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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 1β-METHYLCARBAPENEMS HAVING A NEW MOIETY AT C-2

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Abstract: The synthesis and biological activity of the novel series of 1β-methylcarbapenems **1a-f**, bearing a variety of 3′′,4′′-disubstituted pyrrolidinamides as substituents at C-2, are described. Of these carbapenems, diol **1a** showed the most potent and well balanced antibacterial activity against Gram-positive and Gram-negative. **1a** was also evaluated for pharmacokinetics and *in vivo* therapeutic efficacy in systemic infections.

Carbapenems such as imipenem, panipenem, and meropenem are the most potent β-lactam antibiotics which have a broad spectrum of antibacterial activitiy against both Gram-positive and Gram-negative organisms.[1] Although their activities against resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) are relatively weak, a number of carbapenem antibiotics are currently in huge clinical trial because of their potent antibacterial activity and safety.[2] Meropenem[3] is stable to renal DHP-I[4,5] due to the improved chemical and metabolic stability and it has recently been approved for clinical use in some countries. In recent years, 1β-methylcarbapenems such as BO-2727[6], S-4661[7], ZD-4423[8], ER-35786[9], and FR-21818[10], which have a pyrrolidine-3-yithio group at C-2 in the carbapenem skeleton, have been reported to possess a potent and broad spectrum of antibacterial activity.

Thus, our early efforts[11,12] have been directed toward the synthesis of new 1β-methylcarbapenems derivatized at C-2 side chain with improved properties including antibacterial activity. We are particularly interested in this pyrrolidine-3-ylthio group and focused on the introduction of 3′′,4′′-disubstituted pyrrolidinamide group at C-5′ position of pyrrolidine.

Herein, we wish to report the synthesis of the novel 1β-methylcarbapenems **1a-f** having a new moiety at C-2 and biological evaluation including pharmacokinetics and *in vivo* efficacy.

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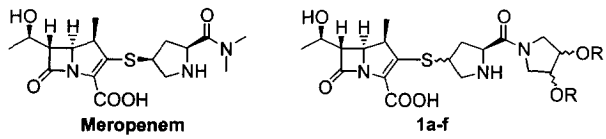
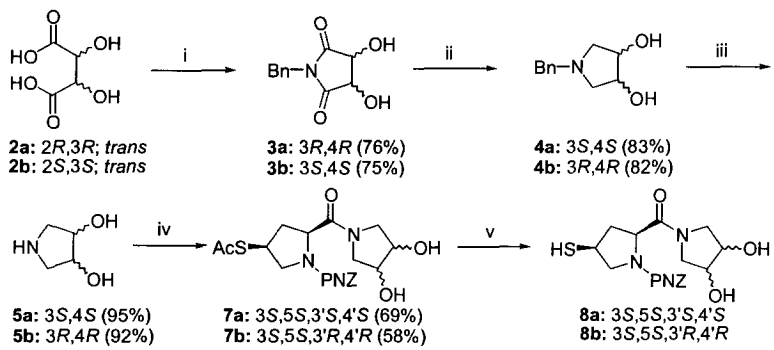


Chemistry

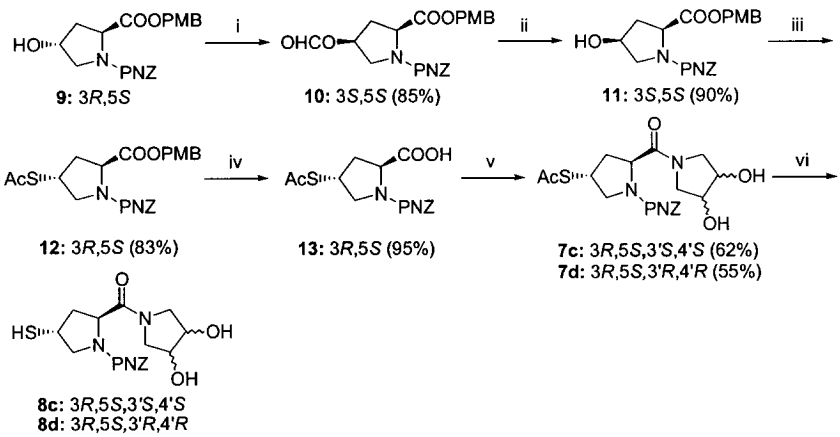
Thiol derivatives **8a-b** having a 3′,4′-disubstituted pyrrolidine moiety were prepared by the sequence of reactions shown in Scheme 1.



