Palladium-Catalyzed Sonogashira Synthesis of Alkynyl Derivatives of Quinoline-5, 8-Dione

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ABSTRACT— The synthesis of various alkynylquinoline-5,8-diones is reported. The intermediate 6,7-dibromoquinoline-5,8-dione was obtained by nitrosation of 8-hydroxyquinoline, followed by reduction and subsequent bromination and oxidation. The coupling reaction of 6,7-dibromoquinoline-5,8-dione with various terminal alkynes via Palladium catalysis gave the alkynylquinoline-5,8-diones in good to excellent yields (50-85%). The chemical structures of the products were confirmed using spectroscopic methods, which include UV/Visible spectrophotometer, Fourier Transform-Infrared (FT-IR) Spectroscopy, \textsuperscript{1}H and \textsuperscript{13}C-NMR Spectroscopy. In vitro antimicrobial activity screening carried out on the compounds against bacterial strains: Escherichia coli 1, Escherichia coli 12, Staphylococcus aureus, Klebsiella pneumonia and Pseudomonas aeruginosa, showed that the synthesized compounds have significant activities (MIC= 0.15-3.20), against the tested organisms. However, compound 5e did not inhibit the growth of Pseudomonas aeruginosa.

Keywords— Alkynylquinoline-5,8-diones, Palladium Catalysis, Sonogashira protocol, Terminal alkynes

1. INTRODUCTION

The chemistry of quinoline-5,8-dione as a functional group is a developing field because of its various biological activities. Quinoline-5,8-dione \textsuperscript{1}, the parent functional group of a large number of medicinal compounds has been of great interest to drug researchers due to its biological functions as antifungal, antibacterial, antiparasitic and antitumor [1]. Lavendamycin and Streptonigrin are known antibiotic and antitumor agents containing the quinoline5,8-dione functional group [1]. Studies have shown that substituted quinoline-5,8-diones are useful antifungicides and antibactericides, whereas some of the polynuclear quinones built on the dihaloquinoline quinones are useful tuberculostatic and cytostatic substances [2]. A number of alkylene-imino quinones have been prepared, which are capable of inhibiting the growth of tumor nuclei [3]. Again, some of the hydroxyl and amino-quinoline-quinones possess marked amoebicidal activity [4].

Among the variety of transition metal catalyzed coupling reactions, Sonogashira coupling reaction of aryl halides with terminal acetylene, provides an effective route for C-C bond formation and has become useful method for the preparation of aryl alkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials [5,6]. Initially, the most common catalytic system for Sonogashira reaction was palladium-phosphine complexes with Cul as the co-catalyst in excess amine [7a-c, 8]. In recent years, significant progress has been made in this reaction and an efficient copper free catalyst system has been developed, which avoided the homocoupling [9, 10]. The copper-free Sonogashira reaction has been intensively investigated with aryl/ heteroaryl iodide and bromine.
derivatives [11]. Though there are various alkylated derivatives of quinoline-5,8-diones with reported facilitating biological activities, the synthesis of its alkynylated derivatives are still yet unknown. In fact no significant work has been done using Sonogashira cross-coupling reaction to extend the conjugation of halogenated quinoline-5,8-diones. It is the interest in these compounds that made us aim at synthesizing the alkynylated quinoline-5,8-diones.

2. MATERIAL AND METHOD

2.1 Reagents and Apparatus

Most of the reactions were carried out under an atmosphere of nitrogen. The regents were analytical grade and purchased from Sigma-Aldrich. Melting points of solids were determined with Fischer John’s melting point apparatus and were uncorrected. UV/Visible spectroscopy were recorded on UV-2500PC series spectrophotometer using 1cm quartz cells, and IR spectra on SHIMADZU FTIR-8400S FOURIER TRANSFORM INFRARED SPECTROPHOTOMETER (KBr, NaCl pallets), (NARICT, ZARIA, Nigeria). Nuclear magnetic resonance (1H-NMR and 13CNMR) spectra were determined using Joel 400MHz at Strathclyde University, Scotland. Chemical shifts are recorded on the δ-scale (neat).

