Chapter 13
Drugs Under Preclinical and Clinical Testing for the Treatment of Infections Caused due to *Staphylococcus aureus*: An Update

Manjulika Shukla, Isha Soni, Arunava Dasgupta, and Sidharth Chopra

Abstract *Staphylococcus aureus* is a significant pathogen of interest worldwide owing to its increasing drug resistance and dwindling antimicrobial armamentarium available against it. Although it typically causes uncomplicated infections, recently increasingly it has been linked to serious community and nosocomial infections ranging from boils to bloodstream infections to endocarditis. Even though there are a number of antibiotics available for the treatment of uncomplicated *S. aureus* infections, the advent of drug resistance has complicated the picture due to decreasing options available for the treatment coupled with increased transmission of drug-resistant strains in the community. Even though the drug discovery pipeline has recently been augmented with the discovery of some new molecules active against *S. aureus*, the true status is anemic owing to lack of molecules acting via new mechanism of action. This chapter describes the various molecules which are in preclinical and clinical development against *S. aureus* and depicts the various challenges as well as lacunae in them.

Keywords Staphylococcus · Preclinical · Drugs · MRSA

13.1 Introduction

Staphylococcus aureus, a typically commensal microflora, is also one of the most notorious pathogens among the so-called "ESKAPE" pathogens (*Enterobacter* sp., *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococcus* sp.) as defined by IDSA and other organizations responsible for causing a variety of serious acute and chronic community as well as

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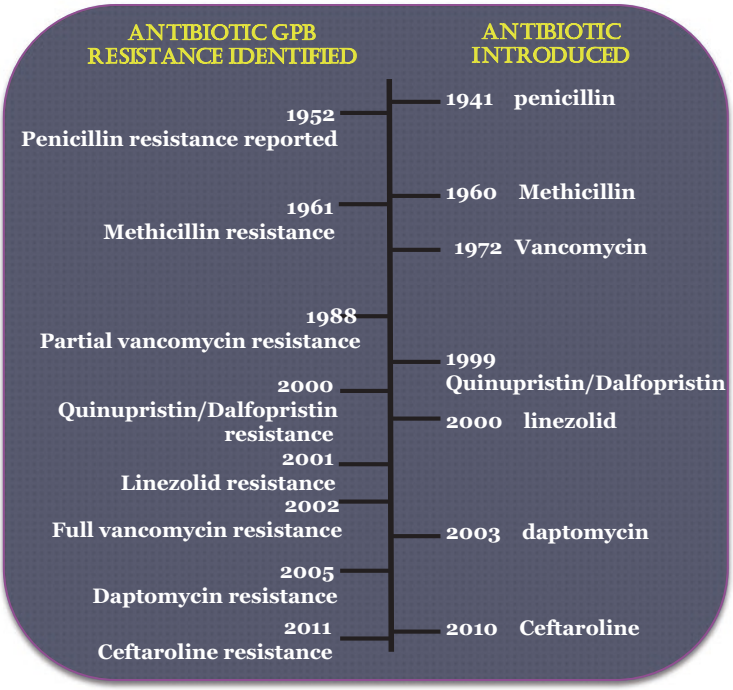


Fig. 13.1 Diagrammatic representation of the introduction of the antibiotic into the clinic and subsequent identification of antibiotic resistance

hospital-acquired infections (HAI) (Boucher et al. 2009). These infections range from skin and skin structure infections such as boils and abscesses to bacteremia, pneumonia, osteomyelitis, endocarditis, meningitis, and toxic shock syndrome. Figure 13.1 (A) depicts a scanning electron micrograph of MRSA (A), as well as cutaneous infection caused due to MRSA in (B).

The treatment of infections caused due to *S. aureus* is typically uncomplicated, but due to the increasing advent of antimicrobial resistance exhibited by *S. aureus* clinical isolates, the discovery and development of new molecules active against *S. aureus* has become a worldwide scientific and medical high priority. This is reflected in the increasingly populated drug discovery pipeline targeting *S. aureus*, although majority of the molecules are from already known classes of drugs (Kumar and Chopra 2013). This is disturbing as increasingly drug-resistant strains of *S. aureus* are being isolated worldwide, thus decreasing the therapeutic options which are available to the attending infectious disease physicians and are directly responsible for increasing morbidity and mortality associated with staphylococcal infections.

