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SYNTHESIS AND ANTIBACTERIAL EVALUATION EXERTED BY TWO ANILINE DERIVATIVES AGAINST ESCHERICHIA COLI OR STAPHYLOCOCCUS AUREUS

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ABSTRACT
Some aniline derivatives have been prepared as antibacterial agents; however, the methods used for their preparation involve several reagents which require special conditions. Therefore, the aim of this study was to synthesize two aniline derivatives using some chemical strategies. The chemical structure was evaluated through both ^{1}H NMR and ^{13}C NMR spectroscopic analysis. In addition, the biological activity of the aniline derivatives against *Escherichia coli* or *Staphylococcus aureus* was evaluated. The results showed that either compounds **5** or **7** inhibit the growth bacterial of both *Escherichia coli* and *Staphylococcus aureus*. In conclusion, it is important to mention that the reagents used in this investigation are not expensive and do not require special conditions for handling. In addition, the results indicate that either compounds **5** or **7** could be a good therapeutic alternative for some infectious diseases.

INTRODUCTION
Epidemiological and clinical data indicate that infectious diseases are serious health problem in worldwide[i-iii]. It is important to mention that several drugs have been used for the treatment of infectious diseases[iv-vi], unfortunately prolonged antibiotic therapy could produce bacterial resistance[vii, viii]. In the search of some therapeutic alternative for treatment of bacteria infectious, some aniline derivatives have been prepared; for example, the preparation of a chloro-salicylideneaniline derivative from salicyladehyde and *p*-chloroaniline as antibac-terial

agent against either *Escherichia coli* or *Staphylococcus aureus*[ix]. Besides, a study showed the synthesis of an aniline copolymer via reaction of 3-aminobenzoic acid with aniline and their biological activity on Gram-negative bacteria[x]. Other data showed the preparation of an azomethine derivative via condensation of aniline with an aldehyde derivative and their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*[xi]. In addition, a report showed the synthesis a benzaldeyde-aniline derivative from chitosan[xii] as antibacterial agent *Escherichia coli* of. All these data show several protocols for preparation of some aniline derivatives with biological activity on both Gram-positive and Gram-negative bacteria. However, the evaluation of antibacterial activity an aniline bound to diazocine ring has not been reported; analyzing these data, the aim of this investigation was to synthesize two aniline derivatives which could be used as therapeutic alternative for treatment of infectious diseases. For this purpose, the biological activity of two aniline derivatives were evaluated against S. aureus and E. coli using the microbial minimal inhibitory concentration (MIC) method[xiii].

Experimental

2.1 General methods

The reagents used in this research were acquired from Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were evaluated with a Thermo Scientific iSOFT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Varian VXR300/5 FT NMR spectrometer at 300 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

2.2 Chemical synthesis

4-[(1*R*)-2-[2-(3-aminophenyl)ethynyl-methyl-amino]-1-hydroxy-ethyl]benzene-1,2-diol (2)

In a round bottom flask (10 ml), epinephrine (90 µl, 0.62 mmol), 3-ethynylaniline (70 µl, 0.62 mmol), and Copper(II) chloride anhydrous (70 mg, 0.52 mmol) and methanol (5 ml) were stirred to room temperature for 48 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane (3:1) system; yielding 65% of product; m.p. 222-224 ºC; IR (V_{max}, cm^{-1}) 3400, 3380 and 1208: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.83 (s, 3H), 3.36-4.72 (m, 3H), 5.24 (broad, 5H), 5.47 (d, 1H, J = 0.40 Hz), 6.45-6.54 (m, 2H), 6.63 (d, 1H, J = 0.40 Hz), 6.66-7.67 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 44.18, 59.12, 73.30, 95.32, 109.12, 111.96, 120.22, 120.50, 121.02, 124.36, 129.22, 131.96, 133.02, 138.44, 145.06, 147.22, 147.34 pm. EI-MS m/z: 300.14. Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33; O, 15.98. Found: C, 67.96; H, 6.70.

