Antimicrobial Activity of the Novel Peptide Deformylase Inhibitor LBM415 (NVP PDF-713) Against an International Collection of Respiratory Tract, and Skin and Soft Tissue Pathogens (2004)

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AMENDED ABSTRACT

Background: LBM415 (LBM) is the first of the peptide deformylase inhibitor (PDI) class compounds being developed for the treatment of community-acquired respiratory tract infections (CARTI) and skin and soft tissue infections (SSTI). In this study, we evaluated the spectrum and potency of LBM against a large, recent (2004) international collection of targeted pathogens.

Methods: Non-duplicate, clinically-significant bacterial isolates (10,733 strains) were collected from > 70 medical centers participating in the global LBM surveillance program, including strains from North America, South America, Europe, and Asia geographic areas. All isolates were tested using NCCLS broth microdilution susceptibility testing methods against LBM and representative comparator agents used in the empiric or directed therapy of the presumed species. Interpretive criteria, where available, were those of CLSI (M100-S15).

Results: The antimicrobial activity and cumulative MIC frequency distributions of LBM for selected species are in the table:

Organisms (no. tested)	MIC (µg/ml) 50%	MIC (µg/ml) 90%	Cum. % of strains inhibited at MIC (µg/ml): 1	2	4	8
S. aureus (SA; 4,931)	1	1	92	99	99	>99
Coag-neg staphylococci (CoNS; 1,190)	0.5	2	87	99	100	-
S. pneumoniae (SPN; 1,423)	0.5	1	91	99	100	-
Viridans group streptococci (122)	0.12	0.5	99	100	-	-
ß-haemolytic streptococci (421)	0.5	1	97	100	-	-
Enterococci (ENT; 1,319)	2	4	33	69	96	100
E. faecalis (916)	2	4	19	58	94	100
E. faecium (361)	1	2	62	93	100	-
Other Gram-positive species (44)	0.25	2	86	100	-	-
H. influenzae (HI; 990)	2	4	48	75	90	98
M. catarrhalis (MCAT; 27)	0.25	0.5	96	100	-	-

Characteristics of the collection included: 40% oxacillin-resistant (OR) SA; 74% OR CoNS; 18% penicillin-R SPN; 15% vancomycin-R ENT; and 23% ampicillin-R HI. LBM displayed potent activity against staphylococci, streptococci, *E. faecium* and MCAT, resulting in a ≥ 99% inhibition at ≤ 4 µg/ml; 94% of *E. faecalis* strains and 90% of HI strains were also inhibited at this level. Inhibition at ≤ 8 µg/ml was also notable for *B. cepacia* (77%) and *S. maltophilia* (80%; data not shown). No differences were noted in the activity of LBM between S and R subsets of SA, CoNS, SPN, ENT and HI for antimicrobials such as oxacillin, penicillin, ampicillin, macrolides, vancomycin and fluoroquinolones. While regional differences were apparent with some comparator agents, LBM activity did not vary significantly between geographic area samples.

Conclusions: The first in class PDI to enter clinical development has consistently shown a wide-spectrum of activity against common pathogens of the respiratory tract and skin and soft tissue, including resistant subsets, with few regional differences detected. Given the unique mode of action and pending favorable pharmacokinetic/pharmacodynamic characterization, PDI compounds promise to be a significant advance for the targeted indications.

INTRODUCTION

The emergence of resistance in bacterial pathogens to currently marketed antimicrobial agents has become a significant medical management crisis. The result has been an increase in morbidity, mortality and health-care costs in both inpatient and outpatient settings. The limited number of antimicrobial classes and the common occurrences of cross-resistance within and between classes create an urgent need to identify new classes of compounds that display novel mechanisms of action.

Peptide deformylase (PDF), a highly conserved metalloproteinase, is required in bacteria for protein maturation. The PDF enzyme can also be present in eukaryotic cells, specifically within mitochondria, but is much less active than in bacteria making inhibitors of PDF promising targets as antibacterial agents.

