Appendix for **Fighting antibiotic resistance –research strategies and (pre)clinical developments to find new antibacterials**

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2. Antibiotics currently approved and marketed in the USA

Appendix Table S 1: Antibiotics currently approved and marketed in the USA (Werth, 2022)

Class	Generation	Antibiotic	Number of natural product derived agents	Number of agents with synthetic origin
Aminoglycoside		Amikacin	8	
		Gentamicin		
		Kanamycin		
		Neomycin[1]		
		Plazomicin		
		Streptomycin		
		Spectinomycin[2]		
		Tobramycin		
Carbapenems		Ertapenem	3	
		Imipenem		
		Meropenem		
Cephalosporins	1st Generation	Cefadroxil	24	
		Cefazolin		
		Cephalexin		
		Cephradine		
	2nd Generation	Cefaclor		
		Cefotetan		
		Cefoxitin		
		Cefprozil		
		Cefuroxime		
	3rd Generation	Cefdinir		
		Cefditoren		
		Cefixime		
		Cefoperazone/sulbactam[3]		
		Cefotaxime		
		Cefpodoxime		
		Ceftazidime		
		Ceftazidime/avibactam		
		Ceftibuten		
		Ceftriaxone		
	4th Generation	Cefepime		
	5th Generation	Ceftaroline/fosamil		
		Ceftobiprole[3]		
	Novel cephalosporins	Cefiderocol		
		Ceftolozane plus tazobactam		
Monobactam		Aztreonam	1	
Penicillins	Natural penicillins	Penicillin G (parenteral/aqueous) or benzathine or procaine	14	
		Penicillin V potassium		
	Amino-penicillins	Ampicillin		

		Ampicillin/sulbactam		
		Amoxicillin		
		Amoxicillin/clavulanate		
	Penicillinase-resistant penicillins	Dicloxacillin		
		Nafcillin		
		Oxacillin		
	Broad-spectrum (anti-pseudomonal)	Carbenicillin		
		Piperacillin		
		Piperacillin/tazobactam		
		Ticarcillin		
		Ticarcillin plus clavulanate		
Chloramphenicol		Chloramphenicol	1	
Daptomycin		Daptomycin	1	
Fluoroquinolons		Ciprofloxacin		7
		Delafloxacin		
		Gemifloxacin		
		Levofloxacin		
		Moxifloxacin		
		Norfloxacin		
		Ofloxacin		
Fosfomycin		Fosfomycin	1	
Pleuromutilins		Lefamulin	1	
Streptogramins		Quinupristin/dalfopristin	1	
Lincosamid		Clindamycin	1	
Oxazolidinones		Linezolid		2
		Tedizolid		
Glycopeptides		Vancomycin	4	
		Telavancin		
		Oritavancin		
		Dalbavancin		
Macrolides		Azithromycin	3	
		Clarithromycin		
		Erythromycin		
Nitroheterocycles		Metronidazol[4]	1	
		Nitrofuranthion		1
Polypeptides		Colistin	2	
		Polymyxin		
Rifamycins		Rifampin	3	
		Rifabutin		
		Rifapentine		
Sulfonamides		Mafenide		9
		Sulfacetamide		
		Sulfadiazine		
		Sulfadoxine		
		Sulfamethizole		
		Sulfamethoxazole		

		Sulfanilamide		
		Sulfasalazine		
		Sulfisoxazole		
Tetracyclines		Doxycycline	5	
		Eravacycline (IV only)		
		Minocycline		
		Omadacycline (novel aminomethylcycline)		
		Tetracycline		
Aminopyrimidines		Trimethoprim		1
Fusidic acid		Fusidic acid[5]	1	

[1] Should be used topically only

[2] Aminoglycoside-related

[3] Not available in the US

[4] Based on natural product

[5] Not approved in the US

3. Analysis of the clinical pipeline

3.1. Recently approved agents

Appendix Table S 2: Antibacterial agents approved between July 2017 and November 2021; adapted from WHO analysis (World Health Organization, 2022)

Name (trade name USA/ EU)	Market authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Indication/s	Expected activity against priority pathogens				Innovation			
						CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela / Quofenix)	Melinta Therapeutics (USA) (Menarini, EU)	FDA (6/2017 ABSSSI, 10/2019 CAP) EMA (12/2019 ABSSSI, 02/2021 CAP)	Fluoroquinolone	iv & oral	ABSSSI, CAP	○	○	○	●	-	-	-	-
Vaborbactam + meropenem (Vabomere/ Vaborem)	Melinta Therapeutics (USA) (Menarini, EU)	FDA (8/2017) EMA (11/2018)	Boronate BLI + β-lactam (carbapenem)	iv	cUTI, (cUTI, cIAI, HAP/VAP in EU)	○	○	●[1]	/	?[2]	✓	-	-
Plazomicin (Zemdri)	Achaogen (Cipla USA/ QiLu Antibiotics, China)	FDA (8/2018)	Aminoglycoside	iv	cUTI	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	?	○	●	/	-	-	-	-
Omadacycline (Nuzyra)	Paratek	FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSSI (iv, oral)	○	○	○	●	-	-	-	-

Rele-bactam + imi-penem / cilastatin (Recar-brio)	Merck Sharp & Dohme	FDA (7/2019 cUTI/cIAI, 7/2020 HAP/VAP) EMA (2/2020 G-ve)	O-BLI + β-lactam (carba-penem) / degradation inhibitor	iv	cUTI, cIAI, HAP/VAP	○	?	●[1]	/	-	-	-	-
Lefa-mulin (Xenleta)	Nabriva (Sunovion Pharmaceuticals Canada)	FDA (8/2019) EMA (7/2020)	Pleuro-mutilin	iv & oral	CAP	/	/	/	●	?	✓[3]	-	-
Lascu-floxacin (Lasvic)	Kyorin Pharmaceutical	PDMA (8/2019)	Fluoro-quinolone	iv & oral	CAP, otorhinolaryngological	WHO EML: not yet evaluated	○	○	○	●	-	-	-
Cefi-derocol (Fetroja)	Shionogi	FDA (11/2019 cUTI, 9/21 HAP/VAP) EMA (4/2020)	Siderophore β-lactam (cephalosporin)	iv	cUTI, HAP/VAP, aerobic G-ve[4]	WHO EML: yes AWaRe: Reserve	●	●	●	/	?	-	-
Levonadi floxacin (Emrok); alalevonadifloxacin (Emrok-O)	Wockhardt	CDSCO (1/2020)	Fluoro-quinolone	iv & oral	ABSSSI	WHO EML: not yet evaluated AWaRe: Watch	○	○	○	●	-	-	-
Conte-zolid (Youxitai); Conte-zolid ace-fosamil	MicuRx	NMPA (6/2021)	Oxazolid-inone	iv & oral	cSSTI	WHO EML: not yet evaluated AWaRe: not yet evaluated	/	/	/	●	-	-	-

Pathogen activity: ● active; ? possibly active; ○ not or insufficiently active; **/** activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. Agents not active against critical priority pathogens were assessed for activity against OPP, which includes the WHO high and medium priority pathogens.

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data; **-** criterion not fulfilled.

