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Design and synthesis of pyranacyclodecaphen-3,6-diyliden)bis(azanylidene))bis(ethan-1-amine) derivative with positive inotropic activity

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ABSTRACT

Several patients with heart failure have been treated with a combination of drugs that usually includes cardiac glycosides, diuretics, and afterload-reducing agents; nevertheless, some drugs can produce adverse effects. The aim of this study was synthesized a new pyranacyclodecaphen-3,6-diyliden)bis(azanylidene))bis(ethan-1-amine) derivative (compound 7) for evaluate their biological activity on perfusion pressure and left ventricular pressure using an rat isolated heart model. The following stage involved the theoretical evaluation of the interaction of compound 7 with the phosphodiesterase-4B (1ror) using a docking model. The results showed that compound 7 increase the perfusion pressure and left ventricular pressure at different doses. Other theoretical data indicated that compound 7 may interact with different type of amino acids residues such as Tyr233, Hys234, Hys238, Hys274, Asp275, Ser282, Asn283, Met347, Asn395, Trp406, Ile410, Phe414, Gln443 and Phe446 on the surface of 1ror protein. All these results indicate that 1) compound 7 have positive inotropic activity on heart; 2) theorethical analysis showed that compound 7 could a high affinity by 1ror protein. This compound is particularly interesting because could constitute a novel therapy for heart failure.

Keywords: *Pyranacyclodecaphen, perfusion pressure, theoretical, docking.*

1. INTRODUCTION

Cardiovascular diseases have been one of the public health problems throughout the world [1-2]. It is noteworthy, that one of the risk factors that condition this type of clinical pathologies is heart failure which is conditioned by an increase in myocardial ischemia; this phenomenon may result in a decrease in cardiac work [3, 4]. There are several drugs for treatment of heart failure such as digoxine (ATP-ase inhibitor) [5], levosimedam (Ca^{++}-sensitizing) [6], dobutamine (β_1- agonist) [7], milrinone (Phosphodiesterase-III inhibitor) [8, 9] and others; however, some these drugs may produce diverse adverse effects such as ischemia, arrhythmia, hyperkalemia, hypopotassemia and others [5]. In the search for new therapeutic alternatives, several drugs with positive inotropic activity have been synthesized via phosphodiesterase inhibition; for example, the preparation of 4-benzylamino-1-chloro-6-substituted phthalazines from piperonyl- amine as phosphodiesterase-5 inhibitor [10]. Another report indicates the preparation of a phosphodiesterase inhibitor (rolipram) from of a nitro-olefin [11]. Additionally, a study showed the reaction of 2-butyl-4-chlorothieno[3,2-d]- pyrimidine with cyclohexylamine to form a thieno[3,2-d]pyrimidines (phosphodiesterase-4 inhibitor) [12]. Another report showed the preparation of a phosphodiesterase-5 inhibitor (sildenafil) from a pyrimidinone [13]. All these data shown the synthesis of several compounds with inotropic activity via phosphodiesterase inhibition; nevertheless, some of these compounds are specific for each phosphodiesterase, which implies that the different functional groups of each drugs employed may condition their biological activity. Analyzing this hypothesis, in this study a pyranacyclodecaphen-3,6-diyliden)bis(azanylidene))bis- (ethan-1-amine) derivative was prepared and their biological activity against both perfusion pressure and left ventricular pressure was evaluated using a ischemic injury model. In addition, a theoretical study was carried out to evaluate their interaction with a phosphodiesterase-4B protein.

2. EXPERIMENTAL SECTION

Chemical synthesis. All reagents used in this investigation were obtained from Sigma-Aldrich Co., Ltd. The melting point for compounds was determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer.^{1}H and ^{13}C NMR (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 obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

General procedure for synthesis of anthracene derivatives

A solution of estrone (**1**) or estradiol (**2**) [0.90 mmol], 5-hexyn-3-ol [100 µl, 0.90 mM] in 2 ml of acetonitrile was stirring for 24 h to reflux. The reaction mixture was evaporated to dryness under reduced pressure. After, the solvent in the mixture was evaporated at reduced pressure and the residue was purified by crystallization from methanol:water system (4:1) in which case two anthracene derivatives (compounds **2** or **3**) were obtained.

8-Amino-10-(3-hydroxy-pentyl)-13a-methyl-1,2,3,3a,3b,4,5,10, 11b,12,13,13a-dodeca hydro-7-oxa-indeno[5,4-a]anthracen-1-ol (3).

Yielding 22 % of product, m.p. 140-142 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 3302 and 1248: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.64 (s, 3H), 0.80 (m, 1H), 0.94 (m, 3H). 1.02-1.31 (m, 4H), 1.36 (m, 1H), 1.38-1.40 (m, 2H), 1.53-1.56 (m, 2H), 1.64 (m, 1H), 1.66 (m, 1H), 1.72-1.88 (m, 3H), 2.00 (m, 1H), 2.10 (m, 1H), 2.16 (m, 1H), 2.17-2.80 (m, 4H), 3.52 (m, 1H), 3.64 (m, 1H), 3.66 (m, 1H), 4.66 (d, 1H, J = -0.5 Hz), 6.10 (broad, 4H), 6.68-7.00 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 9.66, 13.28, 23.88, 25.84, 27.77, 29.76, 30.02, 31.16, 33.70, 34.10, 35.66, 38.91, 39.95, 42.29, 44.37, 49.82, 79.34, 81.24, 92.96, 110.70, 122.18, 123.86, 135.72, 140.44, 148.86, 164.63 ppm. EI-MS m/z: 411.27 Anal. Calcd. for $C_{26}H_{37}NO_3$: C, 75.87; H, 9.06; N, 3.40; O, 11.66. Found: C, 75.80; H, 9.00.

