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ARTICLE

Synthesis, antifungal and antibacterial activity of calix[4]arene-based 1,3,4-oxadiazole derivatives

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Abstract

We describe the synthesis of some novel *p-tert*-butylcalix[4]arene-based (5-aryl-1,3,4-oxadiazol-2-yl)2-chloroethanethioate derivatives (**4a–e**). These compounds were synthesized by the reaction of tetra-*tert*-butyl calix[4]arene (**1**) with (5-aryl-1,3,4-oxadiazol-2-yl)2-chloroethanethioate (**3a–e**) in the presence of potassium carbonate as a weak base and dry acetone as the solvent. All the newly synthesized calix[4]arene derivatives were characterized by elemental analysis and various spectroscopic methods such as FT-IR, ^{1}H NMR,^{13}C NMR, DEPT, and ESI-MS. The synthesized compounds were tested *in vitro* for their antibacterial and antifungal activities against *Escherichia coli* and *Aspergillus fumigates* in comparison with enrofloxacin and amphotericin as reference drugs, which are normally used for treating such infections. The synthesized compounds showed different inhibition zones against the tested bacteria and fungi. Compound **4c** was found to be most effective against *A. fumigates*, whereas compound **4e** was found to be equally effective against *E. coli* and *A. fumigates*.

KEYWORDS

antibacterial activity, antifungal activity, *in vitro*, *S*-(5-aryl-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate, tetra-*tert*-butylcalix[4]arene

1 | INTRODUCTION

Antibiotic resistance is the ability of a microorganism to stand the effect of an antibiotic. Thus the treatment of bacterial infections remains a challenging therapeutic problem, and to overcome the rapid development drug resistance, new classes of antibacterial agents should preferably have chemical characteristics that clearly differ from those of existing agents. This has led to the design and synthesis of many new antimicrobial agents.[1,2]

The calixarenes are a family of macrocyclic compounds with a variable number of phenol units linked by methylene bridges in the ortho position.[3] Calixarenes possess structural features that are desirable for the design and development of new drugs. These compounds are easily synthesized and have variable conformations; for instance, the calix[4]arenes can adopt several different conformers, including the cone, partial cone, 1,2-alternate, and 1,3-alternate. The calix[4]arenes can be functionalized on the upper rim or on the lower rim with several functional groups in a controlled manner. These structural properties allow the use of these compounds in supramolecular chemistry as scaffolds for the construction of various receptors, carriers, and spatial organizers. Calix[4]arenes have been functionalized with different pharmacophoric groups by many researchers and then

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evaluated for their biological activities such as anticancer, antimicrobial, antiviral.[4–8]

Chemical modification of the phenolic oxygen at the lower rim of tetra-*tert*-butylcalix[4]arene is easy and has attracted significant attention due to the increased ability of modified calixarenes to recognize ions, molecules, and biomolecules. Recently, a review paper on the pharmaceutical uses of calixarene derivatives has been published.[9]

1,3,4-Oxadiazole nucleus and its derivatives have attracted much attention because of their pharma applications such as antimicrobials,[10] anticonvulsants,[11] as well as anti-inflammatory,[12] antituberculostatic,[13] fungicidal,[14] insecticidal,[15] and antioxidant[16] agents. In particular, compounds bearing 1,3,4-oxadiazoles have been successfully tested against several disease-causing agents and therefore received special attention in biological studies because of their diverse medicinal potentials.

In our previous works,[17–19] we reported the synthesis and antibacterial properties of a new series of thioglycoside heterocyclic derivatives of 1,2,4-triazole-5-thiones and 1,3,4-oxadiazole-5-thiones.[20]

In the course of our search for new antimicrobial agents with 1,3,4-oxadiazoles and 1,2,4-triazole moieties, in this work we report the synthesis of some (5-aryl-1,-3,4-oxadiazol-2-yl)2-chloroethanethioate derivatives (**3a–e**) that are linked to calix[4]arene (**1**) at the lower rim. We also evaluated the antimicrobial efficacy of these oxadiazole derivatives (**4a–e**) against *Escherichia coli* and *Aspergillus fumigatus*. The oxadiazole pharmacophores (**3a–e**) incorporated into calix[4]arene are excellent bioisosteres of amides and esters and can contribute to enhancing biological activity by participating in hydrogen-bonding interactions. Coupling of the oxadiazole pharmacophores to calix[4]arene causes synergy in the medicinal effects of these compounds.

