F1-1967

In Vitro Activity of the Novel Antibacterial MCB3681 Against Selected Gram-Positive and -Negative Bacteria Compared to Established Antibiotics

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San Francisco, CA, USA
September 27-30, 2006
46th ICAAC

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ABSTRACT

Background: MCB3681, the active metabolite of the water soluble prodrug MCB3837, is a novel antibiotic combining an oxazolidinone and a quinolone linked with a spacer. The objective of this study was to determine the comparative in vitro activities of MCB3681 against a panel of Gram+ and Gram- bacteria in order to characterize the antibacterial spectrum of MCB3681.

Methods: A total of 523 bacterial strains (394 Gram+ and 129 Gram-), most of which were collected during recent multicenter studies in Germany, were tested. MICs of isolates were determined by the broth microdilution method according to the guidelines of the CLSI. Antibacterial agents tested were MCB3681, ampicillin, ciprofloxacin (CIP), erythromycin (ERY), linezolid (LZD), moxifloxacin, oxacillin (OXA), penicillin (PEN), and vancomycin (VAN).

Results: MIC values of MCB3681 for all Gram+ bacteria including resistant isolates such as OXA-resistant staphylococci, VAN-resistant enterococci and streptococci with reduced susceptibility to PEN and/or ERY, ranged from 0.5 to 2 mg/L. It was active against CIP-susceptible- as well as CIP-resistant isolates. Members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* had MIC_{90} values of MCB3681 ranging from 16 to ≥ 64 mg/L, but MIC_{90}s of *Haemophilus influenzae* and *Moraxella catarrhalis* were 2 mg/L. The spectrum of MCB3681 is similar to that of LZD, but MCB3681 proved superior in terms of bactericidal activity. Additionally, MCB3681 was active against a LZD-resistant mutant of *Staphylococcus aureus* (MIC 2 mg/L).

Conclusions: MCB3681 appears to be a promising new antimicrobial agent for the treatment of infections caused by Gram-positive organisms including isolates resistant to currently available drugs.

BACKGROUND

MCB3681, the active component of the prodrug MCB3837, is a novel antibiotic combining the therapeutic moieties of two established antibiotic classes – quinolones (ciprofloxacin) and oxazolidinones (linezolid) – in one molecule. MCB3681 was discovered in the context of a research program for the synthesis of antimicrobial agents for parenteral treatment of infections caused by Gram-positive bacteria.

The present study was performed to provide data on the *in vitro* activities of MCB3681 compared to established drugs against a panel of selected Gram-positive and -negative bacteria including multiply resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA).

MATERIALS AND METHODS

Bacterial strains

A total of 523 aerobic bacterial strains were tested. Five hundred and eighteen isolates, of which 391 and 127 were Gram-positive and Gram-negative bacteria, respectively, were collected during recent multicenter studies in Germany:

- *Enterococcus faecalis* (n=33 including one VRE)
- *Enterococcus faecium* (n=19 including six VRE)
- methicillin-susceptible *Staphylococcus aureus* (MSSA, n=35)
- MRSA (n=33)
- methicillin-susceptible *Staphylococcus epidermidis* (MSSE, n=22)
- methicillin-resistant *Staphylococcus epidermidis* (MRSE, n=39)
- *Staphylococcus haemolyticus* (n=20)
- staphylococci belonging to other species (n=40)
- *Streptococcus pneumoniae* (n=62)
- *Streptococcus pyogenes* (n=41)
- *Streptococcus agalactiae* (n=15)
- streptococci belonging to other species (n=32)
- *Haemophilus influenzae* (n=36, of which 19 were β-lactamase-positive and 17 β-lactamase-negative)
- *Moraxella catarrhalis* (n=33, of which 2 β-lactamase-negative and 31 β-lactamase-positive)
- *Escherichia coli* (n=10), *Klebsiella pneumoniae* (n=13)
- *Proteus mirabilis* (n=10), *Enterobacter cloacae* (n=12)
- *Pseudomonas aeruginosa* (n=13).

