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Aggregation-induced emission active metal complexes: a promising strategy to tackle bacterial infections†

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Bacterial infection is a major global threat to human health and currently one of the leading causes of death worldwide. The development of probes for rapid diagnosis of bacteria with desired sensitivity and selectivity along with antibacterial activity against multidrug-resistant (MDR) bacteria has remained a great challenge. Whilst the traditional methods such as cell culture and colony counting, polymerase chain reaction and immunoassays are used for bacterial infection detection, these are time consuming, laborious and require a skilled operator. On the other hand, the rapid emergence of MDR bacteria is also posing another serious public health threat. Hence, it is an utmost urgency to develop novel therapeutics and rapid diagnostic agents for tackling MDR bacteria. Over the last few years, significant progress has been made towards the development of metal-based aggregation-induced emission luminogens (AIEgens) for bacterial management. These AIEgen materials offer potential applications for simultaneous detection and image-guided elimination of bacteria for the treatment of bacterial infections. In this Feature Article, we have highlighted the recent progress in the development of metal-based AIEgens for detection, discrimination and decimation of bacteria. In addition, the potential challenges in developing antibacterial agents and several future perspectives of metal-based AIEgens in this field have also been discussed.

1. Introduction

Infectious disease is one of the leading causes of death worldwide due to the emergence of antimicrobial resistance (AMR). AMR is a multifaceted problem and poses serious threat to

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† This Feature Article is dedicated to the healthcare professionals fighting against the COVID-2019 pandemic.

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human health, killing 7 million people annually across the globe due to the rapid evolution of drug-resistant bacteria.[1,2] Recent projections suggest that bacterial infections alone will result in 10 million deaths every year by 2050, surpassing the number of deaths caused by cancer presently.[1–3] Bacterial infections can cause diseases like pneumonia, meningitis, typhoid, *etc.* and trigger severe immune response like inflammation, sepsis and septic shock that leads to multiple organ failure.[4] The discovery of the first antibiotic, penicillin, in 1928 by Alexander Fleming has revolutionized medicine by saving millions of lives. Since then, many antibiotics have come into the market but the empirical and rampant use of antibiotics has resulted in the development of multidrug-resistant (MDR) bacteria known as ''superbugs''. According to the Centers for Disease Control and Prevention (CDC) 2019 report, more than 2.8 million antibiotic-resistant infections occur in the United States each year and as a result cause more than 35 000 people deaths each year.[5] The increase of MDR bacteria endangers life-saving surgery, chemotherapy, organ transplants and caesarians. Now days are not far when people will die from common infections like respiratory tract infection, sexually transmitted infection and urinary tract infection if action is not taken soon.[5,6] Over the past 30 years, no new antibiotics have been discovered, and the World Health Organization (WHO) has already warned of dire consequences as we swiftly edge towards the ''post-antibiotic era''.[7] This clearly raises alarm for the urgent development of new classes of antibacterial agents to combat against MDR bacteria.

Along with the discovery of new antibiotics, it is important to develop sensitive techniques for early stage detection and identification of pathogenic bacteria for the effective treatment of bacterial infections. The conventional methods for bacterial detection include cell culture and colony counting, polymerase chain reaction (PCR), and enzyme-linked immunosorbent assay (ELISA).[8] In the recent years, some new methods have been developed for bacterial detection such as colorimetric and electrochemical sensors,[9] surface-enhanced Raman scattering,[10] mass spectrometry,[11] microfluidic based devices, flow cytometric methods,[8] *etc.* However, these methods are time consuming and require expensive equipment, tedious operations with various pre-processing steps and skilled personnel.[8] This scenario clearly projects that there is an urgent and unmet need for the development of new techniques for rapid, selective and sensitive detection of bacteria. In the past few years, aggregation-induced emission luminogens (AIEgens) have gained much attention for detection, imaging and killing of bacteria.[12–16] During the last five years, several excellent review articles on AIEgens have been published, describing their applications in various fields.[12–19] However, among them, only one article has given little emphasis on metal-based AIEgens for the detection and killing of pathogens.[15] In this Feature Article, for the first time, we have systematically summarized the recent development of AIE-active metal complexes for the detection and eradication of bacterial pathogens (Fig. 1). In particular, we have intended to emphasise on the molecular design strategies of metal AIEgens and their interactions with the pathogenic bacteria for imaging and killing, along with the mechanistic aspect of antimicrobial activity. This Feature Article has also highlighted the challenges associated with the discovery of new antibiotics and several future opportunities of metal-based AIEgens as bacterial theranostic agents. We hope that by compiling some exciting developments in this field, this Feature Article will inspire the scientific community for the future design and evolution of metal-based AIEgens.

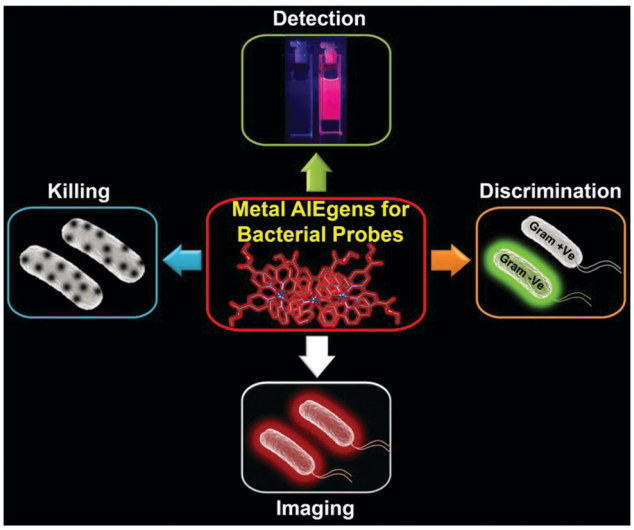

Fig. 1 The metal AIEgens as bacterial theranostic agents.

Pijus K. Sasmal

Pijus K. Sasmal received his PhD in 2010 from IISc Bangalore under the supervision of Prof. Akhil R. Chakravarty. He did his postdoctoral research at the University of Marburg, Germany (October 2010–September 2012), Rutgers University, USA (November 2012–June 2014), and Princeton University, USA (July 2014–September 2015) with Prof. Eric Meggers, Prof. KiBum Lee, and Prof. Robert K. Prud'homme, respectively. He joined the School of Physical Sciences, Jawaharlal Nehru University, New Delhi, India, in 2015 as an Assistant Professor. His main research interest is the design and synthesis of metal-based diagnostic and therapeutic agents for tackling cancer and bacterial infections.

2. Luminogens for sensing and bioimaging

Recently, fluorescent sensors have found wide applications in various fields due to their advantages of excellent sensitivity, rapidness, and easy operation.[20] A variety of fluorescent materials

such as organic dyes, inorganic nanoparticles, fluorescent proteins, *etc.* have been developed for utilization in sensing and imaging applications in the complex biological milieu.[21] Among them, organic dyes such as fluorescein, rhodamine, BODIPY, and cyanine are most widely used and easily accessible. Unfortunately, the traditional organic fluorophores mostly emit brightly in dilute solution and undergo serious photobleaching and self-quenching at high concentration or in the aggregated state because of the strong intermolecular π–π stacking interactions.[22] This notorious effect of organic dyes is termed as aggregation-caused quenching (ACQ), which greatly limits their applications. For example, fluorescein is soluble in water but insoluble in most of the common organic solvents like THF. Fluorescein emits bright green fluorescence when molecularly dissolved in water upon illumination of UV light. However, the fluorescence intensity is gradually quenched as THF is progressively added into water due to the formation of nanoaggregates (Fig. 2a). Owing to the severe aggregate formation, the planar polycyclic structure of fluorescein enables its molecules to pack well and undergo π–π interaction which leads to the generation of excimer species, resulting in the observed ACQ effect. Hence, it is highly desirable to develop new fluorescent sensors that can circumvent the ACQ effect.

In contrast to ACQ fluorophores, AIEgens have emerged as promising alternatives for ''turn-on'' fluorescence sensing and bioimaging.[12–19] The concept of AIE was coined by Tang's group in 2001, who first proposed a new kind of photophysical phenomenon associated with chromophore aggregation, which is the opposite of ACQ.[23] In the AIE process, luminogens exhibit weak or no emission in the dilute solution, but show intense emission in the aggregated or solid state (Fig. 2b). In the past few years, a large number of organic AIEgens such as tetraphenylethene (TPE), tetraphenylpyrazine (TPP), silole, thiophenes, cyanostilbene, 9,10-distrylanthracene (DSA), and organoboron complexes have been developed at an incredible speed and gained enormous attention in the field of chemical and biological sensing and imaging.[12–19] Various hypotheses have been proposed on AIE mechanisms such as restriction of intramolecular rotation (RIR), excimer formation, restriction of intramolecular charge transfer, molecular planarization, J-aggregate formation (JAF), *E–Z* isomerization, twisted intramolecular charge transfer (TICT) and excited state intramolecular proton transfer (ESIPT).[12,24–26] In addition, the π–π stacking interaction in ACQ fluorogens is also hampered in organic AIEgens due to the nonplanar molecular conformation which suppress the dissipation of the excited-state energy *via* non-radiative relaxation and promotes the radiative decay.