1.1 | Bacterial strain

The antibacterial and antifungal activities of the compounds were assayed according to our perviously published method.[21] The mentioned activities were tested against *E. coli* and *A. fumigatus*.

1.2 | Bacterial and fungi culture

The following microorganisms were used in this study to test the antimicrobial activity of the compounds: *E. coli* (PTCC 1399) and *A. fumigatus* (PTCC 5009). All microorganisms were provided by the Persian Culture Collections of Microorganism, Iran. Bacteria were cultured for 24 hr at 37°C in Brain heart infusion broth (Merck, Darmstadt, Germany), and *A. fumigatus* was cultured for 72 hr at 5°C in Saburo Dextrose broth (Merck), and both were used as inoculums.

1.3 | Susceptibility tests

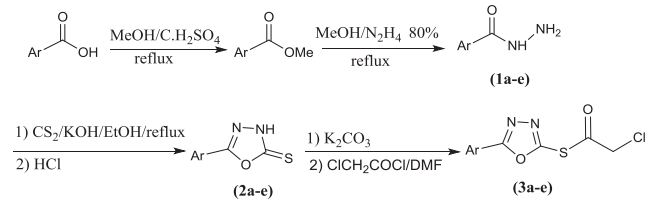
The following methods were used to evaluate the activity of the compounds. Minimum inhibition concentrations (MIC) of the compounds against the tested pathological microorganisms were determined using micro broth dilution method.[21] Briefly, each compound was dissolved in dimethylsulfoxide (DMSO) and a solution with 500 μg/mL concentration was prepared. Stock solutions were added to MHB (BectonDickinson, Franklin Lakes, MD, USA) at 40°C and then poured into Petri plates to obtain dilutions ranging from 7.8 to 100 μg/ml. Control microtiter plates containing the medium and distilled water at similar dilutions were also prepared. Bacterial and fungal suspensions were adjusted to 0.5 McFarland standards (approximately 1–2 × 108 CFU/ml). A fixed amount of the microorganisms was added to all the wells, and the plate was incubated at 37 and 25°C for 24–72 hr for *E. coli* and *A. fumigatus*, respectively (final inoculate was adjusted at 1.5×10^6 CFU per well). Each well was examined for growth by comparing it with the control. The MIC was defined as the lowest concentration of the compounds at which there was no visible growth of the organisms. For each test, enrofloxacin and amphotericin were used as the control antimicrobial agents. The minimum bactericidal concentration (MBC; the lowest concentration of the compounds that resulted in a 99.9% reduction in CFU of the initial inoculums) was determined by plating and counting the contents of wells that showed no visible growth of bacteria onto Mueller Hinton agar and Saburo Dextrose agar plates and incubating at 37 and 25°C for 24–72 hr for *E. coli* and *A. fumigatus*, respectively. MBC was taken as as the lowest concentration of the compounds that prevented any colony formation.

1.4 | Statistical Analysis

All statistical analyses were performed by the SPSS 11.0 (SPSSFW, SPSS Inc, Chicago, IL) statistical package.

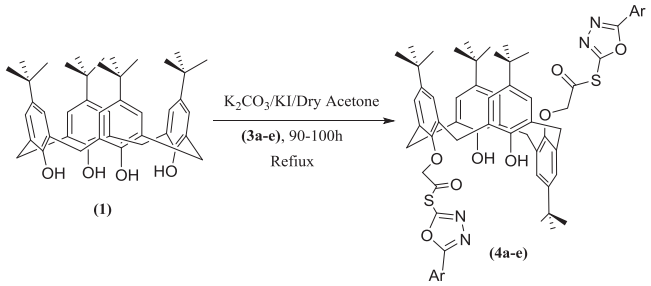
2 | RESULTS AND DISCUSSION

The main synthetic route for substituted 1,3,4-oxadiazole-5-thiones (**2a–e**) involves an initial reaction between a carboxylic acid hydrazide (**1a–e**) and carbon disulfide in basic ethanol solution, followed by acidification with



