Interaction of some chalcone derivatives with calcium channels using a theoretical model

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Abstract

For several years, different drugs have been used to treat heart failure, such as digoxin, captopril, spironolactone, milrinone, levosimedam, dobutamine, and others. However, some of these drugs can produce secondary effects such as arrhythmia, cough, hyperkalemia, and others. Analyzing these data, this study aimed to evaluate the interaction of some chalcone derivatives (1-17) with calcium channels using theoretical models. It is important to mention that 7pjx protein, nifedipine, amlodipine, diltiazem, and verapamil were used as theoretical tools in the DockingServer program. The results showed differences in the interaction of chalcone derivatives compared with nifedipine, amlodipine, diltiazem, and verapamil drugs. Other data indicate that the inhibition constant (Ki) for chalcone analog 1 was lower compared with nifedipine, amlodipine, verapamil, and diltiazem. Besides, other results suggest that Ki for compound 11 was lower compared with nifedipine, verapamil, and diltiazem. All these data suggest that chalcone derivatives 1 and 11 could act as calcium channel inhibitors; this phenomenon could be translated into changes in blood pressure through a decrease in calcium intracellular levels. These data suggest that chalcone derivatives 1 and 11 could be good therapeutic alternatives to treat heart failure.

Keywords: chalcone, derivatives, heart failure, nifedipine, amlodipine

Interação de alguns derivados de chalcona com canais de cálcio usando um modelo teórico

Resumo

Por vários anos, diferentes medicamentos têm sido usados para tratar insuficiência cardíaca, como digoxina, captopril, espironolactona, milrinona, levosimedam, dobutamina e outros. No entanto, alguns desses medicamentos podem produzir efeitos secundários, como arritmia, tosse, hipercalemia e outros. Analisando esses dados, o objetivo deste estudo foi avaliar a interação de alguns derivados de chalcona (1-17) com canais de cálcio usando alguns modelos teóricos. É importante mencionar que a proteína 7pjx, nifedipina, amlodipina, diltiazem e verapamil foram usados como ferramentas teóricas no programa DockingServer. Os resultados mostraram diferenças na interação dos derivados de chalcona em comparação com os medicamentos nifedipina, amlodipina, diltiazem e verapamil. Outros dados indicam que a constante de inibição (Ki) para o análogo de chalcona 1 foi menor em comparação com nifedipina, amlodipina, verapamil e diltiazem. Além disso, outros resultados sugerem que o Ki para o composto 11 foi menor em comparação com nifedipina, verapamil e diltiazem. Todos esses dados sugerem que os derivados de chalcona 1 e 11 podem atuar como inibidores do canal de cálcio; esse fenômeno pode ser traduzido em alterações na pressão arterial por meio de uma diminuição nos níveis intracelulares de cálcio.

Esses dados sugerem que os derivados de chalcona 1 e 11 podem ser boas alternativas terapêuticas para tratar a insuficiência cardíaca.

Palavras-chave: chalcona, derivados, insuficiência cardíaca, nifedipina, amlodipina

1. Introduction

In the literature, several studies indicate that congestive heart failure is the main cause of death worldwide (Bragazzi et al., 2017; Lee et al., 2024; Martin; Aday, 2024; Khan et al., 2024; Yogeswaran et al., 2024). This clinical pathology is conditioned by different risk factors such as alcohol (Wilhelmsen et al., 2024), smoking (Kanimura et al., 2018; Aune et al., 2019), diabetes (Guglin et al., 2014; Ohkuma et al., 2019), lipid concentrations (Velagaleti et al., 2009; Katsiki et al., 2016), hypertension (Vasan; Levy, 1996; Slivnick et al., 2019), coronary artery disease (Lala; Desai, 2014; Mazimba et al., 2023; Nelsen et al., 2024; Huang et al., 2024), and others.

The treatment of patients hospitalized with heart failure often includes the use of different drugs such as captopril (Romankiewicz,1983; Paker et al., 1986), spironolactone (Anton et al., 2003; Huang et al., 2024), valsartan (Cohn; Tognoni, 2001; Maggioni et al., 2005), milrinone (Packer et al., 1991; Akhtar et al., 2022), and levosimedam (Oliva et al., 2018; Massarone et al., 2022). In the search for new therapeutic alternatives, new drugs with biological activity against heart failure have been developed; for example, the synthesis of compound AZD5462 ((1S,4s)-4-(2-Fluoro-4-methoxy-5-(((1S,2R,3S,4R)-3-(((1-methylcyclobutyl) methyl) carbamoyl) bicy-clo[2.2.1]heptan-2-yl) carbamoyl) phenoxy)-1-methylcyclohexane-1-carboxylic acid) as a selective oral allosteric RXFP1 agonist for treatment of heart failure (Granberg et al., 2024).

