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Pillararene-based supramolecular systems for theranostics and bioapplications

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As an emerging type of important macrocycles for supramolecular chemistry, pillararenes and their derivatives have been widely studied and applied in numerous fields, which intensively promotes the development of chemistry, materials science and biology. Pillararene-based theranostic systems are of special interest in the biological and medical areas as they have shown very promising results. Owing to easy preparation, reliable guest affinity, good biocompatibility and stability, pillararenes are frequently used to construct functional biomaterials. On one hand, pillararenes can either be used individually or form diversiform self-assemblies such as micelles, nanoparticles and vesicles to increase water solubility and biocompatibility of drugs. On the other hand, it is promising to modify solid materials like framework materials, silica nanoparticles and graphene oxides with pillararene derivatives to enhance their functions and controllability. In this review, we summarize recent endeavors of pillararene-based supramolecular systems with theranostics and other biological applications comprising drug delivery/chemotherapy, photodynamic/photothermal therapy, antimicrobials, bioimaging, *etc*. By introducing several typical examples, the design principles, preparation strategies, identifications and bio-applications of these pillararene-based supramolecular systems are described. Future challenges and directions of this field are also outlined.

pillararenes, self-assembly, theranostics, drug delivery, supra-amphiphiles

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1 Introduction

Improving the quality of life is a great pursuit which humans have invested tremendous efforts in. However, lots of diseases, including cancer, bacterial and viral infections, diabetes, and vascular diseases, are still life-threatening and hard to treat. Confronting these afflictions, the design of rapid and safe therapeutics with excellent treatment outcomes plays an indispensable role in ensuring the high quality of life for the human race. However, it is still a challenge to apply new treatments in practice because over half of the conceived therapeutics is proven to be inefficient or elicits unpredictable side effects in clinical trials. The failures in effective cure and controllable side effects are caused by many reasons such as limited solubility and stability, unknown toxicity, co-morbidities, poor circulation time, and off-target activity. In order to solve these problems,

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formulations and delivery systems are mainly studied aiming to implement the conversion from proposed therapeutics to clinically feasible drugs.

One actively explored route for new formulations and drug deliveries is using supramolecular systems that are composed of non-covalent interactions, especially macrocycle-based host-guest recognition [1–3]. Early examples of combinations of macrocycles and drugs have highlighted the potential of supramolecular systems in theranostics. For example, the use of hydroxypropyl-*β*-cyclodextrin as an excipient to improve water solubility and stability of drugs has been approved by Food and Drug Administration (FDA). Encouraged by this, macrocycle-based supramolecular systems for drug delivery have become a research hotspot due to the rapid developments of macrocyclic chemistry [4,5].

Pillararenes, which contain repeating phenyl units and methylene bridges, are a class of emerging macrocycles [6,7]. Pillararenes and their derivatives usually possess hydrophobic and electron-rich cavities, rigid pillar-shaped architectures and reliable host-guest recognitions [8,9]. Unlike cyclodextrins, calixarenes and cucurbiturils, the functionalization of pillararenes is relatively easier and can be carried out with the same or different substitutions on both rims, which significantly promotes the diversity of pillararene chemistry [10,11]. Based on manifold types of pillararene derivatives, a large number of pillararene-based supramolecular systems with various applications have been established and continue to thrive. Selected instances comprise absorption [12], separation [13], detection and sensing [14], optical materials [15], catalysis [16] and chirality amplification [17]. More importantly, due to their good biocompatibility, water solubility and selective guest affinity, pillararenes appeal to scientists to investigate their capabilities in theranostics and bioapplications [18,19]. Up to now, tremendous achievements based on pillararenes in the biological field have been accomplished such as construction of pillararene-bearing self-assemblies as nanocarriers for drug delivery [20], decoration of nanomaterials with pillararenes for enhanced biofunctions [21], and even direct use of modified pillararenes for anticancer and antibacterial activities [22,23].

In this review, we summarized the major achievements over the last 3 years in pillararene-based supramolecular systems for bio-applications including drug-loaded host-guest complexes, supramolecular nanoaggregates and pillararene-modified materials with biological functions. To give a comprehensive understanding of the recent developments, we collected reports involving pillararene-based supramolecular systems and discussed these examples thoroughly with design principles, construction methods and detailed functions. The review is categorized according to different biological or biomedical applications including drug delivery and chemotherapy, photodynamic and photothermal therapy, antibacterial activity, and other biological applications (Figure 1).

2 Pillararene-based drug delivery/chemotherapy systems

The main challenges for many of the developed cancer drugs remain in their poor solubility or stability, severe side effect and lack of self-targeting ability. For example, paclitaxel (PTX) and aliskiren exhibited good therapeutic effects against cancer and hypertension, while suffered from limited aqueous solubility. *Cis*-platinum complex-embedded drugs effectively inhibit tumor growth but their systemic toxicity cannot be ignored due to their non-targeting delivery behaviors. Insulin, employed to maintain normoglycemia, requires frequent injections. Thus the development of new formulations with glucose-triggered or controlled release (closed-loop insulin delivery systems) is of high significance. In order to improve the pharmaceutical applications of these drugs, lots of researchers have paid tremendous endeavors in constructing sophisticated drug delivery systems for enhancing therapeutic outcomes and reducing side effects. Pillararenes with ionic or water-soluble substitutions on both perimeters that show good solubility, chemical stability and strong guest affinity in aqueous medium are good candidates for controllable drug delivery systems, and numerous studies have been reported by using pillararene-based host-guest complexation, nanocarriers and composite materials.

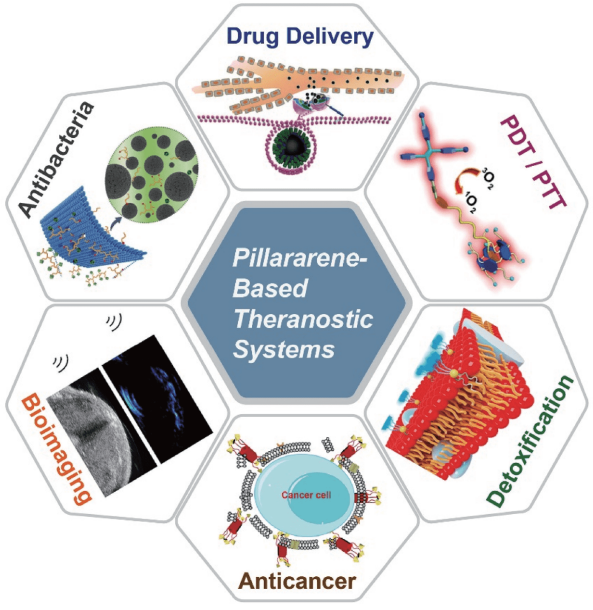


Figure 1 Schematic illustrations of pillararene-based theranostic systems with multiple applications (color online).

2.1 Host-guest complexation-promoted drug delivery

Pillararenes composed of hydrophobic cavities and hydrophilic substitutions have been shown to increase water solubility of hydrophobic drugs and decrease the side effects by forming host-guest complexes [24,25]. Notably, one early example was reported by Sashuk and co-workers [26], elucidating an X-ray structure between carboxyl pillar[5]arene and tetracaine, clearly showing the host-guest complexation to the clinically used drug. Other workers mainly used nuclear magnetic resonance (NMR) and molecular modelling to illustrate the complexation and emphasize the host-guest chemistry promoted bioactivity. For example, Huang and co-workers [27] used carboxyl water-soluble pillar[6]arene (**WP6**) to partially associate tamoxifen (an anticancer drug) for enhanced water solubility and bioactivity. Notti and co-workers [28] described the affinity between carboxyl water-soluble pillar[5]arene (**WP5**) and amikacin (an aminoglycoside antibiotic) against Gram-positive bacteria.

