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Photodynamic therapy with photodegradable photosensitizers

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Photodegradable photosensitizers have gained significant attention in recent years due to their potential advantages in photodynamic therapy. By degrading upon light exposure, these photosensitizers reduce post-treatment drug residues, minimize toxicity, and enhance the safety and precision of therapy. This review provides an overview of the design and current applications of photodegradable photosensitizers, addressing challenges related to light absorption efficiency, toxicity of degradation products, and tissue penetration. Furthermore, future optimization strategies, including chemical modifications, nanocarrier integration, and combination therapies, are discussed.

1 Introduction

Since the introduction of light into modern medicine in the 19th century, significant advances have been made in medical technology, driven by a deeper understanding of light and light-matter interactions. Dr Niels Finsen, who pioneered the use of ultraviolet (UV) light to treat lupus vulgaris, was awarded the Nobel Prize in Physiology or Medicine in 1903.[1,2] The rapid development of photochemotherapy (PUVA) in the 1970s, particularly with the combination of psoralen and ultraviolet A (UVA) for treating psoriasis and vitiligo, marked another milestone.[3] In the 21st century, clinical equipment based on laser diagnosis and treatment has advanced significantly, and modern light therapy is flourishing. Owing to the unique benefits of phototherapy, including anti-tumour and antibacterial activity, non-invasiveness, and spatiotemporal selectivity, it has become a widely studied modality in areas such as cancer therapy, drug-resistant bacterial infections, fungal diseases, and skin disorders.[4–7]

Photodynamic therapy (PDT) operates through the interaction of a photosensitizer, light at a specific wavelength, and oxygen. After selective absorption by target tissues (*e.g.*, tumour cells), the photosensitizer is activated by light, transitioning to an excited state. It then interacts with oxygen molecules to generate singlet oxygen ($^1O_2$) and other reactive oxygen species (ROS), which cause oxidative damage to cellular membranes, proteins, and DNA, ultimately inducing apoptosis or necrosis. Additionally, PDT triggers localized inflammation and immune responses, aiding in the clearance of remaining diseased cells.[8,9]

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Although phototherapy has rapidly advanced in the fields of anti-tumour and antibacterial treatments, many methods have yet to achieve clinical translation. This challenge is closely tied to the limitations of photosensitive materials (photosensitizers) during treatment. For instance, the hypoxic environment within tumours constrains the effectiveness of photodynamic therapy (PDT). These issues can be addressed by employing targeted delivery strategies, developing self-luminescence systems, or combining photocatalytic therapy for PDT. Additionally, integrating phototherapy with other treatment modalities can help enhance its clinical efficacy.[10]

Despite significant efforts toward the development of more efficient and versatile photosensitizers, several inherent limitations continue to impede the clinical advancement of phototherapy. For instance, photodynamic therapy (PDT) has been reported to cause early side effects in the treatment of skin diseases, including pain, erythema, contact dermatitis, and immunosuppression, as well as delayed side effects such as scarring and hyperpigmentation. A particularly concerning issue is the potential for phototherapy to induce or stimulate skin cancer. Furthermore, conventional photosensitizers, which are often in a constantly active state and exhibit low metabolic rates, can cause unintended damage post-therapy.[11–13]

While recently developed activatable photosensitizers have improved the selectivity and safety of phototherapy to some extent,[14] the problem of residual photosensitizers remains unresolved. Upon re-exposure to light, these residual photosensitizers may still generate reactive oxygen species (ROS), causing further damage to healthy tissues and cells. This risk forces patients to remain in low-light environments for extended periods following clinical phototherapy, significantly reducing treatment efficiency and patient compliance. Therefore, optimizing photosensitizer design to minimize adverse

reactions during phototherapy is of critical importance, both for advancing scientific research and improving clinical outcomes.

2 Photodegradable photosensitizers: an innovative approach

Photobleaching refers to the phenomenon where fluorescent molecules or photosensitizers gradually lose their ability to emit light after repeated exposure to excitation light.[15–18] During this process, chemical changes occur in the molecular structure, leading to the loss of fluorescence or other optical properties. This is a common occurrence for dyes under light irradiation. Besides the intrinsic properties of the photosensitizer, the photobleaching rate also depends on the surrounding environment. In many applications, such as fluorescence detection or imaging, photobleaching is undesirable, and efforts are made to enhance the photostability of photosensitizers for more accurate results.[19]

However, in the context of phototherapy discussed in this article, photobleaching serves as a double-edged sword. On one hand, excessively rapid photobleaching may reduce the therapeutic efficacy. On the other hand, residual photosensitizers post-therapy can pose safety risks. Therefore, the optimal scenario for photobleaching is when the photosensitizer "self-degrades" after achieving high therapeutic efficiency, thereby minimizing the side effects of phototherapy and enhancing patient safety.

A novel approach to addressing these challenges is the development of photodegradable photosensitizers. These photosensitizers are designed to break down after exerting their therapeutic effects, thus reducing the risk of residual toxicity. By incorporating controlled photodegradation mechanisms, this strategy ensures that photosensitizers self-degrade once their therapeutic function is complete, thereby minimizing post-treatment side effects and improving the overall safety profile of phototherapy. This emerging technique offers a promising avenue for achieving both high efficacy and enhanced safety in clinical applications (Fig. 1).

2.1 Advances in phototherapy using photodegradable photosensitizers

Cyanine polyene is a crucial fluorescent moiety widely used in the design of small-molecule photosensitizers for photodynamic therapy. While it offers strong light absorption and fluorescence properties, one of its major limitations is susceptibility to photobleaching, which can reduce its effectiveness over prolonged light exposure during treatment. Overcoming this limitation is key to enhancing its clinical utility in PDT applications. Schnermann *et al.*[20] have elucidated the mechanisms underlying the photodegradation of cyanine-like fluorophores (Fig. 2A). These mechanisms include: (1) photoinduced self-degradation, where the chemical instability of the photosensitizer under light induces structural changes *via* photooxidation, leading to degradation; (2) ROS (reactive oxygen species)-triggered

