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Original article

Synthesis and biological evaluation of 1β-methylcarbapenems having cyclic thiourea moieties and their related compounds

T. Han [b], J.-H. Cho [a], C.-H. Oh [a,*]

[a] *Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul 130-650, South Korea*
[b] *Hawon Pharm. Co., Seoul 135-080, South Korea*

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Abstract

The synthesis of a new series of 1β-methylcarbapenems having cyclic thiourea moieties 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. A particular compound (**IIId**) having piperazine thiourea moiety showed the most potent antibacterial activity.

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

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 synthesized and investigated with enthusiasm. Among those compounds, panipenem [2] and meropenem [3] was 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) because of the introduction of a 1β-methyl| group to the carbapenem skeleton for high antibacterial potency. We were also interested in this pyrroldin-3-ylthio group and 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 synthesized and investigated [7–13]. In our previous work [13], the introduction of thiourea moieties showed potent and well-balanced antibacterial activity.

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

2. 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.

The *O*-mesylated compound **1** was treated with sodium triphenylmethylthioate, which was generated in situ from triphenylmethyl mercaptan and sodium hydride in DMF, to provide **2** with inversion of the C-4 configuration. Compound **2** was reduced with lithium borohydride in THF-EtOH and subsequently mesylated to give **4**. The treatment of the mesylated **4** with sodium azide in DMSO gave the azide compound **5**, which was successfully converted into the amine **6** using triphenylphosphine.

The amine **6** was converted to the isothiocyanate compound **7** by treatment of carbon disulfide and ethyl chloroformate. Preparation of the thiourea type compounds (**8**) was accomplished by treatment of compound **7** with corresponding cyclic amine (Scheme 1).

* Corresponding author.
E-mail address: choh@kist.re.kr (C.-H. Oh).

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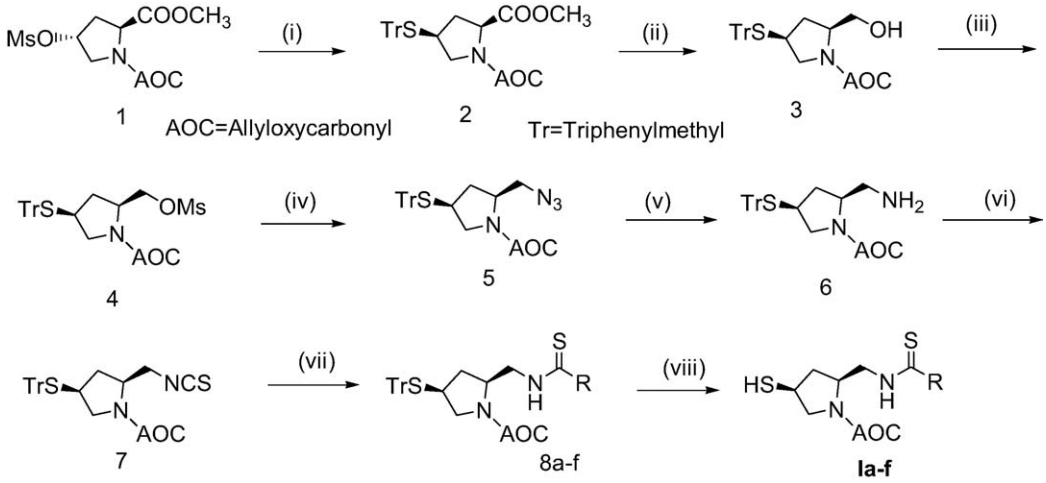
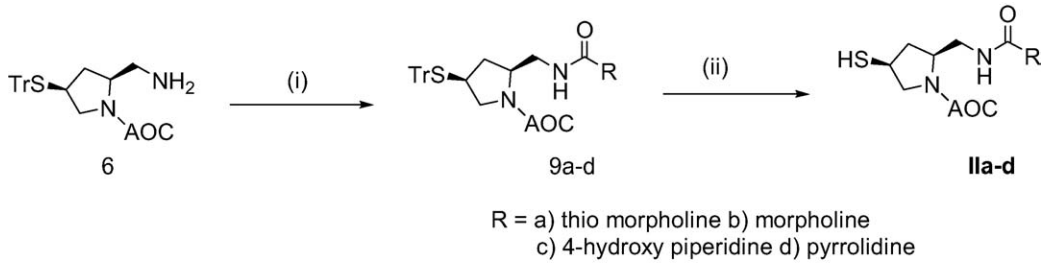


(i) Triphenylmethanethiol, NaH,DMF; (ii) $LiBH_4$, THF/EtOH; (iii) MsCl, TEA, CH_2Cl_2; (iv) NaN_3, DMSO; (v) Ph_3P, H_2O, THF; (vi) CS_2, ethyl chloroformate, TEA, THF; (vii) Cyclic amine, MeOH; (viii) TFA, Et_3SiH, CH_2Cl_2

Scheme 1.



(i) 1) *p*-Nitrophenyl chloroformate, TEA, CH_2Cl_2 2) Cyclic amine, CH_2Cl_2 ; ii) TFA, Et_3SiH, CH_2Cl_2

Scheme 2.