ABSSSI: acute bacterial skin and skin structure infection; AWaRe: Access Watch Reserve; CAP: community-acquired pneumonia; CC: new chemical class; cIAI: complicated intra-abdominal infection; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant *Enterobacterales*; CRPA: carbapenem-resistant *P. aeruginosa*; cSSTI: complicated skin and soft tissue infection; cUTI: complicated urinary tract infection; CDSCO: Central Drugs Standard Control Organization of the Government of India; EMA: European Medicines Agency; EML: WHO Essential Medicines List; G-: Gram-negative; HAP: hospital-acquired pneumonia; iv: intravenous; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; MDR: multidrug-resistant; MoA: new mode of action; N/A: not applicable; NCR: no cross-resistance to other antibiotic classes; NMPA: China National Medical Products Administration; OPP: other priority pathogens; PDMA: Pharmaceuticals and Medical Devices Agency (Japan); T: new target; US FDA: US Food and Drug Administration; VAP: ventilator-associated pneumonia; WHO: world health organisation.

[1] Active against KPC, but not MBL-producing *Enterobacterales*.

[2] New reports suggest that cross-resistance can be obtained when the porin OmpK36 level is varied.

[3] First systemic formulation of this class, which was previously used in animals and topically in humans.

3.2. Antibiotics discontinued from clinical development

Appendix Table S 3: Antibacterial agents discontinued from clinical development between July 2017 and November 2021; adapted from WHO analysis (World Health Organization, 2022)

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
GSK-3342830	1	Siderophore-cephalosporin	Gram-negative	GSK	2017
AIC-499 + unknown BLI	1	β-Lactam + BLI	Gram-negative	AiCuris	2017
SPR-741+ β-lactam	1	Polymyxin (potentiator) + β-lactam	Gram-negative	Spero Therapeutics / Everest Medicines	2018
Cefilavancin (TD-1792, RD-1792)	3	Glycopeptide-cephalosporin hybrid	*S. aureus*	R-Pharm / Theravance Biopharma	2018
Ancremonam (BOS-228, LYS-228)	2	Monobactam	CRE	Boston Pharmaceuticals	2018
RC-01 (T 1228)	1	New class (LpxC inhibitor)	Gram-negative	Recida Therapeutics / Fujifilm Toyama Chemical	2019
GT-1	1	Siderophore-cephalosporin	Gram-negative	Geom Therapeutics	2019
MK-3866	1	BLI	Gram-negative	Merck Sharp & Dohme	2019
Murepavadin (POL7080)[1]	3	Peptide	*P. aeruginosa*	Polyphor	2019
BCM-0184	1	Undisclosed (likely peptide)	*S. aureus*	Biocidium Pharmaceuticals	2019
Iclaprim	3	Trimethoprim	*S. aureus*	Motif Bio	2020
KB109	N/A	Synthetic glycan	Gram-positive and Gram-negative	Kaleido Biosciences	2021
TP-271	1	Tetracycline	*S. aureus* and *S. pneumoniae*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021
TP-6076	1	Tetracycline	*A. baumannii*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021

Underlined: New chemical class.

BLI: β-lactamase inhibitor; CRE: carbapenem-resistant *A. baumannii*; GyrB: DNA gyrase subunit B; MoA: mode of action; WHO: world health organisation.

[1] The development of iv-administered murepavadin was discontinued in 2019. But after merging with Polyphor in September 2021, EnBiotix plans to develop murepavadin as an inhalation treatment for *P. aeruginosa* infections in patients with CF.

4. Analysis of the preclinical pipeline and projects in lead-optimisation

4.1. Novel derivatives of and repurposed approved antibiotic-classes in preclinical development

Appendix Table S 4: Novel derivatives of and repurposed approved antibiotic-classes in preclinical development; adapted from WHO analysis (World Health Organization, 2022)

Product/ program	Company/ Institution	Pre-clinical development stage	Treatment modality	Pathogens	Route of administration	Mode of action	Primary indication
2'-Deoxy-2-thio-5-phenyl-6-azauridine (2b)	Engelhard Institute of Molecular Biology, Russian Academy of Science	Pre-clinical candidate	Small molecule - direct acting	*Staphylococcus aureus*	Parenteral	DNA replication/ synthesis	Other
ABX-605 (Maranmicin)	AGILeBiotics	Pre-clinical candidate	Small molecule - direct acting	*Enterobacterales* (Website: *Pseudomonas aeruginosa, Staphylococcus aureus*, non-tuberculotical *Mycobacteria*)	Parenteral	Protein synthesis	Other
EBL-1463 (Dabocin)	Mutabilis	Pre-clinical candidate	Small molecule - direct acting	*Enterobacterales; Neisseria gonorrhoeae; Salmonella* spp.; *Shigella* spp.	Parenteral	Cell wall synthesis – Other	cUTI
FLX3000	FleurirABX	Pre-clinical candidate	Small molecule - direct acting	*	Oral, parenteral	Cell wall synthesis - Other	cUTI
MET-X	Infex Therapeutics	Pre-clinical candidate	Small molecule - indirect acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales*	Parenteral	Cell wall synthesis - BL and/or BLI	HABP/VABP
PBT2	The University of Queensland	Pre-clinical candidate	Small molecule - indirect acting	*	Oral	Potentiators/ enablers	CAP, URTI
SET-M33	SetLance srl	Pre-clinical candidate	Anti-microbial peptide - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Enterobacterales*	Parenteral	Direct membrane effect	Bloodstream infections
SYNX-0001	Synoxa Sciences, Inc.	Pre-clinical candidate	Small molecule - direct acting	*	Oral, parenteral	Central metabolism	PJI
ULT2	Ultupharma AB	Pre-clinical candidate	Small molecule - direct acting	*	Parenteral	DNA replication/ synthesis	Bloodstream infections
Vancapticin	The University of Queensland	Pre-clinical candidate	Large molecule - direct acting	*Staphylococcus aureus; Streptococcus pneumoniae; Clostridioides difficile*	Parenteral	Cell wall synthesis – Other	PJI

VRP-034 (Novel formulation of Polymyxin B)	Venus Remedies Limited	Pre-clinical candidate	Anti-microbial peptide - direct acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales; Haemophilus influenzae*	Parenteral	Direct membrane effect	cUTI
VRP-035 (Novel formulation of Amikacin)	Venus Remedies Limited	Pre-clinical candidate	Small molecule - direct acting	*Pseudomonas aeruginosa; Enterobacterales; Staphylococcus aureus; Salmonella* spp.; *Streptococcus pneumoniae; Shigella* spp.	Parenteral	Protein synthesis	CAP, URTI, cUTI, uUTI, Bloodstream infections
VRP-044 (Colistin - Renal Guard Program)	Venus Remedies Limited	Pre-clinical candidate	Peptide - direct acting	*	Parenteral	Direct membrane effect	cUTI
VRT001-C (Oral Ceftriaxone)	Venus Remedies Limited	Pre-clinical candidate	Small molecule - direct acting	*	Oral	Cell wall synthesis - BL and/or BLI	CAP, URTI
VRT001-M (Oral Meropenem)	Venus Remedies Limited	Pre-clinical candidate	Small molecule - direct acting	*Pseudomonas aeruginosa; Enterobacterales; Enterococcus faecium; Staphylococcus aureus; Campylobacter* spp.; *Haemophilus influenzae; Streptococcus pneumoniae*	Oral	Cell wall synthesis - BL and/or BLI	HABP/VABP, cUTI, Bloodstream infections
Lefamulin	Nabriva Therapeutics	IND (Investigational New Drug) application subm	Small molecule - direct acting	*Enterococcus faecium; Staphylococcus aureus; Helicobacter pylori; Campylobacter* spp.; *Neisseria gonorrhoeae; Haemophilus influenzae; Streptococcus pneumoniae; Clostridioides difficile*	Parenteral; Oral	Protein synthesis	CAP, URTI
BOS-572 (BLI)	Boston Pharmaceuticals	CTA/IND-enabling studies	Small molecule - indirect acting	*Enterobacterales*	Parenteral	Cell wall synthesis - BL and/or BLI	Other
MBLi (ANT2681)	Antabio	CTA/IND-enabling studies	Small molecule - indirect acting	*Pseudomonas aeruginosa; Enterobacterales; Salmonella* spp.; *Haemophilus influenzae; Shigella* spp.	Parenteral	Cell wall synthesis - BL and/or BLI	cUTI
SBLi (ANT3310)	Antabio	CTA/IND-enabling studies	Small molecule - indirect acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales; Salmonella* spp.; *Haemophilus influenzae; Shigella* spp.	Parenteral	Cell wall synthesis - BL and/or BLI	HABP/VABP
SP1001 (oral cefepime)	Seachaid Pharmaceuticals	CTA/IND-enabling studies	Small molecule - direct acting	*Pseudomonas aeruginosa; Enterobacterales*	Oral	Cell wall synthesis - BL and/or BLI	HABP/VABP

