Full Paper

Novel Iβ-Methylcarbapenems Having Cyclic Sulfonamide Moieties: Synthesis and Evaluation of *in-vitro* Biological Activity – Part II

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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 a substituent on the pyrrolidine ring was investigated. One particular compound **IIIe** having a [1,2,5]thiadiazolidin 1,1-dioxide moiety showed the most potent antibacterial activity.

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

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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] (Fig. 1), and ertapenem **2** [4] (Fig. 1) have been marketed so far. At present, several carbapenem derivatives such as S-4661 **3** [5] (Fig. 1), BO-2727 [6], and E-1010 [7] are under clinical or preclinical studies since the launch of meropenem.

We have also reported that the carbapenem compounds having a pyrrolidin-3-yl-thio 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 [8–13]. In this paper, we describe the synthesis and structure-activity relationships of 1β-methylcarbapenems having a 5′-cyclic sulfonamide moieties at a C-2 side chain and our approach for improvement of antibacterial activity of the carbapenems is discussed.

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Results and discussion

Chemistry

Our general synthetic route leading to new carbapenems involved the preparation of appropriately protected thiols containing a 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 substituted sulfamides **3a–d**, **g** were easily accessible by the condensation of the corresponding diamines **1a–d**, **g** with sulfamide itself in refluxing pyridine (Scheme 1) [13].

The other cyclic sulfamides **3e** and **3f** were also synthesized by the improved procedure shown in Scheme 2. The intermediates **4e** and **4f** were directly synthesized by reaction of the corresponding mustards with *N*-(*t*-butoxycarbonyl)sulfamoyl chloride. The *N*-Boc cyclosulfamides **3e** and **3f** were obtained in high yield by treatment of **4e** and **4f** with K_2CO_3 in DMSO [13].

Compounds **7a–g** were obtained by treatment of carboxylic acids **5** and **3a–g** using oxalyl chloride. Deprotection of the trityl group to mercaptans **Ia–g** were achieved by treatment of **7a–g** with trifluoroacetic acid in the presence of triethylsilane (Scheme 3).

Finally, the reaction of **8** [14] with thiols **Ia–g** in the presence of diisopropylethylamine provided the 2-substi-

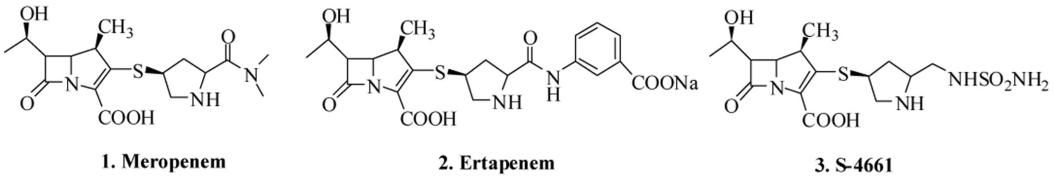
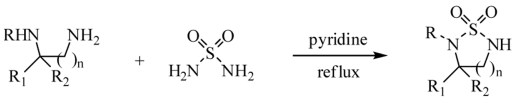
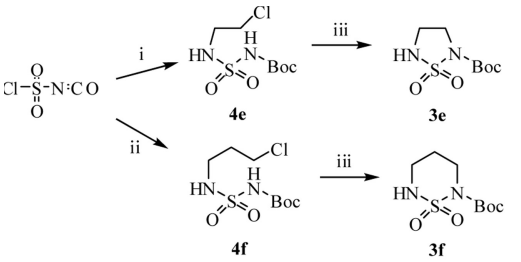


Figure 1. Structures of meropenem, ertapenem, and S-4661.



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
g: n = 2, R = Me, $R_1 = R_2 = H$

Scheme 1. Synthesis of compounds **3a–d**, **g**.



Reagents and conditions: i) BuOH, 2-chloroethylamine, CH_2Cl_2;
ii) BuOH, 2-chloropropylamine, CH_2Cl_2;
iii) K_2CO_3, DMSO.

