








Design and Synthesis of Two Azete Derivatives Using some Chemical Strategies

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Abstract: There are several methods for preparing nitrogen-containing four-membered heterocycles using some reagents that require special conditions such as higher temperatures or differences in the pH. This research aimed to prepare two azete derivatives from 1-Bromo-3,5-dinitrobenzene using some chemical strategies. The chemical structure was characterized by NMR spectroscopic methods. The results indicate that protocols used to synthesize two azete analogs do not require special conditions to give a good yielding. In conclusion, is reported a facile method for the synthesis of two azete derivatives.

Keywords: azete; synthesis; four-membered; heterocyclic.

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1. Introduction

For several years, heterocycles have been of great interest in both biological and chemical fields [1-4]. In this way, several methods have been used for its preparation., for example, azete derivative synthesis from 4-phenylbenzo-1,2,3-triazine under extreme conditions (420 to 450 °C) [5]. Besides, a report showed the intramolecular reaction of *O*-tert-propargylic oximes in the presence of a Chloro(1,5-cyclooctadiene)copper(I) dimer to form an azete-*N*-oxide [6]. Other data display the preparation of an azete derivative by thermolysis of the cyclopropenyl azide [7]. In addition, an azete derivative was synthesized from α -(*O*-nitroaryl)benzylphosphonate, potassium tert-butoxide, and tetrahydrofuran [8]. Other data showed the synthesis of an azete analog from a cyclopenta[a]phenanthren-17-one derivative, 4-Nitrophenylacetonitrile, and CopperII chloride [9]. In addition, a 4-sulfoniminoazet-2-amine was prepared using the three-component system (alkyne, sulfonyl azide, and tetramethylguanidine) in the presence of copper(I) iodide [10]. Recently, an azete-steroid derivative was prepared via an intramolecular reaction of methylidene(methylsulfanyl)amine with an alkyne-derivative using copper(II) chloride as catalyst [11]. All these data show several protocols for synthesizing some nitrogen-containing four-membered heterocycles that require

special conditions such as higher temperatures and different pHs. This study aimed to prepare two azete derivatives using some chemical strategies.

2. Materials and Methods

2.1. General method.

Starting materials were purchased from commercial suppliers (Sigma-Aldrich). 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 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. Synthesis.

6-(3,5-Dinitro-phenyl)-hex-5-yn-1-ol (2)

A solution of 1-Bromo-3,5-dinitro-benzene (200 mg, 0.81 mmol), 5-hexyn-1-ol (100 μl , 0.91 mmol), Copper(II) chloride anhydrous (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using chloroform:hexane (3:1) system; yielding 63% of product; m.p. 86-88 °C; IR (V_{max} , cm^{-1}) 3400 and 1542; ^1H NMR (300 MHz, CDCl_3 -*d*) δ_{H} : 1.60-1.62 (m, 4H), 1.96 (broad, 1H), 2.26-3.64 (m, 4H), 8.52-8.96 (m, 3H) ppm. ^{13}C NMR (300 Hz, CDCl_3) δ_{C} : 19.70, 25.74, 31.82, 62.20, 73.30, 88.80, 121.32, 121.72, 135.74, 147.92 ppm. EI-MS *m/z*: 264.07. Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_5$: C, 54.55; H, 4.58; N, 10.60; O, 30.28. Found: C, 54.52; H, 4.55

11-Nitro-2-oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne (3)

A solution of compound **2** (200 mg, 0.75 mmol), potassium carbonate (110 mg, 0.79 mmol) in dimethyl sulfoxide (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:agua (3:1) system; yielding 44% of product; m.p. 66-68 °C; IR (V_{max} , cm^{-1}) 1542 and 1210; ^1H NMR (300 MHz, CDCl_3 -*d*) δ_{H} : 1.00-3.96 (m, 8H), 6.74-7.74 (m, 3H) ppm. ^{13}C NMR (300 Hz, CDCl_3) δ_{C} : 19.20, 25.82, 26.64, 67.34, 76.42, 89.92, 108.72, 118.60, 122.96, 125.92, 144.10, 155.72 ppm. EI-MS *m/z*: 217.07. Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{NO}_3$: C, 66.35; H, 5.10; N, 6.45; O, 22.10. Found: C, 66.32; H, 5.08.