S. pneumoniae and *S. pyogenes* were categorized based on their susceptibilities to penicillin (pneumococci only) and erythromycin, while isolates of *E. faecalis*, *S. aureus, S. epidermidis,* and *S. haemolyticus* were categorized according to their susceptibility to ciprofloxacin.

Additionally, five characterized strains were tested:

- *S. aureus* Mu50 (VISA),
- *S. aureus* Mu3 (heterogenous VISA)
- *S. aureus* T 1759 (a laboratory-generated linezolid-resistant mutant)
- two linezolid-susceptible mutants of *E. coli*: E. coli 1201, a mutant deficient for efflux and *E. coli* DC2 with a damaged outer membrane

Mu50 and Mu3 were kindly provided by Dr. Hiramatsu (Department of Bacteriology, Juntendo University, Tokyo, Japan) and T 1759 was a gift from T. A. Wichelhaus (Institute for Medical Microbiology, J.-W.-Goethe University, Frankfurt/Main, Germany). DC2 and 1201 were taken from our stock culture collection.

All isolates were identified by routine laboratory methods. For *H. influenzae* and *M. catarrhalis*, β-lactamase production was tested by the Cefinase disk method (Becton Dickinson, Heidelberg, Germany). All strains were stored at – 80°C until studied.

Susceptibility testing

Minimal inhibitory concentrations (MICs) for MCB3681, ampicillin, ciprofloxacin, erythromycin, linezolid, moxifloxacin, oxacillin, penicillin, and vancomycin were determined by the broth microdilution procedure with geometric two-fold serial dilutions in cation-adjusted Mueller-Hinton broth (CAMHB) according to the guidelines of the CLSI (formerly NCCLS, 1) using in-house prepared MIC plates. MCB 3681 and linezolid were provided by the sponsor. Moxifloxacin was obtained from Bayer Healthcare (Leverkusen, Germany), ampicillin and vancomycin were obtained from Sigma Aldrich (Steinheim, Germany), and ciprofloxacin, erythromycin, oxacillin as well as penicillin were obtained from Fluka Chemie (Buchs, Switzerland).

MIC interpretive criteria were those published by the CLSI (2). The accuracy of susceptibility testing was evaluated by MIC testing of quality control organisms.

RESULTS

Comparative activities of MCB3681 against the 518 clinical isolates are shown in **Table 1**. A summary of the in vitro activity of MCB 3681 and the other test items against the tested organisms is presented in **Table 2**. MICs of the five characterized isolates are displayed in **Table 3**.

Table 1: In vitro activity of MCB3681 in comparison to other antimicrobial agents against 518 aerobic bacterial isolates

