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Natural product antibiotics: synthesis and next generation analogues

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**Natural Product Antibiotics:
Synthesis and Next Generation Analogues**

Vladyslav Lysenko

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*“What I cannot create,
I do not understand”*

**Richard
Feynman**

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Abbreviations

A	adenylation	FBMN	feature-based molecular networking
AA	amino acid	FDA	Food and Drug Administration
ABC	ATP-binding cassette	L-FDAA	1-fluoro-2-4-dinitrophenyl-5-L-alanine amide
Ac	acetyl	Fmoc	9-fluorenylmethoxycarbonyl
ACS	American Chemical Society	Fmoc-OSu	<i>N</i> -(9-fluorenylmethoxycarbonyloxy)succinimide
AMR	antimicrobial resistance	FMT	formyltransferase domain
API	atmospheric pressure interface	GCF	gene cluster family
ATCC	American Type Culture Collection	GNPS	global natural product social molecular networking
ATP	adenosine triphosphate	HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
aq.	aqueous	HBTU	hexafluorophosphate benzotriazole tetramethyl uronium
BGC	biosynthetic gene cluster	HFIP	hexafluoroisopropanol
Bn	benzyl	HMBC	heteronuclear multiple bond correlation
Boc	<i>tert</i> -butyloxycarbonyl	HOBt	1-hydroxybenzotriazole
Bu	<i>n</i> -butyl	HPLC	high-performance liquid chromatography
C	condensation	HRMS	high-resolution mass spectrometry
calcd	calculated	HSQC	heteronuclear single quantum correlation
CAMBH	cation-adjusted Mueller-Hinton broth	<i>i</i> -Pr	isopropyl
Cbz	benzyloxycarbonyl	<i>J</i>	coupling constant
CFU	colony-forming units	KHMDS	potassium bis(trimethylsilyl)amide
CLSI	Clinical and Laboratory Standards Institute	LC	liquid chromatography
COVID-19	Coronavirus disease 2019	M	molar (mol/L)
2-CT	2-chloro trityl	<i>mcr</i>	mobile colistin resistance (gene)
Da	dalton	MDR	multi-drug resistant
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	Me	methyl
DCM	dichloromethane	MEA	malt extract agar
Dde	1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl	MEB	malt extract broth
DIC	<i>N,N'</i> -diisopropylcarbodiimide	MHB	Mueller-Hinton broth
DIPEA	<i>N,N</i> -diisopropylethylamine	MHIIB	Mueller-Hinton II broth
DMAP	4-dimethylaminopyridine	MIC	minimum inhibitory concentration
DMF	<i>N,N</i> -dimethylformamide	MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
DMP	Dess–Martin periodinane	MS	mass spectrometry
DMSO	dimethyl sulfoxide	Ms	mesyl
DNA	deoxyribonucleic acid	MT	methyltransferase
E	epimerization	<i>Mtb</i>	<i>Mycobacterium tuberculosis</i>
EDC	<i>N</i> -ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide	MTBE	methyl <i>tert</i> -butyl ether
eq.	equivalent(s)		
ESI	electron-spray ionization		
Et	ethyl		
FAA	fatty amino acid		

<i>m/z</i>	mass-to-charge ratio	THF	tetrahydrofuran
NCTC	National Collection of Type Cultures	TIPS	triisopropylsilane
ND	not determined	TolH	toluene
NDM	New Delhi β -metallo lactamase	t_R	retention time
NF	not found	Trans-AT	trans-acetyltransferase
NMP	<i>N</i> -methyl-2-pyrrolidone	Trt	trityl
NMR	nuclear magnetic resonance	TSA	tryptic soy agar
NOESY	nuclear Overhauser effect spectroscopy	TSB	tryptic soy broth
NR	not relevant	UHPLC	ultra-high performance liquid chromatography
NRP	nonribosomal peptide	UK	United Kingdom
NRPS	nonribosomal peptide synthetase	USA	United States of America
o/n	overnight	UV	ultraviolet
OD ₆₀₀	optical density (at 600 nm)	VISA	vancomycin-intermediate (resistant) <i>Staphylococcus aureus</i>
OM	outer membrane	VRE	vancomycin-resistant Enterococci
Oxyrna	ethyl 2-cyano-2-(hydroxyimino)acetate	VRS	vancomycin-resistant <i>Staphylococcus aureus</i>
Pbf	2,2,4,6,7-pentamethyl-dihydrobenzofuran-5-sulfonyl	WHO	World Health Organization
PBS	phosphate-buffered saline	YPDA	yeast extract peptone dextrose agar
PDA	photo diode array	YPDB	yeast extract peptone dextrose broth
PDB	Protein Data Bank		
PCR	polymerase chain reaction	Amino acids	
PE	petroleum ether	Ala	Alanine
Ph	phenyl	Arg (R)	Arginine
PKS	polyketide synthase	Asp (D)	Aspartic acid
QTOF	quadrupole time of flight	Cit	Citrulline
REMA	resazurin microtiter plate assay	Dab	2,4-diaminobutyric acid
RFU	relative fluorescence units	Dap	2,3-diaminopropionic acid
RNA	ribonucleic acid	Gly (G)	Glycine
RP	reversed phase	Glu (E)	Glutamic acid
rpm	revolutions per minute	His (H)	Histidine
rRNA	ribosomal RNA	Ile (I)	Isoleucine
RT	room temperature	Leu (L)	Leucine
SAR	structure-activity relationship	Lys (K)	Lysine
sat.	saturated	Phe (F)	Phenylalanine
spp.	several species	Ser (S)	Serine
SPPS	solid-phase peptide synthesis	Thr (T)	Threonine
SSN	sequence similarity network	Trp (W)	Tryptophane
tBu	<i>tert</i> -butyl	Tyr (Y)	Tyrosine
T	thiolation	Val (V)	Valine
TB	tuberculosis		
TE	thioesterase		
TFA	trifluoroacetic acid		