BLI: β-lactamase inhibitor; CAP: community acquired pneumoniae; cUTI: complicated urinary tract infections; HABP/VABP: Hospital-acquired or Ventilator-acquired bacterial pneumoniae; PJI: prosthetic joint infections; URTI: upper respiratory tract infections; uUTI: uncomplicated urinary tract infection; WHO: world health organisation.

4.2. Novel traditional antibiotics in preclinical development

Appendix Table S 5: Novel traditional antibiotics in preclinical development; adapted from WHO analysis (World Health Organization, 2022)

Product/ program	Company/ Institution	Pre-clinical development stage	Treatment modality	Pathogens	Route of administration	Mode of action	Primary indication
ABAC-39877	ABAC Therapeutics	Pre-clinical candidate	Small molecule - direct acting	*Acinetobacter baumannii*	Parenteral; Oral	Not disclosed	Other
Avidocin	Pylum Biosciences	Pre-clinical candidate	Large molecule - direct acting	*Enterobacterales*	Unspecified	Direct membrane effect	cUTI
Avidocin	Pylum Biosciences	Pre-clinical candidate	Large molecule - direct acting	*Enterobacterales*	Unspecified	Direct membrane effect	Bloodstream infections
Avidocin	Pylum Biosciences	Pre-clinical candidate	Large molecule - direct acting	*Enterobacterales*	Unspecified	Direct membrane effect	Other
Avidocin	Pylum Biosciences	Pre-clinical candidate	Large molecule - direct acting	*Pseudomonas aeruginosa*	Unspecified	Direct membrane effect	Cystic fibrosis associated infections
Avidocin	Pylum Biosciences	Pre-clinical candidate	Large molecule - direct acting	*Enterococcus faecium*	Unspecified	Direct membrane effect	Bloodstream infections
Corallopyronin A	University Hospital Bonn / Institute for Medical Microbiology, Immunology and Parasitology	Pre-clinical candidate	Small molecule - direct acting	*Staphylococcus aureus; Neisseria gonorrhoeae*	Oral	RNA synthesis	Gonorrhea
Debio 1453	Debiopharm International	Pre-clinical candidate	Small molecule - direct acting	*Neisseria gonorrhoeae*	Oral; Other	Other cellular function	Other
Gyrox	Bugworks	Pre-clinical candidate	Small molecule - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Campylobacter* spp.; *Staphylococcus aureus*	Parenteral	DNA replication/synthesis	cUTI
Hetiamacin E and F	Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russion Academy of Sciences	Pre-clinical candidate	Small molecule - direct acting	*Staphylococcus aureus*	Unspecified	Protein Synthesis	Healthcare-associated infections
LpxC-UTI	Forge Therapeutics	Pre-clinical candidate	Small molecule - direct acting	*	Oral, parenteral	Cell wall synthesis – Other	cUTI
Novo29	Novobiotic	Pre-clinical candidate	Antimicrobial peptide - direct acting	*Staphylococcus aureus; Streptococcus pneumoniae*	Unspecified	Cell wall synthesis – Other	Other
NP108 Luminaderm®	NovaBiotics	Pre-clinical candidate	Antimicrobial peptide - direct acting	*Streptococcus pneumoniae; Staphylococcus aureus; Enterococcus faecium*	Other	Direct membrane effect	Other
NP432 Novarifyn®	NovaBiotics	Pre-clinical candidate	Antimicrobial peptide - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Enterobacterales; Clostridioides difficile*	Parenteral	Direct membrane effect	Other

slm300	Selmod	Pre-clinical candidate	Small molecule - direct acting	Broad spectrum	Parenteral; Oral	Cell wall synthesis – Other	Other
slm400	Selmod	Pre-clinical candidate	Antimicrobial peptide - direct acting	Broad spectrum	Parenteral; Oral	Cell wall synthesis – Other	Other
slm500	Selmod	Pre-clinical candidate	Antimicrobial peptide - direct acting	Broad spectrum	Parenteral; Oral	DNA replication/synthesis	Other
SMT026738 (from DDS-04 series)	Summit Therapeutics	Pre-clinical candidate	Small molecule - direct acting	*	Parenteral	Cell wall synthesis – Other	cUTI
SP2078	Seachaid Pharmaceuticals	Pre-clinical candidate	Small molecule - direct acting	*Enterococcus faecium; Staphylococcus aureus*	Unspecified	Cell wall synthesis – Other	Other
Teixobactin	Novobiotic	Pre-clinical candidate	Antimicrobial peptide - direct acting	*Mycobacterium tuberculosis; Enterococcus faecium; Staphylococcus aureus; Streptococcus pneumoniae; Clostridioides difficile*	Unspecified	Cell wall synthesis – Other	Other
VT-02	Vitas Pharma	Pre-clinical candidate	Small molecule - direct acting	*Staphylococcus aureus*	Parenteral; Oral	Central metabolism	Other
CRS0540	Crestone Pharmaceuticals	CTA/IND-enabling studies	Small molecule - direct acting	*Enterococcus faecium; Staphylococcus aureus; Streptococcus pneumoniae*	Parenteral; Oral	DNA replication/synthesis	Other
CZ-02	Curza	CTA/IND-enabling studies	Small molecule - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Enterobacterales*	Unspecified	Protein Synthesis	Other
ETX-0462	Entasis Therapeutics, Inc	CTA/IND-enabling studies	Small molecule - direct acting	*Pseudomonas aeruginosa*	Unspecified	Cell wall synthesis – Other	Other
NOSO-502	Nosopharm	CTA/IND-enabling studies	Small molecule - direct acting	*Enterobacterales*	Unspecified	Protein synthesis	cUTI
OMN6	Omnix Medical	CTA/IND-enabling studies	Antimicrobial peptide - direct acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales*	Parenteral	Direct membrane effect	HABP/VABP
PLG0206	Peptilogics	CTA/IND-enabling studies	Antimicrobial peptide - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Enterobacterales; Staphylococcus aureus; Enterococcus faecium*	Other	Direct membrane effect	PJI
W5P1 + WXPYY	Alphanosos	CTA/IND-enabling studies	Small molecule - direct acting	*	Oral	Other cellular function	Gonorrhea
APC148	Adjutec Pharma AS	CTA/IND-enabling studie	Small molecule - direct acting	*	Parenteral	Cell wall synthesis - BL and/or BLI	cUTI

BL: β-lactam; BLI: β-lactamase inhibitor; CAP: community acquired pneumoniae; CTA/IND: clinical trial application/ investigational new drug; cUTI: complicated urinary tract infections; HABP/VABP: Hospital-acquired or Ventilator-acquired bacterial pneumoniae; PJI: prosthetic joint infections; URTI: upper respiratory tract infections; WHO: world health organisation.

