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In Vitro Antibacterial Spectrum of BC-3205, a Novel Pleuromutilin Derivative for Oral Use in Humans

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Abstract

Background: BC-3205 [14-*O*-[(*N*-((*R*)-Valyl)-piperidin-3(*S*)-yl)sulfanyl)-acetyl]-mutilin-hydrochloride] is a novel semi-synthetic pleuromutilin derivative that inhibits prokaryotic protein synthesis. BC-3205 is in early stage of clinical development for oral treatment of skin and skin structure infections (SSSI) and community-acquired pneumonia (CAP). We assessed BC-3205 antimicrobial activity against a wide range of clinical isolates.

Methods: BC-3205 and comparators were susceptibility (S) tested by CLSI broth microdilution methods (M07-A8, 2009) against 1063 recent clinical isolates (mainly from 2006-2007) from the USA and Europe that were collected from the SENTRY Antimicrobial Surveillance Program.

Results: BC-3205 was highly active against *Staphylococcus* spp. and *Streptococcus* spp. including methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC_{90} 0.12 µg/ml), community-acquired (CA-MRSA) (MIC_{90} 0.06 µg/ml) and penicillin-resistant *Streptococcus pneumoniae* (PEN-R SPN) (MIC_{90} 0.12 µg/ml). Against *S. aureus*, BC-3205 was 16- to 32-fold more potent than linezolid (LZD). Against PEN-R SPN, BC-3205 was 8-fold more active than levofloxacin (LEV) or LZD. BC-3205 exhibited significant activity against vancomycin (VAN)-resistant (R) *E. faecium* (Efm) (MIC_{90} 0.5 µg/ml), *S. pyogenes* (MIC_{90} 0.03 µg/ml), *S. agalactiae* (MIC_{90} 0.06 µg/ml), *H. influenzae* (MIC_{90} 4 µg/ml) and *M. catarrhalis* (MIC_{90} range, 0.25 µg/ml).

Conclusions: BC-3205 exhibited potent antimicrobial activity against the most prevalent Gram-positive pathogens involved in SSSI and pathogens causing CAP, being more active against staphylococci and streptococci than many antimicrobials currently available for oral use.

Introduction

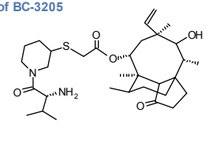
BC-3205 is a novel semi-synthetic pleuromutilin derivative (Figure 1). Pleuromutilin-derived antibiotics are inhibitors of ribosomal protein synthesis interacting with the rRNA of the ribosomal peptidyl transferase cavity. More specifically, foot-printing analysis revealed that pleuromutilins interfere with the central part of domain V of the 23S rRNA, where they prevent the correct positioning of the CCA-ends of tRNAs for peptide transfer and where they are thought to block translation initiation.[1-5]

BC-3205 is being developed for oral treatment of skin and skin structure infections (SSSI) and community-acquired pneumonia (CAP) as it exhibits potent antibacterial activity against common bacterial pathogens causing SSSI and CAP including *Staphylococcus aureus* (MSSA, MRSA and CA-MRSA), *Streptococcus pyogenes*, *S. agalactiae*, *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophilia*.

Of increasing concern is the rising frequency of SSSI caused by MRSA. Being highly endemic in certain geographic regions, especially multi-resistant phenotypes and the high prevalence of community-acquired MRSA (CA-MRSA), in particular the highly virulent clone USA300, are considered to be a substantial threat to public health.

In this study we present the antibacterial activity of BC-3205 against predominant pathogens causing SSSI and CAP including multi-resistant clinical isolates and CA-MRSA.

Figure 1: Structure of BC-3205



Methods

Organism Collection: The activity of BC-3205 was determined against bacterial pathogens causing SSSI and CAP. Organisms included strains isolated from patients in either the United States (USA, 52.3%) or European (47.6%) medical centers (n=67) during 2006 to 2007. Less commonly isolated species and those organisms with characterized resistance mechanism were included from 2005 (7.8%), 2004 (4.7%) and 2000-2003 (7.2%). Most of the isolates were from patients with bloodstream infections (63.1%), respiratory tract infections (29.6%) and skin and skin structure infections (5.6%).

Organisms examined (n=1013) included methicillin-susceptible *S. aureus* (MSSA, 151), methicillin-resistant *S. aureus* (MRSA, 102), community-acquired MRSA (CA-MRSA, 50), *S. pneumoniae* (SPN, 157), penicillin-resistant *S. pneumoniae* (PEN-R SPN, 52), *S. pyogenes* (50), Vancomycin-susceptible *E. faecium* (VAN-S Efm, 51), vancomycin-resistant *E. faecium* (VAN-R Efm, 51), *H. influenzae* (102), *M. catarrhalis* (50), *C. pneumoniae* (2), *Mycoplasma* spp. (6) and *L. pneumophilia* (30).

