Data collection for machine design of novel antibiotics against ESKAPE bacteria

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Antibiotic Resistance Crisis

In 2019 more than 2.8 million antibiotic-resistant infections occurred in the U.S., and more than 35,000 people died

Figure 1 Developing Antibiotic Resistance: A Timeline of Key Events[5]

ANTIBIOTIC RESISTANCE IDENTIFIED		ANTIBIOTIC INTRODUCED
Penicillin-R *Staphylococcus*	1940	
	1943	Penicillin
	1950	Tetracycline
	1953	Erythromycin
Tetracycline-R *Shigella*	1959	
	1960	Methicillin
Methicillin-R *Staphylococcus*	1962	
Penicillin-R pneumococcus	1965	
Erythromycin-R *Streptococcus*	1968	
	1967	Gentamicin
	1972	Vancomycin
Gentamicin-R *Enterococcus*	1979	
	1985	Imipenem and ceftazidime
Ceftazidime-R Enterobacteriaceae	1987	
Vancomycin-R *Enterococcus*	1988	
Levofloxacin-R pneumococcus	1996	1996 Levofloxacin
Imipenem-R Enterobacteriaceae	1998	
XDR tuberculosis	2000	2000 Linezolid
Linezolid-R *Staphylococcus*	2001	
Vancomycin-R *Staphylococcus*	2002	
	2003	Daptomycin
PDR-*Acinetobacter* and *Pseudomonas*	2004/5	
Ceftriaxone-R *Neisseria gonorrhoeae*	2009	
PDR-Enterobacteriaceae		
	2010	Ceftaroline
Ceftaroline-R *Staphylococcus*	2011	

PDR = pan-drug-resistant; R = resistant; XDR = extensively drug-resistant

Dates are based upon early reports of resistance in the literature. In the case of pan-drug-resistant *Acinetobacter* and *Pseudomonas*, the date is based upon reports of health care transmission or outbreaks. Note: penicillin was in limited use prior to widespread population usage in 1943.

1. Old antibiotics are no longer working.

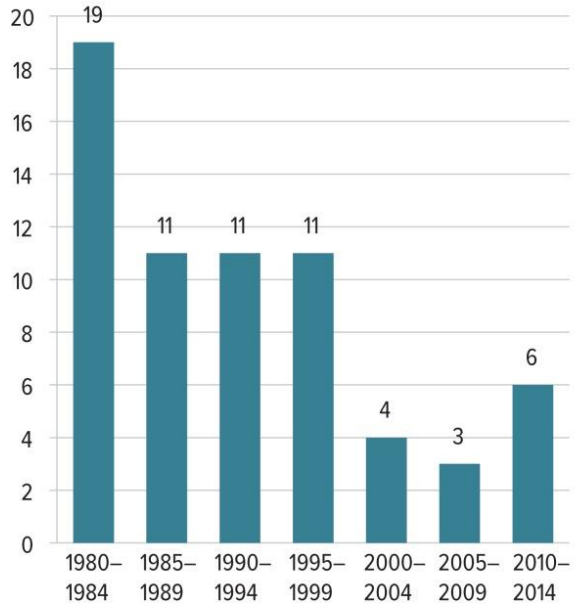
2. Antibiotics are no longer favorable investments.

a. Expensive to research.

b. Doctors are less likely to prescribe new antibiotics .

c. New antibiotics are dedicated to only treating severe infections or resistant infections.

Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



The number of new antibiotics developed and approved has decreased steadily over the past three decades (although four new drugs were approved in 2014), leaving fewer options to treat resistant bacteria.

* Drugs are limited to systemic agents. Data courtesy of the CDC[5] and the FDA Center for Drug Evaluation and Research.

from C. Lee Ventola *PT*, **2015**, *40*, 277

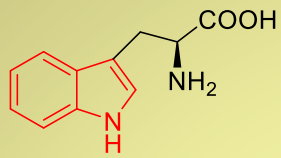
ESKAPE Bacteria -Six Highly Antibiotic Resistance Bacterial Pathogens

Enterococcus faecium - gram-positive bacteria
Staphylococcus aureus - gram-positive bacteria
Klebsilla pneumoniae - gram-negative bacteria
Acinetobacter baumannii - gram-negative bacteria
Pseudomonas aeruginisa - gram-negative bacteria
Enterobacter - gram-negative bacteria