Table 1a

Organism (Number of strains tested)	Antimicrobial agent	MIC (mg/L) Range	MIC_{50}	MIC_{90}	% SUS*	% RES*
Staphylococcus aureus, ciprofloxacin-susceptible MSSA (30)	MCB3681	0.25 - 1	0.5	1	-	-
	Linezolid	1 - 4	2	4	100	-
	Ciprofloxacin	0.125 - 0.5	0.25	0.5	100	0
	Moxifloxacin	0.125 - 0.25	0.125	0.25	100	0
	Oxacillin	0.125 - 2	0.25	0.25	100	0
	Vancomycin	0.5 - 2	1	1	100	0
Staphylococcus aureus, ciprofloxacin-resistant MSSA (5)	MCB3681	0.5	-	-	-	-
	Linezolid	2	-	-	-	-
	Ciprofloxacin	8 - ≥64	-	-	-	-
	Moxifloxacin	1 - ≥64	-	-	-	-
	Oxacillin	0.25 - 0.5	-	-	-	-
	Vancomycin	1	-	-	-	-
Staphylococcus aureus, ciprofloxacin-susceptible MRSA (3)	MCB3681	0.5	-	-	-	-
	Linezolid	2	-	-	-	-
	Ciprofloxacin	0.25 - 0.5	-	-	-	-
	Moxifloxacin	0.125 - 0.25	-	-	-	-
	Oxacillin	4 - 32	-	-	-	-
	Vancomycin	0.5 - 2	-	-	-	-
Staphylococcus aureus, ciprofloxacin-resistant MRSA (30)	MCB3681	0.25 - 1	1	1	-	-
	Linezolid	0.5 - 4	2	4	100	-
	Ciprofloxacin	16 - ≥64	≥64	≥64	0	100
	Moxifloxacin	1 - 32	4	8	0	86,7
	Oxacillin	8 - ≥64	≥64	≥64	0	100
	Vancomycin	0.5 - 2	1	1	100	0
Staphylococcus epidermidis, ciprofloxacin-susceptible MSSE (22)	MCB3681	0.25 - 1	0.5	0.5	-	-
	Linezolid	0.5 - 2	1	1	100	-
	Ciprofloxacin	0.125 - 1	0.25	0.25	100	0
	Moxifloxacin	0.125 - 0.5	0.125	0.25	100	0
	Oxacillin	0.063 - 0.25	0.125	0.125	100	0
	Vancomycin	0.5 - 2	1	2	100	0
Staphylococcus epidermidis, ciprofloxacin-susceptible MRSE (11)	MCB3681	0.25 - 1	0.5	0.5	-	-
	Linezolid	0.5 - 2	1	2	100	-
	Ciprofloxacin	0.125 - 1	0.25	1	100	0
	Moxifloxacin	0.125 - 1	0.125	0.5	90,9	0
	Oxacillin	1 - ≥64	16	≥64	0	100
	Vancomycin	1 - 2	2	2	100	0
Staphylococcus epidermidis, ciprofloxacin-resistant MRSE (28)	MCB3681	0.5 - 1	0.5	0.5	-	-
	Linezolid	0.5 - 2	1	2	100	-
	Ciprofloxacin	4 - ≥64	32	≥64	0	100
	Moxifloxacin	1 - 32	2	32	0	78,6
	Oxacillin	4 - ≥64	32	≥64	0	100
	Vancomycin	1 - 2	2	2	100	0
Staphylococcus haemolyticus, oxacillin-susceptible (8)	MCB3681	0.5 - 1	-	-	-	-
	Linezolid	1 - 2	-	-	-	-
	Ciprofloxacin	0.125 - 1	-	-	-	-
	Moxifloxacin	0.063 - 0.125	-	-	-	-
	Oxacillin	0.031 - 0.25	-	-	-	-
	Vancomycin	0.5 - 1	-	-	-	-
Staphylococcus haemolyticus, oxacillin-resistant (12)	MCB3681	0.25 - 1	0.5	1	-	-
	Linezolid	1 - 2	1	2	100	-
	Ciprofloxacin	0.25 - ≥64	16	≥64	8,3	91,7
	Moxifloxacin	1 - 32	2	32	8,3	66,7
	Oxacillin	4 - ≥64	32	≥64	0	100
	Vancomycin	1 - 2	2	2	100	0

