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Synthesis and Biological Properties of New 1β-Methylcarbapenems

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Abstract:

The synthesis and biological activity of the novel series of 1β-methylcarbapenems, **1** and **2** were described. Most compounds displayed high potent antibacterial activity. The best compound in this series, **2a** (IH201; R^2=NH_2) showed an excellent and a broad spectrum as well as high renal DHP-I stability. It also possessed good *in vivo* efficacy and high safety.

Keywords: Antibiotics; Antibacterials; Substituent effects

β-Lactam antibiotics were in huge clinical use because of their potent antibacterial activity and safety[1]. Especially, carbapenems such as imipenem and meropenem, showed a broad antibacterial spectrum and an excellent bactericidal activity among β-lactams[2]. In spite of its broadest spectrum of antimicrobial activity of all the β-lactam antibiotics in clinical use, imipenem has two serious drawbacks. Those are a high sensitivity to renal dehydropeptidase-I (DHP-I)[3,4] and a convulsive potential[5]. Meropenem, 1β-methylcarbapenem containing a pyrrolidin-3'-ylthio group as C-2 side chain structurally, solved these problems[6-8]. But, increasing incidence of resistant bacterial strains to available antibiotics demands to develop new agents continuously. The structure-activity relationships of imipenem and meropenem are well known that the 6α-hydroxyethyl and 1β-methyl group are necessary for high stability *vs.* β-lactamases and for the high chemical stability as well as stability *vs.* DHP-I, respectively[9-11]. In looking for this point of view, it seems that the 2-position is the only place for further structural modification without the decrease in the chemical and biological stability. Actually, several new 1β-methylcarbapenems which have a pyrrolidin-3'-ylthio group as C-2 side chain, BO-2727 (Banyu)[12], S-4661 (Shionogi)[13], ZD-4433 (Merck)[14], ER-35786 (Eisai)[15], and FR-21818 (Fusisawa)[16], were being investigated in clinical or preclinical stage.

As a part of our research program, we were particularly interested in exploring the effect of the introduction of new amide functions instead of 5'-dimethylaminocarbonyl group in

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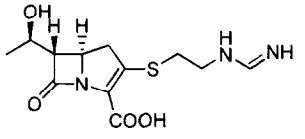
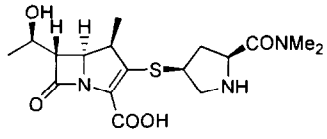
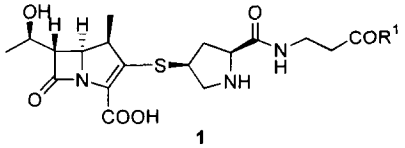
pyrrolidin-3'-ylthio C-2 side chain of meropenem. Our efforts were directed toward the synthesis of new carbapenems **1** and **2** using β- alanine and taurin, which are commercially cheap and available, for the introduction of amide functions at a pyrrolidin-3'- ylthio C-2 side chain. As a result, we discovered new 1β-methylcarbapenem, **2a** (IH201; R^2=NH_2), with a broad anti-microbial spectrum and an excellent *in vivo* efficacy.



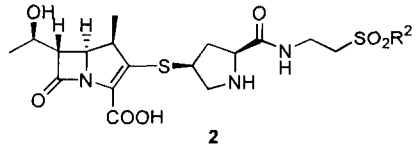
Imipenem



Meropenem



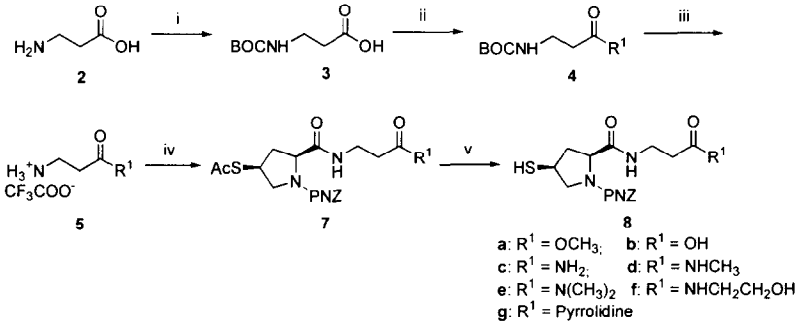
1



2

Synthesis

3-Mercapto-5-(*N*-substituted carbamoyl)pyrrolidines **8a-g** with varying R^1 groups were prepared by the linear route as shown in Scheme 1.



