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Preparation of three Diazocin-derivatives via disconnection A-ring from progesterone.

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ABSTRACT

*Several diazocine-derivatives have been synthesized using several reagents; however, some agents are dangerous and require special conditions. The aim of this study was to synthesize three diazocin-derivatives using progesterone (**1**) as a chemical tool. The first stage was achieved via disconnection of A-ring from steroid nucleus by the reaction of **1** with $NaIO_4/KMNO_4$ to form an isopropenyl-oxo-propionic acid derivative (**2**). Then, the compound **2** was reacted with ethylenediamine or urea or thiourea using boric acid as catalyst to form the compounds **2**-aminoethyl)imino)ethyl-diazonin-5-ol (**3**) or diazocine-9-yl-ethylidene-urea (**6**) or diazocine-9-yl-ethylidene-thiourea (**7**). Following, **3** or **6** or **7** were reacted with 5-hexyn-3-ol in presence of Copper(II) to form the compounds 2-hydroxybutylidene-diazocinol (**5**) or diazocine-2,4(3H)-dione (**8**) or diazocin-4-one (**9**). Finally, diazocine derivatives such as the 1,4-diazocin-dizonin-5-ol (**10**) or prop-2-yn-1-yl)phenoxy)butylidene-diazocine-2,4(3H)-dione (**11**) or 2-(4-(prop-2-yn-1-yl)phe- noxy)butyl-idene)-2-thioxo- diazocin-4-one (**12**) were prepared by the reaction of the compounds **6** or **7** or **8** with (4-nitro-phenyl)-acetonitrile using CooperII chloride as catalyst. The Spectroscopy analyses NMR was used to confirm the chemical structure of compounds. In conclusion, in this study a facile method to synthesis of three diazocin-derivatives is reported.*
Keywords: *Disconnection, diazocine, 4-nitrophenylacetonitrile, progesterone.*

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INTRODUCTION

The development of several strategies for the synthesis of organic molecules plays a central role in the organic chemistry field; for example, the preparation of a series of 5,1l-methano diben zo[*b,f*][1,5]diazocines by the reaction of (2-amino-benzy1)amines with formaldehyde [1]. Other report showed the synthesis of a pseudopeptidic [(5*H*)-6-oxodibenzo[*b,f*][1,5]diazocine-5-yl]arylglycinamide by an Ugi 4CC/Staudinger/aza-Wittig sequence [2]. In addition, the preparation of 3,4-dihydro-l,6-benzodiazocine-2,5 (lH,6H)-dione was made by the reaction of o-phenyl- enediamine with a diethyl derivative [3]. Other study, shown that cyclobutanone reacts with diphenyl-1,2,4,5-tetrazine to give 3,8-diphenyl-6,7-dihydro-1,2-diazocin-4(5H)-one [4]. Also, a series of 2,4,8,10-tetrahalo-6,12-diaryldibenzo [*b,f*][1,5]diazocines were prepared via reaction 3,5-dihalo-2-aminobenzophenones with pyridine [5]. Other data showed the synthesis of a pyrrolodiazocine derivative from pyrrolopyrazine and methyl propiolate [6]. Additionaly, a study showed the synthesis of the pyrrolo[2,1-*c*][1,4]benzodiazocine via a Dieckmann condensation [7]. Additionally, a report indicated the preparation of benzochromeno-diazocines using the three-component system (3-formylchromones, amines and isatoic anhydride or a

dialkyl acetylenedicarboxylate) [8]. Other report indicate the synthesis of a diazocine from the (2-isocyanato- phenyl)(phenyl)methanone and trifluoroacetic acid [9]. All these experimental results show different methods for the preparation of diazocine derivatives; nevertheless, it is important to mention that some protocols require hazardous reagents as well as different experimental conditions for the preparation of these compounds. Therefore, in this study three diazocine derivatives were prepared using some chemical strategies.

MATERIALS AND METHODS

General Methods

The compounds used in this work were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

Synthesis of 3-(3-Isopropenyl-3a,6-dimethyl-7-oxo-dode cahydro-cyclopenta[a]naphtalen-6-yl)-propionic acid (2)

A solution of progesterone (200 mg, 0.63 mmol), sodium periodate (130, 0.60 mmol), potassium permanganate (94, 0.60 mmol), sodium carbonate anhydrous (64 mg, 0.60 mmol), in 5 ml of ethanol was stirring at reflux for 72 h. The precipitate was filtered, washed with water and the filtrate was acidified with 5M HCl and extracted with dichloromethane. The organic phase was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water (4:1) yielding 55 % of product, m.p. 172-174 ^{o}C; IR (V_{max}, cm^{-1}): 1712 and 1380; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.78 (s, 3H), 0.98 (s, 3H), 1.22-1.62 (m, 7H), 1.66 (m, 1H), 1.68-1.70 (m, 2H), 1.71 (m, 1H), 1.72-2.10 (m, 4H), 2.14 (s, 3H), 2.32 (m, 1H), 2.40 (m, 2H), 2.48-2.74 (m, 2H), 11.50 (broad, 1H) ppm. ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 15.00 (C-14), 17.20 (C-18), 20.94 (C-5), 23.08 (C-8), 24.42 (C-9), 26.04 (C-19), 29.90 (C-10), 30.82 (C-23), 32.72 (C-20), 33.68 (C-3), 36.01 (C-11), 38.62 (C-6), 44.28 (C-1), 51.22 (C-13), 53.30 (C-4), 58.88 (C-2), 64.00 (C-7), 177.35 (C-21), 208.42 (C-15), 215.40 (C-12) ppm. EI-MS m/z: 334.21 Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; O, 19.14. Found: C, 71.74; H, 9.00.

Preparation of (1Z,4E,7aR,9aS)-10-(E)-1-((2-aminoethyl) imino)ethyl)-7a,9a-dimethyl-2,3,6,7,7a, 7b,8,9, 9a,10,11,12, 12a,12b,13,14-hexadecahydrocyclopenta[5,6]naphto[2,1-e][1,4]diazonin-5-ol (3).

A solution of **2** (167 mg, 0.50 mmol), ethylenediamine (90 µl, 1.5 mmol), and boric acid (50 mg, 0.80 mmol), in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water (3:1) yielding 66 % of product, m.p. 118-120 ^{o}C; IR (V_{max}, cm^{-1}): 3430 and 3400; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.68 (m, 1H), 0.86 (s, 3H), 1.00 (s, 3H), 1.22-1.70 (m, 6H), 1.80 (s, 3H), 1.82-1.88 (m, 3H), 1.90 (m, 2H), 1.96-2.40 (m, 4H), 2.50 (m, 2H), 2.60-2.64 (m, 2H), 3.10-3.50 (m, 4H), 4.40-4.44 (m, 4H), 4.68 (broad, 3H) ppm. ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 13.20 (C-22), 16.70 (C-29), 17.36 (C-21), 20.70 (C-12), 26.44 (C-19), 26.62 (C-18), 31.54 (C-17), 33.17 (C-14), 33.20 (C-15), 34.10 (C-8), 34.77 (C-16), 38.12 (C-11), 39.62 (C-6), 41.00 (C-27), 42.82 (C-10), 48.60 (C-2), 51.54 (C-3), 51.59 (C-9), 52.40 (C-7), 53.12 (C-26), 63.14 (C-20), 156.70 (C-24), 162.60 (C-13), 183.80 (C-5) ppm. EI-MS m/z: 430.32 Anal. Calcd. for $C_{24}H_{40}N_4O$: C, 71.96; H, 10.06; N, 13.99; O, 3.99. Found: C, 71.82; H, 10.00.