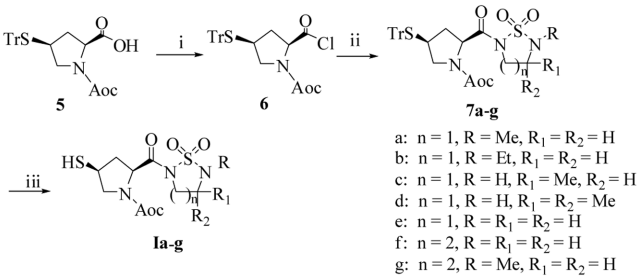
Scheme 2. Synthesis of the compounds **3e** and **3f**.

tuted carbapenems **11a–g**. Deprotection of these compounds was carried out by tetrakis(triphenylphosphine)-palladium(0) and tributyltin hydride to give the crude products, which were purified on a HP-20 column to give the pure carbapenems **IIIa–g** (Scheme 4).

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

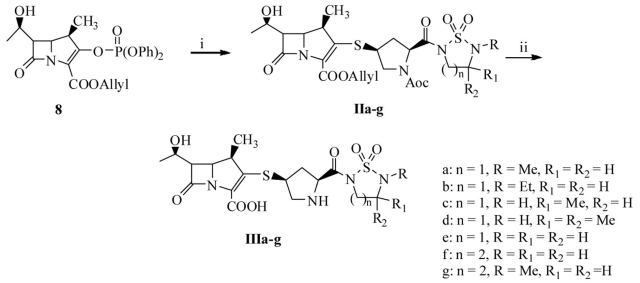
The *in-vitro* antibacterial activities of new carbapenems (sustituents **IIIa–g**) prepared above against both Gram-positive and Gram-negative bacteria are listed in Table 1. For comparison, the MIC values of imipenem and meropenem are also listed. All the compounds displayed superior or similar antibacterial activities against Gram-negative bacteria to imipenem, in particular, against *Escherichia coli, Klebsiella peneumoniae*, *Citrobacter freundii,* and *Enterobactor cloaca.* Most of the compounds except compound **IIId** showed to be 2–4 times more active than imipenem.



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
e: n = 1, R = $R_1 = R_2 = H$
f: n = 2, R = $R_1 = R_2 = H$
g: n = 2, R = Me, $R_1 = R_2 = H$

Reagents and conditions: i) Oxalyl chloride, CH_2Cl_2; ii) **3a-g**, TEA, CH_2Cl_2;
iii) trifluroacetic acid, triethyl silane.

Scheme 3. Synthesis of compounds **Ia–g**.



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
e: n = 1, R = $R_1 = R_2 = H$
f: n = 2, R = $R_1 = R_2 = H$
g: n = 2, R = Me, $R_1 = R_2$ =H

Reagents and conditions: i) *N*,*N*'-diisopropylethyl amine, **Ia-g**, CH_3CN; (ii) tetrakis (triphenylphosphine)palladium, tributyltin hydride, CH_2Cl_2.

Scheme 4. Synthesis of compounds **IIIa–g**.

By comparing the effect of at C-5 of the pyrrolidine side chain on the activity, it was found that compounds **IIIf–g** having thiadiazinane moieties showed minor differences in activity compared to the thiadiazolidine compounds **IIIa**, **e**.

The introduction of an alkyl group at the *N*-position of thiadiazolidines **IIIa**, **b** led to a significantly enhanced antibacterial activity compared to compounds **IIIc**, **d** with an alkyl substitute at the C-3 position. With increasing order of bulkiness of the groups from hydrogen, methyl, ethyl to dimethyl in compounds **Ie**, **Ia**, **Ib**, **Ic**, and **Id**, respectively, it was found that their activities decreased. It could be revealed that any bulky substituent