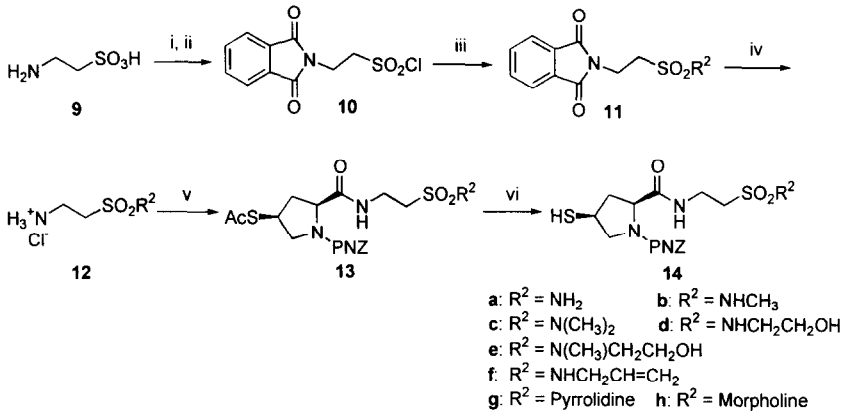
a: R^1 = OCH_3; **b**: R^1 = OH
c: R^1 = NH_2; **d**: R^1 = $NHCH_3$
e: R^1 = $N(CH_3)_2$ **f**: R^1 = $NHCH_2CH_2OH$
g: R^1 = Pyrrolidine

Scheme 1. *Reagents and reaction conditions*: (i) $(Boc)_2O$, 2*N* NaOH, rt (80%); (ii) $ClCOOC_2H_5$, TEA, R^1H, THF, 0°C (**4c**: 72%); (iii) TFA, rt (**5c**: quant.); (iv) (3*S*,5*S*)-3-acetylthio-5-carboxy-1-*p*-nitrobenzyloxycarbonyl pyrrolidine (**6**), $ClCOOC_2H_5$, TEA, THF, 0°C (**7c**: 58%); (v) 2*N* NaOH, MeOH, 0°C (**8c**: 83%)

Boc protection of amino group of β-alanine **2** followed by mixed anhydride coupling with a variety of nucleophiles gave the corresponding compounds **4a-g**, respectively. Amine salt **5** was readily prepared from **4** using trifluoroacetic acid in nearly quantitative yield. With amine salt **5**, thioacetyl proline **6** was coupled using standard coupling procedure to get compound **7**. *N*-Protected 3-thioacetyl proline **6** was prepared from *trans*-4-hydroxy-*L*-proline by the known procedures reported by Sunagawa[17,18]. Subsequent removal of the acetylthio protecting group in **7a-g** was accomplished under basic conditions with 2*N* NaOH in MeOH to give the desired

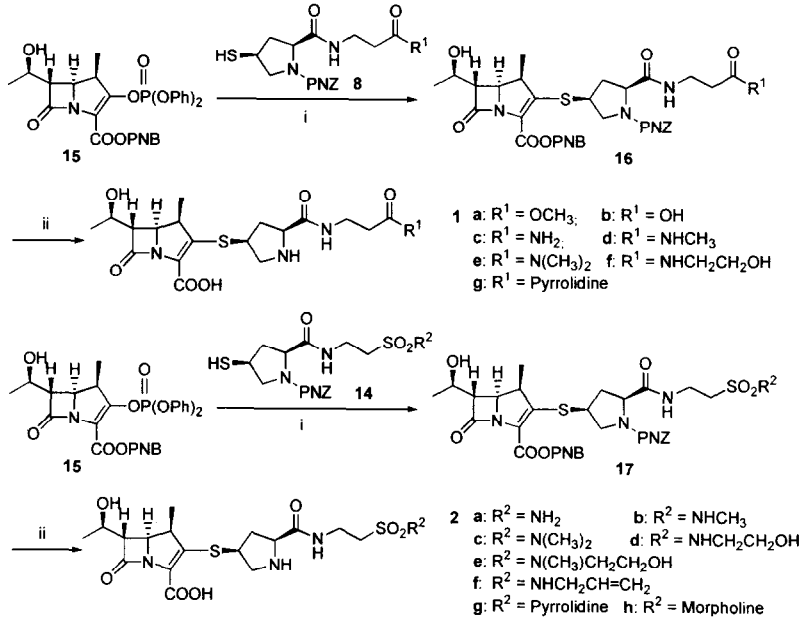
thiol derivatives **8a-g**, respectively.