Footnotes, see end of the table

Table 1b: Cont´d

Organism (Number of strains tested)	Antimicrobial agent	MIC (mg/L) Range	MIC_{50}	MIC_{90}	% SUS*	% RES*
Coagulase staphylococci other than *Staphylococcus epidermidis* or *Staphylococcus haemolyticus* (40°)	MCB3681	0.25 - 2	0.5	1	-	-
	Linezolid	0.5 - 4	2	2	100	-
	Ciprofloxacin	0.125 - 16	0.25	0.5	92,5	7,5
	Moxifloxacin	0.063 - 2	0.125	0.25	92,5	2,5
	Oxacillin	0.125 - ≥64	0.25	2	57,5	42,5
	Vancomycin	0.25 - 4	1	2	100	0
Enterococcus faecalis, susceptible or intermediate to ciprofloxacin (17)	MCB3681	0.5 - 1	1	1	-	-
	Linezolid	1 - 2	2	2	100	0
	Ciprofloxacin	1 - 2	2	2	76,5	0
	Moxifloxacin	0.25 - 2	0.5	1	-	-
	Ampicillin	0.5 - 2	1	2	100	0
	Vancomycin	1 - 2	2	2	100	0
Enterococcus faecalis, resistant to ciprofloxacin (16)	MCB3681	0.5 - 1	0.5	1	-	-
	Linezolid	0.5 - 2	1	2	100	0
	Ciprofloxacin	16 - ≥64	32	≥64	0	100
	Moxifloxacin	8 - 32	16	32	-	-
	Ampicillin	0.5 - 4	1	2	100	0
	Vancomycin	1 - ≥512	2	2	93,8	6,3
Enterococcus faecium (19)	MCB3681	0.5 - 2	1	2	-	-
	Linezolid	1 - 4	2	4	68,4	-
	Ciprofloxacin	1 - ≥64	32	≥64	15,8	73,7
	Moxifloxacin	0.5 - ≥64	8	≥64	-	-
	Ampicillin	1 - 128	64	≥512	15,8	84,2
	Vancomycin	0.5 - ≥512	2	2	68,4	31,6
Streptococcus pneumoniae, susceptible to penicillin and erythromycin (26)	MCB3681	0.125 - 0.5	0.5	0.5	-	-
	Linezolid	0.5 - 2	1	1	100	-
	Ciprofloxacin	0.5 - 16	1	2	-	-
	Moxifloxacin	0.125 - 4	0.25	0.25	96,2	3,8
	Penicillin	≤ 0.008 - 0.031	0.016	0.031	100	0
	Erythromycin	0.031 - 0.25	0.063	0.125	100	0
	Vancomycin	0.5 - 2	1	1	100	-
Streptococcus pneumoniae, susceptible to penicillin and resistant to erythromycin (16)	MCB3681	0.125 - 0.5	0.25	0.5	-	-
	Linezolid	0.5 - 2	0.5	1	100	-
	Ciprofloxacin	1 - 4	2	2	-	-
	Moxifloxacin	0.125 - 0.5	0.25	0.25	100	0
	Penicillin	0.016 - 0.063	0.031	0.063	100	0
	Erythromycin	1 - ≥32	4	≥32	0	100
	Vancomycin	0.5 - 1	0.5	1	100	-
Streptococcus pneumoniae, non-susceptible to penicillin and susceptible to erythromycin (9)	MCB3681	0.5 - 1	1	1	-	-
	Linezolid	1 - 2	-	-	-	-
	Ciprofloxacin	2 - ≥32	-	-	-	-
	Moxifloxacin	0.25 - 4	-	-	-	-
	Penicillin	0.25 - 1	-	-	-	-
	Erythromycin	0.063 - 0.125	-	-	-	-
	Vancomycin	0.25 - 1	-	-	-	-
Streptococcus pneumoniae, non-susceptible to penicillin and resistant to erythromycin (11)	MCB3681	0.125 - 1	0.5	0.5	-	-
	Linezolid	0.5 - 1	1	1	100	-
	Ciprofloxacin	1 - 2	1	2	-	-
	Moxifloxacin	0.125 - 0.25	0.25	0.25	100	0
	Penicillin	0.25 - 0.5	0.5	0.5	100	0
	Erythromycin	16 - ≥32	≥32	≥32	0	100
	Vancomycin	0.25 - 1	0.5	1	-	-