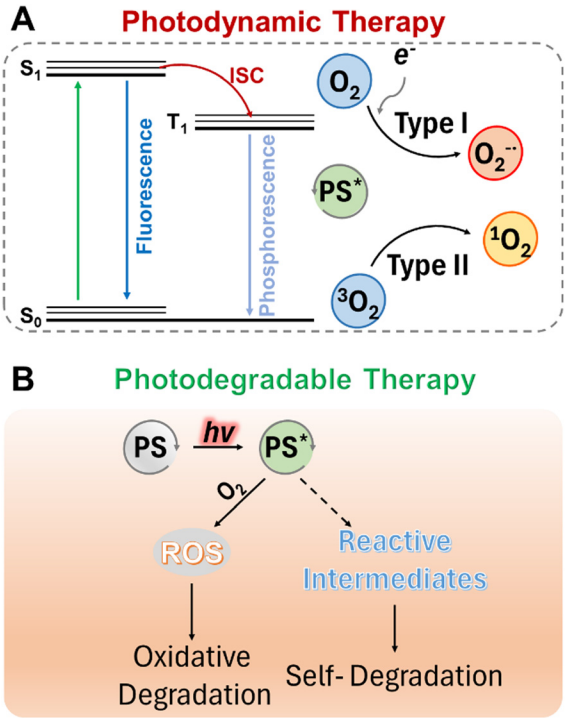

Fig. 1 Mechanisms of photodynamic therapy (A) and photodegradable therapy (B).

self-degradation, in which ROS generated by the photosensitizer upon irradiation react with specific molecular groups, resulting in structural breakdown and degradation; and (3) electron transfer-triggered self-degradation, where electron transfer between the photosensitizer triplet state and oxygen produces reactive species such as superoxide radicals, initiating self-degradation. Below, we summarize recent advancements in the development of photodegradable photosensitizers.

2.1.1 Photodegradable small-molecule photosensitizers. Thiocarbonyl compounds have emerged as a promising class of photosensitizers (PS) due to their heavy atom-free nature, low cytotoxicity, and excellent performance under hypoxic conditions. As type I photosensitizers, they offer distinct advantages, including effective reactive oxygen species generation and reduced potential side effects, making them suitable for photodynamic therapy in challenging tumour microenvironments. Sun *et al.*[21] developed novel thiocarbonyl compounds based on a heavy atom-free methylene blue (MB) structure, exhibiting high ROS production and low cytotoxicity. The results showed that the thioketone and thioester structures oxidize to carbonyl groups upon light irradiation, and the degradation products are minimally toxic. This offers a straightforward solution to the issue of PS residue without compromising PDT efficiency (Fig. 2B).

In recent years, transition metal complexes, particularly Ru(II) complexes, have demonstrated significant potential as photosensitizers (PS) for photodynamic therapy (PDT). Their appeal stems from unique photophysical, photochemical, and electrochemical properties, as well as their structural diversity, enabling tailored designs for enhanced therapeutic

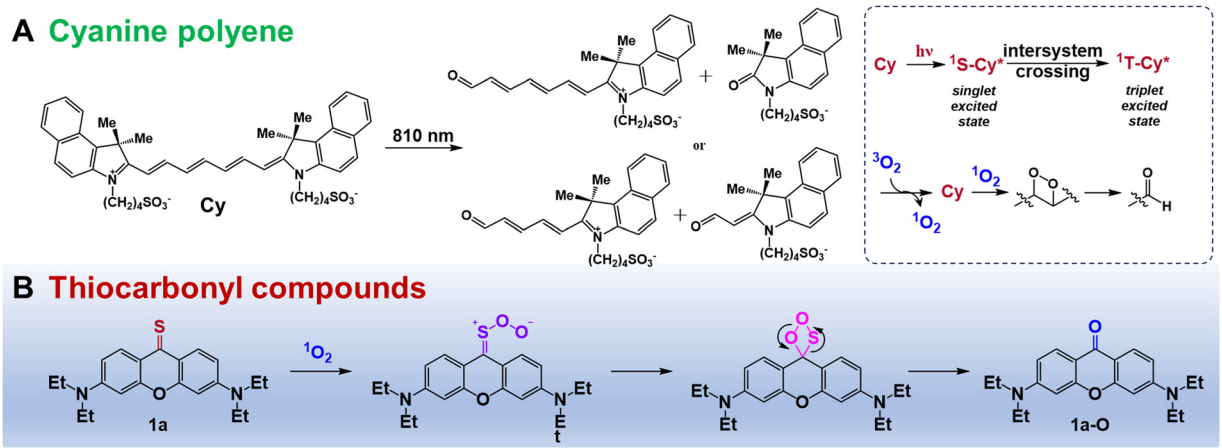

Fig. 2 The photodegradation mechanism of action of cyanine polyene (A) and thiocarbonyl compounds (B).

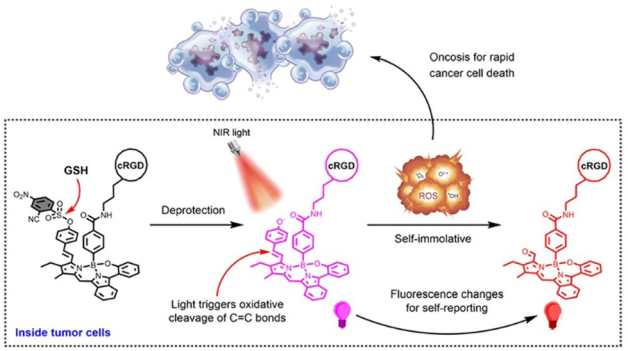

Fig. 3 Photooxidative cleavage of C=C bonds as an effective strategy to develop self-reporting self-immolative photosensitizers in cancer cells. Figure adapted from ref. 23 Copyright: 2023, with the permission from American Chemical Society.

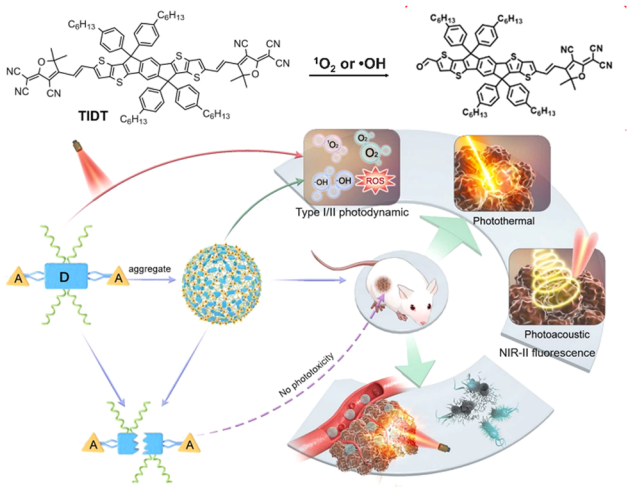

Fig. 4 Structures of TIDT and schematic illustration of photodegradation strategy for antibacterial and cancer phototherapy. Figure adapted from ref. 26 Copyright: 2024, with the permission from Elsevier.

performance. Zhou *et al.*[22] designed and synthesized a novel BODIPY-modified Ru(II) photosensitizer, demonstrating high PDT activity under both normoxic and hypoxic conditions, with a high singlet oxygen yield (Φ = 0.7 in CH_3CN) and excellent superoxide radical ($O_2^{\bullet-}$) generation. It effectively kills cancer cells with low dark toxicity and shows solvent-dependent photodegradation in water. Oxygen presence may accelerate the photolysis process, though the exact mechanism remains unclear.