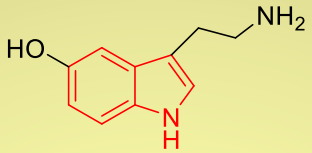
- **700,000 deaths per year are estimated to be caused by gram- negative bacteria world wide.**
- **Most hospital acquired infections are due to ESKAPE bacteria.**

Koulenti, D., et al. (2018). "Infections by multidrug-resistant Gram-negative Bacteria: what's new in our arsenal and what's in the pipeline?“; Peleg, A. Y. , D. C. Hooper, *N. Engl. J. Med*, **2010**, 362, 1804.

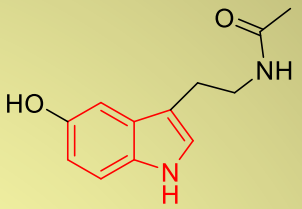
Examples of Natural Compounds and Drugs Containing Indole Core



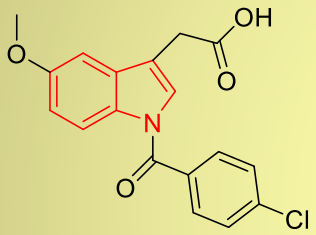
Tryptophan



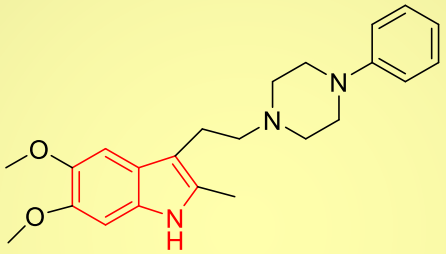
Seratonin



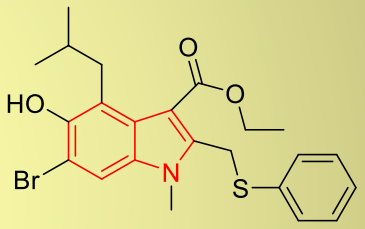
Melatonin



Indometacine



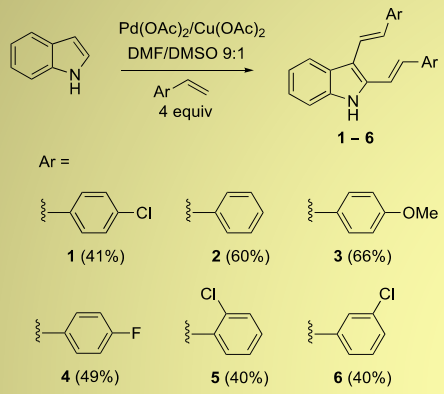
Oxypertine

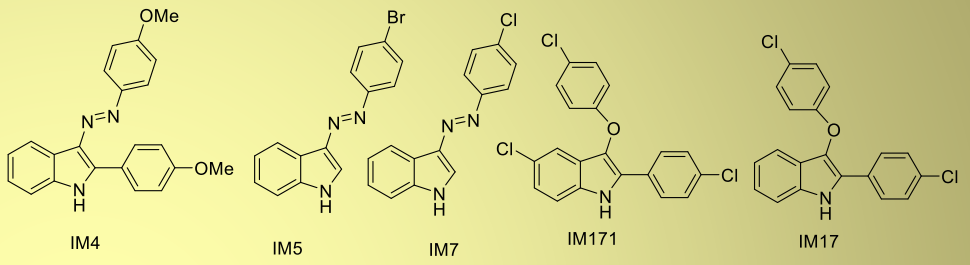


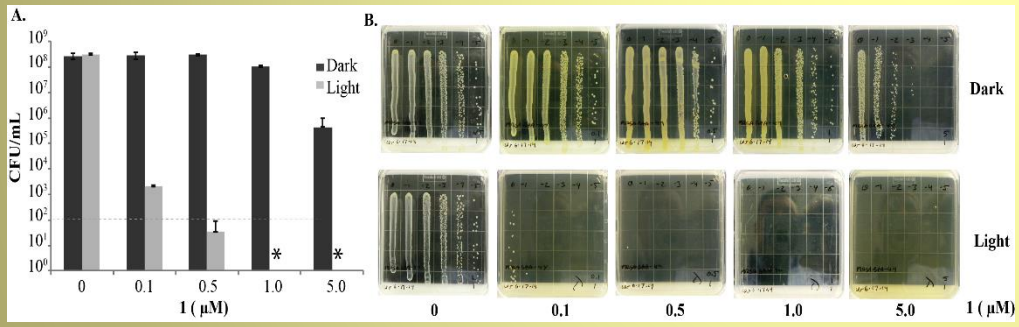
Arbidol

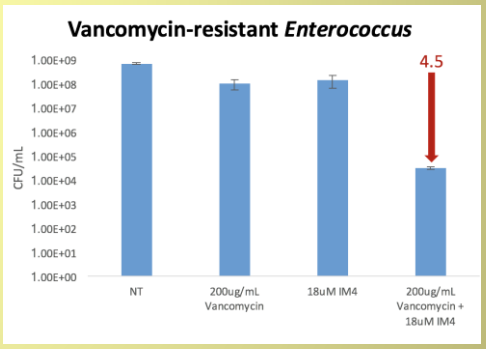
Drug	Application	Drug	Application
Vincristine	Anticancer	**Vincamine**	Vasodilator
Vinblastine	Anticancer	**Roxindole**	Schizophrenia
Reserpine	Antihypertensive	**Delavirdine**	Anti-HIV
Vinorelbine	Anticancer	**Peridopril**	Antihypertensive
Vindesine	Anticancer	**Binedaline**	Antidepressant
Atevirdine	Anti-HIV	**Zafirlukast**	Anti-Asthmatic
Mitraphylline	Anticancer	**Amedalin**	Antidepressant
Cediranib	Anticancer	**Oxypertine**	Antipsychotic

New Antibacterial Compounds Against Resistant Bacteria









Compound **1** eradicates MRSA (ATCC BAA 44) in the presence of light. A: Graph, showing a dose-dependent effect of **1** with and without a 2-minute irradiation with white light. B. Drip-streak plates utilized in the experiment illustrating the CFU counts. The data are derived from a single experiment performed in 3 replicates and serve as an example of 3 independent experiments producing similar results. The stars represent no observable colonies.

The antibacterial activities were determined using an optimized time kill method. The error bars represent technical triplicates in a representative biological replicate carried out at least three times

