Doripenem (S-4661), A Novel Carbapenem: Comparative Activity Against Contemporary Pathogens Including Anaerobes, Bactericidal Action and Methods Evaluations

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ABSTRACT

Background: Doripenem (DOR), is a broad-spectrum carbapenem (CARB) with an activity combining the best features of imipenem (IMP) and meropenem (MER). This potent parenteral compound was studied against clinical isolates (2001-2002) from a worldwide organism collection.

Methods: A total of 859 strains were susceptibility (S) tested by NCCLS methods against DOR and 6 to 28 comparators including IMP, MER and ertapenem (ERT). The organisms included: *Enterobacteriaceae* (ENT; 281), *Acinetobacter* (AC; 33), *P. aeruginosa* (PSA; 35), other non-fermentors (22), *H. influenzae* (HI; 61), *M. catarrhalis* (MCAT; 33), methicillin-S staphylococci (MSS; 39), enterococci (55), streptococci (163), various anaerobes (98), and other Gram-positive spp. (17).

Results: Against ENT, the average DOR MIC_{50} was 0.03 µg/ml (range, ≤ 0.015 - 0.25 µg/ml) 2- to 16X more potent than IMP and comparable to ERT and MER; all DOR MICs were ≤ 4 µg/ml.

Organism (no. tested)	MIC_{50} (µg/ml)/% S (≤ 4 for DOR):			
	DOR	ERT	IMP	MER
AC (33)	16/76	>32/18	>8/76	>8/76
PSA (35)	0.5/100	16/33	2/100	1/100
HI (61)	0.5/100	0.25/100	NT[a]	NT[a]
MCAT (32)	0.03/100	≤0.015/100	NT[a]	NT[a]
MSS (39)	0.06/100	0.5/100	≤0.06/100	NT
S. pneumoniae, PEN-S (20)	≤0.015/100	0.03/100	≤0.06/100	NT
vir. gr. strept, PEN-S (23)	0.06/100	0.25/100	≤0.06/100	NT
ß-strept (61)	0.06/100	0.5/100	≤0.06/100	NT

a. Cefepime and ceftriaxone were tested (HI MIC_{90}: ≤ 0.25; MCAT MIC_{90}: 0.5-2 µg/ml). NT = not tested.

DOR was active against *Aeromonas* (MIC_{50}, 0.03 µg/ml), *Bacillus* spp. (MIC_{50}, 0.03 µg/ml) and all anaerobes (MIC range, ≤0.015-4 µg/ml), but was less active against *Corynebacterium* (MIC_{90}, >32 µg/ml). DOR was bactericidal and broth MICs were slightly elevated compared to agar. In pilot testing, the optimal DOR disk concentration was 10-µg, identical to NCCLS-approved reagents for other CARBs.

Conclusions: DOR appears to be a potent carbapenem with a spectrum resembling currently available CARBs, but with greater activity versus some non-fermentative bacillus strains. Continued development appears warranted against isolates resistant to other ß-lactams.

BACKGROUND

Doripenem (formerly S-4661) is a novel parenteral carbapenem. The chemical formula for doripenem is (+)-(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3[[3S,5S)-S-(sulfamoylaminomethyl) pyrrolidin-3-yl]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate (Shionogi Co., Ltd., Japan; Figure 1), that confers ß-lactamase stability and resistance to inactivation by renal dehydropeptidases. This new carbapenem from earlier *in vitro* studies appears to have a spectrum and potency versus Gram-positive cocci most similar to imipenem, and a Gram-negative activity most like meropenem (e.g. 2- to 4-fold greater than imipenem). A particular feature, attributed to the side chain at position 2, is greater activity among non-fermentative Gram-negative bacilli having multi-drug resistances. However, this new 1ß-methylcarbapenem remains unstable to the L1 enzyme produced by *Stenotrophomonas maltophilia* or metallo-ß-lactamases.

In this report, we summarize the results of testing doripenem and dozens of comparison agents against contemporary, wild-type isolates (2001 - 2002). A total of nearly 1,000 strains was tested by reference NCCLS [2003] methods with resistances interpreted by NCCLS document criteria [2003].

MATERIALS & METHODS

A total of 859 recent clinical isolates were tested from patients with documented infections in hospitals located in the Americas and Europe. The distribution of species and strains was as follows: *Enterobacteriaceae* (281 strains); *Acinetobacter* spp., usually *A. baumannii* (33 strains); *P. aeruginosa* (35 strains); other non-fermentative Gram-negative bacilli (22 strains), *H. influenzae* (61 strains), *M. catarrhalis* (33 strains); oxacillin-susceptible staphylococci (39 strains); *Enterococcus* spp. (55 strains); streptococci (163 strains; three groups); anaerobes (98 strains) and other Gram-positive cocci (17 strains).

