Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Article
Volume 12, Issue 1, 2022, 253 - 263
https://doi.org/10.33263/BRIAC121.253263

Design and Synthesis of Three Tetracyclic-Dione Derivatives and their Biological Activity on Perfusion Pressure Using an Isolated Rat Heart Model

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Received: 25.02.2021; Revised: 2.04.2021; Accepted: 6.04.2021; Published: 20.04.2021

Abstract: Several tetracyclic derivatives have been prepared with different biological activity; however, there are few reports on the effects exerted by the tetracyclic derivatives on the cardiovascular system. The objective of this investigation was to prepare three tetracyclic-dione derivatives (compounds 3 to 5) to evaluate their biological activity on perfusion pressure and coronary resistance. The first stage was achieved by the synthesis of three tetracyclic-dione analogs using some chemical strategies. The second stage involves evaluating biological activity from tetracyclic-derivatives on perfusion pressure and coronary resistance using an isolated rat heart model. The results showed that only compound 5 increases perfusion pressure and coronary resistance compared with the control conditions. In conclusion, the biological activity of compound 5 exerted against perfusion pressure and coronary resistance depends on the functional groups involved in their chemical structure.

Keywords: tetracyclic; derivatives; chemical; perfusion pressure.

1. Introduction

For several years, tetracyclic compounds have been of great interest to the pharmaceutical and chemical industry [1-10]. For example, the synthesis of some tetracyclic 1,5-benzodiazepine derivatives from nevirapine as virus de immunodeficiency human inhibitors using MT-4 cells [11]. Another report displays the preparation of a benzofurane derivative via reaction of 2-Amino-benzoic acid with biological activity against cancer [12]. Also, a study showed the reaction of 3-aryl coumarin aldehydes with malononitrile to form some 3-arylcumarin-tetracyclic derivatives, which were used for the treatment of Parkinson´s [13]. Other studies showed the preparation of a tetracyclic thienopyridone from 4-oxopyrido[3′,2′:4,5]thieno[3,2-*b*]indole-3-carboxylic acid as antibacterial and antitumor agents

[14]. Besides, a report showed the preparation of some tetracyclic fluoroquinolones as antibacterial and anticancer agents [15].

On the other hand, some studies indicate that some tetracyclic exert biological activity on the cardiovascular system; thus, a study suggests that a tetracyclic drug such as imipramine exerts changes in coronary vascular responses in an isolated perfused rat heart model [16]. Other studies showed the synthesis of 2-(4-Substituted-phenyl)sparteine from a 2-dehydrosparteine derivative as an inotropic agent in an isolated guinea pig atria [17]. A report showed some tetracyclic guanines can decrease blood pressure in a spontaneously hypertensive rat model [18]. These data indicate that tetracyclic derivatives can exert an effect on the cardiovascular system; however, there are little data on the biological activity induced by tetracycl-dione derivatives on the cardiovascular system; in this way, this investigation aimed to synthesize three tetracycl-dione derivatives to evaluate their biological activity on perfusion pressure and resistance vascular using an isolated rat heart model.

2. Materials and Methods

2.1. General.

The epoxide derivative (compound 1) was prepared using a previously reported method [19]. Also, the reagents used in this research were acquired from Sigma-Aldrich Co., Ltd. Melting point was determinate using an Electrothermal (900 models) apparatus. Infrared spectra (IR) were obtained with a Thermo Scientific iSOFT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Varian VXR300/5 FT NMR spectrometer at 300 MHz in deutered chloroform ($CDCl_3$) using tetramethylsylane as an internal standard. Electron ionization-mass spectrometry (EIMS) were obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were determinate with a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

2.1.1 Synthesis.

(4R,6S)-11-[hydroxy(phenyl)methyl]-5-oxapentacyclo[7.4.1.02,8.04,6.010,13]tetradec-10(13)-ene-3,7-dione (2).

