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Original article

Novel 1β-methylcarbapenems having cyclic sulfonamide moieties: Synthesis and evaluation of *in vitro* antibacterial activity

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Abstract

The synthesis of a new series of 1β-methylcarbapenems having cyclic sulfonamide 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 (**IIIi**) having 2-methyl-[1,2,6]thiadiazinan-1,1-dioxide moiety showed the most potent antibacterial activity.

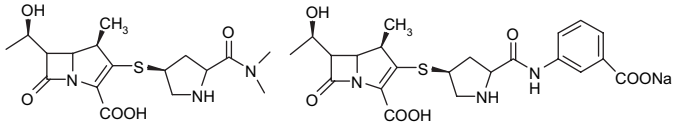
Keywords: 1β-Methylcarbapenems; Antibacterial activity; Substituent effects

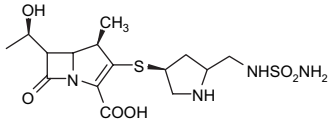
1. Introduction

Carbapenems are one of the most potent types of antibacterial agents and are among those used as a last resort against infections in the clinical field. Three carbapenems, imipenem [1,2], meropenem (**1**) [3], and ertapenem (**2**) [4] have been marketed so far. At present, several carbapenem derivatives such as S-4661 (**3**) [5], BO-2727 [6] and E-1010 [7] are under clinical or preclinical studies since the launch of meropenem.

We were also reported [8–12] that the carbapenem compounds having a pyrrolidin-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity.

In this paper, we describe the synthesis and structure–activity relationships of 1β-methylcarbapenems having a 5′-cyclic sulfonamide moieties 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 coupling reaction with the carbapenem diphenylphosphate, followed by deprotection of the resulting protected carbapenems in a usual manner.

The substituted sulfamides **3a–d**, **3f** and **3i** were easily accessible by the condensation of the corresponding diamines

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1a–d, **1f** and **1i** with sulfamide itself in refluxing pyridine (Scheme 1).

The other cyclic sulfamides **3e** and **3h** were also synthesized by the improved procedure as shown in Scheme 2. The intermediates **5e** and **5h** were directly synthesized by reaction of the corresponding mustards with BOC–sulfamoyl chloride. The *N*-BOC cyclic sulfamides **3e** and **3h** were obtained in high yield by treatment of **5e** and **5h** with K_2CO_3 in DMSO.

The cyclic sulfamidate **3g** ([1,2,3]oxathiadiazolidin-2,2-dioxide) is typically prepared as shown in Scheme 3. The sulfamidite **7** was obtained by reaction of *N*-protected amino ethanol and $SOCl_2$ in CH_3CN at low temperature. The oxidation of the sulfamidite **7** with RuO_4 in CH_3CN gave sulfamidate **8**, which was successfully converted into the deprotected cyclosulfamidate **3g** using trifluoroacetic acid.

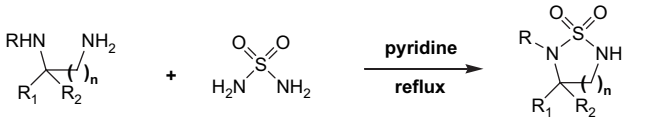
Ester compound **9** was reduced with lithium borohydride in THF/EtOH and subsequently mesylated to give **11**. The O-mesylated compound **11** was treated with cyclosulfamides and sodium hydride in DMF to provide **12a–i**. Deprotection of the trityl group to mercaptans (**Ia–i**) was achieved by treatment of **12a–i** with trifluoroacetic acid in the presence of triethylsilane (Scheme 4).

Finally, the reaction of **13** [13] with thiols **Ia–i** in the presence of diisopropylethylamine provided the 2-substituted carbapenems **IIa–i**. Deprotection of these compounds by tetrakis(triphenylphosphine)palladium(0) and tributyltin hydride gave the crude products, which were purified by HP-20 column to give the pure carbapenems **IIIa–i** (Scheme 5).

2.1. 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/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.

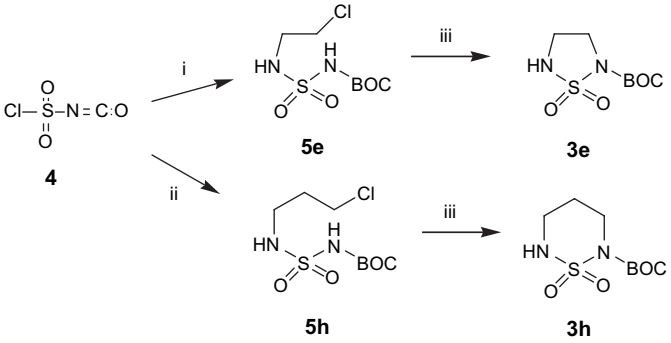
The *in vitro* antibacterial activities of the new carbapenems (**IIIa–i**) prepared above against both Gram-positive and Gram-negative bacteria are listed in Table 1. For comparison, the MIC values of imipenem and meropenem are also listed. All the compounds displayed superior or similar antibacterial



1a-d, 1f and 1i **2** **3a-d, 3f and 3i**

a: n=1, R=Me, R_1=R_2=H
b: n=1, R=Et, R_1=R_2=H
c: n=1, R=H, R_1=Me, R_2=H
d: n=1, R=H, R_1=R_2=Me
f: n=1, R=Bn, R_1=R_2=H
i: n=2, R=Me, R_1=R_2=H

Scheme 1.



i) BuOH, 2 -chloroethylamine, CH_2Cl_2 ii) BuOH, 2-chloropropylamine, CH_2Cl_2 iii) K_2CO_3, DMSO

Scheme 2.

activities against Gram-positive to meropenem, and against Gram-negative bacteria except *Pseudomonas aeruginosa* to imipenem.

