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REVIEW ARTICLE

Antibiotics in the clinical pipeline at the end of 2015

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There is growing global recognition that the continued emergence of multidrug-resistant bacteria poses a serious threat to human health. Action plans released by the World Health Organization and governments of the UK and USA in particular recognize that discovering new antibiotics, particularly those with new modes of action, is one essential element required to avert future catastrophic pandemics. This review lists the 30 antibiotics and two β-lactamase/β-lactam combinations first launched since 2000, and analyzes in depth seven new antibiotics and two new β-lactam/β-lactamase inhibitor combinations launched since 2013. The development status, mode of action, spectra of activity and genesis (natural product, natural product-derived, synthetic or protein/mammalian peptide) of the 37 compounds and six β-lactamase/β-lactam combinations being evaluated in clinical trials between 2013 and 2015 are discussed. Compounds discontinued from clinical development since 2013 and new antibacterial pharmacophores are also reviewed.
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INTRODUCTION

Antibiotics cure disease and save lives. No other class of drugs has so cheaply and effectively prevented death from life-threatening illnesses for over 70 years. Unfortunately, antibiotics are dramatically undervalued by society, receiving a fraction of the yearly revenue per patient generated by next-generation anticancer drugs. It is well documented that antibiotics are becoming an 'endangered species', with older antibiotics rendered impotent by the rise of multidrug-resistant bacteria, and new antibiotics a scarce commodity due to the exit of most major pharmaceutical companies from antibiotic research.[1] Fortunately, since our previous reviews,[2,3] there has been a significant shift in government and public recognition of the potential threat posed by the loss of effective therapies to treat bacterial infections, with well-publicized reports from the World Health Organization,[4,5] and national governments of countries including the UK,[6–8] the USA,[9–13] Canada[14,15] and Australia,[16] among others. Government agencies are incorporating the threat of antibiotic resistance into natural disaster planning scenarios.[17]

A range of reviews and discussions on the antibiotic crisis were published over the past two years. These include articles on the antibiotic crisis[18–22] and possible solutions,[23,24] sources of resistance,[25] surveillance of resistance,[26] restricting non-medical antibiotic use,[27] antibiotic resistance in livestock and the environment,[28,29] possible approaches to address R&D and commercialization challenges,[30–32] difficulties in discovering new antibiotics,[33] development of new antibiotics,[34–36] reviews of therapeutic strategies[37] and new approaches to discover novel antimicrobials[38,39] to combat antibiotic resistance.

This review is an update of our 2011[2] and 2013[3] reviews and details antibiotics launched recently (Table 1; Figures 1–3), as well as the 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)) of antibiotics and β-lactam/β-lactamase inhibitor combinations undergoing clinical development (phase-I, -II or -III trials and regulatory evaluation) as of December 2015 (Tables 2–5; Figures 2–10). Compounds for which no development activity has been reported since our 2013 review[3] are listed in Table 6. The ClinicalTrials.gov NCT codes are listed in parentheses for each trial and trials not in this database are referenced. New trials of approved drugs including new formulations are not discussed in this review. Data in this review were obtained by analyzing the journal literature and internet resources such as company web pages, clinical trial registers and biotechnology-related newsletters. Although every effort has been undertaken to ensure that this data is accurate, it is possible compounds undergoing early clinical development with limited information in the public domain have been overlooked. An overview of the drug development and approval process, antibiotic clinical trial categories and abbreviations are found in the Supplementary Information.

ANTIBACTERIAL DRUGS LAUNCHED SINCE 2000

Since 2000, 30 new antibiotics (two NP, 12 NP-derived and 16 synthetic-derived) and two new β-lactam/β-lactamase inhibitor combinations have been launched worldwide (Table 1). Of the 30 new antibiotics, five were first-in-class antibiotics: linezolid (oxazolidinone, S, 2000), daptomycin (lipopeptide, NP, 2003), retapamulin (pleuromutilin, NP-derived, 2007), fidaxomicin (tiacumicin, NP, 2011) and bedaquiline (diarylquinoline, S, 2012). Importantly, these five new antibiotic classes only target Gram-positive (G+ve) bacteria, which reiterate the importance of identifying new

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Table 1 Antibiotics and β-lactamase inhibitor combinations launched from 2000 to 2015, their antibiotic class, activity spectra, country of first approval, lead source and NP lead source if applicable

Year approved	*Drug name*[a,b]	*Class*	*Bacteria type*	*Country of first approval*	*Lead source*	*NP lead source*
2000	Linezolid	Oxazolidinone	G+ve	USA	S	
2001	Telithromycin	Macrolide	G+ve/G – ve	Germany	NP-derived	Actinomycete
2002	Biapenem	Carbapenem	G+ve/G – ve	Japan	NP-derived	Actinomycete
2002	Ertapenem	Carbapenem	G+ve/G – ve	USA	NP-derived	Actinomycete
2002	Prulifloxacin	Fluoroquinolone	G+ve/G – ve	Japan	S	
2002	Pazufloxacin	Fluoroquinolone	G+ve/G – ve	Japan	S	
2002	Balofloxacin	Fluoroquinolone	G+ve/G – ve	South Korea	S	
2003	Daptomycin[b]	Lipopeptide	G+ve	USA	NP	Actinomycete
2004	Gemifloxacin	Fluoroquinolone	G+ve/G – ve	USA	S	
2005	Doripenem	Carbapenem	G+ve/G – ve	Japan	NP-derived	Actinomycete
2005	Tigecycline	Tetracycline	G+ve/G – ve	USA	NP-derived	Actinomycete
2007	Retapamulin[b,c,d]	Pleuromutilin	G+ve	USA	NP-derived	Fungus
2007	Garenoxacin	Quinolone	G+ve/G – ve	Japan	S	
2008	Ceftobiprole medocaril	Cephalosporin	G+ve/G – ve	Canada	NP-derived	Fungus
2008	Sitafloxacin	Fluoroquinolone	G+ve/G – ve	Japan	S	
2009	Tebipenem pivoxil	Carbapenem	G+ve/G – ve	Japan	NP-derived	Actinomycete
2009	Telavancin	Glycopeptide	G+ve	USA	NP-derived	Actinomycete
2009	Antofloxacin	Fluoroquinolone	G+ve/G – ve	China	S	
2009	Besifloxacin[d]	Fluoroquinolone	G+ve/G – ve	USA	S	
2010	Ceftaroline fosamil	Cephalosporin	G+ve/G – ve	USA	NP-derived	Fungus
2011	Fidaxomicin[b]	Tiacumicin	G+ve	USA	NP	Actinomycete
2012	Bedaquiline[b]	Diarylquinoline	G+ve (TB)	USA	S	
2012	Perchlozone (**1**)	Thiosemicarbazone	G+ve (TB)	Russia	S	
2014	Delamanid (**2**)	Nitroimidazole	G+ve (TB)	Europe	S	
2014	Dalbavancin (**3**)	Glycopeptide	G+ve	USA	NP-derived	Actinomycete
2014	Oritavancin (**4**)	Glycopeptide	G+ve	USA	NP-derived	Actinomycete
2014	Tedizolid phosphate (**5**)	Oxazolidinone	G+ve/G – ve	USA	S	
2014	Ceftolozane (**6**)+tazobactam[e] (**7**)	β-Lactam+β-lactamase inhibitor	G – ve	USA	NP-derived/NP-derived	Fungus/actinomycete
2014	Nemonoxacin (**8**)	Quinolone	G+ve/G – ve	Taiwan	S	
2014	Finafloxacin[d] (**9**)	Fluoroquinolone	G+ve/G – ve	USA	S	
2015	Ceftazidime[e] (**10**)+avibactam[b] (**11**)	β-Lactam+DBO β-lactamase inhibitor	G – ve	USA	NP-derived/S	Fungus
2015	Ozenoxacin (**12**)[d]	Quinolone	G+ve	Japan	S	

Abbreviations: G – ve, Gram negative; G+ve, Gram positive; NP, natural product; S, synthetic; TB, tuberculosis, USA, United States of America.
[a]The structures of the antibiotics approved from 2000 to 2012 can be found in our previous reviews.[2,3]
[b]First member of a new antibiotic or β-lactamase inhibitor class approved for human therapeutic use.
[c]Pleuromutilin derivatives have been previously used in animal health.
[d]Approved for topical use.
[e]Tazobactam and ceftazidime were first launched in 1992 and 1983, respectively.

antibiotic classes with Gram-negative (G – ve) activity. There was one new diazabicyclooctane (DBO)-type β-lactamase inhibitor (avibactam, S, 2015), which when used in combination with selected β-lactams also displays activity against G – ve bacteria.

There has been a steady launch of antibiotics since 2000, averaging three approvals every two years (Figure 1), with a notable spike of seven approvals in 2014. Of the 16 synthetically-derived new antibiotics, eleven were quinolones, two were oxazolidinones, and the remainders were single examples of the nitroimidazole, thiosemicarbazone and diarylquinoline classes. The β-lactam and glycopeptide classes accounted for six and three of the two NP and 12 NP-derived antibiotics respectively with the other five belonging to separate classes.

Since the last review,[3] seven new antibiotics and two new β-lactam/β-lactamase inhibitor combinations (Figure 2) have been approved. These are discussed in detail below, along with perchlozone (**1**) that was approved in Russia in late 2012.

Thioureidoiminomethylpyridinium perchlorate (**1**) (Perchlozone) is an oral treatment developed by JSC Pharmasyntez (Moscow, Russia) and approved in Russia in 2012 for the treatment of multidrug-resistant tuberculosis. Perchlozone (**1**) was synthesized[40] at the Siberian Division of the Russian Academy of Sciences (Novosibirsk, Russia) and is the perchlorate salt of thioureidoiminomethylpyridine, which was first reported in the early 1950s.[41,42] Perchlozone (**1**) is an analog of thiacetazone (**13**), a tuberculosis (TB) drug developed in the 1950s that fell out of favor due to adverse side effects.[43] A recent study has proposed that **1** and thiacetazone (**13**) share a common mode of action: activation by the monooxygenase EthA and inhibition of the FASII dehydratase complex HadABC leading to disruption of mycolic acid biosynthesis.[44]

Delamanid (**2**) (Deltyba, OPC-67683) was developed by the Otsuka Pharmaceutical Co. (Tokyo, Japan) and was approved in Europe and Japan in April and July 2014 respectively as part of an appropriate combination regimen in adult patients with pulmonary multidrug-resistant (MDR)-TB on the basis of phase-IIb data.[45,46] Delamanid (**2**) is currently being evaluated in a phase-III trial for the treatment of multidrug-resistant TB in combination with other TB and retroviral drugs over six months (NCT01424670). Delamanid (**2**)[47,48] is derived

from the anti-TB lead, bicyclic nitroimidazole CGI-17341,[49,50] which was dropped from development due to mutagenicity concerns. Delamanid (**2**) is a prodrug that is reductively activated by a deazaflavin (F_{420}) dependent nitroreductase and inhibits mycobacterial growth through inhibition of mycolic acid biosynthesis.[50]

Dalbavancin (**3**) (Dalvance, Xydalba, BI-397) is one of two new glycopeptides that received FDA approval in 2014 after decades of development.[51–53] It is a semi-synthetic lipopeptide analog of the teicoplanin-like glycopeptide A40926 Factor B, modified by amidation of the C-terminal acid group with *N*,*N*-dimethyl-1,3-diaminopropane. Originally developed at the Lepitit Research Centre of Marion Merrell Dow, it passed through the hands of Hoechst, Biosearch Italia S.p.A, Vicuron Pharmaceuticals, Pfizer (Groton, CT, USA), and finally Durata Therapeutics, who acquired the program in 2009. Durata conducted the final phase-III trials for acute bacterial skin and skin structure infections (ABSSSI) that led to FDA approval in May 2014 for treatment of G+ve ABSSI infections in adult patients caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysagalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*) and *E. faecalis* (vancomycin-susceptible strains). Durata was acquired by Actavis in November 2014, and Actavis by Allergan, plc (Dublin, Ireland) in March 2015. Dalbavancin (**3**) has an extended half-life of over 300 h in humans,[54] allowing for a significant dosing advantage over the twice-daily dosing required for vancomycin. The current prescribing information (Jan 2016) provides for two dosage regimes with different doses depending on renal function: if estimated creatinine clearance (CrCl) is $\geqslant 30$ ml min^{-1} (or on hemodialysis) then a single dose of 1500 mg or a two-dose regimen of 1000 mg followed by 500 mg is recommended. If CrCl is <30 ml min^{-1}, then either a single dose of 1125 or a two-dose regimen of 750 mg followed by 375 mg is recommended. The EU Commission granted marketing authorization for dalbavancin (**3**) in March 2015, with its commercialization partnered with Angelini (Rome, Italy).[55] In October 2015 Allergan filed a supplemental New Drug Application to expand the label to include a single 1500 mg dose administration,[56] based on a phase-III trial in 698 patients (NCT02127970).[57] Like other glycopeptides, dalbavancin (**3**) blocks peptidoglycan synthesis by binding to the precursor Lipid II, though additional mechanisms are proposed to help account for its increased potency.[52,58]

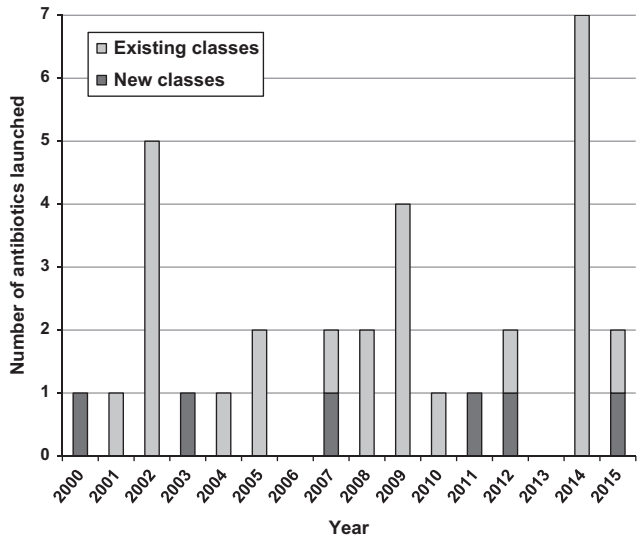

Figure 1 New antibiotic approvals 2000–2015 with new classes highlighted.