LBM415 (also known as NVP PDF-713) is one of the first PDF inhibitors to advance into clinical trials for the oral and parenteral treatment of community-acquired respiratory tract and skin and skin structure infections caused by susceptible Gram-positive and -negative organisms. Recent studies have described QC guidelines for both disk and broth microdilution methods for use in clinical trial testing. Spectrum of activity evaluations of the targeted species, including resistant subsets, has demonstrated a potential role for LBM415 in the treatment of the indicated infections.

In this report, we summarize the results of testing LBM415 and selected comparator agents against a worldwide collection of contemporary (2004) clinical isolates. This collection of 10,733 isolates included predominantly staphylococci, streptococci, enterococci, *Haemophilus influenzae* and *Moraxella catarrhalis* and was tested by standardized reference methodologies (broth microdilution) with categorical interpretations made using current Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) criteria.

MATERIALS AND METHODS

Bacterial strains. The organisms (10,733 strains) included: 6,121 staphylococci (2,853 oxacillin-resistant), 1,423 *Streptococcus pneumoniae* (925, 248 and 250 penicillin-susceptible, -intermediate and -resistant, respectively), 421 ß-haemolytic streptococci, 122 viridans group *Streptococcus* spp., 1,081 vancomycin-susceptible enterococci, 194 vancomycin-resistant enterococci, 990 *Haemophilus influenzae* (226 ampicillin-resistant), 27 *Moraxella catarrhalis,* 22 *Burkholderia cepacia*, 211 *Stenotrophomonas maltophilia* and 44 other gram-positive isolates (see Table 1 for details). All isolates were non-duplicate consecutive clinical isolates submitted from numerous medical centers located in the Americas and Europe that contributed to various surveillance programs for the year 2004. Identifications were performed by the submitting laboratories and confirmed using standard biochemical algorithms, including use of the Vitek System (bioMerieux, Hazelwood, MO).

Antimicrobial agents and susceptibility testing. Compound LBM415 was obtained from Novartis Pharmaceuticals (East Hanover, NJ, USA). All strains were tested by the broth microdilution method [NCCLS, 2003] in cation-adjusted Mueller-Hinton broth (with 2 - 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium (HTM) for testing of *H. influenzae*) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen. Dry-form microdilution panels and broth reagents were purchased from TREK Diagnostics (Ohio, USA). Interpretation of quantitative MIC results was in accordance with CLSI [2005] criteria.

RESULTS

- Among the most common bacterial agents of community-acquired pneumonia and skin and skin structure infections, ≥ 99% of staphylococci, streptococci, *E. faecium*, and *M. catarrhalis* were inhibited at 4 µg/ml or less of LBM415, as were 90% of *H. influenzae* and 94% of *E. faecalis* strains (Table 1).
- All LBM415 MIC values except for one were ≤ 4 µg/ml for *S. aureus* and coagulase-negative staphylococci. MIC_{50} and MIC_{90} values for *S. aureus* were 0.5 and 1 µg/ml for oxacillin-susceptible strains, and both 1 µg/ml for oxacillin-resistant strains (Table 2).
- One isolate (1/4,931; 0.02%) of a methicillin-susceptible *S. aureus* was found during 2004 that demonstrated a MIC of > 32 µg/ml, and represented the first high-level resistant strain ever recovered from a clinical source.
- Among all *S. pneumoniae* strains tested, regardless of penicillin susceptibility patterns, LBM415 was uniformly active with MIC_{50} values of 0.5 µg/ml and MIC_{90} values of 1 to 2 µg/ml (range from ≤ 0.016 to 4 µg/ml).
- LBM415 was also uniformly active against beta-haemolytic and viridans-group streptococci with MIC_{50} values of 0.5 and 0.12 µg/ml, respectively, and MIC_{90} values of 0.5 µg/ml and 1 µg/ml.
- No difference was noted in the activity of LBM415 against vancomycin-susceptible or resistant enterococci, with MIC_{50} and MIC_{90} results for vancomycin-susceptible *E. faecalis* being 2 and 4 µg/ml and vancomycin-resistant *E. faecalis,* 4 and 4 µg/ml. For vancomycin-susceptible and -resistant *E. faecium,* MIC_{50} and MIC_{90} values were 1 and 2 µg/ml.
- LBM415 displayed a broader range (0.03 to 2 µg/ml) of activity against a collection of other Gram-positives including species of *Aerococcus, Bacillus, Corynebacteria, Leuconostoc, Listeria, Micrococcus* and *Rothia*, although the group MIC_{50} and MIC_{90} (0.25 and 2 µg/ml, respectively) remained within achievable plasma concentrations.
- LBM415 displayed activity against both *H. influenzae* and *M. catarrhalis* (Table 3), although the MIC_{50} and MIC_{90} of both ampicillin-susceptible and ampicillin-resistant *H. influenzae* (1 and 4 µg/ml, and 2 and 8 µg/ml, respectively) are 8 to 16-fold higher than those for *M. catarrhalis* (0.25 and 0.5 µg/ml, respectively).
- While LBM415 does demonstrate modest activity against *B. cepacia* and *S. maltophilia*, such activity is not consistent with readily achievable concentrations.
- Regional antibiogram differences were apparent with some species; activity of LBM415 against targeted species did not vary, however, between geographic samples.

