Volume 8, Issue 6, 2018, 3688 - 3694 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

Original Research Article Open Access Journal

Received: 30.10.2018 / Revised: 06.12.2018 / Accepted: 10.12.2018 / Published on-line: 15.12.2018

Synthesis, identification, and investigation of the antibacterial effect of the new derivatives of sulfonamide Calix [4] Arenes based on aliphatic amines

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ABSTRACT

The Calix arens are part of the Supramolecular family and designed as host molecules, so their synthesis has particular importance. In this research, Sulfonamide Calix [4] arene derivatives have been prepared from the reaction of the sulfonyl chloride Calix arene derivative in the presence of aliphatic amines type I and II. The structure of obtained derivatives was investigated using IR and ^{1}HNMR spectroscopy techniques. Antibacterial properties of these compounds were evaluated using MIC, MBC, and Disk Diffusion tests. The results revealed that derivatives have anti-bacterial properties, and substitution at the top rim of the ring is done correctly.

Keywords: *CalixArene, Sulfonamide, Antibacterial Properties, MIC and MBC Tests.*

1. INTRODUCTION

Calixarenes are macromolecules that have been one of the special research areas of the past decades. The presence of specific size, holes and active centers in the upper and lower rims of the ring in the structure of these compounds has caused that it is used as host molecule, in host-guest chemistry in two-dimensional supramolecular. As well, have many applications in various fields, including the separation of ions, molecules, sensors, catalysts, and biological compounds. Guest molecules are known to interact with host molecules. Calixarenes are supramolecular compounds interacting with bioactive molecules and ions, causing changes in biochemical and biophysical processes [1-2]. The calixarenes are highly flexible compounds; the presence of methylene groups between aromatic rings has led to a reduction in their flexibility by placing large aliphatic groups at the top of the rings. Several methods have been reported to substantiate their construction [2]. Before synthesizing the host molecule, it is necessary to select the guest molecule to consider parameters such as size, load, and flexibility for the formation of the complex with the host. In 1872, German Adolf van Baier made a study on the reaction between phenol and formaldehyde in the presence of strong acid, its product was a very hard material, like cement [3]. In 1907, another researcher named Leo Buckland conducted the same reaction in the presence of a small amount of base, obtained a product and called it Bakelite [4]. This material was obtained from the reaction between para tertiary butyl phenol and formaldehyde in the presence of acid or base. The presence of coarse rings such as calixarenes in the structure of drugs increases the selectivity and pharmacological activity of these drugs, thus studying the effect of sulfonamide medications on calixarene units has great importance. Calix [4] arenes, sulfonamide derivatives have a special place in the pharmaceutical industry, so that important parts of antibacterial drugs and antifungal agents have a sulfonamide functional group. Antibacterial properties of sulfonamides occur from the fact that the enzymes in the bacterium are confused with the sulfonamides with para amino benzoic acid, which is the major metabolizing product of bacteria, so that sulfonamides sit on a reactive position of the bacteria during a metabolic controversy and cause bacteria death [5-6]. Although many drugs today have a sulfonamide functional group, it can be said that the most important and first members of this group are initially from the group of antibiotics. Such as sulfacetamide, sulfamethoxazole and silver sulfadiazine [7-8]. The other medicinal properties of these compounds that have been studied are anti-diabetic properties; some type of this group has been known to reduce blood sugar, such as Glibenclamide and Glipizide. Recently, sulfonamide is used to treat Alzheimer's disease. The medicinal properties of sulfonamides, depending on the group R, attached to the N-amino group. The R group should give the proper acidic property to H. Studies have shown that if R is a heterocyclic group, sulfonamide would have a high antibacterial and therapeutic effect. Topiramate, from this family of medicines, is an Anticonvulsant/Anti-Seizure drug [9-11]. In the treatment of hypertension with Thiazide diuretics such as acetazolamide, furosemide, and hydrochlorothiazide. [12] Sulfasalazine is used as an anti-inflammatory drug for gastrointestinal tract [13]. Celecoxib is used with anti-inflammatory and analgesic properties [14-15]. The use of sulfonamide derivative as a protease inhibitor of Dengue 2 virus (mosquito bites) and inhibition of the effects of methazolamide and midazolam the sulfonamide and sulfamate family drug that has been done and has proven on carbon monoxide, on the large volume of gram-negative bacteria an antibiotic film called Pseudoalteromonas haloplanktis. The activity of antimalarial drugs such as benzene sulfonamide examined and verified [16-18]. For recently approved sulfonamide-mediated drugs, it is possible to express amprenavir (a protease inhibitor of HIV) and ultimately a genital medicine in men, such as phosphodiesterase (Phosphodiesterase as a sildenafil inhibitor), which is called Viagra. [19]. Sulfonamide has emerged as

