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Synthesis and antimicrobial activity of some new 1β-methylcarbapenem derivatives having pyrrolidine or piperidine moieties

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A series of 1β-methylcarbapenems having pyrrolidine or piperidine moieties were synthesized and in vitro antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituent on the pyrrolidine ring or piperidine ring was investigated. The antibacterial activity of these carbapenem, **6b** and **6g** showed good results, and were worth further studying.

***Key words*:** synthesis; 1β-Methylcarbapenem; antibacterial activity

INTRODUCTION

The rising emergence of bacteria resistant to existing antimicrobial therapy is responsible for the prevailing interest in new agents for the fight against these threats to human health [1]. Carbapenem is a novel class of β-lactam antibiotics developed in 1970's, which have used in clinical treatment of severe bacterial infections caused by multidrug resistant strains [2]. Carbapenems are one of the most potent types of antimicrobial agents and are among those used as last resort against infections in the clinical field [3], imipenem, panipenem, meropenem, biapenem, doripenem and tebipenem have already been clinically used. In the cases of meropenem, biapenem and ertapenem, doripenem and tebipenem introduction of a 1β-methyl group to the carbapenem skeleton enhances metabolic stability to renal dehydropeptidase-I (DHP-I) and leads to high antimicrobial potency.

The carbapenem compounds which have a 1β-methylcarbapenem skeleton having a potential antimicrobial activity against Gram-negative and Gram-positive bacteria and are useful as medicines or as intermediates for compounds possessing antimicrobial activity, studies on the carbapenem derivatives have been widely develop. We have studied on the synthesis of a variety of 1β-methylcarbapenem derivatives and found that the carbapenem compounds having (3S)-pyrrolidin-3-ylthio group at the C-2 position show good antimicrobial, and a large number of derivatives have been synthesized and investigated [4-9].

In this paper, we described the synthesis and antimicrobial activity of new lβ-methyl-carbapenems having 5′-pyrrolidine and piperidine derivatives substituted pyrrolidin-3′-ylthio group as C-2 side chain and our approach to improve the antimicrobial activity of the carbapenems is discussed.

INVESTIGATIONS AND RESULTS

Synthesis of the target compounds was conducted as shown in Scheme 1 and Scheme 2. The starting material (compound 1), (2S, 4R)-4-acetylthio-1-(allyloxycarbonyl)pyrrolidine-2-carboxylic acid was prepared according to the literature [10]. The starting material, compounds (2a-h) was prepared according to the literature [11-13]. The preparation of compounds (3a-h) was achieved by using followed the method described, Compound 1 was activated with ethyl chloroformate followed by reaction with compounds (2a-h) to afford. Then the compounds