As to the substituent on the pyrrolidine chain, compounds **IIIh–i** having thiadiazinane moieties were generally more potent than the thiadiazolidine compounds **IIIa–b** and **IIIe**. The introduction of alkyl group at N-position of thiadiazolidine (**IIIa** and **IIIb**) led to significantly enhanced antibacterial activity compared to compounds (**IIIc–d**) with alkyl substitute at C-3 position. As expected, the existence of *N*-benzyl group (**IIIf**) significantly lowered the antibacterial activity compared to compounds (**IIIa–b**) with methyl and ethyl groups.

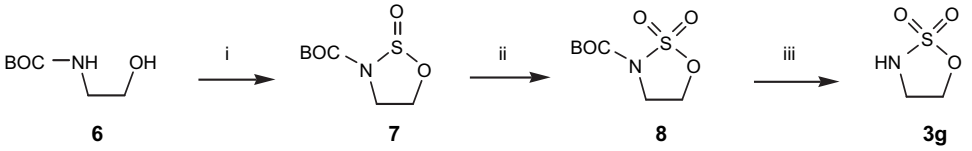
Comparative *in vitro* activities of **IIIi**, meropenem, and imipenem against 40 bacterial strains are summarized in Table 2. The selected carbapenem **IIIi** possessed excellent *in vitro* activity against 40 target pathogens except *P. aeruginosa*, and superior or similar antibacterial activities against Gram-positive bacteria to meropenem, and against Gram-negative bacteria to imipenem. Against *Escherichia coli* and *Corynebacterium diphtheriae*, **IIIi** was 2–3 times more active than the compared meropenem and imipenem.

3. Experimental

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

3.1. 2-Methyl-[1,2,5]thiadiazolidin-1,1-dioxide (*3a*)

To a refluxing solution of sulfamide (1.09 g, 11.3 mmol) in anhydrous pyridine (30 mL) was added dropwise anhydrous *N*-methylenediamine (**1a**, 0.84 g, 11.3 mmol) for over 2 h. The resulting mixture was refluxed for further 16 h under nitrogen before the solvent was removed under vacuum. The residue was triturated with hexane and the solids were collected by



Scheme 3.

filtration and purified by flash chromatography (CH_2Cl_2/MeOH = 20:1) to give 76% yield of **3a** as a white solid: mp 80–83 °C. ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H), 3.37–3.39 (dd, 2H, $J = 1.2$ and 2.1 Hz), 3.52 (q, 2H), 4.79 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 32.67, 39.64, 46.94.

The syntheses of compounds **3b–d**, **3f** and **3i** were carried out by the same procedure as described for the preparation of **3a**.

3b: Yield 57%. ^{1}H NMR ($CDCl_3$): δ 1.24–1.29 (t, 3H, $J = 14.5$ Hz), 3.05–3.12 (q, 2H), 3.34–3.42 (m, 2H), 3.47–3.54 (m, 2H), 5.31 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 13.18, 39.90, 41.53, 48.41.

3c: Yield 46%. ^{1}H NMR ($CDCl_3$): δ 1.34–1.36 (d, 3H, $J = 6.4$ Hz), 3.10–3.13 (m, 1H), 3.60 (m, 1H), 3.89–3.93 (m, 1H), 4.70 (bs, 1H), 4.82 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 18.14, 54.64, 57.94.

3d: Yield 76%. ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 6H), 3.32–3.30 (d, 2H, $J = 7.3$ Hz), 4.18 (bs, 1H), 4.72 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 21.40, 51.91, 56.36.

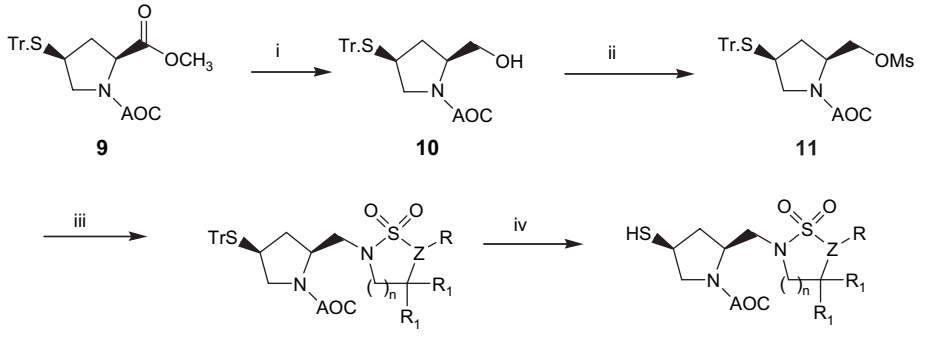
3f: Yield 79%. ^{1}H NMR ($CDCl_3$): δ 3.25–3.29 (t, 2H, $J = 13.2$ Hz), 3.43–3.50 (m, 2H), 4.17 (s, 2H), 4.58 (bs, 1H), 7.26–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 42.37, 49.65, 50.34, 126.98, 128.32, 130.02, 146.17.

3i: Yield 71%. ^{1}H NMR ($CDCl_3$): δ 1.74–1.81 (m, 2H), 2.75 (s, 3H), 3.28–3.32 (t, 2H, $J = 5.8$ Hz), 3.48–3.54 (m, 2H), 4.14 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 28.23, 40.60, 42.11, 44.96.