Another example of supramolecular chemotherapy was reported by Zhang *et al*. [29] (Figure 2). **WP6** was used to associate oxaliplatin, and the host-guest complex was found to show higher bioavailability to cancer cells and less cytotoxicity to normal cells. The association constant (K_a) between **WP6** and oxaliplatin was determined to be 1.66×10^4 M^{-1} in 1:1 binding stoichiometry, and this binding reduced the cytotoxicity of oxaliplatin to colorectal normal cells. Moreover, a lower cytotoxicity to normal cells was found by adding two equivalents of **WP6**, resulting from slightly stronger association in the presence of more host molecules.

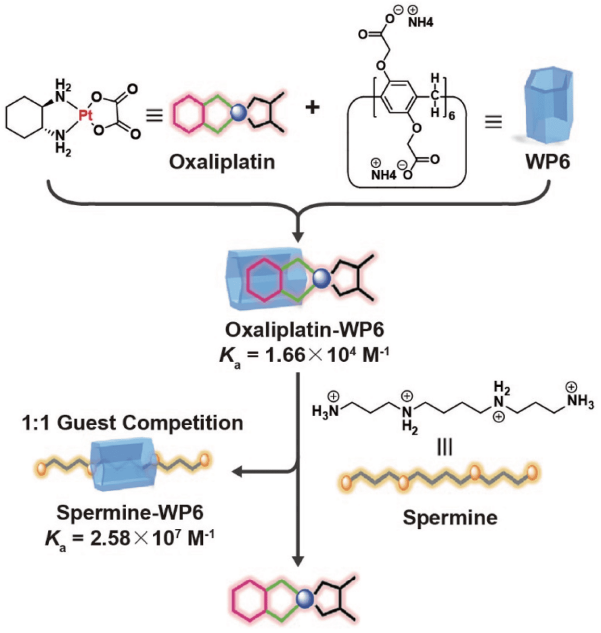


Figure 2 Chemical structures of **WP6**, oxaliplatin and their host-guest complex, and illustration of the release of oxaliplatin upon competitive binding. Reproduced with permission from ref. [29]. Copyright (2018), American Chemical Society (color online).

Because of the stronger binding affinity between **WP6** and spermine ($K_a = 2.58\times10^7$ M^{-1}), competitive replacement and release of oxaliplatin was observed in spermine-overexpressed colorectal cancer cells, leading the high cytotoxicity to cancer cells in the presence of spermine. More importantly, the anticancer activity of the complex was higher than that of free oxaliplatin, which was ascribed to the simultaneous consumption of spermine by **WP6**, since spermine is indispensable for cancer cells growth. This supramolecular chemotherapy also worked well in animal experiments and may have potentials in extending to other clinical drugs.

2.2 Drug release by self-assembled nanocarriers

Apart from directly using host-guest complexes, lots of studies have been dedicated to encapsulating drugs into nanocarriers self-assembled by pillararene-based supramolecular systems, which is also an effective strategy to improve therapeutic efficacy. Such nanocarriers represent various types of self-assemblies that can encapsulate/load drugs including micelles [30], nanoparticles (NPs) [31], vesicles [32,33] and other forms of nanostructures regardless of supramolecular [34] or covalent [35] modes of assembly. One common method is loading hydrophobic drugs in the hydrophobic regions of these self-assemblies or hydrophilic drugs in the intrinsic hollow pores of the vesicles. Pei *et al.* [36] reported a tumor microenvironment-responsive drug delivery system with self-targeting capability based on vesicles formed from a diselenium-bridged pillar[5]arene dimer (**1**, Figure 3). The host-guest recognition of the pillararene facilitated the assembly of vesicles by binding a hydrophilic mannose-containing guest (**2**) and forming a supra-amphiphile. The self-assemblies were used to load doxorubicin (DOX) hydrochloride for enhanced chemotherapy. Moreover, the complex self-assembled into vesicles with the mannose moiety on the exterior surface, rendering vesicles with targeting ability. Meanwhile, the reduction-sensitive diselenium bond provided glutathione (GSH) responsiveness that led to morphological transformation and DOX release in cancer cells. By comparing the intracellular fluorescence of DOX in different cells, a higher uptake of DOX-loaded vesicles by cancer cells was concluded. Additional experiments confirmed evidences of selective cytotoxicity. The cell viability of HepG2 cells was lower than that of 293T cells, mainly resulting from higher levels of intracellular GSH and mannose acceptor in cancer cells.

Loading drugs in nanocarriers by non-covalent interactions is a feasible approach, and some studies show that covalently attaching drugs in supramolecular self-assemblies are also effective to alter physical features and biocompatibility of the drugs. Schmuck and co-workers [37] estab-

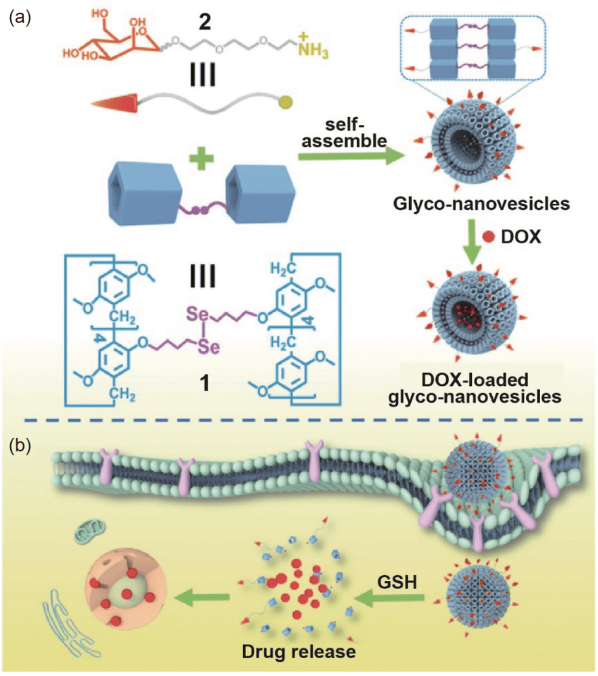


Figure 3 (a) Chemical structures of **1** and **2**. (b) Illustrations of the formation of vesicles and GSH-controlled DOX release. Reproduced with permission from ref. [36]. Copyright (2020), the Royal Society of Chemistry (color online).

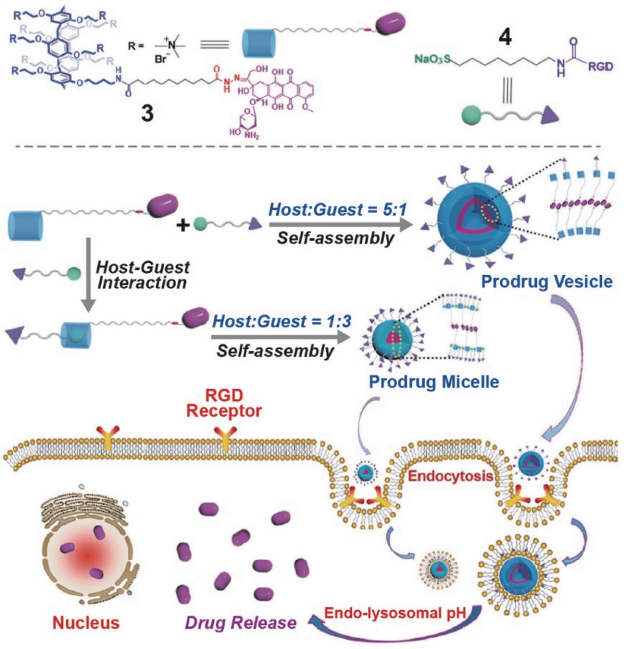


Figure 4 Chemical structures of **3** and **4** and illustrations of vesicle/micelle formation and tumor-targeting drug delivery. Reproduced with permission from ref. [37]. Copyright (2018) John Wiley and Sons (color online).

