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Structural design of porous organic polymers to mitigate π-stacking-induced quenching in porphyrin/phthalocyanine photosensitizers for enhanced antibacterial activity

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Porphyrins and phthalocyanines are cornerstone molecular architectures for photodynamic therapy (PDT), organic photovoltaics, and artificial photosynthesis, prized for their exceptional photophysical properties. However, their extended planar π-conjugated systems inevitably induce aggregation-caused quenching (ACQ) through strong π–π stacking interactions, severely diminishing critical performance metrics like photothermal conversion efficiency and reactive oxygen species (ROS) generation. Porous organic polymers (POPs) have emerged as a transformative platform to overcome this limitation, offering unique capabilities for spatially isolating these photoactive units while maintaining structural integrity and enabling precise porosity control. This comprehensive review systematically analyzes structure-property relationships in porphyrin/phthalocyanine-based POPs. It presents detailed case studies showcasing effective π-stacking suppression strategies and offers forward-looking perspectives for designing next-generation materials optimized for photophysical performance. Key design strategies include host–guest architectures (*e.g.*, β-cyclodextrin-threaded Por-CD-COF), modulating interlayer spacing to enhance photodynamic efficiency, stereochemical engineering (*e.g.*, isomeric iso-CMPs), leveraging steric hindrance to prevent π-stacking while amplifying enzyme-mimetic activities, and dynamic covalent linkages (*e.g.*, imine/boronate bonds), enabling stimuli-responsive chromophore repositioning, multi-component hybrids (*e.g.*, MOF@COF heterostructures), integrating catalytic cores with photoactive shells for synergistic performance enhancement. By summarizing key advances and providing forward-looking perspectives, this review aims to inspire the rational design of next-generation POP-based materials with optimized photophysical properties, paving the way for their broader application in antimicrobial therapy, energy conversion, and beyond.

1 Introduction

Antibiotic resistance (AMR), termed a "silent pandemic" by the WHO, poses a critical global health crisis.[1–3] It directly causes approximately 1.27 million deaths annually, with projections indicating this could soar to 10 million by 2050 without intervention, potentially exceeding cancer mortality and incurring immense economic costs.[4] This crisis stems from decades of antibiotic overuse and misuse in human medicine (*e.g.*, unnecessary prescriptions) and agriculture (*e.g.*, growth promotion), creating vast reservoirs of resistant bacteria and exerting relentless selective pressure.[5] Consequently, multidrug-resistant "superbugs" proliferate, including pathogens resistant to last-resort antibiotics like colistin.[6] With the pipeline for new conventional antibiotics critically depleted, the urgent need for novel antibacterial strategies operating *via* distinct, resistance-circumventing mechanisms is paramount.[7]

In response, numerous antibiotic-free therapeutic alternatives have emerged after years of development, including phototherapy, enzyme therapy, gas therapy, metal ions therapy, cationic therapy, and ultrasonic therapy.[8–13] Among these, antimicrobial phototherapy stands out as a highly promising strategy. It utilizes specific light wavelengths to eliminate pathogens through physicochemical mechanisms, offering a significantly reduced propensity to induce classical genetic resistance compared to traditional antibiotics.[14] Phototherapy, particularly photodynamic therapy (PDT) and photothermal therapy (PTT), has emerged as a promising therapeutic modality due to three distinctive advantages of precise

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spatiotemporal control, non-invasive nature, and localized therapeutic effects.[15] These modalities demonstrate unique activation mechanisms. PDT generates cytotoxic reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$) through photosensitizer-mediated energy transfer, while PTT induces localized hyperthermia *via* efficient photothermal conversion.[16,17] Unlike conventional chemotherapy or radiotherapy which often cause systemic toxicity, both PDT and PTT offer targeted therapeutic effects that are strictly confined to illuminated areas, thereby significantly reducing damage to surrounding healthy tissues.[18] This activation specificity stems from their fundamental working principle that therapeutic effects occur only when and where both photosensitizers and appropriate light irradiation are present simultaneously.[19]

Despite its recognized therapeutic benefits, phototherapy faces several translational challenges that limit its broader clinical adoption. The primary constraint is limited tissue penetration. Visible light (400–700 nm) typically reaches depths of only 1–3 mm. While near-infrared light (700–1100 nm), which can penetrate 5–10 mm, requires photosensitizers specifically optimized for these wavelengths.[20] A further complication arises from the risk of post-treatment photosensitivity, since certain photosensitizers may persist in the skin and induce sunburn-like reactions upon subsequent light exposure.[21] Perhaps the most fundamental bottleneck, however, is the oxygen-dependent mechanism of conventional photodynamic therapy. This dependency severely compromises efficacy in hypoxic environments such as infected wounds, representing a critical limitation that remains to be fully addressed.[22,23] Consequently, developing novel strategies and materials to overcome these limitations constitutes a pivotal direction in the future advancement of phototherapeutic technologies.

2 Porphyrins and phthalocyanines: excellent photosensitizers with inherent aggregation challenges

Porphyrins and phthalocyanines represent two of the most versatile and widely studied molecular frameworks in modern materials science and photochemistry.[24,25] Their unique electronic structures, characterized by highly conjugated macrocyclic systems with delocalized π-electrons, endow them with exceptional light-harvesting capabilities, tunable redox properties, and long-lived excited states.[26] These attributes have established them as indispensable components in a broad spectrum of applications, ranging from biomedical therapies to renewable energy technologies.[27] In PDT, for instance, these chromophores serve as efficient PSs capable of generating cytotoxic ROS upon light irradiation.[28]

Despite their exceptional photophysical properties, porphyrin and phthalocyanine-based systems are fundamentally limited in practical applications by their strong propensity for π–π stacking aggregation. This aggregation-caused quenching (ACQ) phenomenon severely diminishes both photothermal conversion efficiency and photodynamic activity.[29] In photodynamic therapy (PDT), for example, ACQ directly compromises therapeutic efficacy by reducing the yield of ROS.[30] The root of this issue lies in the planar, extended π-conjugated structures of these molecules, which promote intense intermolecular interactions in condensed phases.[31] Consequently, despite optimal molecular designs for light absorption and charge transfer, their solid-state performance is often unsatisfactory.[32]

Conventional approaches to mitigate ACQ primarily rely on steric hindrance, such as attaching bulky substituents or constructing dendritic frameworks, to physically separate the π-systems.[33] While partially effective, these modifications often come with trade-offs, including altered electronic properties, compromised solubility, or reduced loading capacity in composite matrices.[34] Alternative strategies, like encapsulating chromophores within rigid hosts (*e.g.*, metal–organic frameworks or silica), can provide spatial isolation but may inadvertently limit porosity and mass transport.[35] These limitations highlight an urgent need for innovative material platforms that can suppress ACQ without sacrificing key functionalities.

The conventional view of molecular aggregation as a purely detrimental phenomenon is being redefined. It is now recognized that specific aggregation forms, particularly well-defined J-aggregates with characteristic absorption in the 700–730 nm range, can be strategically engineered to direct excited-state dynamics. Such J-aggregates effectively shift the dominant ROS generation pathway from the oxygen-dependent Type II process toward Type I mechanisms, yielding radical species including superoxide ($O_2^{\bullet-}$) and hydroxyl radicals ($^{\bullet}OH$). This pathway switching is especially beneficial for antibacterial PDT under hypoxic conditions, where Type II activity is substantially compromised. However, achieving these functional outcomes, particularly a Type I radical contribution exceeding 60%, demands precise control over molecular and supramolecular organization to steer aggregation into photophysically productive architectures.[36] Accordingly, a central challenge in the field is to develop design strategies that concurrently suppress detrimental ACQ while promoting beneficial J-aggregation with well-defined spectral signatures and high Type I ROS contribution.

In this context, the deliberate extension of the π-conjugated backbone in PSs emerges as a highly promising approach. Rational conjugation engineering not only improves light-harvesting efficiency and promotes intersystem crossing but also offers a versatile route to fine-tune intermolecular interactions in the aggregated state. This strategy enables an optimal balance between monomeric dispersibility and controlled J-aggregation, thereby facilitating efficient energy/electron transfer for enhanced ROS generation. Therefore, the synergistic combination of extended π-conjugation and tailored aggregation guidance represents a forward-looking paradigm for constructing robust and high-performance antibacterial materials, capable of operating effectively across diverse and challenging physiological microenvironments.

3 Porous organic polymers: a transformative platform to address ACQ

Porous organic polymers (POPs) have recently emerged as a groundbreaking platform to address this challenge.[37] As a class of tailor-made functional materials, POPs are characterized by permanent porosity, high specific surface area, and remarkable chemical and thermal stability.[38] Their architectures can be broadly categorized into crystalline covalent organic frameworks (COFs) and amorphous networks, such as hyper-crosslinked polymers (HCPs), conjugated microporous polymers (CMPs), and polymers of intrinsic microporosity (PIMs).[39–42] This structural diversity enables precise tuning of the local environment to achieve optimal chromophore isolation, as demonstrated in several case studies where POPs have significantly enhanced photoluminescence quantum yields, ROS generation, or charge carrier mobility.[43]

The modular nature of POP synthesis allows for deliberate control over pore size, surface area, and functional group distribution, making them ideal scaffolds for immobilizing and isolating photoactive molecules.[44] When porphyrins or phthalocyanines are incorporated as integral building blocks, POPs can effectively suppress detrimental π–π stacking while preserving the intrinsic photophysical properties of the chromophores.[45] Their rigid three-dimensional networks impose spatial separation between aromatic cores, thereby mitigating aggregation-caused quenching (ACQ) without the need for bulky substituents.[46] Additionally, the inherent porosity facilitates efficient diffusion of guest molecules, which is essential for applications in heterogeneous catalysis and gas storage.[47]

Although excellent reviews exist on the general design of POPs, the development of aggregation-induced emission (AIE) photosensitizers, or the use of MOF/COF hybrids in antibacterial therapy, this review offers a unique and timely perspective by focusing on their intersection. Specifically, we present the first systematic analysis of how POPs can be designed to suppress the pervasive ACQ effect in porphyrin and phthalocyanine photosensitizers, a major bottleneck limiting their biomedical performance. Moving beyond a broad overview, we categorize and critically evaluate specific design strategies, including covalent polyrotaxane threading, stereochemical isomer engineering, and spatial distortion control and elucidate their underlying structure–property relationships in enhancing photodynamic and photothermal efficacy. We further link these material-level innovations to their ability to overcome biological barriers in antibacterial therapy, such as hypoxia and biofilm impedance. By concentrating on the role of POP architecture in circumventing ACQ and its implications for antimicrobial applications, this review serves as a targeted resource and a forward-looking guide for developing the next generation of light-activated, non-antibiotic antimicrobial materials.

This review systematically examines the design principles, synthetic routes, and structure–function correlations in porphyrin- and phthalocyanine-based POPs, with an emphasis on their capacity to suppress ACQ and enhance optoelectronic performance. We first outline the origin of ACQ in conventional systems and the limitations of current mitigation strategies. We then discuss how POP frameworks provide a versatile and robust alternative.

Furthermore, we explore emerging strategies for enhancing POP performance, such as post-synthetic modification, hybrid composite formation, and hierarchical pore engineering, which not only counteract ACQ but also introduce advanced functionalities including stimuli-responsiveness and multiphoton absorption. Finally, we offer perspectives on remaining challenges and future opportunities, particularly in the areas of scalable synthesis, material processability, and integration into practical devices. By bridging molecular design with macroscopic performance, this review aims to inspire and direct future research toward the rational construction of next-generation POPs for advanced photonic and electronic applications.

3.1 Host–guest threading strategy for layer spacing regulation

3.1.1 Supramolecular chemistry and polyrotaxane frameworks. Supramolecular chemistry, commonly described as "chemistry beyond the molecular level," represents a paradigm shift in chemical science by focusing on complex systems formed through reversible, non-covalent interactions. This discipline explores intricate molecular assemblies stabilized by multiple interaction modalities, including directional hydrogen bonding networks, hydrophilic/hydrophobic effects, electrostatic (ionic) interactions, metal–ligand coordination, π–π stacking and van der Waals forces, and host–guest molecular recognition.[48] The dynamic and adaptive nature of these interactions enables the formation of sophisticated architectures with emergent properties not found in individual molecular components. This characteristic has propelled supramolecular chemistry to the forefront of interdisciplinary research, bridging fundamental science with cutting-edge applications.[49]

Current research highlights the remarkable versatility of supramolecular chemistry across diverse scientific domains. In advanced materials research, scientists are designing innovative self-healing polymers and stimuli-responsive smart materials.[50] The field of biomedical engineering benefits through the development of precisely targeted drug delivery systems and bioresponsive diagnostic platforms.[51] Nanotechnology applications include the fabrication of sophisticated molecular machines and functional nanostructures with tailored properties.[52] Environmental science applications focus on creating highly selective chemical sensors and advanced separation membranes for pollution control and resource recovery.[53] These wide-ranging applications demonstrate the transformative potential of supramolecular approaches in addressing contemporary scientific and technological challenges.

