Supporting Information

H_2S Donor Functionalized Molecular Machine for Combating Multidrug-Resistant Bacteria Infected Chronic Wounds

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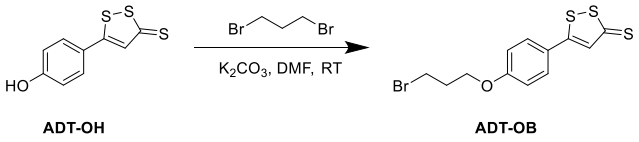
1. Experimental Procedures

1.1 Materials and Instruments

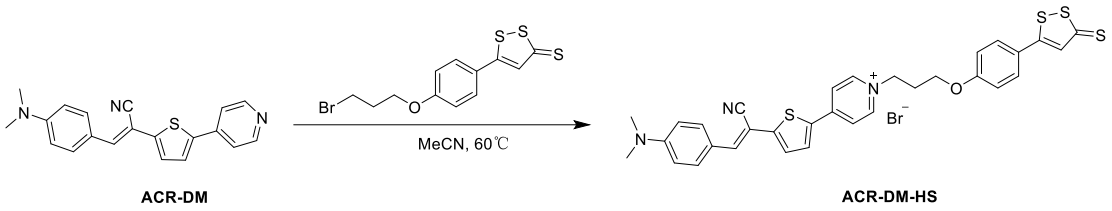
All chemical reagents were obtained from *J&K* Scientific and used without any further purification. The H_2DCF (2,7-dichlorofluorescein diacetate) Detection Kit, Rose Bengal (RB), and 9,10-anthracenediylbis(methylene)dimalonic acid (ABDA) were obtained from Sigma-Aldrich, while the 3'-p-(hydroxyphenyl)fluorescein (HPF) was sourced from Aladdin. For thin-layer chromatography (TLC) analysis, silica gel GF 254 was utilized. Column chromatography purification was conducted using silica gel with a particle size of 200-300 mesh. NMR spectra were recorded on a Bruker AMX-400, with chemical shifts reported in ppm relative to the TMS internal reference. High-resolution mass spectra were recorded using a Bruker Daltonics Bio TOF mass spectrometer. Raman spectra were obtained experiments using a DeepBlue200 confocal micro-Raman spectrometer (Southwest Spectro Technology co.,Ltd). Fluorescence spectra were recorded using a Horiba Duetta spectrofluorimeter with a 10 mm quartz cuvette, while UV-vis absorption spectra were obtained with a Hitachi Pharma Spec UV-1900 UV-visible spectrophotometer. Confocal fluorescence images were captured using a Nikon A1R+ confocal laser scanning microscope. The light source was a white LED illuminator from Opple Lighting Co., with intensities of 5 mW/cm^2 for *in vitro* experiments and 20 mW /cm^2 for *in vivo* studies.

1.2 Synthesis and Characterization of MMs



ADT-OH ADT-OB

ADT-OB: 5-(4-hydroxyphenyl)-3H-1,2-dithiacyclopentene-3-thione (ADT-OH) (200 mg, 0.88 mmol), 1,3-dibromopropane (536 mg, 2.64 mmol), and potassium carbonate (656 mg, 4.79 mmol) were dissolved in 15 mL DMF and stirred at room temperature. The reaction was monitored using thin-layer chromatography (TLC). After completion, the reaction mixture was extracted with ethyl acetate and washed three times with brine. The resulting ethyl acetate solution was dried over anhydrous sodium sulfate and then removed under vacuum to obtain the crude product, which was purified using silica gel column chromatography with a petroleum ether/ethyl acetate eluent (*V*:*V*= 20:1) to obtain ADT-OB (orange solid, 220 mg) with 72% yield.



Scheme S1. Synthetic route to ACR-DM-HS.

(*E*)-4-(5-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)thiophen-2-yl)-1-(3-(4-(3-thioxo-3H-1,2-dithiol-5-yl)phenoxy)propyl)pyridin-1-ium named ACR-DM-HS: ACR-DM was synthesized according to our previous work [1]. ACR-DM (100 mg, 0.3 mmol) and ADT-OB (104 mg, 0.3 mmol) were dissolved in 30 mL of acetonitrile and stirred at 60°C for 24 hours. After removed the solvent, the crude product was purified by silica gel column chromatography using a dichloromethane/methanol eluent (*V*/*V* = 20:1) to obtain 130 mg red solid, with a yield of 64%. ^{1}H NMR (400 MHz, DMSO) *δ*. 9.01 (d, *J* = 6.8 Hz, 2H), 8.29 (dd, *J* = 8.8, 5.2 Hz, 3H), 7.92-7.80 (m, 5H), 7.74 (s, 1H), 7.59 (d, *J* = 4.0 Hz, 1H), 7.00-6.91 (m, 2H), 6.89-6.78 (m, 2H), 4.72 (t, *J* = 6.8 Hz, 2H), 4.22 (t, *J* = 5.6 Hz, 2H), 3.07 (s, 6H) , 2.51-2.39 (m, 2H). ^{13}C NMR (150 MHz, DMSO) *δ*. 214.83, 173.62, 161.37, 152.48, 147.85, 147.33, 144.84, 143.77, 134.84, 134.24, 133.65, 131.90, 128.98, 126.05, 123.93, 121.66, 119.84, 117.98, 115.42, 111.83, 95.21, 65.37, 57.48, 40.43, 29.58. HRMS (ESI): m/z [M - Br $^{-}$] $^{+}$ calcd for $C_{32}H_{28}N_3OS_4$: 598.1110; found 598.1114.

1.3 Quantum Mechanical Calculations

The quantum mechanical calculations were performed using Gaussian 16. Full geometry optimizations and harmonic frequency calculations were conducted for all molecules in DMSO and in both ground and excited states using density functional theory (DFT) and time-dependent density functional theory (TD-DFT) methods, respectively. The absorption spectra and transition densities were calculated using TD-DFT. The vibrationally resolved absorption spectra were obtained within the framework of the Franck-Condon (FC) principle upon TD-DFT based overlap integrals between the vibrational wave functions of the ground and the excited states. The rendered spectra were calculated by convoluting the resonant energy intensity with a Gaussian with a half width at half-maximum (HWHM) of 135 cm^{-1}, which still allows us to assign individual vibronic contributions to the total spectrum.

1.4 Raman Spectroscopy

Raman spectra was obtained using a DeepBlue200 confocal micro-Raman spectrometer (Southwest Spectro Technology co.,Ltd). A single-crystal silicon standard was used for calibration. All spectra were acquired using a 785nm wavelength and a 100× objective lens. A grating of 1200 line with a confocal hole 200 μm were used, resolution of ~6 cm^{-1}. A laser attenuation of 25% provided a power at the sample surface of ~50 mW. Analyses were acquired with an exposure time of 1s for three times. The backscattered Raman radiation was collected between 200-3150 cm^{-1}

1.5 Measurement of ROS Generation Efficiency

10 μM H_2DCF was added to the PBS solution containing 5 μM MM with or without 1000 μM Vc. The mixture was then subjected to light irradiation for 0-210 seconds. The fluorescence intensity at 525 nm was measured using a fluorescence spectrometer, with an excitation wavelength of 488 nm.

1.6 Cyclic Voltammetry Measurements

A cyclic voltammetry experiment was performed utilizing a three-electrode setup. A platinum-carbon composite electrode served as the working electrode, while a platinum wire acted as the auxiliary electrode and an Ag/AgCl electrode functioned as the reference electrode. The measurements were conducted in a 0.01 M PBS solution. The scanning range was established between -1.6 V and 0.6 V, with a scan rate of 20 mV/s.

1.7 Detection Singlet Oxygen Generation Efficiency.

ABDA (50 μM) was mixed with either the MM or RB (5 μM) in water, and then exposed to white light for 0 to 360 seconds. The absorbance of ABDA at 378 nm was recorded at different illumination times to determine the decay rate.

1.8 Detection of Hydroxyl Radicals

5 μM HPF was added to a water solution containing 5 μM MM, which was then irradiated with white light. The fluorescence intensity at 515 nm was recorded to evaluate the ·OH generation efficiency with an excitation wavelength of 488 nm.

1.9 EPR Analysis

For capturing the generation of free radicals, DMPO (100 mM) was mixed with MM (1 mM) in PBS. The solution was exposed to white light irradiation (5 mW/cm^2) for 5 minutes, and the EPR spectra were collected immediately.

1.10 Bacterial Culture

Escherichia coli (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) were sourced from the China General Microbiological Culture Collection Center (CGMCC). Methicillin-resistant *Staphylococcus aureus* (MRSA) was kindly provided by the Sichuan Industrial Institute of Antibiotics at Chengdu University, China. A single bacterial colony from a solid culture medium was transferred to 10 mL of lysogeny broth (LB) and incubated at 37 °C for 12 hours with shaking at 200 rpm. Subsequently, the bacteria were harvested by centrifugation at 8000 rpm for 3 minutes, washed three times with PBS, resuspended in PBS, and diluted to an optical density of approximately 10^8 CFU/mL. The concentration of the bacterial suspension was determined by measuring the absorbance at 600 nm using a cell density meter.

1.11 *In Vitro* Antibacterial Experiments

The antibacterial activity of MMs was assessed using the plate counting method. The bacterial suspension was incubated with different concentrations of MM in the dark for 10 minutes. Subsequently, the suspension was centrifuged at 8,000 rpm for 3 minutes. The bacteria were then washed three times with PBS and re-suspended in PBS. They were further treated either in the dark for 30 minutes or under white light for 30 minutes in the present or absent of 1,000 μM Vc. Subsequently, the bacteria were diluted with PBS to approximately 10^4 CFU/mL, spread on an agar plate, and incubated overnight at 37 °C. Bacterial viability was then determined and quantified through optical density measurements.

1.12 Minimum Inhibitory Concentration

To investigate the minimum inhibitory concentration (MIC) of ACR-DM-HS, different concentrations of ACR-DM-HS were incubated with MRSA or *E. coli* in the dark for 10 minutes, followed by 30 minutes of white light irradiation. The samples were then centrifuged to remove the supernatant, after which 1 mL of LB liquid medium was added. The following day, cultures were inspected for growth, and the MIC was identified as the lowest ACR-DM-HS concentration resulting in no visible growth.

1.13 Scanning Electron Microscopy (SEM) Analysis

The MRSA or *E. coli* with different treatment were fixed with 2.5% glutaraldehyde overnight, washed three times with PBS and sequentially dehydrated using increasing ethanol concentrations (30%, 50%, 75%, 90%, 95%, and 100%) for 15 minutes. Finally, the samples were disposed with metal spraying for SEM analysis (COXEM EM-30).

1.14 Transmission Electron Microscopy (TEM)

1×10^8 CFU/mL MRSA was incubated with 10 μM ACR-DM-HS for 10 minutes, followed by 30 minutes of white light irradiation in the absence or presence of Vc. An untreated bacterial suspension with the same concentration was used as control group. All the suspensions were centrifuged and washed with sterile water. The collected bacteria were mixed with glutaraldehyde solution and fixed at 4 °C overnight. The fixed buffer was removed, and then the bacteria were washed and dehydrated. Additionally, the bacteria were subjected to a 20 minutes treatment with acetone, followed by a 1-hour treatment with a mixture of acetone and embedding agent and another 3-hour treatment with a mixture of acetone and embedding agent. After permeabilization, the bacteria were embedded overnight at 70 °C. Then, the samples were sectioned. The above sections were observed by TEM.

1.15 Detection of Cytoplasmic Materials

1×10^8 CFU/mL MRSA was incubated with different concentrations of ACR-DM-HS for 10 min, and then under 30 min white light irradiation in the absence or presence of Vc. An untreated bacterial suspension with the same concentration was used as control group. After that, the samples were processed through a 0.22-micron filtration membrane to harvest the supernatant. The supernatant was subsequently measured for its absorbance based on UV absorption at 260 nm.

1.16 Bacterial Drug Resistance

Incubate MRSA with different concentrations of Van for 12 hours, or treat it with ACR-DM-HS for 10 minutes followed by 30 minutes of white light exposure, and then evaluate bacterial survival using the plate colony counting method. From the plate where bacteria survive at the highest drug concentration, select a single colony and continue culturing the bacteria until they reach a concentration of 10^8 CFU/mL. Repeat these experimental step MM until MRSA develop MM resistance to the drugs.

1.17 Zeta Potential Measurements

Approximately 10^8 CFU/mL bacteria were incubated with or without 5 μM MM for 10 minutes at room temperature, then harvested by centrifugation at 8,000 rpm for 3 minutes. The bacteria were subsequently resuspended in H_2O and analyzed for zeta potential using a Nano ZS (ZEN3600).

1.18 Fluorescence Imaging

About 1×10^8 CFU/mL bacteria were incubated with 10 μM MM for 10 minutes, after washed with PBS, the bacterial suspensions were either exposed to white light or kept in the dark for 30 minutes in the absent or present of 1,000 μM Vc. Subsequently, counter-stained with 20 μM Hoechst 33342 for 20 minutes. 15 μL of the stained bacterial solution was placed on a confocal laser dish and covered with a coverslip. Fluorescence imaging was conducted using a Nikon A1R+ laser scanning confocal microscope. For Hoechst 33342, a 405 nm laser and a 430-480 nm emission filter were employed. For the MM, a 561 nm laser and a 650-750 nm emission filter were used.

