








# Synthesis and Evaluation Biological Activity of Six Oxapentacyclo Derivatives on Gram Negative and Gram Postive Bacteria

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**Abstract:** There are drugs such as cephalosporin, penicillins, aminoglycosides, quinolones for the treatment of infectious diseases; however, some of these drugs can produce bacterial resistance. This research aimed to synthesize six oxapentacyclo derivatives to evaluate their biological activity against some *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae* using the minimum inhibitory concentration method. The results showed that the methods used in this study produce a good yield of each product. Furthermore, the chemical structure of compounds 2 to 7 was determined using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic techniques. Other data showed that only compounds 3 and 5 decreased the growth bacterial of Gram-negative and Gram-positive bacteria; these data suggest that compounds 3 and 5 could be considered good antibacterial agents against infectious diseases produced by *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*.

**Keywords:** synthesis; oxapentacyclo; derivatives; bacterial.

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## 1. Introduction

There are several drugs for the treatment of infectious diseases around the world [1-3]; however, the appearance of some strains resistant to *Staphylococcus aureus* [4-6], *Escherichia coli* [7-9], *Klebsiella pneumoniae* [10,11], and *Streptococcus pneumoniae* [12,13] has increased deaths in the population. New polycyclic derivatives have synthesized with antibacterial activity against both Gram-positive and Gram-negative bacteria to reduce bacterial resistance. For example, a study showed the preparation of 4-(2,5-Dimethylthiophen-3-yl)-6-(9-ethyl-9H-carbazol-3-yl)-pyrimidin-2-amine as an antibacterial agent against both *Staphylococcus aureus* and *Escherichia coli* bacteria [14]. Other data display that oxysporizoline, a polycyclic extracted of fungus *Fusarium oxysporum* can produce an antibacterial effect against *Staphylococcus aureus* [15]. In addition, another report showed that a polycyclic sulfonamide decreases the growth of bacteria of *Staphylococcus aureus* [16]. Also,

a study displayed the synthesis of a heteroaromatic-polycyclic (GSQ1530) as an antibacterial agent against both *Staphylococcus aureus* and *Streptococcus pneumoniae* [17]. Recently, some polycyclic-anthrabenzoquinones derivatives were synthesized, and their theoretical activity against *Staphylococcus aureus* was evaluated [18]. All these data showed several ways to synthesize several polycyclic derivatives with biological activity against Gram-positive and Gram-negative bacteria. However, there are few reports on the preparation of oxapentacyclo derivatives as antibacterial agents; analyzing these data, in this research, six oxapentacyclo analogs were synthesized to evaluate their antibacterial effect on *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae* using the minimum inhibitory concentration method.

## 2. Materials and Methods

### 2.1. General methods.

Starting materials were purchased from commercial suppliers (Sigma-Aldrich and AKos Consulting & Solutions). NMR spectra were recorded on a Varian VXR300/5 FT apparatus (300 MHz/ $\text{CDCl}_3$ ) using tetramethylsilane as an internal standard. Electron Ionization mass spectrometry (EIMS) was recorded on a Finnigan PolarisQ ion trap mass spectrometer. Melting-point (m.p.) was determined on an electrothermal-900 model apparatus. The infrared spectrum (IR) was determined on a thermo-scientific iSOFT/IR device. Elemental analysis was determined using a PerkinElmer apparatus (Ser. II CHNS / 02400).

### 2.2. Chemical synthesis.

2.2.1. (2R,8S)-11-(4-hydroxybutyl)-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradec-11-ene-3,7-dione (2).

