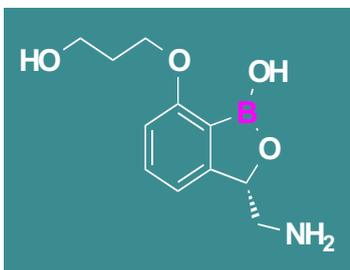


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Introduction

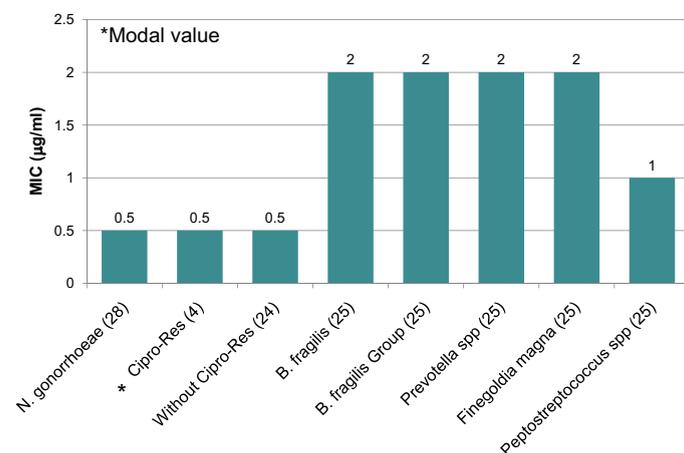
AN3365 (GSK2251052), which has successfully completed phase I clinical trials, is a member of a new class of boron-containing antibacterial protein synthesis inhibitors that inhibits leucyl-tRNA synthetase by a unique mechanism of action. The combination of the oxaborole tRNA trapping (OBORT) mechanism [1] and a clinically unexploited target is likely to escape pre-existing modes of bacterial resistance. AN3365 was advanced due to its broad spectrum of activity against Enterobacteriaceae and non-fermentative Gram-negative bacilli, while its activity against anaerobic bacteria and *Neisseria* species has been largely unexplored. In this study, the activity of AN3365 and 13 comparative agents was investigated against clinical isolates of *Neisseria gonorrhoeae*, and both Gram-negative and Gram-positive anaerobic bacteria including *Bacteroides fragilis* and *B. fragilis* Group, *Prevotella* species, *Peptostreptococcus* species, and *Finegoldia magna*.

Figure 1. Chemical Structure of AN3365 (GSK2251052)

Acknowledgements

This study was funded by GlaxoSmithKline

Results

Figure 2. MIC₉₀ (µg/ml) of AN3365 (GSK2251052)

Methods

- All study organisms were non-replicate, clinical isolates previously collected and frozen at -70° C in the years 2008 and 2009 (anaerobes) and 1997 and 1998 (*N. gonorrhoeae*).
- Minimum inhibitory concentration (MIC) endpoints were determined by agar dilution according to CLSI guidelines [2,3].
- Quality control testing was performed the day of testing according to CLSI guidelines [3,4] using the following strains: *N. gonorrhoeae* ATCC 49226; *B. fragilis* ATCC 25285, and *B. thetaiotaomicron* ATCC 29741.

References

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Results (cont'd)

Table 1. AN3365 and Comparators against 28 Isolates of *Neisseria gonorrhoeae*.

Organism	Drug	MIC (µg/mL)			
		MIC ₅₀	MIC ₉₀	Mode	Range
<i>Neisseria gonorrhoeae</i> (n=24)	AN3365	0.5	0.5	0.5	0.06 - 0.5
	Ciprofloxacin	0.004	0.015	0.004	0.002 - 0.5
	AmoxClav	0.5	1	0.12	0.12 - 2
	AmpSulb	0.25	2	0.25	0.06 - 2
	Ceftazidime	0.06	8	0.06	0.03 - 16
	Ceftriaxone	0.008	2	0.008	≤0.002 - 4
	Cefuroxime	0.06	4	0.06	0.004 - 16
	Trovafloracin	0.008	0.03	0.004	≤0.002 - 1
<i>Neisseria gonorrhoeae</i> (n=4)	AN3365			0.5	0.5 - 0.5
	Ciprofloxacin-Resistant			>2	>2 - >2
	AmoxClav			2	0.06 - 2
	AmpSulb	Not applicable for n's <10		2	0.12 - 2
	Ceftazidime			0.12	≤0.015 - 0.12
	Ceftriaxone			0.008	0.004 - 1
	Cefuroxime			0.12	0.12 - 0.25
	Trovafloracin			16	0.004 - 16