Synthesis of 1-((*E*)-1-((6a*R*,8a*S*,*Z*)-6a,8a-dimethyl-2,4-dioxo-3,4,5,6,6a,6b,7,8,8a,9,10,11, 11a,11b, 12,13-hexadeca hydro-2*H*-cycloocta[5,6]naptho[2,1-*d*][1,3]diazocin-9-yl) ethyli-dene) urea (6).

A solution of **2** (167 mg, 0.50 mmol), urea (50 mg, 1.00 mmol), and boric acid (50 mg, 0.80 mmol), in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water:hexano (4:1:2) yielding 78 % of product, m.p. 88-90 ^{o}C; IR (V_{max}, cm^{-1}): 3420, 3322 and 1680; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (m, 1H), 0.88 (s, 3H), 1.20 (s, 3H), 1.32-1.90 (m, 9H), 1.94 (s, 3H), 1.96 (m, 2H), 2.06-2.40 (m, 4H), 2.68 (m, 2H), 2.94-2.98 (m, 2H), 5.88 (broad, 2H), 9.10 (broad, 1H), ppm. ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 16.04 (C-22), 16.66 (C-23), 20.30 (C-28), 20.70 (C-13), 25.44 (C-18), 26.62 (C-17), 30.64 (C-16), 32.08 (C-6), 32.18 (C-5), 34.07 (C-9), 35.18 (C-15), 37.90 (C-7), 38.16 (C-12), 41.32 (C-11), 51.63 (C-10), 53.17 (C-8), 54.06 (C-19), 158.66 (C-2), 161.30 (C-26), 167.62 (C-4), 182.00 (C-24), 190.70 (C-14) ppm. EI-MS m/z: 400.24 Anal. Calcd. for $C_{22}H_{32}N_4O_3$: C, 65.97; H, 8.05; N, 13.99; O, 11.98. Found: C, 65.90; H, 8.00.

Preparation of 1-((*E*)-1-((6a*R*,8a*S*,*Z*),6a,8a-dimethyl-4-oxo-2-thioxo-3,4,5,6,6a,6b,7,8,8a, 9,10,11, 11a,11b,12,13-hexadecahydro-2*H*-cyclopenta[*5,6*]naphto[2,1-d][1,3]diazocine-9-yl)ethylidene)-thiourea (7).

A solution of **2** (167 mg, 0.50 mmol), tiourea (76 mg, 1.00 mmol), and boric acid (50 mg, 0.80 mmol), in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water (3:2) yielding 70 % of product, m.p. 148-150 ^{o}C; IR (V_{max}, cm^{-1}): 3395, 3322 and 1678; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.88 (s, 3H), 0.96-1.46 (m, 3H), 1.50 (s, 3H), 1.54-1.70 (m, 3H), 1.74 (m, 2H), 1.84-1.98 (m, 5H), 2.06 (s, 3H), 2.14-2.26 (m, 2H), 2.70 (m, 2H), 2.80-2.96 (m, 3H), 7.54 (broad, 2H), 10.30 (broad, 1H) ppm. ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 15.94 (C-22), 16.60 (C-23), 19.78 (C-28), 20.70 (C-13), 25.91 (C-18), 26.62 (C-17), 27.70 (C-7), 31.10 (C-16), 31.54 (C-6), 31.72 (C-5), 34.00 (C-9), 34.84 (C-15), 38.18 (C-12), 42.00 (C-11), 51.63 (C-10), 54.07 (C-19), 54.32 (C-8), 170.34 (C-4), 177.50 (C-24), 181.10 (C-2), 188.30 (C-26), 191.92 (C-14) ppm. EI-MS m/z: 432.20 Anal. Calcd. for $C_{22}H_{32}N_4OS_2$: C, 61.07; H, 7.46; N, 12.95; O, 3.70, S, 14.82. Found: C, 61.00; H, 7.36.

Preparation of (1*Z*,4*E*,7a*R*,9a*S*)-10-((4E,7Z)-7-(2-hydroxy butylidene)-1,2,3,6,7,8-hexahydro-1,4-diazocin-5-yl)-7a,9a-dimethyl-2,3,6,7,7a,7b,8,9,9a,10,11,12,12a,12b,13,14-hexadecahydrocyclo-penta[5,6]naphto[2,1-e][1,4]diazo- nin-5-ol (5)

A solution of **3** (200 mg, 0.50 mmol), 5-hexyn-3-ol (90 µl, 0.81 mmol), and Copper(II) chloride anhydrous (150 mg, 1.11 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water (3:1) yielding 68 % of product, m.p. 142-144 ^{o}C; IR (V_{max}, cm^{-1}): 3430, 3402 and 3324; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.68 (m, 1H), 0.80 (s, 3H), 0.96 (s, 3H), 1.00 (s, 3H), 1.20-1.44 (m, 3H), 1.56-1.58 (m, 2H), 1.70-1.88 (m, 4H), 1.90 (m, 2H), 1.92-2.30 (m, 4H), 2.46 (broad, 3H), 2.50 (m, 2H), 2.52-2.64 (m, 3H), 3.02-3.42 (m, 6H), 3.90 (m, 1H), 3.98 (m, 2H), 4.40-4.44 (m, 4H), 6.14 (d, 1H, J = 0.80 Hz) ppm. ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 9.44 (C-36), 13.23 (C-32), 17.35 (C-34), 20.72 (C-14), 26.62 (C-17), 26.70 (C-16), 27.70 (C-6), 29.72 (C-35), 31.50 (C-18), 33.18 (C-26), 33.20 (C-27), 34.10 (C-12), 34.74 (C-19), 38.16 (C-15), 39.62 (C-28), 42.30 (C-10), 48.22 (C-2), 48.60 (C-23), 49.80 (C-8), 51.57 (C-22), 51.62 (C-11), 52.40 (C-13), 55.32 (C-3), 63.51 (C-9), 67.00 (C-30), 125.94 (C-29), 139.08 (C-7),162.63 (C-25), 164.50 (C-5), 183.80 (C-20) ppm. EI-MS m/z: 496.37 Anal. Calcd. for $C_{30}H_{48}N_4O_2$: C, 72.54; H, 9.74; N, 11.28; O, 6.44. Found: C, 72.46; H, 11.20.

Synthesis of (6a*R*,8a*S*,*Z*)-9-((*Z*)6-(2-hydroxybuthylidene)-2-oxo-2,5,6,7-tetrahydro-1*H*-1,3-diaze-pin-4-yl)-6a,8a-dimethyl-5,6,6a,6b,7,8,8a,9,10,11,11a,11b,12,13-tetradecahydro-2*H*-cyclopenta [5,6]naphto[2,1-*d*][1,3]diazocine-2,4- (3*H*)-dione (8).