2.2. Synthesis of the Key Intermediates

2.2.1. 5-Nitroso-8-hydroxyquinoline hydrochloride 3

The procedure of Pratt and Drake [4] was adopted in the synthesis of this compound. 8-Hydroxyquinoline 2 (40 g, 0.28 mole) was placed in a one litre beaker and water (200 ml) was added to it to form solution. Concentrated hydrochloric acid (75 ml) and Ice (180 g) were added to the solution. This was followed by gradual addition of solution of sodium nitrite (30g) in water (100ml) with vigorous stirring over one hour at 0 °C to 4 °C. The mixture was allowed to stand overnight at 30 minutes, after which the product was filtered off and washed with cold water. The product was air-dried to give 5-nitroso-8-hydroxyquinoline hydrochloride 3 (55.6 g, 96 %) as fine yellow powder, which readily undergoes auto-oxidation. mp 182-183 °C (Lit 181-183 °C) [12].

2.2.2. 5-Amino-8-hydroxyquinoline hydrochloride 4

Freshly prepared 5-nitroso-8-hydroxyquinoline hydrochloride 3 (20 g, 0.10 mole) was dissolved in a mixture of distilled water (80 ml) and 5N-sodium hydroxide solution (130 ml). The solution was warmed to 40 °C and sodium dithionite (47.5 g) was added to it. The temperature of the solution rose spontaneously to 70-80 °C and a rapid flow of nitrogen was passed through it. The solution was allowed to cool slowly to about 50 °C, and 12N hydrochloric acid (12.5 ml) was added to it, and there was evolution of chlorine gas. When the evolution of the gas has subsided, the solution was maintained under diminished pressure with magnetic stirring until most of the dissolved gases had been removed. The mixture was cooled in an ice-salt bath, and the resulting precipitate collected by filtration without washing. More of the precipitate was obtained on further cooling in a freezer at 0 °C for days. Light brown crystals of 5-amino-8-hydroxyquinoline hydrochloride 4 (15.2 g, 81 %) were obtained and the melting point was determined to be 217-219 °C.

2.2.3. 6,7-Dibromoquinoline-5,8-dione, 5.

This compound was prepared according to the literature [2, 4] but some modifications were made. 49% aqueous hydrobromic acid (20 ml) was poured into 2-litre three necked flask equipped with a reflux condenser. 5-Amino-8-hydroxyquinoline dihydrochloride 4 (4 g) was poured into the flask to obtain a solution. The solution was heated, followed by gradual addition of solution of sodium bromate (3.8 g) in water (15 ml) at such a rate that the temperature never rose above 50-60 °C. After the addition, the reaction mixture was heated at that temperature with gentle stirring for 30 minutes, and allowed to cool. The mixture was poured onto an ice block (300 g), and further chilled in an ice-salt mixture. The resulting precipitate was filtered and recrystallized from ethanol to give dark brown precipitate of 6,7-dibromoquinoline-5,8-dione 5 (7.5 g, 86 %); mp 244 °C (Lit. 242-243 °C, 243-245 °C) [12, 13]. UV-Vis λmax (logr) 350.50 (2.35); 539.50 (1.10) and 737.50 (1.11) nm. IR (KBr) νmax: 3057, 1692, 1464, 1376, 696, 756 cm⁻¹.
2.3. General Procedure for Synthesis of Alkynyl Derivatives of 6,7-Dibromoquinoline-5, 8-diones

All the derivatives were synthesized according to Jin Hang et al [14] with some modifications. A mixture of 6,7-dibromoquinoline-5,8-dione (0.5 mmol), alkyne, (0.6-1.2 mmol), PdCl₂(PPh₃)₂ (3 mol %), and TBAF, H₂O (3-6 equiv) was stirred under N₂ at 80 °C for time ranging from 12 and 73 minutes (as monitored by TLC). After the mixture was washed with water, exposed to diethyl ether and evaporated to give the desired products.

2.3.1. 7-Bromo-6-(3-hydroxyprop-1-yn-2-yl) quinoline-5,8-dione 6a

Black solid, yield 82%, mp 202-203 °C, UV-Visible λ max (log ε): 739.5 (1.2), 539 (1.2), 350.5(2.28), 335.5(2.31) nm, IR (KBr) ́: max: 3426cm⁻¹ (O-H); 2128cm⁻¹ (C≡C), 1717cm⁻¹ (C=O), 1461cm⁻¹ (C=C aromatic rings);1399cm⁻¹(C-N);738cm⁻¹(C-Br). 1H-NMR[DSMO-d₆]:6:8.70-8.55(m, 3H, heteroaryl H), 4.23(s,1H,OH),1.57(s,2H,-CH₂).13C-NMR[DSMO-d₆]:176.47(C=O), 142.99-125.81(Ar-C), 58.13,58.09 (C=C), 40.72 (C-Br), 23.65,19.75,14.05 (C-aliphatic).

