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In Vitro Activity of GT-1 and GT-1/GT-055 against Recent Gram-negative Clinical Isolates

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Abstract

Background: GT-1 (previously LCB10-0200), a new siderophore cephalosporin in development by Geom Therapeutics and LegoChem Biosciences, is active against a broad spectrum of gram-negative pathogens. GT-055 (previously LCB18-055) is a new B-lactamase inhibitor (BLI) that improves the activity of GT-1 against many B-lactamase producers. In this study, we evaluated the activity of GT-1 and GT-1/GT-055 against recently collected gram-negative clinical isolates from the USA.

Methods: Minimal inhibitory concentrations (MICs) were determined following CLSI microdilution guidelines against 200 *E. coli*, 200 *K. pneumoniae*, 200 other *Enterobacteriaceae*, 200 *P. aeruginosa*, 200 *A. baumannii* from 2016-2017. Compounds tested included GT-1, GT-055, GT-1+GT-055 in a 1:1 ratio, and comparator agents. As a siderophore antimicrobic, *in vitro* activity of GT-1 may be affected by the presence of iron in the testing medium. All isolates were tested in both cation-adjusted Mueller Hinton broth (CAMHB) and iron-depleted CAMHB; data from CAMHB is presented in this abstract. MIC endpoints were determined at 100% inhibition.

Results: The *in vitro* activity of all antimicrobials tested in CAMHB is shown in the table. MIC50/90 values of GT-1 against *A. baumannii* and *P. aeruginosa* of 2/8 µg/mL and 0.25/1 µg/mL, respectively, were at least 8-fold lower than those of ceftazidime-avibactam and meropenem. The addition of GT-055 to GT-1 reduced the MIC90 values for *Enterobacteriaceae* from 16 µg/mL to 2 µg/mL.

Antimicrobial	MIC$_{50/90}$ (µg/mL)				
	Acinetobacter baumannii N=200	*Pseudomonas aeruginosa* N=200	*Escherichia coli* N=200	*Klebsiella pneumoniae* N=200	Other *Enterobacteriaceae* N=200
GT-1:GT-055 (1:1)	2/8	0.25/1	0.25/1	0.25/2	0.25/2
GT-1	2/8	0.25/1	0.25/16	0.25/8	0.5/16
GT-055	>32/>32	>32/>32	2/4	4/16	8/>32
Meropenem	32/>32	1/16	≤0.06/≤0.06	≤0.06/0.12	≤0.06/0.25
Ceftazidime-avibactam	16/>32	2/8	0.12/0.25	0.12/0.5	0.25/1
Colistin	0.5/1	1/1	0.5/0.5	0.5/1	1/>8

Conclusions: GT-1 exhibited potent *in vitro* activity against recent gram-negative isolates. GT-055 improved the activity of GT-1 against the *Enterobacteriaceae*, but had less effect against *A. baumannii* and *P. aeruginosa*. These findings support further development of GT-1 and GT-055 for use against serious gram-negative pathogens.

INTRODUCTION

GT-1 (LCB10-0200) is a new siderophore cephalosporin in development by Geom Therapeutics and LegoChem Biosciences. GT-1 employs a “Trojan Horse” strategy that uses ferric iron uptake systems as a means to penetrate the outer membrane of gram-negative pathogens. GT-1 is active against a broad spectrum of Gram-negative pathogens including MDR *P. aeruginosa* and *A. baumannii*. GT-055 (LCB18-055) is a new ß-lactamase inhibitor that improves the activity of GT-1 against ß-lactamase-producing *Enterobacteriaceae*. In this study, we evaluated the activity of GT-1 and GT-1/GT-055 against recently collected gram-negative clinical isolates from the USA.

MATERIALS & METHODS

Minimal inhibitory concentrations (MICs) were determined following CLSI microdilution guidelines against 200 *E. coli*, 200 *K. pneumoniae*, 200 other *Enterobacteriaceae*, 200 *P. aeruginosa*, and 200 *A. baumannii* from 2016-2017 [1, 2]. Compounds tested included GT-1, GT-055, GT-1+GT-055 in a 1:1 ratio, and comparator agents. As a siderophore antimicrobic, *in vitro* activity of GT-1 may be affected by the presence of iron in the testing medium. All isolates were tested in both cation-adjusted Mueller Hinton broth (CAMHB) and iron-depleted CAMHB. MIC endpoints were determined at 100% inhibition.

