C-1421

Activity of the Novel Bacterial Topoisomerase II Inhibitor, GSK2140944, Against Select Gram-positive and Gram-negative Bacteria

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ICAAC 2014

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ABSTRACT

Background: GSK2140944 (‘944), a novel bacterial type II topoisomerase inhibitor with a mode of action distinguished from fluoroquinolones, is currently in clinical development. ‘944 has demonstrated activity against the key causative pathogens of respiratory, skin and biothreat infections, including isolates resistant to existing classes of antimicrobials and MRSA. We evaluated the activity of ‘944 and comparator agents against contemporary Gram-positive (GP) and -negative (GN) bacteria.

Methods: A total of 1,008 clinically significant GP and GN bacteria (91.3% from 2012) were tested for susceptibility (S) to ‘944 and comparators by CLSI reference broth microdilution methods. Isolates were from multiple infection types from a global collection.

Results: ‘944 demonstrated activity (0.03 to 1 µg/mL) against all staphylococci. The $MIC_{50/90}$ were as follows: MRSA (0.25/0.5 µg/mL), MSSA (0.25/0.5 µg/mL), coagulase-negative staphylococci (0.12/0.5 µg/mL). For *S. pneumoniae*, including penicillin-non-S isolates, the ‘944 $MIC_{50/90}$ was 0.25/0.25 µg/mL. The ‘944 $MIC_{50/90}$ was 0.25/0.5 µg/mL for β-hemolytic streptococci and 0.12/0.5 µg/mL for viridans group streptococci. *Haemophilus* spp. were inhibited by a ‘944 MIC range of 0.06 to 4 µg/mL. The ‘944 MIC_{50} and MIC_{90} values for all *Haemophilus* spp. isolates were 1 and 2 µg/mL, respectively with similar activity regardless of β-lactamase production. For *E. coli*, *Enterobacter* spp. and *Klebsiella* spp., the ‘944 $MIC_{50/90}$ values were 1/2, 4/32, and 4/8 µg/mL, respectively. For other enterics (10 isolates), ‘944 MIC values ranged from 2 to16 µg/mL.

Conclusions: ‘944 exhibited *in vitro* activity against GP pathogens, (including MRSA), *Haemophilus* spp. and *E. coli*. ‘944 merits further study to evaluate its potential for use in infections where such organisms may be encountered.

	Cumulative % of isolates inhibited at ‘944 MIC (µg/mL) of:								
Organism (No. of isolates)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	≥8
Staphylococci (303)	6.9	8.3	23.8	78.2	98.7	100.0			
MSSA (100)	0.0	1.0	7.0	75.0	99.0	100.0			
MRSA (101)	0.0	1.0	7.9	79.2	99.0	100.0			
CNS 102)	20.6	22.6	55.9	80.4	98.0	100.0			
Streptococcus pneumoniae (299)	1.7	2.0	40.0	93.0	99.7	100.0			
Pen-NS SPN (175)	1.7	2.3	41.7	95.4	100.0				
β-hemolytic streptococci (100)	2.0	3.0	37.0	71.0	90.0	100.0			
Viridans group streptococci (105)	12.4	17.1	51.4	80.0	94.3	100.0			
Haemophilus spp. (101)	0.0	1.0	2.0	11.9	47.5	75.3	95.1	100.0	
Enterobacteriaceae (100)	0.0	0.0	0.0	1.0	5.0	33.0	60.0	84.0	100.0

INTRODUCTION

GSK2140944 is a novel bacterial type II topoisomerase inhibitor with a mode of action distinguished from fluoroquinolones. GSK2140944 selectively inhibits bacterial DNA replication by interacting with the GyrA subunit of bacterial DNA gyrase and the ParC subunit of bacterial topoisomerase IV. This highly specific interaction to bacterial topoisomerases is evidenced by weak inhibition of human topoisomerase II, supporting the selective activity of GSK2140944 against the bacterial targets.

GSK2140944 is currently in clinical development. It has *in vitro* activity against the key causative Gram-positive pathogens of respiratory, skin and soft tissue, and biothreat infections, including MRSA and isolates resistant to existing classes of antimicrobials such as fluoroquinolones and glycopeptides. In this study, we evaluated the *in vitro* activity of GSK2140944 and comparator agents against a global collection of contemporary Gram-positive and -negative bacteria.