Footnotes, see end of the table

Table 1c: Cont´d

Organism (Number of strains tested)	Antimicrobial agent	MIC (mg/L) Range	MIC_{50}	MIC_{90}	% SUS*	% RES*
Streptococcus pyogenes, susceptible to erythromycin (27)	MCB3681	0.25 - 1	0.5	1	-	-
	Linezolid	0.5 - 2	1	2	-	-
	Ciprofloxacin	0.25 - 2	0.25	1	-	-
	Moxifloxacin	0.125 - 0.5	0.125	0.25	-	-
	Penicillin	≤ 0.008 - 0.016	≤ 0.008	0.016	100	-
	Erythromycin	0.063 - 0.25	0.125	0.25	100	0
	Vancomycin	0.25 - 1	0.5	1	100	-
Streptococcus pyogenes, resistant to erythromycin (14)	MCB3681	0.25 - 0.5	0.25	0.5	-	-
	Linezolid	0.5 - 2	1	1	100	-
	Ciprofloxacin	0.25 - 1	0.5	1	-	-
	Moxifloxacin	0.125 - 0.5	0.125	0.25	-	-
	Penicillin	≤ 0.008 - 0.016	≤ 0.008	0.016	100	-
	Erythromycin	1 - ≥32	8	≥32	0	100
	Vancomycin	0.5 - 1	0.5	1	100	-
Streptococcus agalactiae (15)	MCB3681	0.25 - 1	0.5	1	-	-
	Linezolid	1 - 2	2	2	100	-
	Ciprofloxacin	0.5 - 2	1	2	-	-
	Moxifloxacin	0.25 - 0.5	0.25	0.5	-	-
	Penicillin	0.031 - 0.063	0.063	0.063	100	-
	Erythromycin	0.031 - ≥32	0.125	≥32	80	20
	Vancomycin	0.25 - 1	0.5	1	100	-
Other streptococci° (32)	MCB3681	0.25 - 2	0.5	0.5	-	-
	Linezolid	0.25 - 2	1	1	100	-
	Ciprofloxacin	1 - 16	2	4	-	-
	Moxifloxacin	0.125 - 4	0.25	0.5	-	-
	Penicillin	0.016 - 8	0.031	0.25	75,0	6,3
	Erythromycin	0.031 - ≥32	0.125	8	50,0	50,0
	Vancomycin	0.25 - 1	0.5	1	100	-
Haemophilus influenzae, ß-lactamase-negative (19)	MCB3681	0.5 - 2	1	2	-	-
	Linezolid	4 - 16	8	16	-	-
	Ciprofloxacin	≤ 0.016	≤ 0.016	≤ 0.016	100	-
	Moxifloxacin	≤ 0.016 - 0.031	≤ 0.016	0.031	100	-
Haemophilus influenzae, ß-lactamase-positive (17)	Ampicillin	0.25 - 0.5	0.25	0.5	100	0
	MCB3681	0.5 - 2	0.5	1	-	-
	Linezolid	4 - 16	8	16	-	-
	Ciprofloxacin	≤ 0.016	≤ 0.016	≤ 0.016	100	-
	Moxifloxacin	≤ 0.016 - 0.031	≤ 0.016	0.031	100	-
	Ampicillin	16 - 64	32	64	0	100
Moraxella catarrhalis ß-lactamase-negative (2)	MCB3681	0.5 - 1	-	-	-	-
	Linezolid	0.031	-	-	-	-
	Ciprofloxacin	0.031 - 0.063	-	-	-	-
	Moxifloxacin	≤ 0.125	-	-	-	-
Moraxella catarrhalis, ß-lactamase-positive (31)	MCB3681	0.5 - 4	1	2	-	-
	Linezolid	2 - 8	4	8	-	-
	Ciprofloxacin	≤ 0.016 - 0.063	0.031	0.031	-	-
	Moxifloxacin	≤ 0.016 - 0.125	0.031	0.125	-	-
	Ampicillin	0.25 - 8	2	4	-	-

Table 1d: Cont´d

Organism (Number of strains tested)	Antimicrobial agent	MIC (mg/L) Range	MIC_{50}	MIC_{90}	% SUS*	% RES*
Escherichia coli (10)	MCB3681	4 - 32	8	16	-	-
	Linezolid	≥64	≥64	≥64	-	-
	Ciprofloxacin	≤ 0.016 - 0.031	0.031	0.031	100	0
	Moxifloxacin	0.063 - 0.25	0.125	0.125	-	-
	Ampicillin	4 - ≥512	4	256	80,0	20,0
Klebsiella pneumoniae (13)	MCB3681	16 - 32	16	32	-	-
	Linezolid	≥64	≥64	≥64	-	-
	Ciprofloxacin	≤ 0.016 - 0.063	0.031	0.063	100	0
	Moxifloxacin	0.125 - 0.5	0.125	0.5	-	-
	Ampicillin	32 - ≥512	32	256	0	100
Proteus mirabilis (10)	MCB3681	4 - 32	16	32	-	-
	Linezolid	≥64	≥64	≥64	-	-
	Ciprofloxacin	0.031 - 0.063	0.031	0.063	100	0
	Moxifloxacin	0.25 - 0.5	0.5	0.5	-	-
	Ampicillin	1 - 2	1	2	100	0
Enterobacter cloacae (12)	MCB3681	4 - 32	16	32	-	-
	Linezolid	≥64	≥64	≥64	-	-
	Ciprofloxacin	≤ 0.016 - 0.063	0.031	0.063	100	0
	Moxifloxacin	0.125 - 0.25	0.125	0.25	-	-
	Ampicillin	32 - ≥512	128	≥512	0	100
Pseudomonas aeruginosa (13)	MCB3681	≥64	≥64	≥64	-	-
	Linezolid	≥64	≥64	≥64	-	-
	Ciprofloxacin	0.125 - 0.5	0.25	0.5	100	0
	Moxifloxacin	1 - 4	2	4	-	-
	Ampicillin	≥512	≥512	≥512	-	-