A solution of compound 1 (100 µl, 0.52 mmol), 1-phenyl-2-propyn-1-ol (80 µl, 0.65 mmol), Copper(II) chloride anhydrous (130 mg, 0.96 mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then, the solvent of mixture was evaporated under reduced pressure and following the product was purified trough a crystallization using the methanol:agua (3:1:1) system; yielding 54% of product; m.p. 56-58 ^{o}C; IR (V_{max}, cm^{-1}) 3400 and 1712: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.44-1.66 (m, 2H), 2.52 (broad, 1H), 2.56-2.62 (m, 2H), 2.68-2.70 (m, 2H), 3.20-3.32 (m, 4H), 3.60 (m, 2H), 4.36 (m, 1H), 7.14-7.40 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 26.92, 41.20, 46.50, 47.42, 48.74, 52.12, 53.27, 65.96, 80.25, 126.44, 126.48, 128.60, 129.16, 139.80, 139.98, 204.86 ppm. EI-MS m/z: 322.12. Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63; O, 19.85. Found: C, 74.50; H, 5.60.

5-(3-ethynylanilino)-4-hydroxy-10-[hydroxy(phenyl)methyl]tetracyclo[6.4.1.02,7.09,12]tridec-9(12)-ene-3,6-dione (3).

A solution of compound 2 (165 mg, 0.51 mmol), 3-ethynylaniline (100 µl, 0.52 mmol), triethylamine (100 µl, 0.71 mmol), water (5 ml); following the solution was adjusted at a pH of 8.0 and then was stirring for 4 h to reflux. Then, the solvent of mixture was evaporated under reduced pressure and following the product was purified *via* crystallization using the

methanol:hexane:agua (3:1:1) system; yielding 54% of product; m.p. 62-64 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 3312 and 1712: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.44-1.66 (m, 2H), 2.54 (m, 1H), 2.56-2.62 (m, 2H), 2.86 (s, 1H), 2.88 (m, 1H), 3.15 (broad, 3H), 3.20 (m, 1H), 3.22-3.34 (m, 2H), 4.36 (m, 1H), 4.48-4.50 (m, 2H), 6.60- 6.64 (m, 2H), 7.14 (m, 1H), 7.16-7.25 (m, 2H), 7.32-7.40 (m, 4H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 26.92, 41.20, 45.90, 46.50, 50.55, 53.10, 54.70, 67.12, 76.82, 78.20, 80.22, 84.00, 117.84, 121.00, 121.76, 125.50, 126.44, 126.48, 128.60, 129.12, 129.16, 139.80, 139.95, 150.12, 201.44, 202.80 ppm. EI-MS m/z: 439.17. Anal. Calcd. for $C_{28}H_{25}NO_4$: C, 76.52; H, 5.73; N, 3.19; O, 14.56. Found: C, 76.50; H, 5.70.

4-hydroxy-10-[hydroxy(phenyl)methyl]-5-(prop-2-ynylamino)tetracyclo[6.4.1.02, 7.09,12]tridec-9(12)-ene-3,6-dione (4)

A solution of compound 2 (165 mg, 0.51 mmol), propargylamine (50 µl, 0.78 mmol), 5 triethylamine (100 µl, 0.71 mmol), water (5 ml); following the solution was adjusted at a pH of 8.0 and then was stirring for 4 h to reflux. Then, the solvent of mixture was evaporated under reduced pressure and following the product was purified trough a crystallization using the methanol:hexane:agua (3:1:1) system;yielding 54% of product; m.p. 98-100 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 2122 and 1712: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: : 1.44-1.66 (m, 2H), 2.02 (s, 1H), 2.28 (broad, 3H), 2.54 (m, 1H), 2.56-2.62 (m, 2H), 2.76 (m, 1H), 3.20 (m, 1H), 3.22-3.24 (m, 2H), 3.52-3.54 (m, 2H), 3.70 (m, 1H), 4.36 (m, 1H), 4.46 (m, 1H), 7.16-7.40 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 26.92, 35.94, 41.20, 46.50, 49.12, 50.58, 54.74, 55.98, 71.62, 73.44, 76.92, 78.32, 80.20, 126.42, 126.48, 128.60, 129.12, 139.80, 139.96, 197.44, 201.60 ppm. EI-MS m/z: 377.16. Anal. Calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71; O, 16.96. Found: C, 73.16; H, 6.12.