4.3. Non-traditional antibacterial agents in preclinical development

Appendix Table S 6: Non-traditional antibacterial agents in preclinical development; adapted from WHO analysis (World Health Organization, 2022)

Product/ program	Company/ Institution	Pre-clinical development stage	Treatment modality	Pathogens	Route of administration	Mode of action	Primary indication
CF-296	Contrafect Corporation	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Staphylococcus aureus*	Unspecified	Direct membrane effect	PJI
PhM398	PhagoMed Biopharma GmbH	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	Not disclosed	Unspecified	Cell wall synthesis – Other	PJI
PhM754	PhagoMed Biopharma GmbH	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	Not disclosed	Unspecified	Cell wall synthesis – Other	cUTI
PP700	Pherecydes Pharma	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Parenteral	Direct membrane effect	Other
PP814	Pherecydes Pharma	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Parenteral	Direct membrane effect	Other
PP954	Pherecydes Pharma	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Parenteral	Direct membrane effect	Other
PP970	Pherecydes Pharma	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Parenteral	Direct membrane effect	Other
SASPject™ PT3.9	Phico Therapeutics	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Pseudomonas aeruginosa*	Parenteral	DNA replication/ synthesis	Other
SNIPR001	SNIPR BIOME	Pre-clinical candidate	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Unspecified	Direct membrane effect	Bloodstream infections
AR-401	Aridis Pharmaceuticals	Pre-clinical candidate	Biologic	*Acinetobacter baumannii*	Unspecified	Immuno-modulation	Other
ABX01	Centauri Therapeutics	Pre-clinical candidate	Immunomodulators	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales*	Parenteral	Immuno-modulation	Other
ABX02	Centauri Therapeutics	Pre-clinical candidate	Immunomodulators	Not disclosed	Parenteral	Immuno-modulation	Other
PRO-202	Procarta Biosystems	Pre-clinical candidate	Nucleic acid based products	*	Unspecified	Other cellular function	cUTI
F19	Q2Pharma	Pre-clinical candidate	Small molecule - indirect acting	*	Oral, parenteral, topical	Anti-virulence	ABSSSI
Sativa	Vibiosphen	Pre-clinical candidate	Small molecule - indirect acting	Not disclosed	Oral	Potentiators/ enablers	Other
CF-370	Contrafect Corporation	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Pseudomonas aeruginosa*	Unspecified	Direct membrane effect	HABP/VABP
LBP-KP01	Locus Biosciences	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Klebsiella pneumoniae*	Parenteral	Direct membrane effect	uUTI
PN1450	Pherecydes Pharma	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Pseudomonas aeruginosa*	Parenteral	Direct membrane effect	Other

PN1493	Pherecydes Pharma	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Staphylococcus aureus*	Parenteral	Direct membrane effect	Other
PN1777	Pherecydes Pharma	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Pseudomonas aeruginosa*	Parenteral	Direct membrane effect	Other
PN1792	Pherecydes Pharma	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Pseudomonas aeruginosa*	Parenteral	Direct membrane effect	Other
PN1797	Pherecydes Pharma	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Pseudomonas aeruginosa*	Parenteral	Direct membrane effect	Other
PN1815	Pherecydes Pharma	CTA/IND-enabling studies	Bacteriophage/ Bacteriophage products	*Staphylococcus aureus*	Parenteral	Direct membrane effect	Other
CMTX-101, humanized mab	Clarametyx Biosciences, Int.	CTA/IND-enabling studies	Biologic	*	Parenteral	Potentiators/ enablers	Healthcare associated CAP
RESP-X	Infex Therapeutics	CTA/IND-enabling studies	Biologic	*Pseudomonas aeruginosa*	Parenteral	Anti-virulence	HABP/VABP

ABSSI: skin and skin-structure infections; CAP: community acquired pneumoniae; CTA/IND: clinical trial application/ investigational new drug; cUTI: complicated urinary tract infections; HABP/VABP: Hospital-acquired or Ventilator-acquired bacterial pneumoniae; mab: monoclonal antibody; PJI: prosthetic joint infections; URTI: upper respiratory tract infections; uUTI: uncomplicated urinary tract infections; WHO: world health organisation.

4.4. Projects in lead optimisation

4.4.1. Novel derivatives of and repurposed approved antibiotic-classes in lead optimisation

Appendix Table S 7: Novel derivatives of and repurposed approved antibiotic-classes in lead optimisation; adapted from WHO analysis (World Health Organization, 2022)

Product/ program	Company/ Institution	Treatment modality	Pathogens	Route of administration	Mode of action	Primary indication
2'-Deoxy-2-thio-5-phenyl-6-azauridine (2b)	Institute for Experimental Medicine of the Russian Academy of Medical Sciences	Peptide - direct acting	Broad spectrum	Unspecified	Unknown	Healthcare-associated infections
2G-Dabocin	Mutabilis	Small molecule - direct acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales*	Parenteral	Cell wall synthesis – Other	cUTI
NAB739	Northern Antibiotics	Antimicrobial peptide - direct acting	*Acinetobacter baumannii; Enterobacterales*	Parenteral	Direct membrane effect	cUTI
NAB815	Northern Antibiotics	Antimicrobial peptide - direct acting	*Acinetobacter baumannii; Enterobacterales; Enterobacterales*	Parenteral	Direct membrane effect	cUTI
No Name	Chiome Bioscience	Biologic	Not disclosed	Parenteral	Unknown	Unspecified
PBP inhibitors (cyclic Boronate)	Venatorx Pharmaceuticals	Small molecule - direct acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales; Neisseria gonorrhoeae*	Parenteral; Oral	Cell wall synthesis – Other	Gonorrhea
pept_352, pept_1545	Federal Research and Clinical Center of Physical Chemical Medicine of Federal Medical Biological Agency	Peptide - direct acting	*Staphylococcus aureus*	Unspecified	Direct membrane effect	Healthcare-associated infections

cUTI: complicated urinary tract infections; PBP: penicillin binding protein; PJI: prosthetic joint infections; WHO: world health organisation.

4.4.2. Novel traditional antibiotics in lead optimisation

Appendix Table S 8: Novel traditional antibiotics in lead optimisation; adapted from WHO analysis (World Health Organization, 2022)

Product/ program	Company/ Institution	Treatment modality	Pathogens	Route of administration	Mode of action	Primary indication
AI powered next generation AMP	Madam Therapeutics	Peptide - direct acting	*Acinetobacter baumanii*	Unspecified	Direct membrane effect	Other
aaRSIs	Oxford Drug Design	Small molecule - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Enterobacterales*	Unspecified	Protein Synthesis	cUTI
ABAC-40244	ABAC Therapeutics	Small molecule - direct acting	*Staphylococcus aureus*	Parenteral; Oral	Unknown	Other
ABAC-40411	ABAC Therapeutics	Small molecule - direct acting	*Streptococcus pneumoniae*	Oral, parenteral	Unknown	CAP, URTI
ABX-75C	Acurx Pharmaceuticals, Inc.	Small molecule - direct acting	*	Oral, parenteral	DNA replication/ synthesis	ABSSSI
Amurins	Contrafect Corporation	Antimicrobial peptide - direct acting	*Pseudomonas aeruginosa; Acinetobacter baumannii; Enterobacterales*	Unspecified	Direct membrane effect	HABP/VABP,Healthcare associated CAP,Cystic fibrosis associated infections,cUTI,Bloodstream infections
Arylmyxopyronins (APYs)	Ebright Laboratory, Waksman Institute, Rutgers University	Small molecule - direct acting	Broad spectrum	Parenteral; Oral	RNA synthesis	HABP/VABP
BamA-OMPTA	Polyphor AG	Peptide - direct acting	*	Parenteral	Direct membrane effect	HABP/VABP
cystobactamids	Myxobiotics	Small molecule - direct acting	*Pseudomonas aeruginosa; Enterobacterales; Staphylococcus aureus*	Unspecified	DNA replication/ synthesis	cUTI
DDS-01 Series (previous WHO entry SMT-571)	Summit Therapeutics	Small molecule - direct acting	*Neisseria gonorrhoeae*	Oral	Other cellular function	Gonorrhea
Debio 1454/S	Debiopharm International	Small molecule - direct acting	*Acinetobacter baumannii*	Parenteral	Other cellular function	HABP/VABP
GmP	QureTech Bio	Small molecule - direct acting	*Staphylococcus aureus; Enterococcus faecium; Clostridioides difficile*	Parenteral	Unknown	cUTI

