Biological activity of a benzene sulfonamide on perfusion pressure and coronary resistance using an isolated rat heart model

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Abstract

There are studies which indicate that some sulfonamide derivatives can produce changes in the cardiovascular system; however, their biological activity on perfusion presure and coronary resistance is not clear. The aim of this research was to evaluate the effect exerted by benzenesulfonamide, and their derivatives (2,5-dichloro-*N*-(4-nitro-phenyl)-benzene-sulfonamide, 2-hydrazino-carbonyl-benzenesulfonamide, 4-(2-amino-ethyl)-benzene-sulfonamide, and 4-[3-(4-nitro-phenyl)-ureido]-benzene- sulfonamide) on perfusion pressure and coronary reistance. To evaluate the biological activity of benzenesulfonamide and their derivatives on perfusion pressure and coronary reistance an isolated rat heart model was used. Furthermore, theoretical interaction of 4-(2-amino-ethyl)-benzenesul- fonamide with Calcium channel surface was determined using 6jp5 protein, nifedipine, amlodipine, verapamil and BayK 8644 as theoretical tools in a DockingServer program. The Results showed that 4-(2-amino-ethyl)-ben- zenesulfonamide decreased perfusion pressure and coronary resistance compared to benzenesulfonamide, 2,5-dichloro- *N*-(4-nitro-phenyl)-benzene-sulfonamide, 2-hydrazinocarbonyl-benze-nesulfonamide, 4-[3-(4-nitro-phenyl)-ureido]- benenesulfonamide and the control conditions. Besides, theoretical data suggest that 4-(2-aminoethyl)benzenesulfo- namide could interact with aminoacid residues such as Glu_{614} and Ala_{320} involved in 6jp5 protein surface. This phenomenon could result in an ligand-Calcium channel complex formation to produce a decrease in perfusion pressure and vascular resistance. It is noteworthy that biological and experimental models used in this study is an invaluable research tool for investigating questions across the spectrum of physiologic functions of cardiovascular system such as perfusion pressure and coronary resistance

Keywords: benzenesulfonamide, derivatives, perfusion pressure, docking.

Atividade biológica de um benzeno sulfonamida na pressão de perfusão e na resistência coronariana utilizando um modelo isolado de coração de rato

Resumo

Existem estudos que indicam que alguns derivados das sulfonamidas podem produzir alterações no sistema cardiovascular entretanto, sua atividade biológica na pressão de perfusão e na resistência coronariana não está clara. O objetivo desta pesquisa foi avaliar o efeito exercido pela benzenossulfonamida e seus derivados (2,5-dicloro-N-(4-nitro-fenil)-benzeno-sulfonamida, 2-hidrazino-carbonil-benzenossulfonamida, 4-(2-amino-etil)-benzeno-sulfonamida e 4-[3-(4-nitro-fenil)-ureido]-benzeno-sulfonamida) na pressão de perfusão e na

resistência coronariana. Para avaliar a atividade biológica da benzenossulfonamida e seus derivados na pressão de perfusão e na resistência coronariana, foi utilizado um modelo isolado de coração de rato. Além disso, a interação teórica da 4-(2-amino-etil)-benzenossulfonamida com a superfície do canal de Cálcio foi determinada usando a proteína 6jp5, nifedipina, amlodipina, verapamil e BayK 8644 como ferramentas teóricas em um programa DockingServer. Os resultados mostraram que a 4-(2-amino-etil)-benzenossulfonamida diminuiu a pressão de perfusão e a resistência coronariana em comparação com a benzenossulfonamida, 2,5-dicloro-N-(4-nitro-fenil)-benzeno-sulfonamida, 2-hidrazinocarbonil-benze-nessulfonamida, 4-[3-(4-nitro-fenil)-ureido]-benenossulfonamida e as condições de controlo. Além disso, dados teóricos sugerem que a 4-(2-aminoetil)benzenossulfonamida poderia interagir com resíduos de aminoácidos como Glu_{614} e Ala_{320} envolvidos na superfície da proteína 6jp5. Este fenômeno pode resultar na formação de um complexo ligante-canal de Cálcio para produzir uma diminuição na pressão de perfusão e na resistência vascular. Vale ressaltar que, os modelos biológicos e experimentais utilizados neste estudo são uma ferramenta de pesquisa inestimável para investigar questões em todo o espectro de funções fisiológicas do sistema cardiovascular, como pressão de perfusão e resistência coronariana.

Palavras-chave: benzenossulfonamida, derivados, pressão de perfusão, *docking*.