Besides the development and vast applications of organic AIEgens, the last decade has witnessed a rapid evolution of heavy metal complexes in the field of optoelectronics, chemosensors, bioimaging, *etc.*[27–31] The phosphorescence properties of organic AIEgens are limited due to the inefficient spin–orbit coupling because of the presence of light elements.[32–34] The heavy-metal complexes facilitate strong spin–orbit coupling, leading to efficient intersystem crossing from the singlet excited state to the triplet excited state manifold. Transition-metal complexes having metal centres of d^6, d^8 and d^{10} electronic configurations have shown luminescence emission at room temperature.[27–31] In addition, compared to organic AIEgens, metal-based luminogens are interesting since they can exhibit a range of excited states such as metal-to-ligand charge-transfer (MLCT), ligand-to-ligand charge-transfer (LLCT), ligand-to-metal charge-transfer (LMCT), intraligand charge-transfer (ILCT), metal–metal-to-ligand charge-transfer (MMLCT), ligand-to-metal–metal charge-transfer (LMMCT) and metal-to-ligand–ligand charge-transfer (MLLCT) states. These metal complexes provide many superior photophysical properties such as long luminescence lifetimes (100 ns to 1 ms), large Stokes' shift (hundreds of nm), enhanced photostability (lower photobleaching), high quantum yields, high signal-to-noise ratio, easy tunability of light emission wavelength, and straightforward synthetic routes, which makes them attractive alternatives to organic AIEgens for bioimaging, sensing and labeling. Recently, metal complexes such as Ir(III), Ru(II), Os(II), Re(I), Pt(II), Au(I), Cu(I) and Zn(II) have been reported to exhibit excellent AIE properties.[27–31,35] Among these, some AIEgen metal complexes demonstrated potential for use in imaging and decimation of bacterial pathogens which has been discussed in this Feature Article.

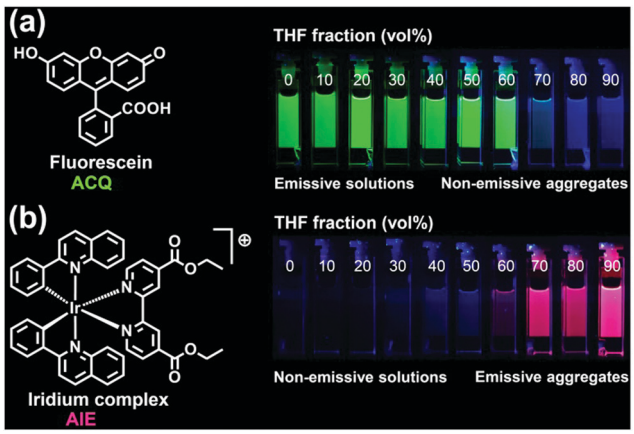

Fig. 2 Fluorescence digital photographs of solutions or suspensions of (a) fluorescein and (b) iridium complex in a water–THF mixture with different fractions of THF, where fluorescein and the iridium complex exhibited aggregation-caused quenching (ACQ) and aggregation-induced emission (AIE) effects, respectively.

3. Interactions of metal-based AIEgens with the bacterial membrane

On the basis of cell wall structure, bacteria are mainly classified into two types: Gram-negative and Gram-positive. Gram-negative bacteria possess a thin peptidoglycan layer (20–50 nm) sandwiched between the cytoplasmic cell membrane and the outer membrane (Fig. 3).[36] The outer membrane (OM) is made up of a lipid bilayer containing lipopolysaccharides (LPS) exposed on the cell surface. The OM serves as a protective layer against various detergents, dyes and hydrophobic antibiotics.[37] LPS are amphiphilic molecules composed of a

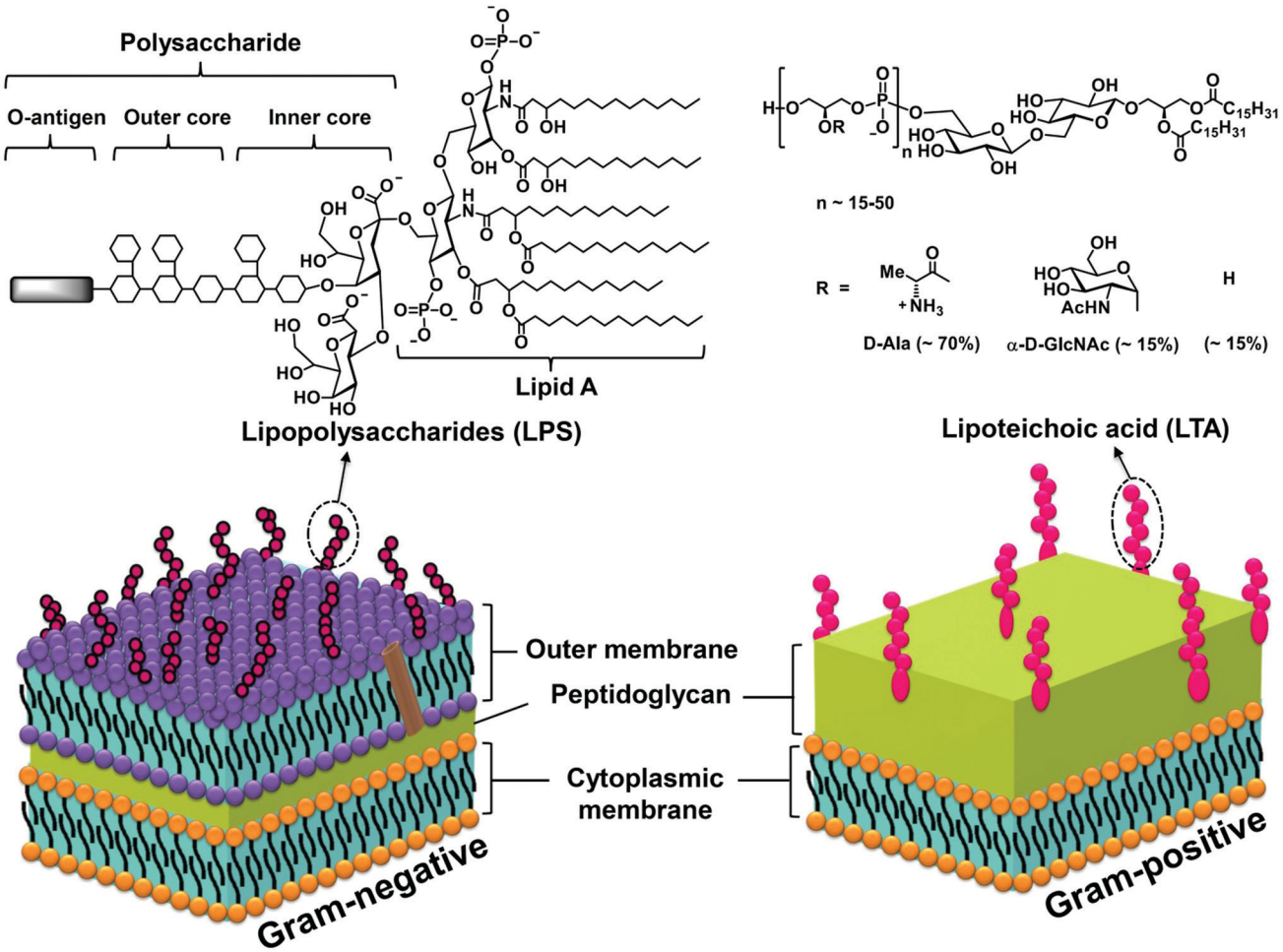

Fig. 3 Schematic illustration depicting the structures of Gram-negative (left) and Gram-positive (right) bacterial cell membranes. (Top) Molecular structure of the pathogenic components, lipopolysaccharides (LPS) and lipoteichoic acids (LTA), that are present on the outer membrane of Gram-negative and Gram-positive bacteria, respectively.

hydrophobic part – lipid A and a hydrophilic core – polysaccharides. Lipid A is a conserved part of Gram-negative bacteria and is responsible for their toxicity.[38] On the other hand, the cell wall of Gram-positive bacteria has a cytoplasmic membrane followed by a thick peptidoglycan layer (15–100 nm) decorated with teichoic acids or lipoteichoic acids (LTA).[36] LPS and LTA are highly negatively charged molecules due to the presence of multiple phosphate groups. LPS also bear additional carboxylate groups attached to the two 2-keto-3-deoxyoctonate (Kdo) units. Further, these molecules contain hydrophobic regions – six alkane chains in LPS and two in LTA per structural unit. The structure of the bacterial cell wall plays a crucial role in determining the interaction of metal-based AIEgens with bacteria.

Metal AIEgens can interact with bacterial pathogens through various noncovalent interactions such as electrostatic interactions, hydrogen bonds, van der Waals forces and hydrophobic interactions. Electrostatic interactions help in disorganization of the bacterial membrane whereas hydrophobic interactions facilitate crossing of the hydrophobic lipid bilayer enhancing membrane insertion and bilayer perturbation.[39] The drug can bind to phosphatidylethanolamines and phosphatidylglycerols present on the phospholipid membranes and/or LPS of Gram-negative bacteria or LTA and teichoic acid organized in multiple layers of peptidoglycan of Gram-positive bacteria, respectively, through electrostatic interactions as well as hydrophobic interactions.[37,40]

4. Antimicrobial mechanism of metal-based AIEgens

The ability of bacteria to gain resistance against existing antibiotics has urged researchers to develop new compounds for the treatment of bacterial infections. For designing a novel antibiotic, one must understand different target sites within the bacterial cell. Antibiotics can kill bacteria either by binding to the component involved in DNA and RNA synthesis or by preventing protein synthesis by binding to subunits of intracellular ribosomes or by disruption of the cell membrane or by inhibition of cell wall synthesis (Fig. 4a).[41] These modes of action can interfere with the normal cellular processes which consequently leads to the death of bacteria. However, bacteria are very smart in altering the regular cellular mechanism to gain resistance against most of the existing