1-(2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yn-11-yloxy)-naphthalen-2-ol (4)

A solution of compound **3** (200 mg, 0.92 mmol), 1-Nitro-naphthalen-2-ol (175 mg, 0.92 mmol), potassium carbonate (130 mg, 0.93 mmol) in dimethyl sulfoxide (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:hexane:benzene (3:1:1) system; yielding 52% of product; m.p. 120-122 °C; IR (V_{max} , cm^{-1}) 3402 and 1212; ^1H NMR (300 MHz, CDCl_3 -*d*) δ_{H} : 1.00-3.96 (m, 8H), 6.34-6.64 (m, 3H), 6.89 (broad, 1H), 7.22-8.10 (m, 6H) ppm. ^{13}C NMR (300 Hz, CDCl_3) δ_{C} : 19.20, 25.80, 26.62, 67.34, 78.36, 89.92, 107.22, 112.42, 117.42, 119.22, 120.72,

121.92, 124.74, 124.82, 125.09, 126.12, 126.49, 129.90, 134.16, 146.10, 161.72, 162.10 ppm. EI-MS *m/z*: 330.12. Anal. Calcd. for C₂₂H₁₈O₃: C, 79.98; H, 5.49; O, 14.53. Found: C, 79.95; H, 5.46.

11-[2-(1-Phenyl-but-3-enyloxy)-naphthalen-1-yloxy]-2-oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne (5)

A solution of compound **4** (200 mg, 0.60 mmol), 1-Phenyl-but-3-en-1-ol (110 μ l, 0.73 mmol), potassium carbonate (130 mg, 0.93 mmol) in dimethyl sulfoxide (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:agua (4:1) system; yielding 48% of product; m.p. 110-112 °C; IR (*V*_{max}, cm⁻¹) 1582 and 1212: ¹H NMR (300 MHz, CDCl₃-*d*) δ _H: 1.00-2.00 (m, 6H), 2.18-2.34 (m, 2H), 3.90-3.96 (m, 2H), 4.96 (m, 1H), 5.14-5.90 (m, 3H), 6.36-6.66 (m, 3H), 7.20-7.40 (m, 3H), 7.44 (m, 1H), 7.48 (m, 2H), 7.60-8.10 (m, 5H) ppm. ¹³C NMR (300 Hz, CDCl₃) δ _C: 19.20, 25.80, 26.62, 44.22, 67.34, 78.36, 81.37, 89.92, 107.95, 113.14, 114.46, 117.40, 118.66, 119.98, 122.16, 122.80, 123.70, 125.02, 126.54, 127.74, 127.96, 128.32, 129.85, 132.30, 138.66, 141.70, 149.92, 151.00, 161.64, 163.14 ppm. EI-MS *m/z*: 460.20. Anal. Calcd. for C₃₂H₂₈O₃: C, 83.45; H, 6.13; O, 10.42. Found: C, 83.42; H, 10.40.

11-(2-Hex-5-ynyloxy-naphthalen-1-yloxy)-2-oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne (6)

A solution of compound **4** (200 mg, 0.60 mmol), 5-hexyn-1-ol (70 μ l, 0.63 mmol) potassium carbonate (70 mg, 0.50 mmol) in dimethyl sulfoxide (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:hexane (3:1) system; yielding 54% of product; m.p. 134-136 °C; IR (*V*_{max}, cm⁻¹) 2138 and 1210: ¹H NMR (300 MHz, CDCl₃-*d*) δ _H: 1.00 (m, 2H), 1.62-1.84 (m, 4H), 1.94 (s, 1H), 1.96-2.00 (m, 3H), 2.22 (m, 2H), 3.94-3.96 (m, 2H), 4.20 (m, 2H), 6.36-6.66 (m, 3H), 7.40-8.10 (m, 6H) ppm. ¹³C NMR (300 Hz, CDCl₃) δ _C: 18.06, 19.20, 25.02, 25.80, 26.62, 28.94, 67.34, 68.62, 70.22, 78.44, 84.13, 89.89, 107.92, 113.14, 117.40, 117.76, 119.94, 122.00, 123.86, 123.92, 126.54, 128.32, 129.88, 130.80, 148.96, 150.78 161.64, 163.30 ppm. EI-MS *m/z*: 410.18. Anal. Calcd. for C₂₈H₂₆O₃: C, 81.92; H, 6.38; O, 11.69. Found: C, 81.90; H, 6.35.

{4-[1-(2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yn-11-yloxy)-naphthalen-2-yloxy]-phe-nyl}-acetonitrile (7)

A solution of compound **4** (200 mg, 0.60 mmol), (4-Nitro-phenyl)-acetonitrile (100 mg, 0.61 mmol) potassium carbonate (70 mg, 0.50 mmol) in dimethyl sulfoxide (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the hexane:methanol (1:2) system; yielding 55% of product; m.p. 108.110 °C; IR (*V*_{max}, cm⁻¹) 3320 and 1212: ¹H NMR (300 MHz, CDCl₃-*d*) δ _H: 1.00-2.00 (m, 6H), 3.62 (m, 2H), 3.92-6.72 (m, 5H), 7.22-7.35 (m, 4H), 7.50-8.22 (m, 6H) ppm. ¹³C NMR (300 Hz, CDCl₃) δ _C: 19.20, 23.42, 25.80, 26.63, 67.38, 78.42, 89.92, 104.00, 109.23, 115.82, 117.30, 117.40, 117.44, 121.45, 122.46, 122.54, 123.10, 123.94, 124.34, 125.12, 125.62, 125.68, 126.20, 136.30, 143.84, 157.52, 161.80, 164.32 ppm. EI-MS *m/z*: 445.16. Anal. Calcd. for C₃₀H₂₃NO₃: C, 80.88; H, 5.20; N, 3.14; O, 10.77. Found: C, 80.85; H, 5.17.

