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Azobenzene quaternary ammonium salt for photo-controlled and reusable disinfection without drug resistance

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ABSTRACT

The abuse of antibiotics causes severe bacterial resistance, and the shortage of antibiotics has created a global public health crisis. This situation has prompted people to develop new antibacterial agents independent of traditional antibiotics. Here, we created a series of photosensitive azobenzene-quaternary ammonium salt smart antibacterial agents by connecting azobenzene with amines with different chain lengths to improve the antibacterial selectivity of quaternary ammonium salt (QAS) and prevent the accumulation of active QAS in the environment. After *trans-cis* isomerization, the solubility of the title compound (compound **4**) increased and the antibacterial property enhanced. The experimental results suggested that the antibacterial effect of compound **4** was significantly enhanced after 365 nm light irradiation, and it had photosensitive intelligent antibacterial activity and could be reused. Notably, we did not obtain any mutants of *Staphylococcus aureus* or *Escherichia coli* resistant to compound **4**. In general, compound **4** has the advantages of high yield, photo-controllable antibacterial properties, reusability, and does not induce bacterial resistance. This photosensitive antibacterial compound provides a new idea for the construction of intelligent disinfectants and is expected to be a candidate for disinfectants in public facilities and medical architecture.

There are many microorganisms in the world. Humans are inevitably in contact with these bacteria in daily work and life. Under certain conditions, bacteria can bring serious infectious diseases and even cause human death. Antibiotics are the main treatment for bacterial infectious diseases currently [1]. However, with the improper use, and environmental residues of antibiotics in medical treatment, agriculture, and livestock husbandry, more and more serious problems have emerged [2,3]. For example, the emergence and intensification of bacterial resistance [4], the flow and accumulation of antibiotics in ecosystems and food chains make food insecure [5,6]. In addition, despite the continuous emergence of new antibiotics, the above-mentioned problems cannot be solved fundamentally. Moreover, developing novel antibiotics take a lot of time and money [7–10].

In the face of the shortage of antibiotics and bacterial resistance crisis, quaternary ammonium salts (QAS) have entered the public view due to their simple structure and special antibacterial mechanism (efficient destruction of bacterial membrane structure) [11,12]. QAS is widely used in trades and professions as surfactants, preservatives, and disinfectants [13]. For instance, under the background of the outbreak of the COVID-19 at the end of 2019, QAS are widely used as disinfectants in goods, family conditions, community facilities, and medical buildings [14,15]. However, QAS is stable, it will inevitable to deposit in the natural environment and occur non-selective sterilization continuously, which brings a series of consequences. For example, severe biological toxicity, cross-resistance, and co-resistance of QAS to antibiotics even potential reproductive toxicity [16–19]. Therefore, to address the bacterial puzzle confronted by the current world, it is very meaningful to design an intelligent QAS antibacterial compound with high antibacterial selectivity and reusable.

Light is an attractive physical factor in the natural environment. It has the advantages of high temporal and spatial resolution, non-biological invasion, and no sample contamination [20]. In the experimental process, it possesses the features of a simple instrument, convenient operation, and low cost [21]. As a common photosensitive group, azobenzene molecule has the advantages of simple synthesis, easy chemical modification, high photo-stability and quantum yield, fast photo-isomerization, and low photo-bleaching

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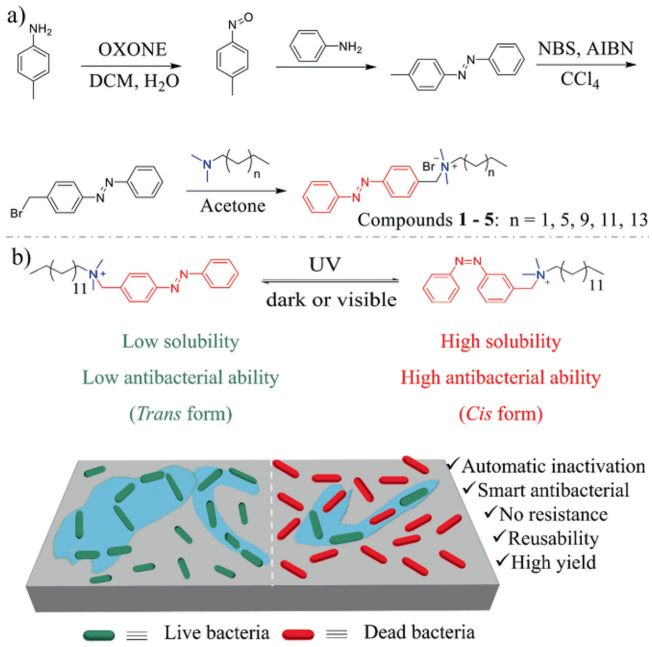

Scheme 1. (a) Synthesis of azobenzene-quaternary ammonium smart antibacterial compounds **1–5** and (b) cartoon characterization of photosensitive antibacterial compound **4**.