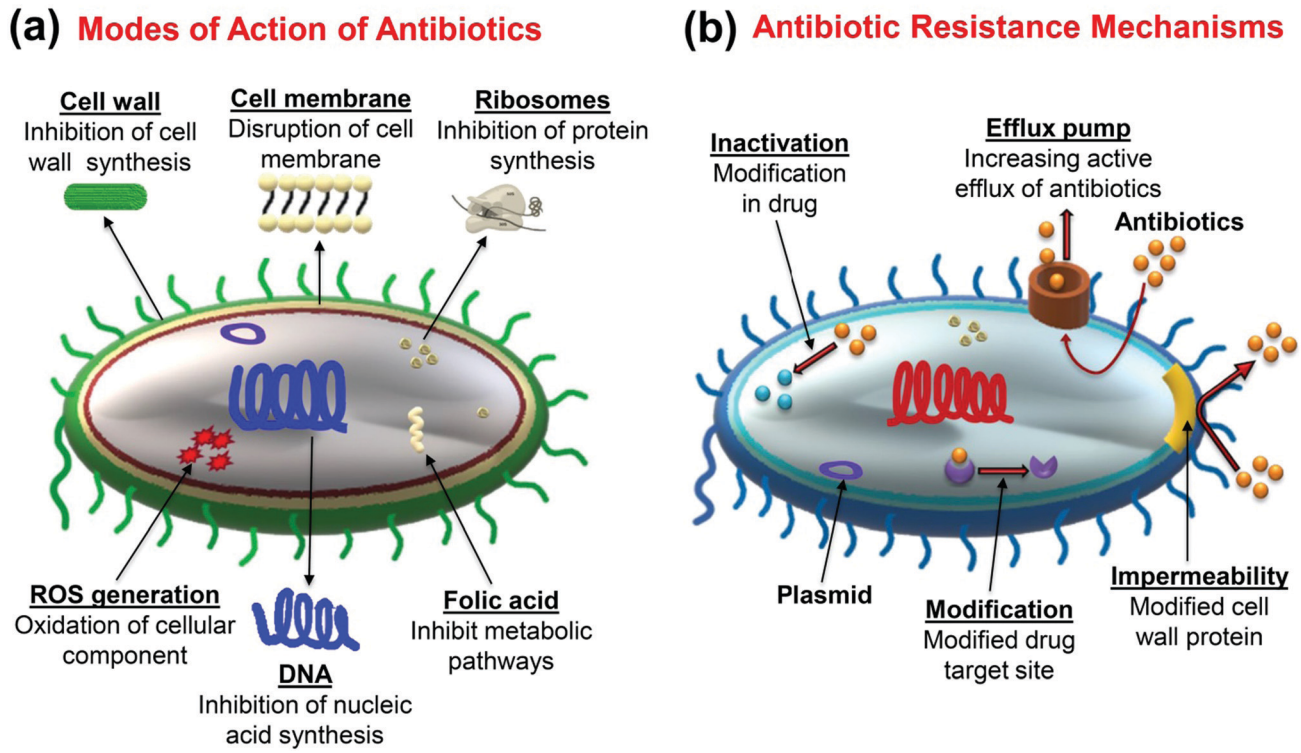

Fig. 4 Schematic diagram showing (a) targets of antibiotics and (b) mechanisms of bacterial resistance to antibiotics.

antibiotics. The mechanisms involved in AMR are (1) enzymatic degradation/modification of antibiotics, (2) alteration of bacterial proteins that are targets of antibiotics, (3) active efflux of antibiotics from the cell and (4) changes in membrane permeability to antibiotics (Fig. 4b).[41,42]

AIEgens have emerged as powerful materials for image-guided therapy and eradication of pathogenic bacteria by the generation of reactive oxygen species (ROS), membrane disruption and binding to bacterial DNA.[15] ROS can kill bacteria by random oxidation of lipids and nucleic acids and damage of proteins which prevents the development of any specific resistance mechanisms in bacteria.

5. Advantages of antibacterial metal-based AIEgens

The traditional luminogens suffer from the ACQ effect at high concentrations or in the aggregated state, which greatly limits their application for sensing and bioimaging. AIEgens possess unique advantages of strong photostability, good biocompatibility, excellent fluorescence properties, high quantum yield, long luminescence lifetimes, high sensitivity, large Stokes' shift, high signal-to-noise ratio and turn-on light-up feature. AIEgens are promising materials for simultaneous imaging and killing of bacteria and have several distinct advantages over conventional luminescent antibacterial agents and other compounds: (1) the AIEgen materials show enhanced antibacterial efficacy due to the formation of nano-aggregates which can colocalize within the bacteria leading to local high drug concentration[43] and (2) the photoactivated AIEgens in the nano-aggregated state can generate high local concentration of ROS for efficient killing of bacteria.[44]

The antibacterial metal-AIEgens are superior to purely organic AIEgens since (1) the metal-AIEgens with longer wavelength emission are particularly appealing due to their low autofluorescence interference which favours both *in vitro* and *in vivo* bacterial imaging,[45] (2) the metal complexes show visible or near-IR light absorption that has deeper tissue penetration, which makes them ideal candidates for photodynamic inactivation (PDI) of bacteria, (3) the photoactivated heavy metal complexes (*e.g.* Ir, Pt, Ru, Rh, *etc.*) could generate high singlet oxygen quantum yields due to strong spin–orbit coupling thereby exhibiting efficient antimicrobial activity, (4) metal-AIEgens can provide a unique mode of action such as ligand exchange or release, redox activation, ROS generation and catalytic generation of toxic species[46] and (5) in addition, the three-dimensional shapes of metal AIEgens enable them to interact with different target sites of bacteria which would be helpful to overcome the drug resistance mechanism in bacteria. Hence, the AIEgen metal complexes bear additional advantages compared with their organic counterparts and conventional luminogens for the development of antibiotics.

6. AIE-Active metal-based luminogens as bacterial theranostic agents

6.1. Ir(III) complexes (d^6 system)

Recently, aggregation-induced phosphorescence emission (AIPE) active iridium(III) complexes have gained immense interest for

their rich photophysical properties and find application in the field of organic light-emitting diodes (OLEDs), bioimaging, chemosensors, *etc.*[24,29,30] In 2015, Laskar and Panwar's groups have demonstrated the application of AIE-active iridium(III) complexes (**1–6**) for sensing and inhibition of bacteria in aqueous solution (Fig. 5a).[47] In this report, they have tested six Ir(III) complexes, out of which three complexes (**1**, **4** and **6**) were found to stain bacterial cells (Fig. 5b). The microscopic imaging studies showed that these Ir(III) complexes can bind and penetrate into the bacterial cells. The complexes exhibited moderate to good antibacterial activity with the minimum inhibitory concentration (MIC) values determined to be 4 and 8 μg mL^{-1} against Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacterial strains, respectively. Notably, the complexes were found to be more effective against Gram-positive bacterial strains due to the strong interactions of the complexes with the thick peptidoglycan component of Gram-positive bacteria that led to the disruption of the cell wall resulting in cell death. Preliminary mechanistic studies revealed that these Ir(III) complexes can interact with DNA through intercalation or major groove binding which were responsible for their antibacterial properties.

The rapid, sensitive and selective diagnosis of bacteria in addition to antibacterial activity against drug-resistant bacteria has remained a great challenge. Towards this endeavor, Sasmal and coworkers have developed a novel class of water soluble metal-based AIEgens, namely cyclometalated iridium(III) polypyridine complexes of the type $[Ir(PQ)_2(N^N)]Cl$ (**7** and **8**), in which PQ = 2-phenylquinoline and N^N = 2,2′-bipyridine derivatives, that demonstrated dual capabilities of simultaneous ultrasensitive detection and elimination of drug-resistant bacteria in aqueous solution (Fig. 5c).[48] The complexes exhibit selective and rapid sensing of pathogenic components, LPS and LTA, which are present in approximately million copies per cell on the outer wall of Gram-negative and Gram-positive bacteria, respectively.[49] These Ir(III) complexes were weakly emissive in aqueous solution, but showed an increase in the emission intensity in the range of 550–800 nm upon binding to LPS/LTA because of the AIE phenomenon (Fig. 5d). The limit of detection (LOD) of LPS and LTA by these Ir(III) complexes was found to be in the lower nanomolar range. The proposed mechanism suggested that these cationic Ir(III) complexes most likely bind to the negatively charged phosphate groups present on LPS/LTA *via* electrostatic interactions that leads to the formation of LPS/LTA–Ir(III) aggregates, resulting in strong intermolecular π–π stacking interactions. After detecting pathogenic components of bacteria, the authors have investigated the interaction of these complexes with the whole bacteria. The complexes enable the detection of bacteria by fluorescence

