Parana Journal of Science and Education (PJSE) – v. 5, n. 1, (7-19) February 1, 2019
ISSN: 2447-6153 *https://sites.google.com/site/pjsciencea*

Design and synthesis of two steroid-oxirane-carboxamide derivatives

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To cite this article:

Lauro Figueroa Valverde, Maria Lopez Ramos, Francisco Diaz Cedillo, Abelardo Camacho Luis, Marcela Rosas Nexticapa, María Virginia del Socorro Mateu Armand, Raquel Estrella-Barron, Eduardo Pool Gómez, Lenin Hau Heredia, Lenin Alfonso Jiménez Alondra, Jhair Cabrera Tuz, "Design and synthesis of two steroid-oxirane-carboxamide derivatives", *Parana Journal of Science and Education*. Vol. 5, No.18, **2019**, pp. 7-19.

Received: January 10, 2019; **Accepted**: January 17, 2019; **Published**: February 1, 2019.

Abstract

There are several studies to preparation of oxirane-derivatives which use several reagents such as chlorophyll, ethyl bromoacetate, *m*-chloroperoxybenzoic acid, potassium hydroxide, dimethyldioxiran and others; nevertheless, expensive reagents and special conditions are required. The aim of this study was synthesizing two novel steroid-oxirane using some reactions; the first stage was achieved by the preparation of two steroid-propargylic-ether (**3** or **4**) via reaction of 2-nitroestrone or 2-nitroestradiol with 5-hexyn-1-ol. The second stage involves the synthesis of two steroid-dioxa derivatives (**5** or **6**) via intramolecular addition from **3** or **4** using Copper(II) as catalyst. Then, **5** or **6** were reacted with ethylenediamine to form two steroid-amino derivatives (**7** or **8**). Following, the compounds **9** or **10** were prepared through of reaction of **7** or **8** with chloroacetylchloride. Finally, **9** or **10** reacted with 2-hydroxy-1-naphthaldehyde to synthesis of two oxirane-steroid derivatives (**11** or **12**). The structure of steroid-oxirane analogs was confirmed via spectroscopic and spectrometric methods. In conclusion, a facile procedure for the preparation of two steroid-oxirane derivatives was developed in this study.

Keywords: Steroid, Oxirane, Cycloaddition, Epoxidation, Amidation, Carboxamide.

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1. Introduction

There are studies which show the preparation of several oxirane derivatives using some methods; for example, the synthesis of 2,3-diphenyl-oxirane-2-carboxylic acid methyl ester from a diazo-carbonyl using NHC-Ag+ as catalyst [1]. Other data showed the epoxidation of 4,4-dimethyl-2-pentyn-1-ol with titanium isopropoxide to form (3-tert-Butyl-2-tributylstannanyl-oxiranyl)-methanol [2]. In addition, the 2-isopropenyl-3-phenyl-oxirane was prepared using the three-component system ((2*R*,5*R*)-dimethylthiolane, allyl halides and aldehyde derivative) [3]. Other study showed the synthesis of an oxirane derivative by reaction of 2,2-dibromomethylquinoxaline with an aromatic aldehyde in the presence of the tetrakis(dimethylamino)ethylene reagent [4]. Also, a 9H-fluorene-2-yl keto-oxirane have been synthesized via epoxidation of the compound 9H-fluorene-2-yl chalcone [5]. Additionally, a spiro-indole-3,2′-oxirane derivative was prepared through epoxidation of 3-aroylmethylene-indole-2-one using an ammonium-bromide derivative as catalyst [6]. Other data shown that a 17-steroid-oxirane was prepared by the reaction of estrone with dimethylsulfonium methylide [7]. In addition, a report indicates the epoxidation of 4-methylene-5-cholestan-3-ol with *m*-chloroperoxybenzoic acid to form a steroid-4-oxirane derivative [8]. Recently, a study showed the preparation of an estrone-17-oxirane by reaction of lactone-steroid derivative with 2-benzothiazol-ylchloromethyl-lithium [9]. All these experimental results indicate that some procedures are available for synthesis of several oxirane analogs; nevertheless, expensive reagents and special conditions are required. Therefore, in this study, two oxirane-steroid derivatives were synthesized using some strategies.

2. Experimental

2.1 General methods

The compounds 2-nitro-estrone was prepared using a previously method reported [10]. Additionally, all the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were determined using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a Varian VXR300/5 FT NMR spectrometer at 300 and 75.4 MHz (megahertz) in $CDCl_3$ (deuterated chloroform) using TMS (tetramethylsilane) as an internal standard. EIMS (electron impact mass spectroscopy) spectra were determined using a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were determined from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

2.2 Preparation of steroid-propargylic-ether (3 or 4)

A solution of 2-nitroestrone or 2-nitroestradiol (0.50 mmol), 5-hexyn-1-ol (70 µl; 0.58 mmol), potassium carbonate (40 mg, 0.30 mmol) in 5 ml of dimethyl sulfoxide was stirring to room temperature for 48 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system.

8-(hex-5-yn-1-yloxy)-11a-methyl-1H,2H,3H, 3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a] phenanthrene-1,7-diol (3)

yielding 44% of product, m.p. 132-134°C; IR (V_{max}, cm^{-1}) 3400, 2160 and 1110. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 0.80-1.40 (m, 7H), 1.60 (m, 2H), 1.66-1.80 (m, 3H), 1.86 (m, 2H), 1.88 (m, 1H), 1.94 (s, 1H), 2.12 (m, 1H), 2.24 (m, 2H), 2.50-3.64 (m, 4H), 4.10 (m, 2H), 6.12 (broad, 2H), 6.40-6.60 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 15.82, 18.02, 24.22, 25.05, 25.35, 27.77, 28.92, 29.68, 32.78, 33.71, 37.28, 44.00, 44.39, 50.72, 68.64, 70.25, 82.44, 84.10, 107.50, 114.04, 128.81, 133.77, 144.70, 144.92 ppm. EI-MS 368.23. Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75; O, 13.02. Found:C, 78.16; H, 8.70.

8-(hex-5-yn-1-yloxy)-7-hydroxy-11a-methyl-2H,3H,3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a]phenan- thren-1-one (4)

yielding 54% of product, m.p. 146-148°C; IR (V_{max}, cm^{-1}) 2162, 1712 and 1112. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.92 (s, 3H), 1.20-1.52 (m, 5H), 1.60 (m, 2H), 1.80 (m, 1H), 1.86 (m, 2H), 1.92 (m, 1H), 1.94 (s, 1H), 2.10-2.20 (m, 4H), 2.24 (m, 2H), 2.46-2.80 (m, 4H), 4.08 (m, 2H), 5.90 (broad, 1H), 6.40-6.60 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C:13.80, 18.02, 21.74, 25.06, 25.87, 26.43, 28.92, 29.66,

31.50, 35.43, 37.53, 46.86, 48.12, 50.42, 68.62, 70.24, 84.12, 107.14, 114.04, 128.42, 133.34, 144.70, 144.91, 220.70 ppm. EI-MS 366.21. Anal. Calcd. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25; O, 13.10. Found: C, 78.60; H, 8.20.

