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Prospects for Antibacterial Discovery & Development

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Abstract

The rising prevalence of multi-drug resistant bacteria is an urgent health crisis that can only be countered through renewed investment in the discovery and development of antibiotics. There is no panacea for the antibacterial resistance crisis; instead, a multi-faceted approach is called for. In this perspective we make the case that, in the face of evolving clinical needs and enabling technologies, numerous validated antibacterial targets and associated lead molecules deserve a second look. At the same time, many worthy targets lack good leads despite harboring druggable active sites. Creative and inspired techniques buoy discovery efforts; while soil screening efforts frequently lead to antibiotic rediscovery, researchers have found success searching for new antibiotic leads by studying underexplored ecological niches or by leveraging the abundance of available data from genome mining efforts. The judicious use of “polypharmacology” (i.e., the ability of a drug to alter the activities of multiple targets) can also provide new opportunities, as can the continued search for inhibitors of resistance enzymes with the capacity to breathe new

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ASSOCIATED CONTENT

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Supporting Information: Lists of selected antibiotic targets and leads.

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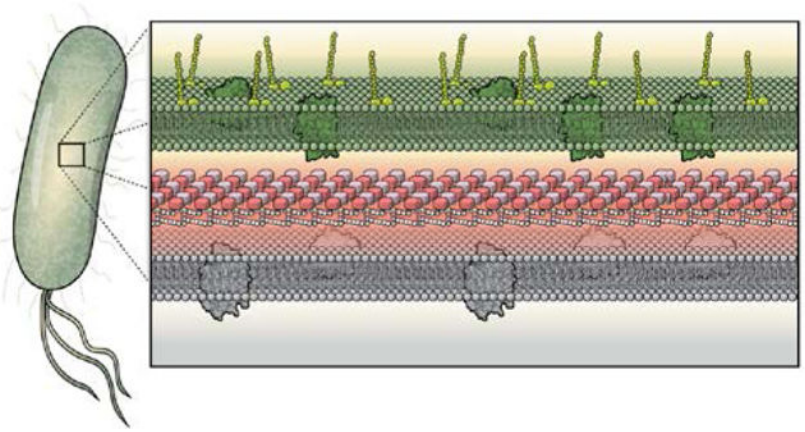
life into old antibiotics. We conclude by highlighting available pharmacoeconomic models for antibacterial discovery and development while making the case for new ones.

Graphical Abstract



Keywords

Antibiotics; Natural Product Discovery; Antibiotic Crisis; Compound Optimization; Pharmacoeconomic Models

The rise of resistance to clinically approved antibacterial agents poses a major threat to the use of these antibiotics in the future. Multidrug-resistant (MDR) organisms are becoming increasingly common and limit our ability to treat infections in the clinic.[1,2] Particularly problematic Gram-positive MDR organisms include *Staphylococcus aureus*, *Enterococcus faecalis*, and *Streptococcus pneumoniae*, whereas Gram-negative pathogens of special concern include *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* (Figure 1).[1] Meanwhile, with MDR tuberculosis accounting for approximately half of the globally diagnosed cases of this infectious disease, *Mycobacterium tuberculosis* remains a perpetual threat. All of these organisms show high rates of not only MDR phenotypes, but also extensive-drug resistance (XDR) and even pan-drug resistance (PDR), leaving few or no available options for treatment.[3] This issue is most pressing for Gram-negative strains, with XDR or PDR strains of all of the bacteria listed above being consistently reported.[3,4,5]

However, the risk in Gram-positive organisms cannot be overlooked. Methicillin-resistant *S. aureus* (MRSA) now commonly carries resistance to multiple other antibiotics as well, as does *S. pneumoniae*.[6,7] While agents such as vancomycin and daptomycin typically retain effectiveness against MRSA, isolated cases of resistance to all of these have been reported, and it seems only a matter of time before many or all of these phenotypes are found in a single strain.[3,6,7] The reduced ability to treat bacterial pathogens leads to worse outcomes for patients with community-derived as well as hospital-acquired infections.[8]

Rising antibiotic resistance is not a new problem, and has plagued medicine since antibiotics were first discovered.[9] Within five years of penicillin (**1**, Scheme 1) entering into the

clinic, 50% of *S. aureus* isolates showed resistance to it.[10] It is assumed that resistance is inevitable once an antibiotic enters widespread use, and that any given antibiotic has a "shelf life" before resistance to it becomes common enough to render the drug ineffective.[11] During the "Golden age" of antibiotic discovery from the 1930s to the 1960s, this problem was mitigated by the ongoing development of new antibiotics.[9,11] Resistance to **1** was answered by the development of methicillin (**2**), and then other agents once resistance to **2** developed.[9,11] However, the rate of antibiotic discovery has dropped significantly, with rediscovery of existing antibiotics or classes of antibiotics being a particular issue with traditional natural product-based approaches.[12,13] Notwithstanding this drought, we argue in this Perspective that there are in fact many excellent protein targets and small molecule leads capable of serving as springboards to reinvigorate the antibiotic drug discovery pipeline.

While scientific advances afford fundamentally new opportunities,[14] perhaps the most significant change in mindset is prompted by mankind's recent experiences with SARS-CoV-2, an unrelated but clearly problematic human pathogen. Despite not being bacterial in nature, the COVID-19 pandemic has taught us two vitally important lessons with profound implications for fighting old and new bacterial pathogens. From a technical standpoint, the value of partially validated targets and leads has never been more compelling. Indeed, the most successful targets (e.g., RNA-dependent RNA polymerase, Spike protein, MPro protease) and leads (e.g., remdesivir, anti-Spike monoclonal antibodies, conformationally stabilized Spike muteins, PF-07321332) for COVID-19 therapy and prophylaxis emerged from relatively mature R&D programs on related RNA viruses. From an economic perspective, public-private partnerships proved essential to de-risking expensive clinical development campaigns necessary for new drug and vaccine approval. Here we draw upon both these lessons to motivate a renewed focus on antibacterial drug discovery.

Many validated target/lead combinations deserve a second look

The search for a novel antibacterial is most efficiently launched from a foundation of a well-studied biological target with a good chemical lead, neither of which have been subjected to the evolutionary pressure of clinical drug resistance. As it turns out, there is a surprisingly long list of such targets and leads. Classic examples can be found among cell membrane inhibitors (Scheme 2) such as the polymyxins including **3**, which were discovered in the 1940s and enjoyed a few decades of clinical use before their usage dropped due to nephrotoxicity issues.[15] However, as resistance to other classes of antibiotics has spiked in the past few decades, **3** has been re-enlisted to treat particularly vexing pathogens such as drug-resistant *A. baumannii* and *P. aeruginosa*.[15,16] More recently, another membrane-targeting antibiotic, daptomycin (**4**), was approved for use against complicated skin and skin structure infections in 2003.[17]

Beyond cell membranes, another example of an under-exploited target with attractive leads is the essential translation factor EF-Tü, which delivers aminoacyl-tRNAs to the ribosome during translation. Unlike its partner elongation factor EF-G, which is targeted by multiple antibiotics that have been approved for human or veterinary use (e.g., fusidic acid (**5**), thiostrepton (**6**)), EF-Tü represents a validated but untapped antibacterial target. At least four families of potent and structurally diverse leads have been identified (Scheme 3), including

kirromycin (**7**), enacyloxin IIa (**8**), pulvomycin (**9**), and GE2270A (**10**).[18] These antibiotics are active against Gram-negative and Gram-positive bacteria.[19,20] Crystal structures of prototypical inhibitors complexed with EF-Tü have been solved; not only do **7** and **9** have distinct binding sites but they also exploit radically different inhibitory mechanisms – while **9** is a competitive inhibitor of aminoacyl-tRNA binding to the ribosome, **7** locks the EF-Tü•GDP complex to the ribosome.[18,19] In light of the fact that bacteria contain fewer than 10,000 ribosomes whereas EF-Tü is one of the most abundant cytoplasmic proteins in the cell, the latter mechanism may be less prone to the evolution of resistance via mere target overexpression.