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

STRAINS	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IPM[a]	MPM[b]
Staphylococcus aureus 1218	6.25	12.5	6.25	25.0	3.125	6.25	12.5	1.563	6.25
Coagulase negative staphylococci	0.390	1.563	0.390	0.781	0.098	0.781	1.563	0.025	0.098
Enterococcus faecalis 2347	6.25	12.5	25.0	12.5	6.25	12.5	12.5	1.56	12.50
Streptococcus pyogenes 9889	0.049	0.025	0.049	0.049	0.025	0.025	0.025	<0.01	0.013
Streptococcus agalaciae 32	0.049	0.098	0.049	0.098	0.025	0.098	0.098	0.01	0.049
Streptococcus pneumoniae 0025	0.049	0.049	0.049	0.049	0.049	0.049	0.049	<0.01	0.010
Haemophilus influenzae 1210	3.125	12.5	12.5	12.5	6.25	6.25	6.25	6.25	3.125
Escherichia coli 04	0.049	0.098	0.098	0.098	0.049	0.025	0.049	0.198	0.049
Klebsiella peneumoniae 523	0.198	0.391	0.198	1.563	0.098	0.098	0.098	0.781	0.025
Citrobacter freundii 323	0.049	0.098	0.198	0.198	0.025	0.025	0.049	0.390	0.025
Enterobactor cloacae 34	0.098	0.198	0.198	0.391	0.049	0.098	0.098	0.781	0.025
Serratia marcescens 3349	0.198	0.781	0.391	0.781	0.098	0.198	0.198	0.781	0.049
Acinetobacter baumannii 2289	12.5	25.0	12.5	25.0	12.5	12.5	6.25	12.5	12.5
Psudemonas aeruginosa 5455	1.563	3.125	3.125	6.25	0.781	0.391	0.781	3.125	1.563

[a] imipenem
[b] meropenem

(**Ic** and **Id**) led to a significant loss in antibacterial activity, which suggests that the bulky substituents are not favorable.

As a result, among all of these derivatives, compound **IIIe** having a [1,2,5]thiadiazolidin 1,1-dioxide moiety showed the most potent antibacterial activity while the thiadiazinane-substituted compounds **IIIf**, **g** exhibited a more potent activity against *Psudemonas aeruginosa* than imipenem and meropenem.

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The authors have declared no conflict of interest.

Experimental

UV spectra: Hewlett Packard 8451A UV-VIS spectrophotometer (Hewlett Packard, Palo Alto, CA, USA). IR spectra: Perkin Elmer 16F-PC FT-IR (Perkin-Elmer, Norwalk, CT, USA). nmR spectra: Varian Gemini 300 spectrometer (Varian, Inc., Palo Alto, CA, USA), tetramethylsilane (TMS), as an internal standard. The mass spectrometry system was based on a HP5989A MS Engine mass spectrometer with a HP Model 59987A (both Hewlett Packard).

Chemistry

*(2S,4S)-2-[(5-Methyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-yl)carbonyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine **7a***

To solution of **5** (1.0 g, 2.1 mmol) in dry CH_2Cl_2 (50 mL) was added drop-wise oxalyl chloride (0.60 mL, 6.3 mmol) and was stirred for 2 h at room temperature. The mixture was evaporated under reduced pressure to give crude **6**. To a stirred solution of cyclic sulfamide (**3a**, 0.30 g, 2.2 mmol) in dry DMF (40 mL) was added dropwise sodium hydride (0.12 g, 3.1 mmol, 60% oil suspension) at 0°C and was stirred for 1 h at room temperature. To the resulting solution was added **6** solution in dry DMF (10 mL) at 0°C and was stirred for 8 h at room temperature. The mixture was diluted with water 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 : 1) to give **7a** (0.52 g, 47%) as a pale yellow oil.

*Compound **7a***

^{1}H-NMR ($CDCl_3$) δ: 1.71–1.79 (m, 2H), 2.29–2.46 (m, 1H), 2.79 (s, 3H), 2.90 (d, *J* = 6.1 Hz, 2H), 3.66–3.72 (m, 1H), 3.87 (bs, 2H), 4.37–4.53 (m, 2H), 5.13–5.29 (m, 2H), 5.73–5.90 (m, 1H), 7.32–7.22 (m, 9H), 7.43 (d, *J* = 9.5 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 30.73, 31.13, 33.01, 42.11, 39.64, 51.24, 52.81, 55.78, 66.87, 118.30, 128.82, 129.02, 135.54, 136.76, 142.61, 179.21.