2.3 Synthesis steroid-dioxecine derivatives

A solution of **3** or **4** (0.50 mmol), Copper(II) chloride anhydrous (40 mg, 0.30 mmol) in 5 ml of methanol was stirring to room temperature for 48 h**.** The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:hexane:water (4:1:1) system.

18-methyl-4,11-dioxapentacyclo[12.11.0.0^{3,12}.0^{15,23}.0^{18,22}]pentacosa-1,3(12),13-trien-5-yn-19-ol (5)

yielding 45% of product, m.p. 162-164^{o}C; IR (V_{max}, cm^{-1}) 3402, 2192 and 1112. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 0.80-1.11 (m, 4H), 1.18 (m, 2H), 1.30-1.40 (m, 3H), 1.60 (m, 2H), 1.66-1.88 (m, 4H), 1.94-1.96 (m, 2H), 2.12-3.64 (m, 5H), 4.16-4.17 (m, 2H), 6.32 (m, 1H), 6.40 (broad, 2H), 6.60 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 15.82, 17.20, 24.22, 25.32, 27.74, 29.67, 29.79, 32.16, 32.78, 33.71, 37.28, 44.02, 44.39, 50.76, 51.94, 67.96, 76.72, 82.46, 109.33, 111.61, 129.78, 134.05, 144.52, 147.30 ppm. EI-MS 366.21. Anal. Calcd. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25; O, 13.10. Found: C, 78.62; H, 8.20.

18-methyl-4,11-dioxapentacyclo[12.11.0.0^{3,12}.0^{15,23}.0^{18,22}]pentacosa-1,3(12),13-trien-5-yn-19-one (6)

yielding 63% of product, m.p. 128-130^{o}C; IR (V_{max}, cm^{-1}) 21.90, 1712 and 1110. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.92 (s, 3H), 1.18 (m, 2H), 1.20-1.52 (m, 5H), 1.60 (m, 2H), 1.80-1.92 (m, 2H), 1.95-1.96 (m, 2H), 2.10-2.80 (m, 8H), 4.16-4.17 (m, 2H), 6.30-6.66 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 13.80, 17.20, 21.75, 25.87, 26.33, 29.67, 29.79, 31.50, 32.14, 35.43, 37.56, 46.87, 48.11, 50.40, 51.94, 67.97, 76.70, 108.96, 111.61, 133.61, 144.50, 147.30, 220.70 ppm. EI-MS 364.20. Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74; O, 13.17. Found: C, 79.00; H, 7.70.

2.4 Preparation of amino-steroid-dioxecine derivative

A solution of **5** (0.50 mmol), ethylenediamine (50 µl, 0.74 mmol) in 5 ml of formaldehyde was stirring to reflux for 12 h**.** The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:hexane:water (4:1:1) system.

2-{[(2-aminoethyl)amino]methyl}-18-methyl-4,11-dioxapentacyclo[12.11.0.0^{3,12}.0^{15,23}.0^{18,22}] pentacosa-1,3(12),13-trien-5-yn-19-ol (7)

yielding 45% of product, m.p. 150-152^{o}C; IR (V_{max}, cm^{-1}) 3400, 3380 and 2190. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 0.80-1.16 (m, 4H), 1.18 (m, 2H), 1.30-1.40 (m, 3H), 1.60 (m, 2H), 1.70-1.88 (m, 10H), 1.95-1.96 (m, 2H), 2.10-2.52 (m, 4H), 2.66-2.80 (m, 4H), 3.60 (broad, 4H), 3.64 (m, 1H), 3.70 (m, 2H), 4.16-4.17 (m, 2H), 6.36 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 15.80, 17.20, 24.22, 25.34, 27.69, 27.70, 29.80, 32.16, 32.78, 33.71, 37.28, 41.57, 44.40, 44.60, 46.10, 50.76, 51.95, 53.32, 67.96, 78.38, 82.46, 109.76, 128.75, 132.11, 132.13, 141.32, 143.30 ppm. EI-MS 438.28. Anal. Calcd. for $C_{27}H_{38}N_2O_3$: C, 73.94; H, 8.73; N, 6.39; O, 10.94. Found:C, 73.88; H, 8.68.

2.5 Reduction of hydroxyl from 7

A solution of 7 (0.50 mmol), pyridinium chlorochromate (100 mg, 0.46 mmol) in 5 ml ethanol:water (4:1) at room temperature for 48 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:hexane:water (4:2:1) system.

2-{[(2-aminoethyl)amino]methyl}-18-methyl-4,11-dioxapentacyclo[12.11.0.0^{3,12}.0^{15,23}.0^{18,22}]pentacosa-1,3(12),13-trien-5-yn-19-one (8)

yielding 53% of product, m.p. 191-193; IR (V_{max}, cm^{-1}) 3380, 2190, 1710 and 1112. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.18 (m, 2H), 1.20-1.54 (m, 5H), 1.60 (m, 2H), 1.80-1.92 (m, 2H), 1.95-1.96 (m, 2H), 2.10-2.54 (m, 8H), 2.64 (m, 2H), 2.66 (broad, 3H), 2.80-3.70 (m, 4H), 4.16-4.17 (m, 2H), 6.44 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 13.82, 17.20, 21.72, 25.72, 27.41, 27.70, 29.79, 31.32, 32.16, 35.12, 37.50, 41.56, 46.10, 47.44, 48.22, 50.54, 51.95, 53.32, 67.96, 78.38, 109.39, 128.38, 131.69, 132.11, 141.32, 143.30, 220.70 ppm. EI-MS 436.27. Anal. Calcd. for $C_{27}H_{36}N_2O_3$: C, 74.28; H, 8.31; N, 6.42; O, 10.99. Found:C, 74.20; H, 8.26.

2.6 Synthesis of chloroamide derivative

A solution of **7** or **8** (0.50 mmol), chloroacetyl chloride (50 µl, 0.63 mmol) and triethylamine (80

µl, 0.57 mmol) in 5 ml methanol at room temperature for 48 h**.** The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:ketone (3:1) system.

2-chloro-N-{2-[({19-hydroxy-18-methyl-4,11-dioxapentacyclo[12.11.0.0^{3,12}.0^{15,23}.0^{18,22}]penta-cosa-1,3(12),13-trien-5-yn-2-yl}methyl)amino] ethyl}acetamide (9)

yielding 83% of product, m.p. 166-168^{o}C; IR (V_{max}, cm^{-1}) 3400, 3310, 2190 and 1110. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 0.80-1.16 (m, 4H), 1.18 (m, 2H), 1.30-1.40 (m,3H), 1.60 (m, 2H), 1.70-1.88 (m, 4H), 1.95-1.96 (m, 2H), 2.10-2.52 (m, 4H), 2.70-3.40 (m, 4H), 3.64 (m, 1H), 3.70 (m, 2H), 4.02 (m, 2H), 4.16-4.17 (m, 2H), 5.94 (broad, 3H), 6.36 (m, 1H). ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 15.80, 17.20, 24.22, 25.35, 27.70, 27.72, 29.80, 32.16, 32.78, 33.71, 37.28, 38.57, 42.43, 44.40, 44.62, 46.10, 50.76, 51.95, 67.96, 78.38, 82.46, 109.76, 128.75, 132.13, 132.37, 141.34, 143.30, 162.60 ppm. EI-MS 514.25. Anal. Calcd. for $C_{29}H_{39}ClN_2O_4$: C, 67.62; H, 7.63; Cl, 6.88; N, 5.44; O, 12.42. Found: C, 67.60; H, 7.58.