Clearly neither any of the above-mentioned leads nor their target is devoid of medicinal challenges. For example, development of **10** encountered difficulties associated with compound solubility and pharmacokinetics.[19] One might also presume that, because human mitochondria contain a homolog of eubacterial EF-Tü, safety considerations must be carefully vetted via comparative structure-activity relationship analysis.[19,21] In this context it is noteworthy that kirromycin is a considerably weaker inhibitor of mitochondrial translation than eubacterial protein translation.[22] As one encouraging example, LFF571 (**11**), a semi-synthetic analog of **10**, showed efficacy in Phase II clinical trials against *C. difficile* infections.[21]

Two more examples of underexploited targets with promising leads are illustrative of this point (Scheme 4). First, the Sec transport system in bacteria exports proteins across the cell membrane and harbors at least one medicinally viable active site in its signal peptidase I (SPase I, also known as the leader peptidase LepB).[23,24] This serine protease utilizes a Ser-Lys catalytic dyad mechanism to cleave the signal sequence of the nascent protein during export, which differentiates it from most eukaryotic serine proteases (including its mammalian ortholog in the endoplasmic reticulum) that have a Ser-His-Asp catalytic triad in their active sites.[25] Arylomycin (**12**) is a potent SPase I inhibitor with narrow-spectrum activity;[26] however, a widespread, naturally occurring mutation was found to confer resistance to **12** in pathogens such as *S. aureus*, *E. coli*, and *P. aeruginosa*.[26] This hurdle was overcome through elegant medicinal chemistry efforts, leading to the development of actinocarbasin (**13**)[27] and G0775 (**14**),[28] both with broad-spectrum activity against MRSA, *K. pneumoniae*, *A. baumannii, P. aeruginosa*, and other pathogens. While **12** is a noncovalent inhibitor,[29] **14** covalently binds the catalytic Lys of SPaseI.[28]

Aminoacyl-tRNA synthetases (AaRSs) are essential for activating amino acids during ribosomal protein translation.[30] They remain a heavily underexploited class of targets with numerous medicinal interesting leads. While safety concerns are legitimate due to the presence of AaRS homologs in humans, many leads do in fact show strong selectivity for bacterial AaRSs.[31,32] Nonetheless, to date the only clinically approved AaRS inhibitor is mupirocin (**15**), a topically used selective inhibitor of bacterial isoleucyl-tRNA synthetase.[30]

The synthetically accessible phenyl-thiazolylurea-sulfonamide (**16**) class of competitivePhe-tRNA synthetases (PheRS) teach a valuable lesson, as they have shown good *in vitro* potency, selectivity, and *in vivo* activity.[31] Enthusiasm for clinical development, however, has been lukewarm because in animal models of infection their activity decreases with

increased dietary phenylalanine. While this limitation is understandable for a competitive enzyme inhibitor, it further underscores the promise of exploring other overlooked classes of AaRS inhibitors in the hope of identifying leads that are less amenable to this deactivation mechanism either through higher affinity binding or allosteric mechanisms.

In addition to those mentioned above, there are many other targets that could be options for further development. We have compiled a list of previously reported targets with at least one known antibacterial lead, as well as a partial list of such leads (see Tables S1 and S2). It is important to note that while many of these antibiotics, especially those produced by nature, possess promising mechanisms of action, or have excellent activity profiles, their structural complexity will necessitate substantial development efforts. There will likely be a need for advances in material availability (such as through metabolic pathway engineering) and significant medicinal chemistry campaigns to modify them for SAR improvements, which could prove challenging due to the limited medicinal chemistry accessibility of many large, complex natural products.

Many worthy targets lack good leads despite harboring druggable active sites

By now there appears to be widespread acceptance of the cliché that good targets fall into two classes – druggable and undruggable – with the existence of an evolutionarily well-sculpted active site being the key differentiator. However, the field of antibacterial drug discovery continues to challenge this dogma with its long and growing list of seemingly druggable targets that lack medicinally useful leads. The Mur ligases involved in peptidoglycan biosynthesis are a classic but often overlooked example. The druggability of the Mur pathway (Scheme 5) is incontrovertible; not only is its first step (MurA) blocked by fosfomycin (**17**),[33] but downstream reactions in peptidoglycan formation are the targets of celebrated antibiotics such as β-lactams[34] and glycopeptides.[35] However, between these clinically validated bookends lie four homologous ATP-dependent amide synthetases (MurC, MurD, MurE and MurF)[36] with a troublesome lack of leads against seemingly simple active sites.[37] While inhibitors against these enzymes have undoubtedly been reported,[33,37,38] none have yielded medicinally viable leads. This paucity of drug-like leads cannot be blamed on a lack of structural insight[38] or assay capabilities.[39,40,41] In fact, a compelling case can be made for MurC-F being universal benchmarks for innovative *in silico* or *in vitro* library technologies that purport to spawn medicinal leads, with pathway assays as a possible tool for facilitating the discovery of such leads. In advance of a future bacterial pandemic, imagine how drug hunters would be empowered by a panel of selective inhibitors of these amide synthetases with excellent *in vitro* and *in vivo* potency, good safety and ADME characteristics, and compatibility with automated synthesis methods!

More recently, several prokaryote-specific macromolecular machines have emerged as attractive drug targets that nonetheless lack medicinally appropriate leads. The Clp proteases are a vivid example; they are proteasome-like, ATP-dependent enzymatic machines in bacteria that degrade misfolded or aggregated proteins.[42] A multimeric ATPase subunit (ClpC) unfolds a protein substrate, which is then funneled to another multimeric proteolytic

subunit (ClpP), where it is degraded. While ClpP homologs are found in both humans and bacteria, the ATPase unit is more variable.[43,44] The chemistry and biology of Clp proteases has been extensively studied in recent years.[45] While Clp function is only essential in mycobacteria,[46] activators of Clp protease action (Scheme 6) have broad-spectrum activity. For example, cyclomarin A (**18**) activates ATPase activity, leading to cell death by uncontrolled protein degradation,[47] while acyl-depsipeptides such as **19** (ADEPs) achieve the same goal through allosteric activation of ClpP.[48,49] While neither is a viable class of lead molecules unto themselves (**18** depends upon reactivity of an electrophilic epoxide, whereas naturally occurring **19** has poor aqueous solubility and high clearance), these molecules set the stage for a more expansive approach toward medicinal lead identification against this target family.[50,51] A particularly intriguing mode of action might involve borrowing a page from proteolysis-targeting chimeras (PROTACS), bifunctional small molecules that facilitate the degradation of specific proteins in eukaryotes.[52] The Clp protease system could be analogously hijacked through the engineering of chimeric molecules that target proteolysis of specific proteins in bacteria.[53] One example of a target protein is FtsZ, discussed below.

FtsZ, an analog of eukaryotic tubulin that is essential for cell division in bacteria,[54] is also an attractive antibiotic target in search of new leads. Polymerization of FtsZ forms the cytokinetic “Z-ring” at the division site, which then recruits accessory factors required for peptidoglycan remodeling and other aspects of cell division (collectively known as the divisome).[55] While analogous to tubulin in function, it differs considerably in sequence and structure.[55] Inhibitors of FtsZ are active against *S. aureus*, *S. pneumoniae*, *M. tuberculosis*, and *P. aeruginosa*, among others.[56,57,58] For example, SRI-3072 (**20)** kills *M. tuberculosis* inside mouse macrophages,[55] while the Zantrins[58] (**21–25**) are synthetic noncompetitive inhibitors with broader spectrum activity.[59] Whereas the FtsZ inhibitor TXA709 (**26**), formulated as a prodrug, has shown good safety in humans,[60] no antibiotic targeting the divisome has been approved to date notwithstanding the identification of at least three druggable sites within this assembly.[61] Undoubtedly, as classical enablers of drug discovery such as improved binding assays[62] and additional X-ray crystal structures[63,64,65] become available, the opportunities for superior clinical candidates will continue to grow. At the same time, the tight geometric constraints for FtsZ function at the cell division plate suggest that an alternative PROTACS-like approach for FtsZ degradation may be particularly promising.