In a round bottom flask (10 ml), 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (150 mg, 0.86 mmol), 5-hexyn-1-ol (120  $\mu\text{l}$ , 1.08 mmol) and Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system. yielding 76% of product; m.p. 136-140  $^{\circ}\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3400, 1712, 1602 and 1070:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -d)  $\delta_{\text{H}}$ : 1.50-1.54 (m, 4H), 1.70-1.96 (m, 4H), 2.08 (m, 2H), 3.00-3.02 (m, 2H), 3.10-3.50 (m, 3H), 3.58 (broad, 1H), 3.60 (m, 2H), 3.66 (m, 2H), 5.70 (d, 1H,  $J = 1.33$  Hz) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 24.42, 32.50, 32.55, 36.54, 39.20, 40.42, 42.20, 50.22, 51.30, 51.85, 62.54, 63.50, 130.60, 148.32, 205.40 ppm. EI-MS m/z: 288.13. Anal. Calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}_4$ : C, 70.81; H, 6.99; O, 22.20. Found: C, 70.78; H, 6.96.

2.2.2. (2S,8R)-11-(aminomethyl)-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradec-11-ene-3,7-dione (3).

In a round bottom flask (10 ml), 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (150 mg, 0.86 mmol), prop-2-yn-1-amine (60  $\mu\text{l}$ , 0.93 mmol) and Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system. yielding 87% of product; m.p. 112-114  $^{\circ}\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ )

3380, 1712, 1602 and 1072:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 2.06 (broad, 2H), 1.70-2.90 (m, 4H), 3.00-3.02 (m, 2H), 3.06 (m, 2H), 3.30-3.40 (m, 2H), 3.60 (m, 2H), 5.90 (d, 1H,  $J = 1.65$  Hz) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 32.14, 38.95, 39.94, 43.96, 48.40, 50.22, 51.56, 53.15, 63.50, 131.84, 144.52, 205.44 ppm. EI-MS  $m/z$ : 245.10. Anal. Calcd. for  $\text{C}_{14}\text{H}_{15}\text{NO}_3$ : C, 68.56; H, 6.16; N, 5.71; O, 19.57. Found: C, 68.53; H, 6.12.

2.2.3. (2R,8S)-11-[(4-hydroxy-3-methoxy-phenyl)methyl]-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradecane-3,7-dione (4).

In a round bottom flask (10 ml), 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (150 mg, 0.86 mmol), eugenol (150  $\mu\text{l}$ , 0.97 mmol) and Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system. yielding 80% of product; m.p. 142-144  $^{\circ}\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3400, 1710, 1604 and 1070:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 1.32-2.30 (m, 7H), 2.60-2.64 (m, 2H), 2.99-3.02 (2H), 3.10-3.48 (m, 2H), 3.62 (m, 2H), 3.84 (s, 3H), 5.47 (broad, 1H), 6.66-6.80 (m, 3H) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 29.70, 33.40, 37.14, 40.62, 41.20, 42.26, 42.40, 49.20, 50.40, 51.52, 55.86, 63.50, 113.34, 114.32, 122.94, 130.90, 144.50, 146.60, 205.40 ppm. EI-MS  $m/z$ : 354.14. Anal. Calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_5$ : C, 71.17; H, 6.26; O, 22.57. Found: C, 71.14; H, 6.22.

2.2.4. (2R,8S)-11-(3-aminophenyl)-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradec-11-ene-3,7-dione (5).

In a round bottom flask (10 ml), 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (150 mg, 0.86 mmol), 3-ethynylaniline (100  $\mu\text{l}$ , 0.94 mmol) and Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system. yielding 69% of product; m.p. 162-164  $^{\circ}\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3382, 1712, 1600 and 1070:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 1.62-1.90 (m, 3H), 3.00-3.02 (m, 2H), 3.20 (m, 1H), 3.60 (m, 2H), 3.62 (m, 1H), 3.66 (m, 1H), 4.04 (broad, 1H), 6.00 (d, 1H,  $J = 1.82$  Hz), 6.56-7.20 (m, 4H) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 33.40, 39.40, 41.32, 42.62, 50.22, 51.70, 52.22, 63.50, 111.90, 114.12, 119.70, 128.60, 135.12, 139.00, 145.60, 146.40, 205.40 ppm. EI-MS  $m/z$ : 307.12. Anal. Calcd. for  $\text{C}_{19}\text{H}_{17}\text{NO}_3$ : C, 74.25; H, 5.58; N, 4.56; O, 15.62. Found: C, 74.22; H, 5.56.

