SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL CARBAPENEMS WITH A CATECHOL OR HYDROXYPYRIDONE MOIETY

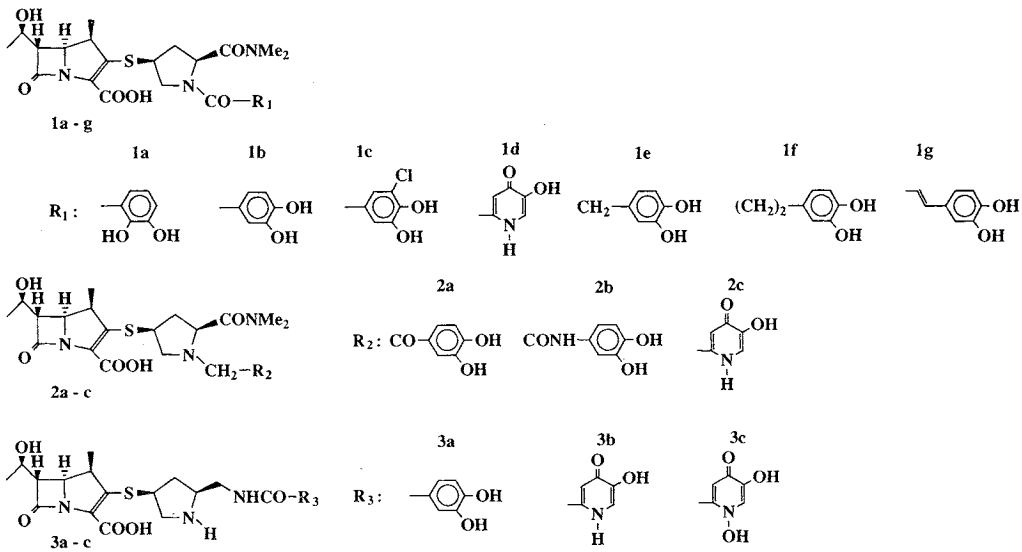
Sir:

During the past decade the opportunistic infections, caused by various Gram-negative bacteria including *Pseudomonas aeruginosa*, have progressively increased and become a serious problem in chemotherapy. Recently there are many reports detailing with β-lactams containing the catechol moiety[1~5]. In addition, it has also been reported that the introduction of a mono- or dihydroxypyridone moiety[6~12] instead of a catechol group as an isostere is effective in improving stability against catechol-*O*-methyltransferase (COMT)[6]. Such compounds show marked activity against Gram-negative organisms, in particular *Pseudomonas aeruginosa*. Apparently these iron-chelating groups allow β-lactams to behave as a siderophore mimic[13,14]. This characteristic enhances penetration of β-lactams through the outer membrane of Gram-negative bacteria by using siderophore transport mechanisms. However, there have been no publications on the successful attachment of catechol units to carbapenems[15]. It was expected that we could create new carbapenems with a broad antimicrobial spectrum and the enhanced potency, especially against *Pseudomonas aeruginosa*. Here we wish to describe synthesis of these carbapenems (1, 2 and 3) and their microbial activities.