Klebicin	Gangagen	Large molecule - direct acting	*Enterobacterales*	Unspecified	Direct membrane effect	HABP/VABP
LptA-OMPTA	Polyphor AG	Peptide - direct acting	*	Parenteral	Direct membrane effect	cUTI
LpxC-lung	Forge Therapeutics	Small molecule - direct acting	*Pseudomonas aeruginosa*	Unspecified	Cell wall synthesis – Other	HABP/VABP
LPxC-STD	Forge Therapeutics	Small molecule - direct acting	*Neisseria gonorrhoeae*	Oral, parenteral	Cell wall synthesis – Other	Gonorrhea
Macrocyles	AiCuris	Small molecule - direct acting	Not disclosed	Unspecified	Not disclosed	Other
NCL195	Neoculi	Small molecule - direct acting	*	Oral	Unknown	ABSSSI
NOSO-2G	Nosopharm	Small molecule - direct acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales; Staphylococcus aureus*	Unspecified	Protein synthesis	HABP/VABP
Novel class	Basilea Pharmaceutica Int. Ltd	Small molecule - direct acting	*	Parenteral	Cell wall synthesis – Other	HABP/VABP
Novel target (DXR inhibitor)	Basilea Pharmaceutica Int. Ltd	Small molecule - direct acting	*	Parenteral	Central metabolism	HABP/VABP
Novel target (IspF inhibitor)	Basilea Pharmaceutica Int. Ltd	Small molecule - direct acting	*	Parenteral	Central metabolism	HABP/VABP
NPI Scaffolds	AiCuris	Small molecule - direct acting	Not disclosed	Unspecified	Not disclosed	Other
OI20-01	Olgram	Antimicrobial peptide - direct acting	Broad spectrum	Parenteral; Other	Direct membrane effect	Other
Stapled Antimicrobial Peptides (StAMPs)	Lytica Therapeutics Inc.	Peptide - direct acting	*	Inhalation, parenteral, topical	Direct membrane effect	HABP/VABP
Trans-translation inhibitors	Microbiotix	Small molecule - direct acting	*Neisseria gonorrhoeae; Haemophilus influenzae; Mycobacterium tuberculosis; Staphylococcus aureus; Streptococcus pneumoniae*	Unspecified	Protein Synthesis	Gonorrhea
TriBE Antibiotics	Evotec	Small molecule - direct acting	Broad spectrum	Unspecified	Not disclosed	cUTI

ULT3	Ultupharma AB	Peptide - direct acting	*	Parenteral	Direct membrane effect	Bloodstream infections
Ureadepsipeptide	Arientis	Small molecule - direct acting	*	Parenteral	Other cellular function	PJI
VT-03	Vitas Pharma	Small molecule - direct acting	*Acinetobacter baumannii*	Parenteral	DNA replication/ synthesis	Other

ABSSI: skin and skin-structure infections; AI: artificial intelligence ; AMP: antimicrobial peptide; CAP: community acquired pneumoniae; cUTI: complicated urinary tract infections; DXR: 1-deoxy-D-xylose-5-phosphate reductoisomerase; IspF: 2-methylerythritol 2,4-cyclodiphosphate synthase (isoprenoid synthesis); HABP/VABP: Hospital-acquired or Ventilator-acquired bacterial pneumoniae; LpxC: UDP-3-O- (R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (lipid A synthesis); LptA: lipopolysaccharide export system protein; PJI: prosthetic joint infections; STD: sexually transmitted disease; WHO: world health organisation.

4.4.3. Non-traditional antibacterials in lead optimisation

Appendix Table S 9: Non-traditional antibacterials in lead optimisation; adapted from WHO analysis (World Health Organization, 2022)

Product/ program	Company/ Institution	Treatment modality	Pathogens	Route of administration	Mode of action	Primary indication
AKT-011	Akthelia	Immunomodulators	*	Oral	Immunomodulation	GI infections
Octapeptin-X	The University of Queensland	Antimicrobial peptide - direct acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales; Neisseria gonorrhoeae*	Parenteral	Unknown	Unknown
OPX-P Octapeptin-X Potentiator	The University of Queensland	Antimicrobial peptide - indirect acting	*Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacterales; Neisseria gonorrhoeae*	Parenteral	Direct membrane effect	Unknown
Artilysins	AiCuris	Bacteriophage/ Bacteriophage products	Not disclosed	Unspecified	Direct membrane effect	Other
Janssen Collaboration with Locus Biosciences	Johnson & Johnson	Bacteriophage/ Bacteriophage products	Not disclosed	Unspecified	Direct membrane effect	HABP/VABP
PM-399	PhagoMed Biopharma GmbH	Bacteriophage/ Bacteriophage products	*Staphylococcus aureus*	Unspecified	Direct membrane effect	PJI
SASPject™ PT4	Phico Therapeutics	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Parenteral	DNA replication/ synthesis	Other
SASPject™ PT5	Phico Therapeutics	Bacteriophage/ Bacteriophage products	*Enterobacterales*	Parenteral	DNA replication/ synthesis	Other
Transmid Technology	Nemesis Bioscience Ltd.	Bacteriophage/ Bacteriophage products	*	Inhalation, oral, parenteral, topical	Anti-virulence	HABP/VABP
FimH	Fimbrion Therapeutics	Biologic	*Enterobacterales*	Unspecified	Anti-virulence	cUTI
CTI-005	Cellics Therapeutics	Large molecule - indirect acting (CARB-X=MACROPHAGE NANOSPONGE)	Broad spectrum	Parenteral	Anti-virulence	Bloodstream infections
CTI-111	Cellics Therapeutics	Large molecule - indirect acting (CARB-X=MACROPHAGE NANOSPONGE)	Broad spectrum	Parenteral	Anti-virulence	Bloodstream infections
OPX	The University of Queensland	Peptide - direct acting	*	Parenteral, topical	Direct membrane effect	PJI
Octapeptin-X Potentiator	The University of Queensland	Peptide - indirect acting	*	Parenteral	Potentiators/ enablers	Not yet determined
ALS-2	Aptorum Group Limited	Small molecule - indirect acting	*Enterococcus faecium; Staphylococcus aureus; Streptococcus pneumoniae*	Parenteral; oral; other	Anti-virulence	Other
ALS-3	Aptorum Group Limited	Small molecule - indirect acting	*Enterococcus faecium; Staphylococcus aureus; Streptococcus pneumoniae*	Parenteral; oral; other	Anti-virulence	Other

