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REVIEW ARTICLE

Antibiotics in the clinical pipeline in 2013

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The continued emergence of multi-drug-resistant bacteria is a major public health concern. The identification and development of new antibiotics, especially those with new modes of action, is imperative to help treat these infections. This review lists the 22 new antibiotics launched since 2000 and details the two first-in-class antibiotics, fidaxomicin (1) and bedaquiline (2), launched in 2011 and 2012, respectively. The development status, mode of action, spectra of activity, historical discovery and origin of the drug pharmacophore (natural product, natural product derived, synthetic or protein/mammalian peptide) of the 49 compounds and 6 β-lactamase/β-lactam combinations in active clinical development are discussed, as well as compounds that have been discontinued from clinical development since 2011. New antibacterial pharmacophore templates are also reviewed and analyzed.
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Keywords: antimicrobial resistance; antibiotic; clinical trials; drug development; drug discovery; natural product

INTRODUCTION

Antibiotics have saved countless lives since the discovery of the sulfonamides and β-lactams in the 1930s. These breakthrough discoveries initiated a "golden era" of antibiotic research that lasted 40 years, during which time most current classes of antibiotics were discovered. However, from the early 1970s to 1999 the innovative antibiotic pipeline dried up. All newly launched antibiotics were analogues of existing drugs except for mupirocin, a Gram-positive only topical antibiotic launched in 1985. Since 2000, the situation has improved, with five more new classes of antibiotics launched (Table 1): linezolid (systemic, approved 2000), daptomycin (systemic, approved 2003), retapamulin (topical, approved 2007), fidaxomicin (**1**; *Clostridium difficile* infections, approved 2010) and bedaquiline (**2**; systemic, approved 2012). Bedaquiline is noteworthy as it was fast-tracked through clinical trials for use in combination with other drugs to treat tuberculosis (TB). Although the launch of these novel antibiotics is a step forward, it must be noted that all of these new antibiotic classes are limited to the treatment of Gram-positive infections with new therapies capable of treating Gram-negative infections desperately needed.

Recent years have seen increasing attention drawn to the convergence of events that may portend a return to the pre-antibiotic era: the increasing threat of drug-resistant 'superbugs', the dearth of new classes of antibiotics and the disengagement of most pharmaceutical companies from antibiotic research because of economic and regulatory challenges. Attempts to highlight the potentially disastrous outcomes are ongoing, including the well-publicized annual report of the Chief Medical Officer of the United Kingdom in March 2013, which addressed the "very real threat" of antimicrobial resistance.[1] Similar discussions in scientific journals since our last review in 2011[2] include both general overviews of the issues,[3,4] as well as articles that address more specific areas of concern, including mechanisms of antibiotic resistance,[5] antibiotic resistance evolution due to sublethal drug concentrations,[6] environmental[7] or antibiotic[8] contributions to resistance development, the overuse of antibiotics in agriculture,[9] surveillance programs monitoring worldwide increases in resistance,[10] and regulatory hurdles for antibiotic drugs.[11] These issues have also been captured in articles in the popular press, such as a 2012 article in *The Atlantic* on: "The Rise of Antibiotic Resistance: Consequences of FDA's Inaction"[12] and articles in *The New York Times* such as "Deadly Bacteria That Resist Strongest Drugs Are Spreading"[13] and "Let's Gang Up on Killer Bugs".[14]

There have been a number of significant developments in improving the atmosphere for antibiotic research, including the US Generating Antibiotic Incentives act (automatic priority review and an additional 5–7 years of market exclusivity for qualified infectious disease products), and the Innovative Medicines Initiative New Drugs for Bad Bugs (IMI ND4BB), a $280 million fund to support the clinical development of new antibiotics and conduct basic research into how antibiotics penetrate Gram-negative bacteria.[15] Other incentives have also been proposed.[16–19] In 2010, the Infectious Diseases Society of America launched the 10 × '20 Initiative to develop 10 new safe and efficacious systemically administered antibiotics by 2020.[20–22] This initiative is focused on developing novel antibiotics to treat Gram-negative bacteria, which are more challenging targets than Gram-positive bacteria because of the presence of an outer membrane permeability barrier, multiple efflux pumps, and antibiotic- and target-modifying enzymes.[23–25] Although

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a 2013 update on the progress of the 10 × '20 Initiative found that there have been advances in some areas, it was reiterated that many of the original obstacles remained.[26]

The commercial landscape for antibiotic development in the last few years has not been encouraging. In 1990, there were 18 large pharmaceutical companies actively engaged in antibiotic research and development, whereas today there are just four: AstraZeneca (London, UK), Novartis (Basel, Switzerland), GSK (London, UK) and Sanofi-Aventis (Paris, France).[16] Depressingly, AstraZeneca CEO Pascal Soriot laid out plans on 21 March 2013 to reduce its future investments in antibiotics,[27] whereas a former major antibiotics player, Pfizer (Groton, CT, USA), closed its antibiotic R&D center in Connecticut in 2011.[28] These decisions highlight the reluctance of drug firms to invest in an area with comparably poor returns and costly phase-III trials that have onerous recruitment requirements needed to fulfill the non-inferiority conditions currently mandated by the Food and Drug Administration (FDA). This is despite an historically high approval rate of antibiotics following the successful completion of phase-I studies.[29]

The net present value for an antibiotic to treat acute infections does not compare to the values ascribed to most other therapeutic areas. Antibiotics are only administered for a few weeks and are priced in the range of hundreds of dollars per day (for example, linezolid 600 mg tablet for $134, daptomycin 500 mg for $362 and Synercid 150–350 mg for $247)[30–32] with some widely used older antibiotics available at much lower prices (for example, vancomycin 1000 mg for $5).[33,34] In contrast, long-term therapies such as cholesterol-lowering drugs and anti-hypertensive agents are taken daily for many years or decades, whereas biological anti-cancer agents and orphan disease treatments are often priced at >$10 000 per treatment. Put simply, we ascribe almost no monetary value to antibiotics in society today and we need a new financial way forward to incentivize the discovery, development and registration of new antibiotics. One solution is government intervention, as suggested in a report from the London School of Economics that proposed a push-pull mechanism to provide a global incentive for more investment in antibiotic R&D.[35] This incentive would be limited to potential drugs that meet stringent criteria for medical need and probability of successful registration. This would lead to a positive net present value for a new antibiotic. The additional risk of slow uptake (often the case for new antibiotics on the market) is ameliorated, as is the development risk at phase-III as the costs are borne by the government. When full economic costing is considered for the estimated two million patients in the Europe (EU) every year that catch hospital-acquired infections (of which 175 000 die), the government receives a significant economic return on investment, in addition to the social and health benefits to society. We also need to think long and hard about antibiotic drug pricing and whether it is ethically acceptable to pay so much for life-extending and lifestyle-associated drugs, but still expect to pay peanuts for life-saving antibiotics. The potential for government contributions to have a key role in the future is illustrated by the May 2013 announcement of a $200 million public–private partnership between the US government Biomedical Advanced Research and Development Authority (BARDA) and GSK to study potential new drugs to treat both conventional pathogens and those that could be developed into weapons.[36] This is on top of a number of recent BARDA awards to smaller companies to develop antibiotics.[37–39]

One facet of antimicrobial therapy that is often overlooked in discussions on antimicrobial resistance to antibiotics is that there are emerging alternative approaches toward treating bacterial infections. Although not discussed in this article, non-antibiotic-based therapies, such as vaccines, neutralizing antibodies, probiotic therapy, phage therapy, immune stimulation and virulence factor neutralization, also show promise for preventing or treating drug-resistant microbial infections.

This review is an update of our 2011 review[2] and details recently launched antibiotics (Table 1, Figures 1 and 2) and compounds and

Table 1 Antibiotics of NP or S origin launched since 2000 with antibiotic class, activity against Gram-positive and/or Gram-negative bacteria, lead source and NP-lead source organism

Year approved	*Drug name*[a,b]	*Class*	*Bacteria type*[c]	*Lead source*	*NP-lead source organism*
2000	Linezolid	Oxazolidinone	G + ve	S	
2001	Telithromycin	Macrolide	G + ve/G − ve	NP derived	Actinomycete
2002	Biapenem	Carbapenem	G + ve/G − ve	NP derived	Actinomycete
2002	Ertapenem	Carbapenem	G + ve/G − ve	NP derived	Actinomycete
2002	Prulifloxacin	Fluoroquinolone	G + ve/G − ve	S	
2002	Pazufloxacin	Fluoroquinolone	G + ve/G − ve	S	
2002	Balofloxacin	Fluoroquinolone	G + ve/G − ve	S	
2003	Daptomycin[b]	Lipopeptide	G + ve	NP	Actinomycete
2004	Gemifloxacin	Fluoroquinolone	G + ve/G − ve	S	
2005	Doripenem	Carbapenem	G + ve/G − ve	NP derived	Actinomycete
2005	Tigecycline	Tetracycline	G + ve/G − ve	NP derived	Actinomycete
2007	Retapamulin[b,d,e]	Pleuromutilin	G + ve	NP derived	Fungus
2007	Garenoxacin	Quinolone	G + ve/G − ve	S	
2008	Ceftobiprole medocaril	Cephalosporin	G + ve/G − ve	NP derived	Fungus
2008	Sitafloxacin	Fluoroquinolone	G + ve/G − ve	S	
2009	Tebipenem pivoxil	Carbapenem	G + ve/G − ve	NP derived	Actinomycete
2009	Telavancin	Glycopeptide	G + ve	NP derived	Actinomycete
2009	Antofloxacin	Fluoroquinolone	G + ve/G − ve	S	
2009	Besifloxacin[e]	Fluoroquinolone	G + ve/G − ve	S	
2010	Ceftaroline fosamil	Cephalosporin	G + ve/G − ve	NP derived	Fungus
2011	Fidaxomicin (**1**)[b]	Tiacumicin	G + ve	NP	Actinomycete
2012	Bedaquiline (**2**)[b]	Diarylquinoline	G + ve (TB)	S	

Abbreviations: NP, natural product; S, synthetic; TB, tuberculosis.
[a]The structures of the antibiotics approved from 2000 to 2010 can be found in our previous review.[2]
[b]First member of a new antibiotic class approved for human.
[c]Gram-positive (G + ve) or Gram-negative (G − ve).
[d]Pleuromutilin derivatives have been previously used in animal health.[157,158]
[e]For topical use only.

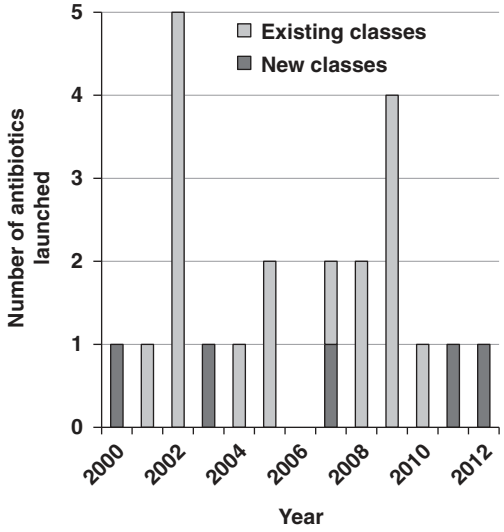
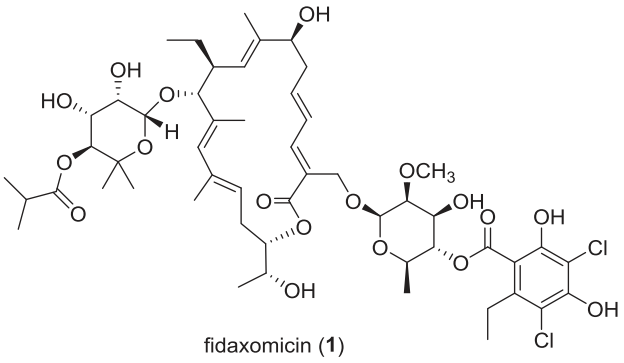


Figure 1 New antibiotic approvals 2000–2012 with new classes highlighted.



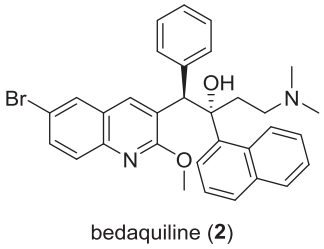


Figure 2 Structures of the recently launched antibiotics, fidaxomicin (**1**) and bedaquiline (**2**).

