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DESIGN AND SYNTHESIS OF TWO STEROID-DIAZOCINE DERIVATIVES

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Abstract
Several azocine derivatives have been prepared; however, some methods use expensive reagents and require special conditions. The aim of this study is to synthesize two new diazocine-steroid derivatives using a series of reactions which involve; *i*) addition (2 +2); *ii*) reduction, *iii*) oxidation and *iv*) imination/cyclization. Chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. In conclusion, in this study, is reported a facile synthesis of two steroid-diazocine derivatives using some strategies chemicals.

Keywords: Steroid, diazocine, addition, cyclization.

Introduction

For several years chemists and pharmacists have developed new heterocyclic derivatives with biological activity[i-iii]; some of these heterocyclic derivatives contain nitrogen in their chemical structure such as the azo- and diazocines which play an important role in medicinal chemistry[iv,v].For example, the synthesis of benzo[6,7][1,5]diazocino[2,1-a]isoindol-12(14H)-one from 3-(2-oxo-2-phenylethyl) isobenzofuran-1(3H)-ones and 2-(aminomethyl)aniline[vi]. In addition, a study showed the preparation of dibenzo[b,f][1,5]diazocines by the reaction of aminobenzophenoneand diphenyl phosphate[vii]. Other report, indicated the synthesis of [(5*H*)-6-oxodibenzo[*b,f*][1,5]diazocine-5-yl]arylglycinamides via an Ugi 4CC/Staudinger/aza-Wittig sequence[viii]. Additionally, a report shown the preparation of seven 6,12-epiiminodibenzo[b,f][1,5]diazocines from o-(triphenylphosphoranylideneamino)benzaldehyde andan amino-derivative[ix]. Other study showed the synthesis of 3,8-diphenyl-6,7-dihydro-1,2-diazocin-4(5H)-one by the reaction of

cyclobutanone with diphenyl-1,2,4,5-tetrazine[x]. All these experimental results showed that some procedures are available for synthesis of several azocine analogs; nevertheless, expensive reagents and special conditions are required. Therefore, in this study, two steroid-diazocine derivatives were synthesized using some chemical strategies.

Results and Discussion

Preparation of two benzocyclobuta-steroid derivatives

Different methods have been used for the synthesis of various cyclobutane analogs using some reagents such asepoxyvinylsulfone-substituted[xi], cyclobutylcarbinyl[xii], cyclopropane derivative[xiii],silver;bis(trifluoromethylsulfonyl)azanide[xiv], trifluoroacetic acid[xv] and others. In this study the first stage was achieved by the reaction of an estradiol-derivative (compound **1**) with 2,4-dinitrophenylhydrazinevia 2 + 2 cycloaddition to form an (3,5-dinitro-bicyclo[4.2.0]octa-1,5-dien-2-yl)-hydrazinemethane-steroid derivative (**3**).

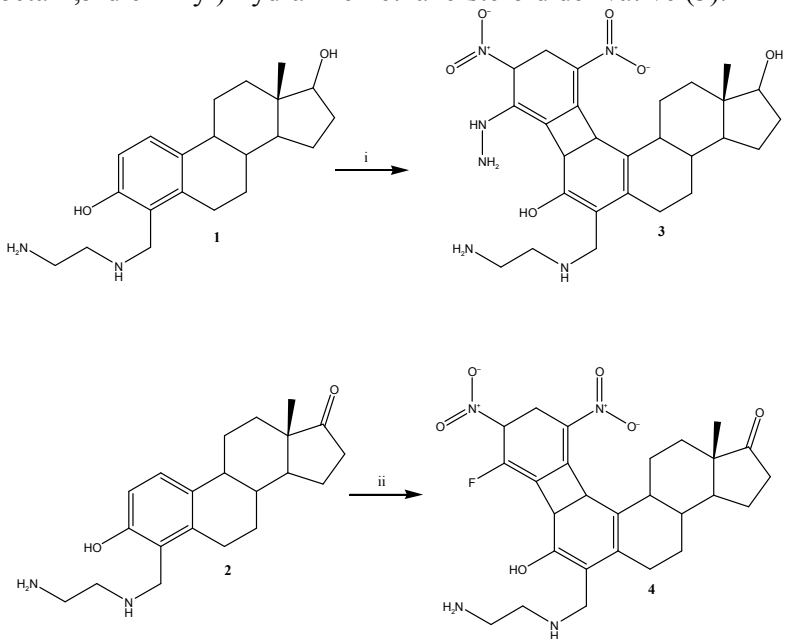

Figure 1. Synthesis of two benzocyclobuta-steroid derivatives (**3** or **4**). Reaction of estradiol-ethylenediamine (**1**) or estrone-ethylenediamine (**2**) with 2-methylimidazol usingCooper(II) chloride (i, ii) as catalyst to form **3** or **4**.