2.2.5. 4-[(2R,8S)-3,7-dioxo-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradec-11-en-11-yl]butanoic acid (6).

In a round bottom flask (10 ml), 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (150 mg, 0.86 mmol), 5-hexynoic acid (100  $\mu\text{l}$ , 0.90 mmol) and Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system. yielding 76% of product; m.p. 38-40  $^{\circ}\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 1710, 1602 and 1072:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 1.70-1.78 (m, 2H), 1.82 (m, 2H), 1.96 (m, 1H), 2.10-2.14 (m, 4H), 3.00-3.02 (m, 2H), 3.10-3.50 (m, 3H), 3.60 (m, 2H), 5.70 (m, 1H,  $J = 1.82$  Hz), 8.20 (broad, 1H) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 22.20, 32.50, 33.74, 36.74,

39.20, 40.40, 42.22, 50.22, 51.30, 51.84, 63.50, 130.62, 147.55, 177.98, 205.40 ppm. EI-MS m/z: 302.11. Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>5</sub>: C, 67.54; H, 6.00; O, 26.46. Found: C, 67.52; H, 6.00.

2.2.6. (2S,8R)-11-[hydroxy(phenyl)methyl]-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]te-tradecane-3,7-dione (7).

In a round bottom flask (10 ml), 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (150 mg, 0.86 mmol), 1-phenyl-2-propyn-1-ol (120  $\mu$ l, 0.98 mmol) and Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system. yielding 80% of product; m.p. 88-90 °C; IR ( $V_{max}$ , cm<sup>-1</sup>) 3400, 1712, 1600 and 1070: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>-d)  $\delta_H$ : 1.70-3.40 (m, 8H), 3.50 (broad, 1H), 3.60 (m, 2H), 5.12 (m, 1H), 5.80 (d, 1H, J = 1.80 Hz), 7.30-7.50 (m, 5H) ppm. <sup>13</sup>C NMR (300 Hz, CDCl<sub>3</sub>)  $\delta_C$ : 32.80, 39.22, 40.68, 42.14, 50.20, 50.84, 51.34, 63.55, 76.60, 127.32, 128.42, 128.46, 134.20, 140.14, 149.32, 205.40 ppm. EI-MS m/z: 322.12. Anal. Calcd. for C<sub>20</sub>H<sub>18</sub>O<sub>4</sub>: C, 74.52; H, 5.63; O, 19.85. Found: C, 74.50; H, 5.60

### 2.3. Pharmacophore model.

3D pharmacophore model for estrone and compounds 2 to 7 was evaluated using LigandScout 4.08 software [19,20]

### 2.4. Biological evaluation.

*Staphylococcus aureus* (ATCC 33591), *Streptococcus pneumoniae* (ATCC 6303), *Escherichia coli* (ATCC 14035), and *Klebsiella pneumoniae* (ATCC 4352) were acquired from the strain bank from Laboratory of Pharmacochimistry, Faculty of Chemical-Biological Sciences of the Autonomous University of Campeche.

### 2.5 Antimicrobial activity.

This stage was carried out using a previously reported technique [21]; in this way, 12 tubes containing 2 mg/2 ml of culture medium (soybean trypticase) were prepared. Then, to the first tube, an aliquot of either of the compounds 2 to 7 (1 mg/ml) was added and was shaken to homogenize the mixture. Then, in the next 11 tubes, different dilutions of either of compounds (2 to 7) at a dose of 0.5 to 0.0004 mg/ml were added with constant stirring (Table 1). Following, each tube was inoculated with 0.1 ml of bacterial suspension, whose concentration corresponded to the McFarland scale ( $9 \times 10^8$  cells/ml), and all the tubes were incubated at 37°C for 24 h. Finally, a sample of any of the compounds was taken with a sterile loop to inoculate them in specific cultures for each bacterial organism at 37 °C for 24 h.

