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REVIEW ARTICLE

Antibiotics in the clinical pipeline in October 2019

Mark S. Butler[1] · David L. Paterson[1]

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Abstract

The development of new and effective antibacterial drugs to treat multi-drug resistant (MDR) bacteria, especially Gram-negative (G−ve) pathogens, is acknowledged as one of the world's most pressing health issues; however, the discovery and development of new, nontoxic antibacterials is not a straightforward scientific task, which is compounded by a challenging economic model. This review lists the antibacterials, β-lactamase/β-lactam inhibitor (BLI) combinations, and monoclonal antibodies (mAbs) first launched around the world since 2009 and details the seven new antibiotics and two new β-lactam/BLI combinations launched since 2016. The development status, mode of action, spectra of activity, lead source, and administration route for the 44 small molecule antibacterials, eight β-lactamase/BLI combinations, and one antibody drug conjugate (ADC) being evaluated in worldwide clinical trials at the end of October 2019 are described. Compounds discontinued from clinical development since 2016 and new antibacterial pharmacophores are also reviewed. There has been an increase in the number of early stage clinical candidates, which has been fueled by antibiotic-focused funding agencies; however, there is still a significant gap in the pipeline for the development of new antibacterials with activity against β-metallolactamases, orally administered with broad spectrum G−ve activity, and new treatments for MDR *Acinetobacter* and gonorrhea.

Introduction

Since their development in the 1940s, antibacterial drugs have become lifesaving medicines that are integral to human health. Unfortunately, antibacterial drug resistance is widespread amongst pathogenic bacteria, which significantly reduces the medical effectiveness of currently marketed drugs. These drug-resistant and multi-drug resistant (MDR) bacteria have been acknowledged by Governments and scientists as one of the world's most pressing health issues; however, the discovery and development of new antibiotics and antibiotic-alternatives to treat these infections is not straightforward. As a consequence, it is important to analyze the antibacterial development pipeline to capture a snapshot of what is happening today and compare it to previous years. This review provides an update to previous reviews in this series in 2015 [1], 2013 [2] and 2011 [3], which are complementary to recent reviews that describe the pre-clinical [4] and clinical pipeline [5–11]. There have also been several important reviews that analyze the lead discovery and development of antibiotics [12–22], antibiotic alternatives [23–25], β-lactam/β-lactamase inhibitors [26, 27], and antibiotic conjugate and prodrug strategies [28]. There has also been reviews that discuss issues with antibiotic stewardship, resistance and, the commercialization challenge [29–41].

This review details antibacterials launched since 2009 (Table 1; Table S1 from 2000 to 2009) and analyzes new antibacterials approved (Figs. 1–3) since the previous 2015 review [1]. Small molecule antibacterials, BLI combinations, and antibody drug conjugates (ADC) that are being evaluated in phase-I, -II, or -III clinical trials and under pre-approval regulatory evaluation as of 31 October 2019 (Tables 2–5, Figs. 4–12) are reviewed highlighting their development status, mode of action, spectra of activity, historical discovery, and origin of the lead compound's pharmacophore. The clinical trial codes, which are predominantly from ClinicalTrials.gov (NCT), are listed in parentheses for each antibacterial,

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✉ Mark S. Butler
mark@msbchem.com

[1] Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Royal Brisbane and Women's Hospital Complex, Herston, Brisbane, QLD 4072, Australia

Table 1 Antibiotics, β-lactamase inhibitor (BLI) combinations, and monoclonal antibodies (mAb) launched from January 2009 to October 2019, their antibiotic class, activity spectra, country of first approval, and lead source

Year approved	Drug name[a,b]	Class	Country of first approval	Lead source
Small molecule antibacterials				
2009	Tebipenem pivoxil	Carbapenem	Japan	NP
2009	Telavancin	Glycopeptide	USA	NP
2009	Antofloxacin	Fluoroquinolone	China	S
2009	Besifloxacin[c]	Fluoroquinolone	USA	S
2010	Ceftaroline fosamil	Cephalosporin	USA	NP
2011	Fidaxomicin[b]	Tiacumicin	USA	NP
2012	Bedaquiline[b]	Diarylquinoline	USA	S
2012	Perchlozone	Thiosemicarbazone	Russia	S
2014	Delamanid	Nitroimidazole	Europe	S
2014	Dalbavancin	Glycopeptide	USA	NP
2014	Oritavancin	Glycopeptide	USA	NP
2014	Tedizolid phosphate	Oxazolidinone	USA	S
2014	Nemonoxacin	Quinolone	Taiwan	S
2014	Morinidazole (**1**)[e]	Nitroimidazole	People's Republic of China	S
2014	Finafloxacin[c]	Fluoroquinolone	USA	S
2015	Zabofloxacin (**2**)	Fluoroquinolone	Republic of Korea	S
2017	Delafloxacin (**3**)	Fluoroquinolone	USA	S
2018	Plazomicin (**4**)	Aminoglycoside	USA	NP
2018	Eravacycline (**5**)	Tetracycline	Europe	NP
2018	Omadacycline (**6**)	Tetracycline	USA	NP
2018	Sarecycline (**7**)[c]	Tetracycline	USA	NP
2019	Pretomanid (**8**)	Nitroimidazole	USA	S
2019	Lefamulin (**9**)	Pleuromutilin	USA	NP
2019	Lascufloxacin (**10**)	Fluoroquinolone	Japan	S
2019	Cefiderocol (**11**)	Cephalosporin siderophore	USA	NP
BLI combinations				
2014	Zerbaxa: ceftolozane + tazobactam[d]	β-Lactam + BLI	USA	NP + NP
2015	Avycaz: avibactam[b] + ceftazidime[d]	DBO BLI + β-lactam	USA	S + NP
2017	Vabomere: vaborbactam[b] (**12**) + meropenem[d] (**13**)	Boronate BLI + β-lactam	USA	S + NP
2019	Recarbrio: relebactam (**14**) + imipenem (**15**)[d] + cilastatin (**16**)[d]	DBO BLI + β-lactam + renal dehydropeptidase inhibitor	USA	S + NP + S
mAbs				
2012	Raxibacumab	mAb	USA	mAb
2016	Obiltoxaximab	mAb	USA	mAb
2016	Bezlotoxumab	mAb	USA	mAb

BLI β-lactamase inhibitor, *DBO* diazabicyclooctane, *mAb* monoclonal antibody, *NP* natural product-derived, *S* synthetic, *USA* United States of America

[a]The structures of the antibiotics approved from 2000 to 2014 can be found in our previous reviews [1–3]

[b]First member of a new antibiotic or β-lactamase inhibitor class approved for human therapeutic use

[c]Approved for topical use

[d]First launches: tazobactam in 1992, ceftazidime in 1983, meropenem (**13**) in 1998, and imipenem (**15**) + cilastatin (**16**) in 1985

[e]Also approved for the treatment of amebiasis and trichomoniasis

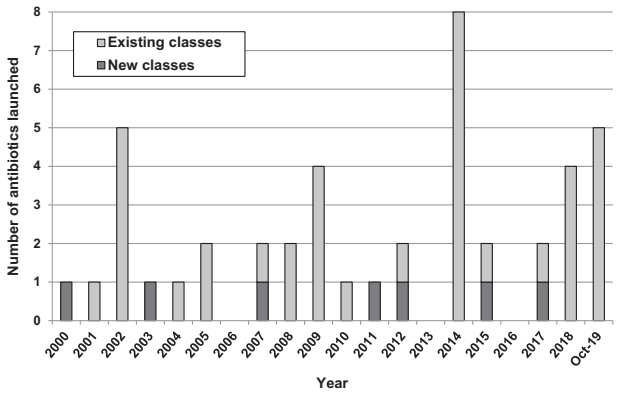
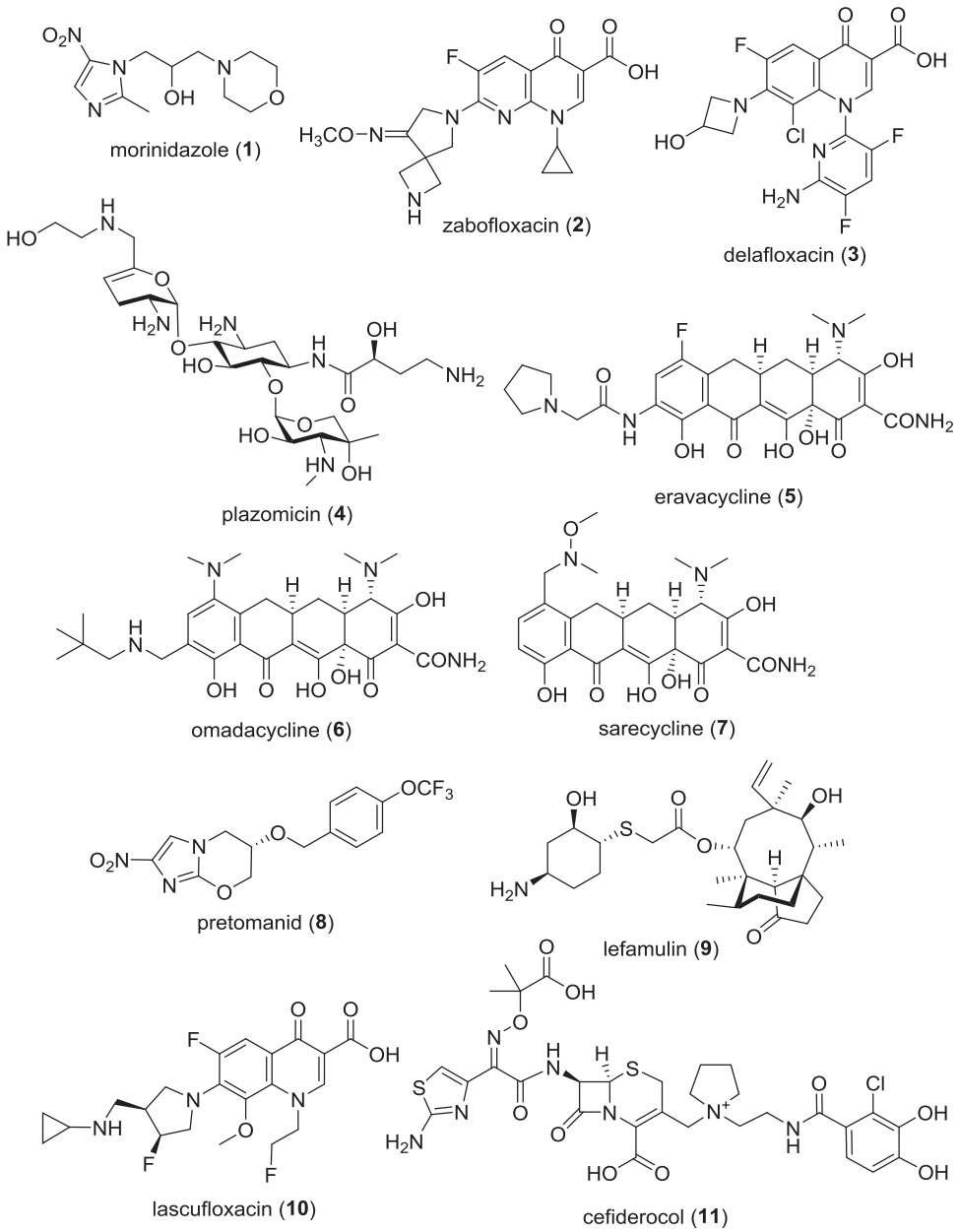


Fig. 1 New antibacterial and BLI classes January 2000 to October 2019 with new classes highlighted

while non-registered trials are referenced at least by a Press Release or peer-reviewed publication. A list of online clinical trial databases can be found in the Supplementary information. Repurposed drugs that have not previously been approved as antibacterials have been included in this analysis. Pro-drugs are grouped together with their active metabolites, while ongoing trials of antibacterial drugs that already approved anywhere in the world are not discussed but are listed in Table S2. Compounds for which no development activity has been reported since 2017 are listed in Table 6. The antibacterials in clinical development have been further analyzed by phase and source derivation (Fig. 13) and to the previous 2011 [3], 2013 [2], and 2015 [1] reviews

Fig. 2 Structures of the recently launched antibacterial drugs



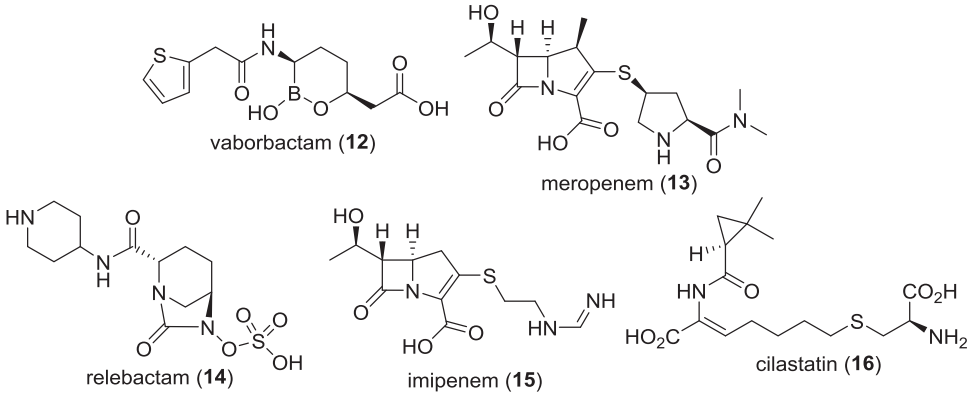


Fig. 3 Structures of the recently β-lactam/β-lactamase inhibitor (BLI) combinations

(Fig. 14). An analysis of new antibacterial pharmacophores (Table 7, Figs. 15 and 16) and administration routes (Figs. S1 and S2) has also been undertaken.

Data in this review were obtained by analyzing the scientific literature and internet resources such as company web pages, clinical trial registers, The Pew Charitable Trusts (Philadelphia, PA, USA) [42, 43] and World Health Organization (WHO) (Geneva, Switzerland) pipeline analyses [5] and biotechnology newsletters. Every effort has been undertaken to ensure that these data are accurate; however, it is possible compounds in the earlier stages of clinical development have been overlooked as there is limited information available in the public domain. An overview of the drug development and approval process, antibiotic clinical trial categories and abbreviations can be found in the Supplementary information.

Antibacterial drugs launched since 2000

Since 2000, 38 new antibacterials (two NP, 16 NP-derived and 20 synthetic-derived), four new β-lactam/BLI combinations and three monoclonal antibodies (mAbs) have been launched worldwide (Tables 1 and S1, Figs. 1 and 2). Of the 38 new antibacterials, five were first-in-class: linezolid (oxazolidinone, S, 2000), daptomycin (lipopeptide, NP, 2003), retapamulin (pleuromutilin, NP-derived, 2007), fidaxomicin (tiacumicin, NP, 2011) and bedaquiline (diarylquinoline, S, 2012). These five antibacterials have Gram-positive (G+ve) activity only; however, bedaquiline is noteworthy as it was the first new drug class approved for tuberculosis (TB) since 1963 [44]. Although the approval of a new class of G-ve antibacterial is still elusive, there has been two new BLI classes launched (diazabicyclooctane (DBO)-BLI (avibactam, S, 2015) and boron-type BLI (vaborbactam (**12**), S, 2017)) that have activity in combination with β-lactams against G-ve bacteria. Two of the approved mAbs, raxibacumab [45] and obiltoxaximab [46], help reduce the effects of anthrax toxins but further work is required to fully establish their efficacy in preclinical and clinical studies [47]. Bezlotoxumab is a mAb that binds and neutralizes *Clostridioides difficile* (formally *Clostridium difficile* [48]) toxin B, which is approved to help reduce the occurrence of *C. difficile* infections (CDI) in patients undergoing antibacterial drug treatments [49, 50].