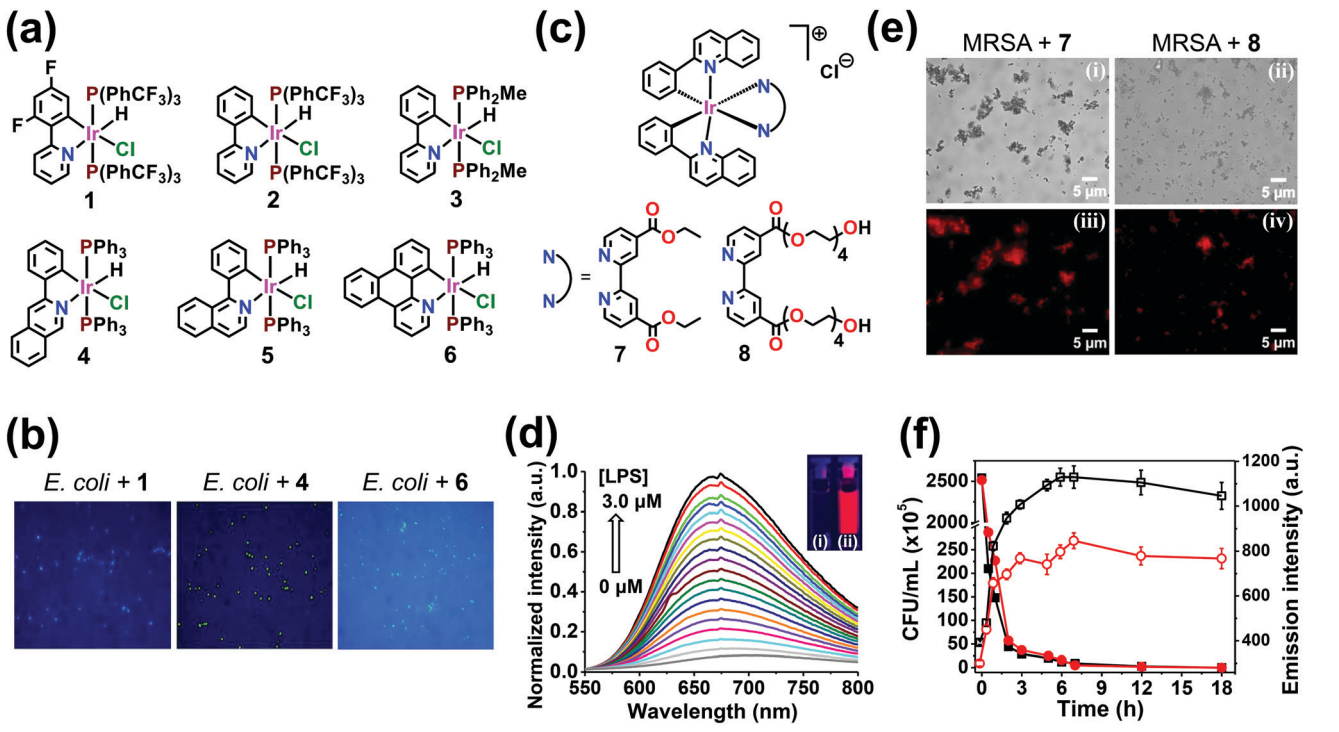

Fig. 5 (a and c) Molecular structures of AIE-active iridium(III) phosphine complexes (**1–6**) and iridium(III) bipyridine complexes (**7** and **8**) utilized as bacterial theranostic agents. (b) Fluorescence microscopy images of *E. coli* treated with the complexes (**1**, **4** and **6**). Reprinted with permission from ref. 47. Copyright 2015 Royal Society of Chemistry. (d) Emission titration spectra of complex **8** in aqueous medium upon gradual addition of LPS. (Inset) Phosphorescent digital photographs of complex **8** (50 μM) in the (i) absence and (ii) presence of LPS (3 μM), respectively. (e) Optical microscopy images of MRSA (10^8 CFU per mL) treated with 400 μg mL^{-1} of complex (**7** and **8**) and observed in complementary bright-field (i,ii) and fluorescence (iii,iv) modes. (f) Kinetics of bacterial detection using fluorescence spectroscopy (hollow data points) and growth inhibition by the counting method using agar plates (solid data points) in CRAB by 15 μg mL^{-1} of complex **7** (□, ■) and complex 8 (○, ●) in aqueous medium. Reprinted with permission from ref. 48. Copyright 2020 American Chemical Society.

microscopy imaging or the naked eye at higher (10^8 CFU per mL) bacterial cell concentrations within 10 min (Fig. 5e). Remarkably, the complexes can detect highly drug-resistant bacteria at extremely low concentrations ($\sim$1.2 CFU per mL) by fluorescence spectroscopy within 5 min in spiked water.

Further, the complexes (**7** and **8**) exhibited potent antibacterial activity (MICs $\leq$ 5 μg mL^{-1}) against a variety of Gram-positive (*E. faecium* and methicillin-sensitive *S. aureus* (MSSA)) and Gram-negative (carbapenem-sensitive *A. baumannii* (CSAB) and *E. coli*) bacteria and the resistant strains, carbapenem-resistant *A. baumannii* (CRAB) and methicillin-resistant *S. aureus* (MRSA). The proposed mechanisms of bacterial cell damage by the complexes were due to cell membrane disintegration and ROS generation. The dual functionality of these Ir(III) scaffolds was

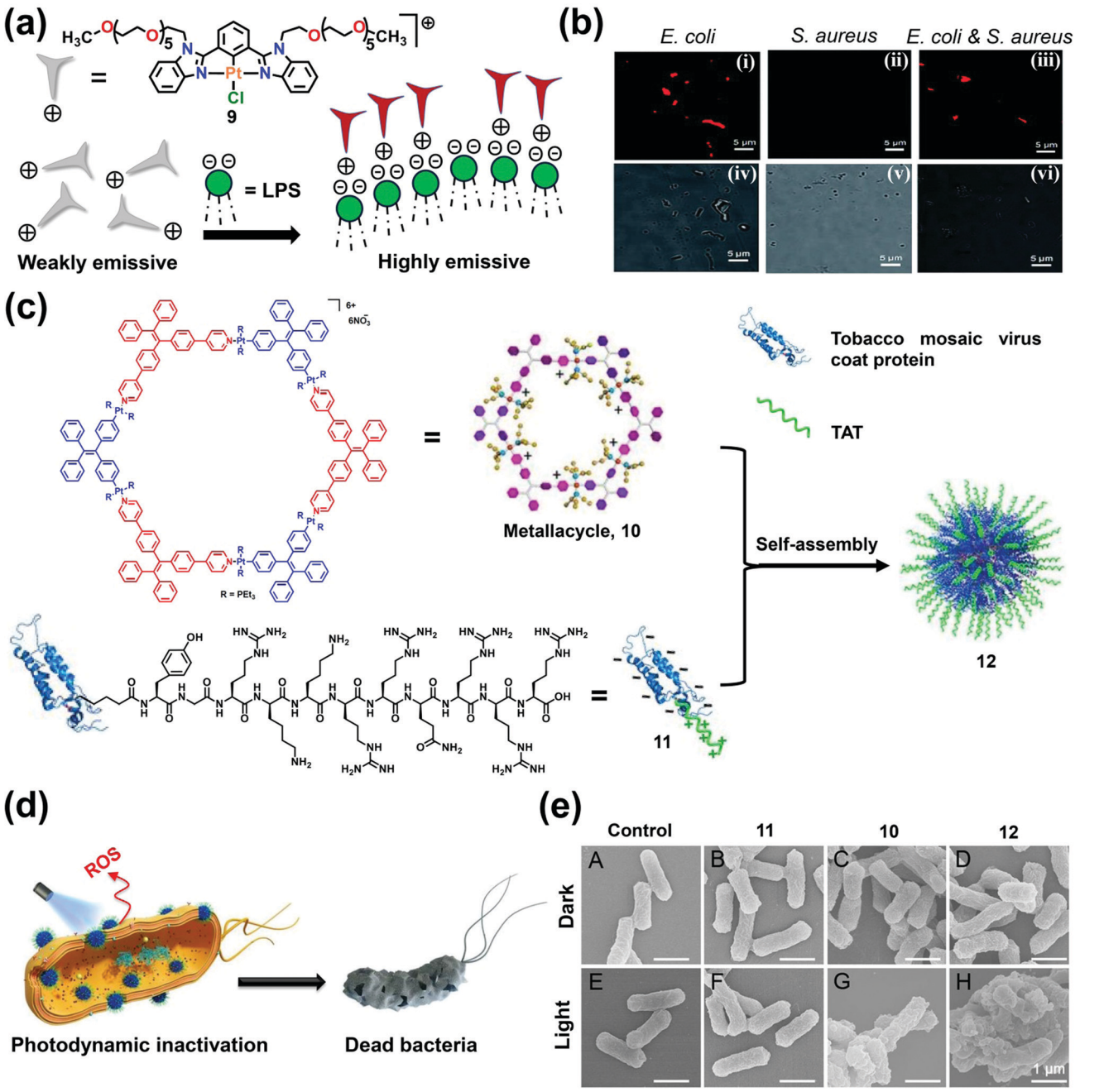

Fig. 6 (a) Molecular structure of the chloroplatinum(II) complex (**9**) used for the detection of LPS. (b) Confocal microscopy images of *E. coli*, *S. aureus* and the mixture of *E. coli* and *S. aureus* treated with the chloroplatinum(II) complex and observed in fluorescence (i–iii) and complementary bright-field (iv–vi) modes. Reprinted with permission from ref. 52. Copyright 2017 Royal Society of Chemistry. (c) Schematic illustration showing the self-assembly of the metallacycle (**10**) and protein (**11**) to provides an assembly (**12**). (d) Mechanism of the antibacterial activity of the assembly (**12**). (e) SEM images of *E. coli* cells without treatment (A) and (E) or after incubation with protein **11** (B) and (F), metallacycle **10** (C) and (G), or assembly **12** (D) and (H) in the dark (A–D) or with 420 nm light (25 mW cm^{-2}) irradiation for 15 min (E–H). Reprinted with permission from ref. 54.

investigated by simultaneously monitoring the detection and eradication of bacteria in aqueous medium in-a-single setup without using any external molecular detection probes (Fig. 5f). These Ir(III) scaffolds could be ideal candidates for monitoring bacterial contamination in aqueous samples and pharmaceutical formulations. More interestingly, these complexes demonstrate higher specificity toward bacterial cells over mammalian cells as examined by cytotoxicity studies for their potential application as antibacterial agents.

6.2. Pt(II) complexes (d^8 system)

In the past few years, square-planar platinum(II) complexes have received considerable attention in the fields of chemical sensors and electro-optical devices due to their intriguing spectroscopic and luminescence properties.[31,50] Several studies showed that the positively charged platinum(II) complexes can interact with negatively charged molecules/species such as single-strand oligonucleotides, polyelectrolytes, and surfactants through electrostatic interactions, leading to the formation of supramolecular aggregates.[51] Keeping this in mind, in 2017, Ding and Yu's groups have reported a cationic Pt(II) complex $[Pt(N^N^N)Cl]^+$ (**9**), where N^N^N is 2,6-bis(benzimidazol-2′-yl)pyridine with hexaethylene glycol methyl ether groups, that demonstrated sensing of the LPS (endotoxin) and rapid discrimination of Gram-negative and Gram-positive bacterial pathogens (Fig. 6a).[52] The luminescence intensity of weakly emissive complex **9** increased upon gradual addition of LPS with the LOD determined to be 5.7 nM. The authors have suggested that the enhancement of luminescence emission was due to the binding of the complex with negatively charged LPS resulting in the formation of LPS–Pt(II) aggregates that enhances the intermolecular Pt···Pt and π–π stacking interactions. The formation of LPS–Pt(II) aggregates was confirmed by determining the hydrodynamic diameter of complex **9** in the absence and presence of LPS.