BFP101	BioFilm Pharma	Small molecule - indirect acting	*Staphylococcus aureus*	Other	Anti-virulence	Local - Diabetic Foot Ulcer
BV200	BioVersys	Small molecule - indirect acting	*Staphylococcus aureus*	Oral, parenteral	Anti-virulence	HABP/VABP
DnaK inhibitors	Arrevus	Small molecule - indirect acting	Broad spectrum	Unspecified	Potentiators/ enablers	Other
Efflux pump inhibitors	Microbiotix	Small molecule - indirect acting	*Enterobacterales*	Unspecified	Anti-virulence	Other
EPI-PA	TAXIS Pharmaceuticals	Small molecule - indirect acting	*Pseudomonas aeruginosa*	Unspecified	Potentiators/ enablers	HABP/VABP
Flurothiazinon	Gamaleya National Reasearch Center of Epidemiology and Microbiology	Small molecule - indirect acting	*Pseudomonas aeruginosa*	Parenteral	Anti-virulence	Healthcare-associated infections
Inhibitors of alpha hemolysin	Helmholtz Centre for Infection Research	Small molecule - indirect acting	*Staphylococcus aureus*	Parenteral	Anti-virulence	HABP/VABP
LasB inhibitors	Helmholtz Institute for Phamaceutical Research Saarland	Small molecule - indirect acting	*Pseudomonas aeruginosa*	Unspecified	Anti-virulence	Cystic fibrosis associated infections
T3SS	Microbiotix	Small molecule - indirect acting	*Pseudomonas aeruginosa*	Unspecified	Anti-virulence	HABP/VABP
Tarocins	Prokaryotics Inc.	Small molecule - indirect acting	*	Oral	Cell wall synthesis – Other	ABSSSI

ABSSI: skin and skin-structure infections; cUTI: complicated urinary tract infections; DnaK: chaperone protein; FimH: type-1 fimbrin D-mannose-specific adhesion; GI: gastro intestinal; HABP/VABP: Hospital-acquired or Ventilator-acquired bacterial pneumoniae; LasB: elastase B; PJI: prosthetic joint infections; T3SS: type 3 secretion system; WHO: world health organisation.

5. Natural product compound distribution by genus

Appendix Table S 10: Natural product compound distribution by genus; based on NPAtlas_v2021_08 (van Santen *et al,* 2022; Gavriilidou *et al,* 2022)

Genus	Phylum	Number of Compounds from Genus	Number of genera in phylum	Number of species in genus
Streptomyces	Actinobacteria	5457	87	1885
Bacillus	Firmicutes	455	24	120
Microcystis	Cyanobacteria	365	64	54
Pseudomonas	Proteobacteria	341	131	118
Lyngbya	Cyanobacteria	296	64	18
Micromonospora	Actinobacteria	296	87	91
Nostoc	Cyanobacteria	216	64	37
Actinomadura	Actinobacteria	166	87	61
Sorangium	Proteobacteria	148	131	30
Nocardiopsis	Actinobacteria	143	87	48
Amycolatopsis	Actinobacteria	137	87	46
Xenorhabdus	Proteobacteria	135	131	32
Nocardia	Actinobacteria	132	87	60
Salinispora	Actinobacteria	124	87	15
Cyanobacterium	Cyanobacteria	108	64	7
Burkholderia	Proteobacteria	96	131	28
Anabaena	Cyanobacteria	93	64	26
Oscillatoria	Cyanobacteria	92	64	24
Pseudoalteromonas	Proteobacteria	80	131	24
Myxococcus	Proteobacteria	79	131	23
Actinomyces	Actinobacteria	78	87	28
Moorea	Cyanobacteria	76	64	4
Saccharothrix	Actinobacteria	74	87	21
Nodularia	Cyanobacteria	72	64	7
Streptoverticillium	Actinobacteria	63	87	33
Actinoplanes	Actinobacteria	62	87	28
Vibrio	Proteobacteria	59	131	22
Cystobacter	Proteobacteria	58	131	14
Hapalosiphon	Cyanobacteria	56	64	7
Actinoalloteichus	Actinobacteria	53	87	8
Symploca	Cyanobacteria	52	64	7
Mycobacterium	Actinobacteria	49	87	14
Chondromyces	Proteobacteria	48	131	8
Scytonema	Cyanobacteria	45	64	16
Kitasatospora	Actinobacteria	44	87	15
Planktothrix	Cyanobacteria	43	64	13
Photorhabdus	Proteobacteria	41	131	7
Serratia	Proteobacteria	40	131	13
Fischerella	Cyanobacteria	40	64	9
Thalassospira	Proteobacteria	39	131	3

Escherichia	Proteobacteria	39	131	5
Flavobacterium	Bacteroidetes	38	26	8
Streptosporangium	Actinobacteria	37	87	13
Phormidium	Cyanobacteria	33	64	6
Saccharopolyspora	Actinobacteria	33	87	15
Nonomuraea	Actinobacteria	32	87	10
Stigmatella	Proteobacteria	31	131	7
Leptolyngbya	Cyanobacteria	31	64	4
Okeania	Cyanobacteria	31	64	5
Pseudonocardia	Actinobacteria	30	87	7
Trichodesmium	Cyanobacteria	30	64	5
Verrucosispora	Actinobacteria	30	87	14
Microbispora	Actinobacteria	28	87	8
Tolypothrix	Cyanobacteria	28	64	4
Lactobacillus	Firmicutes	26	24	13
Archangium	Proteobacteria	25	131	4
Paenibacillus	Firmicutes	22	24	11
Entotheonella	Proteobacteria	21	131	5
Paraburkholderia	Proteobacteria	21	131	3
Actinosynnema	Actinobacteria	21	87	5
Rhodococcus	Actinobacteria	21	87	10
Alteromonas	Proteobacteria	20	131	7
Lysobacter	Proteobacteria	20	131	6
Cytophaga	Bacteroidetes	20	26	8
Chromobacterium	Proteobacteria	19	131	7
Nannocystis	Proteobacteria	19	131	5
Micrococcus	Actinobacteria	19	87	7
Dactylosporangium	Actinobacteria	17	87	7
Methylobacterium	Proteobacteria	17	131	3
Sulfitobacter	Proteobacteria	16	131	1
Kyrtuthrix	Cyanobacteria	16	64	1
Polyangium	Proteobacteria	16	131	6
Ralstonia	Proteobacteria	16	131	3
Corynebacterium	Actinobacteria	16	87	8
Sphaerospermopsis	Cyanobacteria	15	64	3
Natronobacterium	Euryarchaeota	15	8	1
Thermus	Deinococcus-Thermus	14	3	2
Microbacterium	Actinobacteria	14	87	4
Dolichospermum	Cyanobacteria	14	64	2
Helicobacter	Proteobacteria	14	131	1
Marinobacter	Proteobacteria	14	131	4
Actinoallomurus	Actinobacteria	14	87	2
Frankia	Actinobacteria	14	87	1
Staphylococcus	Firmicutes	14	24	7
Corallococcus	Proteobacteria	13	131	3
Acinetobacter	Proteobacteria	13	131	6