Description of antibacterial drugs launched since 2016

Since the 2016, seven new antibacterials (Fig. 2) and two new β-lactam/BLI combinations (Fig. 3) have been approved around the world. These new approvals are discussed, along with morinidazole (**1**) and zabofloxacin (**2**), which were not detailed in the previous review [1].

Small molecules antibacterials

Morinidazole (**1**) was developed by Jiangsu Hansoh Pharmaceutical (Lianyungang, People's Republic of China) and approved in China for the treatment of anaerobic bacterial infections including appendicitis and pelvic inflammatory disease in February 2014 [51]. Morinidazole (**1**), which is also used to treat amebiasis and trichomoniasis [52], belongs to the nitroimidazole class [53] (Table 1, Fig. 2).

Zabofloxacin (**2**) (Zabolante, PB-101, DW-224a) is an orally administered fluoronaphthyridone (fluoroquinolone class) developed by Dong Wha Pharmaceutical (Seoul, Republic of Korea) that was approved in March 2015 in South Korea for the treatment of patients with acute bacterial exacerbation of chronic obstructive pulmonary disease [54, 55]. Zabofloxacin (**2**) has activity against G−ve and G+ve respiratory pathogens, notably *Streptococcus pneumoniae* [56, 57], and drug-resistant *Neisseria gonorrhoeae* [58]. There is ongoing development for the treatment of

Table 2 Antibiotics with NDA/MAA submitted or in phase-III clinical trials

Name (synonym)[a]	Compound class (lead source)	Mode of action	Administration; indication (developer)
NDA/MAA			
Solithromycin (**17**) (T-4288)	Erythromycin (NP)	Protein synthesis inhibition	iv/po; respiratory tract infection (FUJIFILM Toyama)
Iclaprim (**18**)	Trimethoprim (S)	DHFR	iv/po; ABSSSI (Motif Bio)
Phase-III			
Sulopenem (**19**) (IV); oral prodrug: sulopenem etzadroxil (**20**) + probenecid (**21**)	Penem (NP)	PBP (cell wall)	po; uUTI, cUTI, and cIAI (Iterum)
Murepavadin (**22**) (POL7080)	Protegrin I (P)	β-barrel protein LptD (Imp/OstA) inhibition (cell wall)	Inhalation, iv; bronchiectasis and VABP (Polyphor)
SQ109 (**23**)	"Ethambutol analog" (S)	Cell wall synthesis	po; TB (Infectex/Sequella)
Ridinilazole (**24**) (SMT 19969)	*bis*-benzimidazole (S)	Cell division inhibitor	po topical; CDI (Summit)
Gepotidacin (**25**)	Triazaacenaphthylene (S)	DNA gyrase (GyrA)—different to quinolones	po; UTI and gonorrhea (GSK)
Zoliflodacin (**26**) (ETX0914)	Spiropyrimidinetrione (S)	DNA gyrase (GyrB)	po; gonorrhea (Entasis Therapeutics/ GARDP)
Contezolid (**27**) (MRX-I); prodrug: Contezolid acefosamil (**28**)	Oxazolidinone (S)	Protein synthesis inhibition	iv/po; SSSI (phase-III) [ABSSSI phase-II] (MicuRx)
Levonadifloxacin (WCK-771) (**29**); prodrug: alalevonadifloxacin (WCK-2349) (**30**)	Fluoroquinolone (S)	DNA gyrase (GyrA) and Topo IV (ParC)	iv/po; MRSA and G−ve (Wockhardt)

ABSSSI acute bacterial skin and skin structure infections, *CABP* community-acquired bacterial pneumonia, *CDI C. difficile* infection, *cIAI* complicated intra-abdominal infections, *cUTI* complicated urinary tract infections, *DHFR* dihydrofolate reductase, *iv* intravenous, *MRSA* methicillin-resistant *S. aureus*, *NP* natural product, *PBP* penicillin binding protein, *po* per orem (oral), *S* synthetic, *SSSI* skin and skin structure infections, *TB* tuberculosis, *VABP* ventilator-associated bacterial pneumonia

[a]Underlined compounds are new antibacterial pharmacophores

respiratory infections and drug-resistant bacteria [59]. Dong Wha has licensing and supply agreements with China and 12 Middle Eastern and North African countries [60].

Delafloxacin (**3**) (Baxdela, RX-3341, WQ-3034, ABT-492) [61, 62], which is a fluoroquinolone that was being developed by Melinta Therapeutics (New Haven, CT, USA), was approved by the U.S. Food and Drug Administration (FDA) in June 2017 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) using both intravenous (IV) and oral formulations [63]. In addition to activity against G+ve bacteria, delafloxacin (**3**) is also approved for the treatment of the following G−ve bacteria: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [64]; however, **3** is rarely used to treat these G−ve pathogens due to resistance. In October 2019, Melinta announced that the FDA had approved an sNDA for **3** for the treatment of community-acquired bacterial pneumonia (CABP) [65].

Plazomicin (**4**) (Zemdri, ACHN-490), which is a semi-synthetic derivative [66–68] of the aminoglycoside sisomicin [69, 70] developed by Achaogen, Inc. (South San Francisco, CA, USA). An IV formulation of **4** was approved by the FDA in June 2018 for the treatment of cUTI, including pyelonephritis, due to certain Enterobacteriaceae where treatment options are limited [71]. At the same time, Achaogen also sort the approval of plazomicin (**4**) to treat bloodstream infection (BSI), but the FDA indicated further trials would be required to demonstrate its effectiveness. Achaogen had submitted an marketing authorization application (MAA) in October 2018 with The European Medicines Agency (EMA) for complicated urinary tract infections (cUTI), including pyelonephritis, BSI due to certain Enterobacteriaceae, and Enterobacteriaceae in patients with limited treatment options [72]. However, in April 2019, Achaogen filed for bankruptcy [73] and it was announced in June 2019 that Cipla USA Inc. (Sunrise, FL, USA) had purchased the worldwide rights to plazomicin (**4**) except for China where the rights were held by QiLu Antibiotics Pharmaceutical Co. (Jinan, People's Republic of China) [74].

Eravacycline (**5**) (Xerava, TP-434), which is an IV administered, synthetic fluorocycline-type tetracycline derivative [75–77] developed by Tetraphase Pharmaceuticals (Watertown, MA, USA), was approved for treatment of complicated intra-abdominal infections (cIAI) by the EMA in July 2018 [78] and by the FDA in August 2018 [79, 80]. Eravacycline (**5**) had also been evaluated in a cUTI phase-III trial (NCT01978938) but did not achieve statistical non-inferiority to ertapenem and no further development is likely [81].

Omadacycline (**6**) (Nuzyra, amadacycline, PTK-0796) [82], which a semi-synthetic minocycline derivative developed by Paratek Pharmaceuticals (Boston, MA, USA) with both oral and IV administration, was approved by the FDA in October 2018 for the treatment CABP and ABSSSI [83–85]. As a ten-year European market exclusivity starts after a product's first approval, Paratek has decided to re-submit their MAA for CABP and ABSSSI after the completion of their post-marketing CABP study for the FDA; this is because the EMA required an addition CABP study

Table 3 Compounds in, or that have recently completed, phase-II clinical trials

Name (synonym)[a]	Compound class (lead source)	Mode of action	Administration; indication (Developer)
BOS-228 (**31**) (LYS-228)	Monobactam (NP)	PBP (cell wall)	iv; cUTI and cIAI (Boston Pharmaceuticals)
Benapenem (**32**)	Carbapenem (NP)	PBP (cell wall)	iv; UTI (Sihuan Pharmaceuticals)
Nafithromycin (**33**) (WCK 4873)	Macrolide (NP)	Protein synthesis	po; CABP (Wockhardt)
MGB-BP-3 (**34**)	Distamycin A (NP)	DNA minor groove binding	po topical; CDI (MGB Biopharma)
XF-73 (**35**) (exeporfinium chloride)	Porphyrin (NP)	Membrane-perturbing activity	Topical; post-surgical nasal decolonization (Destiny Pharma)
TNP-2092 (CBR 2092) (**36**)	Rifamycin -quinolizinone (ABT719) hybrid (NP-S)	RNA polymerase, DNA gyrase (GyrA) and Topo IV (ParC)	iv (po topical); skin and subcutaneous tissue (TenNor)
Niclosamide (**37**) (ATx201)	Salicylanilide (S)	Oxidative phosphorylation; quorum sensing	Topical; *H. pylori*; impetigo (Union Therapeutics)
Auranofin (**38**)	Auranofin (S)	Thiol-redox homeostasis	po; TB (The Aurum Institute)
MBN-101 (**39**)	Bismuth-thiol (S)	Not reported	Topical; diabetic foot infections and orthopedic-implant infection (Microbion Corporation)
Prodrug: afabicin (**40**) (Debio-1450); afabicin desphosphono (**41**) (Debio 1452, AFN-1252)	Benzofuran naphthyridine (S)	FabI inhibition (cell wall)	iv/po; ABSSSI (Debio/Nobelex)
OPS-2071[b]	Quinolone (S)	Not disclosed	po topical; CDI (Otsuka)
Delpazolid (**42**) (RMX2001, LCB01-0371)	Oxazolidinone (S)	Protein synthesis inhibition	po; TB (HaiHe Biopharma)
Sutezolid (**43**) (PF-2341272, PNU-100480)	Oxazolidinone (S)	Protein synthesis inhibition	po; TB (TB Alliance/Sequella)
Prodrug: DNV-3837 (**44**) (MCB-3837); DNV-3681 (**45**) (MCB-3681)	Oxazolidinone-quinolone hybrid (S-S)	Protein synthesis inhibition, DNA gyrase (GyrA), and topo IV (ParC)	iv; CDI (Deinove)
Telacebec (**46**) (Q203)	Imidazo[1,2-*a*]pyridine amide (S)	Respiratory cytochrome bc1 complex	po; TB (Qurient Co/Infectex)
Macozinone (**47**) (PBTZ 169)	Benzothiazinone (S) (BTZ-043 (**48**))	DprE1 (cell wall)	po; TB (Nearmedic Plus LLC)
OPC-167832 (**49**)	3,4-dihydrocarbostyril (S)	DrpE1 (cell wall)	po; TB (Otsuka)
GSK656 (**50**) (GSK3036656)	Oxaborole (S)	Leucyl-tRNA synthetase (protein synthesis)	po; TB (GSK)

ABSSSI acute bacterial skin and skin structure infections, *CABP* community-acquired bacterial pneumonia, *CDI C. difficile* infection, *cIAI* complicated intra-abdominal infections, *cUTI* complicated urinary tract infections, *iv* intravenous, *NP* natural product, *P* protein/peptide, *PBP* penicillin binding protein, *po* per orem (oral), *S* synthetic, *TB* tuberculosis, *UTI* urinary tract infections

[a]Underlined compounds are new antibacterial pharmacophores

[b]Structure not publically available

Table 4 Compounds in phase-I clinical trials

Name (synonym)[a]	Compound class (lead source)	Mode of action	Administration; indication (developer)
TP-6076[b]	Tetracycline (NP)	Protein synthesis inhibition	iv; G−ve (Tetraphase)
TP-271 (**51**)	Tetracycline (NP)	Protein synthesis inhibition	iv/po; G+ve/G−ve (Tetraphase)
SPR 741 (**52**)[c] + β-lactam	Polymyxin (NP)	Membrane permeabilizer (cell wall)	iv; G−ve (Spero)
SPR 206 (**53**)	Polymyxin (NP)	Membrane disruption (cell wall)	iv; G−ve (Spero)
GT-1 (**54**) (LCB10 0200)	Cephalosporin siderophore (NP)	PBP (cell wall)	iv; not disclosed (Geom)
Apramycin (**55**)	Aminoglycoside (NP)	Protein synthesis inhibition	iv; G−ve (Juvabis)
ACX-362E (**56**)[a]	Dichlorobenzyl guanine (DCBG) (S)	DNA polymerase IIIC	po topical; CDI (Acurx Pharmaceuticals)
Fluorothyazinone (**57**)	Thyazinone (S)	Bacterial type III secretion system (T3SS)	po; G-ve virulence (Gamaleya Research Institute of Epidemiology and Microbiology)
Prodrug: SPR 720 (**58**) (pVXc-486); SPR719 (**59**)	"Ethyl urea benzimidazole" (S)	DNA gyrase (GyrB) and Topo IV (ParE)	po; TB (Spero)
Prodrug: TXA709 (**60**); TXA707 (**61**)	FtsZ benzamide (S)	FtsZ inhibition (cell wall)	po; G+ve (TAXIS)
BTZ-043 (**48**)	Benzothiazinone (S)	DprE1 (cell wall)	po; TB (University of Munich, Hans-Knöll Institute/German Center for Infection Research (DZIF))
TBI-223 (**62**)	Oxazolidinone (S)	Protein synthesis inhibition	po; TB (TB Alliance/Institute of Materia Medica)
TBI-166 (**63**)	Riminophenazine (clofazimine (**64**)) (S)	DNA binding leading to cell cycle disruption	po; TB (Institute of Materia Medica/Chinese Academy of Medical Sciences/Peking Union Medical College)
TBA-7371 (**65**)	Azaindole (S)	DrpE1 (cell wall)	po; TB (TB Alliance)
DSTA4637S (**66**)	mAb rifamycin conjugate (ADC)	RNA synthesis	iv; G+ve (Genentech)
TNP-2098[b]	Undisclosed	Not disclosed	po topical; CDI (TenNor)
BCM-0184[b]	Undisclosed	Not disclosed	po (& topical); G+ve (Biocidium)

ADC antibody drug conjugate, *CDI C. difficile* infections, *G−ve* Gram-negative, *G+ve* Gram-positive, *NP* natural product; *iv* intravenous, *PBP* penicillin binding protein, *po* per orem (oral), *S* synthetic, *TB* tuberculosis

[a]Underlined compounds are new antibacterial pharmacophore

[b]Structure not publically disclosed

[c]SPR741 (**52**) will be used in combination with other antibiotics in subsequent development

