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SYNTHESIS OF TWO *PYRROLIDINE-2,5-DIONE* DERIVATIVES AS ANTIBACTERIAL AGENTS

López-Ramos Maria[1], Figueroa-Valverde Lauro[1,*], Díaz-Cedillo Francisco[2], Rosas-Nexticapa Marcela[3,*], Alvarez-Ramirez Magdalena[3], Mateu-Armad Maria Virginia[3], Lopez Gutierrez Tomas[1], Melgarejo-Gutierrez Montserrat[4], Moo-Kuc Cristina [1].

1 Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México;
2 Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, México, D.F. C.P. 11340;
3 Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México;
** Correspondence: lfiguero@uacam.mx (F.V.L.)*
[4]Facultad de Medicina Universidad Veracruzana, Médicos y Odontologos s/n, Unidad del Bosque, Xalapa, C.P. 91010 Veracruz, México.

Abstract
Various protocols have used for the synthesis of some pyrrolidine-2,5-diones as antibacterial agents; however, these methods involve different reagents which can be dangerous and require special conditions such as different pH and higher temperatures. The aim of this research was to synthesize two pyrrolidine-2,5-dione derivatives (compounds **4** and **5**) using some chemical strategies to evaluate their antibacterial activity against some bacteria. The chemical structure of compounds involved in this study was confirm with both ^{1}H and ^{13}C NMR spectra. The results showed that both **4** and **5** decreased bacterial growth of bacterial strains. However, biological activity of **5** was higher compared with **4**. These data suggest that the biological activity depends on the functional groups involved in the chemical structure of **5**.

Keywords. Synthesis, pyrrol-2,5-dione, derivatives, antibacterial.

Introduction
For years, some pyrrolidione analogs[i] have been used with therapeutic purposes for treat diabetes[ii], inflammation[iii], epileptic[iv], cancer[v], pain[vi], depression[vii]. In addition, new pyrrolidiones have been developed to treat some infectious diseases[viii]. For example, a pyrrolidine-2,5-dione derivative was synthesized from indole, benzaldehyde and succinimide as antibacterial agent against *Escherichia coli* strain[ix]. Besides, a study showed the synthesis of some pyrrolidine-2,5-diones from a α,β-unsaturated anhydride and an amines-derivative with antibacterial activity on *Staphylococcus aureus* strain[x]. Other data indicate the synthesis

of a phenylpyrrolidine-2, 5-dione via reaction of succinic anhydride with a primary aromatic amine as antibacterial agent against *Escherichia coli*strain[xi]. Besides, a study showed the synthesis of 6-substituted benzo[d]thiazol2yl-3-substituted pyrrolidine-2,5-dione from succinic anhydride and a benzothiazole derivative as antibacterial agent[xii]. It is noteworthy that methods used for preparation of several pyrrolidine-2, 5-dione derivatives require special conditions such as different pH and higher temperatures. In this way, the aim of this research was to prepare two pyrrolidine-2,5-dione derivatives to evaluate their biological activity on different bacterial strains.

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/$CDCl_3$) using tetramethylsilane as an internal standard. Electron Ionization mass spectrometry (EIMS) was recorder 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).

Chemical synthesis.

3-Methyl-7-(4-nitro-benzyl)-2,4,6-triaza-bicyclo[3.2.0]hepta-3,6-diene (2)

In a round bottom flask (10 ml), 4-Nitrophenylacetonitrile (150 mg, 0.92 mmol), Copper[II] chloride anhydrous (130 mg, 0.97 mmol) and 2-methylimidazol (80 mg, 0.97 mmol) and methanol (5 ml) was stirring for 12 h at room temperature. Then, the solvent was evaporated under reduced pressure: Following the product was separated using the chloroform:water (4:1) system; yielding 44% of product; m.p. 102-104 ^oC;IR (V_{max}, cm^{-1}) 3432 and 1540: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.92 (s, 3H), 3.32 (m, 2H), 5.40-6.00 (m, 3H), 7.12-7.80 (m, 4H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 20.60, 37.80, 55.90, 69.80, 124.12, 128.56, 141.18, 147.02, 159.80, 179.20 ppm. EI-MS m/z: 244.02. Anal. Calcd. for $C_{12}H_{12}N_4O_2$. C, 59.01; H, 4.95; N, 22.94; O, 13.10. Found: C, 59.00; H, 4.92.