All susceptibility tests were performed by NCCLS dilution methods [2003], were interpreted by M100-S13 [2003] breakpoint criteria, and some disk diffusion tests were attempted to select the appropriate disk content for doripenem. An arbitrary susceptible breakpoint for doripenem was applied (≤ 4 µg/ml), the same as imipenem or meropenem to provide spectrum comparisons only [NCCLS, 2003]. Quality control (QC) was provided by concurrent use of multiple (seven) QC strains recommended by the NCCLS [2003].

Special studies of MBCs, kill-curve analysis and intermethod MIC comparisons were also achieved, generally applying NCCLS published methods.

RESULTS

- Doripenem was very active against strains of *Enterobacteriaceae* (MIC_{90}S, ≤ 0.015 - 0.25; median MIC_{90}, 0.06 µg/ml), a potency greater than imipenem but slightly less than ertapenem or meropenem (Table 1).
- Doripenem exhibited excellent activity against non-fermentative Gram-negative bacilli (MIC_{90}, 0.25 - 0.5 µg/ml), *H. influenzae* (MIC_{90}, 0.5 - 1 µg/ml) and *M. catarrhalis* (MIC_{90}, 0.03 µg/ml). All of these species had doripenem MIC results at ≤ 1 µg/ml, except a subset of multi-drug resistant Acinetobacters (Table 2).
- Against Gram-positive cocci, doripenem was potent against oxacillin-susceptible *S. aureus* (MIC_{90}, 0.06 µg/ml) and oxacillin-susceptible CoNS (MIC_{90}, 0.06 µg/ml). In contrast, *E. faecalis* were marginally inhibited by doripenem ($MIC_{50/90}$ at 4 and 16 µg/ml, respectively; Table 3).
- Streptococci were very susceptible to doripenem with an activity most similar to imipenem. Increased resistance to penicillin among *S. pneumoniae* and viridans group streptococci also resulted in elevated doripenem results, but all MIC values remained ≤ 4 µg/ml (Table 3).
- All anaerobes tested (98 strains) had doripenem MIC values at ≤ 4 µg/ml, e.g. susceptible. *B. fragilis* isolates had a doripenem MIC_{90} at 0.5 µg/ml, lowest among tested carbapenems (Table 4).
- Several other organisms were also susceptible (MIC, ≤ 4 µg/ml) to doripenem including *Aeromonas* spp. (MIC_{50}, 0.03 µg/ml) and *Bacillus* spp. (MIC_{50}, 0.03 µg/ml), but not *Corynebacterium* spp. (MIC_{90}, > 32 µg/ml; data not shown).
- Doripenem was bactericidal versus Gram-negative and -positive organisms (Figure 2 and 3) with MBC values near the MIC results (data not shown).
- Broth and agar dilution doripenem MIC results were similar (Figure 4) and the 10-µg doripenem disk was acceptable for use as a diagnostic reagent, a concentration also used for susceptibility testing of other carbapenems (Table 5).

Figure 1: Biochemical structure of Doripenem.

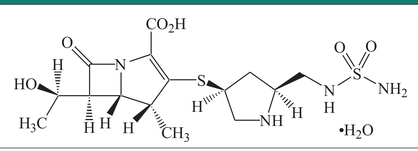

Figure 2: Time killing curves for doripenem tested against *S. pneumoniae* ATCC 49619 (MIC, 0.06 µg/ml).

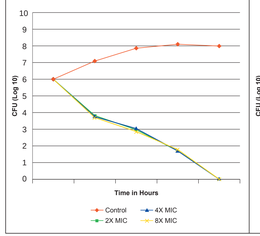

Figure 3: Time killing curves for doripenem tested against *P. aeruginosa* ATCC 27853 (MIC, 0.25 µg/ml).

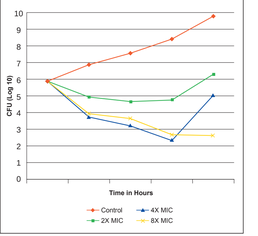

Table 1. Antimicrobial activity of doripenem (S-4661) and five other broad-spectrum ß-lactams tested against contemporary wild-type strains of *Enterobacteriaceae*.