Table 5 β-lactamase inhibitor/β-lactam combinations in clinical trials

Name (synonym)	Compound (lead source)	Administration; indication (developer)
Phase-III		
Enmetazobactam (**68**) (AAI 101) + cefepime (**69**)	Clavulanic acid (**67**) (NP) + cephalosporin (NP)	iv; UTI (Allecra Therapeutics)
ETX2514SUL [durlobactam (**70**) (ETX2514) + sulbactam (**71**)]	DBO (S)[a] + clavulanic acid (**67**) (NP)	iv; MDR *Acinetobacter* infections (Entasis)
Taniborbactam (**72**) (VNRX-5133) + cefepime (**69**)	Boronate (S) + cephalosporin (NP)	iv; cUTI (VenatoRx)
Phase-I		
Nacubactam (**73**) (OP0595) + meropenem (**13**)	DBO (S)[a] + carbapenem (NP)	iv; G−ve (NacuGen Therapeutics)
Zidebactam (**74**) + cefepime (**69**)	DBO (S)[a] & PBP2 + cephalosporin (NP)	iv; G−ve (Wockhardt)
Prodrug: ETX0282 (**75**) + prodrug: cefpodoxime proxetil (**77**); ETX1317 (**76**) + cefpodoxime (**78**)	DBO (S)[a] + cephalosporin (NP)	po; UTI (Entasis Therapeutics)
Prodrug: VNRX-7145 (**79**) + ceftibuten (**80**)	Boronate (S) + cephalosporin (NP)	po; G−ve (VenatoRx)
Prodrug: ARX-1796 (**81**) (ARX-006)	DBO prodrug of avibactam (**82**) prodrug	po; G−ve (Arixa)

cIAI complicated intra-abdominal infections, *cUTI* complicated urinary tract infections, *G−ve* Gram-negative, *iv* intravenous, *NP* natural product, *MDR* multi-drug resistant, *po* per orem (oral), *S* synthetic, *UTI* urinary tract infections

[a]These DBO BLIs also have activity against selected Enterobacteriaceae

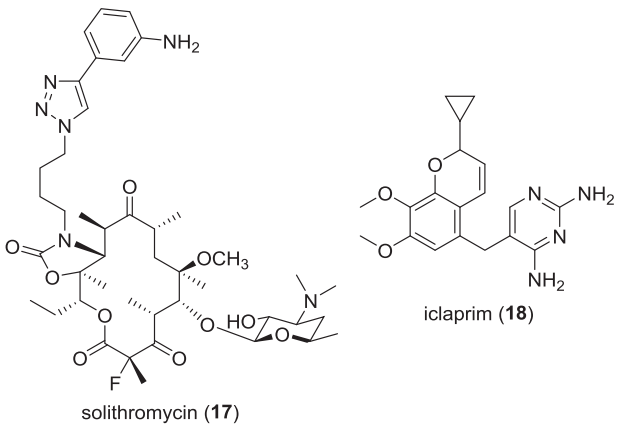


Fig. 4 Structures of antibacterials in the NDA and MAA development stage

but voted to approve **6** for ABSSSI [86]. Omadacycline (**6**) is also being evaluated in phase-II trials as a treatment of acute pyelonephritis (NCT03757234) and cystitis (UTI, NCT03425396).

Sarecycline (**7**) (Seysara, WC-3035, P005672, PTK-AR01) was approved by the FDA in October 2018 as a topical treatment of moderate to severe acne [87–90]. Sarecycline (**7**) is a semi-synthetic tetracycline derivative discovered by Paratek Pharmaceuticals (Boston, MA, USA) and developed by Allergan, plc (Dublin, Ireland), which had its US dermatology assets acquired by Almirall S.A. (Barcelona, Spain) in August 2018.

Pretomanid (**8**) (PA-824) is a nitroimidazole [53] derived from CGI-17341 [91] that was approved by the FDA in August 2019 as an orally-administered treatment for extensively drug resistant (XDR)-TB in combination with bedaquiline and linezolid under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) [92]. The Global Alliance for TB Drug Development (TB Alliance) (New York, NY, USA) has been evaluating pretomanid (**8**) in three phase-III trials: in combination with linezolid and bedaquiline (NCT03086486), linezolid (NCT02333799), and linezolid, bedaquiline, moxifloxacin and clofazimine (NCT02589782). A phase-III in combination with moxifloxacin and pyrazinamide was completed in May 2018 (NCT02342886). Pretomanid (**8**) acts as prodrug that is reductively activated by the deazaflavin (cofactor F_{420})-dependent nitroreductase Rv3547 [93–95]. Pretomanid (**8**) inhibits cell wall growth in aerobic conditions by hindering mycolic acid formation, while its activity involves the induction of respiratory poisoning under anaerobic conditions [93–95]. A recent report has also implicated the production of methylglyoxal using an untargeted metabolomics approach [96].

Lefamulin (**9**) (Xenleta, BC-3781) is a semi-synthetic pleuromutilin [97–99] derivative developed by Nabriva Therapeutics AG (Vienna, Austria) that was approved by the FDA in August 2019 as a treatment for patients with CABP [100]. Nabriva has also submitted an MAA for lefamulin (**9**) to the EMA in June 2019 [101]. Lefamulin (**9**) has had both oral and IV formulations approved, which should lead to shorter hospital stays, and is the second pleuromutilin derivative approved for human use but the first that can be systemically administered. The first approved pleuromutilin in 2007 was retapamulin, which is a topical treatment for impetigo [97, 98].

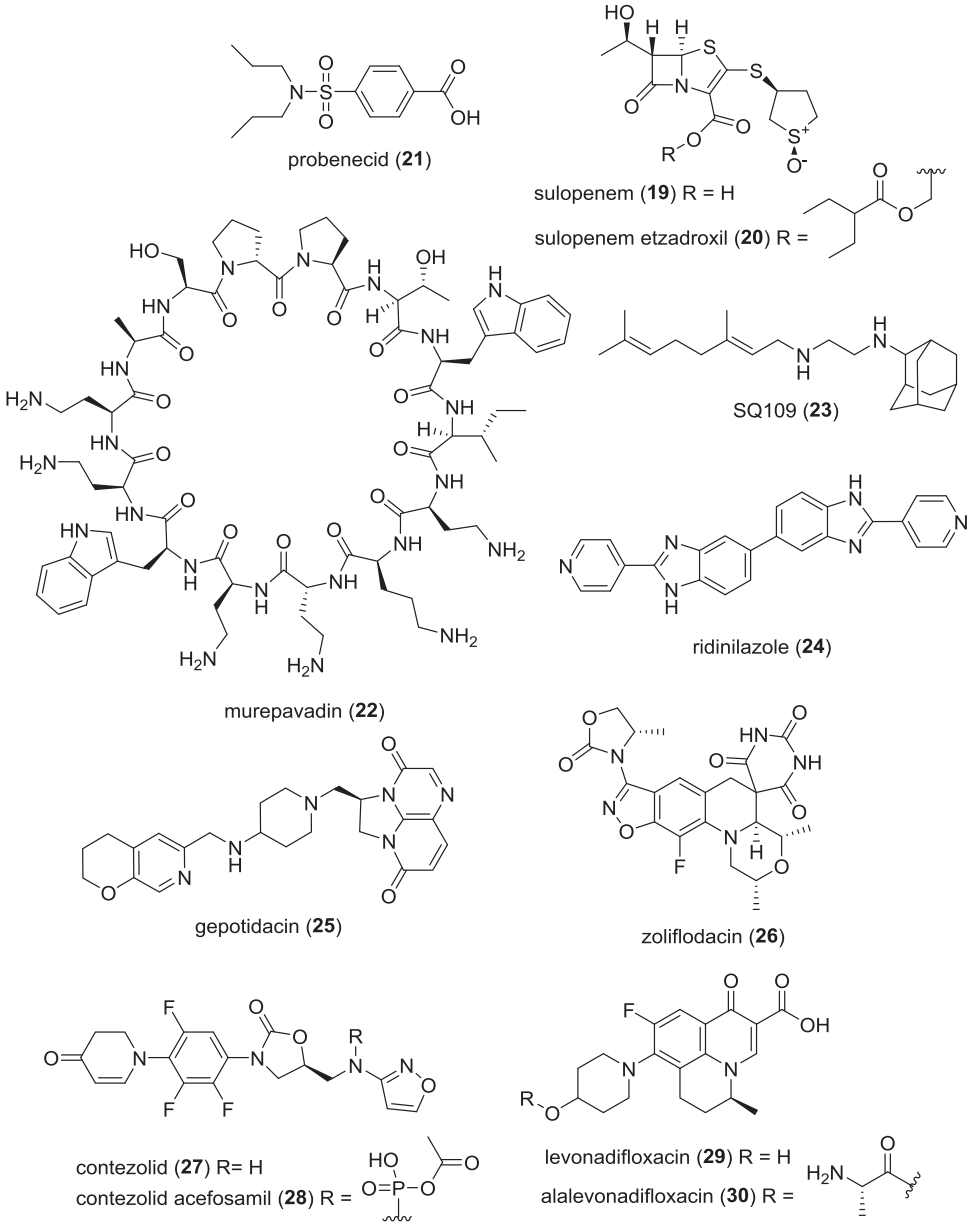


Fig. 5 Structures of compounds in phase-III clinical trials

Like other pleuromutilins, lefamulin (**9**) inhibits bacterial protein synthesis and has activity against a range of skin [102], respiratory [103, 104] and sexually transmitted pathogens [105].

Lascufloxacin (**10**) (Lasvic, KRP-AM1977) is a fluoroquinolone with broad-spectrum activity [106, 107] that was developed by Kyorin Pharmaceutical Co., Ltd (Tokyo, Japan). In September 2019, Kyorin announced that an oral formulation of **10** (called KRP-AM1977X) has been approved for the treatment of CAP, otorhinolaryngological and respiratory tract infections [108], while an NDA for the IV formulation (KRP-AM1977Y) is under preparation.

Cefiderocol (**11**) (Fetroja, S-649266) is an IV administered, semi-synthetic cephalosporin-type β-lactam developed by Shionogi & Co., Ltd. (Osaka, Japan), which incorporates a catechol siderophore that facilitates active transport into the bacteria via iron transporters, that has activity against MDR G-ve pathogens including carbapenemase producers [109–112]. Cefiderocol (**11**) is first approved antibacterial that exploits the iron transport uptake mechanism. Shionogi filed an NDA with the FDA in December 2018 for cUTI including pyelonephritis and an MAA with EMA in March 2019 multi-drug G-ve infections [113]. In November 2019, the FDA approved cefiderocol (**11**) for the treatment of cUTI [114].

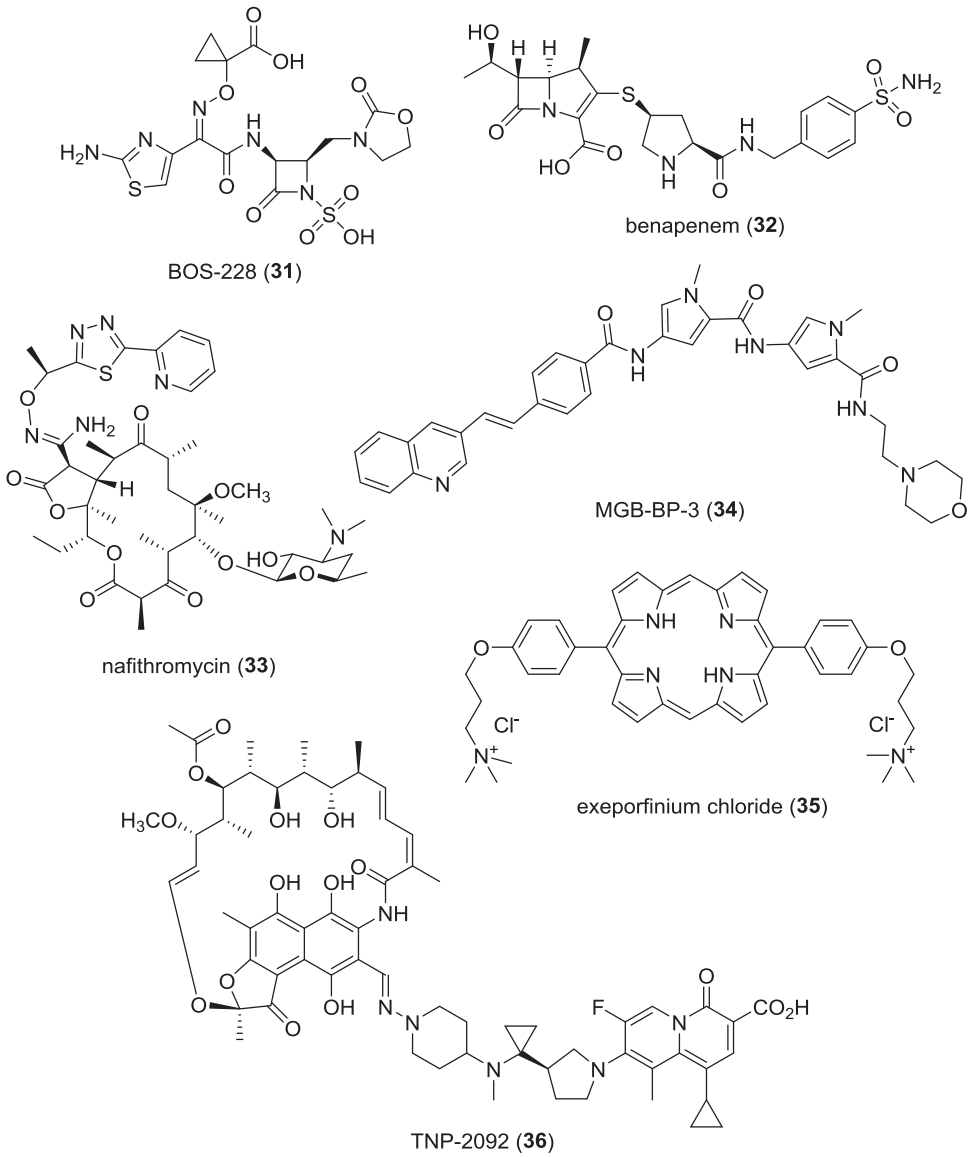


Fig. 6 Structures of NP-derived compounds in phase-II clinical trials

Cefiderocol (**11**) has been evaluated in phase-III trials as a treatment for carbapenem-resistant G-ve pathogens at various sites (NCT02714595) and hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) (NCT03032380). Positive results for a phase-II trial against cUTI (NCT02321800) has recently been published [115].

β-lactam/BLI combinations

Vabomere is an IV administered combination of the first-in-class boronate-type BLI, vaborbactam (**12**) (RPX7009), and meropenem (**13**) that was discovered by Rempex Pharmaceuticals. Rempex were acquired by The Medicines Company (Parsippany, NJ, USA) in December 2013, who were granted FDA approval in the August 2017 for the treatment of G-ve cUTIs (*E. coli*, *K. pneumoniae* and *E. cloacae* species complex), including pyelonephritis [116, 117]. Soon after this approval, The Medicines Company sold its anti-infective business units to Melinta Therapeutics (New Haven, CT, USA) [118]. In November 2017, the EMA approved Vabomere for the treatment of patients with cIAI, HAP/VAP, bacteremia, and other aerobic G-ve organisms with limited treatment options [119]. Vaborbactam (**12**) is noteworthy for its rapid movement from Rempex's 8 August 2011 patent filing [120] to its first approval in just over six years on 29 August 2017 (Table 1, Fig. 3).