3-(3-Amino-phenyl)-5-(3-methyl-2,4,6-triaza-bicyclo[3.2.0]hepta-3,6-dien-7-ylmethyl)-indol-1-ol (3)

In a round bottom flask (10 ml), compound **2** (200 mg, 0.82 mmol), 3-ethynylaniline (100 µl, 0.90 mmol), Copper [II] chloride anhydrous (130 mg, 0.97 mmol) and either methanol or ethanol or dimethyl sulfoxide (5 ml) was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure. Following the product was separated using the chloroform:water (4:1) system; m.p.122-124^oC;IR (V_{max}, cm^{-1}) 3430, 3380 and 3260: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.92 (s, 3H), 3.44 (m, 2H), 5.40-5.72 (m, 2H), 6.56-6.80 (m, 2H), 6.86 (m, 1H), 6.92 (broad, 4H), 7.00-7.04 (m, 2H), 7.10-7.20 (m, 3H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 20.60, 39.50, 55.90, 69.80, 107.50, 112.34, 113.10, 114.90, 116.76, 122.30, 123.52, 124.32, 127.32, 128.96, 130.22, 134.44, 135.70, 144.38, 159.80, 179.20 ppm. EI-MS m/z: 345.15. Anal. Calcd. for $C_{20}H_{19}N_5O$. C, 69.55; H, 5.54; N, 20.28; O, 4.63. Found: C, 69.52; H, 5.52.

1-{3-[1-Hydroxy-5-(3-methyl-2,4,6-triaza-bicyclo[3.2.0]hepta-3,6-dien-7-ylmethyl)-1H-indol-3-yl]-phenylamino}-pyrrolidine-2,5-dione (4)

In a round bottom flask (10 ml), compound **3** (200 mg, 0.58 mmol), Copper[II] chloride anhydrous (80 mg, 0.59 mmol) and *N*-bromosuccinamide (120 mg, 0.61 mmol) and methanol (5 ml) was stirring for 12 h at room temperature. Then, the solvent was evaporated under reduced pressure. Following the product was separated using the chloroform:hexane (4:1)

system; yielding 64% of product; m.p.144-146^{o}C;IR (V_{max}, cm^{-1}) 3430, 3260 and 1712: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.92 (s, 3H), 2.44-2.50 (m, 4H), 3.44 (m, 2H), 5.40-5.72 (m, 2H), 6.20-6.56 (m, 2H), 6.66 (m, 1H), 6.80-7.00 (m, 2H), 7.06 (broad, 3H), 7.12-7.30 (m, 3H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 20.60, 27.80, 39.50, 55.90, 69.80, 107.50, 109.12, 112.44, 114.90, 116.76, 121.95, 123.52, 124.32, 125.60, 128.96, 130.14, 134.06, 134.44, 135.30, 159.80, 165.66, 179.20 ppm. EI-MS m/z: 442.17. Anal. Calcd. for $C_{24}H_{22}N_6O_3$. C, 65.15; H, 5.01; N, 18.99; O, 10.85. Found: C, 65.12; H, 5.00.

1-{3-[5-(3-Methyl-2,4,6-triaza-bicyclo[3.2.0]hepta-3,6-dien-7-ylmethyl)-1-(4-prop-2-ynyl-phenoxy)-1H-indol-3-yl]-phenylamino}-pyrrolidine-2,5-dione (5)