4-hydroxy-10-[hydroxy(phenyl)methyl]-5-(2-phenylhydrazino)tetracyclo[6.4.1.02,7. 09,12]tridec-9(12)-ene-3,6-dione (5)

A solution of compound 2 (165 mg, 0.51 mmol), phenylhydrazine (80 µl, 0.81 mmol), 5 triethylamine (100 µl, 0.71 mmol), water (5 ml); following the solution was adjusted at a pH of 8.0 and then was stirring for 4 h to reflux. Then, the solvent of mixture was evaporated under reduced pressure and following the product was purified *via* crystallization using the methanol:agua (3:1:1) system; yielding 54% of product; m.p. 138-140 ^{o}C; IR (V_{max}, cm^{-1}) 3402, 3380, 3310 and 1710: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.44-1.66 (m, 2H), 2.54 (m, 1H), 2.56-2.62 (m, 2H), 2.76 (m, 1H), 3.20 (m, 1H), 3.22-3.36 (m, 2H), 3.96 (m, 1H), 4.36 (m, 1H), 4.40 (m, 1H), 4.72 (broad, 4H), 6.90-6.92 (m, 3H), 7.12 (m, 1H), 7.24 (m, 2H), 7.32-7.40 (m, 4H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 26.92, 41.20, 46.50, 46.70, 50.58, 54.74, 54.84, 60.32, 73.76, 80.20, 111.40, 121.52, 126.26, 126.44, 126.48, 128.60, 129.12, 139.80, 139.96, 148.10, 200.40, 200.44 ppm. EI-MS m/z: 430.18. Anal. Calcd. for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51; O, 14.87. Found: C, 72.50; H, 6.06.

2.2.2. Pharmacophore evaluation.

The 3D pharmacophore model for both compounds 3-5 was determined using LigandScout 4.08 software [20].

2.1.3. Pharmacokinetic parameters.

SwissADME [21] was used to evaluate some pharmacokinetics parameters for either compounds 3-5.

2.2. Biological activity.

2.2.1. Generalities.

Experimental methods used in this study were are based on rules approved by the Animal Care and Use Committee of University Autonomous of Campeche and accord to Guide for the Care and Use of Laboratory Animals [22]. Male rats Wistar, weighing 200-250 g, were obtained from Laboratory from the pharmacochemistry of University Autonomous of Campeche.

2.2.2. Reagents.

All drugs were dissolved in methanol. Then, the dilutions were carried out using Krebs-Henseleit solution (0.01 %, v/v, which was prepared using a previously reported study [23].

2.2.3. Langendorff method.

Animals) were anesthetized intraperitoneally with pentobarbital (50 mg/Kg). Then the chest was opened, and a loose ligature passed through the ascending aorta. Following, the heart was removed and immersed in Krebs-Henseleit solution. Then, the heart was trimmed of non-cardiac tissue and retrograde perfused through a non-circulating perfusion system at a constant flow rate using a peristaltic pump. An initial perfusion rate of 15 ml/min for 5 min was followed by a 25 min equilibration period at a perfusion rate of 10 ml/min. It is important to mention that all determinations were done after this equilibration period.

2.2.4. Perfusion pressure.

Perfusion pressure changes were carried out in the absence or presence of drugs involved in this study using a pressure transducer connected to the chamber where the hearts were mounted. The records obtained were entered into a computerized data capture system (Biopac).

2.2.5. Experimental design.

Thirty-two animals were used, 8 for each group control and treatment groups. The control group received no drug, while the treatment group functioned as its control.

2.2.5.1. Biological activity exerted by tetracyclic-dione derivatives (3, 4, and 5) on perfusion pressure.

Differences in perfusion pressure (3 to 18 min) in the absence (control) or presence of either compounds 3 or 4, or 5 at a concentration of 0.001 nM were evaluated. It is noteworthy that the effects were obtained in isolated hearts perfused at a constant flow rate of 10 ml/min.

2.2.5.2. Biological activity produced by tetracyclic-dione derivatives (3, 4, and 5)on coronary resistance.

In this investigation, coronary resistance was evaluated in the absence (control) of either compounds 3 or 4, or 5 at a concentration of 0.001 nM. It is noteworthy that coronary resistance was determined as the relationship between coronary flow and perfusion pressure (mm Hg /ml /min).

2.2.6. Statistical analysis.

The data are expressed as average ± SE. The results were put under the variance analysis (ANOVA) with the Bonferroni correction factor using the SPSS 12.0 program [23]. The differences were considered significant when *p* was equal to or smaller than 0.05.