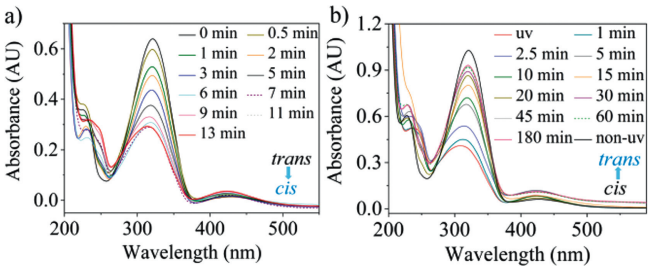

Fig. 1. UV-vis absorption spectra of compound **4** in methanol under 365 nm of UV light (a) and visible light (b) irradiation, respectively.

Table 1
MIC values of the compounds **1–5** before and after UV excitation.

Compd.	Before UV excitation MIC (ppm)		After UV excitation MIC (ppm)	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*
1	>512	>512	>512	>512
2	32	110	32	110
3	32	32	32	32
4	4	128	1	16
5	256	512	32	512

rate [22]. At present, azobenzene molecules was widely applied in the fields of photo-pharmacology [23], surfactants [24], liquid crystal [25], biological macromolecules [26], energy storage compounds [27], anti-tumor [28], supramolecular self-assembly polymers, and nanoparticles [29]. Recently, azobenzene has been used to regulate the antimicrobial activity of molecules *in vitro* [30–32].

Here, we reported a series of azobenzene-quaternary ammonium salt antibacterial agents with photo-sensitive, intelligent, and reusable properties, which were prepared by connecting azobenzene with amines with different chain lengths. The antibacterial performance of the resulting compound (compound **4**) can be easily changed from weak to strong upon 365 nm light irradiation by changing the conformation of azobenzene from the nonpolar *trans*-isomer to the polar *cis*-isomer [33,34]. Compound **4** was selected as the research subject in a series of azobenzene-quaternary ammonium salt antibacterial agents prepared. UV-vis was used to study the *cis-trans* transformation of compound **4** before and after UV excitation. The light-responsive intelligent sterilization of compound **4** was tested in the solution and agar plate antibacterial experiments, the reusability of compound **4** and the possibility of inducing bacterial resistance were studied. The results showed that the minimal inhibitory concentration (MIC) of compound **4** to Gram-negative bacteria, *Escherichia coli* before and after UV excitation was 128 ppm and 16 ppm, and to Gram-positive bacteria, *Staphylococcus aureus* was 4 ppm and 1 ppm, respectively. Finally, this antibacterial agent has the characteristics of good yield, reusability, photosensitive sterilization, and does not induce drug resistance of *E. coli* and *Staphylococcus aureus*. This photosensitive antibacterial compound provides a new thought for the design of smart disinfection antibacterial agents and shows great potential as a candidate for antimicrobial in communal facilities and medical buildings.

Following the idea of designing intelligent antibacterial compounds based on QAS and azobenzene molecules, we first prepared the compounds according to the route shown in Scheme 1a. The chain length of QAS is closely related to its antibacterial effect [35]. To this end, azobenzene-quaternary ammonium salts (**1–5**) with different chain lengths were synthesized by utilizing amines with $n = 1$, 5, 9, 11, 13. Next, successful preparation was verified by ^{1}H NMR, ^{13}C NMR spectroscopy, and high-resolution mass spectrometry (Figs. S1–S15 in Supporting information). Having acquired azobenzene-quaternary ammonium salt compounds, we assessed the photoresponsive properties using UV–vis spectroscopy. 320 nm is the π-π^* absorption wavelength of azobenzene structure. When the azobenzene-quaternary ammonium salt compounds change from *trans*- to *cis*-structure, the absorption peak at 320 nm decreases obviously [26]. The *trans-cis* photoisomerization was also observed by the existence of a weak absorption peak around 440 nm that was consistent with the n–π^* transition of the *cis*-isomer (Figs. S16–S20 in Supporting information). The ratio of isomerization degrees for compounds **1–5** was 50%−70%, which was calculated based on Eq. S1 (Supporting information).