On the other hand, the various 3-mercapto-5-(*N*-substituted carbamoyl)pyrrolidines **14a-h** were prepared *via* the methods outlined in Scheme 2.



Scheme 2. *Reagents and reaction conditions*: (i) CH_3CO_2K, phthalic anhydride, AcOH (90%); (ii) PCl_5, C_6H_6 (85%); (iii) R^2H, THF, 0°C (**11a**: 70%); (iv) $H_2NNH_2\ H_2O$, 95% EtOH (**12a**: >95%); (v) (3*S*,5*S*)-3-acetylthio-5-carboxy-1-*p*-nitrobenzyloxycarbonylpyrrolidine (**6**), $ClCOOC_2H_5$, TEA, THF, 0°C (**13a**: 60%); (vi) 2*N* NaOH, MeOH, 0°C (**14a**: 80%)

Phthalimido protection of commercially available taurine **9** which served as a starting material followed by chlorination provided phthalimidoethanesulfonyl chloride **10** in an excellent yield.



Scheme 3. *Reagents and reaction conditions*: (i) DIPEA, CH_3CN, 0°C (**16c**: 57%; **17a**: 58%); (ii) 10% Pd-C/H_2, 45*psi*, THF/distilled H_2O (1:1), Diaion HP-20 (**1c**: 61%; **2a**: 65%)

The reaction of sulfonyl chloride **10** with various nucleophiles afforded the corresponding sulfoneamides **11a-h** in good yields which were then converted to the amine salts **12a-h** by the treatment with hydrazine monohydrate and 2*N* HCl, respectively. Here we describe the synthesis of **14a-h** from amine salt **12** using the same reaction conditions as in the previous reaction protocols. Amine salts **12a-h** were coupled with thioacetyl proline **6** and subsequently treated with 2*N* NaOH to give the desired compounds **14a-h**, respectively.

Treatment of the enolphosphate **15**[9] with freshly prepared thiol derivatives **8a-g** afforded protected carbapenem esters **16a-g**. Hydrogenolysis of **16a-g** over 10% Pd-C and purification by column chromatography on Diaion HP-20 provided the new carbapenems **1a-g**[1], respectively (Scheme 3). The preparation of another new carbapenems **2a-h**[2] was carried out by the similar procedure to that described above. Coupling of thiol derivatives **14a-h** with the carbapenem nucleus **15** and subsequent removal of PNB and PNZ protecting groups was achieved to give the target carbapenems **2a-h**, after purification by column chromatography.

Biological Properties

The comparative antibacterial activity and DHP-I stability of the various new carbapenems are shown in Table 1. All the compounds were highly active against a wide range of Gram-positive and Gram-negative organisms, including *Pseudomonas*. In a point of view on the structure-activity relationship, the effect of substituents R^1 and R^2 is quite clear. It was shown that the activity decreased with increasing size of R^1 and R^2. Thus, of all compounds synthesized in this work, **1c** and **2a** having the simplest amido substituent, as R^1 and R^2,