2-[[(E)-2-(3-aminophenyl)vinyl]-methyl-amino]-1-(3,4-dihydroxyphenyl)ethenone (3)

In a round bottom flask (10 ml), compound **2** (160 mg, 0.53 mmol), potassium permanganate (80 mg, 0.50 mmol), and ethanol (5 ml) were stirred to room temperature for 12 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:water (4:1) system; yielding 58% of product; m.p. 62-64 ºC; IR (V_{max}, cm^{-1}) 3400, 3382, 1712 and 1210: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.96 (s, 3H), 5.32 (m, 2H), 5.50 (broad, 4H), 5.52 (d, 1H, J = 0.40 Hz), 6.56-6.58 (m, 2H), 6.75 (d, 1H, J = 0.63 Hz), 6.76-7.54 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 44.50, 59.76, 95.42, 109.06, 113.12, 116.96, 120.34, 122.12, 128.66, 128.80, 129.22, 132.18, 141.74, 147.36, 148.90, 149.04, 194.82 ppm. EI-MS m/z: 298.13. Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39; O, 16.09. Found: C, 68.41; H, 6.06.

4-[2-[[(E)-2-(3-aminophenyl)vinyl]-methyl-amino]acetyl]phthalaldehyde (4)

In a round bottom flask (10 ml), compound **3** (100 mg, 0.34 mmol), and dimethyl sulfoxide (5 ml) were stirred to reflux for 24 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:1:1) system; yielding 56% of product; m.p. 126-128 ºC; IR (V_{max}, cm^{-1}) 3380, 1725, 1712 and 1208: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.99 (s, 3H), 4.02 (broad, 2H), 5.30 (m, 2H), 5.50 (d, 1H, J = 0.40 Hz), 6.56-6.58 (m, 2H), 6.75 (d, 1H, J = 0.63 Hz), 6.80-8.36 (m, 5H), 10.50 (s, 1H), 10.60 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 44.96, 59.78, 95.42, 109.06, 113.10, 122.14, 129.22, 129.24, 132.16, 135.20, 137.00, 138.22, 140.90, 141.74, 146.12, 147.36, 187.02, 195.22, 195.24 ppm. EI-MS m/z: 322.13. Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; O, 14.89. Found: C, 70.76; H, 5.60.

3-[(E)-2-[[(2E)-2-(2-aminoethylimino)-2-[(1Z,5Z)-3,4-dihydro-2,5-benzodiazocin-8-yl]ethyl]-methyl-amino]vinyl]aniline (5)

In a round bottom flask (10 ml), compound **4** (100 mg, 0.31 mmol), ethylenediamine (55mg, 0.91 mmol), boric acid (55 mg, 0.89 mmol) and methanol (5 ml) were stirred to room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:water (4:1) system; yielding 69% of product; m.p. 178-180 ºC; IR (V_{max}, cm^{-1}) 3380, 3322 and 1210: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.92, 3.07-3.60 (m, 4H), 3.98 (m, 2H), 4.17 (broad, 4H), 4.19 (m, 4H), 5.57 (d, 1H, J = 0.40 Hz), 6.56-6.81 (m, 3H), 6.87 (d, 1H, J = 0.63 Hz), 6.96-7.80 (m, 4H), 8.67-8.76 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 40.90, 45.82, 49.32, 54.23, 59.02, 92.42, 109.06, 113.12, 122.16, 120.20, 129.62, 129.72, 130.60, 132.92, 133.60, 133.90, 134.66, 134.85, 135.62, 139.40, 147.34, 168.24 ppm. EI-MS m/z: 388.23. Anal. Calcd. for $C_{23}H_{28}N_6$: C, 71.10; H, 7.26; N, 21.63. Found: C, 71,08; H, 7.23.