Carbamoylation of amine was carried out by a conventional method using *p*-nitrophenyl chloroformate to give urea type compounds (**9**) (Scheme 2). Deprotection of the trityl group to mercaptans (**I** and **II**) were achieved by treatment of **8** and **9** with trifluoroacetic acid in the presence of triethylsilane.

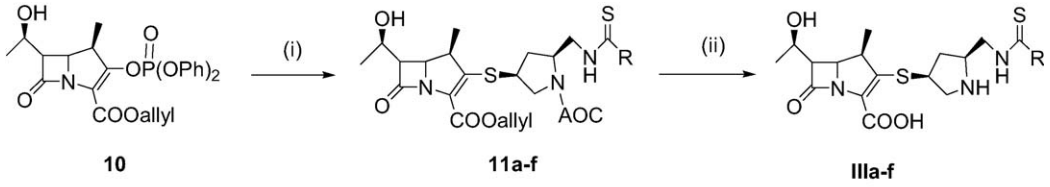
Finally, the reaction of **10** [14] with thiols (**I** and **II**) in the presence of diisopropylethylamine provided the 2-substituted carbapenems (**11**). Deprotection of these compounds were carried out by tetrakis(triphenylphosphine)palladium(0) and tributyltin hydride gave the crude products, which were purified by HP-20 column to give the pure carbapenems (**III** and **IV**) (Scheme 3).

3. Biological activity

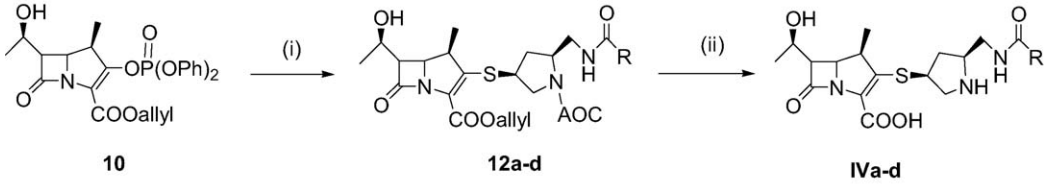
The MICs were determined by the agar dilution method using test agar. An overnight culture of bacteria in tryptosoy broth was diluted to about 10^6 cells per ml with the same broth and inoculated with an inoculating device onto agar containing serial twofold dilutions of the test compounds. Organisms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

The in vitro antibacterial activities of the new carbapenems (**IIIa–f** and **IVa–d**) 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 compounds displayed superior or similar antibacterial activities against Gram-positive to meropenem, and against Gram-negative bacteria except *Pseudomonas aeruginosa* to imipenem.

As to the substituent on the pyrrolidine chain, the compounds **IIIa–f** having cyclic thiourea moieties were generally more potent than the cyclic urea compounds **IVa–d**. Comparing the compounds **IIIa–f** having cyclic thiourea moieties showed slight differences in the antibacterial activities against Gram-positive and Gram-negative bacteria. As expected, the piperazine thio compound **IIId** exhibited the most potent and well-balanced activity. Furthermore we observed that the thiomorpholine thiourea **IIIa** is more potent than the morpholine **IIIb**. Introduction of sulfur atom significantly enhanced antibacterial activity against Gram-negative bacteria compared to that of oxygen atom (Table 2).



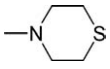
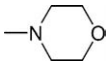
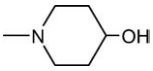
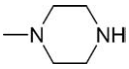
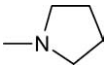
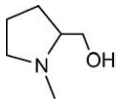
(i) **I** , *N,N*-Diisopropylethyl amine, CH_3CN: (ii) n-Bu_3SnH, cat. $(PPh)_4Pd(0)$, CH_2Cl_2



(i) **II**, *N,N*-Diisopropylethyl amine, CH_3CN: (ii) n-Bu_3SnH, cat. $(PPh)_4Pd(0)$, CH_2Cl_2

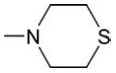
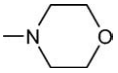
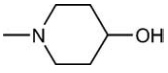
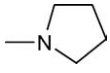
Scheme 3.

Table 1
In vitro antibacterial activities of carbapenem derivatives (**IIIa**–**f**)

R=							IPM[a]	MPM[b]
Organism	**IIIa**	**IIIb**	**IIIc**	**IIId**	**IIIe**	**IIIf**		
Streptococcus pyogenes. 308A	< 0.01	0.01	< 0.01	< 0.01	0.01	<0.01	<0.01	0.01
Streptococcus pyogenes 77A	0.03	0.05	< 0.01	< 0.01	0.03	<0.01	<0.01	0.01
Streptococcus aureus SG 511	0.01	0.05	0.03	0.03	0.05	0.03	0.01	0.05
Streptococcus aureus 503	0.01	0.03	0.03	0.01	0.05	0.03	0.01	0.05
Escherichia coli DC O	0.05	0.05	0.05	0.05	0.05	0.05	0.40	0.03
Escherichia coli 1507 E	0.03	0.05	0.05	0.05	0.05	0.03	0.10	0.03
P. aeruginosa 9027	3.10	3.10	1.50	0.40	6.20	1.50	0.80	0.40
Salmonella typhimurium	0.03	0.10	0.10	0.10	0.10	0.05	0.80	0.05
Enterobacter cloacae P 99	0.05	0.10	0.05	0.05	0.10	0.05	0.10	0.03
Enterobacter cloacae 1321 E	0.01	0.05	0.05	0.05	0.10	0.03	0.20	0.03
DHP-I	2.37	1.67	2.31	1.85	1.54	1.98	0.12	1.00