8-Amino-10-(3-hydroxy-pentyl)-13a-methyl-3,3a,3b,4,5,10, 11b,12,13,13a-decahydro-2H-7-oxa-indeno[5,4-a]anthracen-1-one (4).

Yielding 38 % of product, m.p. 180-182^{o}C; IR (V_{max}, cm^{-1}) 3302, 1712 and 1246:^{1}H NMR (500 MHz, Chloroform-*d*) δ_H:0.92 (s, 3H), 0.94 (s, 3H), 1.20-1.34 (m, 4H), 1.36 (m, 1H), 1.54 (m, 1H), 1.55-1.66 (m, 3H), 1.80-1.92 (m, 2H), 1.98 (m, 1H), 2.10-2.12 (m, 3H), 2.16 (m, 1H), 2.20-2.80 (m, 5H), 3.50 (m, 1H), 3.64 (m, 1H), 4.64 (*d*, *J* = 1.0 Hz, 2H), 6.02 (broad, 3H), 6.66-7.10 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 9.66, 14.10, 21.12, 23.24, 26.44, 29.54, 29.77, 30.04, 32.40, 33.72, 34.10, 36.88, 39.90, 45.10, 49.14, 49.22, 51.64, 79.32, 92.98, 110.67, 121.83, 123.86, 135.34, 140.02, 148.92, 164.64, 220.30 ppm. EI-MS m/z: 409.26 Anal. Calcd.for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42; O, 11.72. Found: C, 76.20; H, 8.56.

Preparation of pyrancyclodecaphene-dioneA solution of **3** or **4** (0.50 mmol), succinic acid (130 mg, 1.10 mmol), boric acid (68 mg, 1.08 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from hexane:methanol:water (1:3:1) system; in which case two pyrancyclodecaphene-dione (**4** or **5**) were obtained.

(13S)-13-methyl-5,6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-6H-17H-cyclopenta[a]phenanthren-17-ol[2,3,e](Z)-8-ethyl-1^{4}H-7-oxa-2-aza-1(2,4)-pyrancyclodecaphene-3,6-dione (5).

Yielding 44 % of product, m.p. 202-204 ^{o}C; IR (V_{max}, cm^{-1}) 3430, 3402, 1710 and 1248:^{1}H NMR (500 MHz, Chloroform-*d*) δ_H:0.66 (s, 3H), 0.80 (m, 1H), 0.84 (s, 3H), 1.02-1.40 (m, 6H), 1.62 (m, 1H), 1.66-1.76 (m, 2H), 1.80 (m, 1H), 1.82 (m, 1H), 1.83 (m, 2H), 1.88 (m, 1H), 2.10 (m, 2H), 2.11 (m, 1H), 2.34-2.42 (m, 4H), 2.56-3.66 (m, 4H), 4.34 (m, 1H), 5.14 (m, 1H), 6.40 (broad, 1H), 6.56 (d, 1H, J = 1.66 Hz), 6.80-7.00 (m, 2H), 8.02 (broad, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 9.52, 13.26, 23.86, 25.84, 27.66, 27.76, 29.36, 29.76, 29.77, 31.16, 35.66, 37.04, 37.05, 38.90, 40.35, 42.29, 44.37, 49.8, 81.24, 82.02, 107.45, 109.90, 121.26, 123.72, 134.70, 138.88, 152.02, 153.62, 171.04, 172.82 ppm. EI-MS m/z: 493.29 Anal. Calcd.for $C_{38}H_{39}NO_5$: C, 72.99; H, 7.96; N, 2.84; O, 18.21. Found: C, 72.90; H, 7.90.

(13S)-13-methyl-5,6,7,8,9,10,11,12,13,14,15,16,-dodecahydro-17H-cyclopenta[a]phe- nanthren-17-one[2,3,e](Z)-8-ethyl-1^{4}H-7-oxa-2-aza-1(2,4)-pyrancyclodecaphene-3,6-dione (6).

Yielding 38 % of product, m.p. 190-192 ^{o}C; IR (V_{max}, cm^{-1}) 3432, 1712 and 1246:^{1}H NMR (500 MHz, Chloroform-*d*) δ_H:0.82 (s, 3H), 0.92 (s, 3H), 1.20-1.54 (m, 5H), 1.62 (m, 1H), 1.78-1.80 (m, 2H), 1.83 (m, 2H), 1.92 (m, 1H), 2.10 (m, 2H), 2.11-2.20 (m, 4H), 2.34-2.42 (m, 4H), 2.46-2.80 (m, 4H), 4.34 (m, 1H), 5.14 (m, 1H), 6.56 (d, 1H, J = 1.66 Hz), 6.80-7.06 (m, 2H), 8.02 (broad, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 9.52, 14.12, 21.12, 23.28, 26.42, 27.66, 29.38, 29.56, 29.76, 29.77, 32.42, 36.85, 37.04, 37.05, 40.35, 45.12, 49.19, 51.62, 82.02, 107.44, 109.90, 120.89, 123.73, 134.33, 138.45, 152.04, 153.63, 171.06, 172.8, 220.30 ppm. EI-MS m/z: 491.26 Anal. Calcd.for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85; O, 16.27. Found: C, 73.20; H, 7.50.

Preparation of azanylylidene-ethanamine derivatives

A solution of **5** or **6** (0.50 mmol), ethylenediamine (50 µl, 0.75 mmol), boric acid (34 mg, 0.54 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from hexane:methanol:water (3:2:1) system; in which case two pyrancyclodecaphene-dione (**7** or **8**) were obtained.