4-[1-[[[(E)-2-(3-aminophenyl)vinyl]-methyl-amino]methyl]-2-oxo-ethyl]phthalaldehy-de (6)

In a round bottom flask (10 ml), compound **2** (100 mg, 0.33 mmol), and dimethyl sulfoxide (5 ml) were stirred to reflux for 24 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane (4:1) system; yielding 44% of product; m.p. 166-168 ºC; IR (V_{max}, cm^{-1}) 3378, 1722 and 1212: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.86 (s, 3H), 3.66-3.86 (m, 3H), 4.02 (broad, 2H), 5.47 (d, 1H, J = 0.40 Hz), 6.48-6.81 (m, 4H), 6.90 (d, 1H, J = 0.63 Hz), 7.83-8.12 (m, 3H), 9.40 (s, 1H), 10.52 (s, 1H), 10.61 (s, 1H) ppm.^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 43.30, 51.50, 55.40, 95.32, 109.06, 111.96, 121.02, 127.90, 128.32, 129.22, 130.87, 133.38, 133.78, 135.32, 140.66, 142.72, 147.36, 189.00, 195.23, 198.46 ppm. EI-MS m/z: 336.14. Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; 14.27. Found: C, 71,39; H, 5.96.

3-[(E)-2-[[(3E)-3-(2-aminoethylimino)-2-[(1Z,5Z)-3,4-dihydro-2,5-benzodiazocin-8-yl]propyl]-methyl-amino]vinyl]aniline (7)

In a round bottom flask (10 ml), compound **6** (100 mg, 0.30 mmol), ethylenediamine (80 mg, 1.32 mmol), boric acid (80 mg, 1.29 mmol) and methanol (5 ml) and methanol (5 ml) were stirred to room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:water (4:1) system; yielding 63% of product; m.p. 177-179 ºC; IR (V_{max}, cm^{-1}) 3382, 3320 and 1208: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.87 (s, 3H), 3.10-3.52 (m, 4H), 3.56-3.76 (m, 3H), 4.17 (broad, 4H), 4.18 (m, 4H), 5.47 (d, 1H, J = 0.40 Hz), 6.48-6.56 (m, 2H), 6.63 (d, 1H, J = 0.40 Hz), 6.74 (m, 1H), 6.75-7.90 (m, 5H), 8.67-8.76 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 40.50, 43.66, 48.72, 49.33, 58.40, 59.24, 95.32, 109.06, 111.96, 121.02, 126.64, 127.60, 129.12, 129.22, 132.00, 133.21, 133.61, 134.64, 137.46, 141.40, 143.82, 147.34, 149.60 ppm. EI-MS m/z: 402.25. Anal. Calcd. for $C_{24}H_{30}N_6$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.60; H, 7.48.

Biological activity

In this study a previously method reported[xiii] was used to evaluate the biological effect exerted by either compound **5** or **7** against *Staphylococcus aureus* (ATCC 49775) and *Escherichia colli* (ATCC 25922). These bacteria were incubated using some growth means such as brain/heart infusion for *Escherichia colli* and Staphylococcus-110 for *Staphylococcus aureus* for 24 h at 37 ºC in the absence or presence of compounds **5** or **7** to determinate the growth bacterial. It is important to mention that minimum inhibitory concentration (MIC) of all compounds involved in this study was evaluated[xiv].

Results and Discussion

Hydroamination reactions for several compounds has been reported using some reagents such as [{HC(C(Me)$_2$N-2,6-^{i}Pr$_2$C$_6$H$_3$)$_2$}-Ca{N(SiMe$_3$)$_2$}(THF)] complex[xv], phosphine-gold(I)-bis-*p*-nitrobenzoate complex[xvi], Palladium[xvii], Rhodium[xviii], dimethyltitanocene[xix] and others. Analyzing these data, in this study, phenylephrine reacted with 3-ethynylaniline in the presence of Copper(II) chloride to form the compound **2** (Figure 1).