2.3.2. 7-Bromo-6-(3-hydroxy-3-methylbut-1-yn-1-yl) Quinoline-5,8-dione 6b

Pink oil, yield 66%. UV-Visible λ max (log ε): 736 (1.15), 351 (2.05) nm, IR (NaCl) V max: 3411cm⁻¹ (O-H ), 2874 cm⁻¹, 2963 cm⁻¹ (C-H aliphatic); 2363 cm⁻¹ (C=C); 1727 cm⁻¹ (C=O); 1464 cm⁻¹(C=C aromatic rings); 1382 cm⁻¹ (C-N stretch); 741 cm⁻¹(C-Br stretch). 1H-NMR[DSMO-d₆]:7:6.61(m,3H,heteroaryl-H),3.19-2.53 (m,3H,-CH₂),1.58-1.35 (m,3H,CH₃), 1.33-1.23(m,3H,-CH₂),0.94-0.69 (m,3H,-CH₃).13C-NMR [DSMO] δ:176.47(C=O), 142.99, 135.28-126.20, (Ar-C), 40.55 (C-Br), 23.62, 19.75, 14.05 (C-aliphatic).

2.3.3. 7-Bromo-6-(phenylethynyl) Quinoline-5,8-dione 6c

Black solid, yield 85%, mp 98-99 °C. UV-Visible λ max (log ε): 737 (1.2), 351 (2.2) nm. IR (KBr) V max: 3078cm⁻¹ (C-H aromatic), 2107cm⁻¹ (C=C); 1625 cm, 1694 cm⁻¹ (C=O), 1462 cm⁻¹ (C=C aromatic rings); 1375 cm⁻¹ (C-N stretch); 637 cm⁻¹, 687 cm⁻¹ (C-Br,stretch). 1H-NMR [DSMO-d₆]:6:9.68-6.94(m,5H,Phenyl-H),7.64-7.07 (m,3H,heteroaryl-H).13C-NMR [DSMO] δ:132.0-129.30 (Ar-C), 40.90 (C-Br).

2.3.4. 7-Bromo-6-(oct-1-yn-1-yl) Quinoline-5,8-dione 6d

Brown oil, yield 50%, UV-Visible λ max (log ε): 361(1.40), 351.5 (1.4) nm. IR (NaCl) V max: 2876cm⁻¹, 2965cm⁻¹ (C-H aliphatic); 2107cm⁻¹ (C=C); 1465cm⁻¹ (C=C aromatic rings); 1381cm⁻¹ (C-N stretch); 736cm⁻¹ (C-Br stretch); 1692cm⁻¹ (C=O). 1H-NMR [DSMO-d₆]:7:8.79-7.84 (m,3H,heteroaryl-H), 7.64-7.07 (m,3H,heteroaryl-H), 3.19-3.15(t,2H,-CH₂),1.90-1.53(m,6H,-CH₃),1.35-1.26(m,2H,-CH₂),0.95-0.89(m,3H,-CH₃).13C-NMR [DSMO] δ:177.23, 175.15, (C=O), 146.63-123.49 (Ar-C), 89.37 (C=C), 40.69 (C-Br), 14.66, 19.78, 23.68 (C-aliphatic).

2.3.5. 7-Bromo-6-(hex-1-yn-1-yl) Quinoline-5,8-dione 6e

Black oil, yield 70%, UV-Visible λ max (log ε): 497 (1.42), 351 (1.7) nm. IR (NaCl) V max: 2171 cm⁻¹ (C=C); 2876 cm⁻¹, 2951 cm⁻¹ (C-H aliphatic); 1641 cm⁻¹ (C=C aromatic rings);1473 cm⁻¹ (C=C aromatic rings);1386 cm⁻¹ (C-N stretch);737 cm⁻¹ (C-Br stretch). 1H-NMR [DSMO-d₆]:6:3.39 (t, 2H,-CH₂), 1.76 (m, 2H,-CH₂), 1.41(q, 2H,-CH₂), 0.97(q, 3H,-CH₃).13C-NMR [DSMO] δ:40.36, 40.30 (C-Br), 23.66, 19.57, 13.15, 13.12 (C-aliphatic).