2-[2-[[1-(2-oxabicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yn-11-yloxy)-2-na-phthyl]oxy]-2-phe-nyl-ethyl]-4-[[4-[[1-(2-oxabicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yn-11-yloxy)-2-naphthyl]oxy]phenyl]methyl]-2,3-dihydroazete (8)

A solution of compound **5** (200 mg, 0.43 mmol), compound **7** (195 mg, 0.43 mmol), Copper(II) chloride (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:agua (4:1) system; yielding 65% of product; m.p. 144-146 °C; IR (V_{\max} , cm^{-1}) 3320 and 1212: ^1H NMR (300 MHz, CDCl_3 -*d*) δ_{H} : 1.00-1.96 (m, 8H), 1.98 (m, 1H), 2.00 (m, 2H), 2.26 (m, 1H), 2.32-2.82 (m, 4H), 3.56 (m, 2H), 3.92-3.96 (m, 2H), 4.66-5.06 (m, 3H), 5.50 (m, 1H), 5.70 (m, 1H), 6.30-6.72 (m, 5H), 6.88-6.96 (m, 4H), 7.32 (m, 3H), 7.42-7.50 (m, 2H), 7.52 (m, 2H), 7.60-8.26 (m, 10H) ppm. ^{13}C NMR (300 Hz, CDCl_3) δ_{C} : 19.20, 25.80, 26.62, 33.42, 40.32, 42.70, 45.96, 67.34, 78.42, 79.24, 89.92, 104.00, 107.98, 109.22, 113.16, 114.70, 115.82, 117.44, 118.34, 119.94, 121.42, 122.12, 122.54, 122.81, 123.13, 123.70, 124.31, 124.37, 125.12, 125.62, 125.68, 125.80, 126.22, 126.52, 126.60, 127.60, 128.34, 129.16, 129.82, 133.10, 136.30, 139.92, 143.86, 149.58, 151.00, 157.54, 161.64, 162.10, 164.26, 166.02 ppm. EI-MS m/z : 905.37. Anal. Calcd. for $\text{C}_{62}\text{H}_{51}\text{NO}_6$: C, 82.19; H, 5.67; N, 1.55; O, 10.59. Found: C, 82.16; H, 5.64.

2-[4-[[1-(2-oxabicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yn-11-yloxy)-2-naphthyl]oxy]butyl]-4-[[4-[[1-(2-oxabicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yn-11-yloxy)-2-naphthyl]oxy]phenyl]methyl]azete (9)

A solution of compound **6** (200 mg, 0.48 mmol), compound **7** (220 mg, 0.48 mmol), Copper(II) chloride (120 mg, 0.89 mmol) in methanol (5 ml) was stirring for 48 h at room temperature. Then the solvent is evaporated on a rotary evaporator and the product is separated using the chloroform:agua (4:1) system; yielding 63% of product; m.p. 128-130 °C; IR (V_{\max} , cm^{-1}) 3322 2 and 1210: ^1H NMR (300 MHz, CDCl_3 -*d*) δ_{H} : 1.00-1.30 (m, 4H), 1.52 (m, 2H), 1.62 (m, 2H), 1.68 (m, 2H), 1.94-2.35 (m, 6H), 2.72 (m, 2H), 2.82 (m, 2H), 3.70 (m, 2H), 3.90-3.94 (m, 2H), 4.12 (m, 2H), 4.96 (d, 1H, $J = 1.79$ Hz), 5.50-6.74 (m, 6H), 6.90-6.96 (m, 4H), 7.40-8.28 (m, 12H) ppm. ^{13}C NMR (300 Hz, CDCl_3) δ_{C} : 19.20, 21.90, 25.80, 26.62, 28.00, 31.34, 45.54, 67.34, 68.50, 78.36, 89.92, 104.00, 107.95, 109.20, 111.34, 113.12, 115.70, 115.84, 117.42, 117.78, 119.94, 121.42, 122.00, 122.54, 123.12, 123.84, 123.92, 124.37, 125.12, 125.62, 125.68, 126.17, 126.20, 126.50, 126.55, 128.34, 129.92, 130.80, 136.30, 143.87, 148.96, 150.74, 153.60, 157.54, 161.64, 162.08, 163.32, 164.24, 165.90 ppm. EI-MS m/z : 445.16. Anal. Calcd. for $\text{C}_{58}\text{H}_{49}\text{NO}_6$: C, 81.38; H, 5.77; N, 1.64; O, 11.21. Found: C, 81.35; H, 5.74.