Furthermore, the authors have demonstrated the rapid discrimination of bacterial strains based on the permeability of complex **9** against the bacterial cell wall for potential application in clinical diagnosis and establishment of therapeutic strategies. To investigate the potential application of complex **9**, Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria were mixed and incubated with **9** for the discrimination of bacterial pathogens (Fig. 6b). The complex could selectively stain Gram-negative bacteria within 5 min, due to the presence of abundant LPS on their outer wall.

Photodynamic therapy (PDT) has emerged as a promising strategy for the effective treatment of various diseases. The PDI of bacteria has become a promising approach for the effective treatment of bacterial infection. PDT requires three essential components such as a photosensitizer (*i.e.* drug), light and molecular oxygen.[53] In PDT, the photosensitizer absorbs light of specific wavelength and becomes excited to the singlet state, which is transformed to the corresponding triplet excited state *via* intersystem crossing. At this stage, the photosensitizer transfers energy to molecular oxygen and generates ROS that induces cell death. In 2019, Stang and coworkers have reported a self-assembled material based on an organoplatinum(II) metallacycle that demonstrated strong membrane-intercalating capability and PDI effect in bacterial cells.[54] The authors have designed an assembly (**12**) that was synthesized by the self-assembly of a positively charged metallacycle (**10**) with the negatively charged transacting activator of transduction (TAT) peptide decorated on tobacco mosaic virus coat protein (**11**) as described in Fig. 6c. The metallacycle (**10**) has the AIE property and acts as a good photosensitizer due to the presence of heavy atoms (Pt), which cause an enhancement of ROS generation. The results of imaging experiments revealed that the assembly (**12**) possessed enhanced membrane-intercalating ability because of the presence of the TAT moiety and accumulated within the cell membrane of *E. coli*, whereas the metallacycle (**10**) accumulated only outside the bacteria.

The antibacterial effect of the metallacycle (**10**) and assembly (**12**) was assessed against Gram-negative bacteria *E. coli* in the dark and upon irradiation of 420 nm light (Fig. 6d). Both the metallacycle and assembly being positively charged could interact with negatively charged bacteria, which resulted in higher toxicity in the dark. However, upon 15 min light irradiation, the cell viability of *E. coli* treated with the assembly decreased from ~55% to nearly 0%. The PDI efficiency of the assembly (96.3%) was significantly higher than that of the metallacycle (46.3%), due to the enhanced bacterial accumulation ability of the assembly. Further, the cell viability of *S. aureus* of Gram-positive bacteria treated with the assembly upon 15 min photoirradiation was decreased from 64% to 30%, suggesting the less effectiveness of the assembly in Gram-positive bacteria. The mechanism of the PDI effect of the assembly against bacteria is mainly due to ROS generation that causes membrane damage as observed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) imaging. The SEM images showed the significant rupture of the bacterial cell membrane after incubation of *E. coli* cells with the assembly under light irradiation (Fig. 6e(H)). This might be due to the oxidation of membrane phospholipids, proteins, DNA and other molecules in the PDI process. However, the surface of bacteria only turned rough after incubation of *E. coli* cells with the metallacycle under irradiation, indicating slight damage of the cell membrane (Fig. 6e(G)).

6.3. Zn(II) complexes (d^{10} system)

Following the discovery of zinc(II)-dipicolylamine (ZnDPA) complexes have a strong affinity to bilayer membranes that are enriched with anionic phospholipids,[55] Smith *et al.* have demonstrated that the bis(Zn^{2+}–DPA) conjugates (**13** and **14**) can efficiently stain the membranes of *E. coli* and *S. aureus* bacteria (Fig. 7a).[56] These conjugates can preferentially bind to the cell membrane over intracellular DNA (Fig. 7b). Furthermore, the probe can selectively stain bacteria over mammalian cells, even in the complex biological medium of saliva. Interestingly, the fluorescence intensity of the probe was enhanced by almost an order of magnitude upon binding to a bilayer membrane, suggesting the AIE property of the conjugates.

In the past few years, fluorogens with ESIPT properties have gained much attention because of their many advantages such as strong fluorescence with a large Stokes' shift and long triplet lifetimes.[57] This strategy motivated Liu *et al.* to develop AIE metal-based bacterial theranostic agents with ESIPT properties.[58] The authors have reported a multifunctional AIE-ZnDPA probe (**15**) based on the salicyladazine fluorogen for image-guided photodynamic killing of bacteria. The positively charged AIE-ZnDPA could bind electrostatically to the negatively charged bacterial membrane to activate AIE plus ESIPT emission *via* restriction of the intramolecular rotation around the N–N bond and formation of intramolecular hydrogen bonds within the salicyladazine moiety (Fig. 7c). The probe showed enhancement of fluorescence in the presence of both Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacteria, suggesting the binding of AIE-ZnDPA with bacteria. The antibacterial activity of AIE-ZnDPA was studied against both the bacteria under dark and light. The probe can kill bacteria even under dark due to the efficient depolarization of the bacterial membrane by the positively charged AIE-ZnDPA and exhibit photocytotoxicity activity through the generation of ROS. The SEM images of *B. subtilis* and *E. coli* bacteria treated with AIE-ZnDPA under dark showed little damage of bacterial cells (Fig. 7d). However, the damage of the bacterial membrane was greatly enhanced after light irradiation of bacteria treated with the probe. On the other hand, the probe did not show cytotoxicity in mammalian cells under both dark and light.

Recently, Liu and coworkers have reported another advanced AIE active Zn(II) complex as a bacterial theranostic agent with significant improvement compared to their AIE-ZnDPA (**15**). In this report, a Zn(II)-tetradentate-coordinated red-emissive probe, TPETH-2Zn (**16**), was synthesized that could selectively image bacteria over mammalian cells and showed potent photocytotoxicity against both Gram-negative and Gram-positive bacteria (Fig. 7e).[59] The probe demonstrated lower background signal and visible light absorptivity which makes TPETH-2Zn better than AIE-ZnDPA. The lower background signal was due to the high binding affinity of the TPETH ligand over DPA with Zn(II), and hence less unbound free probe was left in the detection system. Moreover, longer wavelength

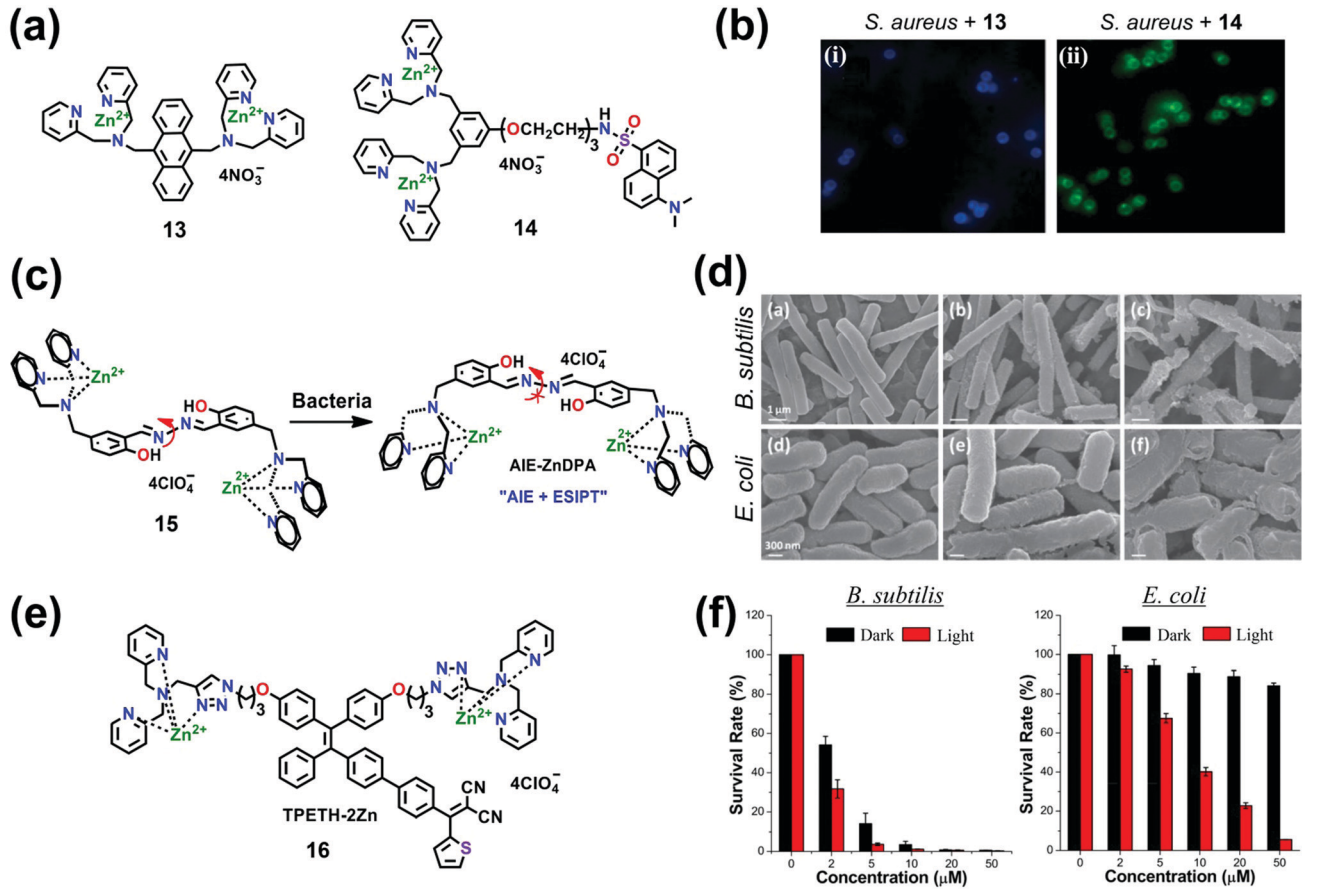

Fig. 7 (a, c and e) The chemical structures of zinc(II)-dipicolylamine (ZnDPA) complexes (**13** and **14**), AIE-ZnDPA (**15**), and Zn(II)-tetradentate-coordinated probe, TPETH-2Zn (**16**), used for selective targeting, imaging and killing of bacteria. (b) Fluorescence microscopy images of *S. aureus* cells stained with (i) **13** and (ii) **14**. Reprinted with permission from ref. 56. Copyright 2006 Royal Society of Chemistry. (d) SEM images showing the morphology of (a–c) *B. subtilis* and (d–f) *E. coli* upon incubation with AIE-ZnDPA (**15**). (a, d) Without AIE-ZnDPA under dark, (b, e) with AIE-ZnDPA (20 μM) under dark and (c, f) with AIE-ZnDPA (20 μM) under white light irradiation (100 mW cm^{-2}, 6 min). Reprinted with permission from ref. 58. Copyright 2015 John Wiley and Sons. (f) Cell survival of *B. subtilis* and *E. coli* treated with TPETH-2Zn (**16**) at different concentrations under dark and white light irradiation (100 mW cm^{-2}, 5 min). Reprinted with permission from ref. 59. Copyright 2017 American Chemical Society.

absorption of TPETH-2Zn enabled high concentrations of ROS to be produced under a white light source leading to enhanced antibacterial activity (Fig. 7f). The probe was almost non-emissive in aqueous solution but became highly red emissive after binding with both Gram-negative (*E. coli*) and Gram-positive (*B. subtilis*) bacteria. Interestingly, the probe could only slightly stain HeLa cells under the same conditions, indicating selectivity towards bacteria over mammalian cells.