To investigate potential photo-degradation of compound **4**, UV–vis spectroscopy of compound **4** was recorded in detail under 365 nm and visible light irradiation, respectively. With the increase of UV excitation time, the absorbance of compound **4** solutions at 320 nm gradually decreased. After 5 min, the absorbance remained constant, indicating that most of compound **4** changed from *trans*- to *cis*-structure at this time (Fig. 1a). Subsequently, under visible light irradiation, the absorbance of compound **4** at 320 nm was gradually higher than that of the solution after complete UV excitation (UV, red line). After 45 min, the absorbance at 320 nm remained unchanged and the peak intensity at 440 nm decreased obviously, indicating that the majority of the compound structure at this moment returned from *cis*- to *trans*-structure (Fig. 1b). These results confirmed that the *trans-cis* isomerization of compound **4** occurred rapidly under UV irradiation, and most of the structures returned from *cis*- to *trans*-structure under white light, which was consistent with the known literature [25].

After the characterization, *E. coli* and *Staphylococcus aureus* were used to test the antibacterial activity of azobenzene-quaternary ammonium salt. The MIC of the compounds **1–5** before and after 365 nm photo-irradiation was tested by the broth dilution method (Table 1). The results showed that when the chain length was too short (compound **1**), the compound had no antibacterial activity against *E. coli* or *Staphylococcus aureus* before and after UV excitation (MIC > 512 ppm). Compounds **2** and **3** had antimicrobial activity against *E. coli* and *Staphylococcus aureus*, but the antibacte-

rial properties of the compounds did not change drastically before and after UV excitation. The antibacterial activity of compound **4** to *Staphylococcus aureus* changed from 4 ppm to 1 ppm before and after UV excitation, and to *E. coli* changed from 128 ppm to 16 ppm. The results represented that when the chain length was too long (compound **5**), the compound had no antibacterial activity against *E. coli* before and after UV excitation (MIC > 512 ppm), while the reverse happened in *Staphylococcus aureus*. This phenomenon can be attributed to the fact that increasing the alkyl chain length in the compounds **1–5** will improve its antibacterial effect [36–38]. However, due to the excessive bending/curling of the long alkyl chain (compound **5**), the quaternary ammonium sites were partially shielded, resulting in reduced antibacterial activity [39,40]. When alkyl chain length was 5 and 9, the *cis-trans* isomerization of azobenzene will not affect the antibacterial effect of the molecule (compounds **2** and **3**). The results suggested that this effect is due to the alkyl chain length and the *cis-trans* isomerization of azobenzene simultaneously affects the antibacterial effect of compounds.

The *cis-trans* isomerization of azobenzene groups changes the physical and chemical properties of substances [24], such as polarity, minimum critical micelle concentration (CMC), surface-active properties, and solubility [21], which could explain why the antibacterial effect of *cis*-isomer was better than *trans*-isomer. In addition, azobenzene-quaternary ammonium salt can interact with bacterial membrane components, such as phosphatidyl lactone, leading to membrane rupture and bacterial death eventually [41]. Due to the different membrane structures of Gram-negative bacteria and Gram-positive bacteria, and *Staphylococcus aureus* lacked outer membrane protection [42,43], it is reasonable that compounds **4** and **5** had better antibacterial effects on *Staphylococcus aureus* than *E. coli* before and after UV irradiation (Table 1). Ideally, the photo-controllable azobenzene-quaternary ammonium salt should exhibit significant antibacterial activity differences between the *trans* isomers and *cis* isomers and display a broad-spectrum antibacterial property. Table 1 clearly showed that compound **4** displays obvious changes in antibacterial activity before and after 365 nm irradiation, and was selected for further studies (Scheme 1b).

To validate the antibacterial mechanism of compound **4**, we hypothesize that the bactericidal activity of compound **4** originates from the QAS group. Utilizing the interaction of positive and negative charges, QAS can be adsorbed on bacterial membrane, and the alkyl chain of QAS can be inserted into bacteria, resulting in membrane damage and bacterial death [44].