MATERIALS AND METHODS

Organism collection: A total of 1,008 clinically significant Gram-negative and Gram-positive bacterial pathogens, mostly collected in 2012 (91.3%), were selected. Some *Streptococcus pneumoniae* and *S. mutans* were collected between 2009 and 2011. The isolates were from patient infections from North America (68.9%), Europe (20.0%), Latin America (4.7%) and Asia-Pacific (6.3%) and were mainly obtained from patients with nosocomial and community-acquired respiratory tract infections (39.9%), bloodstream infections (29.7%) and skin and skin structure infections (21.3%). The following species (number) were tested: *Staphylococcus aureus* (201), coagulase-negative staphylococci (CoNS, 102), *S. pneumoniae* (299), β-hemolytic streptococci (βHS,100; including *S. pyogenes* [75], and *S. agalactiae* [25]), viridans group streptococci (VGS, 105), *Enterobacteriaceae* (100; including *Escherichia coli* [50], *Enterobacter* spp. [20], *Klebsiella* spp. [20], *Citrobacter* spp. [2], Proteeae [5], and *Serratia* spp. [3]), and *Haemophilus* spp. (101; including *H. influenzae* [82] and *H. parainfluenzae* [19]).

Susceptiblity testing: Susceptibility testing was performed using reference broth microdilution following Clinical and Laboratory Standards Institute (CLSI) methods on frozen-form panels produced by JMI laboratories. Susceptibility test panels were produced from a freshly prepared stock of GSK2140944 and the lots of panels were stored frozen at -70 °C until use. Non-fastidious pathogens were tested using Mueller-Hinton broth (MHB). For streptococcal testing, MHB was supplemented with 2.5-5% lysed horse blood. For *Haemophilus* species testing, Haemophilus Test Medium (HTM) was used. QC was performed daily and inoculum density was monitored by colony counts during each batch test run. ATCC QC strains were selected as appropriate for the conditions being tested and included *S. aureus* ATCC 29213, *E. coli* ATCC 25922, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247.

RESULTS

- The chemical structure of GSK2140944 is presented in **Figure 1**. GSK2140944 demonstrated a MIC range of 0.03 to 1 µg/mL against all 303 staphylococci tested (**Table 1**). The MIC range for GSK2140944 against 101 methicillin (oxacillin)-resistant *S. aureus* was 0.06-1 µg/mL and the MIC_{50} and MIC_{90} were 0.25 and 0.5 µg/mL. Against 100 methicillin (oxacillin)-susceptible *S. aureus,* the MIC range was 0.06-1 µg/mL and the MIC_{50} and MIC_{90} were 0.25 and 0.5 µg/mL. The MIC range against CoNS (102) was 0.03-1 µg/mL and the MIC_{50} and MIC_{90} were 0.12 and 0.5 µg/mL.
- For streptococci, the MIC range for GSK2140944 was ≤0.015-1 µg/mL, which was similar to the staphylococcal MIC range. For 299 isolates of *S. pneumoniae,* the MIC_{50} and MIC_{90} were at 0.25 µg/mL including 124 penicillin-susceptible (MIC_{50} and MIC_{90}, 0.25/0.25 µg/mL) and 175 penicillin-nonsusceptible (MIC_{50} and MIC_{90}, 0.25/0.25 µg/mL) isolates (**Table 1**). For 100 isolates of β-hemolytic streptococci (MIC_{50} and MIC_{90}, 0.25 and 0.5 µg/mL; **Table 2**), the MIC range was 0.03-1 µg/mL. For the viridans group streptococci (105 isolates, MIC_{50} and MIC_{90}, 0.12 and 0.5 µg/mL), there was one isolate with a MIC value at ≤0.015 µg/mL, the remainder tested in the range of 0.03-1 µg/mL.
- The MIC_{50} and MIC_{90} for all Gram-positive pathogens tested against GSK2140944 was 0.25 and 0.5 µg/mL, respectively. A total of 91.1% of isolates exhibited MIC values in the range of 0.12-0.5 µg/mL (**Figure 2**).
- *Haemophilus* spp. (101 strains) exhibited a GSK2140944 MIC range of 0.06 to 4 µg/mL. The MIC_{50} and MIC_{90} values for all 82 *H. influenzae* isolates were 0.5 and 2 µg/mL, respectively. The MIC_{50} and MIC_{90} values for the 19 *H. parainfluenzae* isolates were 1 and 4 µg/mL, respectively. MIC values were not affected by β-lactamase status (**Table 1**).
- MIC values for GSK2140944 ranged from 0.25->32 µg/mL for the *Enterobacteriaceae*. MIC_{50} and MIC_{90} values were 2-8 µg/mL, respectively. A total of 79.0% of isolates exhibited MIC values in the range of 1-4 µg/mL (**Figure 3**). For *E. coli* (50 isolates), MIC values ranged from 0.25-8 µg/mL (MIC_{50} and MIC_{90}, 1 and 2 µg/mL, respectively). MIC values for *Enterobacter* spp. (20 isolates) ranged from 1->32 µg/mL (MIC_{50} and MIC_{90}, 4 and 32 µg/mL, respectively). For *Klebsiella* spp. (20 isolates), MIC values ranged from 1->32 µg/mL (MIC_{50} and MIC_{90}, 4 and 8 µg/mL, respectively). For other enterics (10 isolates), MIC values ranged from 2-16 µg/mL.