In a round bottom flask (10 ml), compound **4** (200 mg, 0.45 mmol), potassium carbonate (70 mg, 0.50 mmol) and dimethyl sulfoxide (5 ml) was stirring for 12 h (80 ^{o}C). Then, the solvent was evaporated under reduced pressure. Following the product was separated using the chloroform:hexane (4:1) system; yielding 56% of product; m.p. 102-104 ^{o}C;IR (V_{max}, cm^{-1}) 3430, 2112, 1712 and 1150: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.92 (s, 3H), 2.00 (s, 1H), 2.40-2.50 (m, 4H), 3.44 (m, 2H), 3.48 (m, 2H), 4.10 (broad, 2H), 5.40-5.72 (m, 2H), 6.66 (m, 1H), 6.80-7.12 (m, 4H), 7.20 (m, 2H), 7. 24 (m, 1H), 7.28 (m, 2H), 7.30 (m, 2H), 7.32-7.34 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 20.60, 25.12, 27.00, 39.50, 55.90, 69.80, 71.24, 82.44, 100.34, 109.12, 112.34, 115.70, 115.85, 117.16, 121.85, 123.82, 126.62, 128.16, 128.43, 128.80, 128.82, 130.94, 132.52, 135.06, 135.74, 159.60, 159.64, 165.66, 179.20 ppm. EI-MS m/z: 572.25. Anal. Calcd. for $C_{34}H_{32}N_6O_3$. C, 71.31; H, 5.63; N, 14.68; O, 8.38. Found: C, 71.28; H, 5.60.

***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 Pharmacochemistry, Faculty of Chemical-Biological Sciences of the Autonomous University of Campeche.

***Antimicrobial activity*.**

The antibacterial effect produced by compounds **2** to **5** against Staphylococcus aureus (ATCC 49775), Streptococcus pneumoniae (49136), Escherichia coli (ATCC 25922), and Klebsiella pneumoniae (700603) was evaluated using a previously reported report[xiii]. In this way, the bacteria were incubated using the following growth media as brain/heart infusion for *Escherichia coli* and Staphylococcus 110 for *Staphylococcus aureus* for 24 h to 37 ^{o}C in the absence or presence of either compounds **2** to **5** (at dose of 0.0625 to 1 mg) to determine bacterial growth. Then, several tubes (12) with different characteristics were prepared as follows. The first tube was added 2 mL of culture medium (soybean trypticase protein) at double concentration and the rest (11 tubes) contained the same amount of medium at a single concentration. To first tube (double concentration) a 2 mL aliquot of either compound **2** or **5**was added and shaken, and from this tube a 2 mL aliquot was taken and added to the next tube (single concentration); this process was repeated successively until the solution had been consumed. Then, a bacterial suspension corresponding to the McFarland scale (9×10^8 cells/ml) was added to each tube, and all tubes were incubated at 37 °C for 24 hours.

Results and Discussion

Some pyrrolidine-2,5-dione analogs have been prepared using some protocols which require special condition such as different pH and higher temperatures[x-xii]. The aim of this study was

to synthesize twopyrrolidine-2,5-dione derivatives (compounds **4** and **5**) using some chemical strategies as follows:

Synthesis of a 2,4,6-triaza-bicyclo derivative (2)

Several triazabicyclo derivatives have been prepared using diferent protocols; for example, a study showed the preparation of a serie of 2,6,9-triazabicyclo[3.3.1]nonane derivatives from unsaturated benzyl- or allylimines[xiv]. Other study showed the condensation of 5-aminothieno[2,3-*c*]pyridazine-6-carbaldehyde with aliphatic primary amines to form some 2,6,9-triazabicyclo[3.3.1]nonane derivatives[xv].In addition, Δ^8-triazabicyclo)6.3.0)decene was prepared from 2-(ω-hydroxyalkylamino)- Δ^2-1,3-diazacycloalkene[xvi]. These studies show some methods which require several reagents that can be dangerous and difficult to handle; therefore, in this study a 2,4,6-triaza-bicyclo derivative (compound **2**)was synthesized from 4-Nitrophenylacetonitrile and 2-methylimidazol using Copper[II] chloride as catalyst(Figure 1). The ^{1}H NMR spectrum of **2** showed several signals at 1.92 ppm for methyl group; at 3.32 for methylene group bound to both 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment and phenyl group; at 5.40-6.00 for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fragment; at 7.12-7.80 ppm for phenyl group. The ^{13}C NMR spectra display chemical shifts at 20.60 ppm for methyl group; at 37.80 ppm for methylene group bound to both 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment and phenyl group; at 55.90-69.80 and 159.80-179.30 ppm for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 124.12-142.09 ppm for phenyl group. Besides, the mass spectrum from **2** showed a molecular ion (m/z) at 244.09.

