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REVIEW ARTICLE

Antibiotics in the clinical pipeline in 2011

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The emergence of multi-drug-resistant bacteria and the lack of new antibiotics in the antibiotic drug development pipeline, especially those with new modes of action, is a major health concern. This review lists the 20 new antibiotics launched since 2000 and records the 40 compounds currently in active clinical development. Compounds in the pipeline from new antibiotic classes are reviewed in detail with reference to their development status, mode of action, spectrum of activity and lead discovery. In addition, the NP or synthetic derivation is discussed, with activity against Gram-negative bacteria highlighted.
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Keywords: clinical trials; drug development; drug discovery; natural product; resistance

INTRODUCTION

The discovery of sulfonamides and β-lactam antibiotics in the 1930s had a profound impact on human health by enabling rapid treatment of patients with bacterial infections that previously had often proved fatal.[1,2] Over the next 40 years, now seen as the "golden era" of antibiotic research, the majority of antibiotic drug classes in use today were discovered. Since 1970, most newly approved antibiotics (see Table 1 for antibiotics launched since 2000) have been based on these known scaffolds, with the exception of linezolid (**1**), an oxazolidinone; daptomycin (**2**), a lipopeptide; and the topical antibiotics mupirocin (launched 1985), a pseudomonic acid, and retapamulin (**3**), a pleuromutilin derivative.[3]

The lack of new antibiotics, the emergence of multi-drug-resistant bacteria and the economic and regulatory challenges of antibiotic research have been discussed in depth.[4–20] The potential for a major antibiotic healthcare crisis is best summarized by the Infectious Diseases Society of America (IDSA)[21–23] and the European Centre for Disease Prevention and Control,[16,24] both of which report that there are only a few potential drugs in clinical development that (1) offer significant benefits over existing drugs and (2) that target Gram-negative, hospital-based infections. Gram-negative bacteria are especially difficult to kill as they have an additional outer membrane permeability barrier that compounds need to surmount to be efficacious, as well as often possessing multiple efflux pumps, and antibiotic and target-modifying enzymes.[20,25,26] Despite these considerable challenges, antibiotic drug development is in fact well validated, with a historically high approval rate following successful completion of phase-I studies.[15]

This article reviews all antibiotics that have been launched since 2000, and compounds that are currently undergoing clinical development in phase-I, II or III trials, and under regulatory evaluation as of early 2011. Compounds representing new antibiotic classes are reviewed in detail with reference to their development status, mode of action, spectra of activity and historical discovery. New combinations of previously approved antibiotics have not been included. In addition, the origin of the drug pharmacophore; the natural product (NP) or synthetic derivation, is also reviewed. These data were obtained by reviewing the journal literature and internet resources such as company webpages, clinical trial registers and biotechnology-related newsletters. Some compounds where there has been no evidence of recent development have been excluded from this review. Every endeavor has been undertaken to ensure that these data are accurate, but it is possible that compounds undergoing early clinical development have been overlooked.

The drug development and approval process, as well as commonly used abbreviations associated with antibiotic development used in this review, are summarized as follows:

- Before clinical trials can start, an Investigational New Drug Application (IND) must be approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA) or equivalent agency.
- The clinical indication for clinical trial approval in general falls within one of the following categories of antibacterial infections: *Clostridium difficile* infections (CDI), *C. difficile*-associated diarrhea (CDAD), skin and skin structure infections (SSSi), which are further divided into complicated (cSSSi), uncomplicated (uSSSi) and acute bacterial (ABSSSi), community/hospital acquired pneumonia (CAP/HAP), community-acquired bacterial pneumonia (CABP), urinary tract infections (UTI), complicated intra-abdominal infections (cIAI) and tuberculosis (TB).

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Table 1 New antibacterial drugs launched since 2000 divided into NP- and synthetically-derived listed by antibiotic class

Year	*Name*	*Class*	*Lead (source)*
NP-derived			
2002	Biapenem (**4**)	β-Lactam (carbapenem)	Thienamycin (actinomycete)
2002	Ertapenem (**5**)	β-Lactam (carbapenem)	Thienamycin (actinomycete)
2005	Doripenem (**6**)	β-Lactam (carbapenem)	Thienamycin (actinomycete)
2009	Tebipenem pivoxil (**7**)	β-Lactam (carbapenem)	Thienamycin (actinomycete)
2008	Ceftobiprole medocaril (**8**)	β-Lactam (cephalosporin)	Cephalosporin (fungus)
2010	Ceftaroline fosamil (**9**)	β-Lactam (cephalosporin)	Cephalosporin (fungus)
2001	Telithromycin (**10**)	Macrolide (ketolide)	Erythromycin (actinomycete)
2003	Daptomycin (**2**)[a]	Lipopeptide	Daptomycin (actinomycete)
2005	Tigecycline (**11**)	Tetracycline	Tetracycline (actinomycete)
2007	Retapamulin (**3**)[a,b]	Pleuromutilin	Pleuromutilin (fungus)
2009	Telavancin (**12**)	Glycopeptide	Vancomycin (actinomycete)
Synthetically-derived			
2000	Linezolid (**1**)[a]	Oxazolidinone	Oxazolidinone
2002	Prulifloxacin (**13**)	Fluoroquinolone	Quinolone
2002	Pazufloxacin (**14**)	Fluoroquinolone	Quinolone
2002	Balofloxacin (**15**)	Fluoroquinolone	Quinolone
2004	Gemifloxacin (**16**)	Fluoroquinolone	Quinolone
2007	Garenoxacin (**17**)	Quinolone	Quinolone
2008	Sitafloxacin (**18**)	Fluoroquinolone	Quinolone
2009	Antofloxacin (**19**)[c]	Fluoroquinolone	Quinolone
2009	Besifloxacin (**20**)	Fluoroquinolone	Quinolone

Abbreviation: NP, natural product.
[a]First member of a new antibiotic class approved for human use underlined. Please note that pleuromutilin derivatives had been previously used in animal health.[132]
[b]For topical use only.
[c]Jointly developed by the Shanghai Institute of Materia Medica and Anhui Global Pharmaceutical and approved for use in China in 2009.[133–135]

- Upon successful completion of phase-III clinical trials, a New Drug Application (NDA/FDA and PMDA) or a Marketing Authorization Application (MAA/EMA) must be submitted to seek approval to be able to market the drug.