Other studies showed the preparation of compound BMS-986308 (4-methyl-6-[4-[[(3*S*,5*R*)-3-methyl-5-(4-methyl-1-oxo-3*H*-2-benzofuran-5-yl) piperazin-1-yl] methyl] triazol-2-yl] pyridine-3-carboni-trile) as a potassium channel inhibitor for the treatment of heart failure (Richter et al., 2024). Besides, a report indicates the synthesis of BAY-1021189 (Methyl(4,6-diamino-2-(5-fluoro-1-(2-fluor benzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl) pyrimidine-5-yl) carbamate)) as a guanylate cyclase stimulator for the treatment of heart failure (Follman et al., 2017). Other data displayed the synthesis of several glycyrrhizin derivatives with biological activity against heart failure through Box-1 inhibition (Yan et al., 2013). In addition, a study showed the preparation of a hydroxypyrimidinone analog as a potent apelin agonist for the potential treatment of heart failure (Meng et al., 2021).

On the other hand, it is important to mention that there are studies indicating that chalcone derivatives can produce biological activity on some risk factors involved in heart failure; for example, a study showed that chloride-chalcone and fluoride-chalcone derivatives can reduce myocardial infarction due to ischemia/reperfusion injury using an albino rat model (Annapurna et al., 2012). Other data displayed that chalcone analog ((*E*)-1-(3,4-dimethoxy phenyl)-3-(4-isopropoxy-3-methoxyphenyl)prop-2-en-1-one) produces atheroprotective effects by increasing cholesterol efflux and reducing inflammation-induced endothelial dysfunction (Chen et al., 2020). Other studies indicate that a chalcone analog (Ethyl l2-((4-chloro-6-(quinolin-6-ylamino) pyrimidine-2-yl) thio) hexanoate) decreases heart and kidney injuries via MAPKs/NF-κB signaling pathway inhibition (mitogen-activated protein kinase/nuclear factor kappa-light-chain-enhancer of activated B cells) using in vitro and *in vivo* models (Fang et al., 2015).

Furthermore, a report demonstrates the protective effects of a trans-chalcone on ischemia/reperfusion injuries through phosphoinositide 3-kinase positive regulation (Wang et al., 2024). All these data indicate that some chalcones can produce biological activity in the cardiovascular system; however, the interaction with some biomolecules is unclear. Analyzing these data, this research aimed to evaluate the interaction of seventeen chalcone derivatives on the calcium channel using the 7jpx protein as a theoretical tool. Besides, nifedipine, amlodipine, verapamil, diltiazem, and Bay-8644 drugs were used as controls in the DockingServer program.

2. Materials and Methods

2.1 Chalcone derivatives

Chalcone analogs (Figure 1) were used to evaluate their possible interaction with the calcium channel surface as follows:

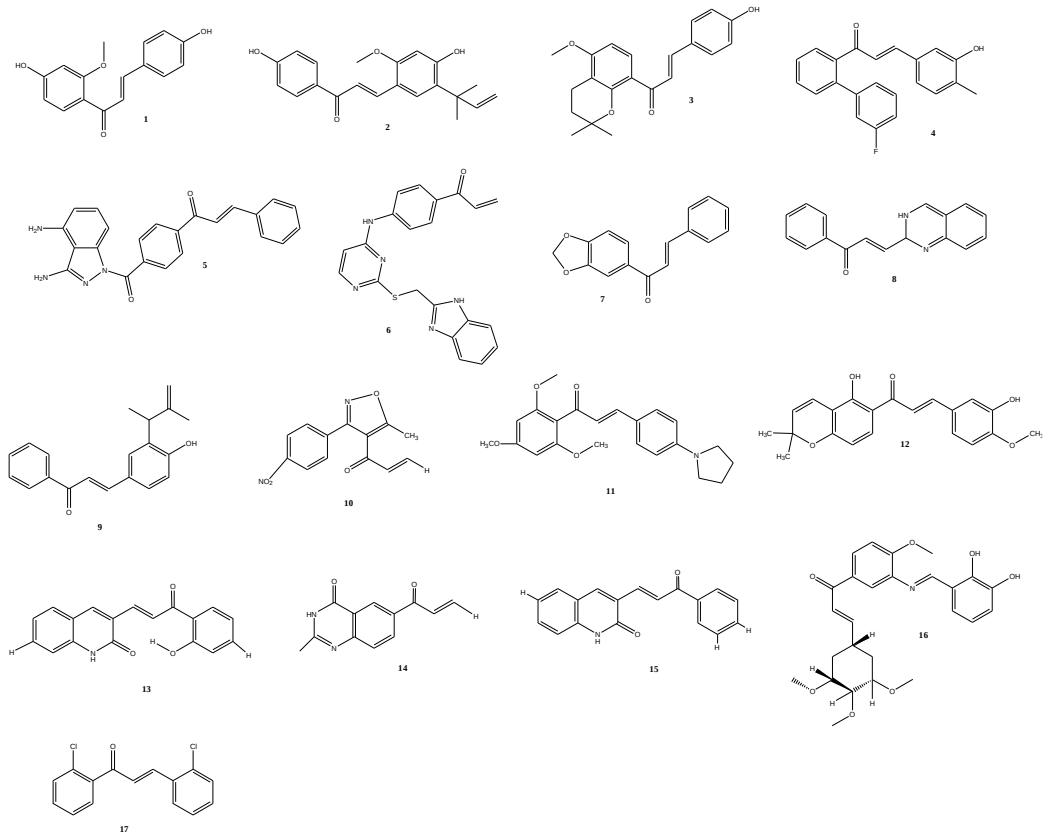

Figure 1. Chemical structure of Chalcone (1-17). Source, PubChem (nih.gov).