The synthesis of compounds **7b–g** were carried out by the same procedure as described for the preparation of **7a**

*Compound **7b***

Yield: 52%. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (s, 3H), 1.72–1.84 (m, 1H), 2.31–2.48 (m, 2H), 3.08–3.16 (m, 3H), 3.36–3.86 (m, 3H), 3.46–3.48 (d, *J* = 6.0 Hz, 2H), 3.87 (bs, 1H), 4.42–4.50 (m, 2H), 5.19–5.23 (m, 2H), 5.80–5.89 (m, 1H), 7.14-7.31 (m, 9H), 7.43 (d, *J* = 7.2 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 15.29, 37.12, 39.16, 41.86, 46.29, 46.45, 46.94, 52.20, 62.56, 66.85, 116.27, 126.19, 130.28, 133.24, 135.46, 146.06, 176.84.

*Compound **7c***

Yield: 46%. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H), 1.68–1.66 (m, 2H), 2.73–2.78 (m, 1H), 2.94–2.97 (m, 1H), 3.22 (q, 1H), 3.40–3.47 (m, 1H), 3.65–3.67 (m, 1H), 3.81 (bs, 1H), 4.18–4.06 (m, 1H), 4.41–4.35 (m, 2H), 4.45 (bs, 1H), 5.01–5.18 (m, 2H), 5.71–5.82 (m, 1H), 7.25-7.12 (m, 9H), 7.36 (d, *J* = 7.5 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 22.94, 34.42, 39.66, 46.02, 46.85, 52.02, 60.17, 66.79, 66.95, 114.32, 126.32, 129.28, 133.10, 150.59, 156.18, 172.48.

*Compound **7d***

Yield: 47%. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 6H), 1.60–1.87 (m, 3H), 2.26–2.47 (m, 1H), 2.81–2.87 (m, 1H), 3.79 (s, 1H), 3.84 (s, 1H), 4.10–4.18 (m, 1H), 4.44–4.49 (m, 2H), 4.64–4.70 (m, 2H), 5.16–5.25 (m, 2H), 7.20–7.32 (m, 9H), 7.43 (d, *J* = 7.0 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 30.29, 35.42, 40.96, 46.32, 48.20, 48.92, 52.10, 57.19, 61.11, 66.75, 116.32, 120.28, 133.10, 150.28, 153.18, 172.39.

*Compound **7e***

Yield: 65%. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (s, 9H), 2.16 (s, 1H), 2.14–2.20 (m, 1H), 2.79 (bs, 1H), 2.79–3.09 (m, 2H), 3.42–3.49 (m, 2H), 3.86 (t, *J* = 12.8 Hz, 2H), 4.03–4.15 (m, 2H), 4.49–4.54 (m, 2H), 5.09–5.28 (m, 3H), 5.75–5.90 (m, 1H), 7.19–7.31 (m, 9H), 7.44 (d, *J* = 7.0 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 38.16, 42.94, 46.29, 48.20, 52.07, 54.25, 62.15, 68.85, 117.32, 124.32, 116.32, 127.51, 127.72, 127.18, 129.28, 131.22, 142.71, 167.14.

*Compound **7f***

Yield: 47%. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 1.88–1.92 (m, 2H), 2.31–2.56 (m, 2H), 2.77–2.94 (m, 2H), 3.04–3.24 (m, 1H), 3.62–3.66 (m,1H), 3.93–4.10 (m, 3H), 4.38–4.50 (m, 2H), 4.96–5.01 (m, 1H), 5.04–5.29 (m, 2H), 5.77–5.91 (m, 1H), 7.19–7.36 (m, 9H), 7.44 (d, *J* = 6.9 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 26.14, 30.18, 37.23, 41.02, 46.39, 48.31, 52.07, 53.36, 56.92, 67.94, 68.76, 81.92, 116.32, 126.19, 127.51, 130.58, 133.10, 153.28, 153.17, 176.03.