1.19 Live/Dead Bacterial Imaging

The bacterial suspension was incubated with different concentrations of MM in the dark for 10 minutes, followed by centrifugation at 8,000 rpm for 3 minutes. The supernatant was discarded, and the bacteria were washed three times with PBS and re-suspended in PBS. The suspension was then irradiated under white light for 30 minutes in the present of 1,000 μM Vc, followed by stained with Sytox Green for 20 minutes. The suspension was centrifuged again at 8,000 rpm for 3 minutes, and the supernatant was discarded. The bacteria were washed three times with PBS and re-suspended in PBS for confocal laser scanning microscopy (CLSM) and flow cytometry detection using a BD Accuri C6 Plus. The emission was collected at 503–563 nm with the excitation of at 488 for Sytox Green.

1.20 Molecular Dynamics Simulations

Molecular dynamics (MD) simulations were performed to investigate the interactions between MMs and simulated bacterial plasma membrane using the free and open-source software GROMACS/2023. Simulations were performed using CHARMM36 force field with the solvent water model of TIP3P, and the charge of the system was neutralized by sodium chloride. The plasma membrane of *S. aureus* was modeled as a mixed lipid bilayer comprising DOPC and DOPG lipids (≈7:3 ratio).

1.21 *In Vitro* Antibiofilm

The bacteria were cultured at 37 °C for 36 hours in LB medium to form biofilm. The biofilm was incubated with MM for 30 minutes, washed with PBS three times, irradiated with white light for 30 minutes. The residual biofilm was stained with 1.0% crystal violet. Subsequently, the stained biofilm was washed three times with PBS, dissolved in 33% glacial acetic acid, and the absorbance was measured at 590 nm to detect the remaining biofilm biomass. Additionally, the biofilm was stained with Sytox

Green and observed under a CLSM to further assess biofilm clearance.

1.22 SEM Images of Bacterial Biofilm

Bacterial biofilms subjected to various treatments were fixed with a 2.5% glutaraldehyde solution, dehydrated using a graded ethanol series, and allowed to dry naturally. Finally, the samples were prepared with metal spraying for SEM analysis.

1.23 Hydrogen Sulfide Detection

Mouse macrophages (RAW264.7) and human umbilical vein endothelial cells (HUVECs) were cultured in DMEM supplemented with 10 % FBS, 100 units/mL of penicillin, and 100 μg/mL of streptomycin in a humidified 5 % CO_2 incubator at 37 °C. Once the cells reached 80-90 % confluence, they were dissociated into single cells with 0.05 % Trypsin-EDTA at 37 °C for 5 min and passaged at a ratio of 1:2 in a new cell culture dish.

RAW264.7 cells were seeded into a 6-well plate to 80% confluency. The cells were detached, centrifuged at 500 rpm for 5 minutes, and the resulting cell pellet was washed three times with cold PBS. The resulting cell suspension was further centrifuged at 500 rpm for 5 minutes, resuspended in passive lysis buffer at a concentration of 1×10^7 cells/mL, and vortexed at 4 °C temperature for 10 minutes. Subsequently, hydrogen sulfide levels of ACR-DM-HS were detected using a hydrogen sulfide detection kit according to the manufacturer's protocol.

20 mL of 1×10^8 CFU/mL MRSA bacterial solution at logarithmic growth stage were centrifuged at 8,000 rpm for 10 minutes. After discarding the supernatant, the bacterial pellet was frozen in liquid nitrogen for 10 seconds and thawed in a 37 °C water bath. This freeze-thaw cycle was repeated five times. Subsequently, hydrogen sulfide levels of ACR-DM-HS were detected using a hydrogen sulfide detection kit according to the manufacturer's protocol.

WSP-5 was used as an intracellular H_2S probe to detect intracellular H_2S. HUVEC cells were seeded into a 48-well plate to 80% confluency. After adding 20 μM ADT-OH or ACR-DM-HS, they were incubated for 12 hours, followed by the addition of WSP-5 and incubation for 30 minutes. 1×10^8 CFU/mL MRSA was treated with 20 μM ADT-OH or ACR-DM-HS for 12 hours, then incubated with 10 μM WSP-5 for 30 minutes. Images were collected using a CLSM (A1R+, Nikon, Japan). For WSP-5: λ_{ex} = 502 nm and λ_{em} = 510-530 nm.

1.24 Cellular Uptake

The HUVECs cells (1×10^5 cells/mL) were cultured in 35 mm culture dishes for 24 hours until the cells reached 80%-90% confluence. After removing the culture medium, 10 μM ACR-DM-HS was added and incubated for 1 hour, followed by three washes with PBS. MRSA (1×10^8 CFU/mL) was incubated with 10 μM ACR-DM-HS for 1 hour, followed by centrifugation to remove the supernatant and washing three times with PBS. Images were collected using a CLSM (A1R+, Nikon, Japan). For ACR-DM-HS: λ_{ex} = 561 nm and λ_{em} = 650-750 nm.

1.25 Selective Bactericidal Experiment

HUVECs (1×10^5 cells/mL) were cultured on 35 mm culture dishes. After 24 h of incubation, 1×10^8 CFU mL−1 of MRSA in 1 mL PBS were added to the cell culture. The mixtures of cells and bacteria were incubated with 10 μM ACR-DM-HS for 10 min at 37 °C. The solution containing the labeled bacteria was carefully transferred into a 1.5 mL centrifuge tube, collected by centrifugation, washed with 1 mL of PBS, and resuspended in 1 mL of PBS. The labeled cells in the culture dish were washed with 2 mL PBS. The labeled bacteria solution was then added back to the culture dish. The mixtures were exposed to white light (5 mW cm^{-2}) for 30 min. After light exposure, the mixtures were stained with 10 μM Sytox Green for 10 minutes. The upper solution containing the labeled bacteria was transferred into a 1.5 mL centrifuge tube and washed with PBS. The labeled cells in the culture dish were also washed with PBS. An appropriate volume of the labeled bacteria solution was added back into the culture dish. Images were collected using a CLSM (A1R+, Nikon, Japan). For ACR-DM-HS: λ_{ex} = 561 nm and λ_{em} = 650-750 nm; Sytox Green: λ_{ex} = 488 nm, λ_{em} = 500-550 nm.

1.26 Hemolysis Assay

Fresh mouse blood was centrifuged at 2,000 rpm for 10 minutes to isolate red blood cells (RBCs). The RBCs were subsequently resuspended in PBS to obtain a 2% RBC suspension.180 μL of the 2% RBC suspension was mixed with 20 μL of PBS containing different concentrations (5, 10, 15, and 20 μM) of ACR-DME or ACR-DM-HS, incubated for 30 minutes at 37°C, followed by 30 minutes of white light irradiation. Triton X-100 and PBS were employed as the positive and negative controls, respectively. After a 10-minute centrifuged at 2,000 rpm, optical density (OD) of the supernatant at 540 nm was measured using a microplate reader. The hemolysis ratio (%) was calculated as follows:

$$\text{Hemolysis rate (\%)} = \frac{OD_{\text{experimental}} - OD_{\text{negative control}}}{OD_{\text{positive control}} - OD_{\text{negative control}}} \times 100\%$$

1.27 Cell Counting Kit-8 (CCK-8) Assay for Evaluating Cell Cytotoxicity

The standard CCK-8 assay was utilized to assess the toxicity of the MM to mammalian cells. Approximately 5000 cells per well were seeded in 96-well plates with 100 μL of culture medium and cultured overnight until reaching 70-80% confluence. The medium was then replaced with 100 μL of fresh medium containing different concentrations of MM (0-20 μM) for 10 minutes. The cells were kept in the dark or exposed to white light for 30 minutes. After 12 hours of incubation, 10 μL of CCK-8 solution mixed with 90 μL of medium was added to each well for an additional 1-hour incubation. The absorbance at 450 nm was measured using an ELISA plate reader. Cell viability was calculated using the formula:

$$\text{Cell viability (\%)} = (OD_{experimental} - OD_{cck8}) / (OD_{control} - OD_{cck8}) \times 100\%$$

1.28 Fluorescence Imaging of Intracellular ROS

HUVECs were seeded in a 48-well plate at an appropriate density and cultured for 12 hours. The cells were then incubated with 100 μM hydrogen peroxide (H_2O_2) for 12 hours. The cells were treated MM or NaHS for an additional 12 hours. Subsequently, the cells were incubated with H_2DCF for 30 minutes, gently rinsed with PBS. The fluorescence images were captured using CLSM. For H_2DCF, a 488 nm laser and a 500-550 nm emission filter were employed.

1.29 *In Vitro* Anti-inflammatory Activity Study

The anti-inflammatory activity of MM was assessed by quantifying the expression levels of the inflammatory cytokines, TNF-α and IL-6, via ELISA assay. RAW264.7 cells were seeded into 96-well plates at an appropriate density, cultured for 24 hours, and subsequently incubated with 0.5 μg/mL LMM for 8 hours to induce inflammation. The cells were treated with MM or NaHS for an additional 12 hours and then exposed to light for 30 minutes. Supernatants from the culture media were then collected. The TNF-α and IL-6 levels were measured using a commercial ELISA kit following the manufacturer's protocol. RAW264.7 cells without any treatment served as the control group.

1.30 Cells Migration Experiments

Mouse fibroblasts (L929) cells were seeded into 12-well plates at a density of 1×10^5 cells per well, and scratch wounds were formed by scraping with a sterile 200 μL pipette tip and washed with PBS to remove unattached cells. The attached cells were then

incubated with MM or NaHS. L929 cells were photographed at 0, 6, 12 and 24 hours. Migration was assessed by calculating the area of closure.

1.31 *In Vitro* Angiogenesis Assay

The *in vitro* pro-angiogenic ability of the MM was evaluated by examining the tube-like structures formed by HUVECs. A matrigel matrix was added to each well of a 48-well plate and pre-incubated at 37 °C for 30 minutes. Subsequently, 1×10^4 HUVECs were seeded onto the matrigel. After cell adherence, the cells were treated with MM or NaHS. The tube-like structures formed by HUVECs were rinsed with PBS and recorded at 2, 6, and 8 hours.

1.32 Establishment of Diabetes Mouse Model and Assessment of Skin Injury

All animal procedures were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of Sichuan Province, and the project protocols were approved by the Animal Ethics Committee of Southwest Jiaotong University (Approval No. SWJTU-2403-NSFC (014)). All tools, instruments, and equipment used have been pretreated with proper disinfection to ensure aseptic conditions (disinfection with 75% ethanol or ultraviolet sterilization). Wistar rats (weighing 200-250 g) were provided by Chengdu Dashuo Experimental Animal Co., Ltd. After one-week acclimatization, they were intraperitoneally injected with 65 mg/kg streptozotocin (STZ) to construct diabetes mouse model. Rats with blood glucose levels exceeding 16.7 mmol/L for over a week were considered successful. Approximately 1 cm in diameter skin wound was created. Bacterial infection was induced by MRSA (10^8 CFU/mL). The rats were randomly divided into five groups. MM: the control group (PBS treatment), the ACR-DM-HS group (treated with 20 μM ACR-DM-HS), the Van group (treated with 20 μM Van),the ACR-DME + L group (treated with 20 μM ACR-DME and irradiated with 20 mW/cm^2 for 30 minutes), and the ACR-DM-HS + L group (treated with 20 μM ACR-DM-HS and irradiated with 20 mW/cm^2 for 30 minutes).

On days 1, 3, 7, and 12, the rat from different group MM were euthanized to obtain infected tissue samples, which were then homogenized in normal saline and diluted 10,000-fold. A 30 μL aliquot of the bacterial suspension was spread on LB agar plates, incubated at 37 °C for 24 hours, and the resulting colonies were counted for analysis. Additionally, tissue samples were fixed in 4% paraformaldehyde for H&E staining, Masson staining and immunohistochemical staining (TNF-α, IL-6, VEGF, CD31 and TGF-β) to evaluate the treatment effects. On day 12, 1 mL blood samples were collected

from the orbital venous plexus of rat from different group MM and allowed to sit at 4 °C for 10-20 minutes before being centrifuged at 3000-3500 rpm for 10-15 minutes. The supernatant was then collected and stored at -20 °C for blood biochemical analysis. Subsequently, the mice were euthanized and dissected to obtain the heart, liver, spleen, lung, and kidney for H&E staining.

To detect the *in vivo* H_2S release from ACR-DM-HS, diabetic rats with MRSA-infected wounds were incubated with ACR-DM-HS for 12 h, followed by euthanasia. The wound tissues were immediately collected and frozen at -80 °C for sectioning. The tissue sections were stained with WSP-5 for 30 min and then subjected to fluorescence imaging analysis using a confocal laser scanning microscope.WSP-5: λ_{ex} = 502 nm and λ_{em} = 510-530 nm.

Blood biochemical analysis was conducted by Chengdu Lilai Biotechnology Co., LTD. H&E staining, Masson staining and immunohistochemical staining were performed at Wuhan Service Biotechnology Co., LTD.

1.33 Statistical Analysis

All reported values were performed using Origin 2018, and the statistical calculations were repeated at least three times independently. All experimental statistics were expressed as means ± standard deviations and analyzed using one-way ANOVA in GraphPad Prism software. The significance levels were denoted as follows: 'ns' denotes no significance; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, ****$p < 0.0001$.

