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# Syntheses and biological activities of calix[4]resorcinarene derivatives modified by sulfonic acid and sulfonamides†

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Functionalization of *C*-propyl-resorcinolcalix[4]arene (**1a**) and *C*-iso-butyl-resorcinolcalix[4]arene (**1b**) with sodium sulfite and formaldehyde solution gave two corresponding sulfonatomethylated calix[4]resorcinarenes **2a/b**. Further modification of **2a/b** with different primary amines afforded three calix[4]resorcinarene sulfonamides **3a/b** and **4c**. Antibacterial and antitumor tests were performed on the starting calix[4]resorcinarenes and their sulfonic acid and sulfonamide derivatives. The results showed that in terms of antimicrobial activity calix[4]resorcinarenes and their derivatives showed bacteriostatic activity against both *Escherichia coli* and *Staphylococcus aureus*. Of which compound **1b** was the most effective against *Escherichia coli* with a MIC value of 6.25 mg mL<sup>-1</sup>; compound **2b** was the most effective against *Staphylococcus aureus* with a MIC value of 3.12 mg mL<sup>-1</sup>. In terms of antitumor activity, calix[4]resorcinarenes and their derivatives showed inhibitory effects on the three tumor cells selected for the experiment. Among them, the survival rate of A549 was 76.03% in the presence of 40 μM **1b**, and the survival rates of HepG2 and MDA-MB-321 were 28.66% and 65.39% in the presence of 40 μM **2b**, respectively.

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## Introduction

Calixarenes have attracted much interest from researchers because of their unique structures and properties. Due to their multiple modification sites, various functional groups can be easily introduced to the upper or lower edge, such as amino acids, amides, amines, alcohols, esters, aldehydes and alkyl derivatives.<sup>1–4</sup> Calixarenes, especially their water-soluble derivatives,<sup>5</sup> have the advantage of having no significant cytotoxicity or immunogenicity in biochemistry.<sup>6,7</sup> The molecules carried by their upper and lower edges may also interact with proteins and nucleic acids to modulate a variety of enzyme activities, cancer cell proliferation, and metabolic pathways,<sup>8–11</sup> which are increasingly being applied in the design and synthesis of biologically active compounds.<sup>12</sup> Among them, the calixarene derivatives are used as drug carriers, which have certain inhibitory activities against bacteria, fungi, and cancer cells. In addition to this, organic substances such as amides, sulfonamides, guanidines, amino acids, thioureas, and other specific moieties have been verified to have a wide range of biological activities such as antiviral, antibacterial, and antitumor activities,<sup>13–16</sup> which can be used as intermediates in the

synthesis of therapeutic drugs. This gives reason to believe that calixarenes modified with nitrogen-containing organics may have future applications in bioactivity. Reports show that calixarenes and their nitrogen-containing derivatives have achieved good results in antibacterial and antitumor applications.<sup>17–21</sup> For example, Kashapov's group synthesized a series of aminoglucosyl calix[4]resorcinarene derivatives with different chemical group compositions at the lower edge, and the biological activity exhibited by these macrocyclic compounds with biocompatible fragments was, in some respects, the first to reveal that the observed hemolytic and antimicrobial activity was dependent on the lipophilicity of the calix[4]resorcinarene structure.<sup>19</sup>

Sulfonamide compounds exhibit a broad spectrum of biological activities, antibacterial mechanisms (Wood-Fields theory)<sup>22,23</sup> and antitumor effects.<sup>24</sup> Moreover, they serve as a carbonic anhydrase inhibitor,<sup>25</sup> cyclooxygenase inhibitor,<sup>25</sup> microtubule inhibitor,<sup>26</sup> and folate-dependent enzyme inhibitor<sup>27</sup> for inhibiting tumor proliferation. Though research on calix[4]resorcinarene and its derivatives has taken an important direction in nanotechnology, separation science, and other areas in the past few decades, its role in biological activity should not be underestimated. There are few reports on calix[4]resorcinarene and its derivatives synthesized from resorcinol, and even fewer studies on biological properties. Therefore, it is of great significance to synthesize calix[4]resorcinarenes and their derivatives modified with a series of biologically active amines containing sulfonamide groups that promote the

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bioactivity of the compounds and explore the changes in their bioactivity. Our group has been studying calix[4]resorcinol for many years with some results in the host-guest chemistry and the organic template for preparation of gold nanoparticles.<sup>28,29</sup> At the same time, we have found that calix[4]resorcinarene often exists as a drug carrier and the few articles that have studied its synthesis have been linked by amide bonds. This paper focuses on the synthesis of methylsulfonamide calix[4]resorcinarene derivatives and initially explores their antibacterial and anti-tumor activities.