1. Introduction

For several years, sulfonamides have been used as therapeutic agents for treat different diseases (apaydin and Torok, 2019) such as antibacterial (Wu et al., 2022; Ibraim et al., 2022), antiviral (Wei et al., 2022; Li et al., 2022), antiprotozoal (Chable et al., 2001), antifungal (Rahavi-Ezabadi et al., 2022), antiinflammatory (Kennedy et al., 1999), anticancer (Niguyen et al., 2022; Lopez-ramos et al., 2023). Besides, other data showeed that some sulfonamide derivatives produce biological activity on cardiovascular system; for example, some studies have shown that hydrochlorothiazide (6-chloro-1,1-dioxo-3,4-dihydro-2H-1lambda-6,2,4-benzothiadiazine-7-sulfo-namide) is an effective diuretic that lowers blood pressure in hypertensive patients (Carey et al., 2022).

Other reports indicate that both chlorthalidone (2-chloro-5-(1-hydroxy-3-oxo-2H-isoindol-1-yl)benzenesulfonamide) and indapamide 4-chloro-N-(2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoylbenzamide are used as antihipertensive drugs (Ernest and Fravel, 2022; Solis-Jimenez et al., 2022; Kobalava et al., 2022). However some these sulfonamide derivatives can produce some secondary effects such as hypercalcemia (Duarte et al., 1971; Wermes et al., 2022), glucose intolerance (kucharczyk et al., 2023), hypokalemia (lin et al., 2022) and others.

In the search for new therapeutic alternatives to treat hypertension or some cardiovascular disorder, several derivatives of sulfonamides have been synthesized to evaluate their pharmacological activity using different biological model (Talley et al., 2000; Harris et al., 2008; Malysz et al., 2009; ren et al., 2020; Pervais et al., 2020;). For example, a study showed that 4-amino-*N*-(1,3-thiazol- 2-yl)benzenesulfonamide decreased rate heart using a rat model (leblond and Hoff, 1994). Other data indicate that a sulfonamide-substituted phenylethylamine (YM-09538) can act as antihypertensive agent through β-receptor blocking using isolated rat right atria tissue model (Takenaka et al., 1982).

Besides, a report display that benzenesulfonamide derivative (4-tert-butyl-N-(5-(3-methoxyphenoxy)-6-{4-[(1-phenyl-methano-l)hydrazono]butoxy}pyrimidin-4-yl)benzene-sulfonamide) decreases the artery blood pressure through endothelin receptor-B blockade using Sprague-Dawley rats (Kanda et al., 2001). Other studies showed the preparation of a series of 4′-[(imidazol- 1-yl)methyl]biphenyl sulfonamides as angiotensin II AT1 and endothelin ETA receptors inhibitors using a hypertensive rat model (Tellew et al., 2003). In addition, a report indicate that Sitaxsentan drug (*N*-(4-chloro-3-methyl-1,2-oxazol-5-yl)-2-[2-(6-methyl-1,3-benzodioxol-5-yl)acetyl]thiophene-3-sulfona-mide) can act as endothelin receptor- A inhibitor (Wu et al., 1999) which can attenuates pulmonary vascular hypertension and cardiac hypertrophy in rats (Tilton et al., 2000).

Another report indicate that a sulfonamide derivative (N-(5-sulfa- moyl-1,3,4-thiadiazol-2-yl)acetamide) is a carbonic anhydrase inhibitor which could be used in patients with severe heart failure (Schwartz et al., 1995). All these data display that sulfonamide derivatives can exert effect on cardiovascular system; however, the biological activity on perfusion pressure is not clear. Analyzing these data, the aim of this research was to evaluate the biological activity produced by benzenesulfonamide and their derivatives (Figure 1) on perfusion pressure and coronary resistance using an isolated rat heart model. Furthermore, the interaction of 4-(2-aminoethyl)benzenesulfonamide with Calcium channel was eavluated using the 6jp5 protein, nifedipine, amlodipine, Bayk 8644 as theoretical tools in a theoretical coupling model.