2.4 Antimicrobial Activity Evaluation

Multi-resistant bacterial strains isolated under clinical conditions and typed strains (ATCC Cultures) were used in the study. The bacterial strains used were Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli 1 and Escherichia coli 12. The antibacterial activities of the monoalkynylated quinoline-5,8-diones against these multi-resistant bacteria were determined using the agar well diffusion method as described by Perez et al [15]. A 10 mg/mL concentration of each compound was constituted by dissolving 0.04 g of each in 1 mL dimethyl sulfoxide (DMSO). A single colony of each test isolate was suspended in 2 mL of sterile nutrient broth. The suspension of each isolate was standardized by adjusting to correspond to 0.5 McFarland turbidity standards corresponding to approximately 10⁵cfu/mL. This was inoculated on the surface of the iso-sensitist nutrient agar, and the excess fluid drained into discard pot containing disinfectant. The inoculated agar surface was allowed to dry, and the plates appropriately labeled. Using a cork borer of 6mm in diameter, wells were bored in the inoculated iso-sensitist nutrient agar. With a micropipette, 50 µL of each test compound solution was delivered into each well. The plates were left on the bench for 30 minutes to allow the compound to diffuse into the agar. Thereafter, the plates were incubated at 37 °C for 24 hours. After incubation, the plates were observed for inhibition zones around the wells. The diameters of the zones were measured with meter rule to the nearest whole millimeter.
The minimum inhibitory concentration (MIC) of the tested compounds was determined using the same method described by Perecz [15]. Serial dilutions of the tested compounds were prepared from 10.0 mg/mL to 0.125 mg/mL. Amended media were incubated overnight at 37 °C to check for sterility. Overnight nutrient broth cultures of the test bacteria were adjusted to contain approximately 10^8 cfu/mL, and 0.025 mL of each of the test organism was spot inoculated on the amended culture media. Inoculated plates were incubated at 37 °C for 24 hours, and observed for presence of visible growth. The minimum inhibition concentration was determined as the value of the lowest concentration that completely suppressed growth of the organism.

3. RESULTS AND DISCUSSION

3.1. Chemistry

The intermediate used for the synthesis of the new alkynylated quinoline-5,8-diones (6a-e), is 6,7-dibromoquinoline-5,8-dione, 4. This was prepared starting from readily available materials in line with reported procedure [4]. The alkynylated quinoline-5,8-diones 6a-e were obtained by palladium-catalyzed coupling of 6,7-dibromoquinoline-5,8-dione 5 and appropriate alkyne using PdCl₂(PPh₃)₂ in the presence of TBAF, 3H₂O and under nitrogen atmosphere. This is a variant of the traditional Sonogashira cross-coupling reaction wherein copper, amine and solvent are not used. The copper was not used in this reaction to avoid homocoupling, which usually occurs in the presence of copper through air oxidation [16]. C=O, C=N, C≡C and C=C aromatics. The use of amine was also avoided in this procedure because amine bases are less environmentally friendly when compared with TBAF·3H₂O. Table 1 shows a summary of the yields and the reaction time for the various derivatives. Among the terminal alkynes 1-hexyne took the least time (12 minutes) to react giving 75% yield (Entry 5), whereas phenyl acetylene which gave the highest yield (85%) required the longest time to complete the reaction (Entry 3). The high yield obtained in the case of phenyacetylene is recognized as exceptional case when compared with other alkynes, which do not give such yield on reaction with electron rich aryl halides [17].

![Scheme 1](image1.png)

Scheme 1. Synthesis of 6,7-dibromoquinoline-5,8-dione, 5.