1 = 1-(4-Hydroxy-2-methoxy-phenyl)-3-(4-hydroxy-phenyl)-propenone
2 = 3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1- (4-hydroxy-phenyl)-propenone
3 = 3-(4-Hydroxy-phenyl)-1-(5-methoxy-2,2-dimethyl-chroman-8-yl)-propenone
4 = 1-(3'-Fluoro-biphenyl-2-yl)-3-(3-hydroxy-4-methyl-phenyl)-propenone
5 = 1-[4-(3,4-Diamino-indazole-1-carbonyl)-phenyl]-3-phenyl-propenone
6 = 1-{4-[2-(1H-Benzoimidazol-2-ylmethylsulfanyl)-pyrimidin-4-ylamino]-phenyl}-propenone
7 = 1-Benzo[1,3]dioxol-5-yl-3-phenyl-propenone
8 = 3-(2,3-Dihydro-quinazolin-2-yl)-1-phenyl-propenone
9 = 3-[3-(1,2-Dimethyl-allyl)-4-hydroxy-phenyl]-1-phenyl-propenone
10 = 1-[5-Methyl-3-(4-nitro-phenyl)-isoxazol-4-yl]-propenone
11 = 3-(4-Pyrrolidin-1-yl-phenyl)-1-(2,4,6-trimethoxy-phenyl)-propenone
12 = 1-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-(3-hydroxy-4-methoxy-phenyl)-propenone
13 = 3-[3-(2-Hydroxy-phenyl)-3-oxo-propenyl]-1H-quinolin-2-one
14 = 6-Acryloyl-2-methyl-3H-quinazolin-4-one
15 = 3-(3-Oxo-3-phenyl-propenyl)-1H-quinolin-2-one
16 = 1-{3-[(2,3-Dihydroxy-benzylidene)-amino]-4-methoxy-phenyl}-3-(3,4,5-trimethoxy-cyclohexyl)-propenone
17 = 1,3-Bis-(2-chloro-phenyl)-propenone

2.2 Pharmacophore model

The pharmacophore model for chalcone derivatives (1-17) was determined using LigandScout 4.08 software (Seidel et al., 2017; Lohachova et al., 2024).

2.3 Protein-ligand

The interaction of chalcone derivatives (1-17) with calcium channels was determined using 7jpx (https://doi.org/10.2210/pdb1GOS/pdb) protein as a theoretical tool. Besides, nifedipine, amlodipine, diltiazem,

and verapamil were used as controls in a DockingServer program (Figueroa-Valverde et al., 2023; Alvarez et al., 2024.

2.4 Pharmacokinetic analysis

Pharmacokinetic factors for chalcone derivatives were determined using the SwissADME software (Hernandez et al., 2024).

2.5 Toxicology analysis

Toxicology evaluation for chalcone analogs was determined using the Gussar software (Figueroa-Valverde et al., 2024).

3. Results and Discussion

There are several theoretical studies indicating that different chalcone derivatives can interact with some biomolecules (Eisenberg et al., 2004Le et al., 2017; Arif et al., 2020; Riswanto et al., 2021); however, these data are not clear, especially regarding heart failure. Analyzing these data, in this study, the interaction of some chalcone derivatives with calcium channels was evaluated using some theoretical models, as follows:

3.1 Pharmacophore Model

There are several theoretical models in the literature to determine some chemical characteristics that serve as support for predicting the interaction of some drugs with different biomolecules, such as pharmacophore (Arsidiacono et al., 2024), QSAR (Madani et al., 2024) and others. This study used the LigandScout 4.4 program to design a pharmacophore for chalcone derivatives. It is important to mention that this program allows for the design of three-dimensional pharmacophores from different functional groups that can act as hydrogen bond donors, hydrogen bond acceptors, lipophilic zones, and positive-negative ionizable chemical groups. The results showed several hydrogen bond donors and acceptors, lipophilic areas, and positively and negatively ionizable chemical groups for chalcone derivatives. It should be noted that the chemical characteristics of each chalcone derivative could be a determining factor for its interaction with some biomolecules, which could result in ligand-protein complex formation (Figure 2-4).