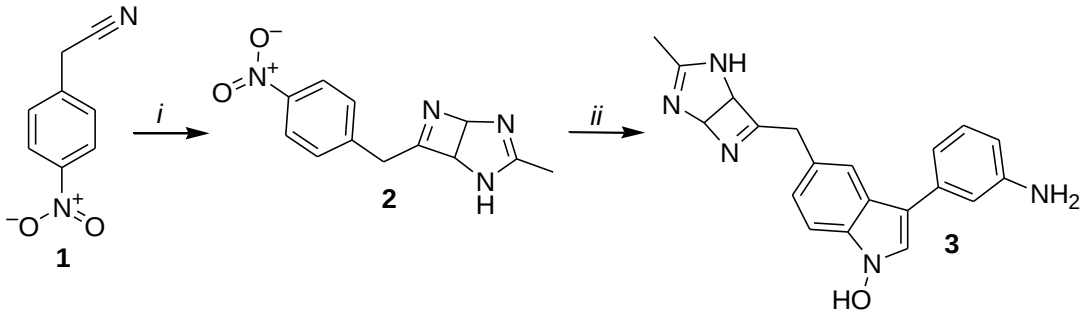


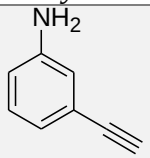
Figure 1. Synthesis of a triaza-bicyclo-indol-1-ol derivative (**3**). *Conditions and reagents*: *i*= 4-Nitrophenyl-acetonitrile, 2-methylimidazol, Copper(II) chloride, 12 h, rt; *ii* = 3-ethynylaniline,Copper(II) chloride anhydrous,rt.
rt =room temperature.

Preparation of a triaza-bicyclo-indol-1-ol derivative

There are several protocols for synthesis of indole derivatives which use some reagents such as ruthenium[xvii], oxiandoles[xviii], tert-butyl isocyanide[xix], palladium[xx], nitroxide[xxi] and others.
In this research, a triaza-bicyclo-indol-1-ol analog (**3**) was prepared from compound **2** and 3-ethynylaniline in the presence of Copper(II) chloride (Figure 1 and 2). It should be noted that this reaction was carried out using three different solvents such as methanol, ethanol and dimethyl sulfoxideto evaluate the yielding of the reaction. The results showed a higher yield with methanol compared to with either ethanol or dimethyl sulfoxide (Table 1).The ^{1}H NMR spectrum of **3** showed several signals at 1.92 ppm for methyl group; at 3.44 for methylene group bound to both 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment and phenyl group; at 5.40-6.72 for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fragment; at 6.56-6.80 and 7.00-7.04 ppm for indole fragment; at 6.86 and 7.10-7.20 ppm for phenyl group; at 6.92 ppm for both hydroxyl and amino groups.. The ^{13}C NMR spectra display chemical shifts at 20.60 ppm for methyl group; at 39.50 ppm for methylene group bound to both 2,4,6-Triaza-

bicyclo[3.2.0]hepta-3,6-diene fregment and phenyl group; at 55.90-69.80 and 159.80-179.20 ppm for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 107.10-114.90-116.76, 123.52-124.32 and 128.96-134.44 ppm for indole fragment; at 112.34-113.10, 122.30,127.32 and 135.70-144.38ppm for phenyl group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) at 345.15.

Table 1. Effect of solvent involved in the synthesis of compound **3**.

Substrate	*Entry*	*Catalyst*	*Solvent*	*Product*	*Yield (%)*
2		Copper(II) chloride	MeOH	3	55
		Copper(II) chloride	EtOH	3	-
		Copper(II) chloride	DMSO	3	12