Oritavancin (**4**) (Orbactiv, LY333328), the second glycopeptide achieving US Food and Drug Administration (FDA) approval in 2014, also navigated a tortuous route to market: initial development by Eli Lilly (Indianapolis, IN, USA) in the 1990s was followed by ownership by InterMune, Inc. (Brisbane, CA, USA), Targanta Therapeutics, and The Medicines Company (Parsippany, NJ, USA), who completed two additional phase-III trials and achieved FDA approval in August 2014.[59] Oritavancin (**4**) is a semi-synthetic derivative of the vancomycin-like glycopeptide chloroeremomycin, which is alkylated on the vancosamine amine with a hydrophobic chlorophenyl-benzyl moiety. Compared to vancomycin it also possesses an additional aminosugar substituent. Like dalbavancin (**3**), an extended >300 h

Table 2 Antibiotics in phase-III clinical trials

Name (synonym)[a]	*Compound class (lead source)*	*Mode of action*	*Bacteria type*	*Indication (developer)*
Solithromycin (**14**)	Erythromycin (NP)	Protein synthesis inhibition	G+ve/G – ve	CABP (Cempra)
Omadacycline (**15**)	Tetracycline (NP)	Protein synthesis inhibition	G+ve/G – ve	ABSSSI (Paratek)
Sarecycline (**16**)	Tetracycline (NP)	Protein synthesis inhibition	G+ve	Acne/rosacea (Allergen)
Eravacycline (**17**)	Tetracycline (NP)	Protein synthesis inhibition	G+ve/G – ve	cIAI (Tetraphase)
Surotomycin (**18**)	Lipopeptide (daptomycin) (NP)	Membrane depolarization	G+ve	CDAD (Merck)
Plazomicin (**19**)	Aminoglycoside (NP)	Protein synthesis inhibition	G+ve/G – ve	cUTI and pyelonephritis (Achaogen)
Cefilavancin (**20**)	Cephalosporin (NP)/vancomycin (NP) heterodimer	Cell wall biosynthesis	G+ve	G+ve (R-Pharm/Theravance Biopharma)
SQ 109 (**21**)	Ethambutol (S)	Cell wall synthesis	G+ve (TB) /G – ve	TB (Infectex/Sequella)
Cadazolid (**22**)	Oxazolidinone (S)/quinolone (S) hybrid	Protein synthesis inhibition/DNA gyrase and topoisomerase IV	G+ve	CDAD (Actelion)
Pretomanid (**23**)	Nitroimidazole (S)	DNA and cellular damage	G+ve (TB)	TB (Global Alliance for TB Drug Development)
Delafloxacin (**24**)	Fluoroquinolone (S)	DNA gyrase and topoisomerase IV	G+ve/G – ve	ABSSI (Melinta)
Lascufloxacin (**25**)	Quinolone (S)	DNA gyrase and topoisomerase IV	G+ve/G – ve	G+ve (Kyorin)
Zabofloxacin (**26**)	Fluoroquinolone (S)	DNA gyrase and topoisomerase IV	G+ve/G – ve	CABP (Dong Wha Pharmaceutical)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; CDAD, *C. difficile*-associated diarrhea; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; G – ve, Gram negative; G+ve, Gram positive; NP, natural product; S, synthetic; TB, tuberculosis; uSSSI, uncomplicated skin and skin structure infections.
[a]Underlined compound is a new antibacterial pharmacophore.

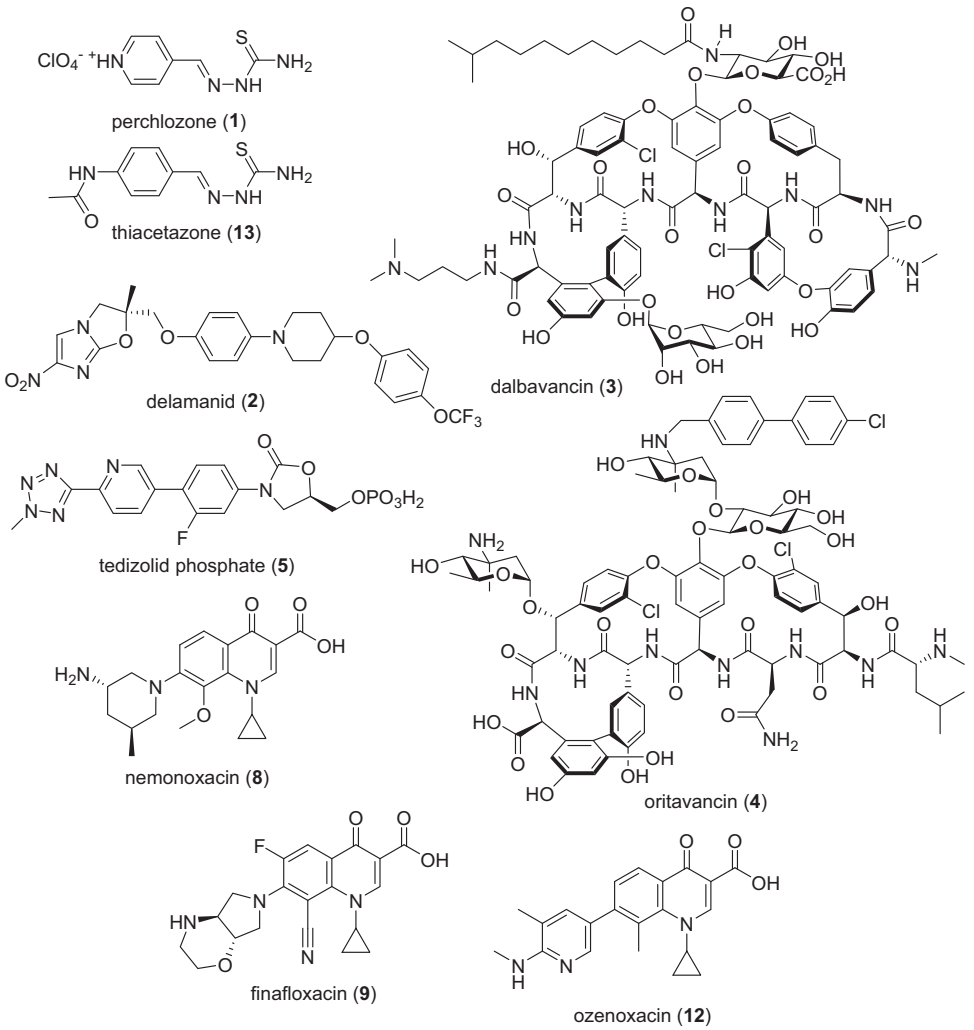

Figure 2 Structures of the recently launched antibiotics, perchlozone (**1**), the 1950s TB drug thiacetazone (**13**), delamanid (**2**), dalbavancin (**3**), oritavancin (**4**), tedizolid phosphate (**5**), nemonoxacin (**8**), finafloxacin (**9**) and ozenoxacin (**12**).

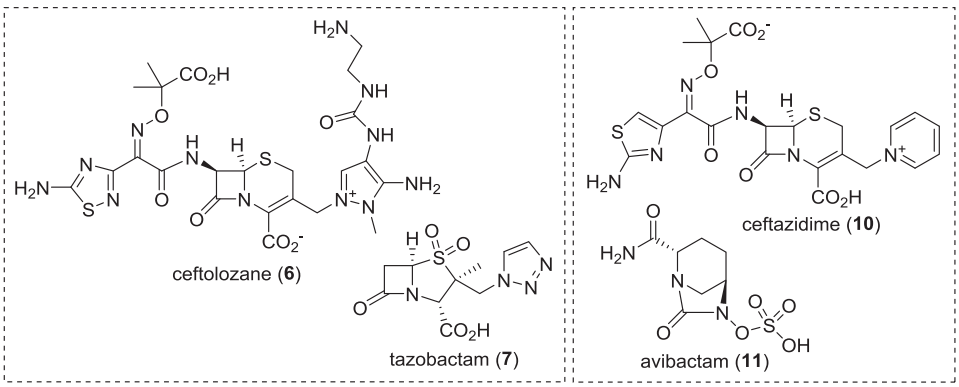

Figure 3 Structures of the recently lauched antibiotics β-lactam/β-lactamase inhibitor combinations ceftolozane (**6**)/tazobactam (**7**) and ceftazidime (**10**)/avibactam (**11**).

half-life[60] allows for treatment of G+ve ABSSSI in adults with *S. aureus* (including methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or *E. faecalis* (vancomycin-susceptible isolates only) with a single 1200 mg dose infused over 3 h. Oritavancin (**4**) is designated as a Qualified Infectious Disease Product (QIDP) under the USA Generating Antibiotic Incentives Now (GAIN) act, providing a five-year extension of non-patent exclusivity. The European Medicines Agency (EMA) provided marketing authorization for

oritavancin (**4**) in the 31 countries of the European Economic Area in March 2015.[61] Multiple mechanisms of action, in addition to Lipid II binding, are proposed to increase the effectiveness of **4**.[62–67]

Tedizolid phosphate (**5**) (Sivextro, torezolid phosphate, TR-701, DA-7218) is an oxazolidinone prodrug that is dephosphorylated *in vivo*. It was approved by the FDA in June 2014 and in EU in June 2015 for the treatment of G+ve ABSSSI,[68–70] and is currently in a phase-III trial for the treatment of presumed G+ve hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) (NCT02019420). Importantly, tedizolid phosphate (**5**) has once-daily dosing using either IV or oral administration and is active against linezolid-resistant strains.[71] Tedizolid was discovered[72] by Dong-A Pharmaceutical (Seoul, South Korea) with later development undertaken by Trius Therapeutics, acquired by Cubist Pharmaceuticals in January 2015, who in turn were acquired by Merck & Co. (Rahway, NJ, USA).[73] Phase-III development has also been undertaken by Bayer Healthcare in Latin American countries and the Asia Pacific Region. Tedizolid (**5**) inhibits bacterial protein synthesis through binding to the 50*S* ribosome, preventing the formation of the 70*S* initiation complex.[74]

Zerbaxa (CXA-201)[75] is an IV-administered combination of the cephalosporin ceftolozane (**6**) (CXA-101, FR264205) and the β-lactamase inhibitor tazobactam (**7**) that was approved by the FDA in December 2014 and the EMA in September 2015 for the treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole,[76] and complicated urinary tract infections (cUTI) including pyelonephritis (kidney infection).[77] Ceftolozane (**6**) is a fifth generation cephalosporin that displays broad-spectrum G − ve activity with potent activity against *Pseudomonas aeruginosa*,[78–80] whereas tazobactam (**7**) is a β-lactamase inhibitor first approved in