Table 1. Cumulative MIC distributions of GSK2140944 tested against a collection of 1,008 Gram-positive and -negative clinical isolates.

Organism	No. of Isolates	MIC in µg/mL (cumulative % inhibited)												
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Staphylococci	303	0 (0.0)	21 (6.9)	4 (8.3)	47 (23.8)	**165** **(78.2)**	**62** **(98.7)**	4 (100.0)	-	-	-	-	-	-
MSSA	100	0 (0.0)	0 (0.0)	1 (1.0)	6 (7.0)	**68** **(75.0)**	**24** **(99.0)**	1 (100.0)	-	-	-	-	-	-
MRSA	101	0 (0.0)	0 (0.0)	1 (1.0)	7 (7.9)	**72** **(79.2)**	**20** **(99.0)**	1 (100.0)	-	-	-	-	-	-
CoNS	102	0 (0.0)	21 (20.6)	2 (22.6)	**34** **(55.9)**	25 (80.4)	**18** **(98.0)**	2 (100.0)	-	-	-	-	-	-
S. pneumoniae	299	0 (0.0)	5 (1.7)	1 (2.0)	114 (40.1)	**159** **(93.3)**	20 (100.0)	-	-	-	-	-	-	-
Pen-susc.	124	0 (0.0)	2 (1.6)	0 (1.6)	45 (37.9)	**65** **(90.3)**	12 (100.0)	-	-	-	-	-	-	-
Pen-non-susc.	175	0 (0.0)	3 (1.7)	1 (2.3)	69 (41.7)	**94** **(95.4)**	8 (100.0)	-	-	-	-	-	-	-
βHS	100	0 (0.0)	2 (2.0)	1 (3.0)	34 (37.0)	**34** **(71.0)**	**19** **(90.0)**	10 (100.0)	-	-	-	-	-	-
Viridans strept.	105	1 (1.0)	12 (12.4)	5 (17.1)	**36** **(51.4)**	30 (80.0)	**15** **(94.3)**	6 (100.0)	-	-	-	-	-	-
Enterobacteriaceae	100	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	4 (5.0)	28 (33.0)	**27** **(60.0)**	24 (84.0)	**8** **(92.0)**	4 (96.0)	2 (98.0)	2 (100.0)
Haemophilus spp.	101	0 (0.0)	0 (0.0)	1 (1.0)	1 (2.0)	10 (11.9)	36 (47.5)	**28** **(75.3)**	**20** **(95.1)**	5 (100.0)	-	-	-	-
β-lact. positive	17	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (11.8)	5 (41.2)	7 **(82.4)**	2 **(94.1)**	1 (100.0)	-	-	-	-
β-lact. negative	84	0 (0.0)	0 (0.0)	1 (1.2)	0 (1.2)	9 (11.9)	31 (48.8)	**21** **(73.8)**	**18** **(95.2)**	4 (100.0)	-	-	-	-

*MIC_{50} and MIC_{90} values in bold

Figure 2. Activity of GSK2140944 tested against contemporary Gram-positive pathogens (n= 807).