A solution of **6** (200 mg, 0.50 mmol), 5-hexyn-3-ol (90 µl, 0.81 mmol), and Copper(II) chloride anhydrous (150 mg, 1.11 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water:hexano (3:2:1) yielding 45 % of product, m.p. 138-140 ^{o}C; IR (V_{max}, cm^{-1}): 3422, 3400 and 1678; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.78 (m, 1H), 0.80 (s, 3H), 0.96 (s, 3H), 1.14 (m, 1H), 1.20 (s, 3H), 1.30-1.44 (m, 3H), 1.56-1.58 (m, 2H), 1.70-1.90 (m, 6H), 196 (m, 2H), 2.06-2.10 (m, 2H), 2.26-2.28 (m, 2H), 2.40-2.42 (m, 2H), 2.68 (m, 2H), 2.94-2.98 (m, 2H), 3.22 (m, 1H), 3.90 (m, 1H), 4.00 (m, 1H), 4.74 (broad, 1H), 6.40 (d, 1H, J = 0.60 Hz), 9.10 (broad, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 9.45 (C-32), 13.22 (C-33), 16.10 (C-36), 20.70 (C-17), 25.78 (C-19), 26.62 (C-20), 29.70 (C-31), 30.60 (C-21), 32.10 (C-29), 32.16 (C-28), 34.00 (C-15), 34.20 (C-6), 35.14 (C-22), 37.14 (C-4), 37.96 (C-30), 38.16 (C-18), 41.60 (C-13), 51.63 (C-14), 53.16 (C-16), 60.60 (C-12), 67.00 (C-10), 126.88 (C-9), 138.80 (C-5), 158.10 (C-2), 158.62 (C-25), 167.60 (C-27), 174.02 (C-7), 190.72 (C-23), ppm. EI-MS m/z: 496.30 Anal. Calcd. for $C_{28}H_{40}N_4O_4$: C, 67.71; H, 8.12; N, 11.28; O, 12.89. Found: C, 67.66; H, 8.08.

(6a*R*,8a*S*,*Z*)-9-((Z)-6-(2-hydroxybuthylidene)-2-thioxo-2, 5,6,7-tetrahydro-1H-1,3-diazepin-4-yl)-6a,8a-dimethyl-2-thioxo-2,3,5,6,6a,6b,7,8,8a,9,10,11,11a,11b,12,13-hexadecahydro-4*H*-cyclopen-ta[*5*,6]naphto[2,1-*d*][1,3]diazocin-4-one (9).

A solution of **7** (200 mg, 0.46 mmol), 5-hexyn-3-ol (90 µl, 0.81 mmol), and Copper(II) chloride anhydrous (150 mg, 1.11 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water:hexano (3:1:1) yielding 66 % of product, m.p. 98-100 ^{o}C; IR (V_{max}, cm^{-1}): 3396, 3458 and 1676; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.80 (s, 3H), 0.94 (m, 3H), 0.96-1.48 (m, 3H), 1.50 (s, 3H), 1.55-1.58 (m, 2H), 1.70 (m, 1H), 1.74 (m, 2H), 1.86-2.28 (m, 8H), 2.58-2.60 (m, 2H), 2.72 (m, 2H), 2.92-

2.96 (m, 3H), 3.00 (m, 1H), 3.10 (broad, 2H), 3.80 (m, 1H), 3.92 (m, 1H), 6.12 (d, 1H, J = 0.80 Hz), 10.30 (broad, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 9.44 (C-32), 13.22 (C-33), 15.94 (C-36), 16.34 (C-6), 20.70 (C-17), 26.20 (C-19), 26.37 (C-6), 26.62 (C-20), 27.73 (C-30), 29.70 (C-31), 31.10 (C-21), 31.55 (C-29), 31.76 (C-28), 34.00 (C-15), 34.84 (C-22), 38.16 (C-18), 42.30 (C-13), 46.14 (C-4), 51.63 (C-14), 54.30 (C-16), 60.30 (C-12), 67.00 (C-10), 123.44 (C-9), 140.82 (C-5), 169.50 (C-7), 170.36 (C-27), 177.52 (C-2), 181.02 (C-25), 191.92 (C-23), ppm. EI-MS m/z: 528.25Anal. Calcd. for $C_{28}H_{40}N_4O_2S_2$: C, 63.60; H, 7.62; N, 10.60; O, 6.05; S, 12.13. Found: C, 63.52; H, 7.54.

Preparation of (1Z,4*E*,7a*R*,9a*S*)-7a,9a-dimethyl-10-((4E,7Z)-7-(2-(4-(prop-2-yn-1-yl)phenoxy) butylidene)-1,2,3,6,7,8-hexahydro-1,4-diazocin-5-yl)-2,3,6,7,7a,7b,8,9, 9a,10,11,12,12a,12b,13,14-hexadecahydrocyclopenta[5,6] naphto [2,1-e][1,4]dizonin-5-ol (10)

A solution of **5** (200 mg, 0.40 mmol), (4-nitro-phenyl)-acetonitrile, potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from methanol:water:hexano (3:1:1) yielding 44 % of product, m.p. 162-164 ^{o}C; IR (V_{max}, cm^{-1}): 3430, 3402, 3320 and 1248; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.68 (m, 1H), 0.80 (s, 3H), 0.98 (s, 3H), 1.00 (s, 3H), 1.22-1.42 (m, 3H), 1.50 (m, 2H), 1.69 (m, 1H), 1.70 (m, 1H), 1.71-1.88 (m, 4H), 1.90 (m, 2H), 1.92-1.96 (m, 2H), 2.06 (s, 1H), 2.08-2.30 (m, 2H), 2.50 (m, 2H), 2.52-2.64 (m, 3H), 3.00-3.06 (m, 4H), 3.12 (broad, 2H), 3.40 (m, 2H), 3.48 (m, 2H), 3.96 (m, 2H), 4.40-4.46 (m, 4H), 4.50 (m, 1H), 6.00 (d, 1H, J = 0.80 Hz) 6.60-7.18 (m, 4H) ppm. ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 9.60 (C-42), 13.26 (C-38), 17.35 (C40), 20.70 (C-14), 25.14 (C-43), 26.62 (C-17), 26.66 (C-16), 28.08 (C-6), 31.18 (C-41), 31.50 (C-18), 33.18 (C-26), 33.20 (C-27), 34.07 (C-12), 34.78 (C-19), 38.16 (C-15), 39.66 (C-28), 42.28 (C-10), 48.20 (C-2), 48.60 (C-23), 50.12 (C-8), 51.53 (C-22), 51.57 (C-11), 52.46 (C-13), 55.36 (C-3), 63.48 (C-9), 71.22 (C-45), 73.56 (C-30), 82.40 (C-44), 117.34 (C-33, C-37), 128.54 (C-34, C-36), 128.66 (C-35), 129.66 (C-29), 139.80 (C-7), 154.00 (C-32), 162.60 (C-25), 164.50 (C-5), 183.80 (C-20) ppm. EI-MS m/z: 610.42 Anal. Calcd. for $C_{39}H_{54}N_4O_2$: C, 76.68; H, 8.91; N, 9.17; O, 5.24. Found: C, 76.56; H, 8.82.