2. Supplementary Figures

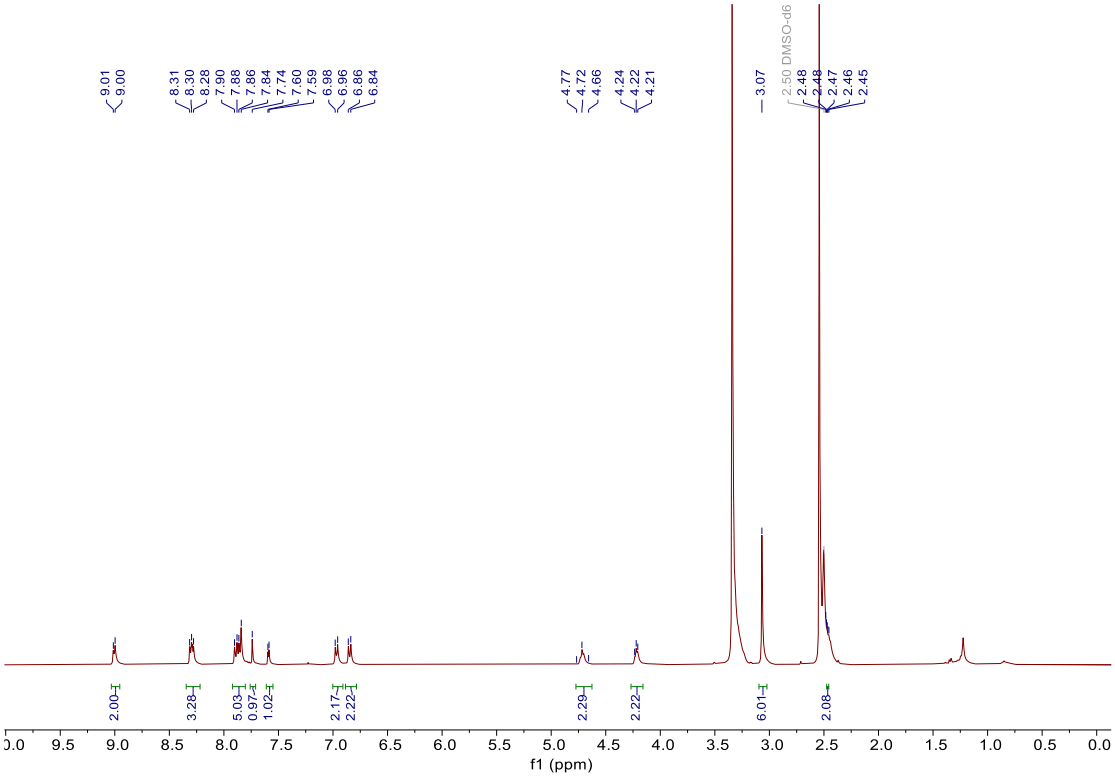


Figure S1. ^{1}H NMR of ACR-DM-HS in DMSO-d_6.

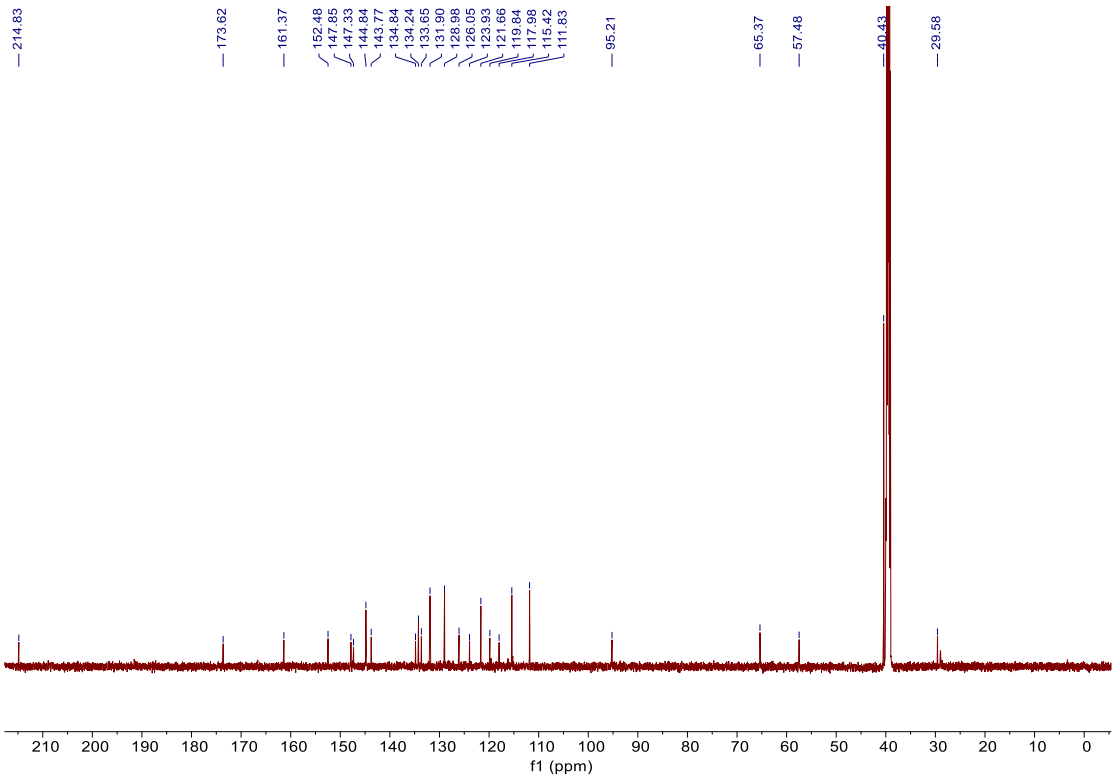


Figure S2. ^{13}C NMR of ACR-DM-HS in DMSO-d_6.

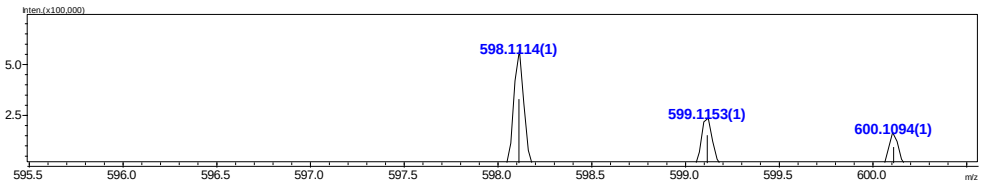


Figure S3. HRMS of ACR-DM-HS.

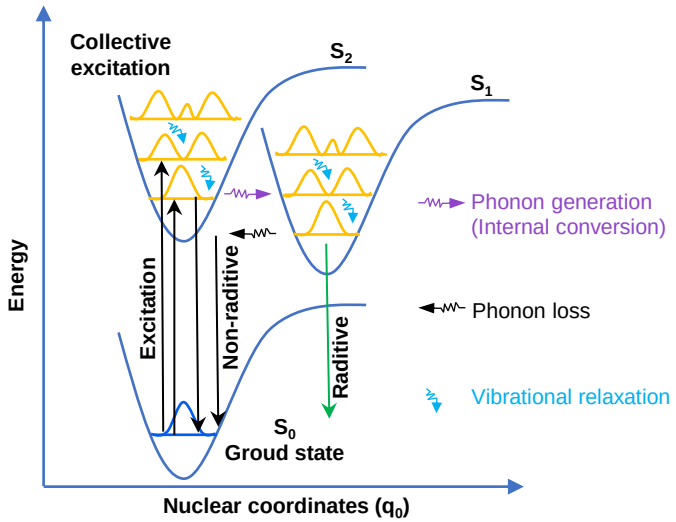


Figure S4. Molecular electron-phonon coupling in a Jablonski diagram.

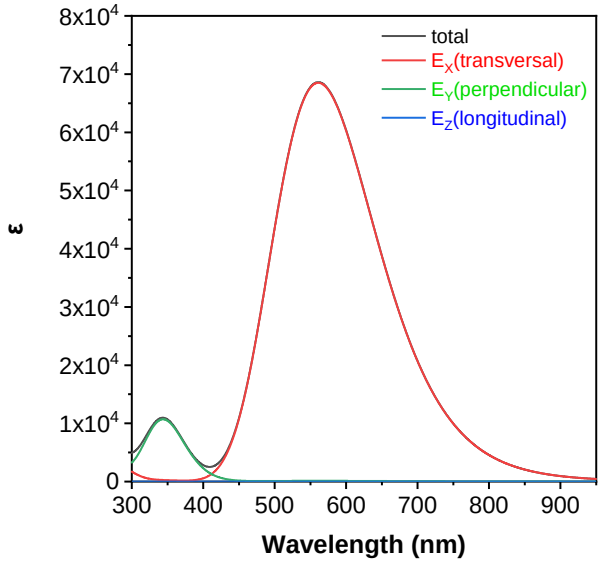


Figure S5. TD-DFT calculated total and partial absorption spectra of ACR-DME.

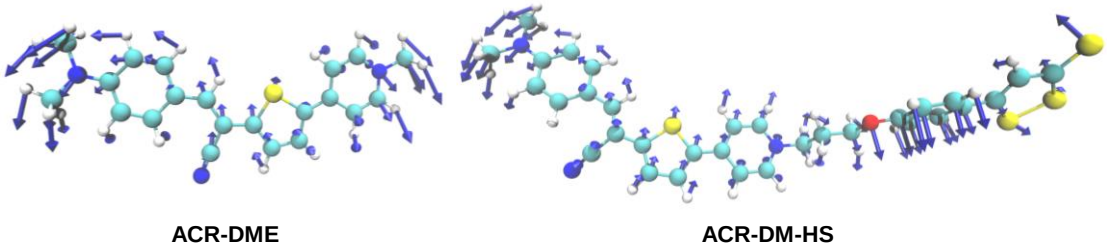


Figure S6. The vibration vectors obtained from TD-DFT calculations and visualized using VMD software.

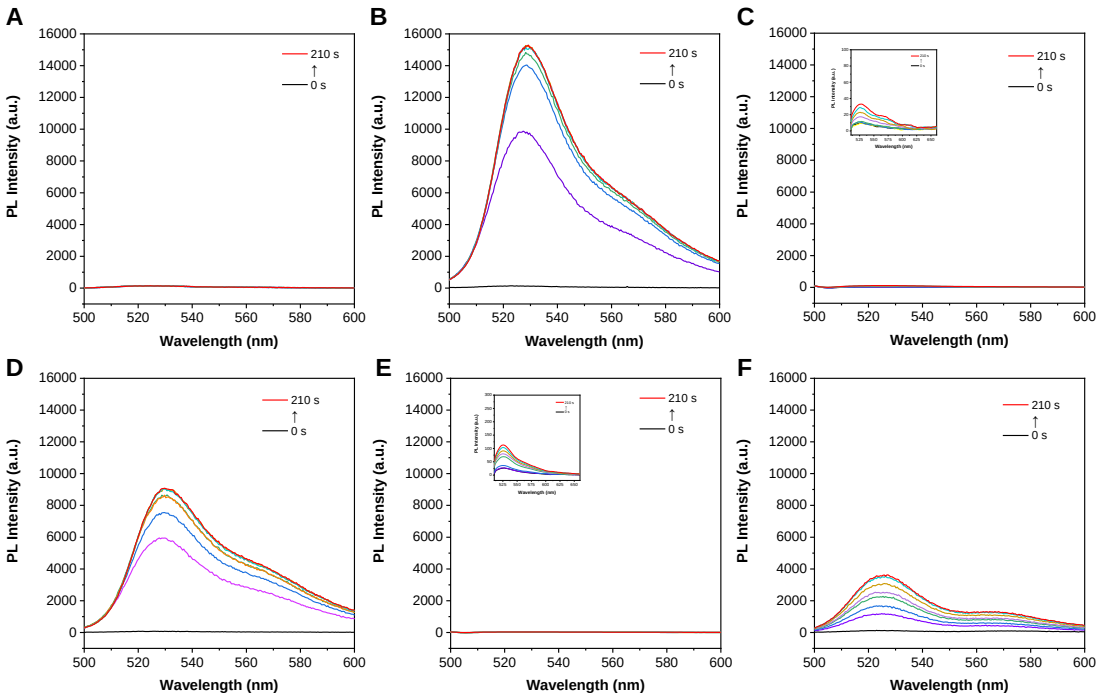


Figure S7. Photoluminescence spectra of H_2DCF in PBS (A) and in the presence of (B) ACR-DM-HS, (C) ACR-DM-HS and Vc, (D) ACR-DME, (E) ACR-DME and Vc, (F) RB under white light irradiation.

