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Combatting Drug-Resistant Bacteria with Gyrase and Topoisomerase IV Inhibitors

Patent Highlight

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Title:	Pyrimidine Gyrase and Topoisomerase IV Inhibitors		
Patent/Patent Application Number:	WO 2012/097269 Al	**Publication Date:**	July 19, 2012
Priority Application:	US 61/432,965	**Priority Date:**	January 14, 2011
	US 61/499,134		June 20, 2011
	US 61/515,174		August 4, 2011
	US 61/515,249		August 4, 2011
Inventors:	Le Tiran, A.; Grillot, A.-L.; Charifson, P. S.; Bennani, Y. L.; O'dowd, H.; Perola, E.		
Assignee Company:	Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139, United States		
Disease Area:	Bacterial Infections	**Biological Target:**	Gyrase and/or Topoisomerase IV

Summary:

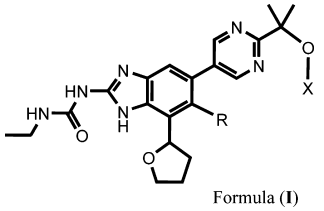
This patent application relates to compounds of formula (I) that act as gyrase and/or topoisomerase IV inhibitors and may possess a broad range of antibacterial activities with favorable toxicological properties. These compounds may either possess the activities or act as prodrugs of compounds possessing the said activities.

Bacterial DNA gyrase is a topoisomerase protein tetramer consisting of two A (GyrA) and two B (GyrB) subunits. GyrA is associated with binding and cleavage of DNA, whereas GyrB binds and hydrolyzes ATP. Topoisomerase IV consists of the ATP-binding subunit, ParE, and the catalytic subunit, ParC. It primarily resolves linked chromosome dimers at the conclusion of DNA replication. Together, these enzymes are necessary for the bacterial DNA replication, cell growth, and division and are associated with the DNA transcription, repair, and recombination. Inhibition of gyrase and/or topoisomerase IV is an attractive strategy to develop new antibiotics with novel mechanisms of action to battle emerging drug-resistant bacteria.

The patent application explains that GyrB and ParE subunits supply the energy necessary for catalytic turnover and resetting of the enzymes via ATP hydrolysis. Inhibitors that target the ATP binding sites in both the GyrB and the ParE subunits would be useful for treating various bacterial infections and treating nosocomial infections in hospitals where the formation and transmission of resistant bacteria are becoming increasingly prevalent. Using existing antibiotics as examples to drive this point, the application mentioned that the widely used quinolone and fluoroquinolones antibiotics that inhibit GyrA and/or ParC develop bacterial resistance. Another class of inhibitors is the coumarin, one of the few antibiotics that bind to GyrB. Its inhibition includes binding the coumarin carbonyl and the surface Arg136 in GyrB. The coumarin-resistant bacteria show mutation at that arginine residue; enzymes with this mutation show lower supercoiling and ATPase activity, but they are also less sensitive to inhibition by coumarin drugs. Coumarins also suffer generally from low permeability in bacteria, eukaryotic toxicity, and poor water solubility.

Thus, with bacterial resistance to antibiotics becoming a serious worldwide health problem, it would be beneficial to introduce new, effective inhibitors of both GyrB and ParE that preferably do not rely on binding to Arg136 for activity. Such inhibitors would be viable antibiotic candidates with probably less chance of developing bacterial resistance.

Important Compound Classes:



Formula (**I**)

Definitions:

R = hydrogen or fluorine

X = H, $-PO(OH)_2-PO(OH)O^-M^+$, $-PO(O^-)_2{\cdot}2M^+$, or $-PO(O^-)_2{\cdot}D^{2+}$

(M^+ is a pharmaceutically acceptable monovalent cation and D^{2+} is a pharmaceutically acceptable divalent cation)

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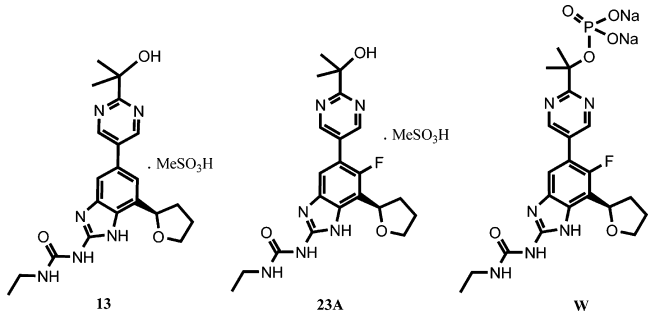
Key Structures: The three compounds shown here were described and claimed specifically in the patent application.



Biological Assay: DNA Gyrase ATPase Assay

Biological Data:

Inhibition of S. *aureus* DNA Gyrase		
Selected Compound	Ki(nM)	ICso (nM)
Compound **23**	9	
Compound **W**	< 9	54
Inhibition of S. *aureus* DNA Topo IV		
Compound **23**	12	
Compound **W**	30	150

Recent Review Articles:

Saravana Kumar, N.; Dhivya, D.; Vijayakumar, B. A focus on quinolones and its medicinal importance. *Int. J. Novel Trends Pharm. Sci.* **2011**, *1* (1), 28−36.

Martins, M.; McCusker, M.; Amaral, L.; Fanning, S. Mechanisms of antibiotic resistance in Salmonella: Efflux pumps, genetics, quorum sensing and biofilm formation. *Lett. Drug Des. Discovery* **2011**, *8* (2), 114−123.

Anderson, A. C.; Pollastri, M. P.; Schiffer, C. A.; Peet, N. P. The challenge of developing robust drugs to overcome resistance. *Drug Discovery Today* **2011**, *16* (17/18), 755−761.

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Notes

The authors declare no competing financial interest.