ANTIBACTERIAL DRUGS LAUNCHED SINCE 2000

Since 2000, 20 new antibiotics have been launched worldwide (Table 1; Figures 1 and 2), of which 11 are NP-derived and nine are synthetically derived. A majority of the NP-derived antibiotics belong to the β-lactam class, with the other five belonging to separate classes. Noteworthy among the NP-derived antibiotics are daptomycin (**2**) and retapamulin (**3**), the first members of the lipopeptide and pleuromutilin classes, respectively, approved for use in humans. Within the synthetically derived antibiotics there is minimal diversity, with eight of the nine antibiotics belonging to the quinolone class and linezolid (**1**), which is the first and, to date, the only representative of the oxazolidinone class.

COMPOUNDS UNDERGOING CLINICAL EVALUATION

This section describes compounds and their structures currently undergoing clinical trials and under regulatory evaluation for the treatment of bacterial infections as of early 2011 (phase-III/(NDA) in Table 2, with structures in Figure 3; phase-II in Table 3, with structures in Figures 3 and 4; and phase-I in Table 4, with structures in Figure 7). Compounds that represent new antibiotic classes are underlined in the tables and a summary of their development status, mode of action and discovery is discussed in detail.

Phase-III trials and NDA/MAA applications

Fidaxomicin (**21**), which is being developed by Optimer Pharmaceuticals (San Diego, CA, USA), is currently undergoing evaluation for market approval by the FDA (NDA finalized in November 2010) and EMA (MAA submitted in September 2010) for the treatment of patients with CDIs.[27,28] *C. difficile* is a spore-forming Gram-positive anaerobe that can cause serious intestinal infections through secreted toxins that cause inflammation of the colon, severe diarrhea, fever with an elevated white blood cell count, and intestinal paralysis and sepsis in widespread infections.[29,30] CDI can be lethal, especially in compromised patients, and there are increasing worldwide outbreaks of new virulent and highly toxic strains of *C. difficile*.[31] Currently only metronidazole and vancomycin are routinely used to treat CDI, and development of new agents is urgently required.[32] Data from two phase-III trials indicated that fidaxomicin (**21**) was able to achieve the primary endpoint of clinical cure, which was defined as patients not requiring any further CDI therapy 2 days after the completion of the fidaxomicin (**21**) course.[33,34] In addition, fidaxomicin (**21**) showed a higher global cure rate than vancomycin and a lower recurrence rate, which was defined as no recurrence within 4 weeks. Fidaxomicin (**21**) belongs to a family of actinomycete-derived macrolactone with a complex history. The structure of **21**, which was named tiacumicin-B, and a series of analogs were reported by Abbott Laboratories in a patent filed in 1986[35] and published in 1987.[36,37] Fidaxomicin (**21**) and analogs have identical structures to the lipiarmycins whose isolation and biological activity, and structure elucidation, were reported in 1975[38–41] and 1987[42,43] respectively, and the clostomicins whose activity and structures were reported in 1986.[44] Early on these macrolactones were shown to be inhibitors of the bacterial DNA-dependent RNA polymerase.[41,45–47] Recent studies have shown that these macrolactones impede the *de novo* initiation of RNA synthesis through binding to the ó70-subunit region-3.2 and the RNA polymerase β′-subunit switch-2 element, which controls the clamping of the promoter DNA in the RNA polymerase active-site cleft.[48] In

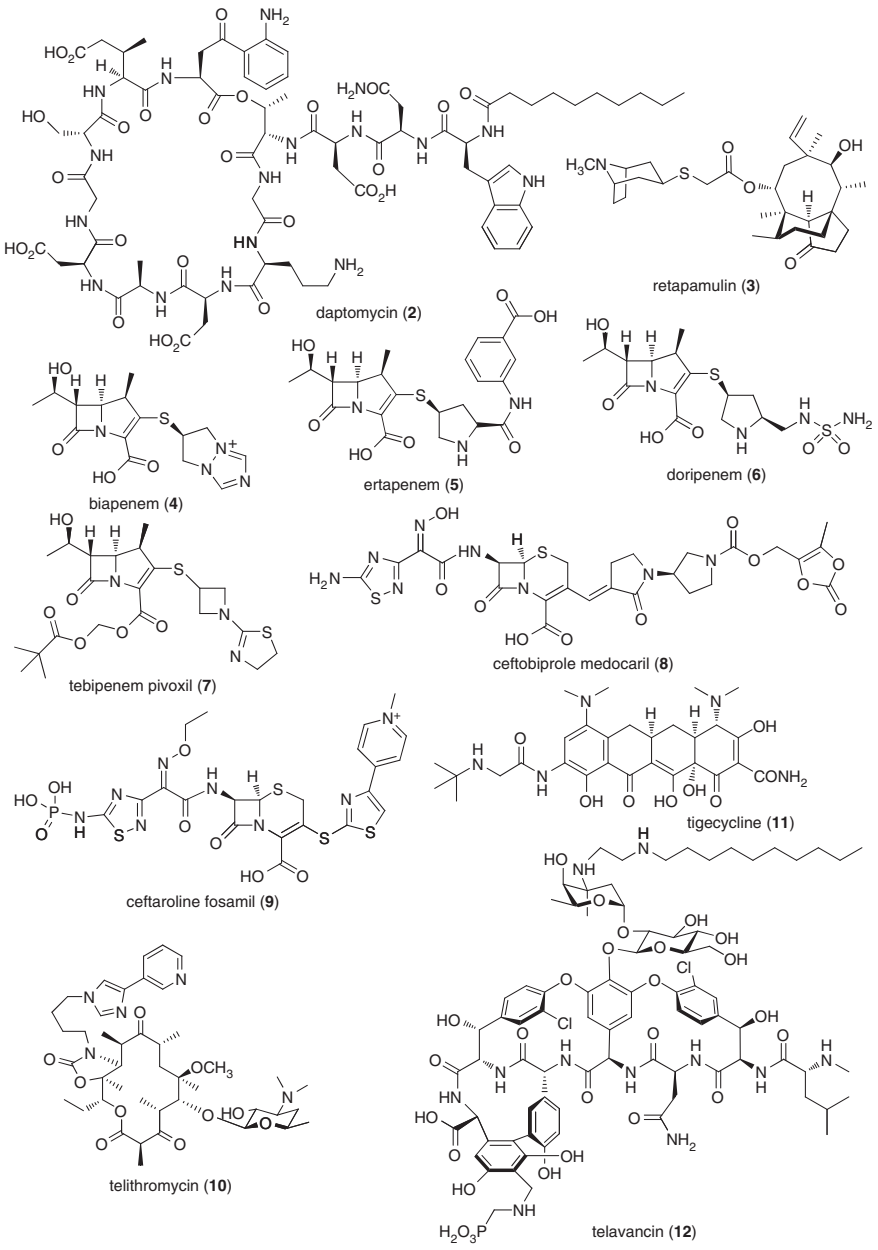


Figure 1 Structures of NP-derived antibiotics launched since 2000.