## Experimental section

### Materials and methods

Compounds **1a/b**<sup>30,31</sup> and **2a/b**<sup>32-34</sup> were prepared according to literature methods. Both *Escherichia coli* and *Staphylococcus aureus* were LB medium, and the conditions were under 37 °C for 24 hours. Human umbilical vein endothelial cell line (HUVEC), human lung adenocarcinoma cell line (A549), hepatocellular carcinoma cell line (HepG2), and human breast cancer cell line (MDA-MB-231) were selected to evaluate the antitumor activity of the compounds. Their culture conditions were HUVEC was cultured in 89% DMEM, 10% FBS, and 1% PS for 24 h at 37 °C in an incubator containing 5% CO<sub>2</sub>; the culture conditions for HepG2 and A549 were in 89% 1640, 10% FBS, and 1% PS in a 37 °C incubator containing 5% CO<sub>2</sub> for 24 hours; MDA-MB-231 was cultured in 89% L-15, 10% FBS and 1% PS for 24 h at 37 °C under 100% air. <sup>1</sup>H NMR was determined by a Bruker AVANCE 400 MHz fully digitized nuclear magnetic resonance spectrometer with chemical shifts ( $\delta$ , ppm) referenced to the reference SiMe<sub>4</sub>. Infrared spectra were recorded on a PerkinElmer 16 PC FT-IR spectrophotometer with use of pressed KBr pellets in the region of 400–4000 cm<sup>-1</sup>. Elemental analysis was determined by a PerkinElmer 2400 CHN analyzer. *In vitro* cellular OD values were determined by Biotek EPOCH2 enzyme labelling assay.

### Syntheses of 3a/b and 4c

Compound **3a** was synthesized by the following procedure: to the ethanol-ethyl acetate (50%) solution of tyramine hydrochloride (638 mg, 3.6 mmol) was added 0.79 mL Et<sub>3</sub>N at 0–5 °C and the mixture was stirred for half an hour. After returning to room temperature, **2a** (240 mg, 0.23 mmol) was added and the reaction mixture was stirred under a nitrogen atmosphere for 3 days. The mixture was filtered and the pH of filtrate was adjusted to weak acidity with 1 M HCl, then the solution was cooled at 0–5 °C to give powder of **3a**. Compounds **3b** and **4c** were synthesized similarly to compound **3a**.

### The microbiological tests of compounds 1a/b, 2a/b, 3a/b, and 4c

The antimicrobial activities of compounds **1a/b**, **2a/b**, **3a/b**, and **4c** were studied with the cultures used for testing: Gram-positive bacteria *Staphylococcus aureus* CMCC(B) 26003 and Gram-negative bacteria *Escherichia coli* ATCC 25922 according to published procedures.<sup>35</sup> Whatman No. 3 filter paper of 6 mm

diameter was soaked in the prepared diluent to obtain the drug paper sheets required for the experiment and the inhibitory properties were studied by observing the size of the inhibitory circles produced by diffusion of the drug sheets on agar plates. An aqueous solution of kanamycin at 1.56 mg mL<sup>-1</sup> was used as a positive control, sterile water and DMSO were used as blank controls, and the results showed that the above solvents had no significant inhibition effect on the bacteria involved in this experiment. Solutions of **1a/b**, **2a/b**, **3a/b**, and **4c** with a concentration of 200 mg mL<sup>-1</sup> were prepared and the antibacterial activity is shown in Table 1. The MIC was defined as the minimum compound concentration that inhibited the growth of the corresponding test microorganism and the corresponding values are listed in Table S2.†

HUVEC cells, MDA-MB-231, A549 and HePG2 cells used for *in vitro* toxicity testing were used as subjects. Anti-tumor properties were indicated through the survival rate of cells in each group detected by MTT assay, cells without any treatment were used as a blank control, and anti-tumor drug cisplatin was used as a positive control. The cells were cultured at 5% CO<sub>2</sub>, 37 °C for 24 h. The cells were incubated in 5% CO<sub>2</sub> at 37 °C for 24 hours, then the medium was removed and 200  $\mu$ L of medium containing different drugs was added to each well to continue treating the cells for 48 hours (final drug concentration 40  $\mu$ M). After removing the medium and rinsing lightly with PBS 2 times, 200  $\mu$ L of medium and 20  $\mu$ L of MTT solution (final concentration of 0.5 mg mL<sup>-1</sup>) were added to each well, and after staining for 4 h, the liquid was removed, the absorbance value at 570 nm was measured by an enzyme marker after adding 150  $\mu$ L of DMSO.