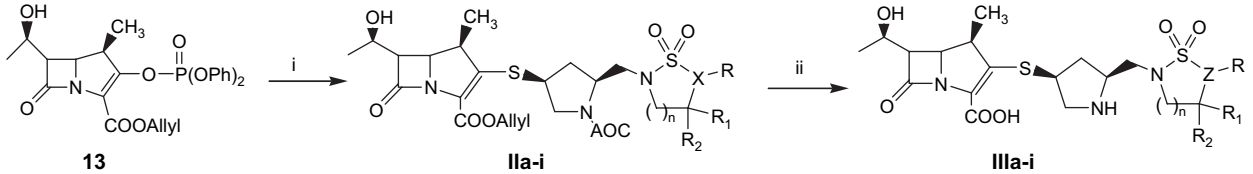
*3.2. 1-tert-Butoxycarbonyl-[1,2,5]thiadiazolidin-1,1-dioxide (**3e**)*

To a stirred solution of chlorosulfonyl isocyanate (CSI) (**4**, 4.00 g, 2.8 mmol) in 80 mL of anhydrous dichloromethane at 0 °C was added 3.3 mmol of absolute *tert*-butyl alcohol in the same solvent. After being stirred for 30 min, the resulting solution of BOC–sulfamoyl chloride and 19.7 mL of triethylamine in 10 mL of dichloromethane were added dropwise to 3.3 mmol of a suspended amino acid ester (2-chloroethylamine or 3-chloropropylamine) hydrochloride in 30 mL of dichloromethane. The reaction temperature did not rise above 5 °C. The resulting reaction solution was allowed to warm up to room temperature for over 2 h. The reaction mixture was diluted with 100 mL of dichloromethane, washed with 0.1 N HCl solution and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Recrystallization from CH_2Cl_2 at low temperature afforded the expected compound **3e** (3.1 g, 71%) as a pale yellow solid. mp 143–144 °C. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.40–3.44 (t, 2H, $J = 12.8$ Hz), 3.79–3.84 (t, 2H, $J = 12.7$ Hz), 4.91 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 29.06, 43.89, 46.32, 83.78, 163.28.

The synthesis of compound **3h** was carried out by the same procedure as described for the preparation of **3e** using the 3-chloropropylamine.



Scheme 4.



i) N,N'-Diisopropylethyl amine, **Ia-i**, CH_3CN (ii) Tetrakis (triphenylphosphine)palladium, tributyltin hydride, CH_2Cl_2.

a: Z=N, n=1, R=Me, R_1=R_2=H
b: Z=N, n=1, R=Et, R_1=R_2=H
c: Z=N, n=1, R=H, R_1=Me, R_2=H
d: Z=N, n=1, R=H, R_1=R_2=Me
e: Z=N, n=1, R= R_1=R_2=H
f: Z=N, n=1, R=Bn, R_1=R_2=H
g: Z=O, n=1, R_1=R_2=H
h: Z=N, n=2, R=R_1=R_2=H
i: Z=N, n=2, R=Me, R_1=R_2=H

Scheme 5.

3h: Yield 57%. ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 9H), 1.82–1.89 (m, 2H), 3.51–3.53 (t, 2H, $J = 5.6$ Hz), 3.91–3.95 (m, 2H), 4.49 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 25.53, 29.06, 41.23, 42.01, 81.92, 161.91.

3.3. 1-tert-Butoxycarbonyl-[1,2,3]oxathiadiazolidin-2,2-dioxide (*8*)

A solution of $SOCl_2$ (2.59 mL, 3.5 mmol) in dry CH_3CN (30 mL) under argon was cooled to −40 °C, and then *N-tert*-butyloxycarbonyl-ethanolamine (**6**, 2.43 mL, 1.4 mmol) in dry CH_3CN (20 mL) was added dropwise for over 12 min. TLC indicated a new product and a trace of **7**. Dry pyridine (6.5 mL) was then added, and the mixture was allowed to warm to room temperature. The solvent volume was reduced to ca. 20 mL, EtOAc (50 mL) was added, the resulting precipitate was filtered off, and the filtrate was concentrated to a residual oil (**7**). The oil was then cooled with an ice-water bath and diluted with CH_3CN (50 mL). $RuCl_3 \cdot H_2O$ (3 mg, 0.03 mmol) and $NaIO_4$ (0.50 g, 0.8 mmol) were added followed by water (75 mL). The resulting orange mixture was stirred at room temperature for 1 h. The mixture was then diluted with ether (100 mL), and the two phases were separated. The organic layer was washed with water (20 mL), saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$, the filtrate was then concentrated to afford **8** as an analytically pure colorless liquid.

7: ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.53–3.60 (m, 1H), 3.84–3.88 (m, 1H), 4.68–4.74 (m, 1H), 4.96–4.98 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 27.03, 47.98, 67.68, 82.12, 162.81.

8: Yield 86%. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 3.26–3.32 (m, 2H), 3.68–3.71 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 28.76, 42.49, 61.31, 81.94, 162.84.