2.3. Physicochemical properties.

Theoretical electronic parameters, such as HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) energy, orbital coefficients distribution, molecular dipole moment, HBD (hydrogen bond donor groups), HBA (hydrogen bond acceptor groups), and TPSA (topological polar surface area) were evaluated using SPARTAN (v.1.4) software [12-15].

2.4. Pharmacophore model.

The 3D-pharmacophore model for both compounds **8** and **9** was determined using LigandScout 4.08 software [16-18].

3. Results and Discussion

There are some protocols for the synthesis of some azete derivatives which require special conditions [5-11]. Analyzing these data, this study aimed to prepare two azete analogs using some chemical tools as follows:

3.1. Coupling of terminal alkynes with benzyl bromide.

There are several studies for the addition of benzyl halide to terminal alkyne using several reagents such as CuI [19], SIMesCuCl [20], Gold(I) [21], Pd/Ni [22]. However, some protocols require different pH and high temperatures. In this investigation, 1-Bromo-3,5-dinitro-benzene reacted with 5-hexyn-1-ol (in the presence of Copper(II) chloride (Figure 1) to form the hexynol (**2**). The ¹H NMR spectra from **2** showed different bands at 1.00-1.62 and 2.26-3.64 ppm for methylene groups bound to both alkyne and hydroxyl groups; at 1.96 ppm for hydroxyl group; at 8.52-8.96 ppm for phenyl group. ¹³C NMR spectra showed chemical shifts at 19.70-62.20 ppm for methylene groups bound to both alkyne and hydroxyl groups; at 73.30-88.80 ppm for alkyne group; at 121.32-147.92 ppm for phenyl group. Besides, the mass spectrum from **2** displays a molecular ion (m/z) at 264.07.

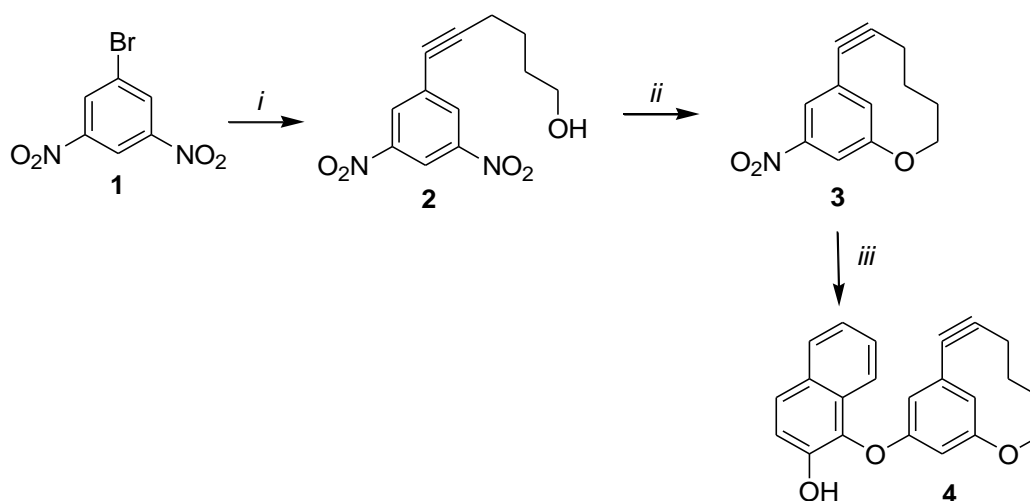


Figure 1. Synthesis of an naphthalenol derivative (**4**). *Reagents and conditions:* *i* = 5-hexyn-1-ol, (Copper(II) chloride, MeOH, room temperature; *ii* = K₂CO₃, DMSO, room temperature; *iii* = 1-Nitro-naphthalen-2-ol, K₂CO₃, DMSO, room temperature. DMSO = dimethyl sulfoxide.

3.2. Preparation of ether derivatives.

Several methods have been employed to the synthesis of some ether analogs using different reagents, such as *p*-toluenesulfonic acid [23], Tetrabutylammonium bromide [24], Cu/ZnO/ZrO₂ [25], lithium aluminum hydride [26]. Besides, other reports have shown the synthesis of ether derivatives via the nitro group's displacement in the presence of dimethyl sulfoxide [27]. In the first stage, compound **3** was prepared from compounds **2** and dimethyl sulfoxide in mild conditions. (Figure 1). The ¹H NMR spectra from **3** different display bands at 1.00-3.96 ppm for methylene groups linked to both alkyne and ether groups; at 6.74-7.74

ppm for phenyl group. ^{13}C NMR spectra showed chemical shifts at 19.20-89.92 for methylene groups bound to both alkyne and ether groups; at 108.72-155.72 ppm for phenyl group. In addition, the mass spectrum from **3** displays a molecular ion (m/z) at 217.07.