structures belonging to the so-called superior structures in pharmaceutical chemistry. The consistent pharmacokinetic properties include metabolic stability [19]. Also has a profound effect in treating urinary problems, intestines, eye pain and eye infections, blistering burns with hot water, ulcers from intestinal inflammation, arthritis and rheumatism, and ultimately high obesity [20-21]. Sulfonamides are inactive when the p-Amino group is acylated and benzene is substituted, and the sulfonamide group does not directly bind to the benzene ring. Other studies have shown that modified sulfonamides tend to favor moderate antibacterial activity. Aliphatic sulfonamides (fatty) have a stronger antibacterial activity for the gram-negative bacteria than gram-positive bacteria, and this antibacterial activity is reduced by increasing the length of the carbon chain [19]. Other preliminary research suggests (bis-sulfonamides) have an antimicrobial activity [22]. Prostaglandin F1a sulfonamides are used for potential osteoporosis treatments. Methanesulfonamide (pentafluoropheny2,3,4,5,6) -N-acyl-N is used as a selective N-acylating agent in chemistry [23-25]. Benzenesulfonamide derivatives have been synthesized with an anti-tumor urea group [26]. An extended green sonography method for sulfonamide transplantation was performed using a natural, stable, and reusable natrolite catalyst at room temperature [27]. In other studies, the silica gel has been used to prepare sulfonamides as a catalyst (reactive chemical interaction agent) that is reusable. This action is carried out by the liquidation of fatty amines with sulfonyl chlorides under soluble conditions at room temperature [28-29]. In this study, para tert butyl phenol was used as the raw material for the synthesis of parent calixarene. After parent calixarene reaction in the presence of chlorosulfonic acid in the reaction of ipso chlorosulfonation, chlorosulfonyl derivative was obtained. In the following, the new sulfonamide derivatives were obtained from the reaction of chlorosulfonyl-Calix-arene obtained with two different aliphatic amines. Antibacterial effects were evaluated using MIC, MBC and Disk Diffusion tests.

2. EXPERIMENTAL SECTION

2.1. Materials and Methods.

Paretashio Butyl Phenol, Sodium hydroxide, Formaldehyde, Diphenyl ether, Ethyl acetate, Dichloromethane, Chlorosulfonic Acid, Diethyl ether, Pyridine, Tetrahydrofuran, and Methanol were purchased from German Merck Company and used without purification. All reactions occurred in a nitrogen atmosphere. All solvents used in the conventional methods were dried before reaction. Antibacterial properties were studied with gram-positive bacteria of Staphylococcus aureus and gram-negative bacteria of Salmonella. The Growth medium used by Muller Hinton, Salmonella Shigella, Broth and Broth Agar were purchased from Merck Company in Germany.