*Compound **7g***

Yield: 47%. ^{1}H-NMR ($CDCl_3$) δ: 1.59–1.63 (m, 2H), 1.73–1.75 (m, 2H), 2.80 (s, 3H), 3.03 (s, 1H), 3.38–3.44 (m, 1H), 3.65 (t, *J* = 11.4 Hz, 2H), 3.81–3.90 (m, 1H), 4.07 (t, *J* = 11.7 Hz, 2H), 4.45–4.52 (m, 2H), 4.93–4.98 (m, 1H), 5.18–5.29 (m, 2H), 5.80–5.91 (m, 1H), 7.19–7.31 (m, 9H), 7.44 (d, *J* = 9.3 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ: 27.74, 36.08, 41.03, 42.94, 46.38, 49.13, 54.24, 58.45, 64.24, 66.75, 67.76, 116.32, 126.27, 128.52, 129.87, 133.11, 153.43, 170.62.

*Allyl (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-{[5-(5-methyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-yl)carbonyl]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio}-1-methylcarbapen-2-em-3-carboxylate **IIa***

To a solution of **7a** (0.61 g, 1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise triethylsilane (0.20 mL, 1.2 mmol) at 5°C, and then TFA (2). 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 **8** (0.40 g, 0.80 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 = 3 : 1) to give **IIa** (0.11 g, 29%) as a yellow amorphous solid.

*Compound **IIa***

^{1}H-NMR ($CDCl_3$) δ: 1.24 (d, *J* = 7.5 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.99–2.04 (m, 1H), 2.81 (s, 2H), 3.25 (bs, 1H), 3.40–3.49 (m, 5H), 3.74 (bs, 1H), 3.09–4.02 (m, 2H), 4.16–4.18 (m, 3H), 4.55–4.59 (m, 4H), 4.71 (dd, *J* = 5.6 and 6.1 Hz, 1H), 4.80 (dd, *J* = 5.5 and 6.0 Hz, 1H), 5.24–5.47 (m, 4H), 4.57 and 5.42 (2s, 1H), 5.92-5.98 (m, 2H).

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

*Compound **IIb***

Yield: 36%. ^{1}H-NMR ($CDCl_3$) δ: 1.23–1.31 (m, 6H), 1.59 (s, 3H), 2.94 (bs, 2H), 3.14–3.18 (m, 3H), 3.40–3.48 (m, 3H), 3.74–3.75 (m, 1H), 3.85–3.97 (m, 3H), 4.08–4.13 (m, 2H), 4.58–4.64 (m, 4H), 4.67 (dd, *J* = 5.2 and 10.2 Hz, 1H), 4.71 (dd, *J* = 6.2 and 10.2 Hz, 1H), 4.98–5.01 (m, 1H), 5.14–5.32 (m, 4H), 5.87–5.95 (m, 2H).

*Compound **IIc***

Yield: 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.23–1.34 (m, 6H), 1.90–1.98 (m, 2H), 2.17 (s, 3H), 2.57–2.71 (m, 2H), 3.11–3.25 (m, 1H), 3.25–3.49 (m, 3H), 3.60–3.69 (m, 1H), 4.07–4.09 (m, 1H), 4.15–4.26 (m, 2H), 4.54–4.71 (m, 4H), 4.74 (dd, *J* = 5.3 and 11.2 Hz, 1H), 4.80 (dd, *J* = 6.1 and 10.1 Hz, 1H), 5.20–5.34 (m, 4H), 5.41 and 5.47 (2s, 1H), 5.89–5.95 (m, 2H).