TABLE 1. Summary of antimicrobial activity at individual MIC values of LBM415 tested against 13 organism groups including 10,903 isolates (all regions).

Organisms (no. tested)	Cumulative % inhibited at MIC (µg/ml): ≤0.25	0.5	1	2	4	8	16	32	>32
Gram-positive									
S. aureus (4,931)	18	48	92	99	99	99	99	99	100
Coagulase-negative staphylococci (1,190)[a]	28	51	87	99	100	-	-	-	-
S. pneumoniae (1,423)	32	69	91	99	100	-	-	-	-
viridans group streptococci (122)	83	93	99	100	-	-	-	-	-
ß-haemolytic streptococci (421)	41	68	97	100	-	-	-	-	-
Enterococci (1,319)[b]	4	12	33	69	96	100	-	-	-
E. faecalis (916)	2	6	20	58	94	100	-	-	-
E. faecium (361)	9	25	63	93	100	-	-	-	-
Other Gram-positive species (44)[c]	73	79	86	100	-	-	-	-	-
Gram-negative									
H. influenzae (990)	3	15	49	75	90	98	99	100	-
M. catarrhalis (27)	89	96	96	100	-	-	-	-	-
B. cepacia (22)	-	-	-	9	32	77	82	86	100
S. maltophilia (211)	<1	1	3	11	44	80	93	98	100

a. Includes *S. auricularis* (four strains), *S. capitis* (18 strains), *S. chromogenes* (one strains), CoNS (531 strains), *S. cohnii* (one strain), *S. epidermidis* (462 strains), *S. haemolyticus* (60 strains), *S. hominis* (50 strains), *S. intermedius* (one strain), *S. lugdunensis* (eight strains), *S. saprophyticus* (14 strains), *S. schleiferi* (one strain), *S. simulans* (six strains), *Staphylococcus* spp. (11 strains), *S. warnerii* (17 strains) and *S. xylosis* (four strains).
b. Includes *E. avium* (14 strains), *E. casseliflavus* (four strains), *E. durans* (one strain), *E. faecalis* (916 strains), *E. faecium* (361 strains), *E. gallinarum* (12 strains), *E. hirae* (three strains), *E. raffinosus* (three strains) and *Enterococcus* spp. (15 strains).
c. Isolates include *Aerococcus* spp. (two strains), *Bacillus* spp. (10 strains), *Corynebacterium* spp. (seven strains), *Leuconostoc* spp. (one strain), *Listeria* spp. (eight strains), *Micrococcus* spp. (10 strains) and *Rothia* spp. (one strain).

TABLE 2. Comparative activity screen of LBM415, a deformylase inhibitor, and selected comparison classes of antimicrobial agents tested against staphylococci (6,066 strains), streptococci (1,966 strains) and enterococci (1,275 strains; all regions).

Antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% susceptible[a]	% resistant[a]
S. aureus					
oxacillin-susceptible (2,963)					
LBM415	0.5	1	0.03->32	-[b]	-[b]
Erythromycin	0.25	>8	≤0.06->8	80.0	18.8
Clindamycin	0.12	0.12	≤0.06->8	96.4	3.1
Doxycycline	≤1	≤1	≤1->8	98.5	0.2
Gentamicin	≤2	≤2	≤2->8	98.5	1.3
Levofloxacin	0.12	0.25	≤0.03->4	94.9	4.9
Linezolid	2	2	0.12-2	100.0	-
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25->2	99.9	0.1
Vancomycin	1	1	0.25-2	100.0	0.0
oxacillin-resistant (1,968)					
LBM415	1	1	≤0.016->8	-[b]	-[b]
Erythromycin	>8	>8	≤0.06->8	10.4	88.9
Clindamycin	>8	>8	≤0.06->8	41.8	58.1
Doxycycline	≤1	4	≤1->8	91.7	1.4
Gentamicin	≤2	>8	≤2->8	74.1	24.9
Levofloxacin	>4	>4	≤0.03->4	17.1	80.3
Linezolid	2	2	0.25-4	100.0	-
Quinupristin/Dalfopristin	0.5	0.5	≤0.25->2	99.8	0.2
Vancomycin	1	1	0.25-4	100.0	0.0
Coagulase-neg. staphylococci					
oxacillin-susceptible (250)					
LBM415	1	2	≤0.016->4	-[b]	-[b]
Erythromycin	0.25	>8	≤0.06->8	65.2	34.8
Clindamycin	≤0.06	0.12	≤0.06->8	92.4	7.2
Doxycycline	≤1	2	≤1->8	94.4	0.8
Gentamicin	≤2	≤2	≤2->8	94.0	3.2
Levofloxacin	0.25	0.5	≤0.03->4	90.4	9.6
Linezolid	1	1	0.5-2	100.0	-[b]
Quinupristin/Dalfopristin	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
Vancomycin	1	2	0.25-2	100.0	0.0
oxacillin-resistant (885)					
LBM415	0.5	2	≤0.016->4	-[b]	-[b]
Erythromycin	>8	>8	≤0.06->8	21.6	77.6
Clindamycin	0.25	>8	≤0.06->8	52.8	46.0
Doxycycline	≤1	4	≤1->8	91.8	2.0
Gentamicin	4	>8	≤2->8	50.2	33.9
Levofloxacin	4	>4	0.06->4	35.1	54.4
Linezolid	1	1	0.25-2	100.0	-[b]
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25->2	99.1	0.3
Vancomycin	1	2	≤0.12-4	100.0	0.0
S. pneumoniae					
penicillin-susceptible (925)					
LBM415	0.5	2	≤0.016-4	-[b]	-[b]
Ceftriaxone	≤0.25	≤0.25	≤0.25-1	100.0	0.0
Erythromycin	≤0.25	2	≤0.25->32	88.0	10.9
Clindamycin	≤0.25	≤0.25	≤0.25->8	95.0	4.5
Quinupristin/Dalfopristin	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Levofloxacin	1	1	0.12->4	98.4	1.6
Chloramphenicol	4	4	≤2->16	99.1	0.9
Rifampin	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Vancomycin	0.25	0.5	≤0.06-0.5	100.0	-
penicillin-intermediate (248)					
LBM415	0.5	1	≤0.016->2	-[b]	-[b]
Ceftriaxone	0.12	0.5	≤0.008-4	99.6	0.4
Erythromycin	1	>32	≤0.06->32	48.8	50.8
Clindamycin	≤0.25	>2	≤0.25->2	74.6	23.8
Quinupristin/Dalfopristin	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Levofloxacin	1	1	0.25->4	99.2	0.8
Chloramphenicol	4	4	≤0.5->2	99.2	0.8
Rifampin	≤0.5	≤0.5	≤0.5->2	99.2	0.8
Vancomycin	0.25	0.5	≤0.06-1	100.0	-
penicillin-resistant (250)					
LBM415	0.5	1	0.06-2	-[b]	-[b]
Ceftriaxone	1	2	≤0.008-8	87.6	2.8
Erythromycin	4	>32	≤0.06->32	30.8	68.8
Clindamycin	≤0.25	>2	≤0.25->2	56.0	42.4