Organism (no. tested)	Antimicrobial	MIC (µg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
E. coli (31)	Doripenem	≤0.015	≤0.015	≤0.015-0.03	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	≤0.015	≤0.015-0.03	100.0	0.0
	Imipenem	0.12	0.25	≤0.06-0.25	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Piperacillin/Tazobactam	2	2	≤0.5-64	96.8	3.2
K. pneumoniae (26)	Doripenem	0.03	0.03	≤0.015-0.06	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	0.03	≤0.015-0.06	100.0	0.0
	Imipenem	0.12	0.25	0.12-0.5	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Piperacillin/Tazobactam	2	4	≤0.5-8	100.0	0.0
K. oxytoca (20)	Doripenem	0.03	0.06	≤0.015-0.06	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	0.03	≤0.015-0.06	100.0	0.0
	Imipenem	0.12	0.25	0.12-0.5	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Piperacillin/Tazobactam	1	4	1-8	100.0	0.0
P. mirabilis (23)	Doripenem	0.06	0.12	0.03-0.12	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	≤0.015	≤0.015	100.0	0.0
	Imipenem	0.5	2	0.12-2	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Piperacillin/Tazobactam	≤0.5	≤0.5	≤0.5	100.0	0.0
Citrobacter spp. (29)	Doripenem	0.03	0.03	≤0.015-0.06	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	0.03	≤0.015-0.03	100.0	0.0
	Imipenem	0.25	1	0.12-4	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12-0.25	100.0	0.0
	Piperacillin/Tazobactam	2	4	1-4	100.0	0.0
Enterobacter spp. (35)	Doripenem	0.03	0.06	≤0.015-0.25	100.0(≤4)	0.0(≥16)
	Ertapenem	0.03	0.25	≤0.015-0.5	100.0	0.0
	Imipenem	0.5	0.5	0.12-1	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
	Cefepime	≤0.12	0.25	≤0.12-0.25	100.0	0.0
	Piperacillin/Tazobactam	2	8	1-16	100.0	0.0
S. marcescens (24)	Doripenem	0.06	0.12	0.03-0.5	100.0(≤4)	0.0(≥16)
	Ertapenem	0.06	0.12	≤0.015-0.25	100.0	0.0
	Imipenem	0.5	2	0.25-2	100.0	0.0
	Meropenem	≤0.06	0.12	≤0.06-2	100.0	0.0
	Cefepime	≤0.12	0.5	≤0.12-2	100.0	0.0
	Piperacillin/Tazobactam	2	8	1-64	95.8	4.2
Indole-positive *Proteae* (39)[b]	Doripenem	0.12	0.25	0.03-0.25	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	0.03	≤0.015-0.5	100.0	0.0
	Imipenem	1	2	0.25-4	100.0	0.0
	Meropenem	≤0.06	0.12	≤0.06-2	100.0	0.0
	Cefepime	≤0.12	0.5	≤0.12-16	97.4	0.0
	Piperacillin/Tazobactam	≤0.5	8	≤0.5-16	100.0	0.0
Salmonella spp. (23)[c]	Doripenem	0.03	0.06	≤0.015-0.12	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	≤0.015	≤0.015	100.0	0.0
	Imipenem	0.25	0.25	≤0.06-0.5	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12-0.25	100.0	0.0
	Piperacillin/Tazobactam	4	4	1-4	100.0	0.0
Shigella spp. (22)[d]	Doripenem	0.03	0.03	≤0.015-0.06	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	≤0.015	≤0.015-0.06	100.0	0.0
	Imipenem	0.12	0.12	≤0.06-0.25	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	0.25	≤0.12-0.5	100.0	0.0
	Piperacillin/Tazobactam	1	2	≤0.5-4	100.0	0.0

a. Susceptibility criteria of the NCCLS [2003], if available.
b. Includes: *M. morganii* (12 strains), *P. vulgaris* (eight strains), *P. rettgeri* (11 strains), and *P. stuartii* (eight strains).
c. Includes: *S. enterica* (one strain), *S. paratyphi* (one strain), and *Salmonella* spp. (21 strains).
d. Includes *S. boydii* (five strains), *S. dysenteriae* (five strains), *S. flexneri* (five strains), and *S. sonnei* (seven strains).

Table 2. Comparative antimicrobial activity of doripenem (S-4661) tested against non-fermentative Gram-negative bacilli, *H. influenzae* and *M. catarrhalis* strains.