(13S)-13-methyl-5,6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-6H-17H-cyclopenta[a]phenanthren-17-ol[2,3,e]2,2'(((1Z, 3Z,6E)-8-ethyl-7,14-dioxa-2-azabicyclo[9.3.1]penta- dec-1(15)-ene-3,6-diylidene)bis(azanylylidene)bis(ethan-1-amine) (7)

Yielding 38 % of product, m.p. 174-176 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 3304 and 1248:^{1}H NMR (500 MHz, Chloroform-*d*) δ_H:0.64 (s, 3H), 0.80 (m, 1H), 0.90 (s, 3H), 1.02-1.40 (m, 6H), 1.42 (m, 2H), 1.56-1.60 (m, 2H), 1.64-1.74 (m, 2H), 1.76 (m, 2H), 1.82-2.76 (m, 5H), 2.79 (m, 2H), 2.80 (m, 1H), 3.04 (m, 2H), 3.12-3.60 (m, 8H), 3.64 (m, 1H), 3.92 (m, 1H), 4.12-5.50 (m, 2H), 5.80 (broad, 6H), 7.00-7.08 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 9.70, 13.26, 21.96, 23.88, 25.78, 25.82, 27.76, 29.76, 29.78, 31.16, 31.58, 35.66, 36.42, 38.90, 40.56, 41.22, 41.29, 42.26, 44.37, 49.82, 50.60, 50.94, 81.22, 82.50, 100.24, 112.02, 122.14, 125.53 135.62, 139.70, 152.22, 153.94, 157.22, 166.22 ppm. EI-MS m/z: 577.39 Anal. Calcd.for $C_{34}H_{51}N_5O_3$: C, 70.68; H, 8.90; N, 12.12; O, 8.31. Found: C, 70.60; H, 8.82.

2-(((13S,E)-13-methyl-5,6,7,8,9,10,11,12,13,14,15,16,-dodecahydro-17H-cyclopenta[a] phenanthren-17-ylidene)amino)ethan-1-amine[2,3,e]2,2'(((1Z,3Z,6E)-8-ethyl-14H-7-oxa-2-aza-1(2,4)-

pyranacyclodecaphen-3,6-diyliden)bis(azanylidene))bis(ethan-1-amine) (8).

Yielding 38 % of product, m.p. 164-166 ^{o}C; IR (V_{max}, cm^{-1}) 3304, 1712 and 1246:^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 0.92 (s, 3H), 1.20-1.36 (m, 4H), 1.42 (m, 2H), 1.54 (m, 1H), 1.56-1.62 (m, 2H), 1.74 (m, 2H), 1.78-2.76 (m, 9H), 2.79 (m, 2H), 2.80 (m, 1H), 3.04 (m, 2H), 3.12-3.60 (m, 8H), 3.94 (m, 1H), 4.12-5.50 (m, 2H), 5.70 (broad, 5H), 7.00-7.14 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 9.72, 14.12, 21.12, 21.94, 23.32, 25.80, 26.42, 29.54, 29.74, 29.76, 31.60, 32.40, 36.44, 36.82, 40.56, 41.22, 41.32, 45.12, 49.16, 50.62, 50.94, 51.62, 82.50, 100.26, 112.00, 121.74, 125.50, 135.20, 139.26, 152.24, 153.94, 157.24, 166.22, 220.30 ppm. EI-MS m/z: 575.38 Anal. Calcd.for $C_{34}H_{49}N_5O_3$: C, 70.92; H, 8.58; N, 12.16; O, 8.34. Found: C, 70.84; H, 8.50.

Physicochemical parameters evaluation

Theoretical electronic properties, such as HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) energy, orbital coefficients distribution, molecular dipole moment and HBD (hydrogen bond donor groups) and HBA (hydrogen bond acceptor groups), TPSA (topological polar surface area) and number of rotatable bonds (RB) were evaluated using the SPARTAN'06 software [14]. In addition, ACD Log P and KOWWIN programs were used to estimate the parameters logP (LogKow), π, were evaluated using previously methods reported [15, 16].

Evaluation of biological activity

Biological method

The animals (male Wistar rats; weighing 200-250 g) used were obtained from the pharmacochemical laboratory of the Autonomous University of Campeche. In addition, the animals were managed in accordance with the guide for the care and use of laboratory animals
[16].

Reagents

The different compounds were dissolved in methanol; in addition, the dilutions were obtained using Krebs-Henseleit.

Experimental design

The animals were anesthetized with pentobarbital (50 mg/Kg body weight) via intraperitoneal injecting. After, the chest was opened to expose the heart, following descending aorta was cut and the heart was immediately flushed with Krebs-Henseleit solution. Then, the heart was trimmed of non-cardiac tissue and retrograde perfused via a non-circulating perfusion system at a constant flow rate (10 ml/min). The perfusion medium was the Krebs-Henseleit solution (pH = 7.4; 35-37 ^{0}C) bubbled with gas mixture (CO2, 5% and O2, 95%). Experimental data were done after of an equilibration period (10 min).

Perfusion pressure

Changes in perfusion pressure and left ventricular pressure produced by the administration of the compounds involved in this investigation were determined using a pressure transducer that was bound to both chamber (where the hearts were mounted) and computerized data capture system (MP-100).

Inotropic activity

To evaluate the inotropic effect, a latex balloon filled with saline solution (0.01 mm, diameter) was inserted into the left ventricle through the left atrium. It is important to mention that latex balloon was bound to pressure transducer which was connected to a computerized data capture system (MP-100). After, inotropic effect produced by compounds involved in this study was evaluated by determine left ventricular developed pressure (LV/dP) [17].

Biological evaluation

First stage

Biological activity exerted by the compounds 6 or 7 against perfusion pressure:

Effects produced by the compounds **6** or **7** (at dose of 0.001 nM) and the conditions control on perfusion pressure through of time (3 to 18 min) were determined.

Second stage

Effects induced by noradrenaline, digoxine, milrinone and compound 7 on left ventricular pressure. Intracoronary boluses (50 µl) of noradrenaline or digoxine or milrinone or the compound 7 (0.001 to 100 nM) were administered and their biological activity against left ventricular pressure was evaluated.