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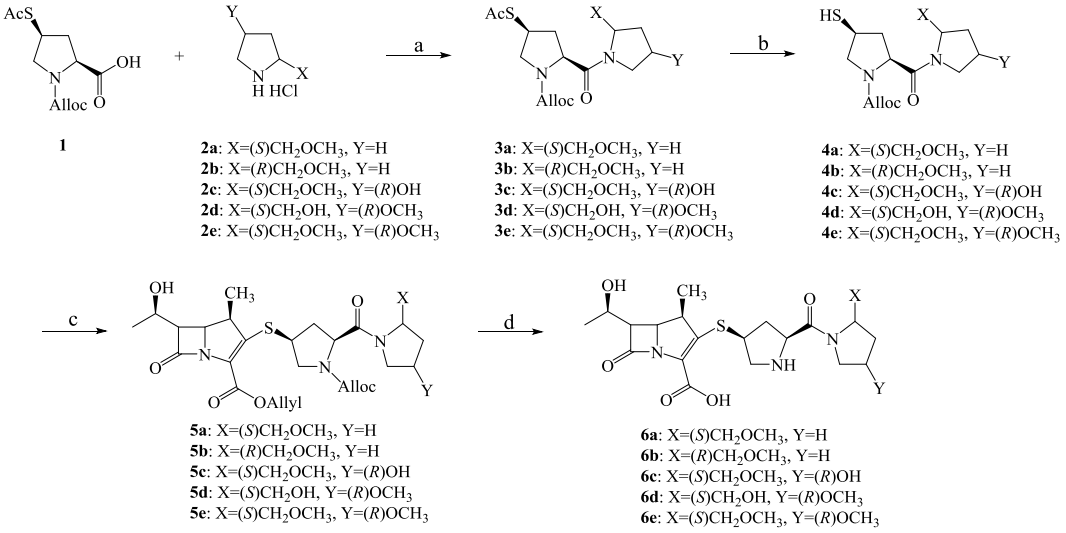
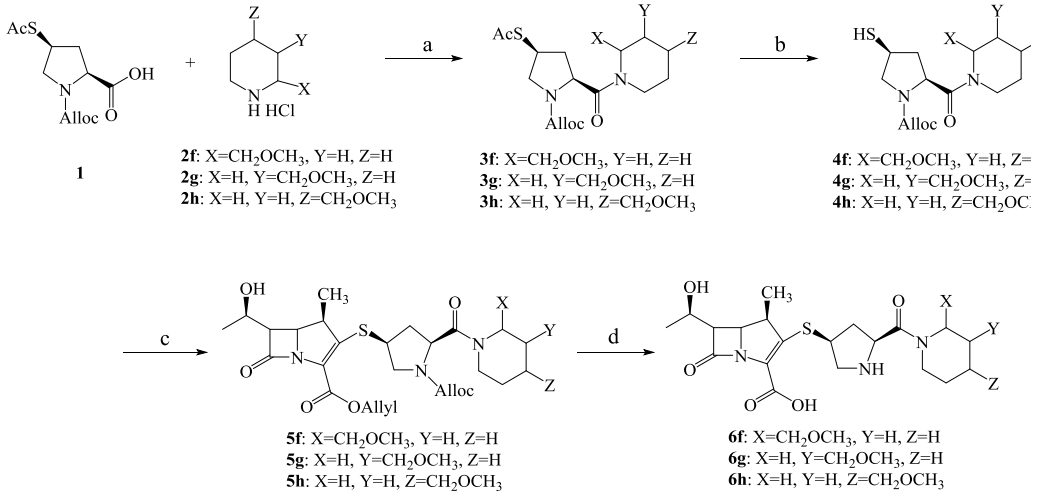


Scheme 1. Scheme of synthesis of 1β-Methylcarbapenem compounds **6a-e** (a) ethyl chloroformate/Et_3N/THF/-5℃/5h; (b) 4N NaOH/MeOH/0-5℃/3h; (c) DIPEA/DCM/-5℃/5h; (d) NDMBA/Ph_3P/$Pd(PPh_3)_4$/THF/-5-0℃/6h.



Scheme 2. Scheme of synthesis of 1β-Methylcarbapenem compounds **6f-h** (a) ethyl chloroformate/Et_3N/THF/-5℃/5h; (b) 4N NaOH/MeOH/0-5℃/3h; (c) DIPEA/DCM/-5℃/5h; (d) NDMBA/Ph_3P/$Pd(PPh_3)_4$/THF/-5-0℃/6h.

were readily hydrolyzed with 4N NaOH aqueous in methanol to give mercaptan compounds (**4a-h**), which were used in the next reaction without purification. A mixture of 1β-methylcarbapenem nucleus allyl (1*R*, 5*S*, 6*S*)-2-(diphenylphosphoryloxy)-6-[(*R*)-1-hydroxy-ethyl]-1-methylcarbapen-2-em-3-carb-oxylate was prepared according to the literature [14] and mercaptan compounds (**4a-h**) in the presence of diisopropylethylamine gave the corresponding carbapenem esters (**5a-h**) in 22.7%–29.3% total yield from compound **1**. Removal of the protecting groups of these compounds by treatment of 1, 3-dimethyl- barbituric acid (NDMBA), Tetrakis-(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) and Ph_3P gave corresponding carbapenems (**6a-h**) [15, 16]. In accordance with the standard agar dilution method, we obtained antimicrobial activity of the derivatives. The in vitro antimicrobial activity of new 1β-methylcarbapenems **6a-h** having pyrrolidine or piperidine moieties are shown in Table 1. The minimal inhibitory concentrations (MIC) of these compounds were compared with meropenem(MPM) as positive controls. All the compounds exhibited superior antimicrobial activity. Some of the target compounds possess similar or superior activity against some Gram-positive organisms or Gram-negative bacteria than MPM. Against most Gram-positive organisms or Gram-negative bacteria, **6b**, **6h** exhibited interesting antimicrobial activities compared to MPM, but poorer against *Pseudomonas aeruginosa*. As to the substituent of the C-5 on the pyrrolidine side chain, the compounds containing introduction of a pyrrolidine or piperidine moieties slightly lower antimicrobial activity than MPM in most cases, presumably due to increased sterics hindrance to penicillin-binding proteins.