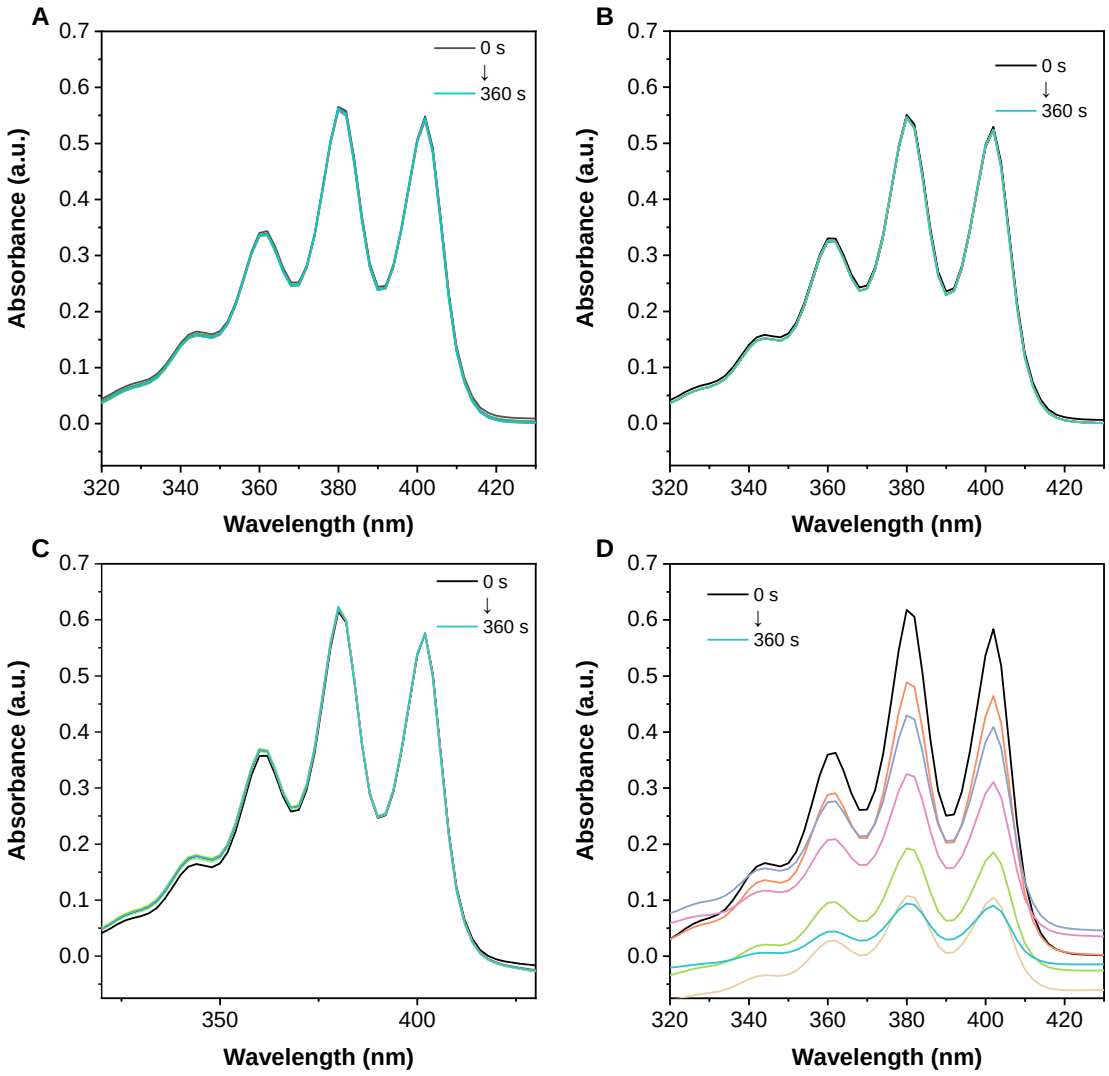


Figure S8. Absorption spectra of ABDA (50 μM) in PBS (A), or in the presence of 5 μM (B) ACR-DM-HS, (C) ACR-DME, (D) RB under white light irradiation.

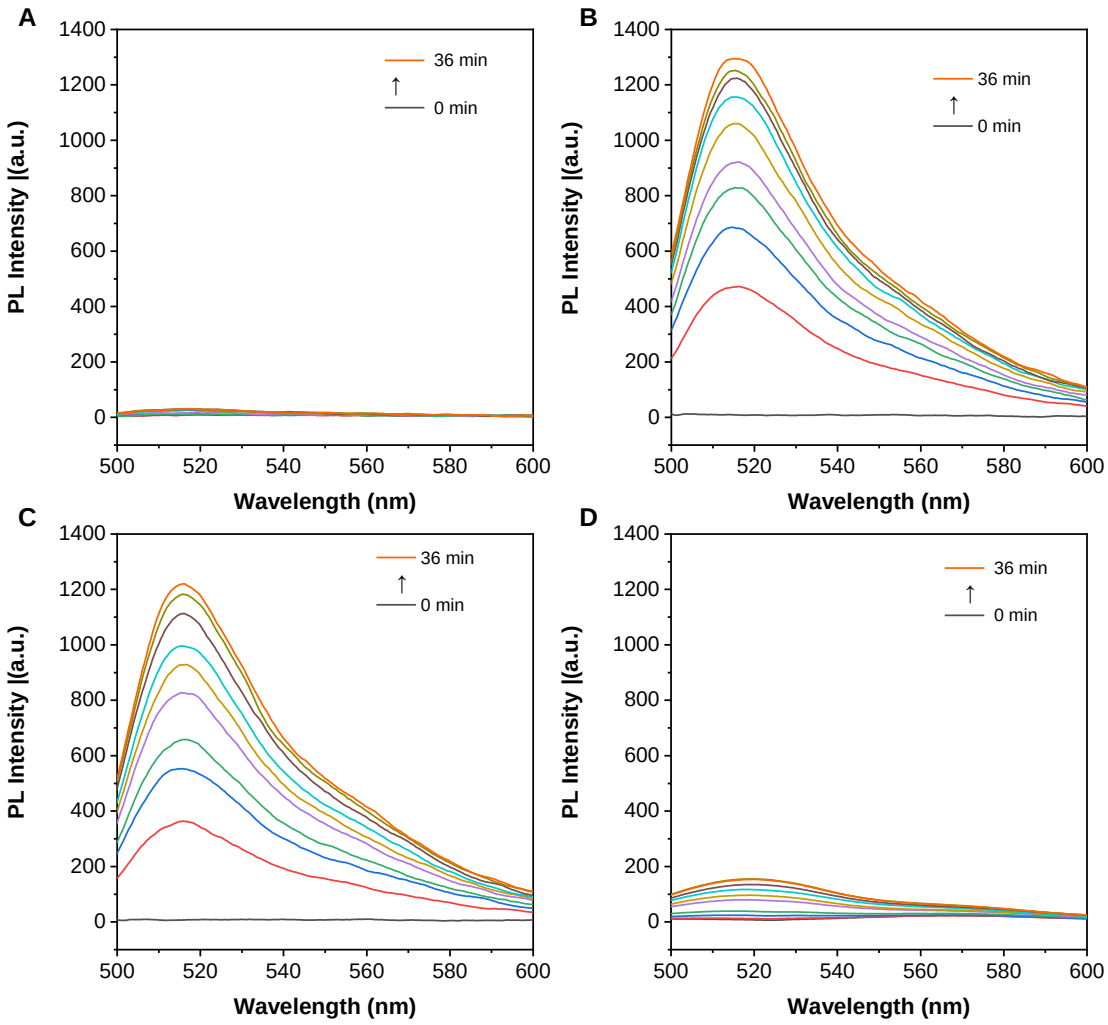


Figure S9. Photoluminescence spectra of HPF in (A) water or in the presence of (B) ACR-DM-HS, (C) ACR-DME, (D) RB under white light irradiation.

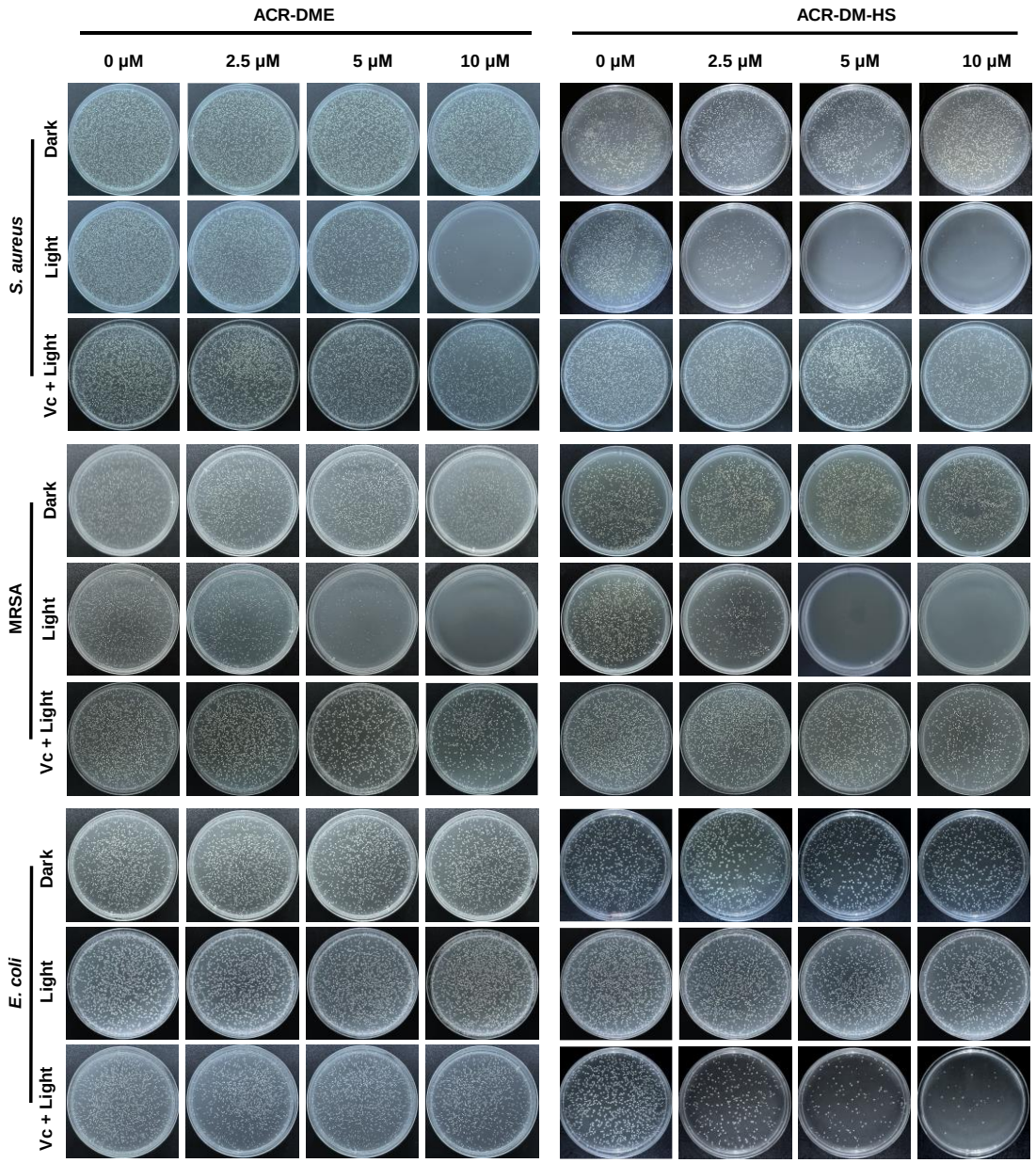


Figure S10. Plate images of *S. aureus,* MRSA and *E. coli* after incubated with different concentrations of ACR-DME or ACR-DM-HS for 10 min and then irradiated with white light or kept under the dark for 30 min in the absence or presence of Vc.

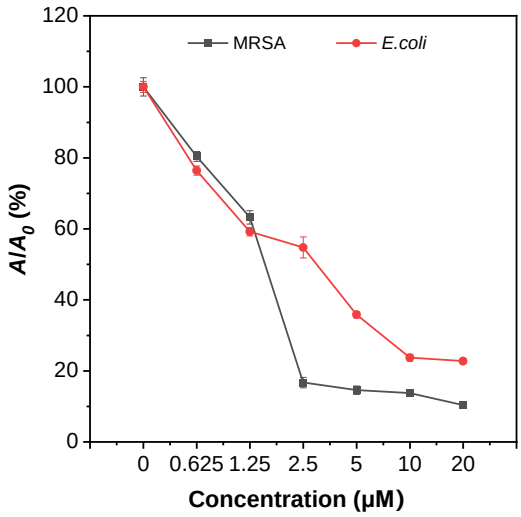


Figure S11. The minimum inhibitory concentration of ACR-DM-HS against MRSA and *E. coli*. The data were presented as the means ± SDs (n = 3).