Accurate assessment of the timing, location, and dosage of photosensitizers is crucial for optimizing treatment efficacy while minimizing toxicity and side effects. Precise monitoring ensures that the photosensitizers are activated in the target tissue at the appropriate moment, reducing off-target effects and enhancing therapeutic outcomes. Zhang *et al.*[23] designed a novel self-immolative photosensitizer based on the photodegradation of traditional photosensitizers, generating a large amount of reactive oxygen species *via* photo-regulated oxidative cleavage of C=C bonds for cancer phototherapy. Red-emitting products are produced during photolysis, enabling real-time monitoring of the photosensitizer's activity. Additionally, glutathione (GSH)-responsive groups were introduced to achieve tumour-specific activation, enhancing phototherapy selectivity (Fig. 3). The presence of oxygen and elevated GSH levels in the tumour microenvironment were found to accelerate the photolysis process.

NIR-absorbing photosensitizers are often formulated as nanoparticles (NPs),[24,25] which are more challenging to photodegrade than their monomeric forms. Liu *et al.*[26] investigated the photodegradation effects in both monodisperse and aggregate states, designing a new A–D–A skeleton photosensitizer that exhibited excellent photosensitivity and photothermal properties. This photosensitizer could oxidize both monodisperse and aggregated states through ROS generated by light. However, the specific degradation mechanisms and products remain largely unexplored (Fig. 4).

Photosensitizers with responsive degradation properties are still rare, primarily due to the absence of a universal design strategy. Additionally, identifying the fragmented components

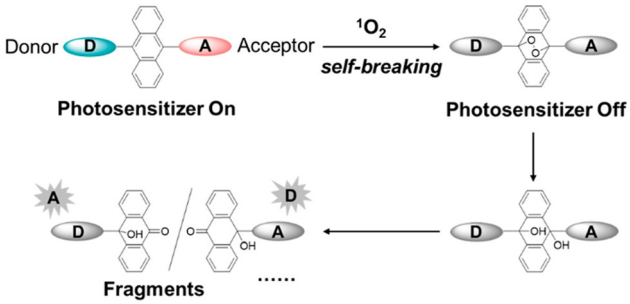

Fig. 5 Chemical structure of anthracene-bridged D–A PSs and self-degradation mechanism. The generated $^1O_2$ could oxidize the anthracene to get the endoperoxide- and anthrone-derived fragments, which break the photosensitizing capacity. Figure adapted from ref. 27 Copyright: 2023, with the permission from American Chemical Society.

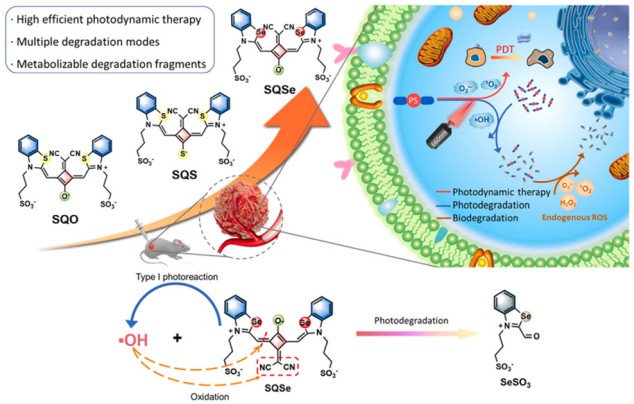

Fig. 6 Schematic illustration of SQO, SQS and SQSe with multiple degradation modes for postoperatively safe PDT. And proposed mechanism for the photodegradation of SQSe. Figure adapted from ref. 28 Copyright: 2023, with the permission from Elsevier.

from decomposed photosensitizers is challenging, hindering the understanding of their pharmacokinetics. Most organic photosensitizers are constructed using π-conjugated units for light absorption and orbital energy regulation. When the π-system is disrupted, ROS generation capacity is lost. For example, anthracene, a π-conjugated unit, is oxidized by singlet oxygen ($^1O_2$) into anthracene peroxides, which further decompose into anthraquinone and oxanthracene. Liu *et al.*[27] developed a series of highly responsive degradable D–A photosensitizers using anthracene as a π-bridge. Coupling D–A units at positions 9 and 10 of anthracene introduces steric hindrance, distorting the π-conjugation and separating the HOMO and LUMO distributions. This increases ROS production for efficient PDT. Simultaneously, the generated singlet oxygen ($^1O_2$) oxidizes anthracene, breaking the π-conjugation, thereby eliminating ROS generation capacity and reducing post-PDT phototoxicity (Fig. 5).

Conjugated double bonds, due to their low bond energy and electron delocalization, are prone to nucleophilic and electrophilic attacks, radical addition, and oxidation reactions, offering potential for instability and degradability. Squaric acid, with its multi-double bond structure, has been used as a π-bridge to design fluorophores and photosensitizers with long-wavelength absorption (600–700 nm). Squaric acid offers several advantages as a biodegradable π-bridge: (1) its substituents can be modified to create photosensitizers more suitable for hypoxic tumour environments; (2) squaric acid dyes are typically hydrophilic, small, and easily metabolized along with their degradation products; (3) the multiple functional groups in squaric acid enable easy adjustment of its photosensitivity and metabolic characteristics. Li *et al.*[28] designed and synthesized several near-infrared-emitting photosensitizers capable of producing various reactive oxygen species (ROS) under light exposure. Singlet oxygen and superoxide anion radicals were used to kill cancer cells, while hydroxyl radicals facilitated the rapid degradation of the photosensitizers. The degradation products were excreted in urine, as confirmed by both *in vivo* and *in vitro* experiments (Fig. 6).