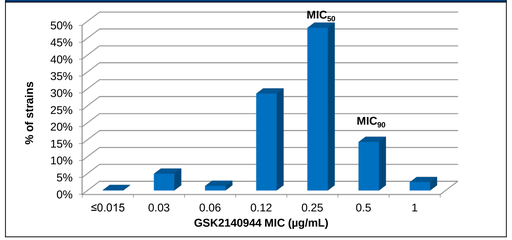


Figure 3. Activity of GSK2140944 tested against contemporary *Enterobacteriaceae* (n= 100).

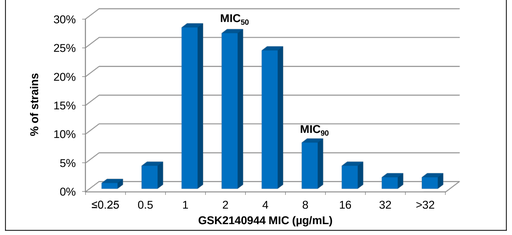


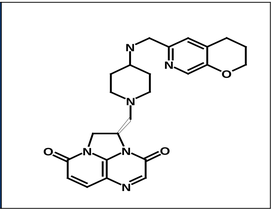
Table 2. Activity of GSK2140944 and comparator antimicrobial agents when tested against Gram-positive and Gram-negative bacteria.

Organism (No. tested)/ Antimicrobial agent	MIC (µg/mL) 50%	MIC (µg/mL) 90%	%S / %I / %R CLSI[a]	%S / %I / %R EUCAST[a]
Staphylococcus aureus (201)				
GSK2140944	0.25	0.5	- / - / -	- / - / -
Oxacillin	>2	>2	49.8 / 0.0 / 50.2	49.8 / 0.0 / 50.2
Levofloxacin	0.25	>32	61.2 / 0.0 / 38.8	61.2 / 0.0 / 38.8
Moxifloxacin	0.06	8	60.7 / 4.5 / 34.8	60.7 / 4.5 / 34.8
Linezolid	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Oxacillin-resistant *S. aureus* (101)				
GSK2140944	0.25	0.5	- / - / -	- / - / -
Oxacillin	>2	>2	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Levofloxacin	8	>32	33.7 / 0.0 / 66.3	33.7 / 0.0 / 66.3
Moxifloxacin	2	32	33.7 / 4.9 / 61.4	33.7 / 4.9 / 61.4
Linezolid	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Oxacillin-susceptible *S. aureus* (100)				
GSK2140944	0.25	0.5	- / - / -	- / - / -
Oxacillin	0.5	0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.25	4	89.0 / 0.0 / 11.0	89.0 / 0.0 / 11.0
Moxifloxacin	0.06	1	88.0 / 4.0 / 8.0	88.0 / 4.0 / 8.0
Linezolid	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Coagulase-negative staphylococci[b] (102)				
GSK2140944	0.12	0.5	- / - / -	- / - / -
Oxacillin	≤0.25	>2	54.1 / 0.0 / 45.9	54.1 / 0.0 / 45.9
Levofloxacin	0.25	32	62.7 / 1.0 / 36.3	62.7 / 1.0 / 36.3
Moxifloxacin	0.12	16	63.7 / 5.9 / 30.4	63.7 / 5.9 / 30.4
Linezolid	0.5	1	96.1 / 0.0 / 3.9	96.1 / 0.0 / 3.9
Streptococcus pyogenes (75)				
GSK2140944	0.25	0.25	- / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -	- / - / -
Meropenem	≤0.06	≤0.06	100.0 / - / -	- / - / -
Penicillin	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	0.5	1	100.0 / 0.0 / 0.0	96.0 / 4.0 / 0.0
Moxifloxacin	0.12	0.25	- / - / -	100.0 / 0.0 / 0.0
Linezolid	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Streptococcus agalactiae (25)				
GSK2140944	0.5	1	- / - / -	- / - / -
Ceftriaxone	0.12	0.12	100.0 / - / -	- / - / -
Meropenem	≤0.06	≤0.06	100.0 / - / -	- / - / -
Penicillin	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	0.5	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Moxifloxacin	0.12	0.25	- / - / -	100.0 / 0.0 / 0.0
Linezolid	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Streptococcus pneumoniae (299)				
GSK2140944	0.25	0.25	- / - / -	- / - / -
Ceftriaxone	2	8	47.2 / 31.1 / 21.7	37.8 / 40.5 / 21.7
Meropenem	1	1	39.5 / 7.4 / 53.1	98.3 / 0.0 / 1.7
Penicillin[c]	4	>4	41.5 / 16.7 / 41.8	- / -
Penicillin[d]	4	>4	27.4 / 10.4 / 62.2	27.4 / 14.1 / 58.5
Levofloxacin	1	1	96.0 / 0.3 / 3.7	96.0 / 0.0 / 4.0
Moxifloxacin	0.12	0.25	96.3 / 1.4 / 2.3	96.0 / 0.0 / 4.0
Linezolid	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Viridans group streptococci[e] (105)				
GSK2140944	0.12	0.5	- / - / -	- / - / -
Ceftriaxone	0.25	1	92.0 / 4.0 / 4.0	78.7 / 0.0 / 21.3
Meropenem	≤0.12	0.25	94.7 / - / -	98.7 / 0.0 / 1.3
Penicillin	0.12	1	62.7 / 34.6 / 2.7	78.7 / 18.6 / 2.7
Levofloxacin	1	2	95.2 / 0.0 / 4.8	- / - / -
Moxifloxacin	0.12	0.25	- / - / -	- / - / -
Linezolid	0.5	1	100.0 / - / -	- / - / -