Synechocystis	Cyanobacteria	13	64	4
Clostridium	Firmicutes	13	24	5
Photobacterium	Proteobacteria	12	131	5
Cylindrospermum	Cyanobacteria	12	64	4
Brevibacillus	Firmicutes	12	24	6
Calothrix	Cyanobacteria	12	64	4
Kibdelosporangium	Actinobacteria	12	87	6
Enterobacter	Proteobacteria	12	131	5
Thermococcus	Euryarchaeota	12	8	4
Saccharomonospora	Actinobacteria	12	87	4
Lechevalieria	Actinobacteria	12	87	2
Ruegeria	Proteobacteria	11	131	3
Aeromonas	Proteobacteria	11	131	5
Marinactinospora	Actinobacteria	11	87	3
Microtetraspora	Actinobacteria	11	87	4
Dermacoccus	Actinobacteria	11	87	4
Shewanella	Proteobacteria	11	131	6
Agrobacterium	Proteobacteria	11	131	8
Halomonas	Proteobacteria	11	131	4
Hyalangium	Proteobacteria	11	131	3
Phaeobacter	Proteobacteria	10	131	2
Chryseobacterium	Bacteroidetes	10	26	3
Microbulbifer	Proteobacteria	10	131	4
Streptoalloteichus	Actinobacteria	10	87	4
Lentzea	Actinobacteria	10	87	3
Pyxidicoccus	Proteobacteria	10	131	4
Chainia	Actinobacteria	10	87	6
Planobispora	Actinobacteria	10	87	1
Pyrococcus	Euryarchaeota	10	8	1
Mooreia	Bacteroidetes	9	26	1
Streptococcus	Firmicutes	9	24	8
Kutzneria	Actinobacteria	9	87	1
Actinosporangium	Actinobacteria	9	87	3
Enhygromyxa	Proteobacteria	9	131	3
Microcoleus	Cyanobacteria	9	64	3
Sphingomonas	Proteobacteria	9	131	6
Arenibacter	Bacteroidetes	9	26	1
Gordonia	Actinobacteria	9	87	5
Pantoea	Proteobacteria	9	131	5
Salegentibacter	Bacteroidetes	9	26	1
Rhizobium	Proteobacteria	9	131	7
Pedobacter	Bacteroidetes	8	26	1
Chitinophaga	Bacteroidetes	8	26	3
Thermomonospora	Actinobacteria	8	87	4
Actinokineospora	Actinobacteria	8	87	3
Jahnella	Proteobacteria	8	131	2
Streptacidiphilus	Actinobacteria	8	87	2

Hormoscilla	Cyanobacteria	8	64	1
Brevibacterium	Actinobacteria	8	87	5
Melittangium	Proteobacteria	8	131	2
Streptomonospora	Actinobacteria	8	87	4
Gynuella	Proteobacteria	8	131	2
Ohtaekwangia	Bacteroidetes	8	26	1
Jiangella	Actinobacteria	7	87	1
Catenulispora	Actinobacteria	7	87	2
Alicyclobacillus	Firmicutes	7	24	2
Erwinia	Proteobacteria	7	131	6
Aphanizomenon	Cyanobacteria	7	64	4
Angiococcus	Proteobacteria	7	131	4
Arthrobacter	Actinobacteria	7	87	5
Erythrobacter	Proteobacteria	7	131	2
Psychrobacter	Proteobacteria	7	131	2
Flexibacter	Bacteroidetes	7	26	5
Klebsiella	Proteobacteria	6	131	4
Haliangium	Proteobacteria	6	131	3
Pelomonas	Proteobacteria	6	131	2
Schizothrix	Cyanobacteria	6	64	2
Synechococcus	Cyanobacteria	6	64	3
Marinispora	Actinobacteria	6	87	2
Caldora	Cyanobacteria	6	64	1
Cylindrospermopsis	Cyanobacteria	6	64	2
Thermoactinomyces	Firmicutes	6	24	4
Jishengella	Actinobacteria	6	87	1
Janthinobacterium	Proteobacteria	6	131	3
Rhodospirillum	Proteobacteria	6	131	1
Roseovarius	Proteobacteria	6	131	2
Bacteroides	Bacteroidetes	6	26	2
Blennothrix	Cyanobacteria	6	64	1
Deinococcus	Deinococcus-Thermus	6	3	2
Loktanella	Proteobacteria	6	131	3
Enterococcus	Firmicutes	5	24	2
Nodosilinea	Cyanobacteria	5	64	3
Xanthomonas	Proteobacteria	5	131	5
Tychonema	Cyanobacteria	5	64	1
Bradyrhizobium	Proteobacteria	5	131	3
Stigonema	Cyanobacteria	5	64	2
Tenacibaculum	Bacteroidetes	5	26	2
Halobacillus	Firmicutes	5	24	3
Sporendonema	Ascomycota	5	2	1
Rhodobacter	Proteobacteria	5	131	3
Limnoraphis	Cyanobacteria	5	64	1
Saprospira	Bacteroidetes	5	26	1
Azotobacter	Proteobacteria	5	131	2

Dickeya	Proteobacteria	5	131	4
Thalassotalea	Proteobacteria	5	131	1
Acetobacter	Proteobacteria	5	131	2
Ochrobactrum	Proteobacteria	5	131	2
Desmonostoc	Cyanobacteria	4	64	3
Sphingopyxis	Proteobacteria	4	131	1
Alcanivorax	Proteobacteria	4	131	2
Kribbella	Actinobacteria	4	87	1
Methylococcus	Proteobacteria	4	131	1
Pseudovibrio	Proteobacteria	4	131	2
Collimonas	Proteobacteria	4	131	1
Raphidiopsis	Cyanobacteria	4	64	2
Hymenobacter	Bacteroidetes	4	26	1
Alcaligenes	Proteobacteria	4	131	2
Labrenzia	Proteobacteria	4	131	3
Tistrella	Proteobacteria	4	131	2
Plectonema	Cyanobacteria	4	64	2
Didemnitutus	Verrucomicrobia	4	2	1
Halobacterium	Euryarchaeota	4	8	3
Fulvivirga	Bacteroidetes	4	26	1
Herpetosiphon	Chloroflexi	4	3	3
Rubritalea	Verrucomicrobia	4	2	1
Paraliomyxa	Proteobacteria	4	131	1
Thermovibrio	Aquificae	4	2	1
Actinopolyspora	Actinobacteria	4	87	2
Thermosporothrix	Chloroflexi	4	3	2
Dichothrix	Cyanobacteria	4	64	2
Tsukamurella	Actinobacteria	4	87	1
Methanobacterium	Euryarchaeota	4	8	1
Carnobacterium	Firmicutes	4	24	3
Methanococcus	Euryarchaeota	4	8	1
Prochlorothrix	Cyanobacteria	4	64	1
Propionibacterium	Actinobacteria	4	87	2
Hormothamnion	Cyanobacteria	3	64	1
Coniella	Ascomycota	3	2	1
Roseobacter	Proteobacteria	3	131	1
Actinomycetospora	Actinobacteria	3	87	1
Allokutzneria	Actinobacteria	3	87	1
Thermobifida	Actinobacteria	3	87	1
Leuconostoc	Firmicutes	3	24	2
Methylocaldum	Proteobacteria	3	131	1
Mycetohabitans	Proteobacteria	3	131	1
Gallaecimonas	Proteobacteria	3	131	1
Conexibacter	Actinobacteria	3	87	1
Rubrobacter	Actinobacteria	3	87	1
Dapis	Cyanobacteria	3	64	1
Actinopolymorpha	Actinobacteria	3	87	1