Tetrapyrrole-based photosensitizers, some of which are clinically approved, are effective in PDT. However, few design strategies consider the link between their molecular structure and self-degradation, which could reduce long-term toxicity. Zhang *et al.*[29] developed a new class of porphyrinolactone photosensitizers and their zinc complexes, which exhibited strong NIR absorption, high fluorescence, and efficient ROS generation. The lactone structure enabled *in situ* conversion into non-cytotoxic products. Using isotopic tracers, they revealed the oxidative degradation mechanism of the photosensitizers, identifying superoxide rather than singlet oxygen as the key intermediary. This system demonstrated effective therapeutic results, rapid metabolism, and minimal phototoxicity (Fig. 7).

2.1.2 Photodegradable polymer photosensitizers. Conventional conjugated polymers are typically non-biodegradable, leading to prolonged metabolic retention and potential adverse side effects. Wei *et al.*[30] developed a self-degrading conjugated polymer based on aggregation-induced emission (AIE) and imidazole units, which demonstrated excellent superoxide anion ($O_2^{-\bullet}$) generation. The generated $O_2^{-\bullet}$ further degrades the imidazole units in CP1, forming biocompatible small molecules that lose the ability to produce ROS under light irradiation (Fig. 8).

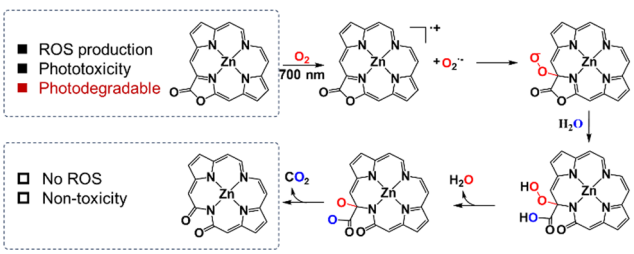

Fig. 7 Schematic illustration of conversion from ZnBPL to ZnBPD. Figure adapted from ref. 29 Copyright: 2022, with the permission from John Wiley and Sons.

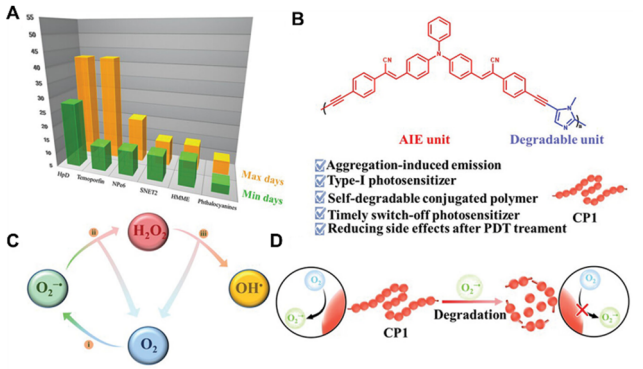

Fig. 8 (A) Therapeutic time in dark room of commercial PSs. (B) $O_2^{-\bullet}$-driven cellular cascaded bio-reactions for reducing the O_2 demand of PDT. (i) Type-I photodynamic process; (ii) disproportionation reaction; (iii) Haber–Weiss/Fenton reaction. (C) Molecular structure of self-degradable conjugated polymer (CP1) with multifunctional performances. (D) Schematic illustration of $O_2^{-\bullet}$ generation from CP1 before and after degradation. Figure adapted from ref. 30 Copyright: 2022, with the permission from John Wiley and Sons.

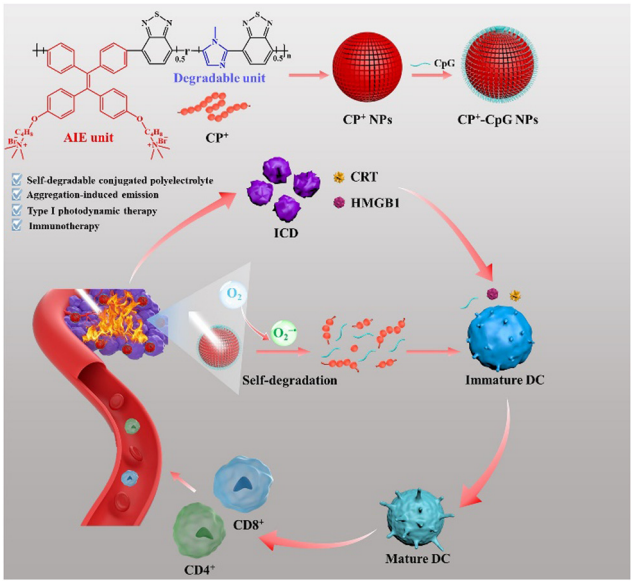

Fig. 9 Schematic illustration of the preparation procedure and the mechanism of CP^+-CpG NPs on the synergistic treatment of PDT and immunotherapy. Figure adapted from ref. 34 Copyright: 2023, with the permission from Elsevier.

Effective cancer therapy should not only target the primary tumour but also stimulate systemic anti-tumour immunity to provide long-term tumour resistance. Immunogenic cell death (ICD) has emerged as a promising concept in cancer treatment. Although certain photodynamic therapy processes have been reported to induce ICD in cancer cells,[31–33] only a few photosensitizers can trigger ICD by inducing oxidative stress. Wei *et al.*[34] developed a self-degrading conjugated polyelectrolyte for photodynamic therapy, incorporating an AIE group and imidazole unit, and capable of loading immunoadjuvants. The positively charged surface of the polyelectrolyte enables electrostatic adsorption of negatively charged cytosine-phosphoguanine (CpG), significantly enhancing cellular uptake. During the photodynamic process, superoxide anion radicals degrade the nanoparticles, resulting in the *in situ* release of CpG, which initiates a robust anti-tumour immune response (Fig. 9).