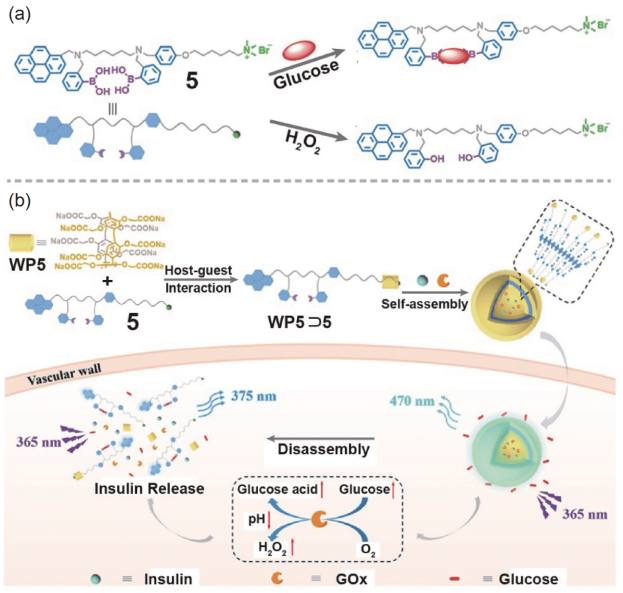


Figure 5 (a) Representations of glucose and H_2O_2-responsiveness of **5**. (b) Formation of vesicles from supra-amphiphile **WP5⊃5** for insulin delivery. Reproduced with permission from ref. [38]. Copyright (2018) John Wiley and Sons (color online).

lished a vesicle-micelle tunable system for drug delivery and covalently modified nanocarriers with a DOX-based prodrug (Figure 4). A cationic pillar[5]arene derived prodrug (**3**) was employed as an amphiphilic host in the system. Driven by the host-guest recognition between **3** and Arg-Gly-Asp (RGD)-modified sulfonate guest (**4**), nanocarriers with tunable size and morphology from vesicles to smaller micelles were obtained by adjusting the molar ratio of the guest. Besides, these nanocarriers were equipped with RGD targeting groups that can promote internalization of nanocarriers by the integrin-overexpressing cancer cells. As expected, *in vitro* experiments suggested that nanocarriers were internalized by cancer cells and the loaded DOX rapidly released resulting from the acid-induced cleavage of the hydrazone moiety. The targeting group on the surfaces of nanocarriers maximized therapeutic efficacy against cancer cells, while the cytotoxicity to normal cells was reduced. The antitumor efficiency was further evaluated by *in vivo* experiments and the results also displayed enhanced tumor inhibition and reduced systematic toxicity.

Supramolecular nanocarriers are not limited to cancer treatments but also have potentials in other diseases. Wang *et al.* [38] reported a supramolecular theranostic nanoplatform for glucose sensing and "closed-loop" insulin delivery (Figure 5). The guest (**5**) was tailored with a pyrene group, a diphenylboronic acid derivative and ternary ammonium, serving as a fluorophore, a glucose binding site and a **WP5** binding site, respectively. Upon the formation of a supra-amphiphile with **WP5**, the self-assembled vesicles were employed for the encapsulation of insulin and glucose oxidase (GOx), realizing simultaneous blood glucose monitoring and "closed-loop" insulin delivery. The insulin-GOx loaded vesicles work with multiple pathways: when exposed to a hyperglycemic condition, the diphenylboronic unit on **5**

selectively bound to glucose, causing partial disassembly and insulin release. Meanwhile, GOx oxidized glucose and produced H_2O_2 accompanied by pH decrease. H_2O_2 further cleaved C–B bond of the guest and an acidic microenvironment protonated **WP5**, which cooperatively destroyed the vesicles and efficiently released the encapsulated cargoes. *In vivo* experiments strongly support that this system works well with a fast response to regulate blood glucose levels of diabetic mice.

Compared to supramolecular self-assemblies, covalently bonded nanocarriers usually possess higher stability and less drug leakage. Ma and co-workers [39] constructed **WP6**-based nanoparticles stabilized by covalent linkers (called "nanosponge") *via* a supra-amphiphilic template for drug delivery (Figure 6). The drug-loaded nanosponge was prepared through four steps that included the formation of nanoparticles composed of a supra-amphiphile based on **WP6** and a ferrocene-bearing guest, covalently cross-linking the nanoparticles by amide condensation, removal of free reagents and loading the cargo through non-covalent interactions. By studying the drug release behaviors under different conditions, the nanosponge showed advantages in stable drug encapsulation and controlled drug release in reductive conditions. Interestingly, except for the satisfactory drug delivery and anticancer effect, the DOX-loaded nanosponge exhibited capability of overcoming multidrug resistance (MDR) in the treatment of MCF-7/ADR cells by decreasing half-maximal inhibitory concentration (IC_{50}) to 3.4 μM, which was explained by avoiding drug efflux through the stable supramolecular encapsulation of cargoes.

2.3 Drug release by hybrid materials

Pillararenes can be tailored as building blocks in the modification of hybrid materials for specific functions. For example, Du *et al.* [40, 41], Yang and Stoddart *et al.* [42–44] separately showed a series of studies in which pillararenes were capped on the surfaces of guest-bearing mesoporous silica nanoparticles (MSNs) or hollow mesoporous carbon nanoparticles (HMCNs) that served as supramolecular nanovalves for drug delivery and controlled release. By modifying mesoporous nanoparticles with pillararenes, surface properties, cargo loading capacity and release process can be handily adjusted. Benefiting from the reversibility of host-guest recognition, the prepared hybrid materials provided a robust reservoir for the storage of cargo molecules and controlled release when they were exposed to certain stimuli such as metal ions, competitive guests, acidic conditions.

Metal-organic frameworks (MOFs) are another class of essential porous materials and they also exhibit a bright future in bioapplications. The surface of MOFs can be modified with the guest that is associated with pillararenes for hybrid materials. Yang and co-workers [45] reported a pillararene nanovalve-operated MOF as a stimuli-responsive release system in 2015. The same group also constructed a core-shell nanocomposite as a theranostic platform by using pillararene-decorated MOFs (Figure 7) [46]. This hybrid material is composed of a Fe_3O_4 core, a UiO-66 Zr-MOF shell and a **WP6** capping structure (Fe_3O_4@UiO-66@**WP6**). The core-shell structure can serve as an MRI tracer and a nanocarrier for the delivery of 5-fluorouracil with controlled

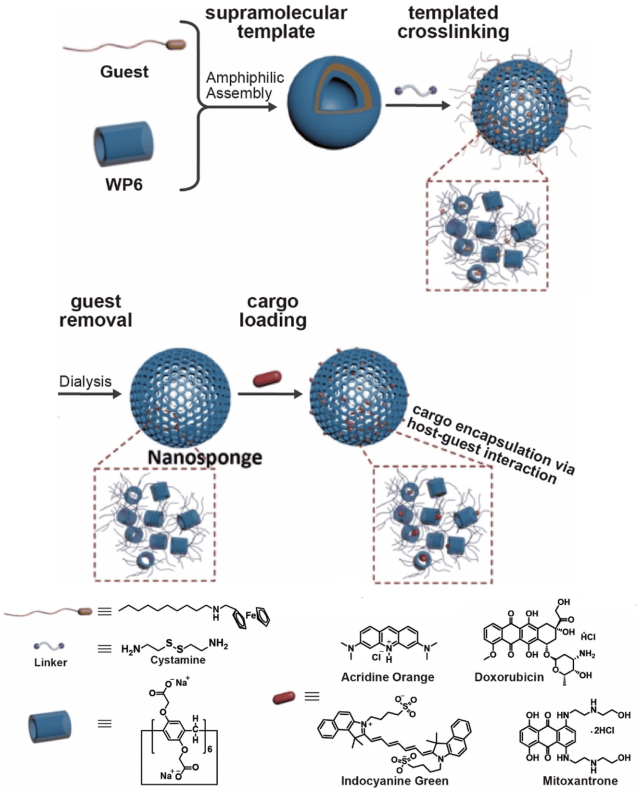


Figure 6 Cartoon representations of the formation of nanosponge *via* the supra-amphiphilic template and chemical structures of building blocks and cargoes. Reproduced with permission from ref. [39]. Copyright (2020), American Chemical Society (color online).