The ^{1}H NMR spectrum of **3** shows signals at 0.80 ppm for methyl group bound to steroid nucleus; at 1.34-2.62, 2.70, 3.12 and 3.64 ppm for steroid moiety; at 2.68, 2.76 ppm for methylene groups bound to both amino groups; at 3.52 ppm for methylene bound to both amino and A ring of steroid nucleus; at 3.66-4.00 and 5.70 ppm for bicyclo[4.2.0]octa-2,4-diene; at 4.70 ppm for amino and hydroxyl groups. The ^{13}C NMR spectra showed chemical shifts at 11.32 ppm for methyl group bound to steroid nucleus; at 23.02-26.02, 30.72-40.50, 42.24-43.62, 49.83, 81.72-113.22, 120.32-121.60 and 150.88 ppm for steroid nucleus; at 28.76, 119.52 and 124.82-147.28 ppm for bicyclo[4.2.0]octa-2,4-diene; at 41.17 and 51.92 ppm for methylene groups bound to both amino groups; at 48.54 ppm for methylene group bound to both A ring of steroid nucleus and amino group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 542.28.

The second stage was achieved by the reaction of an estrone-derivative (compound **2**) with 1-fluoro-2,4-dinitrobenzene via 2 + 2 cycloaddition to form an 2-fluoro-3,5-dinitro-bicyclo[4.2.0]octa-1,5-diene derivative (**4**). The ^{1}H NMR spectrum of **4** shows signals at 0.90

ppm for methyl group bound to steroid nucleus; at 1.42-2.62 and 2.70 ppm for steroid moiety; at 2.68, 2.76 ppm for methylene groups bound to both amino groups; at 3.52 ppm for methylene bound to both amino and A ring of steroid nucleus; at 3.20, 3,70-4.04 and 5.90ppm for bicyclo[4.2.0]octa-2,4-diene; at 4.06 ppm for amino and hydroxyl groups. The ^{13}C NMR spectra showed chemical shifts at 13.90 ppm for methyl group bound to steroid nucleus; at 21.52- 26.55, 31.42, 35.74-37.92, 44.88-47.38, 51.93, 115.96-121.74 and 152.45 ppm for steroid nucleus; at 27.45, 34.35, 42.32, 82.46, 122.77-141.24 and 156.26 ppm for bicyclo[4.2.0]octa-2,4-diene; at 41.17 and 51.92 ppm for methylene groups bound to both amino groups; at 48.56 ppm for methylene group bound to both A ring of steroid nucleus and amino group; at 220.18 ppm for ketone group. In addition, the mass spectrum from **4**showed a molecular ion (m/z) 528.23.

Synthesis of two amino-benzocyclobuta-steroid derivatives

There are some studies which indicate the preparation of amino derivatives using several reagents such as ammonium formate[xvi], TiO 2-graphene hybrids[xvii], $Ag^{++}/NaBH_4$[xviii], hydrazine/ ferrihydrite[xix] and others; however, some of these reagents are expensive and require special conditions. Therefore, in this study, the nitro groups involved in the chemical structure of compounds**3** or **4** were reduced with $Zn_{(dust)}/NaBH_4$ to form two amino-benzocyclobuta-steroid derivatives (compound **5** or **6**).

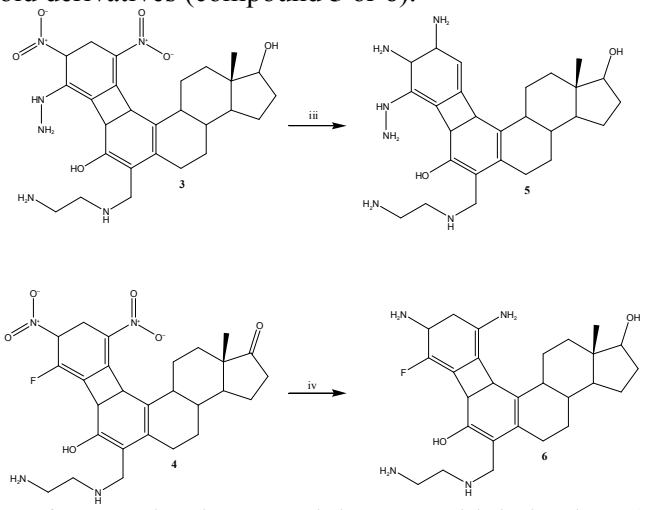

Figure 2. Preparation of two amino-benzocyclobuta-steroid derivatives (**5** or **6**) via reduction of nitro groups of benzocyclobuta-steroid derivatives (**3** or **4**) using the $Zn_{(dust)}/NaBH_4$ system (iii, iv).