Non-traditional strategies for antibacterial discovery must be encouraged

Prior to the COVID-19 pandemic, a vast majority of our repertoire of clinically used antivirals had been engineered against essential targets encoded within the genome of the pathogenic virus. The stunning capacity of SARS-CoV-2 (as well as earlier coronaviruses such as SARS and MERS) to exacerbate from a seemingly innocuous upper respiratory tract infection into a systemic, life-threatening illness has prompted a shift in focus towards the identification of host-acting antiviral mechanisms that could function as broader-spectrum antivirals that might even be less prone to resistance. While the implications of this new approach to antiviral therapy remain to be seen, analogous paradigmatic shifts are starting to gain momentum in antibacterial drug discovery and must be nurtured (Scheme 7).

During the Golden age of antibiotic discovery, new antibiotics were rapidly discovered through systematic screening of secondary metabolites produced by soil-dwelling bacteria, predominantly the actinomycetes.[66] Notwithstanding its immense success, this strategy ultimately led to diminishing returns.[67] With the sequencing of the *Haemophilus influenzae* genome, the prospect of identifying new bacterial targets led to early investment by many pharmaceutical companies.[68,69] Unfortunately, genomics-driven antibacterial discovery failed to quickly spawn a second "golden" era of antibiotic discovery (as discussed in many retrospective analyses[67,68,69,70]) as targets determined to be essential often failed to yield useful leads. This highlights how targets with even a weak lead may be preferable to those without any, regardless of other properties of the targets themselves. Genome mining approaches to new antibacterial lead discovery assist in the discovery of new leads based on the recognition that biosynthetic genes for secondary metabolite production in bacteria and fungi are clustered, which allows educated guesses of both the natural product's broad structural features as well as its antibacterial mode of action.[71] The former guess derives from the identification of putative enzymes involved in polyketide, peptide, or isoprenoid biosynthesis, whereas the latter stems from co-localization of a putative self-resistance enzyme that protects the host from its own natural product.[72] Examples of self-resistance enzymes colocalized with biosynthetic pathways include ones involved in protein biosynthesis,[73] DNA replication,[74] and lipid metabolism.[75] An illustrative case of this kind of genome mining is highlighted by the discovery of thiotetronic acid (**27**), which blocks fatty acid synthesis in bacteria.[76]

Another promising trend in antibacterial drug discovery involves harnessing natural products from under-explored genera and ecological niches. As a simple example, while actinomyces have been extensively screened for new antibiotics, filamentous fungi have been not as thoroughly mined notwithstanding their track record of yielding immensely valuable β-lactams (including of course penicillin).[77]

Similarly, the nematode-inhabiting bacteria *Xenorhabdus* and *Photorhabdus* have gained attention as promising sources of new antibiotics based on the discovery of two promising new antibiotics, odilorhabdin (**28**)[78,79] and darobactin (**29**),[80] respectively. **28** inhibits a new site in the ribosomes of both Gram-positive and Gram-negative bacteria (thus showing no cross-resistance to other clinically used ribosome inhibitors),[78] whereas **29** targets a hitherto unrecognized target BamA, an outer membrane protein in Gram-negative bacteria that catalyzes the folding and insertion of essential outer membrane proteins.[81] The attractiveness of BamA as an antibiotic target has been further underscored by the more-or-less concomitant identification of three other classes of leads, including a murepavadin-polymyxin B chimera,[82] MRL-494 (**30**),[83] and even an antibody.[84] Collectively, these antibiotics have demonstrated potency against many particularly problematic Gram-negative pathogens such as *A. baumannii, P. aeruginosa*, and *K. pneumoniae*.[82] It goes without saying that these antibiotics have the added benefit of acting at the cell surface, thereby circumventing cell permeability issues. While attractive leads are known for these targets, additional medicinal chemistry will be necessary to bring any of them to the clinic.

One final paradigm-shifting approach to antibacterial discovery deserves mention here. While research on *M. tuberculosis* has extensively documented the phenomenon of a

"persister" phenotype in this pathogen (one that achieves antibiotic resistance by persisting in a non-replicating, metabolically inert stage within the human host for long durations), there is growing recognition that persisters represent a major challenge to antibiotic-driven elimination of chronic infections caused by a variety of human pathogens. A better understanding of the bacterial defense system in the persister state holds the key to conquering this phenotype.[85] For example, in response to oxidative stress or antibiotics, bacteria increase the production of NO and H_2S as signaling molecules.[86,87] H_2S is produced en zymatically by orthologues of mammalian cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), or 3-mercaptopyruvate sulfurtransferase.[85] Recently, inhibitors with an indole moiety such as NL1 (**31**) were found to inhibit CSE from *S. aureus* and *P. aeruginosa* and demonstrated promising potentiation effects when dosed in combination with major bactericidal antibiotic classes such as the fluoroquinolones, β-lactams, and aminoglycosides, but not with bacteriostatic antibiotics such as tetracycline or chloramphenicol.[85] While much remains to be learned about the remarkable metabolic networks used by persister bacteria to evade antibiotics, it is likely that these fundamental investigations will shine light on promising targets for future antibacterial drug discovery.

Polypharmacology is under-exploited in antibacterial drug development

A particularly effective strategy to hinder the emergence of drug resistance involves engineering a drug that synergistically blocks more than one target. By now polypharmacology is well established in oncology especially through the emergence of multiple pan-kinase inhibitors as frontline cancer chemotherapeutics.[88,89] In contrast, although combination therapy could be envisioned as a rudimentary flavor of bacterial polypharmacology (e.g., trimethoprim (**32**) and sulfamethoxazole (**33**) in co-trimoxazole[90]), it has received scant attention in anti-infective drug discovery.

In fact, there are many examples of promising antibiotic leads selective for multiple bacterial targets (Scheme 8). For example, kibdelomycin (**34**), a polyketide/non-ribosomal peptide, targets the ATPase activities of type II topoisomerases including GyrB and ParE, both legitimate antibacterial targets in their own right.[91] Structural studies of **34** bound to *S. aureus* GyrB showed that it binds the ATP-binding site pocket with a unique "dual-arm" binding mode with multiple contact points, perhaps explaining the low resistance frequency to this antibiotic observed in *S. aureus*.[92] Kibdelomycin has potent activity in a hamster model of *C. difficile* colitis, conferring 100% protection at a 6.25 mg/kg oral dose with low systemic clearance.[93] Notably, it also has strong activity against a panel of clinical isolates of *A. baumannii*.[94] Another example is teixobactin (**35**), a depsipeptide that binds to lipid II and lipid III and thus blocks peptidoglycan and cell wall teichoic acid synthesis, respectively.[95] This leads to a disorganized, damaged bacterial cell envelope and delocalized autolysins, culminating in cell death.[96,97] Due to its promising mechanism of action and moderate complexity, it has been the subject of multiple SAR studies.[98] Last but not least, corbomycin (**36**) and complestatin (**37**) inhibit multiple autolysins,[99] a class of peptidoglycan hydrolases required for cell wall turnover and cell separation during replication.[100]

While these examples of multitarget agents act on related targets in the same pathway, multifunctional antibiotics acting via unrelated mechanisms are also known. For example, Irresistin-16 (**38**) permeabilizes the bacterial cell membrane while also targeting dihydrofolate reductase (DHFR).[101] DHFR catalyzes the NADPH-dependent production of the tetrahydrofolate, an essential compound used for the de novo synthesis of dTMP involved in DNA building block synthesis.[102] It demonstrates efficacy in Gram-negative and Gram-positive bacteria such as MRSA, *N. gonorrhoeae* and *A. baumannii* with no sign of resistance.[101] Similarly, while the use of rifampin (**39**) is limited to combination therapies owing to the emergence of resistance against this antibiotic at appreciable frequency, TNP-2092 (**40**), combining the pharmacophores of RNA polymerase-targeting **39** with the DNA gyrase-targeting quinolizinone, maintains the potent activity of rifamycin against persistent pathogens and at the same time minimizes the development of rifamycin resistance.[103] Recently, a "tribrid" siderophore-cephalosporin-oxazolidinone conjugate (**41**) was engineered; after internalization via siderophore-mediated uptake, the oxazolidinone is released by the bacteria's inherent β-lactamase activity.[104]

The quest for resistance enzyme inhibitors that breathe new life into old antibiotics must continue