Drug resistance in *S. aureus* is not a new feature. As seen in Fig. 13.2, the identification of resistance usually happens within a couple of years of the commercial release of the drug. This trend started with the introduction of penicillin for the treatment of *S. aureus* infections in 1941, and its resistance was identified in 1952;

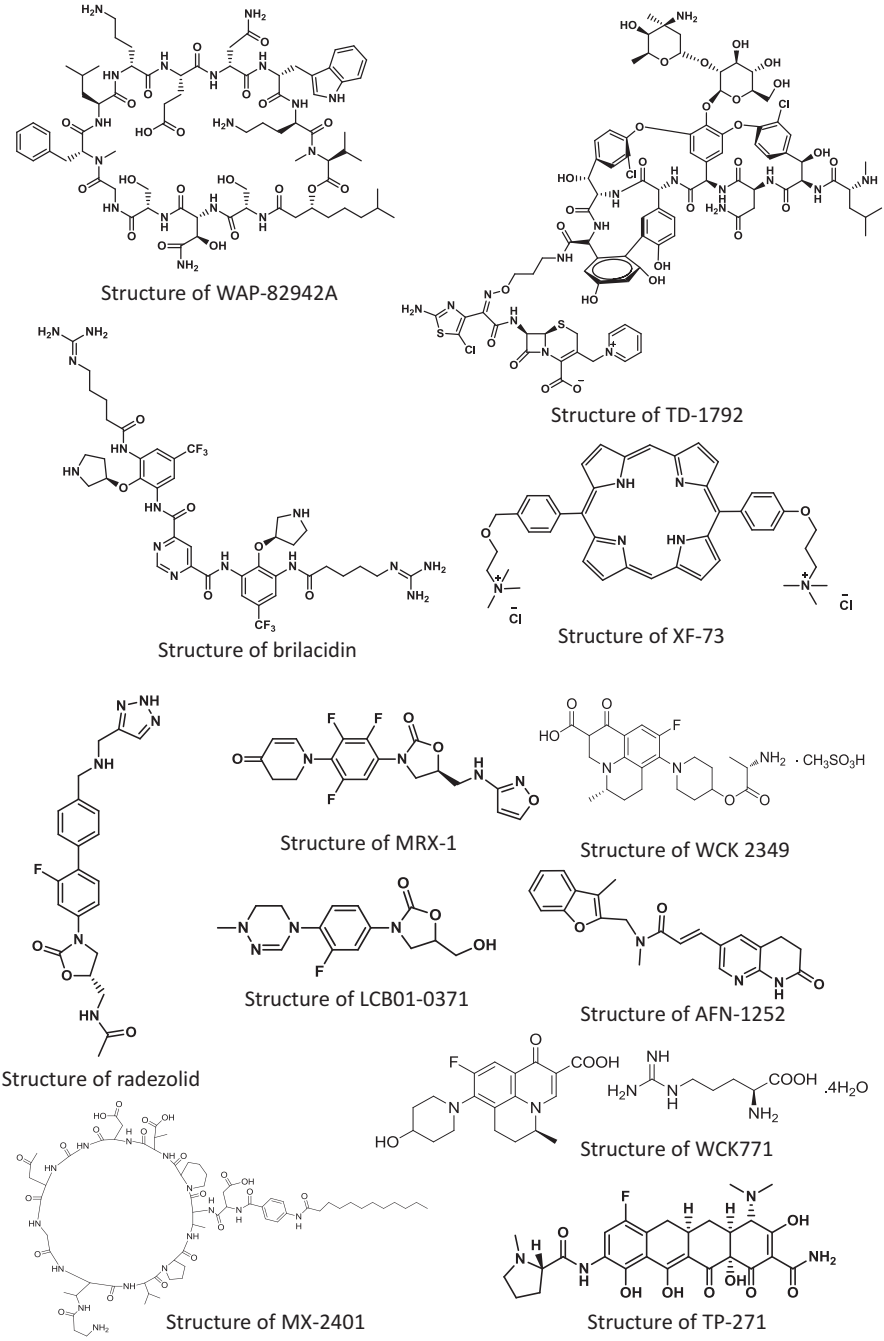
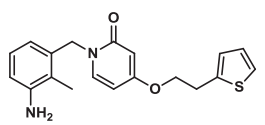
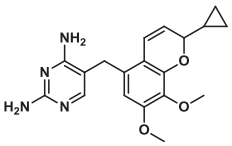
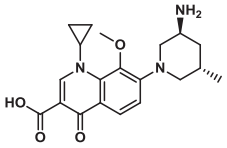
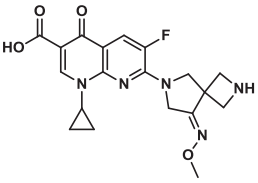