Preparation of (6a*R*,8a*S*,*Z*)-6a,8a-dimethyl-9-((*Z*)-2-oxo-6-(2-(4-(prop-2-yn-1-yl)phe-noxy)butyl-idene)-2,5,6,7-tetrahydro-1H-1,3-diazepin-4-yl)-5,6,6a,6b,7,8,8a,9,10,11,11a,11b,12,13-tetradeca-hydro-2*H*-cyclopenta[5,6]naphto [2,1-*d*][1,3]diazocine-2,4(3H)-dione (11).

A solution of **8** (200 mg, 0.40 mmol), (4-nitro-phenyl)-acetonitrile, potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from methanol:water (3:2) yielding 58 % of product, m.p. 138-140 ^{o}C; IR (V_{max}, cm^{-1}): 3418, 2102, 1676 and 1248; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.78 (m, 1H), 0.80 (s, 3H), 1.00 (s, 3H), 1.20 (s, 3H), 1.30-1.44 (m, 3H), 1.50 (m, 1H), 1.69 (m, 1H), 1.70 (m, 1H), 1.80-1.92 (m, 5H), 196 (m, 2H), 2.04 (s, 1H), 2.06-2.10 (m, 2H), 2.24-2.26 (m, 2H), 2.40-2.42 (m, 2H), 2.66 (m, 2H), 2.94-2.98 (m, 2H), 3.20 (m, 1H), 3.48 (m, 2H), 3.96 (m, 1H), 4.50 (m, 1H), 4.72 (broad, 1H), 6.26 (d, 1H, J = 0.80 Hz), 6.62-7.18 (m, 4H), 9.10 (broad, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 9.60 (C-38), 13.22 (C-42), 16.10 (C-45), 20.70 (C-23), 25.10 (C-39), 25.78 (C-25), 26.60 (C-26), 30.60 (C-27), 31.15 (C-37), 32.06 (C-35), 32.16 (C-34), 34.00 (C-21), 34.60 (C-6), 35.14 (C-28), 37.50 (C-4), 37.94 (C-36), 38.16 (C-24), 41.60 (C-19), 51.63 (C-20), 53.16 (C-22), 60.60 (C-18), 71.20 (C-41), 73.60 (C-10), 82.40 (C-40), 117.34 (C-13, C-17), 128.60 (C-14, C-16), 128.60 (C-15), 130.64 (C-9), 139.50 (C-5), 154.00 (C-12), 158.10 (C-2), 158.66 (C-31), 167.60 (C-33), 174.02 (C-7), 190.72 (C-29), ppm. EI-MS m/z: 610.35 Anal. Calcd. for $C_{37}H_{46}N_4O_4$: C, 72.76; H, 7.59; N, 9.17; O, 10.48. Found: C, 72.68; H, 7.48.

Synthesis of (6a*R*,8a*S*,*Z*)-6a,8a-dimethyl-9-((*Z*)-6-(2-(4-(prop-2-yn-1-yl)phenoxy)butyl-idene)-2-thioxo-2,5,6,7-tetrahydro-1*H*-1,3-diazepin-4-yl)-2-thioxo-2,3,5,6,6a,6b,7,8,8a,9,10,11,11a,11b,12, 13-hexadecahydro-4*H*-cyclopenta [5,6]naphto[2,1-*d*][1,3]diazocin-4-one (12).

A solution of **9** (200 mg, 0.38 mmol), (4-nitro-phenyl)-acetonitrile, potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from methanol:water:hexano (3:2:1) yielding 62 % of product, m.p. 72-74 ^{o}C; IR (V_{max}, cm^{-1}): 3495, 2100 and 1246; ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.80 (s, 3H), 0.94 (m, 1H), 1.00 (s, 3H), 1.40-1.48 (m, 3H), 1.50 (m, 1H), 1.52 (s, 3H), 1.69 (m, 1H), 1.70 (m, 1H), 1.74 (m, 2H), 1.86-1.98 (m, 6H), 2.04 (s, 1H), 2.06-2.28 (m, 2H), 2.54-2.56 (m, 2H), 2.70 (m, 2H), 2.94-2.96 (m, 3H), 2.98 (m, 1H), 3.48 (m, 2H), 3.76 (m, 1H), 4.50 (m, 1H), 5.04 (broad 1H), 6.00 (d, 1H, J = 0.80 Hz), 6.62-7.18 (m, 4H), 10.30 (broad, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ_C: 9.60 (C-38), 13.22 (C-42), 15.94 (C-45), 20.70 (C-23), 25.10 (C-

39), 26.22 (C-25), 26.60 (C-26), 26.70 (C-6), 27.70 (C-36), 31.10 (C-27), 31.15 (C-37), 31.56 (C-35), 31.70 (C-34), 34.00 (C-21), 34.88 (C-28), 38.16 (C-24), 42.30 (C-19), 46.50 (C-4), 51.63 (C-20), 54.30 (C-22), 60.30 (C-18), 71.20 (C-41), 73.60 (C-10), 82.40 (C-40), 117.34 (C-13, C-17), 127.10 (C-9), 128.60 (C-14, C-16), 128.64 (C-15), 141.50 (C-5), 154.00 (C-12), 169.50 (C-7), 170.36 (C-33), 177.52 (C-2), 181.04 (C-31), 191.92 (C-29), ppm. EI-MS m/z: 642.30 Anal. Calcd. for $C_{37}H_{46}N_4O_4S_2$: C, 69.12; H, 7.21; N, 8.71; O, 4.98; S, 9.98. Found: C, 69.06; H, 7.14.

RESULT AND DISCUSSION

Several diazocine derivatives have been synthesized; however, some reagents used for its preparation require special conditions. In this study three diazocine derivatives were synthesized using various strategies. The first stage involves the disconnection of A-ring of progesterone (**1**); it is important to mention that several methods have been used to preparation of different compounds via disconnection of diverse molecules using some protocols [10-14]. In this study, an isopropenyl-propionic acid derivative (**2**) was prepared using a previously method reported [15] which was modified using different conditions (Figure 1). The ^{1}H NMR spectrum of **2** showed several signals at 0.78-0.98 ppm for methyl groups bound to decahydronaphtalen-cyclopentane system; at 1.22-1.67, 1.68-1.70, 1.72-2.10, 2.32, 2.46-2.74 ppm for decahydronaphtalen-cyclopentane system; at 1.66, 1.71 and 2.40 ppm for methylene involved in the arm bound to carboxyl group; at 2.14 ppm for methyl group bound to ketone; at 11.50 ppm for carboxyl group. The ^{13}C NMR spectra displays chemical shifts at 20.94-24.42, 29.90 and 33.68-64.00 ppm for decahydronaphtalen-cyclopentane fragment; at 26.04 and 32.72 ppm for methylene bound to carboxyl group; at 30.82 for methyl group bound to ketone; at 177.30 ppm for carboxyl group; at 20.42-215.40 for ketone groups. Finally, the mass spectrum from **2** showed a molecular ion (m/z) at 334.21.