2.1.3 Supramolecular photodegradable photosensitizers. Supramolecular methods offer another approach to constructing photodegradable materials. These assemblies, stabilized by weak non-covalent interactions, are easily modulated by external stimuli and typically consist of small molecules, favoring the disassembly process. Despite advances in photoresponsive supramolecular assemblies, more efficient photodegradable materials are still needed. Among non-covalent interactions, macrocyclic molecules have garnered significant attention in molecular recognition and assembly due to their host–guest properties, symmetrical structure, adjustable molecular size, and ease of modification.[35–37] *p*-Sulfonatocalix[*n*]arenes (SCnAs), with their high water-solubility and biocompatibility, can modulate the aggregation behavior of aromatic or amphiphilic molecules by lowering the critical aggregation concentration and enhancing aggregate density—this phenomenon is termed calixarene-induced aggregation (CIA). Liu *et al.*[38] constructed a photodegradable supramolecular assembly using SC4A as the host and amphiphilic 9-alkoxy-substituted AnPy as the photoactive guest. SC4A induced tight anthracene packing and inhibited fluorescence quenching of AnPy, enhancing photosensitization. In the presence of exogenous photosensitizers, these assemblies demonstrated effective photolysis under visible light, marking the first report of such a photo dissociable supramolecular system (Fig. 10). The authors proposed two potential mechanisms for the observed photolysis: (1) increased oxygen solubility and/or extended singlet oxygen

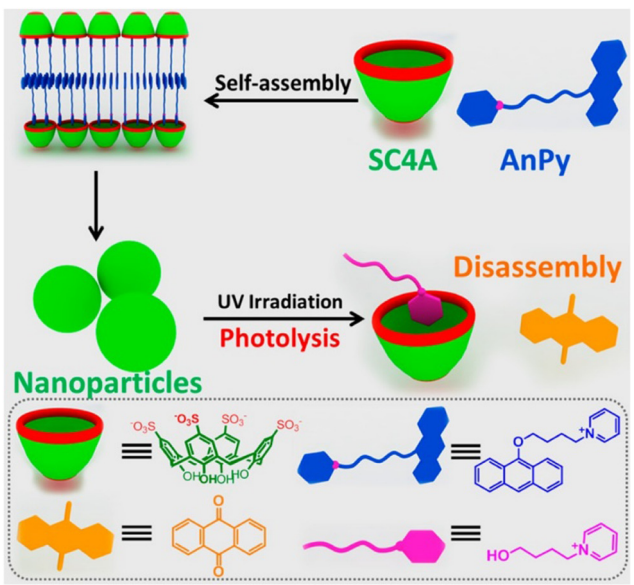

Fig. 10 Schematic illustration of the photolyzable supramolecular amphiphilic assembly. Figure adapted from ref. 38 Copyright: 2015, with the permission from American Chemical Society.

lifetime in the hydrophobic core compared to bulk water; (2) tight anthracene packing within the SC4A-AnPy assembly enhanced interaction with singlet oxygen, facilitating further autoxidation, as photosensitization efficacy relies on proximity to the target.

Pillararenes, a novel class of macrocycles with symmetric columnar frames and π-rich cavities, offer versatile platforms for functional supramolecular materials. Wang *et al.*[39] introduced a photodegradable bola-type super amphiphile featuring 9,10-dialkoxy-anthracene groups and rod-like coil molecules at the ends. These assemblies formed supramolecular complexes with WP5 (pillar[5]arene)-induced aggregation, significantly enhancing photolysis efficiency. Additionally, WP5-G aggregates, co-assembled with exogenous photosensitizers (eosin Y, ESY), exhibited effective decomposition under visible light, confirming that stable singlet oxygen within the aggregates promoted photolysis (Fig. 11). This approach holds promise for applications in phototherapy. Liu *et al.*[40] introduced an innovative method for the efficient photolysis of BODIPY dyes *via* WP5-triggered free radical reactions based on the structure of pillar aromatic compounds. Unlike Wang *et al.*, controlled experiments demonstrated that this photodecomposition process, induced by free radicals, is independent of supramolecular interactions, offering a novel strategy for the efficient photolysis of organic dyes.

Cucurbit[*n*]urils (CB[*n*]), a class of highly symmetric macrocycles made of glycoluril units, can stabilize or activate organic radicals through host–guest complexation in a reversible, controllable, and adaptive manner. Zhang *et al.*[41] explored a cationic iodo-BODIPY derivative with a benzyl group (BDP2IPh)

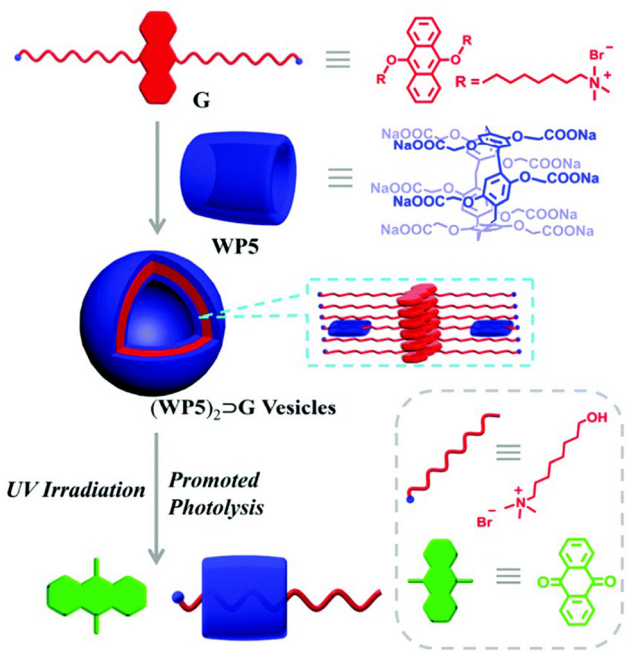

Fig. 11 Schematic illustration of the photolyzable supramolecular amphiphilic assembly. Figure adapted from ref. 39 Copyright: 2016, with the permission from Royal Society of Chemistry.

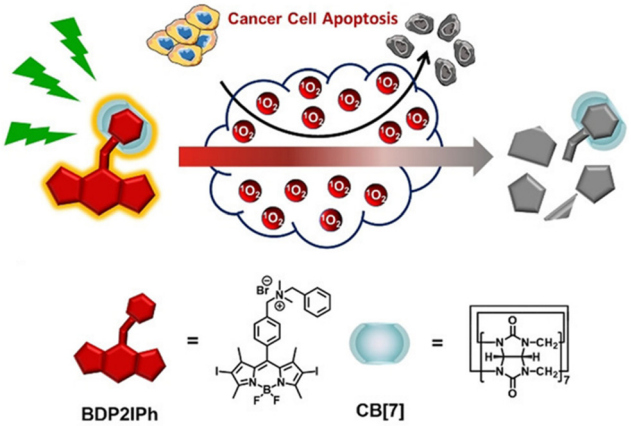

Fig. 12 BDP2IPh and CB[7]: self-degradation pathway for cancer cell apoptosis in photodynamic therapy. Figure adapted from ref. 41 Copyright: 2022, with the permission from John Wiley and Sons.

as a supramolecular photosensitizer in complex with CB[7], characterized by isothermal titration calorimetry (ITC) in ultrapure water. This supramolecular photosensitizer exhibited the same photodynamic therapeutic efficiency but superior biocompatibility compared to the photosensitizer alone. Furthermore, after photodynamic therapy (PDT), the supramolecular complex degraded *via* self-generated ROS, losing its PDT activity, highlighting its potential for safe and efficient cancer treatment (Fig. 12).