Table 2 Compounds in phase-III clinical trials or under NDA/MAA evaluation

Name (synonym)[a]	*Lead compound (lead source)*	*Mode of action*	*Bacteria type*	*Indication and development status (developer)*
Small molecule antibiotics				
Dalbavancin (**3**)	Glycopeptide (A40926) (NP)	Cell wall inhibition	G + ve	Two ABSSSi completed (Durata Therapeutics)
Oritavancin (**4**)	Glycopeptide (chloroeremomycin) (NP)	Cell wall inhibition	G + ve	One ABSSSi completed, one in progress (The Medicines Company)
Omadacycline (**5**)	Tetracycline (NP)	Protein synthesis inhibition	G + ve/G −ve	ABSSSi (Paratek)
Eravacycline (**6**)	Tetracycline (NP)	Protein synthesis inhibition	G + ve/G −ve	cIAI (Tetraphase)
Solithromycin (**7**)	Erythromycin (NP)	Protein synthesis inhibition	G + ve/G −ve	CAP (Cempra)
Surotomycin (**8**)	Lipopeptide (daptomycin) (NP)	Membrane depolarization	G + ve	CDAD (Cubist)
Tedizolid phosphate (**9a**)	Oxazolidinone (S)	Protein synthesis inhibition	G + ve/G −ve	ABSSSi completed (Trius Therapeutics)
Delamanid (**10**)	Nitroimidazole (S)	DNA and cellular damage	G + ve (TB)	NDA and phase-III, TB (Otsuka Pharmaceuticals)
Perchlozone (**11**)	Thiosemicarbazone (S)	Unknown	G + ve (TB)	TB completed (JSC Pharmasyntez)
SQ109 (**12**)	Ethambutol (S)	Cell wall synthesis	G + ve (TB) / G-ve	TB; also *H. pylori*-associated duodenal ulcer (Sequella/Infectex)
Finafloxacin (**13**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	Acute Otitis Media; also completed phase-II *H. pylori* and UTI (MerLion)
Delafloxacin (**14**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	ABSSI (Rib-X Pharmaceuticals)
Avarofloxacin (**15**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	Irritable bowel syndrome; phase-II CABP, ABSSSi completed (Furiex)
Zabofloxacin (**16**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	CAP (Dong Wha Pharmaceutical)
Nemonoxacin (**17**)	Quinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	CAP (TaiGen Biotechnology)
Ozenoxacin (**18**)	Quinolone (S)	DNA gyrase and topoIV	G + ve	Impetigo (Grupo Ferrer Internacional) acne, topical (Maruho Co)
β-Lactam/β-lactamase inhibitor combinations				
CXA-201 (ceftolozane (**19**)/ tazobactam (**20**))	Cephalosporin (NP)/ clavulanic acid (NP)	Penicillin-binding protein/ β-lactamase inhibitor	G + ve/G −ve	cUTI, cIAI; also phase-II HABP/ VABP (Cubist)
CAZ104 (ceftazidime (**21**)/ avibactam (**22**))	Cephalosporin (NP)/ diazabicyclooctane (S)	Penicillin-binding protein/ β-lactamase inhibitor	G + ve/G −ve	cIAI; UTI (AstraZeneca)

Abbreviations: ABSSSi, acute bacterial skin and skin structure infection; CDAD, *C. difficile*-associated diarrhea; cIAI, complicated intra-abdominal infection; CAP, community acquired pneumonia; MAA, Marketing Authorization Application; NDA, New Drug Application; NP, natural product; S, synthetic; TB, tuberculosis; topoIV, topoisomerase IV; UTI, urinary tract infection.
[a]Underlined compounds are new antibacterial templates.

β-lactam/β-lactamase inhibitor combinations undergoing clinical development in phase-I, -II or -III trials or under regulatory evaluation as of May 2013 (Tables 2–4, Figures 3–10). These descriptions include their development status, mode of action, spectra of activity, historical discovery and origin of the drug pharmacophore: natural product (NP), NP-derived, synthetic (S) or protein/mammalian peptide (P). New clinical trials of approved drugs including new formulations are not discussed in this review. The ClinicalTrials.gov NCT codes are listed in parentheses for each trial and trials not in this database are referenced. These data were obtained by analyzing the journal literature and internet resources such as company web pages, clinical trial registers and

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

Name (synonym)[a]	*Lead compound (lead source)*	*Mode of action*	*Bacteria type*	*Indication and development status (developer)*
Small molecule antibiotics				
LFF-571 (**25**)	GE2270 A (NP)	Elongation factor Tu	G+ve	CDAD (Novartis)
Auriclosene (**26**)	*N*-Chlorotaurine (NP)	Oxidation	G+ve/G−ve	Urinary catheter blockage and encrustation, adenoviral conjunctivitis; impetigo asymptomatic bacteriuria completed (Novabay)
Sarecycline (**27**)	Tetracycline (NP)	protein Synthesis inhibition	G+ve	Acne/rosacea (Warner Chilcott)
BC-3781 (**28**)	Pleuromutilin (NP)	Protein synthesis inhibition	G+ve/G−ve	ABSSSi completed (Forest/Nabriva)
Plazomicin (**29**)	Aminoglycoside (NP)	Protein synthesis inhibition	G+ve/G−ve	UTI and pyelonephritis completed (Achaogen)
GSK1322322 (**30**)	Actinonin (NP)	Peptide deformylase	G+ve/G−ve	cSSSi completed (GSK)
Brilacidin (**31**)	Defensin (P)	Bacterial cell membrane lysis	G+ve/G−ve	ABSSSi (PolyMedix)
LTX-109 (**32**)	Cationic peptide (P)	Membrane disruption	G+ve/G−ve	Impetigo (Lytix Biopharma)
DPK-060 (CD-1)[b]	Kininogen subunit (P)	Membrane disruption	G+ve/ G-ve (?)	External otitis, atopic dermatitis completed (Pergamum AB)
LL-37 (**33**)	Cathelicidin subunit (P)	Membrane disruption	G+ve/G−ve	Wound healing in chronic leg ulcers phase-I/II (Pergamum AB)
IMX-942[b]	Indolicidin and IDR-1 (P)	ZZ domain of human p62 (sequestosome-1)	Immuno-modulator	In combination with antibiotic for ABSSSi (Inimex)
PA-824 (**34**)	Nitroimidazole (S)	DNA and cellular damage	G+ve (TB)	TB various drug combinations (Global Alliance for TB Drug Development)
Radezolid (**35**)	Oxazolidinone (S)	Protein synthesis inhibition	G+ve/G−ve	uSSSi, CAP completed (Rib-X)
Sutezolid (**36**)	Oxazolidinone (S)	Protein synthesis inhibition	G+ve (TB)	TB (Pfizer)
Posizolid (**37**)	Oxazolidinone (S)	Protein synthesis inhibition	G+ve (TB)	TB (AstraZeneca)
Cadazolid (**38**)	Oxazolidinone (S)/ quinolone (S) hybrid	Protein synthesis inhibition/ DNA gyrase and topoIV	G+ve	CDAD (Actelion)
AFN-1252 (**39**)	Synthetic lead (S)	FabI inhibition	G+ve	ABSSSi completed (Affinium)
CG400549 (**40**)	Triclosan (S)	FabI inhibition	G+ve	ABSSSi completed (CrystalGenomics)
WCK-771 (**41**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G+ve/G−ve	MRSA and Gram-negatives (Wockhardt Limited)
WCK-2349 (pro-drug WCK-771)[a]	Fluoroquinolone (S)	DNA gyrase and topoIV	G+ve/G−ve	MRSA and Gram-negatives (Wockhardt Limited)
β-Lactam/β-lactamase inhibitor combinations				
CXL (ceftaroline (**23**)/ avibactam (**22**))	Cephalosporin (NP)/ diazabicyclooctane (S)	Penicillin-binding protein/ β-lactamase inhibitor	G+ve/G−ve	MRSA (AstraZeneca)
Imipenem (**42**)/ cilastatin (**43**)/ MK-7655 (**44**)	Carbapenem (NP)/ cilastatin (S)/ diazabicyclooctane (S)	Penicillin-binding protein/ dehydropeptidase inhibition/ β-lactamase inhibition	G+ve/G−ve	UTI and cIAI (Merck)

Abbreviations: ABSSSi, acute bacterial skin and skin structure infection; CDAD, *C. difficile*-associated diarrhea; cIAI, complicated intra-abdominal infection; CAP, community acquired pneumonia; cSSSi, complicated skin and skin structure infection; IDR-1, innate defense regulator-1; MRSA, methicillin-resistant *S. aureus*; NP, natural product; S, synthetic; TB, tuberculosis; topoIV, topoisomerase IV; uSSSi, uncomplicated skin and skin structure infection; UTI, urinary tract infection.
[a]Underlined compounds are new antibacterial templates.
[b]Structure not published.

biotechnology-related newsletters. Compounds have been excluded from this review if there has been no development activity reported since the beginning of 2010 (Table 5). Every endeavor has been undertaken to ensure that these data are accurate, but it is possible compounds undergoing early clinical development with limited information in the public domain have been overlooked.

The drug development and approval process as well as commonly used abbreviations associated with antibiotic development are as follows:

- Before clinical trials can start, an Investigational New Drug Application must be approved by the US FDA, European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency or equivalent national agency. Upon successful completion of phase-III clinical trials, a New Drug Application (NDA: FDA and Pharmaceuticals and Medical Devices Agency) or a Marketing Authorization Application (MAA: EMA) must be approved to be able to market the drug. It is also possible to obtain approval for desperately required drugs under the FDA's accelerated approval program after successful completion of phase-II trials. Some infectious disease antibiotic development programs are assisted by the BARDA, a US government agency mandated to provide an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies and diagnostic tools for public health medical emergencies. Others are assisted by the Division of Microbiology and Infectious Diseases within the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health, and by Europe's Innovative Medicines Initiative.
- Antibacterial clinical trial indications generally fall within one of the following infection categories: *C. difficile* infections (CDIs), *C. difficile*-associated diarrhea (CDAD), skin and skin structure

Table 4 Compounds in phase-I clinical trials

Name (synonym)[a]	*Lead compound (lead source)*	*Mode of action*	*Bacteria type*	*Indication and development status (developer)*
Small molecule antibiotics				
BAL30072 (**45**)	Monobactam (NP)	Penicillin-binding protein	G + ve/G −ve	Gram-negative (Basilea)
Exeporfinium chloride (**46**)	Porphyrin (NP)	Membrane-perturbing activity	G + ve	MRSA topical (Destiny Pharma)
NVB302 (**47**)	Deoxyactagardine B (Type B lantibiotic) (NP)	lipid II binding	G + ve	CDAD completed (Novacta)
S-649266 (GSK-2696266)[b]	cephem (NP)	Penicillin-binding protein	G + ve/G −ve	Gram-negative infections (Shionogi/GSK)
POL7080[b]	Protegrin I (P)	Inhibition of a homolog of the β-barrel protein LptD (Imp/OstA)	G −ve	Phase-I (Polyphor)
LCB01-0371 (**48**)	Oxazolidinone (S)	Protein synthesis inhibition	G + ve	Phase-I (LegoChem Biosciences)
MRX-I (**49**)	Oxazolidinone (S)	Protein synthesis inhibition	G + ve	Phase-I completed (MicuRx)
SMT-19969[b]	Bibenzo[*d*]-imidazole (S)	Unknown	G + ve	CDAD (Summit)
ACHN-975[b]	Unknown (S?)	*N*-Acetylglucosamine deacetylase (LpxC) inhibitor	G −ve	Phase-I (Achaogen)
GSK-214094[b]	Unknown (S?)	Type 2 topoisomerase	Unknown	Phase-I (GSK)
KPI-10 (**50**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	Phase-I (Kalidex)
DS-8587 (**51**)	Fluoroquinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	Phase-I (Daiichi)
KRP-AM1977X (Oral agent) and KRP-AM1977Y (IV agent)[b]	Quinolone (S)	DNA gyrase and topoIV	G + ve/G −ve	Phase-I (Kyorin)
β-Lactam/β-lactamase inhibitor combinations				
ATM-AVI (aztreonam (**24**)/ avibactam (**22**) (NXL104))	Monobactam (NP)/ diazabicyclooctane (S)	Penicillin-binding protein/ β-lactamase inhibition	G + ve/G −ve	Phase-I (AstraZeneca)
Carbavance (biapenem (**52**)/ RPX7009 (**53**))	Carbapenem (NP)/ boron (S)	Penicillin-binding protein/ β-lactamase inhibition	G + ve/G −ve	Phase-I (Rempex)

Abbreviations: CDAD, *C. difficile*-associated diarrhea; MRSA, methicillin-resistant *S. aureus*; NP, natural product; S, synthetic; topoIV, topoisomerase IV.
[a]Underlined compounds are new antibacterial templates, whereas dotted underlined compounds may be new templates.
[b]Structure not published.

infections (SSSi), which are further divided into complicated (cSSSi), uncomplicated (uSSSi) and acute bacterial (ABSSSi), community (CAP)-/hospital-acquired pneumonia, community-acquired bacterial pneumonia (CABP), urogenital gonorrhea, irritable bowel syndrome, ophthalmic indications, such as acute otitis media, urinary tract infections (UTIs) and complicated UTIs (cUTIs), complicated intra-abdominal infections (cIAIs), skin infections, such as acne, rosacea and impetigo, and TB.