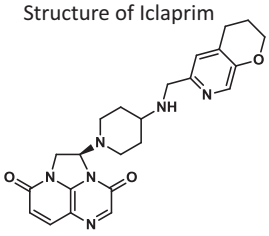
Fig. 13.2 Structure of drugs under preclinical and clinical assessment against *S. aureus*

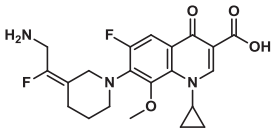

Structure of CG400549

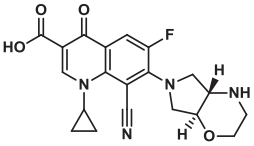

Structure of Iclaprim

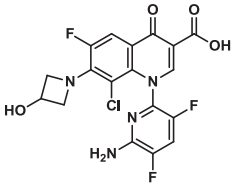

Structure of Nemonoxacin

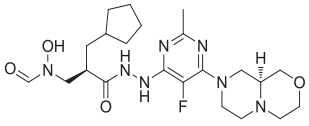

Structure of Zabofloxacin

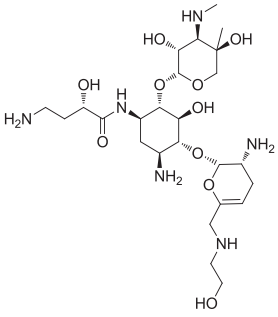

Structure of Gepotidacin


Structure of Avarofloxacin


Structure of Finafloxacin


Structure of Delafloxacin


Structure of GSK-1322322


Structure of 6′-(hydroxyethyl)-1-(haba)-sisomicin

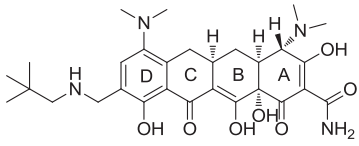

Structure of Omadacycline

Fig. 13.2 (continued)

methicillin was introduced in 1960, and resistance to methicillin was identified in 1961, the so-called MRSA, followed by identification of vancomycin-resistant *S. aureus* (VRSA) in 1988. The latest casualty of this trend was ceftaroline with its introduction in 2010 and the first reported resistance in 2011. In addition, MRSA is listed a high-priority pathogen for which novel drugs are urgently required by WHO in 2017. Taken together, it makes a powerful case for a dedicated drug discovery and development pipeline to continuously address this issue.

The aim of this article is to give an update of drugs in the preclinical and clinical pipeline active against *S. aureus*. In this report, agents are mainly categorized and subcategorized on the basis of their mode of action and chemical class, respectively. Their structures are depicted in Fig. 13.3.

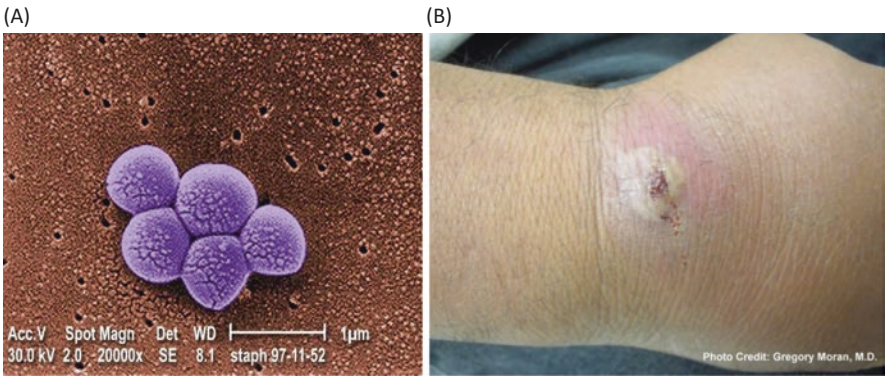


Fig. 13.3 EM of *S. aureus* and cutaneous abscess caused due to methicillin-resistant *S. aureus* (**a**) Colorized SEM depicts MRSA (Magnified 20,000X). (Courtesy: CDC, USA) (**b**) Cutaneous abscess on the foot post packing (front view), caused due to MRSA. (Courtesy: CDC, USA)

13.2 Molecules Acting on Peptidoglycan Biosynthesis and Cell Membrane

Lipopeptide MX-2401 (Migenix Incorporated), a novel semisynthetic analog of amphomycin, is an expanded-spectrum calcium-dependent cyclic lipopeptide possessing bactericidal activity against several clinically relevant Gram-positive bacteria including *Enterococcus*, *S. pneumoniae*, and MRSA (Craig et al. 2010). Despite being structurally similar to daptomycin and possessing a similar mechanism of action by binding to undecaprenyl phosphate (C_{55}-P) and inhibiting cell wall biosynthesis, MX-2401 is not inhibited by lung surfactant. This improves its efficacy for the treatment of pulmonary infections (Rubinchik et al. 2011). Although still in preclinical development phase, MX-2401 seems to be a promising candidate for further evaluation for the treatment of Gram-positive infections, including hospital-acquired pneumonia.