RESULTS

Table 1. *In Vitro* Activity of GT-1 and GT-055 in Cation-adjusted Mueller Hinton Broth and Iron Depleted Mueller Hinton Broth against 600 *Enterobacteriaceae*

Organism (N)	Drug	MIC$_{50}$	MIC$_{90}$	%S	%I	%R	Range
Enterobacteriaceae (600)	GT-1:GT-055 (1:1)	0.25	2	na	na	na	≤0.06 - 64
	GT-1:GT-055 (1:1) ID-MH	0.25	1	na	na	na	≤0.06 - 64
	GT-1	0.25	16	na	na	na	≤0.06 - > 64
	GT-1 ID-MH	0.25	2	na	na	na	≤0.06 - > 64
	GT-055	4	32	na	na	na	0.12 - > 32
	Meropenem	≤0.06	0.12	94.2	0.2	5.7	≤0.06 - > 16
	Ceftazidime-avibactam	0.12	0.5	99.8	--	0.2	≤0.06 - 16
	Colistin	0.5	> 8	84.3	--	15.7	≤0.12 - > 8
Enterobacteriaceae Meropenem NS (35)	GT-1:GT-055 (1:1)	0.25	4	na	na	na	≤0.06 - 8
	GT-1:GT-055 (1:1) ID-MH	0.25	2	na	na	na	≤0.06 - 4
	GT-1	0.5	32	na	na	na	≤0.06 - > 64
	GT-1 ID-MH	0.25	4	na	na	na	≤0.06 - > 64
	GT-055	8	> 32	na	na	na	2 - > 32
	Meropenem	16	> 16	0	2.9	97.1	2 - > 16
	Ceftazidime-avibactam	0.5	2	97.1	--	2.9	0.12 - 16
	Colistin	0.5	> 8	62.9	--	37.1	0.25 - > 8
Enterobacteriaceae Colistin NS (20)	GT-1:GT-055 (1:1)	0.25	2	na	na	na	≤0.06 - 4
	GT-1:GT-055 (1:1) ID-MH	0.25	2	na	na	na	≤0.06 - 2
	GT-1	1	16	na	na	na	≤0.06 - > 64
	GT-1 ID-MH	0.5	4	na	na	na	≤0.06 - > 64
	GT-055	4	8	na	na	na	0.12 - > 32
	Meropenem	≤0.06	> 16	80.0	0	20.0	≤0.06 - > 16
	Ceftazidime-avibactam	0.12	1	100	--	0	≤0.06 - 2
	Colistin	> 8	> 8	0	--	100	8 - > 8

MIC$_{50/90}$ and range in µg/mL; S, susceptible; I, intermediate; R, resistant; ID-MH, iron depleted Mueller-Hinton broth; na, no breakpoint available; NS, non-susceptible

Table 2. *In Vitro* Activity of GT-1 and GT-055 in Cation-adjusted Mueller Hinton Broth and Iron Depleted Mueller Hinton Broth Against 200 *Pseudomonas aeruginosa*