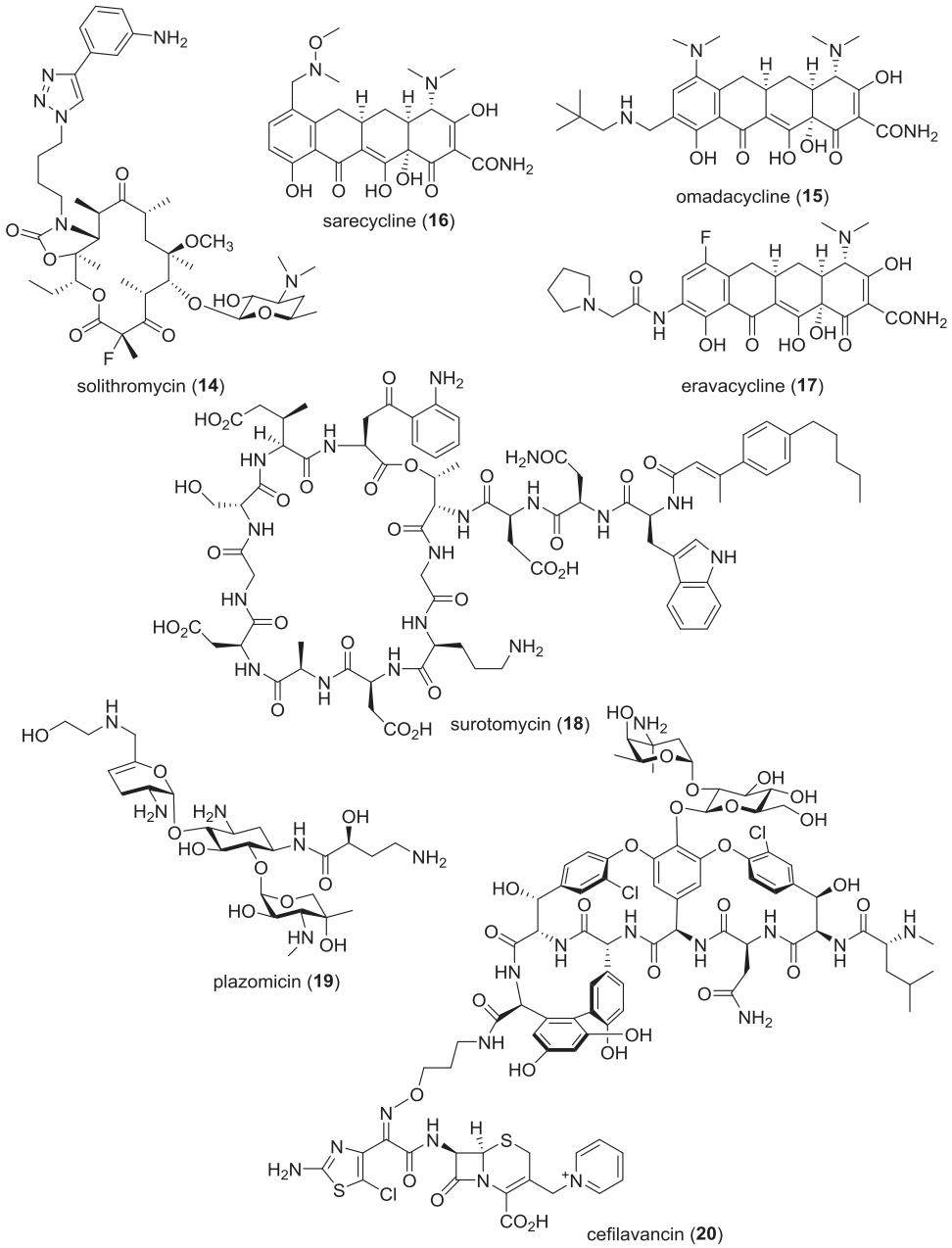

Figure 4 Structures of NP-derived compounds in phase-III clinical trials.

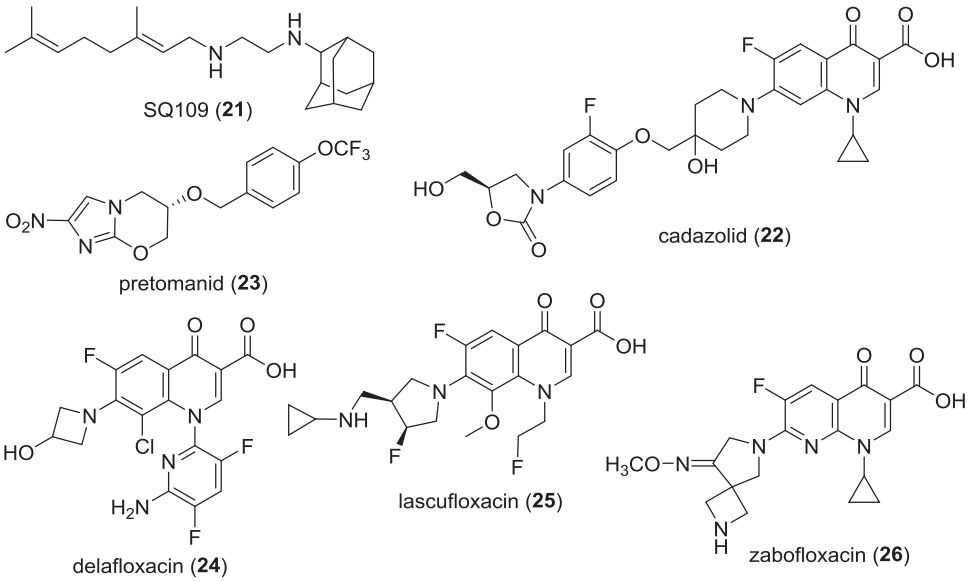

Figure 5 Structures of synthetic compounds in phase-III clinical trials.

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

Name (synonym)[a]	*Compound class (lead source)*	*Mode of action*	*Bacteria Type*	*Indication (developer)*
Exeporfinium chloride (**27**)	Porphyrin (NP)	Membrane-perturbing activity	G+ve	MRSA topical (Destiny Pharma)
Auriclosene (**28**)	*N*-chlorotaurine (NP)	Oxidation	G+ve/G – ve	Urinary catheter blockage and encrustation; Impetigo (Novabay)
Lefamulin (**29**)	Pleuromutilin (NP)	Protein synthesis inhibition	G+ve/G – ve	ABSSSI (Nabriva)
CB-06-01 (**30**)	Thiopeptide (NP)	Peptide elongation factor Tu modulators	G+ve	Acne (Cassiopea S.p.A)
Cefiderocol (S-649266) (**31**)	Catechol-substituted siderophore cephalosporin (NP)	Penicillin-binding protein	G+ve/G – ve	G – ve infections (Shionogi)
POL7080[b]	Protegrin I (P)	Inhibition of a homolog of the β-barrel protein LptD (Imp/OstA)	G – ve	Bronchiectasis and VABP (Polyphor)
Brilacidin (**32**)	Defensin (P)	Bacterial cell membrane lysis	G+ve/G – ve	ABSSSI; head and neck neoplasms; mucositis; stomatitis; mouth diseases (Cellceutix Corporation)
LTX-109 (**33**)	Cationic peptide (P)	Membrane disruption	G+ve/G – ve	Impetigo (Lytix Biopharma)
Radezolid (**34**)	Oxazolidinone (S)	Protein synthesis inhibition	G+ve/G – ve	uSSSI; CABP (Melinta)
MRX-I (**35**)	Oxazolidinone (S)	Protein synthesis inhibition	G+ve	ABSSSI (MicuRx)
Ridinilazole (**36**)	Bibenzimidazole (S)	Unknown	G+ve	CDAD (Summit)
Gepotidacin (**37**)	Gepotidacin (S)	Type 2 topoisomerase	G+ve/G – ve	Infections and gonorrhea (GlaxoSmithKline)
ETX0914 (**38**)	Spiropyrimidinetrione (S)	Type 2 topoisomerase	G+ve/G – ve	Infections and gonorrhea (Entasis Therapeutics)
Debio-1452 (**39**)	Benzodiazepine (S)	FabI inhibition	G+ve	ABSSSI (Debio/Nobelex)
Debio-1450[b]	Benzodiazepine (S)	FabI inhibition	G+ve	ABSSSI (Debio/Nobelex)
WCK-771 (**40**)	Fluoroquinolone (S)	DNA gyrase and topoisomerase IV	G+ve/G – ve	MRSA and G – ve (Wockhardt Limited)
Alalevonadifloxacin (WCK-2349) (**41**)	Fluoroquinolone (S)	DNA gyrase and topoisomerase IV	G+ve/G – ve	MRSA and G – ve (Wockhardt Limited)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; CDAD, *C.* difficile-associated diarrhea; G – ve, Gram negative; G+ve, Gram positive; MRSA, methicillin-resistant *S. aureus*, NP, natural product; P, protein/peptide; S, synthetic; TB, tuberculosis; uSSSI, uncomplicated skin and skin structure infections; VABP, ventilator-associated bacterial pneumonia.
[a]Underlined compounds are new antibacterial pharmacophores.
[b]Structures not published.

1992 in combination with piperacillin.[81,82] Ceftolozane (**6**) was discovered by Astellas (Tokyo, Japan) and late stage clinical development was undertaken by Cubist, now Merck & Co. The combination of ceftolozane and tazobactam is currently under evaluation for the treatment of adult patients with either VABP or HABP (NCT02070757).

Nemonoxacin (**8**) (Taigexyn, TG-873870)[83,84] is a non-fluorinated quinolone from TaiGen Biotechnology Co., Ltd (Taipei, Taiwan) that had an oral formulation approved in Taiwan in March 2014 for the treatment of community-acquired bacterial pneumonia (CABP). In August 2015, TaiGen announced that their partner in China, Zhejiang Medicine Company (Hangzhou, China) had completed an on-site

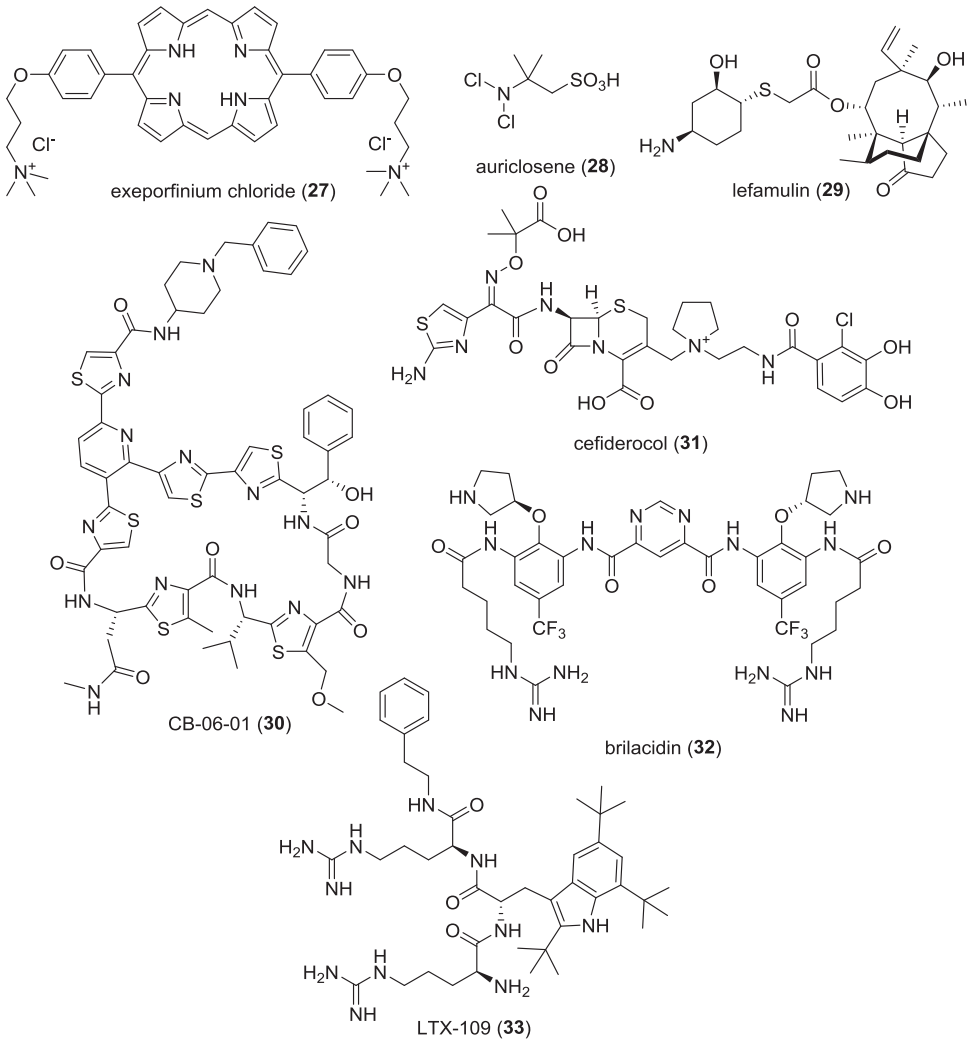

Figure 6 Structures of NP-derived and P-derived compounds in phase-II clinical trials.

inspection by the Chinese FDA with an approval decision pending.[85] TaiGen licensed **8** in 2005 from Procter & Gamble Pharmaceuticals, who were later acquired by Warner Chilcott, now incorporated into Allergan plc (Dublin, Ireland). Nemonoxacin (**8**) has broad-spectrum activity against resistant G+ve and G − ve strains;[86–88] a phase-III trial using IV administration has completed recruitment (NCT02205112), whereas a phase-II trial to treat diabetic foot infections was completed in late 2014 (NCT00685698).