Lotilibcin (WAP-8294A_2; aRigen Pharmaceuticals) is a naturally occurring cyclic lipodesipeptide isolated from Gram-negative bacteria *Lysobacter staphylocidin* that exhibits potent activity against MRSA through selective interaction with bacterial membrane phospholipids (Chen et al. 2015). Lotilibcin has rapidly bactericidal nature and is specific to MRSA, thus expressing a narrow spectrum of action. It has shown 14-fold higher antibacterial activity as compared to vancomycin and has shown potent activity in animal infection models of MRSA. It is being developed for the treatment of ABSSI and is currently under Phase I clinical trials.

Cefilavancin (TD-1792; Theravance Biopharma) is a bactericidal multivalent glycopeptide-cephalosporin heterodimer antibiotic that possesses properties of both a glycopeptide and a beta-lactam and a synergized mode of action (Leuthner et al. 2010). In neutropenic murine thigh infection model and subcutaneous thigh infec-

tion model of *S. aureus*, it has shown severalfold higher activity as compared to vancomycin and linezolid (Hedge et al. 2007). In a randomized, double-blinded, active-controlled Phase II clinical trial, TD-1792 was shown to be safe, efficacious, and non-inferior to vancomycin when injected IV (Stryjewski et al. 2012). It is undergoing a Phase III clinical trial for the treatment of Gram-positive infections and SSI (http://www.theravance.com/bacterial).

TD-1607 (Theravance Biopharma) is a glycopeptide-cephalosporin heterodimer developed for the treatment of serious Gram-positive infections. It is structurally distinct from cefilavancin but demonstrates a similar mode of action, in vitro potency, and bactericidal profile. It has shown potent in vitro activity against numerous contemporary clinical MRSA isolates and has completed Phase I clinical trial where it has been shown to be safe and well tolerated among healthy individuals (https://www.jmilabs.com/data/posters/ICAAC2014/F-970.PDF).

13.3 Cell Membrane Inhibitors

Brilacidin (PMX-30063; Cellceutix) is an arylamide foldamer designed to mimic the amphiphilic properties of antimicrobial peptides and is being developed for the treatment of ABSSSI as IV. In Phase II clinical trials, it has demonstrated clinical response rates comparable to those of daptomycin and was shown to be safe and well tolerated (NCT01211470). Brilacidin causes a dose-dependent depolarization of the *Staphylococcus aureus* membrane comparable to that of daptomycin, thus representing a new class of antibiotics (Mensa et al. 2014).

XF-73 (Destiny Pharma) is a novel dicationic porphyrin that rapidly kills a wide range of Gram-positive bacteria including MRSA by interfering cell membrane, resulting in the loss of vital components from the cell, without bursting the cells themselves. Due to its targeting the bacterial membrane, XF-73 kills bacteria in all growth phases, including nongrowing cultures and bacteria within biofilms (Farrell et al. 2011a, b). Owing to its target, there is a less likely possibility of generating XF-73-resistant mutants. It is being currently investigated for topical use in the treatment of MRSA infections and decolonization and has successfully completed Phase I trial of a nasal formulation for safety and local tolerability for decolonization of *S. aureus*.

13.4 Protein Synthesis Inhibitors

Fusidic acid (CEM-102; Cempra Pharmaceuticals), approved as a topical antibacterial, is being developed as an oral formulation for use in the USA for the treatment of ABSSSI and joint infections. It inhibits protein synthesis by preventing the release of elongation factor-G (EF-G) from the ribosome. In Phase II clinical trial, fusidic acid was shown to be non-inferior to linezolid. In a double-blinded Phase III trial, the oral

formulation has shown non-inferiority to linezolid for the treatment of MRSA infection (https://www.investor.cempra.com/releasedetail.cfm?ReleaseID=1014395). Although approved since the 1960s, there is a significant lack of resistance to fusidic acid among *S. aureus* clinical isolates (McLaws et al. 2011).