Susceptibility test methods: MIC values of SSSI and typical CAP pathogens were determined according to CLSI guidelines (M07-A8, 2009 and M100-S19, 2009).[6] 96-well format panels were produced by JMI Laboratories using Mueller Hinton broth, cation adjusted MHB supplemented with 2-5% lysed horse blood for testing *Streptococcus* spp. or Haemophilus Test Medium for testing *H. influenzae*. Interpretive criteria for comparator antibiotics were used as published by CLSI (M100-S19, 2009).[7] Susceptibility of *C. pneumoniae*, *Mycoplasma* spp. and *L. pneumophilia* was determined by Nabriva Therapeutics and as described earlier.[8, 9, 7]

Quality control was performed as recommended by the CLSI using the following strains: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, *H. influenzae* ATTC 49247 and *E. faecalis* ATCC 29212.

Table 1. Antibacterial spectrum of BC-3205 and comparator antibiotics

Species		MIC_{90} [µg/ml]				
	n	BC-3205	LZD	AZI	CLI	LEV
MSSA	151	0.06	2	8	0.12	0.25
MRSA	102	0.12	2	>16	>16	>16
CA-MRSA[a]	50	0.06	2	>16	0.12	0.5
CoNS	105	0.12	2	>16	>16	>16
SPN	157	0.12	1	>16	>16	1
PEN-R SPN	52	0.12	1	>16	>16	1
S. pyogenes	50	0.03	1	0.12	0.06	0.5
VAN-S Efm	51	4	2	>16	>16	>16
VAN-R Efm	51	0.5	2	>16	>16	>16
H. influenzae	102	4	-	2	-	≤0.06
M. catarrhalis	50	0.25	-	≤0.5	-	≤0.06
C. pneumoniae[b]	2	0.01-0.04	-	0.08-0.16	-	-
Mycoplasma spp.[b, c]	6	≤0.0003-0.04	-	0.00015-6.4	0.2-0.8	-
L. pneumophilia[d]	30	0.5	-	0.12	-	-

Abbreviations: AZI, azithromycin; CLI, clindamycin; LEV, levofloxacin; LZD, linezolid; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CA-MRSA, community-acquired MRSA; CoNS, coagulase negative *Staphylococcus* spp.; SPN, *S. pneumoniae*; PEN-R SPN, penicillin-resistant SPN; VAN-S Efm, vancomycin-susceptible *E. faecium*; VAN-R Efm, vancomycin-resistant *E. faecium*

[a] CA-MRSA include USA300 clone (45) and USA400 clone (5); [b] Range is shown instead of MIC_{90}; [c] *M. pneumoniae* (n=4), *M. hominis* (n=1), *M. genitalium* (n=1); [d] MICs determined by microbroth dilution using charcoal supplemented BCYEα medium

Results

- The antibacterial activity of BC-3205 and comparator antibiotics is presented in Table 1 and the cumulative percentage of strains inhibited by BC-3205 is shown in Table 2.
- With a MIC_{50} value of 0.06 µg/ml and a MIC_{90} value of 0.12 µg/ml, BC-3205 was the most potent compound tested against *S. aureus*; 100.0% of isolates were inhibited by ≤0.12 µg/ml.
- The CA-MRSA isolates (USA300 and USA400 clones) resistant to macrolides and susceptible to the other tested antimicrobial classes were inhibited at BC-3205 concentrations of 0.06 -0.12 µg/ml, identical to that of MSSA isolates.
- *S. pyogenes* and other ß-hemolytic streptococci were highly susceptible to BC-3205 (*S. pyogenes* MIC_{90}, 0.03 µg/ml) with 100% being inhibited at 0.12 µg/ml.
- BC-3205 was also the most potent compound tested against CoNS with MIC_{90} (0.12 µg/ml) values being the same as for *S. aureus*.
- All *S. pneumoniae* were inhibited by ≤0.12 µg/ml of BC-3205, which was equally potent against penicillin-susceptible (MIC_{90}, 0.12 µg/ml), -intermediate (MIC_{90}, 0.06 µg/ml) and -resistant (MIC_{90}, 0.12 µg/ml) isolates. Overall, BC-3205 was the most potent agent tested against this species
- BC-3205 was also shown to be active against the fastidious Gram-negative respiratory pathogens *H. influenzae* (MIC_{90}, 4 µg/ml) and *M. catarrhalis* (MIC_{90}, 0.25 µg/ml) irrespective of ß-lactamase production.
- BC-3205 exhibited potent activity against *C. pneumoniae* (MIC range, 0.01-0.04 µg/ml), *Mycoplasma* spp. (MIC range ≤0.0003-0.04 *µg/ml*) and *L. pneumophilia* (MIC_{90}, 0.12 µg/ml), .
- BC-3205 also exhibited potent activity against vancomycin-susceptible and -resistant *E. faecium* with >90% of isolates being inhibited at ≤4 µg/ml whereas it was less active against *E. faecalis* (MIC_{90}, >16 µg/ml). Resistance to vancomycin had no effect on the MIC values obtained for BC-3205.
- BC-3205 was fully active against bacterial strains resistant to macrolides, clindamycin, fluoroquinolones and vancomycin.

