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Activity Exerted by Fluoro-2,4-Dioxaspiro[Bicyclo[3.3.1]Indene Derivative Against Ischemia/Reperfusion Injury

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Abstract: Several drugs for the treatment of heart failure; however, some of these drugs can produce some secondary effects such as arrhythmias and hypercalcemia and others. The aim of this investigation was to evaluate the biological activity of a Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative against both infarct area and left ventricular pressure. The effect exerted of a Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative against both infarct area and left ventricular pressure was evaluated in an ischemia/reperfusion model using indomethacin and ramatroban as a control. Furthermore, a theoretical study was carried out to determine the interaction of Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with COX-1, COX-2, and thromboxane A_2 using the 5u6x, 3ntg, and 6iiu proteins as controls. The results showed that Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative decrease the infarct and left ventricular pressure; however, this effect was inhibited in the presence of ramatroban. In addition, other data indicated that Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative could interact with both COX-2 and thromboxane A_2 protein surface. All these data indicate that the biological activity of Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative against infarct area and left ventricular pressure was via both COX-2 and thromboxane A_2 inhibition. Therefore, this compound could be s candidate for the treatment of heart failure.

Keywords: Fluoro-2; 4dioxaspiro[bicyclo[3.3.1]indene; ischemia; heart; pressure; docking.

1. Introduction

Heart failure (CHF) is the main risk factor to produce death in a patient of older 60 years old; it is noteworthy that several drugs such as nanpril, nesiritide, digoxin, spironolactone, milrinone, dobutamine, and levosimendan have been used for the treatment of CHF [1]; unfortunately, the use of some these drugs is limited by produce some secondary effects such as arrhythmias and hypercalcemia and others [2-4]. In the search for new therapeutic

alternatives, several compounds have been synthesized to the treatment of CHF; for example, the preparation of compound BAY-1021189 AS for treatment of heart failure via guanylate cyclase activation [5]. Another study showed the preparation of a series of naphthalene derivatives as CYP11B2 enzyme inhibitors for HF [6]. Furthermore, a report has shown the preparation of 1,2,4-triazole derivative as a kinase-2 inhibitor to HF [7]. In addition, a pyridazinone derivative was developed with positive inotropic for the treatment of congestive heart failure [8]. Other reports showed the synthesis of some dihydronaphtalen derivatives with positive inotropic activity in congestive heart failure model [9]. Additionally, some imidazol-pyridazinones derivatives have been developed as positive inotropic agents [10]. Other data showed the synthesis of some (N)-methanocarba phosphonate analogs of 5′-AMP with positive inotropic activity for heart failure [11]. Recently, two steroid derivatives have prepared as positive inotropic agents using a heart failure model [12, 13]. All these data shown the preparation of several compounds with positive inotropic activity for the treatment of heart failure; however, their molecular mechanism is not clear, perhaps this phenomenon is due to different structure chemical of each compound. In this way, the objective of this research was to evaluate the inotropic activity of a fluoride-ether derivative using a biological model. In addition, the theoretical interaction of Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with some biomolecules such as cyclooxygenase (COX) and thromboxane receptor (TXA_2) was evaluated using a Docking software.

2. Materials and Methods

2.1. Generalities.

The compound 8-fluoro-1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]--1(9),5,7-triene (Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative, Figure 1) was prepared using a previously method [14]. In this way, all chemical properties, such as the ^{1}H and ^{13}C NMR spectra for the Fluoride-ether derivative, have already been reported. Furthermore, all reagents used in this investigation were acquired from Sigma-Aldrich Co., Ltd.

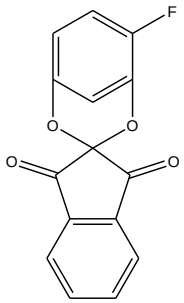

Figure 1. Chemical structure of 8-fluoro-1',3'-dihydro-2,4dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]1(9),5,7-triene [14].

2.2. Animals.

In this study, experimental protocols were reviewed and approved by the Animal care and use committee of University Autonomous of Campeche (UAC) and were in accordance with the guide for the care and use of laboratory animals [15].