3. Results and Discussion

Several compounds have been synthesized to evaluate their activity on the cardiovascular system; however, several protocols use some reagents which require special conditions such as differences in either temperature or pH [11-18]. In this investigation, three tetracyclic derivatives were prepared to evaluate their biological activity against perfusion pressure and vascular resistance using an isolated rat heart model. The first stage was carried out as follows:

3.1. Chemistry.

3.1.1. Preparation of a cyclobutene derivative.

Some studies have shown the preparation of cyclobutene analogs via [2 + 2] cycloaddition of an alkene with alkyne groups or cycloaddition of alkyne groups to alkyne derivatives using some reagents such as ruthenium [24], $Ni(PPh_3)_2Cl_2$ [25], Cobalt [26] and others; however, some protocols require special conditions such as differences in either pH and temperature. In this way, compound 2 was prepared via a reaction of 1 with 1-phenyl-2-propyn-1-ol, in the presence of Copper(II) chloride (Figure 1). The ^{1}H NMR spectrum from 2 showed several signals at 0.80 ppm for methyl group; at 1.44-1.66, 2.56-2.62, 2.68-2.70 and 3.20-3.32 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 2.52 ppm for hydroxyl group; at 4.36 ppm for methylene bound to both hydroxyl and phenyl groups; at 7.14-7.40 ppm for phenyl group. ^{13}C NMR spectra showed chemical shifts at 26.92-53.27 and 128.60 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 65.96 and 139.80 ppm for cyclohexane ring; at 80.25 ppm for methylene bound to hydroxyl and phenyl groups; at 126.44-126.48, 129.16 and 138.98 ppm for phenyl group; at 204.86 ppm for ketone group. Besides, the mass spectrum from 2 showed a molecular ion (m/z) 322.12.

3.1.2. Epoxide ring opening.

There are several reagents used to promote epoxides ring-opening such as alumina [27], transition metal-based Lewis acids [28], lithium bistrifluoromethanesulfonimide [29], bismuth triflate [30], bismuth trichloride [31], zinc(II) perchlorate hexahydrate [32], diisopropoxyaluminium trifluoroacetate [33], vanadium(III) chloride and others. Most of these methodologies use expensive reagents that require special conditions. In this investigation, the epoxide ring-opening (compound 2) was produced under basic conditions via SN_2 mechanism to form either compounds 3 or 4 or 5 (Figure 1). In this way, the ^{1}H NMR spectrum from 3 showed several signals at 0.80 ppm for methyl group; at 1.44-1.66 2.56-2.62 and 3.20-3.34 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 2.54, 2.88 and 4.48-4.56 for cyclohexane ring; at 2.86 ppm for alkyne group; at 3.15 ppm for both hydroxyl and amino groups; at 4.36 ppm for methylene bound to both hydroxyl and phenyl groups; at 6.60-6.64 and 7.16-7.25 ppm for phenyl group bound to both amino and alkyne groups; at 7.14 and 7.32-7.40 ppm for phenyl group bound to a methylene group. ^{13}C NMR spectra showed chemical shifts at 26.92-54.70,

128.60 and 139.80 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 67.12-76.82 ppm for cyclohexane ring; at 78.20 and 84.00 ppm for alkyne group; at 80.22 ppm for methylene group bound to hydroxyl group; at 117.84-125.50, 129.12 and 150.12 ppm for phenyl group bound to both alkyne and amino groups; at 126.44-126.48, 129.16 and 139.95 ppm for phenyl group bound to methylene group; at 201.44 and 202.80 ppm for ketone groups. In addition, the mass spectrum from 3 showed a molecular ion (m/z) 439.17.

Other data showed several signals involved in the ^{1}H NMR spectrum from 4 at 0.80 ppm for methyl group; at 1.44-1.66, 2.54-3.34 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 3.70 and 4.46 ppm for cyclohexane ring; at 2.28 ppm for both hydroxyl and amino groups; at 3.52-3.54 ppm for methylene group bound to both amino and alkyne groups; at 4.36 ppm for methylene bound to both hydroxyl phenyl groups; at 7.16-7.40 ppm for phenyl groups. ^{13}C NMR spectra showed chemical shifts at 26.92, 41.20-76.92, 128.60 and 139.80 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 35.94 ppm for methylene bound to both alkyne and amino groups; at 71.62 and 78.32 ppm for alkyne group; at methylene bound to both hydroxyl and phenyl groups; at 126.42-125.48, 129.12 and 139.96 ppm for phenyl group; at 192.44 and 201.60 ppm for ketone groups. Besides, the mass spectrum from 4 showed a molecular ion (m/z) 377,16.