*Compound **IId***

Yield: 23%. ^{1}H-NMR ($CDCl_3$) δ: 1.24–1.31 (m, 6H), 1.62 (s, 6H), 2.92–3.03 (m, 2H), 3.26–3.28 (m, 1H), 3.35–3.51 (m, 2H), 3.77–3.88 (m, 3H), 4.03–4.17 (m, 2H), 4.22–4.28 (m, 1H), 4.55–4.73 (m, 4H), 4.80 (dd, *J* = 5.2 and 10.2 Hz, 1H), 4.87 (dd, *J* = 6.2 and 10.2 Hz, 1H), 5.11–5.36 (m, 4H), 5.43 and 5.49 (2s, 1H), 5.88–6.01 (m, 2H).

*Compound **IIe***

Yield: 32%. ^{1}H-NMR ($CDCl_3$) δ: 1.22–1.33 (m, 6H), 1.62–1.65 (m, 3H), 2.56–2.67 (m, 2H), 0.03–3.05 (m, 2H), 3.07–3.12 (m, 2H), 3.30–3.42 (m, 1H), 3.71–3.75 (m, 1H), 3.91–4.24 (m, 2H), 4.52-4.62 (m, 4H), 4.64 (dd, *J* = 5.4 and 8.8 Hz, 1H), 4.81 (dd, *J* = 6.0 and 9.7 Hz, 1H), 5.19–5.33 (m, 4H), 5.42 and 5.45 (2s, 1H), 5.85–5.94 (m, 2H).

*Compound **IIf***

Yield: 41%. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (d, *J* = 7.3 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.87–2.00 (m, 2H), 2.60–2.71 (m, 2H), 2.96–2.98 (m, 3H), 3.21–3.26 (m, 1H), 3.37–3.47 (m, 2H), 3.60–3.62 (m, 1H), 4.04–4.07 (m, 2H), 4.21–4.25 (m, 2H), 4.52–4.74 (m, 4H), 4.78 (dd, *J* = 5.4 and 10.3 Hz, 1H), 4.80 (dd, *J* = 5.6 and 9.8 Hz, 1H), 5.16–5.30 (m, 4H), 5.41 and 5.47 (2s, 1H), 5.89–5.97 (m, 2H).

*Compound **IIg***

Yield: 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (d, *J* = 6.2 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.76–1.83 (m, 2H), 1.86–1.98 (m, 1H), 2.90 (s, 3H), 3.24–3.27 (m, 1H), 3.35–3.46 (m, 3H), 3.62–3.69 (m, 2H), 3.86–3.88 (m, 1H), 4.06–4.13 (m, 2H), 4.15–4.26 (m, 2H), 4.52–4.60 (m, 4H), 4.71 (dd, *J* = 5.2 and 10.8 Hz, 1H), 4.80 (dd, *J* = 5.6 and 7.8 Hz, 1H), 5.18–5.34 (m, 4H), 5.41 and 5.47 (2s, 1H), 5.90–5.97 (m, 2H).

(1R,5S,6S)-6-[(1R)-Hydroxyethyl]-2-{5-[(5-methyl-1,1-dioxo-[1,2,5]thiadiazolidin-2-yl)carbonyl]pyrrolidin-3-ylthio}-1-methylcarbapen-2-em-3-carboxylic acid ***IIIa***

To a stirred solution of **IIa** (93 mg, 0.13 mol) and $Pd(PPh_3)_4$ (10 mg) in CH_2Cl_2 (5 mL) was added dropwise *n*-tributytin hydride (0.13 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 amorphorus solid.

Compound ***IIIa***

Yield: 18%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.08 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 5.4 Hz, 3H), 2.34–2.39 (2bs, 1H), 2.58–2.64 (m, 2H), 2.69 (s, 3H), 3.19–3.26 (m, 3H), 3.29–3.39 (m, 4H), 3.54–3.65 (m, 1H), 3.66–3.76 (m, 1H), 3.92–3.86 (m, 3H), 4.08–4.15 (m, 2H). IR (KBr): 3450, 3330, 1750, 1710, 1680, 1340 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{18}H_{26}N_4O_7S_2$: 474.1243. Found: 474.1247.