2-chloro-N-{2-[({18-methyl-19-oxo-4,11-dioxa-pentacyclo[12.11.0.0^{3},^{12}.0^{15,23}.0^{18,22}]pentacosa-1,3(12),13-trien-5-yn-2-yl}methyl)amino]ethyl} acetamide (10)

yielding 78% of product, m.p. 154-156^{o}C; IR (V_{max}, cm^{-1}) 3310, 21.90, 1712 and 1112. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.18 (m, 2H), 1.20-1.54 (m, 5H), 1.60 (m, 2H), 1.80-1.92 (m, 2H), 1.95-1.96 (m, 2H), 2.10-2.54 (m, 8H), 2.70-3.40 (m, 4H), 3.70 (m, 2H), 4.02 (m, 2H), 4.16-4.17 (m, 2H), 5.76 (broad, 2H), 6.44 (m, 1H). ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 13.82, 17.20, 21.72, 25.72, 27.41, 27.70, 29.80, 31.33, 32.16, 35.12, 37.50, 38.57, 42.40, 46.10, 47.45, 48.21, 50.54, 51.94, 52.84, 67.96, 78.38, 109.39, 128.38, 131.69, 132.37, 141.34, 143.32, 162.60, 220.70 ppm. EI-MS 512.24. Anal. Calcd. for $C_{29}H_{37}ClN_2O_4$: C, 67.89; H, 7.27; Cl, 6.91; N, 5.46; O, 12.47. Found:C, 67.80; H, 7.20.

2.7 Preparation of chloroamide derivative

A solution of **9** or **10** (0.50 mmol), 2-hydroxy-1-naphthaldehyde (68 mg, 0.40 mmol), and sodium hydroxide (20 mg, 0.50 mmol) in 5 ml of ethanol was stirring for 72 h at room temperature. 2-hydroxy-1- naphthaldehyde (68 mg, 0.40 mmol), and sodium hydroxide (20 mg, 0.50 mmol) in 5 ml of ethanol was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system.

N-{2-[({19-hydroxy-18-methyl-4,11-dioxapenta cyclo[12.11.0.0^{3,12}.0^{15,23}.0^{15,23}.0^{18,22}]pentacosa-1,3 (12),13-trien-5-yn-2-yl}methyl)amino]ethyl}-3-(2-hydroxy-naphthalen-1-yl)oxirane-2-carbo-xamide (11)

yielding 54% of product, m.p. 175-177^{o}C; IR (V_{max}, cm^{-1}) 3402, 2192, 1632 and 1112. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 0.80-1.16 (m, 4H), 1.18 (m, 2H), 1.30-1.40 (m,3H), 1.60 (m, 2H), 1.70-1.88 (m, 4H), 1.95-1.96 (m, 2H), 2.10-2.52 (m, 4H), 2.70-3.40 (m, 4H), 3.64 (m, 1H), 3.70 (m, 2H), 3.94 (m, 1H), 4.16-4.17 (m, 2H), 4.26 (m, 1H), 6.36 (m, 1H), 6.66 (broad, 4H), 7.22-7.90 ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 15.80, 17.20, 24.22, 25.35, 27.69, 27.70, 29.80, 32.16, 32.78, 33.71, 37.30, 39.14, 44.39, 44.60, 46.04, 50.76, 51.94, 52.82, 53.66, 59.55, 67.94, 78.38, 82.46, 109.76, 118.80, 121.45, 122.58, 123.43, 126.81, 128.00, 128.75, 129.2, 130.35, 132.13, 132.37, 134.34, 141.30, 143.33, 152.77, 172.20 ppm. EI-MS 650.33. Anal. Calcd. for $C_{40}H_{46}N_2O_6$: C, 73.82; H, 7.12; N, 4.30; O, 14.75. Found:C, 73.78; H, 7.08.

3-(2-hydroxynaphthalen-1-yl)-N-{2-[({18-methyl-19-oxo-4,11-dioxapentacyclo[12.11.0.0^{3},^{12}.0^{15,23}.0^{18,22}]penta- cosa-1,3(12),13-trien-5-yn-2-yl}methyl)amino]ethyl}-oxirane-2-carboxamide (12)

yielding 38% of product, m.p. 164-166; IR (V_{max}, cm^{-1}) 21.90, 1712, 1630 and 1110. ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.18 (m, 2H), 1.20-1.54 (m, 5H), 1.60 (m, 2H), 1.80-1.92 (m, 2H), 1.95-1.96 (m, 2H), 2.10-2.54 (m, 8H), 2.70-3.40 (m, 4H), 3.70 (m, 2H), 3.96 (m, 1H), 4.16-4.17 (m, 2H), 4.26 (m, 1H), 6.44 (m, 1H), 6.70 (broad, 3H), 7.22-7.90 (m, 6H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 13.82, 17.20, 21.72, 25.72, 27.41, 27.70, 29.79, 31.30, 32.16, 35.12, 37.49, 39.16, 46.10, 47.45, 48.2 , 50.52, 51.96, 52.84, 53.66, 59.55, 67.96, 78.38, 109.40, 118.80, 121.45, 122.58, 123.43, 126.81, 128.00, 128.38, 129.2, 130.35, 131.70, 132.37, 134.34, 141.30, 143.34, 152.74, 172.20, 220.72 ppm. EI-MS 648.31. Anal. Calcd. for

$C_{40}H_{44}lN_2O_6$: C, 74.05; H, 6.84; N, 4.32; O, 14.80. Found:C, 74.00; H, 6.80.

3. Results and Discussion

Several studies have been showed the preparation of oxirane derivatives; however, some protocols use expensive reagents and their management requires special conditions [11-13]. Therefore, in this study, we report a facile method for the synthesis of two steroid-oxirane derivatives using several strategies.