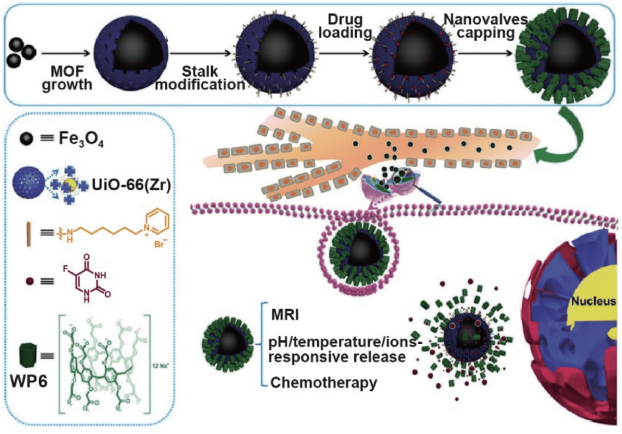


Figure 7 Illustrations of the construction of the pillararene nanovalve-operated MOF and its multiple functions. Reproduced with permission from ref. [43]. Copyright (2018) John Wiley and Sons (color online).

release ability in response to multiple stimuli such as pH, ions, competitive agents and temperature. *In vitro* experiments suggested that the nanocomposite displayed desirable anticancer effect and ideal biocompatibility. Furthermore, when using **WP5** in the supramolecular nanovalve, the drug release of the material was faster than that of Fe_3O_4@UiO-66@**WP6** because the affinity between **WP6** and pyridinium cation was stronger. This observation also revealed that the tightness of the nanovalves could be altered by adjusting host-guest complexation with different host and guest molecules, fulfilling controllable sustained drug release for different requirements.

3 Pillararene-based photodynamic/photothermal therapy

Photodynamic therapy (PDT) and photothermal therapy (PTT) are promising therapeutic modalities against tumors with high efficacy, low cost and minimum invasiveness. Compared to traditional chemotherapy and radiation therapy, drug resistance, severe side effects and cumulative toxicity can be avoided by PDT and PTT. PDT involves transferring the light energy into highly toxic singlet oxygen by a photosensitizer, which induces cell apoptosis and necrosis [47,48]. Usually, photosensitizers are hydrophobic molecules with large π-conjugated structures such as tetraphenylporphyrin (TPP) [49], dipyrromethene boron difluoride (BODIPY) [50] and phthalocyanine derivatives [51], and they suffer from severe π-π stacking in aqueous media. The aggregation of photosensitizers quenches their fluorescence and inhibits the generation of reactive oxygen species (ROS). Therefore, dispersion and delivery of photosensitizers are crucial for PDT. PTT, which is also using light energy, relies on cytotoxic heat generated by photothermal agents under light irradiation. Commonly used photothermal agents are also hydrophobic and sometimes show fast blood clearance. In order to overcome these limitations, sophisticated nanocarriers are required for specific and efficient delivery in physiological environments. Although lots of nanosystems have been elaborated for PDT and PTT, pillararene-based supramolecular approaches are an emerging hotspot owing to their easy preparation, reversibility and high therapeutic outcomes.

3.1 Pillararene-based supramolecular systems for PDT

To prevent hydrophobic aggregation of photosensitizers, Zhang *et al.* [52] presented a host-guest complexation enhanced PDT by using pyridinium guest-bearing pyrophaeophorbide A (**6**) as a photosensitizer, which formed a supra-amphiphile with a pillar[5]arene derivative (**7**, Figure 8). Notably, nanoparticles formed from **6** exhibited negligible emission and singlet oxygen ($^1O_2$) generation ability due to the strong aggregation, whereas nanoparticles of the **7**/**6** complex had enhanced fluorescence and were able to produce $^1O_2$ because the association compensated the free energy of aggregation and overcame the stacking effect. Following studies demonstrated high light cytotoxicity of **7**/**6** assemblies and achieved enhanced PDT. This simple system provides basic design principles of host-guest interactions facilitated PDT.

Targeting ability is one of the most important standards of supramolecular PDT systems. Huang and co-workers [53] constructed a pillar[5]arene-based supramolecular peptide with controllable self-assembly morphologies and PDT capability (Figure 9). The amphiphilic peptide (**8**) bore a pyridinium guest and an ERGDS (E = glutamic acid, R = arginine, G = glycine, D = aspartic acid, S = serine) targeting group that was associated with a thermo-responsive triethylene glycol pillar[5]arene (**9**) with cancer cell targeting ability. The supramolecular peptide was simply prepared by mixing **9** and **8**, and the self-assembly morphologies were controlled by heating and cooling due to the LCST behavior of **9**. Moreover, the nanoparticles of the supramolecular peptide were used for encapsulation of TPP for PDT. Both *in vitro* and *in vivo* studies provided evidences for the high PDT efficiency and biocompatibility. The nanocarriers hold great potential in tumor-targeting therapy benefiting from the targeting sequence on the peptide, The same group also reported a PDT procedure with an adaptive supramolecular photosensitizer [54]. With rational designs, the guest compound (**10**) was composed of an electron-rich tetraphenylethene (TPE) fluorogen, a conjugated electron-deficient pyridinium and another pyridinium unit at the end (Figure 10). The donor-acceptor moiety separates the highest occupied molecular orbital (HOMO) and lowest unoccupied

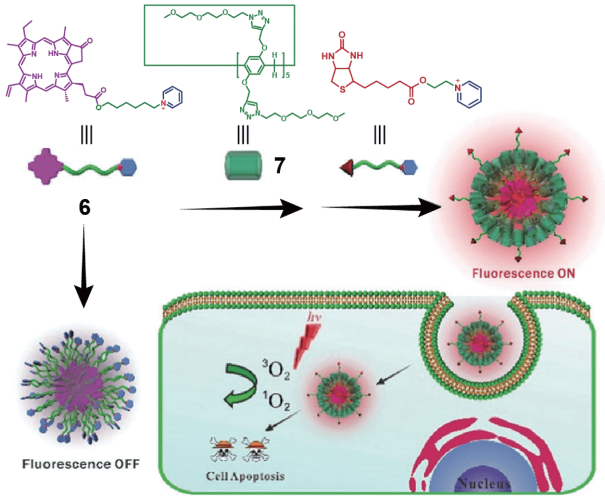


Figure 8 Representations of the fluorescence enhancement by host-guest interactions and the PDT procedure of the nanoparticles. Reproduced with permission from ref. [49]. Copyright (2018), the Royal Society of Chemistry (color online).

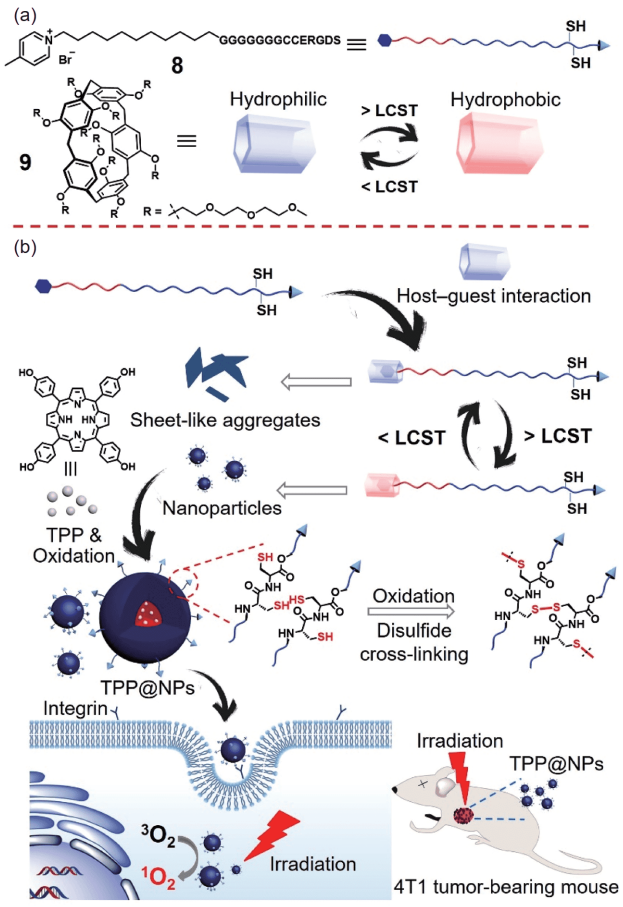


Figure 9 (a) Chemical structures of **8** and **9**. (b) Cartoon illustrations of the programmable peptide self-assembly and PDT. Reproduced with permission from ref. [50]. Copyright (2019), Nature Publishing Group (color online).