The ^{1}H NMR spectrum of **5** shows signals at 0.80 ppm for methyl group bound to steroid nucleus; at 1.34-2.62, 2.70 and 3.64 ppm for steroid moiety; at 2.68 and 2.76 ppm for methylene groups bound to both amino groups; at 3.52 ppm for methylene bound to both amino and A ring of steroid nucleus; at 3.26 and3.683.20 ppm for bicyclo[4.2.0]octa-2,4-diene; at 5.40 ppm for amino and hydroxyl groups. The ^{13}C NMR spectra showed chemical shifts at 11.32 ppm for methyl group bound to steroid nucleus; at 23.02-40.51, 43.61, 49.81, 81.71, 112.47, 118.65, 122.74 and 156.46ppm for steroid nucleus; at 44.00, 50.66, 52.44, 102.51, 117.76, 121.44 and 146.50 ppm for bicyclo[4.2.0]octa-2,4-diene; at 41.16and 51.91 ppm for methylene groups bound to both amino groups; at 48.56ppm for methylene group bound to both A ring of steroid nucleus and amino group. In addition, the mass spectrum from **5** showed a molecular ion (m/z) 484.33.

Other results showed several signals of the ^{1}H NMR spectrum for **6** at 0.80 ppm for methyl group bound to steroid nucleus; at 1.36-2.16 and 2.70 and 3.64 ppm for steroid moiety; at

2.66, 2.76 ppm for methylene groups bound to both amino groups; at 3.52 ppm for methylene bound to both amino and A ring of steroid nucleus; at 3.40-3.42 and 3.98 ppm for bicyclo[4.2.0]octa-2,4-diene; at 4.00 ppm for amino and hydroxyl groups. The ^{13}C NMR spectra showed chemical shifts at 11.32 ppm for methyl group bound to steroid nucleus; at 23.02-31.40, 37.11-37.86, 42.04-43.62, 49.82, 81.72, 115.35-117.90 and 152.44 ppm for steroid nucleus; at 31.46-33.72, 43.76-44.24, 104.64-112.12 and 149.08-151.24 ppm for bicyclo[4.2.0]octa-2,4-diene; at 41.19 and 51.92 ppm for methylene groups bound to both amino groups; at 48.59 ppm for methylene group bound to both A ring of steroid nucleus and amino group. In addition, the mass spectrum from **6**showed a molecular ion (m/z) 470.30.

Preparation of two carbaldehyde derivatives

Several studies have showed the synthesis of aldehyde derivatives from oxidation of primary alcohols using some reagents such chromium(VI), palladium, rhodium or ruthenium and hydrogen peroxide[xx]. However, these reagents could induce some toxic effects from several substances produced on some reaction mixtures.Therefore, in this study a previously reported method[xxi] was used for oxidation of hydroxyl groups involved in the chemical structure of **5** or **6** with dimethyl sulfoxide to form two carbaldehyde derivatives (compounds **7** or **8**).