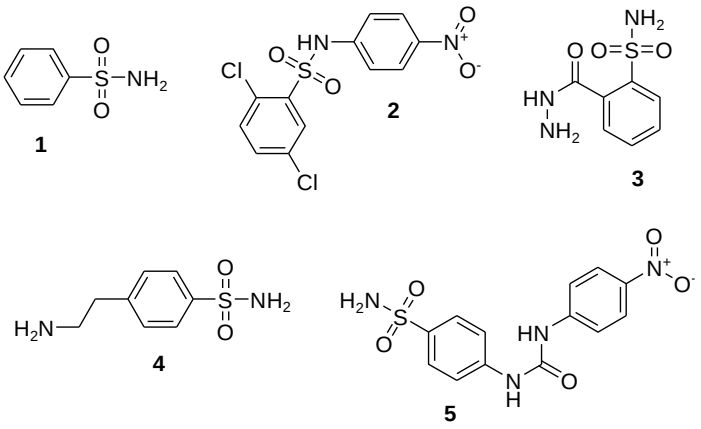

Figure 1. Chemical structure of benzenesulfonamide (**1**), 2,5-Dichloro-N-(4-nitro-phenyl)-benzene-sulfonamide (**2**), 2-Hydrazino- carbonyl-benzenesulfonamide (**3**), 4-(2-Amino-ethyl)-benzenesulfonamide (**4**), and 4-[3-(4-Nitro-phenyl)-ureido]-benzenesulfonamide (**5**). Source: Authors, 2023.

2. Materials and Methods

2.1 General methodology

The experimental procedures and protocols used in this study complied with the research ethics standards used in the Guides for the Care and Use of Animals (Washington, DC: National Academy Press, 1996; Delpire et al., 1999; European Parliament and of the Council of September 22, 2010; Kumar et al., 2021) carried out in the pharmacochemistry laboratory of University Autonomous of Campeche (No. PI-420/12).

2.2 Animals

Wistar; weighing 200-250 g (n = 36) were obtained from Laboratory of Pharmacochemistry Research of University Autonomous of Campeche.

2.3 Reagents

All agents were acquired in Sigma-Aldrich Co. The benzenesulfonamide derivatives and other compounds were dissolved in methanol and, from this solution, dilutions were made by adding *Krebs-Henseleit solution (*v/v*).

*Krebs-Henseleit solution was prepared using a previously reported method (Figueroa-Valverde et al., 2009) with the following reagents such as NaCl (117.8 mM); KCl (6 mM); $CaCl_2$ (1.75 mM); NaH_2PO_4 (1.2 mM); $MgSO_4$ (1.2 mM); $NaHCO_3$ (24.2 mM) ; glucose (5 mM), and sodium pyruvate (5 mM). In addition, the solution was actively bubbled with an O_2/CO_2 (95:5) gas mixture, regulated to pH 7.4 and 37 °C.

2.4 Anesthesia

Pentobarbital (50 mg/kg^{-1}) was via intraperitoneally route to induce anesthesia in rats. Then, the chest was opened, and a loose ligature was passed through the ascending aorta. Then, the heart was removed, and a cannula inserted into the aorta. It is important to mention that cannula was linked to an acrylic chamber, which in turn was bound to a Graham condenser. It is noteworthy that this apparatus was used to retrograde perfuse the heart with Krebs-Henseleit solution at a constant flow (10 mL/min).

2.5 Perfusion pressure evaluation

The recording of the effects produced by benzenesulfonamide and their derivatives on the perfusion pressure was determined using a pressure transducer connected to the chamber where the hearts were mounted. Besides, the pressure transducer was bound to a computerized data system (Biopac).

2.6 Experimental design

Biological activity exerted by benzenesulfonamide and their derivatives on the perfusion pressure. The changes in the perfusion pressure resulting of the increase in time (3-18 min) in the absence or in presence of benzenesulfonamide and their derivatives were determined using the following experimental design (Table 1):

Table 1. Experimental design for the evaluation of biological activity produced by benzenesulfonamide and their derivatives on the perfusion pressure.

Group	Compound	Dose
I	Control	Krebs-Henseleit solution only
II	benzenesulfonamide	0.001 nM
III	Compound 2	0.001 nM
IV	Compound 3	0.001 nM
V	Compound 4	0.001 nM
VI	Compound 5	0.001 nM

Note: Compoun 2 = 2,5-Dichloro-N-(4-nitro-phenyl)-benzene-sulfonamide; compound 3 = 2-Hydrazinocarbonyl-benzenesulfonamide; compound 4 = 4-(2-Amino-ethyl)-benzenesulfonamide and compound 5 = 4-[3-(4-Nitro-phenyl)-ureido]-benzenesulfonamide.

It is important to mention that some compounds at doses of 0.001 nM can produce changes in perfusion pressure (Figueroa-Valverde et al., 2009; Figueroa-Valverde et al., 2011) using some biological models. For this reason, in this research the biological activity of benzenesulfonamide and its derivatives on perfusion pressure was determined using a dose of 0.001 nM.