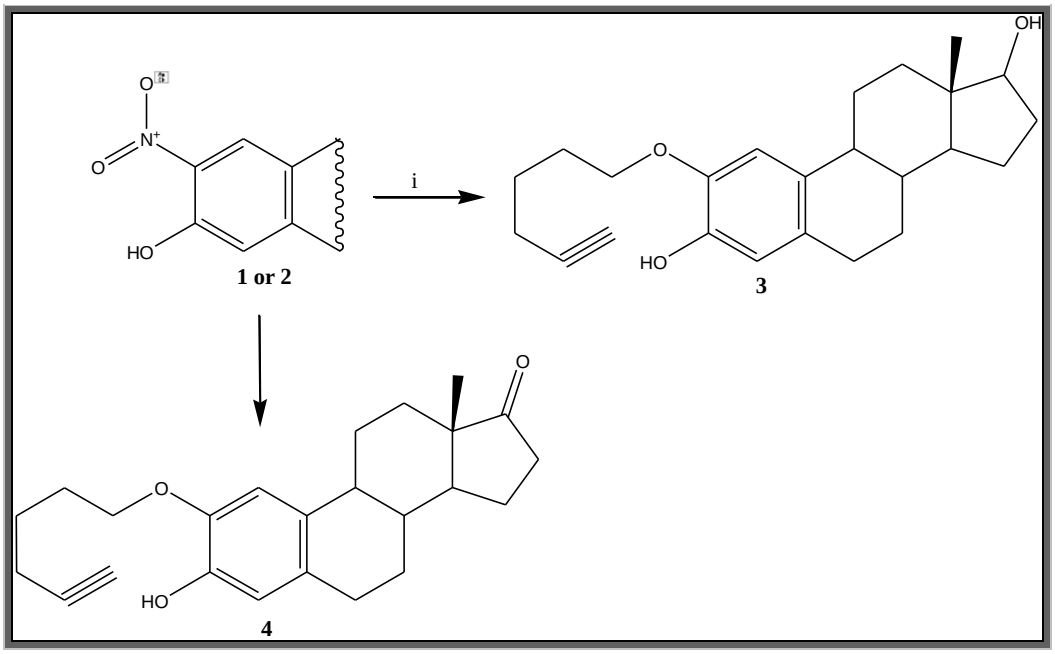

Figure 1. Preparation of steroid-propargylic-ether (**3** or **4**). Reaction of 2-nitroestradiol (**1**) or 2-nitroestrone (**2**) with 5-hexyn-1-ol (i) to form **3** or **4**.

3.1 Preparation of propargyl-ether derivatives

There are several methods for preparation of ether derivatives which involve the use of different reagents such hexyl bromide/sodium cyanide [14], *m*-chloroperoxybenzoic acid [15], hydrazonyl chloride [16], N,N-dimethylbarbituric acid [17] and others. In this study, estrone or estradiol were reacted with 5-hexyn-1-ol in presence of dimethyl sulfoxide at mild conditions.

The ^{1}H NMR spectrum of **3** showed several signals at 0.76 ppm for methyl group bound to steroid nucleus; at 0.80-1.40, 1.66-1.80, 1.88, 2.12, 2.50-3.64 and 6.40-6.60 ppm for steroid moiety; at 1.60, 1.86, 2.24 and 4.10 ppm for methylene groups involved in the arm bound of both ether and alkyne groups; at 1.94 ppm for alkyne group; at 6.12 ppm for both hydroxyl groups. The ^{13}C NMR spectra display several chemical shifts at 15.82 ppm for methyl group bound to steroid nucleus; at 18.02, 25.05, 28.92 and 70.25 ppm for methylene groups o arm bound to both ether and alkyne groups; at 24.22, 23.35-27.77, 29.68-50.72, 82.44 and 107.50-144.92 ppm for steroid moiety, at 68.64 and 84.10 ppm for alkyne group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 368.23.

Other data showed several signals involved in ^{1}H NMR spectrum of compound **4** at 0.90 ppm for methyl group bound to steroid nucleus; at 1.20-1.52, 1.80, 1.92, 2.10-2.20, 2.46-2.80 and 6.40-6.60 ppm for steroid moiety; at 1.60, 1.86, 2.24 and 4.08 ppm for methylene groups involved in the arm bound of both ether and alkyne groups; at 1.94 ppm for alkyne group; at 5.90 ppm for hydroxyl group. The ^{13}C NMR spectra display several chemical shifts at 13.80 ppm for methyl group bound to steroid nucleus; at 18.02, 25.06, 28.92 and 70.24 ppm for methylene groups of arm bound to both ether and alkyne groups; at 21.74, 25.87-26.43, 29.66-50.42 and 107.14-144.91ppm for steroid moiety, at 68.64 and 84.12 ppm for alkyne group; at 220.70 ppm for ketone group.

Finally, the mass spectrum from **4** showed a molecular ion (m/z) 366.21.

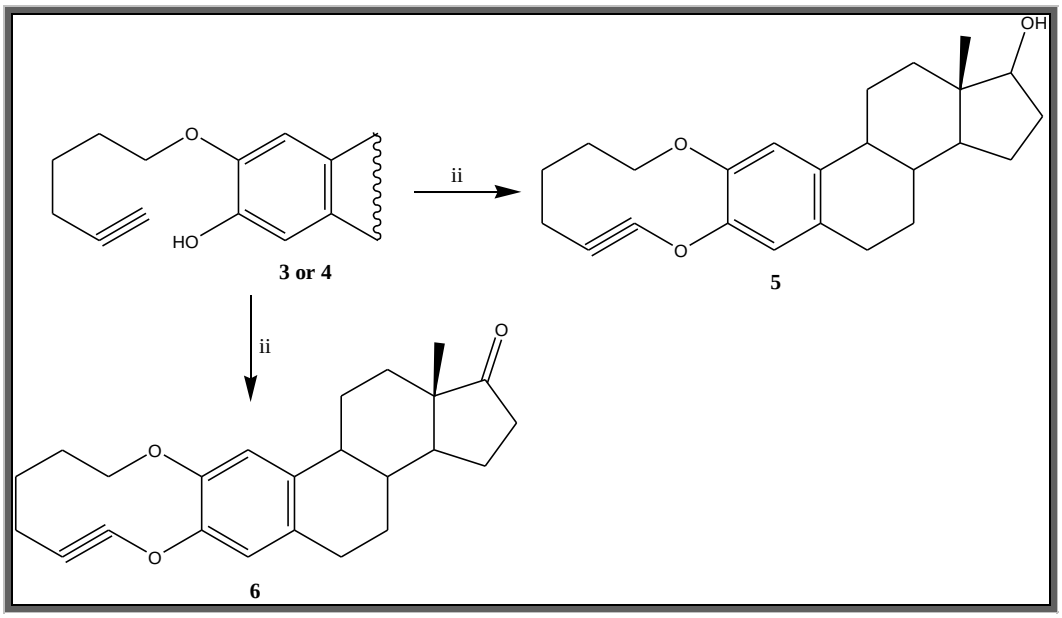

Figure 2. Synthesis of two steroid-dioxecine derivatives (**5** or **6**). Intramolecular reaction of alkyne with the hydroxyl group from 3 or **4** to form the compounds **5** or **6**. ii = Copper(II).