The second step was achieved by the preparation of a diazonine derivative (**3**) from compound **2** (Figure 1). It is noteworthy that some diazonine-derivatives have been prepared using several reagents such as hexame- thylenediamine/dimethylformamide [16], AcOH/HCl [17], CuI [18] and others. In this study **2** was reacted with ethylenediamine using boric acid as catalyst because it is not an expensive reagent and no special conditions are required for their use [19]. Here, it is important to mention that in this study the possibility of forming a dimer as a product of the reaction was analyzed; however, the compound **4** was not obtained (Figure 1). The ^{1}H NMR spectrum of **3** showed several signals at 0.86-1.00 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragement; at 1.80 ppm for methyl group bound to imino group; at 0.68, 1.22-1.70, 1.82-1.88, 1.96-2.40 and 2.60-2.64 ppm for decahydro- naphtalen-cyclopentane fragment; at 1.90, 2.50 and 4.40-4.44 ppm for diazonine ring; at 3.10-3.50 ppm for methylene groups bound to both imino and amino groups; at 4.68 ppm for both hydroxyl and amino groups. The ^{13}C NMR spectra displays chemical shifts at 13.20 and 17.36 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 16.70 ppm for methyl bound to imino group; at 33.17-33.20 and 48.60-51.54 ppm for diazonine ring; at 41.00, 53.12-63.14 ppm for methylene groups bound to both imino and amino groups; at 156.70-183.80 ppm for imino groups. In addition, the mass spectrum from **3** showed a molecular ion (m/z) at 430.32.

The third stage involved the formation of two diazocine-derivatives (**6** or **7**) from of the compound **2** (Figure 3). It is noteworthy, that some diazocine-analogs have been prepared using several reagents [1-9]. In this study, the compound **2** was reacted with urea or thiourea to form **6** or **7** using boric acid as catalyst. The ^{1}H NMR spectrum of **6** showed several signals at 0.88 and 1.20 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 1.94 ppm for methyl group bound o imino group; at 0.76, 1.32-1.90, 2.06-2.40 and 2.94-2.98 ppm for decahydronaphtalen-cyclopentane fragment; 1.96 and 2.68 ppm for diazocine-dione ring; at 5.88 ppm for amino group; at 9.10 for imide group. The ^{13}C NMR spectra displays chemical shifts at 16.04-16.66 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 20.30 for methyl group bound to imino group; at 20.70-30.64 and 34.07-54.06 ppm for decahydronaphtalen-cyclopentane fragment; at 32.08-32.18 ppm for diazocine-dione ring; at 158.66-167.62 ppm for amide groups; at 182.00-190.70 ppm for imino group. Finally, the mass spectrum from **6** showed a molecular ion (m/z) at 400.24.

The ^{1}H NMR spectrum of **7** showed several signals at 0.88 and 1.50 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 2.06 ppm for methyl group bound to imino group; at 0.96-1.46, 1.54-1.70, 1.84-1.98, 2.14-2.26 and 2.80-2.96 ppm for decahydro-naphtalen-cyclopentane fragment; 1.74 and 2.70 ppm for diazocine-dione ring; at 7.54 ppm for amino group; at 10.30 ppm for amide group. The ^{13}C NMR spectra displays chemical shifts at 15.94-16.60 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 19.78 ppm for methyl group bound to imino group; 20.70-31.10 and 34.00-54.32 ppm for decahydronaphtalen-cyclopentane fragment; at 31.54-31.72 ppm for diasazocin-dione ring; at 170.34 and 181.10 ppm for amide groups; at 177.50 and 191.92 ppm for

imino group; at 188.30 for thiourea group. Finally, the mass spectrum from 7 showed a molecular ion (m/z) at 432.20.

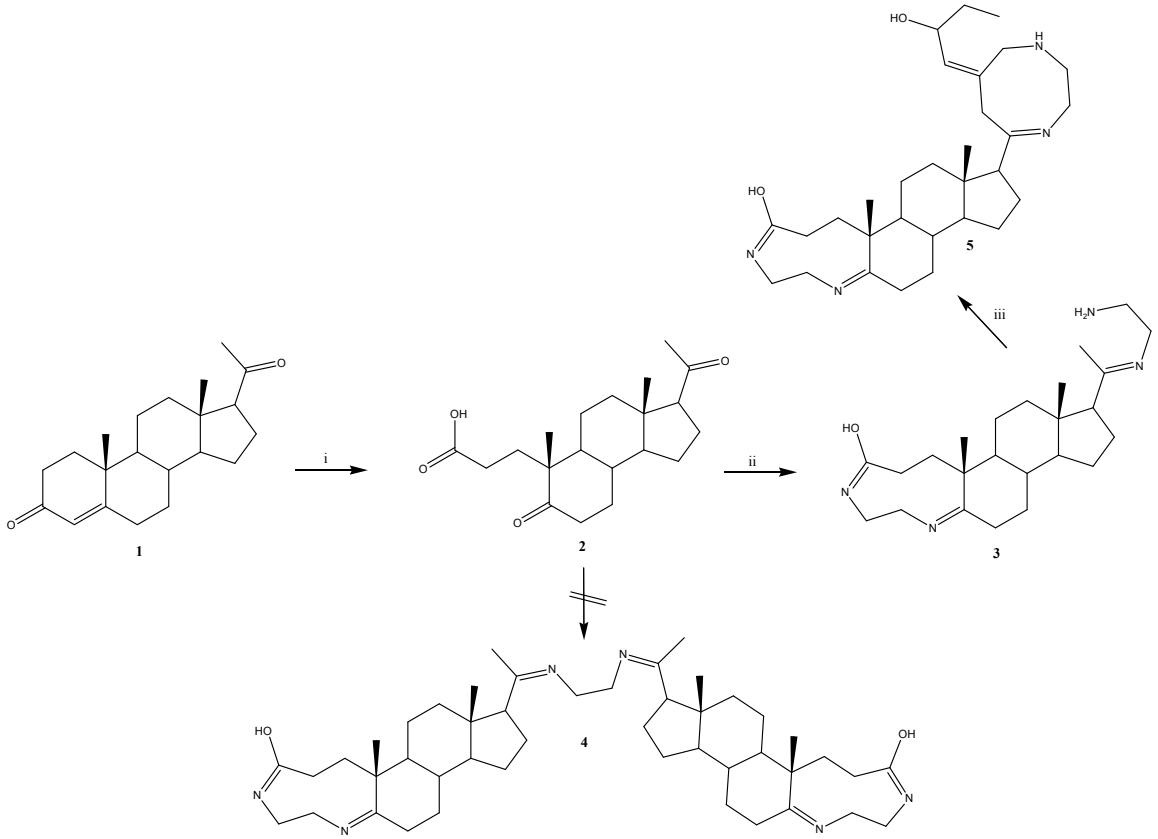

Figure 1. Preparation of a diazonin-5-ol (**5**). The first stage was achieved by opening A-ring of progesterone (1) using $NaIO_4/KMnO_4$ (i) to form an isopropenyl-propionic acid derivative (**2**). Then, **2** was reacted with ethylenediamine (ii) to synthesis of a diazocinol (**3**) analog (3). Finally, **5** was prepared by reaction of **3** with 5-hexyn-3-ol (iii).