13.5 Macrolide

Solithromycin (CEM-101; Cempra Pharmaceuticals), a next-generation semisynthetic ketolide, has been developed for the treatment of CABP and differs from telithromycin in having fluorine substitution at C-2 and an aminophenyl moiety instead of the pyridine moiety, which ameliorates the nicotinic acetylcholine receptor blockage. Solithromycin inhibits protein synthesis by binding to the domain II and domain V of 23S rRNA. Additionally, because of its substitutions, it interacts at a third site on the ribosome and thus is especially active against macrolide-resistant strains (Fernandes et al. 2016). It has successfully completed Phase III trials with both oral and IV formulations, and a NDA has been accepted by the FDA.

13.6 Oxazolidinone

The oxazolidinones, a totally synthetic class of novel antibiotics, have strong activity against nearly all Gram-positive organisms, including those resistant to other drugs. They inhibit protein synthesis by binding to domain V of the 23S rRNA, thereby blocking formation of the initiation complex.

Radezolid (RX-1741; Melinta Therapeutics) is a novel biaryloxazolidinone having improved activity, even against linezolid-resistant strains, and binds to 23S rRNA in the peptidyl transferase center, thus inhibiting protein synthesis by obstructing binding of incoming aminoacyl-tRNA to the A site (Lawrence et al. 2008; Leach et al. 2007; Colca et al. 2003; Ippolito et al. 2008). It is being developed as an oral and topical formulation for the treatment of CAP and uSSSI. It has shown good cure rates and was well tolerated in two completed Phase II trials against uSSSI and CAP. The most commonly reported adverse effects in clinical trial were gastrointestinal symptoms.

MRX-1 (MRX-I; MicuRx Pharmaceuticals), an analog of linezolid, is being developed as an oral formulation to specifically reduce myelotoxicity and monoamine oxidase inhibition, the signature toxicities associated with linezolid (Gordeev and Yuan 2014). MRX-1 has completed Phase II clinical trials with excellent antibacterial activities against MRSA, outpacing linezolid, and demonstrated no significantly adverse side effects. Phase III trials have begun enrolling patients with ABSSSI to compare MRX-1 with linezolid.

LCB01-0371 (LegoChem Biosciences), a novel oxazolidinone with cyclic amidrazone, has been developed for the treatment of infections caused by MRSA, VRE,

and MDR-TB. LCB01-0371 demonstrates potency comparable to torezolid in mouse systemic infection models. It has completed Phase I clinical trial with potency better than linezolid and improved safety in terms of lower myelosuppression and monoamine oxidase inhibition. LCB01-0371 can be administered both parenterally and IV. Combined with its excellent spectrum of activity and multiple routes of administration makes it a good candidate for long-term therapy (Jeong et al. 2010, http://adisinsight.springer.com/drugs/800035856). A Phase II study to explore the EBA, safety, and pharmacokinetics of orally administered LCB01-0371 is about to be initiated.

LCB01-0699 (LegoChem Biosciences) is a new oxazolidinone under preclinical studies for Gram-positive organisms including MRSA, VRE, MDR-TB, and linezolid-resistant strains. It is under preclinical studies and shares most of its properties with LCB01-0371 (http://adisinsight.springer.com/drugs/800027159).

13.7 Aminomethylcyclines

Omadacycline (PTK-0796, Paratek Pharmaceuticals) is a novel, broad-spectrum aminomethyl tetracycline developed for the treatment of ABSSSI, CABP, and cUTI caused due to Gram-positive bacteria. It was designed to circumvent two key mechanisms of tetracycline resistance: ribosome protection and tetracycline efflux, which is reflected in its potent antimicrobial activity against a wide range of drug-resistant clinical isolates. Omadacycline was shown to be efficacious, well tolerated, and non-inferior to linezolid for the treatment of ABSSSI in a Phase II clinical trial (Noel et al. 2012). In a Phase III trial, omadacycline was reported to be safe, efficacious, and non-inferior to linezolid for ABSSSI. Two more Phase III trials are under way, one to compare once-daily oral dose of omadacycline to twice-daily oral dose of moxifloxacin for the treatment of ABSSSI and second to compare safety and efficacy of omadacycline with linezolid for CABP patients.

Eravacycline (TP-434, Tetraphase Pharma) is a broad-spectrum synthetic fluorocycline which retains its activity in the presence of tetracycline efflux pumps and ribosome protection proteins. In vitro studies have shown potent activity against numerous clinical isolates and MDR bacteria such as MRSA (Xiao et al. 2012; Chopra and Dasgupta 2014). It has recently completed a Phase II clinical trial for its use in cIAI when compared with ertapenem where it demonstrated equal efficacy at comparatively lesser dosage. Eravacycline is currently being examined in a multicenter Phase III study to assess the efficacy, safety, and pharmacokinetics of eravacycline compared with meropenem in the treatment of cIAIs (NCT02784704). It is also being examined for its efficacy, safety, and pharmacokinetics as compared to ertapenem and levofloxacin in treating cUTI patients (NCT03032510 and NCT01978938).

