

In Vitro Characterization of a Novel Gyrase Inhibitor (SPR719) Against Nontuberculous Mycobacteria

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ABSTRACT

Background: Nontuberculous mycobacteria (NTM) infections are increasing dramatically globally. *Mycobacterium avium* complex (MAC) and *M. abscessus* are the most frequently encountered NTM among clinical laboratories, and treatment options are extremely limited. In this study, the *in vitro* potency of a novel gyrase inhibitor, SPR719, the microbiologically active form of the orally available prodrug SPR720, was tested against several species of NTM.

Methods: MICs were performed in cation adjusted Mueller Hinton Broth as described and recommended by the Clinical and Laboratory Standards Institute (CLSI M24-A2). Comparator antimicrobials included amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, imipenem, linezolid, minocycline, moxifloxacin, tigecycline, and trimethoprim/sulfamethoxazole (TMP/SMX) for the rapidly growing species (RGM); amikacin and clarithromycin for the MAC; amikacin, ciprofloxacin, clarithromycin, doxycycline, linezolid, moxifloxacin, rifabutin, rifampin and TMP/SMX for the other slowly growing NTM.

Results: Potency of SPR719 against 154 NTM organisms are found in the table.

Conclusions: SPR719 was found to be potent against multiple clinical strains of NTM with an MIC₅₀ range of 0.25 – 4 µg/mL for several species of NTM. These findings support the further advancement of SPR720 for the treatment of NTM disease.

INTRODUCTION

- Infections caused by nontuberculous mycobacteria (NTM) are increasing in prevalence due to improved recognition and diagnosis.
- NTM infections are generally difficult to treat since these organisms are resistant to most of the antituberculous drugs and therefore new agents are needed
- M. avium* complex (MAC) and the *M. abscessus* complex are the most common pathogens found
- Here we describe the *in vitro* activity of SPR719, a novel gyrase inhibitor, against MAC and *M. abscessus* in comparison to other antibacterial agents

METHODS

- MIC testing of SPR719 was performed by microbroth dilution using Mueller Hinton broth, consistent with M24-A2 CLSI methodology
- Comparator antibiotics included amikacin (AMK), cefoxitin (FOX), ciprofloxacin (CIP), clarithromycin (CLR), doxycycline (DOX), imipenem (IPM), linezolid (LZD), minocycline (MIN), moxifloxacin (MXF), tigecycline (TGC), and trimethoprim/sulfamethoxazole (SXT) for the rapidly growing species (RGM)
- Comparator antibiotics included AMK and CLR for the MAC
- Comparator antibiotics included AMK, CIP, CLR, DOX, LZD, MXF, rifabutin (RFB), rifampin (RIF) and SXT for the other slowly growing NTM

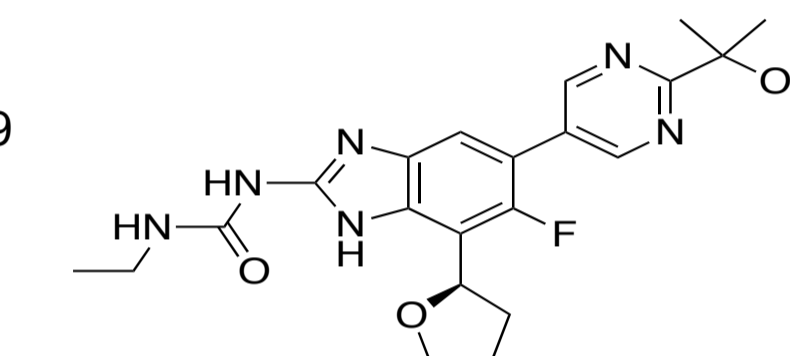
RESULTS

Table 1. SPR719 MIC (µg/mL) values against 161 isolates of nontuberculous mycobacteria