We used *Staphylococcus aureus* as the research object to test the antibacterial mechanism of compound **4** [45]. Next, we observed the morphological changes of *Staphylococcus aureus* after incubation with compound **4** by scanning electron microscopy (SEM) [46]. *Staphylococcus aureus* was prone to wrinkles in the presence of 16 ppm compound **4**, and cracks appeared on the surface of the bacterial membrane, indicating that the integrity of membrane was damaged. In the presence of compound **4** at high concentrations (64 ppm), the bacteria ruptured (Fig. 2a and Fig. S21 in Supporting information). To directly quantify the effect of compound **4** on bacterial membrane integrity, we measured the bacterial membrane permeability and potential of *Staphylococcus aureus* in the presence of fluorescent dyes, PI and $DiSC_3(5)$ [47,48]. Compound **4** increased bacterial membrane permeability observed by PI staining (Fig. 2b and Fig. S22 in Supporting information). $DiSC_3(5)$ is a cationic fluorescent dye, providing a measure of bacterial membrane potential [49,50]. As expected, we observed that with the increase of compound **4** dose, the membrane potential gradually disappeared, which can be demonstrated by the increase of fluorescence (Fig. 2c). These findings suggested that compound **4**, like QAS, significantly disrupts the bacterial membrane potential and permeability barrier. The above results strongly proved that the bactericidal activity of compound **4** was derived from QAS. Previous studies have shown that QAS has the same antibacterial mechanism (destruction of bacterial membrane) against Gram-positive bacteria and Gram-negative bacteria, but shows stronger antibacterial activity against Gram-positive bacteria [51–53].

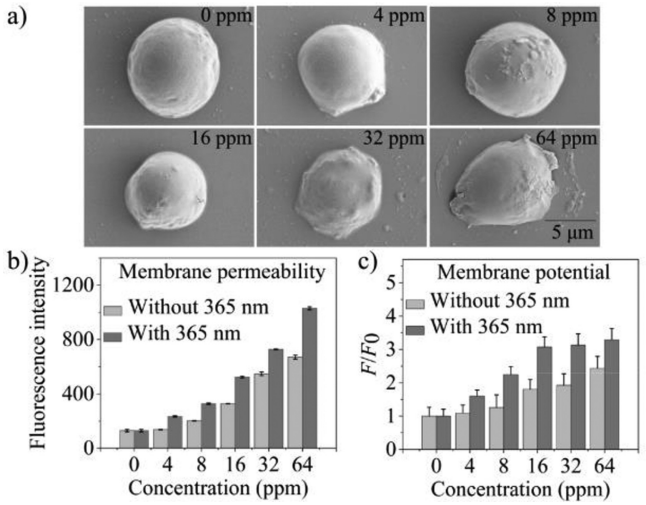

Fig. 2. (a) SEM images of *Staphylococcus aureus* after treatment with UV irradiated compound **4**. (b) Bacterial membrane permeability and (c) membrane potential of *Staphylococcus aureus* after treatment with compound **4**, detected with PI and $DiSC_3(5)$, respectively.

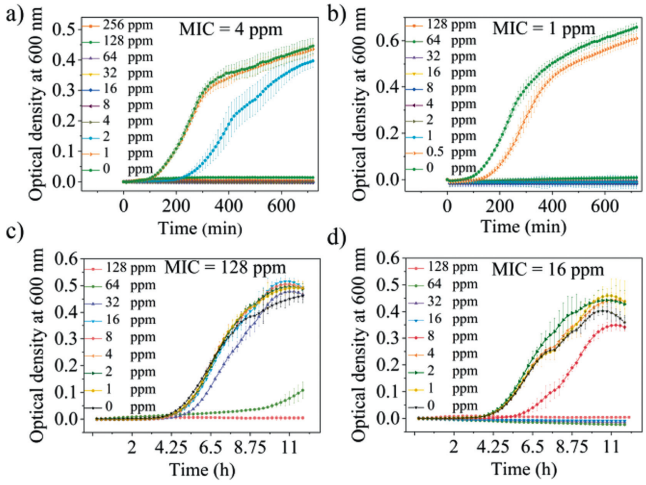

Fig. 3. Growth curves of *Staphylococcus aureus* after incubated with compound **4** before (a) and after (b) photoexcitation, respectively. Growth curves of *Escherichia coli* after incubated with compound **4** before (c) and after (d) photoexcitation, respectively.

