (m, 2H), 2.80–2.96 (m, 2H), 3.28–3.44 (bs, 2H), 3.54 (bs, 1H), 3.88 (bs, 1H), 3.93 (bs, 1H), 4.16 (bs, 1H), 4.45 (m, 1H). IR (KBr): 3397, 1759, 1680, 1591, 1411 cm$^{-1}$. HRMS (FAB) Calc. for $C_{18}H_{27}N_5O_6S$: 441.5031, Found: $[M+H]^+$ 441.3987.

**12g**: Yield 19.9%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.13$ (d, 3H, $J = 7.3$ Hz), 1.20 (d, 3H, $J = 6.6$ Hz), 1.75 (m, 1H), 2.63 (s, 6H), 2.69–2.79 (m, 2H), 2.85–2.96 (m, 2H), 3.28–3.40 (bs, 2H), 3.55 (bs, 1H), 3.85 (bs, 1H), 3.93 (bs, 1H), 4.13 (bs, 1H), 4.45 (m, 1H). IR (KBr): 3390, 1755, 1680, 1590, 1420 cm$^{-1}$. HRMS (FAB) Calc. for $C_{19}H_{29}N_5O_6S$: 455.5297, Found: $[M+H]^+$ 455.3788.

**12h**: Yield 21.5%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.13$ (d, 3H, $J = 7.2$ Hz), 1.20 (d, 3H, $J = 6.3$ Hz), 1.77 (m, 1H), 2.54–2.72 (m, 2H), 2.80–2.92 (m, 2H), 2.99 (t, 2H, $J = 5.1$ Hz), 3.28–3.44 (bs, 3H), 3.54 (bs, 1H), 3.70 (t, 2H, $J = 5.1$ Hz), 3.93 (bs, 1H), 4.16 (bs, 2H), 4.41 (m, 1H). IR (KBr): 3397, 1756, 1685, 1595, 1401 cm$^{-1}$. HRMS (FAB) Calc. for $C_{19}H_{29}N_5O_7S$: 471.5291, Found: $[M+H]^+$ 471.4555.

**12i**: Yield 22.2%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.10$ (d, 3H, $J = 7.0$ Hz), 1.18 (d, 3H, $J = 6.3$ Hz), 1.79 (m, 1H), 2.49–2.67 (m, 3H), 2.92 (m, 1H), 3.08–3.16 (bs, 4H), 3.28–3.43 (bs, 2H), 3.52 (m, 1H), 3.69–3.81 (bs, 4H), 3.91 (bs, 1H), 4.05 (bs, 2H), 4.45 (m, 1H). IR (KBr): 3490, 1740, 1700, 1660, 1400 cm$^{-1}$. HRMS (FAB) Calc. for $C_{21}H_{31}N_5O_7S$: 497.5663, Found: $[M+H]^+$ 497.5670.

**12j**: Yield 20.6%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.12$ (d, 3H, $J = 7.2$ Hz), 1.26 (d, 3H, $J = 6.4$ Hz), 1.88 (m, 1H), 2.45–2.54 (m, 2H), 2.59 (bs, 4H), 2.90 (m, 1H), 3.15 (bs, 1H), 3.28–3.44 (bs, 6H), 3.55 (m, 1H), 3.75 (bs, 1H), 3.88 (bs, 1H), 4.16 (bs, 2H), 4.45 (m, 1H). IR (KBr): 3980, 1710, 1660, 1580, 1405 cm$^{-1}$. HRMS (FAB) Calc. for $C_{23}H_{31}N_5O_6S_2$: 513.6329, Found: $[M+H]^+$ 513.6341.

**12k**: Yield 19.2%. UV $\lambda_{max}$: 298 nm. m.p. 125–136 °C (dec.). $^1$H-NMR ($D_2O$) $\delta = 1.07$ (d, 3H, $J = 7.0$ Hz), 1.14 (d, 3H, $J = 6.2$ Hz), 1.87 (m, 1H), 2.45–2.59 (m, 2H), 2.88 (m, 1H), 2.97 (bs, 8H), 3.15 (bs, 1H), 3.28–3.44 (bs, 3H), 3.55 (m, 1H), 4.06 (bs, 2H), 4.45 (m. 1H). IR (KBr): 3470, 1730, 1660, 1586, 1400 cm$^{-1}$. HRMS (FAB) Calc. for $C_{31}H_{32}N_6O_6S$: 496.5816, Found: $[M+H]^+$ 496.5825.

**12l**: Yield 20.1%. UV $\lambda_{max}$: 298 nm. m.p. 114–131 °C (dec.). $^1$H-NMR ($D_2O$) $\delta = 1.09$ (d, 3H, $J = 7.2$ Hz), 1.16 (d, 3H, $J = 6.4$ Hz), 1.58 (bs, 2H), 1.70–1.88 (m, 4H), 2.01 (m, 1H), 2.45–2.59 (m, 2H), 2.90 (m, 1H), 3.05 (bs, 4H), 3.55 (m, 1H), 3.75 (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 $C_{22}H_{33}N_5O_6S$: 495.5935, Found: $[M+H]^+$ 495.5921.

**12m**: Yield 15.9%. UV $\lambda_{max}$: 298 nm. $^1$H-NMR ($D_2O$) $\delta = 1.07$ (d, 3H, $J = 7.1$ Hz), 1.12 (d, 3H, $J = 6.2$ Hz), 1.52 (bs, 3H), 1.88 (bs, 3H), 2.45–2.49 (m, 1H), 2.90–2.96 (m, 3H), 3.07–3.19 (bs, 5H), 3.55–3.67 (m, 2H), 3.88 (bs, 1H), 4.03 (m, 2H), 4.45 (m, 1H). IR (KBr): 3370, 1755, 1690, 1580, 1430 cm$^{-1}$. HRMS (FAB) Calc.

for $C_{22}H_{33}N_5O_7S$: 511.5929, Found: $[M+H]^+$ 511.5929.

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