		<i>M. abscessus</i> subsp. <i>abscessus</i>	<i>M. abscessus</i> subsp. <i>massiliense</i>	<i>M. abscessus</i> / <i>massiliense</i> hybrid	<i>M. chelonae</i>	<i>M. immunogenum</i>	<i>M. fortuitum</i> group	<i>M. mucogenicum</i> group	<i>M. kansasii</i>	<i>M. marinum</i>	<i>M. simiae</i>	<i>M. avium</i>	<i>M. intracellulare</i>	MAC-X
	N of isolates	33	10	10	10	10	10	10	8	9	10	12	19	10
SPR719	MIC Range	0.25 – 8	0.12 – 4	0.06 – 2	2 – 4	4 – 8	0.06 – 1	0.015 – 0.25	0.002 – 0.015	0.12 – 1	0.5 – 4	0.5 – 2	0.12 – 2	0.12 – 1
	MIC ₅₀	2	2	2	4	4	0.25	0.06	0.015	0.5	1	0.5	0.5	1
	MIC ₉₀	4	2	2	4	8	1	0.25	0.03	0.5	2	2	2	1
AMK	MIC Range	2 - 64	4 – 16	8 – 16	16 – 32	8 – 16	≤1	≤1	2 - 8	≤1 - 2	8 - 32	8 - >64	8 - >64	8 - 32
	MIC ₅₀	8	16	16	16	8	≤1	≤1	4	≤1	16	16	16	8
	MIC ₉₀	16	16	16	32	16	≤1	≤1	8	2	16	64	>64	32
FOX	MIC Range	16 - 64	32 - 64	32 – 64	>128	>128	32 - 64	≤4 – 16						
	MIC ₅₀	64	64	32	>128	>128	64	8						
	MIC ₉₀	64	64	64	>128	>128	64	16						
SXT	MIC Range	4/76 - 8/152	4/76 - 8/152	4/76 - 8/152	≤2/38 - >4/76	2/38 - 8/152	≤0.25/4.75 - 1/19	≤0.25/4.75 - 0.5/9.5	≤0.12 - 0.25/4.75	≤0.25/4.75 - 1/19	1/19 - 4/76			
	MIC ₅₀	4/76	4/76	4/76	≥4/76	4/76	0.5/9.5	≤0.25/4.75	0.25/4.75	0.5/9.5	2/38			
	MIC ₉₀	8/152	8/152	8/152	≥4/76	8/152	1/19	0.5/9.5	0.25/4.75	1/19	4/76			
LZD	MIC Range	2 – 32	2 – 16	2 - 16	2 - 16	4 - 32	≤1 – 8	≤1 - 4	≤1 – 4	≤1 - 2	16 - >64	2 - 64	8 - >64	8 - 64
	MIC ₅₀	8	8	8	8	8	≤1	≤1	≤1	2	32	32	32	32
	MIC ₉₀	16	16	16	16	32	4	4	4	2	64	64	64	64
CIP	MIC Range	2 - >4	≥4	4 - >4	2 - >4	2 - 8	≤0.12	0.25 – 4	2 - 4	1 - 16	4 - >16			
	MIC ₅₀	>4	4	4	≥4	4	≤0.12	0.5	4	8	8			
	MIC ₉₀	>4	>4	>4	≥4	8	≤0.12	2	4	16	>16			
IPM	MIC Range	8 – 64	4 - 32	8 - 32	16 - 64	16 - 64	4 - 8	≤2						
	MIC ₅₀	16	8	16	16	32	4	≤2						
	MIC ₉₀	32	16	32	32	64	8	≤2						
MXF	MIC Range	2 - >8	2 – >8	4 - >8	4 - >8	4 - 8	≤0.25	≤0.25 - 1	≤0.12 - 0.5	0.25 - 4	1 - 8	0.5 - >8	1 - >8	0.5 - >8
	MIC ₅₀	8	8	4	4	4	≤0.25	≤0.25	≤0.12	1	4	1	4	4
	MIC ₉₀	>8	>8	>8	8	8	≤0.25	0.5	0.5	4	8	8	8	>8
DOX	MIC Range	>8	2 - >16	>16	0.12 - >16	8 - >16	0.12 - >16	≤0.12 - >16	1 - 16	2 – 16	≥16			
	MIC ₅₀	>8	>16	>16	>16	>16	>16	≤0.12	8	2	≥16			
	MIC ₉₀	>8	>16	>16	>16	>16	>16	>16	16	16	>16			
MIN	MIC Range	>16	4 - >8	>8	≤1 - >8	>8	≤1 - >8	≤1 - >8						
	MIC ₅₀	>16	8	>8	>8	>8	≤1	≤1						
	MIC ₉₀	>16	>8	>8	>8	>8	>8	>8						
TGC	MIC Range	0.06 - 0.5	0.06 - 0.5	0.06 - 0.25	0.06 - 0.5	0.06 - 0.25	0.03 - 0.12	≤0.25 - 0.25						
	MIC ₅₀	0.25	0.12	0.25	0.25	0.12	0.06	0.12						
	MIC ₉₀	0.5	0.5	0.5	0.5	0.25	0.12	0.25						
CLR	MIC Range	≤2 - >16	≤2	0.12 - 0.25	≤2	≤2	≤0.06 - >16	≤2	0.12 - 0.5	0.5 – 2	8 - >64	0.25 - >64	1 - >64	0.5 - 8
	MIC ₅₀	≥16	≤2	0.06	≤2	≤2	16	≤2	0.25	1	8	2	2	2
	MIC ₉₀	≥16	≤2	0.5	≤2	≤2	>16	≤2	0.5	2	32	8	>64	4
TOB	MIC Range				≤1 - 4	8 - 16								
	MIC ₅₀				≤2	8								
	MIC ₉₀				≤2	16								
RFB	MIC Range								≤0.25	≤0.25	4 - >8			
	MIC ₅₀								≤0.25	≤0.25	8			
	MIC ₉₀								≤0.25	≤0.25	>8			
RIF	MIC Range								≤0.12-1	0.5-1	>8			
	MIC ₅₀								0.25	0.5	>8			
	MIC ₉₀								1	1	>8			

- Comparator MICs were within usual ranges for each species tested
- For NTM tested, including isolates R to CIP or MXF, MICs for SPR719 were at least 1 dilution lower than CIP or MXF
- MIC₅₀ for all RGM (n=93) tested was ≤4 µg/mL
- MIC₉₀ for MAC (n=41), including 10 isolates of MAC-X, was ≤2 µg/mL
- Quality control performed by RGM with *M. peregrinum* ATCC 700686 was 0.25 – 0.5 µg/mL and *Staphylococcus aureus* <0.015 – 0.06 µg/mL
- Quality control performed for slowly growing NTM with *M. marinum* ATCC 927 was 0.12 – 0.5 µg/mL

Figure 1. Structure of SPR719



CONCLUSIONS

- SPR719 was found to be potent against most clinical strains of NTM with an MIC₅₀ range of 0.25–4 µg/mL for several clinically significant species of NTM
- SPR719 may provide a useful treatment alternative to quinolones especially among species that are intrinsically R to quinolones (e.g., *M. abscessus* complex, *M. immunogenum*, *M. simiae*, and most isolates of the MAC)
- These findings support the further advancement of SPR720 for the treatment of NTM disease

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REFERENCE

CLSI, M24-A2, 2011.