2.7 Biological activity produced by benzenesulfonamide and its derivatives on coronary resistance.

Coronary resistance in the absence (control) or presence of either benzenesulfonamide or benzenesulfonamide-derivatives at a concentration of 0.001 nM was determined. The effects were determined in isolated hearts perfused at a constant flow rate of 10 ml/min. It is important to mention that coronary resistance was determined as the relationship between coronary flow and perfusion pressure (mm Hg/mL/min) (Figueroa-Valverde et al., 2011).

2.8 Docking analysis

The interaction of 4-(2-Amino-ethyl)-benzenesulfonamide with Calcium channel surface was determined using 6jp5 (https://doi.org/10.2210/pdb6JP5/pdb) protein as a theoretical model. In addition, nifedipine [*type-L* Calcium channel inhibitor] (Olda et al., 2022), amlodipine [*type-L* calcium channel blocker] (Manson et al., 2003), verapamil [*T-type* Calcium channel inhibitor] (Bergson et al., 2022) and BAYK 8644 [*L-type* Calcium channel activator] (Archana et al., 2022) were used as theoretical tools using DockingServer software (Phopin et al., 2020; Bishst et al., 2021; Figueroa-Valverde et al., 2023).

2.9 Pharmacokinetic parameters

Theoretical pharmacokinetic parameters for 4-(2-Amino- ethyl)-benzenesulfonamide were determined using the SwissADME software (Mahanthesh et al., 2020).

2.10 Toxicology

Toxicity evaluation for 4-(2-Amino-ethyl)-benzenesulfo- namide was determined using GUSARsoftware (Lauro et al., 2023).

2.11 Statistical analysis

The obtained values are expressed as average ± S.E, using each heart (n = 6) as its own control. The data

determined were put under analysis of variance (ANOVA) with the Bonferroni correction factor using the SPSS 12.0 program (Nelson et al., 2022). The differences were considered significant when p was equal or smaller than 0.05.

3. Results and Discussion

There are studies in the literature which indicate that some benzenesulfamide derivatives can produce changes in the cardiovascular system (Takenaka et al., 1982; Schwartz et al., 1995; Kanda et al., 2001); however, the biological activity on both perfusion pressure and coronary resistance is not very clear. Analyzing these data, in this research some compounds were selected whose main characteristic involved sulfonamide groups that were linked to different functional groups. Next, the biological activity exerted by sulfonamide derivatives on perfusion pressure and coronary resistance was determined as follows:

3.1 Evaluation of biological activity

Changes in perfusion pressure through of increase in time (3 to 18 min) in the absence (control) or presence of benzenesulfonamide and their derivatives were determined. The results shows that 4-(2-amimoethyl)-benzenosulfonamide significantly decreased (p = 0.05) the perfusion pressure in a time-dependent manner compared benzenesulfonamide, 2,5-di-chloro-N-(4-nitrophenyl)benzenesulfonamide, 2-Hydrazinocarbonyl-benzenesulfonamide, 4-[3-(4-nitro-phenyl)-ureido-benzenesulfonamide and the conditions control (Figure 2).