[1] **1a:** δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.31 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 2.02-2.09 (m, 1H), 2.68 (t, 2H), 2.90-3.00 (m, 1H), 3.35-3.66 (m, 5H), 3.76 (s, 3H), 4.02-4.07 (m, 1H), 4.25-4.30 (m, 2H), 4.47 (t, 1H). **1b:** δ 1.25 (d, 3H, *J*=7.1 Hz, β-methyl), 1.32 (d, 3H, *J*=6.3 Hz, *CH*$_3$CHOH), 2.04-2.10 (m, 1H), 2.55-2.61 (m, 2H), 2.94-2.99 (m, 1H), 3.35-3.66 (m, 5H), 3.76-3.84 (m, 1H), 4.03-4.08 (m, 1H), 4.25-4.31 (m, 2H), 4.47 (t, 1H). **1c:** δ 1.24 (d, 3H, *J*=7.2 Hz, β-methyl), 1.33 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 2.06-2.11 (m, 1H), 2.56-2.60 (m, 2H), 2.94-2.99 (m, 1H), 3.37-3.65 (m, 5H), 3.76-3.82(m, 1H), 4.04-4.08 (m, 1H), 4.25-4.31 (m, 2H), 4.50 (t, 1H). **1d:** δ 1.22 (d, 3H, *J*=7.1 Hz, β-methyl), 1.33 (d, 3H, *J*=6.3 Hz, *CH*$_3$CHOH), 2.06-2.13 (m, 1H), 2.54-2.68 (m, 2H), 2.77 (s, 3H), 2.78-3.02 (m, 1H), 3.37-3.65 (m, 5H), 3.75-3.83 (m, 1H), 3.98-4.08 (m, 1H), 4.24-4.31 (m, 2H), 4.46 (t 1H). **1e:** δ 1.18 (d, 3H, *J*=7.1 Hz, β-methyl), 1.26 (d, 3H, *J*=6.5 Hz, *CH*$_3$CHOH), 1.96-2.04 (m, 1H), 2.64-2.90 (m, 2H), 2.87 (s, 3H), 3.14 (s, 3H), 3.16-3.19 (m, 1H), 3.25-3.56 (m, 5H), 3.70-3.77 (m, 1H), 3.97-4.01 (m, 1H), 4.19-4.38 (m, 2H), 4.43 (t, 1H). **1f:** δ 1.22 (d, 3H, *J*=7.1 Hz, β-methyl), 1.31 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 2.04-2.09 (m, 1H), 2.54-2.59 (m, 2H), 2.94-2.99 (m, 1H), 3.36-3.65 (m, 7H), 3.76-3.85 (m, 3H), 4.02-4.06 (m, 1H), 4.24-4.30 (m, 2H), 4.47 (t, 1H). **1g:** δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.30 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 1.89-2.07 (m, 5H), 2.64-2.75 (m, 2H), 2.92-2.97 (m, 1H), 3.37-3.65 (m, 9H), 3.72-3.78 (m, 1H), 4.01-4.06 (m, 1H), 4.24-4.39 (m, 2H), 4.42 (t, 1H).