The field of supramolecular chemistry continues to advance through synergistic integration with multiple disciplines. By combining principles from molecular biology, researchers gain deeper insights into complex biomolecular interactions. Collaboration with materials science enables the development of novel functional supramolecular materials with tailored properties. The integration of computational chemistry provides powerful tools for predicting and analyzing assembly thermodynamics.[54] Furthermore, partnerships with device engineering facilitate the creation of innovative molecular-scale devices.[55] This interdisciplinary approach drives continuous progress in supramolecular chemistry research and applications. This multidimensional approach positions supramolecular chemistry as a cornerstone of modern chemical research, offering solutions to challenges in energy, healthcare, and environmental sustainability. The dynamic equilibrium of non-covalent interactions provides unique advantages in designing adaptive, self-regulating systems that respond to environmental stimuli, a feature increasingly valuable in developing next-generation technologies.

Among various supramolecular systems, polymers formed through orthogonal self-assembly based on host–guest interactions are particularly noteworthy. These systems combine excellent molecular selectivity with environmental responsiveness while preserving the intrinsic reactivity of guest molecules and incorporating the characteristics of macrocyclic hosts.[56] Such properties make supramolecular self-assembly particularly promising for developing COFs with precise spatiotemporal control and stimulus-responsive behavior.[57] However, while host–guest assembly techniques have been widely studied for creating interlocked molecules like rotaxanes, most research has focused on linear polymers, leaving the development of structurally novel COFs through simple methods as an ongoing challenge.

The incorporation of host–guest structures offers a pathway to COFs with distinctive topological features and properties (Fig. 1). Current approaches typically involve chemical modification of macrocycles for specific reactivity before their covalent integration into porous frameworks.[58] This strategy faces limitations, as many functional groups cannot be directly introduced due to structural constraints of macrocycles. Moreover, the development of macrocycle-based COFs is hindered by complex modification processes and low molecular utilization rates. These challenges highlight the need for alternative approaches to create macrocycle-containing framework materials. Notably, expanding

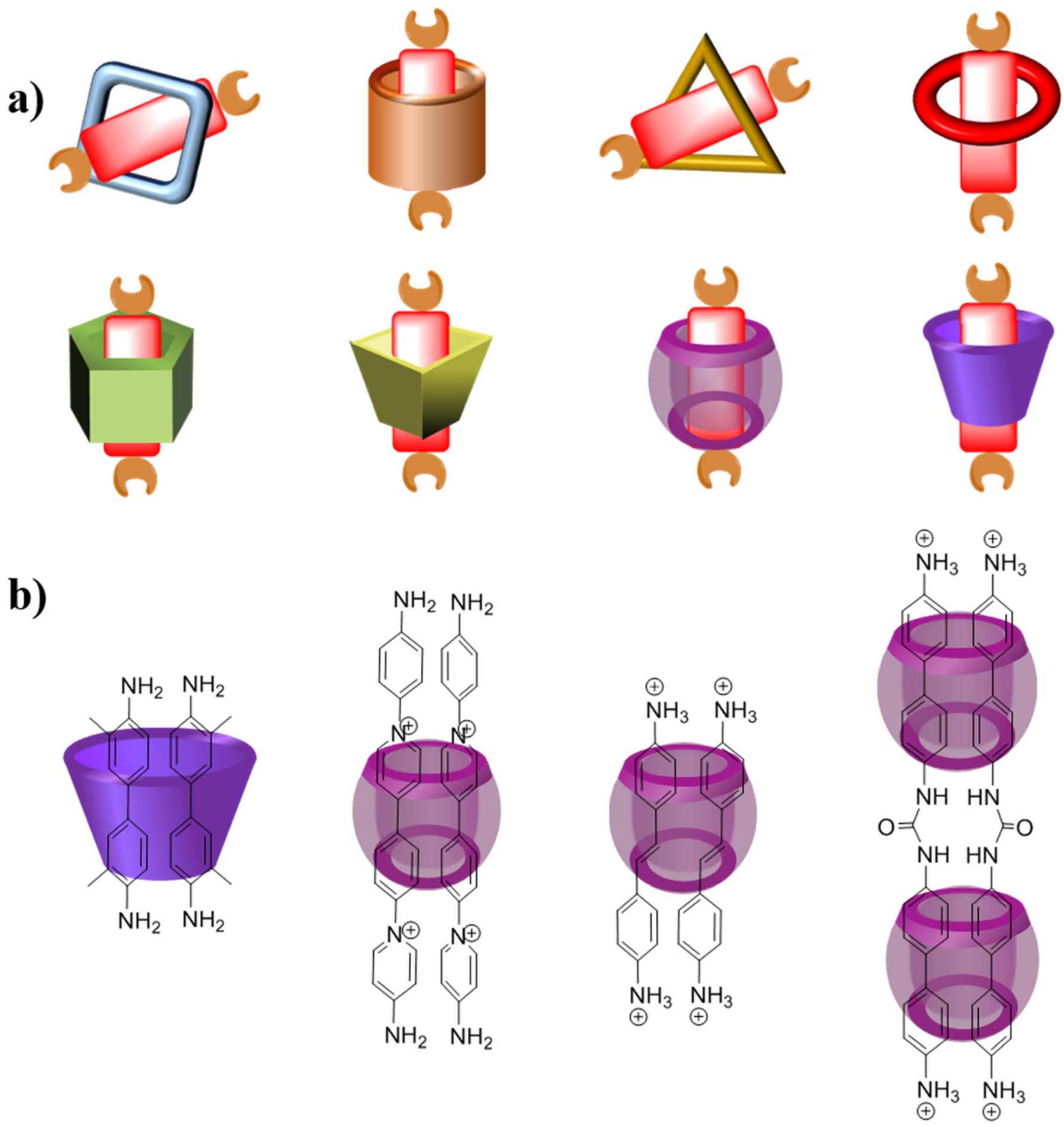

Fig. 1 Possible host–guest complex for the construction of COPRs (a) host–guest complex (1 : 1); (b) host–guest complex (1 : 2 and 2 : 2). Adapted from ref. 57 with permission from Royal Society of Chemistry, *RSC Adv.*, 2024, vol. 14, p. 30077-30083 Copyright 2024.

molecular architectures from discrete points to linear chains and ultimately to planar networks could unlock entirely new material properties and functions.

3.1.2 Strategy of constructing Por-CD-COF *via* β-cyclodextrin (β-CD) threading. Covalent organic polyrotaxanes (COPRs) represent a groundbreaking advancement in COFs, formed through the programmable covalent assembly of pseudorotaxane building blocks with diverse structural units. As an emerging subclass of COFs, COPRs have recently garnered significant attention in materials science due to their unique "hard-soft integration" design strategy.[59] This innovative approach synergistically combines the structural precision of rigid covalent chemistry, and the dynamic adaptability of flexible supramolecular host–guest interactions. This dual integration enables COPRs to function as intelligent materials with exceptional capabilities, including precise generation and detection of molecular signals, sensitive response and amplification of external stimuli and sophisticated structural reorganization in response to environmental changes. The resulting materials exhibit unprecedented control over their architectural properties, making them particularly valuable for advanced applications.[60] Notably, their stimulus-responsive behavior has been successfully implemented in developing multimodal cooperative antibacterial systems, demonstrating the practical potential of these materials.

The Zhou *et al.* pioneered an innovative approach to construct cyclodextrin-incorporated COFs through a sequential mechanochemical-solvothermal synthesis strategy (Fig. 2). By synergistically combining dynamic imine chemistry with host–guest self-assembly, they successfully developed β-cyclodextrin (β-CD)-threaded COFs (Por-CD-COF).[61] The synthesis proceeds through initial formation of pseudorotaxane structures *via* β-CD complexation with aromatic terephthalaldehyde, followed by polymerization with tetraminoporphyrin through mechanochemical grinding and solvothermal crystallization *via* Schiff-base chemistry. The strategic integration of polyrotaxane motifs into the COF architecture delivers multiple structural advantages. This approach enables precise control over interlayer spacing within the π-conjugated framework, effectively preventing photoactivity quenching typically caused by dense π–π stacking while simultaneously optimizing molecular arrangement to enhance photophysical properties. This strategy demonstrates enormous economic and synthetic benefits, which could substantially reduce required porphyrin content (up to 80% reduction), achieving ~5-fold increase in product yield compared to CD-free analogues. Furthermore, the Por-CD-COF system demonstrated remarkable enhancements in both biological performance and antimicrobial mechanisms. Extensive characterization revealed multifaceted improvements, where the incorporated β-CD not only significantly enhanced material biosafety but also exhibited excellent

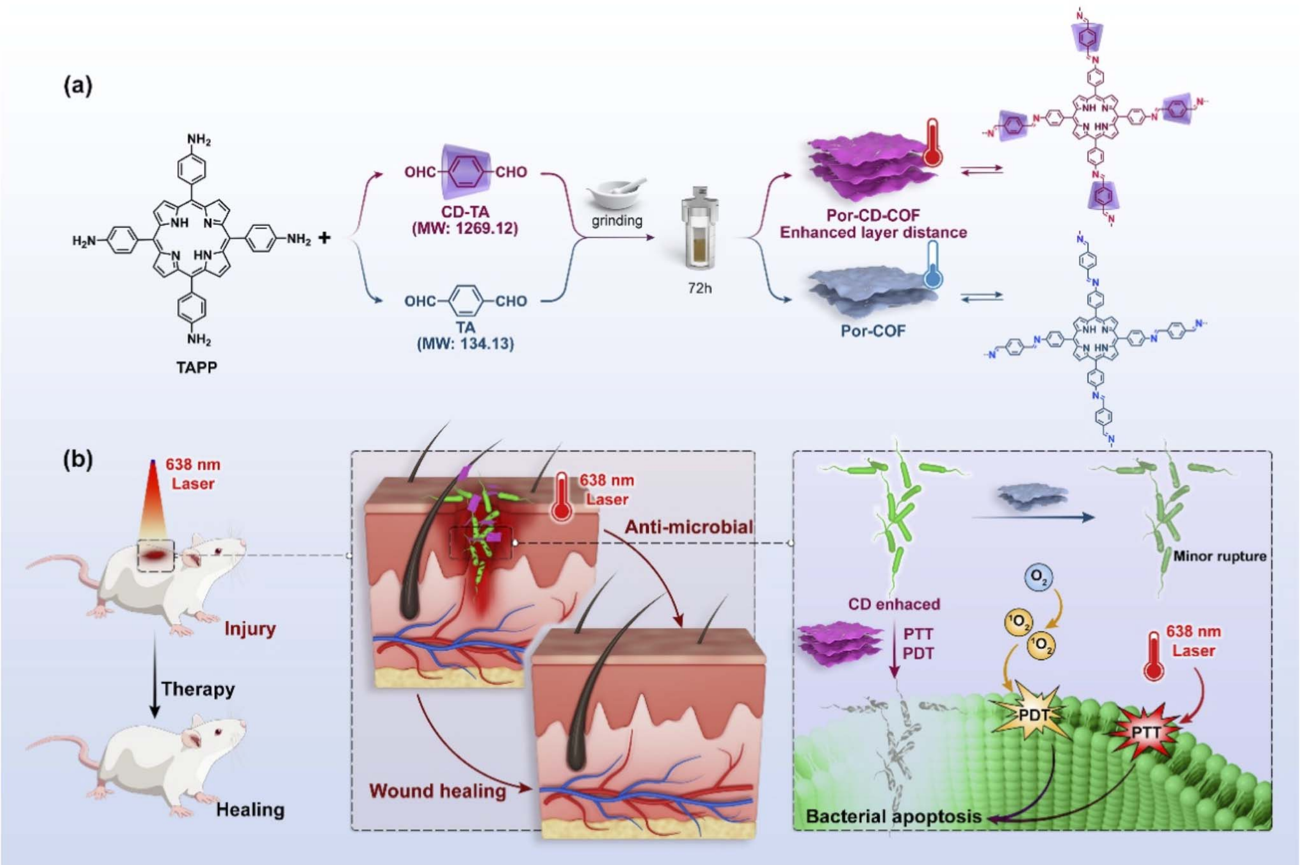

Fig. 2 Schematic illustration of the (a) synthetic pathway and (b) antimicrobial application mechanism of Por-CD-COF, highlighting its multifunctional therapeutic capabilities. Adapted from ref. 61 with permission from Elsevier, *Chem. Eng. J.*, 2024, vol. 486, p. 150345, Copyright 2024.

cytocompatibility across various biological systems. Por-CD-COF exhibits significantly enhanced photothermal and photodynamic therapeutic activities due to its unique β-CD threading mechanism. This structural feature confers three interconnected functional benefits that progressively enhance antibacterial performance. Initially, the threaded β-CD improves bacterial membrane adhesion and concurrently shortens the diffusion path for both ROS and thermal energy. Building on this enhanced interfacial interaction, it further creates a synergistic effect by uniting the intrinsic bacteriostatic property of β-CD with the phototherapeutic action of the COF framework. Collectively, these multi-mechanistic actions culminate in powerfully amplified antibacterial efficacy, enabling the material to achieve potent broad-spectrum activity against diverse bacterial strains including both Gram-positive and Gram-negative bacteria. *In vivo* studies confirmed the outstanding therapeutic performance of Por-CD-COF. The material accelerated wound healing in infected animal models by 40–60% compared to control treatments. It consistently outperformed non-threaded COF counterparts in terms of both antibacterial efficiency and biosafety. Remarkably, Por-CD-COF maintained excellent therapeutic efficacy while reducing photosensitizer dosage requirements by up to 75%. These superior performance characteristics directly result from the material's innovative architecture, which effectively addresses multiple therapeutic challenges in wound management through its integrated design.

