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Synthesis and biological activity of two oxireno-azecin-imidazole derivatives on perfusion pressure via guanylate cyclase inhibition

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ABSTRACT

Some drugs have used in the treatment of heart failure; however, several of these drugs can produce secondary effects such as arrhythmia, hypotension and others. Therefore, the objective of this study was to synthesize two oxireno-azecin-imidazole derivatives (compounds 13 and 14) from two estradiol and estrone analogs through a series of reactions which involving; a) addition; b) acetylation; c) epoxidation; d) formation of two azecine derivatives; e) removal of silyl fragment of the azecines with hydrofluoric acid. Additionally, these compounds were confirmed by NMR spectroscopic data. Then, biological activity of the oxireno-diazepam-imidazole derivatives against perfusion pressure was evaluate in an isolated rat heart model, using the BAY-41-2272 (guanylate cyclase agonist), NS-2028 (guanylate cyclase inhibitor) and nifedipine (calcium channel antagonist) as controls. The results indicate that compounds 13 and 14 increased the perfusion pressure in the absence or presence of BAY-41-2272 and NS-2028; however, this effect was inhibited by nifedipine. These data indicate that compounds 13 and 14 could have a dual effect on perfusion pressure through guanylate cyclase inhibition and calcium channel type-L activation.

Keywords: *estrone, estradiol, oxireno, azecine, imidazole, guanylate cyclase*.

1. INTRODUCTION

Congestive heart failure (CHF) is a main factors involved in the development of cardiovascular diseases worldwide [1, 2]. It is important to mention that, several drugs have used to treatment of CHF; these drugs induces hemodynamic effects that can be beneficial patient with CHF [3-6]. However, some of these medications may produce some secondary effects such as hypotension [7], arrhythmias [8], hyperkalemia [9, 10] and fluid retention [11]. In the search of new therapeutic alternatives to treatment of CHF, several drugs have development: for example, the preparation of a hydroxyphenyl derivative which showed a positive inotropic effect in an isolated pig heart model [12]. Another report indicates that sulmazole (AR-L115BS) can induce a positive inotropic effect in an isolated canine ventricular trabeculae model [13]. Another study shown of that a dihydropyridine-derivative (Bayk 8644) induces a positive inotropic activity in myocardial cells via calcium channels activation [14]. In addition, a study showed that some progesterone-analogs can exert positive inotropic activity in an isolated heart model through glycoside receptor activation [15, 16]. Other study showed that a steroid-derivative (strophanthidine) can exert inotropic activity by increasing intracellular calcium levels "*in vitro*" [17]. In addition, a report shows that compound F90927 (a steroid-analog) induce positive inotropic activity in cardiac muscle through L-type Ca^{2+} channel activation [18]. These experimental reports suggest indicate that several drugs have been used for the treatment of CHF; however, the cell site and the molecular mechanism by which they exert their effect is not very clear; this phenomenon could be due to the different protocols used or to the differences in the chemical structure of each compound. The aim of this study was synthesize a new oxirenodiazecin-imidazole derivative to evaluate their inotropic activity using an isolated heart rat model.

2. EXPERIMENTAL SECTION

Chemical synthesis. The compounds **1** and **2** were synthesized using a method previously reported [19]. 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.

Preparation of two imidazol-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.

(12aS)-1,7-bis((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-1,2,3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-hexadecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazole (3)

yielding 45 %; IR (V_{max}, cm^{-1}) 3490, 3322, 1210, and 1110: ^1H NMR (500 MHz, Chloroform-*d*) δ_H: 0.07 (s, 6H), 0.11 (s, 6H), 0.87 (s, 9H), 0.88 (s, 3H), 0.92 (s, 9H), 1.32-1.92 (m, 13H), 1.94 (s, 3H), 2.00-3.55 (m, 5H), 3.80-3.92 (m, 2H), 5.20 (m, 1H), 8.16 (broad, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: - 4.50, -4.24, 11.38, 18.02, 18.50, 20.62, 22.22, 24.61, 25.41, 25.52, 27.40, 30.67, 31.03, 37.47, 38.45, 43.10, 43.60, 45.51, 46.50, 49.45, 57.03, 68.07, 81.66, 90.10, 124.72, 148.90, 154.70, 161.44 ppm. EI-MS m/z: 582.40. Anal. Calcd. for $C_{34}H_{58}N_2O_2Si_2$: C, 70.04; H, 10.03; N, 4.80; O, 5.49; Si, 9.63. Found: C, 70.00; H, 10.00.

(12aS)-7-((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazol-1(2H)-one (4)

yielding 54 %; IR (V_{max}, cm^{-1}) 3488, 3320, 1712, and 1112: ^1H NMR (500 MHz, Chloroform-*d*) δ_H: 0.13 (s, 6H), 0.90 (s, 3H), 0.92 (s, 9H), 1.37-1.92 (m, 9H), 1.94 (s, 3H), 1.98-2.46 (m, 8H), 3.80-3.92 (m, 2H), 5.20 (m, 1H), 8.16 (broad, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.24, 13.90, 18.50, 20.62, 21.52, 22.26, 25.42, 25.4, 26.02, 27.95, 30.67, 35.74, 37.47, 43.66, 45.51, 47.38, 49.35, 51.92, 57.02, 68.05, 90.10, 127.44, 148.90, 154.70, 157.32, 220.19 ppm. EI-MS m/z: 466.30. Anal. Calcd. for $C_{28}H_{42}N_2O_2Si$: C, 72.05; H, 9.07; N, 6.00; O, 6.86; Si, 6.02. Found: C, 72.00; H, 9.00.

Synthesis of two chloroamide derivatives.

A solution of compounds **3** or **4** (0.50 mmol), chloroacetyl chloride (50 µl; 0.63 mmol), triethylamine (90 µl; 0.64 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 (4:1) system.

1-((12aS)-1,7-bis((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-2,3,3a,3b,4,5,7a,7b,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazol-8-(1H)-yl)-2-chloroethan-1-one (5)

yielding 66 %; IR (V_{max}, cm^{-1}) 3490, 3320, 1630, and 1110: ^1H NMR (500 MHz, Chloroform-*d*) δ_H: 0.06 (s, 6H), 0.11 (s, 6H), 0.86 (s, 9H), 0.88 (s, 3H), 0.92 (s, 9H), 1.32-1.52 (m, 9H), 1.73 (s, 3H), 1.78-3.55 (m, 9H), 4.14-4.20 (m, 2H), 4.42-4.71 (m, 2H), 5.22 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.51, -4.26, 11.34, 18.02, 18.51, 19.76, 22.23, 24.60, 25.41, 25.50, 27.42, 30.67, 31.05, 37.64, 38.44, 42.04, 43.11, 43.61, 44.01 , 46.50, 49.47, 54.76, 66.55, 81.68, 90.29, 128.91, 152.40, 153.00, 157.81, 165.70 ppm. EI-MS m/z: 658.37. Anal. Calcd. for $C_{36}H_{59}ClN_2O_3Si_2$: C, 65.56; H, 9.02; Cl, 5.38; N, 4.25; O, 7.28; Si, 8.52. Found: C, 65.50; H, 9.00.