Recarbrio, which is a combination of the relebactam (**14**), imipenem (**15**) and cilastatin (**16**) developed by Merck & Co (Rahway, NJ, USA; known as Merck Sharp & Dohme (MSD) outside of the USA), was approved by the FDA in

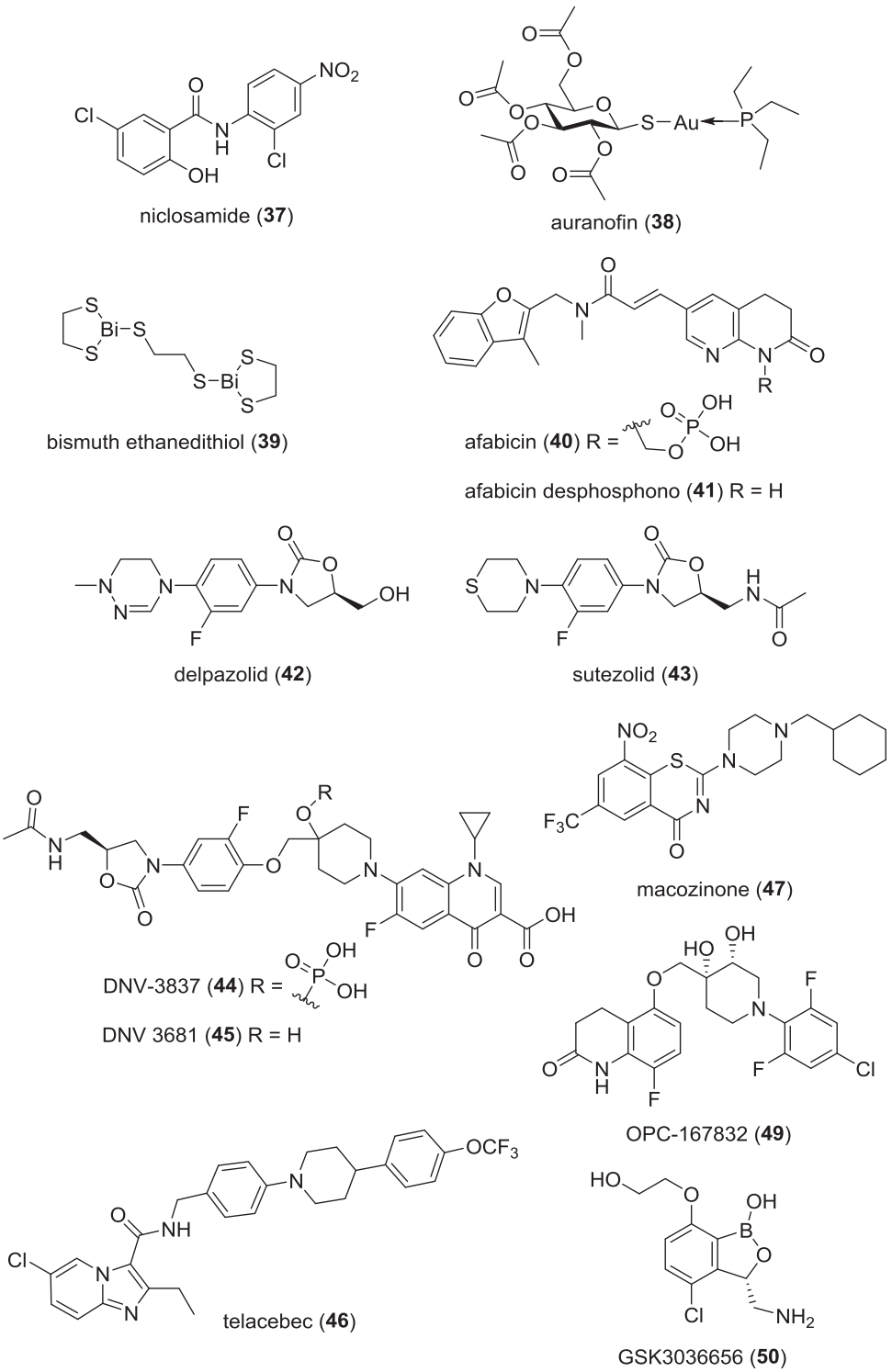


Fig. 7 Structures of synthetic compounds in phase-II clinical trials

July 2019 as an IV administered treatment of cUTI and cIAI [117, 121–123]. Relebactam (**14**) is a DBO-type BLI [124] that is administered with the imipenem (**15**), which is a carbapenem first launched in 1987, and cilastatin (**16**), which is a dehydropeptidase inhibitor that improves the in vivo stability of imipenem (**15**) [125].

Compounds undergoing clinical evaluation

The compounds currently undergoing clinical trials or under regulatory evaluation for the treatment of bacterial infections as of the end of October 2019 are detailed in the following tables and figures: NDA and phase-III in Tables 2

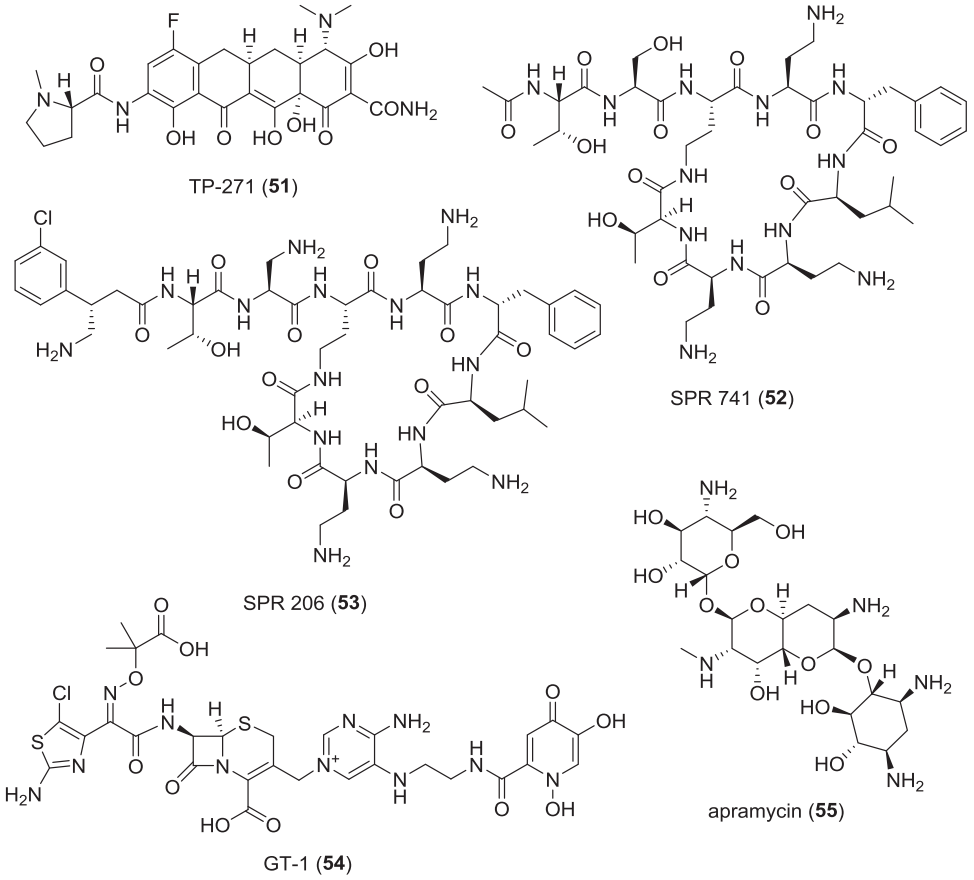


Fig. 8 Structures of NP-derived compounds in phase-I clinical trials

and 5 with structures in Figs. 4, 5, and 11, phase-II in Table 3 with structures in Figs. 6 and 7, and phase-I in Tables 4 and 5 with structures in Figs. 8–10 and 12.

Compounds in NDA/MAA filing

Solithromycin (**17**) (T-4288, CEM-101) is a semi-synthetic 2-fluoroketolide [126] that is being evaluated by FUJIFILM Toyama Chemical Co., Ltd. (Tokyo, Japan) in several phase-III trials in Japan as an oral treatment for sinusitis (JPRN-JapicCTI-173733), otorhinolaryngological (head and neck) infections (JPRN-JapicCTI-163467), respiratory tract infections (JPRN-JapicCTI-163438) and CAP (JPRN-JapicCTI-163439). The National Institute of Allergy and Infectious Diseases (NIAID) (Bethesda, MD, USA) has also been evaluated **1** in a phase-I trial for gonorrhea (NCT02348424). In April 2019, FUJIFILM Toyama applied for a NDA in Japan with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) as a treatment bacterial infections in otorhinolaryngology (ear, nose and throat) [127]. Solithromycin (**17**) was discovered by Optimer Pharmaceuticals (San Diego, CA, USA) and was being developed in the USA by Cempra Pharmaceuticals (Chapel Hill, NC, USA). Cempra submitted an NDA for CABP to the FDA in May 2016 but the FDA sent a Complete Letter Response in December 2016 that requested additional clinical safety information and the satisfactory resolution of manufacturing facility inspection deficiencies [128]. Cempra withdrew the CABP MAA for the EMA in March 2017 [129]. Cempra merged in August 2017 with Melinta Therapeutics (New Haven, CT, USA), who are not currently developing solithromycin (**17**) (Table 2, Fig. 4).

Iclaprim (**18**) is an IV and orally dosed trimethoprim analog that was being developed by Motif Bio plc (London, UK) [130, 131]. Iclaprim (**18**) was discovered by Roche (Basel, Switzerland; coded RO-48-2622) and licensed in 2001 to their anti-infectives spin-out Arpida AG (Reinach, Switzerland; coded AR-100). Arpida completed two phase-III trials evaluating **18** for SSSI but the FDA rejected their NDA in 2009, while their MAA was later withdrawn due to concerns about not reaching non-inferiority to its comparator antibiotic and potential QT interval prolongation issues [132]. Motif Bio started to develop iclaprim (**18**) in 2015 and submitted an NDA with the FDA in June 2018 for ABSSSI from data derived from two phase-III trials (NCT02600611 and NCT02607618) [133] with altered dosing regimens compared with Arpida's trials [131]; however, the FDA required an additional clinical trial before granting approval [134] and Motif Bio have subsequentially halted development.

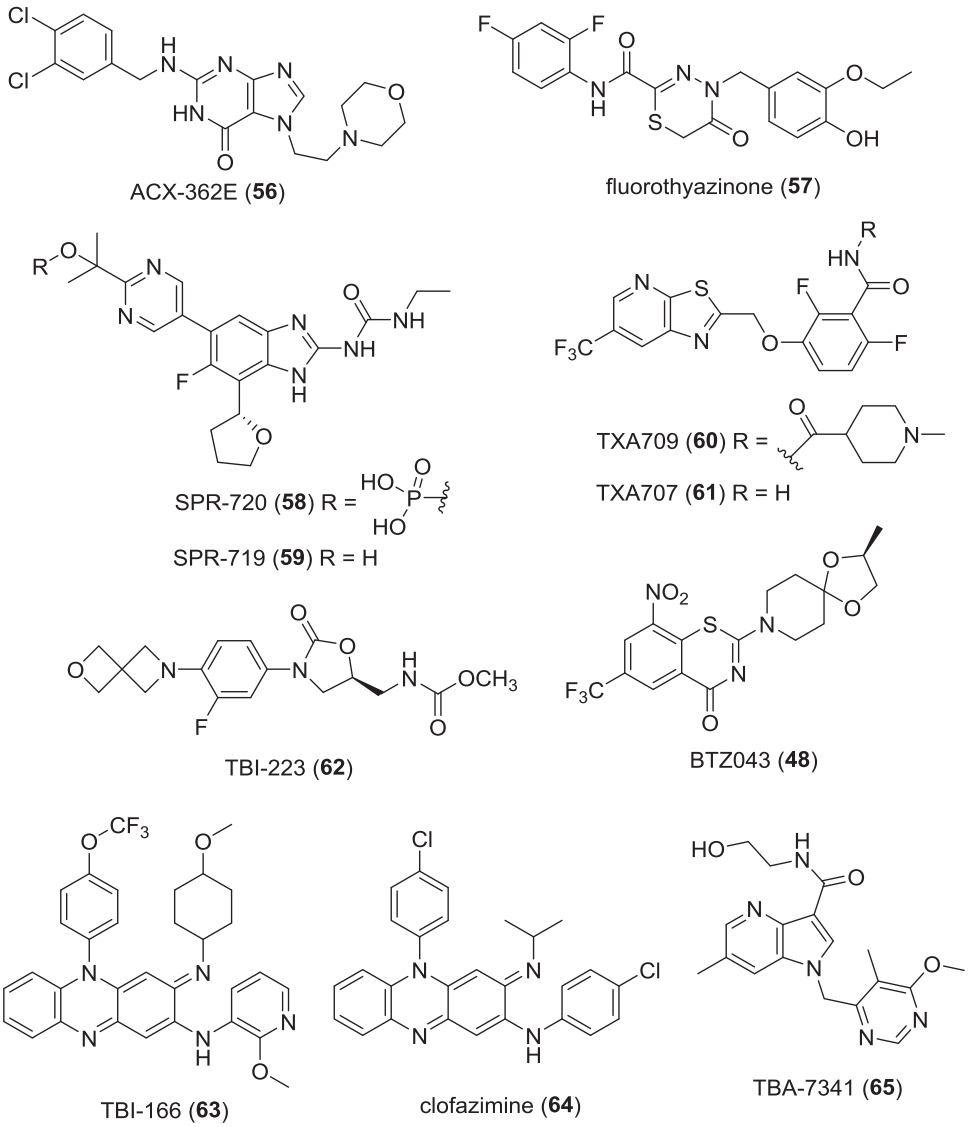


Fig. 9 Structures of synthetic-derived compounds in phase-I clinical trials

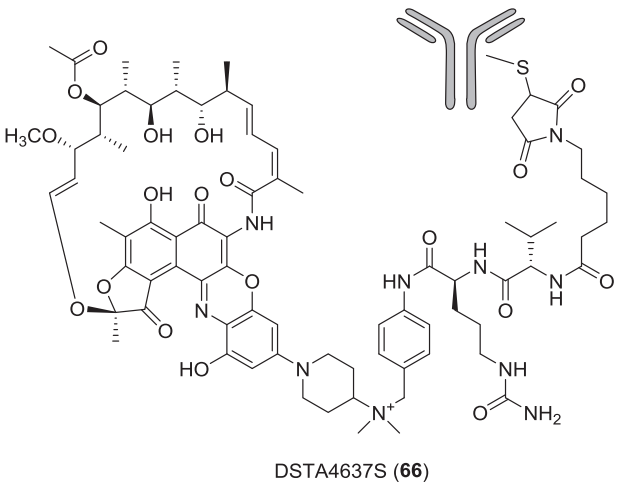


Fig. 10 Structure of the mAb-rifamycin antibiotic conjugate in phase-I trials

Compounds in phase-III trials

Sulopenem (**19**) (CP-70,429) is a synthetic thiopenem β-lactam discovered in Pfizer's Japanese laboratories that underwent clinical evaluation in the mid-1990s but development was discontinued due to high development costs and market return concerns [135]. Interestingly, the *R* enantiomer of sulopenem caused unpleasant sulfurous odors when dosed in human volunteers and the racemate CP65,207 could not be used [136]. Pfizer re-started clinical development in 2003 using a more efficient production-scale synthesis procedure to help alleviate the cost issue [137, 138]. In late 2015, Iterum Therapeutics plc (Dublin, Ireland) licensed sulopenem (**19**) and its prodrug sulopenem etzadroxil (**20**) (PF-03709270) from Pfizer [139]. Iterum are now evaluating **19** using IV administration followed by oral dosing of **20** in phase-III studies for the treatment of cIAI (NCT03358576) and cUTI