addition to showing activity against Gram-positive bacteria, these macrolactones also function against multi-drug-resistant tuberculosis (TB) strains through the same mechanism.[49]

Phase-II trials

In December 2009, Nanotherapeutics (Alachua, FL, USA) acquired ramoplanin (**30**) from Oscient Pharmaceuticals, a company undergoing bankruptcy proceedings that had in turn licensed the North American rights from Vicuron (Figure 5).[50] Ramoplanin (**30**), which is the abbreviation commonly used for ramoplanin-A_2, has been evaluated in phase-II trials for the treatment of *C. difficile*-associated diarrhea, with plans to undertake phase-III trials.[50] The ramoplanin lipopeptide antibiotic complex produced by *Actinoplanes* sp. was first described by Gruppo Lepetit S.p.A. in 1984,[51,52] with structures reported in 1989.[53–55] Ramoplanin (**30**) has been shown to bind to the peptidoglycan intermediate Lipid-II, which disrupts bacterial cell wall synthesis, causing bacterial cell death.[56–58] An X-ray structure of ramoplanin (**30**) in the presence of detergents showed that **30** forms an intimate and highly amphipathic dimer, which allowed a model of **30** binding to Lipid-II to be proposed.[59]

GSK1322322 (**34**),[60–63] which is being developed by GlaxoSmithKline (GSK, Brentford, UK), has recently completed a phase-II trial for acute bacterial skin and skin structure infections (ABSSSis).[64] As well as possessing potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), this compound also shows activity against the respiratory pathogens *Haemophilus influenzae* and *Streptococcus pneumoniae*. GSK1322322 (**34**) targets bacterial peptide deformylase, a metallo-hydrolase enzyme that catalyzes the removal of the formyl group from the *N*-terminal methionine following translation.[65,66] BB83698 (**47**) (Oscient)[66,67] and LBM-415 (**48**) (Novartis, Basel, Switzerland)[66,68,69] were the first peptide deformylase inhibitors to reach phase-I trials, but no further development of either compound

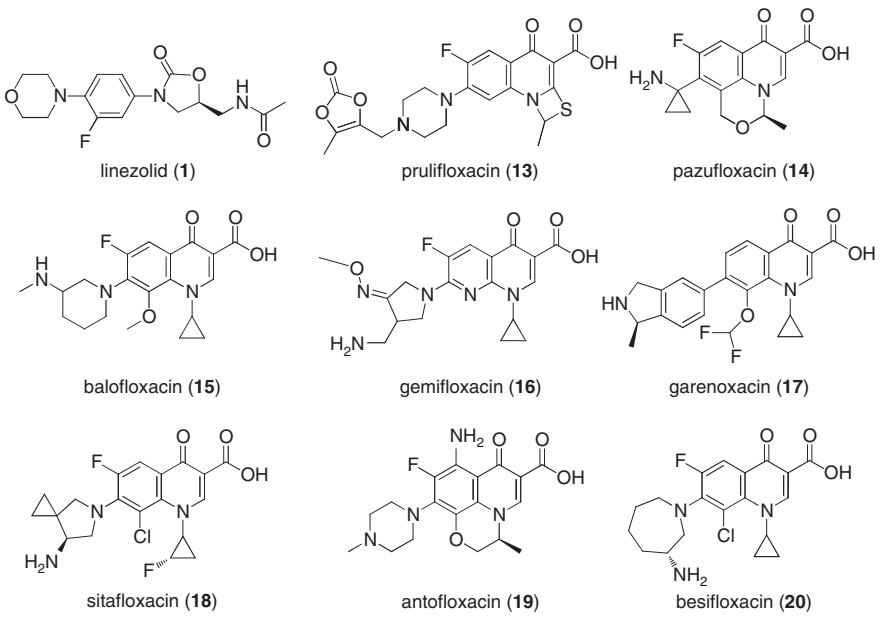


Figure 2 Structures of synthetically derived antibiotics launched since 2000.

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

Name (synonym)	*Lead compound (source)*	*Mode of action*	*Development status, indication (Developer)*
Fidaxomicin (**21**) (tiacumicin-B, difimicin, OPT-80)[27–31,33,34,36,37,48]	Tiacumicin-B (**21**) (NP)	RNA synthesis inhibition	CDI MAA in September 2010 and NDA November 2010 (Optimer)
Amadacycline (**22**) (PTK-0796; MK-2764)[136,137]	Tetracycline (NP)	Protein synthesis inhibition	Phase-III cSSSi (Paratek/Novartis)
Torezolid phosphate (**23**) (TR-701, DA-7218)[138–140]	Oxazolidinone (S)	Protein synthesis inhibition	Phase-III ABSSSI (Trius Therapeutics)
Oritavancin (**24**)[141–145]	Glycopeptide (chloroeremomycin) (NP)	Cell wall production inhibition	Phase-III ABSSSi (The Medicines Company)
Dalbavancin (**25**)[145–149]	Glycopeptide (A40926) (NP)	Cell wall production inhibition	Phase-III ABSSSi (Durata Therapeutics)
Cethromycin (**26**) (ABT-773)[150–154]	Erythromycin (NP)	Protein synthesis inhibition	CAP NDA submitted October 2008 but rejected due to "no efficacy" 2 June 2009 (Advanced Life Sciences)

Abbreviation: NDA/MAA, New Drug Application/Marketing Authorization Application.

