Coordination Chemistry Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Development of fluorescent probes targeting the cell wall of pathogenic bacteria

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ARTICLE INFO

Article history:
Received 22 September 2020
Accepted 8 October 2020
Available online xxxx

Keywords:
Fluorescent probes
Bacterial cell wall
Pathogenic bacteria
Bacterial detection
Antibiotics

ABSTRACT

Contamination of pathogenic bacteria seriously threatens human health and safety, and the types and pathogenicity of bacteria are closely related to cell walls. Fluorescent probes can perform specific and sensitive detection of bacterial cells, and make an important contribution to the diagnosis of bacterial diseases and the development of antibiotics. In this review, we summarized the latest developments in integrating identification elements targeting bacterial cell walls with different chromogenic elements (small molecule fluorophores, conjugated polymers, and fluorescent nanomaterials) to detect and sense pathogenic bacteria. We hope this review paper can provide ideas for the design of new pathogen detection probes with better performance.

Contents

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https://doi.org/10.1016/j.ccr.2020.213646
0010-8545/

1. Introduction

The increase in pathogen infections in clinical practice has become a public health issue that has caused global concern [1]. Pathogenic bacteria are the main cause of human disease and death. Due to the excessive use of antibiotics, the increase of multi-drug resistance (MDR) bacteria has become a global crisis, seriously threatening human health and life safety [2–4]. Quick and accurate infection diagnosis is of great significance to clinical medicine, biological defense, food and water safety, and environmental monitoring. The usual bacterial detection relies on the identification of genes or marker proteins or enzymes. However, due to the excessive abuse of antibiotics, the problem of bacterial multi-drug resistance has become more and more serious. Bacterial detection that relies on markers often cannot reflect the changes of bacteria after adapting to drug resistance.

The pathogenicity of bacteria is usually related to the composition of the cell wall [5]. As the outermost part of pathogen cells, the cell wall is a natural barrier for bacteria to resist external invasion, and its integrity is vital to the survival of cells (Fig. 1a). The cell wall plays a vital role in mediating the initial interaction between cells and the environment, and also affects the exchange of material and information between cells. According to the structure and thickness of the cell wall, bacteria can be divided into gram-positive or gram-negative bacteria. The cell wall of gram-positive bacteria has a thick peptidoglycan layer, underneath the peptidoglycan there is a layer of polymeric teichoic acid and a cytoplasmic membrane. Gram-negative bacteria have a cell wall consisting of a thin layer of peptidoglycan sandwiched between a cytoplasmic membrane and an outer cell membrane. Gram-negative bacteria are not sensitive to many commonly used antibiotics (such as daptomycin and vancomycin). Clinically, the differentiation and

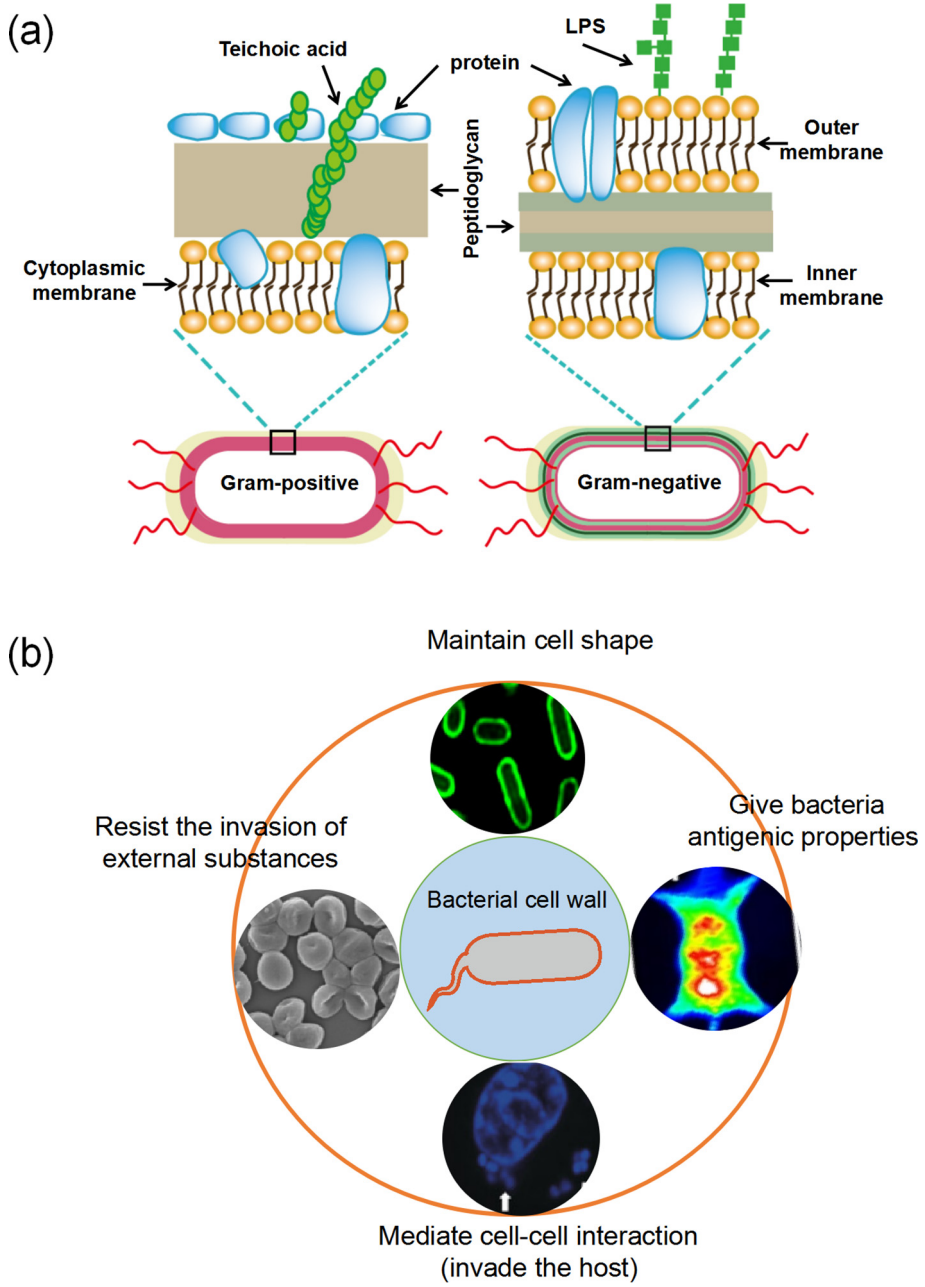


Fig. 1. (a) The schematic structure and (b) physiological function of Gram-negative and Gram-positive bacterial cell wall.

diagnosis of bacteria can provide guidance for further treatment of patients (Fig. 2).

Bacterial cell walls are heterogeneous in composition and dynamic changes. Maintaining membrane function under changing environmental conditions depends on the ability of cells to rapidly adjust their membrane lipid composition (Fig. 1b). When in an unfavorable environment, bacteria have also evolved specific adaptive mechanisms to respond to different physical and chemical conditions. The growth of bacteria requires suitable temperature, pH and other conditions. When in an unfavorable environment, in order to maintain the physiological dynamic balance and ensure the integrity of the membrane, the bacteria will adapt to the changes in the environment by changing the membrane characteristics such as the permeability and fluidity of the cell membrane. This is usually achieved by changing the structure and quantity of membrane proteins, lipids, and the mobility and function of membrane proteins on the bacterial cell wall [6].

Within a certain temperature range, the fluidity of the bacterial cell membrane remains relatively constant at different temperatures, and the cell actively changes its lipid type or the ratio of its hydrocarbon fraction to maintain the membrane function at different temperatures. However, at relatively low temperatures, lipids will be densely arranged and stacked through the hydrocarbon chain perpendicular to the bilayer membrane, which greatly reduces the permeability of the membrane. At relatively high temperatures, lipids will align in a free manner, which will increase the fluidity and permeability of the bacterial membrane. When the lipid accumulation is too messy, the bacterial membrane will have difficulty maintaining the liquid crystal phase and will exist in the form of a liquid phase. In addition, pressure also affects the structure of the membrane. Under greater pressure, the lipids on the bacterial membrane will pack tightly, reducing the fluidity and permeability of the membrane and turning it into a gel phase. Bacteria can also reduce the permeability of the membrane by reversing the membrane potential and changing the structure of membrane lipids under over-acid or over-alkali conditions, thereby hindering the inflow or exudation of protons.