[2] **2a:** δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.31 (d, 3H, *J*=6.5 Hz, *CH*$_3$CHOH), 2.05-2.14 (m, 1H), 2.87-2.98 (m, 1H), 3.34-3.53 (m, 5H), 3.71-3.86 (m, 3H), 4.01-4.05 (m, 1H), 4.25-4.30 (m, 2H), 4.43 (t, 1H). **2b:** δ 1.23 (d, 3H, *J*=7.2 Hz, β-methyl), 1.31 (d, 3H, *J*=6.5 Hz, *CH*$_3$CHOH), 2.08-2.15 (m, 1H), 2.77 (s, 3H), 2.89-2.99 (m, 1H), 3.35-3.58 (m, 5H), 3.67-3.82 (m, 3H), 4.02-4.06 (m, 1H), 4.23-4.31 (m, 2H), 4.46 (t, 1H). **2c:** δ 1.21 (d, 3H, *J*=7.1 Hz, β-methyl), 1.29 (d, 3H, *J*=6.5 Hz, *CH*$_3$CHOH), 2.06-2.16 (m, 1H), 2.88 (s, 6H), 2.92-3.00 (m, 1H), 3.34-3.48 (m, 5H), 3.64-3.87 (m, 3H), 4.02-4.06 (m, 1H), 4.22-4.30 (m, 2H), 4.47 (t, 1H). **2d:** δ 1.26 (d, 3H, *J*=7.1 Hz, β-methyl), 1.35 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 2.16-2.20 (m, 1H), 2.91-3.05 (m, 1H), 3.29 (t, 2H), 3.31-3.54 (m, 5H), 3.71-3.87 (m, 5H), 4.07-4.12 (m, 1H), 4.28-4.33 (m, 2H), 4.54 (t, 1H). **2e:** δ 1.22 (d, 3H, *J*=7.1 Hz, β-methyl), 1.33 (d, 3H, *J*=6.2 Hz, *CH*$_3$CHOH), 2.06-2.21 (m, 1H), 2.89 (s, 3H), 3.01-3.08 (m, 1H), 3.32-3.55 (m, 7H), 3.63-3.91 (m, 5H), 4.05-4.11 (m, 1H), 4.21-4.34 (m, 2H), 4.53 (t, 1H). **2f:** δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.31 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 2.05-2.14 (m, 1H), 2.87-2.98 (m, 1H), 3.34-3.53 (m, 5H), 3.71-3.86 (m, 5H), 3.98-4.05 (m, 1H), 4.25-4.31 (m, 2H), 4.48 (t, 1H), 5.19-5.38 (m, 2H), 5.81-5.98 (m, 1H). **2g:** δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.32 (d, 3H, *J*=6.4 Hz, *CH*$_3$CHOH), 2.00-2.09 (m, 4H), 2.12-2.16 (m, 1H), 2.90-2.98 (m, 1H), 3.35-3.51 (m, 9H), 3.67-3.87 (m, 3H), 4.03-4.07 (m, 1H), 4.24-4.30 (m, 2H), 4.46 (t, 1H). **2h:** δ 1.16 (d, 3H, *J*=7.1 Hz, β-methyl), 1.21 (d, 3H, *J*=6.2 Hz, *CH*$_3$CHOH), 2.06-2.15 (m, 1H), 2.88-2.98 (m, 1H), 3.29-3.53 (m, 9H), 3.71-3.86 (m, 7H), 3.98-4.05 (m, 1H), 4.23-4.30 (m, 2H), 4.43 (t, 1H).

showed the most active properties against organisms tested. The activity of **2a** (IH201) was well balanced over a wide range and almost equal with meropenem. Furthermore, IH201 was more stable to DHP-I than meropenem. In case that R^1 or R^2 is polar substituent, hydroxyethylamido, **1f** and **2d** also showed an excellent activity, but slightly poor compared with their correspondings, **1c** and **2a**, respectively.

Table 1
In vitro antibacterial activity and DHP-I stability.

Organism	MIC (μg/mL)[a]								
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**IPM**[b]	**MEM**[c]
S. pyogens 77A	0.007	0.049	0.007	0.013	0.007	0.007	0.007	0.004	0.002
S. faecium MD 8b	12.5	50	12.5	12.5	12.5	12.5	12.5	1.563	12.5
S. aureus SG 511	0.195	1.563	0.195	0.391	0.195	0.391	0.195	0.013	0.098
E. coli 078	0.025	0.025	0.025	0.049	0.025	0.049	0.025	0.098	0.013
E. coli 1507E	0.025	0.049	0.025	0.025	0.025	0.049	0.025	0.195	0.025
P. aeruginosa 1592E	1.563	6.25	0.391	0.781	1.563	0.391	6.25	0.781	0.195
P. aeruginosa 1771M	0.195	3.125	0.195	0.391	0.391	0.391	0.781	0.195	0.049
S. typhymurium	0.049	0.098	0.049	0.049	0.049	0.098	0.049	0.781	0.025
K. aerogenes 1522E	0.049	0.098	0.049	0.049	0.049	0.098	0.049	0.391	0.049
E. cloacae 1321E	0.025	0.049	0.025	0.025	0.025	0.025	0.025	0.195	0.025
DHP-I stability[d]	NT[e]	NT	26	NT	NT	NT	NT	100	32