was undertaken.[66] The original lead compound, actinonin (**49**),[70,71] was identified by Vicuron as a peptide deformylase inhibitor by searching for NPs that possessed a hydroxamate metal chelating group and methionine-like structures (Figure 6).[72]

NVC-422 (**35**) (*N*,*N*-dichloro-2,2-dimethyltaurine), which was discovered by NovaBay Pharmaceuticals (Emeryville, CA, USA), is being evaluated in a phase-II trial to prevent urinary catheter blockade and encrustation.[73] NovaBay has also been working with Alcon (Hünenberg, Switzerland) for eye, ear and sinus infections, and contact lens care, and with Galderma (Les Templiers, France) for acne, impetigo and other dermatological indications.[74] NVC-422 (**35**) was designed to be a more stable derivative of the naturally occurring oxidant *N*-dichlorotaurine.[75–77] *N*-chloro derivatives of amino acids and peptides can act as oxidants, and are involved in the human immune defense system in the killing of pathogens and control of inflammatory responses.[78] *N*-dichlorotaurine was first identified in 1971, when chlorination of amino acids by the myeloperoxidase system[79,80] was identified as having an important role in the human body because of its relatively high concentration and superior stability over other chlorinated amino acids.[78]

PMX-30063 (structure not released), which was discovered by researchers at the University of Pennsylvania and PolyMedix (Radnor, PA, USA), is currently being evaluated in phase-II trials as a treatment of *Staphylococcus* infections, including MRSA.[81,82] PMX-30063 is a membrane-active antimicrobial arylamide oligomer mimetic of a host defense protein,[83–86] which is bactericidal against both Gram-positive and Gram-negative bacteria, and has a has a very low propensity for resistance development.[82]

Bedaquiline (**36**) (TMC207, R207910, JNJ-16175328) is being developed by Tibotec (Beerse, Belgium) and the Global Alliance for TB Drug Development (New York, NY, USA)[87] for the treatment of patients with pulmonary TB.[88] Bedaquiline (**36**) has successfully completed one phase-II trial and was found to be efficacious against multi-drug-resistant TB.[89,90] Whole-cell screening of *Mycobacterium smegmatis*, a surrogate for screening against *M. tuberculosis*, identified a series of diarylquinolines and structure optimization led to the

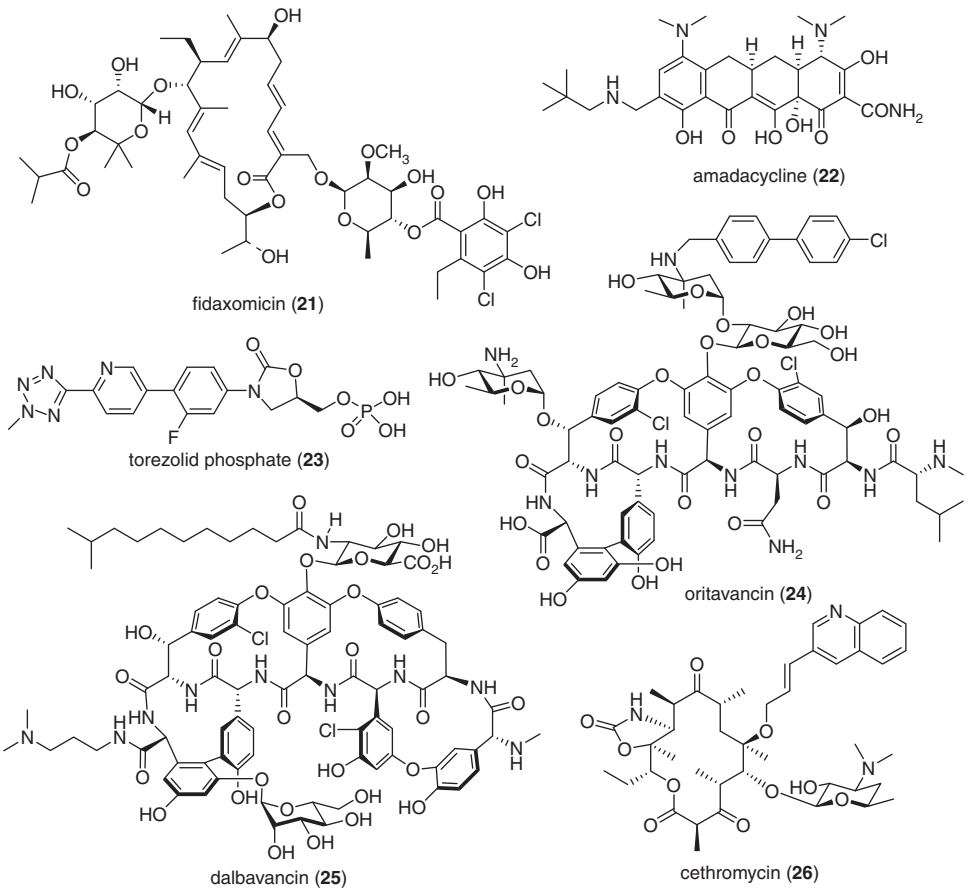


Figure 3 Structures of compounds in phase-III clinical trials or under NDA/MAA evaluation. NDA/MAA, New Drug Application/Marketing Authorization Application.