An otic solution of finafloxacin (**9**) (Xtoro, BAY 35–3377) developed by Alcon Laboratories (Fort Worth, TX, USA) was approved by the FDA in December 2014 to treat acute otitis externa, which is commonly known as 'swimmer's ear', caused by *P. aeruginosa* and *S. aureus* infections.[89] Alcon licensed finafloxacin (**9**) from MerLion Pharmaceuticals (Singapore, Singapore), who recently announced that finafloxacin was more efficacious than ciprofloxacin in phase-II trial for the treatment of cUTI (NCT01928433).[90] Finafloxacin (**9**) is differentiated from other quinolones due to its improved activity at slightly acidic pH, which is more representative of physiological conditions.[91–94]

Avycaz (CAZ104, CAZ-AVI) is a combination of the third-generation cephalosporin ceftazidime (**10**)[95] and the new DBO-type β-lactamase inhibitor avibactam (**11**)[96–98] that has *in vitro* activity against Enterobacteriaceae in the presence of some β-lactamases and extended-spectrum β-lactamases (ESBLs) including AmpC, TEM, SHV, CTX-M, *Klebsiella pneumoniae* carbapenemase (KPCs), AmpC, and certain oxacillinases (OXA), though it is not active against bacteria that produce metallo-β-lactamases or that overexpress efflux pumps. The combination restored the activity of ceftazidime in animal models of infection caused by ESBL, KPC and AmpC producing bacteria. It was approved by the FDA in February 2015 for the treatment of cIAI in combination with metronidazole, and cUTI including pyelonephritis. Actavis (formerly Forest, now Allergan) received this approval in collaboration with AstraZeneca (London, UK). Notably, this β-lactam and β-lactam inhibitor combination was the first antibiotic regimen to be approved by the FDA based only on phase-II data from 169 adult patients. In light of the limited clinical data Avycaz has a label restriction: 'As only limited clinical safety and efficacy data for Avycaz are available, reserve Avycaz for use in patients who have limited or no treatment options.' Two further phase-II trials are testing the combination in children (NCT02497781 and NCT02475733), whereas multiple phase-III trial have recently been completed using ceftazidime-avibactam in hospitalized adults with nosocomial pneumonia (NCT01808092), for cUTI (NCT01644643, NCT01595438, NCT01599806), or for cIAI (NCT01500239, NCT01499290, NCT015002389). In February 2016 Allergan announced the FDA has accepted for filing the company's

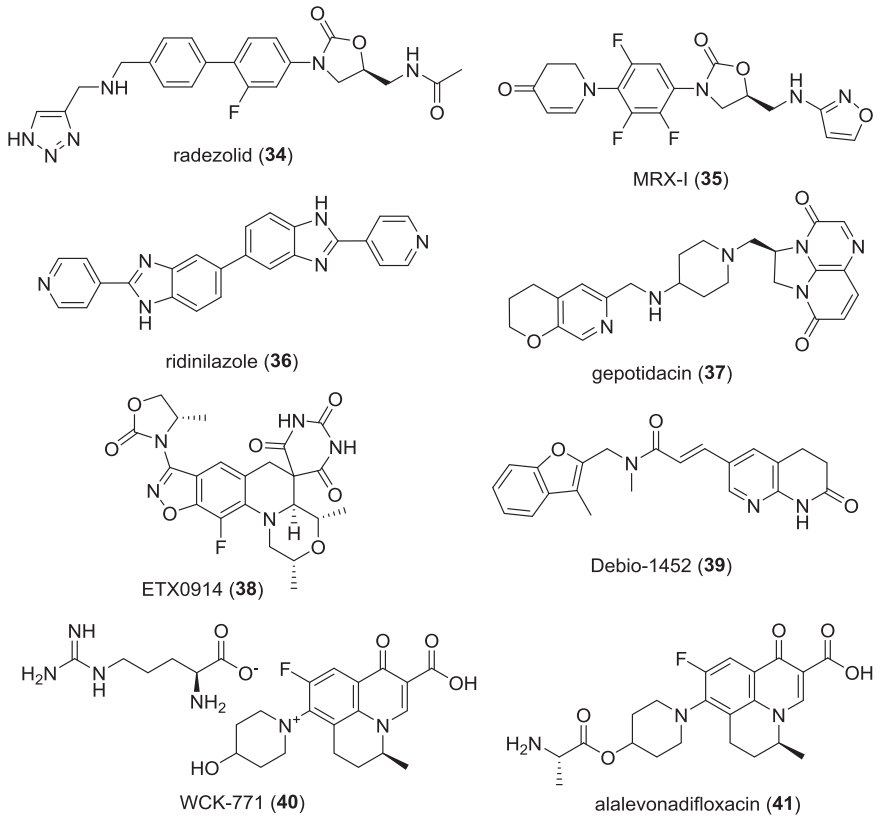

Figure 7 Structures of synthetic compounds in phase-II clinical trials.

Table 4 Compounds in phase-I clinical trials

Name (synonym)[a]	*Compound class (lead source)*	*Mode of action*	*Bacteria type*	*Indication (developers)*
Small molecule antibiotics				
BAL30072 (**42**)/meropenem (**43**)	Monobactam (NP)/ carbapenem (NP)	Penicillin-binding protein	G+ve/G – ve	G – ve (Basilea)
LCB01-0371 (**44**)	Oxazolidinone (S)	Protein synthesis inhibition	G+ve	G+ve (LegoChem Biosciences)
TD-1607 (**45**)	Glycopeptide (NP)-cephalosporin (NP) heterodimer	Cell wall biosynthesis	G+ve	G+ve (Theravance Biopharma)
MGB-BP-03 (**46**)	Distamycin A (NP)	DNA minor groove binding	G+ve	CDI (MGB Biopharma)
CRS3123 (**47**)	Diaryldiamine (S)	Methionyl-tRNA synthetase	G+ve	CDI (Crestone)
TBA-354 (**48**)	Nitroimidazole (S)	DNA and cellular damage	G+ve (TB)	TB (Global Alliance for TB Drug Development)
Q203 (**49**)	Imidazo[1,2-*a*]pyridine amide (S)	Respiratory cytochrome bc_1 complex	G+ve (TB)	TB (Qurient Co/Infectex)

Abbreviations: CDI, *C. difficile* infections, G – ve, Gram negative; G+ve, Gram positive; NP, natural product; S, synthetic; TB, tuberculosis.
[a]Underlined compounds are new antibacterial pharmacophores.

supplemental New Drug Application (NDA) for Avycaz, adding new clinical data to the current label from two of the phase-III trials that evaluated Avycaz, in combination with metronidazole, for the treatment of cIAI, including patients with infections due to ceftazidime-non-susceptible pathogens. The FDA granted priority review status due to a QIDP designation for Avycaz. Avibactam (**11**) has also been evaluated in a phase-II trial (NCT01281462) in combination with ceftaroline fosamil and a phase-I trial with aztreonam (**54**) (NCT01689207) (Table 4; Figure 11).

Ozenoxacin (**12**) (Zebiax, M5120, T-3912), which was discovered by Toyama Chemical (Tokyo, Japan) and later developed by Maruho Co., Ltd (Osaka, Japan) was approved in Japan in September 2015 for the treatment of superficial *S. aureus* and *S. epidermidis* skin infections and acne that is accompanied by purulent inflammation.[99] Ozenoxacin (**12**) is a non-fluorinated quinolone with broad-spectrum activity against a variety of susceptible and quinolone-resistant bacteria.[100,101] Ozenoxacin (**12**) is also being developed in Europe by Ferrer Internacional S.A. (Barcelona, Spain), who has licensed the USA rights to Medimetriks Pharmaceuticals, Inc. (Fairfield, NJ, USA)[102] and the Canadian rights to Cipher Pharmaceuticals (Mississauga, ON, Canada).[103] Ozenoxacin (**12**) has completed a phase-III trial (NCT01397461) and is currently undergoing another phase-III trial (NCT02090764) for the treatment of patients with impetigo.

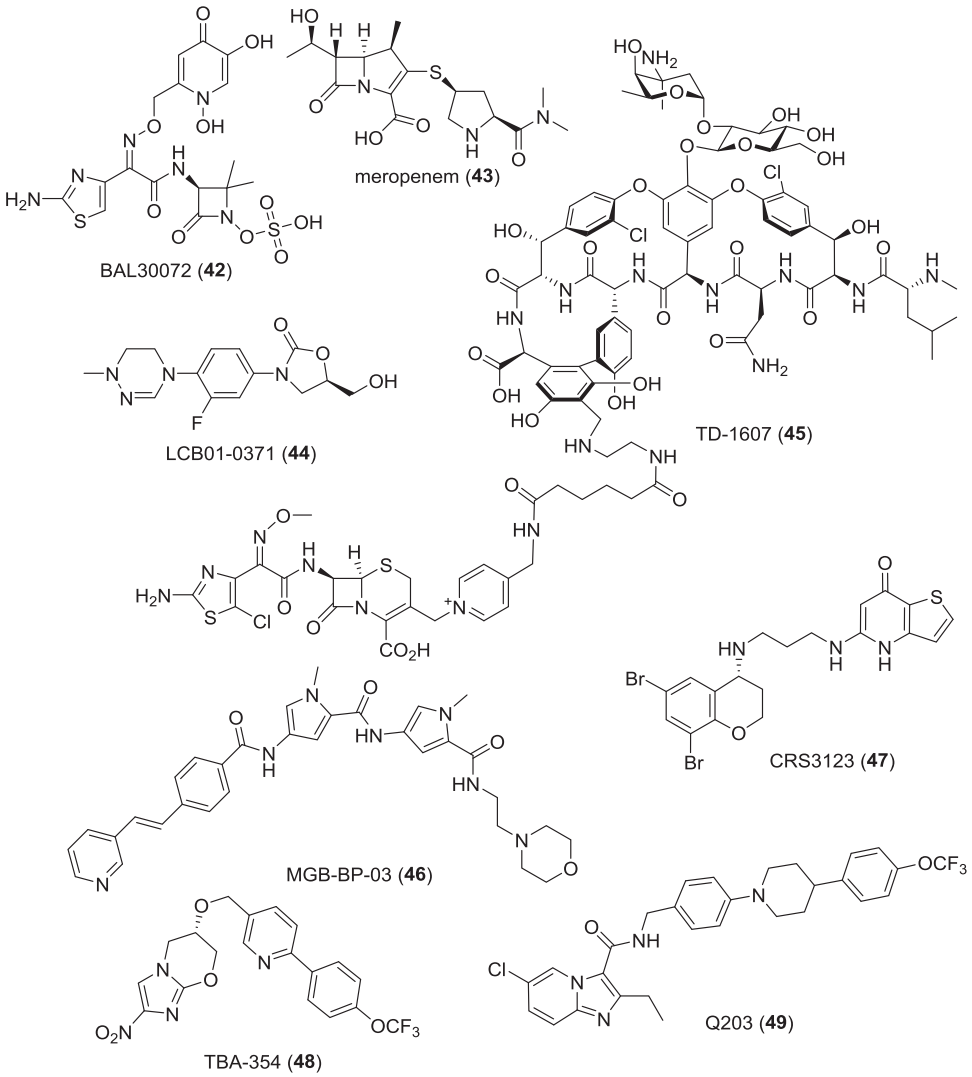

Figure 8 Structures of compounds in phase-I clinical trials.

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 December 2015 are detailed in the following tables and figures: phase-III in Tables 2 and 5 with structures in Figures 4,5 and 9, phase-II in Table 3 with structures in Figures 6 and 7, and phase-I in Tables 4 and 6 with structures in Figures 8 and 10.