2.2 Challenges and potential optimization directions

Compared with the conventional chemotherapy and radiotherapy, the most important clinical therapeutic of PDT lies in the spatiotemporal selectivity towards lesion site while minimizing damage to the surrounding healthy tissues. In addition, PDT is valued for repeatable treatment, low risk, low drug resistance and broad-spectrum against various cancers and infection diseases. However, the residual photosensitizers post treatment may cause damage to normal tissues during systematic circulation and metabolism in the body, due to the non-degradability and slow metabolic rates of photosensitizers. Traditional PSs, especially those that absorb near-infrared light, can be particularly problematic due to their high phototoxicity, as most of the energy of sunlight falls within the phototherapeutic window ranging between 650–850 nm. For example, the clinical used PSs, such as Photofrin and Temoporfin, *etc.*, retain long-lasting photosensitization and have a long clearance time *in vivo*, thus the patients should avoid direct exposure of the skin and eyes to sunlight or strong indoor light sources for several days to weeks after PDT treatment.[28] As a result, the clinical application of PDT is constrained by limited tissue penetration of light and the risk of phototoxic reactions post-treatment, including skin reactions, burning sensations, oxygen dependent-mechanism of action, pain, infection risk, scarring, eye sensitivity, allergic reactions, and prolonged sun sensitivity. Though the severity and occurrence of these side effects vary among individuals, these side effects are primarily due to subsequent

generation of reactive oxygen species, poor tumour selectivity of the PSs, slow metabolic rate, light dosage, and treatment area.[11–13]

To address the above challenges, it's necessary to design novel PSs with the hope to conquer the historical photosensitive reactions that have plagued PDT for over a century. The ideal next-generation PSs should not only effectively produce ROS for high therapeutic efficacy but also undergo rapid metabolism after PDT treatment, thereby mitigating the side effects associated with traditional PSs and improving the safety of phototherapy. This suggests developing a feasible approach to eliminate PS residues in PDT, which is crucial for enhancing the clinical application and safety of phototherapy.

During the past few years, the academic community has witnessed the development of effective and degradable photosensitizers, which is key to promote the clinical application of photodynamic therapy and enhance biosafety. Biodegradable small molecular PS that can be oxidized by substances in the biosystem has been developed. The photodegradation and metabolic pathways of small molecule PSs can be easily analysed by liquid chromatograph mass spectrometer and nuclear magnetic resonance spectroscopy. A specific example given is the water-soluble ZnBPL, which has shown effective therapeutic outcomes, fast metabolism, and minimal phototoxic reactions, despite the degradable mechanism of action should be verified by the relatively complicated isotope labeling.[29] While this strategy reduces phototoxicity to some extent, it does not completely eliminate the risk during the long-term degradation process. Furthermore, the dicyano-modified squaraine PSs SQSe has been designed to enhance NIR absorption and prone to carbon–carbon double bond initiated electrophilic addition, radical addition reaction by superoxide anion during PDT.[28] Importantly, the photodegradation rate and degradation fragments in buffer solution as well as *in vivo* biodegradation and blood biochemical analysis post-treatment were comprehensively investigated to identify the biosafety of SQSe. This study provides a typical example for the discovery of degradable small molecule PS.

In addition to promising photodegradation property, the tumour targeting capability of PSs is another important factor that should be concerned. The phototoxic side effects of traditional PSs are mainly due to low tumour targeting efficiency, which consequently leads to damage to normal tissue.[10] For example, the PpIX prodrug 5-aminolevulinic acid (5-ALA) can be absorbed by rapid proliferating cancer cells and then converted into protoporphyrin IX in mitochondria.[42] However, due to such passive diffusion mechanism, 5-ALA can also be taken up by normal cells, despite the intracellular concentration of PpIX is relatively lower than that in cancer cells. In contrast, NG-cRGD functionalized with c(cRGD) and GSH response functional group provides an example for precise tumour targeting and photodegradable PDT, which may promote the development of precision and personalized photo-medicine. The cyclic pentapeptide of NG-cRGD can specifically bind tumour cells over-expressed integrin $\alpha\nu\beta3$ while the glutathione-responsive group ensure subsequently activated by the high concentration glutathione in cancer cells.[23] Similar to SQSe, NG-cRGD can undergo photodegration *via* light-manipulated oxidative cleavage of C=C bonds. With such self-immolative and photodegradable PSs, NG-cRGD has the potential to visualize the therapeutic process and precisely regulate treatment outcomes for precision and personalized medicine.

Apart from small molecular PSs, photodegradable polymer nanoparticles have also been developed for photodegradable PDT. Nanomaterials exhibit tumour targeting efficiency due to the enhanced permeability and retention effect.[43] Until now, only two polymer nanoparticles functionalized by triphenylamine or tetraphenylethylene have been reported for photodegradable PDT.[30,34] Photosensitizers generally show great tendency for self-aggregation in aqueous media, leading to quenched fluorescence and lower photosensitizing ability. However, both of the polymer PSs showed typical AIE properties, which can overcome the self-aggregation induced excited state quenching and lower photosensitizing ability of small molecular PSs. However, it's necessary to mention that AIE polymer PSs may be challenge for photodegradation process, since aggregation will improve photostability and avoid ROS degradation. Moreover, in contrast to small molecule PSs, nanomaterials contain extended and heterogeneous polymeric chains, which make it much more complicated to identify the degradation mechanism, *in vivo* metabolism profile and evaluate the cytotoxicity of the degraded products towards normal cells. The contemporary research emphasis mainly focus on the development of polymers capable of undergoing oxidative scission by reactive oxygen species. It's necessary to clarify the structural features of photodegraded polymer products and evaluate biosafety profiles in the future. In addition, most of these polymer PSs absorb short wavelength light, with limited photodegradation efficiency under NIR light. Therefore, there is a necessity to develop NIR light activated photodegraded polymer PSs for safe and effective PDT.

