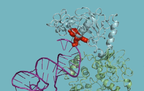

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Potency and Spectrum of Activity of AN3365, a Novel Boron-containing Protein Synthesis Inhibitor, Tested against Enterobacteriaceae

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Abstract

Background: AN3365, which has recently completed Phase I clinical development, is a member of a novel class of boron-containing antimicrobial protein synthesis inhibitors. AN3365 inhibits leucyl-tRNA synthetase via an unique mechanism of action. The *in vitro* activity of AN3365 was evaluated against wildtype and multidrug-resistant (MDR) Enterobacteriaceae.

Methods: 2,029 Enterobacteriaceae collected from USA and European hospitals were selected. Wildtype strains and MDR subsets due to the presence of stably derepressed AmpC, plasmid-borne AmpC, ESBL and KPC enzymes were included. AN3365 and comparators (10) were tested for susceptibility by CLSI broth microdilution methods (M07-A8 and M100-S20-U).

Results: AN3365 exhibited a log-normal MIC distribution with highest MIC_{50} occurrences at 0.5 μg/mL, except for *P. mirabilis* (MIC_{50} 1 μg/mL; Table). AN3365 inhibited all isolates at ≤2 μg/mL except for one *P. vulgaris* (MIC, 4 μg/mL). Among comparators, tigecycline (MIC_{90} 2 μg/mL), imipenem (MIC_{90} 2 μg/mL) and cefepime (MIC_{90} 4 μg/mL) demonstrated highest overall activity. AN3365 was very active against MDR isolates, such as derepressed AmpC (MIC_{90} 1 μg/mL), ESBL (MIC_{90} 1 μg/mL) and KPC producers (MIC_{90} 2 μg/mL). AN3365 and tigecycline (MIC_{90} 2 μg/mL) were the most active compounds tested against KPC-producing *K. pneumoniae*. While AN3365 (MIC_{90} 1 μg/mL) and cefepime (MIC_{90} ≤1 μg/mL) were the most active against Proteae.

Organism/group (Number tested)	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Number (cumulative %) inhibited at MIC (μg/mL) 0.25	0.5	1	2
Enterobacteriaceae (2,029)	0.5	1	84(4.1)	**1342(70.3)**[a]	544(97.1)	58(>99.9)
E. coli (252)	0.5	1	0(0.0)	**131(52.0)**	112(96.4)	9(100.0)
K. pneumoniae (261)	0.5	1	1(0.4)	**151(58.2)**	94(94.2)	15(100.0)
P. mirabilis (250)	1	1	0(0.0)	78(31.2)	**163(96.4)**	9(100.0)
E. aerogenes (250)	0.5	1	5(2.0)	**200(82.0)**	40(98.0)	5(100.0)
E. cloacae (252)	0.5	1	7(2.8)	**194(79.8)**	46(98.0)	5(100.0)
C. freundii (253)	0.5	1	7(2.8)	**208(85.0)**	36(99.2)	2(100.0)
Indole-positive Proteae[b] (259)	0.5	1	23(8.9)	**184(79.9)**	39(95.0)	12(99.6)
S. marcescens (252)	0.5	0.5	41(16.3)	**196(94.1)**	14(99.6)	2(100.0)

a. Modal MIC values are in bold.
b. Includes: *Morganella morganii* (150 strains), *Proteus vulgaris* (41 strains), *Providencia rettgeri* (14 strains), *Providencia stuartii* (43 strains), and unspecified *Providencia* (11 strains).

Conclusions: AN3365 (MIC_{90} 1 μg/mL) was more potent than the most active comparators, tigecycline (MIC_{90} 2 μg/mL), imipenem (MIC_{90} 2 μg/mL) and cefepime (MIC_{90} 4 μg/mL). Also AN3365 was not affected by any β-lactam resistance mechanisms.

Introduction

During the last decades, physicians have faced increasing numbers of seriously-ill patients that have undergone advanced medical procedures, ranging from transplants or advanced surgery to immunosuppressive cancer management. These patients usually have prolonged hospital stays in intensive care units or long-term care facilities and higher occurrences of healthcare-associated infections (HAIs). These infections are frequently caused by multidrug-resistant (MDR) organisms and necessitate a rapid initiation of effective empiric antimicrobial therapy.

