

Figure 1A

Table I
Compounds of Formula A-II

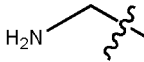
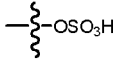
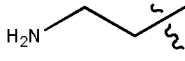
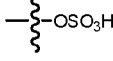
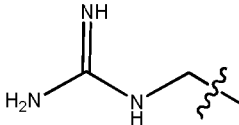
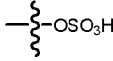
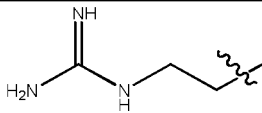
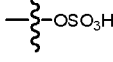
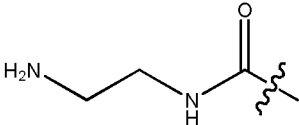
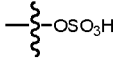
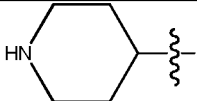
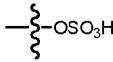
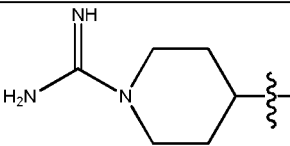
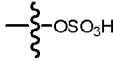
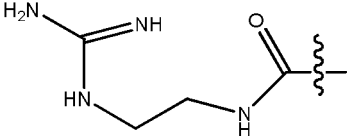
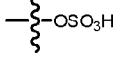
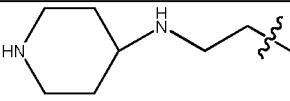
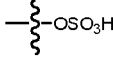
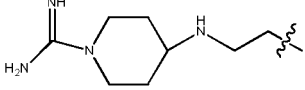
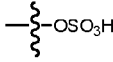
Cmpd. No.	R ¹	R
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609		
610		

Figure 1B

Table I
Compounds of Formula A-II

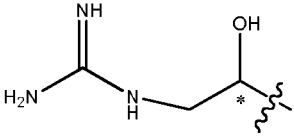
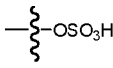
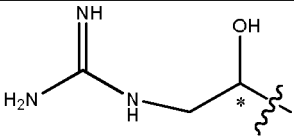
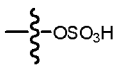
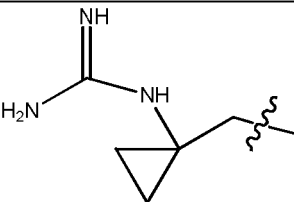
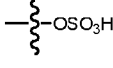
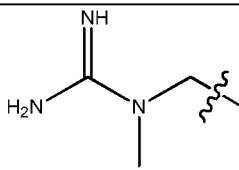
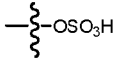
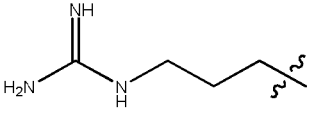
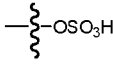
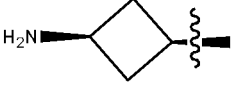
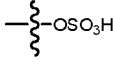
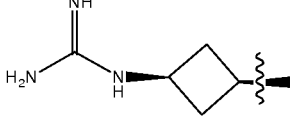
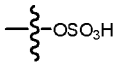
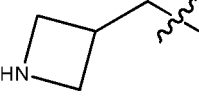
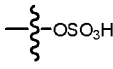
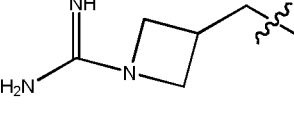
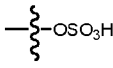
Cmpd. No.	R^1	R
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616		
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619		

