BETA-LACTAMASE INHIBITORS:
SCIENTIFICALLY ELEGANT, JUST COMPLEX

AMBLER CLASSES OF β-LACTAMASES

A	B	C	D
Serine β-lactamases	**Metallo β-lactamases**	**Serine β-lactamases**	**Serine β-lactamases**

• TEM
• SHV
• CTX-M
• KPC
• GES
	• NDM
	• VIM
	• IMP
	• SPM
	• GIM
		• AmpC
		  ◦ CMY
		  ◦ DHA
		  ◦ FOX
		  ◦ ACT
		  ◦ MIR
			• OXA-48
			• OXA-23
			• OXA-58
			• OXA-143
			• OXA-235

Includes common ESBLs & carbapenemases in the US. Inhibitors form tight covalent bonds with these enzymes.	Contains zinc ion(s) at the active site, preventing the formation of a covalent intermediate.	Class C have a shallow pocket, leading to looser binding than class A.	A post-translationally carbamylated lysine creates a hydrophobic pocket that leads to loose binding.

β-LACTAMASE INHIBITOR DISCOVERY TIMELINE

1972 — CLAVULANATE
- First discovered inhibitor

1977 — SULBACTAM
- Class A inhibitor
- Intrinsic activity against *Acinetobacter*

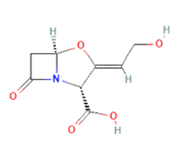
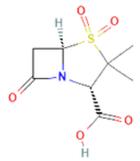
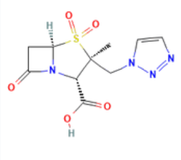
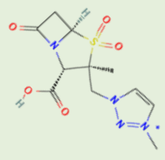
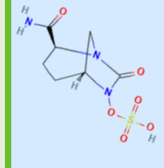
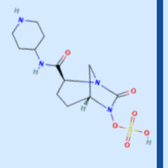
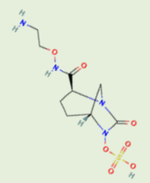
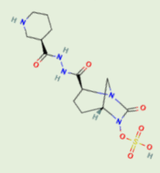
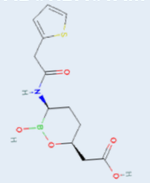
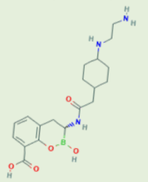
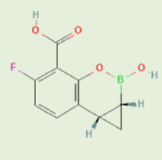
1982 — TAZOBACTAM
- Broader Class A inhibition

2000 to 2010 — DBO INHIBITORS
- Avibactam
- Relebactam
- Durlobactam

2010 to now — BORONATE & MORE
- Vaborbactam
- Taniborbactam
- Xeruborbactam
- Ledaborbactam

One really cool thing about many newer inhibitors is they are recyclable. They bind, inhibit the enzyme, & then can dissociate & bind again. That way, you don't run out of inhibitor.

Pre-2000 Inhibitors	Modern Inhibitors
• Suicide inhibitors (consumed)	• Recyclable (not consumed)
• Irreversible binding	• Reversible binding
• More limited spectrum	• Broad-spectrum

	SUICIDE INHIBITORS (IRREVERSIBLE)			DIAZABICYCLOOCTANE INHIBITORS (REVERSIBLE)				BCH	BORONATE INHIBITORS (REVERSIBLE)			
STRUCTURE	CLAVULANATE 	SULBACTAM 	TAZOBACTAM 	ENMETAZOBACTAM 	AVIBACTAM 	RELEBACTAM 	DURLOBACTAM	NACUBACTAM 	ZIDEBACTAM 	VABORBACTAM 	TANIBORBACTAM 	XERUBORBACTAM 	LEDABORBACTAM
INHIBITS	Class A	Class A	Class A	Class A	Class A (most KPC), C, & some D (OXA-48)	Class A, C	Class A, C & some D (OXA-48 like)	Class A, C, D & some B	Class A, C	Class A (KPC), Class C (AmpC)	Class A, C, & some B & D	Class A, B, C & D	Class A, C & some D
PBP ACTIVITY (AFFINITY*)	None	**PBP 1a (moderate), 3 (high)**	**PBP 2,4 (weak)**	None	**PBP 2 (moderate)**	None	**PBP 2 (high to moderate)**	**PBP 2 (high to moderate)**	**PBP 2 (extremely high)**	None	None	**PBP 1 (high to moderate), 2, 3 (moderate)**	None
PARTNER DRUGS	Amoxicillin. Ticarcillin	Ampicillin, Cefoperazone, Durlobactam	Piperacillin, Ceftolozane	Cefepime	Ceftazidime, Aztreonam	Imipenem/ Cilastin	Sulbactam	Cefepime, Aztreonam	Cefepime	Meropenem	Cefepime	Cefepime, Meropenem, Ceftibuten, Cefiderocol?	Cefepime, Ceftibuten
MISC FACTS	Named after *Streptomyces clavuligerus*	Sometimes used for intrinsic antibacterial activity in *A. baumannii* treatment	Tazobactam was patented in 1982 & came into medical use in 1992	Acts as a serine β-lactamase inhibitor but is reversible A zwitterion that diffuses readily across membranes	The first to lack a β-lactam ring - the DBO structure mimics the ring, but avoids being destroyed	Not as potent as avibactam Inhibits but does not induce AmpC	Not hydrolyzed by metallos, but does not inhibit them	Not hydrolyzed by metallos, but does not inhibit them Not currently being pursued for US approval	New BCH class - very similar to DBO Is not hydrolyzed by metallos, but does not inhibit them	First in its class, utilizes a cyclic boronic acid instead of a β-lactam ring	Submitted to FDA in 2024, additional CMC data was requested, but no further attempts for approval	Inhibits metallos A potential oral option	In phase 2 A potential oral option for ESBLs

Green = Not Yet Commercially Available in the USA , though cefepime/enmetazobactam and cefepime/zidebactam have been approved by the FDA

*Affinity categories are estimations and were derived using average IC_{50} as extremely high (<1 μM), high (<10 μM), moderate (10–100 μM), and weak(>100–1,000 μM). These categories are not standardized because PBPs are not interchangeable across bacterial species, and published affinity measurements often use different assays, units, and experimental conditions.

PBP activity is becoming increasingly important. A partner drug that affects one PBP & an inhibitor that affects another would be ideal, if PK/PD characteristics were aligned.

Combating resistance is increasingly tricky. Bacteria can combine enzymatic & non-enzymatic resistance, and even accumulate PBP mutations. It's a continuous race to outwit the bugs.

The partner β-lactam matters. Inhibitors have their own PK/PD targets. The drug & inhibitor need a high joint probability of target attainment for best results. That's the probability that both drugs achieve their respective PK/PD targets..

Abbreviations: BCH-bicyclo-acyl hydrazide, CMC - Chemistry & Manufacturing Controls, DBO - Diazabicyclooctane, EHR - Electronic Health Record, ESBL - Extended-Spectrum Beta-Lactamase, MISC - Miscellaneous, PBP- Penicillin Binding Protein, PD- Pharmacodynamics, PK - Pharmacokinetics

References:
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