The potency of a failing antibiotic can be preserved by combining it with an agent that inhibits a clinically relevant resistance mechanism. For example, β-lactamase inhibitors (Scheme 9) have found widespread utility. β-lactamases fall into four distinct classes, with Class A and Class C being the most important from a clinical standpoint.[105,106] Classes A, C, and D rely on a serine protease type hydrolytic mechanism, whereas class Bs are zinc metallo-hydrolases.[105,106] Clavulanic acid (**42**) is a prototypical example of a clinically successful β-lactamase inhibitor. Itself a weak β-lactam antibiotic produced by *Streptomyces clavuligerus*, **42** is a potent irreversible inhibitor of common β-lactamase enzymes.[107,108,109] It found initial use in combination with amoxicillin in the early 1980s.[110,111] However, much like with β-lactam antibiotics themselves, **42** has become susceptible to the evolution of resistance.[110,111] In response, newer β-lactamase inhibitors with broader ranges of activities were developed, with one of the most successful being avibactam (**43**).[112] **43** lacks a β-lactam core, but still covalently inhibits β-lactamases, including many of the most important Class A, C, and D enzymes.[112,113,114] It is typically paired with the third-generation cephalosporin ceftazidime (**44**) a combination that retains activity against many key Gram-negative organisms. However, **43** has poor oral bioavailability, and is therefore only used as an injectable. A prodrug variant of **43**, ARX-1796 **(45)**, is entering clinical trials with the companion β-lactam antibiotic ceftibuten (**46)**.[115] Notably, while leads against Class B β-lactamases such as QPX7728 (**47**)[116] and aspergillomarasmine A (**48**)[117,118,119] have been discovered, a clinically useful inhibitor of this class of metalloenzymes has not yet emerged.

Whereas β-lactamase inhibitors represent a clear success in targeting resistance mechanisms to restore activity of existing molecules, similar approaches have not been successful against aminoglycoside antibiotic modifying enzymes (AMEs). Aminoglycosides (Scheme 10) are a diverse class of molecules that typically inhibit protein synthesis through direct

binding to the ribosome.[120] Most aminoglycosides bind inside or very close to the A-site of the ribosome and interfere with the translocation step of protein synthesis,[120] although some like streptomycin are known to bind elsewhere in the ribosome.[121] They were in common use until the late 1970s, when they began to be phased out due to discovery of newer antibiotics with fewer toxicity issues,[120] but have undergone somewhat of a renaissance due to increasing resistance to other antibiotics.[120,122] Three major types of aminoglycoside modifying enzymes are classified by the modification they catalyze: aminoglycoside N-acetyltransferases (AAC), aminoglycoside O-adenyltransferases (ANT), and aminoglycoside O-phosphotransferases (APH).[122,123,124] They are further sub-classified by the actual position on the aminoglycoside, such as kanamycin (**49**), they modify. For instance, an AAC(6') enzyme acetylates the 6' nitrogen of susceptible aminoglycosides. Because a given aminoglycoside modifying enzyme is usually most effective against only a small subset of aminoglycosides,[122] inhibitors need not be broadly active against this superfamily of resistance enzyme in order to be useful. For example, AAC(6') leads to resistance against the second-generation aminoglycoside amikacin (**50**);[122] therefore a medicinally effective inhibitor of this N-acetyltransferase would have considerable clinical impact. Aranorosin (**51**) is an inhibitor of the bifunctional AAC(6')-APH(2") enzyme from methicillin-resistant *S. aureus* that potentiates amikacin activity *in vitro*.[125] More recently, a small-scale screen identified additional inhibitors of AAC(6')-APH(2") enzymes.[126] As a target class though, aminoglycoside modifying enzymes are not as economically attractive as β-lactamases due to their inability to breathe new life into multiple broad-spectrum antibiotics. An alternative approach to rejuvenating the effectiveness of aminoglycosides has already been taken with plazomicin (**52**), a semisynthetic aminoglycoside that is not a substrate for most AMEs.[127] Unfortunately, despite receiving FDA approval, **52** was a major financial failure and partially responsible for the bankruptcy of its developer Achaogen.[128] When attempting to address the problems of antibiotic resistance, economic challenges must be considered as well.

The future of antibacterial discovery will remain bleak absent new pharmacoeconomic models

The growing list of promising antibacterial agents that either failed to complete clinical trials due to insufficient resources or worse became economically non-viable products after gaining new drug approval has prompted calls from experts and laymen for alternative business models to promote innovative antibiotic discovery and development.

At the legislative level, Congress passed the Generating Antibiotic Incentives Now (GAIN) Act of 2012, which provided for an incremental five-year exclusivity period from generic competition (over and beyond the minimum five-year exclusive period for new small molecule drugs as well as any applicable orphan drug or pediatric exclusivity) plus Fast Track and Priority Review incentive programs by the FDA. Many experimental antibiotics have qualified for GAIN Act designation, and a few have even been approved (dalbavancin (**53**, Scheme 11) being a notable example).[129] However, nearly a decade later, most objective assessments would conclude that the impact of the GAIN Act alone on the antibiotic pipeline has been modest at best. The unfortunate example of **52**, which collapsed as

a product (along with its developer, Achaogen) notwithstanding FDA approval following GAIN Act qualification, is a vivid testimonial.

New government-philanthropy partnerships have also been explored over the past decade to fill the void in antibacterial discovery and development created by negligible pharma or venture capital investment. A particularly notable example is the Combating Antibiotic-Resistant Bacteria Accelerator (CARB-X). Over the past five years, CARB-X has curated an impressive pipeline of ca. 50 anti-infective programs including small molecules, proteins, non-traditional agents (e.g., bacteriophages, microbiome therapies), and vaccines.[130] While the roadmap for these agents through pivotal clinical studies and beyond is anything but straightforward, one hopes that judicious stewardship until clinical proof-of-concept is at hand will give these programs their best shot at long-term success.

Looking forward, at least two recently precedented pharmacoeconomic strategies have the potential to rejuvenate our pipeline of innovative antibacterials. One approach would involve expanding the scope of the Priority Review Voucher program created by the United States Congress in 2007 to accelerate drug development for rare pediatric disorders as well as neglected diseases that predominantly burden the developing world. These vouchers, which reduce the time to new drug approval by approximately six months, have been issued for the successful development of more than 50 drugs thus far (including a few anti-infective agents), and have an established value of~$100M (https://sites.fuqua.duke.edu/prioritypreviewvoucher/). If applied more broadly to antibacterial drug development, such an economic bonanza can incentivize both investors and the pharmaceutical industry to invest more heavily in the most promising programs that emerge from the academic sector. An alternative (and complementary) strategy has been successfully test-piloted during the COVID-19 pandemic with the U.S. government substantially de-risking SARS-CoV-2 drug and vaccine development through a three-pronged approach comprising co-investments in clinical trials, an invigorated Emergency Use Authorization (EUA) effort by the FDA, and post-approval purchase guarantees from multiple national governments. The breakneck speeds at which innovative products such as mRNA vaccines and anti-infective monoclonal antibodies have been launched is a vivid testimonial to the power of such an integrated strategy. While scientific advances in microbiology and chemistry will remain the fountainhead for new tools that ward off the persistent threat of new and old bacterial pathogens, the will to translate these discoveries into clinical practice must ultimately come from society. Absent such a collective commitment from all of us, future local or global pandemics will continue to reverse our hard-won gains in life expectancy and quality of life afforded by the Golden Era of Antibiotics in the past century.