The synthesis of compounds **IIIb–g** was carried out by the same procedure as described for the preparation of **IIIa**.

Compound ***IIIb***

Yield: 19%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.10 (s, 3H), 1.12 (d, *J* = 4,6 Hz, 3H), 1.29 (d, *J* = 5.2 Hz, 3H), 1.78–1.90 (m, 1H), 1.98 (bs, 1H), 2.89–2.91 (m, 1H), 3.01–3.09 (m, 2H), 3.18–3.29 (m, 2H), 3.42–3.51(m, 3H), 3.70–3.72 (m, 1H), 3.80–3.85 (m, 1H), 3.87–4.06 (m, 2H), 4.08–4.19 (m, 5H). IR (KBr): 3470, 3300, 1730, 1710, 1670, 1320 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{19}H_{28}N_4O_7S_2$: 488.1399. Found: 488.1400.

Compound ***IIIc***

Yield: 21%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.10 (d, *J* = 4.4 Hz, 3H), 1.21 (d, *J* = 4.0 Hz, 3H), 1.18(s, 3H), 1.70–2.01 (m, 2H), 2.16–2.31 (m, 1H), 2.63–2.71 (m, 1H), 2.92–3.16 (m, 2H), 3.30–3.52 (m, 2H), 3.52–3.55 (m, 3H), 3.93–4.00 (m, 2H), 4.09–4.13 (m, 4H). IR (KBr): 3470, 3350, 1750, 1720, 1680, 1340 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{18}H_{26}N_4O_7S_2$: 474.1243. Found: 474.1244.

Compound ***IIId***

Yield: 15%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.11 (d, *J* = 3.6 Hz, 3H), 1.19 (d, *J* = 5.7 Hz, 3H), 1.26 (s, 6H), 1.62–1.66 (m, 2H), 2.36–2.41 (m, 1H), 2.74–2.70 (m, 2H), 3.23–3.34 (m, 6H), 3.53–3.64 (m, 2H), 3.87–3.89 (m, 1H), 4.05–4.15 (m, 2H). IR (KBr): 3500, 3340, 1730, 1710, 1680, 1340 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{19}H_{28}N_4O_7S_2$: 488.1399. Found: 488.1401.

Compound ***IIIe***

Yield: 15%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.12 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.76–1.81 (m, 1H), 2.32–2.37 (m, 1H), 2.56–2.60 (m, 2H), 3.27–3.45 (m, 5H), 3.55–3.62 (m, 2H), 3.71–3.84 (m, 2H), 4.06–4.14 (m, 5H). IR (KBr): 3470, 3330, 1730, 1710, 1660, 1340 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{17}H_{24}N_4O_7S_2$: 460.1086. Found: 460.1083.

Compound ***IIIf***

Yield: 17%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.14 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.59–1.65 (m, 3H), 2.49–2.61 (m, 2H), 3.44–3.27 (m, 8H), 3.71 (m, 2H), 3.90 (bs., 2H), 4.09–4.13 (m, 3H). IR (KBr): 3450, 3330, 1740, 1710, 1660, 1340 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{18}H_{26}N_4O_7S_2$: 474.1243. Found: 474.1245.

Compound ***IIIg***

Yield: 18%. UV λ_{max}: 298 nm. ^{1}H-NMR (D_2O) δ: 1.11 (d, *J* = 6.7 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.81 (bs, 1H), 2.03–2.11 (m, 1H), 2.64–2.74 (m, 2H), 2.81 (s, 2H), 3.02–3.05 (m, 1H), 3.21–3.25 (m, 1H), 3.35–3.37 (m, 2H), 3.61–3.71 (m, 3H), 4.01–4.15 (m, 4H). IR (KBr): 3470, 3350, 1730, 1700, 1640, 1320 (S=O) cm^{-1}. HRMS(FAB) calcd. for $C_{19}H_{28}N_4O_7S_2$: 488.1399. Found: 488.1400.

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