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

Table 2
In vitro antibacterial activities of carbapenem derivatives (**IVa**–**d**)

R=					IPM[a]	MPM[b]
Organism	**IVa**	**IVb**	**IVc**	**IVd**		
Streptococcus pyogenes 308A	0.01	0.02	0.01	0.01	<0.01	0.01
Streptococcus pyogenes 77A	0.10	0.20	0.05	0.10	<0.01	0.01
Streptococcus aureus SG 511	0.10	0.20	0.10	0.10	0.01	0.05
Streptococcus aureus 503	0.10	0.10	0.05	0.05	0.01	0.05
Escherichia coli DC O	0.20	0.40	0.20	0.20	0.40	0.03
Escherichia coli 1507 E	0.10	0.20	0.10	0.10	0.10	0.03
P. aeruginosa 9027	6.10	12.0	3.10	6.10	0.80	0.40
Salmonella typhimurium	0.20	0.20	0.10	0.20	0.80	0.05
Enterobacter cloacae P 99	0.20	0.40	0.20	0.20	0.10	0.03
Enterobacter cloacae 1321 E	0.10	0.20	0.10	0.10	0.20	0.03
DHP-I	0.80	0.75	1.23	1.14	0.18	1.00

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

Table 3
Comparative in vitro antibacterial activity of **IIId**, meropenem and imipenem against 40 strains (MIC, μg ml^{-1})

Organism	**IIId**	IPM	MPM	Organism	**IIId**	IPM	MPM
***Staphylococcus aureus* giorgio**	0.03	0.01	0.10	***Salmonella paratyphi* A**	0.10	0.10	0.03
***Staphylococcus aureus* 209P**	0.03	0.01	0.10	*Salmonella typhimurium*	0.20	0.40	0.05
***Staphylococcus aureus* 503**	0.01	< 0.01	0.05	*Salmonella oranienberg*	0.20	0.40	0.05
Micrococcus luteus ATCC 9341	0.01	0.01	0.05	*Salmonella typhi*	0.03	0.05	0.01
Streptococcus facium 77A	<0.01	< 0.01	0.01	*Salmonella orion*	0.10	0.20	0.10
Streptococcus agalctiae B	0.03	0.01	0.05	*Salmonella give*	0.10	0.20	0.03
Streptococcus durans D	0.10	0.10	0.80	*Klebsiella pneumonise 477*	0.20	0.20	0.05
Bacillus subtilts ATCC 6633	0.03	0.03	0.05	*Enterobacter cloacae*	0.03	0.10	0.01
Bacillus megatherium	0.05	0.03	0.05	*Enterobacter cloacae 417*	0.05	0.10	0.01
P. aeruginosa 9027	0.80	0.80	0.40	*Serratia marcescens 370*	0.20	0.20	0.05
P. aeruginosa 77/2	0.80	0.80	0.80	*Serratia marcescens 6093*	0.20	0.40	0.05
P. aeruginosa 110/2	0.80	0.80	0.40	*Serratia marcescens 14273*	0.40	0.80	0.20
P. aeruginosa 880/2	0.40	0.80	0.20	*Proteus mirabilis 112/3*	0.20	0.20	0.10
P. cepacia	0.10	0.80	0.40	*Proteus mirabilis 174/3*	0.20	0.10	0.10
Escherichia coli 086	0.05	0.10	0.03	*Proteus vulgaris 868*	0.40	0.10	0.10
Escherichia coli 0114	0.05	0.10	0.01	*Proteus rettgeri 936*	0.40	0.20	0.10
Escherichia coli 0126	0.05	0.10	0.03	*Proteus rettgeri 937*	0.40	0.20	0.05
Escherichia coli V6311/65	0.05	0.05	0.01	*Pasteurella multocida*	0.05	<0.01	0.05
Escherichia coli TEM	0.10	0.20	0.03	*Corynebacterium diphtheriae*	0.01	0.01	0.05
Escherichia coli 1507	0.10	0.10	0.03	*Corynebacterium pyogenes*	0.01	< 0.01	0.03
Streptococcus p. 308A	< 0.01	< 0.01	0.01				
Streptococcus p. 77A	< 0.01	< 0.01	0.01				
Streptococcus a. SG 511	0.03	0.01	0.05				
Streptococcus a. 503	0.01	0.01	0.05				
***Escherichia coli* DC O**	0.05	0.40	0.03				
Pseudomonas a. 9027	0.40	0.80	0.40				
Salmonella typhimurium	0.10	0.80	0.05				
Enterobacter cloacae P99	0.05	0.10	0.03				
Enterobacter c.1321E	0.05	0.20	0.03				
DHP-I	1.85	0.12	1.00				

The stability [13] to DHP-I of most compounds was tested and all the compounds were more stable than meropenem. In particular, the compounds **IIIa** and **IIIc** exhibited the most stability.