The well-defined structure of each component ensures excellent synthetic scalability, and the use of extremely low-cost CD significantly reduces production expenses. However, although solid-phase synthesis is employed, a subsequent solvothermal step is still required, which inevitably involves organic solvents. Therefore, developing green alternatives remains an active research focus.

3.1.3 Strategy of constructing Crown-COPR *via* Crown-ether mechanical interlocking. In a significant advancement, Zhou *et al.* recently pioneered the development of crown ether-based covalent organic polymeric rotaxanes (Crown-COPR) through the polymerization of mechanically interlocked molecules (MIMs), specifically utilizing crown-ether threaded rotaxane building blocks with tetramino-porphyrin.[62] This innovative approach not only modifies the conventional skeleton architecture of COFs but also introduces dynamic mechanical bonds that endow the resulting COPRs with unique functional properties. The synthesized Crown-COPR exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*).This enhanced activity stems from multiple synergistic mechanisms of the inherent antibacterial properties of crown ether moieties, improved bacterial membrane adhesion facilitated by the crown ether structures, and dynamic adjustment of interlayer spacing within the COF framework, which significantly enhances phototherapeutic sensitivity. Further performance optimization was achieved through the incorporation of adaptive multinuclear Zn^{2+} centers, yielding Crown-COPR-Zn. This advanced material demonstrates four synergistic antimicrobial mechanisms: photodynamic therapy (PDT), photothermal therapy (PTT), Zn^{2+} ion toxicity, and crown ether activity, with the added benefit of photo-controlled Zn^{2+} release (Fig. 3). Comprehensive *in vivo* studies confirmed that Crown-COPR-Zn not only effectively eradicates bacterial infections but also significantly accelerates the healing process of infected wounds.

The synthesis strategy demonstrates excellent scalability, enabled by its modular architecture. A mechanochemical pre-assembly step combined with solvothermal crystallization provides a reproducible and scalable route for gram-scale production. The mechanically interlocked structure imparts inherent stability to the framework, reducing the need for strict kinetic control during polymerization. Furthermore, crown ether precursors are commercially available and relatively low-cost compared to many specialized photoactive agents. This threading-based assembly allows precise spatial organization of active sites, resulting in significantly reduction in Zn^{2+} consumption. From an environmental standpoint, the photo-triggered release of Zn^{2+} helps prevent premature metal leaching, while the robust backbone minimizes ecological risks associated with carrier degradation.

3.2 Steric hindrance regulation strategy *via* stereoisomeric engineering

Zhang *et al.* developed a stereochemical engineering strategy that leverages structural isomerism to develop multifunctional nonantibiotic biocides. This approach enables precise modulation of antimicrobial activity through controlled steric hindrance in conjugated microporous polymers (CMPs).[63] Two Fe-phthalocyanine-based CMP isomers (iso-CMP-1 and iso-CMP-2) were synthesized by strategically manipulating the spatial arrangement of reactive groups into neo-iso and *para*-iso configurations. These isomeric polymers demonstrated triple-enzyme-mimetic activities, encompassing peroxidase (POD), oxidase (OXD), and catalase (CAT) (Fig. 3).

These materials demonstrate remarkable adaptability for antibacterial therapy across various wound healing stages. The extended π-conjugation architectures of these iso-CMPs confer broad-band spectral absorption and enhanced photon capture efficiency, synergistically boosting both photothermal and photodynamic performance. Comparative analysis revealed that the neo-iso configuration, with its greater steric congestion, induces significant structural distortion that prevents phthalocyanine π–π stacking while amplifying enzyme-mimetic activities. Mechanistic studies showed the neo-iso stereochemical configuration produces more pronounced structural distortion than the *para*-iso counterpart, thereby disrupting π–π stacking and enhancing peroxidase–mimetic activity.

The iso-CMP system features oxygen-adaptive photodynamic functionality, capable of simultaneously executing Type I and Type II PDT under oxygen-sufficient conditions while selectively activating Type I pathways in hypoxic environments, effectively overcoming oxygen concentration limitations. This system establishes a self-sustaining oxygen metabolic cycle through spatiotemporally programmed enzyme-mimetic cascades: During early infection, the OXD-like activity catalyzes O_2 to generate bactericidal superoxide radicals ($O_2^{\bullet-}$) while producing H_2O_2 Subsequently, CAT-like activity converts accumulated H_2O_2 into O_2, restoring tissue

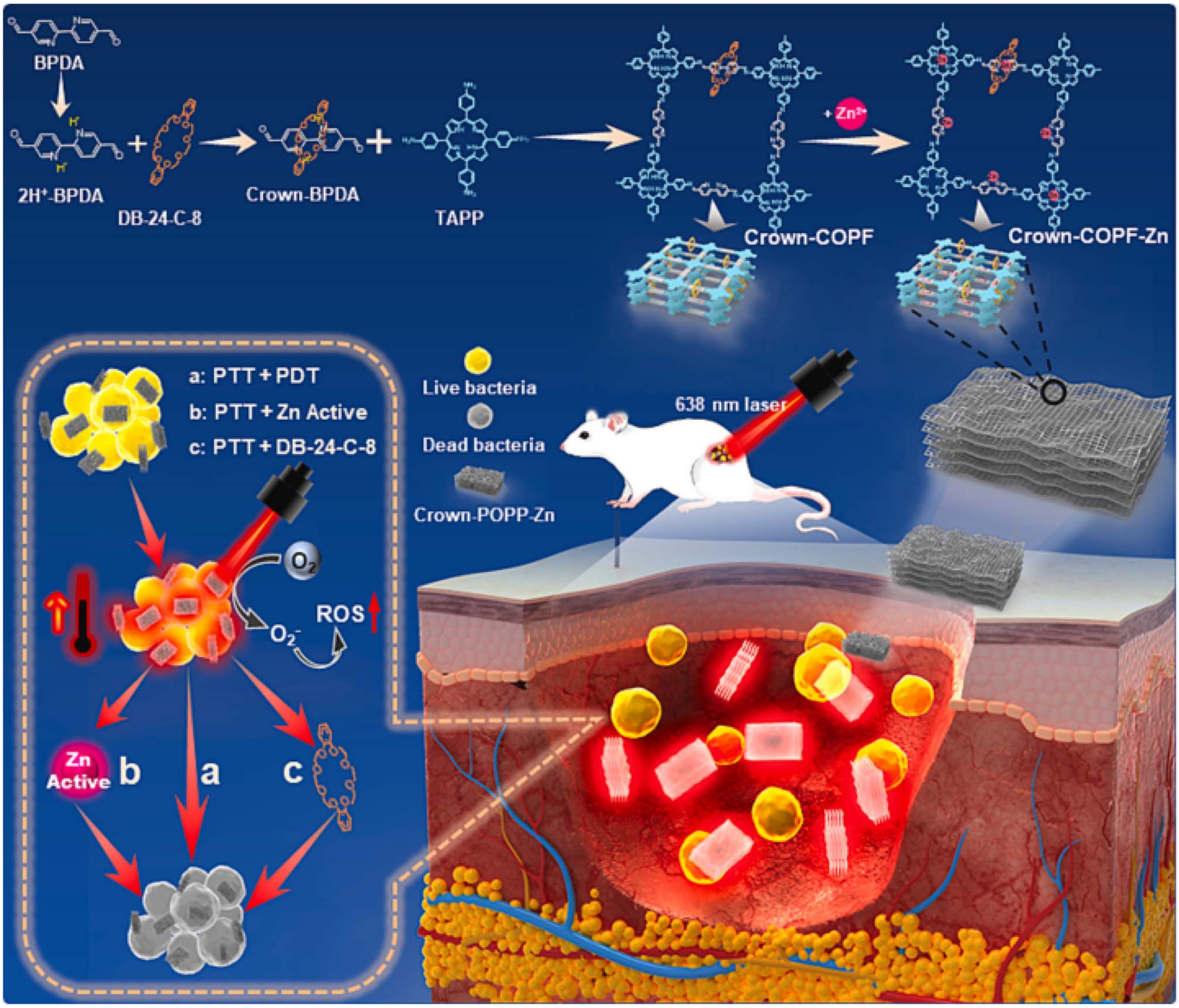

Fig. 3 Schematic diagram of the synthesis and antimicrobial mechanism of Crown-COPR-Zn. PTT, PDT and ROS refer to photothermal therapy, photodynamic therapy, and reactive oxygen species, respectively. Adapted from ref. 62 with permission from Elsevier, *Biomater. Adv.*, 2024, vol. 159, p. 213814. Copyright 2024.

oxygenation and reactivating Type II PDT Meanwhile, POD-like activity processes residual H_2O_2 into $O_2^{\bullet-}$, synergizing with photothermal and PDT effects. This logic-embedded design transforms conventional static materials into intelligent therapeutic systems where bacterial pathogenesis directly triggers self-adaptive antimicrobial responses. The integrated system effectively suppresses bacterial growth and biofilm formation while accelerating wound healing through multiple coordinated mechanisms.

This method adopts an innovative strategy that diverges from conventional approaches by avoiding the use of pre-synthesized, high-cost phthalocyanine monomers as building blocks. Instead, it facilitates the direct formation of phthalocyanine structures during the reaction process. This design considerably streamlines the synthesis, improves overall yield, and lowers production costs. Furthermore, synergistic effects inherent to the process allow for a significant reduction in metal usage, which in turn enhances the biocompatibility of the resulting material. Although the use of organic solvents remains unavoidable in the current protocol, the modular isomer-based synthesis still demonstrates remarkable scalability, supported by reproducible solvothermal conditions and minimal sensitivity to atmospheric variations.

3.3 Stability enhancement strategy *via* flexible linkers and hydrogen-bond interlocking

Xu *et al.* present a hierarchical antimicrobial system that dynamically adapts to the complex pathological microenvironment of infected wounds, overcoming current limitations in antimicrobial efficacy and resistance development. The oxygen-evolving polyphenol-based magnetic porous polymer (FcPor-POP) was rationally designed through three key structural innovations (Fig. 4). At the molecular architecture level, FcPor-POP achieved covalent conjugation of ferrocene-derived enzymatic units with photoactive polyphenol-porphyrin *via*

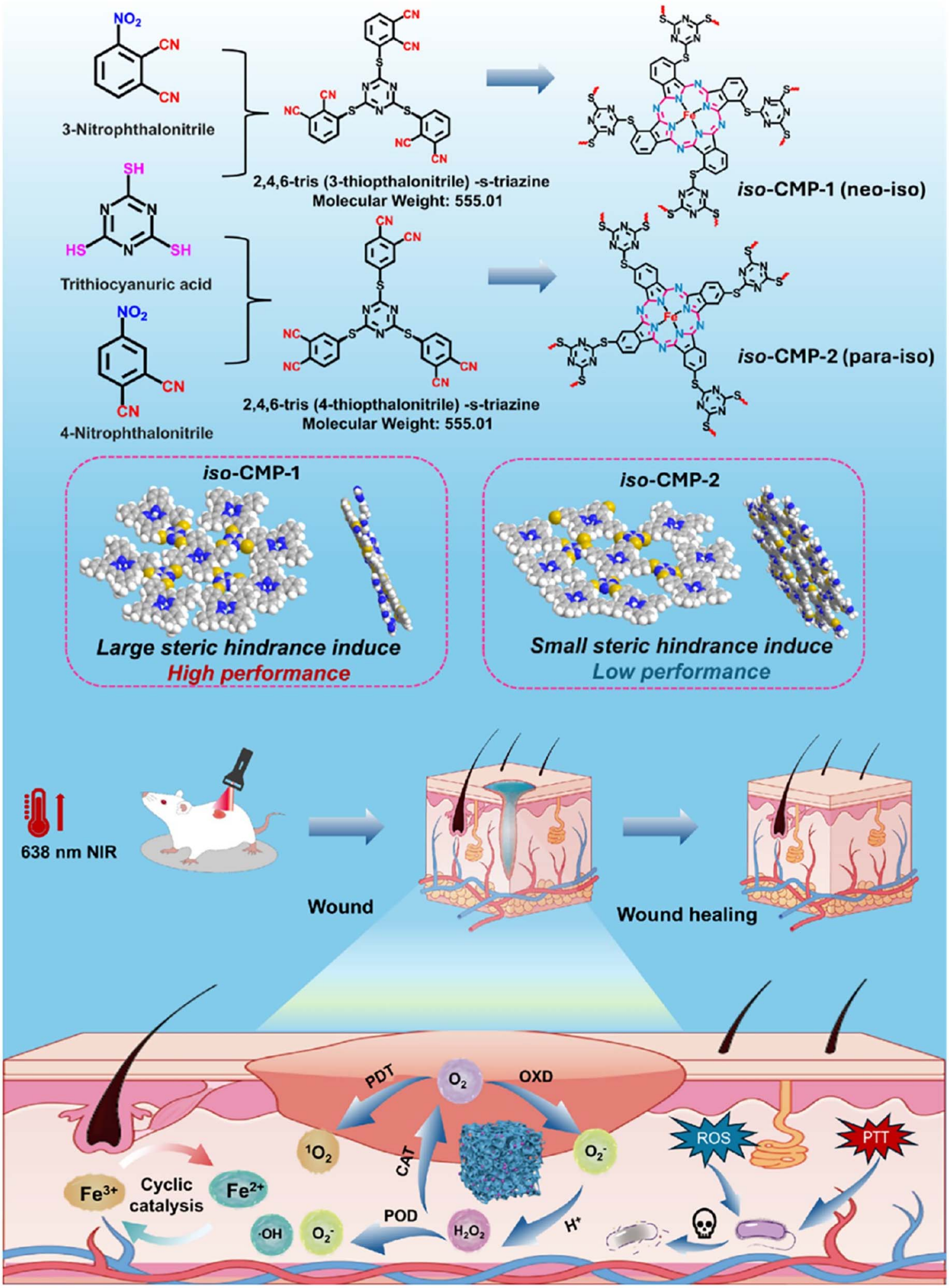

Fig. 4 Schematic route for the synthesis of the iso-CMPs using the isomers with different congestion degrees of reactive monomers. Adapted from ref. 63 with permission from American Chemical Society, *ACS Appl. Mater. Interfaces*, vol. 17, p. 42602. Copyright 2025.