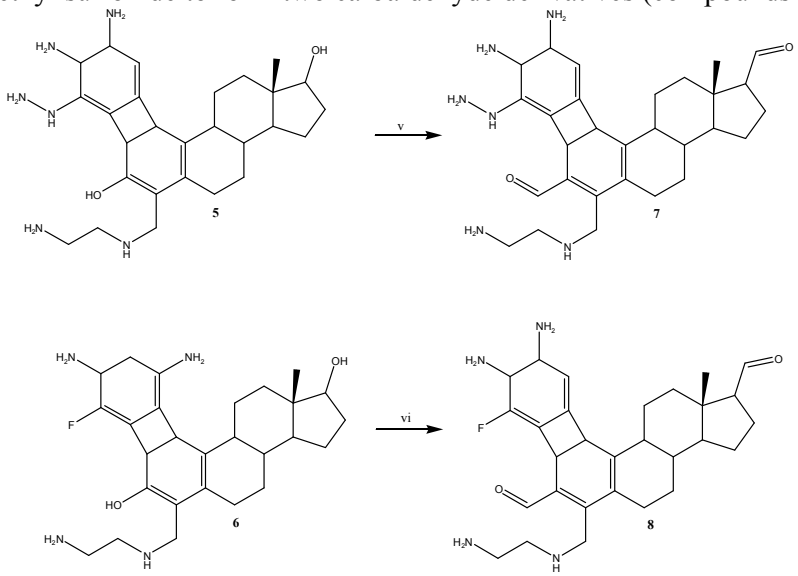

Figure 3. Synthesis of two carbaldehyde derivatives (**7** or **8**) via oxidation of hydroxyl group involved in the chemical structure of amino-benzocyclobuta-steroid derivatives(**5** or **6**) with dimethyl sulfoxide (v, vi).

The ^{1}H NMR spectrum of **7** shows signals at 0.76 ppm for methyl group bound to steroid nucleus; at 1.16-2.12, 2.68 and 2.75 ppm for steroid moiety; at 2.66, 2.76 ppm for methylene groups bound to both amino groups; at 3.60-4.70 ppm for methylene bound to both amino and A ring of steroid nucleus; at 3.10-3.26 and 3.76 ppm for bicyclo[4.2.0]octa-2,4-diene; at 4.90 ppm for amino groups; at 9.84-10.50 for both aldehyde groups. The ^{13}C NMR spectra showed chemical shifts at 14.40 ppm for methyl group bound to steroid nucleus; at 22.44-37.66, 42.68-43.08, 48.60, 55.00, 124.94, and 130.32-144.60 ppm for steroid nucleus; at 50.70, 52.43, 107.28-118.22, 126.34 and 150.40 ppm for bicyclo[4.2.0]octa-2,4-diene; at 41.15 and 51.92 ppm for methylene groups bound to both amino groups; at 48.22 ppm for methylene group bound to both A ring of steroid nucleus and amino group; at 183.92-204.18 for both aldehyde groups. In addition, the mass spectrum from **7** showed a molecular ion (m/z) 506.33.Other results showed several signals of the ^{1}H NMR spectrum from **8** at 0.76 ppm for methyl group bound to steroid nucleus; at 1.16-2.12, 2.68 and 2.75 ppm for steroid

moiety; at 2.66, 2.76 ppm for methylene groups bound to both amino groups; at 3.60 ppm for methylene bound to both amino and A ring of steroid nucleus; at 3.16-3.50 and 3.72-3.86 ppm for bicyclo[4.2.0]octa-2,4-diene; at 4.20 ppm for amino groups; at 9.82-10.52 for both aldehyde groups. The ^{13}C NMR spectra showed chemical shifts at 14.40 ppm for methyl group bound to steroid nucleus; at 22.42-37.18, 42.68, 48.60, 55.00, 123.72-130.66 and 140.82-147.37 ppm for steroid nucleus; at 41.16 and 51.92 ppm for methylene groups bound to both amino groups; at 48.22 ppm for methylene group bound to both A ring of steroid nucleus and amino group; 51.50, 52.47, 110.54-120.50, 134.48 and 159.40 ppm for bicyclo[4.2.0]octa-2,4-diene; at 183.92-204.18 for both aldehyde groups. In addition, the mass spectrum from **8**showed a molecular ion (m/z) 498.30.

Preparation of two diazecine derivatives

Several studies have been carried out to synthesis of diazecine drivatives using several reagents such as hydrochloric acid[xxii] acetic acid[xxiii]formaldehyde[xxiv], pyridine[xxv]Copper(II) oxide[xxvi] and others. In this study, the compounds **7** or **8** reacted with Copper(II) to form two diazocine derivatives (**9** or **10**).