Table 1. In vitro antimicrobial activity (MIC, μg/ml) of the carbapenem derivatives

	6a	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**MPM**
Staphylococcus aureus 26003	0.78	0.39	0.78	3.13	0.39	0.78	6.25	0.39	0.39
pneumococcal pneumonia 31002	0.098	0.098	0.195	0.78	0.39	0.098	1.56	0.098	0.098
Staphylococcus albus 26101	0.78	0.39	1.56	3.13	0.78	1.56	6.25	0.39	0.39
Enterococcus 32220	0.39	0.39	0.195	0.195	0.39	3.13	12.5	6.25	6.25
gamma streptococcus 32206	6.25	12.5	12.5	12.5	12.5	6.25	25	12.5	6.25
Staphylococcus epidermidis 26069	0.78	0.39	1.56	3.13	0.78	0.78	3.13	0.39	0.195
Shigella boydii 51313	0.098	<0.049	0.098	0.195	0.098	0.195	0.39	<0.049	<0.049
Proteus mirabilis 49005	0.098	0.098	0.195	0.195	0.098	0.195	0.78	<0.049	<0.049
Proteus vulgaris 49085	0.195	<0.049	0.195	0.195	0.195	0.195	0.78	<0.049	<0.049
Morgan proteus 49086	0.098	<0.049	0.098	0.195	0.098	0.195	0.39	<0.049	<0.049
Pseudomonas aeruginosa 10124	>25	6.25	>25	12.5	>25	>25	>25	6.25	0.78
Pneumobacillus 46101	0.39	0.195	0.195	0.39	0.39	0.39	0.78	0.098	<0.049
Salmonella enteritidis 50041	0.098	<0.049	0.098	0.195	0.195	0.195	0.39	<0.049	<0.049
Salmonella typhi 50097	0.098	<0.049	0.098	0.195	0.098	0.195	0.39	<0.049	<0.049
Citrobacter 48017	0.098	<0.049	0.098	0.195	0.098	0.39	0.39	<0.049	<0.049
Aerobacter aerogenes 45102	0.195	<0.049	0.39	0.78	0.39	0.78	0.78	<0.049	<0.049
Serratia marcescens 41002	0.195	<0.049	0.195	0.195	0.39	0.78	0.78	<0.049	<0.049
Shigella sonnei 51081	0.098	<0.049	0.195	0.195	0.098	0.195	0.39	<0.049	<0.049
Shigella flexneri 51573	0.098	<0.049	0.098	0.098	0.098	0.098	0.39	<0.049	<0.049
Escherichia Coli 44102	0.098	<0.049	0.39	0.195	0.195	0.195	0.39	<0.049	<0.049

EXPERIMENTAL

All reagents were purchased from commercial sources such as SCRC (www.reagent.com.cn), Aladdin (www.aladdin-reagent.com) and used without further purification. The ^{1}H-NMR spectra (400 MHz) were measured on a DRX-400 spectrometer using DMSO-*d*6 or $CDCl_3$ or D_2O as solvent and TMS as an internal standard. Chemical shifts were expressed in ppm units. Multiplicities were recorded as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were obtained on a LC-MSD 1100 spectrometer with ESI.