## Results and discussion

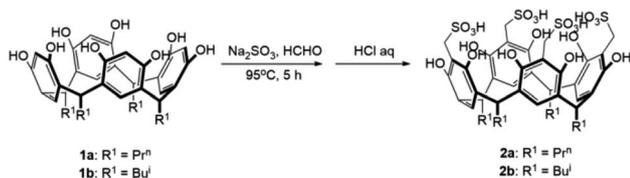
### Synthesis

Compounds **1a/b** and **2a/b** were prepared in high yields (83–90%) according to literature methods (Scheme 1).<sup>30-34</sup> <sup>1</sup>H NMR and IR spectra of compounds **1a/b** and **2a/b** were shown in Fig. S1–S8.† The chemical shift of phenol OH protons appeared at about 8.95 ppm in compounds **1a/b** as a singlet, which moved downfield to 9.73 ppm in compounds **2a/b** by introducing –CH<sub>2</sub>SO<sub>3</sub>H groups at C-2 positions. Compounds **3a/b** and **4c** were

Table 1 MIC values of calix[4]resorcinarenes **1a/b** and their sulfonatomethyl compounds **2a/b** and sulfonamide derivatives **3a/b**, **4c** against two Gram-negative bacteria

Minimum inhibitory concentration (MIC) in mg mL <sup>-1</sup>			
Serial number	Compounds	<i>E. coli</i> ATCC 25922	<i>S. aureus</i> CMCC(B) 26003
1	<b>1a</b>	100	>200
2	<b>1b</b>	6.25	12.5
3	<b>2a</b>	12.5	6.25
4	<b>2b</b>	12.5	3.12
5	<b>3a</b>	200	>200
6	<b>3b</b>	>200	>200
7	<b>4c</b>	25.0	12.5



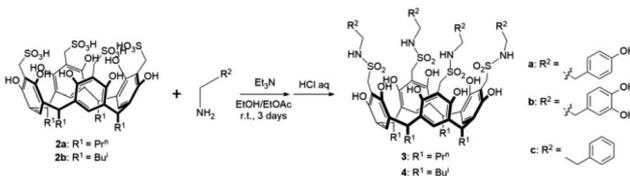


Scheme 1 Synthesis of 5,11,17,23-tetrasulfomethyl calix[4]resorcinarenes.

synthesized by condensation of two sulfonic functionalized calix[4]resorcinarenes **2a/b** and three organic amines in moderate yields (61–69%) (Scheme 2). Generally, the solubility of sulfonamides derivatives of calix[4]resorcinarenes became poor compared with sulfonic derivatives in common organic solvents. <sup>1</sup>H NMR and IR spectra of compounds **3a/b** and **4c** were shown in Fig. S9–S14.† The linking –NHCH<sub>2</sub>CH<sub>2</sub>–Ar protons were observed in the range of 2.69–3.05 ppm in <sup>1</sup>H NMR spectrum of compound **3b** in Fig. S11.† Meanwhile, the typical medium vibration peaks at about 3250 and 1170 cm<sup>-1</sup> for –NHSO<sub>2</sub>– groups were observed in the IR spectra of these sulfonamide compounds.

### Anti-microbial activity

The calix[4]resorcinarenes and their derivatives were tested for their biological activity based on their phenol structures (Table S2†).<sup>36,37</sup> From the experimental results of compounds **1a/b**, it can be seen that the longer the calix[4]resorcinarene R-chain, the better the inhibition effect on *E. coli*, but the effect on *Staphylococcus aureus* appears to be opposite to that of *E. coli*. Comparison of the circles of inhibition produced by compounds **2a/b** reveals that the change of the R group has a much smaller influence on its antimicrobial activity than that of the group modified at the C-2 position. Whereas the compounds synthesized herein, *i.e.*, after modification of the calixarene hydrocarbons with sulfonic acid groups at the C-2 position of the parent hydrocarbons, **2a/b** not only showed good inhibitory effects on Gram-positive *S. aureus*, but also on Gram-negative *E. coli*. In **4c** and **3a/b**, the fewer hydroxyl groups on the benzene ring of R<sup>2</sup>, the better the antibacterial effect, indicating that hydroxyl groups negatively regulate the antibacterial effect. Modifying the sulfonic acid group at the C-2 position could significantly improve the inhibitory effect on Gram-positive *S. aureus* without compromising the inhibitory activity against Gram-negative *E. coli*. Comparing **4c** with **2b**, **4c** with the sulfonamide active fragment exhibited a stronger inhibitory



Scheme 2 Synthesis of calix[4]resorcinarene methylsulfonamide derivatives.

effect against both Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*, yet **2b** demonstrated an even better antibacterial effect. In the reported literature,<sup>38,39</sup> the synthesized calixarenes either inhibited only Gram-positive bacteria or inhibited both Gram-negative and positive bacteria but with average effect. In a word, calix[4]resorcinarenes and their derivatives exhibited better inhibition against *S. aureus* than *E. coli*. Compounds **2a/b** showed good inhibitory effect against *S. aureus* (MIC = 6.25 mg mL<sup>-1</sup>, MIC = 3.12 mg mL<sup>-1</sup>), while compound **1b** showed the best inhibitory effect against *E. coli* (MIC = 6.25 mg mL<sup>-1</sup>).