Statistical analysis

Experimental results are showed as average ± SE, using each heart as its own control. The data were evaluated through an analysis of variance (ANOVA) [18]. The differences were considered significant when $\boldsymbol{p} = 0.05$.

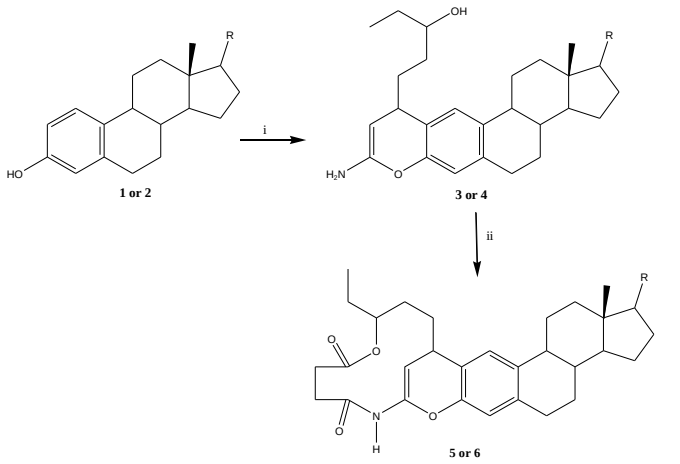
Theoretical evaluation of the interaction between compounds 6 or 7 with phosphodiesterase-4B.

Theoretical analysis was carried out using a docking program (DockingServer) [19]. Phosphodiesterase-4B (ror) was used to determine the interaction of compounds 6 or 7 with the enzyme.

3. RESULTS SECTION

Several anthracene derivatives have been prepared using some reagents such as aliphatic aldehydes/H_2SO_4 [20], chromone/AC_2O [21], pentafluorophenyllithium and tris(pentafluoro-phenyl)boron [22], Pd(II) [23], BF_3-H_20 [24] and others. In this study, two anthracene derivatives were prepared (Figure 1 and 2) using the three-component system (steroid, acetonityl and 5-hexin-3-ol). It is noteworthy that; 1) estrone and estradiol were used as a chemical tool and 2) this reaction did not require any catalyst for its production. The results of ^{1}H NMR spectrum of **3** showed several signals at 0.64 ppm for methyl group which bound to steroid nucleus; at 0.94 ppm for methyl group of arm which attached to 4*H*-pyran ring; at 0.80, 1,02-1.31, 1.38-1.40, 1.64 and 1.72-1.88 ppm for steroid nucleus; at 1.36, 1.53-1.56, 1.66, 2.00, 2.16 and 3.52 ppm for methylene groups of arm which linked to 4*H*-pyran ring; at 3.64 and 4.66 ppm for 4*H*-pyran ring; at 6.10 ppm for both hydroxyl and amino groups. The ^{13}C NMR spectra displays chemical shifts

at 9.66 ppm for methyl involved in the arm which attached to 4*H*-pyran ring; at 13.26 ppm for methyl bound to steroid nucleus; at 23.88-29.76, 31.16, 35.66-38.91, 42,29-49.83 81.24 and 110.70-148.86 ppm for steroid nucleus; at 30.02, 33.70, 35.95 and 79.34 ppm for methylene groups involved in the arm bound to 4*H*-pyran ring; at 34.10, 92.96 and 164.63 ppm for 4*H*-pyran ring. In addition, the mass spectrum from **3** showed a molecular ion (m/z) at 411.27.



R = Hydroyl or Ketone

Figure 1. Synthesis of two pyrancyclodecaphene-dione derivatives (**5** or **6**). Estradiol (**1**) or estrone (**2**) reacted with 5-hexyn-3-ol and acetoni-trile (i) to form the compounds anthracen-ol (**3**) or anthracen-one (**4**). Then, **3** or **4** reacted with succinic acid (ii) to preparation of **5** or **6**.

Another results found showed the following signals of ^{1}H NMR spectrum for **4** at 0.92 ppm for methyl group bound to steroid nucleus; at 0.94 ppm for methyl group of the arm which attached to 4*H*-pyran ring; at 1,20-1.34, 1.54, 1.80-1.92, 2.10-2.12, 2.20-2.80 and 6.66-7.10 ppm for steroid nucleus; at 1.36, 1.55-1.66, 1.98, 2.16 and 3.50 ppm for methylene groups of arm bound to 4*H*-pyran ring; at 3.64 and 4.64 ppm for 4*H*-pyran ring; at 6.02 ppm for both amino an hydroxyl groups. The ^{13}C NMR spectrum showed chemical shifts at 9.66 ppm for methyl involved in the arm which attached to 4*H*-pyran ring; at 14.10 ppm for methyl group attached to steroid nucleus; at 21.16-29.77, 32.40, 36.88, 45.14-51.64 and 110.66-148.92 ppm for steroid nucleus; at 30.04, 33.72, 39.90 and 79.32 ppm for methylene groups attached to 4*H*-pyran ring; at 34.10, 92.98 and 164.64 ppm for 4*H*-pyran ring; at 220.30 for ketone group. Finally, the mass spectrum from **4** showed a molecular ion (m/z) at 409.26.

Preparation of oxa-aza-cyclododecene derivatives (5 or 6)

Some cyclododecene derivatives have synthesized using several reagents such as titanosilicate nano-sheets [25], chloroformate [26], Cu-Al_2O_3 [27], selenocyanatomethyl-benzene/KOH [28] and others; nevertheless, some compounds are difficult to handle and very expensive. Therefore, in this study the compounds **3** or **4** were reacted with succinic acid using boric acid as a catalyst to form **5** or **6** (Figure 1); it is noteworthy that boric acid has been in several reactions to form both ester and amide groups [29].