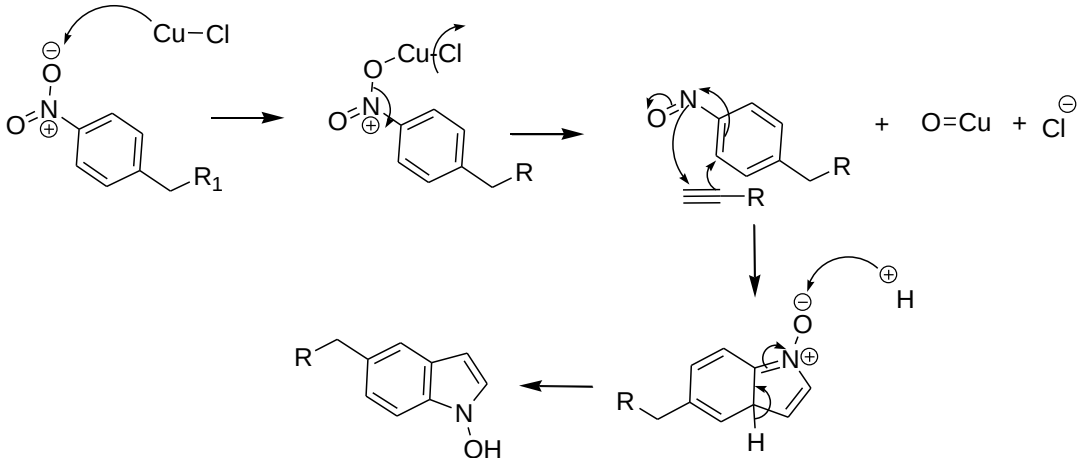


Figure 2. Reaction mechanism involved in the synthesis of compound **3**.

Synthesis of a pyrrolidine-2,5-dione derivative (4)

Several pyrrolidine-2,5-dione have prepared using different methods which require special conditions such diferent pH and higher temperature [ix-xii]. In this researh the compound **4** was prepared from **3**and *N*-bromosuccinamide using Copper[II] chloride as catalyst (Figure 2). The ^{1}H NMR spectrum of **4** showed several signals at 1.92 ppm for methyl group; at 2.44-2.50 ppm for Pyrrolidine-2,5-dione ring; at 3.44 for methylene group bound to both 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment and phenyl group; at 5.40-6.72 for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fragment; at 6.20-6.56 and 6.80-7.00 ppm for indole fragment; at 6.66 and 7.12-7.30 ppm for phenyl group; at 7.06 ppm for both hydroxyl and amino groups. The ^{13}C NMR spectra display chemical shifts at 20.60 ppm for methyl group; at 27.80 and 165.66 ppm for Pyrrolidine-2,5-dione ring; at 39.50 ppm for methylene group bound to both 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment and phenyl group; at 55.90-69.80 and 159.80 and 179.20 ppm for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 107.50, 114.90-116.76, 123.52-124.32, 128.96-130.14 and 134.44 ppm for indole fragment; at 109.12-112.44, 121.95, 125.60, 134.06 and 135.30 ppm for phenyl group. Additionally, the mass spectrum from **4** showed a molecular ion (m/z) at 442.17.