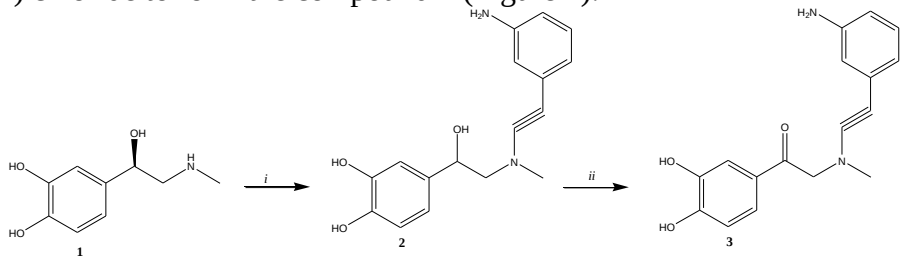

Figure 1. Synthesis of an ethenone derivative (**3**). Reagents and conditions: *i* = 3-ethynylaniline, Copper(II) chloride, room temperature, 12 h; *ii* = potassium permanganate, room temperature, 12 h.

The ^{1}H NMR spectrum from **2** showed several signals at 2.83 ppm for methyl group; at 3.36-4.47 ppm for methylene groups bound to both hydroxyl and amino groups; at 5.24 ppm for both amino and hydroxyl groups; at 5.47 and 6.63 ppm for alkene group; at 6.45-6.54 and 6.66-7.67 ppm for phenyl groups. ^{13}C NMR spectra showed chemical shifts at 44.18 ppm for methyl group; at 59.12-73.30 ppm for methylene groups bound to both hydroxyl and amino groups; at 95.32 and 138.44 ppm for alkene group; at 109.12-133.02 and 145.66-147.34 ppm for phenyl groups. Besides, the mass spectrum from **2** showed a molecular ion (m/z) 300.14.

Preparation of a ketone derivative

Several reagents have used for the synthesis of ketone analogs using some reagents such as PdCl$_2$(PPh$_3$)$_2$[xx], acyl chloride derivatives[xxi], proton exchange membranes[xxii], Palladium[xxiii]. In this study, a ketone derivative (**3**) was prepared via oxidation of **2** with potassium permanganate (Figure 1). The ^{1}H NMR spectrum from **3** showed several signals at 2.96 ppm for methyl group; at 5.32 ppm for methylene groups bound to both hydroxyl and amino groups; at 5.52 and 6.75 ppm for alkene group, at 6.56-6.58 and 6.76-7.54 ppm for phenyl groups. ^{13}C NMR spectra showed chemical shifts at 44.50 ppm for methyl group; at 59.76 ppm for methylene groups bound to both hydroxyl and amino groups; at 95.42 and 141.74 ppm for alkene group; at 109.06-132.18 and 147.36-149.04 ppm for phenyl groups; at 194.82 ppm for ketone group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 298.13.

Preparation of a dialdehyde derivative

There are several studies for preparation of aldehyde derivatives via oxidation of primary alcohols using several reagents such as morpholinium bisulfate[xxiv], calcium hydride[xxv], 2-(hydroxyalky1)dithianes[xxvi], KN(TMS)$_2$[xxvii], chromium(VI)[xxviii] ruthenium[xxix] and others. In this investigation, a method previously reported[xxx] for oxidation of hydroxyl groups was used; in this way, **3** reacted with dimethyl sulfoxide to form the compound **4** (figure 2).

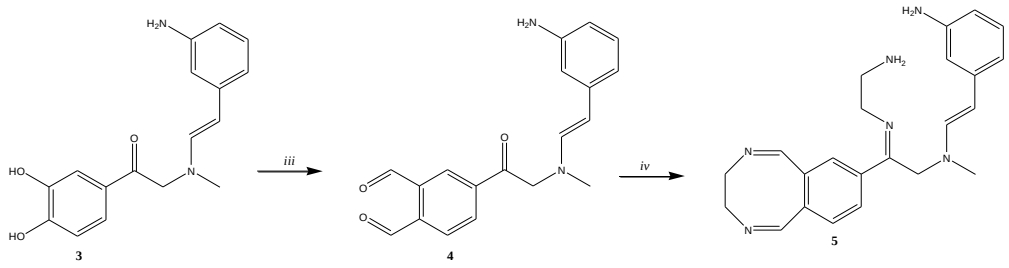

Figure 2. Synthesis of an azocine-aniline derivative (**5**). Conditions and reagents: *iii* = dimethyl sulfoxide, reflux, 24 h; *iv* = ethylenediamine, boric acid, 72 h.