3.4. [1,2,3]Oxathiadiazolidin-2,2-dioxide (*3g*)

Sulfamidate **8** (0.5 g, 2.2 mmol) was dissolved in CH_2Cl_2 (20 mL), and TFA (0.86 mL, 5 equiv) was added. The mixture was stirred for 30 min and then the solvent evaporated under reduced pressure. The residual oil was treated with Et_3N (typically <5 drops), until the mixture tested basic. The mixture was then filtered through a plug of silica using CH_2Cl_2/MeOH = 20:1 to give 82% yield of **3g** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.40–3.44 (t, 2H, $J = 12.8$ Hz),

Table 1
In vitro antibacterial activity (MIC, μg/mL) of the carbapenem derivatives (**IIIa–i**)

Strains	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh	IIIi	IPM[a]	MPM[b]
Staphylococcus aureus 1218	12.5	25.0	25.0	3.12	3.12	3.12	3.12	6.25	6.25	1.560	6.250
Coagulase negative staphylococci	0.098	0.198	0.391	0.098	0.098	0.098	0.098	0.098	0.049	0.025	0.098
Enterococcus faecalis 2347	6.25	6.25	25.0	6.25	6.25	3.12	6.25	6.25	3.12	1.563	12.50
Streptococcus pyogenes 9889	0.02	0.02	0.04	0.01	0.01	0.02	0.02	0.01	<0.01	<0.01	0.013
Streptococcus agalactiae 32	0.02	0.04	0.04	0.02	0.02	0.02	0.02	0.01	<0.01	0.01	0.049
Streptococcus pneumoniae 0025	0.02	0.04	0.04	0.02	0.02	0.025	0.013	0.02	0.01	<0.01	0.01
Haemophilus influenzae 1210	6.25	12.50	12.5	6.25	6.25	12.5	6.25	6.25	3.12	6.250	3.125
Escherichia coli 04	0.049	0.098	0.198	0.049	0.049	0.195	0.049	0.049	0.025	0.195	0.049
Klebsiella pneumoniae 523	0.098	0.198	0.198	0.049	0.049	0.781	0.098	0.049	0.025	0.781	0.025
Citrobacter freundii 323	0.049	0.098	0.198	0.049	0.049	0.781	0.195	0.049	0.025	0.391	0.025
Enterobacter cloacae 34	0.049	0.098	0.195	0.098	0.049	0.781	0.098	0.049	0.025	0.781	0.025
Serratia marcescens 3349	0.098	0.198	0.195	0.049	0.049	6.25	0.198	0.198	0.049	0.781	0.049
Acinetobacter baumannii 2289	12.5	25.0	25.0	12.5	12.5	50.0	12.5	6.25	3.12	12.500	12.5
Pseudomonas aeruginosa 5455	3.125	12.5	25.0	3.125	0.781	100.0	12.5	1.563	1.563	3.125	1.563

[a] Imipenem.
[b] Meropenem.

Table 2
Comparative *in vitro* antibacterial activity of **IIIi**, meropenem and imipenem against 40 strains (MIC, μg/mL)

Organism	**IIIi**	IPM	MPM	Organism	**IIIi**	IPM	MPM
Staphylococcus aureus giorgio	0.05	0.02	0.10	*Salmonella paratyphi* A	0.05	0.10	0.02
Staphylococcus aureus 209P	0.02	0.01	0.10	*Salmonella typhimurium*	0.10	0.40	0.05
Staphylococcus aureus 503	0.01	<0.01	0.05	*Salmonella oranienburg*	0.10	0.40	0.05
Micrococcus luteus ATCC 9341	0.02	0.01	0.05	*Salmonella typhi*	0.03	0.05	0.01
Streptococcus faecium 77A	<0.01	<0.01	0.01	*Salmonella orion*	0.10	0.20	0.10
Streptococcus agalactiae B	0.02	0.01	0.05	*Salmonella give*	0.10	0.20	0.02
Streptococcus durans D	0.10	0.10	0.80	*Klebsiella pneumoniae* 477	0.05	0.20	0.05
Bacillus subtilis ATCC 6633	0.03	0.03	0.05	*Enterobacter cloacae*	0.01	0.10	0.01
Bacillus megatherium	0.05	0.03	0.05	*Enterobacter cloacae* 417	0.02	0.10	0.01
Pseudomonas aeruginosa 9027	1.60	0.80	0.40	*Serratia marcescens* 370	0.10	0.20	0.05
Pseudomonas aeruginosa 77/2	1.60	0.80	0.80	*Serratia marcescens* 6093	0.20	0.40	0.05
Pseudomonas aeruginosa 110/2	0.80	0.80	0.40	*Serratia marcescens* 14273	0.40	0.80	0.20
Pseudomonas aeruginosa 880/2	0.40	0.80	0.20	*Proteus mirabilis* 112/3	0.20	0.20	0.10
Pseudomonas cepacia	0.40	0.80	0.40	*Proteus mirabilis* 174/3	0.20	0.10	0.10
Escherichia coli 086	0.02	0.10	0.05	*Proteus vulgaris* 868	0.40	0.10	0.10
Escherichia coli 0114	0.02	0.10	0.02	*Proteus rettgeri* 936	0.40	0.20	0.10
Escherichia coli 0126	0.02	0.10	0.05	*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	0.01	0.20	0.02	*Corynebacterium diphtheriae*	0.01	0.01	0.05
Escherichia coli 1507	0.02	0.10	0.02	*Corynebacterium pyogenes*	0.01	<0.01	0.02

3.79–3.84 (t, 2H, $J = 12.7$ Hz), 4.91 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 29.06, 43.89, 46.32, 83.78, 163.28.

3.5. (2S,4S)-2-Hydroxymethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**10**)

To a solution of **9** (107.3 g, 0.22 mol) in THF (800 mL) was added slowly $LiBH_4$ (4.8 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 **10** (79.4 g, 78%) 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, $J = 7.5$ Hz).

3.6. (2S,4S)-2-Mesyloxymethyl-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**11**)

A solution of **10** (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 **11** (75.2 g, 93%) 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, $J = 7.7$ Hz).