Finally, the ^{1}H NMR spectrum from 5 showed several signals at 0.80 ppm for methyl group; at 1.44-3.36 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at 3.96 and 4.40 ppm for cyclohexane ring; at 4.72 ppm for both amino and hydroxyl groups; at 6.90-6.92 and 7.26 ppm for phenyl group bound to the amino group; at 7.12 and 7.32-7.40 ppm for phenyl group bound to a methylene group. ^{13}C NMR spectra showed chemical shifts at 26.92-54.84,128.60 and 139.80 ppm for Tricyclo[4.2.1.02,5]non-2(5)-ene; at60.32-73.76 ppm for cyclohexane ring; at 80.20 ppm for methylene bound to both hydroxyl and phenyl group; at 111.40-126.26 and 148.10 ppm for phenyl bound amino group; at 126.44-126.48, 129.12 and 139.96 ppm for phenyl group bound to methylene group; at 200.40 and 200.44 ppm for ketone groups. Finally, the mass spectrum from 5 showed a molecular ion (m/z) 430.18.

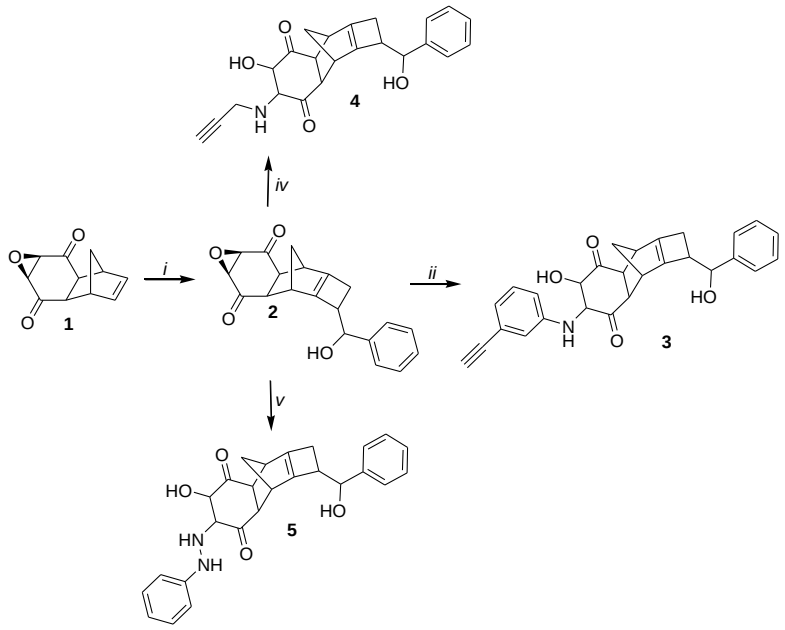

Figure 1. Synthesis of three tetracyclic-dione derivatives (3-5). Reagents and conditions; *i* = 1-phenyl-2-propyn-1-ol, Copper(II) chloride, methanol room temperature, 72 h.; *ii* = 3-ethynilaniline, triethylamine, water; pH = 11.9, reflux, 4h. *ii* = propargylamine, triethylamine, water; pH = 11.9, reflux, 4h. *ii* = phenylhydrazine, triethylamine, water; pH = 11.9, reflux, 4h.

3.1.3. Pharmacophore modeling.

Some theoretical methods have been used to predict the three-dimensional orientation adopted by the interaction protein-ligands [34]. For example, a study showed that the pharmacophore model provides a new perspective to design drugs that can be used to treat any clinical pathology [35]. In this way, in this research, the LigandScout software was used to develop a pharmacophore model for compounds 3-5. The results showed (Figure 2) different types of functional groups involved in the compounds 3-5, which may interact through either hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donors with some biomolecules.

