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Piling up multidecker pyrgos[*n*]cages as antibacterial materials

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The development of antibiotics is regarded as one of the most significant scientific advances in modern medicine. Before the commercialization of antibiotics, infectious diseases were catastrophic throughout history [1]. Penicillin was used to treat serious infections in the 1940s, but unfortunately, with the introduction of antibiotics came the emergence of antibiotic resistance [2,3]. Evolved and adapted methicillin-resistant *Staphylococcus aureus* (MRSA) strains are presently impacting community and healthcare systems across the globe [4]. The steady increase of bacteria becoming resistant to antibiotic agents has led to a shift in research of discovering new approaches for future antibiotics. Drugs, such as sulfonamides, are single-target antibiotics that disrupt folate synthesis by targeting enzymes that are critical for bacterial development [5]. In recent decades, numerous examples of antibiotics with single-protein targets have promoted a pattern of rapid bacterial mutation, shifting the research toward the pursuit of multi-targeted drugs [6,7]. Most drugs in the market act by disrupting the integrity of the bacterial cell membrane while causing no harm to mammalian cells. As an example, Daptomycin is a lipopeptide antibiotic that exhibits properties both in targeting and attacking processes against bacteria [8]. The success of multitarget drugs has given new hope in the search for effective treatments against bacterial infections.

In the search for antibiotics that prevent drug resistance, He and co-workers [9] have introduced recently in *Science Advances* a series of cationic covalent organic cages — namely pyrgos[*n*]cages — which are a class of multidecker cages including evenly localized positive charges through their cylinder conformations. The simplest pyrgos[1]cage (**P1**) can be synthesized through subsequent UV light-induced bromination and *N*-alkylation reactions with an 84% yield. With the intuitive decker-stacking made possible by this synthetic route, yields can reach up to 53% for the two-decker pyrgos[2]cage (**P2**). The three- and four-decker, i.e., pyrgos[3]cage (**P3**) and pyrgos[4]cage (**P4**), have been designed similarly and synthesized (Fig. 1a) stepwise by using analogous precursors with yields of 42% and 2%, respectively. Successful assemblies of these organic covalent cages were confirmed by nuclear magnetic resonance spectroscopy and mass spectrometry. Single-crystal X-ray diffraction structures of three pyrgos[*n*]cages (n = 2, 3, and 4) exhibit (i) paralleled alignments with 5.1–5.4 Å distances between deckers, (ii) D_3 axis throughout centers of benzene rings in all deckers and (iii) uniformly distributed positive charges (Fig. 1b) across perpendicular (benz)imidazolium units. Localized cationic sections interact electrostatically with the anionic bacterial membranes of gram-positive bacteria without endangering animal tissues [10]. The antibacterial efficiency of pyrgos[*n*]cages is enhanced by their diverse sizes contingent on the number of deckers. This research article proposes an alternative pathway for antibacterial action, as pyrgos[*n*]cages work (Fig. 1c) by simultaneously targeting bacterial membranes and DNA, facilitating the interaction of the cationic cages with the negatively charged carboxylic acids found in bacterial cell envelopes and the phosphate groups in the DNA backbone. Pyrgos[*n*]cages may efficiently alter the membrane potential of *S. aureus* through phagocytosis, which further supports this hypothesis of an alternative antibacterial pathway and suggests a revolutionary solution in the continuing fight against antibiotic resistance.

The research results in this article indicate that pyrgos[*n*]cages are highly effective in wound healing and treating antibiotic-resistant *S. aureus* infections. As indicated by the experimental data, the use of pyrgos[*n*]cages in bacteria-infected wounds suggests an increase in healing rate compared with the control groups, which leads to the application of these cationic cages as efficient drugs for treating bacterial infections. Moreover, histological examination with hematoxylin and eosin (H&E) staining of tissue samples taken from treated mice showed normal skin structure with mild inflammation compared with the control groups, which showed partial loss of epidermis and prominent thickening of the skin. The *in vivo* assays indicate that using pyrgos[*n*]cages leads to both the disappearance of infectious bacteria and better tissue development.

The investigation of antimicrobial cationic covalent cages marks a milestone in responding to challenges occasioned by drug-resistant infections. Positive charges in the pyrgos[*n*]cages grant them similar functionalities to antimicrobial peptides (AMPs), allowing selective targeting of anionically charged cells and bacteria to form a net-zero charge complex [11]. This discards any electrostatic interaction with neutrally charged membranes, such as those of mammalian cells, leading to low cytotoxicity. As one of the target sites for pyrgos[*n*]cages, the bacterial cellular membrane allows the cationic structures to target bacteria that are not actively proliferating, namely dormant cells [12]. Fluorescence microscopic characterization of the acting pyrgos[*n*]cages reveals an alteration of the cross-membrane potential to disrupt the cell membrane, instead of the traditional pore-forming mechanism of attack by AMPs used in common antibiotics.