3.7. (2S,4S)-2-(5-Methyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-ylmethyl)-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (**12a**)

To a stirred solution of **3a** (0.30 g, 2.1 mmol) in dry DMF (10 mL) was added dropwise sodium hydride (0.10 g, 2.3 mmol, 60% oil suspension) at 0 °C and was stirred for 1 h at room temperature. To the resulting solution was added **11** (1.0 g, 1.9 mmol) solution in dry DMF (5 mL) at 0 °C and was stirred for 4 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 **12a** (0.67 g, 62%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.79–1.89 (m, 2H), 2.11–2.23 (m, 2H), 2.70 (s, 3H), 3.24–3.41 (m, 5H), 3.43–3.45 (d, 2H, $J = 5.6$ Hz), 3.77 (bs, 1H), 4.42–4.45 (m, 2H), 5.18–5.28 (m, 2H), 5.83–5.85 (m, 1H), 7.18–7.30 (m, 9H), 7.43–7.46 (d, 6H, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$): δ 31.39, 32.83, 33.87, 36.81, 39.64, 46.94, 50.20, 55.78, 67.21, 111.27, 126.82, 128.02, 129.44, 132.66, 144.61, 162.58.

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

12b: Yield 69%. ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3H), 1.83–1.86 (m, 2H), 2.01–2.12 (m, 2H), 2.92 (m, 2H), 3.25–3.41 (m, 5H), 3.42–3.45 (d, 2H, $J = 6.3$ Hz), 3.70 (bs, 1H), 4.41–4.44 (m, 2H), 5.19–5.28 (m, 2H), 5.83–5.86 (m, 1H), 7.18–7.28 (m, 9H), 7.43–7.47 (d, 6H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.19, 33.32, 38.56, 40.96, 44.83, 46.45, 46.94, 52.20, 57.79, 66.81, 112.27, 125.62, 129.03, 129.44, 133.66, 144.21, 162.48.

12c: Yield 60%. ^{1}H NMR ($CDCl_3$): δ 1.56 (s, 3H), 1.83–1.85 (bs, 1H), 2.69–2.79 (m, 2H), 3.07–3.22 (m, 3H), 3.52–3.54 (m, 2H), 3.70–3.74 (m, 3H), 4.13 (bs, 1H), 4.45 (bs, 1H), 5.19–5.29 (m, 3H), 5.85 (m, 1H), 7.26–7.30 (m, 9H), 7.44–7.46 (d, 6H, $J = 7.9$ Hz). ^{13}C NMR ($CDCl_3$): δ 15.19, 34.42, 39.66, 44.83, 46.45, 46.94, 52.20, 55.24, 56.79, 66.85, 114.37, 125.32, 129.43, 129.44, 133.10, 150.21, 162.48.

12d: Yield 66%. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H), 1.86–1.89 (bs, 1H), 2.70–2.72 (m, 3H), 2.95–3.14 (m, 4H), 3.77 (bs, 2H), 4.09–4.11 (m, 1H), 4.44–4.47 (m, 2H), 5.25–5.30 (m, 2H), 5.84–5.87 (m, 1H), 7.22–7.34 (m, 9H), 7.44–7.46 (d, 6H, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$): δ 24.40, 35.42, 40.96, 46.32, 48.20, 49.92, 52.10, 56.91, 59.11, 66.89, 116.21, 126.28, 128.20, 129.17, 132.98, 153.03, 163.23.

12e: Yield 62%. ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H), 1.97–2.01 (m, 1H), 2.62–2.63 (d, 2H, $J = 3.0$ Hz), 2.72–2.75 (m, 2H), 3.21–3.32 (m, 2H), 3.44–3.47 (m, 2H), 3.82–3.84 (bs, 1H), 4.10–4.19 (m, 2H), 4.45–4.47 (m, 2H), 5.19–5.25 (m, 2H), 5.81–5.88 (m, 1H), 7.21–7.31 (m, 9H), 7.43–7.46 (d, 6H, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$): δ 29.98, 41.36, 42.42, 44.12, 46.97, 49.81, 52.32, 55.54, 68.54, 81.34, 116.11, 126.12, 128.89, 129.76, 133.10, 149.99, 152.11, 162.50, 169.11.

12f: Yield 68%. ^{1}H NMR ($CDCl_3$): δ 1.60–1.62 (m, 1H), 2.69–2.72 (m, 2H), 3.11–3.18 (m, 4H), 3.26–3.28 (m, 2H), 3.33–3.34 (d, 2H, $J = 1.6$ Hz), 3.78 (bs, 1H), 4.13–4.18 (m, 2H), 4.44–4.49 (m, 2H), 5.18–5.24 (m, 2H), 5.79–5.88 (m, 1H), 7.19–7.36 (m, 14H), 7.44–7.47 (d, 6H, $J = 8.6$ Hz). ^{13}C NMR ($CDCl_3$): δ 40.96, 45.18, 46.95, 48.20, 49.79, 54.25, 59.45, 68.85, 117.32, 124.32, 126.22, 127.39, 127.72, 128.98, 129.76, 133.72, 144.61, 163.24.