NP and NP-derived compounds in phase-III trials

Solithromycin (**14**) (CEM-101) is a semi-synthetic 2-fluoroketolide discovered by Optimer that is being developed by Cempra Pharmaceuticals (Chapel Hill, NC, USA). It recently completed two phase-III trials for the treatment of CABP (NCT01968733 and NCT01756339). Solithromycin (**14**) demonstrated non-inferiority to moxifloxacin within 72 h, meeting the FDA's primary endpoint, but was inferior in a 5–10 day follow-up required by the EMA. Furthermore, 34% of patients reported adverse events (mainly infusion site related), compared to 13% for moxifloxacin.[104] Solithromycin (**14**) is a protein synthesis inhibitor[105] that has broad-spectrum antibacterial activity including many ketolide/macrolide resistant strains including *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Mycoplasma genitalium*.[106–110] Solithromycin (**14**) is also being investigated in a phase-III trial for the treatment of uncomplicated urogenital gonorrhea (NCT02210325) and as an anti-inflammatory[111] in a phase-II trial for the treatment of nonalcoholic steatohepatitis (NCT02510599). BARDA awarded Cempra a contract in 2013 to develop **14** in pediatric populations and for bioterror threat pathogens.[112,113] Toyama Chemical Co., Ltd (Tokyo, Japan) is also evaluating **14** (coded T-4288) in a phase-II trial in Japan.

Omadacycline (**15**) (amadacycline, PTK-0796) is a semi-synthetic minocycline derivative[114] developed by Paratek Pharmaceuticals (Boston, MA, USA) with broad-spectrum antibacterial activity[115] that can be administered either orally or IV. Omadacycline (**15**) recently started new phase-III trials for the treatment of CABP (NCT02531438) and ABSSSI (NCT02378480). Omadacycline (**15**) inhibits protein synthesis through enhanced ribosome binding compared to tetracycline at a similar site and maintains activity in the presence of the ribosomal protection proteins such as *Tet*(O) and *Tet*(M).[116]

Sarecycline (**16**) (P005672, PTK-AR01) is a semi-synthetic tetracycline derivative[117] discovered by Paratek Pharmaceuticals (Boston, MA, USA) and licensed to Warner Chilcott in July 2007, who were acquired by Actavis now Allergan, plc (Dublin, Ireland) in

October 2013. Sarecycline (**16**) is being evaluated in three phase-III trials for the treatment of acne vulgaris (NCT02413346, NCT02320149 and NCT02322866).

Eravacycline (**17**) (TP-434) is a synthetic fluorocycline-type tetracycline derivative[118–120] developed by Tetraphase Pharmaceutics (Watertown, MA, USA) with broad-spectrum activity, including activity against bacteria that have acquired tetracycline-specific efflux and ribosomal protection through inhibition of protein synthesis.[121–123] Eravacycline (**17**) was evaluated in phase-III trials for the treatment of cIAI (NCT01844856) and cUTI (NCT01978938). In December 2014 tetraphase announced that the IGNITE1 trial in cIAI met its primary endpoint, demonstrating high cure rates in prevalent G − ve pathogens and a favorable safety profile,[124] but in September 2015 the top-line results for the cUTI trial showed **17** did not achieve either the FDA or EMA primary endpoints of statistical non-inferiority compared to levofloxacin.[125] Eravacycline (**17**) was awarded QIDP designation for cUTI and cIAI in 2013.[126]

Surotomycin (**18**) (MK-4261, CB-183,315) is a semi-synthetic daptomycin derivative[127,128] developed by Cubist Pharmaceuticals, which was acquired by Merck & Co. (Rahway, NJ, USA) in December 2014, that completed two phase-III trials (NCT01597505 and NCT01598311) in 2015 for the treatment of *Clostridium difficile* infections (CDI). Surotomycin (**18**) has improved activity against *C. difficile* strains compared to daptomycin,[129–132] and against daptomycin-resistant *S. aureus*, *E. faecalis* and *E. faecium*.[127] Importantly, it was recently reported that surotomycin (**18**) had only a modest disruptive effect on the gut microbiota in a phase-I trial, which could help reduce infection recurrences.[133]

Plazomicin (**19**) (ACHN-490)[134,135] is a semi-synthetic derivative[136] of the aminoglycoside sisomicin[137,138] that has broad-spectrum activity against both G+ve and G − ve bacteria.[139–142] Plazomicin (**19**) is being evaluated by Achaogen, Inc. (South San Francisco, CA, USA) in phase-III trials for the treatment of cUTI and pyelonephritis (NCT02486627) and carbapenem-resistant Enterobacteriaceae VAP, HAP and bloodstream infections (NCT01970371).

Cefilavancin (**20**) (RD-1792, TD-1792) is a cephalosporin/glycopeptide heterodimeric antibiotic developed by Theravance Biopharma, Inc. (South San Francisco, CA, USA) that was licensed to R-Pharm (Moscow, Russia) in October 2012. In March 2015, R-Pharm reported that cefilavancin (**20**) was undergoing a phase-III trial as a treatment of G+ve complicated skin and skin structure infections with data expected in 2016.[143] Cefilavancin (**20**) had previously completed a phase-II trial in 2007 that evaluated two mg/kg/day IV dosing versus vancomycin in 197 patients (NCT00442832), with similar efficacy.[144] Cefilavancin (**20**) consists of vancomycin functionalized with a linker attached to the C-terminal carboxyl group via an amide bond; the other end of the linker is attached through an oxime linkage to the cephalosporin lactam amine substituent, resulting in a hybrid with a dual targeting action against peptidoglycan synthesis.[145]

Synthetic compounds in phase-III trials

SQ 109 (**21**), which was discovered by the National Institute of Allergy and Infectious Diseases (NIAID)[146] and initially developed by Sequella, Inc. (Rockville, MD, USA), is an ethambutol analog that Infectex (Moscow, Russia) is evaluating in a phase-II/III trial for the treatment of MDR pulmonary TB.[147] Recent work has shown that the mode of action of SQ 109 (**21**) is likely to be via dissipation of the transmembrane electrochemical proton gradient.[148] Interestingly, SQ 109 (**21**) has shown potent killing activity of *Trypanosoma cruzi*, which is the parasite that causes Chagas' disease.[149,150]

Cadazolid (**22**) (ACT-179811) is a quinolonyl-oxazolidinone chimeric antibiotic under development by Actelion Pharmaceuticals (Basel, Switzerland) that is being evaluated in two phase-III trials for the treatment of patients with CDI (NCT01983683 and NCT01987895). The FDA has designated cadazolid (**22**) as a Fast Track development program and as a QIDP. Cadazolid (**22**) is a potent inhibitor of *C. difficile* protein synthesis,[151] and also strongly suppresses toxin and spore formation.[152,153]

Pretomanid (**23**) (PA-824), a nitroimidazole derivative being tested by the Global Alliance for TB Drug Development (New York, NY, USA), is in phase-III trials in combination with linezolid (NCT02333799), moxifloxacin and pyrazinamide (NCT02342886) and a multidrug regimen of bedaquiline, moxifloxacin, linezolid and clofazimine (NCT02589782). Pretomanid (**23**) is an analog of CGI-17341, which was found to be too toxic for clinical development,[154] and is a prodrug that is reductively activated by the deazaflavin (cofactor F_{420})-dependent nitroreductase Rv3547. Under aerobic conditions **23** inhibits cell wall growth by hindering mycolic acid formation and under anaerobic conditions its activity involves the induction of respiratory poisoning.[155–157]

Delafloxacin (**24**) (RX-3341, WQ-3034, ABT-492)[158] is being evaluated by Melinta Therapeutics (New Haven, CT, USA) and has completed one phase-III trial (NCT01811732) and is undergoing another (NCT01984684), both for the treatment of G+ve and G−ve ABSSSI. A phase-III trial for the treatment of uncomplicated gonorrhea was terminated (NCT02015637). In the completed ABSSSI study, delafloxacin (**24**) met the study's primary endpoint, reduction in lesion size by at least 20% at 48–72 h in the intent-to-treat population without non-study antibiotics or major procedures, which was comparable to the response in the control arm receiving vancomycin plus aztreonam (**54**).[159] Delafloxacin (**24**) has been assigned QIDP status by the FDA for this therapeutic area, as well as for the treatment of CABP.[158] Delafloxacin (**24**), like finafloxacin (**9**), displays enhanced activity against G+ve bacteria at pH 5 due to its slightly anionic characteristics.[160] The quinolone antibiotic class kill bacteria using 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.[161]

Lascufloxacin (**25**) (KRP-AM1977X)[162] is an orally administered quinolone developed by Kyorin Pharmaceutical Co., Ltd (Tokyo, Japan) that entered phase-III trials in Japan in April 2015 for the treatment of respiratory infections.[163] An IV formulation of **25** called KRP-AM1977Y is currently in phase-II trials.[163]

Zabofloxacin (**26**) (PB-101, DW-224a), which is being developed Dong Wha Pharmaceutical (Seoul, South Korea), completed a phase-III trial in late 2014 for the treatment of patients with acute bacterial exacerbation of chronic obstructive pulmonary disease (NCT01658020).[164] There has been no further update from Dong Wha on the development status of **26**.

NP and NP-derived compounds in phase-II trials

Exeporfinium chloride (**27**) (XF-73) is a porphyrin derivative being developed by Destiny Pharma (Brighton, UK) that has been evaluated in phase-I/II trials for the prevention of post-surgical staphylococcal nasal infections (NCT02282605).[165] Exeporfinium chloride (**27**) is a photosensitizer that has broad-spectrum G+ve activity[166–170] and activity against *Candida albicans*.[171]

Auriclosene (**28**) (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) as an irrigation solution on urinary catheter patency (NCT02130518). It recently

completed a phase-II trial for the treatment of bacterial conjunctivitis (NCT01877694). Auriclosene (**28**) was designed to be a more stable derivative of the naturally occurring oxidant *N*-dichlorotaurine[172–175] and also was recently shown to inactivate *S. aureus* toxins.[176]

Lefamulin (**29**) (BC-3781) is a semi-synthetic pleuromutilin[177,178] derivative originally discovered by Nabriva Therapeutics AG (Vienna, Austria). Nabriva executed an Initial Public Offering of shares in September 2015, raising $92 m to progress lefamulin (**29**) into phase-III trials for CABP.[179] The first, NCT02559310, is currently recruiting 738 patients for a comparison with moxifloxacin +/− linezolid, using IV **29** with potential step-down to oral **29**. A phase-II trial for ABSSSI was completed in 2012 (NCT01119105),[180] whereas further trials in ABSSSI, HABP and VABP are planned.[179] Lefamulin (**29**) is a protein synthesis inhibitor that displays antibacterial activity against a range of skin and respiratory pathogens.[177,181,182]

CB-06-01 (**30**) (NAI-003, BIK-0376, NAI-Acne) is an amide derivative of GE2270, a cyclic thiazole peptide obtained from fermentation of a *Planobispora rosea* strain that is active against G+ve bacteria and anaerobes.[183] CB-06-01 (**30**), licensed from NAICONS (Milan, Italy), is being developed by Cassiopea S.p.A. (Milan, Italy) (formerly Cosmos S.p.A.) as a topical treatment for acne infections. According to the company website, **30** has completed a phase-I study and is currently undergoing phase-III POC trials, expected to be completed in 2Q 2016, though no trials are listed with ClinicalTrials.gov.[183]

Cefiderocol (**31**) (S-649266, GSK-2696266) is a chimeric cephalosporin with a catechol siderophore substituent[184–186] from Shionogi & Co., Ltd (Osaka, Japan) being co-developed with GSK (London, UK). It completed phase-I testing[187–189] and is currently being assessed in a phase-II trial (NCT02321800) for cUTIs caused by G − ve pathogens in hospitalized adults in comparison with IV imipenem/cilastatin.