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

Name (synonym)	*Lead compound (source)*	*Mode of action*	*Development status, indication (Developer)*
ACHN-490 (**27**)[155–157]	Aminoglycoside (NP)	Protein synthesis inhibition	UTI and pyelonephritis (Achaogen)
BC-3781 (**28**)[132,158–160]	Pleuromutilin (NP)	Protein synthesis inhibition	ABSSSi (Nabriva)
CB-183,315 (**29**)[161,162]	Daptomycin (NP)	Membrane depolarization	CDAD (Cubist)
Ramoplanin (**30**)[50–59]	Ramoplanin (NP)	Cell wall production inhibition	CDAD completed (Nanotherapeutics)
TP-434 (**31**)[163,164]	Tetracycline (NP)	Protein synthesis inhibition	cIAI (Tetraphase)
Solithromycin (**32**) (CEM-101)[165–168]	Erythromycin (NP)	Protein synthesis inhibition	CABP (Cempra)
CXA-101 (**33**) (FR264205)[169–171]	Cephalosporin (NP)	Penicillin-binding protein	cIAI (Cubist)
GSK1322322 (**34**)[60–64]	Actinonin (**49**) (NP)	Peptide deformylase	cSSSi completed (GSK)
PMX-30063[81–86]	Defensin (NP)	Bacterial cell membrane lysis	ABSSSi (PolyMedix)
NVC-422 (**35**)[75–78]	*N*-chlorotaurine (NP)	Oxidation	Ophthalmic, impetigo, urinary catheter blockade and encrustation (Alcon/Galderma/Novabay)
ACT-179811[172]	Unknown	Unknown	CDAD (Actelion)
Bedaquiline (**36**) (TMC207, R207910)[87,89–94]	Diarylquinoline (S)	F0 subunit of mycobacterial ATP synthase	TB (Tibotec/Global Alliance for TB Drug Development)
SQ109 (**37**)[173–175]	Ethambutol (S)	Cell wall synthesis	TB, *H. pylori* associated duodenal ulcer (Sequella)
OPC-67683 (**38**)[176,177]	Nitroimidazole (S)	Mycolic acid inhibitor	TB (Otsuka Pharmaceutical)
PA-824 (**39**)[178–181]	Nitroimidazole (S)	DNA and cellular damage	TB (Global Alliance for TB Drug Development)
Delafloxacin (**40**) (RX-3341, ABT-492)[182–184]	Fluoroquinolone (S)	DNA gyrase and topoIV	cSSSi completed (Rib-X)
Finafloxacin (**41**) (BAY 35-3377)[185,186]	Fluoroquinolone (S)	DNA gyrase and topoIV	*H. pylori* and UTI completed (MerLion)
JNJ-32729463 (**42**) (JNJ-Q2)[187,188]	Fluoroquinolone (S)	DNA gyrase and topoIV	CABP, cSSSi (Furiex)
Zabofloxacin (**43**) (PB-101, DW-224a)[189,190]	Fluoroquinolone (S)	DNA gyrase and topoIV	CAP (IASO Pharma/Dong Wha)
Nemonoxacin (**44**) (TG-873870)[191–194]	Quinolone (S)	DNA gyrase and topoIV	CAP, diabetic foot infection completed (TaiGen/Warner Chilcott)
Iclaprim (**45**) (AR-100, Ro 48-2622)[195–198]	Trimethoprim (S)	Dihydrofolate reductase	HAP, cSSSi completed (Acino Holding)
Radezolid (**46**) (RX-1741)[199–202]	Oxazolidinone (S)	Protein synthesis inhibition	uSSSI, CAP completed (Rib-X)

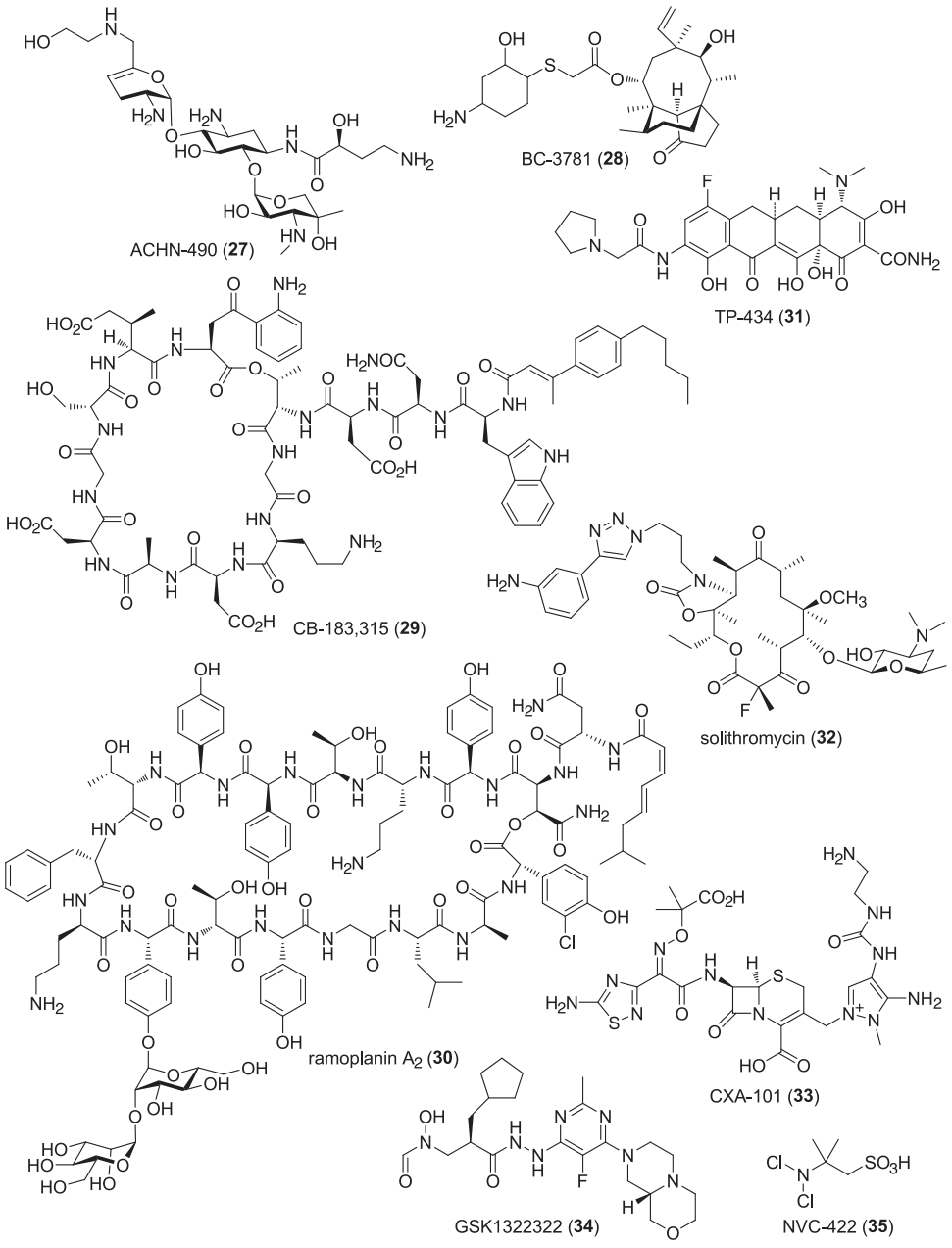


Figure 4 Structures of NP-derived compounds in phase-II clinical trials. NP, natural product.