12g: Yield 61%. ^{1}H NMR ($CDCl_3$): δ 1.70–188 (m, 1H), 1.98–2.10 (m, 1H), 2.68–2.77 (m, 2H), 2.90–2.96 (t, 2H, $J = 7.4$ Hz), 3.28–3.30 (m, 2H), 3.61–3.67 (m, 2H), 3.75–3.80 (m, 2H), 4.47–4.53 (bs, 2H), 5.20–5.28 (m, 2H), 5.81–5.90 (m, 1H), 7.19–7.29 (m, 9H), 7.44–7.46 (d, 6H, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$): δ 36.81, 39.49, 49.21, 50.86, 52.86, 57.92, 62.29, 67.92, 111.29, 127.01, 128.23, 129.83, 133.03, 158.83, 169.32.

12h: Yield 57%. ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9H), 1.64–1.68 (m, 2H), 1.85–1.87 (m, 1H), 2.63–2.70 (m, 2H), 3.08–3.14 (q, 2H), 3.26–3.31 (m, 2H), 3.47–3.76 (m, 2H), 3.99–4.11 (m, 3H), 4.44 (bs, 2H), 5.18–5.22 (m, 2H), 5.80–5.86 (m, 1H), 7.21–7.31 (m, 9H), 7.43–7.46 (d, 6H, $J = 7.7$ Hz). ^{13}C NMR ($CDCl_3$): δ 27.76, 29.98, 37.23, 41.59, 43.99, 48.31, 49.84, 53.36, 56.92, 67.94, 68.76, 81.92, 116.73, 126.12, 127.91, 129.59, 133.10, 153.28, 163.26, 176.01.

12i: Yield 55%. ^{1}H NMR ($CDCl_3$): δ 1.81–1.85 (m, 2H), 2.25–2.26 (bs, 1H), 2.73 (s, 3H), 2.75–2.79 (m, 2H), 2.80–2.81 (bs, 2H), 3.25–3.30 (m, 2H), 3.43–3.50 (m, 4H), 3.72 (bs, 1H), 4.43–4.45 (m, 2H), 5.18–5.21 (m, 2H), 5.84–5.85 (m, 1H), 7.20–7.39 (m, 9H), 7.44–7.46 (d, 6H, $J = 7.7$ Hz). ^{13}C NMR ($CDCl_3$): δ 27.24, 36.08, 41.10, 42.94, 45.37, 49.33, 54.24, 58.45, 64.24, 66.85, 67.75, 116.38, 126.28, 128.52, 129.87, 133.11, 153.43, 163.50.

*3.8. Allyl(1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[5-(5-methyl-1,1-dioxo-[1,2,5]thiadia-zolidin-2-ylmethyl)]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (**IIa**)*

To a solution of **12a** (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% $NaHCO_3$ and brine. The organic layer was concentrated *in vacuo* to give a residue (**Ia**), which was used without further purification. A solution of **13** (0.40 g, 0.80 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 **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 = 3:1) to give **IIa** (0.16 g, 34%) as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.25–1.28 (d, 3H, $J = 5.4$ Hz), 1.34–1.36 (d, 3H, $J = 4.6$ Hz), 2.09–2.02 (m, 2H), 2.53 (bs, 2H), 2.75 (s, 3H), 3.23–3.30 (m, 5H), 3.45 (bs, 1H), 3.95–4.18 (m, 2H), 4.21–4.25 (m, 2H), 4.59–4.67 (m, 4H), 4.69 (dd, 1H, $J = 5.4$ and 13.8 Hz), 4.83 (dd, 1H, $J = 5.7$ and 14.1 Hz), 5.23–5.33 (m, 4H), 5.42 and 5.47 (2 s, 1H), 5.90–6.01 (m, 2H).

The syntheses of compounds **IIb–i** were carried out by the same procedure as described for the preparation of **IIa**.

IIb: Yield 54%. ^{1}H NMR ($CDCl_3$): δ 1.22–1.29 (m, 9H), 1.96–2.10 (m, 2H), 2.17–2.45 (m, 2H), 3.09 (bs, 2H), 3.30–3.39 (m, 3H), 3.66–3.80 (m, 2H), 4.02–4.05 (m, 3H), 4.25–4.27 (m, 2H), 4.56–4.60 (m, 4H), 4.66 (dd, 1H, $J = 5.3$ and 11.2 Hz), 4.81 (dd, 1H, $J = 5.7$ and 12.2 Hz), 5.21–5.24 (m, 4H), 5.42 and 5.45 (2 s, 1H), 5.90–6.01 (m, 2H).

IIc: Yield 57%. ^{1}H NMR ($CDCl_3$): δ 1.27–1.29 (d, 2H, $J = 4.1$ Hz), 1.31–1.33 (d, 2H, $J = 6.3$ Hz), 1.58 (s, 3H), 2.65–2.67 (m, 3H), 3.12–3.27 (m, 2H), 3.36–3.49 (m, 2H), 3.51–3.62 (m, 3H), 3.69–3.77 (m, 2H), 3.90–4.08 (m, 3H), 4.44–4.60 (bs, 5H), 4.62 (dd, 1H, $J = 6.2$ and 10.2 Hz), 4.79 (dd, 1H, $J = 5.2$ and 10.2 Hz), 5.26–5.30 (m, 4H), 5.42 and 5.45 (2 s, 1H), 5.90–6.01 (m, 2H).

IId: Yield 56%. ^{1}H NMR ($CDCl_3$): δ 1.27–1.28 (d, 3H, $J = 2.92$ Hz), 1.31–1.32 (d, 3H, $J = 6.3$ Hz), 1.59 (s, 6H), 2.09–2.12 (m, 1H), 2.63–2.66 (m, 2H), 2.91–2.99 (m, 2H), 3.23–3.25 (m, 4H), 4.13–4.15 (m, 5H), 4.51–4.61 (bs, 4H), 4.71 (dd, 1H, $J = 3.9$ and 7.2 Hz), 4.80 (dd, 1H, $J = 4.3$ and 10.2 Hz), 5.24–5.33 (m, 4H), 5.93–6.96 (m, 2H).