Figure 1C

Table I
Compounds of Formula A-II

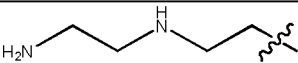
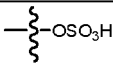
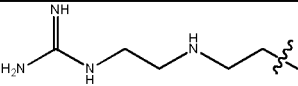
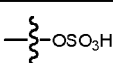
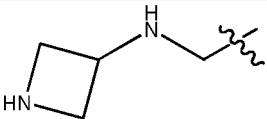
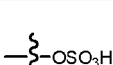
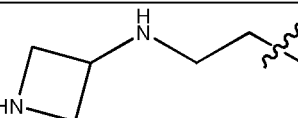
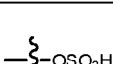
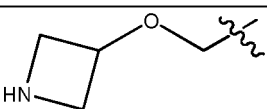
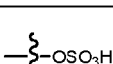
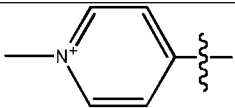
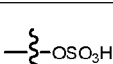
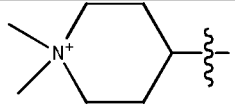
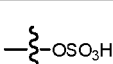
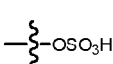
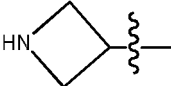
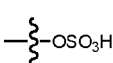
Cmpd. No.	R ¹	R
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625		
626		
627		
628		

Figure 1D

Table I
Compounds of Formula A-II

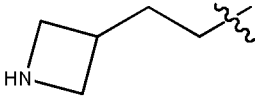
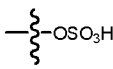
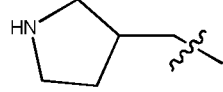
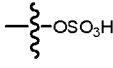
Cmpd. No.	R ¹	R
629		
630		

Figure 2A

Table II Standard BLI Potentiation MIC Assay in Combination with Ceftolozane Against a Panel of Isogenic and Clinical Strains Expressing β -Lactamases.

Strain #	β -Lactamase	Bkgd	No BLI	CCC	612	611	620	621	614	615	613	618	624	622	623	616	617	626
Eco.2806	KPC-2	isogenic	E	B	B	B	A	A	B	B	B	B	A	B	A	B	A	B
Pae.2808	KPC-2	clinical	E	C	B	B	C	C	B	B	C	B	B	C	C	B	C	B
Kpn.2478	KPC-3, TEM+	clinical	E	C	B	B	C	C	B	B	C	B	B	C	C	B	B	C
Kpn.2490	KPC-3, SHV+, TEM+	clinical	E	B	A	A	B	AA	B	A	A	A	B	B	C	B	A	B
Kpn.2783	CTX-M-15, SHV+, TEM+	clinical	E	A	B	A	B	B	B	B	B	B	B	B	B	B	B	B
Kpn.571	TEM-26	clinical	D	AA	A	A	A	A	AA	A	A	A	AA	A	A	A	A	B
Pae.2885	AmpC	clinical	B	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Cfr.568	AmpC	clinical	E	C	B	C	C	C	B	C	C	B	B	C	C	B	B	C
Ecl.569	AmpC	clinical	E	B	B	B	A	B	B	A	B	B	B	A	B	B	A	C
Kpn.2914	KPC-2, SHV+	clinical	D	B	B	B	B	C	B	B	B	B	B	B	B	B	B	B
Kpn.2913	KPC-2, SHV+	clinical	D	A	A	A	B	A	A	A	A	A	A	A	A	A	A	B
Kpn.2917	KPC-2, SHV+	clinical	D	A	A	AA	A	A	A	A	A	A	AA	A	A	A	A	A
Kpn.2918	KPC-3, SHV+, TEM+	clinical	E	C	C	B	C	C	B	C	C	C	B	C	C	C	C	C
Kpn.2909	KPC-3, SHV+, TEM+	clinical	E	B	B	B	B	B	B	B	B	B	B	B	B	B	C	C
Eco.2711	KPC	clinical	D	A	A	A	A	A	A	B	A	A	A	A	A	A	A	B
Eco.2781	KPC-2, TEM+	clinical	C	AA	A	AA	A	A	AA	A	A	A	A	A	A	A	B	A
Kpn.2926	CTX-M-15, OXA-48	clinical	E	B	C	C	C	C	B	C	B	B	B	C	C	C	C	D
Pae.2757	AmpC over-expn	clinical	C	B	B	B	B	B	B	B	B	B	B	B	B	B	B	C
Pae.2863	AmpC de-repress	clinical	C	B	B	B	C	B	B	B	B	B	B	C	B	B	B	B
Eco.2843	DHA-1	isogenic	E	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Eco.2491	CMY-2	clinical	D	A	B	A	A	A	A	A	A	A	A	A	A	A	A	B
Eco.2902	Aba-ADC-33	isogenic	E	B	B	C	C	D	C	C	B	C	C	C	C	B	C	C
Eco.2840	KPC-4	isogenic	E	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Eco.2845	OXA-15	isogenic	E	D	D	C	D	D	C	D	D	D	D	D	D	D	D	D
MIC90			E	C	B	C	C	C	B	C	C	B	B	C	C	B	C	C
MIC50			E	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B

AA=<0.25 μ g/mL; A=0.25-0.5 μ g/mL; B=1-2 μ g/mL; C=4-8 μ g/mL; D=16-32 μ g/mL; E $\geq$ 64 μ g/mL.