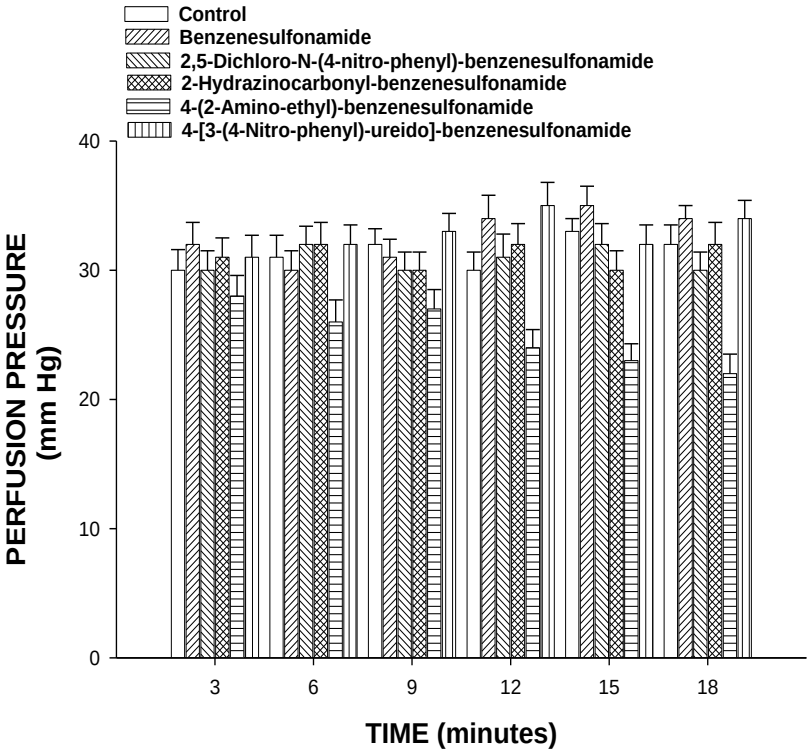

Figure 2. Biological activity produced by benzenesulfonamide derivatives on perfusion pressure. The results shows that compound 4-(2-amimo-ethyl)-benzenosulfonamide decreased the perfufion pressure in a time-dependent manner compared with benzenesulfonamide, 2,5-dichloro-N-(4-nitrophenyl)benzenesulfonamide, 2-Hydrazinocarbonyl-benzenesulfonamide, 4-[3-(4-nitrophenyl)-ureido-benzenesulfona- mide and the conditions control. Each bar represents mean ± S.E of 6 experiments. Source: Authors, 2023.

These results indicate that 4-(2-amimo-ethyl)-benze- nosulfonamide could interact with some biomolecule to produce changes in the cardiovascular system translated as changes in the perfusion pressure. Analyzing these results and other reports, which indicate that some compounds may affect perfusion pressure resulting in changes

in coronary resistance (Figueroa-Valverde et al., 2010; Figueroa-Valverde et al., 2013; Figueroa-Valverde et al., 2023); for this reason, in this research coronary resistance was determined. The results showed that compound 4-(2-amimo-ethyl)-benzenosulfonamide decreased the coronary resistance compared with 2,5-dichloro-N-(4-nitrophenyl)-benzenesulfonamide, 4-(2-amimo-ethyl)-benzenosulfonamide, 4-[3-(4-nitrophe-nyl)-ureido-benze-nesulfonamide and the conditions control (Figure 3).

All these data suggest that 4-(2-aminoethyl)-benzene-sulfonamide could interact with some biomolecule involved in the regulation of blood pressure. This hypothesis is supported by some studies carried out in diferent biological models which suggest that several benzenesulfonamide can produce chamges in blood pressure through release/activation of Calcium channels (Shao et al., 2012; Kim et al., 2016; Grześk et al., 2017).