The fourth stage (Figure 1) involved the preparation of a 2-hydroxybutylidene-diazocin-diazonin-5-ol (**5**) by the reaction of 3 with 5-hexyn-3-ol using Copper(II) chloride as catalyst. This reagent has been used in the reactions of addition from amino group to some alkyne derivatives [20-22]. The reaction mechanism (Figure 2) involves an activated-alkyne group with the Cooper (II) reagent; then, amino group reacts with the activated alkyne to form the enamine. After, a vinyl group is formed via intramolecular from the enamine. Following, vinyl group was intramolecular bound with methyl group. The ^{1}H NMR spectrum of **5** showed several signals at 0.80 and 1.00 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 0.96 ppm for methyl group involved in the arm bound to hydroxyl group; at 0.68, 1.20-1.44, 1.70-1.88, 1.92-2.30 and 2.52-2.64 ppm for decahydronaphtalen-cyclopentane fragment; at 1.56-1.58 and 3.90 ppm for methylene involved in the arm bound to both hydroxyl group and diazocine ring; at 1.90, 2.50 and 4.40-4.44 ppm for diazocinol ring; at 3.02-3.42 and 3.98 ppm for diazocine ring; at 2.46 ppm for both hydroxyl and amino group; at 6.14 ppm for alkene group. The ^{13}C NMR spectra displays chemical shifts at 13.23-17.35 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 9.46 ppm for methyl group involved in the arm bound to hydroxyl group; at 26.70, 48.22, 49.80, 55.32 and 139.08 ppm for diazocine ring; at 20.72-26.62, 31.50, 34.10-42.30, 51.62-52.40 and 63.51 ppm for decahydronaphtalen-cyclopentane fragment; at 33.18-33.20 and 48.60 and 51.57 ppm for diazocinol ring; at 29.72 and 67.00 ppm for methylene involved in the arm bound to both hydroxyl group and diazocine ring; at 125.94 ppm for alkene group; at 162.63-183.80 for imino groups. Finally, the mass spectrum from **5** showed a molecular ion (m/z) at 496.37.

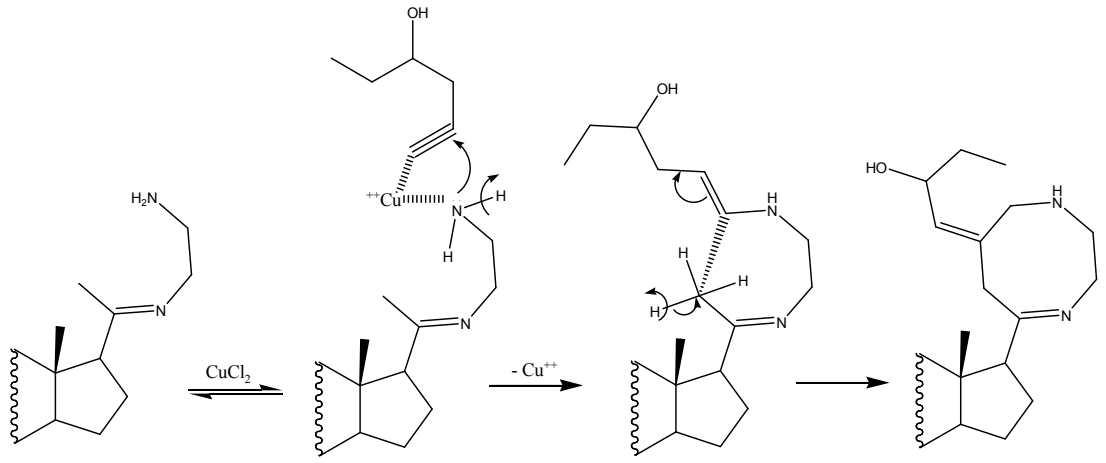

Figure 2. Mechanism of reaction involved in the synthesis of a diazonin-5-ol (**5**).

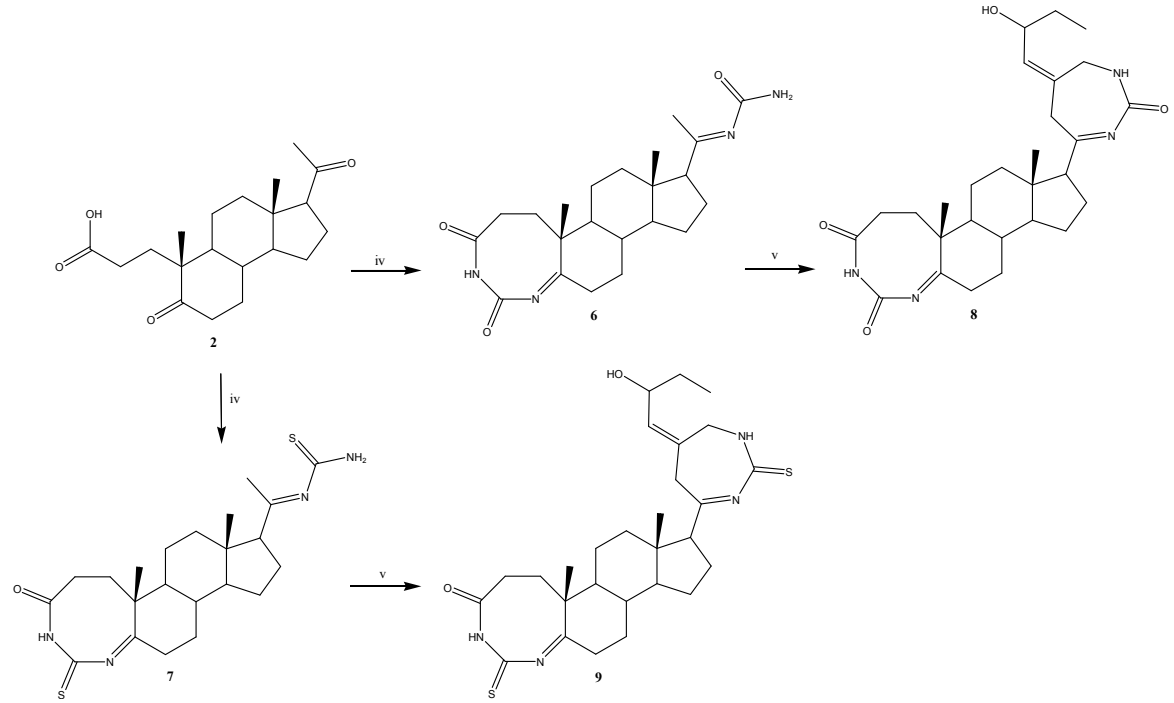

Figure 3. Synthesis of oxo-diazocine-2,4(3*H*)-dione (8) or thioxo-diazocin-4-one (**9**). Reaction of **2** with urea or thiourea (iv) to form the diazocine-urea (**6**) or diazocine thiourea (**7**). Then, **6** or reacted with 5-hexyn-3-ol (v) to form the compounds **8** or **9**.