Figure 2B

Table II Standard BLI Potentiation MIC Assay in Combination with Ceftolozane Against a Panel of Isogenic and Clinical Strains Expressing β -Lactamases.

Strain #	β -Lactamase	Bkgd	No BLI	CCC	627	625	619	609	610	601	602	603	604	605	606	607	
Eco.2806	KPC-2	isogenic	E	B	B	A	A	B	A	B	B	A	A	B	A	B	
Pae.2808	KPC-2	clinical	E	C	C	C	C	C	B	C	C	B	B	C	B	C	
Kpn.2478	KPC-3, TEM+	clinical	E	C	C	C	C	C	C	C	D	B	B	C	B	C	
Kpn.2490	KPC-3, SHV+, TEM+	clinical	E	B	B	A	A	A	A	B	C	A	A	B	B	A	
Kpn.2783	CTX-M-15, SHV+, TEM+	clinical	E	A	B	B	B	B	B	B	C	A	A	B	B	B	
Kpn.571	TEM-26	clinical	D	AA	A	B	A	A	A	A	B	B	A	A	A	A	
Pae.2885	AmpC	clinical	B	A	A	A	A	A	A	B	B	A	A	A	A	A	
Cfr.568	AmpC	clinical	E	C	C	B	B	C	B	B	C	C	C	C	C	C	
Ecl.569	AmpC	clinical	E	B	B	A	B	B	A	B	C	B	A	B	A	A	
Kpn.2914	KPC-2, SHV+	clinical	D	B	B	B	A	B	B	B	C	A	B	B	B	B	
Kpn.2913	KPC-2, SHV+	clinical	D	A	A	B	A	A	A	B	B	A	A	C	A	A	
Kpn.2917	KPC-2, SHV+	clinical	D	A	A	A	AA	A	A	A	B	A	A	B	A	A	
Kpn.2918	KPC-3, SHV+, TEM+	clinical	E	C	C	B	C	C	C	C	D	B	B	C	C	C	
Kpn.2909	KPC-3, SHV+, TEM+	clinical	E	B	C	B	B	C	B	B	C	B	B	C	B	C	
Eco.2711	KPC	clinical	D	A	A	B	A	A	A	A	B	A	A	A	B	A	
Eco.2781	KPC-2, TEM+	clinical	C	AA	A	A	AA	A	A	A	A	AA	AA	A	A	A	
Kpn.2926	CTX-M-15, OXA-48	clinical	E	B	B	C	C	C	C	B	E	B	B	C	C	D	
Pae.2757	AmpC over-exprn	clinical	C	B	B	B	B	B	B	B	B	B	B	B	B	B	
Pae.2863	AmpC de-repress	clinical	C	B	B	B	B	B	A	B	C	B	B	B	B	B	
Eco.2843	DHA-1	isogenic	E	A	A	A	A	A	A	B	B	A	A	B	A	A	
Eco.2491	CMY-2	clinical	D	A	A	B	A	A	A	A	A	A	A	A	A	A	
Eco.2902	Aba-ADC-33	isogenic	E	B	C	C	B	C	B	C	D	B	B	C	B	C	
Eco.2840	KPC-4	isogenic	E	D	D	D	D	D	D	D	E	D	D	D	D	D	
Eco.2845	OXA-15	isogenic	E	D	D	D	D	D	D	D	D	C	C	C	C	C	
MIC90			E	C	C	C	C	C	C	C	D	B	B	C	C	C	
MIC50			E	B	B	B	B	B	A	B	C	B	B	B	B	B	

AA=<0.25 μ g/mL; A=0.25-0.5 μ g/mL; B=1-2 μ g/mL; C=4-8 μ g/mL; D=16-32 μ g/mL; E $\geq$ 64 μ g/mL.