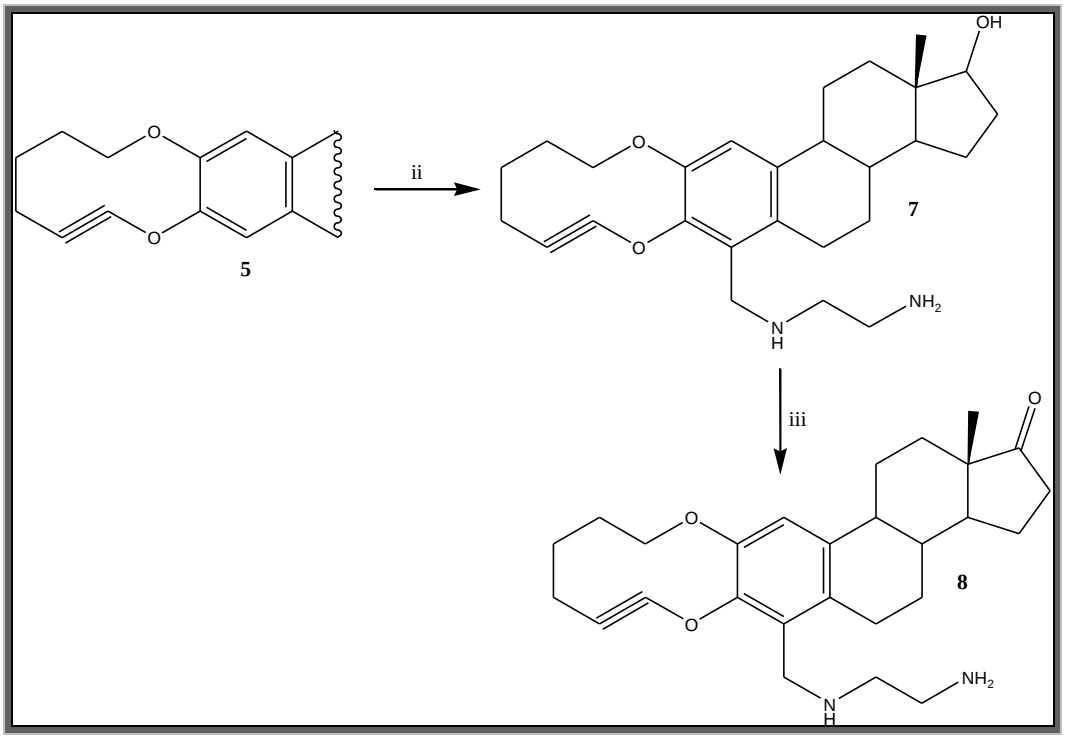

Figure 3. Preparation of two amino-steroid analogs (**7** or **8**). Reaction of oxacine-steroid derivatives (**5**) with ethylenediamine in presence of formaldehyde (ii) to form an amino-ozacine steroid (**7**). Then, **8** was prepared via reduction of **7** with cyanoborohydride/Zn^{+2} (iii).

3.2 Synthesis steroid-dioxa derivatives

There are several reports on the preparation of oxacyclic derivatives using several reagents such as Grubbs catalyst™ 2nd generation [18] urea [19], oxoborane [20], phosphorus trichloride [21], di-ethanolamine [22], *p*-Toluenesulfonamide [23] and others. In this study, two steroid-dioxa

derivatives (**5** or **6**) were prepared via intramolecular from 3 or 4 using Copper(II) as a catalyst (Figure 2); here, is important to mention that this method does not require special conditions.

The ^{1}H NMR spectrum of **5** showed several signals at 0.76 ppm for methyl group bound to steroid nucleus; at 0.80-1.11, 1.30-1.40, 1.66-1.88, 2.12-3.64, 6.32 and 6.60 ppm for steroid moiety; at 1.18, 1.60, 1.94-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 6.40 ppm for hydroxyl group. The ^{13}C NMR spectra display several chemical shifts at 15.82 ppm for methyl group bound to steroid nucleus; at 17.20, 29.79-32.16 and 67.96 ppm for dioxecine ring; at 24.22, 29.79-32.16, 50.76 and 82.46-147.30 ppm for steroid moiety, at 52.95-76.72 ppm for alkyne group. In addition, the mass spectrum from **5** showed a molecular ion (m/z) 366.21.

The ^{1}H NMR spectrum of **6** showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 1.20-1.52, 1.80-1.92, 2.10-2.80 and 6.30-6.66 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 6.40 ppm for hydroxyl group. The ^{13}C NMR spectra display several chemical shifts at 13.80 ppm for methyl group bound to steroid nucleus; at 17.20, 29.79, 32.14 and 67.97 ppm for dioxecine ring; at 21.75-29.67, 31.50, 35.43-50.40 and 108.96-147.30 ppm for steroid moiety, at 51.94-76.70 ppm for alkyne group. In addition, the mass spectrum from **6** showed a molecular ion (m/z) 364.20.

3.3 Synthesis of steroid-amino derivative

There are several studies that show the preparation of some steroid-amino derivatives with Mannich reaction [24]; these reports indicate the reactivity of hydrogen atom (C-4) involved in ring A of steroid nucleus which can be a specific site to introduce an amino group. Therefore, in this study **5** or **6** were reacted with ethylenediamine in presence of formaldehyde to form two steroid-amino derivatives (**7** or **8**).

The ^{1}H NMR spectrum of **7** showed several signals at 0.76 ppm for methyl group bound to steroid nucleus; at 0.80-1.16, 1.30-1.40, 1.70-1.88, 2.10-2.52, 3.64 and 6.36 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 2.66-2.80 ppm for methylene groups bound to both amine groups; 3.60 ppm for both hydroxyl and amino groups; 3.70 ppm for methylene group bound to both ring A (steroid nucleus) and amino group.

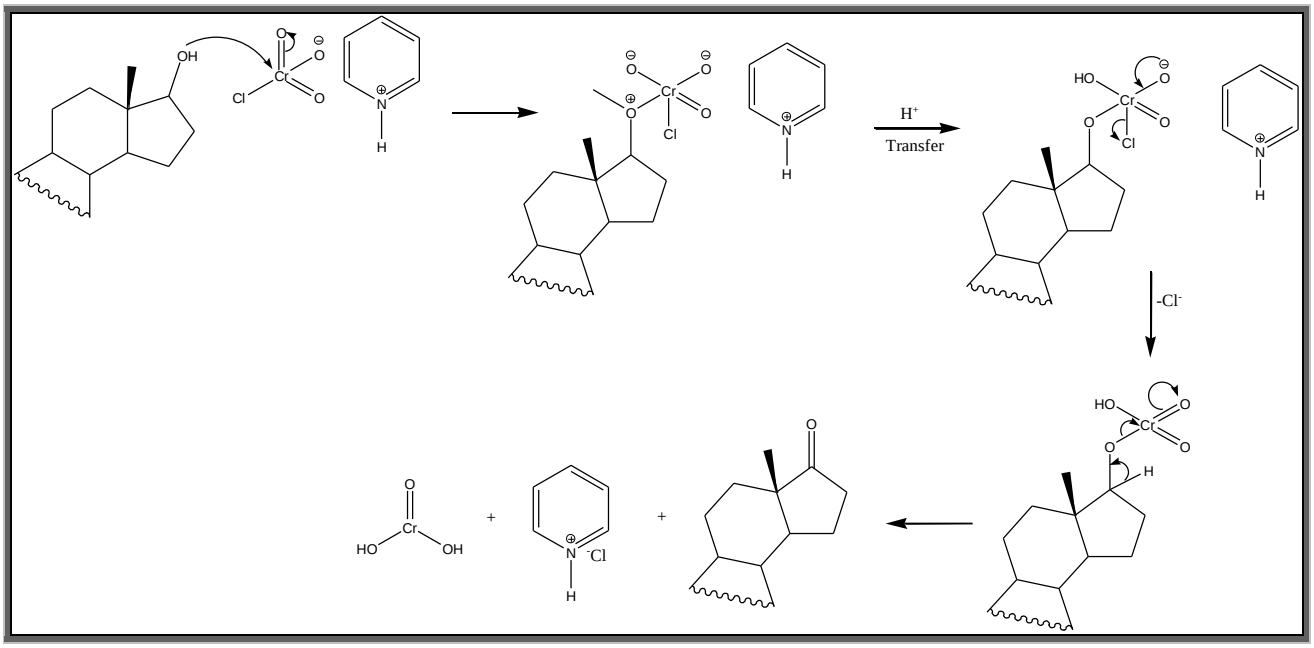

Figure 4. Reaction mechanism involved in the synthesis of an oxacine-steroid derivative (compound **8**) via oxidation of **7** with pyridinium chlorochromate.