Organism (n)	Drug	MIC$_{50}$	MIC$_{90}$	%S	%I	%R	Range
P. aeruginosa (200)	GT-1:GT-055 (1:1)	0.25	1	na	na	na	≤0.06 - 32
	GT-1:GT-055 (1:1) ID-MH	0.12	0.5	na	na	na	≤0.06 - 8
	GT-1	0.25	1	na	na	na	≤0.06 - 64
	GT-1 ID-MH	0.12	0.5	na	na	na	≤0.06 - 32
	GT-055	> 32	> 32	na	na	na	> 32 - > 32
	Meropenem	1	16	63.0	10.0	27.0	≤0.06 - > 32
	Ceftazidime	4	> 32	77.5	6.5	16	0.5 - > 32
	Ceftazidime-avibactam	2	8	98.5	--	1.5	0.5 - > 32
	Colistin	1	1	100	--	0	≤0.12 - 2
P. aeruginosa Meropenem NS (74)	GT-1:GT-055 (1:1)	0.25	2	na	na	na	≤0.06 - 32
	GT-1:GT-055 (1:1) ID-MH	0.12	1	na	na	na	≤0.06 - 8
	GT-1	0.5	2	na	na	na	≤0.06 - 64
	GT-1 ID-MH	0.12	1	na	na	na	≤0.06 - 32
	GT-055	> 32	> 32	na	na	na	> 32 - > 32
	Meropenem	8	32	0	27.0	73.0	4 - > 32
	Ceftazidime	8	> 32	59.5	12.2	28.4	1 - > 32
	Ceftazidime-avibactam	4	8	96.0	--	4.1	1 - > 32
	Colistin	1	1	100	--	0	0.25 - 2

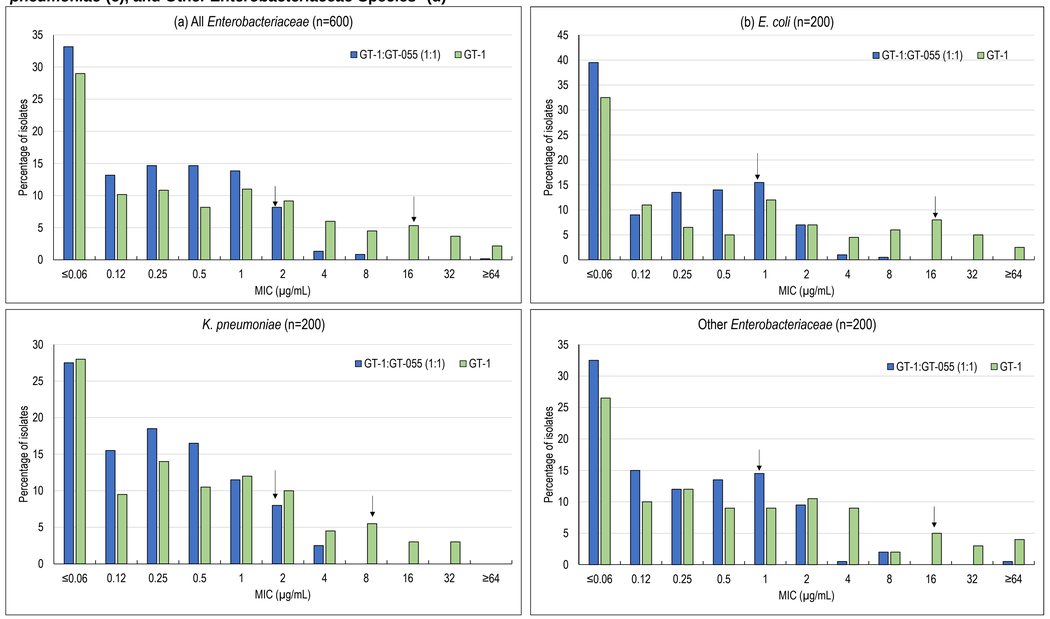
*MIC$_{50/90}$ and range in µg/mL; S, susceptible; I, intermediate; R, resistant; ID-MH, iron depleted Mueller-Hinton broth; na, no breakpoint available; NS, non-susceptible

Table 3. *In Vitro* Activity of GT-1 and GT-055 in Cation-adjusted Mueller Hinton Broth and Iron Depleted Mueller Hinton Broth Against 200 *Acinetobacter baumannii**

Organism (n)	Drug	MIC$_{50}$	MIC$_{90}$	%S	%I	%R	Range
A. baumannii (200)	GT-1:GT-055 (1:1)	2	8	na	na	na	≤0.06 - > 64
	GT-1:GT-055 (1:1) ID-MH	1	8	na	na	na	≤0.06 - > 64
	GT-1	2	8	na	na	na	≤0.06 - > 64
	GT-1 ID-MH	0.5	64	na	na	na	≤0.06 - > 64
	GT-055	> 32	> 32	na	na	na	> 32 - > 32
	Meropenem	32	> 32	38.5	2.0	59.5	≤0.06 - > 32
	Ceftazidime	> 32	> 32	43.5	2.5	54.0	0.5 - > 32
	Ceftazidime-avibactam	16	> 32	na	na	na	0.25 - > 32
	Colistin	0.5	1	94.0	--	6.0	0.25 - > 8