Figure 3A

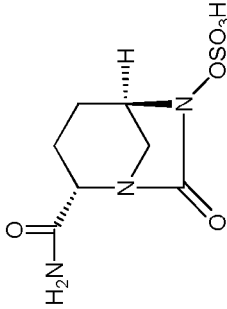
Table III: Synergy MIC (sMIC) Against a Panel of Isogenic and Clinical Strains Expressing β-lactamases

β-Lactamase	Bkgd	Sp	β-Lactam (4 μg/mL)	COMPOUNDS															
				CCC	612	611	620	621	614	615	613	618	624	622	623	616	617	626	627
none	isogenic	Eco	none	D	ND	D	F	F	D	F	F	E	E	F	F	F	F	F	F
KPC-2	isogenic	Eco	CXA-101	B	A	AA	A	A	A	AA	A	AA	A	A	A	A	A	A	A
OXA-15	isogenic	Eco	CXA-101	D	D	C	D	D	C	D	D	C	D	D	D	D	E	D	D
CTX-M-15	isogenic	Eco	CXA-101	A	B	B	C	A	B	B	B	A	B	B	B	A	C	B	C
SHV-12	isogenic	Eco	CXA-101	B	B	B	C	B	B	B	C	B	B	C	C	C	C	D	C
P99	isogenic	Eco	CXA-101	A	AA	A	A	A	AA	A	A	A	A	B	A	A	A	B	A
KPC-3	clinical	Kpn	CXA-101	C	B	B	C	C	B	B	C	B	B	C	C	C	C	C	C
KPC-2	clinical	Pae	CXA-101	B	A	B	B	B	B	B	C	B	B	C	B	B	B	C	B

AA=< 0.25μg/mL; A = 0.25-0.5 μg/mL; B = 1-2 μg/mL; C = 4-8 μg/mL; D = 16-32 μg/mL; E = 64μg/mL; F =≥128μg/mL

CXA-101 is Ceftolozane

Eco is *Escherichia coli*, Kpn is *Klebsiella pneumoniae*, Pae is *Pseudomonas aeruginosa*



CCC is comparator compound

Figure 3B

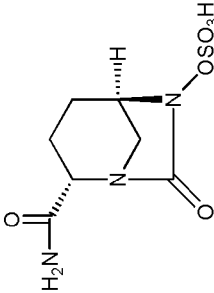
Table III: Synergy MIC (sMIC) Against a Panel of Isogenic and Clinical Strains Expressing β-lactamases

β-Lactamase	Bkgd	Sp	β-Lactam (4 μg/mL)	COMPOUNDS														
				CCC	619	609	610	601	602	603	604	605	606	607	608			
none	isogenic	Eco	none	D	E	F	F	D	E	E	D	F	F	F	F			
KPC-2	isogenic	Eco	CXA-101	B	A	A	A	A	B	A	A	B	A	B	A			
OXA-15	isogenic	Eco	CXA-101	D	D	D	D	D		C	C	D		D	D			
CTX-M-15	isogenic	Eco	CXA-101	A	B	B	B	B	B	A	B	C	B	B	B			
SHV-12	isogenic	Eco	CXA-101	B	D	C	C	B	B	B	B	B	C	C	B			
P99	isogenic	Eco	CXA-101	A	A	B	A	A	A	A	A	B	B	B	A			
KPC-3	clinical	Kpn	CXA-101	C	D	C	C	C	C	B	B	C	C	C	C			
KPC-2	clinical	Pae	CXA-101	B	C	B	C	C	C	A	B	C	C	C	B			

AA=< 0.25μg/mL; A = 0.25-0.5 μg/mL; B = 1-2 μg/mL; C = 4-8 μg/mL; D = 16-32 μg/mL; E = 64μg/mL; F =>128μg/mL

CXA-101 is Ceftolozane

Eco is *Escherichia coli*, Kpn is *Klebsiella pneumoniae*, Pae is *Pseudomonas aeruginosa*

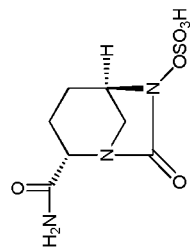


CCC is comparator compound

Table IV: Inhibition Kinetics for the KPC-2 β -lactamase

[illegible]