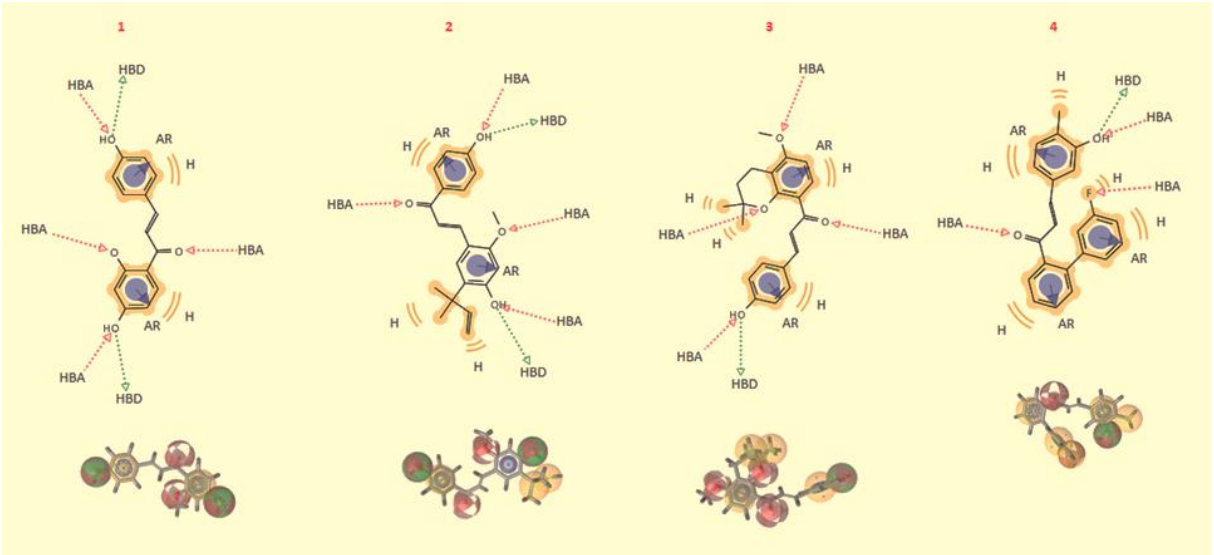

Figure 2. Pharmacophore model for chalcone derivatives (1-4). Visualized with the LigandScout 4.4 program. The scheme showed different types of hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and lipophilic areas. Source: Authors, 2024.

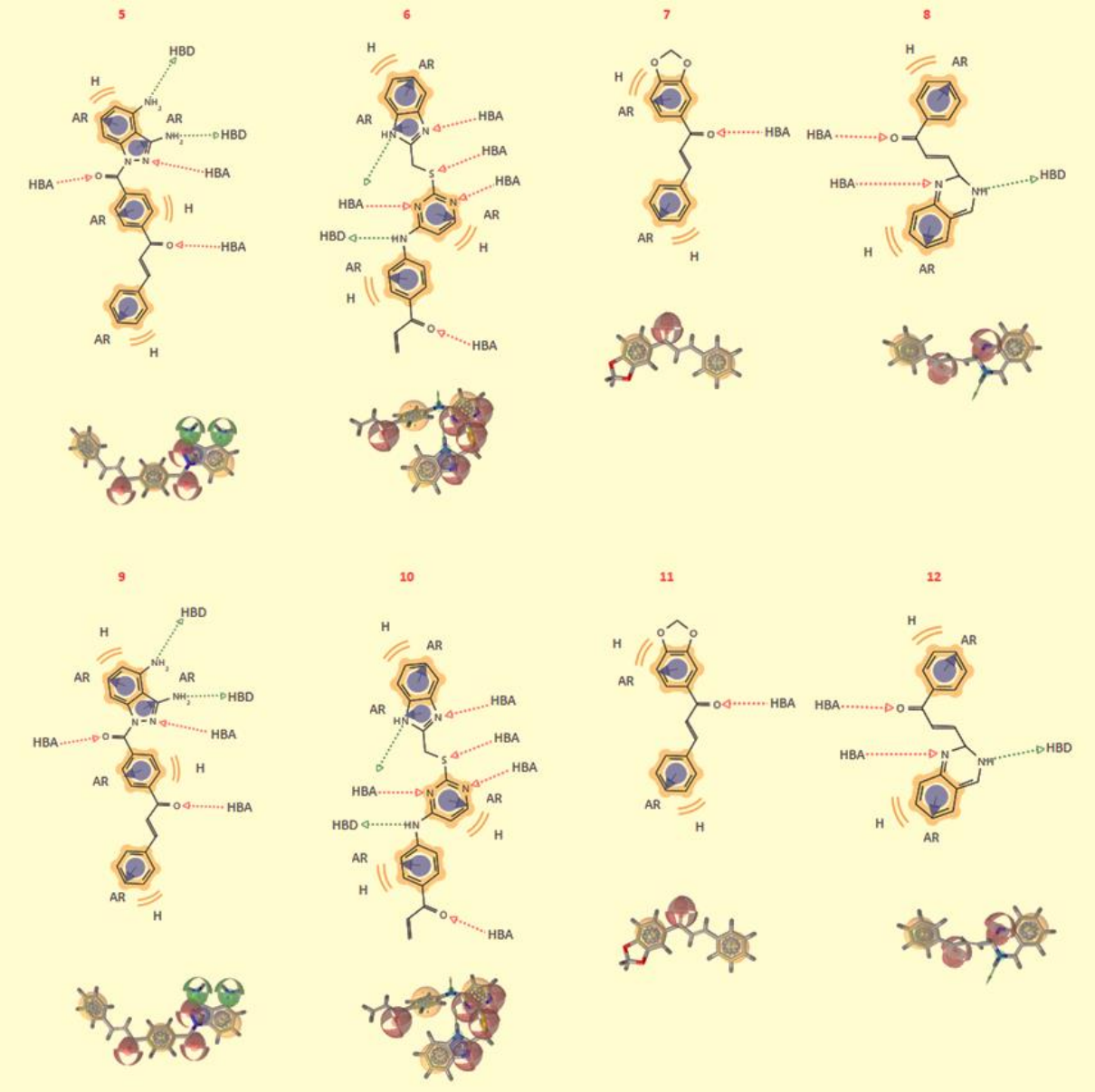

Figure 3. Design a pharmacophore model for chalcone derivatives (5-12). Scheme visualized with the LigandScout 4.4 program. The data displayed hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and lipophilic areas. Source: Authors, 2024.