Ar: Ar= phenyl **(a)**, 2-chlorophenyl **(b)**, Ar=furyl **(c)**, 2-Nitrophenyl **(d)**, 3-Nitrophenyl **(e)**

SCHEME 1 Synthesis of *S*-(5-aryl-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate derivatives



Ar: Ar= phenyl **(a)**, 2-chlorophenyl **(b)**, Ar=furyl **(c)**, 2-Nitrophenyl **(d)**, 3-Nitrophenyl **(e)**

SCHEME 2 Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis *S*-(5-[aryl]-1,3,4-oxadiazol-2-yl) ethanethioate-26,28-dihydroxycalix [4]arene derivatives

dilute hydrochloric acid, which results in the precipitation of oxadiazole. These compounds were synthesized according to the literature[22,23] (Scheme 1).

S-(5-Aryl-1,3,4-oxadiazole-2-yl)-2-chloroethaethioate (**3a–e**) were prepared by the reaction of substituted 1,3,4-oxadiazole-5-thiones (**2a–e**) with choloro actylchloride. The reaction was carried out at 0–5°C in the presence of potassium carbonate in *N*,*N*-dimethylformamide. The reaction mixture was stirred at room temperature. After completion of the reaction, the mixture was poured into cold water and the resulting solid was filtered and crystalized to afford the pure title products (**3a–e**) (Scheme 1).

Tetra-*tert*-butylcalix[4]arene (**1**) was prepared by the Gutsche method as white crystals in good yield through the one-step condensation of *p*-*tert*-butyl phenol with formaldehyde and sodium hydroxide in diphenyl ether under reflux condition.[3]

The synthesis of 5,11,17,23-tetra-tert-butyl-25,27-bis-*S*-(5-[aryl]-1,3,4-oxadiazol-2-yl)ethanethioate-26,28-dihydroxycalix[4]arene derivatives (**4a–e**) was carried out by the reaction of tetra-*tert*-butylcalix[4]arene **(1)** with *S*-(5-aryl-1,3,4-oxadiazole-2-yl)2-chloroethaethioate (**3a–e**) in the presence of anhydrous K_2CO_3/KI in dry acetone under reflux to give the expected products in moderate yields (Scheme 2).

The *in vitro* antibacterial and antifungal activities of the synthesized compounds in CH_3Cl against *E. coli* and *A. fumigatus* are presented in Tables 1 and 2. The minimal inhibition concentration for enrofloxacin as reference antibacterial drug was 36 μg/μl and for amphotericin 28 μg/μl under similar test conditions.

The observed MIC values in Table 1 indicate that these compounds have higher antibacterial effects in comparison with enrofloxacin and amphotericin, which are normally used for treating such infections. The best results were afforded by **3d**, **3a**, and **4e**, which showed high activity against *E. coli*. Preparation of the stock solutions was in the range 10–100 μg/ml. In cases where MIC and MBC were reported as negative (−), it means that this compounds in this concentration range had no antimicrobial activity.

The observed MIC values listed in Table 2 indicate that these compounds have higher antifungal effects in comparison with enrofloxacin and amphotericin, which are normally used for treating such infections. The best results were obtained from **3c**, **4c**, and **4e**, which showed high activity against *Aspergillus fumigates*.

3 | EXPERIMENTAL

3.1 | General

The melting points of all compounds were recorded on a Philip Harris C4954718 apparatus without calibration. FT-IR spectra were recorded on a Thermo Nicolet 670 Nexus spectrometer with KBr pellets. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) measurements were carried out on a Bruker 300 MHz spectrometer in $CDCl_3$ using TMS as the internal reference. ESI-MS measurements were made on a Finnigan MAT 95 double-focusing sector-field mass spectrometer. Thin-layer chromatography (TLC) analyses were carried out on silica gel plates. All chemicals were purchased from Merck (Tehran, Iran) and used as received in all standard procedures. All apparatuses, chemicals, and solvents were dried according to standard methods. Freshly distilled solvents were used throughout the experiments, and anhydrous solvents were dried according to the method of Perrin and Armarego.[24] Microanalyses were performed on a Leco Analyzer 932. 1HNMR, 13C NMR and FT-IR spectra of all products are given in the supporting information section.