Table 2. AN3365 and Comparators against 75 Isolates of Gram-Negative Anaerobes.

Organism	Drug	MIC (µg/mL)			
		MIC ₅₀	MIC ₉₀	Mode	Range
<i>B. fragilis</i> (n=25)	AN3365	2	2	2	1 - 2
	Metronidazole	1	1	1	0.25 - 1
	Cefoxitin	4	16	4	4 - 32
	Clindamycin	0.5	8	0.5	≤0.25 - >8
	Meropenem	≤0.06	0.5	≤0.06	≤0.06 - 4
	PipTazo	0.25	0.5	0.25	≤0.06 - 32
<i>B. fragilis</i> Group (n=25)	AN3365	1	2	1	0.5 - 2
	Metronidazole	1	1	1	0.25 - 2
	Cefoxitin	8	16	8	≤2 - >32
	Clindamycin	4	>8	>8	≤0.25 - >8
	Meropenem	0.12	1	0.12	≤0.06 - 4
<i>Prevotella</i> spp (n=25)	AN3365	1	2	1	0.25 - 2
	Metronidazole	1	2	1	0.25 - 2
	Cefoxitin	≤2	8	≤1	≤2 - 16
	Clindamycin	≤0.25	>8	≤0.25	≤0.25 - >8
	Meropenem	≤0.06	0.12	≤0.06	≤0.06 - 0.5
PipTazo		≤0.06	0.5	≤0.06	≤0.06 - 8

Table 3. AN3365 and Comparators against 50 Isolates of Gram-Positive Anaerobes.

Organism	Drug	MIC (µg/mL)			
		MIC ₅₀	MIC ₉₀	Mode	Range
<i>Finegoldia magna</i> (n=25)	AN3365	1	2	1	0.12 - 2
	Metronidazole	0.5	0.5	0.5	≤0.12 - 1
	Clindamycin	≤0.25	1	≤0.25	≤0.25 - >8
	Meropenem	≤0.06	≤0.06	≤0.06	≤0.06 - 0.25
	Penicillin	≤0.25	0.5	≤0.25	≤0.25 - 0.5
	PipTazo	≤0.06	0.25	≤0.06	≤0.06 - 0.5
<i>Peptostreptococcus</i> spp (n=25)	AN3365	0.5	1	1	≤0.008 - 1
	Metronidazole	0.5	0.5	0.5	≤0.12 - 0.5
	Clindamycin	≤0.25	1	≤0.25	≤0.25 - 8
	Meropenem	≤0.06	0.25	≤0.06	≤0.06 - 0.5
	Penicillin	≤0.25	1	≤0.25	≤0.25 - 1
PipTazo	≤0.06	1	≤0.06	≤0.06 - 16	

Conclusions

- AN3365 had an MIC₉₀ or modal value of 0.5 µg/mL against all isolates of *N. gonorrhoeae* including 4 strains resistant to ciprofloxacin. This value compares favorably with the MIC₉₀ values of amoxicillin-clavulanic acid, ampicillin-sulbactam, ceftriaxone, and cefuroxime.
- AN3365 inhibited the growth of all Gram-negative and Gram-positive anaerobic bacteria at MIC values ≤2 µg/mL.
- AN3365 holds promise for the treatment of *N. gonorrhoeae* and Gram-negative and Gram-positive anaerobic bacterial infections including pathogens with pre-existing resistance mechanisms.