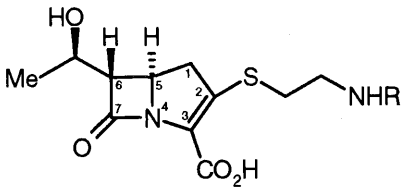
Antibacterial Activity of Some (C2)-Heterobicyclyl Carbapenem Derivatives

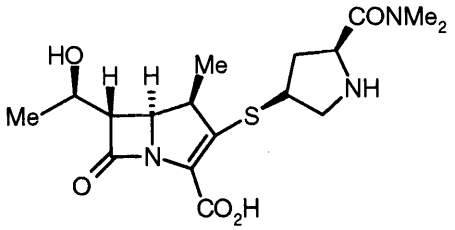
Sir:

The discovery of the natural carbapenem thienamycin (**1**)[1] and its derivative imipenem (**2**)[2] was followed by a considerable amount of research aimed at discovering carbapenem structures that combine the potent antibacterial activities of these antibiotics with improved stability to human renal dehydropeptidase-1 (DHP-1)[†,3]. To date, three stategies have been recognised for modifying the thienamycin nucleus to give synthetic carbapenems with useful levels of antibacterial activity and better stability to DHP-1: incorporation of a 1β-methyl group, as in meropenem (**3**)[4]; fusing a third ring to the nucleus at C-1 and C-2, as in the tribactam (**4**)[5]; and direct attachment of an aromatic or heteroaromatic group at C-2[6,7]. In the latter series, previous work from these laboratories had shown that carbapenems incorporating a five-membered nitrogen-containing aromatic heterocycle at C-2, such as the pyrazole derivative (**5**), combine good stability to DHP-1 with useful activity against penicillin-resistant community pathogens such as *Haemophilus influenzae* and *Streptococcus pneumoniae*.



1 R=H

2 R=CH=NH



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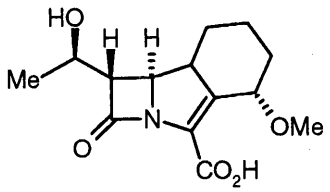

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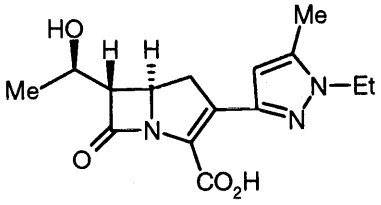

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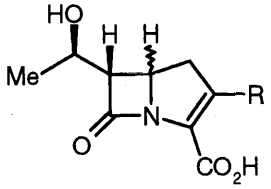
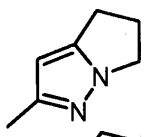
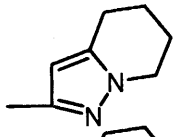


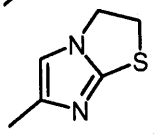
6a R=



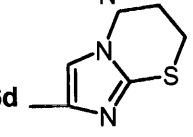
6b



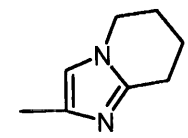
6c R=



6d



6e



† Thienamycin and imipenem have poor stability to DHP-1, and, in clinical use, imipenem is always coadministered with a DHP-1 inhibitor, cilastatin.

Table 1. Primary *in vitro* antibacterial activity (MIC; μg/ml[a]) of carbapenems (**6a**~**e**)

Compound	Organism				
	Escherichia coli	*H. influenzae*[b]	*Moraxella catarrhalis*	*Staphylococcus aureus* Russell	*S. pneumoniae* PU7[b]
6a	0.5	0.5	<0.06	<0.06	0.25
6b	1.0	0.12	<0.06	<0.06	0.12
6c	0.25	0.12	<0.06	<0.06	0.5
6d	0.25	0.25	<0.06	<0.06	0.12
6e	2.0	2.0	0.25	<0.06	<0.06
5	2.0	0.25	<0.06	<0.06	0.25
Imipenem (**2**)	0.12	0.25	<0.06	<0.06	<0.06
Meropenem (**3**)	<0.03	0.13	<0.03	<0.03	1.0

[a] Antibacterial activity was determined by broth microdilution technique in microtitre plates using Hamilton AT and liquid handling technology[7].
[b] Penicillin resistant organisms.

Table 2. MIC_{90} (μg/ml) for carbapenems (**6b**~**d**) against penicillin resistant bacteria.

Compound	Organism	
	H. influenzae[a]	*S. pneumoniae*[b]
Imipenem (**2**)	2.0	0.25
Meropenem (**3**)	0.25	0.25
5	0.25	0.25
6b	0.5	0.12
6c	0.5	0.5
6d	0.5	0.12

[a] 20 non β-lactamase producing strains.
[b] 20~40 penicillin resistant strains.

Table 3. DHP-1 stability of carbapenems (**6a**~**e**).

Compound	Analytical method	
	HPLC[a]	UV[b]
Meropenem (**3**)	88	1.0
5	—	0.6
6a	—	1.6
6b	—	1.1
6c	74	1.1
6d	82	0.7
6e	93	—

[a] Stabilities were measured as described in the literature[7] and are quoted as % compound remaining.
[b] Stabilities were measured as described in the literature[7] and are quoted as hydrolysis rates relative to meropenem, which was given an arbitrary figure of 1.0.

We were interested, therefore, in the effect on activity and stability of elaborating the five-membered heteroaromatic substituent at C-2 to a bicyclic substituent.

Five carbapenems (**6a**~**e**), with bicyclic heterocyclic substituents at C-2, were prepared using the methods previously described[7]. All showed potent, broad spectrum antibacterial activity (Table 1). Of particular note, is the excellent activity against *S. pneumoniae* PU7, a Gram-positive bacterium with altered penicillin binding proteins (PBPs). The imidazopiperidine (**6e**) showed slightly reduced minimum inhibitory concentrations (MIC's) against Gram-negative organisms, but still exhibited greater potency than meropenem (**3**) against *S. pneumoniae* PU7. The carbapenems (**6b**~**d**) were tested against a range (20) of penicillin resistant, non β-lactamase producing strains of *H. influenzae* and exhibited four-fold lower MIC_{90}'s (0.5 μg/ml) than imipenem (2.0 μg/ml). Against a similar range (20~40) of penicillin-resistant *S. pneumoniae*, **6b**~**d** showed similar or slightly improved MIC_{90}'s (0.12~0.5 μg/ml) than imipenem (0.25 μg/ml) (Table 2).

The comparative stabilities of **6a**~**e** against DHP-1 are shown in Table 3. Of these, **6b**~**e** showed comparable DHP-1 stability to meropenem with **6e** showing a slight improvement.

In conclusion, we have described a series of novel C-2-heterobicyclylcarbapenems (**6a**~**e**) exhibiting superior antibacterial activity than imipenem and equivalent to meropenem and the pyrazolyl derivative (**5**). Most of these carbapenems (**6b**~**e**) also demonstrate a stability to DHP-1 equivalent or slightly better than meropenem.

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