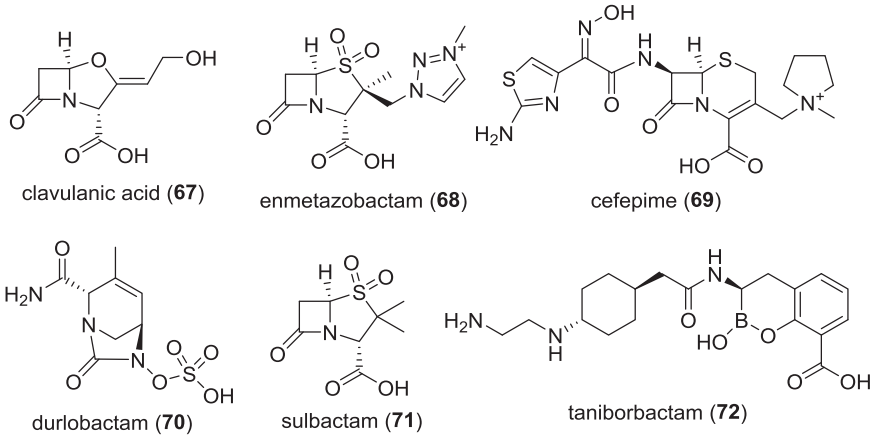


Fig. 11 Structures of BLIs and associated β-lactam antibiotics in phase-III clinical trials and clavulanic acid (**67**)

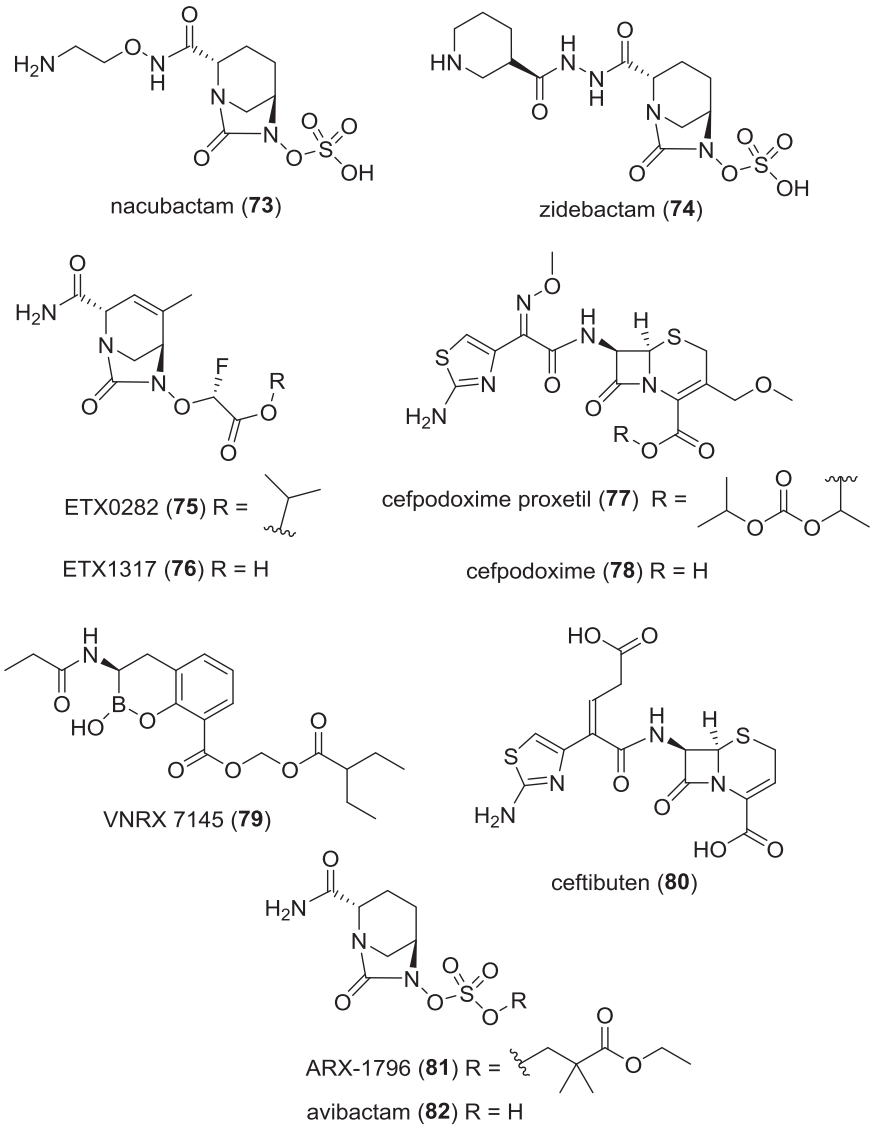


Fig. 12 Structures of BLIs and associated β-lactam antibiotics in phase-I clinical trials

Table 6 Compounds discontinued or likely to have been discontinued from clinical development since 2016 or previous review [1]

Name (synonym)	Compound class (lead source); mode of action	Last known status and indication
AIC499	β-lactam (NP); PBP (cell wall)	Phase-I trial supported by the European Medicines Initiative (IMI) within the COMBACTE-MAGNET project but not in company pipeline (AiCuris Anti-Infective Cures)
Auriclosene	*N*-chlorotaurine (NP); oxidation	Urinary Catheter Blockage and Encrustation; Impetigo (Novabay); looking for phase-II partner, licensed to Virbac for agriculture
BAL30072 + meropenem (**13**)	Monobactam (NP)/carbapenem (NP); PBP (cell wall)	Not in pipeline and no update since 2016 (Basilea)
Brilacidin (PMX30063)	Defensin (P); bacterial cell membrane lysis	Head and neck neoplasms; mucositis (Innovation Pharmaceuticals); completed phase-IIb in Sept 2018 (NCT02324335)
Cadazolid	Oxazolidinone (S) and quinolone (S) hybrid; protein and DNA synthesis	Development discontinued for CDI in March 2018 after phase-III trials (NCT01987895 and NCT01983683) (Actelion, now part of J&J)
CB-06-01 (NAI-003, BIK-0376, NAI-Acne)	GE 2270A (NP); elongation factor Tu (protein synthesis)	Finished phase-II in 2016 as a treatment for acne and development on-hold (Cassiopea S.p.A.)
Cefilavancin	Cephalosporin (NP)/vancomycin (NP) heterodimer; cell wall biosynthesis	No development updates since 2015 (R-Pharm/Theravance Biopharma)
CRS3123	"Diaryldiamine" (S); methionyl-tRNA synthetase (protein synthesis)	Phase-I trials completed in 2014 (CDI) (NCT01551004 and NCT02106338) (Crestone)
DS-2969b	New class (s); gyrase B inhibition	Adverse events from a phase-I trial reported at Infectious Disease Week-2017 (CDI) (Daiichi Sankyo)
Enmetazobactam (**62**) (AAI 101) + piperacillin	Clavulanic acid (NP) + penicillin (NP); BLI and PBP (cell wall)	Phase-I finished January 2014 (Allecra Therapeutics)
GSK 3342830	Cephalosporin siderophore (NP); PBP (cell wall)	Phase-I trial terminated in November 2017 due to some adverse events (NCT02751424) (GSK)
IDP-73152	Actinonin (NP); peptide deformylase inhibition (protein synthesis)	Phase-I completed January 2014 (NCT01904318)
KBP-7072	Tetracycline (NP); protein synthesis inhibition	Two phase-I trials completed in 2015 (KBP Biosciences)
LTX-109	Peptide (P); cell membrane	Phase-II completed NCT01803035 (Lytix Biopharma)
MK3866	Class B metallo-BLI (?)	Phase-I terminated (business and program changes; NCT03295266 and NCT03259087) (Merck & Co)
MK-6183 (CB-238,618, CB-618)	DBO-type BLI (S); PBP (cell wall)	Phase-I trial completed April 2015 (NCT02341599)
Radezolid	Oxazolidinone (S); protein synthesis inhibition	uSSSI (NCT00646958) and CABP (NCT00640926) phase-II trials completed (Melinta)
RC-01 (T 1228)	LpxC inhibitor (S); LpxC (cell wall)	Phase-I terminated (safety; NCT03832517) (Recida Therapeutics and FUJIFILM Toyama Chemical)
Surotomycin	Daptomycin (NP); membrane polarization (cell wall)	CDI phase-III trials completed in 2015 (NCT01597505 and NCT01598311) (Merck & Co)
TBA-354	Nitroimidazole (S); DNA and cellular damage	Discontinued due to mild signs of reversible neurotoxicity (NCT02606214) (TB Alliance)
TD-1607	Glycopeptide (NP)-cephalosporin (NP) heterodimer; cell wall biosynthesis	Discontinued after two phase-I trials (NCT01791049 and NCT01949103) (Theravance Biopharma)

CDI C. difficile infections, *G−ve* Gram-negative, *G+ve* Gram-positive, *MRSA* methicillin-resistant *S. aureus*, *NP* natural product, *PBP* penicillin binding protein, *S* synthetic, *TB* tuberculosis, *uSSSI* uncomplicated bacterial skin and skin structure infections

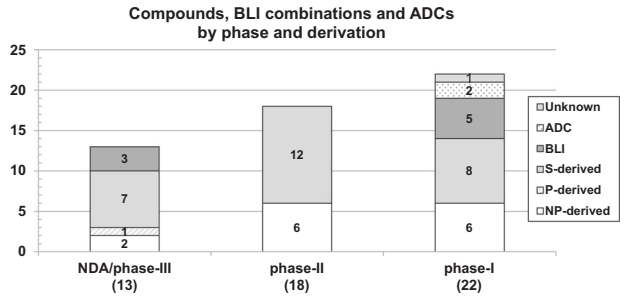


Fig. 13 Compounds under clinical evaluation divided into development phases and their lead derivation source: natural product (NP), synthetic (S), protein/mammalian peptide (P), β-lactam/β-lactamase inhibitor (BLI) combinations, and antibody drug conjugate (ADC)

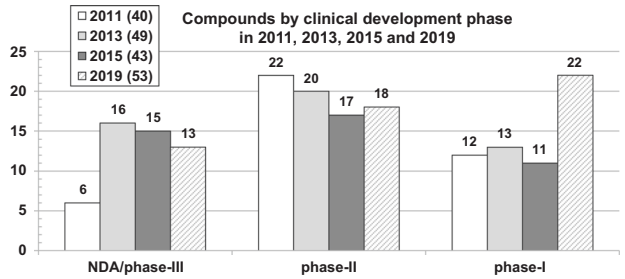


Fig. 14 Comparison of the numbers of compounds undergoing clinical development as of 2011 [3], 2013 [2], 2015 [1], and 2019 by development phase

(NCT03357614) and oral **20** alone for uUTI (NCT03354598). In these trials, sulopenem etzadroxil (**19**) is administered along with probenecid (**21**) [140], which is a marketed drug for gout and hyperuricemia that increases uric acid production, that inhibits the tubular secretion of some β-lactams and leads to a longer drug half-life and higher serum concentrations [141] (Table 3, Figs. 6 and 7).

Murepavadin (**22**) (POL7080, RG7929) is a synthetic cyclic peptide 14-mer based on protegrin I that is being developed by Polyphor, Ltd. (Basel, Switzerland) [142–144]. Murepavadin (**22**) has a new mode of action through binding to the *N*-terminal of the β-barrel protein LptD (Imp/OstA) from *P. aeruginosa* [142, 145], which affects lipopolysaccharide transport to the cell surface and leads to bacterial death [146]. As this binding pocket is only present in *P. aeruginosa* LptD, murepavadin (**22**) displays selective anti-*P. aeruginosa* activity, which should help to reduce resistance and microbiome disturbance. Polyphor have been evaluating murepavadin (**22**) in two phase-III trials for the treatment of *Pseudomonas* nosocomial pneumonia (NCT03582007) and VAP infections (NCT03409679); however, it was announced in May 2019 that there was an increase in serum creatinine and acute kidney injury using IV administration in the nosocomial pneumonia trial [147]. In July 2019, Polyphor announced that this trial had been closed but stressed that the inhaled administration route was not impacted [148].

SQ 109 (**23**) is an ethambutol analog discovered at the NIAID (Bethesda, MD, USA) [149, 150] that was first developed by Sequella, Inc (Rockville, MD, USA), who later licensed the development for the Russian Federation and Commonwealth of Independent States to Infectex (Moscow, Russia). In March 2017, Infectex announced positive results from a phase-II/III trial for the treatment of MDR pulmonary TB [151, 152], but since then there has been no update. Results from a Sequella-sponsored phase-II trial evaluating high range oral doses of rifampicin, moxifloxacin and SQ109 (**23**) for treating TB (NCT01785186) has been published [153]. Although SQ109 (**23**) is structurally derived from ethambutol, SQ109 (**23**) has different modes of action and activity against other bacteria and parasites. Ethambutol targets arabinofuranosyl transferases EmbA and EmbB [154, 155], which are involved in cell wall synthesis, and was recently reported to show synergy with isoniazid targeting a transcriptional repressor of the *inhA* gene [156] and glutamate racemase (MurI) [157]. Conversely, SQ109 (**23**) has been reported to inhibit mMpl3, which is a trehalose monomycolate transporter important in cell wall synthesis [158], as well as inhibit the quinone biosynthesis enzymes MenA and MenG and affect bacterial respiration and electron transfer [159, 160].

Ridinilazole (**24**) (SMT19969) is a synthetic *bis*-benzimidazole [161] that is being developed by Summit Therapeutics plc (Oxford, UK). Ridinilazole (**24**) will be evaluated in two phase-III trials as for the treatment of CDI compared with vancomycin (NCT03595553 and NCT03595566) with assistance from the Biomedical Advanced Research and Development Authority (BARDA) (Washington DC, USA), which is an office of the U.S. Department of Health and Human Services [162]. The mode of action of **24** has not been fully elucidated but has been shown to affect cell division [163]. Importantly, ridinilazole (**24**) has been shown to reduce toxin production [163] and be less harsh on the gut microbiome compared with vancomycin [164].