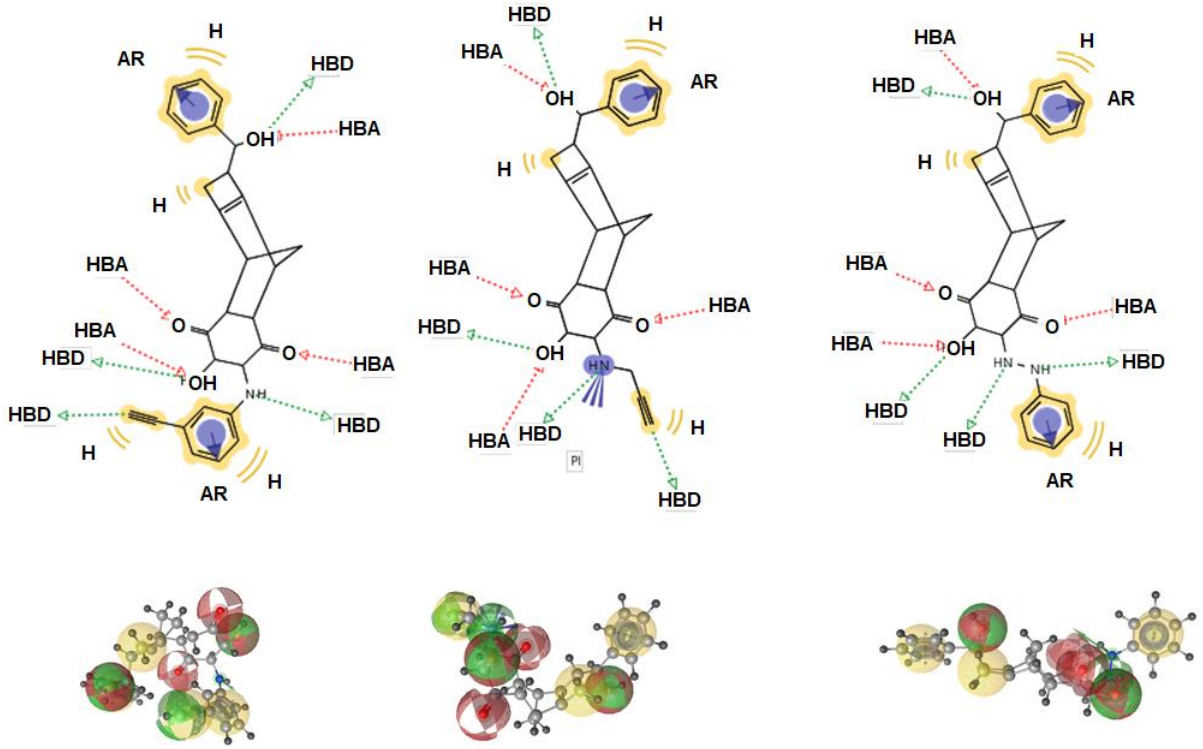

Figure 2. Scheme represents a pharmacophore from compounds 3, 4, and 5 using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red), hydrogen bond donor (HBD, green), and a positive ionizable (PI).

3.2. Biological activity.

3.2.1. General methods.

Changes in perfusion pressure as a consequence of an increase in time in the absence (control) or presence of either tetracyclic-dione derivatives (3, 4, and 5) (Figure 3) were evaluated. The results showed that only compound 5 increase the perfusion pressure ($p = 0.005$) compared with compounds 3, 4, and the conditions control. These data suggest that functional groups involved in the chemical structure of compound 5 are specific for induce changes on perfusion pressure.

By analyzing these data and other studies suggest that the effect exerted by some compounds on perfusion pressure is correlated to changes in coronary resistance [36-38]. In this way, in this research, the coronary resistance was calculated as the ratio of perfusion pressure at the coronary flow assayed (10 ml/min). The results showed that compound 5

increase (p = 0.005) the coronary resistance compared with either compounds 3 or 4 and the control Figure 4.