When bacteria are in an unfavorable environment such as antibiotics or other drugs, they can also trigger the self-protection mechanism and cause changes in the structure of their own cell walls, thereby developing resistance to antibiotics [7]. First of all, bacteria can reduce their affinity with antibiotics by modifying and transforming their targets on the bacterial cell wall [8]. For example, β-lactam antibiotics such as penicillin mainly kill bacteria by binding to the penicillin binding protein on the bacterial cell wall, and the bacteria can change the structure of the penicillin binding protein on the cell wall so that it cannot effectively bind to the antibiotic. Vancomycin targets D-alanine-D-alanine (D-Ala-D-Ala) in the cell wall peptidoglycan of gram-positive bacteria, and bacteria can use D-alanine-D-lactic acid (D-Ala-D-Lac) or D-alanine-D-serine (D-Ala-D-Ser) replace D-Ala-D-Ala to reduce the effect of vancomycin. Polymyxin is mainly sterilized by electrostatic interaction between the positively charged diaminobutyric acid (Dab) residues on polymyxin and the negatively charged phosphoric acid on lipopolysaccharide lipid A [6]. Bacterial cells can reduce the net negative charge on the outer membrane by reducing the amount of lipid A, thereby reducing the electrostatic attraction with polymyxin. Secondly, the outer membrane of gram-negative bacteria and the outer and inner membranes of gram-positive bacteria are usually used as permeation barriers to protect the bacteria from various antibiotics and chemicals. For drugs that act on the internal targets of bacterial cells, such as inhibiting protein synthesis and inhibiting enzyme activity, bacteria can reduce the inflow of antibiotics by reducing membrane permeability or pump antibiotics out of the cell through the active efflux system of the bacterial cell wall in order to block its function. The porin on the outer membrane of gram-negative bacteria is a pore protein that spans the cell membrane and allows antibiotics and other substances to pass through. Bacteria can reduce membrane permeability by reducing the number of porins, so that antibiotics and other drugs cannot flow into the bacteria. In addition, the bacterial cell wall can produce excessive membrane protein which act as an export or efflux pump for the drug, and the drug is pumped out faster than it spreads, so that the drug cannot accumulate in the bacterial cell [9].

Generally speaking, there are significant differences in the surface composition and structure of different pathogens, including the types and ratios of membrane phospholipids and membrane proteins, and the charges on the surface of different bacteria [10]. The cell walls of the bacteria play the role of the fingerprint of the bacteria, and the bacteria can be identified by identifying the cell walls of the bacteria. Fluorescence detection method has been developed and applied to the detection of pathogenic bacteria due to its high detection sensitivity (such as single-molecule detection), fast response speed, and the ability to use multicolor dyes for multiple analysis [11–15]. In this review, we systematically summarize the design methods and performance of fluorescent probes for bacterial cell walls. These probes are classified according to the species that recognize the cell wall, including those that recognize certain cell wall components and those that recognize uncertain cell wall components.

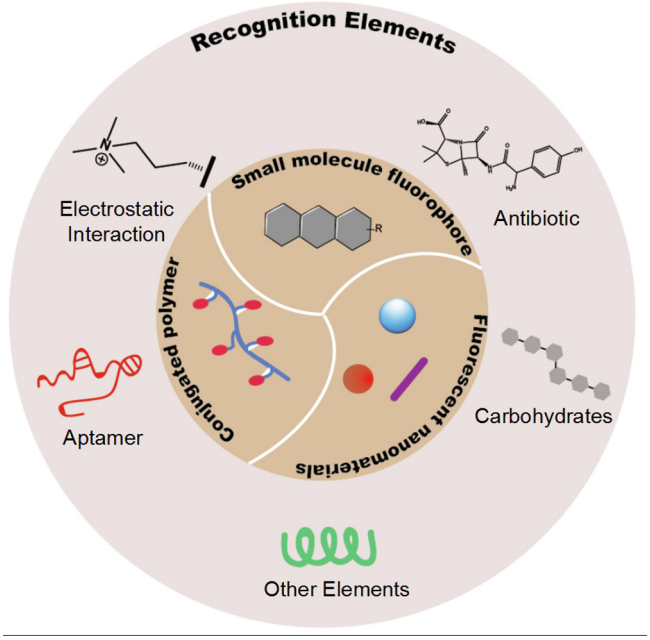


Fig. 2. Construction of Fluorescent probes targeting bacterial cell walls.

2. Fluorescent probes for bacteria cell wall

The construction of fluorescent probes targeting bacterial cell walls usually integrates recognition elements with different chromogenic elements. When the recognition elements recognize the bacterial cell wall, it will transmit the recognition event to the fluorescent chromophore, inducing the fluorescence responses to realize the detection of pathogenic bacteria.

The chromophores of fluorescent probes targeting bacterial cell walls mainly include small molecule fluorescent dyes, conjugated polymers and fluorescent nanomaterials. Fluorescent labeling reagents are an important part of sensitive fluorescence detection. Organic small molecule dyes are often used as marker molecules in

fluorescent biosensors, including fluorescein, rhodamine, bodipy [16], cyanine dyes (Cy3, Cy5 and Cy7) and Alexa dyes. The first dye used as a fluorescent label was fluorescein, followed by rhodamine [17]. Near-infrared (NIR) fluorophores with emission wavelengths of 650–900 nm can penetrate two centimeters or more of tissue for optical imaging of bacterial infections in living animals [18–23]. The incorporation of organic dyes into nanoparticles form more complex dyes, which can be used with metal nanoclusters, quantum dots (QD), etc. However, small molecule fluorescent probes have problems such as low fluorescence output, pH sensitivity, and photobleaching. These shortcomings limit their application in living systems. Conjugated polymers (CPs) have been used as chromophores for bacterial fluorescence detection in recent years due to their excellent light collection and light signal amplification characteristics. In recent years, many luminescent nanomaterials such as silicon nanoparticles (SiNPs), metal nanoparticles, quantum dots (QDs), carbon-based nanomaterials (carbon nanotubes, carbon quantum dots, and graphene), upconversion nanomaterials, and organic nanomaterials have been used as luminescence elements for fluorescent probes for bacterial detection [24–27]. Compared with traditional organic small molecule fluorescent probes, the excitation spectrum of fluorescent nanomaterials are wide and continuously distributed, while the emission spectra are symmetrically distributed and narrow in width, with adjustable colors, that is, nanoparticles of different sizes can be excited by a single wavelength of light to emit light of different colors, and have high photochemical stability and are not easy to be photodegraded. Therefore, fluorescent nanomaterials can be used as a supplement to existing small molecule fluorescent reagents [17].

For the detection of pathogenic bacteria, according to the different components of the surface of the bacteria targeted by the probe, there are two strategies to construct probes: specific target recognition and non-specific target recognition.

3. Specific targets recognition

The selectivity of bacteria is usually mediated by cell surface components. Peptidoglycan, lipopolysaccharide, and teichoic acid that exist on the entire bacterial cell membrane can be used as targets for biological recognition. Many biological receptors have been developed to target a specific one of these moieties, including antibiotics, lectins, sugars (mannose, maltose), aptamers, etc.

3.1. Targeting peptidoglycan of bacteria

3.1.1. Antibiotics

Peptidoglycan of bacterial cell walls can be be recognized by antibiotic conjugated fluorescent probes. Vancomycin is a glycopeptide antibiotic drug that can specifically bind to the D-Ala-D-Ala part of the short peptide chain of the bacterial cell wall peptidoglycan [28]. The famous antibiotic vancomycin was coupled with a near infrared (NIR) fluorophore IRDye 800CW to give probe **1** (Fig. 3), which can be used to selectively image Gram-positive bacteria and distinguish bacterial infection from sterile inflammation in vivo [29]. Piskin *et al.* designed a vancomycin-conjugated fluorescent polymer nanoparticle as a targeting agent as an imaging reagent for MRSA infection in vivo [30]. This study was the first to prove the targeting of vancomycin-conjugated nanoparticles to E. coli in vitro. Vancomycin was also conjugated to Cy3 and rhodamine dayes to development fluorescent antibiotics Cy3-Vanco and Rho-Van [31,32]. Another antiobiotic tridecaptin (TriA) kills bacteria by binding to the peptidoglycan precursor lipid II of gram-negative bacteria. Due to the different structure of lipid II in gram-positive bacteria, the sensitivity of TriA to gram-positive bacteria is much lower. Yang et al. developed an a TriA-based fluorescent probe **2** (Fig. 3) to achieve selective imaging of Gram-negative bacteria [33]. This probe can realize differential labeling of mouse intestinal flora and complex bacterial samples collected from human oral cavity, soil, etc. However, the use of antibiotics as the identification element for bacterial detection will inevitably lead to the development of drug resistance in bacteria and cause immeasurable consequences.