BMCL , **2018**, 28, 1879; *Future Microbiol.*, **2020**, *15*, 579

Design and Development of Next Generation Antibiotics Using Machine Learning Approach

Target identification and validation	Compound screening and lead discovery	Preclinical development
• Target identification and prioritization based on gene–disease associations • Target draggability predictions • Identification of alternative targets (splice variants)	**• Compound design with desirable properties** **• Compound synthesis reaction plans** **• Ligand-based compound screening**	• Tissue-specific biomarker identification • Classification of cancer drug–response signatures • Prediction of biomarkers of clinical end points
• Current data are highly heterogeneous: need standardized high-dimensional target–disease–drug association data sets • Comprehensive omics data from disease and normal states • High-confidence associations from the literature • Metadata from successful and failed clinical trials	**• Large amounts of training data needed** **• Models for compound reaction space and rules** **• Gold standard ADME data** **• Numerous protein structures**	• Biomarkers: reproducibility of models based on gene expression data • Dimension reduction of single-cell data for cell type and biomarker identification • Proteomic and transcriptomic data of high quality and quantity

from J. Vamathevan *Nat. Rev. Drug. Discov.*, **2019**, *18*, 463

First Results

Drug-like parameters and biological data were collected for about 40 indole derivatives. A first library of novel potential antibiotics was synthesized.

	Name of new compound					
Strain of bacteria	4-Aza-H	5-Aza-CN	5-Aza-Br	7-Aza-Gu	7-Aza-F	7-Aza-Br
E. coli	+	-	+	-	-	-
E. carotovora	+	+	+	+	+	-
Klebsiella sp.	+	-	+	-	-	-
S. epidermidis	-	-	+	-	-	-
P. aeruginosa	+	-	+	+	+	+
B. subtilis	+	-	+	-	-	-

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