To confirm whether compound **4** had photo-controlled antibacterial properties, we investigated the differences in bacterial growth curves after incubation with compound **4** before and after light irradiation. The difference in antibacterial activity of compound **4** against *Staphylococcus aureus* before (MIC = 4 ppm) and after (MIC = 1 ppm) photo irradiation was observed directly in Figs. 3a and b. In addition, we found that the MIC value of compound **4** against *E. coli* was 128 ppm when most of the compound was *trans*-structure, and the MIC value was 16 ppm when most of the compound was *cis*-structure as shown in Figs. 3c and d. The *cis*-isomer holds a significantly better antibacterial effect, resulting in 4 times and 8 times antibacterial activity difference. The difference in antibacterial activity appeared in both Gram-negative and Gram-positive bacteria, signifying that compound **4** had broad-spectrum

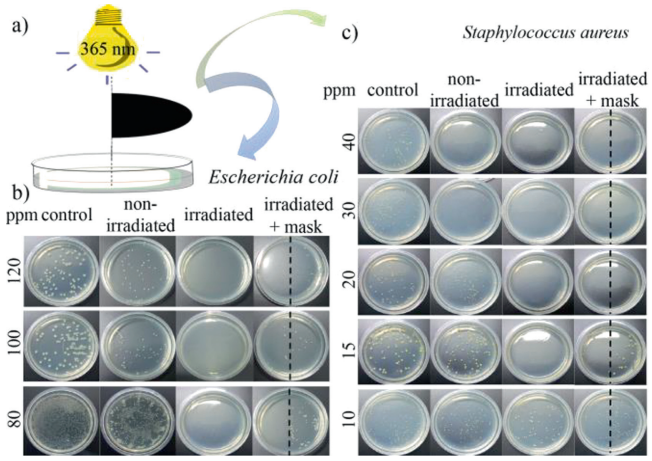

Fig. 4. (a) Schematic diagram of bacterial patterning experiment. (b) Pattern experimental results of *Escherichia coli*. (c) Pattern experimental results of *Staphylococcus aureus*. Compound **4** was mixed with LB solid medium then UV radiation for 30 min at 365 nm before inoculation of bacteria.

antimicrobial activity. These results revealed that compound **4** had photo-controlled antibacterial properties in solution.

Having established that compound **4** had photo-controlled antibacterial ability in solution, it was unknown whether compound **4** also had photo-controlled antibacterial ability under solid conditions. To clarify this, compound **4** at different concentrations was mixed into LB agar plates and divided into non-irradiated and irradiated groups. Subsequently, a baffle was placed above the LB agar plate containing compound **4** as the "irradiation + mask" group (Fig. 4a). In addition, Blank LB medium served as the control group. When the agar plate of the irradiated and the "irradiation + mask" group were exposed to 365 nm light for 30 min, compound **4** in the light region will be transformed into *cis* form with high antibacterial activity. Finally, all plates were coated with bacteria and cultured overnight at 37 °C.

For *E. coli*, the grown bacteria in the non-irradiated group at different concentrations were less than those in the control group, indicating that the non-irradiated compound **4** possesses a weak antibacterial activity, and the higher the concentration, the better the antibacterial effect. The UV radiation group could completely inhibit the growth of bacteria compared with the non-radiation group. Furthermore, bacterial colonies only grew in the agar region covered by the baffle, which can be attributed to the fact that compound **4** in this area is not activated by light and remains inactive. In contrast, there was rare bacterial growth in the ultraviolet radiation area of the agar plate (Fig. 4b).

For *Staphylococcus aureus*, the number of colonies in each radiation group decreased significantly compared with the control group at high concentrations (20–40 ppm), indicating that the antibacterial activity of compound **4** in the radiation group was great and the higher the concentration, the better the antibacterial effect. The growth of bacteria in the UV radiation group was completely inhibited compared with the non-radiation group. Besides, bacterial colonies only grew in the agar region covered by the baffle, which can be attributed to the fact that compound **4** (15 ppm) in this area is not activated by light and remains inactive. When the concentration of compound **4** was 10 ppm, obvious bacterial colonies can be observed in Fig. 4c. This may be the direct consequence of compound **4** mixed with culture medium and bacteria can only contact with compound **4** on the surface of culture medium [20]. In short, the photo-controllable antibacterial of compound **4** was observed in both solution and solid conditions, indicating that compound **4** has a wide range of application characteristics.