Scheme 1. *Reagents and reaction conditions*: (i) $BnNH_2$, xylene, reflux (Dean Stark), 3h; (ii) $BF_3.Et_2O$, diglyme, $NaBH_4$, 70°C, 2h, 6*N* HCl, NaF, 100°C, 30min, 5*N* NaOH; (iii) 10% Pd-C/H_2, 45*psi*, THF; (iv) (3*S*,5*S*)-3-acetylthio-5-carboxy-1-*p*-nitrobenzyloxycarbonylpyrrolidine (**6**), DCC, THF, rt, 3h; (v) 2*N* NaOH, MeOH, rt, 30min

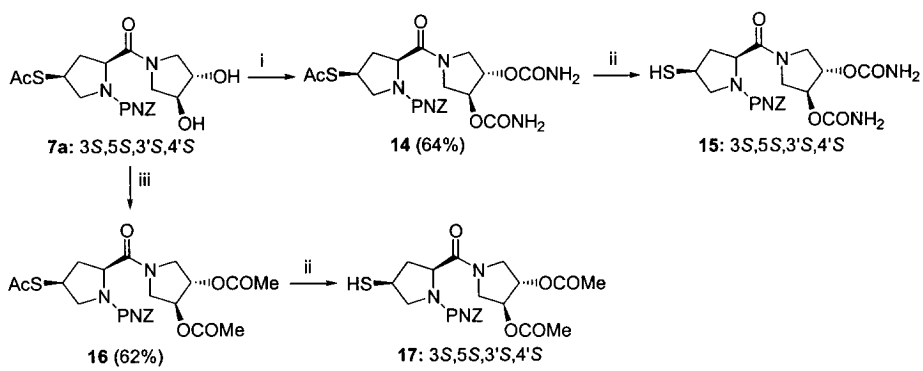
Optically active (3*R*,4*R*)- and (3*S*,4*S*)-*N*-benzyl imines **3a-b** were prepared starting from *L*- and *D*-tartaric acids **2a-b**, respectively.[13] **3a** was then reduced with boron trifluoride diethyl etherate and sodium borohydride in diglyme[13] and subsequently debenzylated to give dihydroxypyrrolidine **5a**. Treatment of **5a** with *N*-protected 3-thioacetyl proline **6**, which was prepared from *trans*-4-hydroxy-*L*-proline by the known procedures reported by Sunagawa[3,14], afforded thioacetate **7a**[15] by standard procedure. **7a** was converted to the desired thiol **8a** by deacetylation under basic condition, applicable for the coupling with carbapenem enolphosphate **18**. The thiol **8b** having (3′*R*,4′*R*)-configuration was prepared from *D*-tartaric acid **2b** in similar manner.

On the other hand, thiols **8c-d** with inversion of configuration at C-3 of pyrrolidine were prepared from protected proline **9** according to Scheme 2. For this end, **9** was treated twice by Mitsunobu reaction[16]. Inversion of hydroxyl group of (3*R*)-**9** using Mitsunobu condition with formic acid followed by hydrolysis of the resulting formate (3*S*)-**10** gave the alcohol (3*S*)-**11** in excellent yield. In order to re-invert the configuration at C-3 of (3*S*)-**11**, treatment of **11** with thiolacetic acid under Mitsunobu condition gave thioacetyl proline (3*R*)-**12**, which upon deprotecting with trifluoroacetic acid provided (3*R*)-**13**. Coupling and deacetylation were carried out by using procedures analogous to those described above to afford the corresponding thiols **8c-d**, respectively.



Scheme 2. *Reagents and reaction conditions*: (i) PPh_3, DEAD, HCOOH, THF; (ii) 1*N* NaOH, EtOH, 0°C, 30min; (iii) PPh_3, DEAD, AcSH, THF; (iv) TFA, anisole, rt, 30min; (v) **5a-b**, DCC, THF, rt, 3h; (vi) 2*N* NaOH, MeOH, rt, 30min

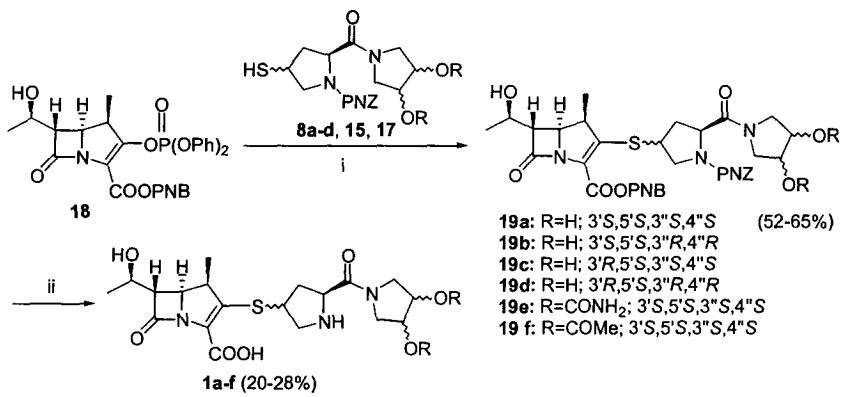
For the formation of carbamate and ester groups at C-3′,4′ of pyrrolidine, thioacetate **7a** was employed as the precursor (Scheme 3).