- Other abbreviations: diazabicyclooctane (DBO), early bactericidal activity (EBA), EU, Gram-positive (G + ve), Gram-negative (G −ve), intravenous (IV), Initial Public Offering, NP, minimum inhibitory concentration, multi-drug resistant (MDR), lipopolysaccharide (LPS), penicillin-binding protein, protein/mammalian peptide (P), Securities and Exchange Commission, structure–activity relationships, synthetic (S) and United States of America (USA).

ANTIBACTERIAL DRUGS LAUNCHED SINCE 2000

Since 2000, 22 new antibiotics (2 NP, 10 NP derived and 10 synthetic) have been launched worldwide (Table 1). Two new antibiotics, fidaxomicin (**1**) and bedaquiline (**2**; Figure 2), have been approved since the last review in this series[2] and are discussed in detail. There has been a steady launch of antibiotics since 2000, averaging one to two launches per year (Figure 1). Five first-in-class antibiotics have been introduced in this period: linezolid (oxazolidinone, S, 2000), daptomycin (lipopeptide, NP, 2003), retapamulin (pleuromutilin, NP-derived, 2007), fidaxomicin (**1**; tiacumicin, NP, 2011) and bedaquiline (**2**; diarylquinoline, S, 2012). The 10 synthetically derived antibiotics are dominated by eight quinolones and this trend is set to continue with six quinolones being evaluated in phase-III (Table 2) and two in phase-II trials (Table 3). Six of the twelve NP and NP-derived antibiotics belong to the β-lactam class with the other six belonging to separate classes. The continued potential of bacteria as a source for antibiotic-lead discovery[40] is reinforced by the list of launched antibiotics, with 9 of the 12 NP-derived antibiotic-lead compounds being derived from actinomycetes and 3 from fungi.

Fidaxomicin (**1**) was developed by Optimer Pharmaceuticals (San Diego, CA, USA) and approved by the US FDA in May 2011 (trade name: Dificid) and by the EMA in December 2011 (trade name: Dificlir) for the treatment of intestinal infections and diarrhea caused by *C. difficile*.[41] *C. difficile* is a spore-forming Gram-positive anaerobe that can overgrow beneficial and commensal gastrointestinal bacteria, secreting toxins that lead to severe diarrhea, inflammation of the colon, fever, intestinal paralysis and sepsis, which can be lethal.[42] *C. difficile*-associated diarrhea has become the leading cause of hospital-acquired infections, a situation aggravated by increasing outbreaks of hypervirulent strains that overproduce the toxins.[43,44] Fidaxomicin (**1**) is an actinomycete-derived macrolactone[45] that was named tiacumicin B when isolated at Abbott Laboratories, with a patent filed in 1986[46] and publication in 1987.[47,48] The tiacumicins have identical structures to the lipiarmycins (isolation reported in 1975[49–52] and structure in 1987[53,54]) and the clostomicins (reported in 1986[55]). Fidaxomicin (**1**) inhibits bacterial RNA polymerase transcription by blocking the initiation of RNA synthesis.[56,57]

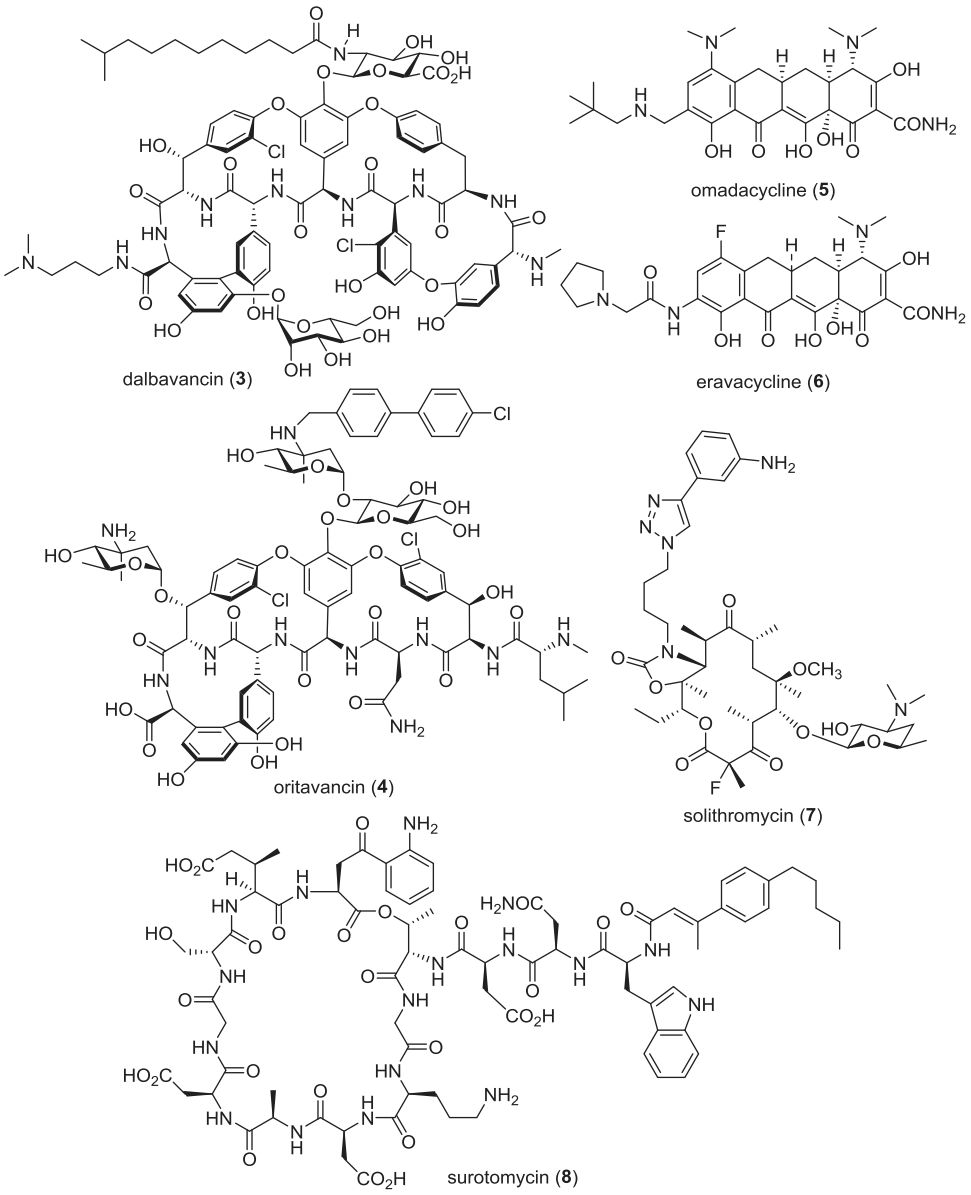


Figure 3 Structures of natural product-derived compounds in phase-III clinical trials.

In late December 2012, the US FDA approved bedaquiline (**2**; trade name: Sirturo) as part of combination therapy to treat adults with MDR pulmonary TB when other alternatives are not available.[58] Bedaquiline (**2**) was approved after the successful completion of two phase-II clinical trials under the FDA's accelerated approval program[59] and was jointly developed by Tibotec (Beerse, Belgium) and the Global Alliance for TB Drug Development (New York, NY, USA).[60,61] Bedaquiline (**2**), derived from a series of diarylquinolines discovered[62] through whole-cell screening against *Mycobacterium smegmatis*, specifically targets the oligomeric subunit c of mycobacterial ATP synthase.[63,64]

COMPOUNDS UNDERGOING CLINICAL EVALUATION

The compounds currently undergoing clinical trials or under regulatory evaluation for the treatment of bacterial infections as of May 2013 are detailed in the following tables and figures: phase-III/NDA in Table 2 with structures in Figures 3–5, phase-II in Table 3 with structures in Figures 6–8 and phase-I in Table 4 with structures in Figures 9 and 10.

Phase-III trials and NDA/MAA applications

NP and NP-derived compounds in phase-III trials. Dalbavancin (**3**) and oritavancin (**4**) are semi-synthetic lipoglycopeptide analogs of the vancomycin/teicoplanin class of antibiotics that are designed for IV treatment of Gram-positive infections. These "second-generation" glycopeptides possess additional lipophilic substituents that significantly increase their biological half-life (approximately 200 and 400 h, respectively) and provide additional mechanisms of action beyond simple inhibition of peptidoglycan synthesis.[65] Both have had a troubled regulatory and commercial pathway, although there now may be a light at the end of the tunnel. Dalbavancin (**3**; BI-397), a semi-synthetic derivative of the teicoplanin-like glycopeptide A40926 Factor B, was originally developed by Vicuron Pharmaceuticals,[66–69] which was acquired by Pfizer (Groton, CT, USA) in 2005.

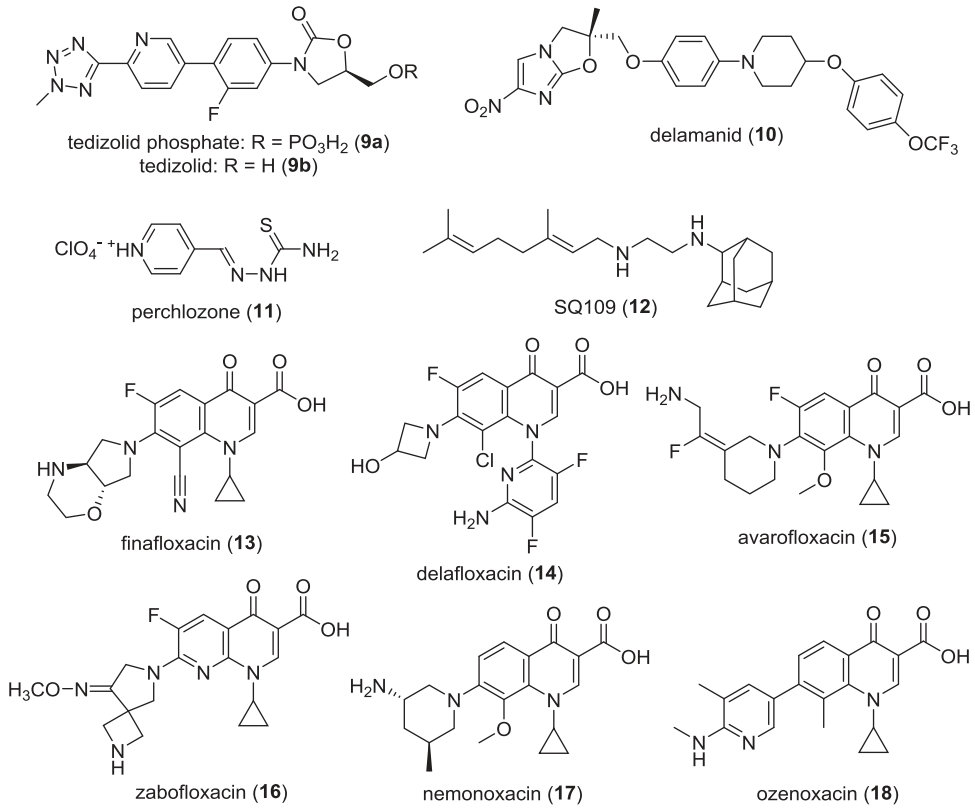


Figure 4 Structures of synthetic compounds in phase-III clinical trials or under New Drug Application/Marketing Authorization Application evaluation.