3.2 | Synthesis of tetra-*tert*-butylcalix[4] arene (1)

It was prepared according to the Gutsche[25] method as white crystals. Yield 3.97 g (62%), mp 340–343°C; IR (KBr) ν/cm^{-1}: 3,158, 2,959, 2,905, 2,868, 2,744, 1,604,

TABLE 1 *In vitro* antibacterial activity of the synthesized compounds against *E. coli*

Compound	MIC (μg/μL)	MBC (μg/μL)	Compound	MIC (μg/μL)	MBC (μg/μL)
3a	10	20	**4a**	—	—
3b	15	30	**4b**	—	—
3c	—	—	**4c**	20	40
3d	10	10	**4d**	20	40
3e	—	—	**4e**	10	20

TABLE 2 *In vitro* antifungal activity of the synthesized compounds against *A. fumigates*

Compound	MIC (μg/μL)	MBC (μg/μL)	Compound	MIC (μg/μL)	MBC (μg/μL)
3a	—	—	**4a**	—	—
3b	—	—	**4b**	20	40
3c	10	20	**4c**	10	20
3d	—	—	**4d**	—	—
3e	20	40	**4e**	10	20

1,482, 1,201, 871, 817, 783, 743, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H:1.22 (s, 36H, $4 \times C[CH_3]_3$), 3.5 (d, 4H, $J =$ 13.8 Hz, $ArCH_2Ar$), 4.26 (d, 4H, $J =$ 13.8 Hz, $ArCH_2Ar$), 7.06 (s, 8H, ArH), 10.34 (s, 4H, $4 \times$ OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):39, 32.60, 34.75, 125.93, 127.68, 144.36, 146.66.

3.2.1 | General procedure for the synthesis of (2a–e)

The main route for the synthesis of 5-substituted-1,-3,4-oxadiazole-2-thiols/thiones (**2a–e**) involves an initial reaction between an acylhydrazide (**1a–e**) (0.1 mol) and carbon disulfide 15.2 g (0.2 mol) in basic alcohol solution (50 ml) followed by acidification of the reaction mixture. The precipitate was filtered, washed thoroughly with cold water, and recrystallized from ethanol to give 1,3,4-oxadiazole-5-thiones (**2a–e**) (yield 60–70%). The following compounds were prepared under analogous procedures.[22,23] Thiol–thione tautomerism is known for the compounds **2a–e**, and one of the forms usually predominates.[26]

3.2.2 | General procedure for the synthesis of *S*-(5-aryl-1,3,4-oxadiazole-2-yl) 2-chloroethanethioate (3a–e)

1,3,4-Oxadiazole-5-thione (0.01 mol) was dissolved in *N*,*N*-dimethylformamide (10 ml), to which potassium carbonate (0.3–0.5 g) was added into the mixture and stirred for 30 min. Then chloroacetyl chloride (0.01 mol) was added dropwise at 0–5°C and the mixture was stirred for 3 hr at room temperature. The formation of the titled intermediate was confirmed by TLC using ethyl acetate/hexane as the mobile phase. After completion of the reaction, the mixture was poured into cold water and the product was collected.

3.2.3 | Synthesis of *S*-(5-phenyl-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate (3a)

Yield: 0.192 g, 75%, m.p. 160–162°C; IR (KBr), υ/ cm^{-1}: 3,440, 2,930, 1,759, 1,622, 1,490, 1,316, 1,051, 968, 753, 689; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.84 (2H, s, CH_2), 7.50–7.66 (3H, m, ArH), 7.94–8.02 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.50, 162.67, 158.81, 133.43, 132.65, 130.33, 128.24, 127.50, 125.49, 43.44. Calcd: C, 47.16; H, 2.77; N, 11.00; S, 12.59%; Found: C, 47.14; H, 2.75; N, 10.98; S, 12.58%.