Gram-negative bacilli are frequently responsible for hospital-acquired pneumonia, surgical site infection, urinary tract infection and bacteremia. Over the last decades, an accumulation of extended-spectrum β-lactamase (ESBL)-encoding genes (bla_{TEM} and bla_{SHV}) has occurred in *Escherichia coli* and *Klebsiella pneumoniae*, and a generalized rise in fluoroquinolone-resistant organisms. More recently, a worldwide dissemination of CTX-M enzymes has been reported in Enterobacteriaceae in the hospital and community settings. Carbapenems are usually the therapeutic options when treating infections caused by ESBL-producers. However, the clinical scenario has been complicated further by the spread of metallo-β-lactamase (MBL; VIM-, IMP- and most recently NDM-like)- and KPC-producing Enterobacteriaceae. The latter organisms are usually only susceptible to tigecycline and polymyxins.

Under these circumstances, new broad-spectrum anti-gram-negative agents would be welcomed. AN3365 is an investigational compound and a member of a novel class of boron-containing antimicrobial protein synthesis inhibitors (Figure 1). During a recently completed Phase 1 trial for AN3365, no safety concerns were identified and this new agent is progressing into further clinical development. In this study, the *in vitro* activity of AN3365 and comparator agents was evaluated against a contemporary collection of wildtype and MDR clinical isolates of Enterobacteriaceae from the United States (USA) and worldwide.

Materials and Methods

Bacterial strain collection. A total of 2,029 non-duplicate Enterobacteriaceae clinical isolates collected during 2006-2009 from USA (50.1%) and European (45.1%) medical centers were selected. The remaining strains tested were recovered from medical centers located in Latin America (4.8%). Strains were selected according to wildtype and MDR phenotypes. Resistant isolates included those with confirmed stably derepressed AmpC, plasmid-borne AmpC (pAmpC), ESBL and KPC enzymes. Sources of recovered organisms included bloodstream (72.9%), respiratory tract (14.2%) and skin and skin-structure specimens (12.7%) with a very small percentage (0.2%) of isolates collected from other clinical specimen types. Species identifications were confirmed by JMI Laboratories using standard algorithms and the automated Vitek 2 system (bioMérieux, Hazelwood, Missouri, USA), when necessary.

Antimicrobial susceptibility testing. Isolates were tested for susceptibility by the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) recommendations. Susceptibility testing was performed by using investigator-prepared 96-well frozen-form panels with cation-adjusted Mueller-Hinton broth. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains: *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853. Interpretation of comparator MIC results was in accordance with published CLSI (M100-S20-U) breakpoint criteria, except for tigecycline where the Food and Drug Administration (FDA) breakpoints were applied.

Results

- AN3365 exhibited a log-normal MIC distribution with highest number of occurrences at 0.5 μg/mL, when tested against Enterobacteriaceae (species or group of species), except for KPC-producing *K. pneumoniae* and *P. mirabilis* (modal MIC, 1 μg/mL; Table 1).
- Overall, AN3365 ($MIC_{50/90}$, 0.5/1 μg/mL) displayed MIC_{90} values two- to four-fold lower than tigecycline ($MIC_{50/90}$, 0.5/2 μg/mL), imipenem ($MIC_{50/90}$, 1/2 μg/mL) and cefepime ($MIC_{50/90}$, ≤1/4 μg/mL), when tested against all Enterobacteriaceae (Table 2).
- AN3365 ($MIC_{50/90}$, 0.5/1 μg/mL) inhibited all *E. coli* at ≤2 μg/mL, where levofloxacin and gentamicin resistance rates were 31.7 and 15.9%, respectively. Tigecycline ($MIC_{50/90}$, 0.25/0.5 μg/mL), imipenem ($MIC_{50/90}$, 0.12/0.25 μg/mL) and polymyxin B ($MIC_{50/90}$, 0.5/1 μg/mL) also had significant activity against this species (Table 2).
- MIC values for AN3365 ranged from 0.25 to 2 μg/mL when tested against *K. pneumoniae* isolates, including pAmpC-, ESBL- and KPC-producers (Table 1). Among KPC-producing *K. pneumoniae*, only AN3365 ($MIC_{50/90}$, 1/2 μg/mL; Table 1) and tigecycline ($MIC_{50/90}$, 1/2 μg/mL; 92.3% susceptible) demonstrated activity towards this population (data not shown).