phenolic-aldehyde condensation. The incorporation of anti-quenching structural motifs including flexible saturated carbon linkages, sandwich-like interleaved units, and hydrogen-bond interlocked structures creates a multi-level design that effectively suppresses photoactivity loss induced by π–π aggregation while maintaining structural integrity.

The system operates through three coordinated action phases that constitute its adaptive antibacterial mechanism. In the first phase of pathological microenvironment sensing, acidic pH triggers POD-like activity from ferrocene units and *in situ* formed Fe_3O_4 nanoparticles, while photothermal heating accelerates H_2O_2 conversion to cytotoxic hydroxyl radicals. When H_2O_2 becomes depleted, the system automatically shifts to the second phase of dynamic activity switching, where multivalent iron centers leverage residual oxygen to produce superoxide radicals, maintaining continuous enzyme-like antibacterial function. The third phase of targeted ROS delivery is achieved through phenolic hydroxyl groups that anchor to bacterial membranes *via* hydrogen bonding, combined with rough surface topography that enhances physical adhesion. This minimizes the distance between reactive oxygen species generation sites and bacterial targets, ensuring efficient membrane disruption by short-lived species.[64]

The polymer matrix orchestrates three self-reinforcing therapeutic circuits that work synergistically. The first circuit establishes an oxygen metabolic cycle where catalase-like activity decomposes H_2O_2 into O_2, alleviating hypoxia while fueling oxidase-like activity and photodynamic therapy in a self-sustaining oxygen supply system. The second circuit provides photothermal amplification that enhances all enzyme kinetics while directly damaging pathogens through thermal effects and accelerating therapeutic cascades. The third circuit reprograms the microenvironment as *in situ* formed Fe_3O_4 consumes protons and hydrogen peroxide, elevating local pH to disrupt bacterial acid tolerance and reduce oxidative stress in host tissue. This hierarchical coordination system achieves temporal control through microenvironment-responsive enzyme switching, spatial precision *via* targeted membrane interactions, energy optimization through light-driven cascades including oxygen self-supply and combined photodynamic and photothermal therapy activation, and material efficiency through multi-enzyme synergy. The FcPor-POP system represents a paradigm shift in antimicrobial design, transforming static materials into dynamic therapeutic systems that intelligently respond to infection dynamics while maximizing antibacterial efficacy through coordinated spatial, temporal, and energy dimensions.

The use of pre-metallated monomers as reaction precursors effectively mitigates metal leaching and enhances material stability, although the synthesis is still performed in organic solvents. The resulting core–shell structure further stabilizes the metal centers and improves the overall robustness of the material. Additionally, the generated metal oxides contribute to the consumption of acid in the local microenvironment, leading to a partial regulation of the pH conditions.

3.4 π–π stacking suppression strategy *via* rigid twisting

Liu *et al.* developed a breakthrough solution through atomic-level structural engineering, combining Knoevenagel polycondensation, post-synthetic methylation, and iron coordination to create a cationic metalloporphyrin COF (MC–COF–I) with precisely controlled photonic and dual enzymatic properties (Fig. 5). This advanced material features a unique architecture of staggered octaaldehyde-porphyrin units connected by π-delocalized vinyl bridges, achieving three fundamental advances in antimicrobial functionality.[65]

The unique design of MC–COF–I confers a cascade of antibacterial functions that operate synergistically across multiple levels. The intentionally distorted porphyrin arrangement prevents π–π stacking interactions, effectively eliminating the ACQ that typically limits photoactivity. Building on this stable photophysical foundation, the embedded iron centers further enable pH-responsive enzymatic switching, allowing the material to autonomously transition between peroxidase-like activity in acidic conditions and catalase-like function at neutral pH, thereby establishing a self-adapting ROS–oxygen cycle. Leveraging this dynamic microenvironment remodeling, the positively charged framework additionally promotes electrostatic targeting of bacterial membranes, enabling localized and precision delivery of photothermal and oxidative stress. Collectively, these coordinated mechanisms empower MC–COF–I to function as an intelligent, biosafe therapeutic agent capable of actively sensing and reprogramming infectious microenvironments for enhanced antibacterial efficacy.

This material orchestrates a cascade of synergistic antibacterial actions combining photothermal, photodynamic, cationic, peroxidase, and catalase therapies, significantly accelerating the healing of infected wounds. This work represents a paradigm shift by resolving the longstanding compromise between phototoxicity and bioactivity in porphyrin-based systems through strategic spatial distortion engineering. The multifaceted therapeutic approach of MC–COF–I addresses current limitations in infection treatment through several key mechanisms. Its microenvironment-responsive behavior ensures appropriate enzymatic activity based on local conditions, while the structural design maximizes both photodynamic efficiency and bacterial targeting specificity. These innovations collectively establish MC–COF–I as a next-generation antimicrobial platform capable of overcoming resistance mechanisms through physical and biochemical interventions rather than conventional antibiotic action.

This modular synthesis demonstrates high scalability by employing industrially well-established Knoevenagel polycondensation to construct a robust framework under mild conditions, followed by sequential functionalization. Although metalloporphyrin precursors dominate costs and solvent use presents environmental challenges, the non-precious iron center ensures low cost and minimal leaching, with solvent recycling offering a path to further improvement.

3.5 Dynamic covalent bond strategy *via* multi-dimensional distortion

Phototherapy has gained recognition as a promising non-antibiotic antimicrobial strategy, characterized by its precise selectivity, non-invasiveness, and minimal risk of inducing drug resistance. However, the widespread application of organic PSs, such as porphyrins, remains constrained by their pronounced tendency to aggregate, leading to severe quenching of photoactivity. To address this limitation, Jiang *et al.* introduced an

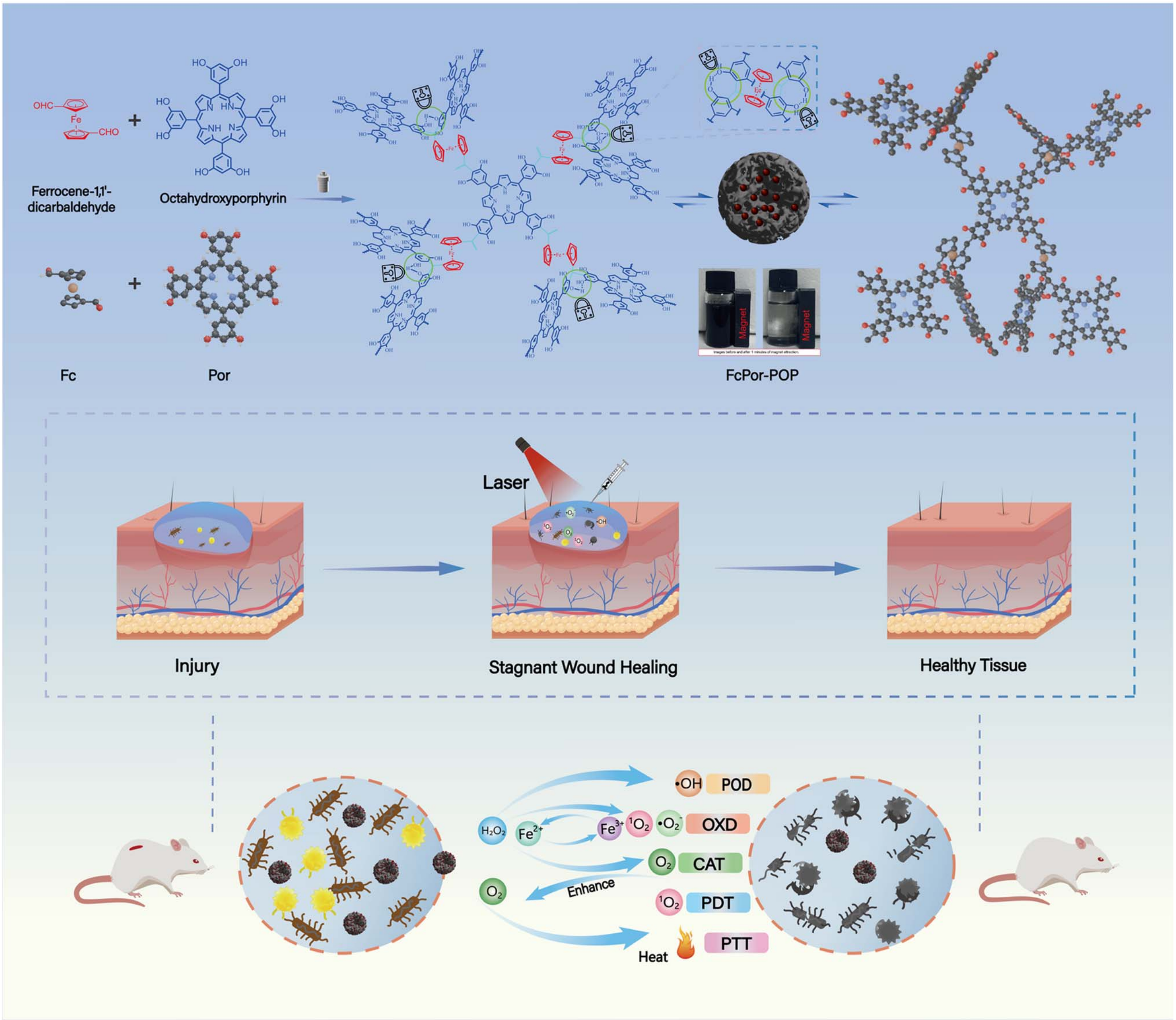

Fig. 5 Schematic route for the synthesis of FcPor-POP, and corresponding mechanism for the boosting the infected wound healing. Adapted from ref. 64 with permission from American Chemical Society, *ACS Appl. Polym. Mater*, vol. 7, p. 9617. Copyright 2025.

innovative three-dimensional multiple-twisted molecular architecture that effectively suppresses such quenching behavior in porphyrin-based systems. Inspired by this approach, a novel crown-ether–based porous organic polymer featuring imidazole linkages, designated Crown-TTEP (Fig. 6), was designed and successfully synthesized.

This advanced material was constructed through the polymerization of a specially designed twisted tetra-1,4-di(4-aldehyde phenyl)phenyl-porphyrin (TTEP) with crown-shaped crown ether building blocks, creating a unique platform for synergistic crown/photothermal/photodynamic combination therapy.[66] The multiple twisted three-dimensional architecture of Crown-TTEP effectively overcomes the photoactivity reduction typically observed in conventional porphyrin systems caused by heavy molecular aggregation. This structural innovation results in significantly enhanced photodynamic and photothermal conversion efficiencies that far surpass those of pure TTEP. Comprehensive *in vitro* and *in vivo* evaluations demonstrated that Crown-TTEP functions as an exceptionally effective broad-spectrum antimicrobial agent, exhibiting outstanding antibacterial performance against both Gram-positive and Gram-negative pathogens. The material's superior antimicrobial efficacy stems from the synergistic combination of photothermal therapy, photodynamic therapy, and the intrinsic antibacterial properties of the crown skeleton under near-infrared light irradiation. This multimodal therapeutic approach not only ensures potent pathogen eradication but also significantly accelerates the healing process of infected wounds. Importantly, this work establishes a new paradigm for enhancing the phototherapeutic performance of porous organic polymer-based antimicrobial agents through rational three-dimensional spatial design, opening new avenues for developing advanced antibiotic-free infection treatments.