identification of bedaquiline (**36**).[91] *In vitro* serial passage experiments generated resistant mutants that suggested that **36** targets the mycobacterial proton pump of ATP synthase.[91] Further mechanistic studies have shown that bedaquiline (**36**) specifically targets the oligomeric subunit-c of mycobacterial ATP synthase.[92–94]

Phase-I trials

Lotilibcin (**53**) (WAP-8294A$_2$), which is being developed by aRigen Pharmaceutical (Tokyo, Japan), is being evaluated as an injectable formulation in phase-I trials (Figure 7).[95] aRigen recently announced that they had licensed **53** to Green Cross Corporation (Yongin, Korea), who will undertake phase-II after completion of the phase-I trial.[95] Lotilibcin (**53**) is the major component of a WAP-8294 antibacterial complex[96] produced by the Gram-negative bacterium *Lysobacter* sp. discovered by Wakamoto Pharmaceutical (Tokyo, Japan).[97–99] Lotilibcin (**53**) has excellent bactericidal activity against MRSA and acne, and has been proposed to interact selectively with phospholipids in the bacterial membrane, which results in membrane damage leading to bacterial cell death.[97–99]

XF-73 (**54**) is a porphyrin derivative being developed by Destiny Pharma (Brighton, UK) that has been evaluated in a phase-I trial as treatment for nasal decolonization of *S. aureus* (including MRSA).[100] XF-73 (**54**) is also being evaluated in pre-clinical studies for the treatment of ulcers and the promotion of wound healing, and CDI. XF-73 (**54**) has activity against a variety of drug-resistant, Gram-positive pathogens that is thought to be mediated by perturbation of the cytoplasmic membrane, although the exact mode of action is unknown.[101–105]

GSK2251052 (**55**) (AN3365) was discovered by Anacor (Palo Alto, CA, USA) and is currently being evaluated in phase-I trials by GSK

Table 4 Compounds in phase-I clinical trials

Name (synonym)	*Lead compound (source)*	*Mode of action*	*Development status, indication (Developer)*
BAL30072 (**50**)[203–205]	Monobactam (NP)	Penicillin-binding protein	Dosing studies, Gram-negative (Basilea)
BC-7013 (**51**)[132,206]	Pleuromutilin (NP)	Protein synthesis inhibition	Topical (Nabriva)
BC-3205 (**52**)[132,207]	Pleuromutilin (NP)	Protein synthesis inhibition	Oral (Nabriva)
Lotilibcin (WAP-8294A_2) (**53**)[95–99]	WAP-8294A_2 (**53**) (NP)	Phospholipid binding resulting in bacterial membrane damage	i.v. formulation (MRSA) (aRigen)
XF-73 (**54**)[100–105]	Porphyrin (NP)	Membrane-perturbing activity	Topical MRSA (Destiny Pharma)
AZD9742[208]	Unknown	Unknown	i.v. dosing and metabolism studies (AstraZeneca)
GSK2251052 (**55**) (AN3365)[106–112]	AN2690 (S)	Aminoacyl-tRNA synthetase	Gram-negative systemic (GSK/ Anacor)
AZD5847[209]	Oxazolidinone (S)	Protein synthesis inhibition	Dosing studies, TB (AstraZeneca)
PNU-100480 (**56**) (PF-02341272)[209–212]	Oxazolidinone (S)	Protein synthesis inhibition	Dosing studies, TB (Pfizer)
AFN-1252 (**57**) (API-1252)[15,113–115,118]	Synthetic lead **58** (S)	FabI inhibition	Oral formulation, MRSA (Affinium)
FAB-001 (**59**) (MUT056399)[117,119]	Triclosan (**60**) (S)	FabI inhibition	Entered phase-I September 2009 (FAB Pharma)
CG400549 (**61**)[117,120–122]	Triclosan (**60**) (S)	FabI inhibition	Dosing studies (CrystalGenomics)

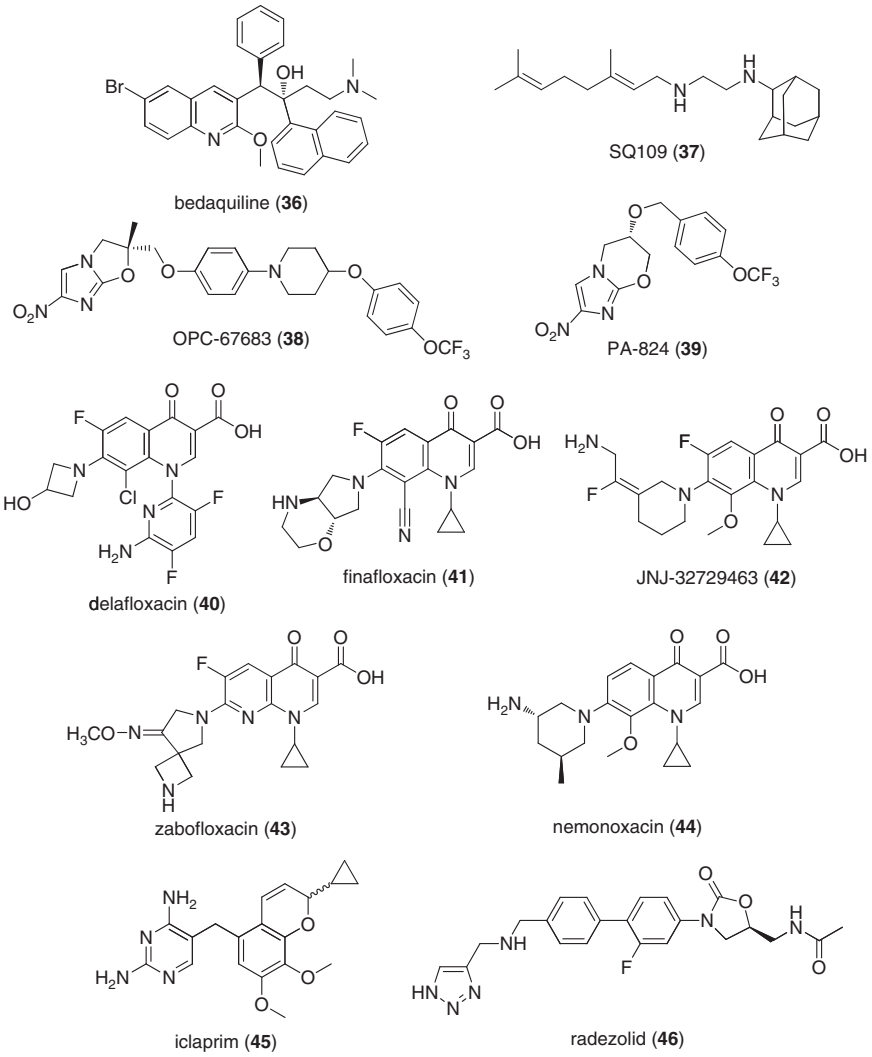
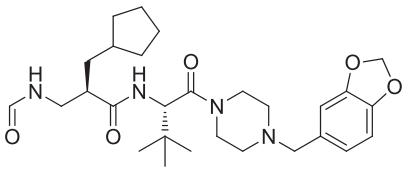
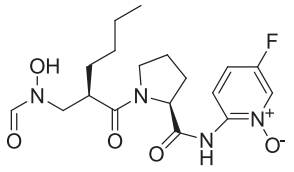