2.2. Preparation of 5, 11, 17, 23-tetrachloro-butyl-Calix [4] arene compound (1).

At the first added 30 gr (0.199 mmol) of 4-tert-Butylphenol granules in a three-neck flask capacity 1000 mL with a mechanical stirrer and add 0.36 gr/ml Sodium hydroxide and 18.6 ml of 37% formaldehyde solution, 30-minute stirring was performed using a mechanical stirrer at ambient temperature. As long as a yellow viscous mass was obtained, Stirring was performed at a temperature of 110 °C to 130 °C. During the mass formation process, by changing the volume and foaming of the contents of the flask, the color changes from beige to dark yellow. After cooling the mixture, 300 ml of diphenyl ether was added to the obtained crude, and the contents of the flask were stirred at ambient temperature for 1 hour. Then the temperature was raised to 120 °C and after about 3 hours under nitrogen gas (to remove water vapor), the color changed from orange to very bright brown. The reflexes were performed for 4 hours at a temperature of 250 °C [30-32]. Finally, by cooling the contents of the flask and reaching the ambient temperature, added 250 ml of ethyl acetate to the obtained solution, and was stirred for about 20 minutes. Sediments were observed after adding ethyl acetate. The contents of the flask were kept steady for 2 days for precipitation action and then the washing was performed with ethyl acetate, acetic acid, water and acetone solvents. In the end, white and White and shiny crystals of Calix [4] arene compound (1) were obtained with a yield of 65 % (Figure 1(A) & (B)).

Mp= 332-340ºC

^{1}HNMR (500MHz, $CDCl_3$) δ(ppm), 1/21(s, 36H, $[CH(CH_3)_3]$), 3/5(d, 4H, $ArCH_2Ar$, j=12/8Hz), 4/26(d, 4H, $ArCH_2Ar$, j= 12/8Hz), 7/04(s, 8H, Ar-H), 10/33(s, 4H, OH);

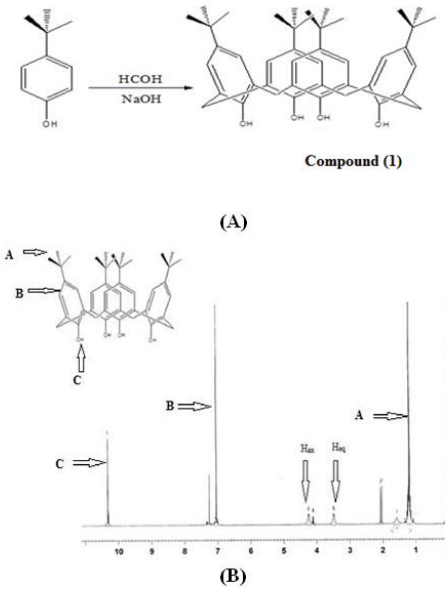

Figure 1. (A) Scheme of synthesis of Compound (1); **(B)** 1HNMR of Compound (1).

2.3. Preparation of 5, 11, 17, 23-tetrachloro sulphonyl-Calix [4] arene compound (2).

Due to the sensitivity of the reaction to the moisture content, all of the containers by the Bunsen burner get dry, after passing the vessels a gentle flow of nitrogen gas was carried out for 5 minutes. In a three-neck flask capacity, 100 ml equipped a condenser and a

nitrogen input, 2.59 gr (3.99 mmol) of compound (1) with 5 ml of dried dichloromethane were added and stirred with a magnetic stirrer for 30 minutes. The flask was then placed in ice and acetone to reduce the temperature to -6 °C, and 10ml (86.2mmol) chlorosulphonic acid dropwise added, the solution being two-phase and its color changed to brown-orange. After that, the bath was removed and the solution should be allowed to warm to room temperature. In this case, the nitrogen gas was passed through a solution for 10 minutes to neutralize the reaction environment, and then the reflux was performed with a paraffin bath for 30 minutes. subsequently, the reaction vessel was placed in an ice bath and acetone (reaction is Exothermic at this stage) and slowly added 60 ml of dry diethyl ether, as soon as adding, the color of the solution changed to cherry red and the diethyl ether as anti-solvent extracts sediments from the reaction solution [33]. The initial sediment was separated and washed with 20 ml of methanol, and the subfiltration solution was kept in the refrigerator for 1 day for re-sedimentation. Finally, the sulfone Calix compound (2) with beige color was obtained with a yield of 91% (Figure 2(A) & (B)).