The thiourea substituted compounds (**IIIa**–**f**) showed more improved stability to DHP-I than the urea analogues (**IVa**–**d**).

Comparative in vitro activities of **IIId**, meropenem, and imipenem against 40 bacterial strains were summarized in Table 3. The selected carbapenem **IIId** possessed excellent in vitro activity against 40 target pathogens except *P. aeruginosa*, and superior or similar antibacterial activities against Gram-positive to meropenem, and against Gram-negative bacteria to imipenem. Against *Pseudomonas cepacia*, **IIId** was two to four times more active than the compared meropenem and imipenem.

4. 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, 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.

*4.1. (2S,4S)-4-Tritylthio-1-(allyloxycarbonyl)pyrrolidine-2-carboxylic acid methyl ester (**2**)*

To a stirred solution of triphenylmethylthiol (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 **1** (76.7 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 = 1:6) to give **2** (100.6 g, 82.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.75–1.85 (m, 1H), 2.01–2.20 (m, 1H), 2.85 (m, 1H), 3.16 (bs, 1H), 3.54 (bs, 1H), 3.77 and 3.80 (2s, 3H), 4.22 (m, 1H), 4.50–4.59 (bs, 2H), 5.20–5.31 (m, 2H), 5.84–5.98 (m, 1H) 7.18–7.26 (m, 9H), 7.48 (d, 6H, J = 7.2).

*4.2. (2S,4S)-2-Hydroxymethyl-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (**3**)*

To a solution of **2** (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 9 h at room temperature. The mixture was diluted with H_2O

(200 ml), 1 N-HCl (200 ml) and 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 (EtOAc/n-hexane = 1:3) to give **3** (79.4 g, 78.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.58 (m, 1H), 1.98 (m, 1H), 2.75–2.89 (m, 2H), 3.01 (m, 1H), 3.55 (bs, 2H), 3.74 (m, 1H), 4.52 (bs, 2H), 5.23–5.30 (m, 2H), 5.80–5.88 (m, 1H), 7.20–7.27 (m, 9H), 7.47 (d, 6H, J = 7.5).

*4.3. (2S,4S)-2-Mesyloxymethyl-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (**4**)*

A solution of **3** (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 (EtOAc/n-hexane = 1:3) to give **4** (75.2 g, 93.2%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.81 (bs, 1H), 2.11 (bs, 1H), 2.75–2.82 (bs, 2H), 2.99 (bs, 4H), 3.95 (bs, 1H), 4.22 (bs, 1H), 4.40–4.50 (bs, 3H), 5.22-5.31 (bs, 2H), 5.80–5.91 (m, 1H), 7.20–7.31 (m, 9H), 7.48 (d, 6H, J = 7.7).

*4.4. (2S,4S)-2-Azidomethyl-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (**5**)*

A mixture of **4** (28.5 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 (EtOAc/n-hexane = 1:5) to give **5** (22.6 g, 85.4%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.92 (m, 1H), 2.15 (m, 1H), 2.77–2.82 (bs, 2H), 2.85–3.01 (m, 2H), 3.88 (m, 1H), 4.52–4.63 (bs, 3H), 5.29–5.38 (bs, 2H), 5.80–5.88 (m, 1H), 7.22–7.31 (m, 9H), 7.46 (d, 6H, J = 7.5).

*4.5. (2S,4S)-2-(2-Aminomethyl-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (**6**)*

A mixture of **5** (9.0 g, 18.0 mmol), triphenylphosphine (5.36 g, 20.0 mmol) and H_2O (0.34 ml, 18.0 mmol) in THF (30 ml) was heated at 40 °C for 4 h. After cooling, the reaction mixture was diluted with H_2O (30 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 (EtOAc/acetone = 2:1) to give **6** (7.29 g, 88.3%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.88 (m, 1H), 2.19 (m, 1H), 2.4–2,80 (d, 2H), 2.85–3.01 (m, 2H), 3.88 (m, 1H), 4.45–4.56 (m, 2H), 5.22–5.30 (bs, 2H), 5.81–5.93 (m, 1H), 7.20–7.30 (m, 9H), 7.45 (d, 6H, J = 7.5).

4.6. (2S,4S)-2-(2-Isothiocyanatomethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (7)

A solution of **6** (2.0 g, 4.4 mmol) and triethylamine (0.66 ml, 4.8 mmol) in dry THF (20 ml) was cooled to 0 °C under nitrogen and treated with carbon disulfide (0.30 ml, 4.8 mmol). The mixture was stirred at 0 °C for 1 h and was dropwise ethyl chloroformate (0.45 ml, 4.80 mmol). The mixture was stirred at room temperature for 1 h, and then diluted with ethyl acetate (100 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 = 1:4) to give **7** (2.0 g, 91.6%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.70–1.77 (m, 1H), 1.94 (m, 1H), 2.81 (m, 1H), 2.89–3.10 (bs, 2H), 3.51 (bs, 1H), 3.78 (bs, 1H), 3.90 (bs, 1H), 4.55–4.62 (m, 2H), 5.26–5.35 (m, 2H), 5.85–5.97 (m, 1H), 7.21–7.34 (m, 9H), 7.50 (d, 6H, J = 7.2).