Gepotidacin (**25**) (GSK-2140944) is an orally bioavailable, first-in-class antibacterial (triazaacenaphthylene class), which is new type of bacterial Type II topoisomerase inhibitor [165], being developed by GlaxoSmithKline (GSK) (London, UK) that has just started phase-III trials as a treatment for uncomplicated UTI (NCT04020341) and uncomplicated urogenital gonorrhea (NCT04010539). Gepotidacin (**25**) has previously completed three phase-II clinical trials: G+ve ABSSSI (NCT02045797), uncomplicated urogenital gonorrhea caused by *N. gonorrhoeae* (NCT02294682) [166, 167] and uncomplicated UTI (NCT03568942). Gepotidacin (**25**) has activity against range of both G+ve and G−ve pathogens [168–170], including several species associated with sexually transmitted infections (STIs) such as *N. gonorrhoeae* [166, 171], *Mycoplasma*, and *Ureaplasma* [172].

Table 7 New antibacterial pharmacophores by compound name, phase, class, lead source, activity, mode of action, and administration

Name—phase	Class (lead source)	Mode of action—administration
Murepavadin (**22**)—III	"Protegrin" (P)	Cell wall (LptD)—inhalation (previously iv)
Afabicin (**40**)—II	Benzofuran naphthyridine (S)	Cell wall (FabI)—iv/po
Macozinone (**47**)—II	Benzothiazinone (BTZ) (S)	Cell wall (DprE1)—po
BTZ-043 (**48**)—I	Benzothiazinone (BTZ) (S)	Cell wall (DprE1)—po
OPC-167832 (**49**)—II	3,4-dihydrocarbostyril (S)	Cell wall (DprE1)—po
TBA-7371 (**65**)I	Azaindole (S)	Cell wall (DprE1)—po
TXA709 (**60**)—I	FtsZ benzamide (S)	Cell wall (FtsZ)—po
Ridinilazole (**24**)—III	*bis*-Benzimidazole (S)	Cell wall (division)—po topical
XF-73 (**35**)—II	Porphyrin (NP)	Cell wall/membrane perturbation—topical
Gepotidacin (**25**)—III	Triazaacenaphthylene (S)	DNA (GyrA)—iv/po
Zoliflodacin (**26**)—III	Spiropyrimidinetrione (S)	DNA (GyrB)—po
MGB-BP-3 (**34**)—II	Distamycin (NP)	DNA (groove binding)—po topical
ACX-362E (**56**)—I	Dichlorobenzyl guanine (S)	DNA (DNA polymerase IIIC)—po topical
SPR 720 (**58**)—I	"Ethyl urea benzimidazole" (S)	DNA (GyrB and ParE)—po
GSK656 (**50**)—II	Oxaborole (S)	Protein synthesis (leucyl-tRNA synthetase)—po
Telacebec (**46**)—II	Imidazo[1,2-*a*]pyridine amide (S)	Oxidative phosphorylation (respiratory complex bc_1)—po
Niclosamide (**39**)[a]—II	Salicylanilide (S)	Oxidative phosphorylation (quorum sensing?)—topical
Auranofin (**38**)[a]—II	"Gold complex" (S)	Thioredoxin reductase—po
Fluorothyazinone (**57**)—I	Thyazinone (S)	Virulence (type III secretion system)—po

[a]Repurposed drugs

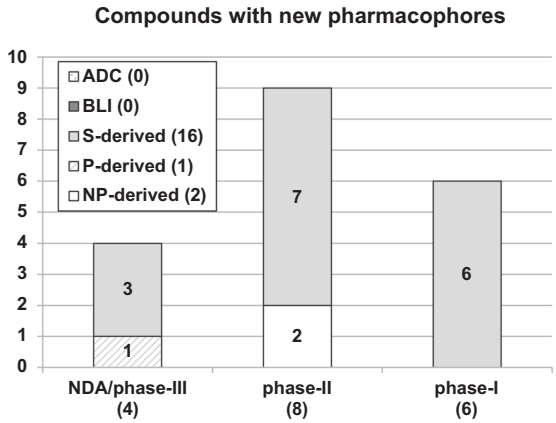


Fig. 15 Antibacterials [natural product (NP), synthetic (S), protein/mammalian peptide (P)], β-lactamase inhibitors (BLI), and antibody drug conjugates (ADCs)] with new antibacterial pharmacophores divided into development phases and their lead derivation source

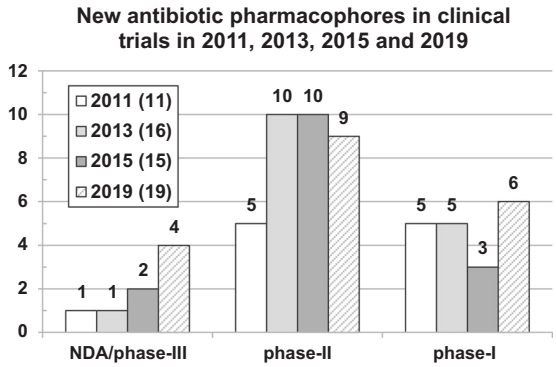


Fig. 16 Comparison of the numbers of novel antibacterial pharmacophores undergoing clinical development in 2011 [3], 2013 [2], 2015 [1], and 2019 by development phase

Zoliflodacin (**26**) (ETX0914, AZD0914) is the first member of a new class of topoisomerase inhibitor class [173] called the spiropyrimidinetriones being developed by Entasis Therapeutics (Waltham, MA, USA) that has started a phase-III trial (NCT03959527) as an orally administered treatment of uncomplicated gonorrhea [174] in collaboration with the Global Antibiotics Research and Development Partnership (GARDP) (Geneva, Switzerland). Zoliflodacin (**26**) also has activity against *Mycoplasma genitalium*, which could enhance its usefulness in treating STIs [175]. Entasis completed a phase-II trial (NCT02257918) that showed that zoliflodacin (**26**) was able to successfully treat uncomplicated urogenital and rectal gonococcal infections but was less efficacious against pharyngeal infections [176].

Contezolid (**27**) (MRX-I) is an oxazolidinone being evaluated by MicuRx Pharmaceuticals (Hayward, CA, USA and Shanghai, People's Republic of China) [177]. MicuRx announced positive results for a China-based phase-III trial for cSSTI and they plan to file an NDA with the Chinese

National Medical Products Administration (NMPA) before the end of 2019 [178]. Contezolid (**27**) has completed a phase-II trial against ABSSSI (NCT02269319) using oral dosing. Contezolid (**27**) was selected for development due to a proposed superior safety profile compared with linezolid [177] and promising activity against G+ve bacteria [179, 180] and TB [181]. The prodrug of contezolid (**27**), contezolid acefosamil (**28**) (MRX-4) [182], is being evaluated in a phase-II trial for the treatment of ABSSSI in both China and the USA (NCT03747497) using an IV to oral switch route.

Levonadifloxacin (**29**) (WCK-771) and its alanine prodrug alalevonadifloxacin (**30**) (WCK-2349) [183] are currently being evaluated in a phase-III trial for CSSSI in India [184, 185] using IV and oral administration. Levonadifloxacin (**29**) is the arginine salt of the fluoroquinolone *S*-(–)-nadifloxacin [186–188]; racemic nadifloxacin has been topically used to treat acne and MRSA [186].

Compounds in phase-II trials

BOS228 (**31**) (LYS228) is an IV-administered monobactam with potent activity against both serine and metallo-β-lactamase expressing [189] discovered by Novartis (Basel, Switzerland) [190–192]. Novartis started phase-II trials of BOS228 (**31**) for G−ve cUTI (NCT03377426) and cIAI (NCT03354754); however, after Novartis exited antibiotic development in July 2018, these trials were halted and **31** was licensed to Boston Pharmaceuticals (Cambridge, MA, USA) for further development [193] (Table 3, Figs. 6 and 7).

Benapenem (**32**) is a carbapenem, which is structurally similar to ertapenem and shares its longer half-life compared with other carbapenems, that is currently being evaluated phase-II trial as a treatment for a cUTI including pyelonephritis by Sihuan Pharmaceutical (Beijing, People's Republic of China) using IV administration (CT20181302) [194]. Benapenem (**32**) has completed three phase-I trials (NCT03570970, NCT03578588, and NCT03588156) and results from these trials indicated that **32** was well tolerated and the PK data supported once-daily IV dosing [195].

Nafithromycin (**33**) (WCK 4873) is an orally bioavailable ketolide being developed by Wockhardt Limited (Mumbai, India) that completed a CABP phase-II trial (NCT02903836) in July 2017. Nafithromycin (**33**) recently started a new multiple dosing phase-I trial (NCT03981887) and has activity against both G+ve (e.g., *S. pneumoniae* and *Staphylococcus aureus*) and G−ve (e.g., *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*) bacteria [196, 197].

MGB-BP-3 (**34**) is a DNA binding antibacterial being developed by MGB Biopharma (Glasgow, UK) that recently started a phase-II trial for the treatment of patients with *C. difficile*-associated diarrhea (CDAD) (NCT03824795). MGB-BP-3 (**34**) was first synthesized at the University of Strathclyde (Glasgow, UK) and its structure is based on the actinomycetes-derived minor groove binders the distamycin, netropsin and thiazotropsin ("lexitropsins") [198].

XF-73 (**35**) (exeporfinium chloride) is a topically administered, photosensitizing porphyrin with derivative broad spectrum G+ve activity [199–202] that is being developed by Destiny Pharma (Brighton, UK). XF-73 (**35**) has recently started a phase-II trial to study its effect on nasal *S. aureus* in patients at risk of post-operative staphylococcal infections (NCT03915470). XF-73 (**35**) has been evaluated in phase-I/II trials for the prevention of postsurgical staphylococcal nasal infections (NCT02282605) and positive data from a phase-I trial have been reported (NCT01592214) [203].

TNP-2092 (**36**) (CBR 2092) is currently being developed by TenNor Therapeutics (Suzhou, People's Republic of China) in a phase-II trial for the treatment of G+ve ABSSSI infections using IV dosing (NCT03964493). TenNor are also evaluating TNP-2092 (**36**) against catheter-related bloodstream infections and prosthetic joint infections [204]. TNP-2092 (**36**) is a rifamycin-quinolizinone hybrid antibacterial discovered by Cumbre Pharmaceuticals [205] that had excellent activity against G+ve pathogens [206]. The rifamycin lead was rifampicin, while the quinolizinone component lead was ABT-719, which had a similar activity profile to quinolones [205]. It was shown that the G+ve antibacterial activity of **36** was via the modes of action of the hybrid components: RNA polymerase (rifamycin) and balanced DNA gyrase and DNA topoisomerase IV (quinolone) inhibition [207].

ATx201 is a topical formulation of niclosamide (**37**), which is a halogenated salicylanilide derivative being developed by UNION Therapeutics A/S (Hellerup, Denmark; previously called AntibioTx) [208, 209]. Niclosamide (**37**) was discovered in the late 1950s by Bayer (Leverkusen, Germany) and is currently used an anthelmintic, predominantly to treat tapeworm infections [210]. ATx201 completed phase-II trials in 2018 for the treatment for impetigo (NCT03429595) and atopic dermatitis (NCT03304470) with its future development being focused on atopic dermatitis (EudraCT2019-002771-33) [211]. In addition to bacterial infections [212–215], there have also been efforts to "re-purpose" **37** as a treatment for Parkinson's disease, Type 2 diabetes, viral infections and oncology [216, 217]. Niclosamide (**37**) has multiple mechanisms in these therapeutic areas [216]. In bacteria, there is evidence that **37** interferes with oxidative phosphorylation in TB, which could affect membrane potential and pH homeostasis [218], and inhibit *P. aeruginosa* quorum sensing [219].

Auranofin (**38**), which is a 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-[triethylphosphine] gold complex first approved as a rheumatoid arthritis drug in 1985 [220–222], is currently being evaluated in a phase-II trial by The Aurum Institute (Johannesburg, Republic of South Africa) as an adjunctive host directed therapies to assess its potential to shorten TB treatment and/or prevent permanent lung damage (NCT02968927). Auranofin (**38**) primarily exerts its biological activity through inhibition of thioredoxin reductase [223–225] but its mode of action in bacteria is more complex [226–228]. There has also been interest in re-purposing auranofin (**38**) for *C. difficile* [229], *Helicobacter pylori* [230], and MRSA, *S. pneumoniae* and *Enterococcus faecalis* [223, 226, 231, 232].

MBN-101 (**39**) (bismuth ethanedithiol, BisEDT) has broad spectrum, topical antibacterial and antibiofilm activity, and is being developed by Microbion Corporation (Bozeman, MT, USA) [233, 234]. MBN-101 is currently being evaluated in a phase-II trial patients diagnosed with an orthopedic infection (NCT02436876), and a phase-Ib/IIa trial as a topical treatment for diabetic foot infection (NCT02723539). Microbion licensed MBN-101 to Haisco Pharmaceutical Group (Chengdu, People's Republic of China) for development in China in February 2016 [235]. Bismuth has some intrinsic antibacterial activity as demonstrated by bismuth subsalicylate (later called Pepto Bismol®), which has been used since 1900 to help treat stomachaches and traveler's diarrhea [236], and Xeroform®, which is a petrolatum-based fine mesh gauze containing 3% bismuth tribromophenate [237]. Bismuth is also used in combinations with other antibiotics and a proton pump inhibitor to treat *H. pylori* infections [238].

Afabicin (**40**) (Debio 1450, AFN 1720), which is a prodrug of afabicin desphosphono (**41**) (Debio 1452, AFN-1252), is being evaluated by Debiopharm Group (Lausanne, Switzerland) in a phase-II trial (NCT03723551) using an IV/oral switch strategy for the treatment of *S. aureus* bone or joint infection [239]. Afabicin (**40**) had previously completed another phase-II ABSSSI trial (NCT02426918). Afabicin (**40**) specifically inhibits staphylococcal FabI [240, 241], which is an essential enzyme in the final step of the fatty acid elongation cycle [242, 243], and the initial lead was discovered [244, 245] by GSK (London, UK) and further developed [246] by Affinium Pharmaceuticals (Austin, TX, USA) before licensing to Debiopharm.

OPS-2071 (structure not disclosed) is a quinolone-based antibacterial being developed by Otsuka Pharmaceutical (Tokyo, Japan) that has completed a phase-II trial against *C. difficile* and enteric infections (NCT02473393) [247]. In February 2019, Otsuka announced an additional phase-II trial evaluating OPS-2071 as an add-on therapy for Crohn's disease where patients show symptoms of active inflammation during ongoing treatment (NCT03850509).

Delpazolid (**42**) (RMX2001, LCB01-0371) is an oxazolidinone discovered by LegoChem Biosciences, Inc. (Daejeon, Republic of Korea), which has activity against G+ve bacteria [248], TB [249] and *Mycobacterium abscessus* [250], that is being evaluated in a phase-II trial for the treatment of TB using oral administration (NCT02836483). Delpazolid (**42**) is being co-developed in China with HaiHe Biopharma (Shanghai, People's Republic of China) and China Shijiazhuang Holding Group Co (Hong Kong, People's Republic of China) [251].