The ^{13}C NMR spectra display several chemical shifts at 15.80 ppm for methyl group bound to steroid nucleus; at 17.20, 29.80-32.16 and 67.96 ppm for dioxecine ring; at 25.34-27.70, 32.78-37.28, 44.40-46.00, 50.76 and 82.46-143.30 ppm for steroid moiety, at 41.57 and 53.32 ppm for methylene groups bound to both amino groups; at 46.10 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 51.95 and 78.38 ppm for alkyne group. In addition, the mass spectrum from **7** showed a molecular ion (m/z) 438.28.

Other data showed several signals involved in ^{1}H NMR spectrum for compound **8** at 0.90 ppm for methyl group bound to steroid nucleus; at 1.20-1.54, 1.80-1.92, 2.10-2.54 and 6.44 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 2.64-2.80 ppm for methylene groups bound to both amine groups; 2.66 ppm for amino groups; 3.70 ppm for methylene group bound to both ring A (steroid nucleus) and amino group;. The ^{13}C NMR spectra display several chemical shifts at 13.82 ppm for methyl group bound to steroid nucleus; at 17.20, 29.79, 32.16 and 67.96 ppm for dioxecine ring; at 21.72-27.70, 31.32, 35.12-37.50, 47.44-50.54 and 109.39-143.30 ppm for steroid moiety, at 41.56 and 53.32 ppm for methylene groups bound to both amino groups; at 46.10 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 51.95 and 78.38 ppm for alkyne group; at 220.70 ppm for ketone group. Additionally, the mass spectrum from **8** showed a molecular ion (m/z) 436.27.

3.4 Preparation of steroid-chloroamide derivatives

Several procedures for synthesis of chloroamide derivatives are reported; these protocols involved some reagents such as trichloroisocyanuric Acid [25], *N*-chlorobenzotriazole [26], chloroacetyl chloride [27-29]. Therefore, in this study two steroid-chloroamide derivatives (**9** or **10**) were prepared using chloroacethyl chloride/triethyl-amine; it is important to mention that with this method the yielding was relatively good.

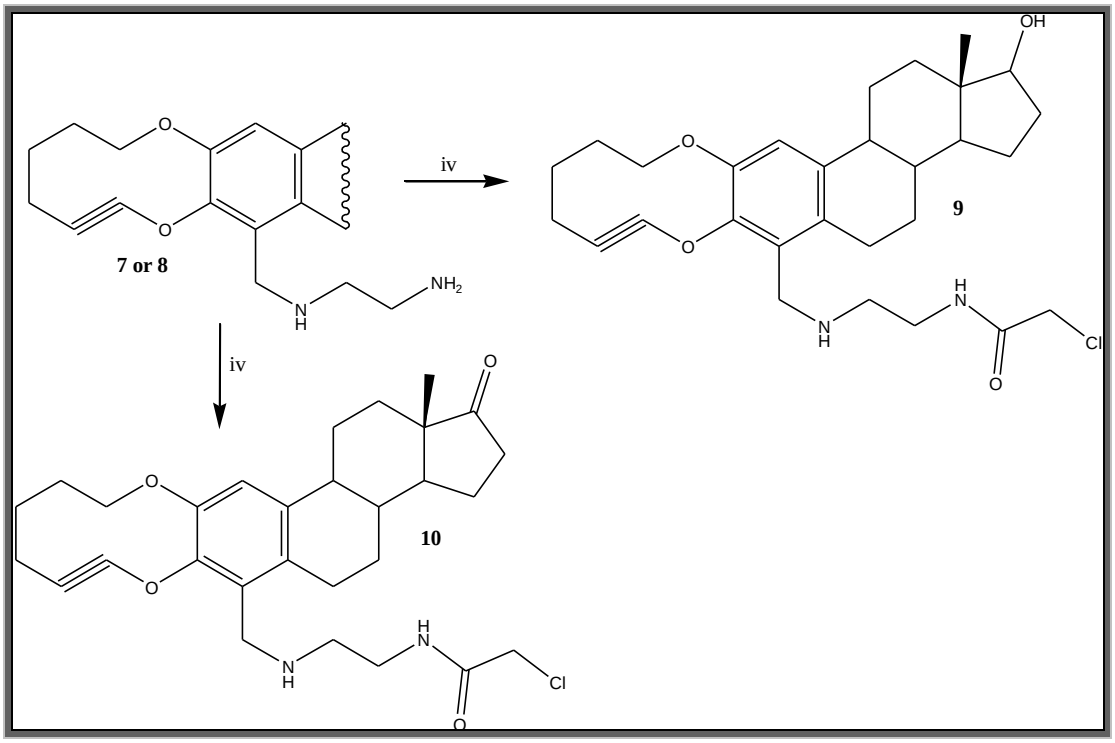

Figure 5. Synthesis of two chloroamide derivatives (**9** or **10**). Compounds **7** o **8** reacted with chloroacetyl chloride (iv) to form **9** or **10**.

The ^{1}H NMR spectrum of **9** showed several signals at 0.76 ppm for methyl group bound to steroid nucleus; at 0.80-1.16, 1.30-1.40, 1.70-1.88, 2.10-2.52, 3.64 and 6.36 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine

ring; at 2.70-3.40 ppm for methylene groups bound to both amine groups; 3.70 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 4.02 ppm for methylene bound chloride; at 5.94 ppm for hydroxyl, amino and amide groups. The ^{13}C NMR spectra display several chemical shifts at 15.80 ppm for methyl group bound to steroid nucleus; at 17.20, 29.80-32.16 and 67.96 ppm for dioxecine ring; at 24.22-27.72, 32.7837.28, 44.40-44.62, 50.76 and 82.46-143.30 ppm for steroid moiety, at 38.57 and 52.84 ppm for methylene groups bound to both amino groups; at 42.43 ppm for methylene group bound to chloride; at 46.10 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 51.95 and 78.38 ppm for alkyne group; at 162.60 ppm for amide group. In addition, the mass spectrum from **9** showed a molecular ion (m/z) 514.25.