*4.7. (2S,4S)-2-[2-(4-Thiomorpholinylthioureido)methyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**8a**)*

To a solution of **7** (1.0 g, 2.0 mmol) in MeOH (10 ml) was added slowly thiomorpholine (0.41 g, 4.0 mmol) at room temperature and was stirred for 2 h. The mixture was diluted with H_2O (30 ml) and ethyl acetate (50 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by silica gel column chromatography (EtOAc/n-hexane = 1:1) to give **8a** (0.98 g, 84.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.54 (m, 1H), 2.12 (m, 1H), 2.43 (bs, 1H), 2.73–2.80 (bs, 4H), 2.83–2.90 (bs, 2H), 2.96–3.17 (bs, 2H), 3.68–3.89 (bs, 1H), 3.85–4.15 (m, 4H), 4.45 (d, 2H, J = 5.5 Hz), 5.23–5.30 (m, 2H), 5.85–5.97 (m, 1H), 7.22–7.32 (m, 9H), 7.46 (d, 6H, J = 7.5), 8.07 (bs, 1H).

The synthesis of compounds **8b**–**f** were carried out by the same procedure as described for the preparation of **8a** using the corresponding amines.

8b: Yield 85.5%. ^{1}H-NMR ($CDCl_3$) δ 1.64 (m, 1H), 2.12 (m, 1H), 2.69–2.77 (m, 2H), 3.01 (bs, 1H), 3.30 (m, 1H), 3.66 (bs, 4H), 3.75 (bs, 4H), 3.89 (m, 2H), 4.44 (d, 2H, J = 5.2 Hz), 5.23–5.29 (m, 2H), 5.72–5.81 (m, 1H), 7.22–7.32 (m, 9H), 7.46 (d, 6H, J = 7.5), 8.13 (bs, 1H).

8c: Yield 83.0%.^{1}H-NMR ($CDCl_3$) δ 1.45–1.50 (bs, 3H), 1.75–1.85 (bs, 2H), 2.18 (m, 1H), 2.68–2.74 (bs, 2H), 2.92–2.98 (bs, 2H), 3.29–3.40 (m, 3H), 3.82–3.90 (bs, 3H), 4.04–4.20 (bs, 2H), 4.35 (d, 2H, J = 5.8), 5.17–5.24 (m, 2H), 5.86 (m, 1H), 7.22–7.32 (m, 9H), 7.46 (d, 6H, J = 7.5), 8.00 (bs, 1H).

8d: Yield 88.8%. ^{1}H-NMR ($CDCl_3$) δ 1.53 (m, 1H), 2.07 (m, 1H), 2.65–2.77 (bs, 2H), 3.02 (bs, 1H), 3.32 (bs, 1H),

3.80–3.95 (bs, 8H), 4.46 (d, 2H, $J = 5.8$), 5.22–5.26 (bs, 2H), 5.90–5.96 (m, 1H), 7.18–7.31 (m, 9H), 7.46 (d, 6H, $J = 7.0$), 8.10 (bs, 1H).

8e: Yield 79.4%. ^{1}H-NMR ($CDCl_3$) δ 1.53 (m, 1H), 1.84–1.95 (bs, 4H), 2.18 (m, 1H), 2.68–2.74 (bs, 2H), 2.97 (bs, 1H), 3.05 (bs, 1H), 3.54–3.69 (bs, 5H), 3.82 (bs, 1H), 4.48 (d, 2H, $J = 5.8$), 5.25–5.34 (m, 2H), 5.86 (m, 1H), 7.22–7.32 (m, 9H), 7.46 (d, 6H, $J = 7.3$), 8.06 (bs, 1H).

8f: Yield 79.4%. ^{1}H-NMR ($CDCl_3$) δ 1.42–1.50 (bs, 2H), 1.80–1.91 (bs, 3H), 2.10–2.21 (m, 1H), 2.68–2.74 (bs, 2H), 2.97 (bs, 1H), 3.15 (bs, 2H), 3.64–3.72 (bs, 5H), 3.82 (bs, 1H), 4.48 (d, 2H, $J = 5.8$), 5.25–5.34 (m, 2H), 5.82–5.89 (m, 1H), 7.22–7.32 (m, 9H), 7.46 (d, 6H, $J = 7.5$), 8.03 (bs, 1H).

*4.8. (2S,4S)-2-[2-(Thiomorpholinylureido)methyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**9a**)*

To a solution of **6** (2.0 g, 4.4 mmol) and triethylamine (1.34 ml, 9.6 mmol) in dry CH_2Cl_2 (30 ml) was added slowly *p*-nitrophenyl chloroformate (1.0 g, 5.0 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 thiomorpholine (0.90 g, 8.7 mmol) and stirred for 1 h at room temperature. The reaction mixture was neutralized with 3 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 (EtOAc/n-hexane = 1:1) to give **9a** (1.4 g, 55.0%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.57 (m, 1H), 2.17 (m, 1H), 2.53–2.57 (bs, 4H), 2.72–2.77 (bs, 2H), 2.95–3.10 (bs, 2H), 3.61 (m, 1H), 3.64–3.69 (bs, 4H), 3.79 (m, 1H), 4.47 (d, 2H, $J = 5.9$ Hz), 5.21–5.26 (d, 2H), 5.80–5.86 (m, 1H), 6.45 (bs, 1H), 7.18–7.32 (m, 9H), 7.46 (d, 6H, $J = 7.5$).