6.4. Au(I) complex (d^{10} system)

Gold(I) complexes are known to exhibit AIE property, which has been utilized for sensing and bioimaging applications.[60,61] The inter- or intra-molecular Au···Au interactions (aurophilic interactions) and the restriction of intramolecular vibrations and rotations of the complexes are responsible for the emissive nature of Au(I) complexes in the aggregated state. In 2019, Zheng and coworkers have reported Pb^{2+} induced fluorometric detection of sulfate-reducing bacteria (SRB) by AIE-active glutathione (GSH)-Au(I) complexes (Fig. 8a).[62] SRB are a group of anaerobic microorganisms that are often found in environments such as freshwater, soil and salt marshes or in the human and animal intestines. SRB use sulfate (SO_4^{2-}) as a terminal electron acceptor which is converted to hydrogen sulfide (H_2S) as the final metabolite in the process of dissimilatory sulfate reduction, leading to the damage of epithelial cells.[63] Thus, the detection of S^{2-} generated from the metabolic activity of SRB is very important for environmental safety. In this work, the Zheng group has demonstrated the Pb^{2+} and S^{2-} induced fluorescence "turn on–off" of GSH-Au(I) complexes which was utilized for the detection of SRB. A non-fluorescent GSH-Au(I) complex was turned to strong fluorescent in solution on addition of Pb^{2+} due to the coordination interactions between Pb^{2+} and GSH ligand that facilitated the formation of a supramolecular structure of the type GSH-Au(I)-Pb(II). The fluorescence was quenched by S^{2-} (generated from the metabolic activity of SRB) due to the formation of PbS which destroyed the GSH-Au(I)-Pb(II) complex.

6.5. Hg(II) complex (d^{10} system)

Development of sensitive techniques for the detection of heavy metal toxins is highly desired since their bioaccumulation could cause serious threat to human health.[64] For instance, the natural bacteria *P. phosphoreum* at a high concentration emit strong bioluminescence based on quorum sensing.[65] However, the bioluminescence of *P. phosphoreum* was quenched in the presence of toxins such as Hg^{2+} which accumulated inside the bacteria and disrupted the quorum sensing process. Recently, Tang and Gao groups have developed a strategy based on an AIE-active probe (**17**) for the turn-on detection of bioaccumulated Hg^{2+} in *P. phosphoreum* (Fig. 8b).[66] The probe could enter the damaged bacteria and turn-on the fluorescence by forming aggregates with Hg^{2+}. The confocal fluorescence microscopy imaging experiments have revealed that almost no fluorescence signal was observed for control groups of *P. phosphoreum* and in the presence of only probe or Hg^{2+}. In contrast, a turn-on fluorescence was observed inside the bacteria in the presence of both Hg^{2+} and probe, indicating the efficient binding of the probe with Hg^{2+} inside the damaged bacteria. Similar experiments were performed in the presence of various other metal ions but no fluorescence enhancement was observed

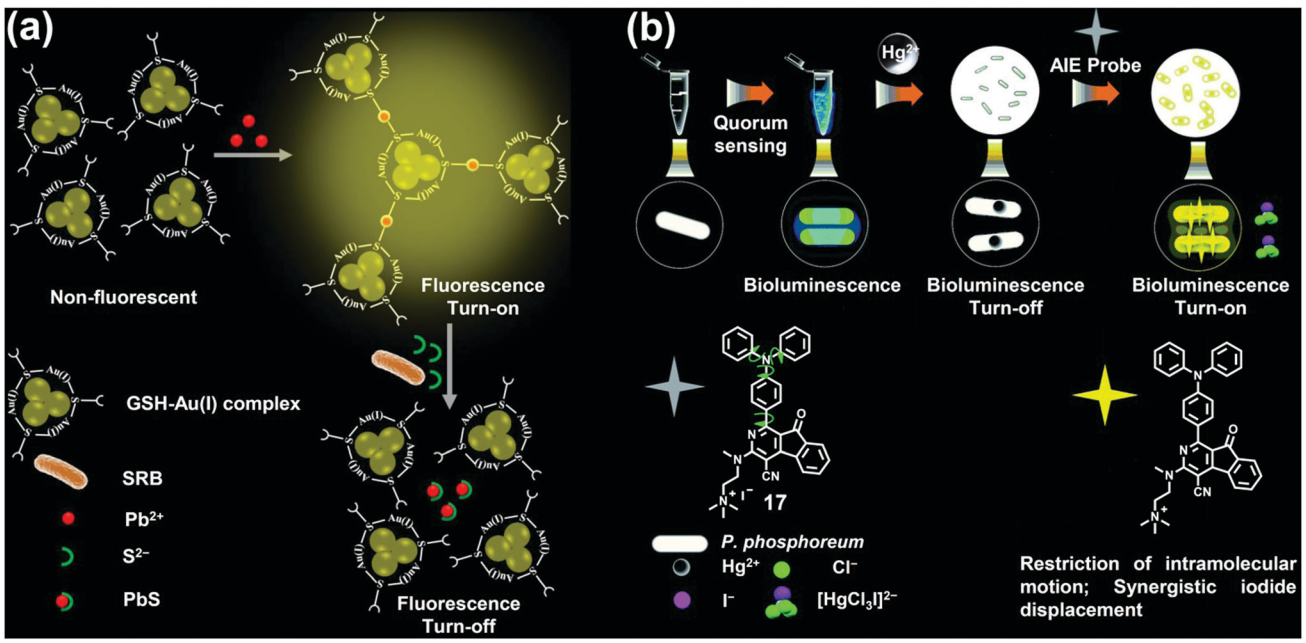

Fig. 8 (a) The schematic illustration of the mechanism of Pb^{2+} and S^{2-} induced fluorescence "turn on–off" of AIE-active GSH-Au(I) complexes utilized for the detection of sulfate-reducing bacteria (SRB).[62] (b) Schematic illustration of the dual detection strategy for Hg^{2+} based on turn-off of the bioluminescence of *P. phosphoreum* bacteria by disrupting the quorum sensing system and turn-on of the photoluminescence of an AIE probe (**17**) by forming aggregates with Hg^{2+} inside the bacteria. Reprinted with permission from ref. 66. Copyright 2019 Royal Society of Chemistry.

signifying the selectivity of the probe towards Hg^{2+}. The mechanism of Hg^{2+} turn-on fluorescence detection was based on restriction of intramolecular motion and synergistic displacement of fluorescence quenching iodide ions.

6.6. Other metal-based systems

In 2014, Liu's group have developed a platform based on an amphiphilic/cationic star copolymer, TPE-*star*-P(DMA-*co*-BMA-*co*-Gd), where TPE, DMA, BMA, and Gd are tetraphenylethylene, 2-(dimethylamino)ethyl methacrylate, butyl methacrylate and T1-type magnetic resonance (MR) imaging contrast agent, DOTA-Gd, respectively, for detection and inhibition of bacteria (Fig. 9).[67] In this platform, the TPE motif has the AIE feature and the amphiphilic/cationic P(DMA-*co*-BMA-*co*-Gd) has an affinity to bind the negatively charged bacterial surface through electrostatic interactions. The binding of the star copolymer to the bacterial surface causes the restriction of intramolecular rotation of the TPE motif and tumbling mobility of anchored Gd moieties which leads to synergistic turn-on fluorescence emission and MR relaxation rate enhancement. The star copolymer demonstrated fluorometric and MR imaging capabilities with LODs of $\sim 8.5 \times 10^5$ CFU per mL and $\sim 5 \times 10^3$ CFU per mL against *E. coli*, respectively. The star copolymer showed the highest antibacterial activity against Gram-negative (*P. aeruginosa*) and Gram-positive (*S. aureus*) bacterial strains with MIC values of ~ 0.1 and 30 μg mL^{-1}, respectively. The mechanism of antibacterial capability of the star copolymer might be due to the deformation of bacterial cell membranes. The star copolymer exhibited selectivity towards bacterial cells over mammalian cells, which was further significantly enhanced by quaternization of DMA units.