The second stage was achieved through reaction of **3** with 1-Nitro-naphthalen-2-ol in the presence of dimethylsulfoxide to form compound **4** (Figure 1). The ^1H NMR spectra from **4** showed several signals at 1.00-6.64 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 6.89 ppm for hydroxyl group; at 7.22-8.10 ppm for naphthalene fragment. ^{13}C NMR spectra showed chemical shifts at 19.20-117.42, 126.90 and 161.72-162.10 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 119.22-126.49 and 134.16-146.10 ppm for naphthalene fragment. Additionally, the mass spectrum from **4** displays a molecular ion (m/z) at 330.12.

The third stage involves the synthesis of compounds **5** from **4** and 1-Phenyl-but-3-en-1-ol, dimethyl sulfoxide in mild conditions (Figure 2).

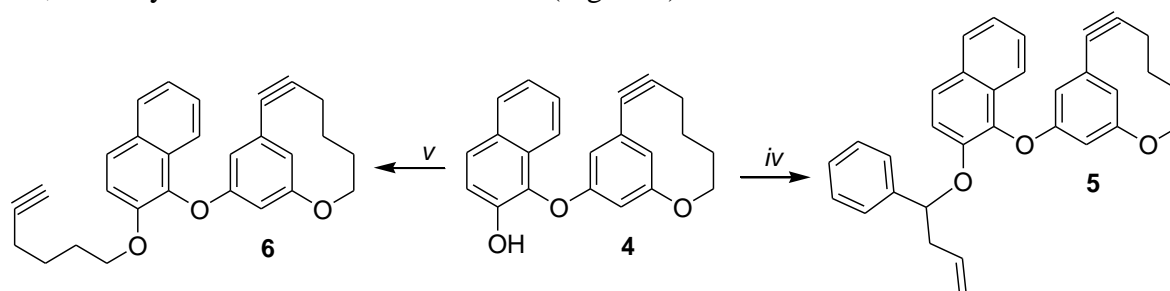


Figure 2. Synthesis of two 2-oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne derivatives (**5** and **6**).

Reagents and conditions: *iv* = 1-Phenyl-but-3-en-1-ol, K_2CO_3 , DMSO, room temperature; *v* = 5-hexyn-1-ol, (K_2CO_3 , DMSO, dimethyl sulfoxide, room temperature. DMSO, dimethyl sulfoxide

The ^1H NMR spectra from **5** showed several signals at 1.00-2.00, 3.90-3.96 and 6.36-6.66 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 2.18-2.34 and 4.96 for methylene groups bound to both alkene and phenyl groups; at 5.14-5.90 for alkene group; at 7.20-7.40 and 7.48 ppm for phenyl group; at 7.44 and 7.60-8.10 ppm for naphthalene fragment. ^{13}C NMR spectra showed chemical shifts at 19.20-26.62, 67.34-78.36, 89.92-113.14, 117.40, 129.85 and 161.64-163.14 for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 44.22 and 81.37 ppm for methylene groups linked to both alkene and phenyl groups; at 114.46, 141.70 ppm for alkene group; at 118.66-123.70, 126.54, 128.32, 132.30 and 149.92-151.00 ppm for naphthalene fragment; at 125.02, 127.74-127.96 and 138.66 ppm for phenyl group. Besides, the mass spectrum from **5** displays a molecular ion (m/z) at 460.20.

The fourth stage was achieved through of reaction of **4** with 5-hexyn-1-ol in the presence of dimethyl sulfoxide to form compound **6** (Figure 2). The ^1H NMR spectra from **6** showed several signals at 1.00-2.00, 3.94-3.96 and 6.36-6.66 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 1.62-1.84, 2.22 and 4.20 ppm for methylene groups linked to both ether and alkyne groups; at 1.94 ppm for alkyne group; at 7.40-8.10 ppm for naphthalene fragment. ^{13}C NMR spectra showed chemical shifts at 18.05, 25.02-28.94 and 70.22 ppm for methylene groups bound to both ether and alkyne groups; at 19.20, 25.80-26.62, 67.34, 78.44, 89.89-117.40, 129.88 and 161.64-163.30 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 68.62 and 84.13 ppm for alkyne group; at 117.76-128.32 and 130.80-150.78 ppm for naphthalene group. Finally, the mass spectrum from **6** displays a molecular ion (m/z) at 410.18.

The fifth stage involves the reaction of **4** with 1-Nitro-4-prop-2-ynyl-benzene in the presence of dimethyl sulfoxide to form compound **7** (Figure 3).

