Studies on the Synthesis and Antibacterial Activity of New Carbamoylpyrrolidinylthio-carbapenems

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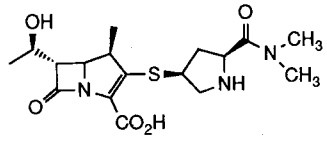
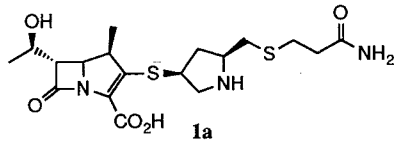
In the preceding paper[1], we reported the synthesis and biological properties of carbapenem compounds having a 5'-aromatic heterocyclic carbamoyl pyrrolidin-3'-yl thio group as the C-2 side chain and their extended antibacterial spectrum. In order to obtain good antibacterial activities against *Pseudomonas aeruginosa* and high stability to renal dehydropeptidase-I (DHP-I), we studied the modification of substituents on the pyrrolidine ring. Some new carbapenem derivatives having a 5'-(substituted or unsubstituted carbamoylalkylthioalkyl)pyrrolidin-3'-ylthio group at the carbapenem C-2 position were synthesized. It is well known that functionalized alkyl pyrrolidine carbapenems show both good antipseudomonal activity and improved stability against DHP-I[2,3].

Synthesis of Carbapenem **1a**, **2c**, **4a** and **4b**

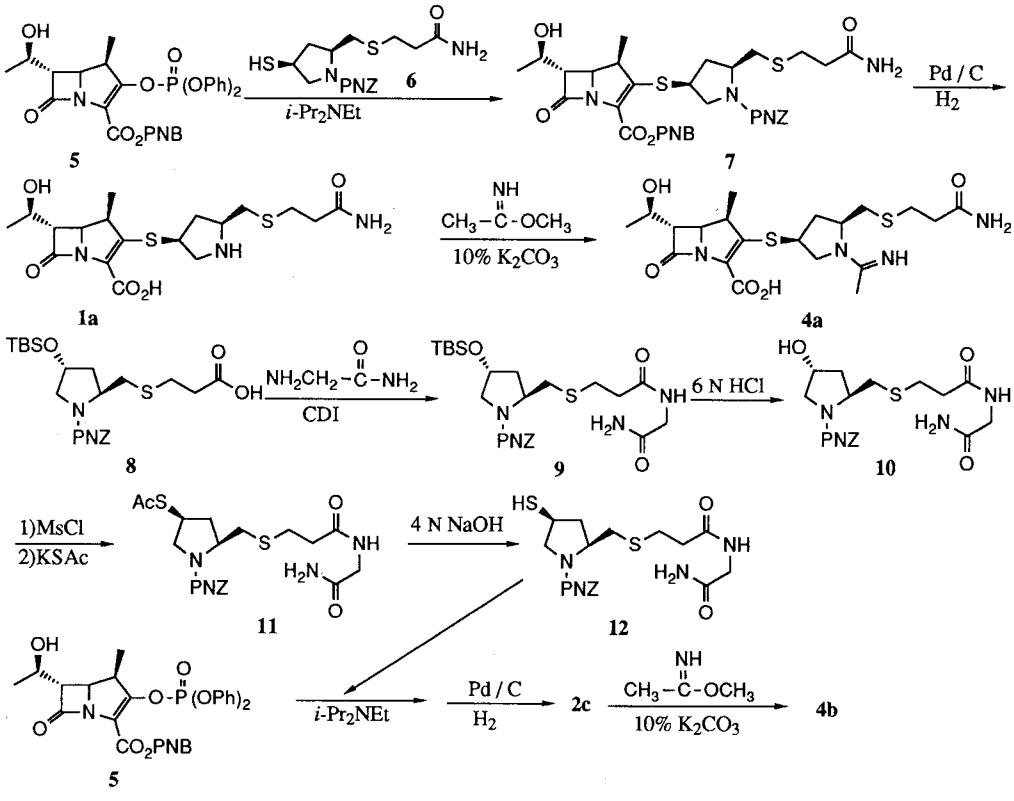
Treatment of enolphosphate[3] with freshly prepared thiol compound (**6**) afforded 2-substituted carbapenem (**7**). Deprotection of (**1a**) by hydrogenolysis over 10% Pd-C in the presence of 3-morpholinopropanesulfonic acid (MOPS) buffer (0.1 M, pH = 7.0) provided the target (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-((carbamoylethyl)mercaptomethyl)pyrrolidin-4-yl]thio-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid (**1a**). After purification of the crude product by column chromatography on diaion HP-20, the carbamoylpyrrolidinyl carbapenem derivative (**1a**)† was obtained as an amorphorous solid. N-Methylimidoylation of compound



Meropenem

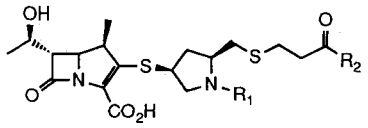


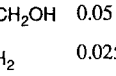
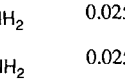
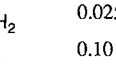
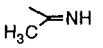
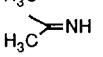
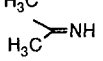
1a



† ^{1}H NMR (D_2O) δ 1.26 (3H, d, J=8 Hz), 1.33 (3H, d, J=8 Hz), 2.17~2.50 (4H, m), 2.65~2.95 (2H, m). UV $\lambda_{max}^{H_2O}$ nm 298.5.