3.2.4 | Synthesis of *S*-(5-[2-chlorophenyl]-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate (3b)

Yield: 0.22 g, 76%, m.p. 149–151°C; IR (KBr), υ/ cm^{-1}: 3,444, 2,949, 1,764, 1,615, 1,591, 1,317, 1,032, 932, 729, 684; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.84 (2H, s, CH_2), 7.44–7.50 (1H, m, ArH), 7.54–7.63 (2H, m, ArH), 7.95–7.97 (1H, d, J = 7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.56, 162.63, 156. 60, 133.72, 132.90, 132.81, 132.00, 129.92, 128.48, 43.30. Calcd: C, 41.54; H, 2.09; N, 9.69; S, 11.09%; Found: C, 41.53; H, 2.07; N, 9.71; S, 11.08%.

3.2.5 | Synthesis of *S*-(5-[furan-2-yl]-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate (3c)

Yield: 0.191 g, 79%, m.p. 105–108°C; IR (KBr), υ/ cm^{-1}: 3,145, 2,942, 1,769, 1,654, 1,466, 1,319, 1,251, 1,071, 945, 589; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.80 (2H, s, CH_2), 6.67 (1H, s, furyl), 7.27 (1H, s, furyl), 7.73 (1H, s, furyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.25, 149.05, 146.39, 116.79, 113.97, 113.79, 43.35. Calcd: C, 39.28; H, 2.06; N, 11.45; S, 13.10%; Found: C, 39.27; H, 2.07; N, 11.43; S, 13.9%.

3.2.6 | Synthesis of *S*-(5-[2-nitrophenyl]-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate (3d)

Yield: 0.23 g, 76%, Lit: m.p. 119–121°C; IR (KBr), υ/ cm^{-1}: 3,440, 2,949, 1,771, 1,657, 1,536, 1,337, 1,304, 1,253, 1,042, 748, 720, 566; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.77 (2H, s, CH_2), 7.85–7.91 (3H, m, ArH), 8.14–8.17 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.68, 162.48, 159.19, 134.70, 133.08, 132.98, 132.71, 132.63, 132.53, 132.18, 43.30. Calcd: C, 40.08; H, 2.02; N, 14.02; S, 10.70%; Found: C, 40.07; H, 2.03; N, 14.01; S, 10.71%.

3.2.7 | Synthesis of *S*-(5-[3-nitrophenyl]-1,3,4-oxadiazol-2-yl) 2-chloroethanethioate (3e)

Yield: 0.21 g, 74%, m.p. 134–138°C; IR (KBr), υ/ cm^{-1}: 3,332, 2,945, 2,875, 1,723, 1,537, 1,470, 1,354, 1,286, 1,196, 1,028, 718; ^{1} H NMR ($CDCl_3$, 300 MHz) δ(ppm): 4.77 (2H, s, CH_2), 7.77 (1H, t, J = 7.8 Hz, ArH), 8.30 (1H, d, J = 7.5 Hz, ArH), 8.45 (1H, d, J = 8.1, ArH), 8.82 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.23, 167.94, 162.94, 133.32, 133.26, 133.16, 124.94, 44.16. Calcd: C, 40.08; H, 2.02; N, 14.02; S, 10.70%; Found: 40.06; H, 2.03; N, 14.00; S, 10.71%.

3.2.8 | General procedure for the synthesis of5,11,17,23-tetra-*tert*-butyl-25,27-bis(*S*-(5-aryl-1,3,4-oxadiazol-2-yl) ethanethioate-26,28dihydroxycalix[4]arene

5,11,17,23-Tetra-*tert*-butyl-25,27-bis-*S*-(5-[aryl]-1,3,4-oxadiazol-2-yl)ethanethioate-26,28-dihydroxycalix[4]arene derivatives (**4a–e**). Calix[4]arene (571 mg, 0.724 mmol), potassium carbonate (100 mg, 0.726 mmol), potassium iodide (50 mg), and *S*-(5-aryl-1,3,4-oxadiazol-2-yl)2-chloro ethanethioate derivatives (400 mg, 1.81 mmol) were refluxed in dried acetone (100 mL) for 80–90 hr. After evaporation of the solvent, the residue was extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was tritrated with methanol to give the product mixture, which was recrystallized from MeOH. Then the precipitate of the compound was submitted to column chromatography (SiO_2, EtOAc/hexane, 2:8).