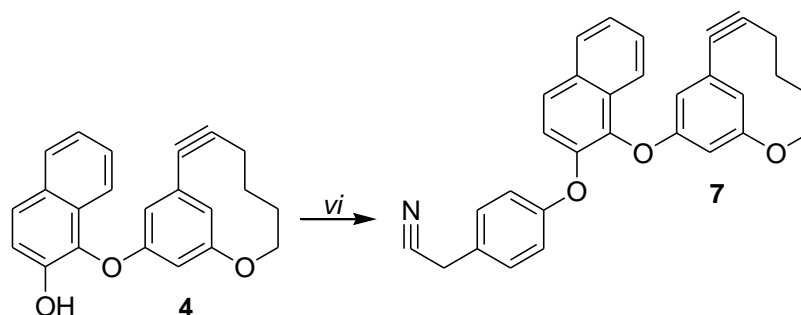


Figure 3. Synthesis of a naphthalen-2-yloxy]-phenyl}-acetonitrile derivative (**7**). *Reagents and conditions:* *vi* = (4-Nitro-phenyl)-acetonitrile, K_2CO_3 , DMSO, room temperature. DMSO, dimethyl sulfoxide

The 1H NMR spectra from **7** showed several signals at 1.00-2.00 and 3.92-6.72 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 3.62 ppm for methylene group bound to both cyanide and phenyl groups; at 7.22-7.35 ppm for phenyl group; at 7.50-8.22 ppm for naphthalene fragment. ^{13}C NMR spectra showed chemical shifts at 19.20, 25.80-109.23, 117.44, 125.68 and 157.52-164.32 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragment; at 23.42 ppm for methylene bound to both phenyl and cyanide groups; at 115.12, 121.45, 122.54-123.10, 124.34-125.62 and 126.20-143.84 ppm for naphthalene fragment; at 117.30, 122.46 and 123.94 for phenyl group; at 117.40 for cyanide group. Besides, the mass spectrum from **7** displays a molecular ion (m/z) at 445.16.

3.3. Synthesis of an azetidine derivative.

There are some methods for the synthesis of azetidine derivatives using some reagents such as Copper(II) chloride [11], tetrakis(acetonitrile)copper(I) tetrafluoroborate [28], 1-azabicyclo[1.1.0]butanes [29], p-toluenesulfonyl chloride [30]. This stage was achieved by preparing compound **8** via reaction of **5** with compound **7** using Copper(II) chloride as catalyst (Figure 4).

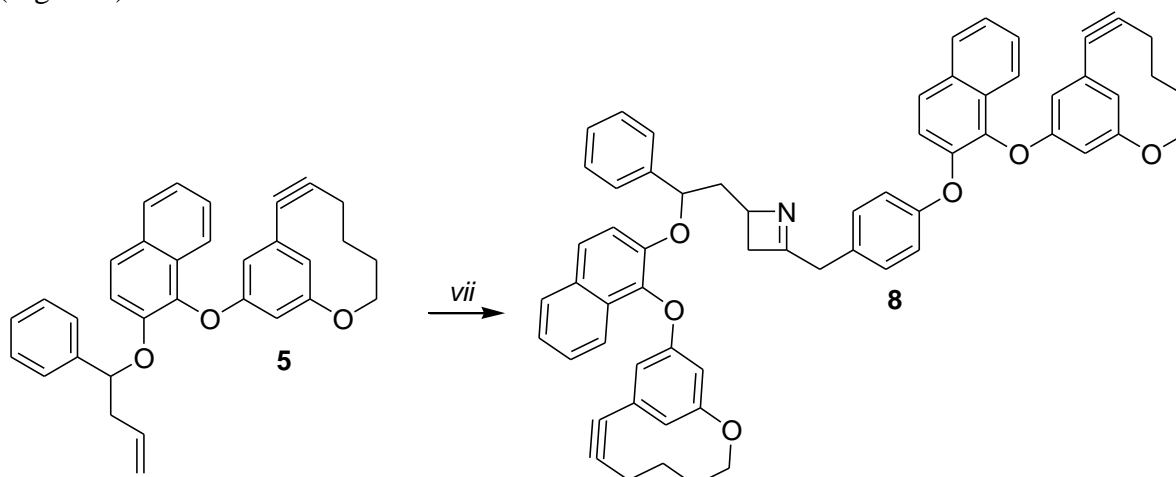


Figure 4. Synthesis of a 2,3-dihydro-azete derivative (**8**). *Reagents and conditions:* *vii* = 2-oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne derivative (**5**), naphthalen-2-yloxy]-phenyl}-acetonitrile derivative (**7**), Copper(II) chloride, room temperature.