Table 1. AN3365 antimicrobial activity and MIC distribution tested against Enterobacteriaceae groups of organisms, species or resistant subsets.

Organism/group (Number tested)	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Number (cumulative %) inhibited at MIC (μg/mL) 0.25	0.5	1	2
Enterobacteriaceae (2,029)	0.5	1	84(4.1)	**1342(70.3)**[a]	544(97.1)	58(>99.9)
E. coli (252)	0.5	1	0(0.0)	**131(52.0)**	112(96.4)	9(100.0)
E. coli (WT; 214)	0.5	1	0(0.0)	**108(50.5)**	98(96.3)	8(100.0)
E. coli (pAmpC; 11)	0.5	1	0(0.0)	**8(72.7)**	3(100.0)	–
E. coli (ESBL; 27)	0.5	1	0(0.0)	**15(55.6)**	11(96.3)	1(100.0)
K. pneumoniae (261)	0.5	1	1(0.4)	**151(58.2)**	94(94.2)	15(100.0)
K. pneumoniae (WT; 159)	0.5	1	0(0.0)	**96(60.4)**	57(96.2)	6(100.0)
K. pneumoniae (pAmpC; 5)	0.5	–	0(0.0)	**3(60.0)**	1(80.0)	1(100.0)
K. pneumoniae (ESBL; 71)	0.5	1	0(0.0)	**43(60.6)**	24(94.4)	4(100.0)
K. pneumoniae (KPC; 26)	1	2	1(3.8)	9(38.5)	**12(84.6)**	4(100.0)
P. mirabilis (250)	1	1	0(0.0)	78(31.2)	**163(96.4)**	9(100.0)
P. mirabilis (WT; 235)	1	1	0(0.0)	74(31.5)	**153(96.6)**	8(100.0)
P. mirabilis (ESBL; 15)	1	1	0(0.0)	4(26.7)	**10(93.3)**	1(100.0)
E. aerogenes (250)	0.5	1	5(2.0)	**200(82.0)**	40(98.0)	5(100.0)
E. aerogenes (WT; 199)	0.5	1	1(0.5)	**163(82.4)**	31(98.0)	4(100.0)
E. aerogenes (AmpC; 51)	0.5	1	4(7.8)	**37(80.4)**	9(98.0)	1(100.0)
E. cloacae (252)	0.5	1	7(2.8)	**194(79.8)**	46(98.0)	5(100.0)
E. cloacae (WT; 202)	0.5	1	2(1.0)	**153(76.7)**	42(97.5)	5(100.0)
E. cloacae (AmpC; 50)	0.5	0.5	5(10.0)	**41(92.0)**	4(100.0)	–
C. freundii (253)	0.5	1	7(2.8)	**208(85.0)**	36(99.2)	2(100.0)
C. freundii (WT; 193)	0.5	1	6(3.1)	**160(86.0)**	26(99.5)	1(100.0)
C. freundii (AmpC; 54)	0.5	1	1(1.8)	**43(81.5)**	9(98.1)	1(100.0)
C. freundii (ESBL; 6)	0.5	–	0(0.0)	**5(83.3)**	1(100.0)	–
Indole-positive Proteae (259)[b]	0.5	1	23(8.9)	**184(79.9)**	39(95.0)	12(99.6)
Indole-positive Proteae (WT; 229)[c]	0.5	1	23(10.0)	**164(81.7)**	35(96.9)	6(>95.5)
Indole-positive Proteae (AmpC; 18)[d]	0.5	2	0(0.0)	**14(77.8)**	2(88.9)	2(100.0)
Indole-positive Proteae (ESBL; 12)[e]	0.5	2	0(0.0)	**6(50.0)**	2(66.7)	4(100.0)
S. marcescens (252)	0.5	0.5	41(16.3)	**196(94.1)**	14(99.6)	2(100.0)
S. marcescens (WT; 226)	0.5	0.5	38(16.8)	**176(94.7)**	11(99.6)	1(100.0)
S. marcescens (AmpC; 26)	0.5	1	3(11.5)	**20(88.5)**	3(100.0)	–

WT, wildtype; pAmpC, plasmid-borne AmpC; ESBL, extended-spectrum β-lactamase.
a. Modal MIC values are in bold.
b. Includes: *M. morganii* (150 strains), *P. vulgaris* (41 strains), *P. rettgeri* (14 strains), *P. stuartii* (43 strains), and unspecified *Providencia* (11 strains).
c. Includes: *M. morganii* (132 strains), *P. vulgaris* (41 strains), *P. rettgeri* (12 strains), *P. stuartii* (35 strains), and unspecified *Providencia* (9 strains).
d. Includes: *M. morganii* (18 strains).
e. Includes: *P. rettgeri* (2 strains), *P. stuartii* (8 strains), and unspecified *Providencia* (2 strains).