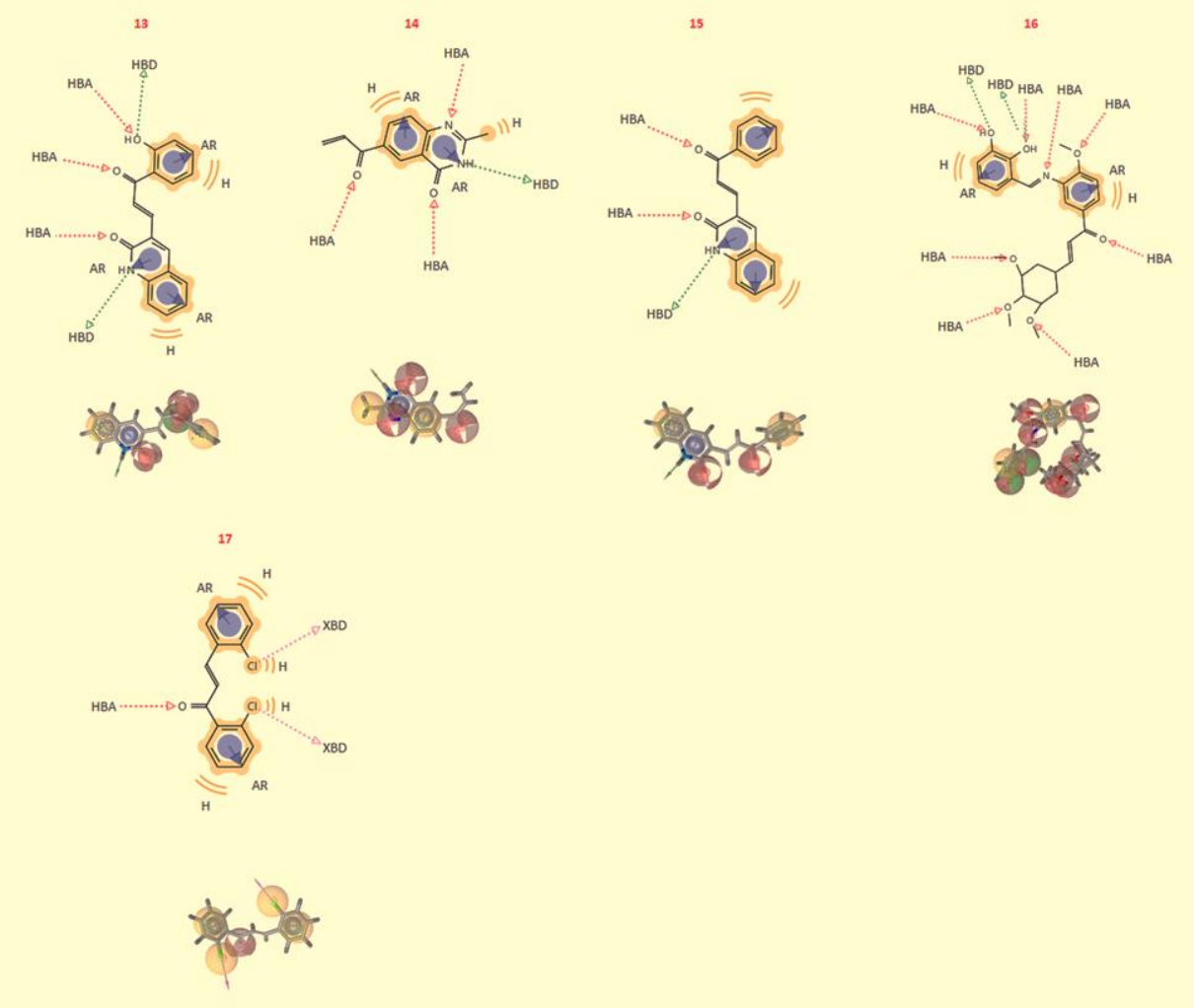

Figure 4. Pharmacophore model for chalcone derivatives (13-17). Visualized with the LigandScout 4.4 program. The results display hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and lipophilic areas. Source: Authors, 2024.

3.2 Ligand-protein complex

Analyzing the data mentioned above and other reports that suggest that ligand-protein complex formation can be determined using some theoretical models such as Gromos (Riniker et al., 2011), HarmonyDOCK (Plewczynski et al., 2014), DockingApp (Di Musio et al., 2017), Prodock (Trosset; Scheraga, 1999), and others. In this study, the interaction of chalcone derivatives with the calcium channel surface was determined using 7jpx protein, nifedipine, amlodipine, diltiazem, and verapamil as theoretical tools in a DockingServer program. It is noteworthy that the DockingServer program uses the MMFF94 model, which is a molecular modeling force field, designed to address condensed phase processes in molecular dynamics simulation and optimization of molecular geometry in proteins and other biological systems (Figueroa-Valverde et al., 2024).