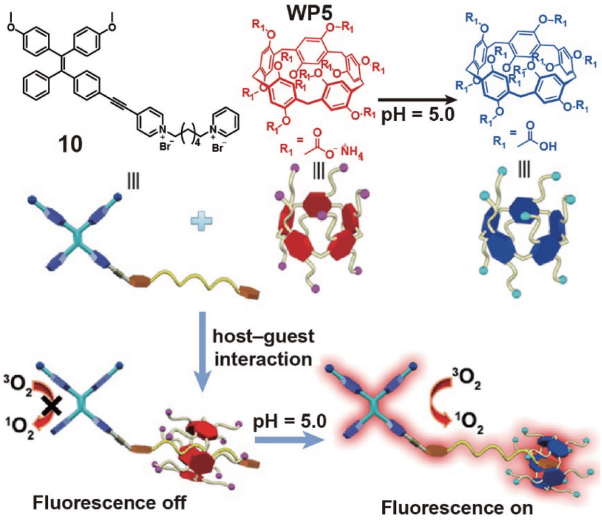


Figure 10 Chemical structures of **WP5** and **10** and the switchable fluorescence and PDT capability. Reproduced with permission from ref. [51]. Copyright (2020) John Wiley and Sons (color online).

molecular orbital (LUMO) distributions and minimizes the energy gap between the S_1 and T_1 states that are helpful for the generation of $^1O_2$. After the host-guest complexation, the cytotoxicity of **10** was reduced and the complex showed a pH-responsive photosensitizing effect. At neutral pH, the complex was non-emissive. In contrast, in an acidic environment, the complex showed red fluorescence and enhanced ROS generation ability, which was applied as a targeting PDT system in response to the acidic tumor microenvironment.

3.2 Pillararene-based supramolecular systems for PTT

PTT, with reduced side effects and invasiveness, is a rapidly developing cancer treatment [55]. Various photothermal agents have been explored including inorganic materials (*e.g.,* gold nanorods and CuS nanoparticles) [56,57], organic materials (*e.g.,* polypyrrole and polydopamine) [58,59] and small molecules (*e.g.,* perylene-3,4,9,10-tetracarboxylic diimide (PDI) and indocynanine green analogies) [60,61]. Fan *et al.* [62] prepared supramolecular vesicles self-assembled by **WP5** and a PDI-containing guest (**11**) for PTT (Figure 11). Compound **11** served as both the guest and the photothermal agent. Upon the formation of a supra-amphiphile, the nanoparticles easily entered cells to achieve a good intracellular accumulation. Moreover, the vesicles were used as nanocarriers for the encapsulation of DOX, resulting in synergistic effects against cancer cells *via* combined chemotherapy and PTT, and hence a better therapeutic efficacy than chemotherapy or PTT alone.

Inorganic photothermal agents such as CuS nanoparticles have been broadly investigated due to their high thermal stability and ease of modification. Yu and co-workers [63] explored a hybrid material for targeting chemotherapy and PTT (Figure 12). CuS nanoparticles were functionalized by **WP5** for monodispersion and stability in an aqueous medium. The nanoparticles were further decorated by a liver cancer cell-targeting galactose guest (**12**) *via* host-guest recognition and loaded with DOX to form the complicated hybrid material (CuS@WPG-DOX). The drug-loaded nanocarriers displayed near-infrared (NIR) absorption and pH-controlled drug release abilities in water that were favorable for combined therapies. As expected, CuS@WPG-DOX was proven to be highly capable of cancer inhibition in both *in vitro* and *in vivo* experiments upon NIR irradiation, which offers a useful approach to construct hybrid materials for potential biomedical applications.

4 Pillararene-based antibacterial systems

The discovery of penicillin nearly a century ago enabled the control of infections caused by Gram-positive bacteria such as *Staphylococcus* that propelled the development of anti-

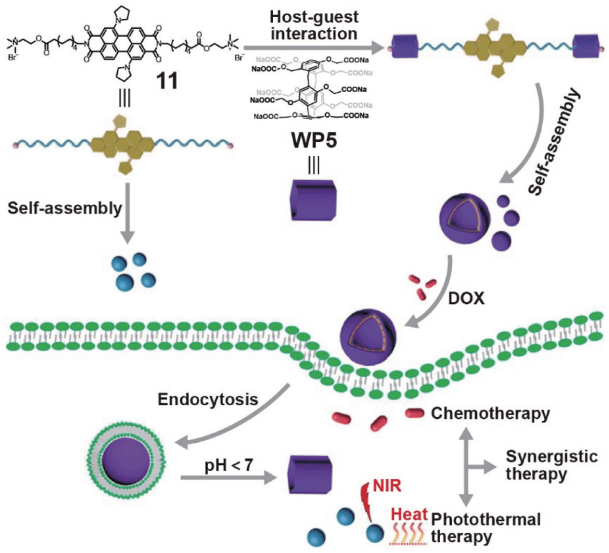


Figure 11 Formation of vesicles from self-assembly of **WP5** and **11** and their use in chemo-photothermal synergistic therapy. Reproduced with permission from ref. [59]. Copyright (2018), American Chemical Society (color online).

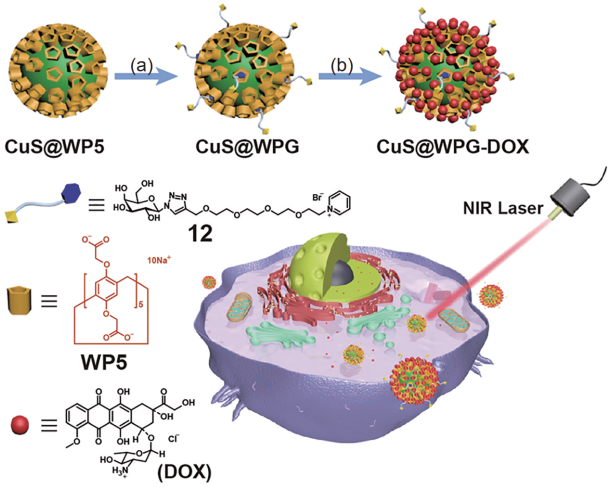


Figure 12 Illustrations of the preparation of the hybrid material CuS@WPG-DOX by host-guest recognition and its therapeutic procedure upon NIR irradiation. Reproduced with permission from ref. [60]. Copyright (2018), American Chemical Society (color online).

biotics. However, the unscientific abuse and continuous overuse of antimicrobials in agriculture, healthcare and clinical treatments escalated the risk of drug resistance that hampers the effectiveness of conventional antibiotics in many situations. Infections and fatal cases caused by MDR bacteria are growing, which show high demands on finding new antibiotics. In addition to the emerging antibiotics based on small molecules and polymers, pillararenes have been actively used to control bacterial infections. For instance, cationic pillararene derivatives with ammonium and phosphonium substituents reported by Cohen *et al.* [64] inhibit the biofilm formation. Transmembrane channels based on pillararenes designed by Hou *et al.* [65] could insert into lipid membranes and showed impressive antibacterial activity. These reports demonstrate the capability of pillararenes as effective building blocks for the preparation of supramolecular antimicrobial agents.