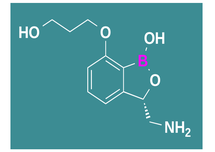
- AN3365 inhibited 96.4% of *P. mirabilis* at ≤1 μg/mL and only nine strains (3.6%) displayed an MIC value of 2 μg/mL (Table 1). AN3365 ($MIC_{50/90}$, 1/1 μg/mL), ceftazidime ($MIC_{50/90}$, ≤1/≤1 μg/mL), cefepime ($MIC_{50/90}$, ≤1/≤1 μg/mL) and piperacillin/tazobactam ($MIC_{50/90}$, 0.5/1 μg/mL; Table 2) were similarly active against *P. mirabilis*.
- *Enterobacter* spp. were very susceptible (≥90.4%) to cefepime, imipenem, levofloxacin, gentamicin and tigecycline. In addition, AN3365 (MIC_{90}, 1 μg/mL), levofloxacin (MIC_{90}, 1 μg/mL), tigecycline (MIC_{90}, 1 μg/mL) and imipenem (MIC_{90}, 1 – 2 μg/mL) showed equivalent potency against *E. cloacae* and *E. aerogenes* (Table 2).
- AN3365 ($MIC_{50/90}$, 0.5/1 μg/mL) was the most active compound tested against indole-positive Proteae, followed by cefepime ($MIC_{50/90}$, ≤1/2 μg/mL), piperacillin/tazobactam ($MIC_{50/90}$, 0.5/4 μg/mL), tigecycline ($MIC_{50/90}$, 1/4 μg/mL) and imipenem ($MIC_{50/90}$, 2/4 μg/mL; Table 2).
- AN3365 ($MIC_{50/90}$, 0.5/0.5 μg/mL) exhibited MIC_{90} results two- to four-fold lower than imipenem ($MIC_{50/90}$, 0.5/1 μg/mL), cefepime ($MIC_{50/90}$, ≤1/2 μg/mL), levofloxacin ($MIC_{50/90}$, ≤0.5/2 μg/mL), gentamicin ($MIC_{50/90}$, 1/2 μg/mL) and tigecycline ($MIC_{50/90}$, 1/2 μg/mL; Table 2), when tested against *S. marcescens*.

Table 2. Activity of AN3365 and comparator antimicrobial agents tested against Gram-negative pathogens.