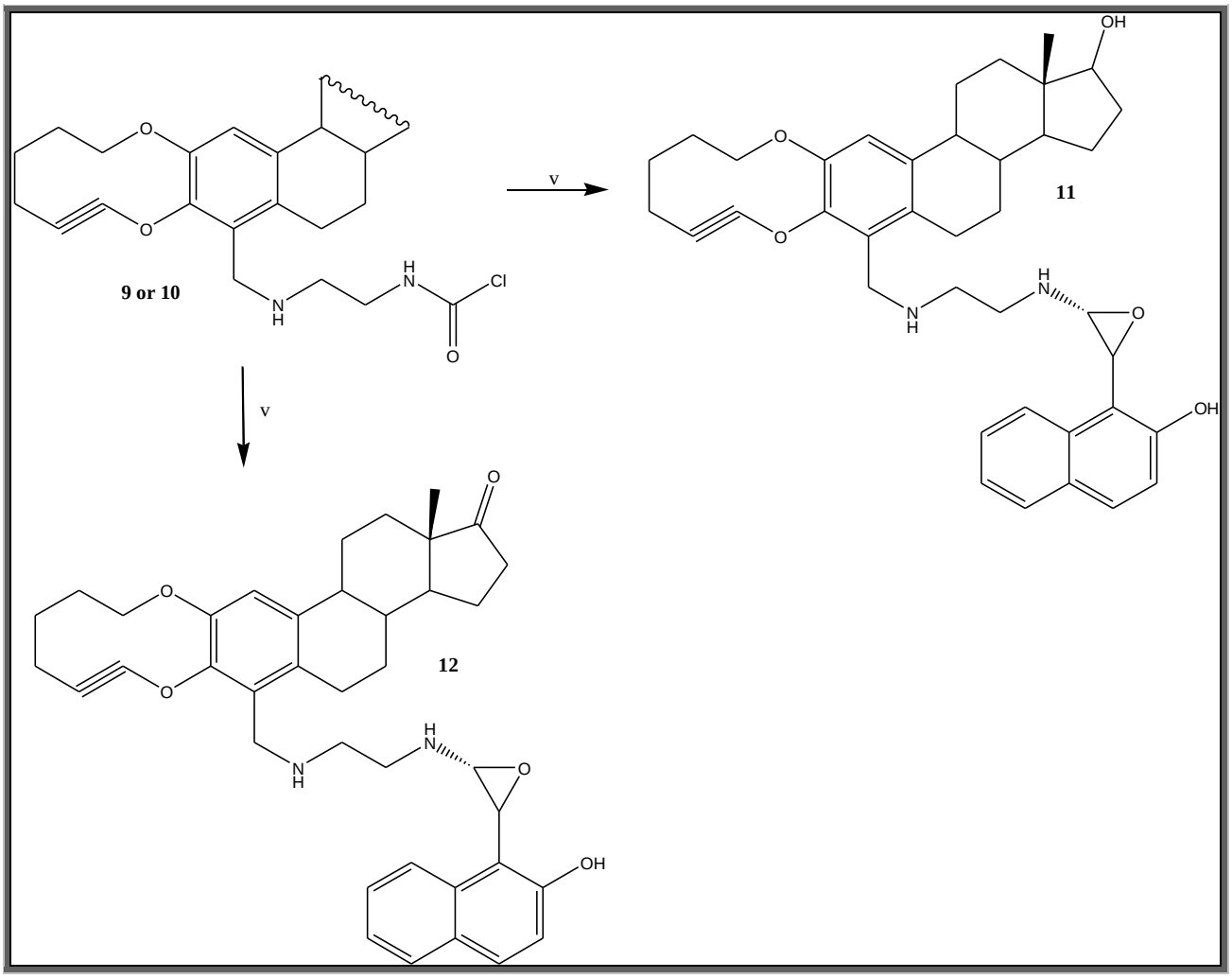

Figure 6. Synthesis of two oxirane-steroid derivatives (**11** or **12**). Compounds **9** or **10** reacted with 2-hydroxy-1-naphthaldehyde (v) to form **11** or **12**.

Other data showed several signals involved in ^{1}H NMR spectrum for the compound **10** at 0.90 ppm for methyl group bound to steroid nucleus; at1.20-1.54, 1.80-1.92, 2.10-2.54 and 6.44 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 2.70-3.40 ppm for methylene groups bound to both amine groups; 3.70 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 4.02 ppm for methylene bound chloride; at 5.76 ppm for both amino and amide groups. The ^{13}C NMR spectra display several chemical shifts at 13.82 ppm for methyl group bound to steroid nucleus; at 17.20, 29.80-32.16 and 67.96 ppm for dioxecine ring; at 21.72-27.70, 31.33, 35.12-37.50, 47.45-50.54 and

109.39-143.32 ppm for steroid moiety, at 38.57 and 52.84 ppm for methylene groups bound to both amino groups; at 42.40 ppm for methylene group bound to chloride; at 46.10 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 51.94 and 78.38 ppm for alkyne group; at 162.60 ppm for amide group; at 220.70 for ketone group. In addition, the mass spectrum from **10** showed a molecular ion (m/z) 512.24.

3.5 Preparation of oxirane-steroid derivatives

Several studies have been reported for synthesis of oxirane derivatives which involve some reagents such as chlorophyll [30], ethyl bromoacetate [31], *m*-chloroperoxybenzoic acid [32], potassium hydroxide [33], dimethyldioxiran [34] and others. In this study, the compounds **9** or **10** were reacted with 2-hydroxy-1-naphthaldehyde in basic medium to form two oxirane-steropid deivatives (**11** or **12**). The ^{1}H NMR spectrum of **11** showed several signals at 0.76 ppm for methyl group bound to steroid nucleus; at 0.80-1.16, 1.30-1.40, 1.70-1.88, 2.10-2.52, 3.64 and 6.36 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 2.70-3.40 ppm for methylene groups bound to both amine groups; 3.70 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 3.94 and 4.26 for oxirane ring; at 6.66 ppm for hydroxyl, amide and amino groups; at 7.22-7.90 ppm for naphthalene. The ^{13}C NMR spectra display several chemical shifts at 15.80 ppm for methyl group bound to steroid nucleus; at 17.20, 29.80-32.16 and 67.94 ppm for dioxecine ring; at 24.22-27.70, 32.78-37.30, 44.39-44.60, 50.76 and 82.46-109.76, 128.75, 132.13-132.37 and 141.30-143.32 ppm for steroid moiety; at 39.14 and 52.82 ppm for methylene groups bound to both amino groups; at 46.04 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 51.94 and 78.38 ppm for alkyne group; at 55.66 and 59.55 ppm for oxirane ring; at 118.80-128.00, 129.20-130.35 and 134.34-152.77 for naphthalene. In addition, the mass spectrum from **11** showed a molecular ion (m/z) 650.33.

Finally, the ^{1}H NMR spectrum of **12** showed several signals at 0.90 ppm for methyl group bound to steroid nucleus; at 1.20-1.54, 1.80-1.92, 2.10-2.54 and 6.44 ppm for steroid moiety; at 1.18, 1.60, 1.95-1.96 and 4.16-4.17 ppm for methylene groups involved in dioxecine ring; at 2.70-3.40 ppm for methylene groups bound to both amine groups; 3.70 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 3.96 and 4.26 for oxirane ring; at 6.70 ppm for hydroxyl, amide and amino groups; at 7.22-7.90 ppm for naphthalene.