3.2.9 | Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis(*S*-(5-phenyl-1,3,4-oxadiazol-2-yl)ethanethioate-26,28-dihydroxycalix[4] arene (4a)

Yield (0.23 g, 60%), m.p. 198°C; IR (KBr), υ/ cm^{-1}: 3,345, 3,406, 2,985, 1,745, 1,624, 1,479, 1,479, 1,123, 801, 569, 461; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 1.22–1.52 (36H, s, 4×C$[CH_3]_3$), 3.00 (1H, d, J = 15), 3.43–3.93 (3H, m), 3.98 (2H, s), 4.00–4.04 (3H, m), 4.29–4.43 (2H, m), 4.96–5.02 (1H, d, J = 18), 6.88 (4H, s, ArH), 7.00 (1H, s), 7.07 (2H, s), 7.29–7.34 (5H, m, ArH), 7.37–7.49 (5H, m, ArH), 7.84–7.95 (5H, m, ArH); DEPT 135^o (125 MHz, CD_2Cl_2) δ (ppm): 29.33, 29.98, 30.71, 30.88, 31.07, 31.15, 31.17, 34.18, 37.63, 124.39, 125.53, 125.78, 125.85, 125.92, 125.99, 126.03, 127.51, 128.13, 128.36, 130.78, 130.99, 131.27; ESI-MS: m/z = 1,088.62 [M + H]; Calcd: C, 70.50; H, 6.39; N, 5.22; S, 5.97%; Found: C, 70.47; H, 6.33; N, 5.23; S, 5.85%.

3.2.10 | Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis *S*-(5-[2-chlorophenyl]-1,3,4-oxadiazol-2-yl) ethanethioate-26,28-dihydroxycalix[4]arene (4b)

Yield (0.84 g, 62%), m.p. 178°C; IR (KBr), υ/ cm^{-1}: 3,410, 3,175, 2,927, 2,861, 1,711, 1,610, 1,669, 1,381, 1,276, 1,250, 1,186, 1,135, 1,186, 1,135, 1,040, 959, 899, 724, 600; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 1.28–1.53 (36H, m, 4×C$[CH_3]_3$), 3.03 (1H, d, J = 12), 3.31–3.57 (3H, m), 4.00–4.03 (4H, m), 4.28–4.40 (2H, m), 4.29–4.43 (2H, m), 4.58 (1H, s), 4.96–5.02 (1H, m), 6.85 (1H, s, ArH), 7.07–7.18 (4H, m, ArH), 7.31 (2H, s), 7.37–7.51 (9H, m, ArH), 7.80–7.89 (2H, m, ArH); DEPT 135^o (125 MHz, CD_2Cl_2) δ (ppm): 29.37, 29.94, 29.37, 29.94, 30.38, 30.41, 30.72, 30.94, 31.10, 31.15, 31.32, 33.72, 33.84, 34.18, 36.74, 37.65, 38.73, 124.40, 125.75, 125.82, 125.87, 125.95, 126.06, 126.22, 126.38, 127.45, 130.12, 130.28, 130.31, 130.35, 130.42, 130.55, 131.49; ESI-MS: m/z = 1,155.22 [M–H]; Calcd: C, 66.25; H, 5.82; N, 4.91; S, 5.61. Found: C, 66.15; H, 5.83; N, 4.85; S, 5.68.

3.2.11 | Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis *S*-(5-[furil]-1,3,4-oxadiazol-2-yl)ethanethioate-26,28-dihydroxycalix[4]arene (4c)

Yield (0.2 g, 52%), m.p. 148°C; IR (KBr), υ/ cm^{-1}: 3,406, 3,166, 2,947, 1,712, 1,617, 1,475, 1,378, 1,290, 1,199, 1,121, 870, 741, 688; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 0.9–1.41 (36H, m, 4×C[CH_3]$_3$), 3.36–3.53 (3H, m), 3.91–4.00 (5H, m), 4.21–4.36 (2H, m), 7.04–7.14 (7H, m), 7.36 (2H, m), 7.05–7.60 (5H, m); DEPT 135^o (125 MHz, CD_2Cl_2) δ (ppm): 29.00, 29.84, 30.69, 30.81, 30.93, 31.11, 37.49, 111.51, 113.05, 113.27, 113.80, 124.28, 125.60, 125.78, 125.83, 125.94, 126.02, 127.43, 145.26; ESI-MS: *m/z* = 1,066.48 [M–H]; Calcd: C, 67.28; H, 6.12; N, 5.32; S, 6.09. Found: C, 67.18; H, 6.10; N, 5.35; S, 6.00.