The following stage was achieved by the reaction of **6** or **7** with 5-hexyn-3-ol in presence of Copper(II) reagent to form the compounds diazepin-2-one (**8**) or diazepin-2-thione (**9**). The ^{1}H NMR spectrum of **8** showed several signals at 0.80 and 1.20 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 0.96 ppm for methyl group involved in the arm bound to hydroxyl group; at 0.78, 1.70-1.90, 1,30-1.44, 2.06-2.10, 2.40-2.42 and 2.94-2.98 ppm for decahydronaphtalen-cyclopentane fragment; at 1.14, 1.56-1.58 and 3.90 ppm for methylene involved in the arm bound to both hydroxyl group and diazopin-2-one ring; at 1.96 and 2.68 ppm for diazocin-2,4-dione ring; at 2.26-2.28, 3.22 and 4.00 ppm for diazopin-2-one ring; at 6.40 ppm for alkene group; at 4.74 and 9.10 ppm for amide groups; at 2.50 ppm for hydroxyl group. The ^{13}C NMR spectra displays chemical shifts at 13.22-16.10 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 9.45 ppm for methyl group involved in the arm bound to hydroxyl group; at 20.70-26.62, 30.60, 34.00, 35.14, 37.96-80.60 ppm for decahydronaphtalen-cyclopentane fragment; at 34.20, 37.14 and 138.80 ppm for diazopin-2-one ring; at 32.10-32.16 ppm for diazocin-2,4-dione ring; at 29.70 and 67.00 ppm for methylene groups involved in the arm bound to both hydroxyl and diazopin-2-one ring; at 174.02-190.72 ppm for imino groups; at 126.88 ppm for alkene group; at 158.10-167.60 ppm for amide groups. Finally, the mass spectrum from 8 showed a molecular ion (m/z) at 496.30.

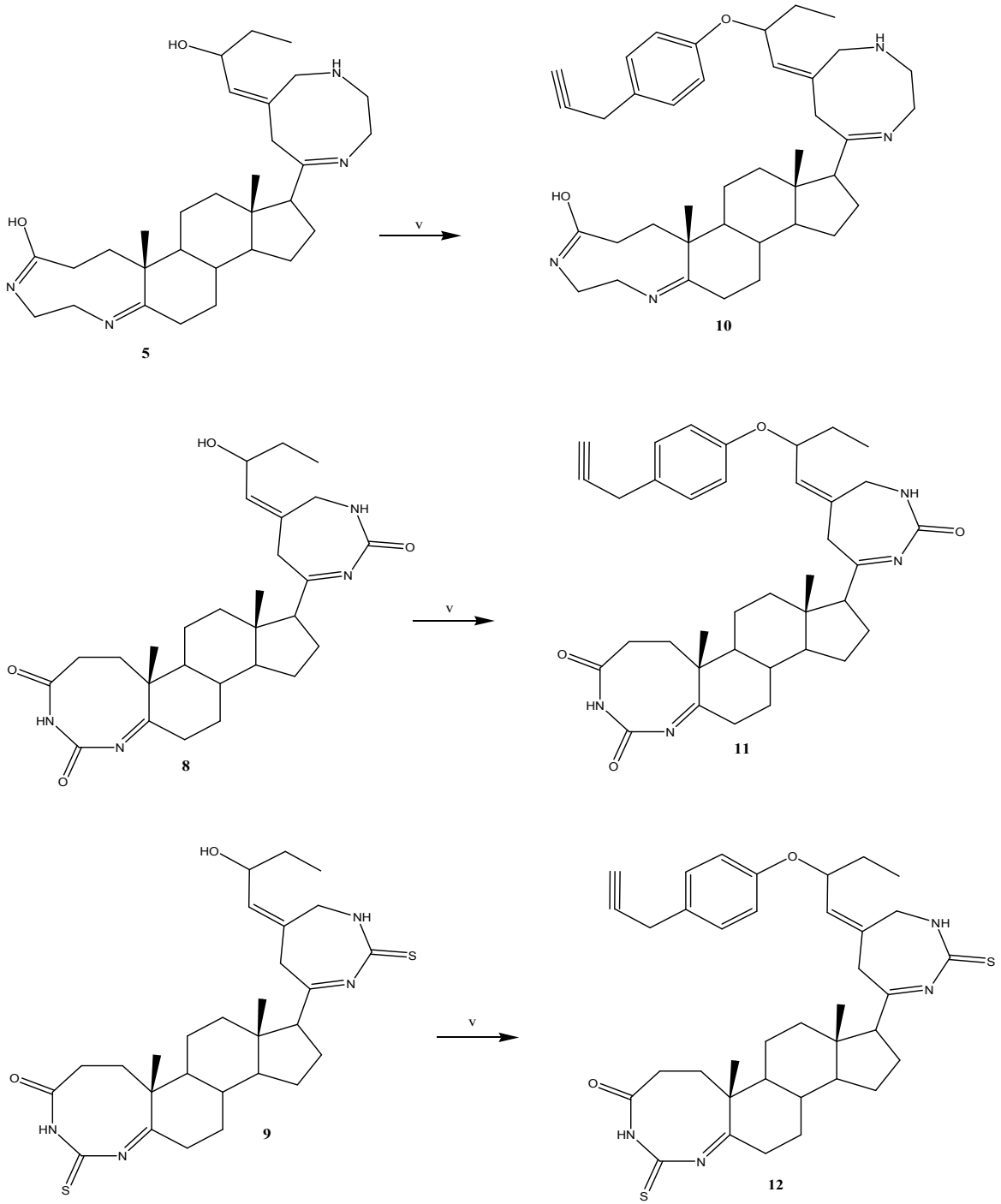

Figure 4. Preparation of diazocine- dizonin-5-ol (**10**) or oxo-diazocine-2,4(3H)-dione (**11**). or thioxo-diazocin-4-one (**12**). Reaction of **5** or **8** or **9** with (4-nitro-phenyl)-acetonitrile (v) to form **10** or **11** or **12**.

The ^{1}H NMR spectrum of **9** showed several signals at 0.80 and 1.50 ppm for methyl groups bound to decahydro-naphtalen-cyclopentane fragment; at 0.94 ppm for methyl group involved in the arm bound to hydroxyl group; at 0.96-1.48, 1.70, 1.86-2.28 and 2.92-2.96 ppm for decahydronaphtalen-cyclopentane fragment; at 1.55-1.58 and 3.92 ppm for methylene involved in the arm bound to both hydroxyl group and diazepine-2-thione ring; at 1.74 and 2.72 ppm for 2-thioxo-diazocin-4-one ring; at 2.58-2.60, 3.00 and 3.80 ppm for diazopin-2-thione ring; at 6.12 ppm for alkene group; at 3.10 ppm for both amino and hydroxyl groups; at 10.30 ppm for amide group. The ^{13}C NMR spectra displays chemical shifts at 13.22-15.94 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 9.44 ppm for methyl group involved in the arm bound to hydroxyl group; at 20.70-26.20, 26.62-27.73, 31.10, 34.00-42.30 and 51.63-60.30 ppm for decahydro- naphtalen-cyclopentane fragment; at 26.37, 46.14 and 140.82 ppm for diazepine-2-thione ring; at 31.55-31.76 ppm for 2-thioxo-diazocin-4-one ring; at 29.70 and 67.00

ppm for methylene groups involved in the arm bound to both hydroxyl and diazepine-2-thione ring; at 169.50 and 191.92 ppm for imino groups; at 170.36-181.02 ppm for amide group; at 172.52-181.02 ppm for thiourea groups. Finally, the mass spectrum from **9** showed a molecular ion (m/z) at 528.25.