Quinupristin/Dalfopristin	≤0.5	1	≤0.5-1	100.0	0.0
Levofloxacin	1	1	0.5->4	99.6	0.4
Chloramphenicol	4	16	≤2->16	81.2	18.8
Rifampin	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
ß-haemolytic streptococci (421)					
LBM415	0.5	1	0.06-2	-[b]	-[b]
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	-[b]
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
Erythromycin	≤0.06	8	≤0.06->8	79.8	19.7
Clindamycin	≤0.06	≤0.06	≤0.06->8	92.7	6.7
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25-1	100.0	0.0
Linezolid	1	1	0.25-2	100.0	-[b]
Levofloxacin	0.5	1	0.12->4	99.0	1.0
Vancomycin	0.5	0.5	≤0.12-1	100.0	-[b]
viridans group streptococci (122)					
LBM415	0.12	0.5	≤0.016-2	-[b]	-[b]
Penicillin	0.06	4	≤0.016-32	61.5	10.7
Ceftriaxone	≤0.25	2	≤0.25-16	89.3	6.6
Erythromycin	1	4	≤0.06->8	47.5	50.8
Clindamycin	≤0.06	4	≤0.06->8	87.7	11.5
Quinupristin/Dalfopristin	0.5	1	≤0.25-2	97.5	0.0
Linezolid	1	1	0.12-2	100.0	-[b]
Levofloxacin	1	1	≤0.03->4	96.7	3.3
Vancomycin	0.5	1	≤0.12-1	100.0	-[b]
Enterococcus faecalis					
vancomycin-susceptible (894)					
LBM415	2	4	0.03-8	-[b]	-[b]
Ampicillin	≤1	2	≤1->16	99.4	0.6
Chloramphenicol	8	>16	≤2->16	78.1	21.4
Levofloxacin	1	>4	0.06->4	68.1	31.7
Gentamicin (high-level)	≤500	>1000	≤500->1000	67.0	33.0
Streptomycin (high-level)	≤1000	>2000	≤1000->2000	69.2	30.8
Quinupristin/Dalfopristin	>2	>2	≤0.5->2	0.3	96.1
Linezolid	2	2	0.5->8	99.8	0.2
Teicoplanin	0.25	0.25	≤0.12-4	100.0	0.0
vancomycin-resistant (21)					
LBM415	4	4	0.5-8	-[b]	-[b]
Ampicillin	2	8	≤1-16	95.2	4.8
Chloramphenicol	8	>16	4->16	52.4	42.9
Levofloxacin	>4	>4	>4	0.0	100.0
Gentamicin (high-level)	>1000	>1000	≤500->1000	14.3	85.7
Streptomycin (high-level)	≤1000	>2000	≤1000->2000	66.7	33.3
Quinupristin/Dalfopristin	>2	>2	1->2	4.8	95.2
Linezolid	1	2	1->8	90.5	9.5
Teicoplanin	>16	>16	≤0.12->16	28.6	71.4
Enterococcus faecium					
vancomycin-susceptible (187)					
LBM415	1	2	0.06-4	-[b]	-[b]
Ampicillin	>16	>16	≤1->16	17.1	82.9
Chloramphenicol	8	16	≤2->16	82.8	6.5
Levofloxacin	>4	>4	0.06->4	21.9	70.6
Gentamicin (high-level)	≤500	>1000	≤500->1000	77.5	22.5
Streptomycin (high-level)	≤1000	>2000	≤1000->2000	55.6	44.4
Quinupristin/Dalfopristin	1	2	≤0.25->2	75.9	7.0
Linezolid	2	2	0.5-2	100.0	0.0
Teicoplanin	0.5	0.5	≤0.12-1	100.0	0.0
vancomycin-resistant (173)					
LBM415	1	2	≤0.016-4	-[b]	-[b]
Ampicillin	>16	>16	2->16	1.7	98.3
Chloramphenicol	8	8	≤2->16	97.1	1.2
Levofloxacin	>4	>4	1->4	2.9	97.1
Gentamicin (high-level)	≤500	>1000	≤500->1000	60.7	39.3
Streptomycin (high-level)	>2000	>2000	≤1000->2000	32.9	67.1
Quinupristin/Dalfopristin	0.5	1	≤0.25->2	94.8	1.2
Linezolid	2	2	0.5-8	98.8	0.6
Teicoplanin	>16	>16	0.25->16	7.5	71.7
Other Gram-pos. species (44)[c]					
LBM415	0.25	2	0.03-2	-[b]	-[b]