Protein/mammalian peptide-derived compounds in phase-II trials

POL7080 (RG7929) is a synthetic cyclic peptide based on protegrin I,[190,191] which was first isolated from porcine leucocytes,[192] but the structure has yet to be made publically available. Developed by Polyphor, Ltd (Basel, Switzerland), POL7080 successfully completed a phase-I trial[193,194] and was partnered with Roche in 2013.[195] POL7080 completed a phase-II trial in 20 patients with exacerbation of non-cystic fibrosis bronchiectasis in November 2015 (NCT02096315) and is currently undergoing another phase-II study in 25 patients with *P. aeruginosa* VABP co-administered with standard of care (NCT02096328). The collaboration with Roche was discontinued in November 2015,[196] with Polyphor continuing the phase-II trial on its own. POL7080 has potent and selective antimicrobial activity against G − ve 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 lipopolysaccharide.[190,194]

Brilacidin (**32**) (PMX-30063), a membrane targeting arylamide oligomer licensed from the University of Pennsylvania that was being developed by Polymedix Inc. (Radnor, PA, USA), completed a phase-IIa trial for the treatment of ABSSSI in 2012 (NCT01211470). The future development of brilacidin (**32**) appeared in doubt as Polymedix filed for bankruptcy on 1 April 2013 and there were reports of possible toxicity concerns,[197] but the assets of Polymedix were acquired by Cellceutix (Beverly, MA, USA) in September 2013 for $US2.1 m plus 1.4 m shares, an apparent bargain considering Polymedix had a market capitalization of over $200 m in 2012.[198] Cellceutix conducted a phase-IIb trial in 2014 (NCT02052388), comparing **32** against daptomycin for treatment of ABSSSI in 215 patients, with no serious adverse events and efficacy similar to daptomycin across all brilacidin treatment groups, including the two single-dose groups.[199] Brilacidin (**32**) received QIDP designation under the GAIN Act in November 2014.[200] Another phase-II trial (NCT02324335) is currently recruiting to test an oral rinse of brilacidin to treat oral mucositis in cancer patients.[201] Cellceutix announced in 2015 that **32** would proceed to a phase-III trial.[202] Brilacidin (**32**) is a member of the family of arylamide foldamers that was designed to mimic cationic antimicrobial peptides and had shown bactericidal activity against both G+ve and G − ve bacteria.[203–205] Cellceutix is also working on a defensin mimetic-compound CTIX-1278 that is still in preclinical testing.[206]

LTX-109 (**33**) (Lytixar), a cationic peptide mimic,[207] is being developed by Lytix Biopharma AS (Oslo, Norway) as a topical antimicrobial peptide. It completed phase-II trials for the treatment of impetigo (NCT01803035) in April 2014 and uSSSI (NCT01223222) in February 2011, and a phase-I/II trial for nasal decolonization of *S. aureus* including MRSA (NCT01158235).[208] LTX-109 (**33**) has rapid bactericidal *in vitro* activity against both G+ve and G − ve drug-resistant strains.[209,210] Lytix planned to develop **33** through a phase-I/II trial for the treatment of mild diabetic foot infections, but in October 2015 announced it had decided not to proceed with the program due to higher costs, a longer than anticipated timeframe, and the company's focus on oncology.[211]

Synthetic compounds in phase-II trials

Radezolid (**34**) is an 'enhanced' oxazolidinone antibiotic, developed by Melinta Therapeutics, Inc. (New Haven, CT, USA), which has activity against G+ve bacteria (including those with resistance to linezolid) in addition to some G − ve bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis*.[212] Radezolid (**34**) was rationally designed from the overlap of sparsomycin and linezolid binding sites on the 50*S* ribosomal subunit.[213–215] Radezolid (**34**) completed two phase-II trials for CABP (NCT00640926, 2009) and uSSSI (NCT00646958, 2008), but no further development has been reported. In January 2015 Melinta licensed radezolid to Malin Corporation plc (Dublin, Ireland) for topical uses.[216]

MRX-I (**35**) is a new oxazolidinone antibiotic being developed by MicuRx (Hayward, CA, USA and Shanghai, China), proposed to possess an improved safety profile compared to linezolid.[217–219] It completed a phase-I trial in April 2012,[220] and is currently undergoing testing in a phase-II comparison with linezolid for the treatment of ABSSSI (NCT02269319: 120 patients, January-October 2015).

Ridinilazole (**36**) (SMT19969) is a synthetic bibenzimidazole compound[221] from Summit Corporation PLC (Oxford, UK) that is being developed for the treatment of CDI in collaboration with the Wellcome Trust (London, UK). Ridinilazole (**36**) completed a phase-I study that showed **36** was 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.[222] The Wellcome Trust awarded Summit an additional Translational Award for further development,[222] leading to a phase-II study comparing **36** with vancomycin in *C. difficile*-associated diarrhea treatment that was initiated in April 2014, with a primary completion in November 2015 (NCT02092935). Positive top-line results were achieved, showing statistical superiority in sustained clinical response rates compared to the standard of care, vancomycin.[223] Ridinilazole (**36**) has already received QIDP designation and has been granted Fast Track status from the US FDA,[224] with phase-III trials being considered. Ridinilazole (**36**) showed good results in a hamster model of CDI.[225]

Gepotidacin (**37**) (GSK-2140944) is a bacterial Type II topoisomerase inhibitor[226,227] being investigated by GlaxoSmithKline (London, UK) that has completed multiple phase-I clinical trials (NCT01706315, NCT01615796, NCT01934205, NCT02000765, NCT02045849, NCT02202187 and NCT02257398), with both oral and IV dosing. A phase-II study investigating gepotidacin (**37**) with IV/oral switch therapy in G+ve ABSSSI was completed in June 2015 (NCT02045797), with a second phase-II study treating uncomplicated urogenital gonorrhea caused by *N. gonorrhoeae* initiated in April 2015 (NCT02294682).

ETX0914 (**38**) (AZD0914) is an orally available topoisomerase inhibitor developed by AstraZeneca (London, UK) that is in a phase-II clinical trial that was initiated in November 2014 (NCT02257918) to investigate efficacy in treating uncomplicated gonorrhea. It received FDA QIDP designation in June 2014,[228] and formed one of the key assets of AstraZeneca's anti-infective spinout company, Entasis Therapeutics (Waltham, MA, USA), in 2015.[229] ETX0914 (**38**) is a novel spiropyrimidinetrione that targets bacterial topoisomerase II with a mode of inhibition distinct from the fluoroquinolones and aminocoumarins, meaning it retains activity against fluoroquinolone resistant isolates.[230,231]

Debio-1452 (**39**) (AFN 1250) was being developed by Affinium Pharmaceuticals (Austin, TX, USA) and successfully completed a phase-IIa trial in August 2012 (NCT01519492) as an oral formulation for the treatment of staphylococcal ABSSSI. Debio-1452 (**39**) disrupts fatty acid biosynthesis by inhibiting staphylococcal FabI,[232,233] an essential enzyme in the final step of the fatty acid elongation cycle,[234,235] and was derived from a benzodiazepine identified at GSK (London, UK) using a high-throughput screen looking for inhibitors of *S. aureus* FabI.[236,237] Structure-based design led to the identification of a 3,4-dihydro-1,8-naphthyridin-2(1*H*)-one core with good *in vitro* and *in vivo* antibacterial activity with no significant cytotoxicity.[236] Affinium licensed the program in 2002 and conducted further structure optimization leading to AFN-1252 (**39**).[232,238–245] In February 2014, Debiopharm Group (Lausanne, Switzerland) acquired Affinium's antibiotic assets, including both **39** and a prodrug of AFN-1252, Debio-1450 (AFN-1720).[246] The prodrug, Debio-1450, was assessed in two phase-I studies (NCT02162199 and NCT02214433), with a third (NCT02595203) scheduled for completion in December 2015. A phase-II study was initiated in May 2015 that is examining IV switch oral therapy compared with IV vancomycin and oral linezolid in the treatment of patients with staphylococcal ABSSSI, estimated to be completed by June 2016 (NCT02426918). The FabI inhibitor platform is being used to generate other antibiotic candidates Debio 1453 and Debio 1454, for *N. gonorrhoeae* and Enteric species, respectively,[247] in collaboration with Nobelex Biotech Inc. (Toronto, Canada), founded by Affinium's former management.[248]

The fluoroquinolone WCK-771 (**40**), which is the arginine salt of *S*-(−)-nadifloxacin, and its prodrug alalevonadifloxacin (WCK-2349) (**41**)[249] completed four phase-I trials between 2013 and August 2015 (NCT01875939, NCT02244827, NCT02217930, NCT02253342). Its developer, Wockhardt Limited (Mumbai, India) received QIDP status for WCK-771 (**40**) and alalevonadifloxacin (**41**) in August 2014,[250] the first for an Indian company. Nadifloxacin is a racemic fluoroquinolone with a previous history of clinical use in Japan in 1993 as a topical antibiotic to treat acne and methicillin-resistant staphylococcal infections.[251] The *S* enantiomer of nadifloxacin was found to be more active than the racemic mixture and had pharmacokinetic properties amenable for systemic use,[251–254] whereas the prodrug is used to provide oral availability.

Compounds in phase-I trials

BAL30072 (**42**)[255–257] is a chimeric monobactam derivative with an iron-chelating dihydroxypyridone moiety developed by Basilea Pharmaceutica (Basel, Switzerland) for use as monotherapy or in combination with carbapenems. In 2013 Basilea was awarded a $US89 m contract by BARDA for the development of an IV dosage form,[258,259] leading to a phase-I study initiated in June 2014 to evaluate multiple-ascending doses of IV-administered **42** alone and in combination with meropenem (**43**).[260] In September 2015, Basilea announced that an inhaled dosage form of **42** would be developed as part of the European iABC (inhaled Antibiotics in Bronchiectasis and Cystic fibrosis) program.[261] This inhaled form of BAL30072 (**42**), a targeted treatment for chronic lung infections, will initially undergo preclinical development activities in preparation for phase-I studies.[262] BAL30072 (**42**) displays activity against many G−ve bacteria[255] including *P. aeruginosa*,[263] *Acinetobacter baumannii*[264,265] and *Burkholderia pseudomallei*[266] and is rapidly absorbed into bacteria via the essential iron uptake systems.[255,263] BAL30072 (**42**) was found to be effective against a series of clinical isolates from New York City hospitals.[267]

LCB01-0371 (**44**)[268] is another new oxazolidinone, with a cyclic amidrazone substituent, belonging to LegoChem Biosciences, Inc. (Daejeon, South Korea). Purported to be more safe than linezolid or tedizolid, it has completed three phase-I trials (NCT01554995, NCT01842516 and NCT02540460) and has recently completed a phase-II trial (NCT01554995). Two additional phase-I trials are either currently recruiting (NCT02529241) or planned (NCT02538003).

TD-1607 (**45**), like cefilavancin (**20**) (TD-1792), is a heterodimeric antibiotic developed by Theravance Biopharma, Inc. (South San Francisco, CA, USA) consisting of vancomycin covalently linked to a cephalosporin, providing a dual targeting action against peptidoglycan synthesis. Although cefilavancin (**20**) forms the linkage with the C-terminal carboxyl group of vancomycin and an oxime group attached to the cephalosporin lactam amine substituent, TD-1607 (**45**) is aminomethylated on an aromatic ring (like telavancin) and this handle is used to attach the glycopeptide to the cephalosporin, which itself is attached via a pyridinyl substituent off the six-membered ring of the cephalosporin bicyclic ring system.[269] TD-1607 (**45**) entered two phase-I trials, testing single IV dosing in 64 patients in April 2013 (NCT01791049), with the study completed in August 2013, and an additional 48 patients in September 2013-July 2014 (NCT01949103). No further development has been reported, though it is listed in the 2015 Theravance Biopharma annual report as 'midstage' candidate for MRSA.[270]

MGB-BP-3 (**46**) is a novel compound with G+ve activity being developed by MGB Biopharma (Glasgow, UK). It is based on the University of Strathclyde's DNA minor groove binding technology[271] and derived from distamycin A.[272] A phase-I trial (NCT02518607) of **46** was initiated in July 2015 with an oral formulation being developed to treat CDI; IV and topical treatments are in preclinical development.[273]

CRS3123 (**47**) (REP-3123), a small molecule protein synthesis inhibitor that acts on the novel target methionyl-tRNA synthetase (MetRS) originally developed by Replidyne just under 10 years ago,[274] is being developed by Crestone Inc. (Boulder, CO, USA) for the treatment of CDI. CRS3123 (**47**) is potent against a range of *C. difficile* clinical isolates, but has a relatively narrow spectrum of activity that may help to spare the normal gut bacteria during therapy. The first phase-I trial (NCT01551004), sponsored by the NIAID, enrolled 40 patients from May 2012-April 2014 to test a single dose. A second trial,

also sponsored by NIAID, was initiated in April 2014 (NCT02106338) to test multiple doses in up to 30 subjects.[275]

TBA-354 (**48**)[276] is a next-generation nitroimidazole being developed to treat TB by the TB Alliance, in conjunction with the University of Auckland and University of Illinois-Chicago.[277] TBA-354 (**48**), shown to be more potent than pretomanid (**23**) in preclinical testing,[278] is currently in two phase-I trials (NCT02288481 and NCT02606214), the first new TB drug candidate to begin a phase-I trial since 2009.[279]

Q203 (**49**) is a new imidazo[1,2-*a*]pyridine amide[280,281] with potent anti-tubercular activity that is being evaluated in a phase-I trial (NCT02530710) by Qurient Co., Ltd (Seongnam-si, South Korea). Qurient has also licensed **49** to Infectex (Moscow, Russia). Two imidazo[1,2-*a*]pyridine amides were identified from screening 121 526 compounds using a phenotypic high-content assay in infected macrophages.[217] Structure optimization led to the identification of Q203 (**49**) that has excellent *in vivo* activity and pharmacokinetic and safety profiles compatible with once-daily dosing.[217,218] Q203 (**49**) and analogs inhibit *Mycobacterium tuberculosis* growth by targeting the respiratory cytochrome bc_1 complex.[217]