Supplementary Material

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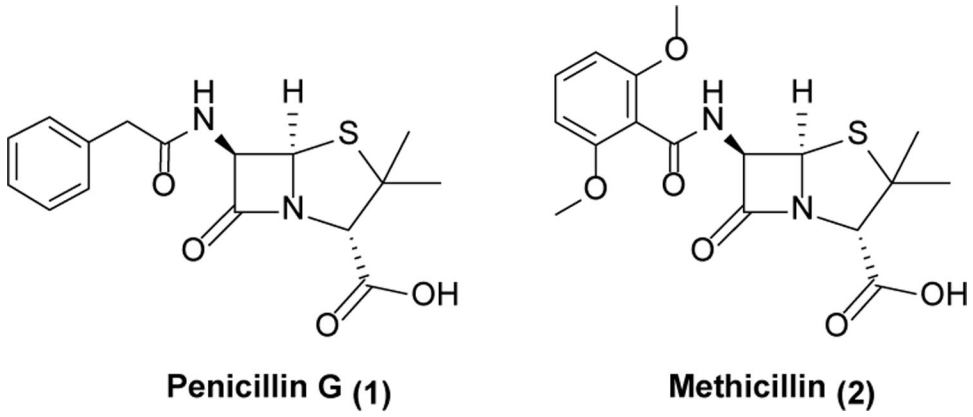


Scheme 1.
Penicillins

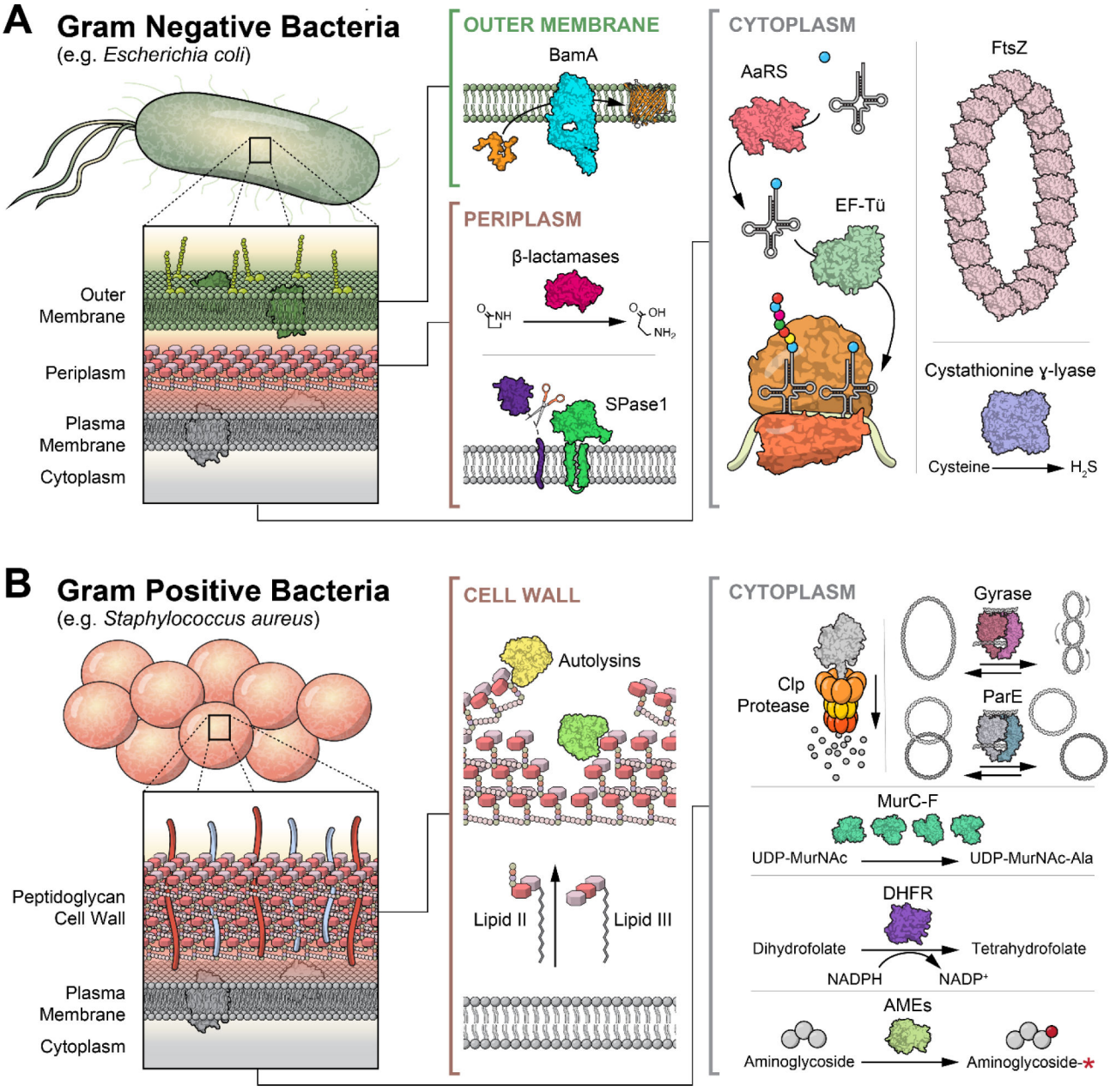
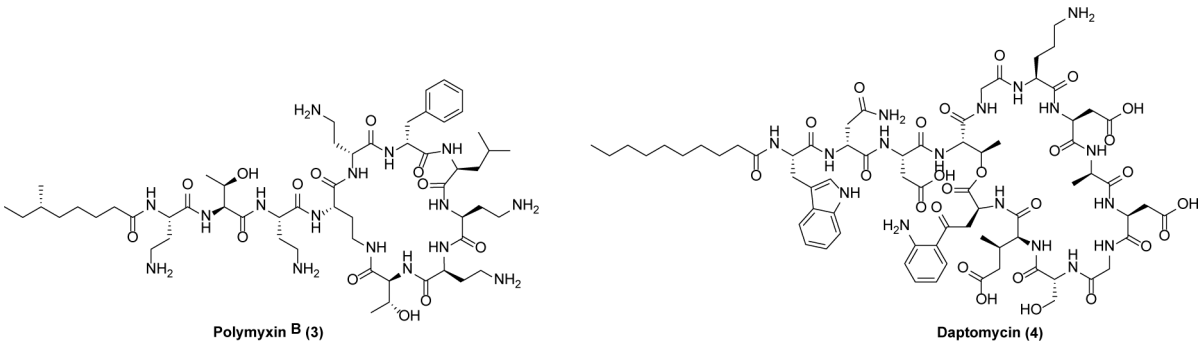
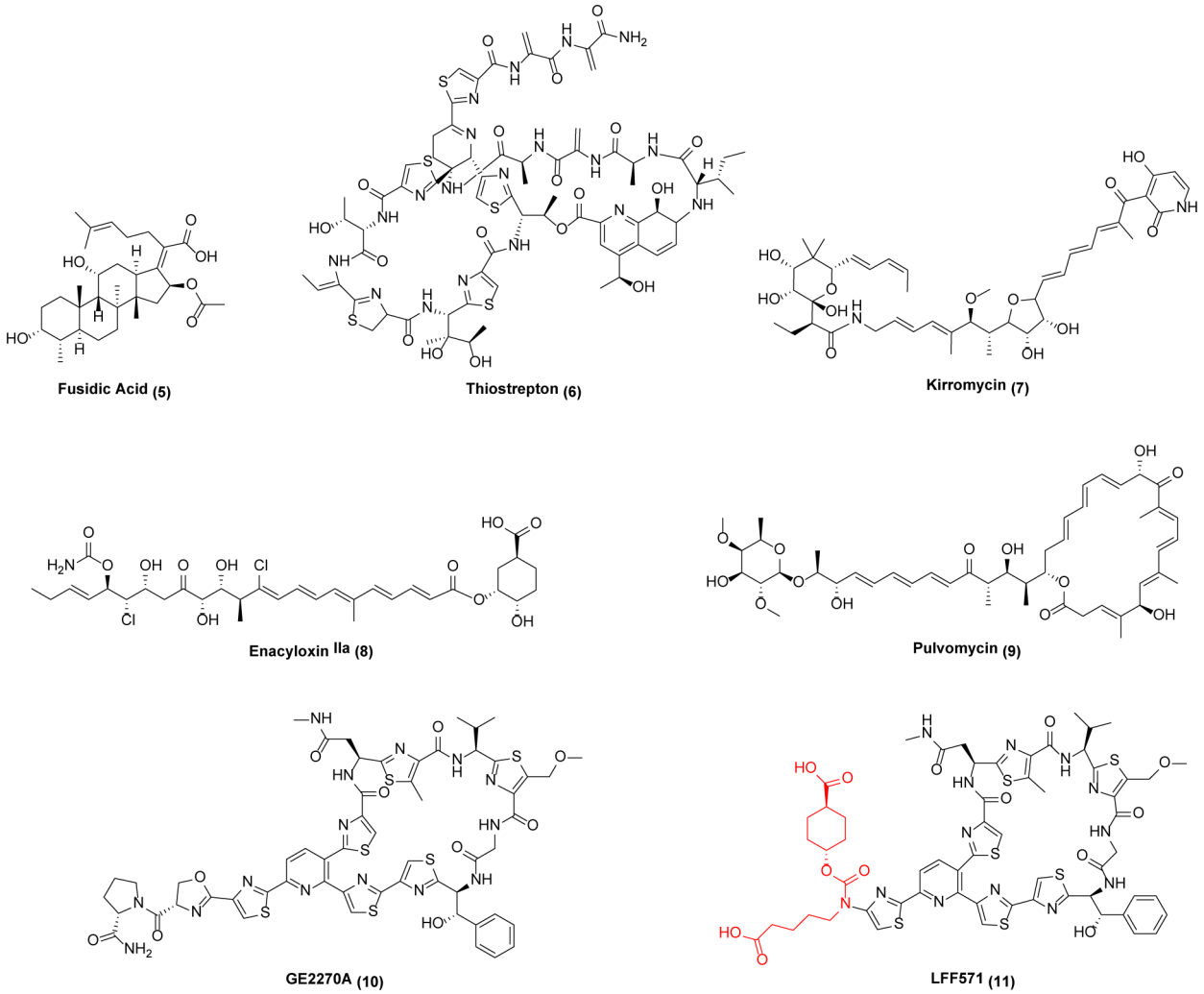


Figure 1.