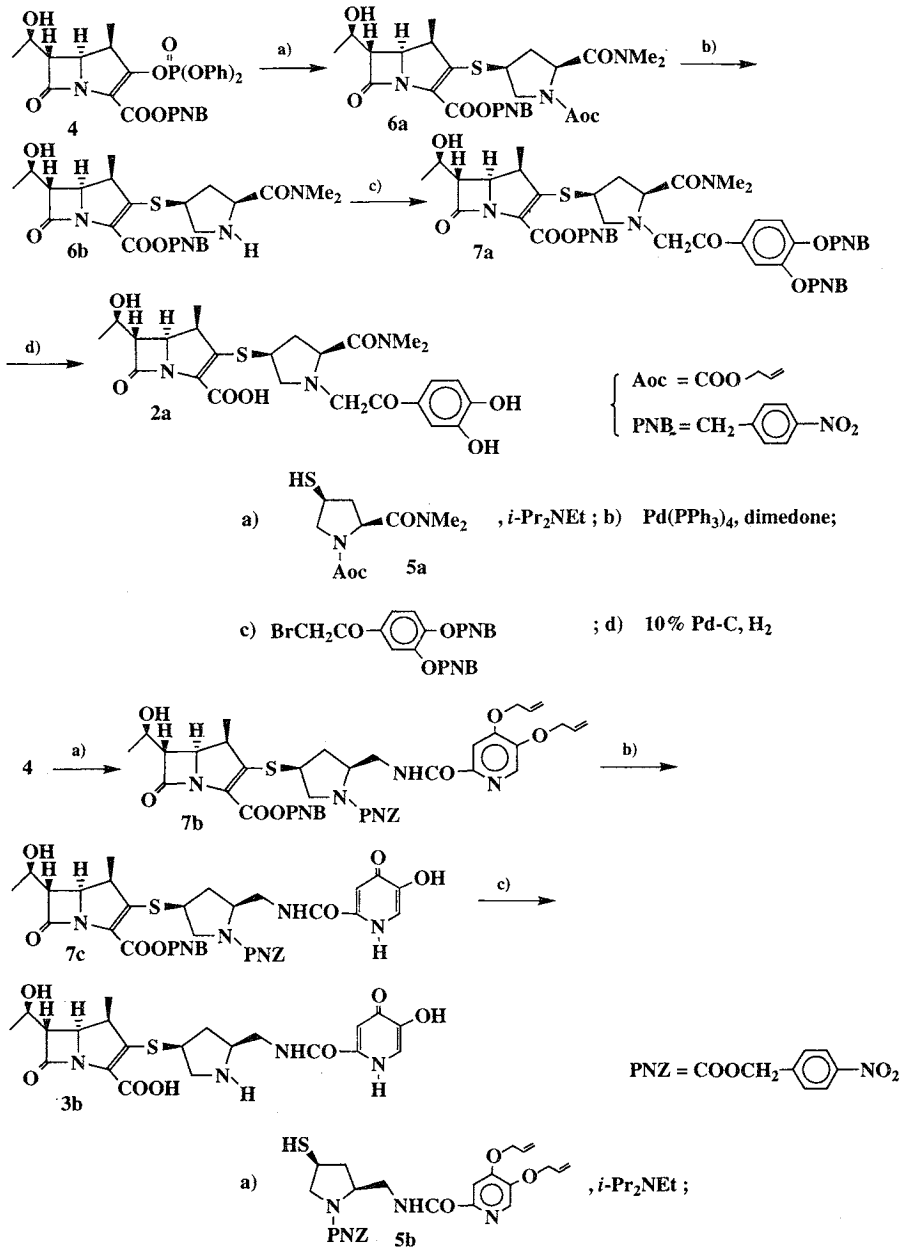
The synthetic routes employed for the title compounds are similar to those reported before[16,17] and the typical two procedures are shown in the Scheme. First, the synthesis of compound **2a** was performed as follows. Treatment of the enolphosphate (**4**)[18] with freshly prepared mercaptan (**5a**) afforded 2-substituted carbapenem ester (**6a**). Compound **6b** was obtained by removal of the allyloxycarbonyl (Aoc) group in **6a** with tetrakis(triphenylphosphine)palladium as catalyst. The introduction of the catechol-containing group could be achieved by *N*-alkylation of **6b** with the corresponding bromide to give **7a**. Hydrogenolysis of **7a** over 10% Pd-C and purification by column chromatography on Diaion CHP-20P provided the desired carbapenem **2a**. **2a**: IR (KBr) cm^{-1} 3400 (br), 1754, 1620, 1594; ^1H NMR (270 MHz, D_2O) δ 1.19 (3H, d, J=6.9 Hz), 1.30 (3H, d, J=6.3 Hz), 1.72 (3H, m), 2.80 (1H, m), 2.90 (3H, s), 3.01 (3H, s), 3.24 (3H, m), 3.40 (2H, m), 3.87 (1H, m), 3.95~4.50 (5H, m), 6.91 (1H, d, J=8.3 Hz), 7.45 (1H, s), 7.52 (1H, d, J=8.3 Hz); UV λ_{max} (H_2O) nm 220, 263, 297.

A second synthetic route was applied to obtain the carbapenem **3b**. Treatment of **4** with mercaptan **5b**, that already had the catechol-type substituent, afforded compound **7b**. Cleavage of the allyl groups with tetrakis(triphenylphosphine)palladium, successive hydrogenolysis over 10% Pd-C and purification as described above provided the final product **3b**. **3b**: IR (KBr) cm^{-1} 3358 (br), 1752, 1654, 1560; ^1H NMR (270 MHz, D_2O) δ 1.22 (3H, d, J=6.6 Hz),

Fig. 1.



Scheme 1.



1.30 (3H, d, J=6.3 Hz), 1.78 (1H, m), 2.76 (1H, m), 3.25~4.35 (10H, m), 7.12 (1H, s), 7.76 (1H, s); UV λ_{max} (H_2O) nm 295.

The mercaptans (**5**) used in this work were prepared starting from *trans*-4-hydroxy-L-proline in similar procedures as described in the preceding papers[16,17]. And the catechol or hydroxypyridone fragments were synthesized according to the literature[1~12,19].

The *in vitro* antibacterial activities (MIC's) of the prepared carbapenems are shown in Table 1~2. Some of the trends with regard to the effects of structural variations on intrinsic activity can be gleaned from an examination of the MIC's for 1'-*N*-substituted analogues (Table 1). All compounds (**1a~1g** and **2a~2c**) showed equal or

Table 1. Antimicrobial activity of carbapenem compounds having the catechol-type moiety at 1'-*N*-position.