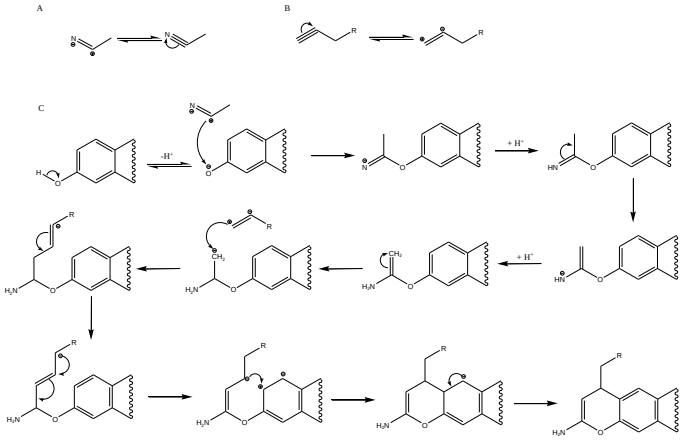


Figure 2. Mechanism of reaction involved in the synthesis of anthracenederivatives (**3** or **4**).

The results of ^{1}H NMR spectrum of **5** display several signals at 0.66 ppm for methyl group. Another results found showed the following signals at 0.84 ppm for methyl group of arm which attached to oxa-aza-cyclododecene system; at 0.80, 1.02-1.40, 1.66-1.76 1.82, 1.88, 2.11, 2.56-3.66 and 6.80-7.00 ppm for steroid nucleus; at 1.62 and 1.80 ppm for methylene group bound to oxa-aza-cyclododecene system; at1.83, 2.10, 2.34-2.42 and 5.14 ppm for oxa-aza-cyclododecene system; at 4.34 and 6.56 ppm for 4*H*-pyran ring; at 6.40 ppm for hydroxyl group; at 8.02 for amino group. The ^{13}C NMR spectra showed several signals at 9.52 ppm for methyl group of arm which attached to oxa-aza-cyclododecene system; at 13,26 ppm for methyl group bound to steroid nucleus; at 23.86-25.84, 27.76, 29,77-35.66, 38.90, 44,37-81.24, 109.90, 122.26-138.88 and 153.62 ppm for steroid nucleus; at 27.66 ppm for methylene group attached to oxa-aza-cyclododecene system; at 29.36-29.76, 37.04-37.05 and 82-02 ppm for the oxa-aza-cyclododecene system; at 40.35, 107.45 and 152.02 ppm for 4*H*-pyran ring; at 171.04-172.82 ppm for ketone groups. Finally, the mass spectrum from **4** showed a molecular ion (m/z) 493.29.

Another results found showed the following signals of ^{1}H NMR spectrum for **6** at 0.92 ppm for methyl group attached to steroid nucleus; at 0.82 ppm for methyl group of arm which attached to oxa-aza-cyclododecene system; at 1.20-1.54, 1.78-1.80, 1.92, 2.11-2.20, 2.46-2.80, and 6.80-7.06 ppm for steroid nucleus; at 1.62 ppm for methylene group bound to oxa-aza-cyclododecene system; at 1.83, 2.10, 2.34-2.42 and 5.14 ppm for oxa-aza-cyclododecene system; at 4.34 and 6.56 ppm for 4*H*-pyran ring; at 8.02 for amino group. The ^{13}C NMR spectra displays chemical shifts at 9.52 ppm for methyl group of arm which bound to oxa-aza-cyclododecene system; at 14.12 ppm for methyl group bound to steroid nucleus; at 21.12-26.42, 29,56, 29.77-36.85, 46.12-51.62, 109.90-138.45 and 153.63 ppm for steroid nucleus; at 27.66 ppm for methylene bound to oxa-aza-cyclododecene system; at 29.38, 29.76, 37.04-37.05 and 82-02 ppm for the oxa-aza-cyclododecene system; at 40.35, 107.44 and 152.04 ppm for 4*H*-pyran ring; at 171.06-220.30 ppm for ketone groups. Finally, the mass spectrum from 5 showed a molecular ion (m/z) at 491.26.

Formation of oxa-aza-cyclododecene-amino-imino system (7 or 8)

Several methods for preparation of imino groups derivatives have been previously reported; however, some reagents involved in its production require special conditions [30. 31]. In this sense, two oxa-aza-cyclododecene-amino-imino (**7** or **8**) were prepared from **5** or **6** (Figure 3) using boric as a catalyst.

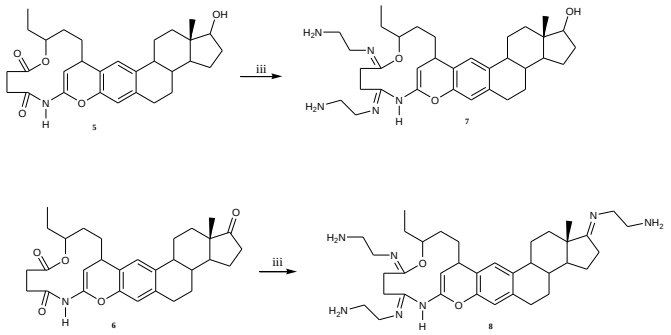


Figure 3. Preparation of azanylylidene-ethanamine derivatives (**7** or **8**). 17-ol-pyrancyclodecaphene-3,6-dione (**5**) or 17-one-pyrancyclodecaphene-3,6-dione (**6**) reacted with ethylenediamine (iii) to form **7** or **8**.