2.3. Modified Langendorff method.

Animals were anesthetized with (50 mg / Kg) via intraperitoneal. In the following, the chest was opened, and a loose ligature was passed through the ascending aorta; the heart was then removed and immersed in a Krebs-Henseleit* solution (pH 7.4, 35-37 ^{o}C and bubbled with an O_2/CO_2 mixture [5% / 95%]). Then a cannula was inserted into the aorta to fix the cardiac tissue. It is important to mention that the cannula was bound to a pressure transducer that was connected to a data acquisition system.

* Krebs-Henseleit was prepared using a previous method [16].

2.4. Heart failure.

It is noteworthy that the heart was stabilized for a period of 15 minutes at a coronary flow of 10 ml/min; following, the hearts were subjected to ischemia/reperfusion process for 40 minutes by turning off the perfusion system [13]. Then, the perfusion system was restarted, and the hearts were reperfused by 40 minutes with Krebs-Henseleit solution. The hearts were randomly divided into 6 major treatment groups with n = 9 and follows:

2.5. Biological activity.

2.5.1. Effects exerted by fluoride-ether derivative against infarct area.

Group I. Hearts were subjected to ischemia/reperfusion but received vehicle only (Krebs-Henseleit solution).

Group II. Hearts were subjected to ischemia/reperfusion and treated with the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative at a dose of 0.001 to 100 nM before ischemia period and during the entire period of reperfusion. In this way at the end of each experiment, the perfusion pump was stopped, and 0.5 ml of fluorescein solution (0.10%) was injected slowly through a sidearm port connected to the aortic cannula. The areas of the normal left ventricle non-risk region, area at risk, and infarct region were determined using methods previously reported [13].

2.5.2. Effects exerted by Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative or indomethacin or ramatroban against infarct area.

Group III. Hearts were subjected to ischemia/reperfusion but received vehicle only (Krebs-Henseleit solution).

Group IV. Hearts were subjected to ischemia/reperfusion and treated with the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative at a dose of 0.001 before ischemia period and during the entire period of reperfusion.

Group V. Hearts were subjected to ischemia/reperfusion and treated with the indomethacin* at a dose of 1 nM (before the ischemia period and the entire period of reperfusion).

Group VI. Hearts were subjected to ischemia/reperfusion and treated with the ramatroban** at a dose of 0.001 (before the ischemia period and the entire period of reperfusion).

*Dose of both indomethacin and ramatroban drugs was established using a previously method reported [17, 18].

2.6. Inotropic activity.

To evaluate the effects exerted by fluoride-ether derivative against left ventricular pressure, a saline-filled latex balloon (0.01 mm, diameter) was inserted into the left ventricle via the left atrium. It is noteworthy that the latex balloon was linked to a cannula, which is linked to a pressure transducer [16].

2.6.1. Effects exerted by fluoride-ether derivative against ventricular pressure.

Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative was administered via intracoronary (boluses, 50 µl) at dose of 0.001 to 100 nM and their effect on the left ventricular pressure was evaluated. The dose-response curve (control) was re-determined in the presence of ramatroban, a concentration of 100 nM (duration of preincubation with ramatroban was by a 10 min equilibration period).

2.6.2. Biological activity induced by either the U46619 drug against ventricular pressure.

Intracoronary boluses (50 µl) of either U46619 were administered at a dose of 0.001 to 100 nM, and biological activity on the left ventricular pressure was determined.

2.6.3. Statistical analysis.

The data were expressed as average ± SE, using each heart (n = 7) as its own control. The results were put under an analysis of variance with the Bonferroni correction factor using the SPSS 12.0 software [19], and the values were considered significant when p = 0.05.

2.7. Protein-ligand interaction.

The interaction of the fluoride-ether with COX-1, COX-2, and thromboxane A_2 with CK2- the surface was evaluated using 5u6x, 3ntg, and 6iiu proteins [20] as tools. Furthermore, a docking Server software [21] was used to calculate both binding energy and distance between amino acid residues of 5u6x, 3ntg, and 6iiu proteins and Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative.

2.8. Pharmacokinetics parameter.

To evaluate some pharmacokinetic factors of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative**,** the SwissADME software was used [22].