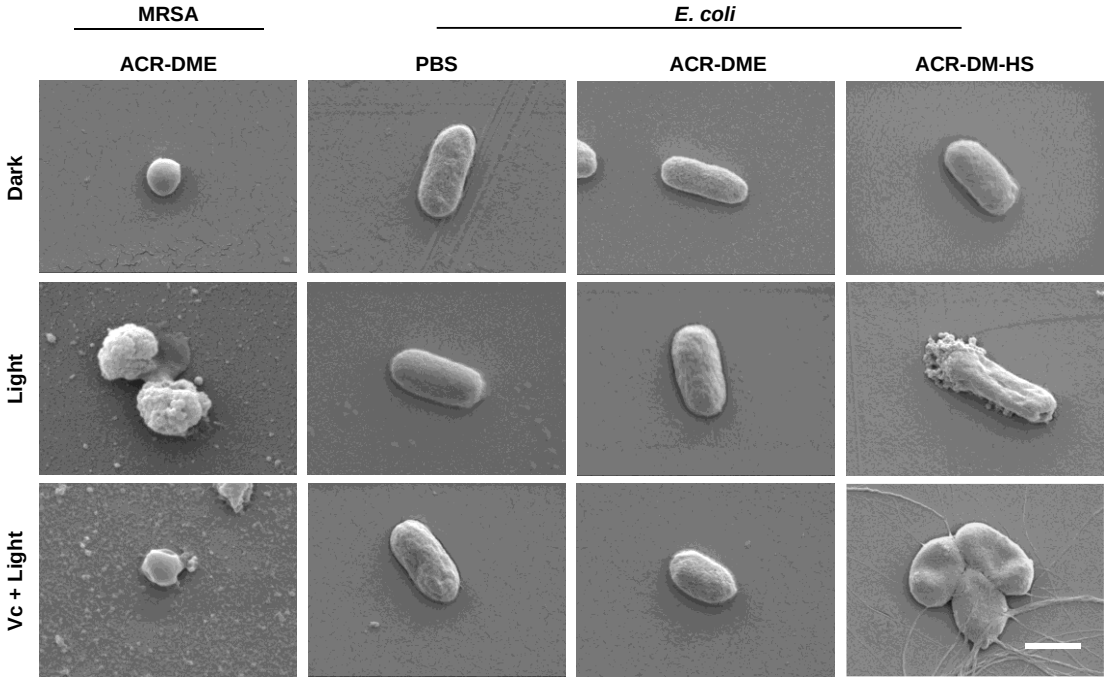


Figure S12. SEM images analysis the morphology changes of MRSA and *E. coli* after incubated with ACR-DM-HS or ACR-DME under dark or white light in the absence or presence of Vc. Scale bars: 1 μm.

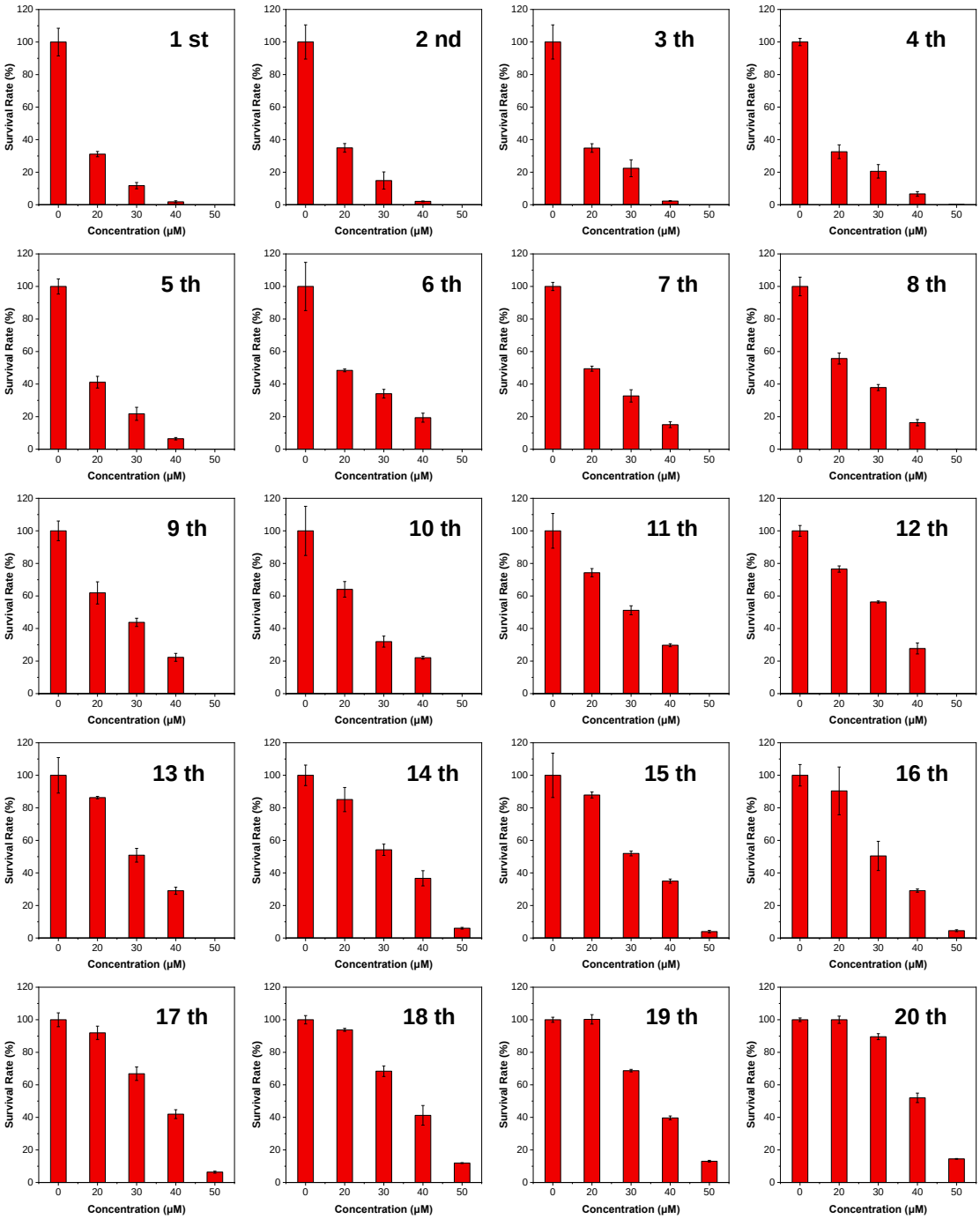


Figure S13. Drug susceptibility test of MRSA to vancomycin. Different concentrations of vancomycin were incubated with MRSA for 12 hours, and bacterial survival rate was assessed by plate colony counting. A single colony was selected from the plate where the bacteria survived at the highest drug concentration to continue the culture. The bacterial survival rate was recorded for 20 consecutive cycles of treatment. The data were presented as the means ± SDs (n = 3).

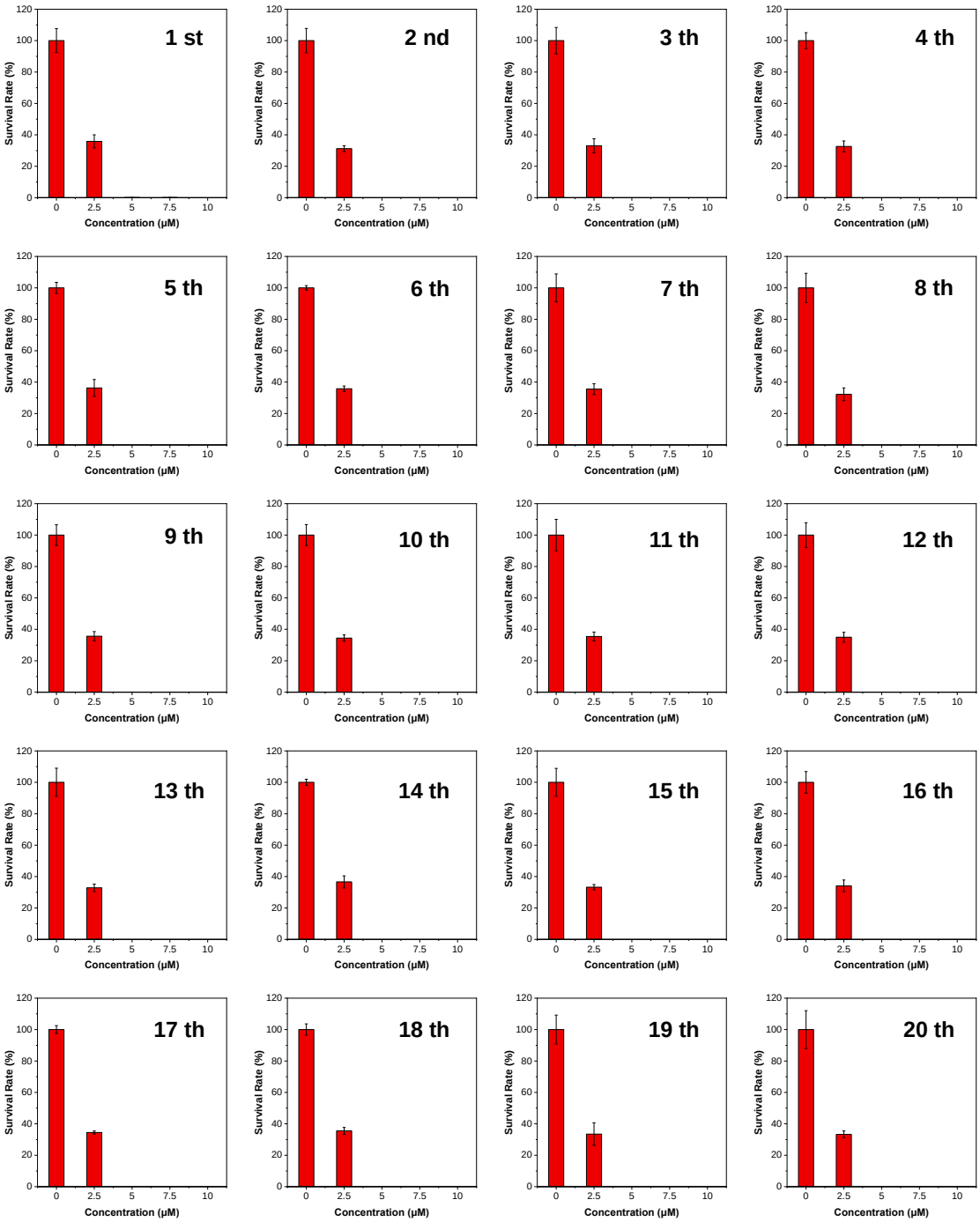


Figure S14. Drug susceptibility test of MRSA to ACR-DM-HS. MRSA was incubated with different concentrations of ACR-DM-HS for 10 minutes, followed by 30 minutes of white light irradiation, and bacterial survival rate was assessed by plate colony counting. A single colony was selected from the plate where the bacteria survived at the highest drug concentration to continue culture. The bacterial survival rate was recorded for 20 consecutive treatment cycles. The data were presented as the means ± SDs (n = 3).

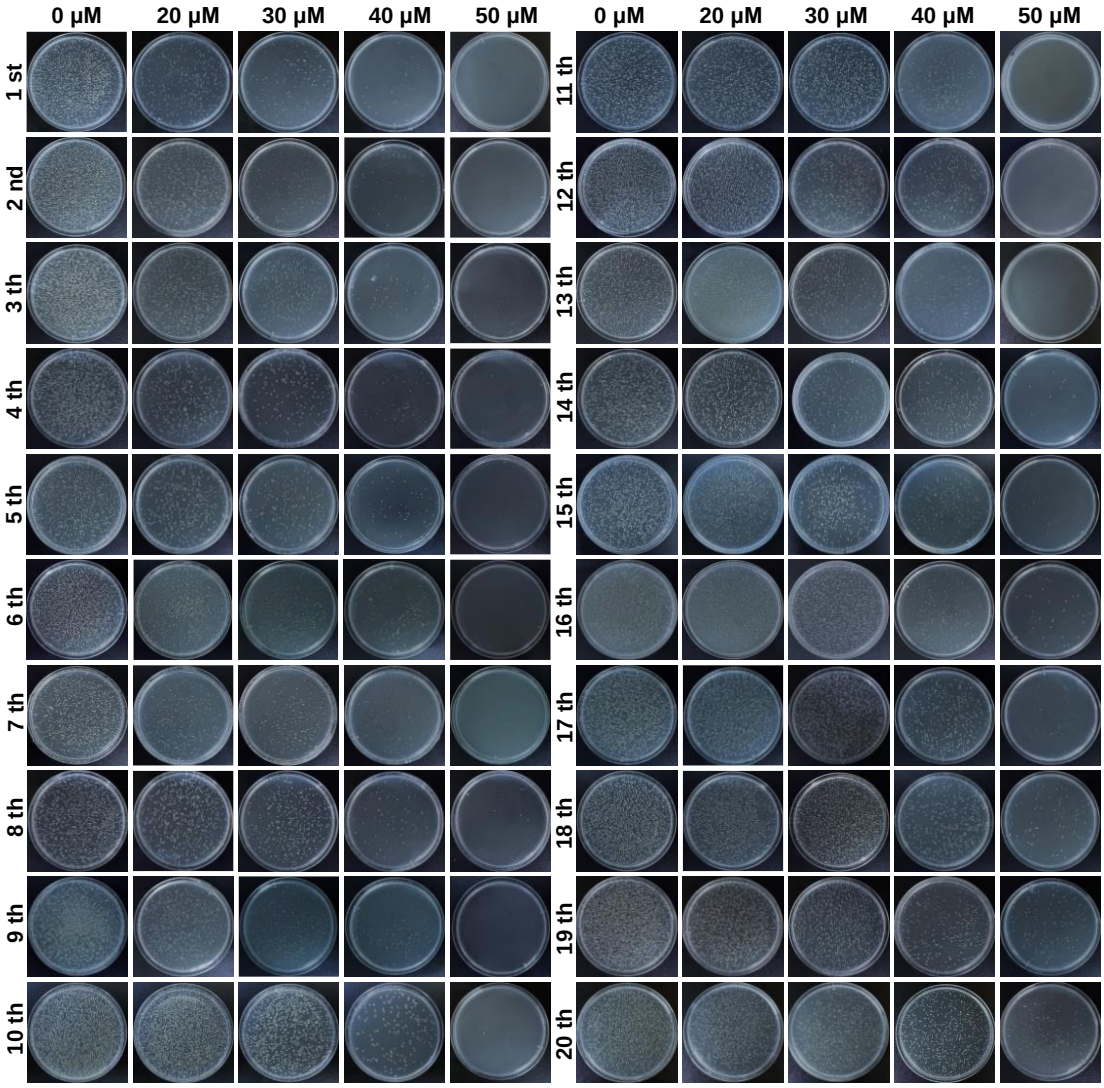


Figure S15. Plate images of MRSA from Figure S13.