It is noteworthy that boric acid does not require special conditions for its handling [32]. The results of ^{1}H NMR spectra of **7** showed several signals at 0.64 ppm for methyl group attached to steroid nucleus; at 0.90 ppm for methyl group of arm which attached bound to oxa-aza-cyclododecene system; at 0.80, 1.02-1.40, 1.64-1.74, 1.82-2.76, 2.80, 3.64 and 7.00-7.08 ppm for steroid nucleus; at 1.42, 1.76, 2.79, 3.04 and 3.92 ppm for oxa-aza-cyclododecene system; at 1.56-1.60 ppm for methylene group attached to oxa-aza-cyclododecene system; at 3.12-3.60 ppm for methylene groups to both amines; at 4.12-5.60 ppm for 4*H*-pyran ring; at 5.80 for both amino and hydroxyl groups. The ^{13}C NMR spectra showed several signals at 9.70 ppm for methyl group of arm which bound to oxa-aza-cyclododecene system; at 13.26 ppm for methyl group attached to steroid nucleus; at 23.88, 25.82, 29.76, 31.16, 35.66, 38.90, 42.26-49.82, 81.22, 112.02-139.70 and 153.94 ppm for steroid nucleus; at 25.78 ppm for methylene groups attached to oxa-aza-cyclododecene system; 21.96, 29.78, 38.58, 36.42 and 82.50 ppm for the oxa-aza-cyclododecene system; at 40.56, 100.24 and 152.22 ppm for 4*H*-pyran ring; at 41.22-41.29 and 50.60-50.94 ppm for methylene groups attached to both amine groups; at 157.22-166.22 ppm for imino groups. In addition, the mass spectrum from **7** showed a molecular ion (m/z) at 577.39.

In addition, the results of ^{1}H NMR spectrum of **8** showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 0.90 ppm for methyl group of arm which attached to oxa-aza-cyclododecene system; at 1.20-1.36, 1.54, 1.78-2.76, 2.80 and 7.00-7.08 ppm for steroid nucleus; at 1.42, 1.74, 2.79, 3.04 and 3.94 ppm for oxa-aza-cyclododecene system; at 1.56-1.62 ppm for methylene group bound to oxa-aza-cyclododecene system; at 3.12-3.60 ppm for methylene groups to both amines; at 4.12-5.50 ppm for 4*H*-pyran ring; at 5.30 ppm for amino groups. The ^{13}C NMR spectra display chemical shifts at 9.70 ppm for methyl group of arm which attached to oxa-aza-cyclododecene system; at 14.12 ppm for methyl group attached to steroid nucleus; at 21.12, 23.32, 26.42-29.74, 32.40, 36.82, 45.12-49.16, 51.62-82.50, 112.00-139.26 and 153.94 ppm for steroid nucleus; at 25.80 ppm for methylene groups attached to oxa-aza-cyclododecene system; 21.94, 29.76-31.60 and 36.44 ppm for the oxa-aza-cyclododecene system; at 40.56, 100.26 and 152.24 ppm for 4*H*-pyran ring; at 41.22-41.32 and 50.62-50.94 ppm for methylene groups bound to both amine groups; at 157.24-166.22 ppm for imino groups; at 220.30 ppm for ketone group. Finally, the mass spectrum from 8 showed a molecular ion (m/z) at 575.38.

Electronic parameters evaluation (HOMO and LUMO)

The molecular orbitals HOMO and LUMO (Figure 4, Table 1) for the compounds **7** and 8 were theoretically evaluated with SPARTAN'06 software package (Wavefunc-tion Inc. Irvine, CA, 2000), using Hartree-fock method at 321-G level. The results showed in table 1 indicated that HOMO and LUMO values were lower for the compound **7** compared with **8**; these data indicate that **8** have a strong electro donating ability in comparison with **7**.

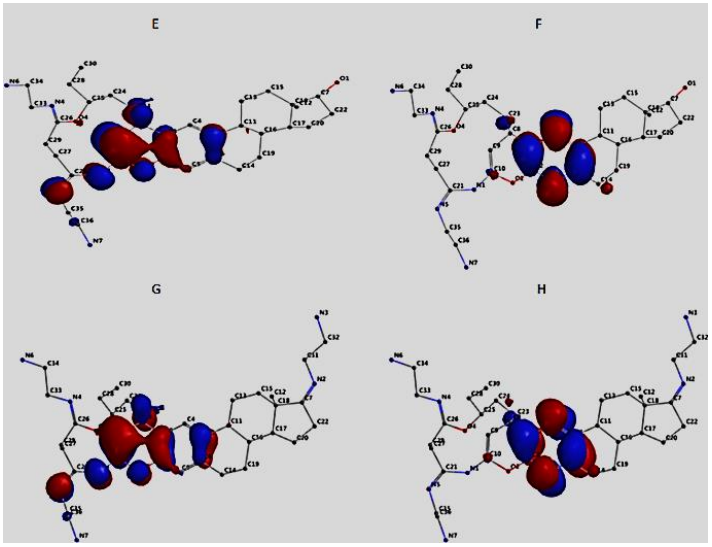


Figure 4. The scheme shown electronic parameters such as HOMO and LUMO for the compounds **7** (G) and **8** (H). Visualized with Spartan 6.0 software.

Table 1. Electronic parameters involved in the compound **7** and **8**.

Parameter	Compound 7	Compound 8
Energy (kcal/mol)	-1803.84	-1915.36
Energy HOMO (ev)	-7.31	-7.82
Energy LUMO (ev)	3.72	3.70
Energy-gap = E. HOMO – E. LUMO (ev)	-11.03	-11.52

Lipophilicity degree of compound 7 and 8.

A theoretical analysis on lipophilicity degree of compound **7** and **8** was evaluated using the parameters log P and π [33]. It is noteworthy that logP (logKow) determinate the lipophilicity degree; in addition, therefore, logKow represents the lipophilic effects of all molecule [14]. It is important to mention that π value for a particular compound can conditioned the lipophilicity degree [15]. The results shown in Table 2 indicated that logKow and π were higher for compound **8** compared to **7**, which translates to more lipophilicity. This phenomenon could be conditioned by other chemical involved in the chemical structure of **7** or **8** such as volume (V_m) and molar refractivity (R_m) that are two

physicochemical parameters which could produce several changes in some biological models.

Table 2. Physicochemical factors **(**logKow and π) involved in the compounds **7** and **8**.