Overall, the ingeniously designed structures of the pyrgos[*n*]cages present opportunities for the development of organic cationic antibiotics. The intuitive synthesis of the cationic cages allows for further elongation of the molecule by piling additional deckers using analogous building blocks. Increasing the spectrum of cationic antibiotics to include fungal bacteria, using distinct antibiotics and medicines properly are mere examples of

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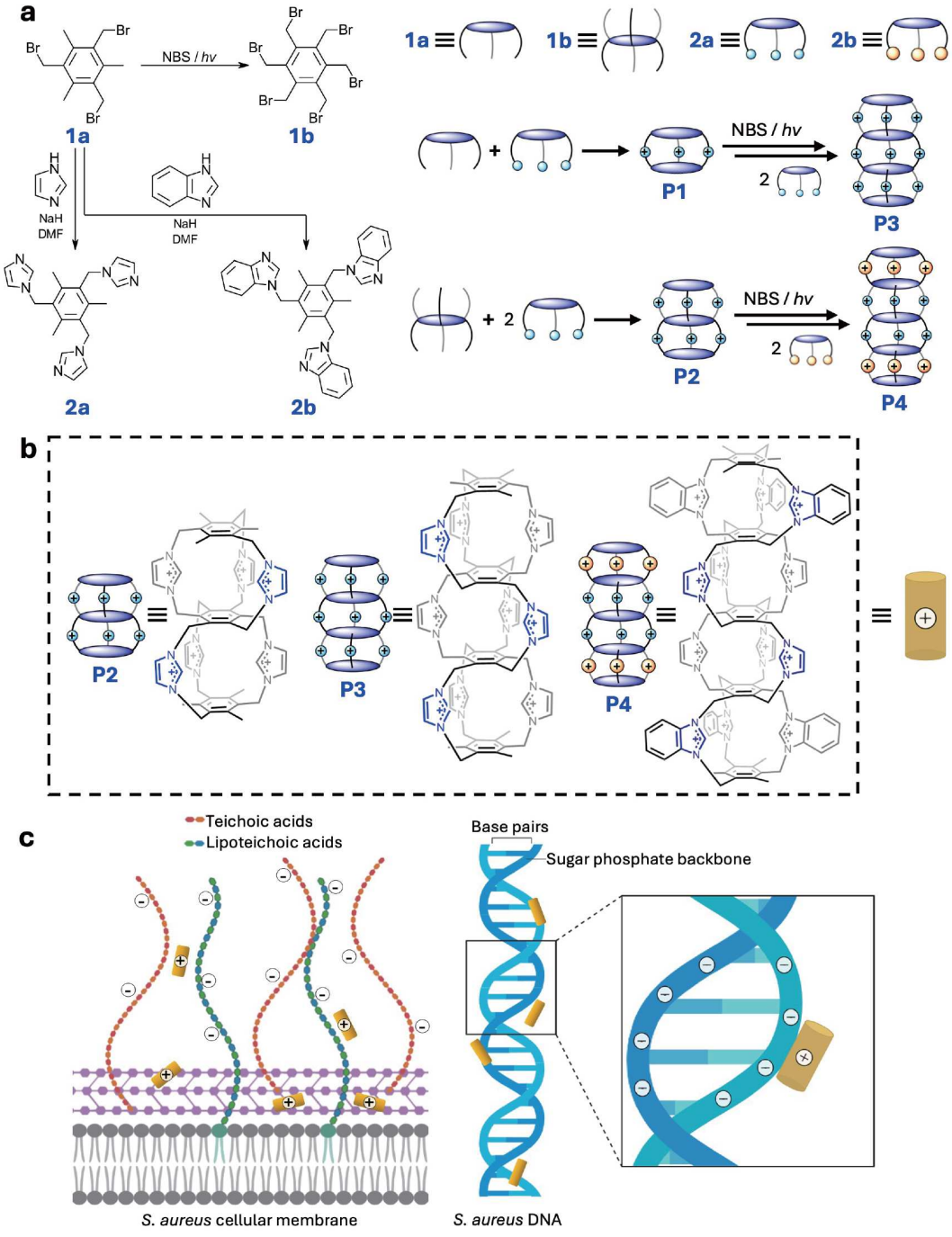

Figure 1 (a) Schematic representation of the syntheses of building blocks and pyrgos[*n*]cages with one, two, three, and four deckers, namely **P1**, **P2**, **P3**, and **P4**, respectively. (b) Structural formulas of pyrgos[*n*]cages including evenly localized positive charges throughout the cylindrical conformation. (c) Proposed mechanism of general pyrgos[*n*]cages targeting *S. aureus* cellular membranes (left) and DNA (right). Adapted from Ref. [9]. Copyright 2024, the Authors.

attempts to delay the development of drug resistance. The current race for drug development, bolstered by curiosity and determination, will undoubtedly help to answer the call to the rising antibiotic healthcare crisis by providing innovative solutions to drug-resistant infections.

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