*% SUS, % susceptible; % RES, % resistant
°intermediate to penicillin

°S. auricularis (n=2), S. capitis (n=4), S. hominis (n=8), S. lugdunensis (n=2), S. saprophyticus (n=6), S. sciuri (n=1), S. simulans (n=6), S. warneri (n=6), S. xylosus (n=4)

°S. acidominimus (n=1), S. anginosus (n=2), S. bovis (n=4), S. dysgalactiae (n=2), S. intermedius (n=1), S. mitis (n=8), S. oralis (n=8), S. salivarius (n=1), S. sanguinus (n=1), S. vestibularis (n=1), Streptococcus sp. (n=3)

Table 2: Summary of MIC_{90} values (in mg/L)

Organism	MCB3681	linezolid	ciprofloxacin	moxifloxacin	vancomycin
CS-MSSA	1	4	0,5	0,25	1
CR-MRSA	1	4	≥64	8	1
CS-MSSE	0,5	1	0,25	0,25	2
CS-MRSE	0,5	2	1	0,5	2
CR-MRSE	0,5	2	≥64	32	2
MRSH	1	2	≥64	32	2
Other CNS	1	2	0,5	0,25	2
CS *E. faecalis*	1	2	2	1	2
CR *E. faecalis*	1	2	≥64	32	2
E. faecium	2	4	≥64	≥64	≥512
S. pneumoniae	0,5	1	2	0,25	1
S. pyogenes	0,5 - 1	1 - 2	1	0,25	1
S. agalactiae	1	2	1	0,5	1
Other streptococci	0,5	1	4	0,5	1
H. influenzae	2	16	≤ 0,016	0,031	-
M. catarrhalis	2	16	0,031	0,125	-
E. coli	16	≥64	0,031	0,125	-
K. pneumoniae	32	≥64	0,063	0,5	-
P. mirabilis	32	≥64	0,063	0,5	-
E. cloacae	32	≥64	0,063	0,25	-
P. aeruginosa	≥64	≥64	0,5	4	-

Abbreviations: CS, ciprofloxacin-susceptible; CR, ciprofloxacin-resistant; MRSH, methicillin-resistant *Staphylococcus haemolyticus* ; CNS, coagulase-negative staphylococci

Table 3: In vitro activity of MCB3681 in comparison to other antibacterial agents against five characterized strains (MICs in mg/L)

Organism	MCB3681	linezolid	ciprofloxacin	moxifloxacin	vancomycin
S. aureus Mu50 (VISA)	1	2	32	4	8
S. aureus Mu3 (heterogenous VISA)	1	2	32	2	2
S. aureus T 1759 (linezolid-resistant)	2	≥64	0,25	0,063	2
E. coli 1201 (deficient for efflux)	2	4	2	1	-
E. coli DC2 (damaged outer membrane)	2	4	0,063	0,031	-

Gram-positive bacteria

MCB3681 was consistently active against all Gram-positive pathogens tested, regardless of resistance to comparator agents. It inhibited all strains at a concentration of 2 mg/L, while 386 (98.7%) isolates were inhibited by concentrations between 0.125 and 1 mg/L.