TP-271 (Tetraphase Pharma) is a novel broad-spectrum synthetic fluorocycline developed for the treatment of respiratory tract infections caused by susceptible and antibiotic-resistant public health pathogens, including *Francisella tularensis*, *Yersinia pestis*, and *Bacillus anthracis* (Liu and Myers 2016 (http://adisinsight.springer.com/drugs/800044518)). It has received the QIDP designation from FDA, and Phase I trial to assess the safety, tolerability, and pharmacokinetics of TP-271 has been initiated.

13.8 Aminoglycosides

Plazomicin (ACHN-490; Achaogen Incorporated), a neoglycoside derived from sisomicin, has been developed to overcome the effects of aminoglycoside-modifying enzymes (AMEs), which are the primary mode of resistance to aminoglycosides (Tenover et al. 2011). It has shown potent efficacy against MDR Gram-negative bacteria as well as MRSA. In a Phase II clinical trial for the treatment of cUTI, plazomicin was shown to be safe and non-inferior to levofloxacin. Similarly, in Phase III clinical trial termed EPIC (Evaluating Plazomicin in cUTI), it has met the primary goal of non-inferiority to meropenem.

13.9 Peptide Deformylase Inhibitors

Lanopepden (GSK 1322322; GlaxoSmithKline) is a selective peptide deformylase inhibitor with potent activity against MRSA (Ross et al. 2011). In a randomized, double-blinded, placebo-controlled Phase I clinical trial, it was shown to be safe and well tolerated among healthy individuals. In another Phase II clinical trial, it was shown to be safe, well tolerated, and efficacious for the treatment of confirmed cases of ABSSSI. However, GlaxoSmithKline has terminated the lanopepden program (http://adisinsight.springer.com/drugs/800030124).

13.10 DNA Synthesis Inhibitors

13.10.1 Fluoroquinolones

Delafloxacin (Baxdela, Melinta Therapeutics) is an anionic fluoroquinolone that acts on both DNA topoisomerase II and topoisomerase IV and thus is designed to exhibit potency against MDR pathogens (Remy et al. 2012). It is being developed for the treatment of ABSSSI and is available as both oral and IV formulations. In a

Phase II clinical trial, where it was compared to tigecycline, delafloxacin met its primary and secondary efficacy end points and is currently being evaluated in a Phase III clinical trial versus vancomycin and aztreonam for the treatment of ABSSSI; no results are posted yet (NCT01984684). It is also undergoing a Phase III trial to evaluate the safety and efficacy of delafloxacin compared to moxifloxacin in the treatment of adult patients with CAP (NCT02679573).

Finafloxacin (Xtoro, MerLion Pharmaceuticals) is a novel fluoroquinolone designed to be activated under acidic conditions, thus eliminating the reservoirs of intracellular infection (Stubbings et al. 2011). Under acidic conditions, finafloxacin demonstrates superior activity when compared to moxifloxacin. A finafloxacin suspension was recently approved by FDA for the treatment of acute *otitis externa* or swimmer's ear caused due to *P. aeruginosa* and *S. aureus*. Various formulations are in Phase I and II evaluation for the treatment of uUTI, cUTI, and pyelonephritis.

Avarofloxacin (JNJ-Q2, Johnson and Johnson) is an aminoethylidenylpiperidine fluoroquinolone with a zwitterion structure that demonstrates antibacterial effect against numerous MDR Gram-negative and Gram-positive bacteria including MRSA and is being developed as both oral and IV formulations (Farrell et al., 2011a, b). During one Phase II trial conducted to study its safety and efficacy for treating ABSSSI caused by MRSA, JNJ-Q2 was found to be highly active, well tolerated, and non-inferior to linezolid.

Gepotidacin (GSK 2140944; GlaxoSmithKline) is a novel triazaacenaphthylene DNA topoisomerase II inhibitor (Bouchillon et al. 2013). Its mechanism is different from fluoroquinolone binding to DNA gyrase; thus it demonstrates efficacy against fluoroquinolone-resistant isolates. In addition, it is especially active against various MDR isolates of *N. gonorrhoeae* (Farrell et al. 2017). It is currently being evaluated for bioavailability, food effect, and pharmacokinetics of gepotidacin in a Phase I trial in healthy subjects (NCT02853435).