After establishing the light-controlled antibacterial effect of compound **4** under different conditions, it is curious whether compound **4** can be reused. We speculated that the transformation of antibacterial ability of compound **4** caused by *cis-trans* isomerization of azobenzene could be reproducible. To verify this hypothesis, we designed a complete antibacterial cycle test (see Supporting information for the details). The antibacterial cycle experiment was performed by determining the change of antibacterial activity caused by structure of the compound **4** under different conditions and contained 4 steps (Fig. 5a). (i) The MIC of Compound **4** to *Staphylococcus aureus* after the first UV irradiation was 1 ppm (Fig. S23a in Supporting information). (ii) When exposed to different conditions, the MIC values of compound **4** gradually increased from 1 ppm to 4 ppm (Figs. S23b-d in Supporting information). It indicated that most of the structures of compound **4** gradually changed from *cis*-structure to *trans*-structure, and the antibacterial performance decreased. (iii) When subjected to UV radiation again, most of the structure of compound **4** rapidly changed from the *trans*-isomer with poor antibacterial performance to the *cis*-isomer with high antibacterial performance, which reduced the MIC value of compound **4** against *Staphylococcus aureus* (Fig. S23e in Supporting information). (iv) After dark or visible light irradiation, the structures of compound **4** from *cis* form change to *trans* form. Subsequently, we verified that compound **4** could achieve 4 *cis-trans* reverse cycles (Fig. 5b), which is consistent with previous studies [20,54], suggesting that compound **4** can be reused.

The cyclic experiments clarified that compound **4** could spontaneously change from *cis*-isomer to *trans*-isomer under dark or visible light irradiation [55]. These results approve that the sterilization of compound **4** is photo-controllable and reusable.

Due to the unreasonable use of antibiotics in the world, the problem of bacterial drug resistance is extremely serious [3]. QAS is difficult to cause bacterial drug resistance due to its abnormal antibacterial mechanism. Compound **4** contains a quaternary ammonium group and has excellent antibacterial performance. Based on this, it is necessary to detect whether compound **4** can induce common pathogens to produce drug resistance. We compared the antibacterial activity of compound **4** against pathogens with three common antibiotics, namely amoxicillin, ampicillin, and erythromycin [47]. Amoxicillin (40 ppm), ampicillin (40 ppm), and UV-irradiated compound **4** (40 ppm) had the same antibacterial kinetics against *E. coli* (Fig. 6a). Furthermore, we tested the resistance of *E. coli* to amoxicillin, ampicillin, and irradiated compound **4** [9]. As expected, *E. coli* was rapidly developed resistance to amoxicillin within a few days. The maximum concentration of antibiotics in the test was 512 ppm, and the MIC value increased by nearly 128 times (Table S1 in Supporting information). The antibacterial activity of ampicillin fluctuated, and the MIC value increased by about 15 times. It is worth noting that compound **4** after UV radiation did not produce obvious drug resistance in *E. coli* during the 30 days experiment (Fig. 6b).

Amoxicillin (10 ppm), erythromycin (10 ppm), and irradiated compound **4** (5 ppm) had the same antibacterial kinetics against *Staphylococcus aureus* (Fig. 6c). It should be clear that the higher the concentration of compound **4**, the greater the initial absorption value of OD 600 nm. In addition, we tested the resistance of *Staphylococcus aureus* to amoxicillin, erythromycin, and compound **4**. As predicted, *Staphylococcus aureus* was rapidly resistant to amoxicillin and erythromycin in a short time. The MIC value of amoxicillin and erythromycin increased by about 512 times. Surprisingly, *Staphylococcus aureus* was not resistant to compound **4** after UV irradiation within 30 days (Fig. 6d). All of these results indicated that compound **4** after ultraviolet radiation was an excellent antibacterial agent that did not produce resistance to Gram-negative bacteria and Gram-positive bacteria. In summary, the antibacterial activity of compound **4** can be regulated by the photo-