(12aS)-7-((tert-butyldimethylsilyl)oxy)-8-(2-chloroacetyl)-9,12a-dimethyl-3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazol-1(2H)-one (6)

74 %; IR (V_{max}, cm^{-1}) 3322, 1712, 1632, and 1112: ^1H NMR (500 MHz, Chloroform-*d*) δ_H: 0.11 (s, 6H), 0.90 (s, 3H), 0.92 (s, 9H), 1.38-1.70 (m, 6H), 1.73 (s, 3H), 1.87-2.80 (m, 11H), 4.12-4.20 (m, 2H), 4.42-4.71 (m, 2H), 5.22 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.26, 13.86, 18.51, 19.77, 21.51, 22.26, 25.42, 26.03, 27.95, 30.67, 35.74, 37.64, 42.02, 43.66, 44.02, 47.38, 49.35, 51.93, 54.74, 66.56, 90.29, 131.62, 152.40, 153.01, 153.66, 165.70, 220.20 ppm. EI-MS m/z: 542.27. Anal. Calcd. for $C_{30}H_{43}ClN_2O_3Si$: C, 66.33; H, 7.98; Cl, 6.53; N, 5.16; O, 8.84; Si, 5.17 Found: C, 66.28; H, 7.92.

Preparation of oxiran derivatives.

A solution of compounds **5** or **6** (0.30 mmol), 2-hydroxy-1-naphthaldehyde (55 mg; 0.32 mmol), 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.

((12aS)-1,7-bis((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-2,3,3a,3b,4,5,7a,7b,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazol-8-(1H)-yl)((2R)-3-(2-hydroxynaphthalen-1-yl)oxiran-2-yl)methanone (7)

yielding 44 %; IR (V_{max}, cm^{-1}) 3400, 3320, 1630, and 1110: ^1H NMR (500 MHz, Chloroform-*d*) δ_H: 0.07 (s, 6H), 0.11 (s, 6H), 0.86 (s, 9H), 0.88 (s, 3H), 0.92 (s, 9H), 1.32-1.62 (m, 9H), 1.73 (s, 3H), 1.78-3.55 (m, 9H), 4.10 (m, 1H), 4.42-4.47 (m, 2H), 4.48 (m, 1H), 5.22 (m, 1H), 7.22-7.90 (m, 6H), 9.08 (broad 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.50, -4.26, 11.35, 16.83, 17.82, 18.52, 22.23, 24.62, 25.42, 25.74, 27.42, 30.67, 31.05, 37.64, 38.45, 43.11, 43.61, 11.4, 46.49, 49.45, 53.46, 53.90, 56.54, 66.56, 81.66, 90.29, 118.84, 121.45, 122.58, 123.43, 126.81, 127.85, 128.93, 129.22, 130.35, 134.66, 153.92, 154.20, 157.81, 159.12, 171.10 ppm. EI-MS m/z: 794.45. Anal. Calcd. for $C_{47}H_{66}N_2O_5Si_2$: C, 70.99; H, 8.37; N, 3.52; O, 10.06; Si, 7.06. Found: C, 70.92; H, 8.30.

(12aS)-7-((tert-butyldimethylsilyl)oxy)-8-((2R)-3-(2-hydroxynaphthalen-1-yl)oxirane-2-carbonyl)-9,12a-dimethyl-3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazol-1-(2H)-one (8)

yielding 55 %; IR (V_{max}, cm^{-1}) 3400, 3320, 1712, 1630 and 1110: ^1H NMR (500 MHz, Chloroform-*d*) δ_H: 0.11 (s, 6H), 0.90 (s, 3H), 0.92 (s, 9H), 1.38-1.70 (m, 6H), 1.73 (s, 3H), 1.86-2.80 (m, 11H), 4.10 (m, 1H), 4.42-4.47 (m, 2H), 4.48 (m, 1H), 5.22 (m, 1H), 7.22-7.90 (m, 6H), 9.10 (broad 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.26, 13.86, 16.82, 18.51, 21.52, 22.26, 25.42, 26.02, 27.95, 30.67, 35.74, 37.64, 43.66, 44.01, 47.37, 49.34, 51.91, 53.46, 53.90, 56.54, 66.56, 90.29, 118.86, 121.45, 122.58, 123.43, 126.81, 127.86, 129.22, 130.36, 131.63, 134.66, 153.67, 153.92, 154.17, 159.12, 171.07, 220.20 ppm. EI-MS m/z: 678.34. Anal. Calcd. for $C_{41}H_{50}N_2O_5Si$: C, 72.53; H, 7.42; N, 4.13; O, 11.78; Si, 4.14. Found: C, 72.48; H, 7.40.

Preparation of two imidazole-oxiran-naphthaldehyde-steroid complex.

A solution of compounds **7** or **8** (0.50 mmol), and 2 ml of dimethyl sulfoxide was stirring to reflux for 24 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:benzene:hexane (3:1:1) system.

1-((3R)-3-((12aS)-1,7-bis((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-1,2,3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-hexadecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta-[1,2-d]imidazole-8-carbonyl)oxiran-2-yl)-2-naphthaldehyde (9)

yielding 54 %; IR (V_{max}, cm^{-1}) 3322, 1724, 1630 and 1110: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.07 (s, 6H), 0.11 (s, 6H), 0.86 (s, 9H), 0.88 (s, 3H), 0.92 (s, 9H), 1.32-1.62 (m, 9H), 1.73 (s, 3H), 1.78-3.55 (m, 9H), 3.86 (m, 1H), 4.42-4.47 (m, 2H), 4.48 (m, 1H), 5.22 (m, 1H), 7.22-8.46 (m, 6H), 10.00 (s, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.52, -4.26, 11.35, 16.84, 17.82, 18.52, 22.22, 25.22, 25.42, 25.74, 27.43, 30.67, 32.97, 37.64, 38.45, 41.82, 43.11, 43.61, 44.02, 46.49, 49.47, 54.70, 56.54, 66.56, 82.61, 90.28, 123.32, 127.98, 128.91, 129.42, 129.52, 129.57, 130.15, 130.86, 133.9, 142.28, 146.00, 154.19, 157.81, 159.13, 171.10, 191.60 ppm. EI-MS m/z: 806.45. Anal. Calcd. for $C_{48}H_{66}N_2O_5Si_2$: C, 71.42; H, 8.24; N, 3.47; O, 9.91; Si, 6.96. Found: C, 71.38; H, 8.20.