Differ from polymer PSs, supramolecular assembly established *via* multiple weak intermolecular interactions provide another strategy to void self-aggregation of hydrophilic PSs. Host–guest complexation is particularly convenient and advantageous in constructing water-soluble supramolecular architectures.[35–37] Typical water-soluble and photolysable supermolecule PSs architectures use the amphiphilic anthracene or BODIPY type PSs as the guest and SCnAs, CB[n] or CB[n] as the host.[38–41] The supramolecular assembly systems showed highly photoreactive and photolysis with visible light during PDT, despite that short wavelength visible light is needed to excite the PSs and limited cancer targeting efficiency. Though supramolecular assembly extended the design of photodegradable PDT, photodegradable supermolecular system with high tumour targeting ability and strong near-infrared light triggered therapeutic efficiency still remain to be discovered.

The photodegradable PSs or system reviewed above require a strict balance between the photoreactivity and photodegrading rate of PSs. However, as the old saying goes, no one can have the cake and eat it too. In this case, blocking the phototoxicity of PSs after PDT treatment maybe an alternative solution to

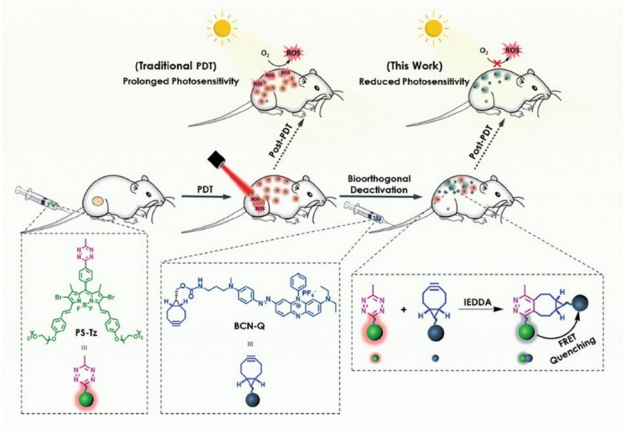

Fig. 13 Working principle of the bioorthogonal antidote **BCN-Q** for deactivation of the residual photosensitizer **PS-Tz** after the photodynamic treatment. Figure adapted from ref. 44 Copyright: 2024, with the permission from John Wiley and Sons.

enhance the safety of PDT. Ng *et al.* proposed a novel bioorthogonal chemistry strategy, where PSs will be inactivated by an antidote containing quencher.[44] This strategy can neutralize the photosensitization activity of PSs under physiological conditions without disrupting natural biochemical processes (Fig. 13). However, though the reaction yield and selectivity of bioorthogonal chemistry are high in biological environments without side reactions, it's still very challenging to achieve 100% quenching of PSs in extremely complicated pathological environments. In addition, the introduction of quencher and formation of the bioorthogonal adduct make it even more complicated to evaluate the safety, toxicity and drug metabolism than small self-photodegradable PSs.

It introduces tumor-targeting functional groups to NIR-absorbing PSs and develop intelligent PSs specifically activated by tumour microenvironment (*e.g.*, pH, over-expressed protein or enzymes) to enhance the targeting efficiency in complex pathological environments.

3 Summary and outlook

In this review, we have highlighted the potential of photodegradable photosensitizers to enhance the safety profile of photodynamic therapy (PDT). These photosensitizers degrade upon light activation, reducing the accumulation of residual substances post-treatment, and thereby minimizing potential side effects. With advancements in photodegradable photosensitizers, not only can the specificity and efficacy of phototherapy be improved, but photochemical stability and degradation kinetics can also be optimized through structural modifications and fine-tuning of reaction conditions.

Despite promising results from both *in vitro* and *in vivo* studies, several challenges remain. First, a thorough evaluation of the toxicity of the degradation products is crucial to ensure safety in clinical applications. Second, the degradation rate must be synchronized with the therapeutic window to maintain treatment efficacy. Furthermore, enhancing the light absorption efficiency and tissue penetration depth of these photosensitizers will be critical areas for future research.

The integration of novel materials and nanotechnology is expected to further advance the field of photodegradable photosensitizers, especially in precision medicine. For example, the combination of photosensitizers with smart nanocarriers could enable controlled release and targeted delivery. Additionally, the development of multifunctional photosensitizers will likely expand their applications in theragnostic. We believe that photodegradable photosensitizers hold significant potential to revolutionize both the safety and effectiveness of PDT and other phototherapy modalities.

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Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 R. Roelandts, *J. Am. Acad. Dermatol.*, 2002, **46**, 926–930.
2 K. I. Møller, B. Kongshoj, P. A. Philipsen, V. O. Thomsen and H. C. Wulf, *Photodermatol., Photoimmunol. Photomed.*, 2005, **21**, 118–124.
3 M. A. Pathak and T. B. Fitzpatrick, *J. Photochem. Photobiol., B*, 1992, **14**, 3–22.
4 D. Dolmans, D. Fukumura and R. K. Jain, *Nat. Rev. Cancer*, 2003, **3**, 380–387.
5 K. Liu, Y. L. Liu, Y. X. Yao, H. X. Yuan, S. Wang, Z. Q. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 8285–8289.
6 X. S. Li, H. T. Bai, Y. C. Yang, J. Y. Yoon, S. Wang and X. Zhang, *Adv. Mater.*, 2019, **31**, 1805092.
7 J. P. Celli, B. Q. Spring, I. Rizvi, C. L. Evans, K. S. Samkoe, S. Verma, B. W. Pogue and T. Hasan, *Chem. Rev.*, 2010, **110**, 2795–2838.
8 U. Chilakamarthi and L. Giribabu, *Chem. Rec.*, 2017, **17**, 775–802.
9 S. Kwiatkowski, B. Knap, D. Przystupski, J. Saczko, E. Kędzierska, K. Knap-Czop, J. Kotlińska, O. Michel, K. Kotowski and J. Kulbacka, *Biomed. Pharmacother.*, 2018, **106**, 1098–1107.
10 X. Y. Deng, Z. W. Shao and Y. L. Zhao, *Adv. Sci.*, 2021, **8**, 2002504.
11 F. Borgia, R. Giuffrida, E. Caradonna, M. Vaccaro, F. Guarneri and S. P. Cannavò, *Biomedicines*, 2018, **6**(1), 12.
12 S. H. Ibbotson, T. H. Wong, C. A. Morton, N. J. Collier, A. Haylett, K. E. McKenna, R. Mallipeddi, H. Moseley, L. E. Rhodes, D. C. Seukeran, K. A. Ward, M. F. M. Mustapa and L. S. Exton, *Br. J. Dermatol.*, 2019, **180**, 715–729.
13 S. Ibbotson, *Photochem. Photobiol. Sci.*, 2018, **17**, 1885–1903.
14 J. C. Gao, Y. Tian, Y. G. Li, F. Hu and W. B. Wu, *Coord. Chem. Rev.*, 2024, **507**, 215756.
15 R. Bonnett and G. Martínez, *Tetrahedron*, 2001, **57**, 9513–9547.
16 J. S. Dysart and M. S. Patterson, *Photochem. Photobiol. Sci.*, 2006, **5**, 73.
17 C. X. Duan, V. Adam, M. Byrdin, J. Ridard, S. Kieffer-Jaquinod, C. Morlot, D. Arcizet, I. Demachy and D. Bourgeois, *J. Am. Chem. Soc.*, 2013, **135**, 15841–15850.
18 A. P. Demchenko, *Methods Appl. Fluoresc.*, 2020, **8**, 022001.