Organism (number tested) / Antimicrobial agent	Range	MIC (μg/mL) 50%	MIC (μg/mL) 90%	% Susceptible/Resistant[a]
Enterobacteriaceae (2,029)[b]				
AN3365	0.25 – 4	0.5	1	– [c] / –
Ampicillin	0.5 – >64	>64	>64	16.0 / 81.3
Amoxicillin/clavulanate	0.5 – >64	64	>64	30.5 / 63.8
Ceftazidime	≤1 – >16	≤1	>16	82.7 / 16.1
Cefepime	≤1 – >32	≤1	4	92.9 / 6.1
Piperacillin/tazobactam	≤0.06 – >128	2	64	86.4 / 8.1
Imipenem	≤0.03 – >64	1	2	73.5 / 8.1
Levofloxacin	≤0.5 – >16	≤0.5	16	81.4 / 15.9
Gentamicin	≤0.5 – >16	1	16	87.2 / 11.1
Tigecycline	0.06 – 8	0.5	2	92.2 / 0.6
Polymyxin B	≤0.25 – >8	1	>8	58.7 / 41.3
Escherichia coli (252)				
AN3365	0.5 – 2	0.5	1	– / –
Ampicillin	0.5 – >64	>64	>64	38.5 / 61.1
Amoxicillin/clavulanate	1 – >64	8	32	64.7 / 17.1
Ceftazidime	≤1 – >16	≤1	16	85.7 / 12.7
Cefepime	≤1 – >32	≤1	2	90.1 / 9.5
Piperacillin/tazobactam	0.12 – >128	2	32	87.3 / 7.5
Imipenem	0.06 – 16	0.12	0.25	99.6 / 0.4
Levofloxacin	≤0.5 – >16	≤0.5	>16	66.7 / 31.7
Gentamicin	≤0.5 – >16	1	>16	83.3 / 15.9
Tigecycline	0.06 – 1	0.25	0.5	100.0 / 0.0
Polymyxin B	≤0.25 – 8	0.5	1	97.6 / 2.4
Klebsiella pneumoniae (261)				
AN3365	0.25 – 2	0.5	1	– / –
Ampicillin	1 – >64	>64	>64	1.5 / 94.3
Amoxicillin/clavulanate	1 – >64	8	64	61.3 / 25.3
Ceftazidime	≤1 – >16	≤1	>16	64.7 / 34.1
Cefepime	≤1 – >32	≤1	>32	75.9 / 20.3
Piperacillin/tazobactam	0.25 – >128	8	>128	69.3 / 24.9
Imipenem	≤0.03 – >64	0.25	1	90.0 / 10.0
Levofloxacin	≤0.5 – >16	≤0.5	>16	64.8 / 31.4
Gentamicin	≤0.5 – >16	≤0.5	>16	75.5 / 21.5
Tigecycline	0.12 – 4	0.5	2	96.2 / 0.0
Polymyxin B	0.5 – >8	0.5	2	95.8 / 4.2
Proteus mirabilis (250)				
AN3365	0.5 – 2	1	1	– / –
Ampicillin	0.5 – >64	2	>64	70.0 / 30.0
Amoxicillin/clavulanate	0.5 – >64	1	8	90.8 / 3.6
Ceftazidime	≤1 – >16	≤1	≤1	98.4 / 1.2
Cefepime	≤1 – >32	≤1	≤1	95.6 / 4.0
Piperacillin/tazobactam	0.12 – 8	0.5	1	100.0 / 0.0
Imipenem	0.06 – 4	2	4	80.8 / 14.4
Levofloxacin	≤0.5 – >16	≤0.5	16	78.4 / 17.2
Gentamicin	≤0.5 – >16	1	16	86.8 / 10.4
Tigecycline	0.5 – 8	2	4	62.0 / 3.6
Polymyxin B	>8	>8	>8	0.0 / 100.0
Enterobacter aerogenes (250)				
AN3365	0.25 – 2	0.5	1	– / –
Ampicillin	1 – >64	>64	>64	2.8 / 95.6
Amoxicillin/clavulanate	1 – >64	64	64	2.4 / 97.2
Ceftazidime	≤1 – >16	≤1	>16	79.6 / 20.4
Cefepime	≤1 – >32	≤1	≤1	98.4 / 1.2
Piperacillin/tazobactam	≤0.06 – >128	4	64	81.2 / 6.0
Imipenem	≤0.03 – 16	1	2	62.4 / 1.6
Levofloxacin	≤0.5 – >16	≤0.5	1	90.4 / 8.8
Gentamicin	≤0.5 – >16	≤0.5	1	98.4 / 0.4
Tigecycline	0.12 – 4	0.5	1	98.8 / 0.0
Polymyxin B	≤0.25 – >8	1	4	86.8 / 13.2
Enterobacter cloacae (252)				
AN3365	0.25 – 2	0.5	1	– / –
Ampicillin	4 – >64	>64	>64	4.8 / 90.9
Amoxicillin/clavulanate	1 – >64	64	64	2.8 / 94.0
Ceftazidime	≤1 – >16	≤1	>16	80.2 / 19.8
Cefepime	≤1 – >32	≤1	4	96.4 / 2.4
Piperacillin/tazobactam	0.12 – >128	2	128	84.9 / 10.3
Imipenem	0.06 – 8	0.5	1	94.8 / 0.4
Levofloxacin	≤0.5 – >16	≤0.5	1	93.3 / 4.8
Gentamicin	≤0.5 – >16	≤0.5	4	91.3 / 7.9
Tigecycline	0.25 – 4	0.5	1	96.0 / 0.0
Polymyxin B	≤0.25 – >8	1	>8	83.3 / 16.7
Citrobacter freundii (253)				
AN3365	0.25 – 2	0.5	1	– / –
Ampicillin	2 – >64	64	>64	4.3 / 87.7
Amoxicillin/clavulanate	1 – >64	64	64	3.2 / 94.1
Ceftazidime	≤1 – >16	≤1	>16	77.9 / 21.3
Cefepime	≤1 – >32	≤1	2	95.3 / 4.0
Piperacillin/tazobactam	1 – >128	4	128	79.8 / 12.6
Imipenem	0.12 – 4	1	1	91.3 / 0.4
Levofloxacin	≤0.5 – >16	≤0.5	2	92.1 / 6.7
Gentamicin	≤0.5 – >16	1	1	92.1 / 7.9
Tigecycline	0.25 – 4	0.5	1	98.0 / 0.0
Polymyxin B	≤0.25 – 4	0.5	1	98.8 / 1.2
Indole-positive Proteae [d] (259)				
AN3365	0.25 – 4	0.5	1	– / –
Ampicillin	0.5 – >64	>64	>64	5.8 / 92.3
Amoxicillin/clavulanate	0.5 – >64	>64	>64	17.4 / 81.1
Ceftazidime	≤1 – >16	≤1	8	86.9 / 8.1
Cefepime	≤1 – >32	≤1	2	92.7 / 6.2
Piperacillin/tazobactam	≤0.06 – 128	0.5	4	98.5 / 0.8
Imipenem	0.5 – 8	2	4	24.7 / 35.9
Levofloxacin	≤0.5 – >16	≤0.5	>16	73.4 / 22.4
Gentamicin	≤0.5 – >16	1	>16	79.2 / 17.4
Tigecycline	0.25 – 8	1	4	88.8 / 0.8
Polymyxin B	0.5 – >8	0.5	>8	0.8 / 99.2
Serratia marcescens (252)				
AN3365	0.25 – 2	0.5	0.5	– / –
Ampicillin	8 – >64	>64	>64	1.2 / 97.6
Amoxicillin/clavulanate	2 – >64	>64	>64	1.2 / 98.4
Ceftazidime	≤1 – >16	≤1	16	89.3 / 10.3
Cefepime	≤1 – >32	≤1	2	98.0 / 2.0
Piperacillin/tazobactam	0.5 – 128	2	16	90.6 / 2.4
Imipenem	0.25 – 64	0.5	1	94.8 / 0.8
Levofloxacin	≤0.5 – >16	≤0.5	2	93.3 / 3.1
Gentamicin	≤0.5 – >16	1	2	91.0 / 8.2
Tigecycline	0.25 – 8	1	2	97.6 / 0.4
Polymyxin B	0.5 – >8	>8	>8	6.7 / 93.3