3. Results and Discussion

3.1. Biological activity.

Several compounds have been prepared for the treatment of heart failure [5-13]; however, the biological activity is very confusing; perhaps this phenomenon could depend on the chemical structure of each compound. Analyzing these data, the aim of this investigation was to evaluate the biological activity exerted by a Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative (Figure 1) against using an ischemia/reperfusion model (Figure 1). In this way, all chemical properties, such as the ^{1}H and ^{13}C NMR spectra for the Fluoride-ether derivative, have already been reported [14]. The results (Figure 2) showed that the Fluoro-

2,4dioxaspiro[bicyclo[3.3.1]indene derivative decrease the infarct area in a dose-dependent manner compared with conditions control (Krebs-Henseleit solution).

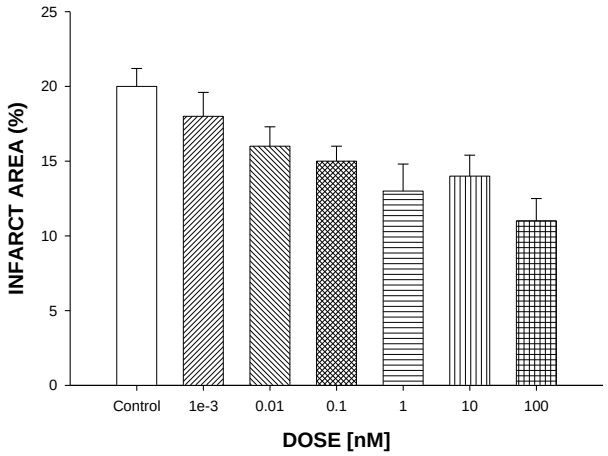

Figure 2. Effect exerted by the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative at a dose of 0.001-100 nM on the functional recovery of rat hearts subjected to ischemia and reperfusion. The results indicate that Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative can reduce the area infarct to different doses compared with control conditions. Bars indicate the mean ± S.E. of 9 experiments.

This phenomenon suggests that Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative could induce changes in some biological systems. Analyzing this hypothesis and other studies which indicate that prostaglandins produce beneficial effects on the heart [23, 24]; some experimental alternative was carried out; in this way, the biological activity of either indomethacin (cyclooxygenase 1 and 2 inhibitors) [25] and ramatroban (non-selective thromboxane A_2 antagonist) [26] was evaluated. The results showed that both indomethacin and ramatroban decrease the infarct area compared with the conditions control; however, the biological activity of both indomethacin and ramatroban was in a similar manner to the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative (Figure 3).

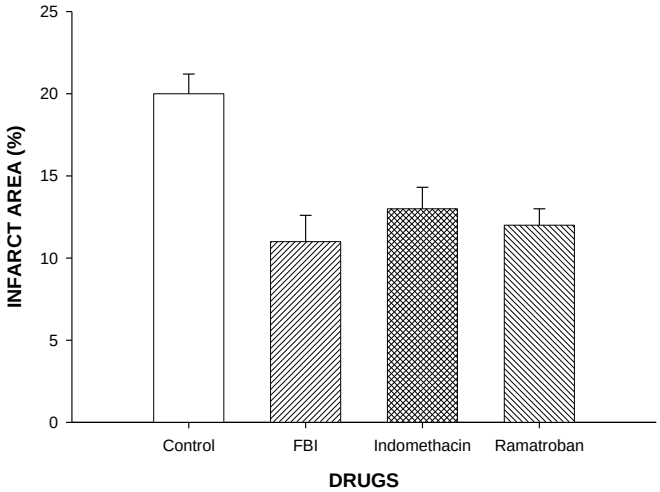

Figure 3. Biological activity exerted by either Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative (FBI) or indomethacin or ramatroban at a dose of 0.01 nM on the functional recovery of rat hearts subjected to ischemia and reperfusion. The results indicate that the FBI significantly ($p = 0.05$) reduces the area infarct compared with the indomethacin [1 nM] or ramatroban [100 nM] and control conditions. Bars indicate the mean ± S.E. of 9 experiments.

Analyzing these data, the biological activity of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative against left ventricular pressure was evaluated in the absence or presence of ramatroban using the U46619 drug (thromboxane A_2 agonist) [27] as a pharmacological tool; the results showed that U46619 increase the left ventricular pressure in a dose-dependent manner. Furthermore, the biological activity exerted by the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative was inhibited by ramatroban (Figure 4).