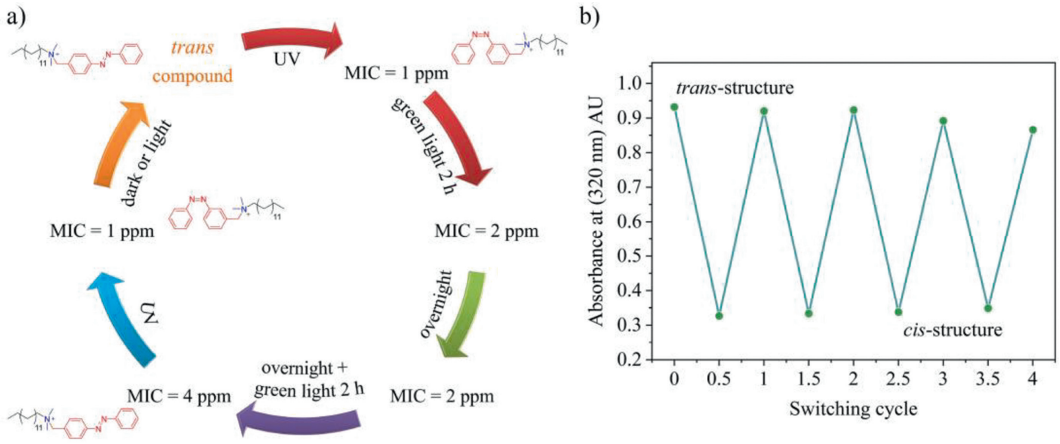

Fig. 5. (a) Schematic diagram of the antibacterial cycle test. (b) Reversible photochromism of compound **4**, observed by monitoring the absorbance at $\lambda = 320$ nm.

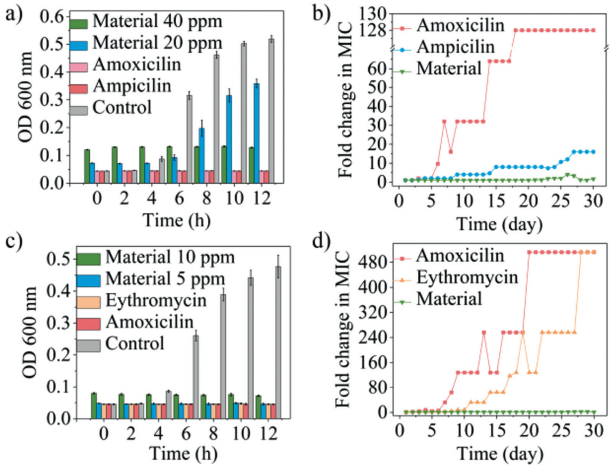

Fig. 6. Time-kill kinetics of compound **4** against *Escherichia coli* (a) and *Staphylococcus aureus* (c), respectively. Fold increase in MIC of *Escherichia coli* (b) and *Staphylococcus aureus* (d) to compound **4**, antibiotics after 30 days of serial passaging in each drug.

induced *cis-trans* isomerization, and the antibacterial activity of compound **4** can be automatically inactivated after action. These all contribute to the sterilization of compound **4** without inducing drug resistance.

In conclusion, azobenzene-quaternary ammonium salt antibacterial agents with photosensitivity and automatic inactivation characteristics were prepared to improve the antibacterial selectivity of QAS and reduce the residue of QAS with high antibacterial. UV–vis spectroscopy showed that compound **4** rapidly changed from *trans*- to *cis*-structure after UV excitation. Bacterial membrane permeability, membrane potential experiments, and scanning electron microscopy images confirmed that the antibacterial property of compound **4** originated from the efficient destruction of bacterial membrane structure by QAS. The growth curve of bacteria manifested that the MICs of compound **4** to *Staphylococcus aureus* before and after UV irradiation were 4 ppm and 1 ppm, and to *E. coli* were 128 ppm and 16 ppm, respectively. The photo-controllable antibacterial test reflected that the antibacterial effect of compound **4** was significantly enhanced after UV excitation. Compound **4** has photosensitive antibacterial property, and the antibacterial ability is proportional to the concentration. The reusability assay proved that compound **4** could be reused. Besides, compound **4** after UV radiation did not produce obvious drug resistance in *E. coli* and *Staphylococcus aureus* during the 30 days experiment. This photosensitive antibacterial compound provides a new thought for the design of intelligent disinfection antibacterial agents and shows great potential as a candidate for disinfection antibacterial agents in communal facilities and healthcare buildings.

Declaration of competing interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.05.057.

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