The results showed differences in the interaction of chalcone derivatives with amino acid residues involved in the 7jpx protein surface compared with nifedipine, amlodipine, diltiazem, and verapamil drugs (Table 1, Figure 5). It is noteworthy that compound 1 could interact with the 7jpx protein surface through polar bonds with Thr_{1255} and Asp_{1400}. Besides, it could also interact hydrophobically with Trp_{1258} and Ile_{1261}. Other results suggest that compound 11 may interact with the 7jpx protein surface via polar bonds with Trp_{1182} and Arg_{1254}. In addition, this chalcone derivative may interact through hydrophobic bonds with Pro_{1181}, Val_{1184}, Phe_{1185}, Leu_{1247}, Leu_{1257}, Trp1258, and Ile_{1261}.

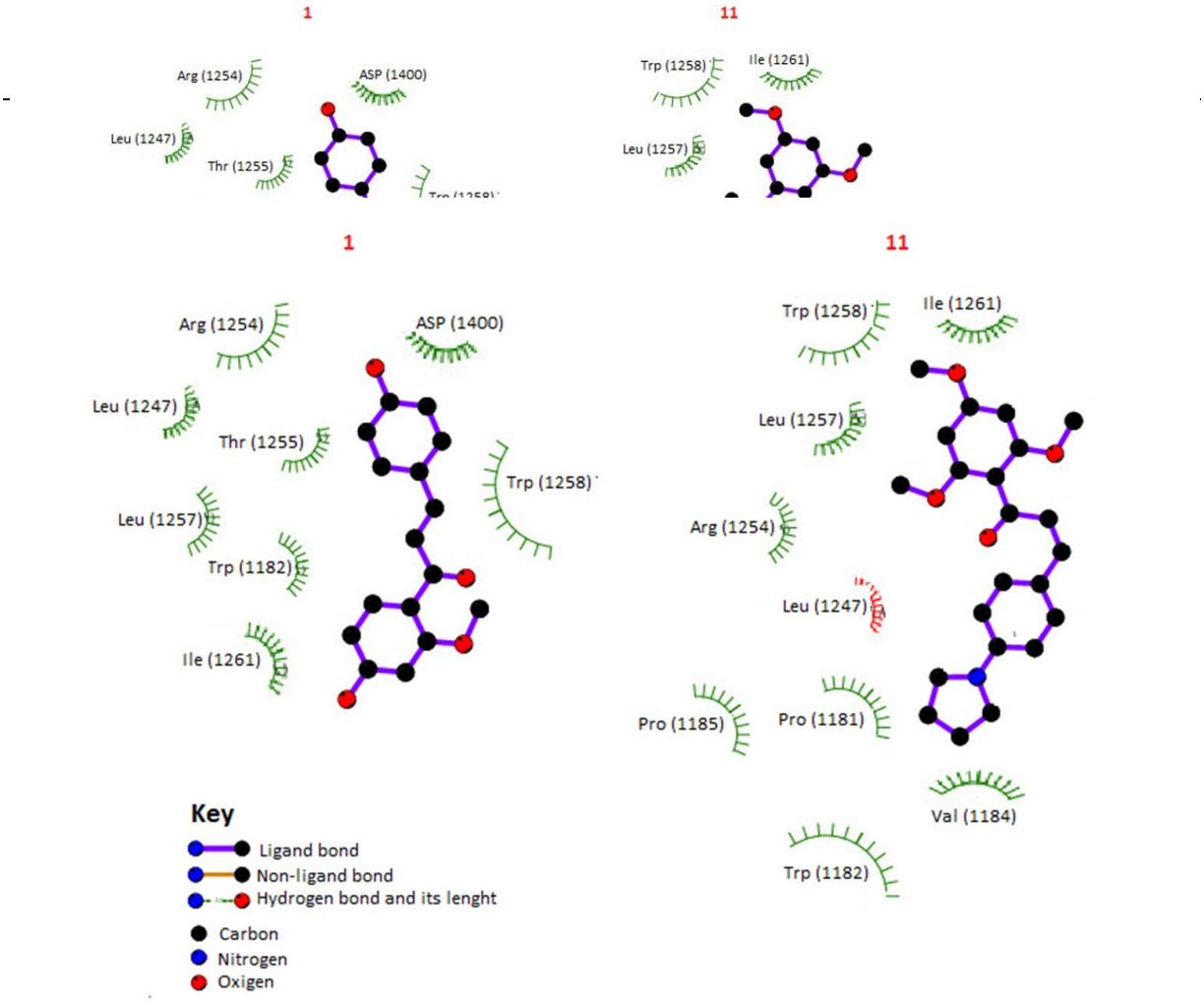

Figure 5. Interaction of chalcone derivatives (1 and 11) with some amino acid residues involved in the 7jpx protein surface. The scheme is visualized using the LigandScout 4.4 program. Source: Authors, 2024.

Table 1. Interaction of chalcone derivatives (1-17), nifedipine, amlodipine, diltiazem, and verapamil with 7jpx protein surface.