![Scheme 2](image2.png)

Scheme 2: Synthesis of 6,7-dibromoquinoline-5,8-diones alkynyl derivatives 6a - e

R = –C₆H₄, –C₆H₁₃, –CH₃OH, –C₆H₆O, –C(CH₃)₂OH
In the formation of the alkynylated derivatives of 6,7-dibromoquinoline-5,8-dione, the 6-position of 6,7-dibromoquinoline-5,8-dione 4, is favoured for nucleophilic attack by the alkyne. The reactions of 6,7-dibromoquinoline-5,8-dione depend primarily on the heterocyclic nitrogen atom which withdraws electrons from the quinonoid ring. Moreover, the site of nucleophilic attack on a quinone depends upon which of the carbonyl carbon atom more strongly attracts the electrons of the ethylenic double bond [18]. The 8-carbonyl carbon atom of 6, 7-dibromoquinoline-5,8-dione 4, is located at the α-position with respect to the pyridine ring and more electron-deficient than the 5-carbonyl carbon atom which occupies the β-position[18]. This deficiency of C-8 is transferred to C-6 via inductive effect by withdrawal of electrons from the double bond between the 6- and 7-carbon atoms making the bromine in 6-position a better leaving group than that at 7-position. This leads to preferential attack by a nucleophile at 6-position forming 7-bromo-6-alkynylated quinoline-5,8-diones (6a-e). This reaction is fast due to availability of electron density on the triple bond of the alkyne, which is responsible for the nucleophilic attack on the 6-position of the quinoline.

The possible working mechanism of the catalyzed reactions follows the general copper, amine and solvent free Sonogashira cross-coupling reactions as represented in Figure 1. Although the effect of TBAF in these reactions was not clear, TBAF acting as a base, and phase-transfer catalysis (PTC) to favour the desired reaction is confirmed [14]. The mechanism outlined in Figure 1 was formulated on the basis of the mechanism reported earlier [7a, 19]. The Pd(0) species could be generated readily from the reaction of Pd(pph$_3$)$_2$Cl$_2$ with substrates, followed by the oxidative addition of Pd(0) with 6,7-dibromoquinolin-5,8-dione [13] to form intermediate (T$_1$). Ligand exchange between intermediate and the acetylene anion, which was generated by the reaction of terminal alkyne with TBAF, occurred to afford intermediates (T$_2$) (T$_3$). Finally, the reductive elimination of the intermediates (T$_2$) (T$_3$) took place to regenerate the active Pd (0) species and give the desired products (6a-e). Thus, several beneficial roles of TBAF might occur in the reaction as reported [20, 21]. For the present reaction, these include: (1) activation of the active Pd(0) species with the formation of anionic Pd species, (2) stabilization of the low concentration Pd(0) species (T$_1$ &T$_2$), (3) deprotonation of the acidic hydrogen in the alkyne in pathway (ii), and (4) Phase-transfer catalysis for the inorganic base/substrate/product phases[21, 22, 23].

The establishment of the structures of the new compounds (6a-e), were on the basis of the FT-IR and NMR Spectroscopy. The peaks at 2128-2363cm$^{-1}$, 1641-1727cm$^{-1}$, 1461-1473 cm$^{-1}$ and 1375-1399cm$^{-1}$ were assigned to stretching vibrations of C=C, C=O, C=C aromatics and C=N respectively. The $^1$H-NMR Spectra in each case showed signal at 8.78-7.07ppm assigned to Ar-H. The assigned structure was further supported by C-NMR spectra. The peaks at 176.47-177.15ppm and 125.81-146.63ppm were due to C=O and C=C aromatic respectively. Other peaks are in agreement with the rest of carbons in the structure of the compounds.

**Table 1:** Synthesis of Quinoline-5,8-diones Alkynylated Derivatives under Copper, Amine, and Solvent Free Conditions$^{(a)}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Terminal Alkynes</th>
<th>Products</th>
<th>Time (Mins)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HC≡C—OH</td>
<td>![Image] 6a</td>
<td>51</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>HC≡C—CH$_3$OH</td>
<td>![Image] 6b</td>
<td>25</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>HC≡C—Ph</td>
<td>![Image] 6c</td>
<td>60</td>
<td>85</td>
</tr>
</tbody>
</table>

$^{(a)}$
(a) Reaction conditions: 6,7-dibromoquinoline-5,8-dione (0.5 mmol), alkyne, (0.6-1.2 mmol), PdCl$_2$(PPh$_3$)$_2$ (3 mol %), and TBAF,3H$_2$O (3-6 equiv), stir under N$_2$ at 80 °C, 12-73 minutes (as monitored by TLC).