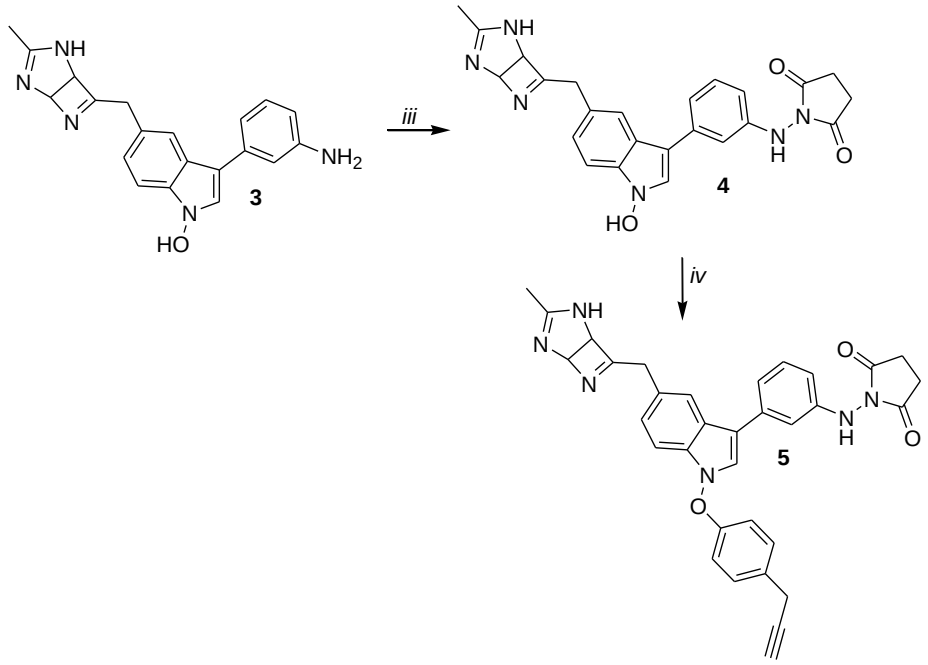


Figure 2. Synthesis of two pyrrolidine-2,5-dione derivatives (**4** and **5**).*Conditions and Reagents*: *iii* = *N*-bromosuccinamide, Copper[II] chloride, 12 h, rt; *iv* = dimethyl sulfoxide, potasium carbonate, 12 h, reflux at 80 ^{o}C.rt = room temperature.

Preparation of an ether derivative (5)

There are some protocols for synthesis of ether analogs which use some reagents, such as *p*-toluenesulfonic acid[xxii], tetrabutylammonium bromide[xxiii], Cu/ZnO/ZrO_2[xxiv], lithium aluminum hydride[xxv], dimethyl sulfoxide[xxvi] and others. In the study, **5** was prepared from compounds **4** and dimethyl sulfoxide in mild conditions.The ^{1}H NMR spectrum of **5** showed several signals at 1.92 ppm for methyl group; at 2.00 ppm for alkyne group; at 2.40-2.50 ppm for Pyrrolidine-2,5-dione ring; at 3.44 ppm for methylene group bound to both indole ring and 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 3.48 ppm for methylene group linked to both phenyl and alkyne groups; at 4.10 for amino groups; at 5.40-5.72 ppm for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 6.66, 7.24 and 7.32-7.34 ppm for phenyl group bound to both indole ring and amino group; at 7.20 and 7.30 ppm for phenyl group linked to ether group. The ^{13}C NMR spectra display chemical shifts at 20.60 ppm for methyl group; at 25.12 ppm for methylene bound to both alkyne and phenyl group; at 27.00 ppm for Pyrrolidine-2,5-dione ring; at 39.50 ppm for methylene group bound to both indole ring and 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 70.24-82.44 ppm for alkyne group; at 55.90-69.80, 159.64 and 179.20 ppm for 2,4,6-Triaza-bicyclo[3.2.0]hepta-3,6-diene fregment; at 100.34, 115.70, 117.16, 123.82, 128.16-128.80 and 130.94 ppm for indole ring; at 109.12-118.34, 121.85 and 126.62 and 135.06-135.74 ppm for phenyl group linked to both indole ring and amino group; at 115.80, 128.82, 132.52 and 159.60 ppm for phenyl group bound to ether group; at 165.66 ppm for ketone groups. Finally, the mass spectrum from **4** showed a molecular ion (m/z) at 572.25

Antibacterial activity

There are various studies which indicate that some pyrrolidine-2,5-dione derivativesmay decrease bacterial growth ofdifferent bacterial strains[ix-xii]. Analyzing these data, in this studythe antibacterial activity produced by both compounds **4** to **5** against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *Klebsiella pneumoniae* was evaluated, using

the compounds **2**and **3** as control with minimum inhibitory concentration method. The results showed that bacterial growth of either Gram-negative or Gram-positive bacteria only was inhibited by the compounds**4** and **5**.It is noteworthy that antibacterial activity produced by compound **5** was higher compared with **4**. These data suggest that bacterial activity of both compounds **4** and **4**could depend onfunctional groups involved in their chemical structure.

Table 2. Antibacterial activity of compounds **4** and **5**against four bacterial strains

Compound	Staphylococcus aureus (mg)	Streptococcus pneumoniae (mg)	Escherichia coli (mg)	*Klebsiella pneumoniae (mg)*
2and**3**(controls)	-	-	-	-
4	0.25	0.25	0.25	0.25
5	0.5	0.5	1.0	1.0

CONCLUSIONS

In this research, a facile synthesis of two pyrrolidine-2,5-diones (**4** and **5**) is reported using some chemical strategies. Besides, the compounds **4** and **5** decrease the bacterial growth of both Gram-negative and Gram-positive bacteria and this effect depend of functional groups involved in their chemical structure. In this way, these compounds could be considered as good antibacterial agents.

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None

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