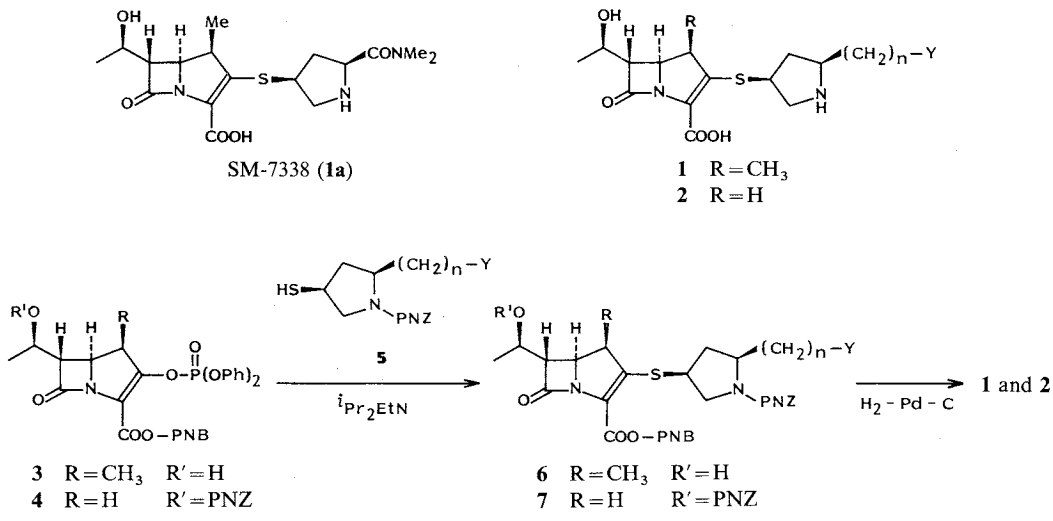
A NEW SERIES OF CARBAPENEM ANTIBIOTICS WITH 5'-SUBSTITUTED PYRROLIDINYLTHIO GROUP AT C-2 POSITION

Sir:

In the preceding paper[1], we reported the synthesis and biological properties of carbapenem compounds having 5'-aminocarbonyl pyrrolidin-3'-ylthio group as C-2 side chain and demonstrated that SM-7338, (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-dimethylaminocarbonyl-pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid (**1a**), exhibited an extended antibacterial spectrum including anti-pseudomonal activity and high stability to renal dehydropeptidase-I (DHP-I)[2]. With the aim of further improving the stability to DHP-I, we studied the modification of the substituent on the pyrrolidine ring, that is, introducing a methylene spacer between aminocarbonyl group and pyrrolidine ring at the 5' position and exchanging the aminocarbonyl group with other functional groups such as hydroxyl and cyano groups.

We wish to describe here the microbiological activity of a new series of the carbapenems of the general formulae **1** and **2**. The synthetic route employed for the title compounds is similar to that developed by the Merck group for the production of thienamycin[3] and L-646591[4] as shown in Scheme 1. Enol phosphate (**3** and **4**) which was treated with freshly prepared mercaptans (**5**) afforded protected carbapenems (**6** and **7**). Deprotection of **6** and **7** by hydrogenolysis over 10% Pd-C in the presence of 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (0.1 M, pH 7.0) provided the target 2-[3-(5-substituted pyrrolidinyl)thio]carbapenem carboxylic acids (**1** and **2**), after purification by column chromatography on Diaion CHP-20P. The mercaptans (**5**) used in this work were prepared starting from *trans*-4-hydroxy-L-proline. For example, the preparation of mercaptan (**5b**) was achieved by the synthetic route as shown in Scheme 2. Compound **8**, obtained from *trans*-4-hydroxy-L-proline, was treated with benzoyl chloride and then removal of *p*-methoxybenzyl (PMB) group of **9** was carried out with TFA and anisole to give carboxylic acid (**10**). Activation of **10** with ethyl chloroformate followed by sodium borohydride reduction afforded alcohol (**11**). After tosylation of **11**, the tosyloxymethyl group of **12** was converted into the iodomethyl group with sodium iodide in DMF to give compound **13**. Treatment of **13** with sodium cyanide followed by hydrolysis with HCl in AcOH provided carboxylic acid (**15**), which was transformed into thioacetate (**19b**): $[\alpha]_D^{25}$ −63.2° (*c* 1.00, $CHCl_3$); IR (neat) cm^{-1} 1700, 1635; ^1H NMR (270 MHz, $CDCl_3$) δ 1.90 (1H, m), 2.33 (3H, s), 2.71 (1H, m), 2.92 (6H, s), 3.02 (2H, s), 3.30 (1H, dd, J=7.0 and 11.0 Hz), 3.92 (1H, m), 4.09 (1H, dd, J=7.0 and 11.0 Hz), 5.21 (2H, s), 7.51 (2H, d, J=9.0 Hz), 8.23 (2H, d, J=9.0 Hz) in a similar procedure to that described in our preceding paper[1]. Finally the

Scheme 1.