Organism (no. tested)	Antimicrobial	MIC (µg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Acinetobacter spp. (33)	Doripenem	0.5	16	0.03->32	75.8(≤4)	21.2(≥16)
	Ertapenem	8	>32	≤0.015->32	-	-
	Imipenem	0.5	>8	0.12->8	75.8	24.2
	Meropenem	2	>8	≤0.06->8	75.8	24.2
	Cefepime	8	>16	≤0.12->16	51.5	33.3
	Piperacillin/Tazobactam	>64	>64	≤0.5->64	39.4	48.5
P. aeruginosa (35)	Doripenem	0.25	0.5	0.06-1	100.0(≤4)	0.0(≥16)
	Ertapenem	4	16	0.25-16	-	-
	Imipenem	1	2	0.5-2	100.0	0.0
	Meropenem	0.25	1	≤0.06-2	100.0	0.0
	Cefepime	2	8	1-16	91.7	0.0
	Piperacillin/Tazobactam	4	16	≤0.5->64	91.7	8.3
Haemophilus influenzae ß-lactamase-negative (33)	Doripenem	0.12	1	≤0.015-1	100.0(≤4)	0.0(≥16)
	Ertapenem	0.06	0.25	≤0.015-0.5	100.0	0.0
	Amoxicillin/Clavulanate	0.5	2	0.12-2	100.0	0.0
	Piperacillin/Tazobactam	≤1	≤1	≤1	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Cefepime	≤0.06	0.12	≤0.06-0.25	100.0	0.0
Haemophilus influenzae ß-lactamase-positive (28)	Doripenem	0.12	0.5	0.12-1	100.0(≤4)	0.0(≥16)
	Ertapenem	0.06	0.12	0.03-0.12	100.0	-
	Amoxicillin/Clavulanate	1	2	0.25-4	100.0	0.0
	Piperacillin/Tazobactam	≤1	≤1	≤1	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0	0.0
Moraxella catarrhalis (33)[c]	Doripenem	≤0.015	0.03	≤0.015-0.03	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	≤0.015	≤0.015-0.03	100.0	-
	Amoxicillin/Clavulanate	≤0.06	0.25	≤0.06-0.25	100.0	0.0
	Piperacillin/Tazobactam	≤1	≤1	≤1	100.0	0.0
	Ceftriaxone	0.25	0.5	≤0.008-1	100.0	0.0
	Cefepime	0.5	2	≤0.06-2	100.0	0.0

a. Susceptibility criteria of the NCCLS [2003], if available.
b. Includes: *A. caviae* (two strains), *A. hydrophila* (two strains), and *Aeromonas* spp. (one strain).
c. Penicillin susceptibility determined by lack of ß-lactamase production and interpretive criteria used for *H. influenzae* [NCCLS, 2003] were applied.

Table 3. Antimicrobial activity of doripenem (S-4661) tested against Gram-positive organisms, compared to selected ß-lactam agents.