Nemonoxacin (TG-873870) is a C-8-methoxy nonfluorinated broad-spectrum quinolone. The C-8-methoxy substituent on the quinolone ring increases antibacterial effectiveness against Gram-positives and reduces selection of resistant mutants (Guo et al. 2012). When tested in vitro against clinical fluoroquinolone-resistant isolates of Gram-negative and Gram-positive bacteria including staphylococci, streptococci, enterococci, *N. gonorrhoeae*, and *H. influenzae*, nemonoxacin demonstrates better activity than ciprofloxacin, levofloxacin, and moxifloxacin (http://adisinsight.springer.com/drugs/800022726). It has been tested in a Phase II to determine the safety and efficacy of nemonoxacin in diabetic foot infections (NCT00685698). It has also been evaluated in Phase II trial for the treatment of CAP in comparison to levofloxacin (NCT00434291). It has been tested against levofloxacin to determine its efficacy and safety in CAP patients (NCT01529476).

Zabofloxacin (DW-224a, Dong Wha) is a broad-spectrum fluoroquinolone active against fluoroquinolone-resistant bacteria including MRSA and *Neisseria gonorrhoeae* (Kim et al. 2004). In a double-blinded, double-dummied, randomized, parallel-grouped Phase III clinical trial, zabofloxacin was shown to be non-inferior

to moxifloxacin (DW224a-II-1; KCT0001343). It has also been evaluated for the treatment of CAP in a Phase II trial, but the studies have been terminated due to financial considerations (NCT01081964). It also demonstrates excellent activity against intracellular pathogens such as *Legionella pneumophila* (http://adisinsight.springer.com/drugs/800019661).

WCK 771/WCK 2349 (Wockhardt) is a broad-spectrum bactericidal fluoroquinolone drug derived from benzoquinolizine levonadifloxacin. It targets bacterial DNA gyrase and DNA topoisomerase IV and inhibits *NorA* and thus exhibits potent activity against levofloxacin- and moxifloxacin-resistant MRSA. In various animal infection models, it has shown superior activity as compared to other quinolones (Patel et al. 2004). In Phase I clinical trial, it was shown to be safe and well tolerated among healthy individuals (http://adisinsight.springer.com/drugs/800016734).

13.11 Dihydrofolate Reductase (DHFR) Inhibitors

Iclaprim (AR-100 and RO-48-2622, Arpida Limited) is a novel diaminopyrimidine and has been shown to possess strong antagonistic activity against the bacterial DHFR enzyme. It is also active against trimethoprim-resistant MRSA (Schneider et al. 2003). In Phase II and Phase III trial studies, iclaprim was shown to be equally safe and non-inferior to vancomycin and linezolid for treating ABSSSI and cSSSI when compared to linezolid (NCT00299520) caused by MRSA, respectively.

13.12 Fatty Acid Synthesis Inhibitors

CG400549 (Crystal Genomics) belongs to a novel structural scaffold that targets the fatty acid biosynthesis enzyme called FabI within the FASII pathway, a critical enzyme in generating bacterial cell membrane. It has displayed superior in vitro efficacy and four- to eightfold higher potency when compared with linezolid, daptomycin, and vancomycin in treating MRSA, VRSA, and VISA (Park et al. 2007a, b). It has successfully completed a Phase II trial for the treatment of cABSSSI caused due to MRSA and has been demonstrated to be more potent in comparison to linezolid and vancomycin (Kim and Sohn 2011; Yum et al. 2007; Park et al. 2007a, b) (NCT01593761), but there is no further information available publically as to its future.

Debio1450 (AFN-1720; Debiopharm), the prodrug of Debio1452 (AFN-1252), is a highly potent and selective agent against several staphylococcal species and MDR strains such as MRSA and VISA. Both chemical entities inhibit the enzyme FabI enoyl reductase, the acyl carrier protein, resulting in a bacteriostatic mode of

action (Kaplan et al. 2012). A preclinical study of Debio1452 in several murine models of infection has validated its effectiveness. It has completed a Phase II clinical trial evaluating the efficacy of both intravenous (IV) and oral formulations in comparison with IV vancomycin switched to oral linezolid for the treatment of ABSSSI (NCT02426918). It is predicted that this entity will preserve human microbiota and reduce adverse effects associated with antibiotics such as *Clostridium difficile* overgrowth because of its specificity for staphylococcal species.