Scheme 3. *Reagents and reaction conditions*: (i) $Cl_3CCONCO$, *cat.* $Bu_2Sn(OAc)_2$, CH_2Cl_2, rt, 5-6h, Al_2O_3; (ii) 2*N* NaOH, MeOH, rt, 30min; (iii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 5-6h

Treatment of **7a** with trichloroacetyl isocyanate in the presence of dibutyltindiacetate and then aluminum oxide led to the carbamate **14**[15], which was deacetylated under basic condition to afford the desired thiol **15**. For the preparation of ester compound **17**, **7a** was reacted with acetic anhydride. **16**[15] was then converted to the thiol **17** by saponification with aqueous 2*N* NaOH.

Reaction of carbapenem enolphosphate **18**[17] with thiol derivatives **8a-d**,**15**,**17** afforded the protected 1β-methylcarbapenems **19a-f**, respectively (Scheme 4). Hydrogenolysis of **19a-f** over 10% Pd-C and purification by column chromatography on Diaion HP-20 provided the corresponding carbapenems **1a-f**[18] as an amorphous solid by lyophilization, respectively.



Scheme 4. *Reagents and reaction conditions*: (i) DIPEA, CH_3CN, 0°C; (ii) 10% Pd-C/H_2, 45*psi*, THF/distilled H_2O (1:1), Diaion HP-20

Biological Properties

Table 1 shows the antibacterial activity and stability to porcine renal DHP-I of the novel carbapenems prepared above, together with those of imipenem and meropenem as reference compounds.

Table 1
In vitro antibacterial activity and DHP-I stability of carbapenem compounds **1a-f**.

Organism	MIC (μg/mL)[a]							
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**IPM[b]**	**MEM[c]**
S. pyogens 77A	0.007	0.007	0.025	0.013	0.025	0.007	0.004	0.002
S. faecium MD 8b	6.25	6.25	25	12.5	6.25	6.25	1.563	12.5
S. aureus SG 511	0.098	0.195	0.195	0.195	0.195	0.195	0.013	0.098
E. coli 078	0.013	0.013	0.098	0.098	0.025	0.025	0.098	0.013
E. coli 1507E	0.025	0.025	0.098	0.195	0.025	0.025	0.195	0.025
P. aeruginosa 1592E	0.195	0.098	100	100	0.781	1.563	0.781	0.195
P. aeruginosa 1771M	0.098	0.098	0.781	0.391	0.391	0.195	0.195	0.049
S. typhymurium	0.049	0.049	0.195	0.391	0.049	0.049	0.781	0.025
K. aerogenes 1522E	0.049	0.049	0.195	0.195	0.049	0.049	0.391	0.049
E. cloacae 1321E	0.013	0.013	0.195	0.195	0.025	0.013	0.195	0.025
DHP-I stability[d]	0.63	0.50	NT[e]	NT	0.53	0.66	0.19	1.00

[a] MIC was determined by agar dilution method using Mueller-Hinton.
[b] IPM=imipenem.
[c] MEM=meropenem.
[d] Relative $t_{1/2}$ of hydrolysis to meropenem by partially purified porcine renal DHP-I.
[e] Not tested.

All the compounds displayed potent antibacterial activity against the target organisms. In our series, the promising compounds were unsubstituted diols **1a** and **1b**. The diols **1a-b** exhibited excellent antibacterial activities against a wide range of both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. They showed potent activity similar to meropenem, but their stabilities to DHP-I were slightly poorer than meropenem. According to expectation, there appeared to be significant difference in potency

between **1a-b** and **1c-d**, which are diasteromers at C-3′ of pyrrolidine ring. Namely, **1c-d** with 3′R-configuration exhibited 2-4 fold inferior activity against Gram-positives and very poor activity against Gram-negatives compared to diasteromer **1a-b**.[19] The carbamate **1e** and the ester **1f** displayed similar activity each other but reduced activity compared to the unsubstituted diol compounds **1a-b**. They showed similar or slightly inferior activities to meropenem against most of Gram-positive and Gram-negative bacteria. And also the compound **1a** possessed highly effective *in vitro* potency against respiratory tract pathogens, especially such as *S. aureus* 241, *S. pneumoniae* PN020, *K. pneumoniae* 2011E, *H. influenzae*, and *M. catarrhalis* 25240. **1a** exhibited potent activity as much as meropenem and several fold better than cefpirome against those β-lactam resistant strains.[20]