Organism (no. tested)	Antimicrobial	MIC (µg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Staphylococcus aureus oxacillin-susceptible (20)	Doripenem	0.06	0.06	0.03-0.06	100.0(≤4)	0.0(≥16)
	Ertapenem	0.25	0.25	0.12-0.5	100.0	0.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Amoxicillin/Clavulanate	≤2	≤2	≤2	100.0	0.0
	Penicillin	8	32	0.03-32	15.0	85.0
	Ceftriaxone	2	4	2-4	100.0	0.0
	Cefepime	2	2	0.5-4	100.0	0.0
Coag.-neg. staphylococci oxacillin-susceptible (19)	Doripenem	0.03	0.06	≤0.015-0.06	100.0(≤4)	0.0(≥16)
	Ertapenem	0.25	0.5	0.12-0.5	100.0	0.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Amoxicillin/Clavulanate	≤2	≤2	≤2-4	100.0	0.0
	Penicillin	0.5	16	0.03-32	15.8	84.2
	Ceftriaxone	2	4	1-4	100.0	0.0
	Cefepime	1	2	0.25-2	100.0	0.0
E. faecalis (45)[a]	Doripenem	4	16	≤0.015->32	80.0(≤4)	13.3(≥16)
	Ertapenem	16	>32	0.12->32	-	-
	Imipenem	1	4	0.12->8	-	-
	Ampicillin	≤2	4	≤2->16	97.8	2.2
	Amoxicillin/Clavulanate	≤2	≤2	≤2->16	97.8	2.2
	Penicillin	4	8	1->32	91.1	9.6
S. pneumoniae penicillin-susceptible (20)	Doripenem	≤0.015	≤0.015	≤0.015	100.0(≤4)	0.0(≥16)
	Ertapenem	≤0.015	0.03	≤0.015-0.03	100.0	0.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Amoxicillin/Clavulanate	≤2	≤2	≤2	100.0	0.0
	Penicillin	≤0.06	0.03	≤0.015-0.03	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
	Cefepime	≤0.12	0.25	≤0.12-0.5	100.0	0.0
S. pneumoniae penicillin-intermediate (10)	Doripenem	0.03	0.25	≤0.015-0.5	100.0(≤4)	0.0(≥16)
	Ertapenem	0.06	0.5	≤0.015-1	100.0	0.0
	Imipenem	≤0.06	0.12	≤0.06-0.12	100.0	0.0
	Amoxicillin/Clavulanate	≤2	≤2	≤2	100.0	0.0
	Penicillin	0.5	1	0.12-1	0.0	0.0
	Ceftriaxone	0.5	1	≤0.25-1	100.0	0.0
	Cefepime	0.5	1	≤0.12-1	100.0	0.0
S. pneumoniae penicillin-resistant (23)	Doripenem	0.5	1	0.25-2	100.0(≤4)	0.0(≥16)
	Ertapenem	1	2	0.5-4	69.6	8.7
	Imipenem	0.25	2	0.12-2	44.4	22.2
	Amoxicillin/Clavulanate	4	8	1-8	43.5	39.1
	Penicillin	4	4	2-4	0.0	100.0
	Ceftriaxone	1	4	0.5-4	60.9	17.4
	Cefepime	1	2	0.5-4	52.2	4.3
viridans gr. streptococci penicillin-susceptible (23)	Doripenem	0.03	0.06	≤0.015-0.12	100.0(≤4)	0.0(≥16)
	Ertapenem	0.12	0.25	0.03-1	100.0	-
	Imipenem	≤0.06	≤0.06	≤0.06-0.12	-	-
	Penicillin	≤0.06	0.12	0.03-0.12	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Cefepime	≤0.12	0.25	≤0.12-0.25	100.0	0.0
viridans gr. streptococci penicillin-intermediate (13)	Doripenem	0.25	0.5	≤0.015-2	100.0(≤4)	0.0(≥16)
	Ertapenem	0.5	1	0.12-4	92.3	-
	Imipenem	≤0.06	0.12	≤0.06-0.25	-	-
	Penicillin	0.25	1	0.25-1	0.0	0.0
	Ceftriaxone	≤0.25	0.5	≤0.25-16	92.3	7.7
	Cefepime	0.5	1	≤0.12-2	92.3	0.0
viridans gr. streptococci penicillin-resistant (13)	Doripenem	2	4	0.25-4	100.0(≤4)	0.0(≥16)
	Ertapenem	4	8	1-8	7.7	-
	Imipenem	2	4	0.12-4	-	-
	Penicillin	8	32	≤4->32	0.0	100.0
	Ceftriaxone	4	>32	2->32	0.0	69.2
	Cefepime	4	>16	1->16	23.1	61.5
ß-haemolytic streptococci (61)[a]	Doripenem	≤0.015	0.06	≤0.015-0.12	100.0(≤4)	0.0(≥16)
	Ertapenem	0.03	0.5	≤0.015-0.5	100.0	-
	Imipenem	≤0.06	≤0.06	≤0.06	-	-
	Penicillin	≤0.015	0.06	≤0.015-0.12	100.0	-
	Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
	Cefepime	≤0.12	0.25	≤0.12-0.5	100.0	-

a. Susceptibility criteria of the NCCLS [2003], if available.
b. Includes four *van A* and two *van B* strains.
c. Includes: group A (20 strains), group B (20 strains), group C (seven strains), group F (five strains), group G (seven strains) and untyped (two strains).

Figure 4: Comparison of doripenem MIC results from agar dilution and broth microdilution methods (106 isolates) [NCCLS, 2003].

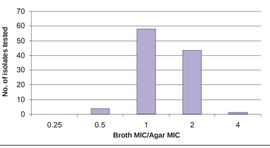

Table 4. Results of testing 98 anaerobic bacteria against doripenem and four comparison agents.