The ^{1}H NMR spectrum from **4** showed several signals at 2.99 ppm for methyl group; at 4.02 ppm for amino group; at 5.30 ppm for methylene groups bound to both ketone and amino groups; at 5.50 and 6.75 ppm for alkene group; at 6.56-6.58 and 6.80-8.30 ppm for phenyl groups; at 10.50-10.60 ppm for aldehyde groups. ^{13}C NMR spectra showed chemical shifts at 44.76 ppm for methyl group; at 59.78 ppm for methylene groups bound to both ketone and amino groups; at 95.12 and 141.74 ppm for alkene group; at 109.06-140.90 and 146.12-147.36 ppm for phenyl groups; at 187.02-195.22 ppm for aldehyde groups; at 195.24 ppm for ketone group. Finally, the mass spectrum from **4** showed a molecular ion (m/z) 322.13.

Synthesis of a diazocine-aniline derivative

In the literature have been reported several methods for preparation of azocine derivatives using some reagents such as rhodium[xxxi], dimethyl acetylenedicarboxilate[xxxii], tetrahydropyridine[xxxiii], tetrahydrothieno[3,2-c]pyridines[xxxiv], Copper(II)[xxxv]. In this research, **4** reacted with ethylenediamine in the presence of boric acid to form the compound **5** (Figure 2). The ^{1}H NMR spectrum from **5** showed several signals at 2.92 ppm for methyl group; at 3.07-3.60 ppm for methylene groups bound to both imino and amino groups; at 3.98 ppm for methylene groups bound to phenyl and amino groups; at 4.17 ppm for amino group; at 4.19 and 8.67-8.76 ppm for methylene groups involved in 2,3-Dihydro-[1,4]diazocine ring; at 6.56-6.81 and 6.96-7.80 ppm for phenyl groups. ^{13}C NMR spectra showed chemical shifts at 40.90 and 54.23 ppm for methylene groups bound to both imino and amino groups; at 45.82 ppm for methyl group; at 49.32 ppm for methylene groups involved in 2,3-Dihydro-[1,4]diazocine ring; at 59.02 ppm for methylene groups bound to both amino and phenyl groups; at 92.42 and 134.85 ppm for alkene group; at 109.06-132.92, 133.90 and 135.62-147.34 ppm for phenyl groups; at 133.60, 134.66 and 168.24 ppm for imino groups. Besides, the mass spectrum from **5** showed a molecular ion (m/z) 388.23.

Synthesis of an aldehyde derivative.

This stage was achieved via reaction of **5** with dimethyl sulfoxide to form the compound **6** Figure 3). The ^{1}H NMR spectrum from **6** showed several signals at 2.86 ppm for methyl group; at 3.02-3.86 ppm for methylene groups bound to both amino and aldehyde groups; at 4.02 ppm for amino groups; at 5.47 and 6.90 ppm for alkene group; at 6.98-6.81 and 7.83-8.12 ppm for phenyl groups; at 9.40-10.61 ppm for aldehyde groups. ^{13}C NMR spectra showed chemical shifts at 43.30 ppm for methyl group; at 51.50-55.40 ppm for methylene groups bound to both aldehyde and amino groups; at95.32 and 135.32 ppm for alkene group; at 109.06-133.78 and 140.66-147.36 ppm for phenyl groups; at 189.00-198.86 ppm for aldehyde groups. In addition, the mass spectrum from **6** showed a molecular ion (m/z) 336.14.