Organism (No. tested)/ Antimicrobial agent	MIC (µg/mL) 50%	MIC (µg/mL) 90%	%S / %I / %R CLSI[a]	%S / %I / %R EUCAST[a]
Enterobacteriaceae[f] (100)				
GSK2140944	2	8	- / - / -	- / - / -
Ceftazidime	0.25	8	87.0 / 4.0 / 9.0	87.0 / 0.0 / 13.0
Ceftriaxone	≤0.06	8	87.0 / 0.0 / 13.0	87.0 / 0.0 / 13.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.06	16	80.0 / 5.0 / 15.0	78.0 / 2.0 / 20.0
Moxifloxacin	0.06	16	- / - / -	75.0 / 2.0 / 23.0
Escherichia coli (50)				
GSK2140944	1	2	- / - / -	- / - / -
Ceftazidime	0.25	1	92.0 / 2.0 / 6.0	92.0 / 0.0 / 8.0
Ceftriaxone	≤0.06	8	88.0 / 0.0 / 12.0	88.0 / 0.0 / 12.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.03	16	72.0 / 4.0 / 24.0	72.0 / 0.0 / 28.0
Moxifloxacin	0.03	32	- / - / -	70.0 / 2.0 / 28.0
Enterobacter spp. (20)				
GSK2140944	4	32	- / - / -	- / - / -
Ceftazidime	0.25	>32	65.0 / 5.0 / 30.0	65.0 / 0.0 / 35.0
Ceftriaxone	0.25	>8	65.0 / 0.0 / 35.0	65.0 / 0.0 / 35.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.06	4	80.0 / 10.0 / 10.0	70.0 / 10.0 / 20.0
Moxifloxacin	0.06	8	- / - / -	70.0 / 0.0 / 30.0
Klebsiella spp. (20)				
GSK2140944	4	8	- / - / -	- / - / -
Ceftazidime	0.12	0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftriaxone	≤0.06	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.06	0.5	95.0 / 0.0 / 5.0	95.0 / 0.0 / 5.0
Moxifloxacin	0.06	1	- / - / -	85.0 / 5.0 / 10.0
Haemophilus influenzae (82)				
GSK2140944	0.5	2	- / - / -	- / - / -
Ceftazidime	0.06	0.25	100.0 / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -	98.7 / 0.0 / 1.3
Meropenem	≤0.06	0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	0.015	0.03	100.0 / - / -	100.0 / 0.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	100.0 / - / -	100.0 / 0.0 / 0.0
H. influenzae (β-lactamase-positive;16)				
GSK2140944	1	2	- / - / -	- / - / -
Ceftazidime	0.06	0.12	100.0 / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Meropenem	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	0.015	0.015	100.0 / - / -	100.0 / 0.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	100.0 / - / -	100.0 / 0.0 / 0.0
H. influenzae (β-lactamase-negative;66)				
GSK2140944	0.5	2	- / - / -	- / - / -
Ceftazidime	0.06	0.25	100.0 / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -	98.4 / 0.0 / 1.6
Meropenem	≤0.06	0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	0.015	0.03	100.0 / - / -	100.0 / 0.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	100.0 / - / -	100.0 / 0.0 / 0.0
H. parainfluenzae (19)				
GSK2140944	1	4	- / - / -	- / - / -
Ceftazidime	0.03	0.12	100.0 / - / -	- / - / -
Ceftriaxone	≤0.06	≤0.06	100.0 / - / -	- / - / -
Meropenem	≤0.06	0.12	100.0 / - / -	- / - / -
Levofloxacin	0.03	>4	89.5 / - / -	- / - / -
Moxifloxacin	-	-	100.0 / - / -	- / - / -