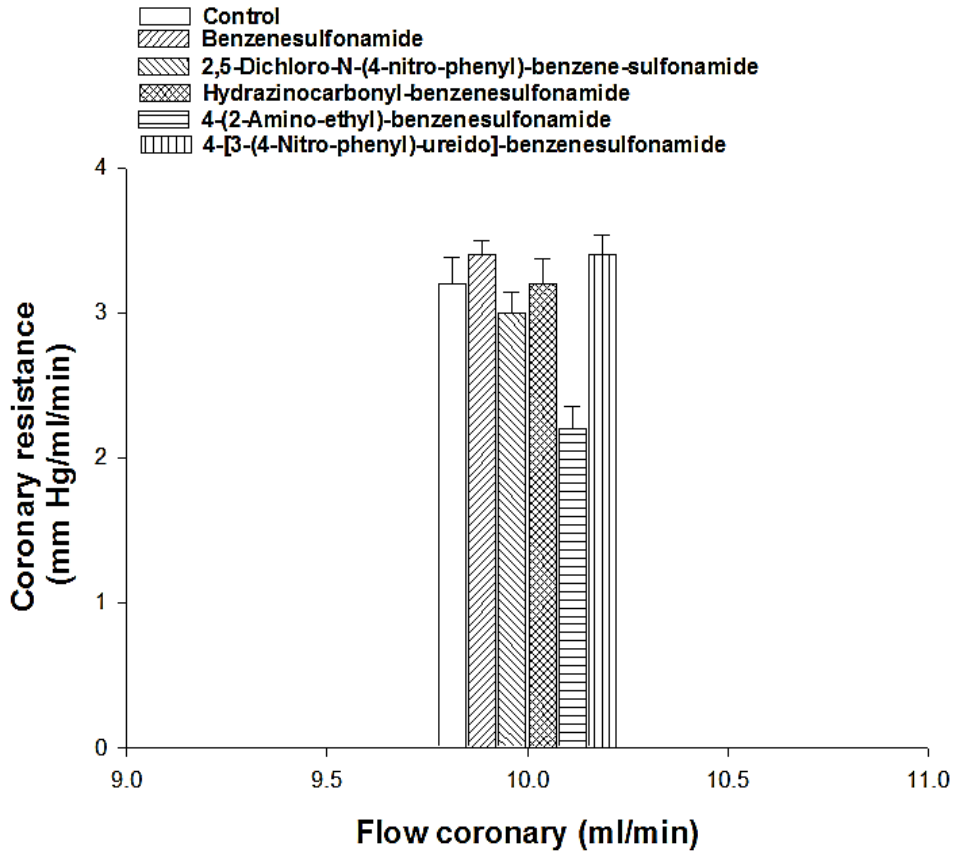

Figure 3. Biological Activity produced by benzenesulfonamide derivatives on coronary resistance. The results show that coronary resistance was lower ($p = 0.05$) in the presence of 4-(2-amimo-ethyl)-benzenosulfonamide in comparison with the other benzenesulfonamide derivatives and control conditions. Each bar represents the mean ± SE of eight experiments. Source: Authors, 2023.

3.2 Docking analysis

In the literature there are several reports indicating that some sulfonamides can act as Calcium channel inhibitors (Shao et al., 2012; Zhang et al., 2015; Kim et al., 2016). For example, a theoretical-experimental study showed the preparation of Calcium channel antagonists containing a biaryl sulfonamide core using the patch clamp assay and a theoretical model (Hangeland et al., 2008).

For this reason, in this investigation, the interaction of 4-(2-aminoethyl)-benzenesulfonamide with Calcium channel surface was evaluated using 6jp5 protein, nifedipine, amlodipine as theoretical tools in DockingServer program. The results (Table 2 and Figure 4) showed that ligand-protein complex formation could involve hydrogen bonding interactions between the amino acid residues Glu_{614} and Ala_{320} from 6jp5 protein surface with the chemical structure of 4-(2- aminoethyl)-benzenesulfonamide. This phenomenon may be the key to protein-ligand binding affinity, which is essential to produce changes in perfusion pressure and coronary resistance through Calcium channels inhibition. However, to support this hypothesis was necessary to evaluate

some thermodynamic parameters.

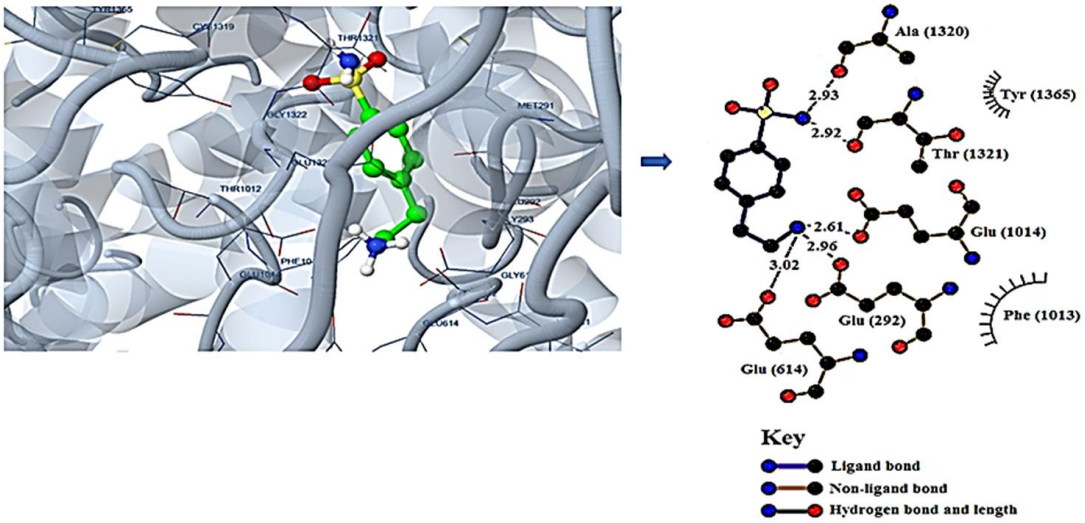

Figure 4. Interaction of 4-(2-Aminoethyl)benzene sulfonamide with 6jp5 protein surface. Visualized with DockingServer program. Source: Authors, 2023.

Table 2. Aminoacid residues involved in theoretical interaction of 4-(2-Aminoethyl)benzene sulfonamide BAY-8644 nifedipine, amlodipine and verapamil with 6jp5 protein surface.