IIe: Yield 45%. ^{1}H NMR ($CDCl_3$): δ 1.26–1.28 (d, 3H, $J = 7.2$ Hz), 1.35–1.38 (d, 3H, $J = 6.2$ Hz), 2.07–2.13 (m, 1H), 2.59 (bs, 2H), 2.76–2.83 (m, 2H), 3.25–3.49 (m, 3H), 3.50–3.74 (m, 3H), 3.89 (m, 1H), 4.08–4.15 (m, 2H), 4.22–4.24 (m, 1H), 4.59–4.66 (m, 4H), 4.67 (dd, 1H, $J = 5.2$ and 10.8 Hz), 4.80 (dd, 1H, $J = 5.7$ and 11.1 Hz), 5.21–5.24 (m, 4H), 5.42 and 5.47 (2 s, 1H), 5.87–6.00 (m, 2H).

IIf: Yield 43%. ^{1}H NMR ($CDCl_3$): δ 1.26–1.28 (d, 3H, $J = 7.2$ Hz), 1.35–1.37 (d, 2H, $J = 6.2$ Hz), 2.04–2.11 (m,

2H), 2.45–2.51 (m, 2H), 3.16–3.20 (m, 2H), 3.23–3.39 (m, 4H), 3.35 (m, 1H), 3.54 (bs, 1H), 4.08–4.26 (m, 5H), 4.60–4.64 (m, 4H), 4.71 (dd, 1H, $J = 5.5$ and 7.8 Hz), 4.81 (dd, 1H, $J = 2.6$ and 8.1 Hz), 5.22–5.30 (m, 4H), 5.42 and 5.47 (2 s, 1H), 5.90–5.99 (m, 2H), 7.30–7.37 (m, 5H).

IIg: Yield 54%. ^{1}H NMR ($CDCl_3$): δ 1.14–1.17 (bs, 3H), 1.35–1.37 (d, 3H, $J = 6.1$ Hz), 1.66–1.71 (m, 2H), 2.00–2.04 (m, 2H), 3.28–3.35 (m, 4H), 3.67 (bs, 1H), 3.97–4.11 (m, 3H), 4.13–4.23 (m, 2H), 4.51–4.60 (m, 4H), 4.67 (dd, 1H, $J = 5.6$ and 9.8 Hz), 4.84 (dd, 1H, $J = 5.4$ and 10.3 Hz), 5.23–5.33 (m, 4H), 5.42 and 5.47 (2 s, 1H), 5.89–6.02 (m, 2H).

IIh: Yield 45%. ^{1}H NMR ($CDCl_3$): δ 1.23–1.26 (d, 3H, $J = 7.1$ Hz), 1.32–1.35 (d, 3H, $J = 7.2$ Hz), 1.64–1.67 (m, 2H), 2.17–2.23 (m, 2H), 2.59 (bs, 2H), 3.25–3.49 (m, 6H), 3.69–3.74 (m, 1H), 3.99 (bs, 2H), 4.08–4.15 (m, 2H), 4.22–4.24 (m, 1H), 4.59–4.66 (m, 4H), 4.67 (dd, 1H, $J = 5.2$ and 10.8 Hz), 4.80 (dd, 1H, $J = 5.7$ and 11.1 Hz), 5.21–5.24 (m, 4H), 5.87–6.00 (m, 2H).

IIi: Yield 49%. ^{1}H NMR ($CDCl_3$): δ 1.19–1.21 (m, 3H), 1.26–1.28 (m, 3H), 1.35–1.36 (d, 3H, $J = 6.2$ Hz), 1.74–1.76 (m, 2H), 2.52–2.54 (bs, 2H), 2.76 (s, 3H), 3.23–3.29 (m, 3H), 3.49–3.50 (m, 2H), 3.59 (bs, 1H), 4.01–4.09 (m, 2H), 4.21–4.24 (m, 2H), 4.57–4.59 (m, 4H), 4.67 (dd, 1H, $J = 6.6$ and 9.0 Hz), 4.81 (dd, 1H, $J = 5.4$ and 11.2 Hz), 5.23–5.36 (m, 4H), 5.84–6.02 (m, 2H).

*3.9. (1R,5S,6S)-6-[(1R)-Hydroxyethyl]-2-[5-(5-methyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-ylmethyl)]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (**IIIa**)*

To a stirred solution of **IIa** (80 mg, 0.13 mol) and $Pd(PPh_3)_4$ (10 mg) in CH_2Cl_2 (5 mL) was added dropwise *n*-tributyltin hydride (0.12 mL, 0.22 mmol) at 0 °C and was stirred for 1 h at same temperature. The resulting solution was diluted with water (10 mL) and the organic layers were 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 **IIIa** as an amorphous solid. Yield 18%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.09 (d, 3H, $J = 6.4$ Hz), 1.18–1.21 (d, 3H, $J = 6.9$ Hz), 1.50–1.57 (m, 1H), 2.11 (m, 2H), 2.55–2.59 (m, 2H), 2.64 (s, 3H), 3.16–3.19 (m, 1H), 3.26–3.35 (m, 7H), 3.45–3.48 (m, 2H), 3.71–3.87 (m, 2H), 4.09–4.16 (m, 2H). IR (KBr): 3400, 3250, 1710, 1680, 1325 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{18}H_{28}N_4O_6S_2$ 460.1450, found 460.1455.