The 1H NMR spectra from **8** showed several signals at 1.00-11.96, 2.00, 2.32-2.82, 3.92-3.96, 5.50, 6.30-6.72 and 7.42-7.50 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragments; at 1.98, 2.26 and 5.70 ppm for methylene groups bound to both azete ring and ether groups; at 3.56 ppm for phenyl group linked to methylene group; at 4.66-5.06

ppm for azete ring; at 6.88-6.96, 7.32 and 7.52 ppm for phenyl groups bound to ether groups at 7.60-8.26 ppm for naphthalene fragment. ^{13}C NMR spectra showed chemical shifts at 19.20-26.62, 67.34-78.42, 88.92-113.16, 117.44, 125.68, 129.82, 157.54-161.64 and 164.26 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragments; at 40.32, 45.96 and 79.24 ppm for phenyl groups linked to ether groups; at 114.70, 125.80, 126.60 and 162.10 ppm for phenyl group bound to ether group; at 115.82, 118.34-123.70, 124.37-125.62 126.22-126.52, 128.34, 133.10-136.30 and 143.86-151.00 ppm for naphthalene fragments; at 124.31, 127.60, 129.16 and 139.92 for phenyl group bound to methylene group. In addition, the mass spectrum from **8** displays a molecular ion (m/z) at 905.37.

Preparation of an azete derivative

Several studies have showed the preparation of some azete analogs using some reagents such as $\text{Rh}_2(\text{OAc})_4$ [31], *N*-nitrenes [32], 2,3-dibromopropylamine [33], 1-aminoacetylenes [34]. In this investigation, an azete derivative (**9**) was synthesized. This stage was achieved via 2 + 2 addition of **6** to compound **7** in the presence of copper(II) chloride (Figure 5). The ^1H NMR spectra from **9** showed several signals at 1.00-1.30, 1.62, 1.94-2.35, 2.82, 3.90-3.94 and 5.50-6.74 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragments; at 1.52, 1.68, 2.72 and 4.12 ppm for methylene groups bound to both azete ring and ether group; at 3.70 ppm for methylene group bound to azete ring; at 4.96 ppm for azete ring; at 6.90-6.96 ppm for phenyl group; at 7.40-8.18 ppm for naphthalene fragments. ^{13}C NMR spectra showed chemical shifts at 19.20, 25.80-26.62, 67.34, 78.36-109.20, 113.12, 125.68, 117.42-125.62, 129.92, 157.54-161.64 and 163.32-164.24 ppm for 2-Oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne fragments; at 21.90, 28.00-31.34 and 68.50 ppm for methylene groups bound to both azete ring and ether group; at 45.54 ppm for methylene group bound to azete ring; at 11.34, 153.60 and 165.90 ppm for azete ring; at 115.70, 126.17, 126.55 and 162.08 ppm for phenyl group; at 115.84, 117.78, 126.20-126.50, 128.34 and 130.80-150.74 ppm for naphthalene fragments. Besides, the mass spectrum from **9** displays a molecular ion (m/z) at 855.35.

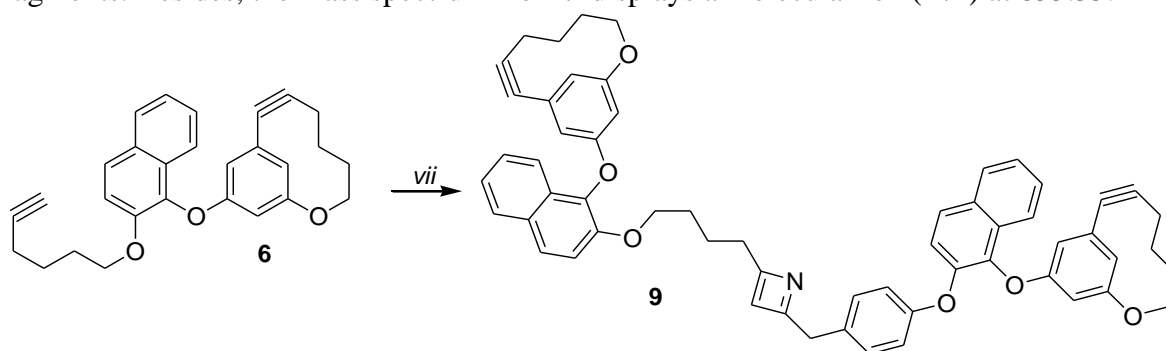


Figure 5. Synthesis of a 2-naphthyl-oxy-phenyl-methyl-azete derivative (**9**). *Reagents and conditions:* *vii* = 2-oxa-bicyclo[7.3.1]trideca-1(12),9(13),10-trien-7-yne derivative (**6**), naphthalen-2-yloxy-phenyl-acetonitrile derivative (**7**), Copper(II) chloride, room temperature.

3.4. Electronic factors.

The molecular orbitals and their physicochemical properties, such as energy and the frontier electronic density, have been used to predict the reactivity of several compounds, which involves the π -electron system and several types of reactions on conjugated systems [35]. Some studies suggest that the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) values and their energy gap could be related to the

chemical activity of several compounds. By analyzing these data, both HOMO and LUMO involved in the chemical structure of either compounds **8** or **9** were evaluated in this study. The results showed that the HOMO-LUMO gap values were different for **8** compared to **9** (Figure 6 and Table 1). This process could be conditioned by π orbital, which is localized in either 2,3-Dihydro-azete or azete rings.