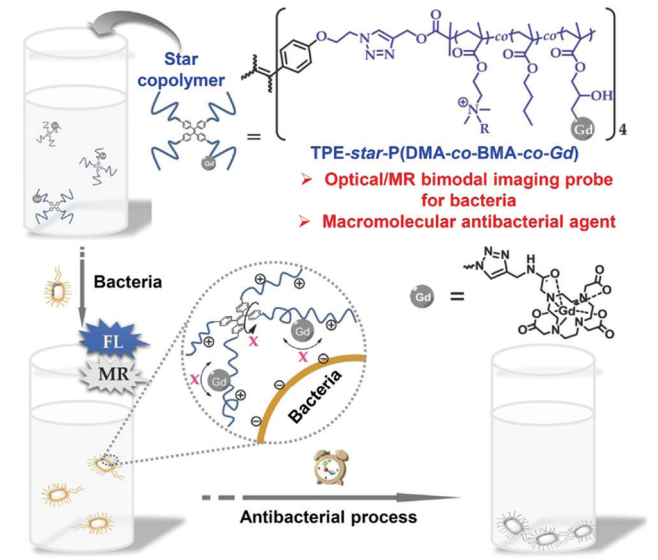

Fig. 9 Schematic illustration of fluorometric/magnetic resonance (MR) bimodal detection of bacteria by amphiphilic star copolymers (TPE-*star*-P(DMA-*co*-BMA-*co*-Gd)). The star copolymers also act as potent macromolecular antibacterial agents. Reprinted with permission from ref. 67. Copyright 2014 John Wiley and Sons.

7. Challenges to the development of new antibacterial agents

Despite the increasing antibiotic resistance in bacteria, no new drugs are being commercialized in the market over the past three decades. According to WHO's 2019 report, the majority of the large number of pharmaceutical companies have exited the field of antibiotic R&D and currently there are alarmingly few new drugs in the pipeline to deal with the worsening crisis of antibiotic resistance.[68] The recent report by the AMR Industry Alliance evidently stated that the low price of antibiotics worldwide along with the challenge to maintain the efficacy of the drug has dampened the industry investment against evolving MDR superbugs.[69] Moreover, there has been a dearth in discovery of new antibiotics possibly due to the poor return on investment and the limited market of the drug as soon as bacteria gain resistance against that drug. This clearly projects that the antibiotics do not attract the industry and R&D sector for the investment. On the other hand, it is financially more beneficial to modify the existing antibiotics instead of the development of new drugs.[70] Currently only a few companies are investing in the development of new antibiotics, whereas others prefer developing generic drugs as there is low risk in returns from the market. Most of the big pharmaceutical companies have preferred to invest on drugs for chronic diseases (*e.g.* cancer, diabetes, cardiovascular diseases, hypertension, *etc.*) that require prolonged treatment to get maximum profitability. In contrast, bacterial infections are mostly acute and, thus, much less attention has been drawn in the context of financial benefits. However, the development of new antibacterial drugs is extremely important rather than only the modification of existing antibiotics since it will be easier for bacteria to gain resistance against these modified antibiotics. This can be achieved by identifying new possible drug targets and new chemical entities. In addition, it requires a strategy to develop *in vitro* high-throughput screening assay for the identification of antibiotic potential.

8. Conclusions

In this Feature Article, we have summarized the development of metal-based AIEgens for the detection and elimination of bacteria. With the success of organic AIEgens as antimicrobial agents, the scientific community has gradually started focusing on transition metal-based AIEgens as antibacterial agents. The first report appearing in this area was with a Zn(II)-based metal complex. Since then, scientists have begun to explore other metal AIEgens and recently significant progress has been made in this field. In this article, we have discussed AIE-active metals such as Ir(III), Pt(II), Zn(II), Au(I) and Hg(II) for sensing and killing of bacteria. Several interesting reports have been discussed which include an Ir(III)-based system that can detect bacteria at extremely low concentrations with potent antibacterial activity against drug-resistant bacteria through membrane disruption and ROS generation. Pt(II)-based AIEgens

demonstrate bacterial discrimination and selective staining of Gram-negative bacteria. Further, the Pt(II)-based self-assembled metallacycle showed higher accumulation within bacterial cells due to the membrane-intercalating properties, consequently demonstrating a high PDI effect through the generation of ROS. In other reports, Zn(II)-based systems were reported to stain bacteria with excellent antibacterial activity upon photoactivation through membrane depolarization and ROS generation. In another interesting report, Au(I) AIEgens could identify sulfate-reducing bacteria due to Pb^{2+} and S^{2-} induced fluorescence "turn on–off" of GSH-Au(I) complexes. Though some advances have been made using metal-based AIEgens, the application of these materials as antimicrobial agents is still in its infancy.

9. Future perspectives

On the basis of progress achieved so far and for the further development of metal-based AIEgens to a new height, more intense research efforts are needed in this area in the coming years. The strategies to develop metal AIEgens with their future opportunities as potent antibacterial agents are as follows:

(1) The development of new metal-based AIEgens is highly desired for antibacterial applications. For example, the AIE-active Ru(II), Os(II), Re(I), Pd(II) and Cu(I) systems are totally untouched for bacterial sensing and/or killing, which would open up an opportunity to design and synthesize new complexes for the scientific community.

(2) The selective discrimination of Gram-negative and Gram-positive bacteria is another important parameter for efficient treatment by narrowing down the antibiotic's regimen. To date, only one example has been reported on metal AIEgens for bacterial discrimination. The selective discrimination could be achieved by properly designed metal complexes through ligand functionalization or modification around the metal center.

(3) *In vivo* bacterial detection and treatments have been hardly explored with the reported AIE metal-based systems, which need to be developed and studied in the near future.

(4) The metal-AIEgens can be encapsulated/conjugated with nanoparticles (*e.g.* polymeric nanoparticles, gold nanoparticles, *etc.*) for targeted delivery at the infection sites.

(5) In addition, a greater number of reports should be discussed on endotoxin detection in real samples such as human serum and urine. Also, these systems should be studied for monitoring bacterial contamination in aqueous samples and pharmaceutical formulations.

(6) Further, a large number of AIE-based metal complexes need to be developed and studied for their antibacterial activity against Gram-negative and Gram-positive bacteria in order to predict the structure–activity relationship, as this will be of help for further designing and exploration in this field.

In general, many metal complexes suffer from poor solubility in water and phosphate buffer saline (PBS) which limits their biological applications. This can be tackled by carefully designing the ligands around the metal centre. For example, the ligands can be functionalized with hydrophilic moieties such as polyethylene glycol (PEG) chain, glucose scaffold, small peptides, cationic linkers or polar substituents (hydroxy, amino, sulfonate and carboxylic acid termini) to improve the solubility of the metal complexes in water or PBS solution.

In summary, metal-based AIEgens are powerful materials for the detection and eradication of bacteria. The unique properties of metal complexes such as varied coordination geometry, structural diversity, and easy functionalization of ligands, versatile redox states and distinct photophysical characteristics can produce a vast number of complexes which makes them excellent candidates for diagnostic and therapeutic application in bacterial management. Further, the metal complexes can eradicate bacteria through various modes of action such as ligand exchange or release, redox activation, catalytic generation of toxic species and binding to various bacterial target sites, including ROS generation. These mechanisms are difficult to replicate with purely organic compounds to overcome resistance in bacteria. These unique properties of metal complexes may offer untapped opportunities for the development of bacterial diagnostic agents and antibiotics. Due to the scarcity of new antibiotics in the clinic, we expect to see a large number of attractive reports on AIE-metal complexes as antibacterial agents in the years to come. We hope that we are able to contribute to the realization of the impact of metal complexes in this unexplored area and open up new opportunities for the development of metal AIEgens by integrating with functional moieties and nanomaterials for tackling problems associated with AMR.

Conflicts of interest

The authors declare no conflict of interest.

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Notes and references

1 C. Willyard, *Nature*, 2017, **543**, 15.
2 A. Tagliabue and R. Rappuoli, *Front. Immunol.*, 2018, **9**, 1068.
3 J. O'Neill, Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations, 2014, https://amr-review.org/Publications.html (Accessed Oct 2018).
4 R. S. Hotchkiss, L. L. Moldawer, S. M. Opal, K. Reinhart, I. R. Turnbull and J. L. Vincent, *Nat. Rev. Dis. Primers*, 2016, **2**, 16045.
5 CDC, *Antibiotic Resistance Threats in the United States*, Centers for Disease Control and Prevention, Atlanta, GA, U.S., 2019, www.cdc.gov/DrugResistance/Biggest-Threats.html.
6 C. L. Ventola, *Pharmacol. Ther.*, 2015, **40**, 277–283.
7 WHO, *Antimicrobial Resistance: Global Report on Surveillance*, World Health Organization, Geneva, Switzerland, 2014, http://www.who.int/drugresistance/documents/surveillancereport/en/(accessed Sept 3, 2015).
8 P. Rajapaksha, A. Elbourne, S. Gangadoo, R. Brown, D. Cozzolino and J. Chapman, *Analyst*, 2019, **144**, 396–411.