The syntheses of compounds **IIIb–i** were carried out by the same procedure as described for the preparation of **IIIa**.

IIIb: Yield 16%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.11 (s, 3H), 1.13–1.14 (d, 3H, $J = 5.8$ Hz), 1.17–1.20 (d, 3H, $J = 6.3$ Hz), 1.64–1.66 (m, 1H), 2.13 (bs, 2H), 2.68–2.70 (m, 2H), 3.03–3.07 (m, 2H), 3.25–3.42 (m, 6H), 3.44–3.59 (m, 2H), 3.57–3.62 (m, 2H), 3.57–3.59 (m, 2H), 4.15–4.17 (m, 2H). IR (KBr): 3450, 3300, 1720, 1670, 1355 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{19}H_{30}N_4O_6S_2$ 474.1607, found 474.1607.

IIIc: Yield 19%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.11–1.12 (d, 3H, $J = 6.3$ Hz), 1.13–1.15 (d, 3H, $J = 6.7$ Hz), 1.17 (s, 3H), 1.50–1.53 (bs, 1H), 2.51–2.53 (m, 2H), 2.76 (q, 2H), 3.06–3.08 (m, 2H), 3.46–3.62 (m, 6H), 3.71–3.73 (dd, 2H, $J = 5.4$ and 6.8 Hz), 3.93–3.99 (m, 2H), 4.05–4.10 (m, 2H). IR (KBr): 3430, 3260, 1710, 1660, 1340 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{18}H_{28}N_4O_6S_2$ 460.1450, found 460.1452.

IIId: Yield 17%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.09–1.10 (d, 3H, $J = 6.9$ Hz), 1.13–1.14 (d, 3H, $J = 7.4$ Hz), 1.29 (s, 6H), 1.62–1.65 (m, 2H), 2.10–2.12 (m, 2H), 2.64–2.67 (m, 1H), 3.24–3.35 (m, 8H), 3.54–3.56 (m, 1H), 3.83–3.90 (m, 2H), 4.04–4.11 (m, 2H). IR (KBr): 3470, 3280, 1720, 1680, 1310 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{19}H_{30}N_4O_6S_2$ 474.1607, found 474.1609.

IIIe: Yield 20%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.15–1.18 (d, 3H, $J = 6.6$ Hz), 1.20–1.23 (d, 3H, $J = 7.0$ Hz), 1.67–1.83 (m, 3H), 2.32–2.37 (m, 1H), 2.60–2.69 (m, 2H), 3.27–3.30 (m, 1H), 3.39–3.43 (m, 7H), 3.52–3.55 (m, 2H), 3.76–3.87 (m, 2H), 4.06–4.15 (m, 2H). IR (KBr): 3490, 3280, 1710, 1670, 1310 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{17}H_{26}N_4O_6S_2$ 446.1294, found 446.1299.

IIIf: Yield 16%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.05–1.08 (d, 3H, $J = 7.0$ Hz), 1.11–1.12 (d, 3H, $J = 6.7$ Hz), 1.56–1.66 (m, 1H), 2.07 (bs, 2H), 2.58–2.63 (m, 2H), 3.01–3.02 (m, 1H), 3.01–3.33 (m, 9H), 3.35–3.37 (m, 2H), 3.52–3.54 (m, 2H), 4.01–4.06 (m, 2H), 7.27–7.30 (m, 5H). IR (KBr): 3400, 3360, 1710, 1680, 1325 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{24}H_{32}N_4O_6S_2$ 536.1763, found 536.1770.

IIIg: Yield 18.3%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.08–1.11 (d, 3H, $J = 5.4$ Hz), 1.15–1.16 (d, 3H $J = 6.7$ Hz), 1.18–1.20 (s, 1H), 1.21–1.22 (m, 2H), 2.72–2.82 (m, 2H), 3.07–3.09 (m, 5H), 3.27–3.40 (m, 2H), 3.73 (dd, 2H, $J = 2.4$ and 5.3 Hz), 4.05–4.16 (m, 5H). IR (KBr): 3440, 3220, 1710, 1670, 1370 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{17}H_{25}N_3O_7S_2$ 447.1134, found 447.1134.

IIIh: Yield 15%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.12–1.14 (d, 3H, $J = 7.2$ Hz), 1.19–1.21 (d, 3H, $J = 6.3$ Hz), 1.57–1.68 (m, 4H), 2.58–2.68 (m, 3H), 3.24–3.46 (m, 9H), 3.53–3.58 (m, 2H), 3.85 (bs, 2H), 4.12–4.14 (m, 2H). IR (KBr): 3470, 3330, 1710, 1680, 1340 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{18}H_{28}N_4O_6S_2$ 460.1450, found 460.1453.

IIIi: Yield 15%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.09–1.11 (d, 3H, $J = 7.2$ Hz), 1.16–1.18 (d, 3H, $J = 6.3$ Hz), 1.59–1.62 (m, 1H), 1.77–1.79 (m, 2H), 2.10–2.11 (bs, 1H), 2.62–2.64 (m, 2H), 2.68 (s, 3H), 3.27–3.34 (m, 4H), 3.36–3.39 (m, 4H), 3.55–3.59 (m, 2H), 3.83–3.85 (bs, 1H), 3.91–3.93 (bs, 1H), 4.10–4.15 (m, 3H). IR (KBr): 3420, 3290, 1720, 1680, 1390 (S=O) cm^{-1}. HRMS(FAB) Calcd. for $C_{19}H_{30}N_4O_6S_2$ 474.1607, found 474.1610.

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