1-((3R)-3-((12aS)-7-((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-1-oxo-1,2,3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-hexadecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta-[1,2-d]imidazole-8-carbonyl)oxiran-2-yl)-2-naphthaldehyde (10)

yielding 43 %; IR (V_{max}, cm^{-1}) 3322, 1722, 1712 and 1110: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.11 (s, 6H), 0.90 (s, 3H), 0.92 (s, 9H), 1.38-1.70 (m, 6H), 1.73 (s, 3H), 1.85-2.80 (m, 11H), 3.86 (m, 1H), 4.42-4.47 (m, 2H), 4.48 (m, 1H), 5.22 (m, 1H), 7.22-8.46 (m, 6H), 10.00 (s, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.24, 13.86, 16.85, 18.52, 21.52, 22.26, 25.4, 25.42, 26.03, 27.95, 30.67, 35.72, 37.62, 41.81, 43.66, 44.02, 47.38, 49.35, 51.92, 54.70, 56.54, 66.56, 90.29, 123.32, 127.98, 129.42, 129.53, 129.57, 130.15, 130.84, 131.64, 133.91, 142.28, 146.01, 153.68, 154.20, 159.12, 171.10, 191.60, 220.18 ppm. EI-MS m/z: 690.34. Anal. Calcd. for $C_{42}H_{50}N_2O_5Si$: C, 73.01; H, 7.29; N, 4.05; O, 11.58; Si, 4.06. Found: C, 73.00; H, 7.20.

Synthesis of two steroid-oxireno-diazecine derivatives.

A solution of compounds **9** or **10** (0.50 mmol), ethylenedimine (50 µl, 0.74 mmol)) and boric acid (40 mg, 0.65 mmol) and 5 ml of methanol was stirring to reflux for 12 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system.

(1E,5Z,13aS)-1-((12aS)-1,7-bis((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-2,3,3a,3b,4,5,7a,7b,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta-[1,2-d]imidazol-8(1H)-yl)-3,4,12c,13a-tetrahydronaphtho[2,1-f]oxireno[2,3-h][1,4] diazecine (11).

yielding 44 %; IR (V_{max}, cm^{-1}) 3322, 1162 and 1110: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.07 (s, 6H), 0.11 (s, 6H), 0.86 (s, 9H), 0.88 (s, 3H), 0.92 (s, 9H), 1.32-1.86 (m, 12H), 1.88 (s, 3H), 1.90-3.05 (m, 5H), 3.32 (m, 1H), 3.54 (m, 1H), 4.22-4.34 (m, 4H), 4.41 (m, 1H), 4.68 (m, 1H), 5.22 (m, 1H), 5.81 (m, 1H), 7.40-7.92 (m, 2H), 7.94 (m, 1H), 8.05-8.18 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.50, -4.50, -4.26, 11.37, 18.02, 18.52, 22.22, 22.36, 24.60, 25.42, 25.51, 27.42, 30.67, 31.05, 37.74, 38.45, 43.11, 43.61, 45.03, 46.50, 48.81, 49.49, 50.90, 52.64, 54.94, 59.02, 67.60, 81.68, 95.50, 119.22, 124.40, 125.18, 125.24, 126.75, 127.33, 127.41, 128.24, 130.27, 135.62, 140.97, 142.24, 143.88, 151.35, 153.79, 162.10 ppm. EI-MS m/z: 830.49. Anal. Calcd. for $C_{50}H_{70}N_4O_3Si_2$: C, 72.24; H, 8.49; N, 6.74; O, 5.77; Si, 6.76. Found: C, 72.18; H, 8.40.

(12aS)-7-((tert-butyldimethylsilyl)oxy)-9,12a-dimethyl-8-((1E,5Z,13aS)-3,4,12c,13a-tetrahydronaphtho[2,1-f]oxireno[2,3-h][1,4]diazecin-1-yl)-3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d] imidazol-1(2H)-one (12)

yielding 65 %; IR (V_{max}, cm^{-1}) 3320, 1712, 1162 and 1110: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.11 (s, 6H), 0.90 (s, 3H), 0.92 (s, 9H), 1.38-1.86 (m, 7H), 1.88 (s, 3H), 1.90-3.05 (m, 10H), 3.32 (m, 1H), 4.22-4.34 (m, 4H), 4.41 (m, 1H), 4.68 (m, 1H), 5.22 (m, 1H), 5.81 (m, 1H), 7.40-7.92 (m, 2H), 7.94 (m, 1H), 8.05-8.18 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: -4.26, 13.86, 18.50, 21.52, 22.26, 22.33, 25.42, 26.03, 27.95, 30.67, 35.74, 37.74, 43.66, 45.03, 47.40, 48.80, 49.35, 50.91, 51.93, 52.64, 54.94, 59.02, 67.59, 95.50, 119.25, 124.42, 125.24, 126.75, 127.33, 127.40, 127.90, 128.24, 130.29, 135.60, 141.00, 142.24, 143.86, 151.35, 153.80, 157.94, 220.20 ppm. EI-MS m/z: 714.39. Anal. Calcd. for $C_{44}H_{54}N_4O_3Si$: C, 73.91; H, 7.61; N, 7.84; O, 6.71; Si, 3.93. Found: C, 73.88; H, 7.58.

Preparation of two tetrahydronaphto-oxireno-imidazol-diazocine derivatives.

A solution of compounds **11** or **12** (0.50 mmol) and hydrofluoric acid (5 ml) was stirring to reflux for 48 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:hexane:water (3:2:1) system.

(12aS)-9,12a-dimethyl-8-((1E,5Z,13aS)-3,4,12c,13a-tetrahydronaphtho[2,1-f]oxireno[2,3-h][1,4]diazecin-1-yl)-1,2,3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-hexadecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazole-1,7-diol (13)

yielding 69 %; IR (V_{max}, cm^{-1}) 3400, 3320 and 1160: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.80 (s, 3H), 1.32-1.86 (m, 12H), 1.88 (s, 3H), 1.96-3.64 (m, 7H), 4.20 (broad, 2H), 4.22-4.34 (m, 4H), 4.41 (m, 1H), 4.68 (m, 1H), 5.30 (m, 1H), 5.81 (m, 1H), 7.40-7.92 (m, 2H), 7.94 (m, 1H), 8.04-8.18 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 11.32, 22.22, 22.32, 23.02, 27.42, 30.67, 30.71, 37.01, 37.1, 41.65, 43.60, 43.62, 46.50, 48.80, 49.82, 50.90, 52.64, 54.94, 58.32, 67.62, 81.72, 101.20, 119.22, 124.42, 125.24, 126.75, 126.85, 127.33, 127.41, 128.24, 130.29, 135.62, 141.00, 142.24, 143.88, 153.80, 160.60, 161.82 ppm. EI-MS m/z: 602.32. Anal. Calcd. for $C_{38}H_{42}N_4O_3$: C, 75.72; H, 7.02; N, 9.29; O, 7.96. Found: C, 75.68; H, 7.00.