3.2.12 | Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis *S*-(5-[2-nitrophenyl]-1,3,4-oxadiazol-2-yl) ethanethioate-26,28-dihydroxycalix[4]arene (4d)

Yield (0.19 g, 65%), m.p. 188°C; IR (KBr), υ/ cm^{-1}: 3,451, 2,956, 1,759, 1,538, 1,475, 1,356, 1,297, 1,189, 1,132, 876, 723, 563; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 1.22–1.41 (36H, m, 4×C[CH_3]$_3$), 3.50 (1H, d, *J* = 12), 3.33–3.69 (3H, m), 3.98–4.04 (5H, m), 4.18–4.23 (2H, m), 4.52 (1H, s), 7.07(2H, s), 7.15 (1H, s), 7.27 (1H, s), 7.43–7.49 (2H, m, ArH), 7.69–7.2 (6H, m), 7.82–7.86 (2H, m, ArH), 7.88–8.01 (3H, m, ArH); DEPT 135^o (125 MHz, CD_2Cl_2) δ (ppm): 30.55, 30.61, 30.74, 33.79, 124.14, 124.74, 124.79, 124.89, 125.06, 125.53, 125.73, 126.03, 126.13, 131.02, 131.25, 131.79, 131.91, 132.47, 132.51, 132.64; ESI-MS: *m/z* = 1,178.48 [M + H]; Calcd: C, 65.04; H, 5.72; N, 7.22; S, 5.51. Found: C, 65.00; H, 5.64; N, 7.25; S, 5.44.

3.2.13 | Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis *S*-(5-[3-nitrophenyl]-1,3,4-oxadiazol-2-yl)ethane thioate-26,28-dihydroxycalix[4]arene (4e)

Yield (0.16 g, 61%), m.p. 158°C; IR (KBr), υ/ cm^{-1}: 3,513, 2,956, 1,760, 1,536, 1,473, 1,355, 1,297, 1,184, 1,132, 1,061, 873, 723, 565; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm): 0.95–1.39 (36H, m, 4×C[CH_3]$_3$), 3.69(2H, d, *J* = 15), 3.85–3.95 (2H, m), 4.01–4.05 (5H, m), 7.2–7.24 (2H, s), 4.5 (2H, s), 6.70 (1H, s), 7.03–7.2 (4H, m, ArH), 7.26 (2H, s), 7.70–7.86 (8H, m, ArH), 7.97 (2H, s, ArH), 7.98–8 (4H, m, ArH); DEPT 135^o (125 MHz, CD_2Cl_2) δ (ppm): 30.39, 30.67, 30.70, 30.74, 30.80, 30.89, 30.99, 31.07, 31.27, 31.31, 34.14, 35.06, 36.75, 38.01, 38.62, 67.48, 123.95, 123.98, 124.19, 124.36, 125.91, 125.99, 126.11, 127.53, 130.85, 131.01, 131.83, 131.90, 132.48, 132.59, 132.68; ESI-MS: *m/z* = 1,178.43 [M + H]; Calcd: C, 65.04; H, 5.72; N, 7.22; S, 5.51. Found: C, 65.00; H, 5.67; N, 7.25; S, 5.47.

4 | CONCLUSIONS

A series of new tetra-*tert*-butyl calix[4]arene derivatives (**4a–e**) were prepared by the reaction of *S*-(5-aryl-1,-3,4-oxadiazol-2-yl)2-chloroethanethioate moieties (**3a–e**) with calix[4]arene (**1**) in the presence of potassium carbonate. The antimicrobial results obtained from novel calix[4]arene derivatives (**4a–e**) revealed that among the synthesized compounds, **4c** was most effective against *A. fumigates*. Compound **4e** was found to be most effective against E. *coli* and *A. fumigates*.

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SUPPORTING INFORMATION

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