4.1 Pillararenes with antibacterial activities

Biofilms that can insulate bacteria from antibiotics and host immune response are considered as one of the major reasons for chronic infections. Many reports have focused on the inhibition of biofilm formation and killing of planktonic bacteria, while only a few are aimed to disrupt the established biofilms. By using zwitterionic pillar[5]arene (**13**), Haag and co-workers [66] reported a method to combat planktonic bacteria and destroy pre-existing biofilms (Figure 13). Compound **13** self-assembled into weakly positive-charged nanoaggregates by binding the hexyl sulfate group. The antibiotic activity was evaluated using Gram-positive *Staphylococcus aureus* (*S. aureus* (SH1000)) and Gram-negative *Escherichia coli* (*E. coli* (DH5α)) bacterial strains. Unlike the previously reported cationic pillararenes that mainly killed Gram-positive bacterial strains, **13** performed as antibiotics against both strains. Cryo-transmission electron microscope (cryo-TEM) images provided evidences for the interactions between **13** nanoaggregates and *E. coli* (DH5α) membranes that finally caused deformation of the membrane. Furthermore, treating pre-cultivated *E. coli* (DH5α) biofilms with **13** nanoaggregates efficiently disrupted the established biofilms. Studies of the resistance development against *E. coli* (DH5α) biofilms revealed that it was hard for bacteria to rapidly generate resistance against **13**, giving **13** the edge as a long-lasting antibacterial agent.

4.2 Pillararene-involved materials with antibacterial activities

Pillararene derivatives-coated inorganic/organic matrices are versatile tools with various applications, especially for the nanostructured multilayer films. Pisagatti and co-workers [67] successfully prepared **WP5** and poly(allylamine hydrochloride)-coated glass slides with multilayer films *via* a layer-by-layer assembly approach for the combat against pathologically relevant bacterial strains. The obtained multilayer films were loaded with antibiotic levofloxacin and amikacin by host-guest recognition. *In vitro* studies demonstrated a steady release of antibiotics during the experimental period and an effective inhibition of the surface adhesion and the bacterial proliferation.

Recently, cationic polymers that can effectively bind to negatively charged bacterial membranes have attracted considerable attention. The electrostatic and hydrophobic interactions between cationic polymers and membranes de-

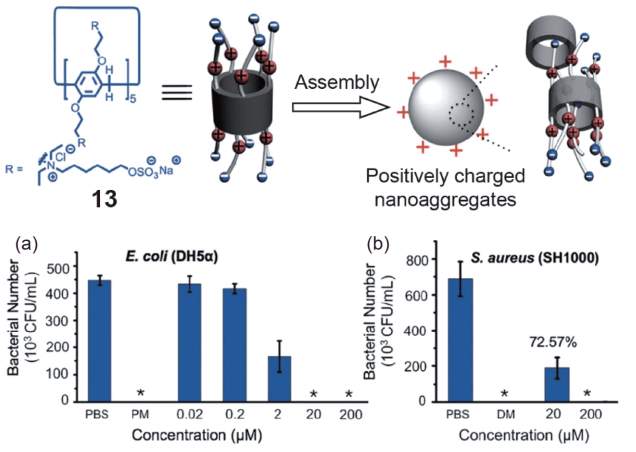


Figure 13 Cartoon representation of the formation of positively charged nanoaggregates from **13**. The antibacterial ability of **13** against (a) *E. coli* (DH5α) and (b) *S. aureus* (SH1000). Reproduced with permission from ref. [63]. Copyright (2019) John Wiley and Sons (color online).

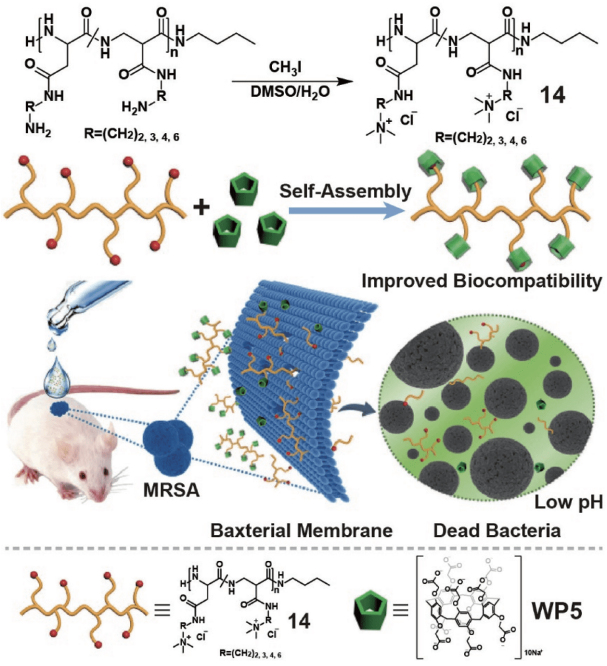


Figure 14 Chemical structures of **WP5** and **14** and illustration of the biodegradable supramolecular material with antibacterial ability for healing MRSA-infected wound. Reproduced with permission from ref. [65]. Copyright (2019) John Wiley and Sons (color online).

stroy the membrane integrity, thus leading to bacterial death. Quaternary ammonium compounds (QACs) are a class of cationic polymers which have a broad-spectrum of antibacterial activity and seldom induce the generation of resistance. Although QACs may be good candidates for curing MDR bacterial infections, most of the reported QACs are dependent on non-biodegradable backbones, which increase risks of the unpredictable side effect and potentially accumulative toxicity. To solve these problems, Gao and coworkers [68] described a biodegradable supramolecular material based on **WP5** and QACs against Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and for mitigating resistance (Figure 14). Cationic polyaspartamide derivatives (**14**) were used as QACs whose biocompatibility was increased by the association with **WP5** and forming quaternary ammonium/**WP5** complexes. However, under inflammated tissue with the bacterial infection, quaternary ammonium moieties were released in response to an acidic microenvironment and protonation of **WP5**, showing specific membranolysis to Gram-positive bacteria. This pH-responsiveness promoted the antibacterial activity when treating MRSA-infected wound *in vivo*. Moreover, polyaspartamides are biodegradable, which avoids the long-term toxicity and mitigates antimicrobial resistance.

5 Other biological applications based on pillararenes

5.1 Pillararene-based supramolecular systems for bioimaging

Pillararenes with multiple substitutions are favorable for stabilizing nanoparticles by either adding anionic carboxylate/phosphate pillararenes during the preparation procedures, or post-modifying nanoparticles *via* ligand-exchange methods and host-guest recognitions. For example, **WP6** can serve as both a reducing agent and a stabilizing agent when preparing gold nanoparticles (AuNPs) through a reversed Turkevich approach, with the obtained **WP6**-stabilized AuNPs possessing sensing and catalysis abilities [69]. Phosphate-bearing pillar[5]arenes with water solubility can be attached on the surface of magnetic nanoparticles for enhanced aqueous dispersion and separation of guest-labelled proteins [70]. Recently, rare-earth upconversion nanoparticles (UCNPs), which hold great advantages in thermal and optical stability, larger anti-stokes shifts, high quantum yields, *etc*, are promising tools for probing and bioimaging, albeit confronting challenges in colloidal and aqueous-medium stability. To solve these problems, **WP5** modified UCNPs with good water dispersibility for controlled drug release and cell imaging were separately reported by Sun *et al.* [71] (Figure 15) and Yang *et al.* [72]. The decoration of **WP5** is a feasible strategy for dispersing UCNPs, which offers a transparent and stable solution in a physiological environment. Under NIR irradiation, the nanoparticles realize upconversion luminescence for cell imaging, which provides an insight for developing stable UCNPs for bioimaging.