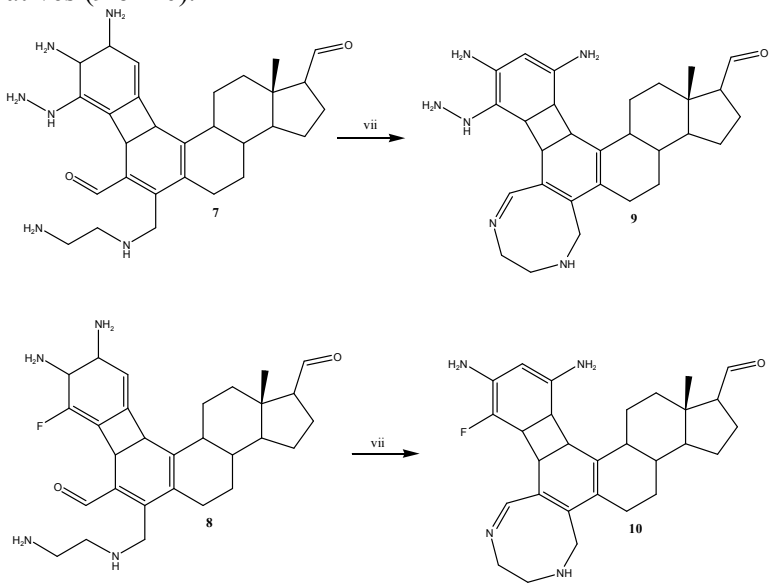

Figure 4. Synthesis of two diazecine derivatives (**9** or **10**). Reaction of two carbaldehyde derivatives (**7** or **8**) with Copper(II) chloride (vii, viii) to form **9** or **10**.

The ^{1}H NMR spectrum of **9** shows signals at 0.76 ppm for methyl group bound to steroid nucleus; at 1.16-2.12, 2.66-2.74 ppm for steroid moiety; at 2.34, 3.20-3.46 and 4.42-4.82 for bicyclo[4.2.0]octa-2,4-diene; at 2.86 and 3.54-3.66 ppm for diazocine ring; at 6.30 ppm for amino groups; at 9.22 ppm for imino group; at 9.80 ppm for aldehyde group. The ^{13}C NMR spectra showed chemical shifts at 14.40 ppm for methyl group bound to steroid nucleus; at 22.42-35.02, 42.66-44.50, 48.60, 55.00, 119.60-132.44 and 165.34 ppm for steroid nucleus; at 38.22-42.12, 98.33-101.30, 134.74 and 141.87 ppm for bicyclo[4.2.0]octa-2,4-diene; at 45.92-47.98 and 52.52 ppm for diazocine ring; at 140.36 ppm for imino group; at 204.18 ppm for aldehyde group. In addition, the mass spectrum from **9** showed a molecular ion (m/z) 488.32.

Other results showed several signals of the ^{1}H NMR spectrum for**10** at 0.76 ppm for methyl group bound to steroid nucleus; at 1.16-2.72, 2.90 and 3.64 ppm for steroid moiety; at 4.25-4.92 for bicyclo[4.2.0]octa-2,4-diene; at 2.86 and 3.56 and 3.66 ppm for diazocine ring; at

5.12 ppm for amino groups; at 9.26 ppm for imino group; at 10.52 ppm for aldehyde group. The ^{13}C NMR spectra showed chemical shifts at 14.40 ppm for methyl group bound to steroid nucleus; at 22.42-35.04, 42.68, 44.51, 48.60, 117.12, 130.36-135.22 and 158.70 ppm for steroid nucleus; at 38.72-42.14, 43,46, 100.74, 127.02 and 142.60-149.97 ppm for bicyclo[4.2.0]octa-2,4-diene; at 45.92-47.96 and 52.00 ppm for diazocine ring; at 140.37 ppm for imino group; at 204.18 ppm for aldehyde group. In addition, the mass spectrum from **10**showed a molecular ion (m/z) 476.29.

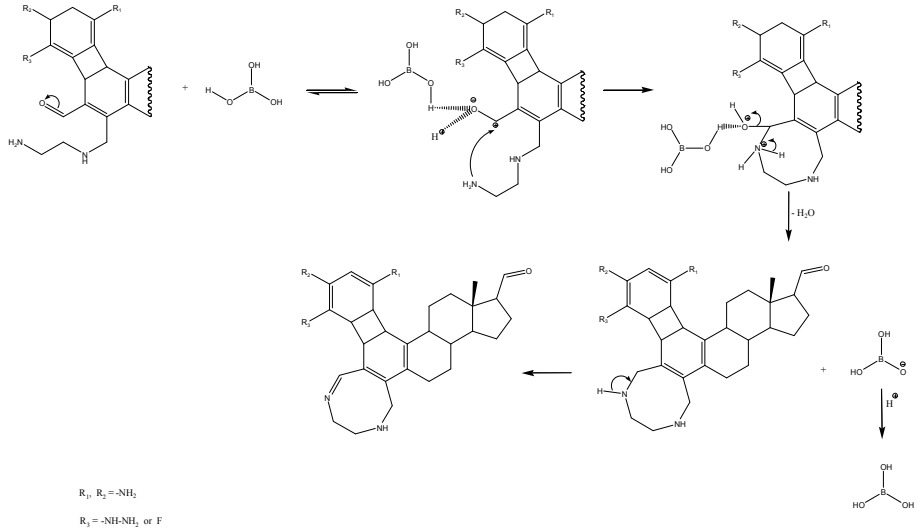

Figure 5. Reaction mechanism involved in the synthesis of two diazacine-steroid derivatives (compounds **9** or **10**).