β-LACTAM/β-LACTAMASE INHIBITORS UNDERGOING CLINICAL EVALUATION

The β-lactam antibiotics, which have evolved over multiple generations of improved subclasses, include penicillins, cephalosporins and carbapenems. They have been one of the most successful antibiotic classes ever discovered. Resistance to the β-lactams is generally caused by lactam ring opening by β-lactamase enzymes, inactivating the antibiotics so they are unable to inhibit their target, the bacterial penicillin-binding proteins involved in cell wall synthesis. This resistance can be overcome by co-administration of a β-lactamase inhibitor that provides the first clinical example of a 'resistance-breaker' strategy. The first β-lactamase inhibitor, clavulanic acid,[282–284] was isolated from *Streptomyces clavuligerus* and is still used today as a combination therapy with amoxicillin, most commonly known as Augmentin. New β-lactam/β-lactamase inhibitor combinations were reviewed in 2013[285,286] and 2011,[285,286] whereas β-lactam antibiotics and β-lactamase inhibitors that are approved, in the clinic, and under development, were reviewed in 2014.[287]

β-Lactam/β-lactamase inhibitor combinations in phase-III trials

Carbavance is a combination of meropenem (**43**), a carbapenem first launched in Italy in 1994, and vaborbactam (RPX7009) (**50**), a novel boron-containing β-lactamase inhibitor,[288] initially developed by Rempex Pharmaceuticals (San Diego, CA, USA), which was subsequently bought by The Medicines Company (Parsippany, NJ, USA) in 2013.[289] Carbavance has completed multiple phase-I trials (NCT01702649, NCT01751269, NCT01772836, NCT02020434 and NCT02073812) and is currently recruiting two phase-III trials, comparing Carbavance to piperacillin+tazobactam in cUTIs (NCT02166476) and against best available therapy for carbapenem-resistant Enterobacteriaceae serious infections (cUTI, acute pyelonephritis, HABP, VABP, bacteremia; NCT02168946).

A combination therapy of imipenem (**51**), cilastatin (**52**) and relebactam (**53**) (MK-7655) that is being developed by Merck & Co. (Rahway, NJ, USA) has completed phase-II trials for cUTI (NCT01505634; completed July 2015) and cIAI (NCT01506271, completed August 2014). A phase-III trial comparing the combination against colistimethate sodium+imipenem+cilastatin in imipenem-resistant bacterial infection is currently recruiting 64 patients (NCT02452047) with an estimated completion in October 2016. A comparison with piperacillin+tazobactam for treatment of bacterial pneumonia in 536 patients is in preparation (NCT02493764), with an estimated completion in January 2018. Relebactam (**53**) is a DBO β-lactamase inhibitor related to avibactam (**11**),[290] whereas imipenem (**51**) is a carbapenem first launched in 1987 that needs to be co-administered with the dehydropeptidase inhibitor cilastatin (**52**) in order to impede imipenem metabolism.[291]

β-Lactam/β-lactamase inhibitor combinations in phase-I trials

ATM-AVI[292] is a combination of aztreonam (**54**), a monobactam first launched in 1984, and avibactam (**11**) (NXL104) that was being evaluated by AstraZeneca (London, UK) and Forest Laboratories (now part of Allergan, plc) in a phase-I trial (NCT01689207) that started in September 2012 but was not completed until December 2014. ATM-AVI was selected by the Innovative Medicines Initiative (IMI) 'New Drugs for Bad Bugs' (ND4BB) program in 2013. The IMI solicited proposals to evaluate the combination in a phase-IIa pharmacokinetic/pharmacodynamic analysis of ATM-AVI in patients with serious infections caused by G − ve pathogens, and in a phase-III randomized, multicenter, clinical study to evaluate the efficacy and safety of ATM-AVI in the treatment of serious infections caused by G − ve pathogens.[293] AstraZeneca recently announced a new phase-II trial (NCT02655419) that will evaluate the PK, safety and tolerability of ATM-AVI for the treatment of cIAIs in hospitalized adults.

OP0595 (**55**) (RG6080) is another DBO β-lactamase inhibitor[294] developed by Meiji Seika Pharma, Co. Ltd (Tokyo, Japan) and Fedora Pharmaceuticals (Edmonton, AB, Canada) and partnered with Roche in January 2015.[295,296] OP0595 (**55**) completed a phase-I trial (NCT02134834) in November 2014.

AAI101 is a novel extended-spectrum β-lactamase inhibitor developed by Allecra Therapeutics Gmbh (Weil am Rhein, Germany)/Allecra SAS (Saint Louis, France), an anti-infective company established in 2013 by Orchid Chemicals and Pharmaceuticals Ltd (Chennai, India) and lead investors Forbion Capital Partners (Naarden, The Netherlands) and Edmond de Rothschild Investment Partners (Paris, France).[297,298] Phase-I results were presented at ICACC 2014.[299] Preclinical testing has examined the combination with cefepime (**56**).[300,301] Allecra has a second β-lactam antibiotic/β-lactamase inhibitor combination, AAI202 that has also completed phase-I trials,[302] but no further information is available. No structures have been disclosed but they are likely to be a clavulanic acid-type inhibitors.[298]

Zidebactam (**57**) (WCK 5107)[303] is a β-lactamase inhibitor being developed by Wockhardt Biopharm (Mumbai, India). It is being tested in a phase-I trial initiated in August 2015 alone and in combination with cefepime (**56**) (NCT02532140).

COMPOUNDS DISCONTINUED FROM CLINICAL DEVELOPMENT

Compounds and β-lactam/β-lactamase inhibitor combinations that have been discontinued from clinical development or have had their development halted since the 2013 review[3] are listed in Table 6 with comments on the reasons for the cessation of development if known.

ANALYSIS OF COMPOUNDS UNDERGOING CLINICAL TRIALS

Numbers of compounds undergoing clinical evaluation and their source derivation

There are a total of 37 compounds and six β-lactam/β-lactamase inhibitor combinations currently undergoing clinical trials (Figure 11). Of the 37 compounds, 13 are in phase-III (Table 2; Figures 4 and 5), 17 in phase-II (Table 3; Figures 7 and 8) and seven in phase-I (Table 4;

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

Name (synonym)[a]	*Compound (lead source)*	*Mode of action*	*Bacteria type*	*Indication (developer)*
Phase-III				
Carbavance (meropenem (**43**)+vaborbactam (**50**))	Carbapenem (NP)/boron (S)	Penicillin-binding protein/β-lactamase inhibition	G+ve/G – ve	cUTI, Enterobacteriaceae infections (The Medicines Co)
Imipenem (**51**)+cilastatin (**52**)+relebactam (**53**)	Carbapenem (NP)/cilastatin (S)/diazabicyclooctane (S)	Penicillin-binding protein/dehydropeptidase inhibition/β-lactamase inhibition	G+ve/G – ve	UTI and cIAI (Merck)
Phase-I				
ATM-AVI (aztreonam (**54**)+avibactam (**11**))	Monobactam (NP)/DBO (S)	Penicillin-binding protein/β-lactamase inhibition	G – ve	Phase-I completed; phase-II announced (AstraZeneca)
OP0595 (**55**)	Not disclosed/DBO (S)	β-lactamase inhibitor	G+ve/G – ve	Phase-I (Roche)
Cefepime (**56**)+AAI101[b]	Cephalosporin (NP)/clavulanic acid[b] (NP)	β-lactamase inhibitor	G – ve	Phase-I (Allecra Therapeutics)
Cefepime (**56**)+zidebactam (**57**)	Cephalosporin (NP)/DBO (S)	β-lactamase inhibitor	G – ve	Phase-I (Wockhardt)

Abbreviations: cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; G – ve, Gram negative; G+ve, Gram positive; NP, natural product; S, synthetic.
[a]Underlined compound are new β-lactamase inhibitor pharmacophore.
[b]Structure not published but likely to be clavulanic acid-type.[298]

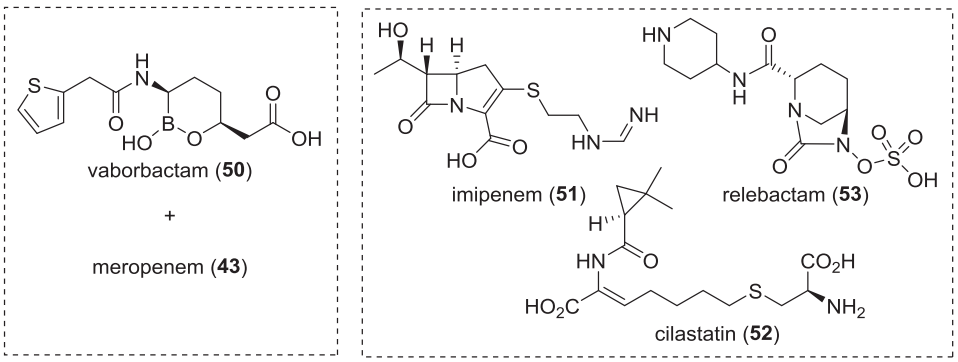

Figure 9 Structure of the β-lactamase inhibitor and β-lactam antibiotic combinations in phase-III clinical trials.

Figure 10), whereas there are two β-lactam/β-lactamase inhibitor combinations in phase-III and four in phase-I (Table 5; Figures 9 and 11). Nineteen antibiotics were synthetically-derived (S), 15 were NP-derived (NP), and three were protein/mammalian peptide-derived (P) (Figure 11). There is approximately the same number of compounds in each development phase in 2015 compared to 2013 (Figure 12). The only notable difference is between the number in phase-III trials in 2011 (6) compared to 2013 (16) and 2015 (15). Importantly, new antibiotics (ETX0914 (**38**), CB-06-01 (**30**), TD-1607 (**45**), CRS3123 (**47**; Replidyne had previously developed **47** as REP-3123 in phase-III trials in 2008), TBA-354 (**48**) and Q203 (**49**)) and β-lactamase inhibitors (OP0595 (**55**), AAI101 and zidebactam (**57**)) have entered the clinic to counteract those no longer being evaluated (Table 6).

New antibacterial pharmacophore analysis

The NP- and protein/mammalian peptide (P)-derived compound derivation is quite diverse but there are only four new antibacterial pharmacophores derived from NPs and three from P pharmacophores (Figure 13). The new NP and P pharmacophores are derived from porphyrin (phase-II; exeporfinium (**27**)/ porphyrin), *N*-chlorotaurine (auriclosene (**28**)/ *N*-chlorotaurine), thiopeptide (CB-06-01 (**30**)/ GE2270-A), and distamycin A (phase-I; MGB-BP-03 (**46**)), whereas brilacidin (**32**), LTX-109 (**33**) and POL7080 are derived from or inspired by naturally occurring cationic peptides. Similarly, the new synthetically-derived antibacterial pharmacophores are diverse: cadazolid (**22**; phase-III, oxazolidinone and quinolone chimera), ridinilazole (**36**; phase-II; bibenzimidazole), gepotidacin (**37**; phase-II, 'gepotidacin' class); ETX0914 (**38**; phase-II, spiropyrimidinetrione), Debio-1452 (**39**)/ Debio-1450 (both phase-II; benzodiazepine), CRS3123 (**47**; phase-I, diaryldiamine) and Q203 (**49**; phase-I, imidazo[1,2-*a*]pyridine amide). After the recent approval of the DBO class β-lactamase inhibitor avibactam (**11**) there is only one class of new pharmacophores: the boron class exemplified by vaborbactam (**50**), which is part of a combination with meropenem (**43**) called Carbavance. Although these classes have been classified as synthetically-derived for this review, they are inspired by the NP clavulanic acid, which was the first β-lactamase inhibitor reported.[282,283]

The total number of new pharmacophores rose from 11 in 2011 to 17 in 2013 and then back slightly to 15 in 2015 (Figure 14). Since 2013, five compounds with new antibacterial pharmacophores, LFF-571, lanopepden (GSK1322322), DPK-060 and ACHN-975 are not currently being actively pursued; whereas the peptide-derived LL-37 and IMX-942 have been retooled for anti-inflammatory purposes (Table 6).