3.1.2. Lectin

The lectin wheat germ agglutinin (WGA) can specifically bind *N*-acetylmuramic acid and *N*-acetylglucosamine residues on the cell surface of bacteria. Fluorescently labeled WGA, such as

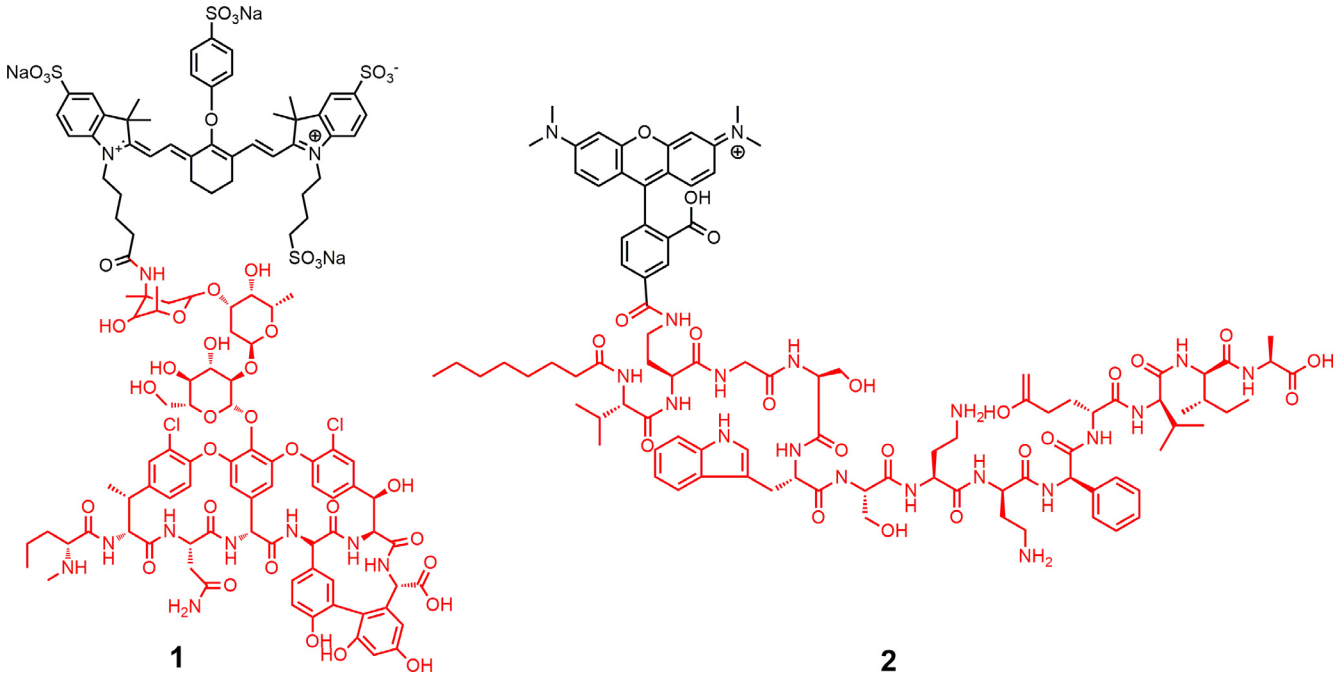


Fig. 3. Structure of the probes **1** and **2**.

WGA-fluorescein isothiocyanate (FITC), WGA-488, WGA-647 and WGA quantum dots, were used to stain bacterial cell walls [34,35]. Gram-positive bacteria contain many peptidoglycans in the cell wall which can be accessed directly by WGA molecules. In contrast, the peptidoglycan layer of gram-negative bacteria is shielded by the outer membrane, which contains lipopolysaccharide (LPS) and lipoprotein that WGA cannot recognize it. Therefore, the WGA conjugates can selectively stain Gram-positive bacteria but not Gram-negative bacteria.

3.1.3. Metabolizable compounds

Another commonly used method of labeling peptidoglycans of bacterial cell walls is based on bacterial metabolic pathways (Fig. 4) [36]. This strategy includes direct labeling and indirect labeling. Direct labeling method is to incubate bacteria with fluorophore-modified bioorthogonal precursors. Fluorescent probes can be directly labeled on the surface of bacteria through a proprietary metabolic pathway of bacteria; indirect labeling method is to use bacteria and bioorthogonal functional groups (such as alkynes or azides) modified metabolic precursors are incubated together, and then fluorescent probes derived with bioorthogonal groups are introduced. The fluorophores can effectively label bacteria through a click chemistry reaction. The general method for labeling gram-positive bacteria is the maltodextrin transport mechanism of bacteria. Commonly used metabolic precursors include D-amino acids which can be incorporated into bacterial peptidoglycan. Small molecule fluorophores [37,38] and near-infrared fluorophores [39] were then labeled metabolic precursors for bacterial imaging. For example, VanNieuwenhze *et al.* synthesized a series of fluorescently labeled D-amino acids **3**–**5** to image the synthesis of peptidoglycan in living bacterial cells in situ [40]. Yang et al. used fluorescently labeled D-amino acids **6** to sequentially label bacteria to assess the viability of the gut flora after transplantation [37]. Liu et al. used AIE fluorophore labeled D-amino acid and the probe **7** was reported to image in situ ablation of bacteria in living cells [41]. Tan *et al.* used near-infrared fluorescent probe **8** to image intestinal flora through a way of peptidoglycan metabolization [39].

3.1.4. Lysozyme

Lysozyme can destroy the β-1,4 glycosidic bond between *N*-acetyluric acid and *N*-acetylglucosamine in the cell wall to kill bacteria. Because the outer layer of gram-positive bacteria is a thick peptidoglycan layer, the ability of lysozyme to recognize gram-positive bacteria is stronger than that of gram-negative bacteria. The fluorescein isothiocyanate-labeled lysozyme (FITC-LYZ) designed by Zhang et al. can provide quantitative information on the binding of the probe to Gram-positive bacteria [42].

3.2. Targeting lipopolysaccharide of gram-negative bacteria

3.2.1. Antibiotic

Polymyxin antibiotics are a group of peptide antibiotics, consisting of five derivatives A, B, C, D, and E. The most commonly used in clinic are Polymyxin B (PxB) and Polymyxin E (PxE). They can specifically bind lipopolysaccharide (LPS) molecules in the outer membrane of gram-negative bacteria. Chen et al. used PxB labeled a cyanine dye and the probe **9** can specifically stain gram-negative bacteria (Fig. 5) [33,43]. PxB was also used to label other fluorophores and various probes were developed.

3.2.2. Metabolizable compounds

3-deoxy-D-mannose caprylic acid (Kdo) plays an important role during the membrane lipopolysaccharide synthesis in almost all Gram-negative bacteria. Fluorescently labeled Kdo was then used as a precursor for membrane synthesis and the LPS of Gram-negative bacteria can then be labeled through the metabolic pathway. This monosaccharide does not exist in Gram-positive

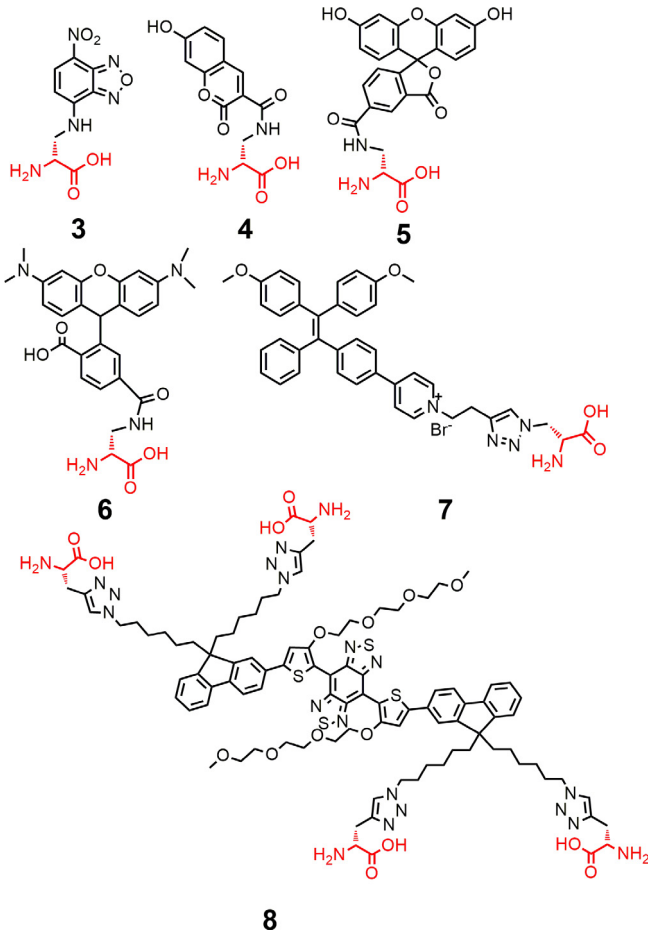


Fig. 4. Structure of the probes **3**–**8**.