PNB: *p*-Nitrobenzyl, PNZ: *p*-nitrobenzyloxycarbonyl.

Table 1. Antibacterial activity and DHP-I stability of carbapenem compounds having $(CH_2)_n$ spacer between aminocarbonyl group and pyrrolidine ring at 5'-position.

Organism	MIC (μg/ml)											
No.	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**	**2j**	**2k**	**1k**
R:	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	CH_3
Y:	$CON(CH_3)_2$	$CON(CH_3)_2$	$CON(CH_3)_2$	$CONHCH_3$	$CONHCH_3$	$CONHCH_3$	$CONHCH_3$	$CONH_2$	$CONH_2$			
n:	0	1	2	1	2	3	4	1	2	0	1	1
S.a. FDA 209P	<0.013	<0.013	<0.013	<0.013	<0.013	0.025	<0.013	<0.013	<0.013	<0.013	<0.013	<0.013
S.p. Cook	<0.013	ne	<0.013	<0.013	<0.013	<0.013	<0.013	<0.013	<0.013	<0.013	ne	ne
E.c. NIHJ JC-2	<0.013	<0.013	<0.013	0.025	<0.013	0.05	0.025	<0.013	<0.013	<0.013	0.025	0.05
K.p. ATCC 10031	<0.013	<0.013	<0.013	<0.013	<0.013	0.05	0.025	<0.013	<0.013	<0.013	0.025	0.05
P.m. GN 2425	<0.013	0.20	0.025	0.10	0.05	0.10	0.10	0.10	0.025	0.05	0.10	0.10
P.a. IFO 3451	0.10	0.78	0.78	0.78	0.78	1.56	1.56	1.56	0.78	0.78	6.25	6.25
S.m. X 100	<0.013	0.025	<0.013	0.025	<0.013	0.10	0.05	0.025	<0.013	0.025	0.05	0.05
E.c. ML 1410/RP4[a]	<0.013	ne	0.05	0.05	0.05	0.20	0.10	0.10	0.05	0.025	ne	ne
E.c. GN 5482[a]	<0.013	<0.013	0.025	<0.013	<0.013	0.05	0.025	<0.013	<0.013	<0.013	0.025	0.05
P.v. GN 7919[a]	<0.013	0.05	0.025	0.05	<0.013	0.20	0.20	0.025	0.025	0.05	0.10	0.10
S.m. GN 6473[a]	<0.013	0.05	0.025	0.025	<0.013	0.10	0.10	0.025	0.025	0.20	0.20	0.10
DHP-I[b] $T_{1/2}$ (minutes)	310	1,800	960	1,200	1,100	2,100	2,200	980	1,200	16	230	2,000

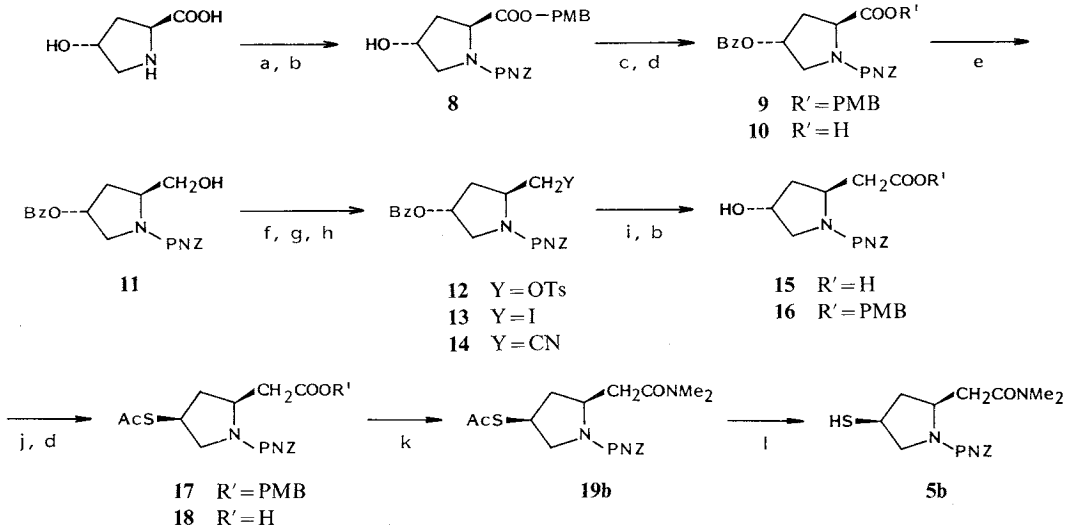
[a] β-Lactamase producing strain.