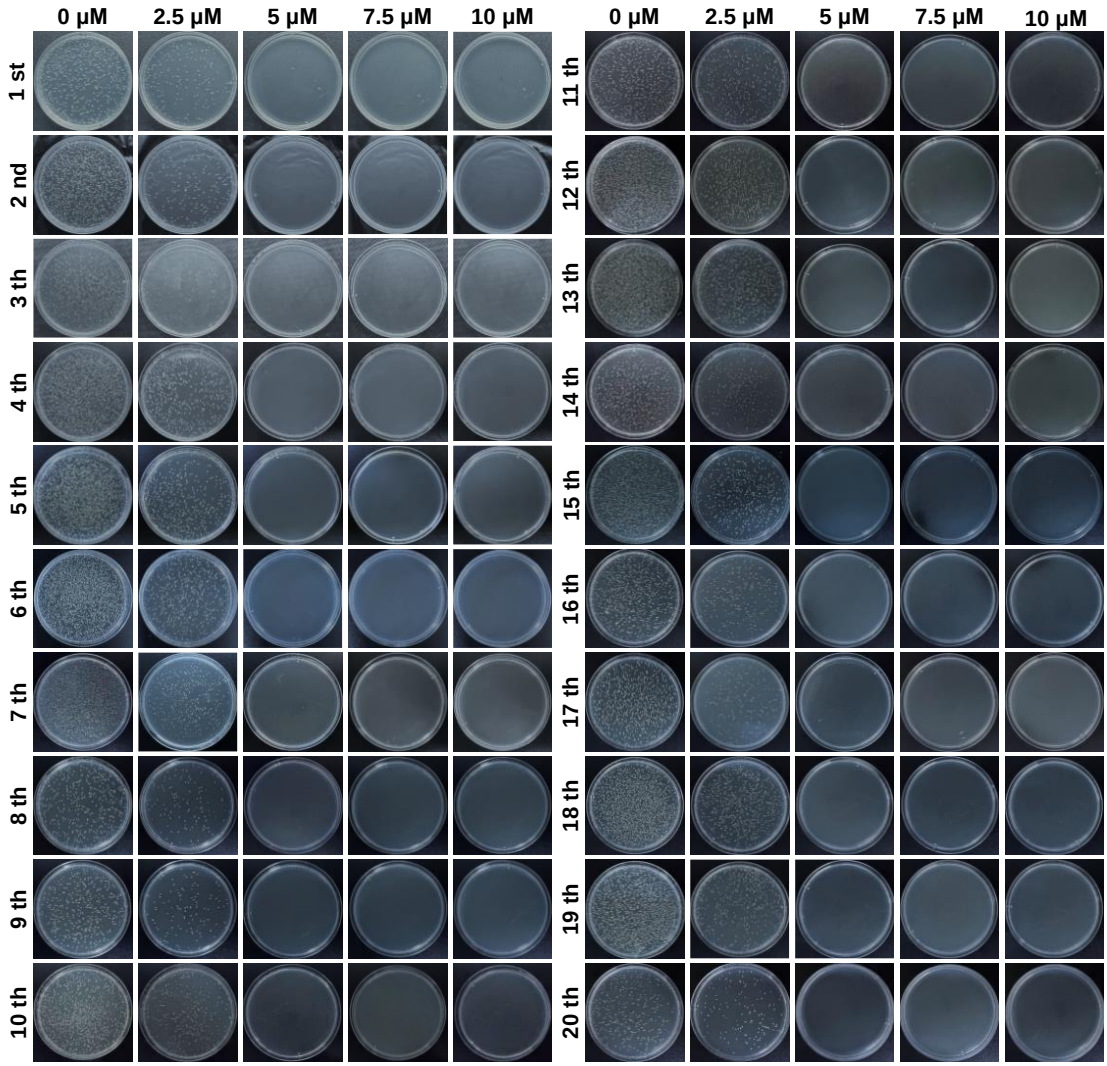


Figure S16. Plate images of MRSA from Figure S14.

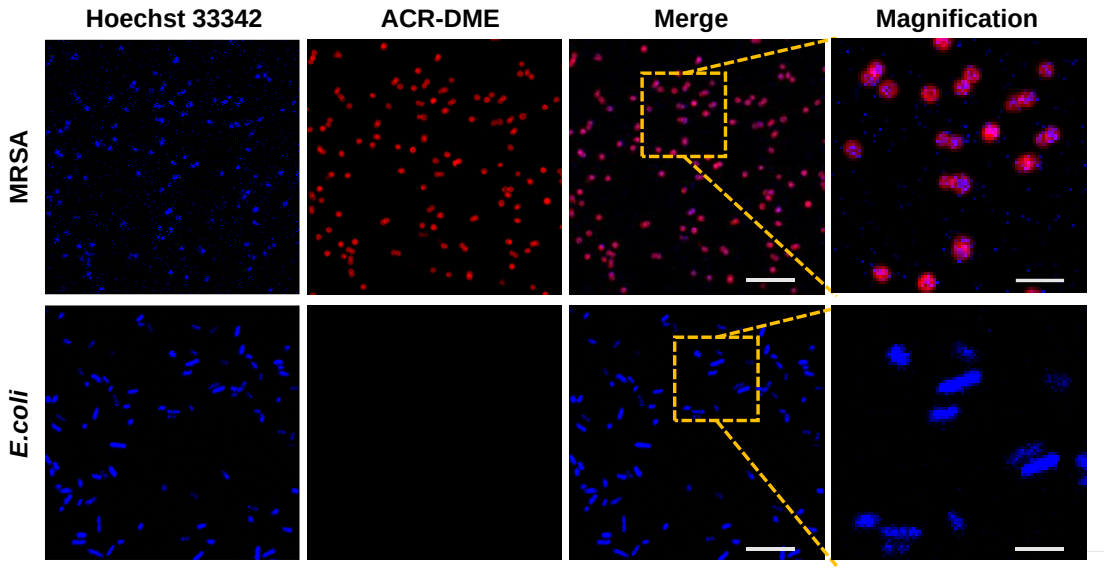


Figure S17. Fluorescence images of MRSA or *E. coli* treated with 5 μM ACR-DME under dark conditions. Scale bars: 10 μm. Magnification scale bars: 3 μm. ACR-DM-HS: λ_{ex} = 561 nm, λ_{em} = 650-750 nm. Hoechst 33342: λ_{ex} = 405 nm, λ_{em} = 430-480 nm.

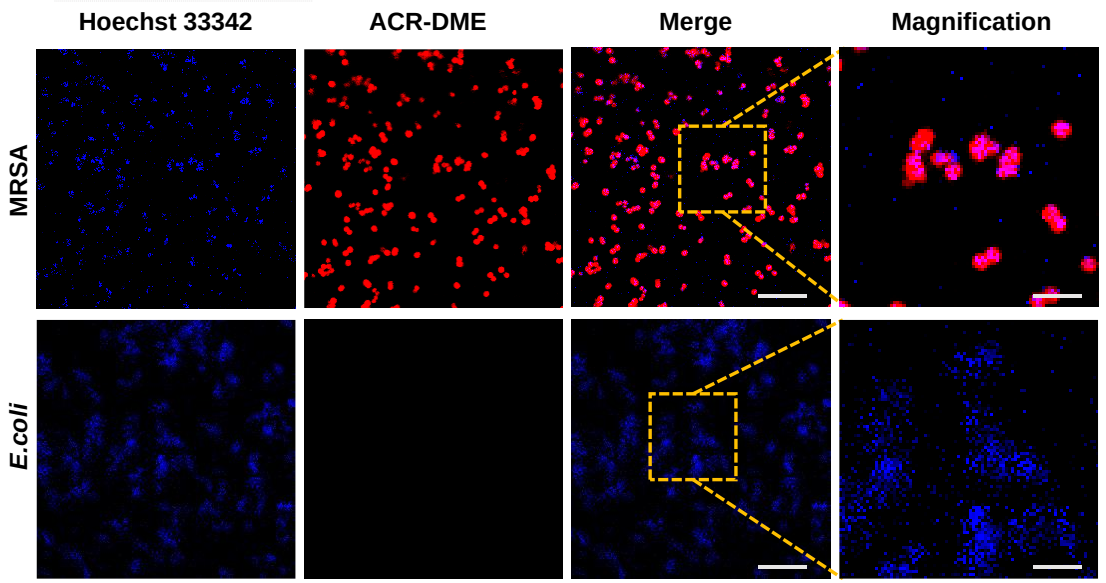


Figure S18. Fluorescence images of MRSA or *E. coli* pretreated with Vc (1000 μM) and then treated with 5 μM of ACR-DME and light illumination for 30 minutes. Scale bars: 10 μm. Magnification scale bars: 3 μm.

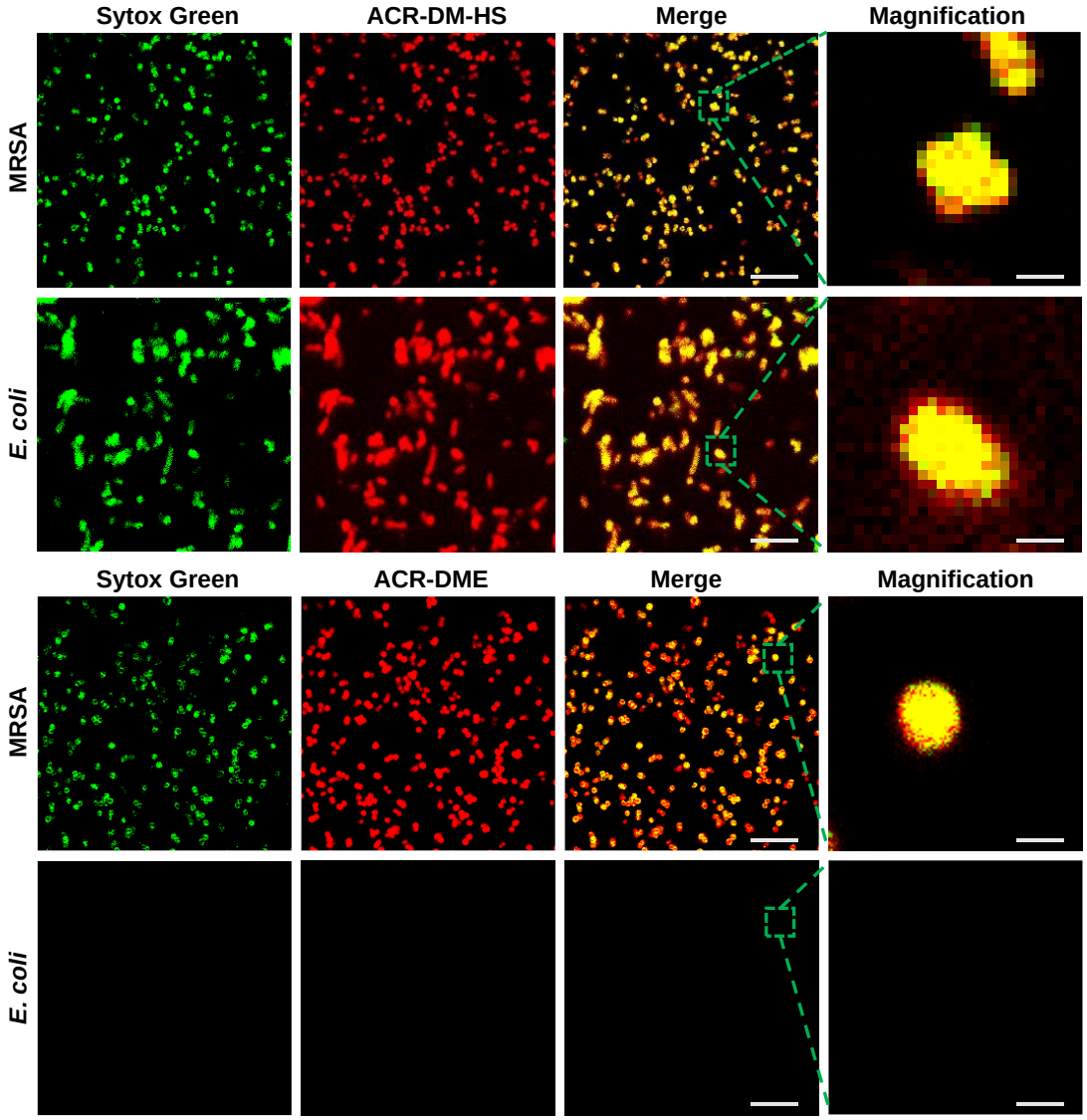


Figure S19. Fluorescence images of MRSA or *E. coli* pre-treatment with 1000 μM Vc, incubated with 10 μM ACR-DME or ACR-DM-HS and irradiated with light for 30 minutes, followed by co-staining with Sytox Green. The red and green fluorescence channels were merged and magnified to assess colocalization of the two signals. Scale bars: 10 μm. Magnification scale bars: 3 μm. Sytox Green: λ_{ex} = 488 nm, λ_{em} = 503-563 nm.