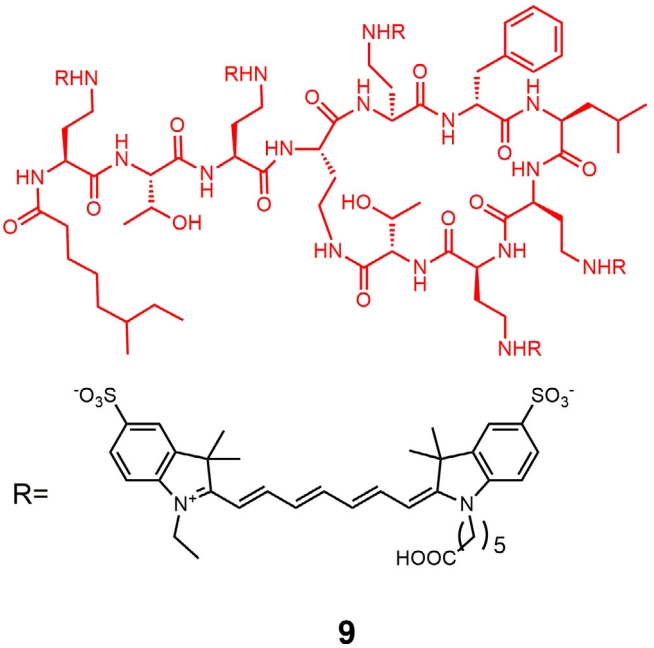


Fig. 5. Structure of the probe **9**.

bacteria, and stands as a selective target for Gram-negative bacteria recognition. Chen *et al.* used fluorescently labeled azido analogue of Kdo-8-azido-8-deoxy-Kdo (8AzKdo) **10** to selective image Gram-negative bacteria in the intestinal flora (Fig. 6) [31].

3.2.3. Cationic complex

Cationic platinum(II) complexes can bind negatively charged LPS to form LPS–Pt(II) aggregates. Yu *et al.* synthesized [Pt(N^N^N)Cl]$^+$ **11** which can identify Gram-negative Escherichia coli and Gram-positive Staphylococcus aureus quickly without washing within 5 min (Fig. 7) [44].

3.3. Targeting other components of the cell wall

3.3.1. Lectins

Lectins can have high affinity for cell surface mannose residues and other polysaccharides in the cell walls of Gram-positive and Gram-negative bacteria. The identification of these carbohydrates on the surface of bacteria can be used for the specific identification of target bacteria. For example, the lectin concanavalin A (Con A) has high affinity for the D-mannosyl specific group on the bacterial cell wall and can also be used as a bacterial targeting ligand [45].

3.3.2. Boronic acid

Boronic acid can be selectively bound to cis-diol groups through the formation of cyclic esters, and has been widely used to detect sugars and glycosylated biomolecules. Due to the thick peptidoglycan layer on the surface of gram-positive bacteria, boronic acid has been proven to be a recognition molecule for bacterial detection. Chang *et al.* developed fluorescent probes **12** and**13** with boronic acid as the recognition group as staining reagents for Gram-positive bacteria (Fig. 8) [46]. Rosal et al. synthesized a boronic acid copolymer-poly(4-vinylphenylboronic acid-methyl-2-acrylic acid-(2-dimethylamino)ethyl methyl ester-n-butyl methacrylate) (pVDB)) **14** for rapid detection of bacteria (Fig. 8), it can form acrylate with the glycol-rich sugar-based part found on the bacterial membrane [47].

3.3.3. Carbohydrates

Large sugar molecules such as maltose, maltotriose and maltohexose are the main sources of bacterial glucose. Fluorescent probes that use these molecules as recognition groups can label bacterial cells by the maltodextrin transporter on the bacterial surface. Therefore, it can be used to distinguish bacterial infections from other diseases. Gambhir et al. used maltotriose as a recognition group to synthesize probe **15** for fluorescence and photoacoustic imaging of bacterial infections(Fig. 9) [48]. Pili are

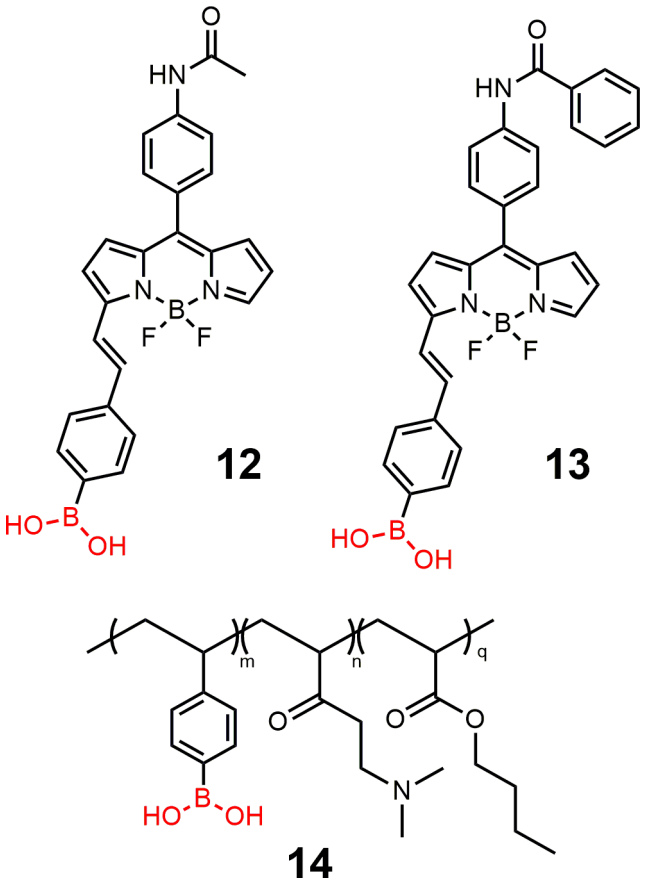


Fig. 8. Structure of probe **12**–**14**.

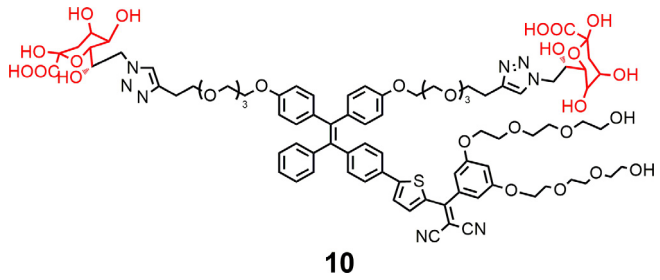


Fig. 6. Structure of the probe **10**.

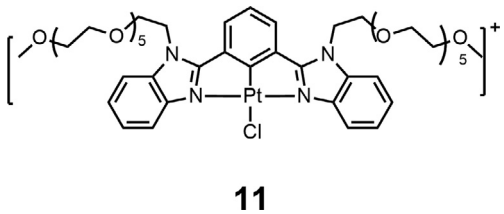
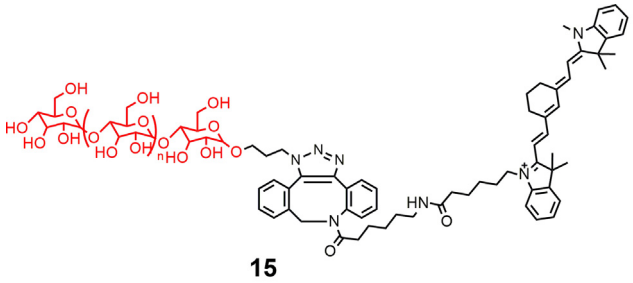


Fig. 7. Structure of the probe **11**.



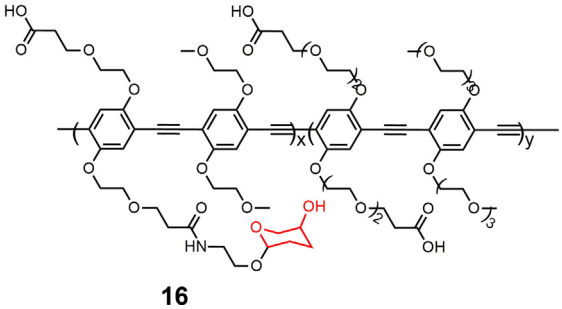


Fig. 9. Structure of the probe **15** and**16**.