The compounds **9b**–**d** were also prepared as described for the preparation of **9a** using the corresponding amines.

9b: Yield 60.2%. ^{1}H-NMR ($CDCl_3$) δ 1.42 (bs, 1H), 2.05 (bs, 1H), 2.67 (bs, 1H), 2.97 (bs, 1H), 3.07 (bs, 2H), 3.24 (bs, 4H), 3.75 (bs, 5H), 3.82 (bs, 1H), 4.45 (bs, 2H), 5.25 (bs, 2H), 5.75–5.80 (m, 1H), 6.65 (bs, 1H), 7.13–7.22 (m, 9H), 7.40 (d, 6H, $J = 7.5$).

9c: Yield 58.8%. ^{1}H-NMR ($CDCl_3$) δ 1.45–1.52 (bs, 3H), 1.76–1.84 (bs, 2H), 2.11 (m, 1H), 2.68–2.77 (bs, 1H), 2.90–2.95 (bs, 2H), 3.33–3.45 (bs, 2H), 3.82–3.94 (bs, 4H), 4.04–4.10 (bs, 2H), 4.39 (bs, 2H), 5.25–5.32 (m, 2H), 6.55 (bs, 1H), 7.14–7.20 (m, 9H), 7.42 (d, 6H, $J = 7.5$).

9d: Yield 52.9%. ^{1}H-NMR ($CDCl_3$) δ 1.45 (m, 1H), 1.69–1.85 (bs, 4H), 2.12 (bs, 1H), 2.68–2.94 (bs, 4H), 3.29 (m, 1H), 3.75–3.82 (bs, 4H), 3.90 (bs, 1H), 4.45 (bs, 2H), 5.25–5.34 (m, 2H), 5.79–5.83 (m, 1H), 6.60 (bs, 1H), 7.14–7.20 (m, 9H), 7.42 (d, 6H, $J = 7.8$).

*4.9. Allyl (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[5-(thiomorpholinylthioureido)methyl]-1-(allyloxycarbonyl) pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (**11a**)*

To a solution of **8a** (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 (**Ia**), 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 (**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 diisopropylethyl amine (0.13 g, 1.0 mmol) and a solution of the mercapto compound **Ia** 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 = 2:1) to give **11a** (0.38 g, 59.5%) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, $J = 7.0$ Hz), 1.37 (d, 3H, $J = 6.2$ Hz), 1.88–1.96 (bs, 2H), 2.19 (bs, 2H), 2.66–2.85 (bs, 4H), 3.10 (bs, 1H), 3.25–3.36 (m, 2H), 3.49–3.59 (bs, 2H), 3.71–3.84 (bs, 4H), 3.95 (m, 1H), 4.10–4.23 (bs, 2H), 4.40–4.52 (bs, 2H), 4.85 (dd, 1H, $J = 5.2$ and 5.6 Hz), 4.98 (dd, 1H, $J = 5.2$ and 5.6 Hz), 5.12–5.50 (m, 4H), 5.69–6.01 (bs, 2H), 8.08 (s, 1H).

The synthesis of compounds **11b**–**f** and **12a**–**d** were carried out by the same procedure as described for the preparation of **11a**.

11b: Yield 61.4%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, $J = 7.1$ Hz), 1.33 (d, 3H, $J = 6.4$ Hz), 1.74 (bs, 1H), 2.02 (bs, 1H), 2.56 (m, 1H), 3.10–3.30 (bs, 2H), 3.49–3.59 (bs, 2H), 3.65–3.74 (bs, 4H), 3.81–3.90 (bs, 5H), 4.10–4.23 (bs, 2H), 4.40–4.52 (bs, 2H), 4.59 (dd, 1H, $J = 5.2$ and 5.6 Hz), 4.68 (dd, 1H, $J = 5.2$ and 5.6 Hz), 5.13–5.45 (m, 4H), 5.69–6.00 (bs, 2H), 8.09 (bs, 1H).

11c: Yield 49.8%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, $J = 7.0$ Hz), 1.34 (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), 3.23–3.39 (m, 2H), 3.49–3.69 (bs, 4H), 3.80–3.95 (m, 2H), 4.10–4.20 (bs, 5H), 4.40–4.52 (bs, 2H), 4.59 (dd, 1H, $J = 5.1$ and 5.5 Hz), 4.68 (dd, 1H, $J = 5.1$ and 5.5 Hz) , 5.20–5.49 (m, 4H), 5.89–6.00 (bs, 2H), 7.99 (bs, 1H).

11d: Yield 51.4%. ^{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, 2H), 4.55 (bs, 2H), 4.59 (m, 2H), 4.78 (m, 2H), 5.12–5.50 (m, 6H), 5.65–6.01 (bs, 3H), 8.20 (bs, 1H).