a. Criteria as published by the CLSI [2014] and EUCAST [2014]. "-" indicates no interpretive criteria available for that category.
b. Includes: *Staphylococcus capitis* (9 strains), *Staphylococcus caprae* (4 strains), *Staphylococcus cohnii* (2 strains), *Staphylococcus epidermidis* (61 strains), *Staphylococcus haemolyticus* (11 strains), *Staphylococcus hominis* (10 strains), *Staphylococcus intermedius* (1 strain), *Staphylococcus saprophyticus* (1 strain), *Staphylococcus simulans* (1 strain), and *Staphylococcus warneri* (2 strains).
c. Penicillin breakpoints - parenteral non-meningitis.
d. Penicillin breakpoints - oral penicillin V.
e. Includes: *Streptococcus anginosus* (7 strains), *Streptococcus australis* (3 strains), *Streptococcus constellatus* (1 strain), *Streptococcus cristatus* (5 strains), *Streptococcus gordonii* (7 strains), *Streptococcus infantarius* (3 strains), *Streptococcus infantis* (3 strains), *Streptococcus intermedius* (1 strain), *Streptococcus massiliensis* (2 strains), *Streptococcus mitis/oralis* (5 strains), *Streptococcus mitis* group (7 strains), *Streptococcus mutans* (13 strains), *Streptococcus oralis* (8 strains), *Streptococcus parasanguinis* (7 strains), *Streptococcus salivarius* (22 strains), *Streptococcus sanguinis* (8 strains), and *Streptococcus vestibularis* (3 strains).
f. Includes: *Citrobacter freundii* (1 strain), *Citrobacter koseri* (1 strain), *Enterobacter aerogenes* (7 strains), *Enterobacter cloacae* (13 strains), *Escherichia coli* (50 strains), *Klebsiella oxytoca* (5 strains), *Klebsiella pneumoniae* (15 strains), *Morganella morganii* (2 strains), *Proteus mirabilis* (2 strains), *Providencia rettgeri* (1 strain), and *Serratia marcescens* (3 strains).

Figure 1. Chemical structure of GSK2140944.



CONCLUSIONS

- GSK2140944, a novel bacterial type II topoisomerase inhibitor, exhibited *in vitro* activity against Gram-positive pathogens (including MRSA) and Gram-negative pathogens including *Haemophilus* spp. and *Enterobacteriaceae*.
- GSK2140944 merits further study to evaluate its potential for use in infections where such organisms may be encountered.

ACKNOWLEDGEMENT

This project was sponsored by GlaxoSmithKline and has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under OTA Agreement No. HHSO100201300011C.

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