Mp>230ºC

^{1}HNMR (500MHz, DMSO-d_6, TMS), δ(ppm) 3/95(s, 8H, $ArCH_2Ar$), 7/39(s, 8H, Ar-H), 11/55(s, 4H, OH);

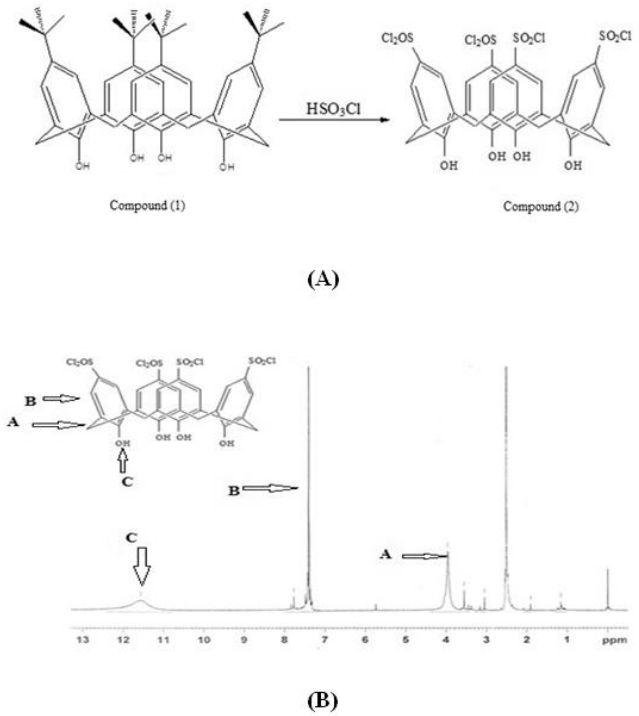

Figure 2. (A) Scheme of synthesis of Compound (2); **(B)** 1HNMR of Compound (2).

2.4. The general method for the preparation of sulfonamide calix[4] arene derivatives.

In order to carry out these two reactions, in a flask capacity 100 ml, poured 0.3 gr (0.36 mmol) of the compound (2) with 12.5 ml of tetrahydrofuran, after that the color of the solution changed to beige-pink. The Intended amines were added to the mixture with considering the ratio 1:4 of amine and compound (2). To remove chlorine substituted by an amine, pyridine was used to complete the reaction Finally, pyridinium chloride sedimentation showed the completion of the reaction. To purify the obtained product methanol was used as an anti-solvent.

2.4.1.Sulfonamide Hexadecyl Calix [4] Arene Derivative

Mp > 125℃,

1HNMR (500MHz, DMSO) δ (ppm): 1/19 (t,12H, CH3), 1/36(M, 112H, CH2), 3/32(t, 8H, CH2-NH), 5.06(d-d, 8H, Ar-CH2-Ar), 7/77(s, 8H, Ar-H), 8/21(t, 4H, NH), 8.82(s, 4H, OH);

IR : $\mathcal{V}$ (cm-1)=2593, 2127, 2254, 825, 630 CM-1, Yeild:37%

2.4. 2. Sulfonamide Cyclohexyl Calix [4] Arene Derivative

Mp> 180℃,

^{1}HNMR (500MHz, DMSO) δ(ppm): 1/12(m, 8H, CH_2), 1/62(m, 16H, CH_2-CH_2-CH_2), 1/76(m, 16H, CH_2β), 2/71(m, 4H, CH-NH), 3/6(d, 8H, Ar-CH_2-Ar), 4/63(s, 4H, NH), 7/32(s, 8H, Ar-H), 8/58(s, 4H, OH);

IR: $\mathcal{V}$(cm^{-1})=3174, 2930, 2855, 2528, 2076, 1387, 1240, 1140, 1037 CM^{-1}, Yeild:45%

2.5. Antibacterial Properties Analysis Method

2.5.1. Method of preparing the applied growth medium. Growth medium provided according to the instruction which has been placed in the containers and then placed inside the autoclave to be sterilized, after cooling, considering that the growth medium was intended for bacterial cell culture or tests carried out, they were poured respectively, in 8 and 10 cm plates. Then placed next to the flame, and finally, put it in the refrigerator to be tightened. To prepare the used liquid growth medium, after being made according to the instructions it was poured into test tubes and it was placed into autoclave [34].