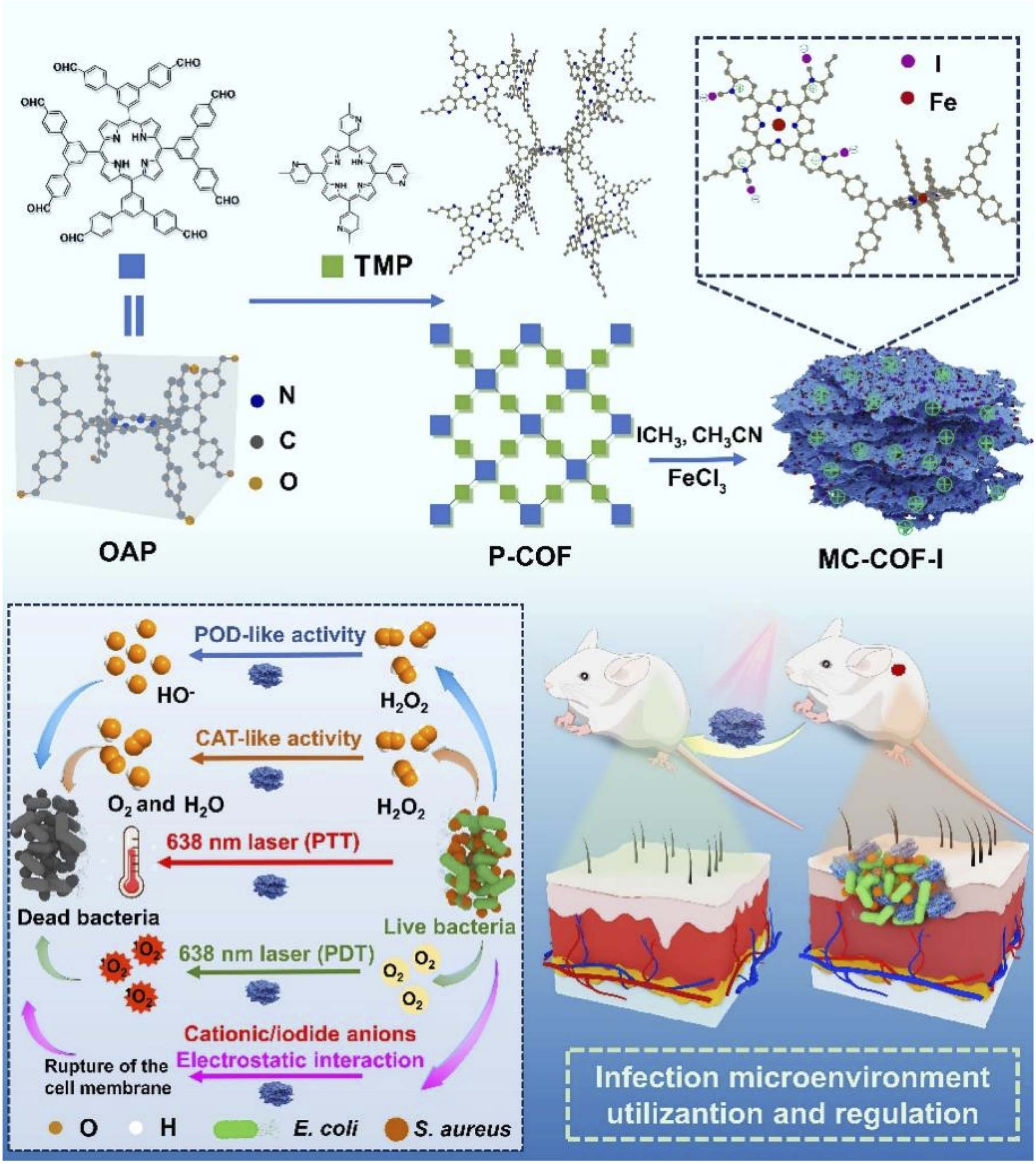

Fig. 6 Schematic route for the synthesis of antimicrobial cationic COF (MC–COF–I) with infection microenvironment utilization and regulation capacities and corresponding cascaded five in one antimicrobial and promoting wound healing modes. Adapted from ref. 65 with permission from American Chemical Society, *ACS Appl. Polym. Interfaces*, vol. 17, p. 56 786. Copyright 2025.

The one-pot hydrothermal synthesis of Crown-TTEP shows good scalability, with oxygen/moisture tolerance and enhanced monomer solubility ensuring consistent quality. While the long reaction time (5 day) and multi-step TTEP synthesis pose challenges, scale-up is economically viable with much enhanced conversion efficiency and potential cost reduction through process intensification.

3.6 Synergistic targeting strategy *via* cationic engineering and spatial distortion

Wei *et al.*, have developed a breakthrough cationic metallo-covalent organic framework (CRuP–COF) through an innovative solvent-mediated dual-reaction synthesis strategy (Fig. 7).

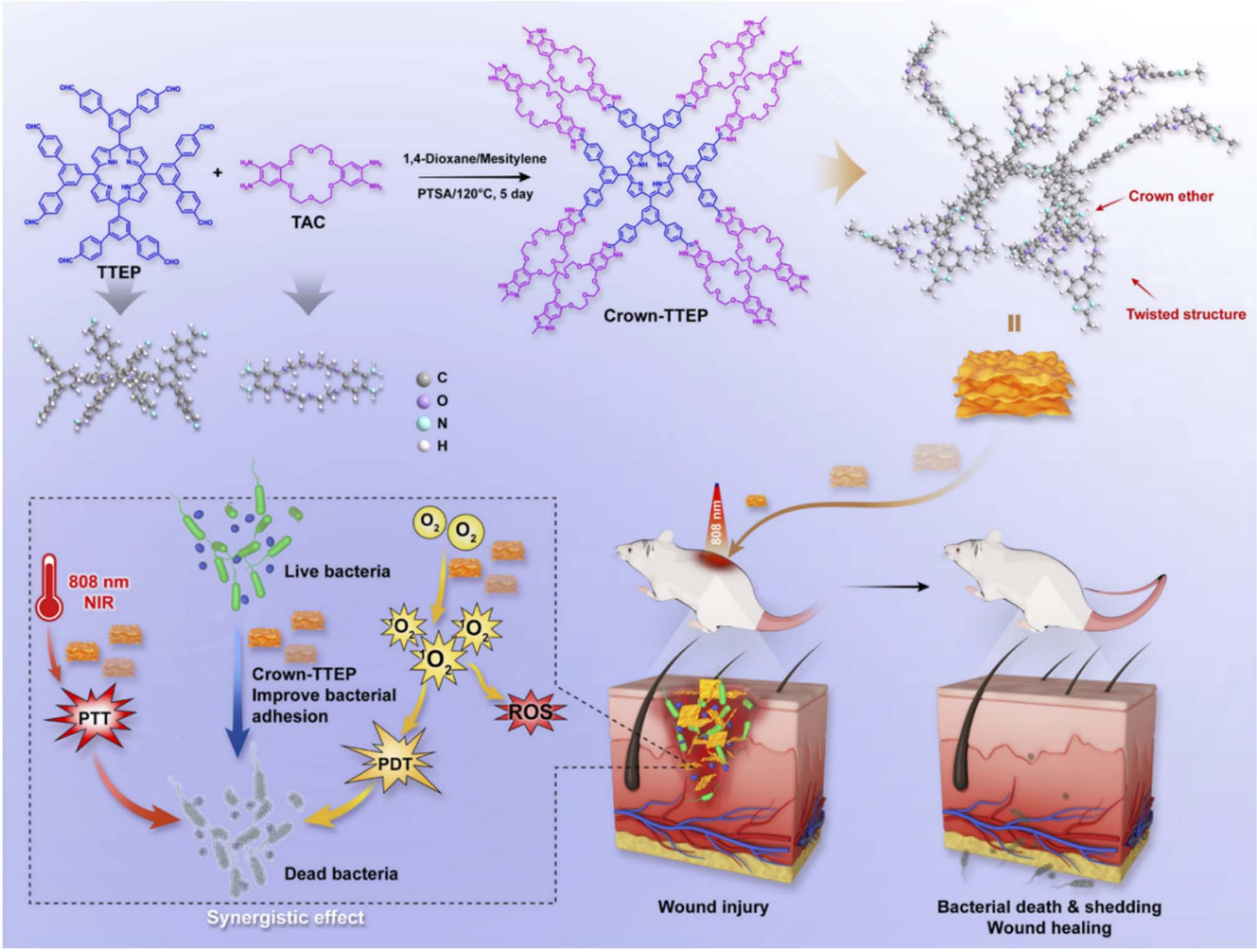

Fig. 7 Schematic diagram of the route and synergistic antimicrobial properties of Crown-TTEP synthesized by hydrothermal synthesis. Adapted from ref. 66 with permission from Springer Nature, *Sci. Rep.*, vol. 15, p. 33397. Copyright 2025.

This advanced material ($\zeta = +21.07 \pm 1.04$ mV) is engineered *via* the synergistic combination of Knoevenagel polycondensation and SN2 nucleophilic substitution, using bromoethane as a bifunctional modulator to copolymerize tris(4,4′-dicarboxaldehyde-2,2′-bipyridine)Ru(II) (Rubpy-6CHO) and *meso*-tetrakis(6-methylpyridin-3-yl)porphyrin (TMPP). The resulting structure incorporates three fundamental innovations that synergistically overcome existing therapeutic limitations. First, the strategic structural engineering significantly enhances photodynamic performance. By incorporating spatially distorted Ru(II) centers, the material forms staggered π-conjugation networks that effectively prevent π–π stacking interactions. This crucial modification addresses a long-standing challenge in photodynamic therapy by eliminating the photoactivity decay typically observed in conventional porphyrin systems, thereby preserving optimal antimicrobial photodynamic efficiency. Second, the cationic surface engineering enables precise targeted therapy. Through pyridinic *N*-ethylation, the material acquires a permanent cationic surface potential that facilitates selective electrostatic adhesion to negatively charged bacterial membranes. This targeting capability, when combined with the material's hierarchical porous architecture and exceptionally high specific surface area, creates an optimal environment for efficient mass and energy transport while simultaneously minimizing unwanted thermal dissipation and reactive oxygen species loss. Third, the material exhibits powerful multimodal antimicrobial action. CRuP–COF demonstrates superior photothermal conversion efficiency coupled with sustained reactive oxygen species generation through mixed Type I and II mechanisms. These properties translate to remarkable therapeutic performance, showing 50% greater potency compared to its non-cationic counterpart RuP–COF. The combination of these three innovations creates a comprehensive solution that addresses multiple aspects of antimicrobial therapy, from molecular–level interactions to macroscopic therapeutic effects.[67]

At 200 μg mL^{-1}, CRuP–COF achieves remarkable >99.9% eradication rates against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) pathogens. The system further demonstrates self-amplifying therapeutic effects, where localized photothermal heating accelerates ROS production, which in turn enhances bacterial membrane permeability to facilitate cationic targeting. Comprehensive biosafety assessments confirm excellent biocompatibility, with minimal hemolytic activity and high cellular viability at therapeutic concentrations. CRuP–COF represents a transformative antimicrobial platform that simultaneously addresses three critical challenges.

This organic solvent-mediated dual-reaction strategy exhibits excellent scalability through its orthogonal one-pot design, which combines Knoevenagel polycondensation and SN2 substitution without intermediate purification. Although Ru(II) complexes raise material costs, their high efficiency and recyclability improve economic viability. The process features high atom economy and a simplified supply chain, but solvent use leads to environmental threat. The framework securely confines Ru(II), minimizing leaching and ecological risk.

3.7 Intelligent degradation and repair strategy *via* microenvironment responsiveness

Hu *et al.* report the development of Cu–B–COF, an infection microenvironment-responsive covalent organic framework designed for intelligent wound healing applications (Fig. 8). This innovative material is constructed through the dynamic assembly of a bidentate *N*-substituted salicylimine–Cu complex [Cu(SALANIH-boronic acid)2] with 5,10,15,20-tetrakis(2,3-dihydroxyphenyl)porphyrin, combining advantageous features of both metal–organic frameworks and COFs.[68]

The Cu–B–COF platform demonstrates remarkable adaptability through several key features. Its pH/H_2O_2-responsive boronate esters enable dynamic structural reconfiguration, including size modulation and controlled biodegradation. The incorporated Cu-based catalytic centers exhibit dual enzymatic activities, functioning as both glutathione peroxidase and peroxidase mimics. The three-dimensional twisted architecture, induced by bidentate salicylimine-Cu units, significantly enhances light energy utilization efficiency while preventing aggregation-induced quenching effects. This unique structural design results in superior photothermal performance compared to conventional porphyrin systems, along with dual-mode photodynamic capabilities (Type I/II mechanisms) that enable adaptive therapeutic responses. The material operates through three coordinated phases. This innovative structural configuration endows the material with exceptional therapeutic properties that surpass conventional porphyrin-based systems. The precisely engineered architecture achieves remarkable photothermal conversion efficiency while simultaneously supporting dual-mode photodynamic action through both Type I and Type II mechanisms. These complementary photochemical processes work in concert to create an adaptive therapeutic system capable of dynamically responding to infection conditions. The therapeutic action unfolds through three precisely coordinated phases that progressively address infection control and tissue repair.