Compound	**Aminoacid Residues**
Nifedipine	Asn_{649}; Leu_{652}; Leu_{653}; Phe_{656}; Leu_{657}; Phe_{1013}; Phe_{1054}; Asn_{1058}; Val_{1061}
Amlodipine	Met_{291}; Glu_{292}; Phe_{1013}; Glu_{1014}; Thr_{1321}; Gly_{1322}; Tyr_{1365}; Ala_{1369}
Verapamil	Leu_{326}; Val_{329}; Leu_{330}; Asn_{649}; Leu_{653}; Phe_{656}; Phe_{1013}; Phe_{1054}; Met_{1057}; Asn_{1058}
BAYK 8644	Asn_{649}; Leu_{652}; Leu_{653}; Phe_{656}; Leu_{657}; Phe_{1013}; Phe_{1054}; Asn_{1058}
4-(2-Aminoethyl)-benzene sulfonamide	Glu_{292}; Glu_{614}; Phe_{1013}; Glu_{1014}; Ala_{1320}; Thr_{1321}; Tyr_{1365}

Source: Authors, 2023.

3.3 Thermodynamic parameters

In the literature there are studies indicating that some benzenesulfonamide derivatives can interact with several biomolecules (Krishnamurthy et al., 2007; Zubrienė et al., 2017; Gökce et al., 2018); this phenomenon could involve different thermodynamic parameters such as such as free energy of binding, electrostatic energy, total intermolecular energy, and Van-Der Waals (vdW) + hydrogen bond (Hbond) + desolvation energy (Figueroa-Valverde et al., 2023).

For this reason, the aim of this investigation was to evaluate some theoretical thermodynamic factors involved in the interaction of 4-(2-Aminoethyl)benzene sulfonamide with 6jp5 protein surface using DockingServer program. In Table 3 are shown some thermodynamic parameters which indicate that there are differences in the energy's levels for 4-(2-Aminoethyl)benzene sulfonamide compared with nifedipine, amlodipine, verapamil and BayK 8644. Besides, inhibition constant (Ki) for 4-(2-Aminoethyl)benzene sulfonamide was lower compared with nifedipine, verapamil and BayK 8644.

Table 3. Evaluation of thermodynamic parameters involved in the interaction of 4-(2-Aminoethyl)benzene sulfonamide, BAY-6035, nifedipine, amlodipine and verapamil with 6jp5 protein surface.

Parameters	**Nifedip.**	**Amlodip.**	**Verapamil**	**BayK8644**	**ABS**
A	-5.67	-7.65	-4.96	-6.27	-7.41
B	69.90	2.49	230.77	25.36	3.71
C	-7.01	-6.42	-8.22	-7.62	-5.08
D	0.00	-2.74	-0.33	-0.04	-3.81
E	-7.01	-9.16	-8.55	-7.65	-8.89
F	667.20	817.58	990.06	658.48	468.4

Note: A = Est: Free Energy of Binding (kcal/mol); B = Inhibition Constant, Ki (mM); C = vdW + Hbond + desolv Energy (kcal/mol); D = Electrostatic Energy (kcal/mol); E = Total Intermolec. Energy (kcal/mol); F = Interact. Surface; *ABS = 4-(2-Aminoethyl) benzene-sulfonamide*. Source: Authors, 2023.

All these experimental and theoretical data suggests that the compound 4-(2-aminoethyl)benzene sulfonamide could produce changes in perfusion pressure and coronary resistance through Calcium channels inhibition. However, it is important to mention that it would be necessary to determine some pharmacokinetic parameters, which could determine its biological activity.

3.4 Pharmacokinetic parameters

There several theoretical methods to determine some pharmacokinetics parameters of different dugs such as ADME/PK (Roy et al., 2022), ADME/tox (Chalkha et al., 2022) and SwissADME (Mahanthesh et al., 2020). In this study, pharmacokinetic parameters for 4-(2-Aminoethyl)benzene sulfonamide were evaluated using Admetlab 2.0 program (Azis et al., 2022; Nie et al., 2022). Theoretical results (Table 4) showed differences in permeability for 4-(2-Aminoethyl)benzene sulfonamide using Caucasian colon adenocarcinoma cells and Madin-Darby canine kidney as theoretical models. Other theoretical data indicate that a high concentration of 4-(2-aminoethyl)- benzenesulfonamide does not bind to plasma (72.9 percent) translated as optimal volume distribution and and short half-life; this phenomenon could due to lipophylicity degree (Concensus LogPO/W = 0.28) which was calculated using SwissADME [43].

On the other hand, analyzing these data and other study which indicate that a sulfonamide derivative (sulfaphenazole) can act as CYP 2C6 and CYP 2C9 inhibitor, which result in a decrease in post-ischemic vascular dysfunction and increase blood flow (Turner et al., 2022). For this reason in this research the possibility that 4-(2-aminoethyl)benzenesulfonamide could interact with some member of the P450 family was analyzed using SwissADME software (Mahanthesh et al., 2020).