*MIC$_{50/90}$ and range in µg/mL; S, susceptible; I, intermediate; R, resistant; ID-MH, iron depleted Mueller-Hinton broth; na, no breakpoint available

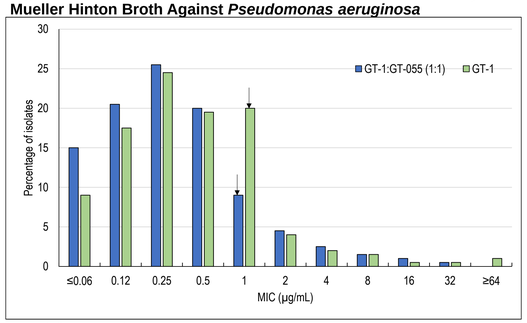
Figure 1. MIC Distribution of GT-1 and GT-055 in Cation-adjusted Mueller Hinton Broth Against All *Enterobacteriaceae* (a), *E. coli* (b), *K. pneumoniae* (c), and Other *Enterobacteriaceae* Species* (d)



Arrows indicate MIC$_{50}$ values

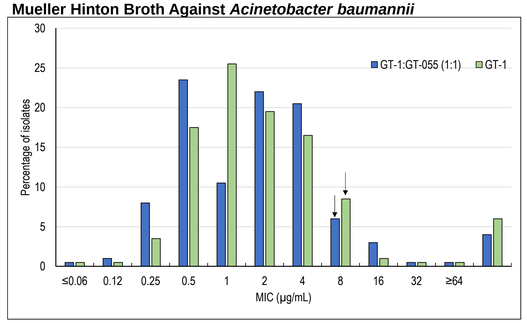
*Other *Enterobacteriaceae* species include (n): *Citrobacter freundii* (22), *Citrobacter koseri* (13), *Enterobacter asburiae* (7), *Enterobacter cloacae* (47), *Klebsiella (Enterobacter) aerogenes* (11), *Klebsiella oxytoca* (22), *Serratia liquefaciens* (1), *Serratia marcescens* (77)

Figure 2. MIC Distribution of GT-1 and GT-055 in Cation-adjusted Mueller Hinton Broth Against *Pseudomonas aeruginosa*



Arrows indicate MIC$_{50}$ values

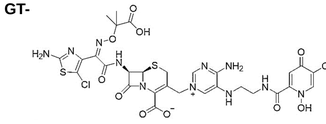
Figure 3. MIC Distribution of GT-1 and GT-055 in Cation-adjusted Mueller Hinton Broth Against *Acinetobacter baumannii*



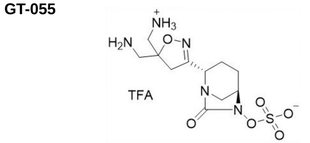
Arrows indicate MIC$_{50}$ values

STRUCTURE

GT-



GT-055



CONCLUSIONS

- GT-1 exhibited potent *in vitro* activity against recent gram-negative isolates.
- The addition of GT-055 improved the activity of GT-1 against the *Enterobacteriaceae*, but had less effect against *A. baumannii* and *P. aeruginosa*.
- There was an 8-fold decrease in the MIC$_{90}$ value of GT-1 for *Enterobacteriaceae* in iron deficient medium, and an 8-fold increase for *A. baumannii* owing to increased trailing. (Reading *A. baumannii* MICs at 80% inhibition reduced the MIC$_{90}$ in ID-MHB to 4 ug/mL). Iron-effects were less pronounced for *P. aeruginosa*.
- These findings support further development of GT-1 and GT-055 for use against serious gram-negative pathogens.

REFERENCES

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