2.6. Methods used to cultivate bacteria

2.6.1.Lawn cultivation. In order to perform a Disk Diffusion test, should use the growth medium that is suitable for the growth of most bacteria, thus used the Muller Hinton growth medium, which is the general growth medium. Lawn cultivation used for this test was performed with swap and loop. Previously, in order to obtain a uniform growth medium, it is necessary to have single colonies of the tested bacterium, which was grown in a proprietary growth medium and placed in an incubator for 18 hours. poured single-cloned bacteria in distilled water and compared with a half-MAC (containing about 1.5×10^8 standard bacteria), were poured on the growth medium. Lines were drawn, by means tool, on the medium horizontally, vertically and diagonally. It was placed in an incubator for 24 hours [35].

2.6.2. Four stage cultivation. A special growth medium needs to be prepared for the growth of bacteria. After preparing the medium, single-colonies of the bacteria taken from the hospitals and laboratories were taken and growth on the growth Medium withdraw lines diagonally. Several points were made by a loop to create single-colonies [35].

2.6.3. Liquid Growth Medium. After the preparation of half Mac, some of it was injected into the liquid medium and then placed in an incubator [35].

2.7. Antibacterial Tests

2.7.1. Disk Diffusion Test. After lawn cultivation, the disk diffusions impregnated with the derivatives were placed on it and put it in the incubator for 16 to 18 hours. This test was performed

for both synthesized derivatives. The amount of bacterial growth halo around the disk was measured by the Coliseum. The growth temperature of the studied bacteria in this study is 35-37 °C [35].

2.7.2. MIC and MBC Tests. This test used to control antibacterial properties. MIC means the lowest concentration of antibacterial agent that inhibits bacterial growth, and MBC means the lowest concentration of antibacterial agent that causes the death of bacteria. 0.04 g of hexadecyl and cyclodecyl derivatives dissolved in 2cc of dimethyl sulfoxide. Provided Nine test tubes containing 1cc sterilized growth medium. Then added 1cc of dilution of antibiotic to tube 1. stirrer it with a vertex for the solution homogeneity, then from tube No.1 to tube No.8, respectively added 1cc to the next test tube. Thus, the antibiotic dilution gradually decreases with increasing number of tubes. The next step is to prepare a bacterial suspension. Single-colonies of bacteria growth for 14 to 18 hours were taken with loop and dipped into sterilized water tubes and each time compared to half Mac. After equalizing with half Mac opacity, added 1cc of it to all tubes. In this case, the tube number 9, which contains only the growth medium and the bacteria, as a positive control, and the tube number 8, which only contains growth medium and antibiotic, was considered as a negative control. Finally, it was placed in the incubator at 37 °C for 24 hours. This was done for both grams positive and gram-negative bacteria [35-38].

3. RESULTS SECTION

The ^{1}HNMR spectrum of compound (2) is performed in dimethyl sulfoxide solvent (Figure.2 (B)). The presence of larger groups of ethyl stabilizes the conformation of the Cone. In this case, the methylene protons are in the longest distance and the cone conformation is preserved; as a result, two peaks in the doublet-doublet form existed. In the case of observing a single wavelength peak in the ^{1}HNMR spectrum for methylene protons, it can be concluded that calixarene has another conformation other than the cone. Since the SO_2 group at the top of the ring makes the group flexible, even at ambient temperature the conformation changes, it can be concluded that factors such as polarity of solvent and temperature can be impressive on the displacement of methylene bridge protons. The ^{1}HNMR solvent for compound (2) is DMSO, that is polarized solvent. As a result, the reason for seeing a single peak in this fast-moving spectrum is the methylene protons in the polar solvent at ambient temperature, which is so fast that the device displays a single peak. Therefore, it can be concluded that the peak of the methylene protons will appear doublet if the solvent is nonpolar and the temperature is low. By replacing the SO_2Cl group, the peak of tertbutyl phenol was eliminated in the 1.21 ppm range, and respectively the 8-proton related to the methylene bridge in 3.95 ppm was a single wide spectrum. Due to having two symmetry plates in the structure 8 protons in the aromatic region, 7.39 ppm gave single peak and in 11.55 ppm, there is a single peak of the phenol group, which represents 4 phenol protons. In the IR spectrum, this combination of adsorbs is related to the chlorosulfonyl group at 1164 and 1363 cm^{-1}, the region of 1200 to 1400 cm^{-1} represents the aromatic region. The broad peak 3231 cm^{-1} is for phenolic OH, and the vibrational frequency of the tartaric Butyl group is also eliminated.