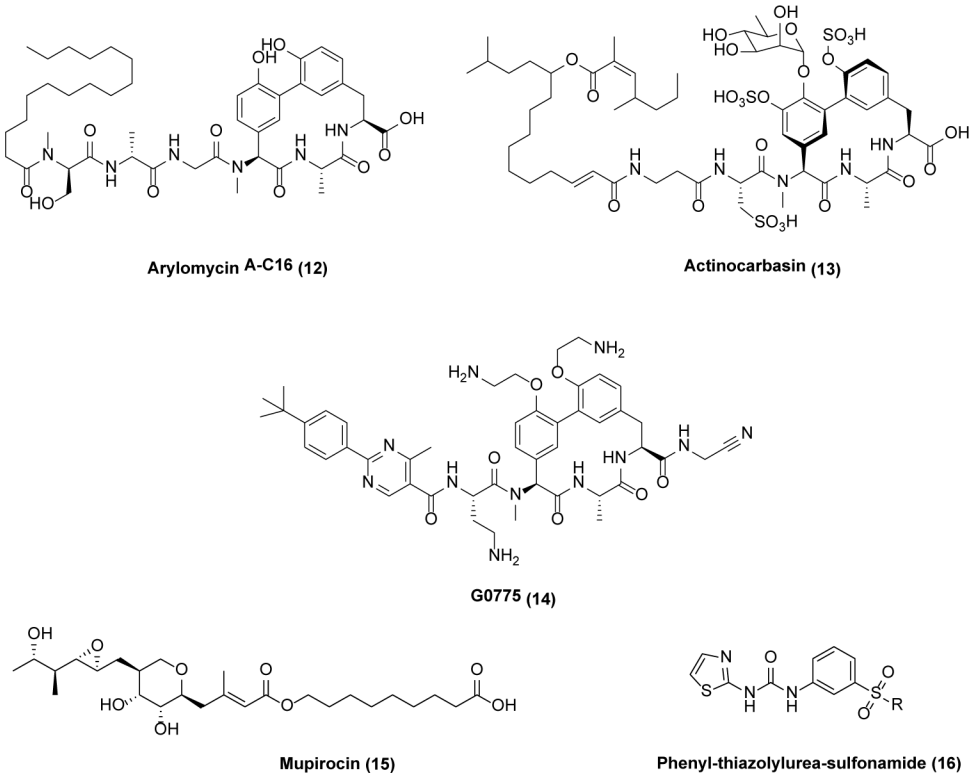
(a) The cell wall of a Gram-negative bacterium is composed of an outer membrane, the peptidoglycan, and the periplasm, all of which localize many antibiotic targets. (b) Gram-positive bacterium have a thick peptidoglycan layer surrounding its plasma membrane and cytoplasm. Illustrations courtesy of Eric Smith.



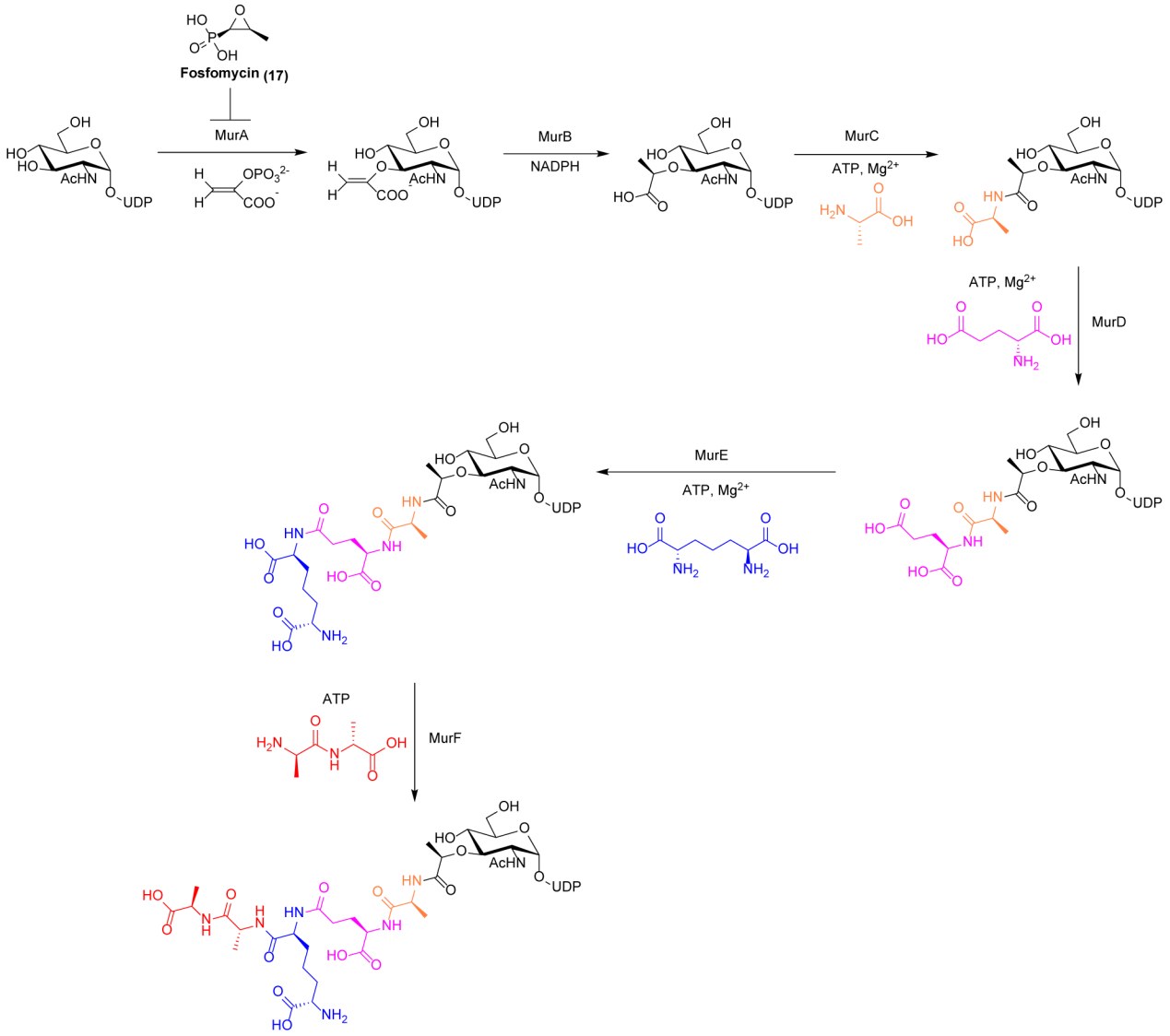
Scheme 2.
Cell membrane targeting antibiotics