### 2.6. Pharmacokinetics parameter.

Pharmacokinetic parameters were determined using the SwissADME software [22,23].

## 3. Results and Discussion

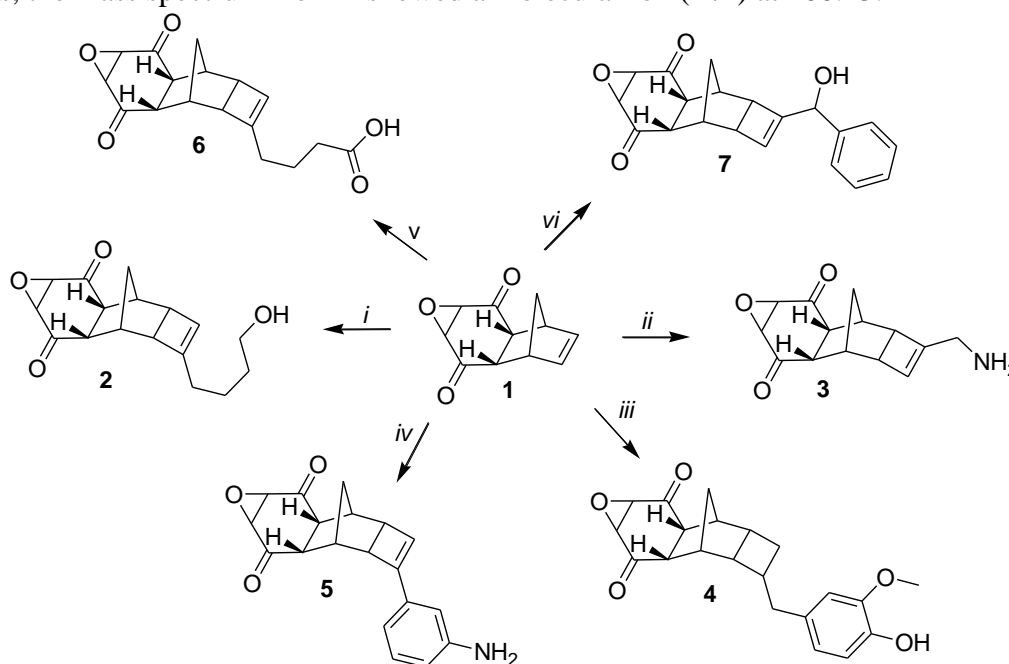
Several pentacyclic analogs have been prepared using different chemical tools [24-27]; however, some protocols used involve require special conditions such as different pH and higher temperatures. Therefore, in this research, six oxapentacyclo-derivatives were

synthesized from 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (compound 1) to evaluate their antibacterial activity against Gram-negative and Gram-positive bacteria; the first stage was achieved as follows:

### 3.1. Chemical synthesis.

3.1.1. (2R,8S)-11-(4-hydroxybutyl)-5-oxapentacyclo[7.4.1.0<sup>2,5</sup>,8.0<sup>4,6</sup>,13]tetradec-11-ene-3,7-dione (2).

Compound 2 was prepared from 1, 5-hexyn-1-ol, and Copper(II) chloride (Figure 1). The <sup>1</sup>H NMR spectrum of 2 showed several signals at 1.50-1.54, 2.08, 3.60 and 3.66 ppm for methylene groups linked to both Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment and hydroxyl group; at 1.70-1.96 and 3.00-3.50 for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 3.60 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 5.70 ppm for alkene group. The <sup>13</sup>C NMR spectra display chemical shifts at 24.42, 36.54, and 62.54 ppm for methylene groups linked to both Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment and hydroxyl group; at 32.50 and 39.20-51.85 for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 63.50 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 130.60-148.32 ppm for alkene group; at 205.40 ppm for ketone groups. Besides, the mass spectrum from 2 showed a molecular ion (m/z) at 288.13.