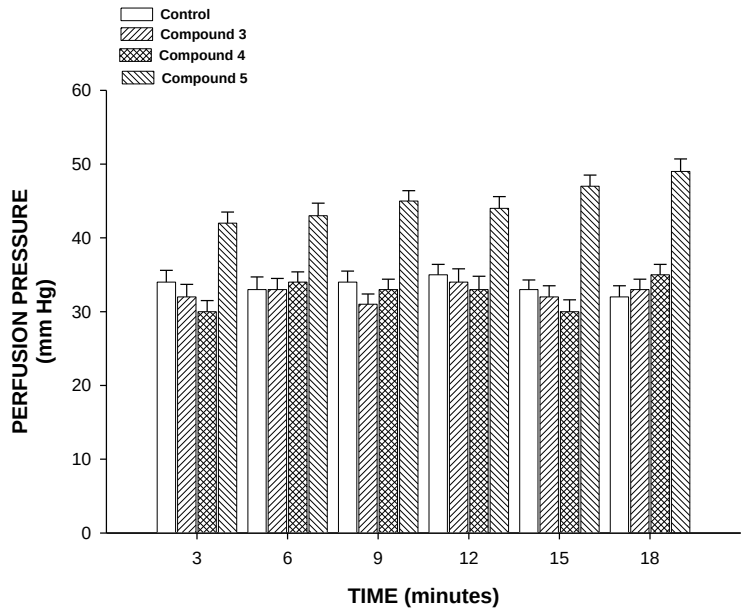

Figure 3. Effect exerted by the tetracyclic-dione derivatives (compounds 3, 4, and 5) at a dose of 0.001 nM on perfusion pressure. The results showed that compound 5 significantly increase the perfusion pressure (p= 0.006) over time compared to control conditions and compounds 3 and 4. Each bar represents the mean ± S.E. of 8 experiments.

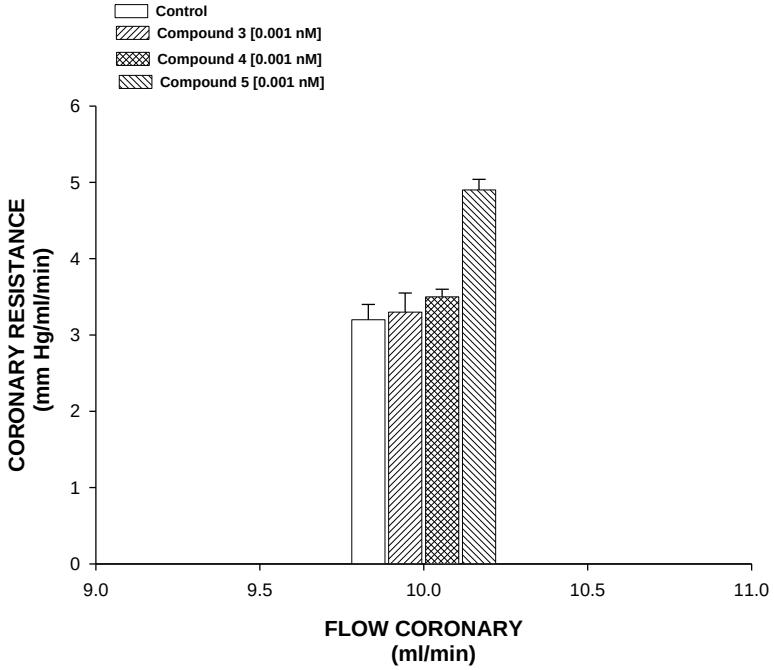

Figure 4. Activity induced by tetracyclic-dione derivatives (compounds 3, 4, and 5) on coronary resistance. The results showed that compound 5 increase (p = 0.005) the coronary resistance compared with either compounds 3 or 4 and the control conditions. Each bar represents the mean ± S.E. of 8 experiments.

3.3. Pharmacokinetic theoretical evaluation.

Some pharmacokinetic parameters of compounds 3-5 were evaluated using SWISSADME software. The results showed that compounds 3-5 could be absorbed via oral, and compounds 3 and 5 show higher lipophilicity compared with compound 4 (Table 1).

Besides, other data indicate differences in the interaction with CYP proteins, resulting in changes in their metabolism, such as happening with other drugs [39-41].

Table 1. The pharmacokinetics properties of compounds 2–4. The values determinate using the SwissADME software.

Comp.	Comp GI (absorption)	BBB (permeant)	P-gP (substrate)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	LogKp (skyn permeation) cm/s
3	High	No	Yes	No	No	No	Yes	No	-7.55
4	High	No	Yes	No	No	No	No	No	-8.76
5	high	No	yes	No	No	No	Yes	No	-7.83

4. Conclusions

It's interesting the biological activity exerted by the tetracyclic-dione derivative (compound 5) on both perfusion pressure and vascular resistance. This effect could be translated as a good candidate to be evaluated as an inotropic agent. Besides, the effect exerted by this compound depends on functional groups involved in chemical structure.

Funding

This research received no external funding.

Acknowledgments

Acknowledgments to Benjamin Valverde and Raquel Anzurez for their unconditional support of this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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