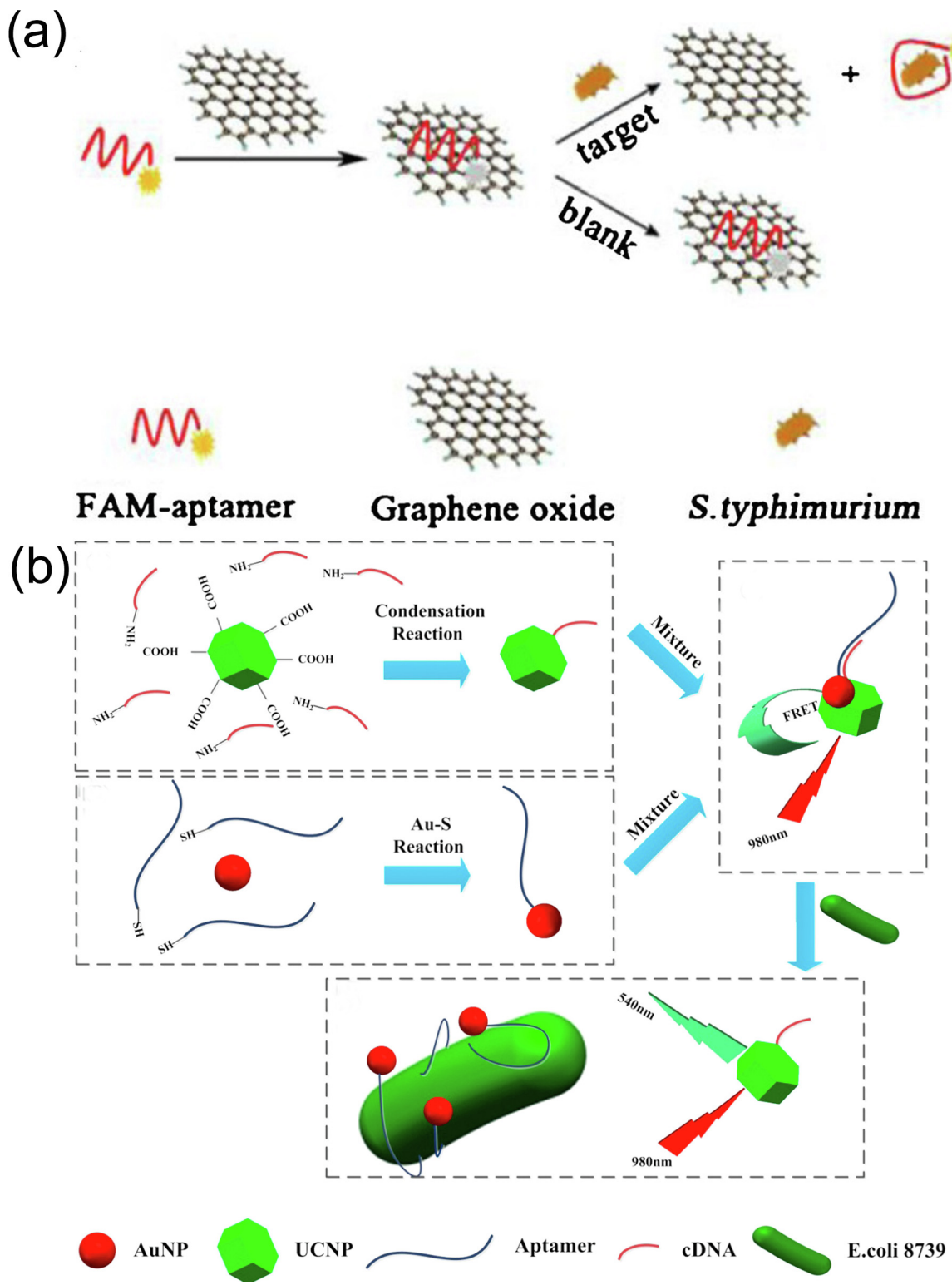


Fig. 10. Nanoprobe with aptamer as recognition elements and its application in bacterial detection. Wherein, Fig. 10a is reprinted from Ref. 53 with permission from Copyright 2014, Springer. Fig. 10b is reprinted from Ref. 55 with permission from Copyright 2017, Elsevier.

hair-like structures emitted from the surface of bacteria rich in lectins (carbohydrate binding proteins) that can bind to mannose. Specific recognition of bacteria can be modified by carbohydrates on CPs. Mannose-based polymers can interact multivalently with mannose receptors located on the pili. Seeberger et al. reported a carbohydrate functionalized poly(p-phenylene acetylene) (PPE) **16** that can be used to detect E. coli (Fig. 9). Brightly fluorescent aggregates of bacteria were yielded by incubation of mannose-functionalized polymer with E.coli [49]. Due to the presence of an Ara-binding lectin on mycobacteria, Yan et al. functionalized fluorescein-doped silica nanoparticles (FSNPs) with D-arabinose (Ara). The multivalent Ara-presenting nanoparticles were

visualized under microscopy to interact with Mycobacterium smegmatis to form clusters [50].

3.3.4. Aptamer

Many recent studies have focused on the application of aptamer-conjugated nanomaterials for the detection of pathogenic bacteria [51]. Aptamers are single-stranded nucleic acids (DNA or RNA) and have high binding affinity to target bacterial cells. The targeting of nucleic acid aptamers to bacteria is based on the properties of DNA or RNA that can bind to proteins and polysaccharides on the surface of pathogenic bacteria. The systematic evolution of ligands through exponential enrichment (SELEX) can be used to design aptamers for various target bacteria. Fluorescence resonance energy transfer (FRET) is a simple, fast and sensitive signal transduction technique. When the donor and acceptor are in close proximity, energy transfer occurs from the energy donor to the energy acceptor. This energy transfer will cause a characteristic change in the fluorescence of the donor or acceptor. Nanomaterials, for example gold nanoparticles (AuNPs) and graphene oxide (GO), can be used as energy acceptors for fluorescence resonance energy transfer (FRET). Song *et al.* used aptamer-modified AuNPs and Van-functionalized gold nanoclusters as the energy acceptor and donor, respectively. A linear variation was obtained between FRET signals and the Staph. aureus concentration (in the range from 20 to 10^8cfu/mL with a detection limit of 10 cfu/mL) [52]. Nanomaterials can also form complexes with small molecule fluorophores and conjugated polymers to detect bacteria through fluorescence resonance energy transfer. Nanomaterials can be used as fluorescence quenchers to effectively quench the fluorescence of adsorbed fluorophores. When these complexes were destroyed by the analyte, the fluorescence would be recovered. Based on this principle, Deng et al. constructed a system to detect Salmonella typhimurium (Fig. 10a). When the FAM-labeled aptamer was adjacent to the graphene oxide (GO), the fluorescence was quenched. When the target bacteria contacted with the material, the fluorophore was released from the GO due to the formation of the target-aptamer complex, and the fluorescence intensity increased greatly [53]. Wang et al. also reported anotherr method using FRET to detect bacteria. In this study, organic dyes and GO were replaced by QD and carbon nanoparticles (CNPs) to achieve high quenching efficiency [54]. Lu et al. coupled UCNPs (donors) with corresponding complementary DNA (cDNA) and AuNPs (acceptors) with aptamers (Fig. 10b). When the targeting aptamer hybridizes to cDNA, the upconversion fluorescence was quenched. The aptamer preferentially binded the bacteria to form a three-dimensional structure, thereby releasing UCNPs to restore upconversion fluorescence [55].

4. Non-specific target

The main components of bacterial cell membranes are negatively charged phospholipids, including phosphatidylglycerol and cardiolipin. Phosphatidylglycerol and cardiolipin in the outer membrane of Gram-negative bacteria and lipopolysaccharide on the cell wall all make the entire surface of the bacteria negatively charged. Gram-positive bacteria have no outer membrane, and the teichoic acid embedded in the cell wall also shows a negative charge [56]. Non-specific detection was then realized to identify bacteria through the fluorescent signal generated by the electrostatic and hydrophobic interaction between the probes and the bacteria (Fig. 11).

4.1. Small molecule probes

Tang et al. proposed the concept of aggregation-induced luminescence (AIE) in 2001 [57]. In contrast to aggregation induced fluorescence quenching, AIE is a unique photophysical phenomenon. These fluorophores show weak or no emission when dissolved in solution, but when forming aggregates, the intramolecular movement is restricted, which will be accompanied by significant fluorescence enhancement. AIE luminescent agents (AIEgens) usually use tetrastyrene derivatives as chromophores which have attractive features such as aggregated high emission efficiency, large stokes shift, and excellent light stability in biological imaging. In recent years, many positively charged AIE probes have been synthesized for fluorescence-on imaging of Gram-positive and Gram-negative bacteria [58–63]. Different molecules have different charge groups and hydrophobicity, and can exhibit different interactions with bacteria [64]. Tang et al. synthesized a series of aggregation-induced luminescence molecules **17**–**20** with orderly enhanced D-A conjugation (Fig. 12). Because the probe was positively charged, it can achieve selective imaging and photodynamic killing of Gram-positive bacteria [59]. Zhou et al. designed a quaternaryammonium functionalized tetraphenylethenes (TPEs) **21** (Fig. 12), which were successfully used to stain eight different kinds of bacteria. And these types of probes can also determine all tested bacteria through linear discriminant analysis in the form of fluorescent sensor arrays [65]. Jiang et al. successfully differentiated eight kinds of bacteria, including normal bacteria and multi-drug resistant bacteria, using a fluorescent sensor array composed of five AIE probes **22**–**26** (Fig. 12) [66]. Tang et al. synthesized an AIE molecule **27** that can be used for no-wash imaging of bacteria, and further used for bacterial susceptibility research and high-throughput antibiotic screening (Fig. 12) [63].