In the initial pathogen elimination phase, the system orchestrates a powerful antimicrobial response through combined glutathione depletion and photothermal-enhanced peroxidase activity. This synergistic approach generates intense bursts of $^{\bullet}OH$ and ROS storms that penetrate deep into infected tissues, effectively eradicating pathogenic microorganisms. Following pathogen clearance, the system transitions to microenvironment remodeling, where it actively neutralizes acidic conditions through proton consumption while simultaneously scavenging excess hydrogen peroxide. This dual action restores physiological pH balance and alleviates oxidative stress, creating favorable conditions for tissue recovery. The pH-regulating capacity is particularly valuable in infected wounds where acidosis typically impairs healing processes. The final regeneration phase harnesses the sustained release of copper ions to stimulate new blood vessel formation, while the antioxidant polyhydroxyl components actively support extracellular matrix reconstruction and promote epithelial cell migration. This comprehensive approach addresses both microbial control and the subsequent tissue repair processes, overcoming the common limitation of antimicrobial therapies that often neglect the healing phase. The coordinated transition between these therapeutic phases ensures optimal treatment outcomes throughout the entire wound healing continuum. Synergistic pathogen elimination through GSH depletion and photothermal-enhanced peroxidase activity, generating potent hydroxyl radical bursts and ROS storms with deep tissue penetration. Microenvironment remodeling *via* acid neutralization (H^+ consumption) and H_2O_2 scavenging, restoring physiological pH while reducing oxidative stress. Tissue regeneration promoted by sustained Cu^{2+} release (stimulating angiogenesis) and antioxidant polyhydroxyl activity (supporting matrix reconstruction and epithelial migration). This multiscale engineering approach successfully addresses critical limitations of conventional enzyme therapies, including inadequate ROS production in hypoxic conditions, self-limiting catalytic efficiency, and insufficient vascular support during tissue repair. The Cu–B–COF system represents a significant advancement in adaptive therapeutic materials for infectious wound management.

This scalable synthesis features a self-correcting mechanism, enabling consistent gram-scale production. Although precise stoichiometric control and the cost of starting materials remain as the primary obstacles, the method offers significant advantages, including the utilization of inexpensive copper, high reaction yields, and minimal purification. The resulting material demonstrates exceptional copper retention and undergoes favorable environmental degradation. While the process still involves organic solvents, their moderate usage substantially enhances the environmental profile (Fig. 9).

3.8 Heterojunction synergy strategy *via* modular assembly

The construction of heterojunction and hybrid nanostructures represents a powerful materials design paradigm, enabling the integration of functionally distinct components into a single composite with enhanced or even emergent properties. By rationally combining materials at the nanoscale, it becomes possible to exploit synergistic effects, such as improved charge separation, enhanced light harvesting, and cascaded catalytic activities, that are unattainable by any single component alone, thereby opening new avenues for advanced biomedical applications.

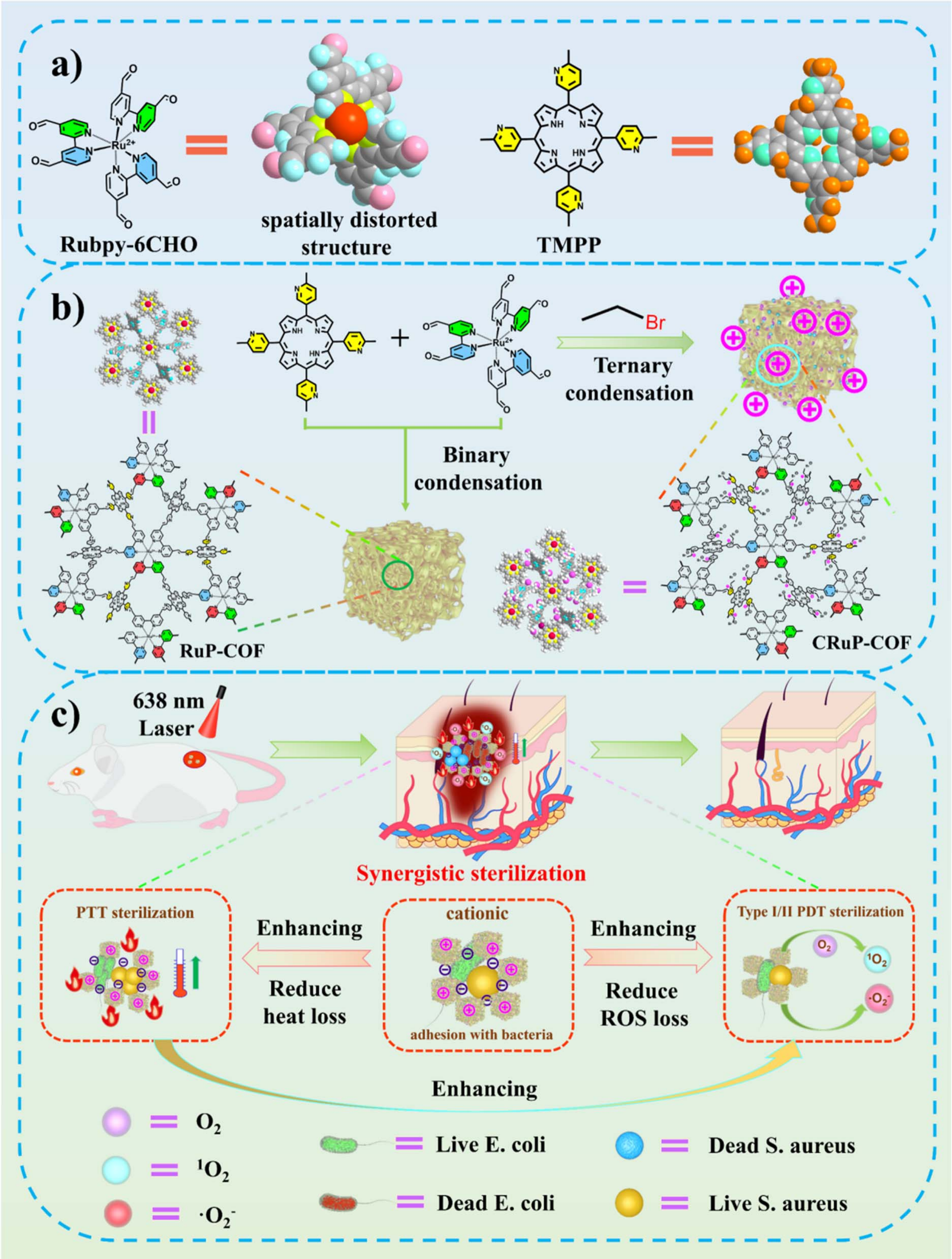

Fig. 8 (a) Schematic representation of the stereo structures of Rubpy-6CHO and TMPP; (b) schematic diagram of the synthesis process of CRuP–COF and RuP–COF; (c) schematic diagram of the antibacterial mechanism of CRuP–COF. Adapted from ref. 67 with permission from American Chemical Society, *ACS Appl. Mater. Interfaces*, vol. 17, p. 13566. Copyright 2025.

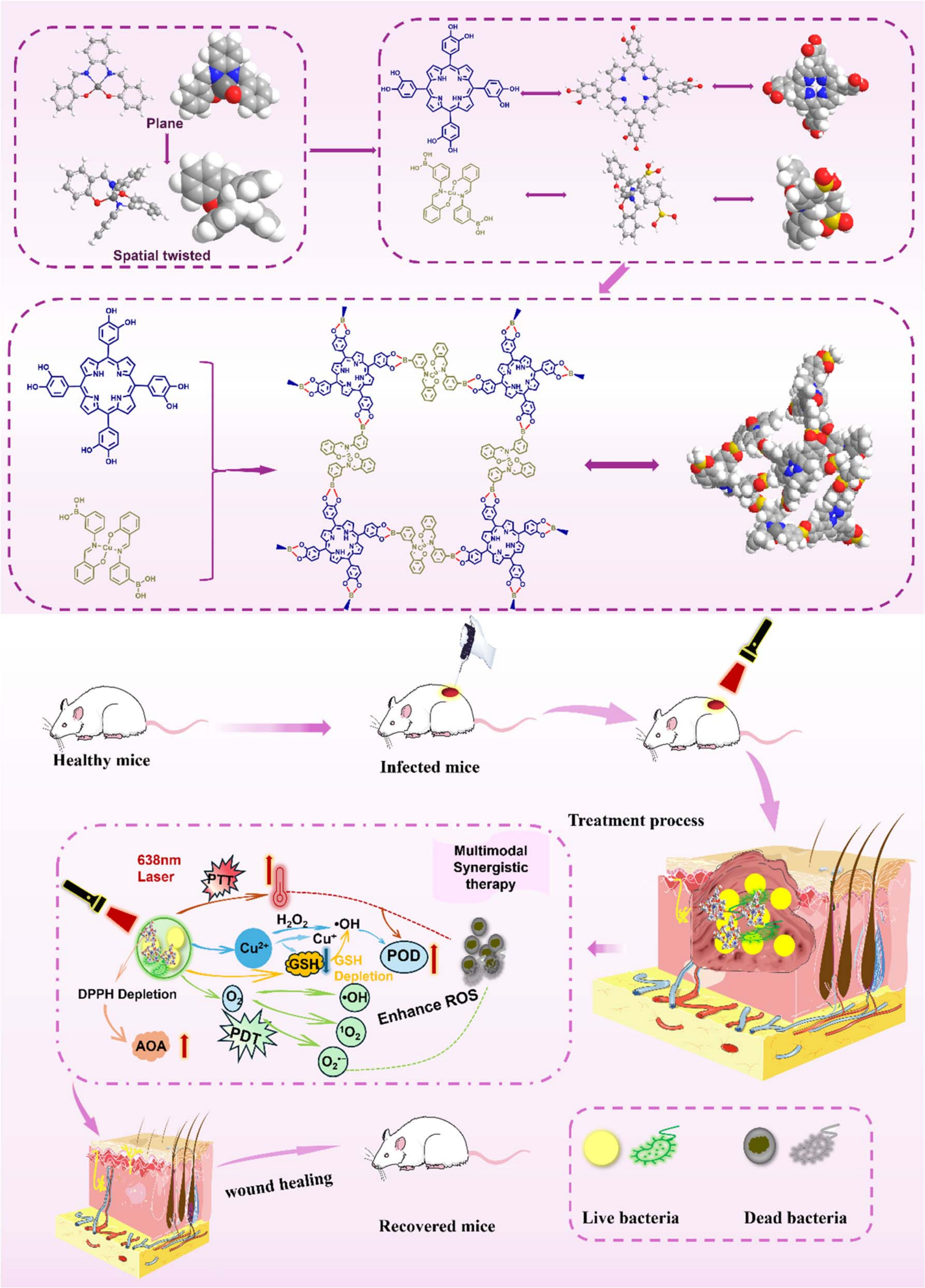

Fig. 9 Schematic representation of a Cu–B–COF capable of light-triggered combined antimicrobial therapy and wound healing. Adapted from ref. 68 with permission from American Chemical Society, *ACS Appl. Polym. Interfaces*, vol. 7, p. 13566. Copyright 2025.