Spectra data of compounds **6a-6h**: the titled compounds were new compounds and their structures were fully confirmed by 1H NMR and ESI-MS. **6a**: Yield: 33.1% ^{1}H-NMR (400Hz, D_2O): δ1.16 (d,3H, *J*=7.2Hz, β-CH_3), 1.24(d,3H,*J*=6.4Hz, CH_3CHOH), 1.77~1.94 (m,5H, pyrrolidine H), 3.03~3.10(m, 1H, pyrrolidine H), 3.25~3.33(m,4H, -CH_2O- and pyrrolidine H and H_6), 3.42~3.65(m, 6H, and pyrrolidine H and -OCH_3), 3.80~3.84(m,2H, pyrrolidine H), 3.94~3.98(m, 2H, H_1 and pyrrolidine H), 4.10~4.16 (m,2H, H_5 and H_8); ESI-MS: *m/z* = 454.12 $[M+H]^+$. **6b**: Yield: 34.8%; ^{1}H-NMR(400Hz, D_2O):δ1.22 (d,3H,*J*=7.2Hz, β-CH_3), 1.30(d,3H,*J*=6.4Hz, CH_3CHOH), 1.88~2.06 (m,5H, pyrrolidine H), 3.04~3.11(m,1H, pyrrolidine H), 3.32~3.39(m,4H, -CH_2O- and pyrrolidine H and H_6), 3.45~3.61(m,6H, pyrrolidine H and -OCH_3), 3.75~3.79(m,2H, pyrrolidine H), 4.01~4.06(m,2H, H_1 and pyrrolidine H), 4.23~4.28(m, 2H, H_5 and H_8) ; ESI-MS: *m/z* = 454.17 $[M+H]^+$. **6c**: Yield: 37.3%; ^{1}H-NMR (400Hz, D_2O): δ1.13(d,3H,*J*=7.2Hz,β-CH_3), 1.24(d,3H, *J*=6.4Hz,CH_3CHOH), 1.82-1.99 (m, 3H), 2.93-2.98(m, 1H, pyrrolidine H), 3.22-3.27(m, 2H, -CH_2O-), 3.39-3.46(m,3H, pyrrolidine H and H_6), 3.45(s, 3H, –OCH_3), 3.59-3.63(m, 2H, pyrrolidine H), 3.71-3.74(m, 1H, pyrrolidine H), 3.90-3.95(m, 2H, pyrrolidine H), 4.08-4.13(m, 2H, H_1 and pyrrolidine H), 4.28-4.33(m, 2H, H_5 and H_8). ESI-MS: *m/z* = 470.22 $[M+H]^+$. **6d**: Yield: 45.1%; ^{1}H-NMR (400Hz, D_2O): δ1.13(d,3H, *J*=7.2Hz,β-CH_3), 1.24(d,3H, *J*=6.4Hz, $\underline{CH_3}$CHOH), 2.09-2.23(m, 3H), 2.99-3.06(m, 1H, pyrrolidine H), 3.14-3.23 (m, 2H, -CH_2O-), 3.25(s, 3H, –OCH_3), 3.40-3.48(m,3H, pyrrolidine H and H_6), 3.60-3.74(m, 3H, pyrrolidine H), 3.79-3.86(m, 2H, pyrrolidine H), 4.03-4.06(m, 2H, H_1 and pyrrolidine H), 4.20-4.27(m, 2H, H_5 and H_8). ESI-MS: *m/z* = 470.23 $[M+H]^+$. **6e**: Yield: 42.3%; ^{1}H-NMR(400Hz, D2O): δ1.13(d,3H,J=7.2Hz, β-CH_3), 1.18(d,3H,J=6.4Hz,CH_3CHOH), 1.76-1.99 (m, 3H, pyrrolidine H), 2.84-2.89(m, 1H, pyrrolidine H), 3.18~3.32(m,5H, -CH_2O- H and –OCH_3), 3.39-3.46(m,6H, and pyrrolidine H and -OCH_3 and H_6), 3.57-3.66(m, 3H, pyrrolidine H), 3.87-3.90(m, 2H,