11e: Yield 59.2%. ^{1}H-NMR ($CDCl_3$) δ 1.28 (d, 3H, $J = 7.0$ Hz), 1.37 (d, 3H, $J = 6.1$ Hz), 1.43–1.52 (bs, 2H), 1.63–1.88 (bs, 3H), 1.98 (m, 1H), 2.46 (bs, 1H), 3.10 (bs, 1H), 3.20–3.44 (m, 3H), 3.49–3.69 (bs, 4H), 3.95–4.08 (m,

1H), 4.11–4.23 (bs, 2H), 4.26–4.69 (bs, 6H), 5.13–5.49 (m, 4H), 5.76–5.98 (bs, 2H), 8.02 (bs, 1H).

11f: Yield 58.3%. ^{1}H-NMR ($CDCl_3$) δ 1.22 (d, 3H, J = 6.7 Hz), 1.30 (d, 3H, J = 6.2 Hz), 1.36–1.44 (bs, 2H), 1.76–2.03 (bs, 3H), 2.39 (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), 4.09–4.24 (bs, 2H), 4.40–4.76 (bs, 6H), 5.10–5.51 (m, 4H), 5.79–6.00 (bs, 2H)), 8.08 (bs, 1H).

12a: Yield 61.2%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 7.0 Hz), 1.35 (d, 3H, J = 6.2 Hz), 1.78–1.86 (bs, 1H), 2.15 (bs, 2H), 2.60–2.70 (bs, 4H), 3.10–3.24 (bs, 2H), 3.49–3.69 (bs, 6H), 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), 4.66 (dd, 1H, J = 5.2 and 5.6 Hz), 5.12–5.50 (m, 4H), 5.81–6.01 (bs, 2H), 6.60 (bs, 1H).

12b: Yield 53.8%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 7.1 Hz), 1.33 (d, 3H, J = 6.4 Hz), 1.74 (bs, 1H), 2.09 (bs, 1H), 2.56 (m, 1H), 3.10–3.27 (bs, 2H), 3.40–3.59 (bs, 3H), 3.65–3.79 (bs, 6H), 4.02–4.13 (bs, 2H), 4.20–4.32 (bs, 2H), 4.40–4.52 (bs, 2H), 4.59 (dd, 1H, J = 5.2 and 5.6 Hz), 4.68 (dd, 1H, J = 5.2 and 5.6 Hz), 5.13–5.49 (m, 4H), 5.79–5.97 (bs, 2H), 6.65 (bs, 1H).

12c: Yield 48.8%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 7.0 Hz), 1.34 (d, 3H, J = 6.1 Hz), 1.43–1.59 (bs, 2H), 1.66–1.98 (bs, 3H), 2.04 (m, 1H), 2.46 (bs, 1H), 3.23–3.39 (m, 2H), 3.49–3.77 (bs, 5H), 3.80–3.95 (m, 2H), 4.10–4.26 (bs, 5H), 4.40–4.52 (bs, 2H), 4.59 (dd, 1H, J = 5.1 and 5.5 Hz), 4.68 (dd, 1H, J = 5.1 and 5.5 Hz), 5.20–5.49 (m, 4H), 5.89–6.00 (bs, 2H), 6.69 (bs, 1H).

12d: Yield 51.7%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 7.0 Hz), 1.35 (d, 3H, J = 6.0 Hz), 1.45–1.58 (bs, 2H), 1.79–1.92 (bs, 3H), 1.98 (m, 1H), 2.46 (bs, 1H), 3.16–3.44 (bs, 4H), 3.49–3.71 (bs, 5H), 3.90–4.08 (m, 2H), 4.11–4.23 (bs, 2H), 4.26–4.69 (bs, 4H), 5.13–5.49 (m, 4H), 5.76–5.98 (bs, 2H), 6.61 (bs, 1H).

*4.10. (1R,5S,6S)-6-[(1R)-Hydroxyethyl]-2-{5-[5-(thiomorpholinylthioureido)methyl] pyrrolidin-3-ylthio}-1-methylcarbapen-2-em-3-carboxylic acid (**IIIa**)*

To a stirred solution of **11a** (0.42 g, 0.68 mol) and $Pd(PPh_3)_4$ (60 mg) in CH_2Cl_2 (10 ml) was added dropwise *n*-tributytin hydride (0.36 ml, 1.32 mmol) at 0 °C and was stirred for 1 h at same temperature. To the resulting solution was diluted with water (20 ml) and the organic layers was washed with water (2 × 220 ml). The combined aqueous layers were washed with ethyl ether (2 × 20 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 **IIIa** as an amorphous solid. Yield 24.3%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.01 (d, 3H, J = 5.3 Hz), 1.12 (d, 3H, J = 6.5 Hz), 1.58 (m, 1H), 2.48–2.57 (bs, 2H), 2.85–3.11 (bs, 5H), 3.24–3.48 (bs, 3H), 3.53–3.65 (bs, 2H), 3.70–3.90 (bs, 6H), 3.96–4.11 (m, 2H). IR (KBr): 3480, 1710, 1660, 1210 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{30}N_4O_4S_3$ 486.1429, Found 486.1428.

The synthesis of compounds **IIIb**–**f** and **IVa**–**d** were carried out by the same procedure as described for the preparation of **IIIa**.