Organism	MIC (μg/mL)[a]									
	2a[f]	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**IPM**[b]	**MEM**[c]
S. pyogens 77A	0.004	0.013	0.007	0.007	0.013	0.007	0.004	0.013	0.004	0.002
S. faecium MD 8b	6.25	12.5	12.5	12.5	12.5	6.25	6.25	12.5	1.563	12.5
S. aureus SG 511	0.098	0.195	0.195	0.195	0.391	0.195	0.098	0.391	0.013	0.098
E. coli 078	0.025	0.025	0.025	0.025	0.025	0.025	0.013	0.025	0.098	0.013
E. coli 1507E	0.013	0.025	0.025	0.025	0.025	0.025	0.013	0.049	0.195	0.025
P. aeruginosa 1592E	0.195	0.391	1.563	0.391	1.563	1.563	6.25	50	0.781	0.195
P. aeruginosa 1771M	0.195	0.391	0.195	0.391	0.781	0.781	0.391	1.563	0.195	0.049
S. typhymurium	0.025	0.025	0.049	0.049	0.049	0.049	0.025	0.098	0.781	0.025
K. aerogenes 1522E	0.049	0.049	0.049	0.049	0.049	0.049	0.025	0.098	0.391	0.049
E. cloacae 1321E	0.025	0.025	0.025	0.025	0.025	0.025	0.013	0.049	0.195	0.025
DHP-I stability[d]	24	NT	NT	NT	NT	NT	NT	NT	100	32

[a] MIC was determined by agar dilution method using Mueller-Hinton.
[b] IPM=imipenem.
[c] MEM=meropenem.
[d] Relative rate of hydrolysis to imipenem by partially purified porcine renal DHP-I.
[e] Not tested.
[f] IH201.

So we carried out further biological test for new carbapenem **2a** (IH201). Pharmacokinetic study in mice indicated that the AUC value of IH201 was approximately 3-4 fold higher than that of meropenem (Table 2). And also, the *in vivo* protective activity of IH201 against *S. pyogenes* 77A, *E. coli* 078, and *P. aeruginosa* 1771M was investigated as shown in Table 3. As a result, IH201 displayed approximately 3 times more active values against *S. pyogenes* 77A and *E. coli* 078, but slightly less active value against *P. aeruginosa* 1771M in comparison with those for meropenem. It seems to be due to its better bioavailability.

Furthermore, in acute toxicity test, LD_{50} for IH201 was acceptable high value, 2000-4000

mg/kg (Table 4). These biological properties indicate that IH201 is a promising new carbapenem with a good potential for treatment of broad infections and high safety.

Table 2
Pharmacokinetic parameters[a] of IH201

	IH201	Meropenem
Cmax (μg/mL)	16.04 ± 0.96	7.6 ± 0.55
Tmax (hr)	< 0.33	0.21 ± 0.04
t1/2 (hr)	0.32 ± 0.04	0.24 ± 0.02
AUC (μg/mL)	11.89 ± 1.13	3.29 ± 0.29
AUC (hr)	0 - 3 hr	0 - 2 hr

[a] at a single subcutaneous administration of 40 mg/kg in mice (n=4).

Table 3
In vivo protective activity[a,b] of IH201

	IH201	Meropenem
S. pyogens 77A	2.31 (1.36 - 3.94)	7.16 (4.13 - 2.43)
E. coli 078	0.47 (0.3 - 0.74)	1.24 (0.74 - 2.08)
P. aeruginosa 1771M	2.60 (1.53 - 4.39)	1.76 (1.14 - 2.72)

[a] at a single subcutaneous administration in mice.
[b] PD_{50} (mg/kg), parenthesis: 95% confidence limits.

Table 4
Acute toxicity of IH201

	Dose (mg/kg)[a]				Predicted LD_{50} (mg/kg)
	500	1000	2000	4000	
Lethality (dead/total)	0/5	0/5	0/5	5/5	2000 - 4000

[a] at a single intravenous administration in mice.

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