Sutezolid (**43**) (PF-2341272, PNU-100480) [252] is an oxazolidinone-type antibacterial that was originally developed alongside linezolid by Upjohn & Co (later Pharmacia & Upjohn), which was later absorbed into Pfizer (New York, NY, USA) in 1995. Sutezolid (**43**) has potent activity against TB [253–255] and Sequella (Rockville, MD, USA) licensed **43** from Pfizer in 2013 and a phase-II trial was completed as a treatment for naive patients with drug-sensitive pulmonary tuberculosis using oral administration (NCT01225640) [256]. Sequella and the TB Alliance (New York, NY, USA) have recently started a phase-II trial evaluating sutezolid (**43**) in combination with bedaquiline, delamanid, and moxifloxacin against a combination of bedaquiline, delamanid, and moxifloxacin (NCT03959566).

DNV-3837 (**44**) (MCB-3837) is an oxazolidinone–quinolone hybrid prodrug of DNV-3681 (**45**) (MCB-3681) developed by Morphochem AG/Biovertis AG, which was acquired in 2018 by Deinove (Montpellier, France). that recently started a phase-II trial as a potential treatment of CDI (NCT03988855) [257]. DNV-3837 (**44**) is administered intravenously, which differentiates it from other antibacterials being developed for CDI that are delivered orally with little or no systemic distribution (po topical). DNV-3837 (**44**) shows activity against G+ve bacteria including MRSA, *C. difficile, Francisella tularensis*, and *Bacillus anthracis* [258–261].

Telacebec (**46**) (Q203) is an orally bioavailable imidazo[1,2-*a*]pyridine amide [262, 263] that is currently being developed by Qurient Co., Ltd. (Seongnam-si, Republic of Korea) in a phase-II trial for treatment of TB (NCT03563599). The imidazo[1,2-*a*]pyridine amide pharmacophore was identified during phenotypic high-content assay in infected macrophages and inhibits TB growth via targeting QcrB, which is a subunit of the menaquinol cytochrome c oxidoreductase (bc_1 complex) [262, 264, 265]. Infectex (Moscow, Russia), who has licensed **46** from Qurient, announced the successful completion of a Russian phase-I trial in June 2017 [266].

Macozinone (**47**) (PBTZ169) is a benzothiazinone (BTZ) derivative being evaluated by Nearmedic Plus LLC (Moscow, Russia) in a phase-II trial for the treatment of TB in Russia and Belarus but the trial was discontinued due to slow enrollment in February 2018 (NCT03334734).

The Innovative Medicines for Tuberculosis (iM4TB) Foundation (Lausanne, Switzerland) is leading the development in the rest of the world and are currently evaluating oral dosing of macozinone (**47**) in a phase-I trial (NCT03776500). Macozinone (**47**) is a second generation BTZ043 (**48**; Fig. 8) analog, which had potent in vitro activity against TB but suboptimal in vivo efficacy, that has enhanced physico-chemical properties [267]; however, macozinone (**47**) still has relatively poor solubility, which could affect oral bioavailability [268]. The nitro group present BTZs is reduced in vivo and the reactive nitroso intermediate forms a covalent semi-mercaptal adduct with cysteine-387 of *Mycobacterium tuberculosis* decaprenylphosphoryl-β-D-ribose (DPR) 2′-oxidase (DprE1), which is an essential enzyme used to cell wall synthesis [269–271]. Macozinone (**47**) has activity against a range of *Mycobacterium* species but resistance can arise through amino acid polymorphism of cysteine-387 [271, 272]. It has been recently shown that macozinone (**47**) and BTZ043 (**48**) can be de-aromatized in vivo through formation of a Meisenheimer complex, which could also reduce their in vivo half-lives [273].

OPC-167832 (**49**) is an orally bioavailable 3,4-dihyrdocarbostyril derivative being developed by Otsuka Pharmaceutical (Tokyo, Japan) as a potential treatment for uncompleted pulmonary TB in a phase-I/II trial (NCT03678688) [274, 275]. OPC-167832 (**49**) exerts its antimycobacterial activity through inhibition of cell wall synthesis target DprE1 [274], which is the same target as the BTZ-043 (**48**) and macozinone (**47**) [269, 273, 276].

GSK656 (**50**) (GSK3036656) is a boron containing leucyl t-RNA synthetase inhibitor [277, 278] being developed by GSK (London, UK) that is currently being evaluated in a phase-II trial as a treatment for patients with drug-sensitive pulmonary TB using oral dosing (NCT03557281). GSK3036656 (**50**) was discovered in collaboration with Anacor Pharmaceuticals (Palo Alto, CA, USA), who had identified that 3-aminomethylbenzoxaboroles inhibit leucyl-tRNA synthetase [277, 279]. The closely related epetraborole (AN3365, GSK 2251052), which is the dechloro-derivative GSK656 (**50**), entered phase-II clinical trials in 2012 but was discontinued to the rapid emergence of resistance [280, 281].

Compounds in phase-I trials

TP-6076 (structure not disclosed) is an IV administered, fully synthetic fluorocycline (tetracycline class) being developed by Tetraphase Pharmaceuticals (Watertown, MA, USA) that is being evaluated in a phase-I trial (NCT03691584). TP-6076 has shown promising activity against carbapenem-resistant *Acinetobacter baumannii* clinical isolates [282] and Tetraphase has received support from CARB-X (Boston, MA, USA) to help with development [283] (Table 4, Figs. 8–10).

TP-271 (**51**) is another fully synthetic fluorocycline being developed by Tetraphase Pharmaceuticals (Watertown, MA, USA) that completed two phase-I trials investigating oral administration (NCT03450187 and NCT03024034) and two phase-I trials evaluating IV administration (NCT02724085 and NCT03234738). TP-271 (**51**) has activity against G +ve and G −ve pathogens associated with respiratory tract infections [284] and the biothreat pathogens *F. tularensis* [285] and *B. anthracis* [286].

SPR 741 (**52**) (NAB 741), which is a polymyxin derivative with antibiotic potentiating activity being developed by Spero Therapeutics (Cambridge, MA, USA), has completed two phase-I trials (NCT03022175 and NCT03376529). SPR 741 (**52**) will need to be partnered with another antibacterial and be administered using an IV route to show clinical effect. The mode of action of polymyxins involves membrane disruption but is complex [287]. SPR 741 (**52**) was initially developed by Northern Antibiotics (Helsinki, Finland) and designed to have less nephrotoxicity by reducing the number of positive charges [288–290]. The replacement of the 3-hydroxyoctanoate group with an acetate leads to a significant reduction in antibacterial activity, while maintaining Lipid A binding in a similar way to polymyxin nonapeptide; the combination of these effects leads to strong synergisms and enhanced G-ve activity of several antibacterials [290–293].

SPR 206 (**53**) is an IV administered polymyxin derivative [294] with activity against MDR G-ve bacteria being developed by Spero Therapeutics (Cambridge, MA, USA) that has recently started a phase-I trial (NCT03792308). In January 2019, Spero announced that Everest Medicines (Shanghai, People's Republic of China) had licensed SPR 206 (**53**), along with an exclusive option to rights to SPR741 (**52**), in China, South Korea and several Southeast Asian countries [295].

GT-1 (**54**) (LCB10 0200) is an IV administered cephalosporin siderophore β-lactam being developed by Geom Therapeutics (San Francisco, CA, USA), which is a joint venture with LegoChem Biosciences (Seoul, Republic of Korea). GT-1 (**54**) started a phase-I trial (ACTRN12618001980224) in Australia in March 2019 but the trial has been stopped due to safety concerns. There has been no subsequent update about whether development will continue.

Apramycin (**55**) is an aminoglycoside-type protein synthesis inhibitor being developed by Juvabis Therapeutics (Zurich, Switzerland) that recently started a phase-I trial evaluating IV dosing (NCT04105205). Apramycin (**55**) was discovered at Eli Lilly & Co (Indianapolis, IN, USA) in the 1960s [296] and its structure was published in 1976 [297]. Apramycin (**55**) is currently being used as veterinary antibiotic to treat *E. coli* infections [298] and it will be interesting

to follow the impact of the possible re-purposing a veterinary drug into a human medicine and how this could impact its future animal use. Apramycin (**55**) has activity against carbapenem- and aminoglycoside-resistant Enterobacteriaceae, *A. baumannii* and *P. aeruginosa* [299–301].

ACX-362E (**56**) is a *bis*-substituted guanine derivative [302, 303] that is being evaluated in a phase-I trial by Acurx Pharmaceuticals (White Plains, NY, USA) [304, 305]. ACX-362E (**56**) inhibits bacterial DNA polymerase IIIC and will be evaluated as potential treatment for CDI [306]. DNA polymerase IIIC, which is a new target for clinical development, is an essential enzyme in low guanine and cytosine classes of bacteria such as *Bacillus*, *Clostridioides*, *Enterococcus*, *Mycoplasma*, *Lactobacillus*, *Listeria*, *Pneumococcus*, *Staphylococcus* and *Streptococcus*. The discovery of ACX-362E (**56**) and a historical overview of the development of DNA polymerase IIIC inhibitors has recently been reviewed [305].

Fluorothyazinone (**57**) (C-55, fluorothyazinon) recently completed a phase-I trial (NCT03205462), which was sponsored by Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation (Moscow, Russia). Fluorothyazinone (**57**) is an orally administered inhibitor the bacterial type III secretion system (T3SS) [307–309], which is highly conserved in many G−ve pathogens that is considered to be a promising antivirulence target [310]. It will be interesting to follow the clinical development and later stage clinical trial design of this antivirulence agent.

SPR720 (**58**) (pVXc-486) is a prodrug of the DNA gyrase inhibitor SPR719 (**59**) (VXc-486) that is being evaluated in a phase-I trial by Spero Therapeutics (Cambridge, MA, USA) as a potential oral treatment for TB and nontuberculous *Mycobacterium* (NTM) infections such as *Mycobacterium avium* complex and *M. abscessus* (NCT03796910) [311–314]. SPR720 (**58**) inhibits DNA synthesis via DNA gyrase GyrB and Topoisomerase IV parC, which is similar to novobiocin [315]. The development of SPR720 (**58**) is being supported by the Novo REPAIR Fund (Copenhagen, Denmark) and the Bill & Melinda Gates Medical Research Institute (Cambridge, MA, USA), who fund the TB development [316]. SPR720 (**58**) and SPR719 (**59**) were discovered by Vertex Pharmaceuticals (Boston, MA, USA) [311, 312].

TXA709 (**60**) is an orally bioavailable prodrug of TXA707 (**61**) that belongs to the new FtsZ benzamide class, which inhibits an essential enzyme FtsZ (bacterial homolog of tubulin) in bacterial cell wall division in both G+ve and G−ve bacteria [317, 318]. TXA709 (**60**) is currently being evaluated in a phase-I trial by TAXIS Pharmaceuticals (Monmouth Junction, NJ, USA) [319]. The benzamide class, as exemplified by PC190723 [320–322] that has a Cl in place of the CF_3 in TXA707 (**61**), was discovered by Prolysis Ltd (Oxford, UK). Prolysis were bought in November 2009 by Biota Holdings (Melbourne, Australia) and Biota's FtsZ IP portfolio was licensed to TAXIS in August 2014 [323]. The development of PC190723 and its prodrug TXY541 [324] was hindered by poor physicochemical and PK properties; however, TXA709 (**60**) has enhanced metabolic stability, PK properties and superior in vivo efficacy against *S. aureus* compared with TXY541 [325, 326].

BTZ-043 (**48**), which is a member of the anti-TB BTZ class, has recently completed a phase-I trial (NCT03590600). This trial was sponsored by the University of Munich (Munich, Germany), Hans-Knöll Institute (Jena, Germany) and the German Center for Infection Research (DZIF) (Heidelberg, Germany). As with macozinone (**47**), BTZ-043 (**48**) inhibits the essential mycobacterial cell wall biosynthesis enzyme DprE1 [269, 273, 276].

TBI-223 (**62**) is an oxazolidinone being developed by the TB Alliance (New York, NY, USA) and the Institute of Materia Medica (Shanghai, People's Republic of China) that is currently being evaluated in a phase-I trial using oral dosing (NCT03758612). TBI-223 (**62**) has similar in vitro TB activity and in vivo properties in mouse models but has a higher safety margin in pre-clinical studies and enhanced metabolic properties compared to linezolid [327, 328].

TBI-166 (**63**) (pyrifazimine) is an orally bioavailable clofazimine (**64**) analog [329] (riminophenazine class) that is being evaluated in a phase-I trial (ChiCTR1800018780) as a treatment for TB by the Global Alliance for TB Drug Development (New York, NY, USA) in partnership with the Institute of Materia Medica (Shanghai, People's Republic of China), Chinese Academy of Medical Sciences (Beijing, People's Republic of China) and Peking Union Medical College (Beijing, People's Republic of China). Clofazimine (**64**) has been used to treat leprosy since 1962 and has more recently been incorporated into short-course MDR-TB regimens [330, 331]; however, clofazimine (**64**) has suboptimal PK/PD that leads to tissue accumulation, which due to its red color causes skin discoloration that can take months to clear. TBI-166 (**63**) was designed to have improved PK/PD properties, while maintaining potent anti-TB activity with less skin discoloration [332, 333].

TBA-7371 (**65**) is a 1,4-azaindole that is being developed by the Global Alliance for TB Drug Development (New York, NY, USA), which has completed a phase-I trial (NCT03199339) that evaluated safety, tolerability, PK, and PK interactions using oral dosing. TBA-7371 (**65**) is a non-covalent DprE1 inhibitor that was discovered by researchers at AstraZeneca's Bangalore site in India by scaffold hopping from telacebec (**46**), which has a different mechanism [334–336].

TNP-2198 (structure not disclosed but likely to be hybrid like TNP-2092 (**36**)) is being developed by TenNor Therapeutics (Suzhou, People's Republic of China) for diseases of anaerobic infections, which includes gastrointestinal diseases associated with *H. pylori*, bacterial vaginosis and CDAD [337]. TNP-2198 is being evaluated in a phase-I trial examining an ascending dose regimen and the effect of eating (CTR20190734).

BCM-0184 (structure not disclosed) is currently being evaluated by Biocidium Biopharmaceuticals (North Vancouver, BC, Canada) in a phase-I trial [338]. BCM-0184 has activity against MRSA and has oral and topical formulations, but no further information is available.

DSTA4637S (**66**) (RG7861, Sym009) is an IV administered thiomab-type *S. aureus* mAb-rifamycin ADC [339, 340] being developed by Genentech (South San Francisco, CA, USA) that has successfully completed a phase-1 trial in healthy volunteers (NCT02596399) [341] and is currently being evaluated in a phase-I trial in patients with *S. aureus* bacteremia that are receiving antibacterials (NCT03162250). DSTA4637S (**66**) is designed to cleave in phagocytic cells, which can be a reservoir for *S. aureus* infections, and being developed for the treatment of serious *S. aureus* infections including MRSA. DSTA4637S (**66**) has an engineered human immunoglobulin G1 (IgG1) anti-*S. aureus* mAb (MSTA3852A) that was discovered in collaboration with Symphogen (Ballerup, Denmark), which binds to teichoic acid β-*O*-linked *N*-acetylglucosamine sugars in the cell wall, attached via a protease-cleavable valine–citrulline linker to a rifamycin derivative (dmDNA31) with an average stoichiometry of two antibiotic units to one mAb [339, 340, 342, 343]. The rifamycin derivative dmDNA31 exerts is activity through inhibition of RNA synthesis.