Finally, the diazocine ether-derivatives (**10** or **11** or **12**) were prepared. It is noteworthy that some ether analogs have been synthesized using several reagents; however, some agents are dangerous and require special conditions [20]. In this study, the preparation of compounds **10** or **11** or **12** was carried out via displacement of nitro from (4-nitro-phenyl)-acetonitrile with the compounds **5** or **8** or **9** using a previously method reported for synthesis of ether-groups [21, 22]. The ^{1}H NMR spectrum of **10** showed several signals at 0.80 and 1.00 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 0.98 ppm for methyl group involved in the arm bound to both ether group and diazocine ring; at 0.68, 1.22-1.42, 1.69, 1.71, 1.92-1.96, 2.08-2.30 and 2.52-2.64 ppm for decahydro- naphtalen-cyclopentane fragment; at 2.06 ppm for alkyne group; at 1.50, 1.70 and 4.50 ppm for methylene involved in the arm bound to both ether group and diazocine ring; at 1.90, 2.50 and 4.40-4.46 ppm for diazocine-ol ring; 3.00-3.06, 3.40 and 3.96 ppm for diazocine ring; at 3.12 ppm for both hydroxyl and amino group; at 3.48 for methylene group bound to alkyne group; at 2.06 ppm for alkyne group; at 6.00 ppm for alkene group; at 6.60-7.18 ppm for phenyl group. The ^{13}C NMR spectra displays chemical shifts at 13.26-17.35 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 9.60 ppm for methyl group involved in the arm bound to ether group; at 28.08, 48.20,50.12, 55.36 and 139.80 ppm for diazocine ring; at 20.70, 26.62-26.66, 31.50, 34.07-42.28, 51.59-52.46 and 63.48 ppm for decahydro-naphtalen-cyclopentane fragment; at 25.14 for methylene group bound to alkyne group; at 33.18-33.20 and 48.60 and 51.53 ppm for diazocinol ring; at 31.18 and 73.56 for methylene involved in the arm bound to both ether group and diazocine ring; at 71.22 and 82.40 for alkyne group; 117.34-128.66 and 154.00 ppm for phenyl group; at 129.66 ppm for alkene group; at 162.62-183.80 for imino groups. Finally, the mass spectrum from **10** showed a molecular ion (m/z) at 610.42.

The ^{1}H NMR spectrum of **11** showed several signals at 0.80 and 1.20 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 1.00 ppm for methyl group involved in the arm bound to ether group; at 0.78, 1.30-1.44, 1.69, 1.80-1.92, 2.06-2.10, 2.40-2.42 and 2.94-2.98 ppm for decahydronaphtalen-cyclopentane fragment; at 1.46 and 1.70 ppm for methylene involved in the arm bound to both ether group and diazepin-2-one ring; at 1.96 and 2.68 ppm for diazocine-2,4-dione ring; at 2.04 ppm for alkyne group; at 3.48 and 4.50 ppm for methylene group bound to alkyne group; at 2.24-2.26, 3.20 and 3.96 ppm for diazepin-2-one ring; at 6.26 ppm for alkene group; at 6.62-7.18 for phenyl group; at 4.72 and 9.10 ppm for urea groups. The ^{13}C NMR spectra displays chemical shifts at 13.22, 20.70 ppm for methyl group bound to decahydro- naphtalen-cyclopentane fragment; at 9.60 ppm for methyl group involved in the arm bound to ether group; at 16.10, 25.78-30.60, 34.00, 35.14 and 37.94-60.60 ppm for decahydronaphtalen-cyclopentane fragment; at 34.60, 37.50 and 138.50 ppm for diazepin-2-one ring; at 25.10 ppm for methylene ring bound to alkyne group; at 32.06-32.16 ppm for diazocin-2,4-dione ring; at 31.15 and 73.60 ppm for methylene groups involved in the arm bound to both ether and diazepin-2-one ring; at 71.20 and 82.40 ppm for alkyne group; at 117.34-125.60 and 154.00 pp for phenyl group; at 130.64 ppm for alkene group; at 174.02-190.72 ppm for imino groups; at 167.60 ppm for amide group; 158.10-158.66 ppm for urea group. Finally, the mass spectrum from **11** showed a molecular ion (m/z) at 610.35.

The ^{1}H NMR spectrum of **12** showed several signals at 0.80 and 1.52 ppm for methyl groups bound to decahydronaphtalen-cyclopentane fragment; at 1.00 ppm for methyl group involved in the arm bound to ether group; at 0.94, 1.44-1.48, 1.69, 1.86-1.98, 2.06-2.28 and 2.94-2.96 ppm for decahydronaphtalen-cyclopentane fragment; at 1.50, 1.70, and 4.50 ppm for methylene involved in the arm bound to both ether group and diazepine-2-thione ring; at 174 and 2.70 ppm for 2-thioxo-diazocin-4-one ring; at 2.04 ppm for alkyne group; at 3.48 ppm for methylene group bound to alkyne group; at 2.54-2.56 and 2.98-3.76 ppm for diazepin-2-thione ring; at 6.00 ppm for alkene group; at 6.62-7.18 ppm for phenyl group; at 5.04 and 10.30 ppm for amide groups. The ^{13}C NMR spectra displays chemical shifts at 13.22-15.94 ppm for methyl group bound to decahydronaphtalen-cyclopentane fragment; at 9.60 ppm for methyl group involved in the arm bound to ether group; at 20.70, 26.22-26.60, 27.70-31.10, 34.00-42.30 and 51.63-60.30 ppm for decahydronaphtalen-cyclopentane fragment; at 26.70, 46.50, 141.50 ppm for diazepine-2-thione ring; at 31.15 and 73.60 ppm for methylene groups involved in the arm bound to both ether and diazopine-2-thione ring; at 25.10 ppm for methylene bound to alkyne group; at 31.56-31.70 ppm for 2-thioxo-diazocin-4-one ring; at 71.20 and 82.40 ppm for alkyne group; at 127.10 ppm for alkene group; at 170.36 ppm for amide group; at 169.50 and 191.92 ppm for imino groups; at 177.52-181.04 ppm for thiourea groups; at 117.34, 128.60-128.64 and 154.00 ppm for phenyl group. Finally, the mass spectrum from **12** showed a molecular ion (m/z) at 642.30.

CONCLUSION

In this study a facile method to synthesis of three diazocin-derivatives is reported.

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No none

CONFLICT 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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