Compound	Aminoacid Residues
Nifedipine	Pro_{1181}; Trp_{1182}; Arg_{1254}; Leu_{1257}; Trp_{1258}
Amlodipine	Trp_{1182}; Leu_{1247}; Arg_{1254}; Leu_{1257}; Trp_{1258}; Ile_{1261}; Gln_{1265}
Bayk-8644	Pro_{1181}; Trp_{1182}; Leu_{1247}; Arg_{1254}; Leu_{1257}; Trp_{1258}; Ile_{1261}
Diltiazem	Pro_{1181}; Trp_{1182}; Phe_{1185}; Leu_{1188}; Ile_{1244}; Ile_{1261}
Verapamil	Trp_{1182}; Leu_{1247}; Arg_{1254}; Leu_{1257}; Trp_{1258}; Ile_{1261}; Lys_{1262}; Gln_{1265}; Asp_{1400}
1	Trp_{1182}; Leu_{1247}; Arg_{1254}; Thr_{1255}; Leu_{1257}; Trp_{1258}; Ile_{1261}; Asp_{1400}
2	Trp_{1182}; Leu_{1247}; Arg_{1254}; Leu_{1257}; Trp_{1258}; Ile_{1261}
3	Pro_{1181}; Trp_{1182}; Ile_{1244}; Leu_{1247}; Arg_{1254}
4	Pro_{1181}; Trp_{1182}; Val_{1184}; Phe_{1185}; Leu_{1247}; Arg_{1254}; Trp_{1258}
5	Trp_{1182}; Phe_{1185}; Ile_{1244}; Leu_{1247}; Arg_{1254}; Thr_{1255}; $Leu_{1257;}$ Trp_{1258}
6	Pro_{1181}; Trp_{1182}; Phe_{1185}; Ile_{1244}; Arg_{1254}; Leu_{1257}; Ile_{1261}
7	Pro_{1181}; Trp_{1182}; Phe_{1185}; Arg_{1254}; $Leu_{1257;}$ Trp_{1258}; Ile_{1261}
8	Pro_{1181}; Trp_{1182}; Phe_{1185}; Leu_{1247}; Arg_{1254}; $Leu_{1257;}$ Trp_{1258}; Ile_{1261}
9	Phe_{205}; Ile_{209}; Leu_{320}; Ile_{1244}; Leu_{1246}; Leu_{1247}; Leu_{1257}; Ile_{1261}
10	Pro_{1181}; Trp_{1182}; Phe_{1185}; Arg_{1254}; $Leu_{1257;}$ Trp_{1258}
11	Pro_{1181}; Trp_{1182}; Val_{1184}; Phe_{1185}; Leu_{1247}; Arg_{1254}; $Leu_{1257;}$ Trp_{1258}; Ile_{1261}
12	Leu_{320}; Pro_{1181}; Trp_{1182}; Ile_{1244}; Leu_{1247}; Arg_{1254}; $Leu_{1257;}$ Trp_{1258}; Ile_{1261}
13	Trp_{1182}; Val_{1184}; Phe_{1265}; Leu_{1247}; $Leu_{1257;}$ Trp_{1258}
14	Pro_{1181}; Trp_{1182}; Phe_{1185}; Arg_{1254}; $Leu_{1257;}$ Trp_{1258}; Ile_{1261}
15	Pro_{1181}; Trp_{1182}; Val_{1184}; Phe_{1185}; Arg_{1254}; Leu_{1257}
16	Pro_{1181}; Trp_{1182}; Phe_{1185}; Ile_{1244}; Leu_{1247}; Arg_{1254}; Leu_{1257}
17	Pro_{1181}; Trp_{1182}; Phe_{1185}; Arg_{1254}; Leu_{1257}; Trp_{1258}; Ile_{1261}

Source: Authors, 2024.

3.3 Thermodynamic parameters

For several years, different thermodynamic factors have been evaluated to determine the possible ligand-protein formation (Prozzo et al., 2004; Homans, 2007). In this study, some thermodynamic parameters were determined to evaluate the possibility of the interaction of chalcone derivatives with calcium channels using the 7jpx protein as a theoretical tool. The results (Table 2) showed differences in energy levels compared to nifedipine, amlodipine, verapamil, and diltiazem drugs. Besides, constant inhibition (Ki) for chalcone analog 1 was lower compared with nifedipine, amlodipine, verapamil, and diltiazem. Other data indicate that Ki for compound 11 was lower compared with nifedipine, verapamil, and diltiazem. All these data suggest that chalcone derivatives 1 and, 11 could act as calcium channel inhibitors; this phenomenon could be translated as changes in blood pressure through a decrease in calcium intracellular levels. These data suggest that chalcone derivatives 1, and 11 could be good therapeutic alternatives for the treatment of heart failure.

