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Spectrum and Potency of a New Peptide Deformylase Inhibitor, NVP-PDF386

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ABSTRACT

Background: Peptide deformylase (PDF) has been recognized as a novel new target and several PDF inhibitors have been described. NVP-PDF386 is a new PDF candidate that exhibits inhibitory qualities against this essential bacterial metalloprotease. The spectrum and activity was assessed by reference (NCCLS) methods against recent clinical isolates.

Methods: NVP-PDF386 was obtained from Novartis Pharmaceuticals and was diluted in broth microdilution trays with seven comparison agents. The clinical strains were isolated in 2001-2002, and included over 1,000 organisms such as *S. aureus* (104), CoNS (49), *Streptococcus* spp. (320), enterococci (104), *H. influenzae* (308), *M. catarrhalis* (103), Enterobacteriaceae (112) and non-fermentative Gram-negative bacilli (107). NCCLS methods were used throughout with recommended controls and medium supplements.

Results: The $MIC_{50/90}$ (in µg/ml) for NVP-PDF386 were: *S. aureus* 0.5/1, CoNS 0.5/1, *S. pneumoniae* 0.25/0.5, *S. pyogenes* 0.5/0.5, *S. agalactiae* 0.25/0.25, other ß-haemolytic spp. 0.5/1, viridans gr. streptococci 0.25/0.5, enterococci 1/2, *M. catarrhalis* 0.25/0.25, *H. influenzae* 8/32, enteric and non-fermentative bacilli >32/>32. No differences in NVP-PDF386 MIC distributions were observed between MRSA and MSSA, MR-CoNS and MS-CoNS, penicillin susceptible (S) and less-S streptococci and macrolide S and R strains. NVP-PDF386 spectrum and potency compared favorably to control glycopeptides (2), oxazolidinones (2), streptogramin combinations (1) and other agents focused against Gram-positive cocci (GPC).

Conclusions: NVP-PDF386, a novel PDF-inhibitor possesses a potency equal or greater than linezolid against key GPC (MIC_{90}, 0.25-2) and *M. catarrhalis*, but a more limited activity was identified versus Gram-negative bacilli and *H. influenzae*. Further studies appear warranted for the PDF class against multi-R GPC.

INTRODUCTION

Peptide deformylase (PDF) is a prokaryotic metalloprotease that is essential for bacterial growth. This enzyme deformylates the N-terminal formyl group of new bacterial polypeptides. PDF is highly conserved across bacterial species and intracellular pathogens including *Chlamydia* and mycoplasma. There is no evidence of cross resistance between PDF inhibitors and any other class of antimicrobial agent, making these agents attractive prospects for clinical development.

MATERIALS AND METHODS

NVP-PDF386 laboratory standard powder was obtained from Novartis Pharmaceuticals (Summit, NJ), and diluted into broth and incorporated into microdilution trays for susceptibility testing. Twenty comparator agents were tested from the glycopeptide, streptogramin, oxazolidinone, penicillin, macrolide, lincosamide, quinolone, aminoglycoside, tetracycline, phenicols, and folate pathway inhibitor classes. A total of 1,264 recent clinical strains from the SENTRY Antimicrobial Surveillance Program (2001 - 2002) were tested. Isolates were selected to over represent key resistance mechanisms within individual species (see Tables 2-5).

National Committee for Clinical Laboratory Standards (NCCLS) susceptibility methods (2000) and interpretative criteria (2002) were utilized. All testing was performed in cation-adjusted Mueller-Hinton broth, except Haemophilus (Haemophilus Test Medium) and streptococci (Mueller-Hinton broth supplemented with 3 to 5% lysed horse blood). Concurrent quality control was performed with *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619, and *Haemophilus influenzae* ATCC 49247.

RESULTS

- NVP-PDF386 was most active against *M. catarrhalis*, *S. pneumoniae*, and *Streptococcus* spp., not pneumococci with 100, 98, and 97% of strains inhibited at ≤ 0.5 µg/ml MIC, respectively (Table 1).
- Antimicrobial activity of NVP-PDF386 was generally equal to vancomycin, teicoplanin, linezolid, and quinupristin/dalfopristin against most Gram-positive cocci. Multidrug-resistant phenotypes among various species did not show increased MIC values to NVP-PDF386.
- NVP-PDF386 activity was superior to vancomycin, teicoplanin, quinupristin/dalfopristin, and linezolid against enterococci.
- The widest range of NVP-PDF386 MIC values was observed for *H. influenzae* (≤ 0.016 - > 32 µg/ml). The MIC_{50} (8 µg/ml) was identical for ß-lactamase-positive and -negative isolates, results similar to clarithromycin.

Table 1. Summary of antimicrobial activity at individual MIC values of NVP-PDF386 tested against 11 organism groups.