3.1. The reaction between various amines, with chlorosulfonyl derivative.

Selection and connection of the first and second type of aliphatic amines have done in terms of polarity, considering that the compound (2) as a host molecule does not have a high polarization, in order to increase the size of the Calix [4] arene cavity, and the special properties of derivatives. Initially, due to the good solubility of the compound (2), its dried form was used in tetrahydrofuran solvent, taking into account the ratio of 1: 4 basic materials with an amine, calculated the amount of required ammonium (mmol) and added the calculated amount to the solution. Finally, used pyridine base for the removal of substituted Cl, pyridinium chloride sediment indicate the reaction progression at this stage. Finally, the product was washed with methanol for recrystallization. Subsequently, their melting points were obtained and their spectral information was obtained. Both achieved derivatives have two symmetry plates it was raveled that the prepared derivatives were tetra sulfonamide. Bridge protons appear as a singlet. The aromatic protons have been a peak in one place. The used aliphatic amines have aromatic positioning peaks in the area. Hexadecylamine, cyclohexylamine, are used amines. The efficiency obtained for the synthesis of the derivative hexadecyl Calix [4] arenes sulfonamide was 37% (Compound 3; Figure.3 (A)).

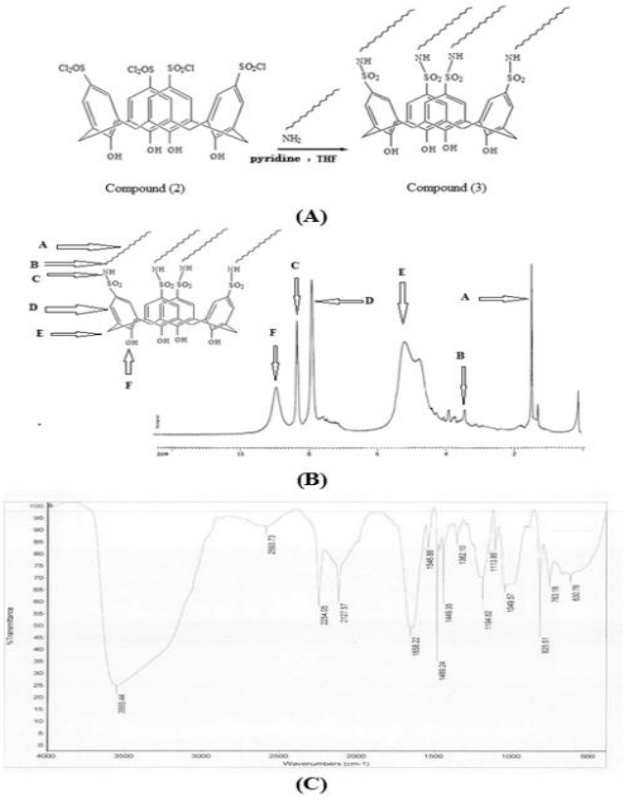

Figure 3. (A) Scheme of synthesis of Compound (3);**(B)** ^{1}HNMR of Compound (3);**(C)** IR of Compound (3).