Conclusions.

In this study, is reported a facile synthesis of two steroid-diazocine derivatives using some strategies chemicals.

Acknowledgements

None

Experimental

General methods

The compounds amino-estradiol (**1**) and amino-estrone (**2**) were synthesize using a previously method reported[xxvii]. In addition, all the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. 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.

Chemical synthesis

Preparation of two benzocyclobuta-steroid derivatives

A solution of compounds **1** or **2** (0.40 mmol), 2-methylimidazol (40 mg; 0.49 mmol), Cooper(II) chloride anhydrous (67 mg, 0,5), and 5 ml of methanol 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.

(13aS)-6-(((2-aminoethyl)amino)methyl)-8-hydrazinyl-13a-methyl-9,11-dinitro-2,3,3a,3b,4,5,7a,9,10,11b,11d,12,13,13a-tetradecahydro-1H-benzo[3,4]cyclobuta[1,2-g]cyclopenta[a]phenanthrene-1,7-diol (3)

yielding 65 %; IR (V_{max}, cm^{-1}) 3460, 3380, 3200, and 1542: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.80 (s, 3H), 1.34-2.62 (m, 14H), 2.68 (m, 2H), 2.70 (m, 1H), 2.76 (m, 2H), 3.12 (m, 1H), 3.52 (m, 2H), 3.64 (m, 1H), 3.66-3.82 (m, 3H), 4.00 (m, 1H), 4.70 (broad, 8H), 5.70 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 11.32, 23.02, 25.04, 26.02, 28.76, 30.72, 31.42, 34.82, 37.12, 37.85, 40.50, 41.16, 42.24, 43.62, 48.54, 49.83, 51.92, 81.72, 81.86, 113.22, 119.52, 120.32, 121.60, 124.82, 133.14, 147.28, 150.88 ppm. EI-MS m/z: 542.28. Anal. Calcd. for $C_{27}H_{38}N_6O_6$: C, 59.76; H, 7.06; N, 15.49; O, 17.69. Found: C, 59.70; H, 7.00.

(13aS)-6-(((2-aminoethyl)amino)methyl)-8-fluoro-7-hydroxy-13a-methyl-9,11-dinitro-2,3,3a,3b,4,5,7a,9,10,11b,11d,12,13,13a-tetradecahydro-1H-benzo[3,4]cyclobuta[1,2-g]cyclopenta[a]phenanthren-1-one (4)

yielding 48 %; IR (V_{max}, cm^{-1}) 3460, 3380, 1542, and 1012: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.42-2.62 (m, 14H), 2.68 (m, 1H), 2.70 (m, 1H), 2.76 (m, 2H), 3.20 (m, 1H), 3.52 (m, 2H), 3.70 (m, 1H), 3.88-4.04 (m, 2H), 4.06 (broad, 4H), 5.90 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 13.90, 21.52, 25.11, 26.03, 26.55, 27.45, 31.42, 34.35, 35.74, 37.92, 41.17, 42.32, 44.88, 47.38, 48.56, 51.92, 51.93, 82.46, 115.96, 117.78, 121.74, 122.77, 127.09, 141.24, 152.45, 156.26, 220.18 ppm. EI-MS m/z: 528.23. Anal. Calcd. for $C_{27}H_{33}FN_4O_6$: C, 61.35; H, 6.29; F, 3.59; N, 10.60; O, 18.16. Found: C, 61.30; H, 6.21.

Synthesis of two amino-benzocyclobuta-steroid derivatives

A solution of compounds **3** or **4** (0.50 mmol), sodium borohydride (20 mg; 0.53 mmol), Zn dust (1 mmol), and 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:hexane:water (4:1:1) system.