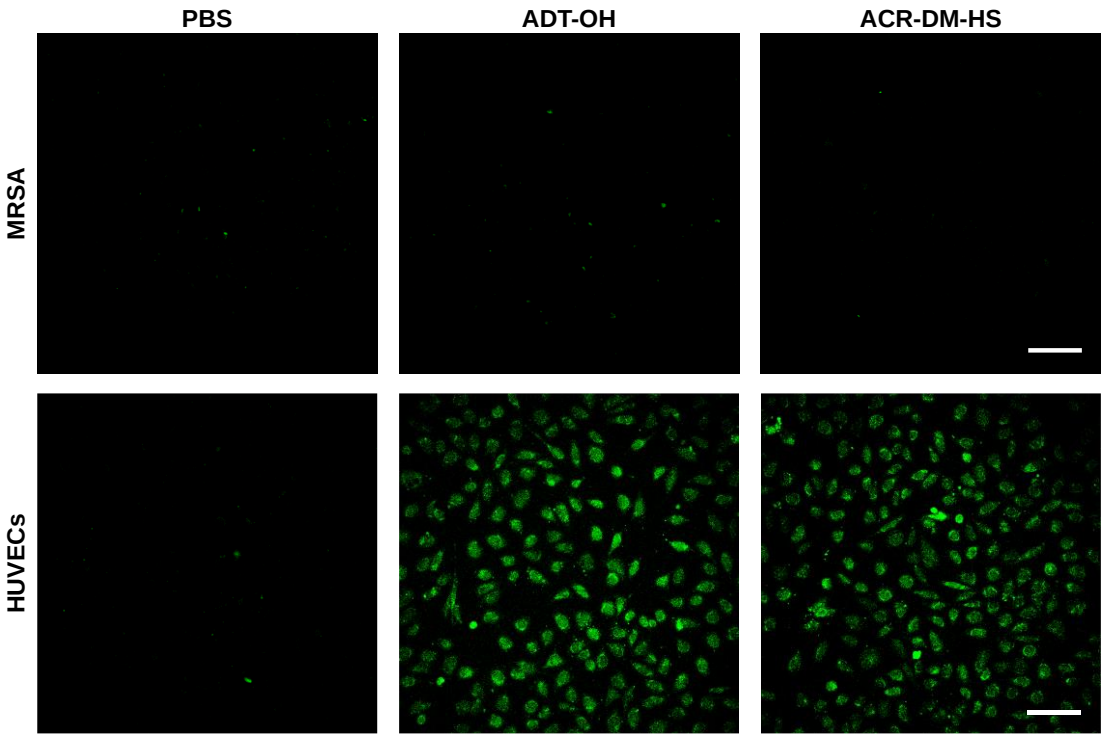


Figure S20. Intracellular H_2S detection in MRSA and HUVECs using WSP-5 as a probe after treatment with 20 μM ADT-OH or ACR-DM-HS for 12 hours. Scale bar = 200 μm (top), Scale bar = 100 μm (bottom). WSP-5: λ_{ex}= 502 nm, λ_{em} = 510-530 nm.

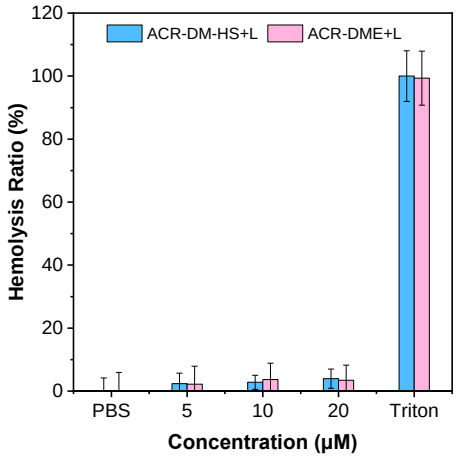


Figure S21. Hemolysis rate of ACR-DM-HS or ACR-DME incubated with 2% red blood cells for 30 minutes and then exposed to light for 30 minutes. The data were presented as the means ± SDs (n = 3).

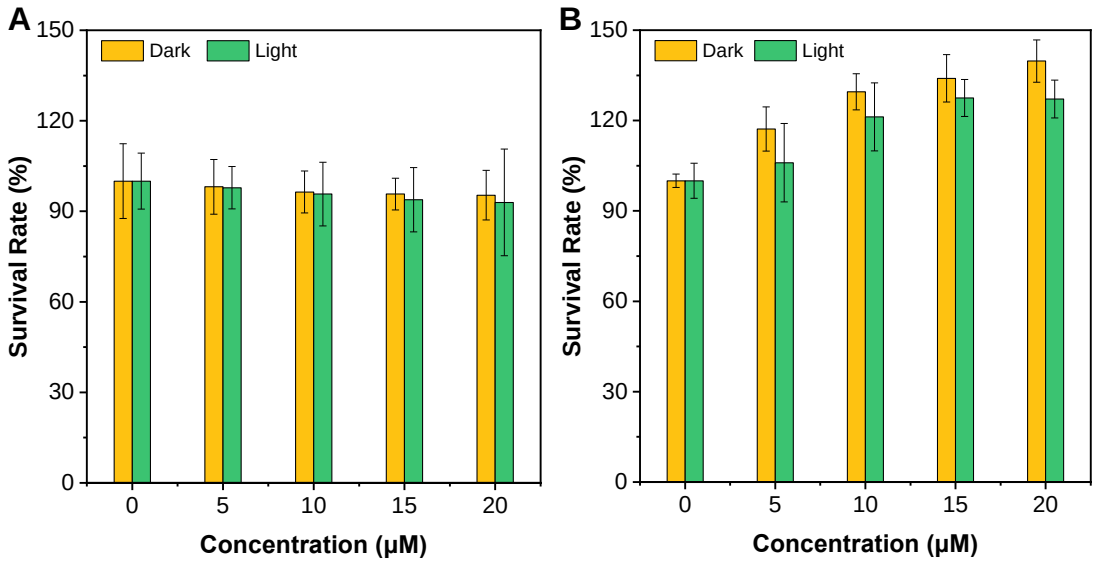


Figure S22. Cell viability of HUVECs were incubated with different concentrations of ACR-DME (A) and ACR-DM-HS (B) and then kept under dark or light irradiation conditions. The data were presented as the means ± SDs (n = 3).

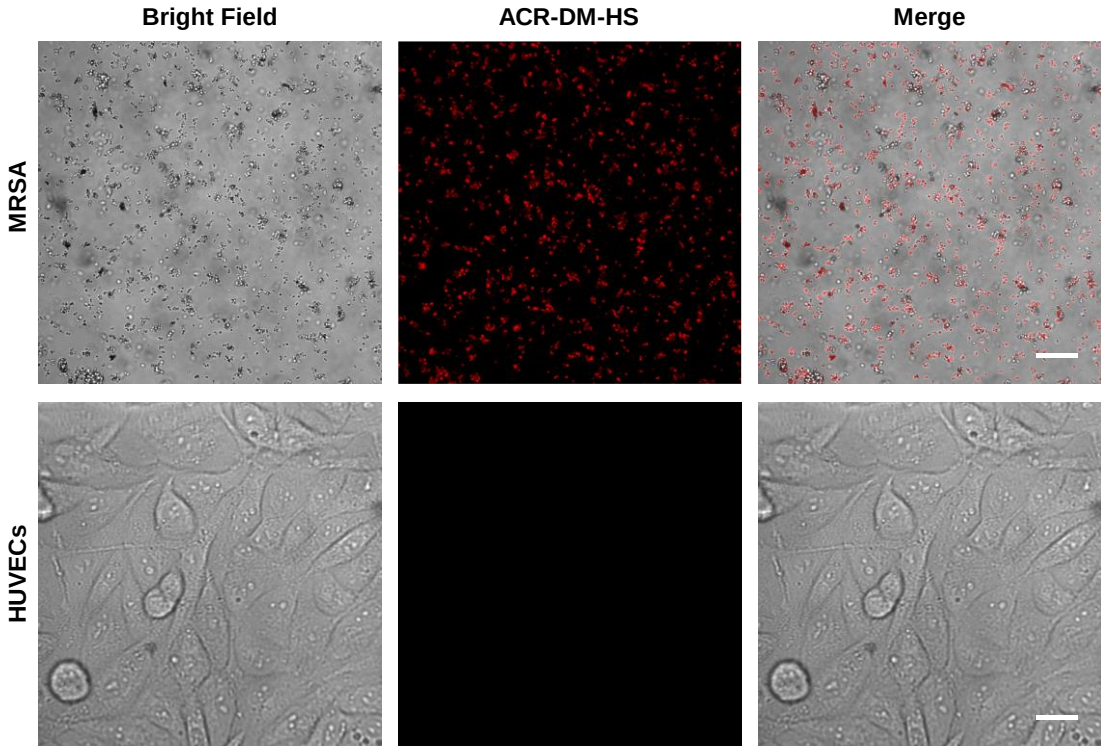


Figure S23. CLSM images of MRSA or HUVECs after incubated with ACR-DM-HS for 1 h. ACR-DM-HS: λ_{ex} = 561 nm, λ_{em} = 650-750 nm scale bar = 20 μm (top), scale bar = 25 μm (bottom).

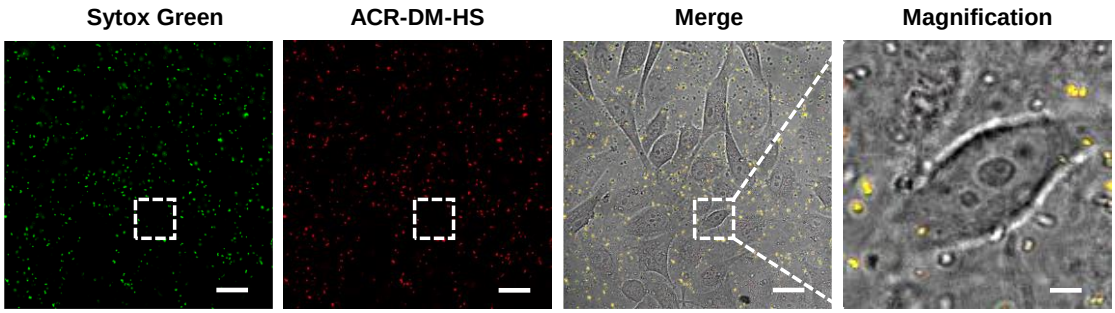


Figure S24. Fluorescence images of mixed HUVEC cells with MRSA after incubation with 10 μm ACR-DM-HS for 30 min, followed by white light irradiation for 30 min. Mixed cells and bacteria were then stained with 10 μM Sytox Green and recorded with CLSM. ACR-DM-HS: λ_{ex} = 561 nm, λ_{em} = 650-750 nm; Sytox Green: λ_{ex} = 488 nm, λ_{em} = 500-550 nm. Scale bar: 25 μm, magnification scale bar: 5 μm.

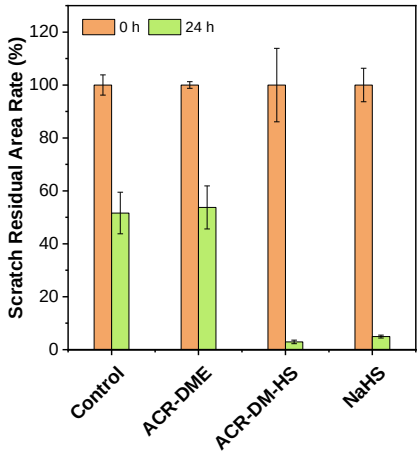


Figure S25. Scratch residual area rate of L929 cells treated with ACR-DME, ACR-DM-HS or NaHS. The data were presented as the means ± SDs (n = 3).

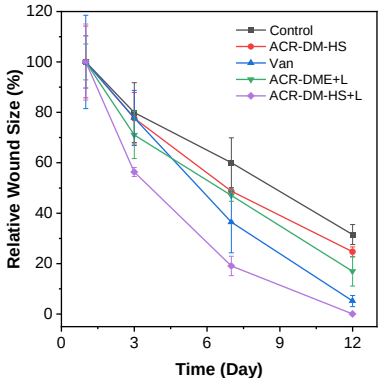


Figure S26. Relative wound sizes of rat with different treatments on day 1, 3, 7, and 12 from the corresponding images in Figure 8B. The data were presented as the means ± SDs (n = 3).

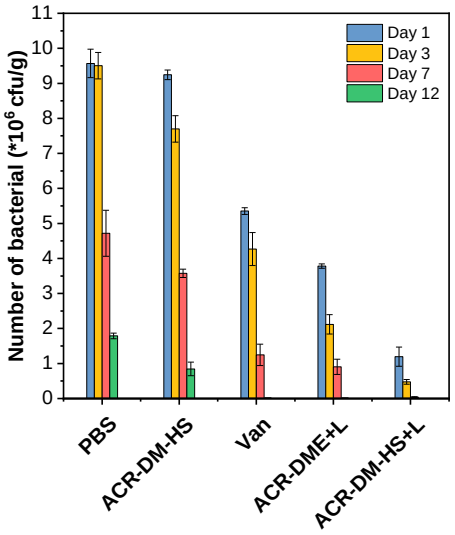


Figure S27. Quantitative analysis of bacterial colonies in wound tissues of different group on days 1, 3, 7, and 12. The data were presented as the means ± SDs (n = 3).