19 T. Komatsu, D. Oushiki, A. Takeda, M. Miyamura, T. Ueno, T. Terai, K. Hanaoka, Y. Urano, T. Mineno and T. Nagano, *Chem. Commun.*, 2011, **47**, 10055–10057.
20 A. P. Gorka, R. R. Nani and M. J. Schnermann, *Org. Biomol. Chem.*, 2015, **13**, 7584–7598.
21 T. G. Chen, X. Q. Zhang, J. F. Ge, Y. J. Xu and R. Sun, *Spectrochim. Acta, Part A*, 2022, **270**, 120783.
22 Y. T. Peng, X. W. Da, W. P. Zhou, Y. L. Xu, X. L. Liu, X. S. Wang and Q. X. Zhou, *Dalton Trans.*, 2024, **53**, 3579–3588.
23 C. F. Wang, Y. J. Sun, S. J. Huang, Z. X. Wei, J. Y. Tan, C. F. Wu, Q. Chen and X. J. Zhang, *J. Am. Chem. Soc.*, 2023, **145**, 13099–13113.
24 X. Y. Li, X. D. Guo, L. X. Cao, Z. Q. Xun, S. Q. Wang, S. Y. Li, Y. Li and G. Q. Yang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7809–7813.
25 D. Casanova, D. Giaume, M. Moreau, J. L. Martin, T. Gacoin, J. P. Boilot and A. Alexandrou, *J. Am. Chem. Soc.*, 2007, **129**, 12592–12593.
26 H. Y. Chen, S. J. Yan, L. Zhang, B. Zhao, C. Q. Zhu, G. W. Deng and J. Liu, *Sens. Actuators, B*, 2024, **405**, 135346.
27 J. C. Gao, H. Yang, Y. R. Lu, Q. K. Shi, S. D. Xu, W. B. Wu, F. Hu and B. Liu, *Chem. Mater.*, 2023, **35**, 1229–1237.
28 Y. G. Li, P. Zhang, Y. J. Xie, J. P. Yang, Y. Q. Yang, L. L. Shi, W. B. Wu and Z. Li, *Biomaterials*, 2023, **299**, 122182.
29 M. L. Zhu, H. Zhang, G. L. Ran, Y. H. Yao, Z. S. Yang, Y. Y. Ning, Y. Yu, R. J. Zhang, X. X. Peng, J. H. Wu, Z. F. Jiang, W. K. Zhang, B. W. Wang, S. Gao and J. L. Zhang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204330.
30 H. Y. Huang, W. S. Xie, Q. Wan, L. C. Mao, D. N. Hu, H. Sun, X. Y. Zhang and Y. Wei, *Adv. Sci.*, 2022, **9**, e2104101.
31 C. Chen, X. Ni, S. R. Jia, Y. Liang, X. L. Wu, D. L. Kong and D. Ding, *Adv. Mater.*, 2019, **31**, 1904914.
32 X. D. Li, M. Y. Guo and C. Y. Chen, *Chem. Res. Chin. Univ.*, 2021, **37**, 83–89.
33 J. C. Li, D. Cui, J. G. Huang, S. S. He, Z. B. Yang, Y. Zhang, Y. Luo and K. Y. Pu, *Angew. Chem.*, 2019, **131**, 12810–12817.
34 H. Y. Huang, W. S. Xie, D. N. Hu, X. Z. He, R. X. Li, X. Y. Zhang and Y. Wei, *Chem. Eng. J.*, 2023, **451**, 138617.
35 Y. Liu, C. Y. Yu, H. B. Jin, B. B. Jiang, X. Y. Zhu, Y. F. Zhou, Z. Y. Lu and D. Y. Yan, *J. Am. Chem. Soc.*, 2013, **135**, 4765–4770.
36 D. S. Guo and Y. Liu, *Chem. Soc. Rev.*, 2012, **41**, 5907–5921.
37 D. S. Guo, T. X. Zhang, Y. X. Wang and Y. Liu, *Chem. Commun.*, 2013, **49**, 6779–6781.
38 Y. X. Wang, Y. M. Zhang and Y. Liu, *J. Am. Chem. Soc.*, 2015, **137**, 4543–4549.
39 S. W. Guo, X. Liu, C. H. Yao, C. X. Lu, Q. X. Chen, X. Y. Hu and L. Y. Wang, *Chem. Commun.*, 2016, **52**, 10751–10754.
40 H. F. Zhang, L. Wang, P. Y. Dong, S. Q. Mao, P. Mao and G. X. Liu, *RSC Adv.*, 2021, **11**, 7454–7458.
41 B. Yuan, H. Wu, H. Wang, B. H. Tang, J. F. Xu and X. Zhang, *Angew. Chem., Int. Ed.*, 2021, **60**, 706–710.
42 M. Ishizuka, F. Abe, Y. Sano, K. Takahashi, K. Inoue, M. Nakajima, T. Kohda, N. Komatsu, S. Ogura and T. Tanaka, *Int. Immunopharmacol.*, 2011, **11**, 358–365.
43 Y. Takakura and Y. Takahashi, *J. Controlled Release*, 2022, **350**, 486–493.
44 E. Y. Xue, C. X. Yang, Y. M. Zhou and D. K. P. Ng, *Adv. Sci.*, 2024, **11**, 2306207.