IIIb: Yield 22.6%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.05 (d, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.5 Hz), 1.68 (m, 1H), 2.45–2.59 (bs, 2H), 2.85–3.19 (bs, 2H), 3.29–3.48 (bs, 5H), 3.53–3.65 (bs, 2H), 3.70–3.85 (bs, 6H), 3.96–4.11 (m, 2H). IR (KBr): 3460, 1710, 1670, 1210 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{30}N_4O_5S_2$ 470.1658, Found 470.1658.

IIIc: Yield 21.5%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.08 (d, 3H, J = 5.5 Hz), 1.15 (d, 3H, J = 6.7 Hz), 1.36–1.47 (bs, 2H), 1.69 (m, 1H), 1.76–1.97 (bs, 2H), 2.48–2.59 (m, 1H), 3.23–3.38 (bs, 4H), 3.53–3.65 (m, 2H), 3.76–3.96 (bs, 6H), 4.04–4.29 (bs, 3H). IR (KBr): 3430, 1720, 1710, 1210 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{21}H_{32}N_4O_5S_2$ 484.1814, Found 484.1811.

IIId: Yield 21.2%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.01 (d, 3H, J = 7.0 Hz), 1.14 (d, 3H, J = 6.2 Hz), 1.40–1.57 (m, 1H), 2.45–2.56 (bs, 2H), 2.96–3.18 (bs, 5H), 3.21–3.44 (bs, 2H), 3.51–3.58 (bs, 2H), 3.64–3.88 (bs, 6H), 4.14 (bs, 2H). IR (KBr): 3400, 1720, 1670, 1220 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{31}N_5O_4S_2$ 469.1817, Found 469.1820.

IIIe: Yield 18.6%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.10 (d, 3H, J = 6.9 Hz), 1.21 (d, 3H, J = 6.2 Hz), 1.77–1.86 (bs, 4H), 2.44 (m, 1H), 3.13–3.30 (bs, 5H), 3.34–3.45 (m, 2H), 3.54–3.69 (bs, 4H), 3.82 (bs, 1H), 3.95 (m, 1H), 4.16 (m, 2H). IR (KBr): 3390, 1710, 1680, 1220 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{30}N_4O_4S_2$ 454.1708, Found 454.1708.

IIIf: Yield 16.0%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.03 (d, 3H, J = 6.4 Hz), 1.11 (d, 3H, J = 6.2 Hz), 1.33–1.46 (bs, 2H), 1.65–1.96 (bs, 3H), 2.46 (m, 1H), 3.05–3.26 (bs, 4H), 3.45–3.54 (bs, 2H), 3.60–3.78 (bs, 5H), 3.95–4.08 (bs, 2H), 4.18 (m, 2H). IR (KBr): 3490, 1720, 1680, 1190 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{21}H_{32}N_4O_5S_2$ 484.1814, Found 484.1812.

IVa: Yield 24.6%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.06 (d, 3H, J = 5.0 Hz), 1.13 (d, 3H, J = 6.2 Hz), 1.56 (m, 1H), 2.48–2.55 (m, 1H), 2.58–2.65 (bs, 5H), 2.85–3.01 (bs, 2H), 3.24–3.48 (bs, 5H), 3.53–3.65 (bs, 4H), 3.70–3.82 (bs, 1H), 4.11 (m, 1H). IR (KBr): 3480, 1710, 1690, 1660, 1210 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{30}N_4O_5S_2$ 470.1658, Found 470.1656.

IVb: Yield 29.2%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.07 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.2 Hz), 1.55 (m, 1H), 2.45–2.55 (m, 1H), 3.21–3.42 (bs, 6H), 3.45–3.51 (bs, 2H), 3.55–3.69 (bs, 6H), 3.76–3.83 (m, 1H), 3.86–3.94 (m, 1H), 3.98–4.11 (m, 2H). IR (KBr): 3490, 1730, 1710, 1670, 1210 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{30}N_4O_6S$ 454.1886, Found 454.1883.

IVc: Yield 21.0%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.08 (d, 3H, J = 5.5 Hz), 1.15 (d, 3H, J = 6.7 Hz), 1.38–1.49 (bs, 2H), 1.60 (m, 1H), 1.75–1.98 (bs, 2H), 2.48–2.59 (m, 1H), 3.23–3.38 (bs, 4H), 3.53–3.65 (m, 2H), 3.76–3.96 (bs, 6H), 4.04–4.20 (bs, 3H). IR (KBr): 3430, 1730, 1720, 1670, 1210

(C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{21}H_{32}N_4O_6S$ 468.2043, Found 468.2040.

IVd: Yield 23.2%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ 1.09 (d, 3H, $J = 7.0$ Hz), 1.19 (d, 3H, $J = 6.2$ Hz), 1.67 (m, 1H), 1.80 (bs, 4H), 2.45–2.56 (m, 1H), 3.09–3.18 (bs, 4H), 3.21–3.34 (bs, 2H), 3.45–3.58 (bs, 4H), 3.74–3.83 (bs, 1H), 3.85–3.98 (bs, 1H), 4.14 (bs, 2H). IR (KBr): 3480, 1720, 1700, 1670, 1220 (C=S) cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{30}N_4O_5S$ 438.1937, Found 438.1940.

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