Table 2. MIC frequency distributions of BC-3205 against 1013 bacterial isolates

Organism (no. tested)	Cumulative percentage of strains inhibited at each MIC [µg/ml]												
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
S. aureus (303)	-	-	0.3	87.5	100.0	-	-	-	-	-	-	-	-
Oxacillin-susceptible (151)	-	-	-	90.7	100.0	-	-	-	-	-	-	-	-
Oxacillin-resistant (102)	-	-	1.0	78.4	100.0	-	-	-	-	-	-	-	-
CA-Oxacillin-resistant (50)	-	-	-	96.0	100.0	-	-	-	-	-	-	-	-
Coagulase-negative staphylococci (105)	-	-	3.8	71.4	90.5	93.3	95.2	96.2	96.2	96.2	99.1	99.1	100.0
Oxacillin-susceptible (50)	-	-	6.0	88.0	98.0	98.0	98.0	98.0	98.0	98.0	100.0	-	-
Oxacillin-resistant (55)	-	-	1.8	56.4	83.6	89.1	92.7	94.6	94.6	94.6	98.2	98.2	100.0
E. faecium (102)	-	1.0	6.9	65.7	79.4	83.3	85.3	87.3	89.2	95.1	98.0	100.0	-
Vancomycin-susceptible (51)	-	-	2.0	54.9	70.6	78.4	78.4	78.4	82.4	92.2	98.0	100.0	-
Vancomycin-resistant (51)	-	2.0	11.8	76.5	88.2	88.2	92.2	96.1	96.2	98.0	98.0	100.0	-
Enterococcus spp. (22)	4.6	4.6	9.1	31.8	31.8	31.8	40.9	40.9	40.9	59.1	77.3	90.9	100.0
S. pneumoniae (157)	0.6	1.9	20.4	80.3	100.0	-	-	-	-	-	-	-	-
Penicillin-susceptible (54)	-	1.9	13.0	57.4	100.0	-	-	-	-	-	-	-	-
Penicillin-intermediate (51)	2.0	3.9	35.3	96.1	100.0	-	-	-	-	-	-	-	-
Penicillin-resistant (52)	-	-	13.5	88.5	100.0	-	-	-	-	-	-	-	-
Viridans group streptococci. (20)	5.0	15.0	55.0	85.0	100.0	-	-	-	-	-	-	-	-
Beta-hemolytic streptococci (152)	-	3.3	68.4	98.0	100.0	-	-	-	-	-	-	-	-
H. influenzae (102)	-	-	-	-	-	1.0	2.9	48.0	87.3	100.0	-	-	-
Beta-lactamase negative (51)	-	-	-	-	-	-	-	43.1	92.2	100.0	-	-	-
Beta-lactamase positive (51)	-	-	-	-	-	2.0	5.9	52.9	82.4	100.0	-	-	-
M. catarrhalis (50)	-	-	2.0	32.0	84.0	100.0	-	-	-	-	-	-	-

Conclusions

- BC-3205 shows promising activity against the most prevalent Gram-positive pathogens producing skin and skin structure infections, and also Gram-negative pathogens causing community-acquired respiratory tract infections.
- BC-3205 was very active against *S. aureus*, methicillin-susceptible and –resistant isolates including CA-MRSA, *S. pyogenes*, *S. pneumoniae* and other streptococcal species with 100% of strains being inhibited ≤0.12 µg/ml.
- Modest activity was found against *H. influenzae* and *E. faecium.*
- BC-3205 exhibited potent activity against the atypical pathogens: *C. pneumoniae*, *M. pneumoniae* and *L. pneumophilia*.
- No cross-resistance was observed with macrolides, lincosamides, fluoroquinolones and vancomycin.
- Overall, BC-3205 showed an activity profile being superior to many antibiotics currently in use for oral treatment of SSSI and CAP.

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