(12aS)-7-hydroxy-9,12a-dimethyl-8-((1E,5Z,13aS)-3,4,12c,13a-tetrahydronaphtho[2,1-f]oxireno[2,3-h][1,4]diazecin-1-yl)-3,3a,3b,4,5,7a,7b,8,10a,10b,10d,11,12,12a-tetradecahydrocyclopenta[7',8']phenanthro[3',4':3,4]cyclobuta[1,2-d]imidazol-1(2H)-one (14)

yielding 54 %; IR (V_{max}, cm^{-1}) 3400, 3320, 1712 and 1162: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.38-1.86 (m,

8H), 1.88 (s, 3H), 1.92-2.98 (m, 7H), 3.22 (m, 1H), 4.22-4.34 (m, 4H), 4.41 (m, 1H), 4.68 (m, 1H), 5.30 (m, 1H), 5.81 (m, 1H), 7.40-7.92 (m, 2H), 7.94 (m, 1H), 8.04-8.18 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 13.86, 21.50, 22.28, 22.35, 26.00, 27.95, 30.67, 35.74, 37.00, 41.65, 43.66, 47.40, 48.80, 49.35, 50.90, 51.93, 52.64, 54.94, 58.30, 67.60, 101.20, 119.25, 124.42, 125.24, 126.75, 127.33, 127.41, 128.22, 129.52, 130.30, 135.62, 141.00, 142.22, 143.88, 153.80, 157.68, 160.60, 220.20 ppm. EI-MS m/z: 600.31. Anal. Calcd. for $C_{38}H_{40}N_4O_3$: C, 75.97; H, 6.71; N, 9.33; O, 7.99. Found: C, 75.90; H, 6.68.

Biological evaluation. Animals were anesthetized using pentobarbital (50 mg/Kg body weight) through intraperitoneal administration. Then, the animal was opened via a thoracic abdominal laparotomy and the heart was perfused via retrograde with the Krebs-Henseleit solution* through a non-circulating perfusion system with a constant flow rate. It is noteworthy, that the study population involved in each group was n = 9.

*Krebs-Henseleit system composed by following substances in mmol concentrations per liter; 117.8 NaCl; 6 KCl; 1.75 CaCl2; 1.2 NaH2PO4; 1.2 MgSO4; 24.2 NaHCO3; 5 glucose, and 5 sodium pyruvate [27]. The solution was then bubbled with a mixture of O_2/CO_2 (95:5/5 %) and the mixture was regulated to a pH of 7.4 (37°C). The coronary flow (10 mL/min) was adjusted with a peristaltic pump for an equilibration period of 15 min [20].

Perfusion pressure.

Measurements of perfusion pressure changes induced by drugs administration in this study was assessed using a pressure transducer connected to the chamber where the hearts were mounted and the results entered into a computerized data capture system (Biopac) [21].

Experimental design

Evaluation of biological activity of adenosine, sodium nitroprusside (NP), BAY-41-2272, NS-2028, compounds 13 and 14 on perfusion pressure. The compounds following; a) adenosine; b) sodium nitroprusside (NP); c) BAY-41-2272; d) NS-2028; e) compound **13**; and e) compound **14** were perfused at a dose of 0.01 nM and changes on perfusion pressure* through of time (3-18 min) were evaluated.

*The effects were determined using an isolated hearts model at a constant-flow rate of 10 ml/min.

Evaluation of effects exerted by both compounds 13 and 14 on perfusion pressure via guanylate cyclase inhibition. The biological activity of both compounds **13** or **14** at a dose of 0.01 nM (in a period of 3-18 min) on the perfusion pressure was determinate. The dose-response curve (control)* was repeated in the presence of the compounds sodium nitroprusside (NP), BAY-41-2272 and NS-2028 and the effects were evaluated.

*Duration of preincubation with compounds **13** or **14** was by a 10 min equilibration period.

Evaluation of biological activity of both compounds 13 or 14 via calcium channel.

The effect exerted by both compounds **13** or **14** at a dose of 0.01 nM (in a period of 3-18 min) on the perfusion pressure was determinate. The dose-response curve (control)* was repeated in the presence of nifedipine and the effects were evaluated.

*Duration of preincubation with compounds **13** or **14** was by a 10 min equilibration period.

Statistical analysis.

The values determinate were expressed as average ± SE, using each heart (n = 9) as its own control. The results were put under Analysis of Variance (ANOVA) with the Bonferroni correction factor [21] using the SPSS 12.0 program. The significant differences were considered when ***p*** was equal or smaller than 0.05.

3. RESULTS SECTION

In this study two oxirenodiazecin-imidazole derivatives were prepared as follows:

Preparation of a steroid imidazol-derivative.

Some methods have been reported for the synthesis of imidazole-derivatives using reagents such as cupric bromide [22], Copper(II) acetate [23], L-proline [24], indium(III) chloride [25], thiazolium [26] and others. It is important to mention that some of these substances are corrosive and require specific conditions. The objective of this study was to synthesize two indole-steroid derivatives (compound **3** or **4**) from two estradiol or estrone derivatives and 2-methylimidazoe using Copper(II) chloride as a catalyst. The ^{1}H NMR spectrum of **3** (Figure 1) showed several signals at 0.07-0.87 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.88 ppm for methyl group bound to steroid nucleus; at 1.94 ppm for methyl bound to imidazole ring; at 1.32-1.92, 2.00-3.55 and 5.20 ppm for steroid moiety; at 3.80-3.90 and 8.16 ppm for imidazole ring. The ^{13}C NMR spectra displays chemical shifts at -4.50, -4.24, 18.02-18.50 and 25.41-25.52 ppm for terbuthyldimethylsylane fragment; at 11.38 ppm for methyl group bound to steroid nucleus; at 20.62 ppm for methyl bound to imidazole ring; at 22.22-24.61, 27.40-49.45, 81.66-148.90 and 161.44 ppm for steroid moiety; at 57.00-68.07 and 154.70 ppm for imidazole ring. In addition, the mass spectrum from **3** showed a molecular ion (m/z) at 582.40.

On the other hand the ^{1}H NMR spectrum of **4** (Figure 1) showed several signals at 0.13 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.90 ppm for methyl group bound to steroid nucleus; at 1.37-1.92, 1.98-2.46 and 5.20 ppm for steroid moiety; at 1.94 ppm for methyl bound to imidazole ring; at 3.80-3.92 ppm for imidazole ring; at 8.16 ppm for amino group. The ^{13}C NMR spectra displays chemical shifts at -4.24, 18.50 and 25.42 ppm for terbuthyldimethylsylane fragment; at 13.90 ppm for methyl group; at 20.62 ppm for methyl bound to imidazole ring; at 21.52-22.26, 26.02, 27.94-51.92, 90.10-148.90 and 157.32 ppm for steroid moiety; at 57.02-68.05 and 154.70 ppm; at 220.19 ppm for ketone group. Finally, the mass spectrum from **4** showed a molecular ion (m/z) at 582.40.

