STUDIES ON THE SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW ZWITTERIONIC CARBAPENEMS

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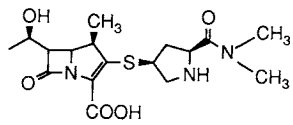
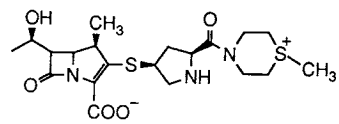
In the preceding papers[1,2], we reported the syntheses and biological properties of carbapenem compounds having a 5'-(hydroxyalkylaminocarbonyl)pyrrolidin-3'-ylthio group as the C-2 side chain and their an extended antibacterial spectrum. In order to obtain good antibacterial activities against *Pseudomonas aeruginosa* and high stability to renal dehydropeptidase-I (DHP-I), we studied the modification of substituent on the pyrrolidin ring. Some new carbapenem compounds having a 5'-(*S*-methylthio morpholinylcarbonyl)pyrrolidin-3'-yl thio group at the carbapenem C-2 position were synthesized. It is well known that zwitterionic carbapenems show both good antipseudomonal activity and improved stability against DHP-I[3].

Synthesis of Carbapenems **1a** and **2a**

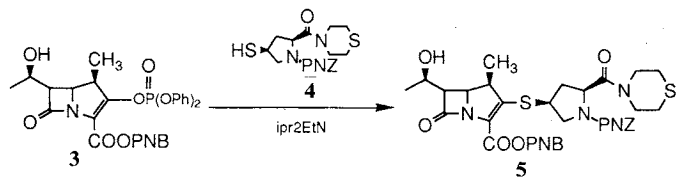
Treatment of enolphosphate[3] (**3**) with freshly prepared thiol compound (**4**) afforded 2-substituted carbapenem (**5**). *S*-methylation of the thiomorpholine ring was accomplished by the action of trimethyloxoniumtetrafluoroborate at room temperature. There was no indication of reaction between the alkylating agent and the sulfur atom of the C-2 side chain. The decreased reactivity of the sulfur atom of the C-2 side chain appears to be due to the conjugation of the sulfur atom with the α,β-unsaturated ester functionality[4]. Deprotection of compound **6** was carried out by catalytic hydrogenation over 10% Pd-C in the phosphate buffer.

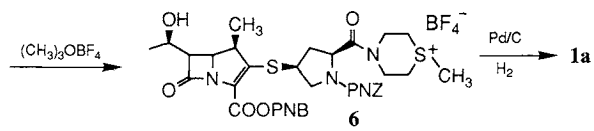


Meropenem



1a





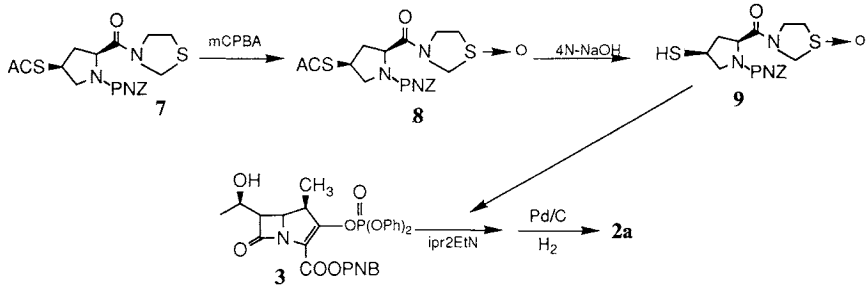
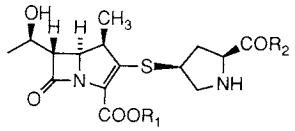
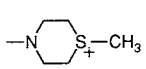
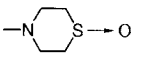
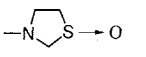
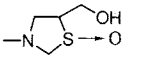
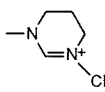


Table 1. Antibacterial activity and DHP-I stability of the carbapenems.



Compound	R_1	R_2	MIC (μg/ml)[a]						DHP-I $T_{1/2}$ (minutes)
			S.p.[b]	*S.a.*	*E.c.*	*P.a.*	*K.a.*	*En.c.*	
1a			<0.01	0.05	0.05	0.20	0.05	0.03	2058.3
1b	H		<0.01	0.40	0.05	3.12	0.10	0.05	1468.5
1c	H		<0.01	0.05	0.03	1.56	0.03	0.01	1578.6
2a	H		<0.01	0.20	0.05	0.78	0.05	<0.01	1016.0
2b	H		<0.01	0.05	0.03	0.40	0.03	0.01	1366.9
3a	H		<0.01	0.10	0.03	1.56	0.03	0.01	1923.1
3b	H		<0.01	0.20	0.05	6.25	0.10	0.03	1824.3
4a			<0.01	0.20	0.10	0.40	0.10	0.10	1959.9
4b	H		<0.01	0.20	0.05	1.56	0.05	0.05	1550.8
Imipenem			<0.01	0.01	0.20	0.80	0.40	0.20	134.8
Meropenem			<0.01	0.05	0.03	0.20	0.03	0.01	1789.4

[a] Agar dilution method.

[b] *S.p.*; *Streptococcus pyogenes* 77A, *S.a.*; *Staphylococcus aureus* 503, *E.c.*; *Escherichia coli* DC0, *P.a.*; *Pseudomonas aeruginosa*, *K.a.*; *Klebsiella aerogenes* 1522E, *En.c.*; *Enterobacter cloacae* 1321E.

After purification of the crude product by column chromatography on Diaion HP-20, the zwitterionic product (**1a**)[†] was obtained as an amorphous solid. Oxidation of compound **7** with *m*-chloroperbenzoic acid in CH_2Cl_2 afforded sulfoxide compound **8** (MS *m/z* 470 (M+1)), whose acetylthio group was readily hydrolyzed with 4N NaOH to give thiol compound (**9**). Compound **2a** was prepared by the same procedure as described above.

Biological Studies

The MICs and the stability to DHP-I of the new series of carbapenems are shown in Table 1. The zwitterionic compounds (**1a**, **4a**) exhibited superior antibacterial activity to nonzwitterionic compounds (**1c**, **4b**) against *P. aeruginosa*. The positive charge on sulfonium ion of thiomorpholine ring might cause a marked improvement in antipseudomonal activity. There was no significant difference between

[†] ^{1}H NMR (D_2O) δ 1.27 (d, 3H, J=7.5 Hz), 1.31 (d, 3H, J=6.5 Hz) 2.05 (m, 1H), 2.95 (m, 1H), 3.08 (s, 3H, S^+–CH_3), 3.35 (m, 3H), 3.50 (m, 2H), 3.75 (br s, 2H), 3.80 (dd, 2H), 4.15 (br s, 4H), 4.25 (m, 3H); UV $\lambda_{max}^{H_2O}$ nm 298: LC-MS *m/z* 458 (M+2).

the activity of meropenem and that of compound **1a**. Oxidized compounds (**1b**, **2a**) exhibited lower activities than nonoxidized compounds (**1c**, **2b**).

Introduction of a hydroxyethyl group (**3a**, **3b**) significantly lowered the antibacterial activity against *P. aeruginosa*, whereas they possessed good stability to DHP-I[5]. The zwitterionic compounds (**1a**, **4a**), which shows excellent antibacterial activities as well as high stability to the enzymatic hydrolysis by renal dehydropeptidase, were chosen for the further evaluation.

Acknowledgement

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