Compound	Fragment	Values
7	-CH3 [aliphatic carbon]	1.0946
	-CH2- [aliphatic carbon]	7.3665
	-CH [aliphatic carbon]	2.5298
	C [aliphatic carbon - No H, not tert]	2.9169
	-OH [hydroxy, aliphatic attach]	-1.4086
	-O- [oxygen, aliphatic attach]	-1.2566
	-NH2 [aliphatic attach]	-2.8296
	-NH- [aliphatic attach]	-1.4962
	Aromatic Carbon	1.7640
	-O- [oxygen, one aromatic attach]	-0.4664
	-tert Carbon [3 or more carbon attach]	0.2676
	-N=C [aliphatic attach]	-0.0020
	Fused aliphatic ring unit correction	-0.6842
	Equation Constant	0.2290
	π	1.2948
	Log Kow	8.0248
8	CH_3 [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	8.3487
	-CH [aliphatic carbon]	2.1684
	C [aliphatic carbon - No H, not tert]	3.8892
	-O- [oxygen, aliphatic attach]	-1.2566
	$-NH_2$ [aliphatic attach]	-4.2444
	-NH- [aliphatic attach]	-1.4962
	Aromatic Carbon	1.7640
	-O- [oxygen, one aromatic attach]	-0.4664
	-tert Carbon [3 or more carbon attach]	0.2676
	-N=C [aliphatic attach]	-0.0030
	Fused aliphatic ring unit correction	-0.6842
	>C=N-C [cyclic-type imine, ali carbon att]	-1.5500
	Equation Constant	0.2290
	π	0.0359
	LogKow	8.0607

Table 3. Physicochemical parameters involved in the compound **7** and **8**.

Parameter	Compound 7	Compound 8
Molar refractivity (cm^3)	160.73 ± 0.5	174.07 ± 0.5
Molar volume (cm^3)	429.4 ± 7.0	465.6 ± 7.0
Parachor (cm^3)	115.70 ± 8.0	1254.2 ± 8.0
Index of refraction	1.671 ± 0.5	1.670 ± 0.5
Density (kg/cm^3)	1.34 ± 0.1	1.32 ± 0.1
Surface tension (dyne/cm)	52.40 ± 7.0	52.60 ± 7.0
Dipole moment (debye)	-2.23	-2.54
PSA (Å)	102.92	115.28
HBA	1.0	2.0
HBD	8.0	9.0
Polarizability	88.47	92.37

These physicochemical factors are tools for the correlation of different properties that depend on characteristics of substituents attached to a constant reaction center. To evaluate both V_m and R_m descriptors in this study, a previously method reported was used [34]. The theoretical results showed (Table 3) that R_m and V_m were higher for **8** compared with **7**. These data suggest that steric hindrance, conformational preferences, and internal rotation could be factors that influence the biological activity by compound **8** on some biological model. Analyzing these data and a study which indicate that some physiochemical factors of several drugs such as hydrogen bond donor groups (HBD) and hydrogen bond acceptor groups (HBA), topological polar surface area (TPSA) are used to predict the biological activity of some compounds in different theoretical models [35]; in this study these physicochemical parameters (Table 3) were evaluated using the Spartan 6.0 software. The results indicate that HBA was < 5, < HBD 5 and values these data indicate that **8** could be well absorbed such happening with another type of compounds [36]. Another result showed that TPSA for8 was higher compared the compound **7**; It is noteworthy, that there are studies which indicate that this physicochemical parameter could condition the ability of drugs to penetrate the blood-brain barrier affinity and exhibit biological activity on intestine nervous central system [37]. All these data suggested that compound **7** could be a good prospect as a new drug in some biological system.

Biological activity.

Analyzing the hypothesis above mentioned, in this study the inotropic activity of compound **8** against perfusion pressure was evaluated using the Langendorff method. In the first stage, the biological activity of **8** was asses and compared with the effect of the compound **7** and control conditions. The results showed (Figure 5) that **8** significantly increased (***p*** = 0.05) the perfusion pressure compared with the compound **7** and control conditions.

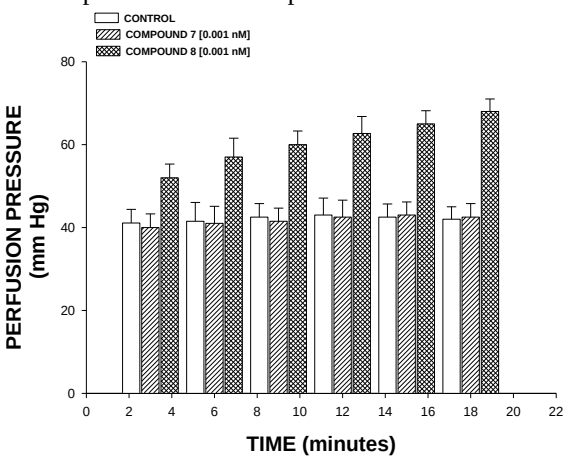


Figure 5. Biological activity induced by the compounds **7** and **8** on perfusion pressure through of time. The experimental data found shown that compound **8** significantly increased (***p*** = 0.05) the perfusion pressure compared with the compound **7** and conditions control. Each bar represents the mean ± S.E. of 9 experiments.

These data indicated that compound **8** exert a positive inotropic effect in heart.

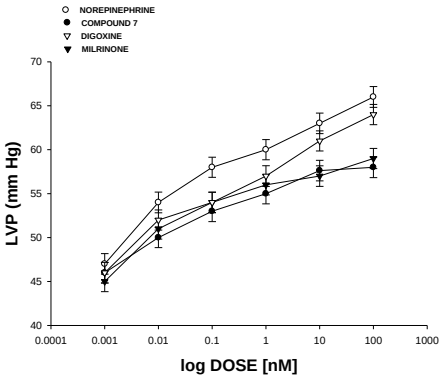


Figure 6. Effect induced by norepinephrine, digoxine, milrinone and the compound **8** against left ventricular pressure (LVP). The scheme shows that compound **8** significantly increase LVP (**p** = 0.05) in a similar form; however, this effect was different from the biological activity exerted by

norepinephrine and digoxine. Each bar represents the mean ± S.E. of 9 experiments.