The selected carbapenem **1a** was evaluated for pharmacokinetic and *in vivo* therapeutic efficacy in systemic infections in mice. The pharmacokinetics of **1a** was compared with meropenem in mice and the results were listed in Table 2. Profiles of **1a** were almost equal to those of meropenem. Based on good bioavailability and potent antibacterial activity, **1a** showed excellent *in vivo* therapeutic efficacy in systemic infections caused by *E. coli*, *S. aureus*, *S. pyogens*, and *P. aeruginosa* in mice (Table 3). Especially, therapeutic efficacy of **1a** was approximately 5 fold better than that of meropenem against *S. aureus*.

Table 2
Pharmacokinetic parameters[a] of **1a**

	1a	Meropenem
Cmax (μg/mL)	16.58 ± 0.21	15.57 ± 2.01
Tmax (hr)	0.17	0.17
$t_{1/2}$ (hr)	0.25 ± 0.05	0.27 ± 0.01
AUC (μg.h/mL)	6.83 ± 0.50	6.86 ± 0.39
AUC (hr)	0 - 4 hr	

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

Table 3
In vivo protective effects[a,b] of **1a** and Meropenem

	1a	Meropenem
E. coli 078	0.94 (0.38 – 2.35)	0.65 (0.37 – 1.13)
S. aureus Y-80-1953	2.18 (0.98 – 4.83)	11.1 (5.90 – 20.5)
S. pyogens 77A	4.79 (2.9 – 8.0)	4.55 (1.5 – 13.9)
P. aeruginosa 1771M	3.93 (2.29 – 7.07)	4.26 (1.94 – 9.37)