(13aS)-9,10-diamino-6-(((2-aminoethyl)amino)methyl)-8-hydrazinyl-13a-methyl-2,3, 3a,3b,4,5,7a,9,10,11b,11d,12,13,13a-tetradecahydro-1H-benzo[3,4]cyclobuta[1,2-g] cyclopenta[a]phenanthrene-1,7-diol (5)

yielding 56 %; IR (V_{max}, cm^{-1}) 3460, 3382, and 3200: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.80 (s, 3H), 1.34-2. 2.62 (m, 15H), 2.68 (m, 2H), 2.70 (m, 1H), 2.76 (m, 2H), 3.26 (m, 1H), 3.52 (m, 2H), 3.64 (m, 1H), 3.68 (m, 1H), 3.76-5.20 (m, 2H), 5.40 (broad, 12H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 11.32, 23.02, 25.08, 26.03, 30.71, 31.43, 37.04, 37.102, 37.86, 40.51, 41.16, 43.61, 44.00, 48.56, 49.81, 50.66, 51.91, 52.44, 81.71, 102.51, 112.47, 117.76, 118.65, 121.44, 122.72, 146.50, 159.46 ppm. EI-MS m/z: 484.33. Anal. Calcd. for $C_{27}H_{42}N_6O_2$: C, 67.19; H, 8.77; N, 17.41; O, 6.63. Found: C, 67.12; H, 8.70.

(13aS)-9,11-diamino-6-(((2-aminoethyl)amino)methyl)-8-fluoro-13a-methyl-2,3,3a,3b,4,5,7a,9,10,11b,11d,12,13,13a-tetradecahydro-1H-benzo[3,4]cyclobuta[1,2-g]cyclopenta[a]phenanthrene-1,7-diol (6)

yielding 45 %; IR (V_{max}, cm^{-1}) 3462, 3380, 3200, and 1012: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.80 (s, 3H), 1.36-2.16 (m, 3H), 2.66 (m, 2H), 2.70 (m, 1H), 2.76 (m, 2H), 3.40-3.42 (m, 2H), 3.52 (m, 2H), 3.64 (m, 1H), 3.98 (m, 1H), 4.00 (broad, 9H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 11.32, 23.02, 25.08, 26.02, 30.72, 31.40, 31.46, 33.72, 37.11, 37.86, 41.19, 42.04, 43.62, 43.76, 44.24, 48.59, 49.82, 51.92, 81.72, 104.64, 112.12, 115.35, 116.76, 117.90, 149.08, 151.24, 152.44 ppm. EI-MS m/z: 470.30.

Anal. Calcd. for $C_{27}H_{39}FN_4O_2$: C, 68.91; H, 8.35; F, 4.04; N, 11.90; O, 6.80. Found: C, 68.86; H, 8.30.

Preparation of two carbaldehyde derivatives

A solution of compounds **5** or **6** (0.50 mmol) and 5 ml of dimethyl sulfoxide was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water:acetone (4:1:1) system.

(13aS)-9,10-diamino-6-(((2-aminoethyl)amino)methyl)-8-hydrazinyl-13a-methyl-2,3, 3a,3b,4,5,7a,9,10,11b,11d,12,13,13a-tetradecahydro-1H-benzo[3,4]cyclobuta[1,2-g] cyclopenta[a]phenanthrene-1,7-dicarbaldehyde (7).

yielding 63 %; IR (V_{max}, cm^{-1}) 3460, 3382 and 1740: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 1.16-2.12 (m, 14H), 2.66 (m, 2H), 2.68 (m, 1H), 2.75 (m, 1H), 2.76 (m, 2H), 3.10-3.26 (m, 2H), 3.60 (m, 2H), 3.76 (m, 1H), 4.12 (m, 1H), 4.70 (m, 1H), 4.90 (broad, 10H), 9.84 (d, 1H, J = 1.80 Hz), 10.50 (d, 1H, J = 1.05 Hz) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 14.40, 22.44, 23.70, 25.41, 26.16, 32.07, 32.32, 35.04, 37.66, 41.15, 42.68, 42.75, 43.08, 48.22, 48.60, 50.70, 51.92, 52.43, 55.00, 107.28, 118.22, 124.94, 126.34, 130.32, 139.23, 144.60, 150.40, 183.92, 204.18 ppm. EI-MS m/z: 506.33. Anal. Calcd. for $C_{29}H_{42}N_6O_2$: C, 68.74; H, 8.36; N, 16.59; O, 6.32. Found: C, 68.68; H, 8.30.