Synthesis of two chloroamide derivatives.

There are several studies for the preparation of chloroamides using some reagents such as trichloroisocyanucic acid [27], N-chlorobenzotriazole [28] and chloroacetyl chloride [29, 30]. In this study, two chloroamides (compounds **5** and **6**) were synthesized

from **3** or **4** and chloroacetyl in presence of triethylamine. The ^{1}H NMR spectrum of **5** (Figure 6) showed several signals at 0.06-0.86 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.88 ppm for methyl group bound to steroid nucleus; at 1.73 ppm for methyl bound to imidazole ring; at 1.32-1.62, 1.78-3.55 and 5.22 ppm for steroid moiety; at 4.14-4.20 ppm for methylene group bound to amide; at 4.42-4.71 ppm for imidazole ring. The ^{13}C NMR spectra displays chemical shifts at -4.51, -4.26, 18.02-18.51 and 25.41-25.50 ppm for terbuthyldimethylsylane fragment; at 11.34 ppm for methyl group bound to steroid nucleus; at 19.76 ppm for methyl group bound to imidazole ring; at 22.23-24.60, 27.42-38.44, 43.11-49.47, 81.68-128.91 and 153.00-157.81 ppm for steroid moiety; at 42.04 ppm for methylene group bound to amide; at 54.76-66.55 and 152.40 ppm for imidazole ring; at 165.70 ppm for amide group. Finally, the mass spectrum from **5** showed a molecular ion (m/z) at 658.37.

Other data showed several signals of ^{1}H NMR spectrum for **6** (Figure 6) at 0.11 and 0.92 ppm terbuthyldimethylsylane fragment; at 0.90 ppm for methyl group bound to steroid nucleus; at 1.73 ppm for methyl bound to imidazole ring; at 1.38-1.70, 1.87-2.80 and 5.22 ppm for steroid moiety; at 4.14-4.20 ppm for methylene group bound to amide; at 4.42-4.71 ppm for imidazole ring. The ^{13}C NMR spectra displays chemical shifts at -4.26, 18.51 and 25.42 ppm for terbuthyldimethylsylane fragment; at 13.86 ppm for methyl group bound to steroid nucleus; at 19.77 ppm for methyl bound to imidazole ring: at 21.51-22.26, 26.03-37.64, 43.66-51.93, 90.29-131.62 and 153.00-153.66 ppm for steroid moiety; at 42.04 ppm for methylene bound to amide group; at 54.74-66.56 and 152.40 ppm for imidazole ring; at 165.70 ppm for amide group; at 220.20 ppm for ketone group. Additionally, the mass spectrum from **6** showed a molecular ion (m/z) at 542.27.

Preparation of oxiran derivatives.

Some reagents have used for the preparation of oxirane derivatives such as Co(III) [31], KOAc [32] and polycicloctane [33]. Analyzing these data in this study two oxiran derivatives (compounds **7** or **8**) were prepared by the reaction of **5** or **6** with 2-hydroxy-1-naphthaldehyde under mild conditions. The ^{1}H NMR spectrum of **7** (Figure 6) showed several signals at 0.07-0.86 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.88 ppm for methyl group bound to steroid nucleus; at 1.73 ppm for methyl bound to imidazole; at 1.32-1.62, 1.78-3.55 and 5.22 ppm for steroid moiety; at 4.10-4.48 ppm for oxirane ring; at 4.42-4.47 ppm for imidazole ring; at 7.22-7.90 for phenyl groups; at 9.08 ppm for hydroxyl group. The ^{13}C NMR spectra displays chemical shifts at -4.50, -4.26, 17.82-18.52 and 25.42-25.74 ppm for terbuthyldimethylsylane fragment; at 11.35 ppm for methyl group bound to steroid nucleus; at 1.83 ppm for methyl bound imidazole ring; at 22.23-24.62, 27.42-49.45, 81-66-90.29, 128.93 and 154.20-157.81 ppm for steroid moiety; at 53.46-53.90 ppm for oxirane ring; at 56.54-66.56 and 159.12 ppm for imidazole ring; at 168.84-127.85 and 129.22-153.92 ppm for phenyl groups; at 171.10 ppm for amide group. Finally, the mass spectrum from **7** showed a molecular ion (m/z) at 794.45.

Other data showed several signals of ^{1}H NMR spectrum for **8** (Figure 2) at 0.11 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.90 ppm for methyl group bound to steroid nucleus; at 1.73 ppm for methyl bound to imidazole ring; at 1.38-1.70, 1.86-2.80 and 5.22 ppm for steroid moiety; at 4.10 and 4.48 ppm for oxirane ring; at 4.42-4.47 ppm for imidazole ring; at 7.22-7.90 ppm for phenyl groups at 9.10 ppm for hydroxyl group. The ^{13}C NMR spectra displays chemical shifts at -4.26, 18.51 and 25.42 ppm for terbuthyldimethylsylane fragment; at 13.86 ppm for methyl group bound to steroid nucleus; at 16.82 ppm for methyl bound to imidazole ring; at 21.52-22.26, 26.02-51.91, 90.29, 131.63, 153.67 and 154.17 for steroid moiety; at 53.46-66.56 and 159.12 ppm for imidazole ring; at 118.86-130.36, 134.66 and 153.92 ppm for phenyl groups; at 171.07 ppm for amide group; at 220.20 ppm for ketone group. In addition, the mass spectrum from **8** showed a molecular ion (m/z) at 678.34.