**Figure 1:** Proposed Mechanism of Synthesis of Alkynylated Derivatives of 6,7-Dibromoquinoline-5,8-dione

3.2 Antimicrobial Properties

Due to considerable biological and pharmaceutical activities of quinones, it becomes necessary to evaluate the antibacterial activity of the synthesized compounds. Moreover, the precursors, 8-hydroxyquinoline, 2 and 6,7-dibromoquinoline-5,8-dione, 6 are known to have antibacterial activities [24]. An effective approach of antimicrobial therapy of an infection is based on the isolation and identification of the infected organism and determining its sensitivity to antibacterial drugs. The micro-organisms tested in this study include the following: *Escherichia coli* 1, *Escherichia coli* 12, *Klebsiella pneumonia*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, using the agar diffusion method [15]. The choice of ampicillin and gentamycin as Clinical standards is due to the fact that they possess broad spectrum of antibacterial activities. The results of the antimicrobial activities tests are as shown in Table 2. The higher the IZD, the higher the sensitivity of the compound. The IZD range 9-12 indicates less sensitive, 13-16 indicates moderate sensitive
and 17-20 indicates highly sensitive. In all, the results show that all the compounds exhibited some level of activity against the tested organisms, with the exception of 5e, which did not inhibit the growth of *Pseudomonas aeruginosa*.

The MIC values of the synthesized compounds against *E.coli* 1 ranges from 0.16 mg/mL to 1.41 mg/mL while the MIC value for the gentamycin and ampicilin under similar condition was 100 mg/mL. The least activity was observed in compounds 6a and 6c with MIC value of 1.41 mg/mL. The MIC values of the synthesized compounds against *klebsiella pneumonia* ranges from 0.16 to 2.80 mg/mL while that of gentamycin and ampicilin under similar condition was 5.00 mg/mL. Therefore, all the synthesized compounds (MIC 0.16 to 2.80 mg/mL) were more active than gentamycin and ampicilin (5.00 mg/mL). The highest activity was observed on compounds 6a and 6d (MIC 0.16 mg/mL). The MIC test for the synthesized compounds against *staphylococcus aureus* showed that the highest activity was observed on compound 6c (MIC 0.15 mg/mL) and least activity on compound 6d (MIC 2.80 mg/mL). The different alkynylated derivatives of quinoline-5,8-diones exhibited varying MIC values ranging from 0.15 to 2.80 mg/mL showing better activity than gentamycin and ampicilin (2.5 mg/mL) except compound 6d (MIC 2.8 mg/mL). The MIC values ranging from 0.13 to 3.20 mg/mL was observed for the synthesized compounds against *pseudomonas aeruginosa* while the MIC value of gentamycin and ampicilin under similar condition was 10 mg/mL and 20 mg/mL respectively. Compound 6b (MIC 3.20 mg/mL) showed the least activity, while *pseudomonas aeruginosa* was resistant to compound 6e. The MICs of the compounds are low when compared to the standard drugs, and since the bacteria strains used in these tests are actually very resistance to conventional drugs, these compounds could serve as lead for multi-resistant bacteria drugs [25].

<table>
<thead>
<tr>
<th>Bacteria strain</th>
<th>E.coli 1</th>
<th>E.coli 2</th>
<th>Klebsiella pneumonia</th>
<th>Staphylococcus aureus</th>
<th>Pseudomonas aeruginosa</th>
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<tr>
<td>Compounds</td>
<td>IZD (mm)</td>
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<tr>
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<td>14</td>
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<td>14</td>
<td>1.41</td>
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<tr>
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<td>0.16</td>
<td>18</td>
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<tr>
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<td>0.32</td>
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4. CONCLUSION

The Syntheses of alkynylated quinoline-5,8-diones have been achieved successfully using modified Sonogashira protocol. The assigned structures were supported by the spectra data. The alkynylated quinoline-5,8-diones have good antibacterial activity against some of the tested organisms. However, there is need for further research in order to determine the toxicity of the synthesized products since they show signs of potential antimicrobial drugs.

5. ACKNOWLEDGEMENTS

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6. REFERENCES