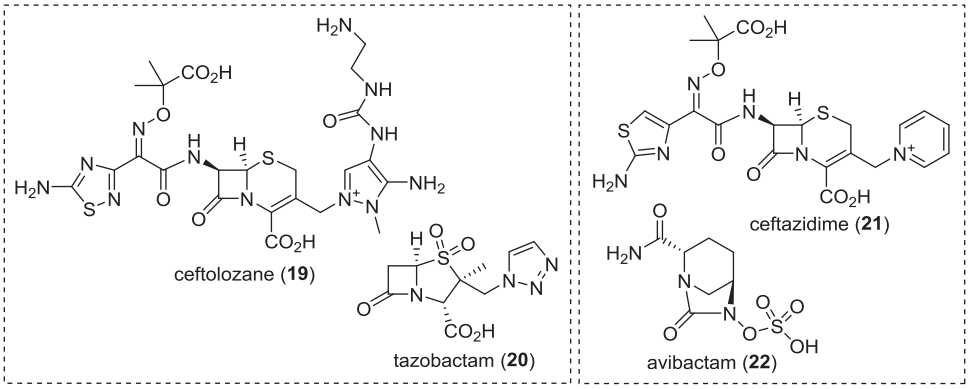


Figure 5 Structures of β-lactamase inhibitor/antibiotic combinations in phase-III clinical trials.

Three phase-III trials were successfully completed between 2003 and 2005 but the FDA requested additional non-inferiority data in 2007.[65] Little progress was made until 2009, when Durata Therapeutics (Chicago, IL, USA) acquired the program and initiated two additional phase-III trials (NCT01339091 and NCT01431339). In December 2012[70] and February 2013,[71] Durata announced that the DISCOVER 1 and 2 ("Dalbavancin for Infections of the Skin COmpared to Vancomycin at an Early Response") phase-III studies (573 patients at 92 sites and 739 patients at 139 sites) met their primary end point of non-inferiority, comparing two IV doses of dalbavancin (**3**) given 1 week apart with twice-daily vancomycin doses for 14 days. The company also indicated it intends to submit an NDA with the FDA by mid-2013 and an MAA with the EMA at year-end 2013.[71]

Oritavancin (**4**; LY333328) was initially developed by Eli Lilly in the 1990s and is a semi-synthetic derivative of the vancomycin-like glycopeptide chloroeremomycin.[69,72,73] InterMune, Inc. acquired the rights in 2001, followed by Targanta Therapeutics in 2005. Two phase-III trials were successfully completed, with the results disclosed in 2001 and 2003, but the FDA rejected an NDA in December 2008 because of concerns over safety and effectiveness.[65,73] In January 2009, Targanta was acquired by the Medicines Company (Parsippany, NJ, USA), which initiated two phase-III trials (NCT01252719 and NCT01252732) for Gram-positive ABSSSi (SOLO I, 968 patients at 46 centers globally, successfully completed by October 2012;[74] SOLO II, currently recruiting 960 patients at 100 centers globally with enrollment expected by mid-2013), as well as two phase-I safety trials

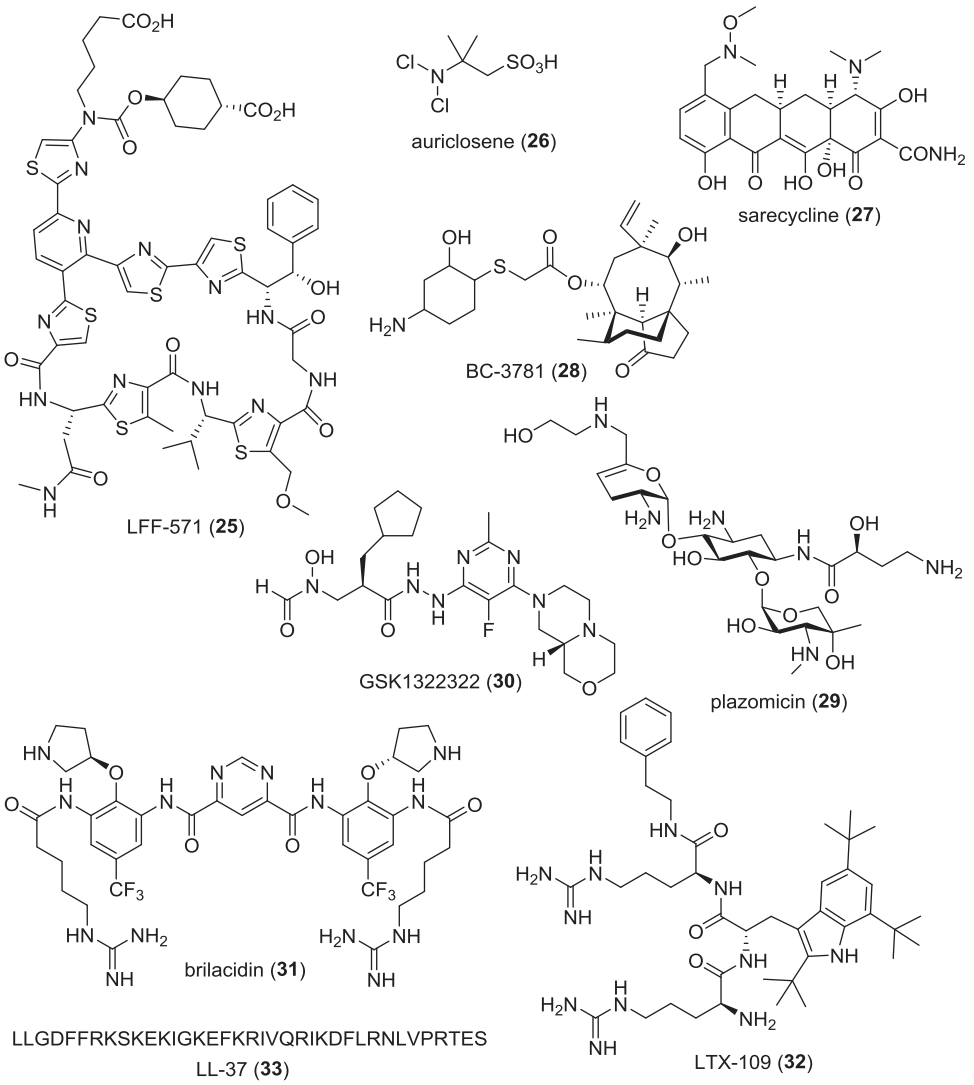


Figure 6 Structures of natural product-derived and P-derived compounds in phase-II clinical trials.

(NCT01784536 and NCT01762839) to assess cardiotoxicity and CYP450 activity (completed by January 2013).

Omadacycline (**5**; amadacycline, PTK-0796) is a semi-synthetic tetracycline derivative[75,76] developed by Paratek Pharmaceuticals (Boston, MA, USA) with a complex development history. Omadacycline (**5**) has been licensed to Bayer (Leverkusen, Germany), Merck (Rahway, NJ, USA) and then Novartis (Basel, Switzerland), who started a phase-III trial for the treatment of cSSSi in 2009 but discontinued the studies in 2011 (NCT00865280). Paratek is planning phase-III trials for omadacycline (**5**) for the treatment of ABSSSi and CABP using both oral and IV formulations,[76] as well as planning studies for the treatment of UTIs. It is presumed that Paratek will fund these studies from a planned initial public offering that was registered with the US Securities and Exchange Commission in September 2012.[77]

Eravacycline (**6**; TP-434) is a synthetic tetracycline derivative[78–80] developed by Tetraphase Pharmaceutics (Watertown, MA, USA) that recently entered into a phase-III trial for the treatment of cIAI (NCT01844856) after successfully completing a phase-II trial (NCT01265784). Eravacycline (**6**) is the first member of the new fluorocycline tetracycline subclass with broad-spectrum activity that includes bacteria with tetracycline-specific efflux and ribosomal protection. As with other tetracyclines, eravacycline (**6**) inhibits bacterial protein synthesis.[81]

Solithromycin (**7**; CEM-101) is a semi-synthetic 2-fluoroketolide being developed by Cempra Pharmaceuticals (Chapel Hill, NC, USA) that is currently being evaluated in a phase-III trial for the treatment of CABP (NCT01756339) and a phase-II trial for the treatment of uncomplicated urogenital gonorrhea (NCT01591447). Solithromycin (**7**), which was discovered by Optimer Pharmaceuticals (San Diego, CA, USA)[82] and then licensed to Cempra in 2006, is a protein synthesis inhibitor that has broad-spectrum antibacterial activity including many ketolide/macrolide-resistant strains.[83–85] Solithromycin (**7**) differs from telithromycin, a ketolide launched in the EU (2001) and USA (2004) that has had some safety issues including visual disturbances and hepatotoxicity. These side effects could be due to inhibition of nicotinic acetylcholine receptors via the pyridine moiety on its side chain.[86] Solithromycin (**7**) does not contain the pyridine moiety and, as a consequence, is not predicted to display these side effects. In May 2013, Cempra was awarded $58 million to develop **7** for pediatric use and for biodefense by BARDA.[39]

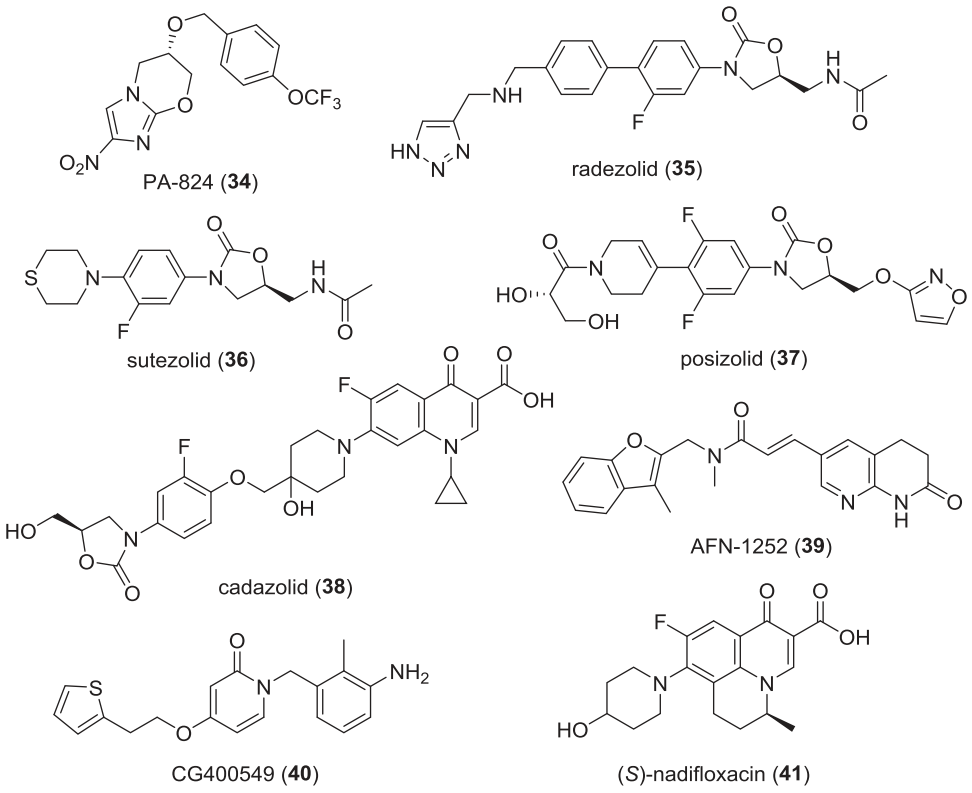


Figure 7 Structures of synthetic compounds in phase-II clinical trials.