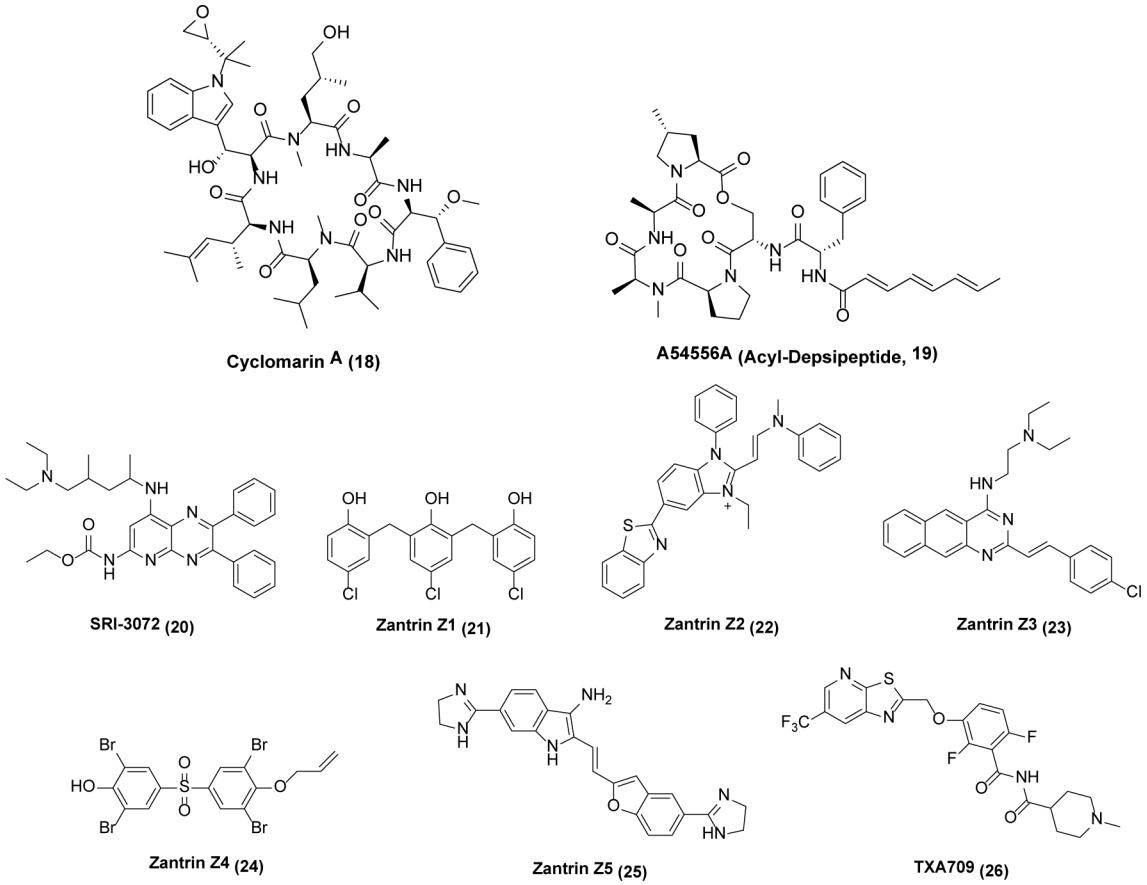
Scheme 3.
EF-G and EF-Tü inhibitors



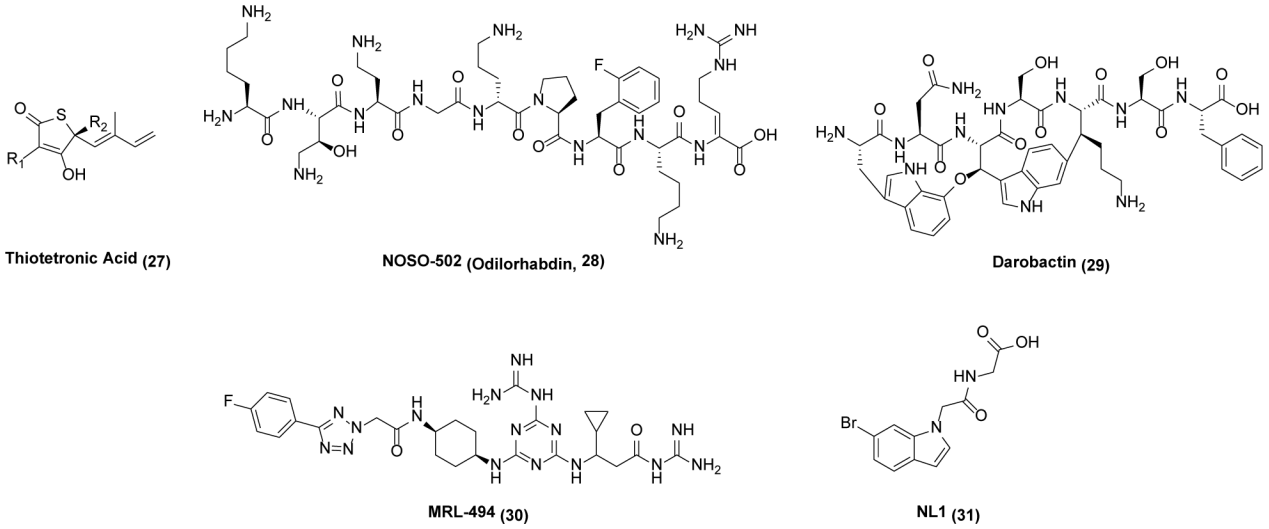
Scheme 4.
Signal peptidase and aminoacyl-tRNA synthetase inhibitors



