ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

pubs.acs.org/acsmedchemlett

Combatting Resistant Bacteria with the Help of Beta-Lactamase Inhibitors

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

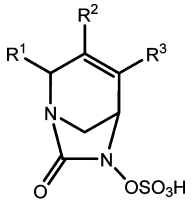
Title:	Heterobicyclic Compounds as Beta-Lactamase Inhibitors		
Patent Application Number:	WO 2013/150296 A1	**Publication Date:**	October 10, 2013
Priority Application:	US 61/618,993	**Priority Date:**	April 2, 2012
Inventors:	McGuire, H.; Bist, S.; Bifulco, N.; Zhao, L.; Wu, Y.; Huynh, H.; Xiong, H.; Comita-Prevoir, J.; Dussault, D.; Geng, B.; Chen, B.; Durand-Reville, T.; Guler, S.		
Assignee Company:	Astrazeneca AB, SE-151 85 Södertälje (SE)		
Disease Area:	Bacterial Infections	**Biological Target:**	β-Lactamase

Summary: The invention in this patent application is related to heterobicyclic compounds represented generally by formula (Ia), which are β-lacatamase inhibitors. These compounds may potentially be useful for the treatment of bacterial infections, including infections caused by drug and multidrug resistant organisms.

β-lactam antibiotics treat infections with a broad spectrum of Gram-positive and Gram-negative bacteria by inhibiting the cell wall synthesis of the bacterium. They are generally safe and well-tolerated drugs that exhibit low toxicity because their biological target has no eukaryotic analogue. However, there are many infectious bacterial strains that show significant resistance to these drugs, causing patient morbidity and mortality. Examples of resistant strains include methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug resistant (MDR) strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumonia*, and other Enterobacteriaceae. The bacterial resistance is primarily caused by extended-spectrum β-lactamases (ESBLs). β-lactamases are bacterial enzymes that cleave the β-lactam rings rendering the antibiotic drugs inactive. There are currently four known classes of β-lactamases denoted Class A, Class B, Class C, and Class D. Classes A, C, and D are serine β-lactamases, while Class B enzymes are metallo-β-lactamases (MBLs).

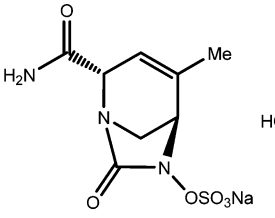
To improve the effectiveness of β-lactam antibiotics, they may be used in conjunction with β-lactamase inhibitors. Most β-lactamase inhibitors have little antibiotic activity of their own, but they can block the activity of β-lactamases to allow the β-lactam antibiotics to work and overcome bacterial resistance. Currently available β-lactamase inhibitors, clavulanic acid, tazobactam, and sulbactam, are only effective against certain Class A enzymes. Other β-lactamase inhibitors such as Avibactam and MK7655, currently in clinical trials, work primarily on Classes A and C enzymes but show minimal effect against Class D enzymes. In order to effectively combat the significant β-lactam antibiotics resistance seen today by different bacteria strains, there is a need to develop β-lactamase inhibitors that can effectively block all three serine β-lactamases classes. There is also a need to develop new β-lactamase inhibitors which are effective against class D β-lactamases.

Important Compound Classes:

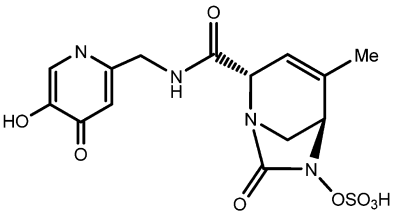


Formula (**Ia**)

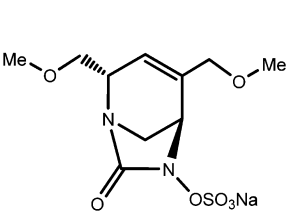
Key Structures: The inventors listed the structure and synthesis of 29 examples of the compounds of formula (I) including these three compounds:



1



8



13

Received: December 11, 2013
Published: December 20, 2013

Biological Assay: Minimum Inhibitory Concentrations (MICs) were determined by the broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Biological Data: The inventors assessed the synergy of compounds of formula (I) with β-lactams against several organisms producing a variety of β-lactamases belonging to different classes. MIC values were determined according to the CLSI guidelines. The data from the above three examples are listed in the following table:

	MIC (μM)			
	Klebsiella pneumoniae	Pseudomonas aeruginosa	Pseudomonas aeruginosa	Pseudomonas aeruginosa
	KPC2	AmpC	PER-1, OXA-10	AmpC
Ceftazidime	256	128	256	32
+ Example **1** (4μg/L)	≤ 0.50	4	2	4
+ Example **8** (4μg/L)	≤ 0.50	64	4	8
+ Example **13** (4μg/L)	≤ 0.50	64	64	16

Synergy was defined as a 4-fold or more reduction in the MIC of the β-lactam in the presence of the compound of formula (I), compared to the β-lactam alone.

Claims: Claims 1−15: composition of matter; variations of formulas Ia

Claim 16−18: composition of matter; specific examples of formula Ia

Claim 19: pharmaceutical composition

Claim 20−23: use of compounds as a medicament for the treatment of bacterial infection

Recent Review Articles:

Chen, J.; Shang, X.; Hu, F.; Lao, X.; Gao, X.; Zheng, H.; Yao, W. *Mini-Rev. Med. Chem.* **2013**, *13* (13), 1846−1861.

Bebrone, C.; Lassaux, P.; Vercheval, L.; Sohier, J.-S.; Jehaes, A.; Sauvage, E.; Galleni, M. *Drugs* **2010**, *70* (6), 651−679.

Toney, J. H.; Moloughney, J. G. *Curr. Opin. Invest. Drugs* **2004**, *5* (8), 823−826.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.