**Figure 1.** Synthesis of six oxapentacyclo derivatives (2 to 7). *Conditions and reagents:* *i* = 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (1), 5-hexyn-1-ol, Copper(II) chloride, 48 h, rt; *ii* = compound 1, prop-2-yn-1-amine, Copper(II) chloride, 48 h, rt; *iii* = compound 1, eugenol, Copper(II) chloride, 48 h, rt; *iv* = compound 1, 3-ethynylaniline, Copper(II) chloride, 48 h, rt; *v* = compound 1, 5-hexynoic acid, Copper(II) chloride, 48 h, rt; *vi* = compound 1, 1-phenyl-2-propyn-1-ol, Copper(II) chloride, 48 h, rt. rt = room temperature

3.1.2. 2S,8R)-11-(aminomethyl)-5-oxapentacyclo[7.4.1.0<sup>2,5</sup>,8.0<sup>4,6</sup>,13]tetradec-11-ene-3,7-dione (3).

This stage was achieved *via* a reaction of 1 with prop-2-yn-1-amine and Copper(II) chloride anhydrous to form 3. The <sup>1</sup>H NMR spectrum from 3 showed several signals at 2.06 ppm for the amino group; at 1.70-3.02 and 3.30-3.40 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 3.06 ppm for methylene bound to the amino group; at 3.60 ppm for 7-Oxa-

bicyclo[4.1.0]heptane-2,5-dione fragment; at 5.90 ppm for alkene group. The  $^{13}\text{C}$  NMR spectra display chemical shifts at 32.14-50.22 for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 138.44-144.52 ppm for alkene group; at 51.56 ppm for methylene group bound to the amino group; at 53.15-63.50 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 205.40 ppm for ketone groups. Finally, the mass spectrum from **2** showed a molecular ion (m/z) at 245.10.

3.1.3. (2R,8S)-11-[(4-hydroxy-3-methoxy-phenyl)methyl]-5-oxapentacyclo[7.4.1.0<sub>2</sub>,8.0<sub>4</sub>,6.0<sub>10</sub>,1<sub>3</sub>]tetradecane-3,7-dione (**4**).

Compound **4** was prepared from **1**, eugenol, and Copper(II) chloride anhydrous under mild conditions. The  $^1\text{H}$  NMR spectrum from **4** showed several signals at 1.32-2.30 and 3.10-3.48 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]nonane fragment; at 2.60-2.64 ppm for methylene group linked to both Tricyclo[4.2.1.0<sup>2,5</sup>]nonane fragment and phenyl group; at 2.99-3.02 and 3.62 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 3.84 ppm for methyl group; at 5.47 ppm for hydroxyl group; at 6.66-6.80 ppm for phenyl group.  $^{13}\text{C}$  NMR spectra display chemical shifts at 29.70-37.14 and 41.20-51.52 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]nonane fragment; at 40.62 ppm for methylene group bound to both Tricyclo[4.2.1.0<sup>2,5</sup>]nonane fragment and phenyl group; at 55.86 ppm for methyl group; at 63.50 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 113.34-146.60 ppm for phenyl group; at 205.40 ppm for ketone groups. In addition, the mass spectrum from **4** showed a molecular ion (m/z) at 354.14.

3.1.4. (2R,8S)-11-(3-aminophenyl)-5-oxapentacyclo[7.4.1.0<sub>2</sub>,8.0<sub>4</sub>,6.0<sub>10</sub>,1<sub>3</sub>]tetradec-11-ene-3,7-dione (**5**).

Preparation **5** was carried out from **1**, 3-ethynylaniline, and Copper(II) chloride anhydrous. The  $^1\text{H}$  NMR spectrum from **5** showed several signals at 1.62-3.20 and 3.62-3.66 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 3.60 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 4.00 ppm for the amino group; at 6.00 ppm for alkene group; at 6.56-7.20 ppm for phenyl group.  $^{13}\text{C}$  NMR spectra display chemical shifts at 33.40-52.22 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 63.50 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 111.90-128.60 and 139.00-145.60 ppm for phenyl group; at 135.12-146.40 ppm for alkene group; at 205.40 ppm for ketone groups. Besides, the mass spectrum from **5** showed a molecular ion (m/z) at 307.12.