Unlike traditional fluorescent imaging, photoacoustic imaging utilizes laser irradiation and detection of ultrasonic waves from thermoelastic expansion to acquire high-resolution images with deep penetration. In order to proceed with high-performance photoacoustic imaging, optical-to-

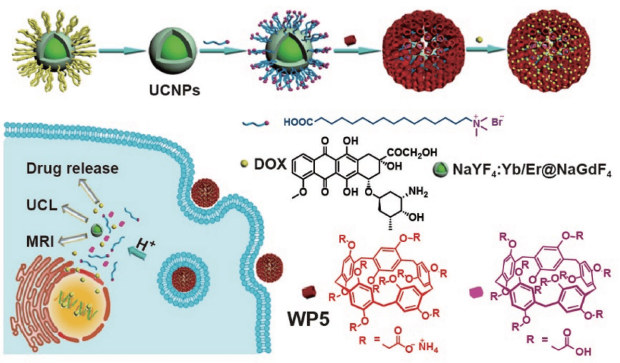


Figure 15 The preparation of **WP5**-modified UCNPs and multiple biological applications. Reproduced with permission from ref. [68]. Copyright (2018), American Chemical Society (color online).

acoustic efficiency and photoacoustic signal must be amplified. Chen *et al.* [73] described the preparation of a supramolecular hybrid material composed of graphene oxide (GO), a pillar[6]arene derivative (**15**) with bicarbonate counterions and a pyrene-bearing guest (**16**) as a contrast agent for ultrasonography and photoacoustic imaging (Figure 16). Driven by host-guest recognition and π-π interactions between GO and pyrene, ternary components formed the hybrid material (GO@**15**⊃**16**). Compared to uncoated GO, GO@**15**⊃**16** exhibited better water dispersibility and increased NIR absorption, favorable for photothermal effect. Upon NIR irradiation, bicarbonate counterions decomposed into CO_2 nanobubbles along with the temperature rise caused by photothermal effect. CO_2 nanobubbles could scatter and reflect ultrasound, which further increased the vibration of the medium and enhanced the photoacoustic signal. Employing GO@**15**⊃**16** in *in vivo* experiments demonstrated significantly increased photoacoustic signals of tumors, which provided new perspectives to prepare imaging agents and pillararene-decorated hybrid materials.

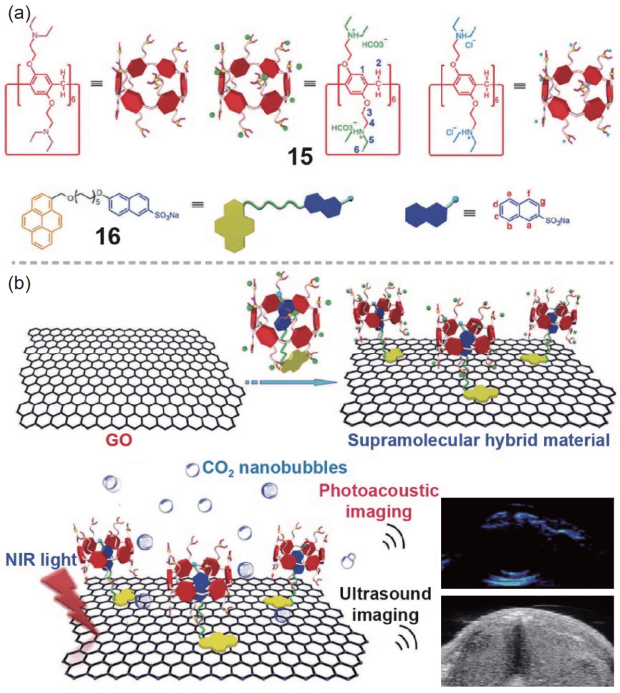


Figure 16 (a) Chemical structures of **15** and **16**. (b) Representation of the preparation of GO@**15**⊃**16** with ultrasonography and photoacoustic imaging enhancement. Reproduced with permission from ref. [69]. Copyright (2018), the Royal Society of Chemistry (color online).

5.2 Detoxification *via* pillararene-based host-guest recognition

Fast decreasing the levels of toxicants in the body is still a widely approved guideline for poisoning treatment. Current methods for toxicant removal mainly depend on porous materials such as activated charcoal that can adsorb toxic compounds without selectivity. Such "passive and non-selective absorption" limit therapeutic outcomes. Therefore, positive and customized strategies designed at the molecular level for detoxification should be developed. Among numerous toxicants, paraquat is nearly the most harmful due to its fast accumulation in tissues and organs resulting in poor therapeutic efficiency. Due to the two positive charges and the linear structure of paraquat, Huang *et al.* [74,75] and Wang *et al.* [76] separately reported supramolecular ways for the treatment of paraquat poisoning by pillararene- and cucurbituril-based host-guest recognitions. The binding affinities between these two hosts and paraquat are so strong that can effectively decrease the concentration of free paraquat and retard paraquat-involving redox cycling. By supramolecular association, the toxicity of paraquat at cellular level is reduced, which provides a potential approach for detoxification. However, when paraquat enters the body, the treatment is complicated because the paraquat concentration in serum is consistently low and thus only a small amount of paraquat can be eliminated by passive blood purification. Besides, after blood purification, the redistribution of paraquat from stored tissues to plasma and then to kidney and lung still takes place. To continuously reduce the amount of paraquat, Sun and co-workers [77] modified red blood cells (RBC) with **WP6** and a Janus dendrimer amphiphile (JDA) to inherit a long circulation time for continuous detoxification (Figure 17). The JDA molecule contained cationic pyridinium moieties and hydrophobic chains that acted as both an amphiphile and pillararene guest. Pre-assembly between **WP6** and JDA produced vesicles, which promoted the loading of the host-guest complex onto RBC membranes (**WP6**@JDA@RBC) by cell-liposome interactions. *In vivo* experiments on paraquat poisoned mice suggested that the injection of **WP6**@JDA@RBC for 1 h post-poisoning (first aid) steadily decreased the concentration of paraquat in plasma with a 75% removal rate, and the toxicant removal was still effective in delayed aid (after 3 days of poisoning).

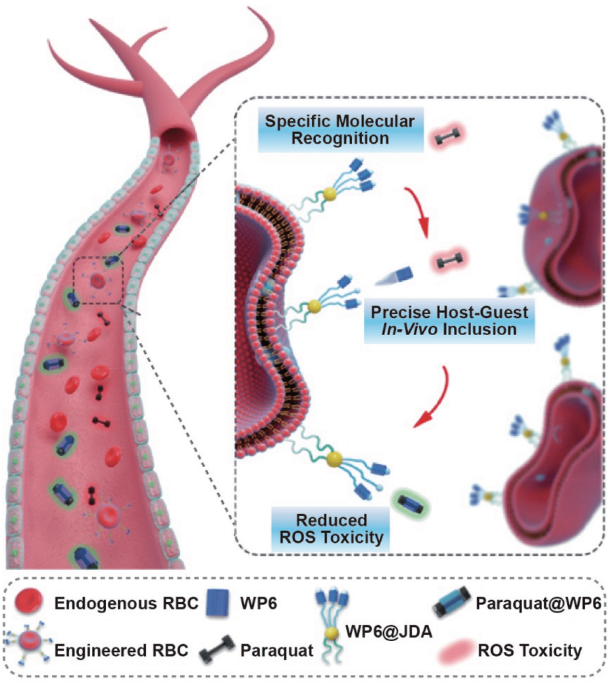


Figure 17 Cartoon illustrations of the host-guest complex-loaded RBC for paraquat detoxification in the blood. Reproduced with permission from ref. [73]. Copyright (2020), American Chemical Society (color online).