Figure.3 (B) shows the ^{1}HNMR of compound (3). The solvent of compound (3) is a 3-dimethyl sulfoxide (DMSO 2.53) which is due to the polarity of the observed peaks for the methylene bridge protons in the form of a single one, indicating the high velocity of the transformation of equatorial and axial protons and displays disintegrating Cone conformation. The peak at 5.06 ppm represents 8 protons of Methylene Bridge. The triplet peak at 1.19 ppm represents 12 protons of the methyl group at the end of the chain in hexadecylamine and peak at 1.36 ppm related to 112 hydrogen amino chain. The peak at 3.32 ppm corresponds to 8 proton-methylene-linked nitrogen that is deshield. 8 aromatic hydrocarbons have peak at 7.77 ppm. Four Hydrogen attached to N have peak at 8.21 ppm, and split by the effect of CH_2 as a triplet, and eventually, the peak of the phenyl group's hydrogen appear at 8.82 ppm. In the IR spectrum (Figure.3 (C)), the corresponding composition in the 2593 cm^{-1} frequency is related to the amine group type 1, and at 2254, 2127 cm^{-1}, the frequency is related to the C-H aliphatic chain and at 630 to 825 cm^{-1}, the observed peak is related to the N-H group. The derivative yield of sulfonamide cyclohexyl Calix [4] arene (Compound (4)) was 45% (Figure.4 (A)). The ^{1}HNMR spectrum of compound (4) was performed in a solvent (DMSO), Figure.4 (B). shows 8 types of protons in the structure of this compound. The range of 1 / 12ppm to 1 / 76ppm, which represents 3 protons in the loop, consists of protons in the parietal rim of the ring, split into a multiple, and contains 8 protons in the whole structure. 16 protons placed in the meta-ring position and split into M, and 16 protons in the ring's orthogonal position, which are also split as multi, a wide peak at 2.71ppm are related to hydrogen bound to nitrogen, which is de shield due to joining to this group. In addition, a single peak at 3 / 6ppm for methylene hydrogen at the bridge, which indicates the collision of the Cone configuration is related to 8 protons in the whole structure. The wide peak at 4.63ppm is related to 4 NH hydrogen and aromatic H which have the peak at the range of 7.32ppm, corresponding to 8 hydrogens. Finally, phenolic de shield hydrogens that are four in the structure and can be seen at 8.58ppm. In the IR spectrum (Figure.4(C)), the 4 bands of 3174 cm^{-1} are related to the C-H loop. 2930, 2855cm^{-1} the symmetric frequency is related to the amine group type 1. The frequency of the aliphatic C-H structures is shown in 2528, 2076cm^{-1}. The frequency of 1240, 1037 cm^{-1} is related to the C-N bond in the structure, and finally, 1140, 1387 cm^{-1} frequency is observed for the SO_2 group.

3.2. Analyze the Antibacterial effects of the derived derivatives

Antibacterial properties were evaluated by Disk Diffusion test as well as MIC (Figure.5 (A-D)) and MBC (Figure.5 (E-H)) tests on cyclohexyl and hexadecyl synthesized compounds. Specified that sulfonamide compounds merely inhibit the growth of bacteria, and then in the disc test, single colonies were observed around the blank disk (containing the sample). According to the tables (1 & 2), the diameter of the bacteria's lack of growth holes indicates that almost two synthesized compounds were susceptible to tested bacteria and caused their lack of growth. But in a series, the bacteria non-growth halo was bigger and indicates the greater effect of the compound on the bacteria. In Plate 1 with a gram-negative bacteria, the halo of the hexadecyl derivative is greater than the hexyl derivative, which can be interpreted as the reason for that is the high-chain C compound compared to another sulfonamide, which has a higher sensitivity to Salmonella bacteria. And with the gram-positive bacteria, the same assumption could be made that the long chain of this compound had an effect on its antibacterial properties. MIC and MBC test had done. The lowest antibacterial concentration that caused the lack of bacteria growth (MIC) was number 3 for both tubes. MBC is negative for both because we know that sulfonamide compounds do not kill bacteria [35-40].