Figure 5 Structures of synthetically derived compounds in phase-II clinical trials.

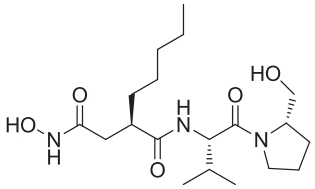
for the treatment of hospital-acquired Gram-negative infections, including *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter* species.[106,107] GSK2251052 (**55**) is a new type of protein synthesis inhibitor[108,109] that binds to the active editing site of LeuRS through coordination of the Boron atom to the *cis*-diols of the ribose on the terminal nucleotide of $tRNA^{Leu}$ GSK2251052 (**55**), which was



BB83698 (**47**)



LBM-415 (**48**)

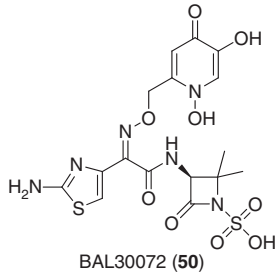


actinonin (**49**)

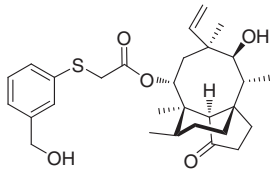
Figure 6 Structures of peptide deformylase inhibitors 47 and 48, and lead compound actinonin (49).

discovered using a structure-based design approach that was initiated with a co-crystal of $tRNA^{Leu}$ and AN2690,[108–112] is noteworthy as being one of the first truly novel antibiotics with Gram-negative activity that has successfully completed a phase-I trial.

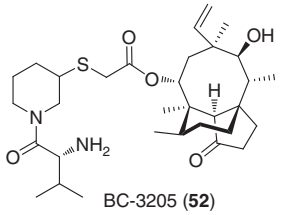
AFN-1252 (**57**)[113,114] is being evaluated in a phase-I trial using an improved oral formulation by Affinium Pharmaceuticals (Austin, TX, USA), having successfully completed other phase-I trials that used single and multiple ascending doses.[115] AFN-1252 (**57**) selectively disrupts staphylococcal bacterial fatty acid biosynthesis through inhibiting FabI, 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.[116,117] The activity of **57** is restricted to *S. aureus*, *Staphylococcus epidermidis* and a few other bacterial species due to the specificity and the restricted distribution of FabI.[113,114] Although this narrow spectrum of activity may impart a safety advantage over conventional antibiotics that can indiscriminately kill non-pathogenic microorganisms, it will also limit the compound's use, and as a consequence, potential market size. AFN-1252 (**57**) is a synthetically derived antibiotic that had its genesis in a high-throughput screen undertaken at GSK that tested 305 189 compounds against the *S. aureus* FabI and identified a benzodiazepine **58** with micromolar range activity.[15,118] The use of a crystal structure-based design led to the discovery of the 3,4-dihydro-1,8-naphthyridin-2(1H)-one **62**, which had selective, potent activity against FabI, and good *in vitro* and *in vivo* antibacterial



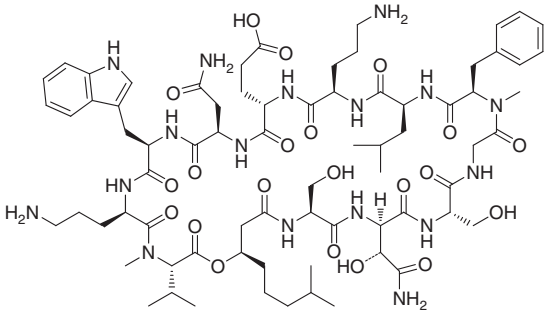
BAL30072 (**50**)



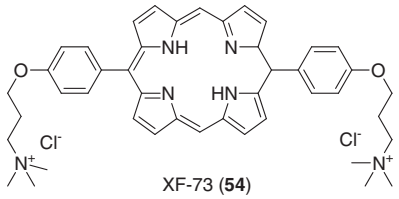
BC-7013 (**51**)



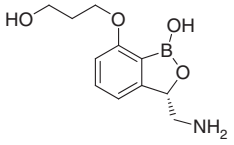
BC-3205 (**52**)



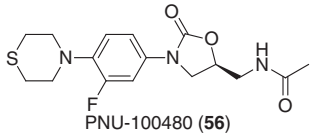
Iotilibcin (**53**)



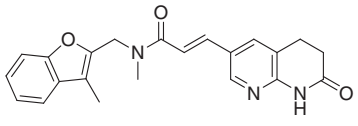
XF-73 (**54**)



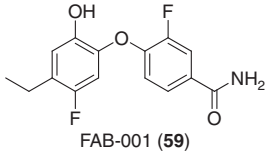
GSK2251052 (**55**)



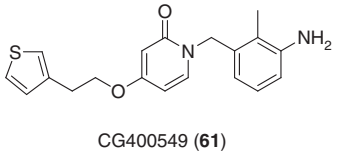
PNU-100480 (**56**)



AFN-1252 (**57**)



FAB-001 (**59**)



CG400549 (**61**)

Figure 7 Structures of compounds in phase-I clinical trials.