pyrrolidine H), 3.94-4.00(m, 2H, H_1 and pyrrolidine H), 4.09-4.15(m, 2H, H_5 and H_8). ESI-MS: *m/z*=484.23 $[M+H]^+$. **6f**: Yield: 39.6%; ^{1}H-NMR(400Hz, D_2O):δ1.21(d, 3H,*J*=7.6Hz, β-CH_3), 1.30(d,3H,*J*=6.0Hz, CH_3CHOH), 1.47~1.58(m,1H, piperidine H), 1.73~1.85(m,4H, piperidine H), 2.85~3.04(m,2H, pyrrolidine H), 3.15~3.22(m,4H,-CH_2O- and pyrrolidine H and H_6), 3.42~3.57 (m,6H,–OCH_3 and piperidine H), 3.59~3.64(m,1H, pyrrolidine H), 3.73~3.78 (m,2H, pyrrolidine H), 3.87~4.02(m,2H, H_1 and pyrrolidine H), 4.10~4.17(m,2H, H_5 and H_8) ; ESI-MS: *m/z* =468.21 $[M+H]^+$. **6g**: Yield: 35.4%; ^{1}H-NMR(400Hz, D_2O):δ1.24(d, 3H, *J*=7.2Hz, β-CH_3), 1.32(d,3H, *J*=6.4Hz, CH_3CHOH), 1.51~1.57(m,1H, piperidine H), 1.78~2.02 (m,4H, piperidine H), 2.98~3.13 (m, 2H, pyrrolidine H), 3.16-3.26(m,1H, H_6), 3.34~3.46(m,7H, –OCH_3 and piperidine H and -CH_2O-), 3.48~3.52(m,2H, piperidine H), 3.61~3.71(m,1H, pyrrolidine H), 3.76~3.83(m,2H, pyrrolidine H), 4.05~4.12(m,2H, H_1 and pyrrolidine H), 4.16~4.30(m,2H, H_5 and H_8) ; ESI-MS: *m/z* =468.17 $[M+H]^+$. **6h**:Yield: 41.2%; ^{1}H-NMR(D_2O):δ1.14(d, 3H, *J*=6.8Hz, β-CH_3), 1.22(d,3H, *J*=7.6Hz, CH_3CHOH), 1.62~1.82(m,5H, pyrrolidine H), 2.72~2.78 (m,1H, pyrrolidine H), 3.04~3.09 (m, 3H, pyrrolidine H and - CH_2-$NHSO_2NH_2$), 3.18~3.21(m, 1H, H_6), 3.56~3.64(m, 3H, pyrrolidine H), 3.77~3.83 (m,2H, pyrrolidine H), 3.93~3.97(m,2H, H_1 and pyrrolidine H), 4.09~4.16(m,2H, H_5 and H_8) ; ESI-MS: *m/z* =468.27 $[M+H]^+$.

CONCLUSIONS

A series of 1β-methylcarbapenems having pyrrolidine or piperidine moieties have been prepared from (2*S*, 4*R*)-4-acetylthio-1-(allyloxycarbonyl) pyrrolidine-2-carboxylic acid (**1**) in the reaction with the corresponding pyrrolidine or piperidine derivatives (**2a-h**). Obtained derivatives were determined their antimicrobial activity by the standard agar dilution method. Then the MIC values were calculated and compared with standard (MPM). We have found the derivatives exhibited superior antimicrobial activity, among these compounds **6b** and **6h** have antimicrobial activities higher than others, and were worth further studying. Due to increased sterics hindrance to penicillin-binding proteins, the derivatives slightly lower antimicrobial activity than MPM in most cases.

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СИНТЕЗА И АНТИ-МИКОТИЧНА АКТИВНОСТ НА НЯКОИ НОВИ 1β-МЕТИЛ-КАРБАПЕНЕМ‘ОВИ ПРОИЗВОДНИ С ПИРОЛИДИНОВИ ИЛИ ПИПЕРИДИНОВИ ПОЛОВИНИ

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(Резюме)

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Синтезирани са серия от 1β-метил-карбапенеми с пиролидинови или пиперидинови половини. Изследвана е *in vitro* антибактериалната им активност спрямо Грам-положителни и Грам-отрицателни бактерии. Изследван е ефектът на заместителите в пиролидиновите или пиперидиновите пръстени. Антибактериалната активност на карбапенемите **6b** и **6g** показва добри резултати и си струва бъдещи изследвания.