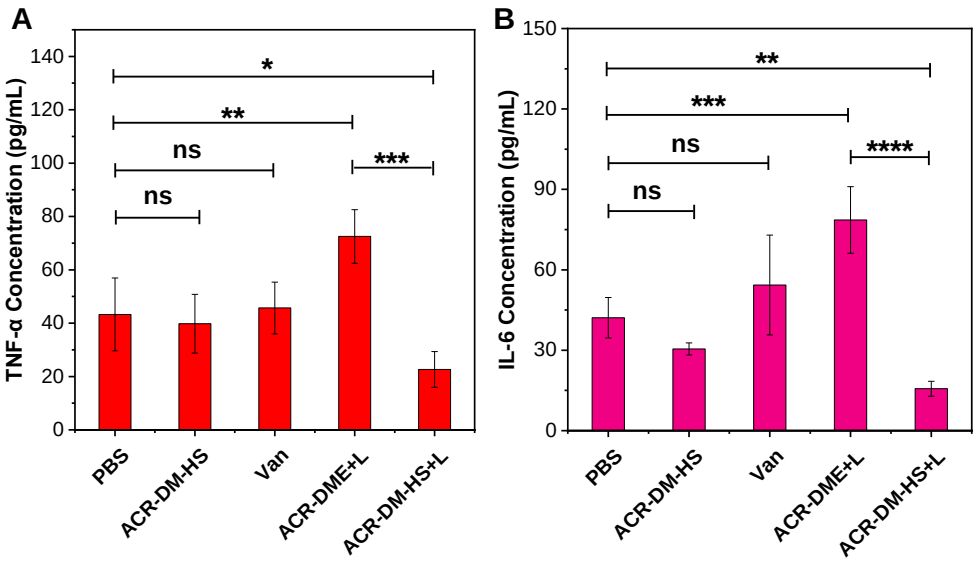


Figure 28. The levels of TNF-α (A) and IL-6 (B) in serum of rat with different treatment on day 3. The data were presented as the means ± SDs (n = 3) and were analyzed by one-way ANOVA with GraphPad Prism software. ns means no significance; *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.

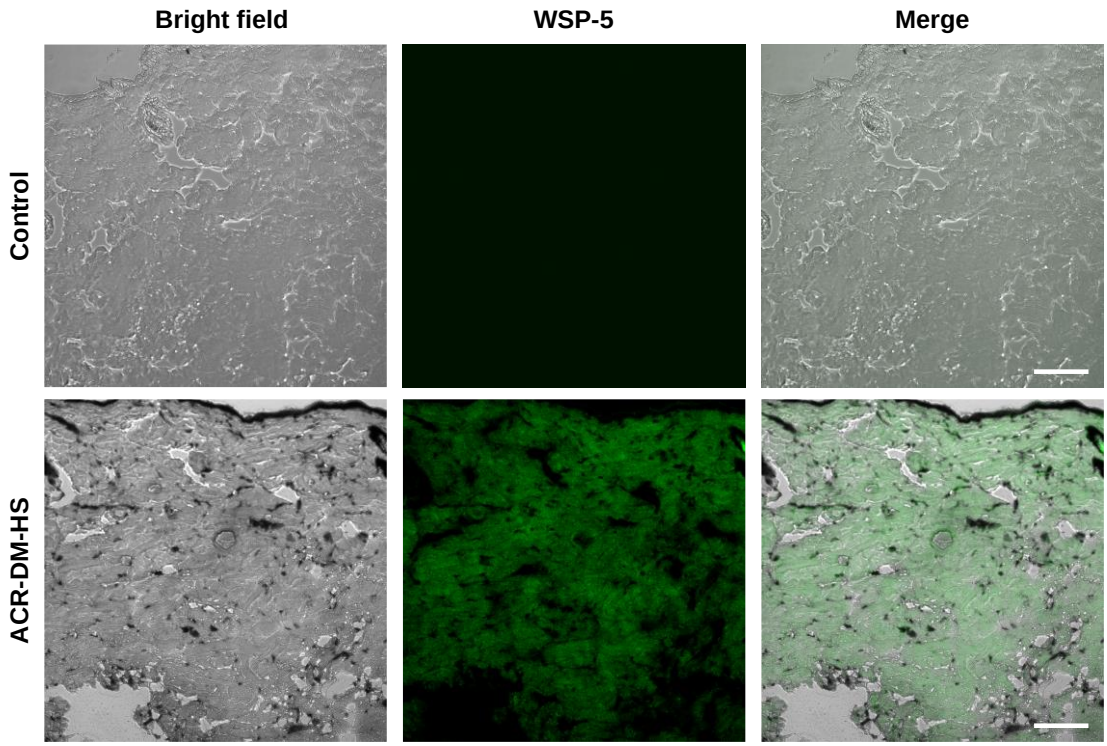


Figure S29. *Ex vivo* H_2S detection from tissue of MRSA infected rat after treatment with ACR-DM-HS + L using WSP-5 as a probe. Scale bar: 100 μm. WSP-5: λ_{ex} = 502 nm, λ_{em} = 510-530 nm.

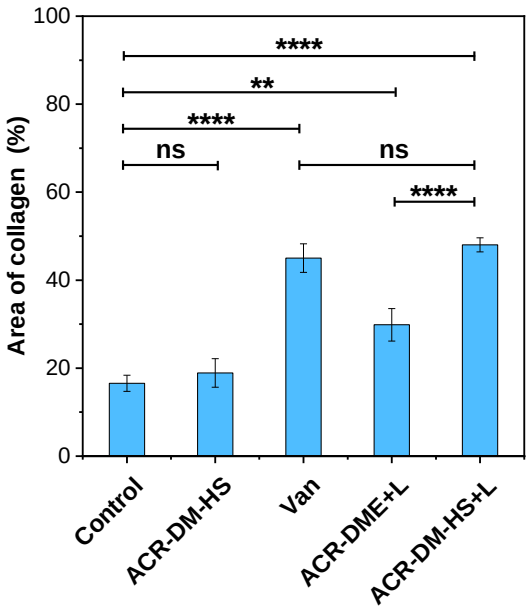


Figure 30. Quantitative analysis of the collagen fiber area in different groups. The data were presented as the means ± SDs (n = 3) and were analyzed by one-way ANOVA with GraphPad Prism software. ns means no significance; **p < 0.01; ****p < 0.0001.

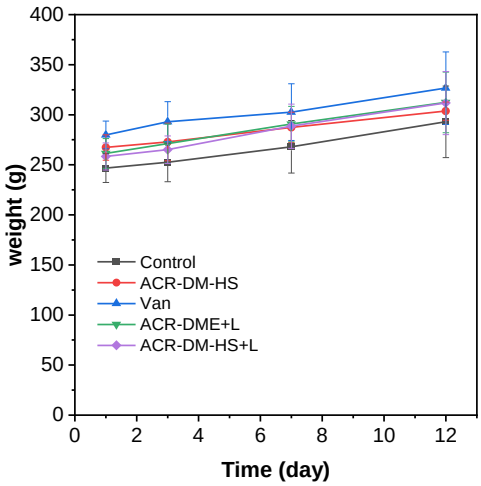


Figure S31. Body weight changes of rat in different group. The data were presented as the means ± SDs (n = 3).

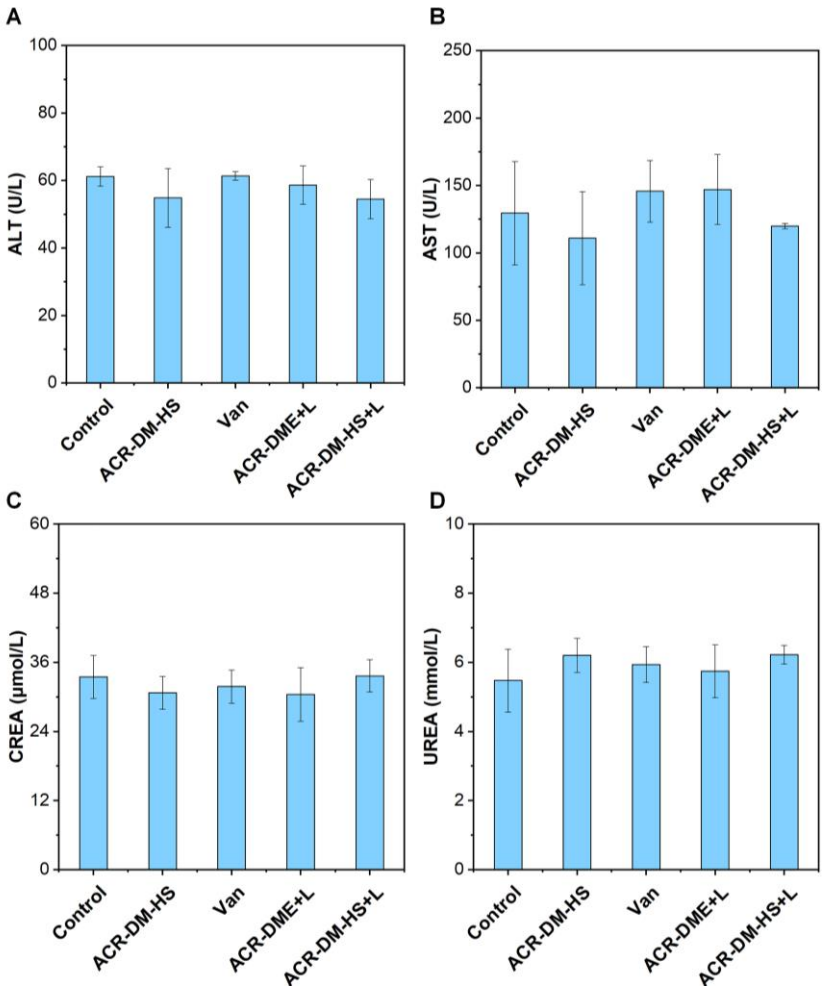


Figure S32. Blood biochemical analysis of rats from each group on day 12. (A) Alanine aminotransferase (ALT), (B) Aspartate aminotransferase (AST), (C) Creatinine (CREA), (D) Urea (UREA). The data were presented as the means ± SDs (n = 3).

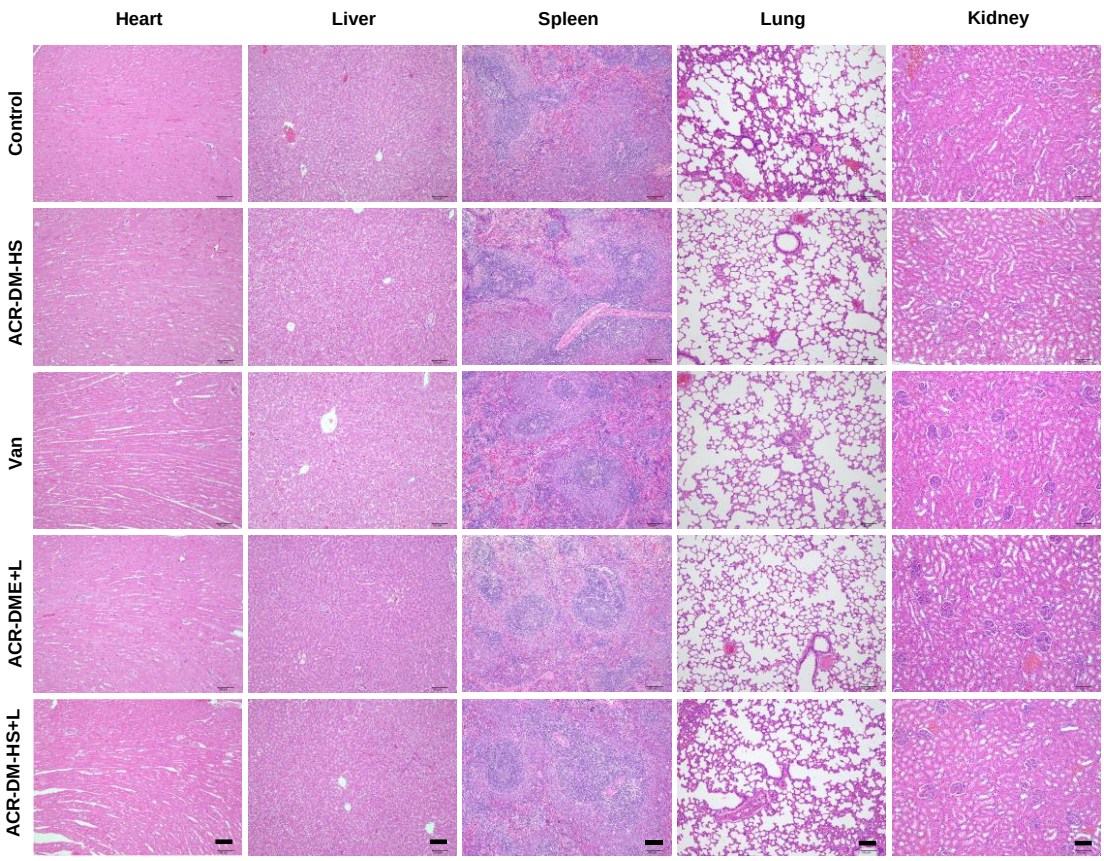


Figure S33. H&E staining of major organs (heart, liver, spleen, lung, kidney) of in rat with different treatment on day 12. Scale bar: 100 μm.

3. Reference

1. F W. Xia, B. W. Guo, Y. Zhao, J.-L. Wang, Y. Chen, X. Pan, X. Li, J. X. Song, Y. Wan, S. Feng, M.-Y. Wu, *Adv. Mater.* 2023, *35*, 2309797.