9 J. Sun, A. R. Warden, J. Huang, W. Wang and X. Ding, *Anal. Chem.*, 2019, **91**, 7524–7530.
10 W. Gao, B. Li, R. Yao, Z. Li, X. Wang, X. Dong, H. Qu, Q. Li, N. Li, H. Chi, B. Zhou and Z. Xia, *Anal. Chem.*, 2017, **89**, 9836–9842.
11 Y. Zhu, N. Gasilova, M. Jović, L. Qiao, B. Liu, L. T. Lovey, H. Pick and H. H. Girault, *Chem. Sci.*, 2018, **9**, 2212–2221.
12 M. Gao and B. Z. Tang, *ACS Sens.*, 2017, **2**, 1382–1399.
13 J. Mei, N. L. C. Leung, R. T. K. Kwok, J. W. Y. Lam and B. Z. Tang, *Chem. Rev.*, 2015, **115**, 11718–11940.
14 D. D. La, S. V. Bhosale, L. A. Jones and S. V. Bhosale, *ACS Appl. Mater. Interfaces*, 2018, **10**, 12189–12216.
15 X. W. He, L. H. Xiong, Z. Zhao, Z. Y. Wang, L. Luo, J. W. Y. Lam, R. T. K. Kwok and B. Z. Tang, *Theranostics*, 2019, **9**, 3223–3248.
16 X. Cai and B. Liu, *Angew. Chem., Int. Ed.*, 2020, **132**, 9952–9970.
17 H. Wang and G. Liu, *J. Mater. Chem. B*, 2018, **6**, 4029–4042.
18 C. Zhu, R. T. K. Kwok, J. W. Y. Lam and B. Z. Tang, *ACS Appl. Bio Mater.*, 2018, **1**, 1768–1786.
19 G. Feng and B. Liu, *Acc. Chem. Res.*, 2018, **51**, 1404–1414.
20 A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515–1566.
21 M. Y. Berezin and S. Achilefu, *Chem. Rev.*, 2010, **110**, 2641–2684.
22 J. Mei, Y. Hong, J. W. Y. Lam, A. Qin, Y. Tang and B. Z. Tang, *Adv. Mater.*, 2014, **26**, 5429–5479.
23 J. D. Luo, Z. L. Xie, J. W. Y. Lam, L. Cheng, H. Y. Chen, C. F. Qiu, H. S. Kwok, X. W. Zhan, Y. Q. Liu, D. B. Zhu and B. Z. Tang, *Chem. Commun.*, 2001, 1740–1741.
24 P. Alam, G. Kaur, S. Chakraborty, A. R. Choudhury and I. R. Laskar, *Dalton Trans.*, 2015, **44**, 6581–6592.
25 N. L. C. Leung, N. Xie, W. Yuan, Y. Liu, Q. Wu, Q. Peng, Q. Miao, J. W. Y. Lam and B. Z. Tang, *Chem. – Eur. J.*, 2014, **20**, 15349–15353.
26 T. Zhang, H. Ma, Y. Niu, W. Li, D. Wang, Q. Peng, Z. Shuai and W. Liang, *J. Phys. Chem. C*, 2015, **119**, 5040–5047.
27 Q. Zhao, C. H. Huang and F. Y. Li, *Chem. Soc. Rev.*, 2011, **40**, 2508–2524.
28 V. W.-W. Yam and K. M.-C. Wong, *Chem. Commun.*, 2011, **47**, 11579–11592.
29 D.-L. Ma, S. Lin, W. Wang, C. Yang and C.-H. Leung, *Chem. Sci.*, 2017, **8**, 878–889.
30 P. Alam, C. Climent, P. Alemany and I. R. Laskar, *J. Photochem. Photobiol., C*, 2019, **41**, 100317.
31 A. Haque, L. Xu, R. A. Al-Balushi, M. K. Al-Suti, R. Ilmi, Z. Guo, M. S. Khan, W. Y. Wong and P. R. Raithby, *Chem. Soc. Rev.*, 2019, **48**, 5547–5563.
32 M. S. Kwon, Y. Yu, C. Coburn, A. W. Phillips, K. Chung, A. Shanker, J. Jung, G. Kim, K. Pipe, S. R. Forrest, J. H. Youk, J. Gierschner and J. Kim, *Nat. Commun.*, 2015, **6**, 8947.
33 W. Zhao, Z. He, J. W. Y. Lam, Q. Peng, H. Ma, Z. Shuai, G. Bai, J. Hao and B. Z. Tang, *Chem*, 2016, **1**, 592–602.
34 J. Yang, Z. Ren, Z. Xie, Y. Liu, C. Wang, Y. Xie, Q. Peng, B. Xu, W. Tian, F. Zhang, Z. Chi, Q. Li and Z. Li, *Angew. Chem., Int. Ed.*, 2017, **56**, 880–884.
35 L. Ravotto and P. Ceroni, *Coord. Chem. Rev.*, 2017, **346**, 62–76.
36 A. Gupta, S. Mumtaz, C.-H. Li, I. Hussain and V. M. Rotello, *Chem. Soc. Rev.*, 2019, **48**, 415–427.
37 A. H. Delcour, *Biochim. Biophys. Acta, Proteins Proteomics*, 2009, **1794**, 808–816.
38 P. Prasad, S. Sachan, S. Suman, G. Swayambhu and S. Gupta, *Langmuir*, 2018, **34**, 7396–7403.
39 J. Wang, C. Lu, Y. Shi, X. Feng, B. Wu, G. Zhou, G. Quan, X. Pan, J. Cai and C. Wu, *ACS Appl. Mater. Interfaces*, 2020, **12**, 18363–18374.
40 R. M. Epand, C. Walker, R. F. Epand and N. A. Magarvey, *Biochim. Biophys. Acta*, 2016, **1858**, 980–987.
41 G. Kapoor, S. Saigal and A. Elongavan, *J. Anaesthesiol. Clin. Pharmacol.*, 2017, **33**, 300–305.
42 M. Laws, A. Shaaban and K. M. Rahman, *FEMS Microb. Rev.*, 2019, **43**, 490–516.
43 S. Xie, S. Manuguri, G. Proietti, J. Romson, Y. Fu, A. K. Inge, B. Wu, Y. Zhang, D. Häll, O. Ramström and M. Yan, *Proc. Natl. Acad. Sci. U. S. A.*, 2017, **114**, 8464–8469.
44 W. Wu, D. Mao, F. Hu, S. Xu, C. Chen, C. J. Zhang, X. Cheng, Y. Yuan, D. Ding, D. Kong and B. Liu, *Adv. Mater.*, 2017, **29**, 1700548.
45 S. Xu, Y. Duan and B. Liu, *Adv. Mater.*, 2020, **32**, 1903530.
46 A. Frei, J. Zuegg, A. G. Elliott, M. Baker, S. Braese, C. Brown, F. Chen, C. G. Dowson, G. Dujardin, N. Jung, A. P. King, A. M. Mansour, M. Massi, J. Moat, H. A. Mohamed, A. K. Renfrew, P. J. Rutledge, P. J. Sadler, M. H. Todd, C. E. Willans, J. J. Wilson, M. A. Cooper and M. A. T. Blaskovich, *Chem. Sci.*, 2020, **11**, 2627–2639.
47 N. Jain, P. Alam, I. R. Laskar and J. Panwar, *RSC Adv.*, 2015, **5**, 61983–61988.
48 A. Gupta, P. Prasad, S. Gupta and P. K. Sasmal, *ACS Appl. Mater. Interfaces*, 2020, **12**, 35967–35976.
49 E. T. Rietschel, T. Kirikae, F. U. Schade, U. Mamat, G. Schmidt, H. Loppnow, A. J. Ulmer, U. Zahringer, U. Seydel, F. Di Padova, M. Schreier and H. Brade, *FASEB J.*, 1994, **8**, 217–225.
50 J. A. G. Williams, S. Develay, D. L. Rochester and L. Murphy, *Coord. Chem. Rev.*, 2008, **252**, 2596–2611.
51 N. Liu, B. Wang, W. Liu and W. Bu, *Chem. Commun.*, 2011, **47**, 9336–9338.
52 Y. Zhu, C. Xu, Y. Wang, Y. Chen, X. Ding and B. Yu, *RSC Adv.*, 2017, **7**, 32632–32636.
53 L. K. McKenzie, H. E. Bryant and J. A. Weinstein, *Coord. Chem. Rev.*, 2019, **379**, 2–29.
54 S. Gao, X. Yan, G. Xie, M. Zhu, X. Ju, P. J. Stang, Y. Tian and Z. Niu, *Proc. Natl. Acad. Sci. U. S. A.*, 2019, **116**, 23437–23443.
55 C. Lakshmi, R. G. Hanshaw and B. D. Smith, *Tetrahedron*, 2004, **60**, 11307–11315.
56 W. M. Leevy, J. R. Johnson, C. Lakshmi, J. Morris, M. Marquez and B. D. Smith, *Chem. Commun.*, 2006, 1595–1597.
57 J. Ma, J. Zhao, P. Yang, D. Huang, C. Zhang and Q. Li, *Chem. Commun.*, 2012, **48**, 9720–9722.
58 M. Gao, Q. Hu, G. Feng, N. Tomczak, R. Liu, B. Xing, B. Z. Tang and B. Liu, *Adv. Healthcare Mater.*, 2015, **4**, 659–663.
59 G. Feng, C.-J. Zhang, X. Lu and B. Liu, *ACS Omega*, 2017, **2**, 546–553.
60 A. Pinto, N. Svahn, J. C. Lima and L. Rodríguez, *Dalton Trans.*, 2017, **46**, 11125–11139.
61 J. Zhang, H. Zou, J. P. Lei, B. Z. He, X. W. He, H. H. Y. Sung, R. T. K. Kwok, J. W. Y. Lam, L. Zheng and B. Z. Tang, *Angew. Chem., Int. Ed.*, 2020, **59**, 7097–7105.
62 L. Zheng, X. Ye, P. Qi, D. Zhang and Y. Sun, *Microchim. Acta*, 2019, **186**, 382.
63 J. Kováč, M. Vítězová and I. Kushkevych, *Open Med.*, 2018, **13**, 344–349.
64 K.-H. Kim, E. Kabir and S. A. Jahan, *J. Hazard. Mater.*, 2016, **306**, 376–385.
65 N. B. Turan, D. S. Chormey, Ç. Büyükpınar, G. O. Engin and S. Bakirdere, *TrAC, Trends Anal. Chem.*, 2017, **91**, 1–11.
66 L. Huang, S. Li, X. Ling, J. Zhang, A. Qin, J. Zhuang, M. Gao and B. Z. Tang, *Chem. Commun.*, 2019, **55**, 7458–7461.
67 Y. Li, H. Yu, Y. Qian, J. Hu and S. Liu, *Adv. Mater.*, 2014, **26**, 6734–6741.
68 WHO, *Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline*, Geneva, Switzerland, 2019, https://www.who.int/publications/i/item/9789240000193 (accessed Jan, 2020).
69 Health Policy Watch, Geneva, Switzerland. https://healthpolicy-watch.news/low-antibiotics-prices-dampen-industry-investment-in-vital-new-tools-to-combat-superdrugs-says-amr-industry-alliance/ (Published 16 Jan 2020).
70 M. Kumar, A. Curtis and C. Hoskins, *Pharmaceutics*, 2018, **10**, 11.