Theoretical results showed that 4-(2-aminoethyl)benzenesulfonamide may not interact with P_{450}; these data indicate that sulfonamide derivative may not be metabolized through this metabolic pathway; perhaps, it could be metabolized through phase 2 which involving enzymatic bioconjugation reactions. Analyzing these data, it would be interesting to perform some experiments to evaluate metabolism of this compound.

Table 4. Evaluation of pharmacokinetics parameters calculated for 4-(2-Aminoethyl)benzene sulfonamide. The values were determined using ADMETLab 2.0 program.

Caco-2 permeability	-5.473	Low permebility
MDCK permeability	0.0003	Higher permeability.
HIA	0.032	Low absorption
CYP1A2 inhibitor	0.016	Non-inhibitor
CYP1A2 sustrato	0.485	Non-substrate
CYP2C19 inhibitor	0.025	Non-inhibitor
CYP2C19 sustrato	0.287	Non-substrate
CYP2C9 inhibitor	0.016	Non-inhibitor
CYP2C9 sustrate	0.403	Non-substrate
CYP2D6 inhibitor	0.097	Non-inhibitor
CYP2D6 sustrato	0.645	Non-substrate
CYP3A4 inhibitor	0.014	Non-inhibitor
CYP3A4 sustrato	0.352	Non-substrate
PPB	27.41	Low protein-bound
Fu	72.09	Higher Fraction unbound to plasma
Pgp-inhibitor	0.001	Pgp-inhibitor
VD (ml/min)	1.887	Optimal
$T_{1/2}$ (h)	0.257	Short half-life
CL (ml/min/kg)	1.127	Low clearence rate

Note: Caco-2 = Caucasian colon adenocarcinoma Cells; MDCK = Madin–Darby canine kidney; CYP = P_{450} family; PPB = plasma protein binding; VD = volume distribution; $T_{1/2}$ = ; CL = clearance; Fu = Higher Fraction unbound un plasms; HIA = human intestinal absorption. Source: Authors, 2023.

3.5 Toxicity analysys

There are studies which indicate that some sulfonamide derivatives can produce toxicity in different biological systems (Vilter et al., 1944; Lehr, 1957; Hess et al., 1999). Analyzing these data, in this investigation the possible toxicity produced by 4-(2-aminoethyl)benzenesulfonamide was determined using a theoretical model [44]. The results showed that the administration of compound 4-(2-aminoethyl)- benzenesulfonamide through oral route requires higher doses to produce toxicity in comparison with the intraperitoneal, intravenous and subcutaneous routes (Table 5).

Table 5. Rate acute toxicity predicted using GUSAR program.

Rat IP (mgkg)	Rat IV (mgkg)	Rat Oral (mgkg)	Rat SC (mgkg)
303.70	586.80	2100.00	321.00

Note: IP = Intraperitoneal route of administration (LD_{50}); IV = Intravenous route of administration (LD_{50}); Oral - Oral route of administration (LD_{50}): SC = Subcutaneous route of administration (LD_{50}). Source: Authors, 2023.

4. Conclusions

In this research biological activity of 4-(2-aminoethyl)benzenesulfonamide on perfusion pressure using an isolated rat heart model is reported. It is noteworthy that biological model used in this study is an invaluable research tool for investigating questions across the spectrum of physiologic functions of cardiovascular system

such as perfusion pressure and coronary resistance.

The results suggest that compound 4-(2-aminoethyl)ben- zenesulfonamide decrease perfusion pressure through L-type Calcium channel inhibition; this phenomenon could be translated as a good inotropic negative agent. In addition theorethical data suggest that 4-(2-aminoethyl)- benzenesulfonamide could interact with some aminoacid residues involved in 6jp5 protein surface (Glu_{614} and Ala_{320}); this phenomenon could result in 4-(2-aminoethyl)-benzenesulfonamide-Calcium channel complex formation to produce a decrease in perfusion pressure.

5. Authors' Contributions

Alvarez-Ramirez Magdalena: reading, writing, and evaluating data. *Figueroa Valverde Lauro*: article writing, data evaluation and corrections. *Rosas Nexticapa Marcela*: article writing, data evaluation and corrections. *López-Ramos Maria*: analysis data. *Mateu-Armad Maria Virginia*: analysis data. *Garcimarrero-Espino E. Alejandra*: software usage, data analysis. *Hau-heredia Lenin*: data analysis. *Cauich-Carrillo Regina*: software usage, data analysis. *Mijangos-Sanchez Julliete*: software usage, data analysis.

6. Conflicts of Interest

No conflicts of interest.

7. Ethics Approval

Yes

8. References

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