a. Criteria for susceptibility as published by the Clinical and Laboratory Standards Institute (M100-S20-U; Update June 2010) and FDA approved breakpoints for tigecycline.
b. Includes: *C. freundii* (253 strains), *E. aerogenes* (250 strains), *E. cloacae* (252 strains), *E. coli* (252 strains), *K. pneumoniae* (261 strains), *Morganella morganii* (150 strains), *P. mirabilis* (250 strains), *Proteus vulgaris* (41 strains), *Providencia rettgeri* (14 strains), *Providencia stuartii* (43 strains), *S. marcescens* (252 strains), and unspecified *Providencia* (11 strains).
c. –, no breakpoint available.
d. Includes: *M. morganii* (150 strains), *P. vulgaris* (41 strains), *P. rettgeri* (14 strains), *P. stuartii* (43 strains), and unspecified *Providencia* (11 strains).

Figure 1.
Chemical structure of AN3365 [GSK2251052].



Conclusions

- Overall, AN3365, tigecycline and imipenem were the most potent agents tested against this selected bacterial population; however, the Anacor compound was usually more potent (approximately two-fold) than tigecycline and imipenem.
- AN3365 demonstrated *in vitro* potency advantages when compared to the other agents tested. This *in vitro* activity was observed regardless of species or antimicrobial resistance phenotype expressed, suggesting lack of pre-existing resistance due to novel MoA.
- In summary, AN3365 exhibited high potency against this contemporary collection of Enterobacteriaceae species, inhibiting all strains at 2 μg/mL, except for one *P. vulgaris*, which has an MIC of 4 μg/mL. With the rise of MDR Enterobacteriaceae, these *in vitro* data calls for further clinical development of AN3365

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