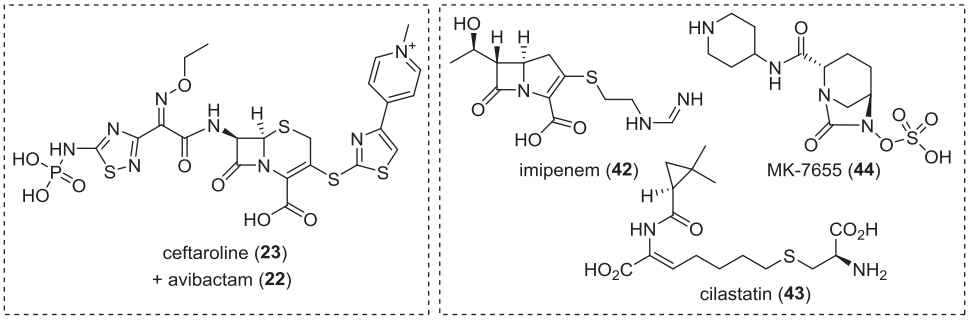


Figure 8 Structures of β-lactamase inhibitor/antibiotic combinations in phase-II clinical trials.

Surotomycin (**8**; CB-183 315) is a semi-synthetic daptomycin derivative[87] that is being evaluated by Cubist Pharmaceuticals (Lexington, MA, USA) in two identical phase-III trials (NCT01597505 and NCT01598311) for the treatment of *C. difficile*-associated diarrhea. Surotomycin (**8**) has good bactericidal activity against a panel of *C. difficile* strains that include the highly virulent NAP1 strain, has negligible systemic absorption and has a minor impact on the levels of key normal bowel bacteria such *Bacteroides* spp.[88–90]

Synthetic compounds in phase-III trials. Tedizolid phosphate (**9a**)[91–93] (torezolid phosphate, TR-701, DA-7218) is an oxazolidinone being developed by Trius Therapeutics (San Diego, CA, USA) that has completed a phase-III trial for the treatment of Gram-positive ABSSSi (NCT01170221).[94] Discovered by Dong-A Pharmaceutical (Seoul, South Korea), it is a pro-drug that is dephosphorylated *in vivo* to give tedizolid (**9b**), which is active against various Gram-positive bacteria including linezolid-resistant strains.[95] Like linezolid, tedizolid (**9b**) binds to the 50S ribosome preventing the formation of the 70S initiation complex, which in turn blocks the initiation of protein synthesis.[96]

Delamanid (**10**; OPC-67683) is being evaluated by Otsuka Pharmaceutical Co. (Tokyo, Japan) in a phase-III trial for the treatment of MDR TB in combination with other TB drugs over 6 months (NCT01424670). Otsuka has filed an MAA with the EMA in 2011 and a Pharmaceuticals and Medical Devices Agency in March 2013 in Japan on the basis of phase-II data including trial NCT00685360.[97] Delamanid (**10**)[98,99] is derived from the bicyclic nitroimidazole CGI-17341,[100,101] which was a promising TB lead compound dropped from development because of mutagenicity concerns. Delamanid (**10**) and PA-824 (**33**, phase-II section, Figure 7) are both non-mutagenic in the Ames mutagenicity assay. Both **10** and **33** are pro-drugs that are reductively activated by a deazaflavin (F_{420})-dependent nitroreductase.[101]

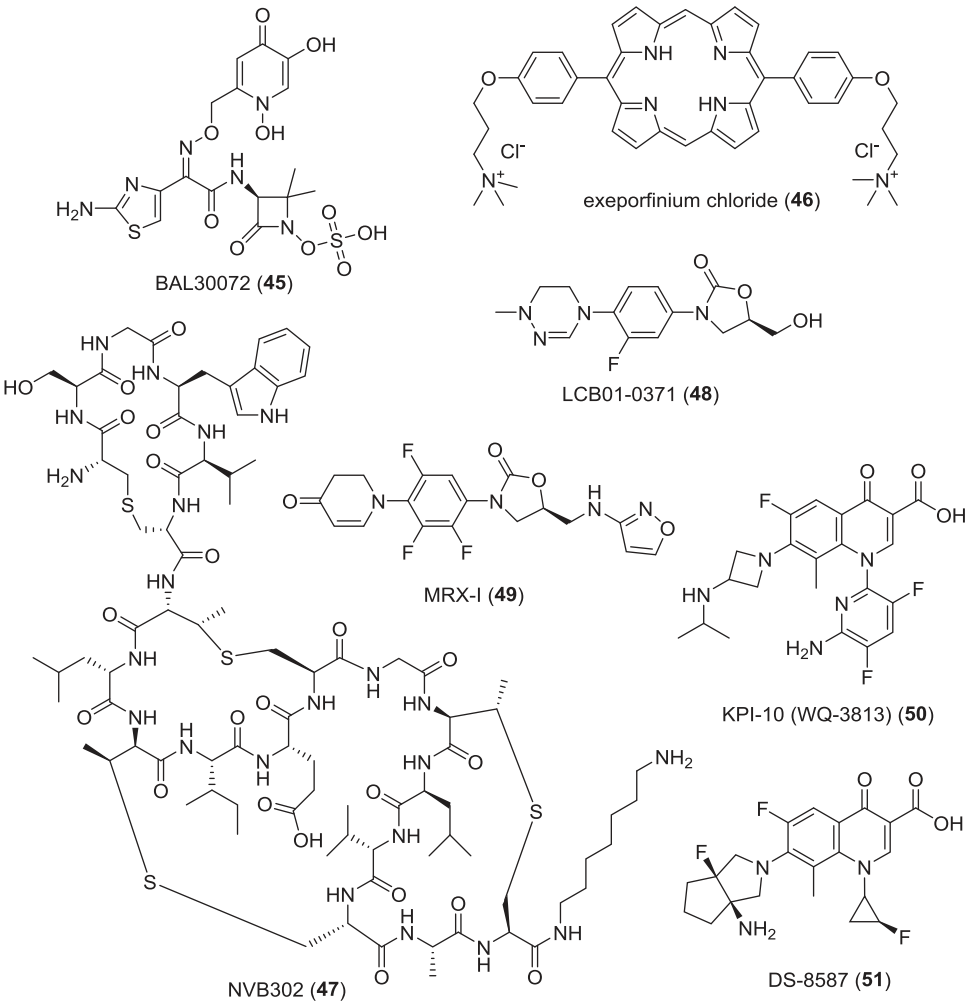


Figure 9 Published structures of compounds in phase-I clinical trials.

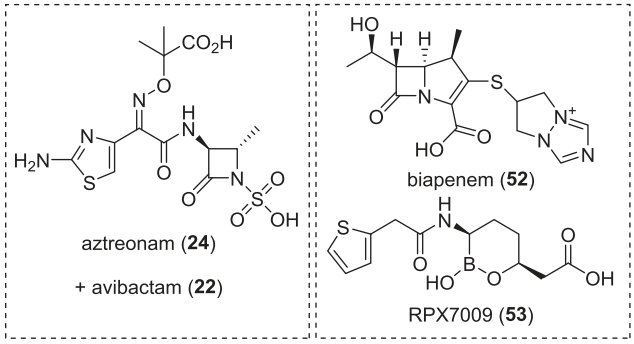


Figure 10 Structures of β-lactamase inhibitor/antibiotic combinations in phase-I clinical trials.

Thioureidoiminomethylpyridinium perchlorate (**11**; Perchlozone) is under development by JSC Pharmasyntez (Moscow, Russia) and has completed a phase-II/III trial for the treatment of patients with TB. The perchlorate salt of thioureidoiminomethylpyridine (**11**) was synthesized at the Siberian Division of the Russian Academy of Sciences (Novosibirsk, Russia)[102,103] and is the salt form of thioureidoiminomethylpyridine, which was discovered to have anti-TB activity in the early 1950s.[104,105]

SQ109 (**12**) is an ethambutol analog developed by the NIAID and Sequella (Rockville, MD, USA) that has recently completed a phase-II trial for EBA in patients with pulmonary TB (NCT01218217). In December 2012, SQ109 (**12**) started a phase-II/III trial in collaboration with Infectex (Moscow, Russia) for the treatment MDR-TB.[106] SQ109 (**12**) was chosen as the lead candidate after the synthesis and biological evaluation of 63 000 analogs synthesized using a combinatorial solid-phase approach.[107] Although SQ109 (**12**) was designed as an ethambutol analogue, it was recently shown that these compounds differ in their mode of action with SQ109 (**12**) inhibiting MmpL3, a transporter of mycobacterial trehalose monomycolate.[108] An X-ray structure of SQ109 (**12**) binding to *Staphylococcus aureus* dehydrosqualene synthase has also been published.[109]

There are currently four fluoroquinolones, finafloxacin (**13**), delafloxacin (**14**), avarofloxacin (**15**) and zabofloxacin (**16**), and two quinolones, nemonoxacin (**17**) and ozenoxacin (**18**), being evaluated in phase-III trials. Quinolone antibiotics kill bacteria through a dual mechanism of DNA gyrase (GyrA) and topoisomerase IV (ParC) inhibition, with the GyrA/ParC activity ratios depending on the compound and microorganism target.[110]

Finafloxacin (**13**; BAY 35–3377) is being tested in phase-III trials by MerLion Pharmaceuticals (Singapore, Singapore) for the treatment of acute otitis media (inner and outer ear infections).[111] Finafloxacin

Table 5 Compounds discontinued or likely to have been discontinued from clinical development since 2011

Name (synonym)[a]	*Lead compound (lead source); mode of action*	*Reason for discontinuation; indication and development status*
AZD5099	Unknown; GyrB inhibition	AstraZeneca (London, UK) suspended participant recruitment in November 2011 during phase-I
AZD9742	Unknown; unknown	Developed discontinued in August 2010 by AstraZeneca (London, UK) after phase-I with no reasons given
BC-3205	Pleuromutilin (NP); protein synthesis inhibition	Completed phase-I oral but no update from Nabriva Therapeutics AG (Vienna, Austria) since 2010
BC-7013	Pleuromutilin (NP); protein synthesis inhibition	Completed phase-I oral in 2010 but no update from Nabriva Therapeutics AG (Vienna, Austria)
CB-182 804	Polymyxin (NP); membrane disruption	Cubist Pharmaceuticals (Lexington, MA, USA) discontinued development after phase-I in September 2010
Cethromycin (ABT-773)	Erythromycin (NP); protein synthesis inhibition	Advanced Life Sciences terminated operations in May 2011; CAP NDA submitted October 2008 but rejected due to "no efficacy" on 2 June 2009
FAB-001	Triclosan (S); FabI inhibition	Phase-I started in September 2009 but no update from FAB Pharma S.A.S. (Paris, France)
GSK-2251052 (AN3365)	AN2690 (S); aminoacyl-tRNA synthetase	GSK (London, UK) discontinued development in 2012 after increased resistance was observed in bacterial isolates from a subpopulation of patients in a phase-IIa trial and the rights have reverted back to Anacor Pharmaceuticals, Inc. (Palo Alto, CA, USA)
Iclaprim (AR-100, Ro 48–2622)	Trimethoprim (S); dihydrofolate reductase inhibition	No update from Acino Holding Ltd. (Basel, Switzerland) since December 2010; NDA filed for cSSSi in March 2008 by Arpida Ltd (Muenchenstein, Switzerland) but further clinical trials were requested in January 2009
Lotilibcin (WAP-8294A_2)	WAP-8294A_2 (NP); phospholipid binding resulting in bacterial membrane damage	Green Cross Corporation (Yongin, South Korea) licensed lotilibcin from aRigen Pharmaceuticals, Inc. (Tokyo, Japan) in January 2011 but not listed in Green Cross pipeline; IV formulation (MRSA) was in phase-I in 2010
Ramoplanin	Ramoplanin (NP); cell wall production inhibition	No update from Nano therapeutics, Inc. (Alachua, FL, USA) since December 2009; CDAD phase-II trails completed before 2006
TP-2758	Tetracycline (NP); protein synthesis inhibition	Tetraphase (Watertown, MA, USA) was in phase-I for UTI in 2012 but is no longer listed on the company's website

Abbreviations: CDAD, *C. difficile*-associated diarrhea; cSSSi, complicated skin and skin structure infection; MRSA, methicillin-resistant *S. aureus*; NP, natural product; S, synthetic; UTI, urinary tract infection.
[a]Underlined compounds were new antibacterial templates.