Chromatium	Proteobacteria	3	131	2
Herbaspirillum	Proteobacteria	3	131	1
Zymomonas	Proteobacteria	3	131	1
Nitrosomonas	Proteobacteria	3	131	1
Sulfolobus	Crenarchaeota	3	1	2
Byssovorax	Proteobacteria	3	131	1
Polymorphospora	Actinobacteria	3	87	1
Aequorivita	Bacteroidetes	3	26	1
Kitasatoa	Actinobacteria	2	87	1
Allostreptomyces	Actinobacteria	2	87	1
Janibacter	Actinobacteria	2	87	2
Planococcus	Firmicutes	2	24	2
Catenuloplanes	Actinobacteria	2	87	1
Variovorax	Proteobacteria	2	131	2
Aphanothece	Cyanobacteria	2	64	1
Sphaerimonospora	Actinobacteria	2	87	1
Chlorobium	Chlorobi	2	1	1
Nesterenkonia	Actinobacteria	2	87	2
Pelagiobacter	Abditibacteriota	2	1	1
Pseudanabaena	Cyanobacteria	2	64	1
Roseofilum	Cyanobacteria	2	64	1
Thioalkalivibrio	Proteobacteria	2	131	1
Williamsia	Actinobacteria	2	87	2
Massilia	Proteobacteria	2	131	2
Aquimarina	Bacteroidetes	2	26	1
Cuspidothrix	Cyanobacteria	2	64	1
Trichormus	Cyanobacteria	2	64	1
Geitlerinema	Cyanobacteria	2	64	1
Hydrocoleum	Cyanobacteria	2	64	1
Labilithrix	Proteobacteria	2	131	1
Prochloron	Cyanobacteria	2	64	1
Stenotrophomonas	Proteobacteria	2	131	2
Delftia	Proteobacteria	2	131	1
Faenia	Actinobacteria	2	87	1
Sandaracinus	Proteobacteria	2	131	1
Lactococcus	Firmicutes	2	24	2
Chloroflexus	Chloroflexi	2	3	1
Enteractinococcus	Actinobacteria	2	87	1
Solwaraspora	Actinobacteria	2	87	1
Serinicoccus	Actinobacteria	2	87	2
Kocuria	Actinobacteria	2	87	2
Planomonospora	Actinobacteria	2	87	2
Ampullariella	Actinobacteria	2	87	2
Rivularia	Cyanobacteria	2	64	1
Hassallia	Cyanobacteria	2	64	1
Dietzia	Actinobacteria	2	87	1
Rhodopseudomonas	Proteobacteria	2	131	2

Hahella	Proteobacteria	2	131	1
Spiribacter	Proteobacteria	1	131	1
Mesorhizobium	Proteobacteria	1	131	1
Hydrogenobacter	Aquificae	1	2	1
Legionella	Proteobacteria	1	131	1
Vitiosangium	Proteobacteria	1	131	1
Colwellia	Proteobacteria	1	131	1
Sporotalea	Firmicutes	1	24	1
Haloferax	Euryarchaeota	1	8	1
Sarcina	Firmicutes	1	24	1
Edwardsiella	Proteobacteria	1	131	1
Acrocarpospora	Actinobacteria	1	87	1
Azospirillum	Proteobacteria	1	131	1
Haemophilus	Proteobacteria	1	131	1
Beneckea	Proteobacteria	1	131	1
Eubacterium	Firmicutes	1	24	1
Gluconacetobacter	Proteobacteria	1	131	1
Roseivirga	Bacteroidetes	1	26	1
Westiellopsis	Cyanobacteria	1	64	1
Porphyromonas	Bacteroidetes	1	26	1
Pediococcus	Firmicutes	1	24	1
Virgibacillus	Firmicutes	1	24	1
Actinospica	Actinobacteria	1	87	1
Mumia	Actinobacteria	1	87	1
Rhodovulum	Proteobacteria	1	131	1
Zobellia	Bacteroidetes	1	26	1
Cobetia	Proteobacteria	1	131	1
Pontibacter	Bacteroidetes	1	26	1
Rapidithrix	Bacteroidetes	1	26	1
Jejuia	Bacteroidetes	1	26	1
Rhodobium	Proteobacteria	1	131	1
Algoriphagus	Bacteroidetes	1	26	1
Hyella	Cyanobacteria	1	64	1
Microvirgula	Proteobacteria	1	131	1
Kamptonema	Cyanobacteria	1	64	1
Alkalimonas	Proteobacteria	1	131	1
Paracoccus	Proteobacteria	1	131	1
Gloeotrichia	Cyanobacteria	1	64	1
Sulfurospirillum	Proteobacteria	1	131	1
Gluconobacter	Proteobacteria	1	131	1
Cupriavidus	Proteobacteria	1	131	1
Blastobacter	Proteobacteria	1	131	1
Cyanobium	Cyanobacteria	1	64	1
Amycolata	Actinobacteria	1	87	1
Meiothermus	Deinococcus-Thermus	1	3	1
Thermoplasma	Euryarchaeota	1	8	1

Mechercharimyces	Firmicutes	1	24	1
Empedobacter	Bacteroidetes	1	26	1
Nocardioides	Actinobacteria	1	87	1
Spirulina	Cyanobacteria	1	64	1
Teredinibacter	Proteobacteria	1	131	1
Aphanocapsa	Cyanobacteria	1	64	1
Yersinia	Proteobacteria	1	131	1
Endobugula	Proteobacteria	1	131	1
Methylobacter	Proteobacteria	1	131	1
Hyphomonas	Proteobacteria	1	131	1
Brenneria	Proteobacteria	1	131	1
Aulosira	Cyanobacteria	1	64	1
Phytohabitans	Actinobacteria	1	87	1
Salmonella	Proteobacteria	1	131	1
Comamonas	Proteobacteria	1	131	1
Salinibacter	Rhodothermaeota	1	2	1
Thermosynechococcus	Cyanobacteria	1	64	1
Microseira	Cyanobacteria	1	64	1
Glycomyces	Actinobacteria	1	87	1
Promicromonospora	Actinobacteria	1	87	1
Eucapsis	Cyanobacteria	1	64	1
Trinickia	Proteobacteria	1	131	1
Aerobacter	Proteobacteria	1	131	1
Salisaeta	Rhodothermaeota	1	2	1
Azoarcus	Proteobacteria	1	131	1
Petrotoga	Thermotogae	1	1	1
Frateuria	Proteobacteria	1	131	1
Borrelia	Spirochaetes	1	1	1
Providencia	Proteobacteria	1	131	1
Clavibacter	Actinobacteria	1	87	1
Arcicella	Bacteroidetes	1	26	1
Geobacillus	Firmicutes	1	24	1
Lysinibacillus	Firmicutes	1	24	1
Rubrivivax	Proteobacteria	1	131	1
Geobacter	Proteobacteria	1	131	1
Marinomonas	Proteobacteria	1	131	1
Curtobacterium	Actinobacteria	1	87	1
Achromobacter	Proteobacteria	1	131	1
Amphibacillus	Firmicutes	1	24	1
Ectothiorhodospira	Proteobacteria	1	131	1

6. Natural product compound distribution by phylum

Appendix Table S 11: Natural product compound distribution by phylum; based on NPAtlas_v2021_08 (van Santen *et al,* 2022; Gavriilidou *et al,* 2022)

Phylum	Number of compounds in phylum	Number of genera in phylum
Actinobacteria	7490	87
Actinobacteria (w/o Streptomyces)	2031	86
Cyanobacteria	1920	64
Proteobacteria	1907	131
Firmicutes	594	24
Bacteroidetes	164	26
Euryarchaeota	51	8
Deinococcus-Thermus	21	3
Chloroflexi	10	3
Verrucomicrobia	8	2
Ascomycota	8	2
Aquificae	5	2
Crenarchaeota	3	1
Abditibacteriota	2	1
Chlorobi	2	1
Rhodothermaeota	2	2
Spirochaetes	1	1
Thermotogae	1	1

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