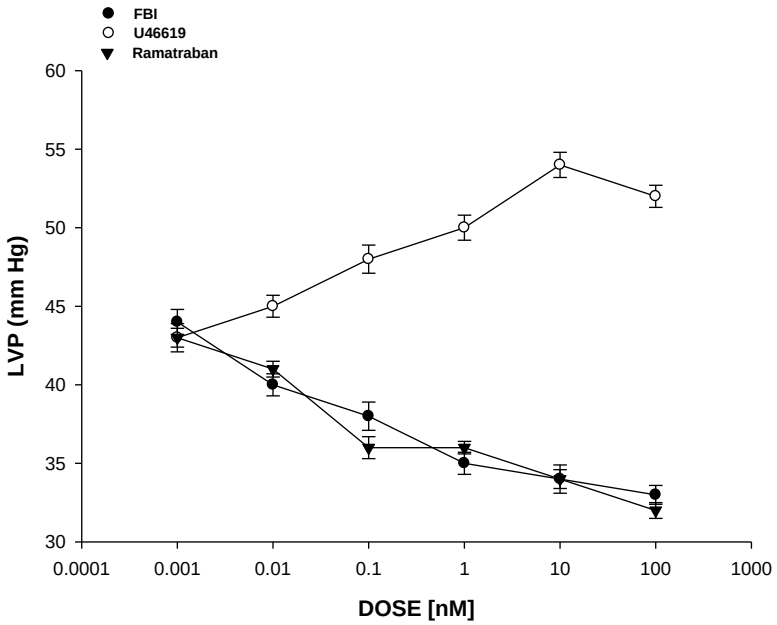

Figure 4. Biological activity exerted by the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative (FBI) against left ventricular pressure. The compound FBI [0.001 to 100 nM] was administered (intracoronary boluses, 50 µl), and the corresponding effect on left ventricular pressure was evaluated in the absence and presence of ramatroban. Besides, the effect exerted by U46619 against left ventricular pressure was evaluated. The results display that activity exerted by the compound FBI against left ventricular pressure was inhibited in the presence of ramatroban. In addition, U46619 increase LVP in a dose-dependent manner. Bars indicate the mean ± SE of 9 experiments.

All these data suggest that Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative could decrease the infarct area via interaction with either cyclooxygenase enzyme or thromboxane-A_2 receptor.

3.2. Protein-ligand interaction.

To evaluate the possibility of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative could interact with the COX-1, COX-2 enzymes, or thromboxane A_2 receptor surface, a theoretical study was carried out, using the following proteins 5u6x, 3ntg, and 6iiu as chemical tools [20]. The results showed several of amino acid residues of either 5u6x, 3ntg and 6iiu proteins surface could interaction with Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative (Figures 5-7; Tables 1-3); it is noteworthy that probably the aminoacid residues involved on 5u6x, 3ntg and 6iiu proteins surface could interact with carbonyl groups of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative via hydrogen bond. This phenomenon may be conditioned by some thermodynamic parameters involved in the interaction protein-ligand, such as happening with another type of biomolecules [28, 29].

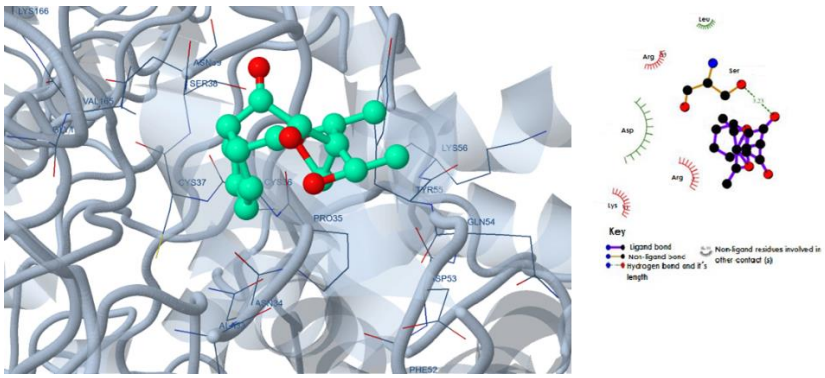

Figure 5. The scheme shows the binding sites of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with some amino acid residues involved in the 5u6x protein surface. The visualization was carried out using DockingServer software [21].