### Anti-tumor activity

As shown in Fig. 1, by comparing the cell survival rate against HUVEC cells in the presence of compounds **1a/b** and **2a/b**, it can be found that the compounds with R as isobutyl are much less toxic to HUVEC than propyl, and the survival rate of HUVEC in the presence of compounds **3a/b** and **4c** modified by organic amines is even not less than 90%. Generally, these compounds have minimal damage to normal cells, their inhibitory effects on three types of tumor cells *in vitro* proliferation A549, HepG2, and MDA-MB-321 are performed. It can be found that calix[4]resorcinarene raw material **1a** showed high inhibitory properties against cancer cells at a concentration of 40 mM, compound **1b** showed strong inhibitory activity against the three strains of cancer cells selected for the experiments (cell survival rate: A549: 76.03%; HepG2: 82.86%; MDA-MB-321: 71.90%). Modification of the sulfonic acid group improved the inhibition of cancer cells HepG2 and MDA-MB-231, for example, compound **2b** showed a decrease in relative survival to 28.66% for HepG2 cells. The tumor cell inhibitory effects of compounds modifying the sulfonamide structure varied depending on the R and amine groups: modification of compound **2a** to compounds **3a/b** effectively improved the inhibitory effects on A549 and

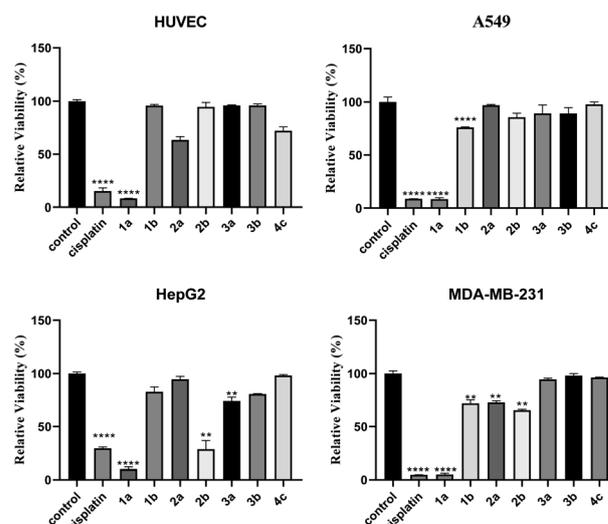


Fig. 1 Calix[4]resorcinarenes **1a/b** and their sulfonatomethyl compound **2a/b** and sulfonamides derivatives **3a/b**, **4c** on the activity of HUVEC (40 mM), A549, HepG2 and MDA-MB-321 cells (\**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001, vs. blank group).



HepG2. As can be seen from Fig. 1, both calix[4]resorcinarene raw materials and their sulfonic acid derivatives showed good inhibitory activity against MDA-MB-231, with cell survival rates ranging from 5.09% to 72.83, but the introduction of amide groups resulted in the increase of the survival rate of the MDA-MB-231 cells up to 96.31%. The inhibitory effect of sulfonic acid-modified compound **2b** on HepG2 was comparable to cisplatin and significantly stronger than that of the other two sulfonamide derivatives with the same R<sup>2</sup> group. Compared to previous studies,<sup>40</sup> a series of compounds exhibited a more effective inhibitory effect on HepG2, with **2b** being the most effective. The possible reasons for this result may be that the introduction of the sulfonamide group disrupts the hydroxyl structure of the sulfonic acid, which may have tumor inhibitory activity.

## Conclusions

A series of supramolecular compounds were synthesized from calix[4]resorcinarenes by sequential modification of sulfonic acid group and sulfonamide structures. Their antibacterial and antitumor activities were tested by disk diffusion test and MTT assay, respectively. The results showed that compound **1b** had a significant inhibitory effect on the growth of *Escherichia coli*; compound **2b** had a significant inhibitory effect on the growth of *Staphylococcus aureus*. The results of the relevant anti-tumor experiments suggested that compound **1b** showed the highest cytotoxicity on A549, and the best inhibitory effect was observed on HepG2 and MDA-MB-321 with compound **2b**. Generally, the sulfonamide derivatives lack strong antibacterial and anti-tumor properties possibly due to the introduction of the sulfonamide group disrupts the important hydroxyl group of the sulfonic acid structure.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data can be obtained upon request from the corresponding author.

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