(13aS)-9,10-diamino-6-(((2-aminoethyl)amino)methyl)-8-fluoro-13a-methyl-2,3,3a, 3b,4,5,7a,9,10,11b,11d,12,13,13a-tetradecahydro-1H-benzo[3,4]cyclobuta[1,2-g] cyclopenta[a]phenanthrene-1,7-dicarbaldehyde (8)

yielding 54 %; IR (V_{max}, cm^{-1}) 3462, 3380, 1742, and 1012: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 1.16-2.12 (m, 14H), 2.66 (m, 2H), 2.68 (m, 1H), 2.75 (m, 1H), 2.76 (m, 2H), 3.16 (m, 1H), 3.50 (m, 1H), 3.60 (m, 2H), 3.72 (m, 1H), 3.86 (m, 1H), 4.20 (broad, 7H), 4.82 (m, 1H), 9.82 (d, 1H, J = 1.80 Hz), 10.52 (d, 1H, J = 1.80 Hz) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 14.40, 22.42, 23.71, 25.42, 26.16, 32.06, 32.37, 35.04, 37.18, 41.16, 42.68, 43.09, 44.26, 48.22, 48.60, 51.50, 51.92, 52.47, 55.00, 110.54, 120.50, 123.72, 130.66, 134.48, 140.82, 147.37, 159.40, 183.92, 204.18 ppm. EI-MS m/z: 494.30. Anal. Calcd. for $C_{29}H_{39}FN_4O_2$: C, 70.42; H, 7.95; F, 3.84; N, 11.33; O, 6.47. Found: C, 70.38; H, 7.90.

Preparation of two diazecine derivatives

A solution of compounds **8** or **9** (0.50 mmol), boric acid (50 mg, 0.80 mmol) and 5 ml of methanol was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:2) system.

(17aS,Z)-13,15-diamino-12-hydrazinyl-17a-methyl-2,3,3a,3b,4,5,6,7,8,9,11b,11c,15a, 15b,15d,16,17,17a-octadecahydro-1H-benzo[3',4']cyclobuta[1',2':3,4]cyclopenta[7,8] phenanthro[1,2-f][1,4]diazocine-1-carbaldehyde (9)

yielding 44 %; IR (V_{max}, cm^{-1}) 3462, 3380, 3320 and 1740: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 1.16-2.12 (m, 14H), 2.34 (m, 1H), 2.66-2.74 (m, 2H), 2.86 (m, 2H), 3.20-3.46 (m, 2H), 3.54 (m, 2H), 3.66 (m, 2H), 4.42-4.82 (m, 2H), 6.30 (broad, 8H), 9.22 (m, 1H), 9.80 (d, 1H, J = 1.80 Hz) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 14.40, 22.42, 23.71, 25.42, 26.38, 32.56, 35.02, 38.32, 42.12, 42.66, 42.82, 43.01, 43.41, 44.51, 45.92, 47.98, 48.60, 52.52, 55.00, 98.33, 101.30, 119.60, 128.76, 132.44, 134.74, 140.36, 141.87, 165.34, 204.18 ppm. EI-MS m/z: 488.32. Anal. Calcd. for $C_{29}H_{40}N_6O$: C, 71.28; H, 8.25; N, 17.20; O, 3.27. Found: C, 71.20; H, 8.20.

(17aS,Z)-13,15-diamino-12-fluoro-17a-methyl-2,3,3a,3b,4,5,6,7,8,9,11b,11c,15a,15b, 15d,16,17,17a-octadecahydro-1H-benzo[3',4']cyclobuta[1',2':3,4]cyclopenta[7,8]phenanthro[1,2-f][1,4]diazocine-1-carbaldehyde (10)

yielding 54 %; IR (V_{max}, cm^{-1}) 3460, 3382, 3320, 1742 and 1012: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 1.16-2.72 (m, 17H), 2.86 (m, 2H), 2.90 (m, 1H), 3.56 (m,

2H), 3.64 (m, 1H), 3.66 (m, 2H), 3.72 (m, 1H), 3.86 (m, 1H), 4.25 (m, 1H), 4.92 (m, 1H), 5.12 (broad, 5H), 9.26 (m, 1H), 10.52 (d, 1H, J = 1.80 Hz) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 14.40, 22.42, 23.71, 25.42, 26.38, 32.56, 35.04, 38.72, 42.14, 42.68, 42.82, 43.46, 43.48, 44.51, 45.92, 47.96, 48.60, 52.55, 55.00, 100.74, 117.12, 127.02, 130.36, 135.22, 140.375, 142.60, 149.97, 158.70, 204.18 ppm. EI-MS m/z: 476.29. Anal. Calcd. for $C_{29}H_{37}FN_4O_2$: C, 73.08; H, 7.82; F, 3.99; N, 11.75; O, 3.36. Found: C, 73.00; H, 7.76.

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