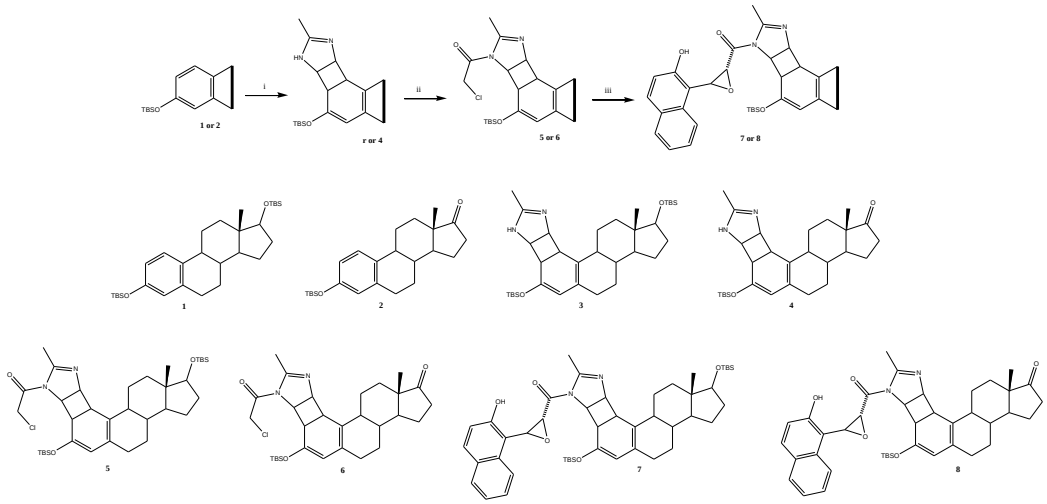

Figure 1. Preparation of two oxirane-derivatives (**7** or **8**). Two steroid-imidazole analogs (**3** or **4**) were prepared from estradiol (**1**) or estrone (**2**) derivatives and 2-methylimidazole (i). Then, **3** or **4** reacted with chloroacetyl chloride (ii) to synthesis of two chloroamides (**5** or **6**). Finally, **7** or **8** were prepared by the reaction of **5** or **6** with 2-hydroxy-1-naphthaldehyde (iii).

Preparation of two carbaldehyde derivatives.

It is noteworthy that there are several reports on the oxidation of primary alcohols to form the corresponding aldehydes. These compounds can be prepared with some techniques which are accomplished by stoichiometric amounts of metallic oxidants such as chromium(VI) palladium, rhodium or ruthenium and hydrogen

peroxide reagents [34]. However, these reagents may induce risks of toxicity by the generation of several substances involved on some reaction mixtures. Therefore, in this study, a method previously reported [35] for oxidation of hydroxyl groups was used for formation of **9** and **10** by the reaction of **7** or **8** with DMSO. The ^{1}H NMR spectrum of **9** (Figure 6) showed several signals at 0.07-0.86 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.88 ppm for methyl group bound to steroid nucleus; at 1.73 ppm for methyl bound to imidazole ring; at 1.32-1.62, 1.78-3.55 and 5.22 ppm for steroid moiety; at 3.86 and 4.48 ppm for oxirane ring; at 4.42-4.47 ppm for imidazole ring ; at 7.22-8.46 ppm for phenyl groups; at 10.00 ppm for aldehyde group. The ^{13}C NMR spectra displays chemical shifts at -4.52, -4.26, 17.82-18.52 and 25.42-25.74 ppm for terbuthyldimethylsylane fragment; at 11.35 ppm for methyl group bound to steroid nucleus; at 16.84 ppm for methyl bound to imidazole ring; at 22.22-25.22, 27.43-38.45, 43.11-49.47, 81.61-90.28, 128.91 and 154.19-157.81 ppm for steroid moiety; at 41.82 and 54.70 ppm for oxierane ring; at 56.54-66.56 and 159.13 ppm for imidazole ring; at 132.32-127.98 and 129.42-146.00 ppm for phenyl groups; at 171.10 ppm for amide group; at 191.60 ppm for aldehyde group. Additionally, the mass spectrum from **9** showed a molecular ion (m/z) at 806.45.

Other data showed several signals of ^{1}H NMR spectrum for **10** (Figure 6) at 0.11 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.90 ppm for methyl group bound to steroid nucleus; at 1.73 ppm for methyl bound to imidazole ring; at 1.38-1.70, 1.85-2.80 and 5.22 ppm for steroid moiety; at 3.46 and 4.48 ppm for oxirane ring, at 4.42-4.47 ppm for imidazole ring; at 7.22-8.96 ppm for phenyl groups; at 10.00 ppm for aldehyde group. The ^{13}C NMR spectra displays chemical shifts at -4.24, 18.52 and 25.42 for terbuthyldimethylsylane fragment; at 13.86 ppm for methyl group bound to steroid nucleus; at 16.85 ppm for methyl bound to imidazole ring; at 21.52-22.26, 26.02-37.62, 43.66-51.92, 90.29, 131.64 and 153.68-154.20 ppm for steroid moiety; at 41.81 and 54.70 for oxirane ring; at 56.54-66.56 and 159.12 ppm for imidazole ring; at 123.32-130.84 and 133.91-146.00 ppm for phenyl groups; at 171.10 ppm for amide group; at 191.60 ppm for aldehyde group; at 220.18 ppm for ketone group. Finally, the mass spectrum from **10** showed a molecular ion (m/z) at 690.34.

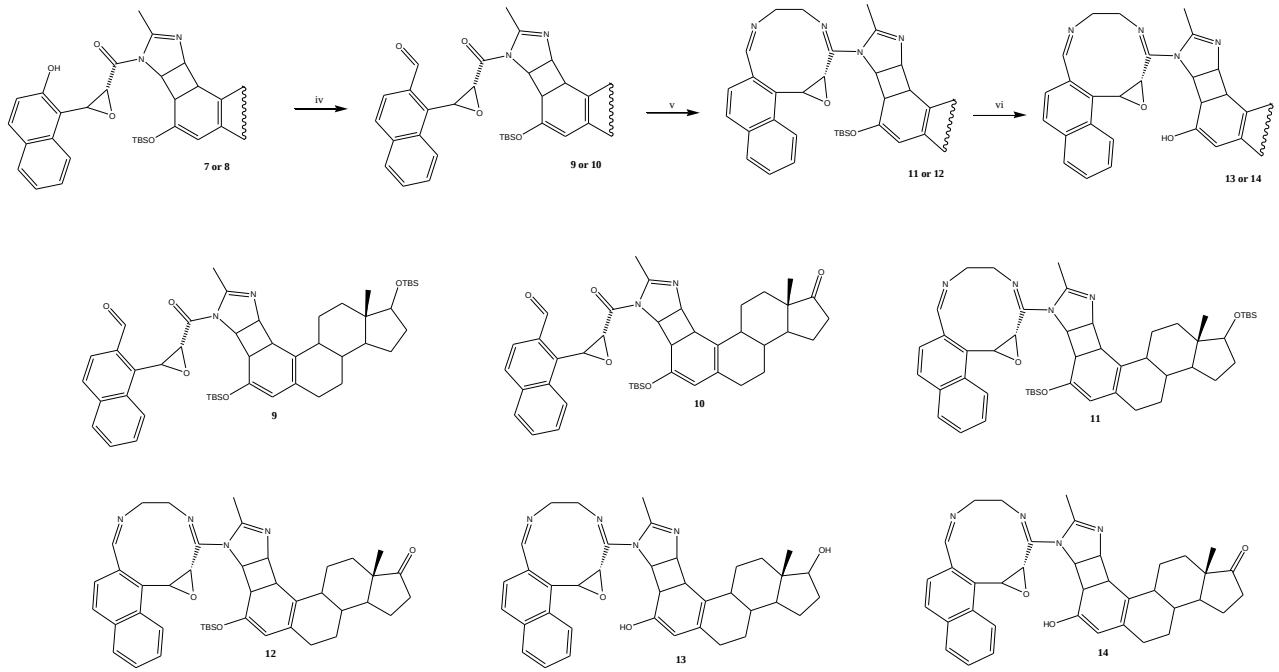

Figure 2. Synthesis of two diazocine-steroid-derivatives (13 or 14). Two carbaldehyde-analogs (9 or 10) were prepared from oxirane-derivatives (7 or 8) in presence of dimethyl sulfoxide (iv). Then 9 or 10 reacted with ethylenediamine (v) to form two azecine derivatives (11 or 12). Finally, 13 or 14 were prepared by the reaction of 11 or 12 in presence of hydrofluoric acid (vi).