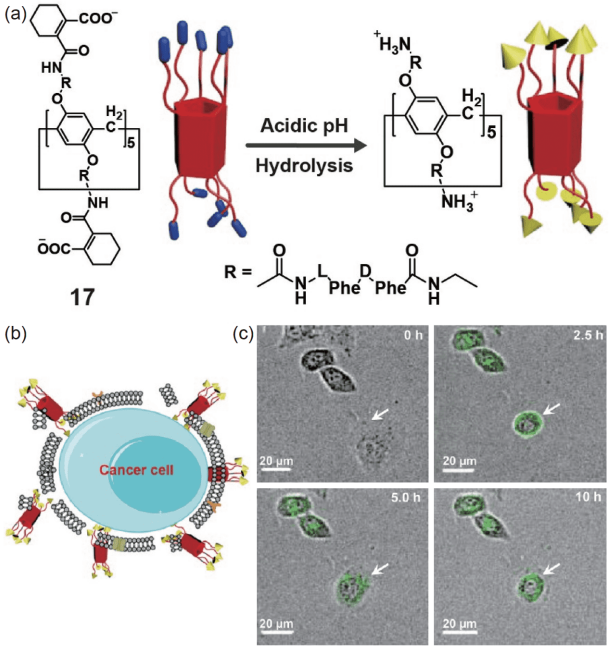


Figure 18 (a) Mechanism of charge reversal process of **17**. (b) Cartoon representation of the interactions between **17** and cancer cell membrane. (c) CLSM images of HepG2 cells upon treatment with 5 μM of **17** after a certain period. Reproduced with permission from ref. [74]. Copyright (2019), American Chemical Society (color online).

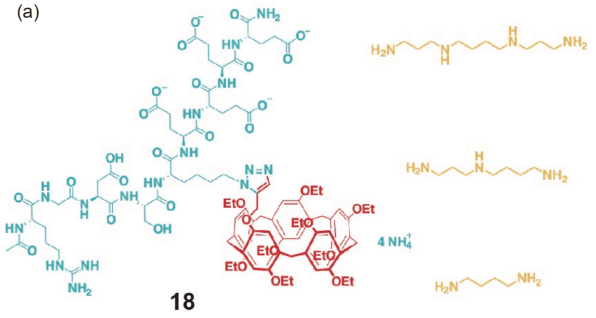
Besides, decorated RBC exhibited prolonged circulation capability, which was suitable for continuous detoxification. Compared to the injection of free **WP6**, treatment with **WP6**@JDA@RBC achieved lung and kidney protection without obvious systematic toxicity. These engineered RBC can perform as a potentially clinical strategy for early-staged paraquat detoxification.

5.3 Pillararene derivatives as anticancer molecules

In virtue of facile functionalization, pillararenes can be substituted with any desired group for manifold functions, supporting rationally designed pillararenes for prospective anticancer activity. Tailoring pillararenes with multiple cationic substitutions showed great potential for binding cell membranes and inducing cell death *via* a synergistic effect of multi-positive charges. During this procedure, reducing cytotoxicity to normal cells is the hinge. To improve the cancer cell targeting ability, Zhang and co-workers [78] designed a charge-reversal amphiphilic pillararene derivative (**17**) for selectively eliminating cancer cells (Figure 18). Note that the anionic heading group synthesized from 1,2-dicarboxylic-cyclohexene anhydride is a pH-sensitive moiety that hydrolyses in an acidic microenvironment and produces a cationic ammonium head, accomplishing charge reversal. Examining the zeta potential of nanoaggregates from **17** at pH 6.5 evidenced the charge changes from the negative state to the positive state, whereas assemblies at pH 7.4 hold negative charges. Such a pH-responsive charge-reversal property is crucial for selectivity towards cancer cells. Owing to exposed cationic head groups in the acidic tumor region, positively charged hosts bind cell membranes by electrostatic interactions followed by insertion into membranes, resulting in membrane disruption. Further experiments illustrated tumor targeting and antitumor abilities accompanied with limited systematic toxicity of **17**, broadening the scope of anticancer drugs.

Apart from directly killing cancer cells, regulating intracellular molecules that are critical for cell survival is also a viable way for designing antitumor systems. Essential molecules including ATP, oxygen, and carbohydrates for cell proliferation and metabolism have been regarded as targets. Recently, Li *et al.* [79] proposed a supramolecular trap for depleting intracellular polyamines such as spermine, spermidine and putrescine by host-guest recognitions of pillar[5]arene (Figure 19). Rapidly growing cancer cells need a higher amount of polyamines for division than normal cells, and thus depletion of polyamines can induce the apoptosis of cancer cells. A peptide-pillararene conjugate (**18**) was designed as the supramolecular trap with the peptide sequence consisted of RGD for cancer cell-specific internalization and anionic EEEE residue for enhanced complexation. Studies of host-guest recognition suggested high affinities to polyamines, which was further evidenced by *in vitro* experiments, where enzymes for polyamine biosynthesis were overexpressed after incubation with **18**. More importantly, *in*

(a)



(b)

IC50 values of 18 against selected cell lines (μM)

Tumor types	Cell lines	IC_{50} (μM) P1P5A
Breast cancer	MCF-7	18.40
Glioma	C6	30.16
	U87	22.53
Neuroma	Neuro-2a	8.52
Lung cancer	A549	34.81
Hepatocellular carcinoma	HepG-2	30.85
Normal	LO2	49.17
	HUVEC	52.15

Figure 19 (a) Chemical structures of **18** and polyamines. (b) IC_{50} values of **18** against selected cell lines. Reproduced with permission from ref. [75]. Copyright (2020), Nature Publishing Group (color online).

vivo experiments demonstrated that **18** inhibited the growth of several tumor models with low systematic toxicity and prolonged median survivals of the tumor-bearing mice. This supramolecular trap proved the potentials of macrocyclic derivatives instead of assemblies as antitumor agents.

6 Summary and outlooks

In summary, we reviewed the recent progress in the bioapplications of pillararene-based supramolecular systems. Useful features of pillararenes, including rigid structures, facile functionalization, high affinities to various guests, and good biocompatibility, have attracted considerable interest, as they are promising candidates for the construction of novel and high-performance functional systems. Theranostics and other bio-related applications are desired directions of pillararene-based systems. Owing to multiple non-covalent interactions, pillararenes strongly hold their position in fabricating self-assemblies, hybrid materials and even therapeutic host-guest complexes with high stability and controllability, which are highly favorable for bioapplications. The most popular bioapplication is using pillararene-based self-assemblies as nanocarriers to deliver hydrophobic drugs with enhanced water solubility and stability. Similarly, this strategy is also useful for the encapsulation of photosensitizers for phototherapies. In addition, modifying pillararenes with bioactive groups broaden the scope of function accompanied by enhanced bioactivity because of the synergic effect of multiple substitutions. All these examples indicate that pillararene-based supramolecular systems are rising stars in both the chemistry and the biology fields. Besides, compared with other macrocycles, pillararenes integrally possess easy functionalization, high guest affinity and broad guest structures. Pillararene-based supramolecular systems also exhibit dynamic and reversible nature that potentially has better controllability and degradability than covalent-bonded systems.

Although lots of excellent reports have been published based on the supramolecular systems of pillararenes showing high therapeutic efficiency and biocompatibility, it is still difficult to push these theranostics towards real applications and clinical research. Several approaches may be addressed to get closer to clinical applications including: first, investigations of larger pillar[*n*]arenes (n>6) may help to associate bulky drug molecules for better solubility and stability as these pillararenes have larger cavities. Second, applying more noncovalent interactions and even covalent linking in supramolecular self-assemblies can improve the *in vivo* stability of nanostructures, which further prevents unwanted drug release. Third, the target ability can be improved by testing different functionalizations on the pillarene systems especially when it comes to possible adjuvant effect for immunotherapy. Finally, rigorous *in-vivo* testing can be applied to understand the interaction of pillararenes with biointerfaces, which can figure out the biological safety of pillararenes. Doing *in-vitro* testing can give us more information about a system but it is less critical than *in-vivo* testing when it comes to clinical translation. The era of supramolecular systems like pillararenes to be used in multiple biomedical applications is just starting with a little less than a decade under the belt. There is definitely plenty of room for this field of research to grow in order to significantly understand the actual role that supramolecular macrocycles can play in the clinical field in the near future.

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Conflict of interest The authors declare no conflict of interest.

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