CONCLUSION AND FUTURE OUTLOOK

There was a steady state of compounds entering and leaving antibiotic clinical trials (Figure 12) and those with new pharmacophores (Figure 14) from 2013 to 2015. Of the 15 new pharmacophores, only a few have activity against G – ve bacteria: the topically-administered auriclosene (**28**) and LTX-109 (**33**), and the IV-administered

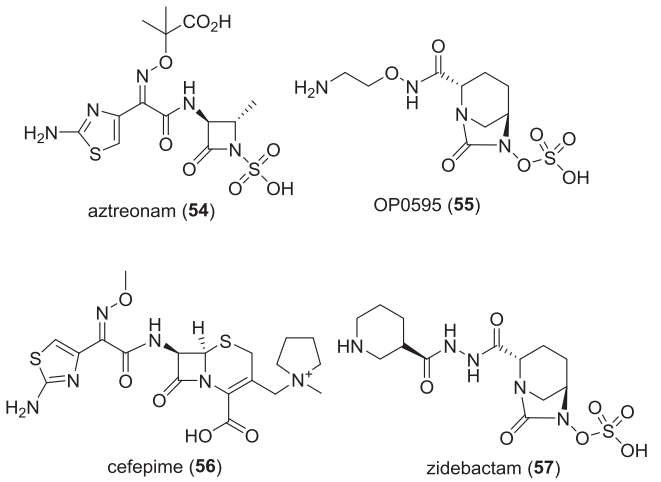

Figure 10 Structures of β-lactamase inhibitors and associated β-lactam antibiotics in phase-I clinical trials.

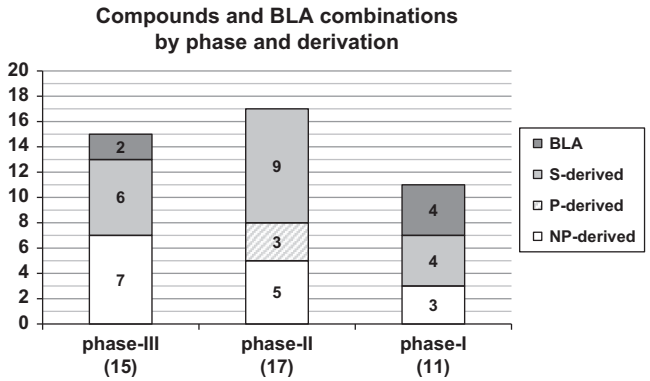

Figure 11 Compounds under clinical evaluation divided into development phases and their lead derivation source (natural product (NP), synthetic (S), protein/peptide (P)) with the β-lactam/β-lactamase inhibitor (BLA) combinations listed separately.

POL7080, brilacidin (**32**), gepotidacin (**36**) and ETX0914 (**38**). Other non-quinolone G − ve actives are the aminoglycoside plazomicin (**27**), the β-lactam-siderophore hybrids S-649266 (**31**) and BAL30072 (**44**) and the six β-lactamase inhibitor/β-lactam combinations that includes vaborbactam (**50**), which is a novel boron-containing β-lactamase inhibitor in phase-III trials with meropenem (**43**). A worrying trend is that there is only one G − ve active, BAL30072 (**44**), in phase-I development, which started its first trial in 2010 and was re-booted in late 2015 to evaluate an inhaled dosage form. Hopefully, some of these compounds will move forward into phase-III trials so that new G − ve drugs will be available to physicians to treat MDR infections.

Unfortunately, as this review illustrates, the acute positive trend of new approvals masks a chronic underlying malaise in antibiotic discovery and development. While there are a number of antibiotics in late stage trials near approval, the pipeline feeding further New Drug Applications is drying up, with relatively few early stage candidates. There is still interest in antibiotics from large pharmaceutical companies, as evidenced by Roche partnering with several small biotech antibiotic companies in the past few years (Polyphor 2013—discontinued 2015[196], RQx 2013, Spero Therapeutics 2014, Discuva Ltd 2014, GeneWeave 2015, Meiji Seika Pharma and Fedora 2015) and the Merck acquisition of Cubist for

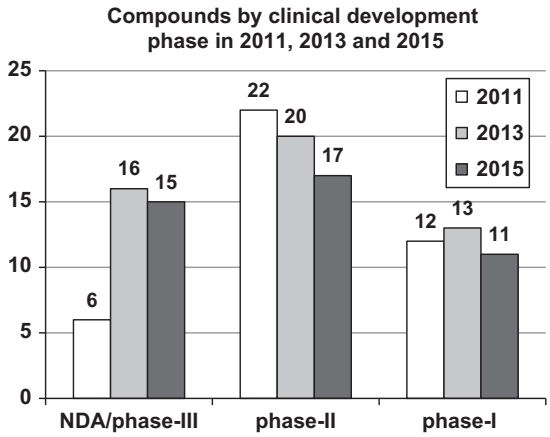

Figure 12 Comparison of the numbers of compounds undergoing clinical development as of 2011[2], 2013[3] and 2015 by development phase.

nearly $10 bn in 2014, although this is tempered by AstraZeneca shedding its antibiotic discovery group into Entasis Therapeutics (Waltham, MA, USA) in mid-2015. Many new antibiotics have arisen from smaller biotech companies, and this trend appears likely to continue with a number of new biotech startups forming such as Macrolide Pharmaceuticals (Watertown, MA, USA), Kaleido Biosciences (Cambridge, MA, USA) and Spero Therapeutics (Cambridge, MA, USA);[304] there are nearly 40 European biotech companies in the BEAM (Biotechs from Europe innovating in Anti-Microbial Resistance; http://beam-alliance.eu) alliance.[305]

Antibiotics remain at the forefront of treating infections, but there is also a growing trend towards alternatives to antibiotics, which includes 'non-compound' approaches such as antibodies, probiotics, lysins, phage therapy, immune stimulation and vaccines,[306] as well as a search for small molecule 'resistance breakers' designed to assist existing antibiotics overcome resistance,[307] much as β-lactamase inhibitors help β-lactams retain activity. Attempts are being made to re-invigorate traditional antibiotic discovery by creating more effective ways to isolate novel natural products,[308] such as assessing extremophiles or marine organisms grown under unusual conditions (for example, the Marine Bioproducts Engineering Center, Honolulu, HI, USA and Berkeley, CA, USA) or utilizing genomic screening technologies to look for specific sequences in gene expression libraries from DNA extracted from environmental samples that may be manipulated to produce novel antimicrobials[309] (for example, Warp Drive Bio LLC, Cambridge, MA, USA). NovoBiotic Pharmaceuticals (Cambridge, MA, USA) is using an 'iChip' to culture and isolate bacteria *in situ* in soil, which led to the highly publicized discovery of teixobactin.[310] Sanofi has partnered with the Fraunhofer Institute for Molecular Biology and Applied Ecology (Aachen, Germany) in a joint effort to explore natural products, mining Sanofi's collection of $>100\,000$ different microorganisms to cultivate them under various conditions and stimulate them to produce active substances.[311] The Community for Open Antimicrobial Drug Discovery (Brisbane, Australia) is a Wellcome Trust and the University of Queensland initiative that is attempting to mine the chemical diversity contained in millions of organic chemist's laboratories around the world to uncover new synthetic chemotypes.[312,313]

The current clinical trial status of new antibiotics outlined in this review indicates we still face a serious threat from new extremely drug-resistant G − ve bacteria, including the polymyxin-resistant strains that

Table 6 Compounds discontinued or likely to have been discontinued from clinical development since 2013

Name (synonym)[a]	*Compound class (lead source); mode of action*	*Last known status and indication*
Acorafloxacin (avarofloxacin, JNJ-32729463, JNJ-Q2)	Fluoroquinolone (S); DNA gyrase and topoisomerase IV	Irritable bowel syndrome and available for licensing; phase-II CABP, ABSSSI completed (Furiex)
LFF-571	GE2270-A (NP); elongation factor Tu	CDAD phase-II completed but not listed in Novartis pipeline
Sutezolid (PF-2341272, PNU-100480)	Oxazolidinone (S); protein synthesis inhibition	TB phase-II; no update from Sequella and Pfizer since 2013
Posizolid (AZD 2563, AZD-5847)	Oxazolidinone (S); protein synthesis inhibition	TB phase-II completed and not in AstraZeneca pipeline
Lanopepden (GSK1322322)	Actinonin (NP); peptide deformylase	cSSSI phase-II completed; other phase-I trials halted in early 2015 and not in GSK pipeline
Ceftaroline/avibactam (**11**)	Cephalosporin (NP)/diazabicyclooctane (S); penicillin-binding protein/β-lactamase inhibitor	Completed phase-II against MRSA and no update since January 2014 (Actavis)
CG400549	Triclosan (S); FabI inhibition	ABSSSI completed in 2013 (CrystalGenomics)
DPK-060 (CD-1)	AMP-derived from human protein kininogen (P)	Phase-II (external otitis, atopic dermatitis) completed October 2013 Pergamum AB (DermaGen AB)
LL-37	Cathelicidin subunit (P)	Wound healing in chronic leg ulcers phase-I/II (Pergamum AB)
IMX-942	Indolicidin and IDR1 (P); ZZ domain of human p62 (sequestosome-1)	Immuno-modulator in combination with antibiotic for ABSSSI (Inimex); now being pursued in phase-II trial by Soligenix as treatment for oral mucositis as SGX-942 (NCT02013050)
KPI-10	Fluoroquinolone (S); DNA gyrase and topoisomerase IV	In phase-I trials in 2012 but no update (Kalidex)
NVB-302	Deoxyactagardine B (NP); cell wall biosynthesis	G+ve; completed phase-I in 2012 and available for licensing (Novacta Biosystems)
ACHN-975	New class (S); *N*-acetylglucosamine deacetylase (LpxC) inhibitor	G – ve; observation of inflammation at the infusion site in some of phase-1 subjects (Achaogen)
DS-8587	Fluoroquinolone (S); DNA gyrase and topoisomerase IV	Phase-I; discontinued in 2014 (Daiichi)
Ramoplanin	Ramoplanin (NP); cell wall-production inhibition	G+ve; no update from Nano therapeutics, Inc. (Alachua, FL, USA) since December 2009; CDAD phase-II trials completed before 2006; planning Phase-IIb in 2016

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CDAD, *C.* difficile-associated diarrhea; cIAI, complicated intra-abdominal infections; cSSSI, complicated bacterial skin and skin structure infections; G – ve, Gram negative; G+ve, Gram positive; MRSA, methicillin-resistant *S. aureus*; NP, natural product; P, protein/peptide; S, synthetic; TB, tuberculosis.
[a]Underlined compounds were potential new antibacterial pharmacophores.

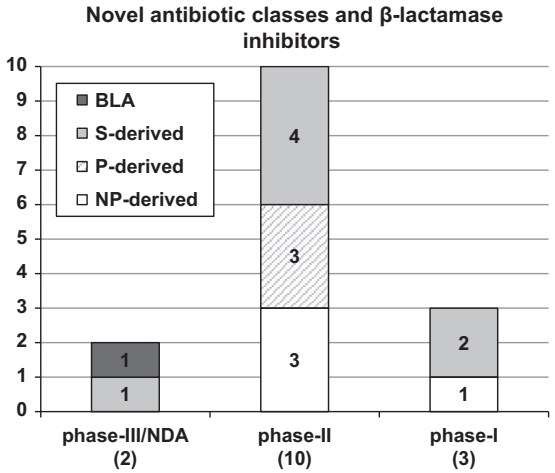

Figure 13 Compounds [natural product (NP), synthetic (S), protein/peptide (P)] and β-lactamase (BLA) inhibitors with new antibacterial pharmacophores divided into development phases and their lead derivation source.

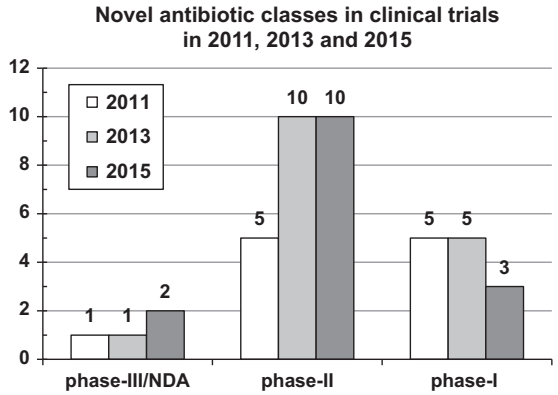

Figure 14 Comparison of the numbers of novel antibacterial pharmacophores undergoing clinical development in 2011[2], 2013[3] and 2015 by development phase.

generated a great deal of publicity in late 2015. There are few novel therapies in the pipeline, and innovative approaches for G – ve bacteria are scarce. The only light on the horizon is the continued increase in public and political awareness of the issue. Much of the innovation now appears to be driven by small biotech companies, with later stage partnerships with large pharma companies. However, with the continued retirement and retrenchment of experienced, qualified antibiotic development professionals, we potentially face a generational knowledge gap. It is now more important than ever to continue to search for and develop new antibacterial drug leads to stem a MDR bacteria tsunami that threatens to push us into a human health era where most G – ve infections will not be able to be treated. Equally importantly we need incentives to retain the few antibiotic researchers left today.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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