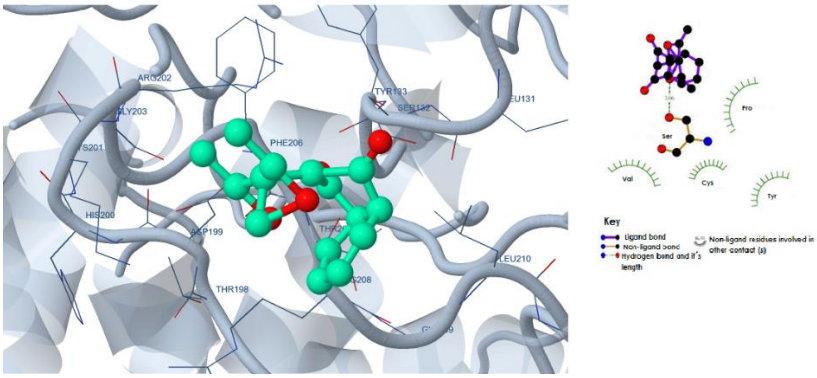

Figure 6. Binding sites of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with some amino acid residues involved of the 3ntg protein surface. The visualization was carried out using DockingServer software [21].

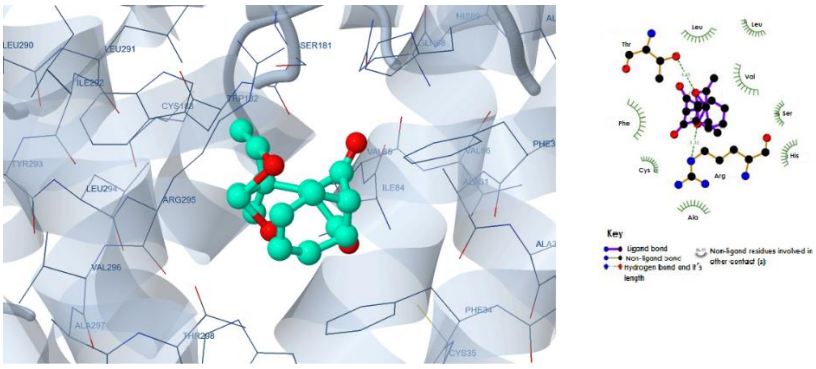

Figure 7. The scheme shows the binding sites of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with some amino acid residues involved in the 6iiu proteins surface. The visualization was carried out using DockingServer software [21].

Table 1. Residues of amino acid residues involved in the interaction between the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 5u6x (COX-1) protein surface.

Fluoride-ether derivative	**Indomethacin**	**Hyperforin**
Ser_{132}	Pro_{35}	Ser_{38}
Asp_{199}	Ser_{38}	Pro_{40}
Lys_{201}	Tyr_{55}	Gln_{42}
Arg_{208}	Glu_{67}	Tyr_{55}
Leu_{210}		Glu_{67}
		Asn_{68}
		Ser_{132}
		Lys_{201}
		Arg_{202}
		Arg_{208}
		Leu_{210}

Table 2. Residues of aminoacid residues involved in the interaction between the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 3ntg (COX-2) protein surface.

Fluoride-ether derivative	**Indometahacin**	**Colecoxib**
Ser_{132}	Trp_{125}	His119
Asp_{199}	Glu_{126}	Tyr120
Lys_{201}	Ser_{129}	Glu126
Arg_{208}	Asn_{130}	Asn130
Leu_{210}	Leu_{131}	Tyr133
	Ser_{132}	Arg202
	Arg_{202}	Phe206

Table 3. Residues of aminoacid residues involved in the interaction between the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 6iiu (thromboxane A2) protein surface.