3.1.5. 4-[(2R,8S)-3,7-dioxo-5-oxapentacyclo[7.4.1.0<sub>2</sub>,8.0<sub>4</sub>,6.0<sub>10</sub>,1<sub>3</sub>]tetradec-11-en-11-yl]butanoic acid (**6**).

Compound **1** reacted with 5-hexynoic acid and Copper(II) chloride anhydrous under mild conditions. The  $^1\text{H}$  NMR spectrum from **6** showed several signals at 1.70-1.78, 1.96 and 3.00-3.50 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 1.82 and 2.10-2.14 ppm for methylene groups bound to both Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment and carboxyl group; at 3.60 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 5.70 ppm for alkene group; at 8.20 ppm for carboxyl group.  $^{13}\text{C}$  NMR spectra display chemical shifts at 22.20 and 33.74-36.74 ppm for methylene groups bound to both Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment and carboxyl group; at 32.50, 39.20-51.84 and 130.62 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; 63.50 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 130.62-147.55 ppm for alkene group; at 177.98 ppm for carboxyl group; at 205.40 ppm for ketone groups. In addition, the mass spectrum from **6** showed a molecular ion (m/z) at 302.11.

3.1.6. (2S,8R)-11-[hydroxy(phenyl)methyl]-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradecane-3,7-dione (7).

Finally, compound 7 was synthesized *via* a reaction of 1 with 1-phenyl-2-prpy-1-ol in the presence of Copper(II) chloride anhydrous. The  $^1\text{H}$  NMR spectrum from 7 showed several signals at 1.70-3.40 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 3.50 ppm for hydroxyl group; at 3.60 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 5.12 ppm for methylene group linked to hydroxyl group; at 5.80 ppm for alkene group; at 7.30-7.50 ppm for phenyl group.  $^{13}\text{C}$  NMR spectra display chemical shifts at 32.80-51.34 ppm for Tricyclo[4.2.1.0<sup>2,5</sup>]non-3-ene fragment; at 63.55 ppm for 7-Oxa-bicyclo[4.1.0]heptane-2,5-dione fragment; at 76.60 ppm for methylene group linked to hydroxyl group; at 127.32-128.46 and 140.14 ppm for phenyl group; at 134.20 and 149.32 ppm for alkene groups; at 205.40 ppm for ketone groups. Besides, the mass spectrum from 7 showed a molecular ion (m/z) at 322.12.

### 3.2. Physicochemical parameters.

There are theoretical methods that are used to determine several physicochemical parameters of different compounds; in this way, in this investigation, some physicochemical factors involved in the chemical structure of compounds 2 to 7 were evaluated using SwisADME software [22,23]. Table 1 shows different physicochemical parameters involved in each of the compounds studied.

**Table 1.** Physicochemical parameters involved in the chemical structure of compounds 2 to 7.

Parameter	Compounds					
	2	3	4	5	6	7
Heavy atoms	21	18	26	23	22	24
Arom. heavy atoms	0	0	6	6	0	6
Fraction Csp <sup>3</sup>	0.76	0.71	0.62	0.47	0.71	0.50
Rotatable bonds	4	1	3	1	4	2
Hydrogen bond acceptors	4	4	5	3	5	4
Hydrogen bond donors	1	1	1	1	1	1
Molar Refractivity	75.44	62.56	93.33	84.73	76.05	85.50
TPSA (Å <sup>2</sup> )	66.90	72.69	76.13	72.69	83.97	69.90