(**13**) is also being evaluated in a phase-II trial to treat patients with complicated UTI[112] and has previous completed phase-II trials for uncomplicated UTI (NCT00722735) and *Helicobacter pylori* eradication (NCT00723502). The pre-clinical development of finafloxacin (**13**) was focused on reducing toxicity issues associated with other fluoroquinolones and an excellent safety profile has been observed in the clinical trials to date.[113,114] Finafloxacin (**13**) was also highly effective in *in vivo* infection models and this could be due to the improved activity at slightly acidic pH, which is more representative of physiological conditions.[115–118] This is in contrast to marketed quinolones that are less efficacious at acidic pH.[119]

Delafloxacin (**14**; RX-3341, WQ-3034, ABT-492) is being evaluated by Rib-X Pharmaceuticals (New Haven, CT, USA) for the treatment of ABSSSi, with patients soon to be enrolled in a phase-III trial (NCT01811732). Similar to finafloxacin (**13**), delafloxacin (**14**) displays enhanced activity against Gram-positive bacteria at more acidic pH (pH 5). This has been proposed to be due to the lack of a basic residue in the pendant heterocycle providing an overall weakly anionic character.[120]

Avarofloxacin (**15**; JNJ-32729463, JNJ-Q2) is being developed by Furiex Pharmaceuticals, Inc (Morrisville, NC, USA) in phase-III trials for the treatment of irritable bowel syndrome (NCT01553747 and NCT01553591). Avarofloxacin (**15**) has successfully completed phase-II trials for cSSSi (NCT01130272) and irritable bowel syndrome (NCT01128530), whereas a phase-II trial for CABP was terminated because of slow enrollment (NCT01198626). Avarofloxacin (**15**) displays equipotent activity against GyrA and ParC, which has been suggested to improve the spectrum of activity and lower the potential for resistance.[121] In addition, the presence or absence of the NorA efflux pump did not alter the minimum inhibitory concentrations of avarofloxacin (**15**), which suggested reduced susceptibility to bacterial efflux.[122]

Zabofloxacin (**16**; PB-101, DW-224a) is undergoing phase-III trials conducted by Dong Wha Pharmaceutical (Seoul, South Korea) for the treatment of patients with acute bacterial exacerbation of chronic obstructive pulmonary disease (NCT01658020). Dong Wha had licensed zabofloxacin (**16**) to IASO Pharma, Inc. (San Diego, CA, USA, formally Pacific Beach Biosciences) but their phase-III trial for CAP was halted in May 2012 due to financial reasons (NCT01081964). Zabofloxacin (**16**) has broad-spectrum antibacterial activity[123,124] and inhibits both GyrA and ParC.[125]

Nemonoxacin (**17**; TG-873870) is being evaluated in a phase-III trial by TaiGen Biotechnology Co., Ltd. (Taipei, Taiwan) for the treatment of patients with CAP (NCT01529476). TaiGen secured the full worldwide rights to nemonoxacin (**17**) in December 2011, after originally licensing it from Procter & Gamble Pharmaceuticals, which was acquired by Warner Chilcott (Rockaway, NJ, USA) in October 2009. Nemonoxacin (**17**) is a non-fluorinated quinolone that has broad-spectrum activity against susceptible and resistant Gram-positive and Gram-negative strains.[126,127]

Ozenoxacin (**18**; T-3912) recently completed a phase-III trial by Ferrer Internacional S.A. (Barcelona, Spain) for patients with impetigo (NCT01397461), whereas a phase-III trial for acne by Maruho Co. (Osaka, Japan) is ongoing.[128] Ozenoxacin (**18**) is also a non-fluorinated quinolone with broad-spectrum activity against a variety of susceptible and resistant Gram-positive bacteria.[129]

β-Lactam/β-lactamase inhibitor combinations in phase-III trials. The β-lactam antibiotics, which include penicillins, cephalosporins and carbapenems, have been one of the most successful antibiotic classes ever discovered. A common resistance mechanism for β-lactams is ring opening by β-lactamase enzymes, inactivating the antibiotics and rendering them unable to inhibit the bacterial penicillin-binding proteins. The co-administration of a β-lactamase inhibitor with a β-lactam considerably prolongs the antibiotic activity. The first β-lactamase inhibitor, clavulanic acid,[130–132] was isolated from *Streptomyces clavuligerus* and is still used today in combination with amoxicillin, which is most commonly known under GSK's trade name Augmentin. The new β-lactam/β-lactamase inhibitor combinations have been recently reviewed.[133,134]

CXA-201 (ceftolozane (**19**; CXA-101, FR264205)/tazobactam (**20**)) is a cephalosporin/β-lactamase inhibitor combination that is being developed by Cubist Pharmaceuticals (Lexington, MA, USA) in phase-III trials for cUTI (NCT01345929) and pyelonephritis (NCT01345955) and in two phase-III trials for cIAI (NCT01445665 and NCT01445678). CXA-201 is administered IV and has activity against Gram-negative bacteria including MDR *Pseudomonas aeruginosa*. Ceftolozane (**19**) is a cephalosporin discovered by Astellas (Tokyo, Japan) with broad-spectrum Gram-negative activity,[135–137] whereas tazobactam (**20**) is a clavulanic acid-type β-lactamase inhibitor first approved in 1992 in combination with piperacillin.[138,139]

CAZ104 (ceftazidime (**21**)/avibactam (**22**; NXL104, AVE1330A)) is a cephalosporin/β-lactamase inhibitor combination[140] that is being assessed by AstraZeneca (London, UK) in three phase-III trials for the treatment of cUTI (NCT01644643, NCT01599806 and NCT01595438). Ceftazidime (**21**) is a third-generation cephalosporin first launched in 1983 with activity against Gram-negative bacteria including the *Enterobacteriaceae* and *P. aeruginosa*.[141] Avibactam (**22**) is a non-β-lactam β-lactamase inhibitor of the DBO class, which displays activity against class A and C serine β-lactamases.[142–144] Avibactam (**22**) was discovered by Hoechst Marion Roussel, which eventually formed part of Sanofi-Aventis (Paris, France). Sanofi-Aventis spun out anti-infective discovery into Novexel in 2004, which was acquired by AstraZeneca (London, UK) in 2010. Avibactam (**22**) is also being evaluated in phase-II and phase-I trials in combination with ceftaroline (**23**; Figure 8) and aztreonam (**24**; Figure 10), respectively.

Phase-II trials

NP and NP-derived compounds in phase-II trials. LFF-571 (**25**) is a semi-synthetic derivative of the thiopeptide GE2270-A being developed by Novartis (Basel, Switzerland) and is currently undergoing phase-II testing for the treatment of moderate CDIs (NCT01232595). LFF-571 (**25**) has broad-spectrum activity against Gram-positive bacteria including anaerobic and aerobic intestinal bacteria[145] and was well tolerated in a phase-I trial.[146] GE2270-A is an actinomycetes-derived antibiotic first described by the Lepetit Research Institute (formally Gerenzano, Italy) in 1991 that inhibited protein synthesis via bacterial elongation factor Tu (EF-Tu). Scientists at Novartis recognized the potential of GE2270-A, leading to the synthesis of the dicarboxy derivative LFF-571 (**25**), which was considerably more soluble than GE2270-A.[147] LFF-571 (**25**) also inhibits bacterial EF-Tu.[148]

Auriclosene (**26**; NVC-422, *N*,*N*-dichloro-2,2-dimethyltaurine) is an *N*-dichlorotaurine analog being evaluated in phase-II trials by NovaBay Pharmaceuticals, Inc. (Emeryville, CA, USA) to prevent urinary catheter blockage and encrustation (NCT01243125), as an ophthalmic solution for the treatment of adenoviral conjunctivitis (NCT01532336) and for the treatment of impetigo in partnership with Galderma SA (Lausanne, Switzerland).[149] Auriclosene (**26**) has also completed a phase-II trial for the treatment of bacteriuria in catheterized patients (NCT00781339). Auriclosene (**26**) was designed to be a more stable derivative of the naturally occurring oxidant *N*-dichlorotaurine;[150–152] the *N*-chloramine antibiotic class has been recently reviewed.[153]

Sarecycline (**27**; P005672, PTK-AR01), a semi-synthetic tetracycline derivative[154,155] discovered by Paratek Pharmaceuticals (Boston, MA, USA) and licensed[156] to Warner Chilcott (Rockaway, NJ, USA) in July 2007, recently completed a phase-II trial for the treatment of facial acne vulgaris (NCT01628549).

BC-3781 (**28**), a semi-synthetic pleuromutilin[157,158] derivative discovered by Nabriva Therapeutics AG (Vienna, Austria), is being developed in collaboration with Forest Laboratories (New York, NY, USA). It completed a phase-II trial for ABSSSi in 2012 (NCT01119105).[159] BC-3781 (**28**) is a protein synthesis inhibitor and displays antibacterial activity against skin and respiratory pathogens such as *S. aureus*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *C. difficile*, *Moraxella catarrhalis*, *Legionella pneumophila* and *Mycoplasma pneumoniae*.[158,160,161]

Plazomicin (**29**; ACHN-490) is a semi-synthetic derivative[162] of the aminoglycoside sisomicin[163,164] developed by Achaogen, Inc. (South San Francisco, CA, USA) that has completed phase-II trials for the treatment of UTI and pyelonephritis (NCT01096849). Plazomicin (**29**) displays excellent activity against methicillin-resistant *S. aureus* (MRSA)[165] and the MDR Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter* spp.[166] Plazomicin (**29**) displayed similar activity against *P. aeruginosa* as amikacin, another semi-synthetic aminoglycoside, but lower than average activity against *Acinetobacter baumannii* compared with other aminoglycosides.[167] The biological activity and spectrum of activity of plazomicin (**29**) has been recently reviewed.[168]

GSK1322322 (**30**), under development by GlaxoSmithKline (GSK; London, UK), has completed a phase-II trial for ABSSSi (NCT01209078) with two further phase-I trials enrolling volunteers (NCT01803399 and NCT01818011). GSK1322322 (**30**) displays promising activity against the Gram-positive pathogens such as *S. aureus*, *S. pneumoniae*, *Streptococcus pyogenes*, as well as against the Gram-negatives *H. influenzae* and *M. catarrhalis*.[169] It targets bacterial peptide deformylase, a metallo-hydrolase enzyme that catalyzes the removal of formyl groups from *N*-terminal methionines following translation.[170] Two previous peptide deformylase inhibitors, BB83698 and LBM-415, reached phase-I but their development was discontinued.[171–174] These compounds were based on the NP lead, actinonin,[175,176] which was identified by virtual searching for NPs that possessed a hydroxamate metal-chelating group and methionine-like structures as potential peptide deformylase inhibitors.[177]

Protein/mammalian peptide-derived compounds in phase-II trials. Brilacidin (**31**; PMX-30063), a membrane targeting arylamide oligomer that was being developed by Polymedix Inc. (Radnor, PA, USA), recently completed a phase-IIa trial for the treatment of ABSSSi (NCT01211470). However, the future development of brilacidin (**31**) is in doubt as Polymedix filed for bankruptcy on 1 April 2013 and there have been reports of possible toxicity concerns.[178] Brilacidin (**31**) is a member of the family of arylamide foldamers that was designed to mimic cationic antimicrobial peptides and had shown bactericidal activity against both Gram-positive and Gram-negative bacteria.[179–181]

LTX-109 (**32**; Lytixar) is another cationic peptide mimic[58] that is being developed by Lytix Biopharma AS (Oslo, Norway) in a phase-II trial for the treatment of impetigo (NCT01803035). LTX-109 (**32**) has completed a phase-II trial for the treatment of uSSSi (NCT01223222) and a phase-I/II trial for nasal decolonization of *S. aureus* including MRSA (NCT01158235). LTX-109 (**32**) is metabolically stable and has rapid bactericidal *in vitro* activity against both Gram-positive and Gram-negative drug-resistant strains.[182] An in-depth study of **32** against a large panel of *S. aureus* strains, including MRSA, vancomycin-intermediate *S. aureus* and vancomycin-resistant *S. aureus*, was reported in 2012.[183]

DPK-060 (CD-1) is an antimicrobial peptide being developed by Pergamum AB (Solna, Sweden) that has completed phase-II trials for the treatment of external otitis (NCT01447017) and atopic dermatitis (NCT01522391). The structure of DPK-060 has not been published but is likely to be a derivative of the antibacterial domain of kininogen.[184–186]