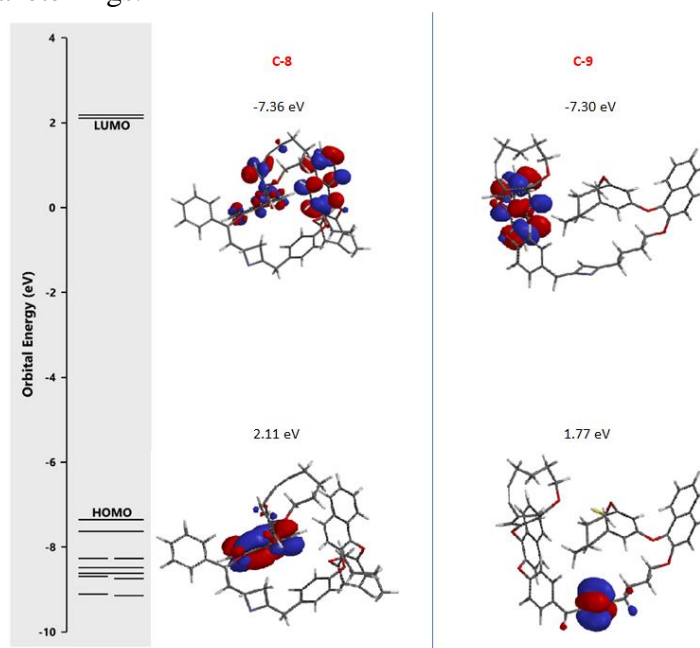


Figure 6. Molecular orbitals (HOMO and LUMO) involved in the compounds **8** (left) and **9** (right), visualized with SPARTAN'06 software

Table 1. Physicochemical parameters involved in the chemical structure of compounds **8** and **9**. The values were calculated using Spartan software.

Parameters	Compounds	
	8	9
HOMO (eV)	-7.36	-7.30
LUMO (eV)	2.11	1.77
LogP	12.98	11.73
HBD	0	0
HBA	7	7

3.5. Pharmacophore ligand model.

Some chemical models have been used to determine the three-dimensional orientation adopted by the functional groups of several compounds to predict its binding with different biomolecules [36]. In this way, in this research, a pharmacophore model for both compounds **8** and **9** was determined using the LigandScout 4.1 (Figure 7). The data indicate that functional groups of compounds **8** and **9** could interact via hydrophobic contacts, hydrogen bond acceptors, or hydrogen bond donors with some biomolecules.

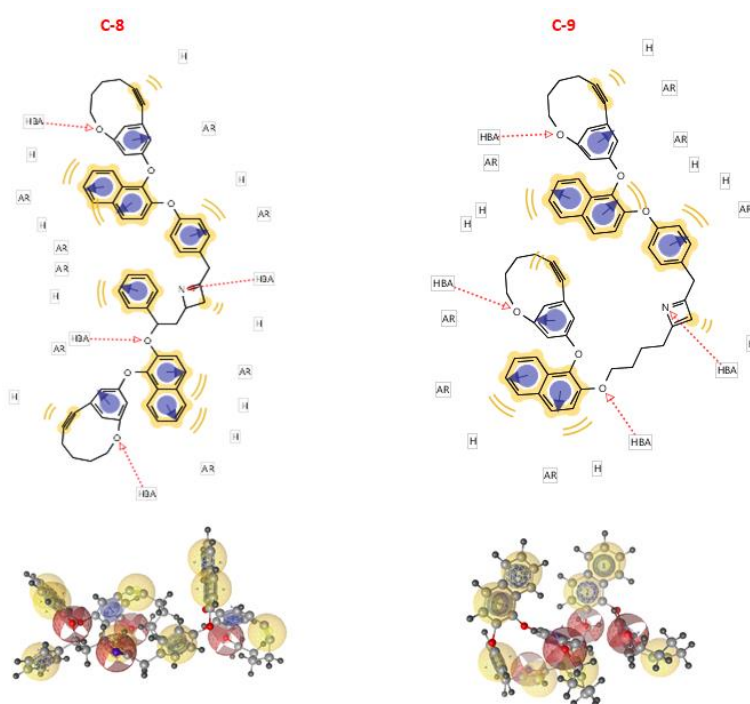


Figure 7. The scheme representing a pharmacophore from both compounds 8 (left) and 9(right) using the LigandScout 4.1 software. The model involves a methyl group (yellow), hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, yellow).

4. Conclusions

This research reports the synthesis of two azete derivatives that do not require special conditions to give a good yielding. Besides, the differences of parameters electronic such as HOMO and LUMO values and their energy gap may be associated with the chemical activity produced by these compounds; this is supported by other studies carried out in some biological models [37, 38].

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Conflicts of Interest

The authors declare no conflict of interest.

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