Organism	Compound No.	MIC (μg/ml)					
		1a	**1b**	**1c**	**1d**	**1e**	**1f**
S.a. FDA 209P		6.25	1.56	3.13	1.56	0.78	3.13
S.p. Cook		0.78	0.20	0.39	0.39	0.05	0.20
E.c. NIHJ JC-2		3.13	1.56	0.39	0.39	0.39	3.13
K.p. ATCC 10031		0.78	0.025	<0.013	<0.013	0.025	0.10
P.m. GN 2425		1.56	0.39	0.20	0.05	0.20	0.78
P.a. IFO 3451[a]		12.5	1.56	0.39	1.56	3.13	6.25
P.a. TL-2666[a]		6.25	3.13	0.39	1.56	6.25	12.5
P.a. TL-2667[b]		6.25	1.56	0.39	0.78	1.56	6.25
S.m. X 100		6.25	1.56	0.20	0.20	0.39	3.13
E.c. ML 1410/RP4[c]		3.13	0.39	0.20	0.10	0.39	6.25
P.v. GN 7919[c]		6.25	3.13	1.56	1.56	1.56	12.5
S.m. GN 6473[c]		6.25	3.13	0.78	0.78	0.78	6.25

Organism	Compound No.	MIC (μg/ml)				
		1g	**2a**	**2b**	**2c**	IPM
S.a. FDA 209P		0.78	0.20	0.39	0.78	<0.013
S.p. Cook		0.05	<0.013	0.10	0.10	<0.013
E.c. NIHJ JC-2		0.78	0.05	0.39	0.20	0.10
K.p. ATCC 10031		<0.013	0.025	0.10	0.025	0.10
P.m. GN 2425		0.10	0.10	0.20	0.10	0.78
P.a. IFO 3451[a]		1.56	0.39	1.56	1.56	0.78
P.a. TL-2666[a]		1.56	0.78	1.56	1.56	3.13
P.a. TL-2667[b]		1.56	0.20	1.56	1.56	25
S.m. X 100		0.78	0.05	0.39	0.20	0.20
E.c. ML 1410/RP4[c]		0.78	0.05	0.20	0.20	0.39
P.v. GN 7919[c]		3.13	0.10	0.78	0.39	0.78
S.m. GN 6473[c]		3.13	0.10	0.39	1.56	0.20

[a] IPM-susceptible strain.
[b] IPM-resistant strain.
[c] β-Lactamase producing strain.
Abbreviations: *S.a.*, *Staphylococcus aureus*; *S.p.*, *Staphylococcus 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*.

stronger antipseudomonal activity against imipenem (IPM) resistant strain (*Pseudomonas aeruginosa* TL-2667) compared with IPM susceptible ones (*Pseudomonas aeruginosa* IFO 3451 and TL-2666). This fact proves that the introduction of catechol or hydroxypyridone moiety is effective in the field of carbapenem derivatives as well as other β-lactam antibiotics. Concerning the substitution pattern in the benzene ring, a 3,4-dihydroxyphenyl group was better for the enhancement of the antimicrobial activity than a 2,3-substituted one (compare **1a** with **1b**). It was also observed that the introduction of the electron-withdrawing group, such as chlorine atom, in the catechol residue (compare **1b** with **1c**) or the utilization of the hydroxypyridone moiety instead of the catechol group (compare **1b** with **1d**), that might also contribute to increased stability against

Table 2. Antibacterial activity of carbapenem compounds having the catechol-type moiety at 5'-position.

Organism	Compound No.	MIC (μg/ml)		
		3a	**3b**	**3c**
S.a. FDA 209P		0.05	0.05	0.20
S.p. Cook		0.013	<0.013	0.025
E.c. NIHJ JC-2		0.10	0.10	0.20
K.p. ATCC10031		0.025	<0.013	<0.013
P.m. GN 2425		0.10	0.10	0.10
P.a. IFO 3451[a]		1.56	0.78	0.39
P.a. TL-2666[a]		1.56	1.56	0.20
P.a. TL-2667[b]		3.13	1.56	0.39
S.m. X 100		0.10	0.05	0.10
E.c. ML 1410/RP4[c]		0.20	0.10	0.20
P.v. GN 7919[c]		0.39	0.20	0.39
S.m. GN 6473[c]		0.39	0.20	0.39

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

COMT[6,10] *in vivo*, enhanced the potency against Gram-negative bacteria including IPM resistant *Pseudomonas aeruginosa*. The 1′-*N*-alkylated carbapenems (**2a**～**2c**), that had basic character, were more active than the 1′-*N*-acylated ones. The effects of the spacer length, which was considered as an important factor, was not clear on the basis of these investigations. Although the orientation of the catechol moiety could be an important factor, because the caffeic acid derivative (**1g**), that had more rigid conformation, showed better anti-pseudomonal activity than the phenylpropionic acid derivative (**1f**), it was estimated that the increase of acidity (pK_a) by the supplementary conjugated bonding might also affect the antibacterial activity in this case. In order to find the more appropriate position for the catechol-type substituent, 5′-substituted analogues were also prepared. Among them, the derivatives (**3a**～**3c**), that have the iron-chelating moiety via the amidomethyl-spacer, showed enhanced antimicrobial activities against Gram-negative strains including IPM resistant *Pseudomonas aeruginosa* (Table 2).

In conclusion, the title compounds show the expected improvements in antimicrobial spectrum and strong activity against IPM resistant *Pseudomonas aeruginosa*. Further evaluation of **2** and **3** is in progress.

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