Preparation of azecine derivatives.

Several azecine analogs have been prepared using some reagents such as lithium hexamethyldisilazide [36], cyanogen bromide [37], trifluoroacetic acid [38], tetrahydropyridine [39] and others. In this study, two azecine derivatives were prepared from 9 or 10 and ethylenediamine in presence of boric acid. The ^{1}H NMR spectrum of **11** (Figure 6) showed several signals at 0.07-0.86 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.88 ppm for methyl bound to steroid nucleus; at 1.88 ppm for methyl bound to imidazole; at 1.32-1.86, 1.90-3.05, 3.54 and 5.22 ppm for steroid moiety; at 7.40-7.92 and 8.05-8.18 ppm for phenyl groups; at 3.32 ppm for imidazole ring; at 4.22-4.34, 4.68 and 7.94 ppm for tetrahydro-[1,4]-diazecine ring; at 4.41 and 5.81 ppm for oxirane ring. The ^{13}C NMR spectra displays chemical shifts at -4.50, -4.26, 18.02-18.52 and 25.42-25.51 ppm for terbuthyldimethylsylane fragment; at 11.37 ppm for methyl group bound to steroid nucleus; at 22.36 ppm for methyl bound to imidazole ring; at 22.2, 24.60, 27.42-46.50, 49.49, 81.68-95.50, 125.18, 153.35 and 162.10 ppm for steroid moiety; at 48.81, 52.64-54.94, 135.62 and 143.88 ppm for tetrahydro-[1,4]-diazecine ring; at 50.90 ppm for oxirane ring; at 59.02-67.60 and 153.79 ppm for imidazole ring; at 119.22-124.40, 125.24-130.27 and 140.97-142.24 ppm for phenyl groups. In addition, the mass spectrum from **11** showed a molecular ion (m/z) at 830.49.

Other results showed several signals of ^{1}H NMR spectrum for **12** (Figure 6) at 0.11 and 0.92 ppm for terbuthyldimethylsylane fragment; at 0.90 ppm for methyl group bound to steroid nucleus; at 1.38-1.86, 1.90-3.05 and 5.22 ppm for steroid moiety; at 1.88 and 3.32 ppm for imidazole ring; at 4.22-4.34, 4.68 and 7.94 ppm for tetrahydro-[1,4]-diazecine ring; at 4.41 and 5.81 ppm for oxirane ring; at 7.40-7.92 and 8.05-8.18 ppm for phenyl groups. The ^{13}C NMR spectra displays chemical shifts at -4.26, 18.50 and 25.42 ppm for terbuthyldimethylsylane fragment; at 13.86 ppm for methyl group bound to steroid nucleus; at 22.33 ppm for methyl bound to imidazole ring; at 21.50-22.26, 26.03-47.40, 49.35, 51.93, 95.50, 127.90, 151.35 and 157.94 for steroid moiety; at 48.80, 52.64, 135.60 and 143.86 ppm for tetrahydro-[1,4]-diazecine ring; at 50.91 and 43.94 for oxirane ring; at 59.02-67.59 and 153.80 ppm for imidazole ring; at 119.25-127.40, 128.24 and 141.00-142.24 ppm for phenyl groups; at 220-20 ppm for ketone group. Finally, the mass spectrum from **12** showed a molecular ion (m/z) at 714.39.

Removal of silyl protecting groups.

Some reagent has used for removal of silyl protecting groups from hydroxyl such as ammonium fluoride [40], tris(dimethylamino)sulfonium/difluorotrimethylsilicate [41], hydrofluoric acid [42] and others. In this study, hydrofluoric acid was used to the removal of the silyl-protecting group from hydroxyl of the compounds **11** or 12 to form **13** or **14** (Scheme 2). The ^{1}H NMR spectrum of **13** showed several signals at 0.80 ppm for methyl group bound to the steroid nucleus; at 1.88 ppm for methyl bound to imidazole ring; at 4.20 ppm for hydroxyl group; at 1.32-1.86, 1.96-3.64 and 5.30 ppm for steroid moiety; at 4.22-4.34 and 7.94 ppm for tetrahydro-[1,4]-diazecine ring; at 4.41 and 5.81 ppm for oxirane ring; at 4.68 ppm for imidazole ring; at 7.40-7.92 and 8.04-8.18 ppm for phenyl groups. The ^{13}C NMR spectra displays chemical shifts at 11.32 ppm for methyl group bound to steroid nucleus; at 23.32 ppm for methyl boun to imidazole ring; at 22.22, 23.02-46.50, 49.82, 81.72-119.20, 126.85 and 160.60-161.82 ppm for steroid moiety; at 48.80, 52.64, 135.62 and 143.88 ppm for tetrahydro-[1,4]-diazecine ring; at 50.90 and 54.94 ppm for oxirane ring; at 58.32-67.62 and 153.80 ppm for imidazole ring; at 119.22-126.75, 127.33-130.29 and 141.00-142.24 ppm for phenyl groups. Additionally, the mass spectrum from **13** showed a molecular ion (m/z) at 602.32.

Finally, the ^{1}H NMR spectrum of **14** (Figure 6) showed several signals at 0.90 ppm for methyl group bound to the steroid nucleus; at 1.88 ppm for methyl bound to imidazole ring; at 1.38-1.86, 1.92-2.98 and 5.30 ppm for steroid moiety; at 4.22-4.34, 4.68 and 7.94 ppm for tetrahydro-[1,4]-diazecine ring; at 4.41 and 5.81 ppm for oxirane ring; at 3.22 and 4.68 ppm for imidazole ring; at 7.40-7.92 and 8.04-8.18 ppm for phenyl groups. The ^{13}C NMR spectra displays chemical shifts at 13.86 ppm for methyl group bound to steroid nucleus; at 22.34 ppm for methyl bound to imidazole ring; at 21.50-22.80, 26.00-47.40, 49.35, 51.93, 101.20, 129.52 and 157.68-160.60 ppm for steroid moiety; at 48.80, 52.64, 135.62 and 143.88 ppm for tetrahydro-[1,4]-diazecine ring; at 50.90-54.94 ppm for oxirane ring; at 58.30-67.60 and 53.80 ppm for imidazole ring; at 119.26-128.22, 130.30 and 141.00-142.22 ppm for phenyl groups; at 220.00 ppm for ketone group. Finally, the mass spectrum from **14** showed a molecular ion (m/z) at 600.31.