Table 2. Thermodynamic parameters involved in the coupling of chalcone derivative (1-17) to 7pjx protein.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
Nifedipine	-4.11	969.99	-5.22	-0.08	-5.30	515.74
Amlodipine	-3.67	2.02	-4.52	0.13	-4.39	613.32
Bayk-8644	-4.74	332.79	-6.02	-0.01	-6.03	548.33
Diltiazem	-5.00	217.37	-6.34	0.15	-6.19	719.11
Verapamil	-2.96	6.81	-5.79	0.10	-5.68	777.20
1	-3.57	2.43	-5.21	-0.03	-5.25	561.70
2	-4.44	557.31	-6.63	-0.09	-6.72	671.98
3	-4.99	221.06	-6.23	-0.03	-6.26	658.11
4	-5.62	76.28	-6.93	-0.02	-6.94	607.40
5	-5.86	50.81	-7.08	0.01	-7.07	734.02
6	-6.10	33.89	-6.45	0.01	-6.44	640.85
7	-4.79	307.01	-5.64	0.02	-5.62	530.72
8	-5.01	214.13	-5.84	0.09	-5.75	542.07
9	-6.51	16.78	-8.32	0.02	-8,30	751.20
10	-4.32	685.46	-5.65	0.07	-5.58	474.28
11	-4.02	1.14	-6.06	0.06	-6.00	706.84
12	-4.97	226.89	-5.31	-0.04	-5.34	709.08
13	-5.50	93.07	5.90	-0.01	-5.91	573.79
14	-4.27	736.61	-4.81	0.00	-4.81	479.57
15	-5.42	106.23	-6.18	-0.02	-6.20	567.89
16	-5.34	120.86	-7.59	-0.02	-7.61	862.38
17	-5.52	90.32	-6.29	0.00	-6.29	562.91

Note: **A =** Est: Free Energy of Binding (kcal/mol^{-1}); **B** = Inhibition Constant, Ki (mM); **C** = vdW + Hbond + desolv Energy (kcal/mol^{-1}); **D** = Electrostatic Energy (kcal/mol^{-1}); **E** = Total Intermolec. Energy (kcal/mol^{-1}); **F** = Interact. Surface. Source: Authors, 2024.

3.6 Pharmacokinetic parameters

There are several studies to determine different pharmacokinetic properties, such as absorption, distribution, metabolism, and elimination, using some theoretical programs such as PKQuest (Levit, 2002), PharmPK (Ishaku et al., 2020), SwissADME (Sicak, 2021), and others. In this research, some pharmacokinetic factors for chalcone derivatives (1 and 11) were determined using the SwissADME program to compare with nifedipine, amlodipine, verapamil, and diltiazem drugs. The results (Table 3) indicate that the metabolism of chalcone derivatives could involve different Cyps (P450 family). This phenomenon may be due to differences in the chemical structure or lipophilicity of the compounds.

Table 3. Pharmacokinetic parameters for chalcone derivatives, nifedipine, amlodipine, diltiazem and verapamil.

Compound	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VII**	**Consensus Log $P_{o/w}$**
Nifedipine	High	No	No	Yes	Yes	Yes	Yes	Yes	2.55
Amlodipine	Low	No	Yes	No	No	No	No	No	3.69
Diltiazem	High	No	No	No	Yes	Yes	Yes	Yes	2.19
Verapamil	High	Yes	Yes	No	No	No	Yes	Yes	2.79
1	High	Yes	No	Yes	No	Yes	No	Yes	2.81
11	High	Yes	No	No	Yes	Yes	Yes	Yes	3.69

Source: Authors, 2024.

3.7 Toxicity analysis

For several years, different methods have been used to predict the toxicity degree of new drugs (Dix et al., 2007; Judson et al., 2009; Toropov et al., 2014). This study aimed to determine the possible toxicity produced by chalcone derivatives (1 and 11) using nifedipine, amlodipine, diltiazem, and verapamil as controls in the GUSAR program. The results (Table 4) indicated that the degree of toxicity could depend on the dose administered to chalcone derivatives through different routes of administration. Perhaps, this phenomenon could depend on the different functional groups involved in the chemical structure of each chalcone.

Table 4. Theoretical toxicity analysis for chalcone derivatives (1 and 11) using the GUSAR software.

Compound	**IP LD_{50} (mg kg^{-1})**	**IV LD_{50} (mg kg^{-1})**	**Oral LD_{50} (mg kg^{-1})**	**SC LD_{50} (mg kg^{-1})**
Nifediíne	571.60	60.61	768.10	238.30
Amlodipine	567.10	567.10	567.10	567.10
Diltiazem	332.20	53.96	990.80	338.60
Verapamil	244.70	9.33	946.20	173.70
1	518.80	184.20	3333.00	3120.00
11	277.80	81.96	722.20	747.70

Source: Authors, 2024.

4. Conclusions

This research aimed to evaluate the possibility that some chalcone derivatives could interact with the calcium channel using some theoretical models that can help to predict the possible biological activity produced by chalcone derivatives. The results indicate that compounds 1 and 11 can interact with different types of amino acids involved in the 7pjx protein surface. Therefore, these chalcone derivatives could act as calcium channel inhibitors; this data suggests that chalcone derivatives 1 and 11 could be a good therapeutic alternative for the treatment of heart failure.

5. Acknowledgments

None.

6. Authors' Contributions

Lauro Figueroa Valverde: article writing, data evaluation, and corrections. *Magdalena Alvarez-Ramirez*: reading, writing, and evaluating data. *Marcela Rosas Nexticapa*: article writing, data evaluation, and corrections. *Emilio Aguilar-Sanchez*: analysis data. *Maria Virginia Mateu-Armad* and *Enrique Bonilla-Zavaleta*: analysis data.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Does not apply.

9. References

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