	% inhibited at MIC values (µg/ml):					
Organism (no. tested)	≤0.25	0.5	1	2	4	8
Gram-positive						
S. aureus (104)	44	65	96	100	100	100
Coagulase-negative staphylococci (49)	29	65	96	100	100	100
S. pneumoniae (170)	82	98	100	100	100	100
Streptococcus spp., not *S. pneumoniae* (150)	75	97	99	100	100	100
Enterococci (104)	17	24	58	91	100	100
Other Gram-positive species (26)	46	58	81	85	89	92
Gram-negative						
H. influenzae (308)	2	2	4	15	41	75
M. catarrhalis (103)	90	100	100	100	100	100
Enterobacteriaceae (112)	0	0	0	0	0	0
Non-fermentative GNR (107)	0	0	0	0	1	2
Gram-positive/-negative						
Anaerobes (31)	58	84	84	94	100	100

Table 2. Comparative antimicrobial activity screen of NVP-PDF386, a deformylase inhibitor, tested against *S. aureus* (104 strains).

	MIC (µg/ml):			
Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
NVP-PDF386	0.5	1	0.06-2	(-/-)[b]
Vancomycin	1	1	0.5-4	100/0
Teicoplanin	0.5	2	0.25-4	100/0
Quinupristin/dalfopristin	0.25	0.5	0.12-2	99/0
Linezolid	2	2	0.5-2	100/0
Oxacillin	2	>8	0.25->8	51/49
Erythromycin	>8	>8	0.12->8	47/51
Clindamycin	0.12	>8	≤0.06->8	64/36
Ciprofloxacin	0.5	>2	0.03->2	60/39
Chloramphenicol	8	>16	≤2->16	78/19
Tetracycline	≤4	>8	≤4->8	80/19
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	84/15

a. Susceptibility criteria of the NCCLS [2002].
b. No criteria have been established.

Table 3. Comparative antimicrobial activity screen of NVP-PDF386, a deformylase inhibitor, tested against *Enterococcus* spp. (104 strains).

	MIC (µg/ml):			
Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
NVP-PDF386	1	2	0.06-4	(-/-)[b]
Vancomycin	2	>16	0.5->16	71/28
Teicoplanin	0.25	>16	≤0.12->16	79/19
Quinupristin/dalfopristin	4	>8	0.25->8	26/59
Linezolid	2	2	0.5->8	96/4
Ampicillin	≤2	>16	≤2->16	71/29
Gentamicin[c]	≤500	>1000	≤500->1000	32/46
Streptomycin[c]	≤1000	>2000	≤1000->2000	63/37
Ciprofloxacin	>2	>2	0.5->2	40/56
Chloramphenicol	8	>16	≤2->16	77/18
Tetracycline	>8	>8	≤4->8	43/57
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	64/35

a. Susceptibility criteria of the NCCLS [2002].
b. No criteria have been established.
c. High-level resistance screens among Enterococcus spp. only.

Table 4. Comparative antimicrobial activity screen of NVP-PDF386, a deformylase inhibitor, tested against *S. pneumoniae* (170 strains).

	MIC (µg/ml):			
Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
NVP-PDF386	0.25	0.5	≤0.016-1	(-/-)b
Vancomycin	0.25	0.5	≤0.12-1	100/0
Quinupristin/dalfopristin	0.5	0.5	0.12-1	100/0
Linezolid	0.5	0.5	0.25-1	100/0
Amoxicillin/clavulanate	0.25	4	≤0.06->	89/5
Penicillin	0.25	4	≤0.03->4	38/31
Erythromycin	≤0.25	>32	0.25->32	61/38
Clindamycin	≤0.12	>8	≤0.12->8	77/22
Levofloxacin	1	1	0.5-2	100/0
Chloramphenicol	4	16	≤2->16	82/18
Tetracycline	≤2	>16	≤2->16	61/39
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	50/42

a. Susceptibility criteria of the NCCLS [2002].
b. No criteria have been established.

Table 5. Comparative antimicrobial activity screen of NVP-PDF386, a deformylase inhibitor, tested against *H. influenzae* (308 strains).

	MIC (µg/ml):			
Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
NVP-PDF386	8	32	≤0.016->32	(-/-)[b]
Quinupristin/dalfopristin	4	4	0.12->8	(-/-)[b]
Amoxicillin/clavulanate	1	2	≤0.06->8	97/1
Ampicillin	≤2	>4	≤2->4	60/40
Azithromycin	1	2	≤0.12->16	>99/<1
Clarithromycin	8	16	≤0.25->32	86/2
Ciprofloxacin	≤0.03	≤0.03	≤0.03-0.25	100/0
Levofloxacin	≤0.03	≤0.03	≤0.03-0.25	100/0
Chloramphenicol	≤2	≤2	≤2-16	>99/<1
Tetracycline	≤2	≤2	≤2-8	>99/<1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	77/22

a. Susceptibility criteria of the NCCLS [2002].
b. No criteria have been established.

CONCLUSIONS

- NVP-PDF386 is a novel PDF inhibitor that possesses a potency equal to or greater than that of the new oxazolidinone class of antimicrobials when tested against staphylococci, streptococci and enterococci.
- NVP-PDF386 demonstrates no evidence of cross resistance to other antimicrobials including penicillins (ampicillin, oxacillin, penicillin), macrolides, vancomycin, linezolid, or ciprofloxacin.
- The potency and spectrum of activity of this PDF inhibitor class of antimicrobial agents warrants further evaluation.

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