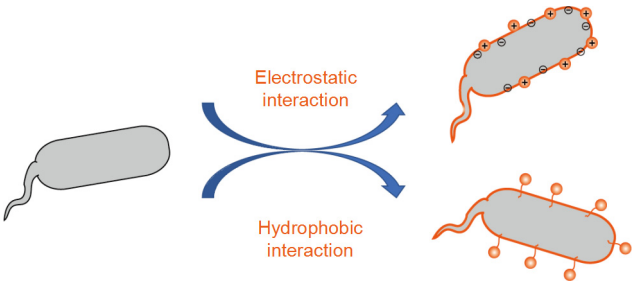


Fig. 11. Schematic diagram of non-specific interaction between probe and bacteria.

Due to the presence of many phosphate compounds on the surface of bacteria, coordination bonds can be formed between the metal ion acceptor and the negatively charged phosphate oxygen atom, thereby achieving recognition of the bacteria. Among them, dimethylpyridine amine (DPA) is the most commonly used metal coordination ligand. Positively charged zinc (II)-lutidine amine (ZnDPA) analogs can interact electrostatically with the surface of negatively charged bacteria [67–69]. Single ZnDPA dimers, ZnDPA tetramers, and ZnDPA multimers have been developed for fluorescent imaging of bacterial infections in vivo [18,70]. Smith et al. designed a series of fluorescent probes **28**–**30** with bis (zinc(II)-lutidine amine) as the recognition group, and proved that the probes can selectively associate with the cell membrane of bacteria by the titration method of fluorescence resonance energy transfer (Fig. 13). And these probes can image the sites infected with gram-positive and gram-negative bacteria in living mice [71]. Smith et al. used zinc(II)-dipicolylamine BODIPY conjugates **31** for bacterial imaging and photodynamic inactivation (Fig. 13) [67]. Dye-labeled ZnDPA with aggregation-induced luminescence (AIE) fluorophores can be used for bacterial cell imaging. For example, Liu et al. designed the AIE-ZnDPA probe **32**–**33** (Fig. 13), which binded bacteria through electrostatic interaction, and can produce reactive oxygen species to kill bacteria under the irradiation of a certain wavelength of light [62,72]. Smith *et al.* used Zn-DPA

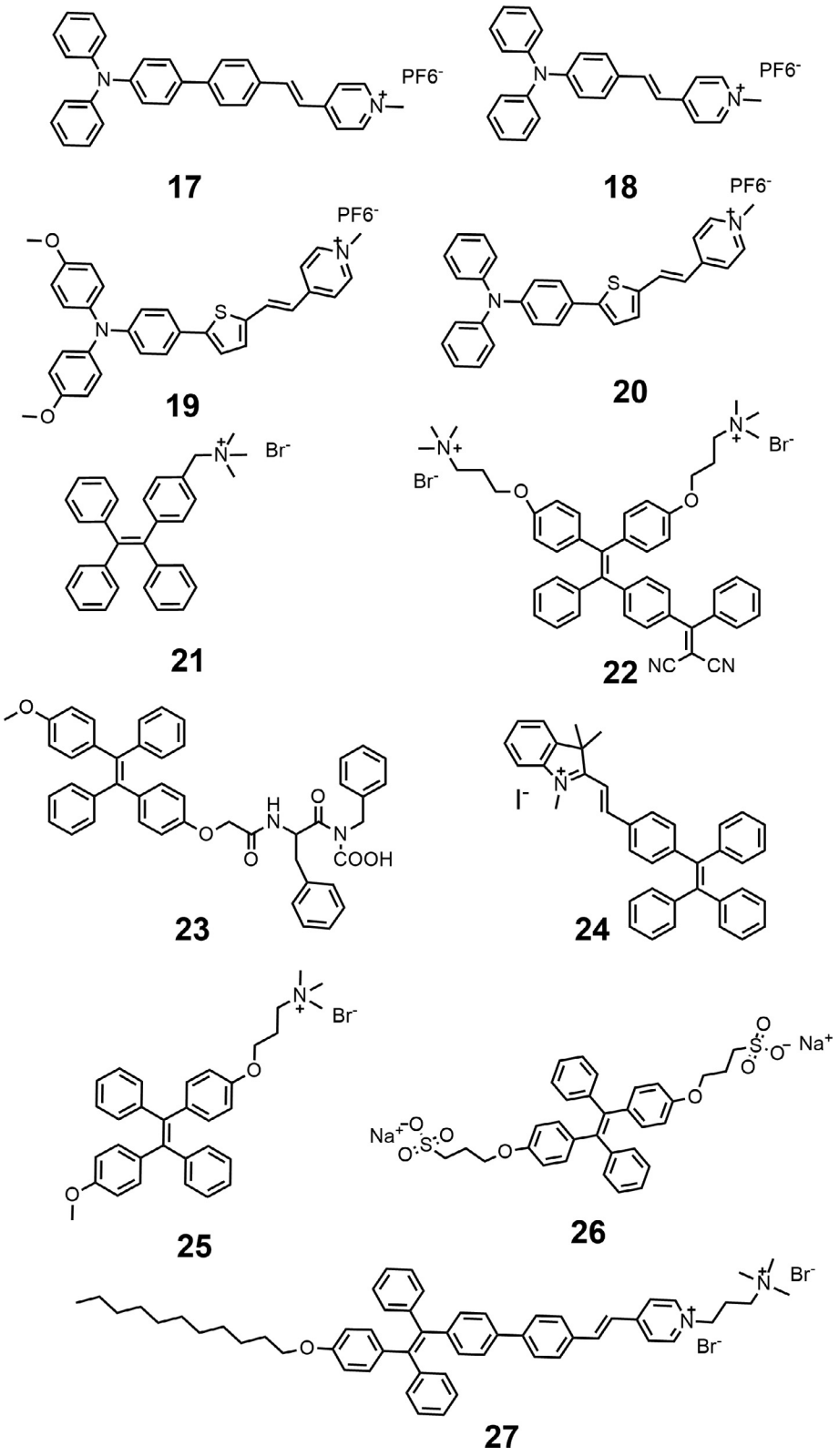


Fig. 12. Structure of the probe **17**–**27**.

labeled with the near-infrared dye Cy7 and the probe 34 was used to image the infected parts of mice. The NIR fluorescent probe selectively accumulated in the thighs of mice infected with bacteria [73].

Antibacterial peptides are a class of positively charged amphiphilic peptides, usually composed of dozens of amino acid residues. Due to the electrostatic attraction between the negative charge of the bacterial membrane lipid and the positive charge of the antimicrobial peptide, as well as the hydrophobic interaction between the bacterial membrane and the hydrophobic end of the antimicrobial peptide, the antimicrobial peptide can selectively bind and penetrate the bacterial cell membrane [74]. Fluorescently