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

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15. **7a:** ^{1}H NMR ($CDCl_3$) δ 1.92-2.02 (m, 1H), 2.33 (s, 3H), 2.62-2.78 (m, 1H), 3.35-3.52 (m, 3H), 3.61-3.82 (m, 2H), 3.85-3.97 (m, 1H), 4.08-4.17 (m, 3H), 4.51-4.55 (m, 1H), 5.12-5.21 (m, 2H), 7.48 (d, 2H), 8.18 (d, 2H). **7b:** ^{1}H NMR ($CDCl_3$) δ 1.89-2.01 (m, 1H), 2.34 (s, 3H), 2.58-2.77 (m, 1H), 3.32-3.49 (m, 3H), 3.62-3.78 (m, 2H), 3.84-3.95 (m, 1H), 4.10-4.16 (m, 3H), 4.50-4.56 (m, 1H), 5.12-5.20 (m, 2H), 7.38 (d, 2H), 8.20 (d, 2H). **7c:** ^{1}H NMR ($CDCl_3$) δ 2.14-2.28 (m, 1H), 2.38-2.46 (m, 1H), 2.32 (s, 3H), 3.36-3.56 (m, 2H), 3.61-3.82 (m, 1H), 3.96-4.25 (m, 1H), 4.52-4.66 (m, 1H), 5.17 (q, 2H), 7.50 (d, 2H), 8.22 (d, 2H). **7d:** ^{1}H NMR ($CDCl_3$) δ 2.15-2.25 (m, 1H), 2.37-2.44 (m, 1H), 2.34 (s, 3H), 3.34-3.48 (m, 2H), 3.58-3.80 (m, 1H), 3.92-4.42 (m, 1H), 4.48-4.66 (m, 1H), 5.18 (q, 2H), 7.52 (d, 2H), 8.23 (d, 2H). **14:** ^{1}H NMR ($CDCl_3$) δ 1.62-1.82 (m, 1H), 2.33 (s, 1H), 2.73-2.86 (m, 1H), 3.08-3.18 (m, 1H), 3.15-3.52 (m, 1H), 3.48-3.64 (m, 2H), 3.68-3.82 (m, 1H), 3.84-4.02 (m, 1H), 4.59 (t, 1H), 5.18 (q, 2H), 6.62-6.82 (m, 2H), 7.62 (d, 2H), 8.24 (d, 2H). **16:** ^{1}H NMR ($CDCl_3$) δ 1.92-2.08 (m, 1H), 2.08 (s, 6H), 2.34 (s, 3H), 2.64-2.78 (m, 1H), 2.46 (t, 1H), 3.56-3.84 (m, 4H), 3.83-4.06 (m, 3H), 4.04-4.18 (m, 1H), 4.50 (t, 1H), 5.21 (q, 2H), 7.46 (d, 2H), 8.22 (d, 2H).
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18. **1a:** ^{1}H NMR (D_2O) δ 1.22 (d, 3H, *J*=7.1 Hz, β-methyl), 1.31 (d, 3H, *J*=6.4 Hz, C*H*$_3$CHOH), 2.04-2.08 (m, 1H), 3.07-311 (m, 1H), 3.36-3.41 (m, 1H), 3.42-3.52 (m, 2H), 3.54-3.64 (m, 2H), 3.77-3.83 (m, 3H), 4.05-4.10 (m, 1H), 4.24-4.35 (m, 4H); FABHRMS *m/z* Calcd for $C_{19}H_{27}N_3O_7S$ $(M+H)^+$ 442.1570, Found 442.1646. **1b:** ^{1}H NMR (D_2O) δ 1.26 (d, 3H, *J*=7.2 Hz, β-methyl), 1.34 (d, 3H, *J*=6.3 Hz, C*H*$_3$CHOH), 1.88-2.02 (m, 1H), 2.98-3.14 (m, 1H), 3.36-3.56 (m, 3H), 3.57-3.81 (m, 3H), 3.87-3.96 (m, 1H), 3.98-4.10 (m, 1H), 4.22-4.42 (m, 4H), 4.43-4.53 (m, 2H); FABHRMS *m/z* Calcd for $C_{19}H_{27}N_3O_7S$ $(M+H)^+$ 442.1570, Found 442.1630. **1c:** ^{1}H NMR (D_2O) δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.30 (d, 3H, *J*=6.4 Hz, C*H*$_3$ CHOH), 2.38-2.50 (m, 1H), 2.51-2.63 (m, 1H), 3.33-3.50 (m, 1H), 3.43-3.56 (m, 3H), 3.53-3.68 (m, 1H), 3.73-3.81 (m, 2H), 3.81-3.92 (m, 1H), 4.12-4.18 (m, 1H), 4.26-4.34 (m, 4H). **1d:** ^{1}H NMR (D_2O) δ 1.28 (d, 3H, *J*=7.1 Hz, β-methyl), 1.34 (d, 3H, *J*=6.5 Hz, C*H*$_3$CHOH), 2.43-2.58 (m, 1H), 2.58-2.72 (m, 1H), 3.42-3.64 (m, 3H), 3.64-3.83 (m, 3H), 3.86-4.04 (m, 3H), 4.21-4.46 (m, 5H). **1e:** ^{1}H NMR (D_2O) δ 1.23 (d, 3H, *J*=7.1 Hz, β-methyl), 1.31 (d, 3H, *J*=6.4 Hz, C*H*$_3$CHOH), 1.99-2.07 (m, 1H), 3.03-3.12 (m, 1H), 3.37-3.50 (m, 3H), 3.67-3.81 (m, 1H), 4.28 (d, 2H), 4.61-4.75 (m, 1H); FABHRMS *m/z* Calcd for $C_{21}H_{29}N_5O_9S$ $(M+H)^+$ 528.1686, Found 528.1755. **1f:** ^{1}H NMR (D_2O) δ 1.25 (d, 3H, *J*=7.1 Hz, β-methyl), 1.33 (d, 3H, *J*=6.3 Hz, C*H*$_3$CHOH), 1.98-2.11 (m, 1H), 2.14 (s, 6H), 3.04-3.18 (m, 1H), 3.38-3.50 (m, 3H), 3.56-3.87 (m, 4H), 3.91-4.04 (m, 1H), 4.05-4.10 (m, 1H), 4.28 (d, 2H), 4.45-4.50 (m, 1H), 4.62-4.71 (m, 1H).
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20. MIC (μg/mL) data. *S. aureus* 241: 16 (**1a**), 64 (Cefp), 16 (MPM); *S. pneumoniae* PN020: 1 (**1a**), 1 (Cefp), 0.25 (MPM); *K. pneumoniae* 2011E: 0.031 (**1a**), 0.25 (Cefp), 0.031 (MPM); *H. influenzae*: 0.25 (**1a**), 0.25 (Cefp), 0.13 (MPM); *M. catarrhalis* 25240: ≤0.008 (**1a**), 0.031 (Cefp), ≤0.008 (MPM).