LL-37 (**33**), the C-terminal peptide of the human antimicrobial cathelicidin peptide hCAP-18, is being developed in a phase-I/II trial for the wound healing in chronic leg ulcers by Pergamum AB (Solna, Sweden).[187] Although cathelicidins have been identified in a variety of species, hCAP-18 is the only human cathelicidin and consists of a 30-amino-acid signal peptide domain, a 103-amino-acid cathelicidin domain and a 37-amino-acid C-terminal peptide designated as LL-37.[188,189] LL-37 (**33**) has broad-spectrum antibacterial activity[190] and kills bacteria through membrane disruption.[191] Interestingly, LL-37 (**33**) displayed equipotent activity with its enantiomer D-LL-37, which suggested a nonspecific mode of action, whereas a structure activity relationship study showed that antibacterial activity can be retained down to 19 residues.[192]

IMX-942 is a five-amino-acid synthetic cationic peptide loosely based on indolicidin, which is derived from bovine neutrophils,[193] and the synthetic peptide innate defense regulator-1.[194,195] Inimex Pharmaceuticals, Inc. (Coquitlam, BC, Canada)[196] is evaluating IMX-942 in a phase-II clinical trial in combination with a standard antibiotic therapy with severe ABSSSi to investigate whether this combination can shorten clearance time of the bacterial infection in these patients.[197] Although the structure and mode of action of IMX-942 has not been published, the anti-inflammatory mode of action of innate defense regulator-1 is via sequestosome-1/p62.[195]

Synthetic compounds in phase-II trials. PA-824 (**34**) is a nitroimidazole derivative being tested by the Global Alliance for TB Drug Development (New York, NY, USA) in phase-II trials in combination with other TB drugs (NCT01691534 and NCT01498419). PA-824 (**34**) was originally synthesized by PathoGenesis Corporation (acquired by Chiron in 2002, who in turn were acquired by Novartis (Basel, Switzerland) in 2006) as an analog of the TB-lead CGI-17341, which was found to be too toxic for further development.[198] The mode of action of PA-824 (**34**) is complex but under anaerobic conditions **34** is reductively activated by a deazaflavin-dependent nitroreductase and then acts as a nitric oxide donor in a similar manner to delamanid (**10**, phase-III section, Figure 4).[199,200]

There are currently three oxazolidinones[45,93,201] that have been studied in phase-II trials: radezolid (**35**), sutezolid (**36**) and posizolid (**37**). Radezolid (**35**; RX-1741)[202–205] has completed phase-II studies for the treatment of both cSSSi (NCT00646958) and CAP (NCT00640926) and is similar in structure to tedizolid phosphate (**9a**), which has completed phase-III studies. Radezolid (**35**) has activity against Gram-positive bacteria including those with resistance to linezolid, as well activity against some Gram-negatives such as *H. influenzae* and *M. catarrhalis*,[206] and was rationally designed from the overlap of sparsomycin- and linezolid-binding sites on the 50S ribosomal subunit.[202,203,207]

Sutezolid (**36**; PNU-100480, PF-02341272) is being developed by Pfizer (Groton, CT, USA) and recently completed a phase-IIa trial looking for EBA in naive patients with drug-sensitive pulmonary TB (NCT01225640). Sutezolid (**36**) was discovered at Upjohn (now part of Pfizer) and its structure optimized for activity against TB.[208] Sutezolid (**36**) displays promising *in vitro* and *in vivo* activity against TB,[209,210] and was well tolerated in phase-I trials.[211,212]

Posizolid (**37**; AZD5847, AZD2563) is an oxazolidinone developed by AstraZeneca (London, UK) that the NIAID is sponsoring in a phase-IIa trial for EBA with newly diagnosed pulmonary TB patients (NCT01516203). Posizolid (**37**) was originally developed as a broad-spectrum Gram-positive antibiotic[213,214] and was later found to have activity against TB.[215]

Cadazolid (**38**; ACT-179811) is a quinolonyl-oxazolidinone chimeric antibiotic being developed by Actelion Pharmaceuticals (Basel, Switzerland) that successfully completed a phase-II trial for the treatment of patients with CDI (NCT01222702) in 2013. Actelion recently announced plans to commence phase-III trials.[216] Cadazolid (**38**) is a potent inhibitor of *C. difficile* protein synthesis, leading to strong suppression of toxin and spore formation.[217,218]

AFN-1252 (**39**) is being developed by Affinium Pharmaceuticals (Austin, TX, USA) and successfully completed a phase-IIa trial (NCT01519492) as an oral formulation for the treatment of staphylococcal infections in 2012. AFN-1252 (**39**) disrupts fatty acid biosynthesis by inhibiting staphylococcal FabI,[219,220] an essential enzyme that catalyzes the reduction of *trans*-2-enoyl-ACP to acyl-ACP in the final step of the fatty acid elongation cycle.[221,222] AFN-1252 (**39**) is a synthetically derived antibiotic elaborated from a benzodiazepine hit initially identified at GSK (London, UK) using a high-throughput screen looking for inhibitors of *S. aureus* FabI.[29,223] Structure optimization using X-ray crystal structure-based design led to the identification of a 3,4-dihydro-1,8-naphthyridin-2(1*H*)-one core, which had selective, potent activity against FabI, and good *in vitro* and *in vivo* antibacterial activity with no significant cytotoxicity.[223] In 2002, GSK licensed this discovery to Affinium who undertook further structure optimization that culminated in the discovery of AFN-1252 (**39**).[224,225]

CG400549 (**40**) is being developed by CrystalGenomics, Inc. (Seoul, South Korea) and recently successfully completed a phase-IIa trial for the treatment of ABSSSi caused by MRSA (NCT01593761). CG400549 (**40**)[226–229] is another FabI inhibitor, derived from the topical biocide triclosan, a broad-spectrum antibiotic used in cleaning and personal care products first launched in the early 1970s.[230]

The fluoroquinolone WCK-771, which is the arginine salt of *S*-(−)-nadifloxacin (**41**), and its pro-drug WCK-2349 (structure not published) are undergoing testing in phase-II trials by Wockhardt Limited (Mumbai, India). Nadifloxacin is a racemic fluoroquinolone launched as a topical antibiotic in Japan in 1993 to treat acne and methicillin-resistant staphylococcal infections.[231] Scientists at Wockhardt discovered that the *S* enantiomer of nadifloxacin, WCK-771 (**41**), was more active than the racemic mixture and had pharmacokinetic properties amenable for systemic use.[231–234]

β-*Lactam*/β-*lactamase inhibitor combinations in phase-II trials.* CXL (ceftaroline (**23**)/avibactam (**22**; NXL104)) is being developed by AstraZeneca (London, UK) in a phase-II trial for the treatment of MRSA.[235] Avibactam (**22**) is a DBO-type β-lactamase inhibitor

described in detail earlier in the phase-III section, whereas ceftaroline fosamil (**23**) is a cephalosporin approved in 2010 for the treatment of CABP and ABSSSi.[236] The CXL combination has activity against Enterobacteriaceae with class A and C β-lactamases and MRSA.[133,237,238]

A combination therapy of imipenem (**42**), cilastatin (**43**) and MK-7655 (**44**) is being developed by Merck (Rahway, NJ, USA) and is being evaluated in phase-II trials for UTI (NCT01505634) and cIAI (NCT01506271). MK-7655 (**44**) is a DBO β-lactamase inhibitor related to avibactam (**22**),[239] whereas imipenem (**42**) is a carbapenem first launched in 1987 that needs to be co-administered with the dehydropeptidase inhibitor cilastatin (**43**) in order to slow down the metabolism of imipenem.[240] The imipenem (**42**) and MK-7655 (**44**) combination therapy displays *in vitro* activity against carbapenem-resistant Gram-negative bacteria.[241]

Phase-I trials

NP and NP-derived compounds in phase-I trials. BAL30072 (**45**)[242–244] is a monobactam derivative with an iron-chelating dihydroxypyridone moiety that is being tested by Basilea Pharmaceutica (Basel, Switzerland) in phase-I trials. BAL30072 (**45**) displays activity against many Gram-negative bacteria[242] including *P. aeruginosa*,[245] *A. baumannii*[246,247] and *Burkholderia pseudomallei*[248] and is rapidly absorbed into bacteria via the essential iron uptake systems.[242,245]

Exeporfinium chloride (**46**; XF-73) is a porphyrin derivative being developed by Destiny Pharma (Brighton, UK) that is being investigated in collaboration with the NIAID in a phase-I trial as an intranasal gel formulation for the nasal decolonization of *S. aureus* (NCT01592214). XF-73 (**46**) has successfully completed three phase-I/IIa trials in the United Kingdom[249] and has broad-spectrum Gram-positive activity,[250–254] as well as activity against the fungus *Candida albicans*.[255]

NVB302 (**47**) is a semi-synthetic aminoheptylamido derivative[256,257] of the new Type B lantibiotic deoxyactagardine B being developed by Novacta Biosystems Limited (Welwyn Garden City, UK) in collaboration with the Wellcome Trust (London, UK) that has completed a phase-I trial as a treatment for CDI.[258] Deoxyactagardine B is produced by *Actinoplanes liguriae* NCIMB41362 and its biosynthetic cluster has been characterized.[259] NVB302 (**47**) has displayed activity in an *in vitro C. difficile* gut model.[260] Like other related lantibiotics,[261] NVB302 (**47**) exerts its antibacterial activity through binding to the cell wall peptidoglycan precursor lipid II.

S-649266 (GSK-2696266) is a cephem derivative from Shionogi & Co., Ltd (Osaka, Japan) being co-developed with GSK (London, UK) that is in phase-I.[262–264] The structure has not been publically released. [262,263]

Protein/large peptide-derived compounds in phase-I trials. POL7080 is a synthetic cyclic peptide based on protegrin I, which was first isolated from porcine leucocytes.[265] Developed by Polyphor Ltd (Basel, Switzerland), POL7080 has successfully completed a phase-I trial.[266,267] POL7080 has potent and selective antimicrobial activity against Gram-negative bacteria including *P. aeruginosa* and has a novel mode of action through targeting the β-barrel protein LptD (Imp/OstA), which is involved in the outer-membrane biogenesis of LPS.[267,268]

Synthetic compounds in phase-I trials. There are two oxazolidinones, LCB01-0371 (**48**) and MRX-I (**49**), in phase-I trials. LCB01-0371 (**48**)[269] belongs to LegoChem Biosciences, Inc. (Daejeon, South Korea) and is currently being investigated in one phase-I trial (NCT01842516) and has recently completed another phase-I trial (NCT01554995). MRX-I (**49**)[270] is being developed by MicuRx (Hayward, CA, USA, and Shanghai, China) and completed a phase-I trial in April 2012.[271]

SMT-19969 is a synthetic compound[272] from Summit Corporation PLC (Oxford, UK) that is being developed for the treatment of CDI in collaboration with the Wellcome Trust (London, UK). It recently completed a phase-I study[273] that showed SMT 19969 was well tolerated at therapeutically relevant doses and was highly sparing of gut flora with only the clostridia bacterial family being reduced to levels below the limit of detection.[273] The Wellcome Trust has awarded Summit an additional Translational Award for further development.[273]

ACHN-975 is an LpxC (UDP-3-*O*-(3*R*)-hydroxymyristoyl)-*N*-acetylglucosamine deacetylase) inhibitor[274] being developed by Achaogen, Inc. (South San Francisco, CA, USA) that has completed one phase-1 trial (NCT01597947) and recently started another phase-I trial (NCT01870245). LpxC is an essential zinc-dependent metalloamidase involved in the biosynthesis of lipid A, the subunit of LPS that anchors the LPS to a phospholipid layer to form the outer membrane of Gram-negative bacteria.[275,276] ACHN-975 has broad-spectrum activity against Gram-negative bacteria including MDR *P. aeruginosa*, MDR *E. coli* and *Yersinia pestis* (the cause of the Black Death plague and a potential biological warfare agent).[277]

GSK-2140944 is a bacterial type II topoisomerase inhibitor being investigated by GSK (London, UK) in two phase-I clinical trials (NCT01706315 and NCT01615796). There is no further information available about GSK-2140944.[264]

KPI-10 (**50**; WQ-3813) is a fluoroquinolone discovered by Wakunaga Pharmaceutical Co., Ltd. (Osaka, Japan) being developed by Kalidex Pharmaceuticals, Inc. (Menlo Park, CA, USA). It has completed a phase-I trial.[278,279]

Daiichi-Sankyo (Tokyo, Japan) is investigating DS-8587 (**51**), another fluoroquinolone, in a phase-I trial.[280] DS-8587 (**51**) is less affected by efflux pumps and induces a lower frequency of single-step mutations compared with ciprofloxacin, and has potential as a treatment for *A. baumannii* infections.[281]

AM1977X (oral agent) and KRP-AM1977Y (IV agent) are quinolones that are being developed by Kyorin Pharmaceutical Co., Ltd (Tokyo, Japan) and are currently in phase-I trials.[282]

β-Lactam/β-lactamase inhibitor combinations in phase-I trials. ATM-AVI is a combination[283] of aztreonam (**24**), a monobactam first launched in 1984, and avibactam (**22**; NXL104), a DBO β-lactamase inhibitor previously discussed in the phase-II and -III sections, being developed by AstraZeneca (London, UK). ATM-AVI was being evaluated in a phase-I trial (NCT01689207) but the study was recently suspended because of poor participant recruitment.