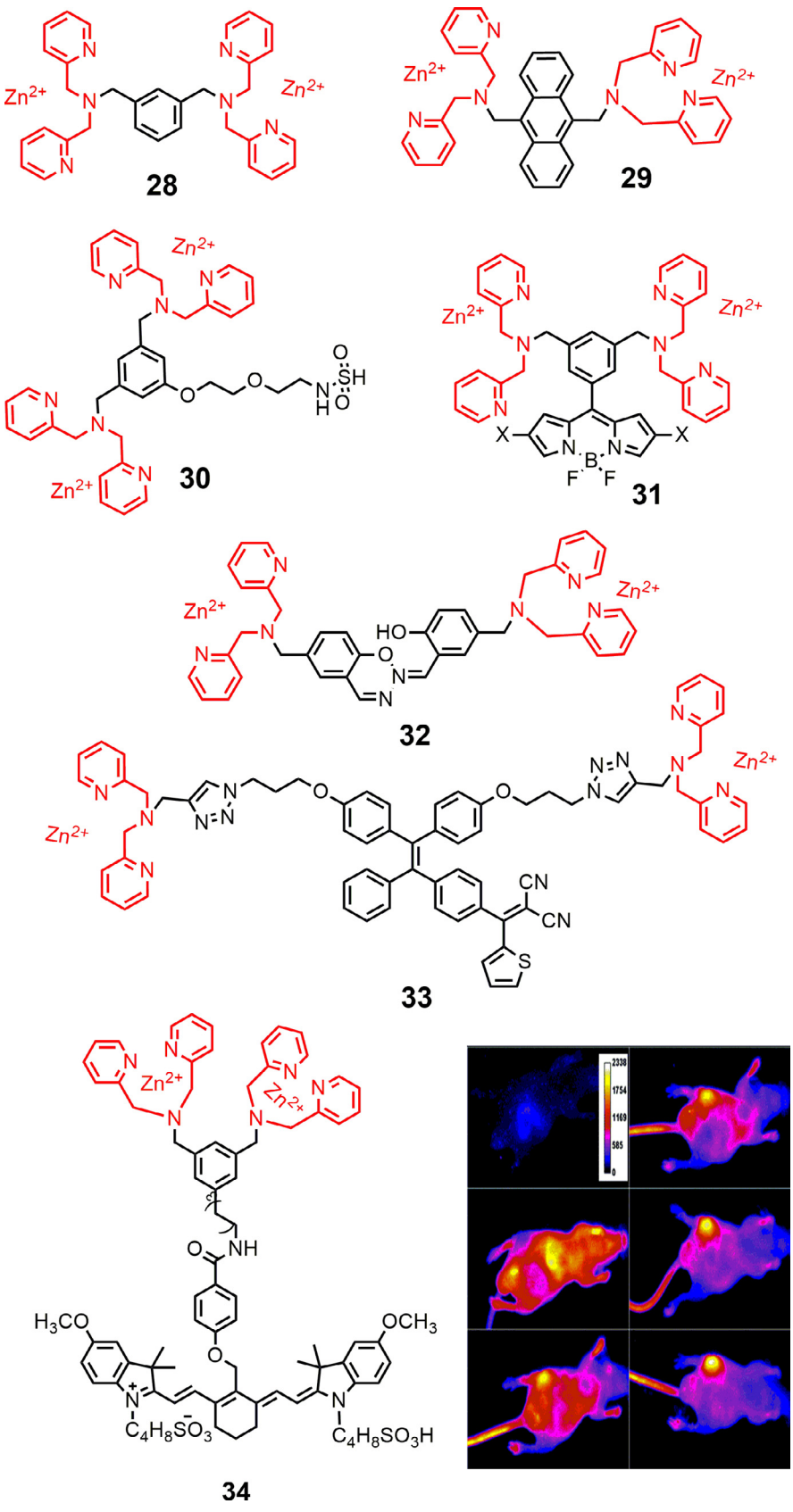


Fig. 13. Structure of the probe **28**–**34**. Fig. 13 is reprinted from Ref. 73 with permission from Copyright 2006, American Chemical Society.

labeled cationic antimicrobial peptides have been successfully used for bacterial imaging [75]. Among all the antimicrobial peptides, Ubiquitin (UBI) has attracted the most attention on infection imaging. In 1999, UBI was purified from mouse macrophages for the first time, and it showed very strong antibacterial activity against a variety of pathogens including bacteria and fungi.

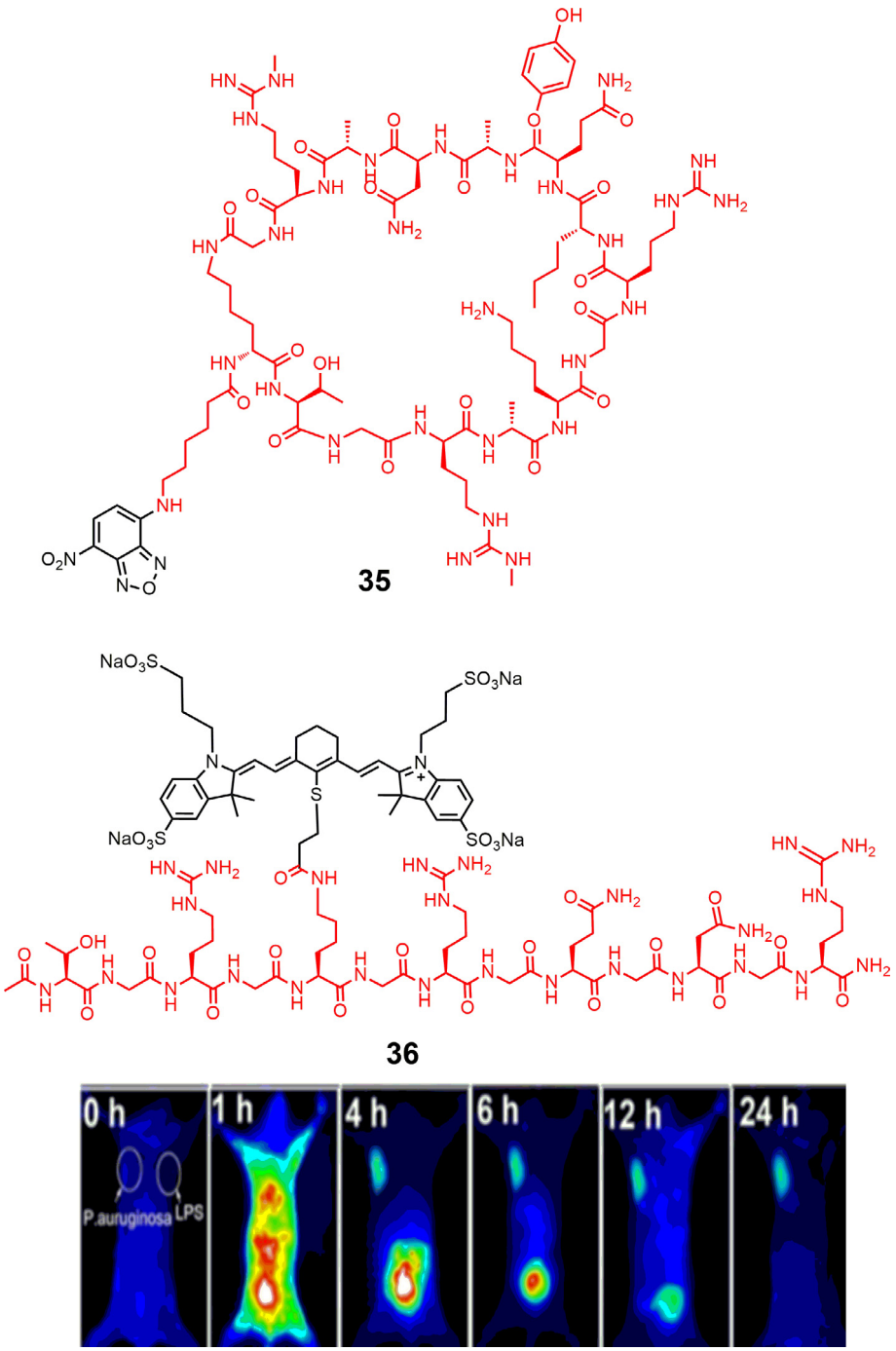


Fig. 14. Structure of the probe **35** and **36**. Fig. 14 is reprinted from Ref. 76 with permission from Copyright 2015, American Chemical Society.

UBI_{29-41} is a synthetic peptide derivative of UBI and has become one of the most promising new imaging agents for imaging of bacterial-specific infections. Dhaliwal *et al.* used NBD-labeled antimicrobial peptide fragments (UBI_{29-41}) **35** to quickly image live bacteria in human lung tissue (Fig. 14) [74]. Gu et al. designed a near-infrared fluorescent dye (ICG02) to label UBI_{29-41} **36** and studied its target in different bacteria (Staphylococcus aureus, Escherichia coli and Pseudomonas aureus) and bacterial infection mouse models (Fig. 14) [76].