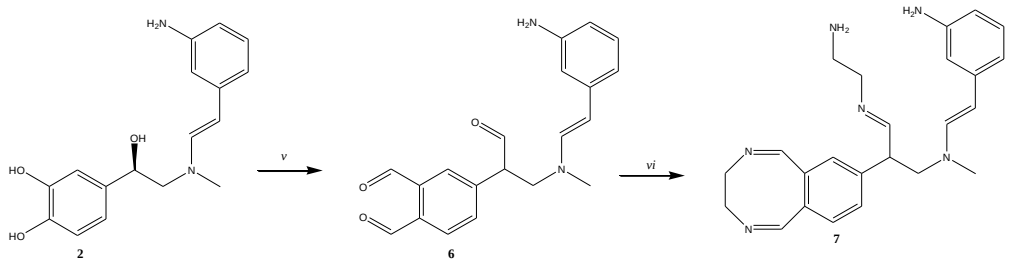

Figure 3. Synthesis of amino-azocine aniline derivative (7). Conditions and reagents: *v* = dimethyl sulfoxide, reflux, 24 h; *vi* = ethylenediamine, boric acid, 72 h.

Preparation of a second diazocine derivative

The compound **6** reacted with ethylene diamine using boric as catalyst to form the compound **7** (Figure 3). The ^{1}H NMR spectrum from **7** showed several signals at 2.87 ppm for methyl group; at 3.10 and 3.52 ppm for methylene groups bound to both amino and imino groups; at 3.56-3.76 for methylene groups bound to both amino and phenyl groups; at 4.18 ppm for methylene groups involved in 2,3-Dihydro-[1,4]diazocine ring; at 5.47 and 6.63 ppm for alkene group; at 6.48-6.56 and 6.75-7.90 ppm for phenyl groups; at 6.74 and 8.67-8.76 ppm for imino groups. ^{13}C NMR spectra showed chemical shifts at 40.50 and 58.40 ppm for methylene bound to both imino and amino groups; at 43.66 ppm for methyl group; at 49.33 ppm for methylene groups of 2,3-Dihydro-[1,4]diazocine ring; at 95.32 and 143.82 ppm for alkene group; at 109.06-133.21, 137.46-141.40 and 147.04 ppm for phenyl groups; at 133.61-134.64 and 149.60 ppm for imino groups. Finally, the mass spectrum from **7** showed a molecular ion (m/z) 402.25.

Activity biological

Antibacterial effect exerted by either compound 5 or 7 against *Escherichia colli* and *Staphylococcus aureus* (Figure 4 and 5) was evaluated using gentamicin, ciprofloxacin, and cefotaxime as controls. The results showed that growth of *Escherichia coli* was inhibited in the presence of CEFOT (MIC = 2.61×10^{-4} mmol), CIPROF (1.5×10^{-3} mmol) and GENT (MIC = 2.68×10^{-4} mmol). In addition, both compounds **5** (MIC = 2.57×10^{-3} mmol) and **7** (MIC = 1.24×10^{-3} mmol) decreased the bacterial growth of *Escherichia coli*.