Organism (no. tested)	Antimicrobial	MIC (µg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Bacteroides fragilis (26)	Doripenem	0.25	0.5	0.12-1	100.0(≤4)	0.0(≥16)
	Ertapenem	0.5	1	0.12-2	100.0	0.0
	Meropenem	0.12	1	0.06-2	100.0	0.0
	Metronidazole	2	2	0.5-4	100.0	0.0
	Clindamycin	4	>16	1->16	30.8	50.0
Prevotella spp. (20)	Doripenem	0.12	0.25	0.03-1	100.0(≤4)	0.0(≥16)
	Ertapenem	0.25	1	0.03-2	100.0	0.0
	Meropenem	0.12	0.25	0.03-1	100.0	0.0
	Metronidazole	4	16	0.5->32	90.0	5.0
	Clindamycin	≤0.12	>16	≤0.12->16	70.0	30.0
Other Gram-negative species (12)[b]	Doripenem	0.25	1	≤0.015-4	100.0(≤4)	0.0(≥16)
	Ertapenem	1	2	≤0.015-8	90.0	10.0
	Meropenem	0.25	1	≤0.015-4	100.0	0.0
	Metronidazole	2	2	0.5-2	100.0	0.0
	Clindamycin	>16	>16	0.12->16	25.0	75.0
Clostridium difficile (10)	Doripenem	1	2	1-2	100.0(≤4)	0.0(≥16)
	Ertapenem	4	4	4-8	90.0	0.0
	Meropenem	2	2	1-4	100.0	0.0
	Metronidazole	0.5	1	≤0.12-1	100.0	0.0
	Clindamycin	4	8	0.5-16	60.0	40.0
Other *Clostridium* spp. (16)[c]	Doripenem	0.03	0.06	≤0.015-0.25	100.0(≤4)	0.0(≥16)
	Ertapenem	0.06	0.12	0.03-0.12	100.0	0.0
	Meropenem	≤0.015	0.5	≤0.015-1	100.0	0.0
	Metronidazole	4	4	0.5-4	100.0	0.0
	Clindamycin	0.5	8	≤0.12->16	68.8	12.5
Other Gram-positive species (14)[d]	Doripenem	0.12	0.25	≤0.015-0.5	100.0(≤4)	0.0(≥16)
	Ertapenem	0.12	0.25	≤0.015-0.25	100.0	0.0
	Meropenem	0.12	0.12	≤0.015-0.12	100.0	0.0
	Metronidazole	>32	>32	1->32	7.1	92.9
	Clindamycin	0.25	2	0.12->16	92.9	7.1

a. Susceptibility criteria of the NCCLS [2003], if available.
b. Includes: *Bacteroides ovatus* (three strains), *Bacteroides* spp. (one strain), *Bacteroides thetaiotaomicron* (six strains), *Fusobacterium nucleatum* (one strain), and *Fusobacterium* spp. (one strain).
c. Includes: *Clostridium perfringens* (12 strains), *Clostridium* spp. (one strain), and *Clostridium septicum* (three strains).
d. Includes: *Propionibacterium acnes* (two strains), *Propionibacterium* spp. (nine strains), and *Peptostreptococcus* spp. (three strains).

Table 5. Average zone diameters (triplicate determinations x 2 MIC readers) for three candidate doripenem disk concentrations compared to ertapenem (10-µg), imipenem (10-µg) and meropenem (10-µg) disk results (five QC strains).

Organism	Disk zone diameter (mm): Doripenem 5-µg	Doripenem 10-µg[a]	Doripenem 20-µg	Ertapenem 10-µg	Imipenem 10-µg	Meropenem 10-µg
E. coli ATCC 25922	27.3	29.3	30.7	32.8	27.6	27.6
P. aeruginosa ATCC 27853	27.0	30.3	32.5	18.2	23.7	28.2
S. pneumoniae ATCC 49619	28.7	31.2	32.8	28.8	34.2	29.0
S. aureus ATCC 25923	31.3	33.3	34.8	29.5	38.3	28.5
E. faecalis ATCC 29212	15.3	19.0	22.2	12.7	25.5	15.2

a. Proposed disk concentration was 10-µg, consistent with that concentration used for other carbapenems.

CONCLUSIONS

- Doripenem was identified as a potent carbapenem with a spectrum of activity resembling currently marketed, pseudomonas-active carbapenems such as imipenem and meropenem.
- Doripenem's potency was superior overall to other carbapenems primarily versus many non-fermentative Gram-negative bacillus isolates and some Gram-positive cocci (streptococci).
- Doripenem, with anti-anaerobic activity and the above noted features with cidal action, represents a very broad and balanced spectrum of activity for use against difficult to treat infections caused by resistant organisms. Further development in human clinical trials appears warranted.

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