4.2. Conjugated polymers probes

The structure of conjugated polymers (CPs) is usually a conjugated main chain with electron delocalization structure and a side chain modified by cationic functional groups such as quaternary ammonium and imidazolium [10]. In the non-specific detection of pathogenic bacteria, the main driving force is the electrostatic interaction between the positively charged side chain of modified conjugated polymer and the bacterial cell wall, as well as the hydrophobic interaction between the polymer backbone and the bacterial cell wall. By adjusting the conjugated main chain, CPs can almost cover the entire absorption wavelength spectra [10]. The diversity of side chain modifications can adjust its solubility and functionality in aqueous media. The addition of bacteria can enhance or quench the fluorescence of the conjugated polymer, which was used to distinguish bacteria [77–80]. Wu et al. used FITC-labeled glycol chitosan polymer as a universal cell surface imaging probe for

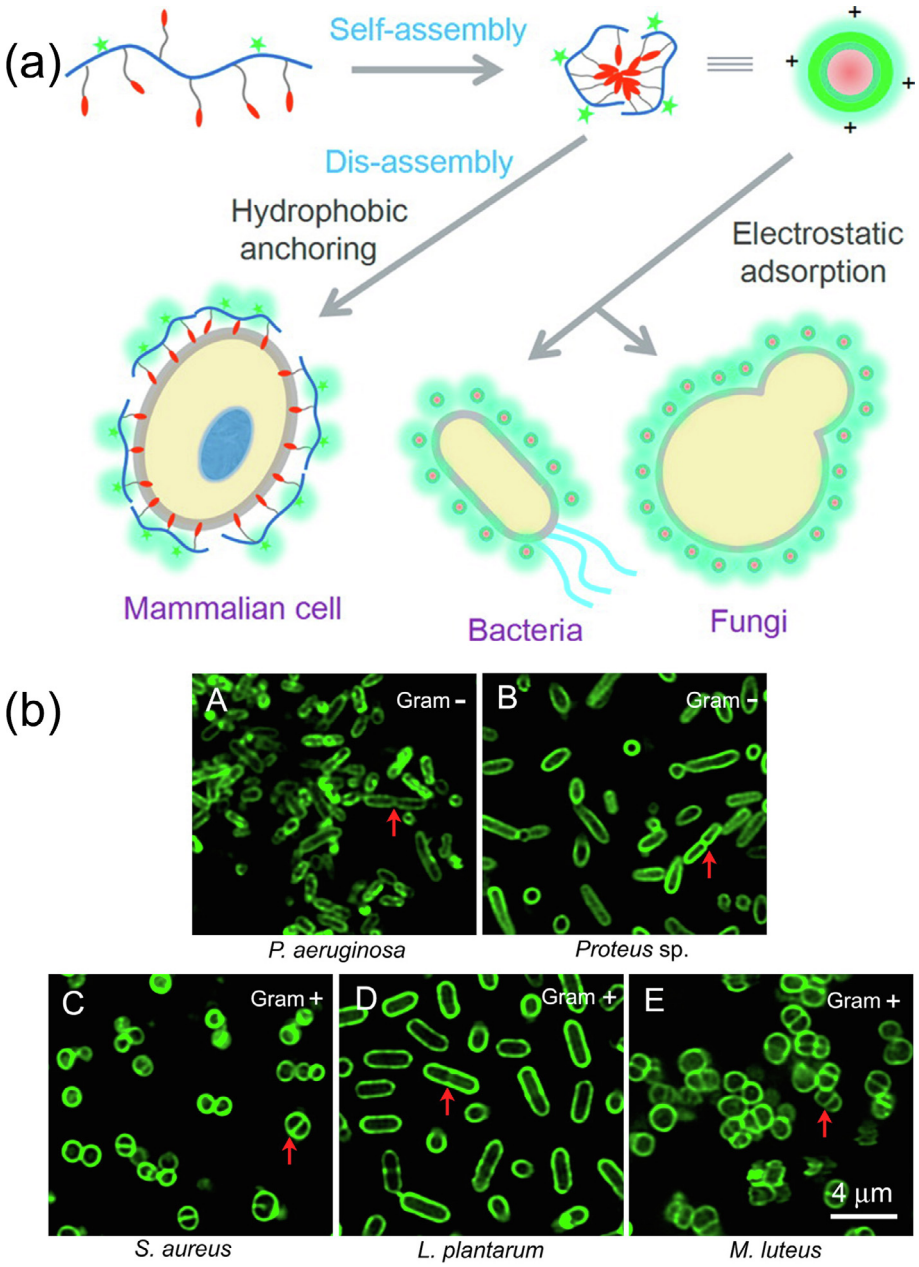


Fig. 15. Cationic conjugated polymers for bacterial imaging. Fig. 15 was reprinted from Ref. 81 with permission from Copyright 2016, American Chemical Society.

mammalian, fungal and bacterial cells through the hydrophobic interaction of cholesterol with bacterial cell walls (Fig. 15) [81]. Wang et al. developed a new cationic PPV derivative, which exhibited different interactions with fungi, gram-negative bacteria and gram-positive bacteria in buffer solutions of different ionic strength. The differentiation of fungi, gram-positive bacteria and gram-negative bacteria can be realized by changing the ionic strength of the buffer [77]. Wang et al. also developed an aggregation-directed intramolecular förster resonance energy transfer (FRET) conjugated polymer PFDBT-BIMEG [82]. After adding bacteria, the bacteria will induce FRET from PF to DBT. The different aggregation degree of PFDBT-BIMEG reflected the difference of their interaction with PFDBT-BIMEG. PFDBT-BIMEG's aggregation-oriented FRET changed within 15 min, which can be used as a fluorescent signal to distinguish bacterial types.

4.3. Nanoprobes

The surface of nanoparticles can also be functionalized with cations, which can be combined with bacteria through electrostatic interaction and then used for bacterial imaging and detection. In addition, some functional group-modified nanomaterials can also form hydrogen bonds with components on the bacterial cell wall. For example, the quaternized carbon dots (CDs) and quaternized SiNPs designed by Wu et al. can both realize the imaging of Gram-positive bacteria [83,84]. Zhang et al. used the positively charged Guanidine-Functionalized Upconversion Fluorescent Nanoparticles (UFNPs) to simultaneously detect seven kinds of pathogenic bacteria. The luminescence intensity of UFNPs in the presence of bacteria has been effectively enhanced, so pathogenic bacteria can be non-specifically quantified [85]. Gu et al. developed a fluorescent nano-probe named ZnO @ PEP-MPA by conjugating

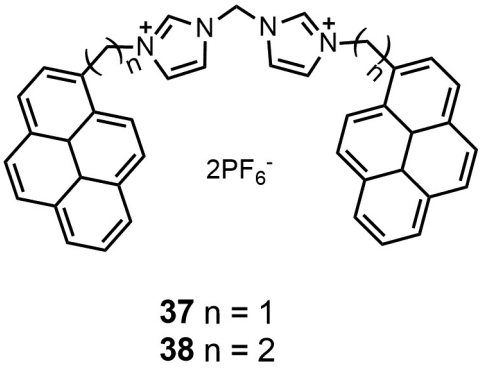


Fig. 16. Structure of the probes **37** and **38**.

BSA-stabilized ZnO QDs (ZnO @ BSA) with UBI_{29-41}, and MPA, a near infrared (NIR) dye which could discriminate the bacterial infection from sterile inflammation or cancer in vivo [86]. Phosphonic acid fluorescent organic Nanoparticles designed by Ishow et al. can selectively stain Gram-Positive Bacteria. The driving force was believed to be the hydrogen bonds between the acidic unit and the peptidoglycan (PG) layer of the outer wall of Gram-positive bacteria [87].

Except the structure and composition, the amount of net charge on the cell wall of Gram-positive bacteria and Gram-negative bacteria is also different. Fluorescence detection method can be used to amplify these subtle differences with high sensitivity to realize the identification of bacteria. Although many probes targeting bacterial cell walls have been developed, they usually only recognize one type of bacteria and cannot respond to differences between different bacteria. Although some probes can have a weak response to the difference between different bacteria, it is necessary to use more than two probes to distinguish them by means of a sensor array [64,66]. Xu et al. have developed imidazolium-pyrene self-assembling nanoprobes **37** and **38** (Fig. 16), which form aggregates in water to quench the fluorescence. The probes can interact with the surface of the bacteria through electrostatic and hydrophobic interactions to disassemble the probe aggregates and display bright fluorescence, which can be used as a bacterial imaging reagent [88]. It's worthy to point out that the fluorescence of the probe molecule will switch between the pyrene monomer and the excimer after binding to the bacteria, and the fluorescence signals act as the fingerprints of different bacteria. The rapid identification and detection of pathogenic bacteria can be achieved by converting the fluorescent signal into a two-dimensional image [89,90].

5. Conclusion

In this review, we summarized the construction strategies of cell wall-targeted fluorescent probes used in the fluorescent detection of pathogenic bacteria in recent years. The study of bacterial cell walls is of great significance for bacterial identification and combating multi-drug resistant bacteria. Fluorescence-based bacterial detection methods are still under development. In the future, more new biological receptors that specifically recognize bacterial components need to be developed. In addition, combining fluorescence detection with other modes such as photoacoustic and radiological imaging can further improve the accuracy of diagnosis. Finally, targeted bacterial imaging can also be combined with treatment, such as targeted photodynamic therapy, which is of great significance for the treatment of bacterial infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (21878286, 21908216, 21576043) and Dalian Institute of Chemical Physics (DICPI201938, DICP I202006).

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