Carbavance™ is a combination of biapenem (**52**; RPX2003), a carbapenem first launched in Japan in 2001, and RPX7009 (**53**), a novel boron-containing β-lactamase inhibitor,[284] being developed by Rempex Pharmaceuticals (San Diego, CA, USA). Carbavance has completed one phase-I trial (NCT01702649) and is being evaluated in two other phase-I trials (NCT01751269 and NCT01772836). The combination is active against β-lactamase containing Gram-negative bacteria including *K. pneumoniae* carbapenemase.[285]

COMPOUNDS DISCONTINUED FROM CLINICAL DEVELOPMENT

Compounds that have been discontinued from clinical development since the 2011 review[2] are listed in Table 5 along with the reasons for their discontinuation.

ANALYSIS OF COMPOUNDS UNDERGOING CLINICAL TRIALS

Numbers of compounds undergoing clinical evaluation and their source derivation

There are a total of 49 compounds and 6 β-lactam/β-lactamase inhibitor combinations currently undergoing clinical trials (Figure 11). There is 1 compound being evaluated in a NDA/MAA (Table 2), 15 compounds in phase-III (Table 2), 20 compounds in phase-II (Table 3) and 13 compounds in phase-I (Table 4), with two β-lactam/β-lactamase inhibitor combinations in each of phase-I, -II and -III (Tables 2–4). Twenty-five antibiotics are synthetically derived (S), sixteen NP-derived (NP), six protein/mammalian peptide-derived (P) and two compounds are of unknown derivation. The distribution between NP-, P- and S-derived compounds is relatively similar in phase-I and -II, as was observed in 2011.[2] The number of synthetic compounds (nine) in phase-III and NDA/MAA has now surpassed the NP-derived compounds (six), which is in contrast to 2011 when the NP-derived compounds dominated the synthetic compounds five to one.[2] There are 10 more compounds undergoing phase-III and NDA/MAA evaluation in 2013 compared with 2011 (Figure 12) and this is due to a surge in recent trials starting for both the NP-derived (eravacycline (**6**), solithromycin (**7**) and surotomycin (**8**)) and S-derived compounds (delamanid (**10**), perchlozone (**11**), SQ109 (**12**), finafloxacin (**13**), delafloxacin (**14**), avarofloxacin (**15**), zabofloxacin (**16**), nemonoxacin (**17**) and ozenoxacin (**18**)). It is striking that the number of compounds across phase-I/II/III is relatively constant, compared with the normal 'pyramid' seen in other therapeutic areas. This may reflect a low attrition rate for antibiotics progressing through phase-I to -III trials, but is more likely to be representative of the lack of new antibiotics entering the pipeline over the past decade. With only 13 compounds and 2 β-lactam/β-lactamase inhibitor combinations currently in phase-I, the number of compounds in phase-III in 5 years does not look promising.

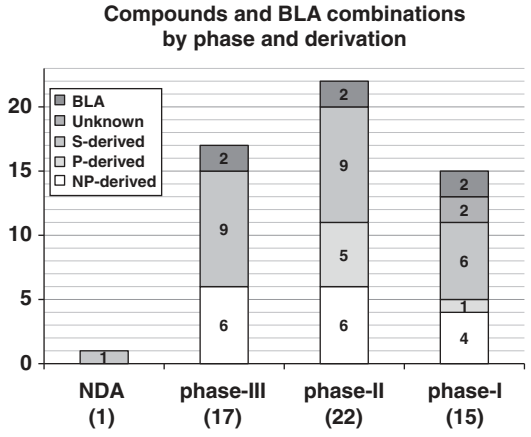


Figure 11 Compounds under clinical evaluation divided into development phases and their lead derivation source (natural product (NP), synthetic (S), protein/peptide (P)) with the β-lactam/β-lactamase inhibitor (BLA) combinations listed separately.

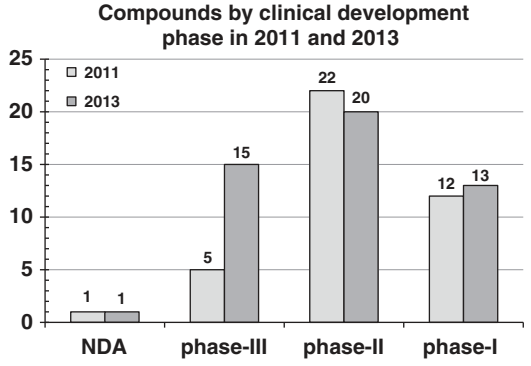


Figure 12 Comparison of the numbers of compounds undergoing clinical development between in 2011 and 2013 by development phase. NDA, New Drug Application.

New antibacterial template analysis

The NP- and P-derived compound derivations are quite diverse but there are only five new antibacterial templates derived from NPs, whereas there are six from protein/mammalian peptide (P) templates (Figure 13). The new NP templates are derived from thiopeptide (LFF-571 (**25**)/GE2270-A), *N*-chlorotaurine (auriclosene (**26**)/*N*-chlorotaurine), actinonin (GSK1322322 (**30**)/actinonin), porphyrin (exeporfinium (**46**)/porphyrin) and type B lantibiotic (NVB302 (**47**)/deoxyactagardine B). Deoxyactagardine B is the only recently discovered lead compound but is an analog of a previously discovered lantibiotic.[260] Although there are no new NP-derived templates currently in late-stage development, the new template NP fidaxomicin (**1**) was launched in 2011 (Table 1). The newly created subclass of natural occurring protein/mammalian peptide leads introduced into this review accounts for six new antibacterial templates with all of the compounds (brilacidin (**31**), LTX-109 (**32**), DPK-060, LL-37 (**33**), IMX-942, POL7080) derived from or inspired by naturally occurring cationic peptides. NPs have traditionally been the main source of most new antibiotic drug leads and further investment in NP drug discovery may help reinvigorate the antibiotic field.[24,286–288]

Similarly, the new synthetically derived antibacterial templates are diverse: perchlozone (**11**; thiosemicarbazone), cadazolid (**38**; oxazolidinone and quinolone chimera), AFN-1252 (**39**; benzodiazepine), CG400549 (**40**; triclosan) and SMT-19969 (bibenzo[*d*]imidazole). The derivation of ACHN-975 has not been published but it is likely to be a new template, whereas the lead for GSK-214094 has not been published.

There are three new β-lactamase inhibitors with two new templates: avibactam (**22**) and MK-7655 (**44**) from the DBO class and RPX7009 (**53**) from the boron class. Both have been classified as synthetically derived but are inspired by the NP clavulanic acid, which was the first β-lactamase inhibitor reported.[130,131]

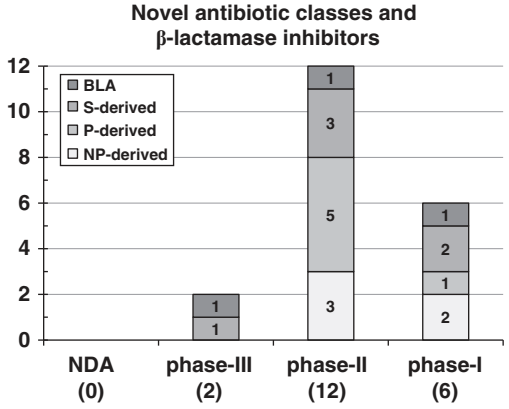


Figure 13 Compounds and β-lactamase (BLA) inhibitors with new antibacterial templates divided into development phases and their lead derivation source. NDA, New Drug Application; NP, natural product; P, protein/peptide; S, synthetic.

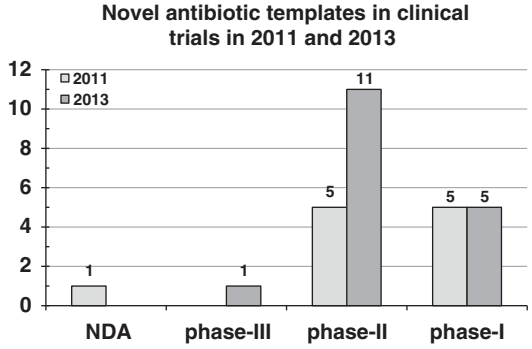


Figure 14 Comparison of the numbers of novel antibacterial templates undergoing clinical development in 2011 or 2013 by development phase. NDA, New Drug Application.

The total number of new templates has risen from 11 in 2011 to 17 in 2013 (Figure 14), which is predominantly due to the increase in protein/peptide (P)-derived cationic antimicrobial peptides undergoing clinical evaluation. Since 2011, three compounds with new antibacterial templates, GSK-2251052, ramoplanin and lotilibcin (Table 5), are not currently being actively pursued.

CONCLUSION AND FUTURE OUTLOOK

These are challenging, but exciting times for antibiotic research. Around 5 years ago the FDA changed the regulatory framework of phase-III clinical trials, which resulted in a re-evaluation of many late-stage clinical programs and the demise of many antibiotic-focused biotech companies. These uncertainties, along with the costs of these large late-stage trials and comparably poor returns, were a contributing factor in the exodus of many large companies from antibiotic research. However, there is now hope on the horizon with the FDA and companies starting to agree on feasible clinical trial designs. There has been an upsurge in recently initiated phase-III trials, and a push for more innovative ways to discover, develop and register new antibiotics. The EU's EMA has been slightly ahead of the FDA and has publically recognized the need for new antibiotics and the issues holding back antibiotic development. However, the FDA has just released new draft guidelines that address many of these pressing issues.[289] Another advance has been the advent of public–private partnerships in the development of TB drugs. A partnership between Tibotec (Beerse, Belgium) and the Global Alliance for TB Drug Development (New York, NY, USA) culminated in the December 2012 approval of bedaquiline (**2**) for the treatment of TB, which was the first new TB treatment launched for over 40 years. There are six other potential TB drugs in clinical development, delamanid (**10**; NDA, phase-III), perchlozone (**11**; complete phase-II/III), SQ109 (**12**; phase-III), PA-824 (**34**; phase-II), sutezolid (**36**) and posizolid (**37**) and a number of others in pre-clinical development.[290] The Wellcome Trust (London, UK) has also been supporting antibiotic research and has been helping to fund the clinical trials of two compounds, NVB302 (**47**) and SMT-19969, for the treatment of CDIs. The US government organizations, BARDA and NIAID, have provided additional support for clinical development programs.

Although there has been a slow but steady stream of new compounds entering the clinical pipeline, the difficulty of finding a truly novel antibacterial cannot be overstated. As noted in our previous review[2] and by others,[20,25,26,291] this is especially the case for Gram-negative bacteria where there is a dearth of new antibiotics to treat these bacteria. Other than the quinolones, which already have resistance issues, the only other compounds in development with activity against Gram-negative bacteria are the topically administered *N*-chlorotaurine mimic auriclosene (**26**), the systematically administered aminoglycoside plazomicin (**28**), the peptide deformylase inhibitor GSK1322322 (**30**), the monobactam-siderophore hybrid BAL30072 (**45**), the cationic peptide POL7080 and the LpxC inhibitor ACHN-975. Importantly, the six β-lactamase inhibitor/β-lactam combination therapies in clinical trials have activity against Gram-negative bacteria and will significantly bolster the antibiotic armamentarium if approved.

The real and extremely serious threat of totally antibiotic-resistant bacteria is starting to capture the attention of the public and policy makers. Although the challenges of antibiotic drug discovery are great, there is a dedicated group of researchers actively trying to identify the next generation antibiotics to treat these superbugs. It is imperative that we continue to search for new antibacterial drugs through innovative screening methods of both synthetic and NP libraries and undertake rational drug design from the advances afforded by protein crystal structures.

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