3.8.1 MOF@COF core–shell heterostructures for self-reinforcing Cascades. Artificial enzymes that mimic natural enzymatic activities have garnered significant attention for combating pathogenic infections. However, their clinical translation remains challenging due to complex synthetic routes and limited therapeutic efficiency. To address these

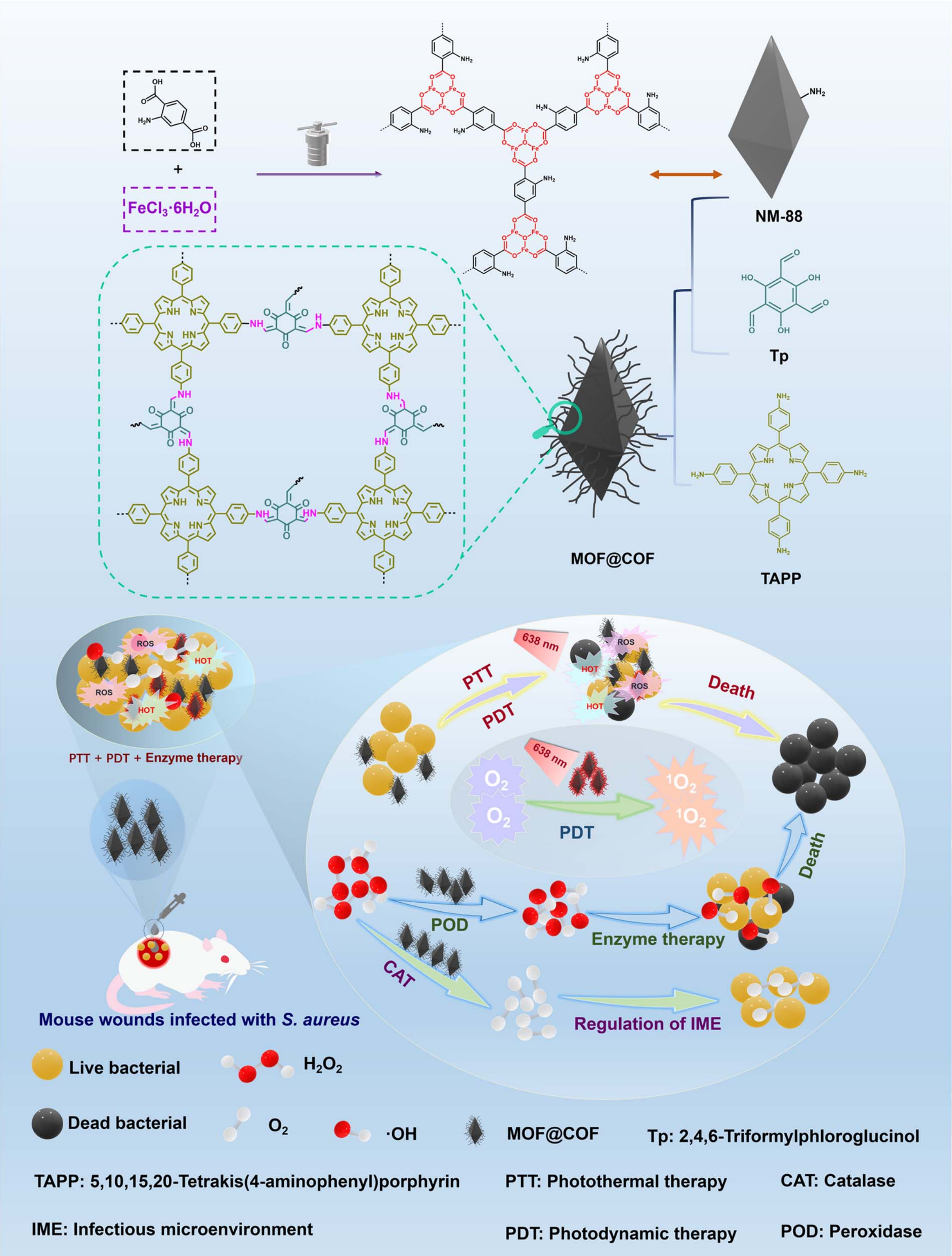

Fig. 10 Schematic representation of the synthesis and antimicrobial application of MOF@COF. Adapted from ref. 69 with permission from Elsevier (Cell Press), *iScience* vol. 28, p. 113414. Copyright 2025.

limitations, Guo *et al.* developed a modular assembly strategy for constructing hierarchical MOF@COF heterostructures *via* covalent interface engineering, circumventing the need for de novomonomer synthesis while amplifying functionality through synergistic interactions (Fig. 10). A key innovation in this work is the morphology-controlled core–shell architecture, achieved through the in situgrowth of a porphyrin-based covalent organic framework (COF) on an amino-functionalized metal–organic framework (MOF, Fe-MIL-88A-NH_2). The NH_2-MOF surface facilitates oriented COF assembly *via* Schiff base condensation, ensuring a well-defined heterojunction with uniform shell thickness.[69] Critically, the thin-layer COF growth on the MOF surface effectively mitigates the issue of deep-layer photosensitizer underutilization, a common limitation in bulk COF materials where inner active sites remain inaccessible to light excitation. By confining the COF to a thin, well-defined shell, we maximize light penetration and ensure efficient utilization of the photodynamic components. The MOF@COF hybrid integrates the dual peroxidase (POD)– and catalase (CAT)-like activities of the MOF core with the photoactive COF shell, enabling a self-reinforcing cascade therapeutic effect. Within the infectious microenvironment (IME), the composite selectively catalyzes the photothermal-sensitized conversion of endogenous H_2O_2 into Bactericidal $^{\bullet}$OH radicals (*via* POD-like activity), and O_2 (*via* CAT-like activity). This dual functionality not only enhances photodynamic therapy (PDT) by improving light harvesting and charge separation but also alleviates hypoxia-induced PDT resistance through in situself-oxygenation. The MOF@COF heterostructure acts as a broad-spectrum antimicrobial agent, simultaneously utilizing and remodeling the IME to exert precise therapeutic effects. By combining photodynamic, photothermal, and enzymatic activities, the system achieves enhanced bacterial eradication (Gram-positive and Gram-negative strains) and accelerated wound healing in infected wounds. Hybrid presents a rational design strategy for constructing biocompatible, multifunctional artificial enzymes with synergistic catalytic sites, enabling a cascaded self-reinforcing therapeutic effect for infectious wound therapy. The thin-shell COF growth on MOF not only optimizes photodynamic efficiency but also provides

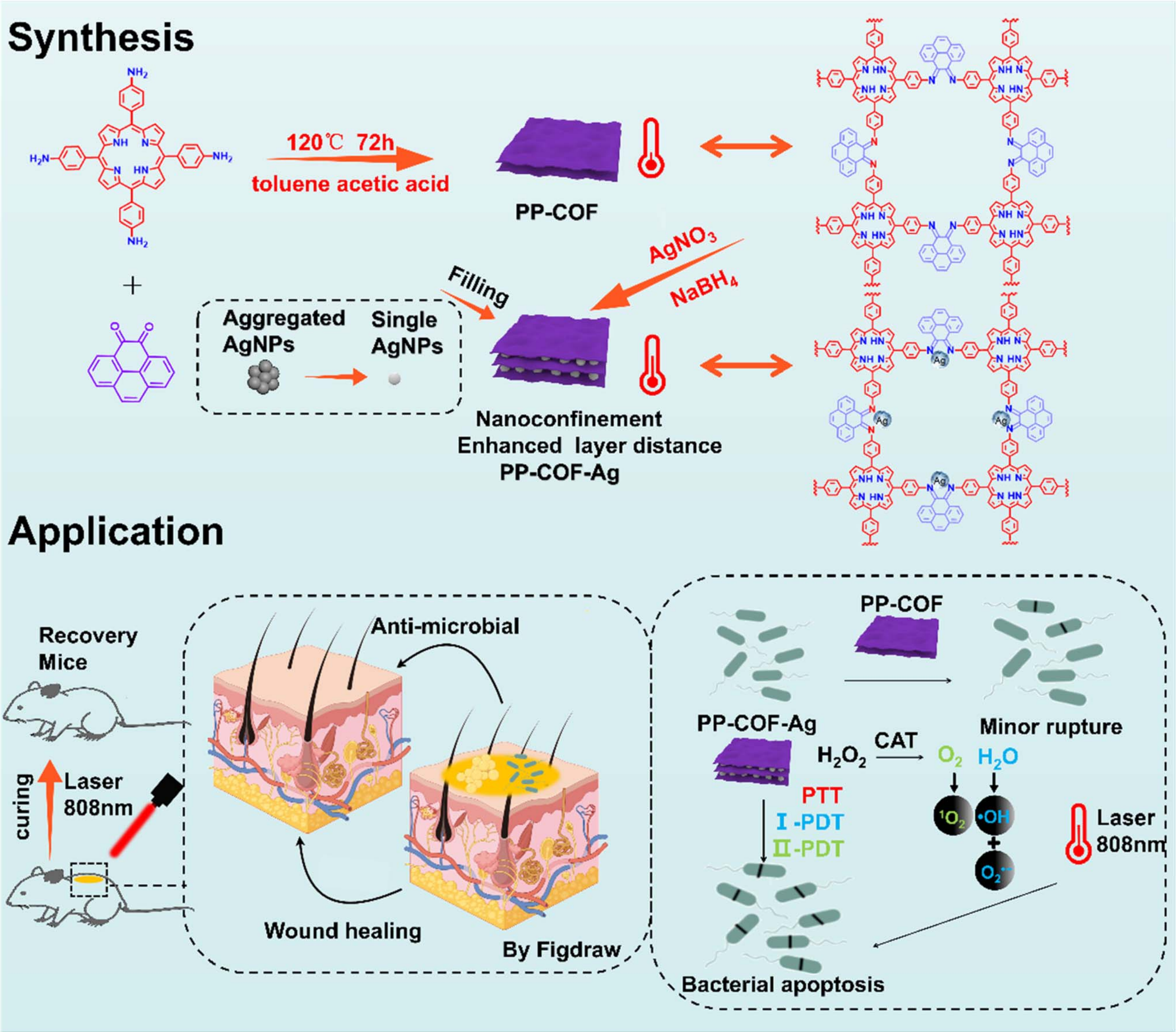

Fig. 11 Schematic representation of the synthesis of PP–COF–Ag and its.antimicrobial and anti-biofilm applications in wounds. Adapted from ref. 70. With permission from Elsevier, Inorg. *Chem. Commun.*, vol. 183, p. 115666. Copyright 2025.

a generalizable approach for developing high-performance hybrid nanomaterials for biomedical applications.

This work develops a scalable core–shell architecture by growing a porphyrin COF shell on an amino-functionalized Fe-MOF. The stepwise, organic solvent-compatible synthesis ensures a uniform heterojunction and high batch-to-batch consistency on a multi-gram scale. The approach uses low-cost iron and minimizes synthetic steps, greatly cutting material costs while achieving high yield. The unqiue core–shell structure ensured negligible Fe leaching. The process is efficient and environmentally benign. Crucially, the thin COF shell maximizes light utilization, overcoming the limited activation of deep-layer photosensitizers in bulk COFs.

3.8.2 COF-metal nanocomposites for smart therapeutic switching.

Wang *et al.* presented PP–COF–Ag, an intelligent antibacterial artificial enzyme system that demonstrates infection microenvironment-driven therapeutic modality switching (Fig. 11).[70] This innovative platform combines the structural advantages of covalent organic frameworks (COFs) with precisely encapsulated silver nanoparticles (AgNPs) to achieve

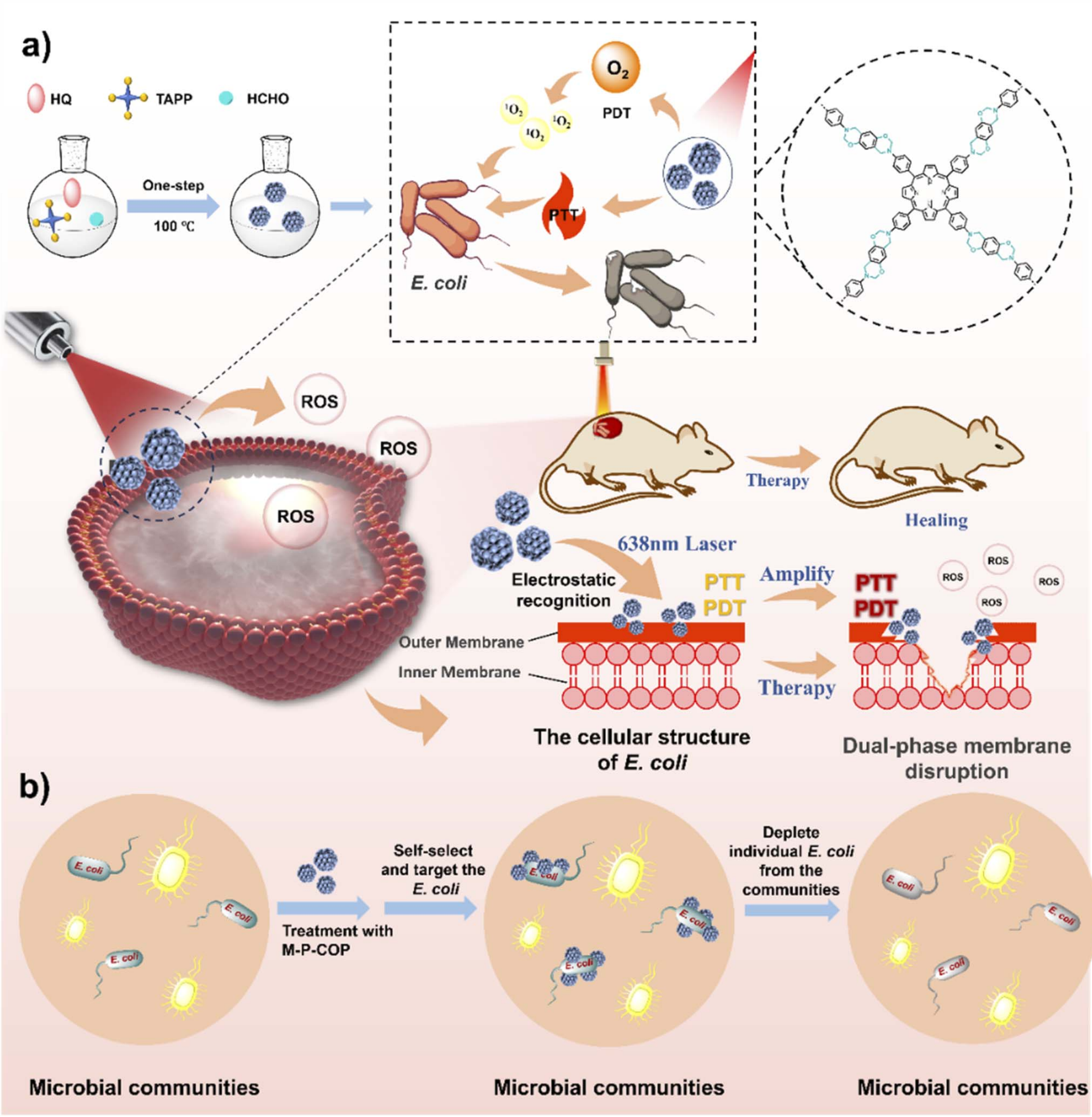

Fig. 12 (a) Schematic representation of the synthesis and antimicrobial application of M-P-COP. (b) Schematic representation of *E. coli* removal from microbial communities by M-P-COP. Adapted from ref. 71 with permission from Elsevier, A *Chem. Eng. J.*, vol. 517, p. 164311. Copyright 2025.