In the search of molecular mechanism involved in the biological activity exerted by compound **8**, several pharmacological tools such as norepinephrine (adrenergic receptors agonist), digoxine (ATP-ase inhibitor) and milrinone (phosphodiesterase III inhibitor) were used.The results showed (Figure 6) that compound increased the left ventricular pressure in a different manner compared with norepinephrine and digoxine; however, in a similar form compared with milrinone.

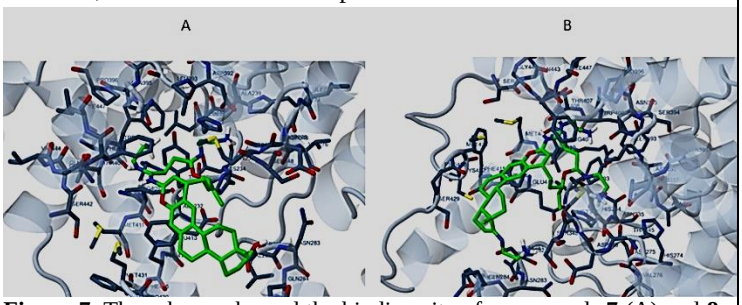


Figure 7. The scheme showed the binding site of compounds **7** (A) and **8** (B) with phosphodiesterase-4B (1ror) surface. Visualized with GL- mol Viewer.

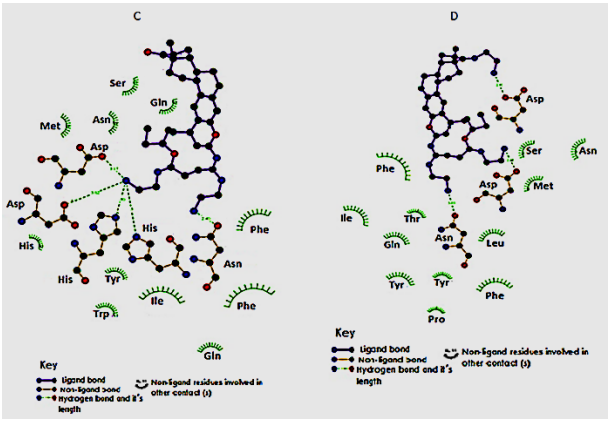


Figure 8. The scheme showed the binding site of amino acid residues involved in the interaction of phosphodiesterase-4B (1ror) with the compound **7 (C)** and **8 (D)**. Visualized with GL mol Viewer, dockingserver.

This phenomenon suggests that biological activity could be via inhibition of phosphodiesterase; analyzing these data and others that indicate that phosphodiesterase-4B is involved in the inotropic activity [38], a theoretical study on the interaction of compound **8** with phosphodiesterase-4B (1ror) was evaluated using a docking model [39]. The results (Figure 7 and 8) showed the possible interaction of compound **7** with the amino acid residues involved in the structure of phosphodiesterase-4B such as Tyr_{233}, Hys_{234}, Hys_{238}, Hys_{274}, Asp_{275}, Ser_{282}, Asn_{283}, Met_{347}, Asn_{395}, Trp_{406}, Ile_{410}, Phe_{414}, Gln_{443}, Phe_{446}. Analyzing these data, also the possible interaction of compound **7** with the 1ror protein was evaluated to compare with compound **8**. Theoretical data found showed that **7** could interact with several amino acid residues such as Tyr_{233}, Asn_{283}, Asp_{346}, Met_{347}, Ser_{348}, Asp_{392}, Leu_{293}, Asn_{395}, Pro_{396}, Tyr_{403}, Thr_{407}, Ile_{410}, Phe_{414}, Gln_{443}, Phe_{446}.

All this data indicates that compounds **7** or **8** could interact in a manner different with amino acids residues on the surface of phosphodiesterase-4B. This phenomenon could involve other type intramolecular interactions due to changes in the energy levels.

Thermodynamic parameters involved in the interaction of compounds 7 or 8 with the phosphodiesterase-4B (1ror)

In addition, other studies shown that also some thermodynamic parameters are evidences for confirming the interaction drug-protein [40], in this study a theoretical evaluation was carried out on some thermodynamic parameters such as free energy of binding, electrostatic energy, total intermolecular energy, vdW + on some thermodynamic parameters such as free energy of binding, electrostatic energy, total intermolecular energy, vdW + Hbond + desol energy and inhibition constant. The results showed differences in the intramolecular energy involved in the interaction for compound **7** or **8** (Table 4) with the phosphodiesterase-4B. Finally, other data shown that inhibition constants were lower for **7** compared with the Ki for **8**. These data are interesting, which implies a higher interaction of the compound **8** with the phosphodiesterase-4B which could is related to positive inotropic effect.

Table 4. Energy levels.

Comp	Est. Free Energy of Binding (kcal/ mol)	Est. Inhib. Const. Ki (nM)	vdW + Hbond + desolv Energy (kcal/mol)	Electrost. Energy (kcal/ mol)	Total Intermol Energy (kcal/ mol)	Inter. Surface
7	-10.88	10.66	-8.65	-5.18	13.84	1254.50
8	-10.38	24.56	-8.87	-4.96	-13.83	1439.13

4. CONCLUSIONS

The results shown that compound **8** exert a positive inotropic effect in an isolated heart model. In addition, theoretical data indicated that this phenomenon could involve inhibition of the phosphodiesterase-4B which opens the possibility that this compound would be used to heart failure; however, it is important to conduct toxicity studies of the compounds involved in this study.

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