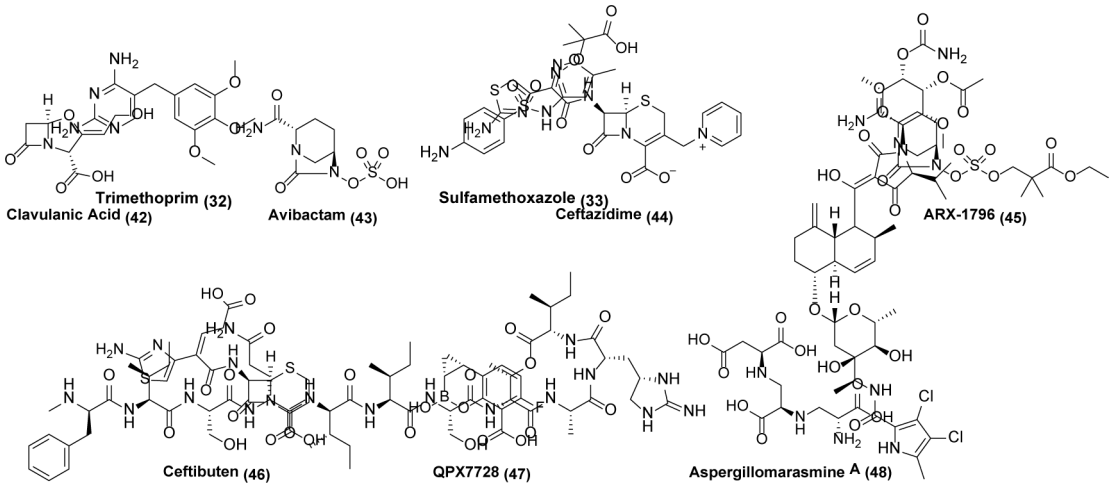
Scheme 5.
Mur ligase pathway



Scheme 6.
Clp protease activators and FtsZ inhibitors

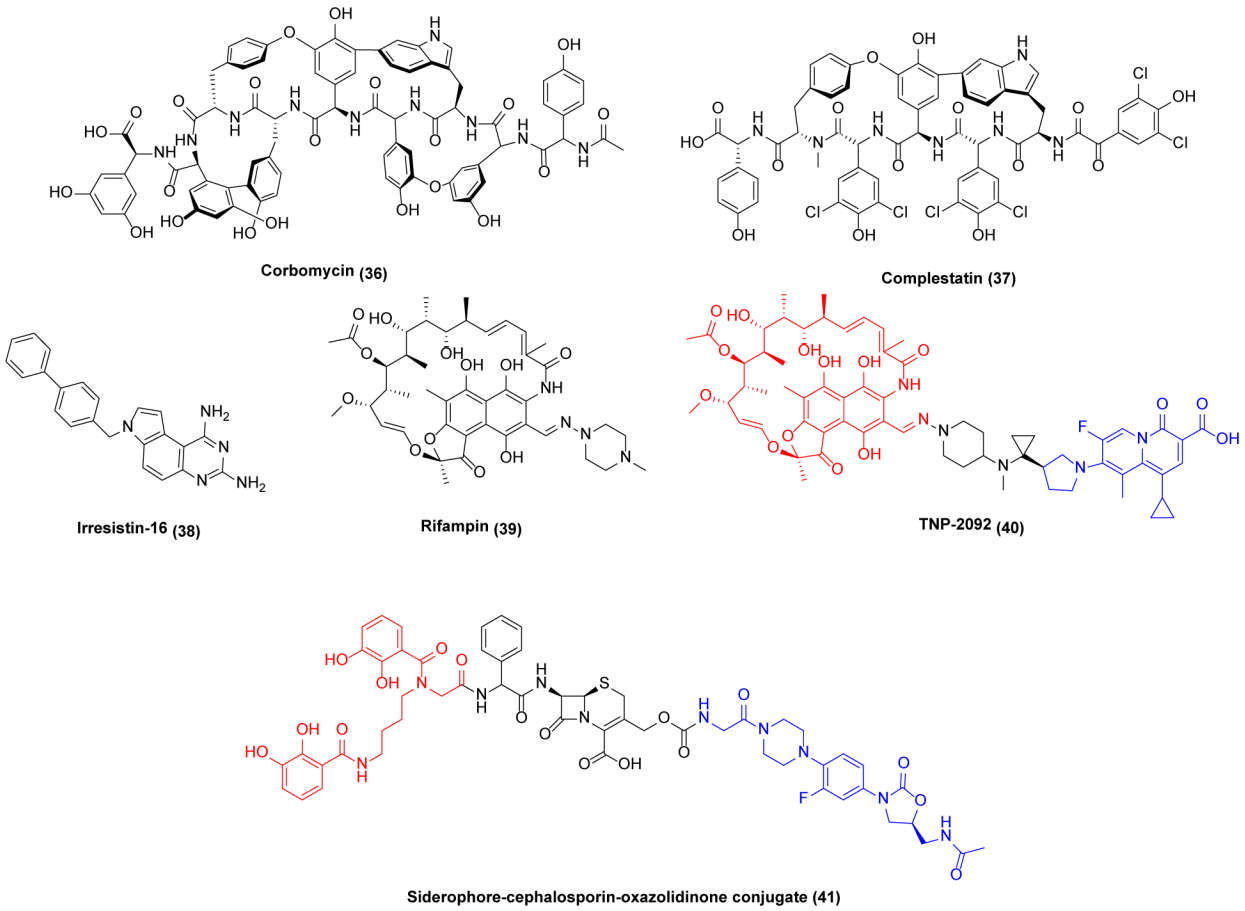


Scheme 7.
Antibiotics discovered from non-traditional approaches

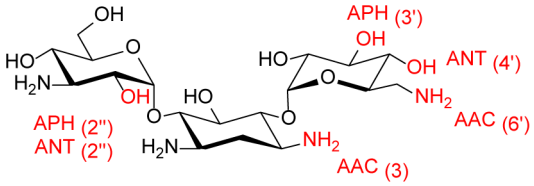


Scheme 9.

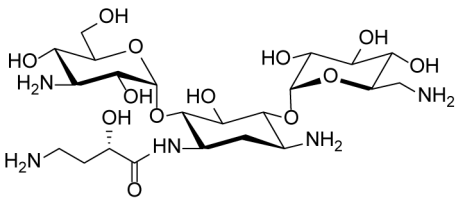
β-lactamase inhibitors and relateds molecules



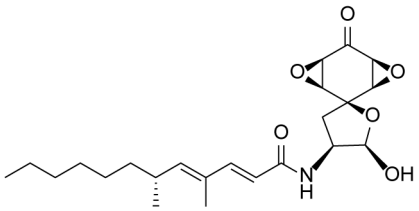
Scheme 8.
Antibacterial agents exhibiting polypharmacology



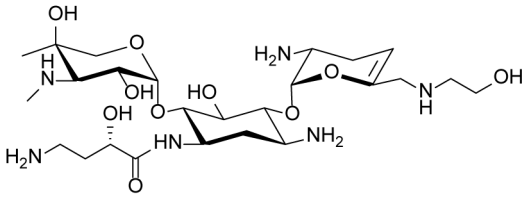
Kanamycin A (49)



Amikacin (50)



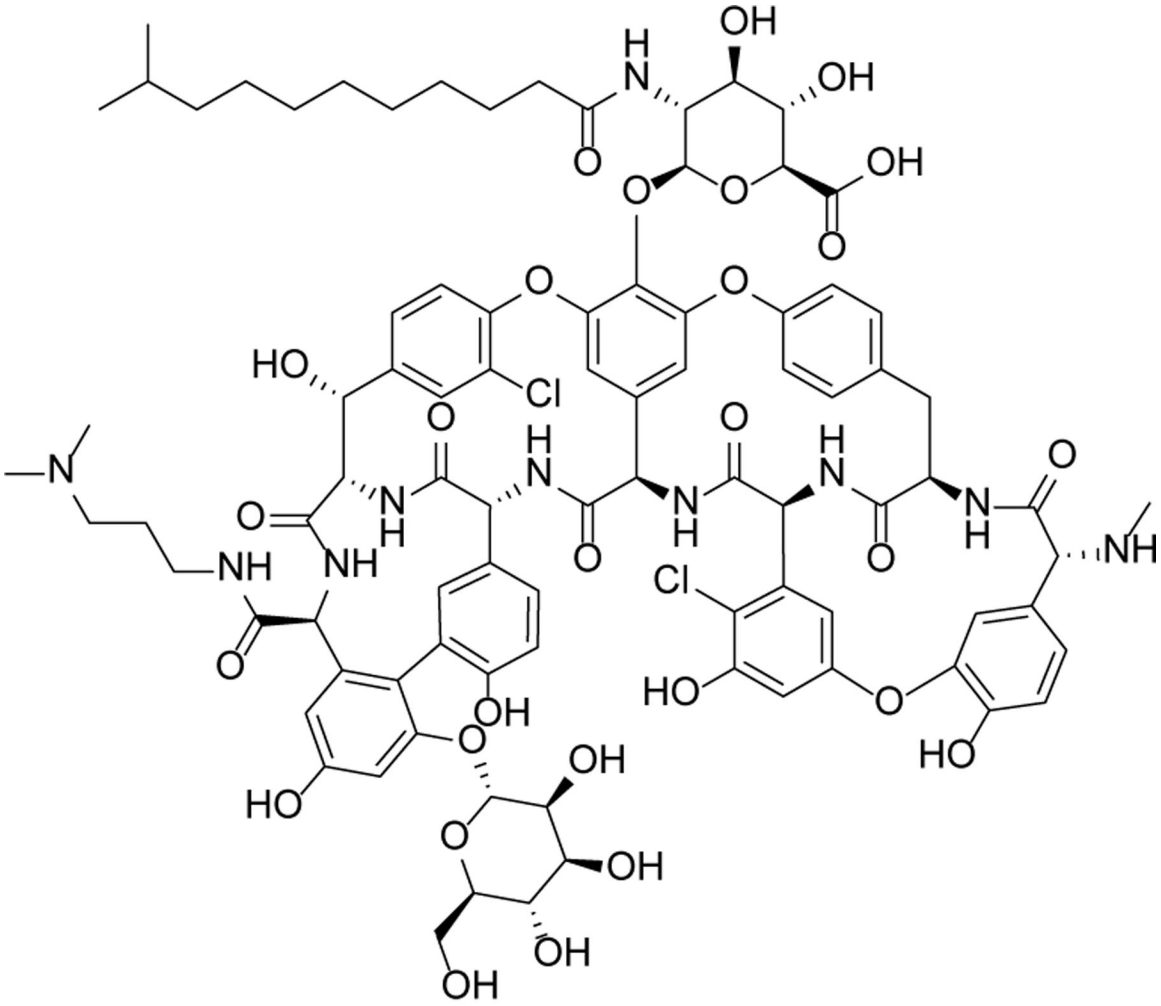
Aranorosin (51)



Plazomicin (52)

Scheme 10.

Aminoglycosides and aminoglycoside modifying enzyme inhibitors



Scheme 11.
Dalbavancin