MCB3681 was uniformly active against ciprofloxacin-susceptible- and ciprofloxacin-resistant staphylococci. The MIC_{90}s against groups with at least ten strains tested (i.e. ciprofloxacin-susceptible MSSA, ciprofloxacin-resistant MRSA, ciprofloxacin-susceptible MSSE, ciprofloxacin-susceptible MRSE, ciprofloxacin-resistant MRSE, oxacillin-resistant *S. haemolyticus*, staphylococci belonging to other species than *S. epidermidis* or *S. haemolyticus*) ranged from 0.5 to 1 mg/L. Based on MIC_{90}s MCB3681 was 2-4-fold more active than linezolid against these groups of organisms. MCB3681 also had significant potency against VISA strains Mu50 and Mu3 (MICs 1 mg/L) as well as against linezolid-resistant strain T 1759 (MIC 2 mg/L).

MCB3681 had good activity against *E. faecalis*, with an MIC_{90} of 1 mg/L for both ciprofloxacin-susceptible and ciprofloxacin-resistant isolates. *E. faecium* had an MIC_{90} of 2 mg/L. Notably, 14 and six out of the 19 *E. faecium* strains were resistant to ciprofloxacin and vancomycin, respectively. The potency of MCB3681 against both species was 2-fold greater than that of linezolid.

MCB3681 was a potent inhibitor of streptococcal species, including isolates with reduced susceptibility to penicillin and/or erythromycin, with MIC_{90}s ranging from 0.5 to 1 mg/L. It was more active than linezolid or ciprofloxacin, but a less potent inhibitor of streptococci than moxifloxacin. Notably, MCB3681 also demonstrated high activity against two isolates of *S. pneumoniae* (L6-06-11 and L6-06-10) highly resistant to ciprofloxacin (MICs 16 and ≥ 64 mg/L), with MICs of 0.25 and 0.5 mg/L, respectively. The MIC of moxifloxacin for either isolate was 4 mg/L.

Gram-negative bacteria

MCB3681 was equally active against ß-lactamase-positive and -negative isolates of *H. influenzae*. Based on MIC_{90}s (2 mg/L), it was 8-fold more potent than linezolid (16 mg/L), but less potent than ciprofloxacin (MIC_{90} ≤ 0.016 mg/L) or moxifloxacin (MIC_{90} 0.031 mg/L).

MCB3681 also inhibited *M. catarrhalis*, with MICs of individual isolates ranging from 0.5 to 4 mg/l (MIC_{90} 2 mg/L). MCB 3681 was more potent than linezolid (MIC_{90} 4 mg/L), but less active than ciprofloxacin (MIC_{90} 0.031 mg/L) or moxifloxacin (MIC_{90} 0.125 mg/L).

MCB 3681 exhibited only moderate activity against members of the family *Enterobacteriaceae* (MIC_{90}s 16-32 mg/L). However, half of the *E. coli* isolates were inhibited at 4 mg/L. In contrast, MICs against linezolid were consistently ≥ 64 mg/L. Notably, MCB3681 had increased activity against linezolid-susceptible *E. coli* strains DC2 and 1201, with MICs of 2 mg/L.

All isolates of *P. aeruginosa* had MICs ≥ 64 mg/L for MCB 3681 and linezolid.

CONCLUSIONS

- MCB3681 was a potent inhibitor of Gram-positive organisms, with MIC_{90} values ranging from 0.5 to 2 mg/L. The highest MIC recorded was 2 mg/L.
- Notably, it was equally active against ciprofloxacin-susceptible- and cipro-floxacin-resistant strains. Additionally, MCB 3681 had activity against a linezolid-resistant mutant of *S. aureus*.
- Members of the family *Enterobacteriaceae* were moderately susceptible, while MCB3681 had greater activity against *H. influenzae* and *M. catarrhalis*. MCB3681 was not active against *P. aeruginosa*.
- In general, the spectrum of activity of MCB3681 was similar to that of linezolid, but MCB3681 was consistently more potent.
- A potential advantage of MCB 3681 over linezolid would be the activity against linezolid-resistant *S. aureus* and enterococci, which have emerged during linezolid treatment and can be transmitted from patient-to-patient (3-11).
- MCB3681 appears to be a promising new antimicrobial agent for the treatment of infections caused by Gram-positive organisms including isolates resistant to currently available drugs.

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