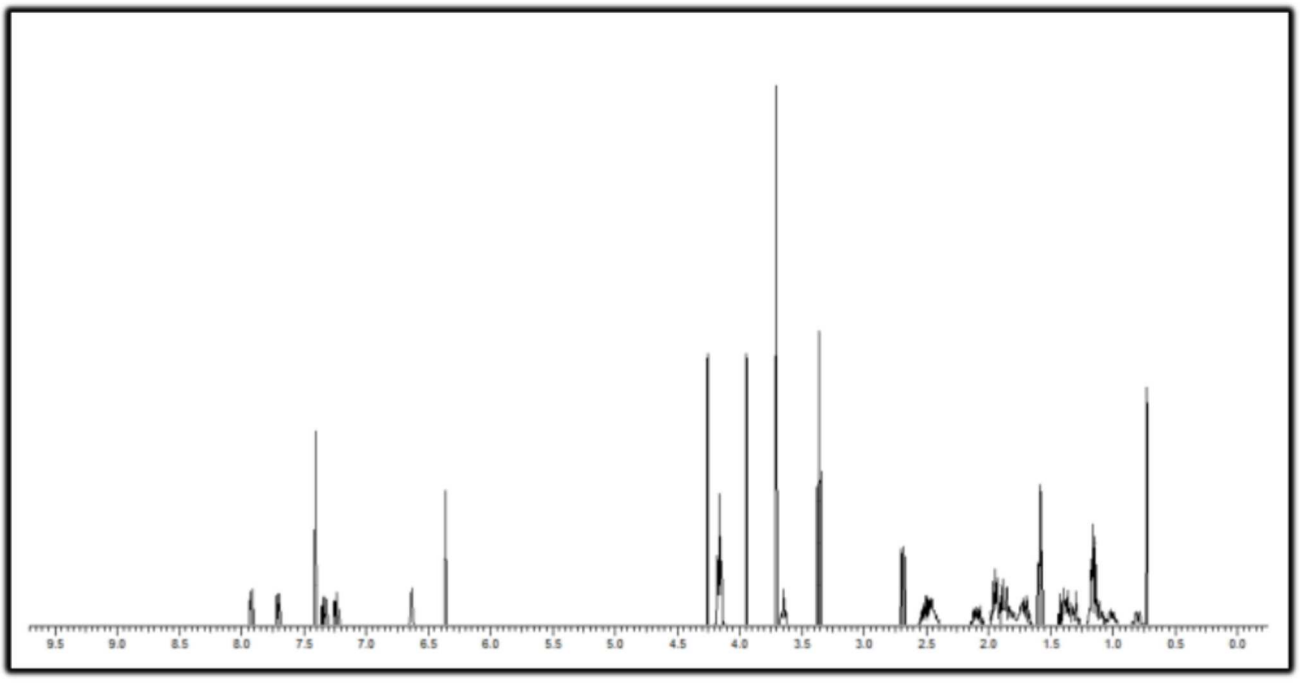

Figure 7. The scheme shown ^{1}H NMR spectrum from **11.** Analyzed with a Varian VXR300/5 FT NMR apparatus at 300 and 75.4 MHz in $CDCl_3$. Axis abscissa (ppm); ppm = parts per million.

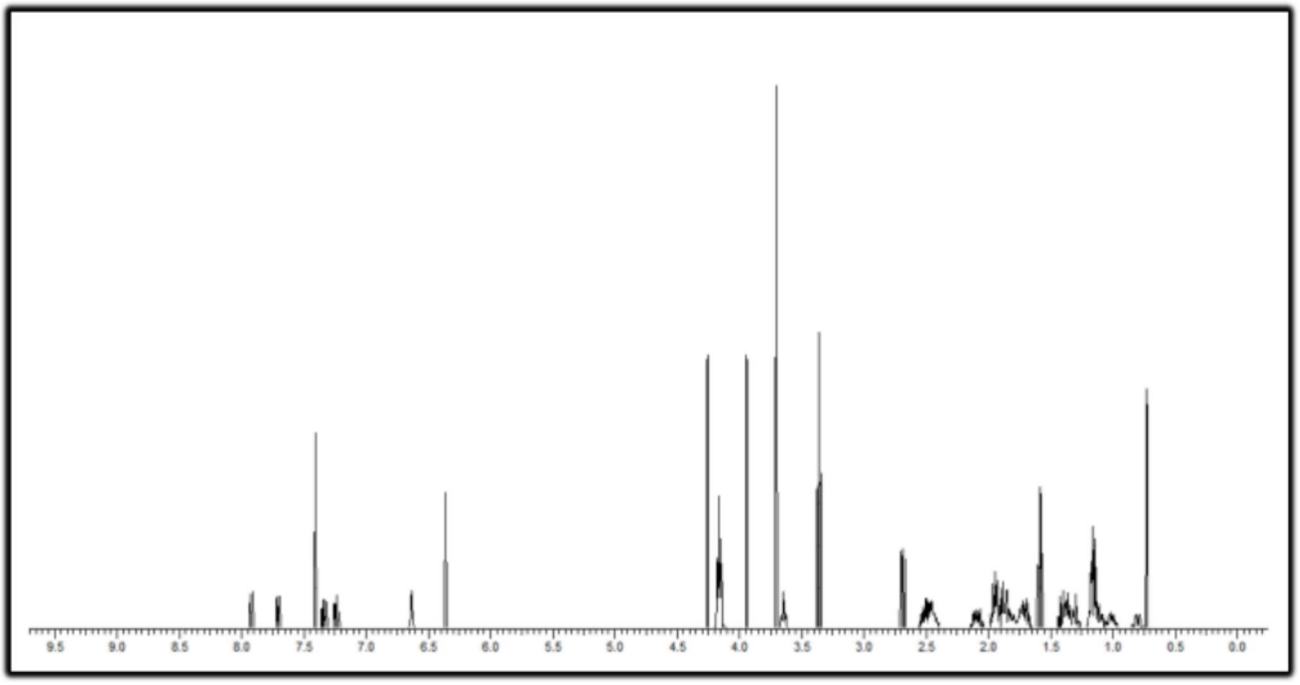

Figure 8. Visualization of ^{1}H NMR spectrum from **12.** Analyzed with a Varian VXR300/5 FT NMR apparatus at 300 and 75.4 MHz in $CDCl_3$. Axis abscissa (ppm); ppm = parts per million.

The ^{13}C NMR spectra display several chemical shifts at 13.82 ppm for methyl group bound to steroid nucleus; at 17.20, 29.79, 32.16 and 67.96 ppm for dioxecine ring; at 21.72-27.70, 31.30, 35.12-37.49, 47.45-50.52, 109.40, 128.38, 131.70-132.37 and 141.34-143.30 ppm for steroid moiety; at 39.16 and 52.84 ppm for methylene groups bound to both amino groups; at 46.10 ppm for methylene group bound to both ring A (steroid nucleus) and amino group; at 51.96 and 78.38 ppm for alkyne group; at 55.66 and 59.55 ppm for oxirane ring; at 118.80-128.00, 129.22, 130.35, 134.34 and152.74 for naphthalene; at 172.20 ppm for amide group; at 220.70 ppm for ketone group. In addition, the mass spectrum from **12** showed a molecular ion (m/z) 648.31.

Conclusions

There are several reports for the preparation of oxirane derivatives; however, some protocols use some reagents that can be *i*) expensive; *ii*) difficult to handle; *iii*) expansive and *iv*) require special conditions. Therefore, in this study is reported a facile method for the preparation of two oxiran-steroid derivatives using some strategies. It is important to mention that reagent used for their preparation was not require special conditions and are facile of handled.

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