13.13 Summary

This chapter provides a detailed overview of current anti-MRSA drug pipeline and summarizes the excitements and loopholes in the current experimental therapies, which are tabulated in Table 13.1. It is important to keep in mind that the drug pipeline for most of the infectious disease pathogens including *S. aureus* is facing a severe deficit of putative drug candidates. In the past decades, the overly misuse of antibiotics has led to severe healthcare crises as the cases of MRSA are growing in both developed and developing countries with very little options available for their treatment. Recent Phase III trials for investigative drugs including MRX-1, omadacycline, plazomicin, zabofloxacin, and iclaprim have raised the hope for their promising effects against a range of the clinical isolates of MRSA. There have been some bright spots such as the discovery and development of TD-1792 and TD1607 and other novel modes of action antibiotics; however much still needs to be done to stem this burgeoning crisis.

Apart from these although the drug pipeline against MRSA has multiple potent candidates, there is a massive void which still exists in the discovery of new antibacterial chemical classes. Post-marketing surveillance and judicious use of new antimicrobial agents are necessary to ensure the effectiveness and longevity of the currently approved drugs. Presently, the drug pipeline is occupied with the focus on the single target. In the future, focusing on multiple targets and other avenues including combination therapy and identification of newer targets is the need of time for the generation of effective antimicrobials to combat resistance.

The discovery and development of molecules exhibiting anti-MRSA activity is a highly active field with a number of agents under preclinical and clinical development. Despite its appearance, the drug discovery pipeline is extremely anemic and requires a continuous resupply effort to be able to ameliorate the antimicrobial resistance crises.

Table 13.1 The various compounds active against *S. aureus* are listed along with their status above

Drug name	Company	Chemical class	Indication	Development phase	Mechanism of action (known or novel)
Cell wall and cell membrane inhibitors					
MX-2401	Migenix Incorporated	Lipopeptide	Gram-positive infections	Preclinical	Known
WAP-8294A2 (lotilibcin)	aRigen Pharmaceutical	Lipopeptide	ABSSI	Phase I	Known
TD-1792	Theravance	Cephalosporin/vancomycin heterodimer	ABSSI	Phase III	Known
TD-1607	Theravance	Cephalosporin/glycopeptide heterodimer	Gram-positive infections	Phase I	Known
Brilacidin	Cellceutix Corporation	Defensin mimetic	ABSSI, mucositis, stomatitis	Phase II	Known
XF-73	Destiny Pharmaceutical	Porphyrin	Gram-positive infections	Phase I	Novel
Protein synthesis inhibitors					
Fusidic acid	Cempra Pharmaceutical	Cholestadienes	ABSSI and joint infections	Phase III	Known
Solithromycin	Cempra Pharmaceutical	Macrolide	CABP	Phase III	Known
Radezolid	Melinta Therapeutics	Oxazolidinone	uSSSCI; CABP	Phase II	Known
MRX-I	MicuRx Pharmaceutical	Oxazolidinone	ABSSI	Phase III	Known
LCB01-037	LegoChem Biosciences	Oxazolidinone	Gram-positive infections; TB	Phase II	Known
Omadacycline	Paratek	Aminomethylcycline	ABSSI	Phase III	Known

(continued)

Table 13.1 (continued)

Drug name	Company	Chemical class	Indication	Development phase	Mechanism of action (known or novel)
Eravacycline	Tetraphase Pharmaceutical	Aminomethylcycline	cIAI	Phase III	Known
TP-271	Tetraphase Pharmaceutical	Aminomethylcycline	Respiratory infections	Phase I	Known
Plazomicin	Achaogen	Aminoglycosides	cUTI and pyelonephritis	Phase III	Known
Lanopepden	GSK	Cyclopentanes	cSSSI	Phase II	Known
Nucleic acid inhibitors					
Delafloxacin	Melinta Therapeutics	Fluoroquinolone	ABSSSI (Melinta)	Phase III	Known
Finafloxacin	MerLion Pharmaceutical	Fluoroquinolone	cUTI and pyelonephritis	Phase II	Known
Avarofloxacin	Furiex	Fluoroquinolone	ABSSSI	Phase II	Known
Gepotidacin	GSK	Fluoroquinolone	Gram-positive infections and *N. gonorrhoeae*	Phase I	Known
Nemonoxacin	TaiGen Biotech	Fluoroquinolone	ABSSSI and CABP	Phase III	Known
Zabofloxacin	Dong Wha Pharma	Fluoroquinolone	CABP	Phase III	Known
Iclaprim	Arpida Ltd.	Dihydrofolate reductase inhibitors	ABSSSI	Phase III	Known
Fatty acid inhibitors					
CG400549	Crystal genomics	Fatty acid synthesis inhibitor	ABSSSI	Phase II	Known
Debio1450	Debio/Nobelex	Benzodiazepine	ABSSSI	Phase II	Known

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