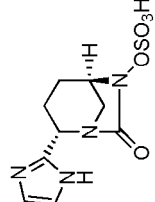
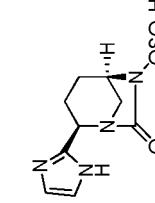
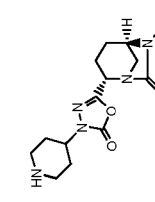
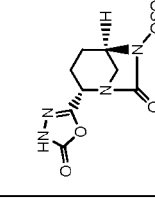
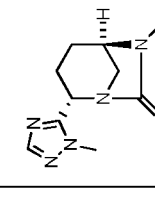
	Compound								
	CC C	601	602	603	604	605	606	607	608
	Kinact/K mM ⁻¹ s ⁻¹	C	B	C	B	A	B	B	A

$$A = 1000\text{--}5000 \text{ mM}^{-1}\text{s}^{-1}; B = 100\text{--}999 \text{ mM}^{-1}\text{s}^{-1}; C = 1\text{--}99 \text{ mM}^{-1}\text{s}^{-1}$$


CCC is comparator compound

Figure 5A

Table V: Synergy MIC (sMIC) of Comparator Compounds Against a Panel of Isogenic and Clinical Strains Expressing β -lactamases

β -Lactamase	Bkgd	Sp	β -Lactam (4 μ g/mL)					
none	isogenic	Eco	D	F	F	F	F	F
KPC-2	isogenic	Eco	C	F	C	C	C	C
OXA-15	isogenic	Eco	ND	ND	ND	ND	ND	F
CTX-M-15	isogenic	Eco	C	F	D	D	B	D
SHV-12	isogenic	Eco	C	F	D	D	C	D
P99	isogenic	Eco	C	F	B	B	B	C
KPC-3	clinical	Kpn	D	F	C	C	D	E
KPC-2	clinical	Pae	F	F	D	D	F	D

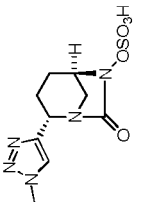
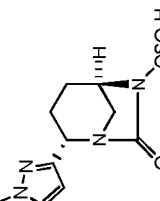
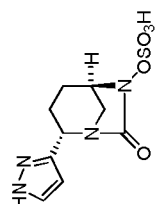
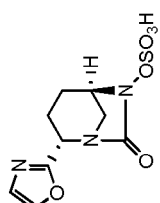
AA= $<0.25\mu\text{g/mL}$; A = $0.25\text{--}0.5\mu\text{g/mL}$; B = $1\text{--}2\mu\text{g/mL}$; C = $4\text{--}8\mu\text{g/mL}$; D = $16\text{--}32\mu\text{g/mL}$; E = $64\mu\text{g/mL}$; F = $\geq 128\mu\text{g/mL}$

CXA-101 is Cefotolozane

Eco is *Escherichia coli*, Kpn is *Klebsiella pneumoniae*, Pae is *Pseudomonas aeruginosa*

Figure 5B

Table V: Synergy MIC (sMIC) of Comparator Compounds Against a Panel of Isogenic and Clinical Strains Expressing β -lactamases

β -Lactamase	Bkgd	Sp	β -Lactam (4 μ g/mL)				
none	isogenic	Eco	none	E	F	F	F
KPC-2	isogenic	Eco	CXA-101	A	D	C	B
OXA-15	isogenic	Eco	CXA-101	ND	F	F	D
CTX-M-15	isogenic	Eco	CXA-101	D	F	D	B
SHV-12	isogenic	Eco	CXA-101	B	C	C	B
P99	isogenic	Eco	CXA-101	A	C	B	A
KPC-3	clinical	Kpn	CXA-101	E	F	F	D
KPC-2	clinical	Pae	CXA-101	E	F	F	D

AA= $<0.25\mu$ g/mL; A = $0.25-0.5\mu$ g/mL; B = $1-2\mu$ g/mL; C = $4-8\mu$ g/mL; D = $16-32\mu$ g/mL; E = 64μ g/mL; F = $\geq 128\mu$ g/mL

CXA-101 is Ceftolozane

Eco is *Escherichia coli*, Kpn is *Klebsiella pneumoniae*, Pae is *Pseudomonas aeruginosa*