Biological evaluation.

There are several reports which indicate that some drugs can exert effects on heart failure [12-17]; however, there are not insufficient data on the inotropic activity exerted by these compounds.

In the search of a therapeutic alternative for treatment of heart failure, in this study the biological activity of two oxirenodiazecin-imidazole (compounds 12 and 13) derivative on perfusion pressure was evaluated in an isolated rat heart model using adenosine (purinergic-receptor agonist; guanylate cyclase stimulator) [43] and sodium nitroprusside (guanylate cyclase activator) [44] as controls.

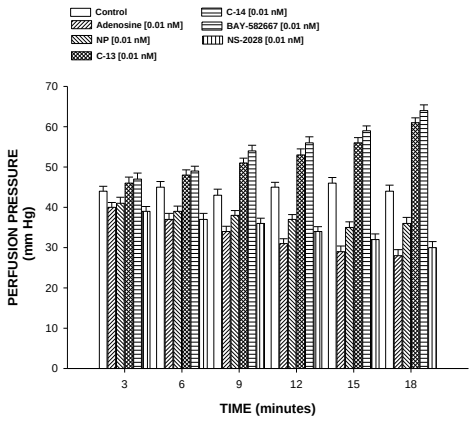

Figure 3. Biological activity* of adenosine, sodium nitroprusside (NP), BAY-41-2272, NS-2028, compounds 13 and 14 at a dose of 0.01 nM on perfusion pressure. The scheme shown that both compound 13 and 14 increase the perfusion pressure by increases in time (3 to 18 min) compared with NP, BAY-41-2272, NS-2028 and control conditions. *The effects were determined using an isolated hearts model at a constant-flow rate of 10 ml/min.

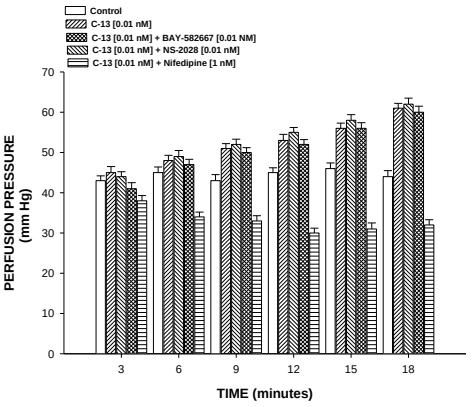

Figure 4. Effect exerted by the compound **13** at a dose of 0.01 nM (in a period of 3-18 min) on the perfusion pressure in absence or presence of sodium nitroprusside (NP), BAY-41-2272 and NS-2028. The scheme shown that compound **13** increase the perfusion pressure through of time and this effect was not inhibited by nitroprusside (NP) or BAY-41-2272 or NS-2028. However, the nifedipine inhibited their biological activity (***p*** = 0.05).

*Duration of preincubation with compounds **13** was by a 10 min equilibration period.

The results showed (Figure 3) that both compounds increase the perfusion pressure through time (3-18 min) compared with the adenosine and sodium nitroprusside. This data opens the

possibility of the compounds 13 or 14 guanylate cyclase activator could modulate the biological activity of guanylate cyclase enzyme in the heart.

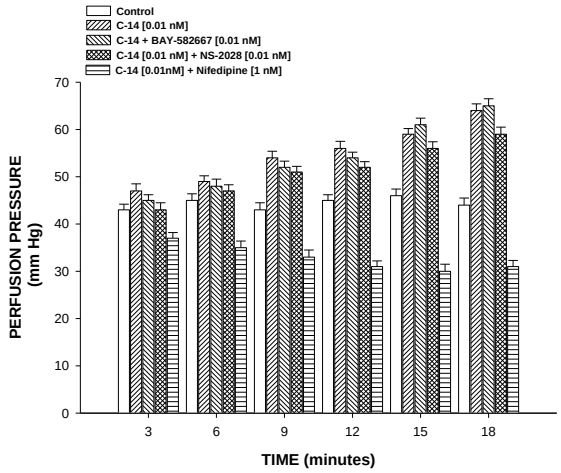

Figure 5. Biological activity produced by the compound **14** at a dose of 0.01 nM (in a period of 3-18 min) on the perfusion pressure in absence or presence of sodium nitroprusside (NP), BAY-41-2272 and NS-2028. The results showed that compound **14** increase the perfusion pressure through of time and this effect was not inhibited by nitroprusside (NP) or BAY-41-2272 or NS-2028. However, the nifedipine inhibited their biological activity ($\boldsymbol{p} = 0.05$).
*Duration of preincubation with compounds **14** was by a 10 min equilibration period.

To evaluate this hypothesis, in this study the biological activity of the compounds BAY-41-2272 (guanylate cyclase agonist) [45] and NS-2028 (guanylate cyclase inhibitor) [46] on the perfusion pressure was evaluated.

The results showed that NS-2028 increase in a similar manner that both compounds 13 or 14 and this effect was different to biological exerted by BAY-41-2272; these data confirm that both compounds 13 or 14 can modulate the biological activity of guanylate cyclase.

However, to evaluate if these compounds may act as inhibitors of the enzyme, the biological activity of both compounds 13 or 14 was evaluated in the absence or presence of BAY-41-2272 and NS-2028. The results showed (Figure 4 and 5) that both compound 13 or 14 increasing the perfusion pressure and this effect was inhibited by BAY-41-2272; in addition, the biological activity exerted by two steroid derivatives was similar in absence or presence of NS-2028.

In the search of and additional mechanism molecular other reports were analyzed, these reports indicate that some drugs can exert their effect through of calcium channels, for this razon the biological activity produced by compounds **13** and **14** on perfusion pressure was evaluated in absence or presence of nifedipine (calcium channel type-L agonist) [46, 47].

The results indicate that both compounds **13** and **14** increase the perfusion pressure; however, this effect was inhibited with nifedipine. All, this data suggests that; 1) compounds **13** and **14** may induce changes on perfusion pressure through guanylate cyclase inhibition and calcium channel type-L activation; 2) the biological activity could depend on both oxirane and azocine ring.

4. CONCLUSIONS

(The results found suggest that compounds **13** or **14** exert effects on perfusion pressure through two molecular mechanisms compared to other drugs; this phenomenon can be translated as a cardioprotective effect produced by these compounds in heart failure.

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