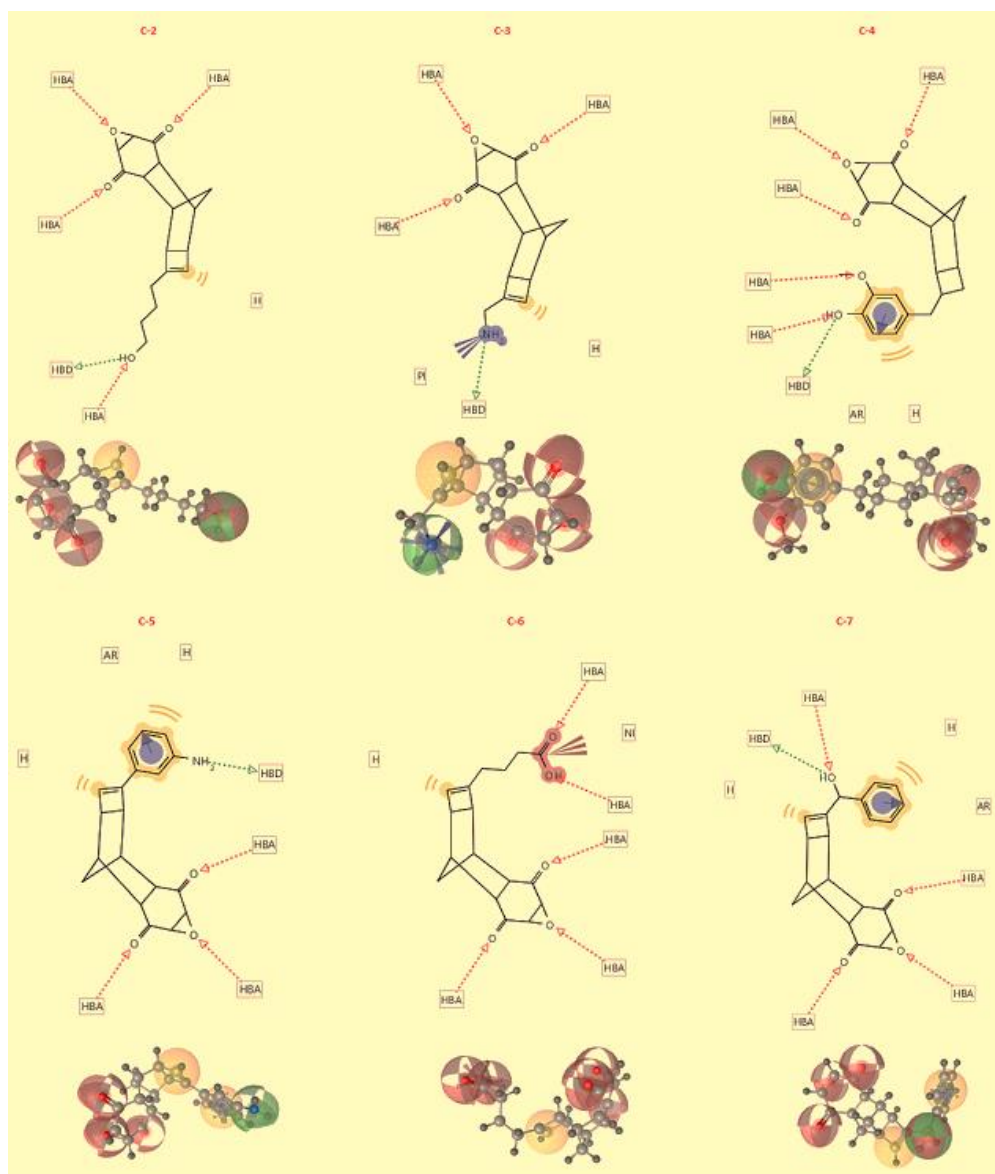
### 3.3. Pharmacophore model.

In this study, a pharmacophore model was designed using a previously reported method [19] to support the possibility that functional groups involved in the chemical structure of the studied compounds could interact with some biomolecule through hydrophobic interactions or as hydrogen bond acceptors or bond hydrogen donors. The results showed that these interactions could condition the biological activity of each compound with some biomolecule (Figure 2).