β-lactam and β-lactamase inhibitor (BLI) combinations undergoing clinical evaluation

The discovery of the first β-lactamase inhibitor clavulanic acid (**67**) [344–346], which was isolated from *Streptomyces clavuligerus*, was an important breakthrough that rescued β-lactams antibacterial activity. Augmentin, which is combination of clavulanic acid (**67**) and amoxicillin, is still heavily used today after 38 years of being sold. There have been four new BLI combinations approved in the last five years (Table 1, Fig. 3): Zerbaxa in 2014 (new cephalosporin ceftolozane), Avycaz in 2015 (new DBO-type BLI avibactam), Vabomere in 2017 (new boronate-type BLI vaborbactam (**12**)), and Recarbrio in 2019 (new DBO-type BLI relebactam (**14**)). In this section, new BLI combinations undergoing clinical evaluation are discussed (Table 5, Figs. 11 and 12).

β-lactam/BLI combinations in phase-III trials

Enmetazobactam (AAI 101) (**68**) is a clavulanic acid (**67**)-type BLI [347–349] with activity against extended spectrum β-lactamases (ESBLs) and some class A and D carbapenemases that is currently being evaluated by Allecra Therapeutics Gmbh (Weil am Rhein, Germany)/Allecra SAS (Saint Louis, France) in combination with cefepime (**69**) in a phase-III trial for cUTI using IV administration (NCT03687255) (Table 5, Fig. 11).

ETX2514SUL is an IV administered combination of the DBO-type BLI durlobactam (**70**) (ETX2514) [350–352], which also has antibacterial activity, and clavulanic acid-type BLA inhibitor sulbactam (**71**), which was first launched in 1986. ETX2514SUL is active against MDR *Acinetobacter* spp. [353, 354] and is being evaluated by Entasis Therapeutics (Waltham, MA, USA) is a phase-III trial as a treatment for infections caused by *A. baumannii–calcoaceticus* complex (NCT03894046). ETX2514SUL has also been evaluated in a phase-II trial for acute pyelonephritis and cUTI (NCT03445195).

The boronate-type BLI taniborbactam (**72**) (VNRX-5133) [355] and cefepime (**69**), which is a fourth-generation cephalosporin first approved in 1994, are being evaluated by VenatoRx Pharmaceuticals (Malvern, PA, USA) in a phase-III trial (NCT03840148) as an IV treatment for cUTI and acute pyelonephritis. Taniborbactam (**72**) has activity against both serine- and metallo-β-lactamases, including ESBL, OXA, KPC, NDM and VIM enzymes, and it was recently shown by X-ray crystallography that **72** bound to NDM-1 though cyclization of its acylamino oxygen onto the boron of the bicyclic core [356].

β-Lactam/BLI combinations in phase-I trials

Nacubactam (**73**) (OP0595, FPI-1459, RG6080, RO7079901), which is a DBO-type BLI [357–359], and meropenem (**13**), which is a carbapenem first approved in 1998, was developed by Meiji Seika Pharma, Co. Ltd. (Tokyo, Japan) and Fedora Pharmaceuticals (Edmonton, AB, Canada). Meji and Fedora formed the joint venture NacuGen Therapeutics (Edmonton, AB, Canada) in January 2019 for further development of nacubactam (**73**) [360]. Meiji Seika and Fedora had previously partnered with Roche (Basel, Switzerland) [361, 362] and several phase-I trials using IV dosing have been completed (Meiji Seika: NCT02134834; Roche: NCT02972255, NCT02975388 and NCT03174795) (Table 5, Fig. 12).

A DBO-type BLI, zidebactam (**74**) (WCK 5107), is being developed in combination with the fourth generation cephalosporin cefepime (**69**) (combination WCK 5222, FEP-ZID) by Wockhardt Limited (Mumbai, India) and has completed five phase-I trials using IV dosing (NCT02532140 [363], NCT02674347, NCT02707107,

NCT02942810, NCT03630094). Zidebactam (**74**) inhibits PBPs and several β-lactamases while enhancing β-lactam activity [364] and the combination shows in vitro and in vivo activity against G−ve bacteria such as *A. baumannii*, *P. aeruginosa* and CRE [364–368].

ETX0282CPDP, which is a combination of the DBO-type BLI ETX0282 (**75**) and cefpodoxime proxetil (**77**), is currently being evaluated in a phase-I trial using oral dosing (NCT03491748) by Entasis Therapeutics (Waltham, MA, USA) with partial CARB-X (Boston, MA, USA) funding [369]. Both ETX0282 (**75**) and cefpodoxime proxetil (**77**) are prodrugs that are hydrolyzed in vivo releasing their active metabolites, ETX1317 (**76**) and cefpodoxime (**78**) [370, 371]. ETX0282 (**75**) is noteworthy as the *N*-oxy-sulfonic acid group previously found in DBO BLIs has been replaced with (*R*)-2-(*N*-oxy)-2-fluoroacetic acid; ETX0282 (**75**) also displays antibacterial activity against *E. coli* in addition to BLI activity.

A combination of the boronate-type BLI VNRX-7145 (**79**) [372, 373] and ceftibuten (**80**), which is a third generation cephalosporin first approved in 1995, is currently being developed by VenatoRx Pharmaceuticals (Malvern, PA, USA) [374]. VNRX-7145 (**79**) has activity against CRE (KPC and OXA carbapenemases) and ESBLs. Both VNRX-7145 (**79**) and ceftibuten (**80**) are orally bioavailable, which is a differentiator to VenatoRx's more advanced IV administered, phase-III taniborbactam (**72**) and cefepime (**69**) program.

ARX-1796 (**81**) (ARX-006) is an orally bioavailable prodrug derivative of the approved DBO-type BLI avibactam (**82**) [375, 376] being developed by Arixa Pharmaceuticals (Palo Alto, CA, USA) that recently started a phase-I trial (NCT03931876).

Compounds discontinued from clinical development

Compounds and β-lactam/BLI combinations that have been discontinued from clinical development or have had their development halted since the 2015 review [2] are listed in Table 6 with comments about their the development halt or cessation noted if known.

Analysis of compounds undergoing clinical trials

Numbers of compounds undergoing clinical evaluation and their source derivation

There are currently 44 compounds, eight β-lactam/BLI inhibitor combinations currently and one ADC undergoing clinical trials (Figs. 13 and 14). Of the 44 compounds, two are in NDA/MAA (Table 2, Fig. 4), eight are in phase-III (Table 2; Fig. 5), 18 in phase-II (Table 3; Figs. 6 and 7) and 16 in phase-I (Table 4; Figs. 8 and 9), three β-lactam/BLI combinations in phase-III (Table 5; Fig. 11) and five in phase-I (Table 5; Fig. 12) and one ADC in Phase-I (Table 4, Fig. 10). Of the 44 compounds, 27 antibacterials were synthetically-derived (S), 14 were NP-derived (NP), one protein/mammalian peptide-derived (P), one ADC and the derivation of two are not known (Fig. 13).

There has been a similar number of compounds in the different development phases between 2011, 2013 and 2015, except for in phase-III trials in 2011 (6) compared with 2013 (16) and 2015 (15). In 2019, the number in phase-III/NDA (13) and phase-II (18) is similar to previous years, but the number in phase-I trials (22) in 2019 has increased from an average 12 compounds in the previous reviews [1–3]. Thirteen of the phase-I compounds target G−ve bacteria (seven compounds including one anti-virulence and five BLI combinations), while there are nine with G+ve activity (including five against TB and one for CDI). It will be interesting to monitor how many of the current phase-I antibacterials move to phase-II studies and beyond in the next few years and whether this higher number of antibacterials in phase-I level will be maintained or even increased.

New antibacterial pharmacophore analysis

The modes of action of nearly all antibacterial drugs can be categorized into four major "macro" level classes: cell wall, protein synthesis, DNA synthesis and RNA synthesis inhibitors [377]. In the TB field, there is also an emerging mode of action around the mycobacterial respiratory system, which is inhibited by bedaquiline (launched 2012) and the clinical candidate telacebec (**46**) [378]. Recent work has also shown that inhibition of the respiratory system in other bacteria is an important factor in bacteria cell death [379]. The "macro" mode of action classes (e.g., cell wall inhibitors) are further divided into structure classes (e.g., β-lactam), which and sometimes further into structure sub-classes (e.g., penicillins, cephalosporins, carbapenems, and monobactams). A pharmacophore is the common sub-unit of active molecules that interacts with the biological target (e.g., the β-lactam subunit of the β-lactam antibacterials).

In this review, new pharmacophores not previously used in a human antibacterial drug have been analyzed as a measure of antibacterial structure innovation (Table 7). There are 19 different compounds with six in phase-I, 9 in phase-II and 4 in phase-III (Fig. 15) and this is slightly higher than previous reviews: 11 in 2011, 17 in 2013 and 15 in 2015 (Fig. 16). Fifteen of these compounds have new structure classes and/or new mode of action of the well-

established "macro" targets: cell wall (9), DNA (5) and protein synthesis inhibition (1). There are no new RNA synthesis inhibitors in clinical development. There are no new BLI classes in development after the recent approvals of the DBO (avibactam, 2015) and boronate classes (vaborbactam, (**12**), 2017). The ADC DSTA4637S (**66**) was not classified as a new pharmacophore as the payload is a rifamycin derivative; however, if approved, it would be a first antibacterial ADC alongside and would add to the three approved mAbs, raxibacumab, obiltoxaximab, and bezlotoxumab (Table 1).

Existing antibacterial classes that inhibit the bacterial cell wall include the β-lactams, glycopeptides, fosfomycin, cylcloserine; daptomycin (lipopeptide) and polymyxin. The new cell wall antibacterials inhibit several different targets (LptD: murepavadin (**22**), FabI: afabicin (**40**), 3 × DprE: macozinone (**47**)/BTZ-043 (**48**), OPC-167832 (**49**), and TBA-7371 (**65**), and FtsZ: TXA709 (**60**)) and two that have less defined mechanisms (ridinilazole (**24**) and XF-73 (**35**)) (Table 7).

There is currently one class of DNA synthesis inhibitors (DNA gyrase GyrA and Topoisomerase IV parC), the quinolones, in clinical use. Novobiocin has not been clinically used for many years but it inhibits DNA gyrase GyrB and Topoisomerase IV parE [313, 315]. SPR720 (**58**) is an "ethyl urea benzimidazole" that also inhibits GyrB and parE, while geptotidacin (**25**) inhibits GyrB at a different site to the quinolones and zoliflodacin (**26**) inhibits GyrB [315]. The dichlorobenyl guanine ACX-362E (**56**) inhibits a new target DNA polymerase IIIC. MGB-BP-03 (**34**) belongs to the distamycin class that is a DNA groove binder, which is the mechanism also found in several anticancer drugs, such as daunorubicin, dactinomycin, and bleomycins.

The protein synthesis inhibitor class has many representatives that include the macrolides, aminoglycosides, tetracyclines, lincosamides, chloramphenicol, oxazolidinones, pleuromutilins, and streptogramins. Other protein synthesis inhibitors include fusidic acid, which inhibits elongation factor G, and mupirocin that inhibits isoleucine t-RNA synthetase (IleRS). The oxaborole GSK656 (**50**) is a new pharmacophore that inhibits leucine t-RNA synthetase (LeuRS), which would be a new antibacterial mechanism.

Telacebec (**46**) and bedaquiline both have inhibitory effects on the bacterial electron-transport chain (respiration). Auranofin (**38**) targets thiol-redox homeostasis through thioredoxin reductase inhibition, while niclosamide (**39**) inhibits oxidative phosphorylation (amongst other mechanisms) but also has been reported to inhibit quorum sensing in *P. aeruginosa*. Fluorothyazinone (**57**) inhibits the G−ve type III secretion system, which is an antivirulence target that has not been previously explored in the clinic.

Administration analysis

The antibacterial clinical pipeline's administration routes (po, oral; iv/po intravenous oral switch; iv, intravenous; po topical, CDI oral; topical, topical or drops) was analyzed by development phase (Fig. S1) and lead source (Fig. S2). Oral administration is the most predominate route (27) with just under 50% (13) being 13 TB clinical candidates, for which oral administration route is almost mandatory. The second highest category is iv administration with 17, while there are six candidates that use iv/po; the iv/po switch strategy is used when patients move from iv administration in intensive care to oral afterwards. Eight of the 15 iv administered drugs are derived from NP lead, which is not unexpected due their physico-chemical properties [21, 380]. The po topical (5) administration route is used to treat for gastrointestinal infections, such as *C. difficile* and *H. pylori*. For po topical, the clinical candidates are taken orally as tablets, but are not significantly systemically absorbed; this contrasts with po administered compounds that are taken orally but pass through the gut and into blood for delivery throughout the body. Interestingly, one of the CDI clinical candidates, DNV-3837 (**44**) is being developed using iv administration, which differentiates it to the other five CDI clinical candidates in development and marketed drugs that use the po topical route. Finally, there are three topical delivered candidates that can be delivered as creams and eye drops.

Conclusion and outlook

The antibacterial pipeline composition (number, phase breakdown, and pharmacophores) is similar previous numbers in 2011 [3], 2013 [2], and 2015 [1] except for a spike in the number of phase-I candidates from 11 in 2015 to 21 in 2019 (Fig. 14). It is likely that this increase in phase-I candidates has been helped by increased funding and the development expertise offered by organizations like the Wellcome Trust (London, UK), BARDA (Washington DC, USA), GARDP (Geneva, Switzerland), CARB-X (Boston, MA, USA) and the Novo Holdings's REPAIR Impact Fund (Copenhagen, Denmark), as well as funding provided for the development of new anti-*Mycobacterium* drugs by organizations such as the TB Alliance (New York, NY, USA) and Bill & Melinda Gates Foundation (Seattle, WA, USA). However, despite this increase, there are also some unmet medical needs that need to be addressed in the clinical pipeline: new antibacterials with activity against β-metallolactamases, orally administered that have broad spectrum G−ve activity, and new treatments for MDR *Acinetobacter* and gonorrhea. It is imperative that we discover and develop new antibacterials, especially against these unmet medical needs, to keep replenishing the pipeline and help limit the health impacts of MDR bacteria.

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Compliance with ethical standards

Conflict of interest DLP has received grants and/or personal fees from Achaogen, AstraZeneca, Bayer, Cubist, Entasis Therapeutics, GlaxoSmithKline, Leo Pharmaceuticals, Merck Sharp & Dohme (Merck & Co), Pfizer, and Shionogi & Co. MSB declares no conflicts of interest.

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