Table 1. Antibacterial activity and DHP-1 stability of carbapenem.



Comp.	R_1	R_2	MIC (μg/ml)[a]						DHP-1[c] ($T_{1/2}$)min
			S.a.[b]	*S.p.*	*E.c.*	*P.a.*	*K.a.*	*En.c.*	
1a	H	NH_2	0.05	0.013	0.05	0.10	0.20	0.025	568
1b	H	$NHCH_3$	0.05	0.013	0.05	0.20	0.20	0.025	490
1c	H	$N(CH_3)_2$	0.05	0.013	0.20	0.78	0.20	0.05	463
1d	H	$N(CH_3)CH_2CH_3$	0.05	0.013	0.39	1.56	0.39	0.05	405
2a	H	$NHCH_2CN$	0.05	0.013	0.20	0.78	0.20	0.05	309
2b	H	$NH(CH_2)_2OH$	0.05	0.013	0.20	1.56	0.39	0.05	385
2c	H	$NHCH_2CONH_2$	0.05	0.013	0.05	0.20	0.20	0.025	521
2d	H	$NHCH(OH)CH_2OH$	0.05	0.013	0.20	1.56	0.39	0.05	425
3a	H		0.025	0.013	0.025	3.13	0.39	0.20	512
3b	H		0.025	0.013	0.025	6.25	0.39	0.20	523
3c	H		0.10	0.013	0.39	1.56	0.20	0.05	386
4a		NH_2	0.10	0.013	1.56	3.13	0.39	0.20	520
4b		$NHCH_2CONH_2$	0.10	0.013	1.56	6.25	0.39	0.20	490
4c			0.10	0.013	3.13	6.25	0.39	0.20	476
Imipenem			0.10	0.013	0.10	0.20	0.39	0.20	34
Meropenem			0.10	0.013	0.013	0.10	0.05	0.025	152

[a] Agar dilution method

[b] *S.a.; Staphylococcus aureus SG51, S.p.; Streptococcus pyrogenes A77, E.c.; Escherichia coli O55, P.a.; Pseudomonas aeruginosa 1771M, K.a.; Klebsiella aerogenes 1522E, En.c.; Enterobacter cloacae 1321E*

[c] DHP-1; Dehydropeptidase-1 (Sigma Chemical Co.: Kidney acetone powder - porcine, type II)

(**1a**) with methyl acetimidate·HCl in 10% K_2CO_3 solution provided the compound (**4a**). Substitution of compound (**8**) with glycinamide in acetonitrile afforded carbamoylmethylcarbamoylalkylpyrrolidine compound (**9**). Desilylation of compound (**9**) carried out with 6N HCl in methanol to give hydroxymethylcarbamoylpyrrolidine compound (**10**). After mesylation of compound (**10**), the mesylated carbamoylpyrrolidine compound was converted into the acetylthiocarbamoylmethyl carbamoylpyrrolidine compound (**11**) with potassium thioacetate in DMF, whose acetythio group was readily hydrolyzed with 4N NaOH to give thiol compound (**12**). The compounds (**1b**)~(**4c**) also were prepared by the same procedure as described above.

Biological Studies

The MICs of the novel carbapenems for Gram-positive and Gram-negative bacteria and the stability data (T1/2) to DHP-I are shown in Table 1. The nonheterocyclic-carbamoyl compounds (**1a**~**2d** and **4a**, **4b**) exhibited enhanced antibacterial activity compared to the heterocycliccarbamoyl compounds (**3a**~**3c**) against *P. aeruginosa*. It is interesting that compounds with N-acetimidoylated pyrrolidine at C-2 side chain (**4a**~**4c**) did not show high activity against *P. aeruginosa*. The novel compounds (**1a**, **1b**, **2c**) exhibited enhanced or similar antibacterial activity to imipenem against *P. aeruginosa*. As the extent of alkyl group in the carbamoyl group increased, antibacterial activity generally decreased against Gram-negative bacteria, as shown by compound (**1a**) which exhibited higher activity against *P. aeruginosa* than compounds (**1b**~**1d**). There was no significant difference between the activity of meropenem and that of compound (**1a**). Carbamoylalkylsubstituted compound (**2c**) exhibited higher activity than hydroxy or cyanoalkyl substituted compounds (**2a**, **2b**). Introduction of a heterocyclic carbamoyl group (**3a**, **3b**, **3c**) significantly lowered the antibacterial activity against *P. aeruginosa*, whereas they possessed good stability to DHP-I[3]. Carbamoylmethylsubstituted carbamoyl compounds (**1a**, **2c**), which show high resistance to enzymatic stability by renal dehydropeptidase (DHP-I) chosen for further evaluation. Most carbapenem derivatives showed enhanced or similar antibacterial activity to imipenem against Gram-positive and Gram-negative bacteria except *P. aeruginosa*.

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