spatiotemporally controlled bacterial inactivation. AgNP intercalation induces COF layer expansion, simultaneously preventing nanoparticle aggregation while enhancing near-infrared (NIR, 808 nm) photothermal conversion efficiency. The periodic structure of COF provides spatial restriction and interfacial stabilization, maintaining AgNPs monodispersity even under physiological conditions. The system enables NIR-triggered Ag^+ release with glutathione (GSH)-responsive amplification. PP–COF–Ag exhibits selective catalase-like activity in H_2O_2-rich infected regions, alleviating hypoxia to enhance photodynamic therapy. PP–COF–Ag simultaneously depletes GSH (85% reduction) while generating ROS ($^{\bullet}OH$, $^1O_2$), overwhelming bacterial antioxidant defenses. PP–COF–Ag with synergistic eradication effect combines chemical attack (ROS/Ag^+) with photothermal ablation for complete biofilm penetration and destruction. In Staphylococcus aureus-infected wound models, PP–COF–Ag demonstrated 99.97% bacterial reduction within 24 h with complete biofilm eradication, accelerated wound closure and excellent biosafety. This work establishes a new paradigm for smart antibacterial materials by integrating three key functional capabilities: autonomous pathological sensing that responds to infection biomarkers like pH, H_2O_2, and GSH; dynamic therapeutic switching between chemical and physical modalities; and spatiotemporal precision through NIR-controlled activation in deep tissues. The demonstrated multi-lock-and-key design principle provides a blueprint for developing next-generation antimicrobials that can effectively navigate complex host–pathogen interactions while maintaining precise therapeutic control.

The intercalation of AgNPs during COF crystallization expands the layered structure, which simultaneously prevents nanoparticle aggregation and enhances NIR photothermal conversion efficiency. The framework structure of the COF provides spatial confinement, ensuring AgNP monodispersity and reducing Ag^+ leaching. This modular one-pot synthesis is scalable, achieving high Ag loading and composite yield with less silver consumption than conventional methods. Although organic solvents are employed, the overall environmental impact is mitigated by the low effective dosage and the stable encapsulation that minimizes silver release.

3.9 Structure-oriented targeting strategy for precision inactivation of gram-negative bacteria

E. coli, a ubiquitous pathogen in soil and aquatic environments, poses significant public health risks largely attributable to its widespread multidrug resistance (MDR). A major contributor to this resistance in Gram-negative (G-) bacteria, including *E. coli*, is their complex cellular architecture. Their lipopolysaccharide (LPS)-rich outer membrane (OM) coupled with selective porin barriers presents a formidable defense against conventional antibiotics and many phototherapeutic agents, limiting treatment efficacy. To overcome this critical challenge, Yue *et al.* introduce a novel porphyrin-integrated covalent organic polymer, designated M-P-COP. This material is specifically engineered to exploit a unique architectural vulnerability inherent to the G-bacterial OM. Synthesized efficiently *via* a one-pot Mannich reaction using tetra-aminoporphyrin (TAPP), hydroquinone (HQ), and paraformaldehyde as building blocks, M-P-COP forms a stable, rigid benzoxazine-linked backbone (Fig. 12).[71]

This robust structure not only ensures exceptional photostability and enhanced photosensitivity but also crucially enables precise molecular recognition of G-bacterial membranes. The core innovation of M-P-COP lies in its

Table 1 Comparative analysis of POP design strategies suppressing ACQ

Materials	Key mechanism to suppress ACQ	Antibacterial mechanism	Photothermal conversion efficiency (η)	Synthetic approach	Advantages	Limitations and challenges
Por-CD-COF	β-CD threading	Mixed type I and II PDT/PTT/CD	64.9%	Mechanical lapping & Solvent thermal	Enhanced biosafety	Complex synthesis
Crown-COPR-Zn	Crown-ether mechanical interlocking	Mixed type I and II PDT/PTT/Crown/Zn	49.6%	Solvent thermal	Enhanced biosafety	Complex synthesis
Iso-CMP-1, iso-CMP-2	Crown-ether mechanical interlocking	Mixed type I and II PDT/PTT/POD/CAT/OXD	79.96% 52.64%	Solvent thermal	Oxygen self-supply	Complex synthesis
FcPor-POP	Crown-ether mechanical interlocking	Mixed type I and II PDT/PTT/POD/CAT	63.58%	Solvent thermal	Oxygen self-supply, pH-responsive	Complex synthesis
MC–COF–I	Rigid twisting	Mixed type I and II PDT/PTT/POD/CAT/Cation	50.14%	Solvent thermal	Oxygen self-supply	Complex synthesis
Crown-TTEP	Multi-dimensional distortion	Mixed type I and II PDT/PTT/Crown	44.6%	Solvent thermal	NIR	Complex synthesis
CRuP–COF	Spatial distortion-engineered	Mixed type I and II PDT/PTT/POD/Cation	53.43%	Solvent thermal	Enhanced biosafety	High cost
Cu–B–COF	Distortion degradation	Mixed type I and II PDT/PTT/POD/GPx	64.9%	Solvent thermal	Biodegradable	Complex synthesis
MOF@COF	Hybrid	Mixed type I and II PDT/PTT/POD/CAT/	84.25%	Solvent thermal	pH-responsive	Complex synthesis
PP–COF–Ag	Interlayer-engineered Ag/COF heterostructures	Mixed type I and II PDT/PTT/POD/Ag	85.0%	Solvent thermal	pH-responsive	Potential long-term toxicity
M-P-COP	Membrane structure matching	Mixed type I and II PDT/PTT	71.4%	Solvent thermal	High selectivity	—

structure-selective bactericidal activity. Through precise physicochemical matching with the LPS-porin complex characteristic of *E. coli*'s outer membrane, M-P-COP achieves remarkable species specificity. Upon light activation, it generates abundant reactive oxygen species (ROS), synergistically disrupting both the outer membrane integrity and vital intracellular components of the target bacterium. Crucially, this potent activity is highly selective: M-P-COP mediates light-activated, species-specific inactivation, effectively eliminating nearly 100% of *E. coli* cells at ultra-low doses. Experimental results unequivocally demonstrate this exceptional selectivity. M-P-COP achieves outstanding bactericidal efficacy against *E. coli* (>99.94% inactivation at 100 μg mL^{-1} under light irradiation). In stark contrast, it exhibits negligible antimicrobial activity (only ∼5.32% inactivation) against the Gram-positive (G+) bacterium *Staphylococcus aureus* under identical conditions. Furthermore, M-P-COP shows minimal impact on representative environmental microbiota, highlighting its targeted action. This breakthrough directly addresses the longstanding inefficiency of traditional phototherapeutic agents against Gram-negative pathogens. Moreover, by enabling precise pathogen targeting, M-P-COP circumvents the indiscriminate disruption of microbial communities typically caused by broad-spectrum antibiotics. Consequently, our study presents an innovative and highly promising strategy for the precise removal of specific pathogenic threats within complex environmental or clinical settings, offering significant potential for applications in water treatment, food safety, and targeted antimicrobial therapy.

M-P-COP is efficiently synthesized *via* a scalable one-pot Mannich reaction, forming a rigid benzoxazine-linked framework that ensures high photostability and precise recognition of Gram-negative bacterial membranes. This process uses organic solvents, but achieves high yields with excellent reproducibility. While TAPP is the primary cost driver, the one-pot method reduces synthetic steps, enabling a projected cost reduction. Crucially, M-P-COP exhibits light-activated, species-specific bactericidal activity at ultra-low doses, while minimally impacting Gram-positive bacteria and environmental microbiota, underscoring its targeted efficacy and environmental safety (Table 1).

4 Research challenges and future perspectives

The development of POPs for suppressing ACQ has shown considerable promise in laboratory settings. However, several key challenges must be systematically addressed to advance these materials toward real-world implementation. This section outlines the major translational barriers and proposes future research trajectories.

4.1 Scalability and processability

A primary translational gap for POPs lies not in their inherent photophysical properties, but in their scalability and processability. Moving from milligram-scale syntheses to gram- or kilogram-level production remains a critical hurdle. Future efforts should prioritize the development of solvent-free or green-solvent routes, such as mechanochemical polymerization, alongside the optimization of film-forming properties to enable uniform coating deposition. These advances are essential for integrating POPs into practical devices such as biomedical coatings and flexible optoelectronics.

4.2 Dynamic responsiveness

Most current POP architectures are structurally static. Introducing dynamic covalent linkages (*e.g.*, imine, boronate esters) can enable stimulus-responsive frameworks capable of post-synthetic rearrangement under pH or light triggers. Such dynamic behavior not only improves chromophore dispersion and mitigates ACQ but also allows real-time tuning of π-stacking distances, offering spatiotemporal control over photophysical properties for adaptive and smart material systems.

4.3 Multifunctional integration

Emerging POP systems have begun to combine photodynamic and photothermal therapies with enzymatic or ionic functionalities. Future designs should pursue more sophisticated synergistic platforms, integrating immunotherapy or gene delivery mechanisms, to enable comprehensive and programmable antimicrobial strategies. Such multifunctionality could significantly broaden the application scope of POP-based materials.

4.4 Machine learning optimization

The discovery of POPs with optimized pore-chromophore ratios and excitation energy transfer pathways currently relies on trial-and-error experimentation. Machine learning approaches present a promising alternative, enabling predictive modeling of photophysical behavior and accelerating the design of materials with tailored light-harvesting and ROS-generation performance.

4.5 Considerations for translation

While the proof-of-concept studies presented herein demonstrate remarkable antibacterial efficacy, their translation to practical applications hinges on addressing scalability, cost, and environmental footprint. Currently, these syntheses are predominantly performed on a milligram scale using solvothermal methods, which involve high-boiling-point organic solvents and raise concerns for large-scale solvent consumption and waste. A thorough cost analysis must consider the expense of specialized monomers, particularly metalloporphyrins and phthalocyanines, and the energy-intensive nature of prolonged high-temperature reactions. Furthermore, the environmental impact, especially the potential for metal leaching (*e.g.*, Zn, Fe, Cu, Ru, Ag) from these porous frameworks into biological or ecological systems, requires rigorous long-term assessment. Future research must prioritize developing greener, solvent-free or aqueous-based synthetic routes (*e.g.*, mechanochemical synthesis), utilizing more abundant and cheaper metal centers, and engineering robust frameworks with minimal leaching potential to ensure these promising materials can be sustainably scaled for real-world antimicrobial applications.

5. Conclusions

PSs play vital roles in photodynamic therapy, solar energy conversion, and photocatalysis, yet their performance is often hampered by aggregation-caused quenching and photodegradation. This review systematically outlines the underlying mechanisms, current mitigation strategies, and future research trajectories aimed at overcoming these limitations. Advanced POP architectures, such as polyrotaxane-threaded covalent organic frameworks (Por-CD-COF), spatially distorted frameworks (CRuP–COF), and enzyme-mimetic hybrids (MOF@COF), demonstrate that rational molecular engineering can effectively suppress aggregation and enhance photodynamic output. Key design principles include spatial isolation *via* rigid 3D networks (*e.g.*, staggered porphyrins in MC–COF–I), dynamic distance modulation through host–guest chemistry (*e.g.*, β-cyclodextrin in Por-CD-COF), and multicomponent synergy (*e.g.*, ferrocene–polyphenol integration in FcPor-POP). These materials not only achieve exceptional antibacterial performance but also counteract hypoxia and biofilm resistance through mechanisms such as self-oxygenation (*e.g.*, CAT-like activity in Cu–B–COF), microenvironment adaptation (*e.g.*, pH-responsive enzymatic switching in MC–COF–I), and energy cascade optimization.

6 Future directions

Emerging research paradigms point toward bioorthogonal POPs capable of *in vivo* catalysis, closed-loop therapeutic systems with integrated pathogen sensing, and biodegradable constructs for transient antimicrobial interventions. Computational design and automated synthesis are poised to play a pivotal role in accelerating the transition of these materials from laboratory prototypes to clinically viable solutions. Looking forward, several priorities stand out, including enhancing material processability, conducting rigorous *in vivo* biosafety assessments, and leveraging artificial intelligence to guide synthesis and optimization. By systematically integrating structural control, functional synergy, and scalable fabrication, POP-based antimicrobial platforms hold exceptional potential to move beyond conventional antibiotics and address the growing challenge of multidrug-resistant infections.

Conflicts of interest

There are no conflicts to declare.

Data availability

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

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