### 3.4. Antibacterial activity.

There are reports which indicate that several oxapentacyclo can exert biological activity against some bacterial strain [31,32]; analyzing these data, the antibacterial activity of compounds 2 to 7 against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Klebsiella pneumoniae* was evaluated using 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione as control with minimum inhibitory concentration method (MIC). The results showed in Tables 2, and 3 indicate that bacterial growth of either Gram-negative or Gram-positive bacteria only was inhibited by compounds 3 and 5; however, this

effect was higher in the presence of compound 5 compared with 3. All these data suggest that the bacterial activity of compounds 3 and 5 depends on amino groups involved in their chemical structure. This hypothesis is supported by some studies which suggest that group amino involved in the chemical structure of a pregnenolone-vitamin B1 derivative is the responsibility of their antibacterial activity against *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli* [33]. However, the effect exerted by 5 on this type of bacteria could be due to the amino group being linked to the phenyl group, which could result in a hydrophobic interaction with some biomolecule present in the bacteria.



**Figure 2.** Pharmacophore from compounds 2 (C-2), 3 (C-3), 4 (C-4), 5 (C-5), 6 (C-6) and 7 (C-7) using the LigandScout software. Hydrogen bond acceptors (HBA, red), hydrogen bond donor (HBD, green).

**Table 2.** Antibacterial activity of compounds 1 to 7 against four bacterial strains.

Compound	<i>Staphylococcus aureus</i> (mg)	<i>Streptococcus pneumoniae</i> (mg)	<i>Escherichia coli</i> (mg)	<i>Klebsiella pneumoniae</i> (mg)
1 (control)	-	-	-	-
2	-	-	-	-
3	1	1	1	1
4	-	-	-	-
5	0.5	0.5	0.5	0.5
6	-	-	-	-
7	-	-	-	-



**Table 3.** Antibacterial activity of compounds 3 and 5 against four bacterial strains.

Compound	<i>Staphylococcus aureus</i> (mmol)	<i>Streptococcus pneumoniae</i> (mmol)	<i>Escherichia coli</i> (mmol)	<i>Klebsiella pneumoniae</i> (mmol)
3	$4.07 \times 10^{-3}$	$4.07 \times 10^{-3}$	$4.07 \times 10^{-3}$	$4.07 \times 10^{-3}$
5	$1.62 \times 10^{-3}$	$1.62 \times 10^{-3}$	$1.62 \times 10^{-3}$	$1.62 \times 10^{-3}$

### 3.5. Pharmacokinetic evaluation.

There are several methods to predict some pharmacokinetic factors [28-30]. In this way, some pharmacokinetic parameters for compounds 3 and 5 were determined using SwissADME software [22,23]. The results showed differences in gastrointestinal absorption and metabolism (involving different types of cytochrome P<sub>450</sub> systems), which could depend on differences in chemical structure (Table 4) of each compound on the chemical structure of compounds 3 and 5 and the degree of lipophilicity (Table 5).

**Table 4.** The pharmacokinetics properties of compounds 3 and 5. The values were determined using the SwissADME software.

Parameter	Compound 3	Compound 5
GI absorption	High	High
BBB permanent	No	Yes
P-gp substrate	Yes	Yes
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	Yes
CYP3A4 inhibitor	No	No

**Table 5.** Values of lipophilicity degree for compounds 3 and 5 using SwissADME software.

Parameter	Compound 3	Compound 5
iLOGP	1.62	2.06
XLOGP3	-0.93	1.16
WLOGP	-0.08	1.71
MLOGP	0.55	1.78
SILICOS-IT	0.92	2.12
Consensus Log Po/w	0.42	1.77

## 4. Conclusions

This investigation reports an easy way to synthesize six oxapentacyclo derivatives (compounds 2 to 7) using some chemical strategies. Besides, compounds 3 and 5 showed that they can exert antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Klebsiella pneumoniae* which suggest that these compounds could be considered as a good antibacterial agent against infectious diseases produced by these organisms.

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## Conflicts of Interest

We declare that this manuscript does not have any conflict of financial interests (political, personal, religious, ideological, academic, intellectual, commercial, or otherwise) for its publication.

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