a. Susceptibility criteria of the CLSI [2005].
b. No criteria have been established.
c. Isolates include *Aerococcus* spp. (two strains), *Bacillus* spp. (10 strains), *Corynebacterium* spp. (seven strains), *Leuconostoc* spp. (one strain), *Listeria* spp. (eight strains), *Micrococcus* spp. (19 strains) and *Rothia* spp. (one strain).

Table 3. Comparative antimicrobial activity screen of LBM415, a deformylase inhibitor, tested against *H. influenzae* (982 strains) and *M. catarrhalis* (27 strains; all regions).

Antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% susceptible[a]	% resistant[a]
H. influenzae					
ampicillin-susceptible (756)					
LBM415	1	4	0.03-32	-[b]	-[b]
Amoxicillin/Clavulanate	0.5	1	≤0.06-4	100.0	0.0
Ceftriaxone	≤0.008	0.016	≤0.008-1	100.0	-[b]
Chloramphenicol	≤2	≤2	≤2-8	99.6	0.1
Rifampin	≤0.25	0.5	≤0.25->2	99.5	0.1
Levofloxacin	≤0.03	≤0.03	≤0.03-0.25	100.0	-[b]
Azithromycin	1	2	≤0.06-4	100.0	-[b]
Clarithromycin	8	16	≤0.25->32	89.4	0.1
Quinupristin/Dalfopristin	4	>4	≤0.5->4	-[b]	-[b]
ampicillin-resistant (226)					
LBM415	2	8	0.06-16	-[b]	-[b]
Amoxicillin/Clavulanate	0.5	2	0.25-4	100.0	0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	-[b]
Chloramphenicol	≤2	≤2	≤2-16	95.1	3.1
Rifampin	≤0.25	≤0.25	≤0.25-1	100.0	0.0
Levofloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0	-[b]
Azithromycin	1	2	0.12->8	98.7	-[b]
Clarithromycin	8	16	≤0.25->32	87.0	2.2
Quinupristin/Dalfopristin	4	>4	≤0.5->4	-[b]	-[b]
***M. catarrhalis* (27)**					
LBM415	0.25	0.5	0.03-2	-[b]	-[b]
Amoxicillin/Clavulanate	≤1	≤1	≤1-2	100.0	0.0
Levofloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0	-[b]
Azithromycin	≤0.06	-	≤0.06-0.12	100.0	-
Clarithromycin	≤0.25	-	≤0.25-0.5	100.0	0.0
Rifampin	≤0.25	≤0.25	≤0.25	100.0	0.0
Tetracycline	≤0.25	0.5	≤0.25-0.5	100.0	0.0
Quinupristin/Dalfopristin	≤0.5	-	≤0.5-4	-[b]	-[b]

a. Susceptibility criteria of the CLSI [2005]. Breakpoints for *H. influenzae* were applied for interpretation of *M. catarrhalis* results.
b. No criteria have been established.

CONCLUSIONS

- LBM415 displays a broad-spectrum of activity against the common Gram-positive pathogens, including resistant subsets, with no regional differences in potency apparent.
- The majority of Gram-negative fastidious species (*H. influenzae* and *M. catarrhalis*) were also inhibited by LBM415.
- As a class of antimicrobials, the peptide deformylase inhibitor compounds exhibit a spectrum of activity and unique mode of action that promises to be a significant advance in chemotherapy targeting infections of the respiratory tract and skin and skin structure.
- Examination of additional candidate compounds to optimize spectrum and potency is warranted.

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