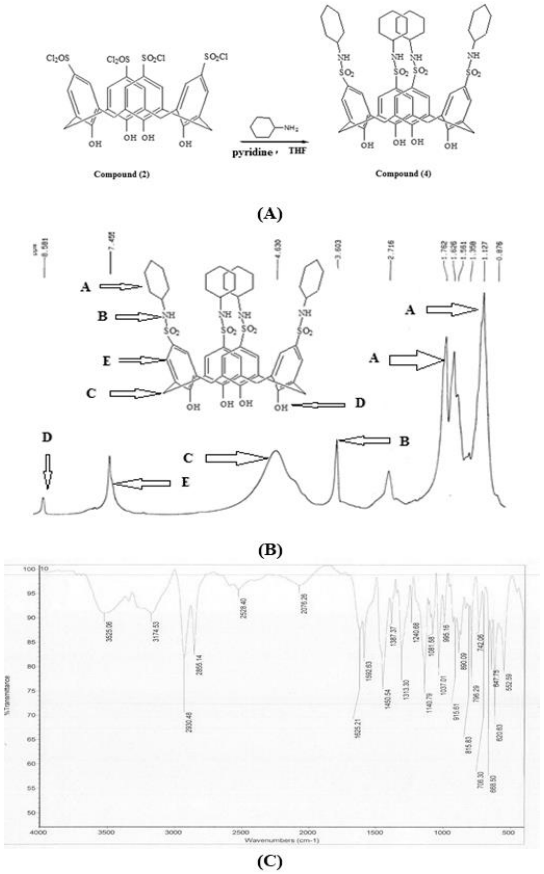

Figure 4. (A) Scheme of synthesis of Compound (4);**(B)** ^{1}HNMR of Compound (4);**(C)** IR of Compound (4).

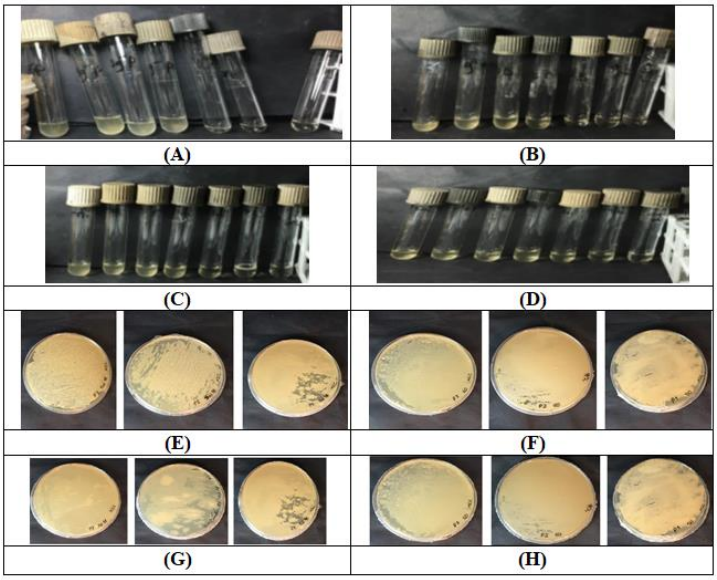

Figure 5. (A) MIC Test of hexadecyl derivatives to g- bacteria;**(B)** MIC Test of hexadecyl derivatives to g+ bacteria;**(C)** MIC Test of cyclodecyl derivatives to g- bacteria; **(D)** MIC Test of cyclodecyl derivatives to g+ bacteria**(E)** MBC Test of hexadecyl derivatives to g- bacteria;**(F)** MBC Test of hexadecyl derivatives to g+ bacteria;**(G)** MBC Test of cyclodecyl derivatives to g- bacteria; **(H)** MBC Test of cyclodecyl derivatives to g+ bacteria.

Table 1. Salmonella bacteria 18 (Evaluation of the sensitivity of two derivatives to g- bacteria**).**

Plate 1	Compound	Halo of lack of growth	Evaluation of the sensitivity
A	Hexylamine	12mm	sensitive
B	Hexadecylamine	13mm	sensitive

Table 2. Staphylococcus aureus (Evaluation of the sensitivity of two derivatives to g + bacteria**).**

Plate 1	Compound	Halo of lack of growth	Evaluation of the sensitivity
A	Hexylamine	10.9mm	sensitive
B	Hexadecylamine	11.9mm	sensitive

4. CONCLUSIONS

In this study, two useful compounds based on sulfonamide calix[4]arene were synthesized. the results revealed that the aliphatic derivatives exhibit a more complete antibacterial behavior on gram-positive bacteria than gram-negative bacteria. It can be concluded that the aliphatic branch has an important medicinal effect for the gram-negative bacteria. In addition, the long chain combinations show more antibacterial effects for both tested bacteria. Noteworthy also is the property of calix[4]arene synthesized derivatives could be exploited to improve the pharmaceutical formulation of antibacterial application.

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