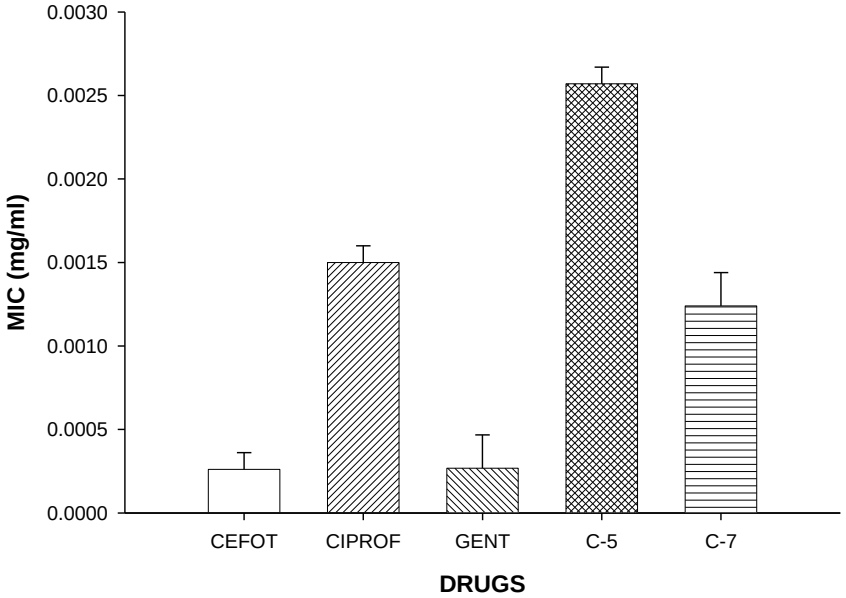

Figure 4. Effect induced by both compound **5** (C-5) and **7** (C-7) and the controls (cefotaxime, CEFOT; gentamicin, GENT; CIPROF, ciprofloxacin) against *Escherichia coli*. The results

showed that growth of *Escherichia coli* was inhibited in the presence of CEFOT (MIC = 2.61 × 10^{-4} mmol), CIPROF (1.5 × 10^{-3} mmol) and GENT (MIC = 2.68 × 10^{-4} mmol). In addition, both compounds **5** (MIC = 2.57 × 10^{-3} mmol) and **7** (MIC = 1.24 × 10^{-3} mmol) decreased the bacterial growth of *Escherichia coli*. MIC = minimum inhibitory concentration.

In addition, other data showed that *Staphylococcus aureus* was susceptibly to cefotaxime (MIC = 5.23 × 10^{-4} mmol), ciprofloxacin (MIC = 1.5 × 10^{-3} mmol) and gentamicin (MIC = 2.68 × 10^{-5} mmol). Besides, the bacterial growth of this microorganism in presence of both compound **5** (MIC of 1.28 × 10^{-3} mmol) and **7** (MIC = 1.24 × 10^{-3} mmol) was inhibited.

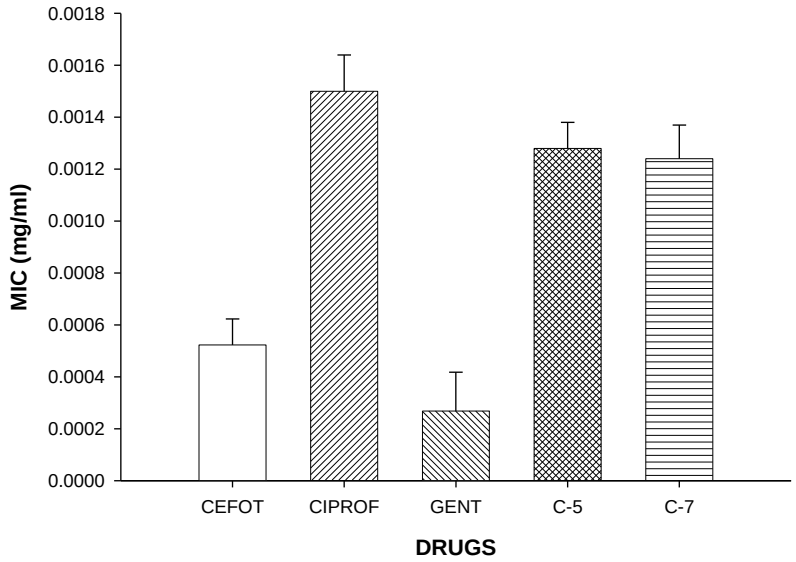

Figure 5. Antibacterial effects exerted by both compounds **5** and **7** and the controls (cefotaxime, CEFOT; ciprofloxacin, CIPROF and gentamicin, GENT) against *Staphylococcus aureus*. The results showed that *Staphylococcus aureus* was susceptibly to cefotaxime (MIC = 5.23 × 10^{-4} mmol), ciprofloxacin (MIC = 1.5 × 10^{-3} mmol) and gentamicin (MIC = 2.68 × 10^{-5} mmol). Besides, the bacterial growth of this microorganism in presence of both compound **5** (MIC of 1.28 × 10^{-3} mmol) and **7** (MIC = 1.24 × 10^{-3} mmol) was inhibited. MIC = minimum inhibitory concentration.

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