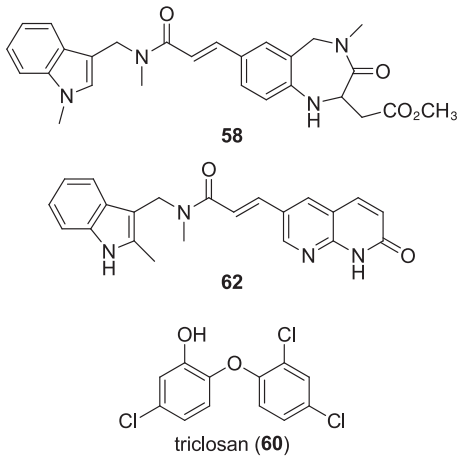


Figure 8 Structures of GSK's FabI HTS hit 59 and optimized lead 62, and triclosan (60). GSK, GlaxoSmithKline.

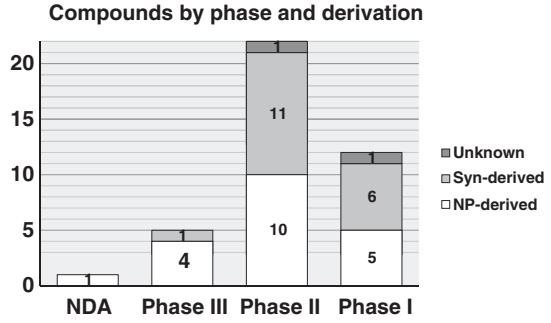


Figure 9 Compounds under clinical evaluation divided into development phases and their lead derivation source.

activity with no significant cytotoxicity.[118] GSK licensed this discovery to Affinium in 2002, with further structure optimization leading to the clinical candidate AFN-1252 (**57**) (Figure 8).[113,114]

There are two further FabI inhibitors, FAB-001 (**59**) (MUT056399) and CG400549 (**61**), under clinical evaluation for the treatment of drug-resistant staphylococci whose structures were derived from triclosan (**60**).[117] FAB Pharma (Paris, France) started a phase-I trial of FAB-001 (**59**) in September 2009,[117,119] whereas CrystalGenomics (Seoul, Korea) have completed a single ascending-dose phase-I trial of CG400549 (**61**)[120–122] and are currently studying **61** in a multiple ascending-dose phase-I trial. Triclosan (**60**) is a trichloro-phenoxy phenol topical antibiotic[123–125] launched in the early 1970s with broad spectrum activity against a variety of Gram-positive and Gram-negative bacteria that is present in a variety of cleaning and personal care products.[126] At lower concentrations, triclosan (**60**) was found to be bacteriostatic, and in 1999 various groups showed that this was because of FabI inhibition,[125,127–130] whereas the bactericidal activity observed at high concentrations has been proposed to be caused by membrane destabilization.[131]

ANALYSIS OF COMPOUNDS UNDERGOING CLINICAL TRIALS

There are a total of 40 compounds currently undergoing clinical trials (Figure 9), with one being evaluated in an NDA/MAA (Table 2), five in phase-III (Table 2), 22 in phase-II (Table 3) and 12 in phase-I (Table 4). There are slightly more NP-derived compounds (20) compared with those synthetically derived (18), with two compounds of unknown derivation. The distribution between NP-derived and synthetically derived is relatively similar in phase-I and II, whereas NP-

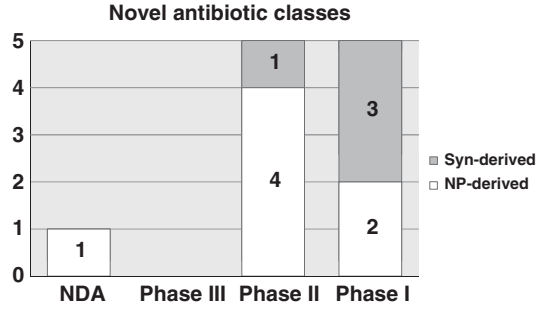


Figure 10 Compounds with new antibacterial templates divided into development phases and their lead derivation source.

derived compounds predominate in phase-III and NDA/MAA. The synthetically derived compounds classes are quite diverse (4 oxazolidinones, 1 diarylquinoline, 1 ethambutol, 2 nitroimidazole, 5 quinolones, 1 trimethoprim and 2 different types of FabI inhibitors), with strong influences from increased TB research (oxazolidinones, diarylquinoline, ethambutol and nitroimidazole) and leads from the screening of synthetic libraries combined with X-ray structure design (diarylquinoline and AFN-1252-type FabI inhibitors).

The difficulty in identifying new antibacterial templates to treat Gram-positive bacteria has been well documented. It is pleasing to note that GSK2251052 (**55**) represents a new antibiotic template, which is being actively pursued in clinical trials to treat various drug-resistant, Gram-negative bacteria. In addition, the monobactam-siderophore hybrid BAL30072 (**50**), the aminoglycoside ACHN-490 (**27**) and various quinolones are being developed to treat Gram-negative bacteria. GSK1322322 (**34**), NVP-422 (**35**), iclaprim (**45**), XF-73 (**54**), PMX-30063 and selected oxazolidinones have also been reported to have *in vitro* activity against Gram-negative bacteria.

There are also more NP-derivative new antibiotic templates (7) compared with those synthetically derived (4) (Figure 10). It must be noted, however, that three of the NP-derived lead compound templates (porphyrin, *N*-chlorotaurine and defensin) are not classic secondary metabolites, as is the case with the actinomycetes-derived fidaxomicin (**21**), ramoplanin (**30**) and actinonin (**49**), and the bacterial-derived lotilibcin (**53**).

The predominance of NP-derived compounds in late-stage trials (Table 2; Figure 10) and the lack of recently launched antibiotics outside the quinolones (Table 1) is rather striking. Whether this predominance is biased by historical screening methods, or a hint that NP-derived compounds (outside of the quinolones) are more likely to prove efficacious and safe in late-stage clinical trials, is a key question. We will need to observe the progress of compounds through the clinical pipeline in the years to come, while continuing to promote scientific, regulatory and economic mechanisms to promote antibiotic discovery, development, approval, stewardship and appropriate use in the market.

ACKNOWLEDGEMENTS

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