[b] Partially purified renal DHP-I of swine[5].

Abbreviations: *S.a.*, *Staphylococcus aureus*; *S.p.*, *Streptococcus pyogenes*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *P.m.*, *Proteus mirabilis*; *P. a.*, *Pseudomonas aeruginosa*; *S.m.*, *Serratia marcescens*; *P.v.*, *Proteus vulgaris*.

ne: Not examined.

Scheme 2.



a: PNZ-Cl, NaOH, b: PMB-Cl, NEt_3, C: BzCl, NEt_3, cat. DMAP, d: TFA-anisole, e: 1) ClCOOEt; NEt_3, 2) $NaBH_4$, f: TsCl, pyridine, g: NaI-CH_3COEt, h: NaCN-DMF, i: HCl-AcOH, j: AcSH, =$(NCOOEt)_2$, PPh_3, k: 1) $(COCl)_2$; 2) $HN(CH_3)_2$, l: NaOH.

PNZ: *p*-Nitrobenzyloxycarbonyl, PNB: *p*-nitrobenzyl, DMAP: 4-dimethylaminopyridine, TsCl: *p*-toluenesulfonyl chloride.

Table 2. Antibacterial activity and DHP-I stability of carbapenem compounds having hydroxyalkyl or cyanomethyl groups at 5'-position.

Organism	MIC (μg/ml)						
	No.	**1l**	**1o**	**1p**	**2l**	**1q**	**2q**
	R:	CH_3	CH_3	CH_3	H	CH_3	H
	Y:	OH	OH	OH	OH	CN	CN
	n:	1	2	3	1	1	1
S.a. FDA 209P		<0.013	<0.013	0.025	<0.013	<0.013	<0.013
S.p. Cook		<0.013	<0.013	<0.013	<0.013	<0.013	<0.013
E.c. NIHJ JC-2		<0.013	<0.013	0.05	0.05	<0.013	<0.013
K.p. ATCC 10031		<0.013	<0.013	0.05	0.025	<0.013	<0.013
P.m. GN 2425		<0.013	0.05	0.10	0.10	0.025	<0.013
P.a. IFO 3451		0.39	0.78	1.56	3.13	3.13	3.13
S.m. X 100		<0.013	0.025	0.05	0.10	<0.013	<0.013
E.c. ML 1410/RP4[a]		0.05	0.10	0.20	0.20	0.025	<0.013
E.c. GN 5482[a]		<0.013	<0.013	0.025	0.10	<0.013	<0.013
P.v. GN 7919[a]		<0.013	0.10	0.39	0.20	0.05	<0.013
S.m. GN 6473[a]		<0.013	0.05	0.10	0.20	0.025	<0.013
DHP-I[b] $T_{1/2}$ (minutes)		1,700	1,375	1,355	42	250	12

[a,b] and abbreviations: See a footnote in Table 1.

acetylthio group of **17b** was readily hydrolyzed with 4 N-NaOH to give mercaptan (**5b**).

The MICs and the stability to DHP-I of the new series of carbapenems synthesized are shown in Tables 1 and 2 with those of the reference compounds **1a** and **2j**. The carbapenem compounds having a spacer $(CH_2)_n$ between the aminocarbonyl group and the pyrrolidine ring exhibited potent antibacterial activities against Gram-positive and Gram-negative bacteria comparable to the reference compounds or only slightly reduced though the anti-pseudomonal activity was distinctly reduced

by the presence of the methylene spacer. The introduction of the spacer resulted in remarkable improvement in stability to DHP-I regardless of the length of the spacer. Introduction of the spacer resulted in a 6~14-fold increasing stability to DHP-I.

Next, the carbapenem compounds having hydroxy(C-1~C-3)alkyl group and a cyanomethyl group at the 5' position also exhibited well balanced antibacterial spectra. The 5'-hydroxyalkyl derivatives similarly possessed high stability to DHP-I after the substitution by the 1β-methyl group. That of the cyanomethyl derivative was also improved by the same substitution, but not as much.

As mentioned above, we have found that the introduction of a methylene spacer further enhanced the stability to DHP-I in addition to that introduced by substitution of 1β-methyl group and this effect was not influenced by the length of spacer. Slight to marked diminution of antibacterial activity was observed depending upon the species studied.

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