Fluoride-ether derivative	Ramatroban
Ala_{31}	Phe_{30}
Phe_{34}	Phe_{34}
Cys_{35}	Cys^{35}
Val_{85}	Leu_{78}
His_{89}	Thr_{81}
Ser_{181}	Val_{85}
Leu_{291}	Met_{112}
Leu_{294}	Ser_{181}
Ar_{295}	Trp_{182}
Thr_{298}	Trp_{258}
	Leu_{294}
	Arg_{295}
	Thr_{298}
	Gln_{301}

3.3. Thermodynamic parameters.

Analyzing data above mentioned, in this investigation, a theoretical ass was carried out to evaluate some thermodynamic factors involved between the interaction of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 5u6x, 3ntg and 6iiu proteins surface using indomethacin (non-selective COX-1 and COX-2 inhibitor) [25], hyperforin (selective COX-1 antagonist) [30], celecoxib (selective COX-2 inhibitor) [31], and ramatroban (thromboxane A_2 antagonist) [26] as chemical tools. Furthermore, Docking Server software [21] was used to calculate binding energies between amino acid residues of 5u6x, 3ntg, and 6iiu proteins surface with the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative. The results showed differences in the thermodynamic parameters of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative compared to either indomethacin or hyperforin celecoxib or ramatroban (Tables 4-6); furthermore, the inhibition constant (Ki) involved on the interaction of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with the 5u6x protein surface was higher compared with the Ki for either indomethacin or hyperforin. However, the Ki involved in the interaction of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative with the 3ntg, or 6iiu proteins surface, was lower compared with both indomethacin, celecoxib, and ramatroban. All these data suggest that these differences could be translated as a higher inhibition of biological activity against COX-2 and thromboxane A_2, which could be translated as a decrease of infarct area.

Table 4. Thermodynamic parameters involved in the interaction of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 5u6x (COX-1) protein surface.

Compound	Est. Free energy of Binding	Est. Inhibition Constant (Ki)	vdW + H-bond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Interact Surface
*F-E	-4.57	447.23	-4.57	0.00	-4.57	397.66
Indomethacin	-3.69	1.97	-4.87	0.03	-4.83	493.56
Hyperforin	-2.52	14.20	-4.93	-0.0.17	-4.76	631.76

*F-E = Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative

Table 5. Thermodynamic factors involved in the interaction of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 3ntg (COX-2) protein surface.

Compound	Est. Free energy of Binding	Est. Inhibition Constant (Ki)	vdW + H-bond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Interact Surface
*F-E	-3.91	1.36	-4.06	0.15	-3.91	471.53
Indomethacin	-3.34	3.57	-4.60	-0.18	-4.78	501.86
Celecoxib	-3.36	3.43	-4.76	-0.38	-5.14	485.14

*F-E = Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative

Table 6. Thermodynamic parameters involved in the interaction of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative and 6iiu (thromboxane A2) protein surface.

Compound	Est. Free energy of Binding	Est. Inhibition Constant (Ki)	vdW + H-bond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Interact Surface
*F-E	-7.15	5.77	-7.05	0.10	7.15	685.97
Ramatroban	-8.94	281.09	-9.98	-0.49	-10.47	880.51

*F-E = Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative

3.4. Pharmacokinetic evaluation.

There are several studies to evaluate some pharmacokinetic parameters of several drugs using theoretical models such as PKQuest [32], PharmPK [33] Gitub [34], SwissADME [35]. In this way, in this study, some pharmacokinetic parameters involved in the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative were evaluated using SwissADME software. The results showed in Table 7 indicate that these compounds could have higher gastrointestinal absorption and, consequently, higher metabolism exerted by cytochrome P450 (CYP1A2 and CYP2C9) system.

Table 7. The pharmacokinetics properties of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative. The values determine using SwissADME software.

Parameter	****F-E**
GI absorption	Higher
BBB permeant	Yes
*Pg-substrate	No
CYP1A2	Yes
CYP2C19	No
CYP2C9	Yes
CYP2D6	No
CYP3A4	No
Log K_p (skyn permeation)	-5.36 cm/seg

*pg-substrate = protein-g substrate; **F-E = Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative.

4. Conclusions

All these data indicate that the biological activity of Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative against infarct area and left ventricular pressure was via both COX-2 and thromboxane A_2 inhibition. Therefore, this compound could be s candidate for the treatment of heart failure.

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Conflicts of Interest

The authors declare no conflict of interest.

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