

Comprehensive bioinformatic analysis identifies some indole derivatives for treating cTnT-associated hypertrophic cardiomyopathy

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Abstract

Alterations in cardiac troponin (cTnT) levels have been observed to be associated with the development of hypertrophic cardiomyopathy. It is worth noting that some drugs have been used to treat hypertrophic cardiomyopathy; however, these drugs act as myosin inhibitors. In the search for a therapeutic alternative for the treatment of this clinical pathology, this study aimed to determine the interaction of some indole derivatives (1-43) with cTnT using the 2n7l protein as a theoretical tool in the DockingServer program. Besides, the compounds indole, bepridil, levosimendan, and DPISTA were used as controls. The results showed differences in the number of amino acid residues involved in the docking of indole derivatives with the 2n7l protein surface compared to the controls. Other results indicate that the K_i values for indole derivatives 2, 4, 11, and 43 were lower compared with compounds 1, 3, 5-10, 12-42, bepridil, indole, and levosimendan. All these data suggest that compounds 2, 4, 11, and 43 may have good affinity for the 2n7l protein surface, which could lead to changes in the biological activity of cTnT. Therefore, these compounds could represent promising candidates for further experimental evaluation using a hypertrophic cardiomyopathy model.

Keywords: hypertrophic cardiomyopathy, indole derivatives, docking server.

Uma análise bioinformática abrangente identifica alguns derivados de indol para o tratamento da cardiomiopatia hipertrófica associada à cTnT

Resumo

Alterações nos níveis de troponina cardíaca (cTnT) têm sido associadas ao desenvolvimento de cardiomiopatia hipertrófica. Vale ressaltar que alguns fármacos têm sido utilizados para tratar a cardiomiopatia hipertrófica; entretanto, esses fármacos atuam como inibidores da miosina. Na busca por uma alternativa terapêutica para o tratamento dessa patologia clínica, o objetivo deste estudo foi determinar a interação de alguns derivados de indol (1-43) com a cTnT utilizando a proteína 2n7l como ferramenta teórica no programa DockingServer. Além disso, os compostos indol, bepridil, levosimendan e DPISTA foram utilizados como controles. Os resultados mostraram diferenças no número de resíduos de aminoácidos envolvidos na interação dos derivados de indol com a superfície da proteína 2n7l em comparação com os controles. Outros resultados indicam que os valores de K_i para os derivados de indol 2, 4, 11 e 43 foram menores em comparação com os compostos 1, 3, 5-10, 12-42, bepridil, indol e levosimendan. Todos esses dados sugerem que os compostos 2, 4, 11 e 43 podem ter boa afinidade pela

superfície da proteína 2n7l, o que poderia levar a alterações na atividade biológica da cTnT. Portanto, esses compostos podem representar candidatos promissores para avaliação experimental adicional utilizando um modelo de cardiomiopatia hipertrófica.

Palavras-chave: cardiomiopatia hipertrófica, derivados de indol, *dockingserver*.

1. Introduction

Cardiomyopathy is a disease associated with structural changes in the heart muscle, resulting in a decreased ability of the heart to pump blood throughout the body (Brieler et al., 2017; Wexler et al., 2009). Some studies have been classified as cardiomyopathy according to their etiology [acquired cardiomyopathy and hereditary cardiomyopathy] and depending on their clinical manifestations [dilated cardiomyopathy, restrictive cardiomyopathy, and hypertrophic cardiomyopathy] (Jin et al., 2025). The main characteristic of hypertrophic cardiomyopathy is left ventricular dysfunction, which may be caused by mutations in certain genes that encode sarcomeric proteins of the heart muscle (Bazan et al., 2020; Geske et al., 2018; Lorenzine et al., 2020; Maron et al., 2022; Semsarian et al., 2015).

For example, a study conducted on 57 individuals from southern Lebanon showed that the p.Arg21Cys mutation of the TNNI3 gene (which encodes troponin C of cardiac muscle, cTnT) was associated with malignant hypertrophic cardiomyopathy and sudden cardiac death (Fahed et al., 2020). In addition, a study carried out in patients with hypertrophic cardiomyopathy showed mutations in the Arg145Gly and Lys206Gln regions of the TNNI3 gene by DNA conformation polymorphism sequencing analysis by polymerase chain reaction (Kimura et al., 1997).

Other studies conducted in patients from different regions of the Netherlands indicate that some mutations in the p.Arg145Trp and p.Ser166Phe fragments of the TNNI3 gene are associated with hypertrophic and restrictive cardiomyopathy (Vanden Wijngaard et al., 2011). Another report that included 113 South African patients with hypertrophic cardiomyopathy identified several mutations associated with this disease, including the variants c.244C>T (p.Pro82Ser), c.485G>A (p.Arg162Gln), and c.509G>A (p.Arg170Gln) by high-resolution fusion analysis (Mouton et al., 2015). In addition, a direct sequence analysis of the gene for cTnT was performed in a family with hypertrophic cardiomyopathy and multiple cases of sudden infant death at Brigham and Women's Hospital, using PCR analysis; the results revealed a homozygous mutation in exon 11 with a phenylalanine to serine substitution at residue 179 (Ser179Phe) in the cTnT gene, associated with hypertrophic cardiomyopathy (Ho et al., 2000).

Another study was conducted at Kanazawa University Hospital to analyze cTnI gene mutations in 130 patients with hypertrophic cardiomyopathy. The results showed that 25 individuals had a lysine 183 deletion mutation (Lys183 del) in exon 7 of the cTnI gene (Kokado et al., 2000). Finally, a study was conducted in forty-six patients with hypertrophic cardiomyopathy to evaluate some mutations involved in the cTnT gene using PCR. The data revealed a Phe110Ile mutation in the cardiac troponin T gene (Anan et al., 1998). All this data indicates that mutations in the gene that codes for cTnT may influence the development of hypertrophic cardiomyopathy.

It is important to mention that some drugs have been approved to treat hypertrophic cardiomyopathy, such as aficamtem and mavacamtem (Dicorato et al., 2025; Möbius-Winkler et al., 2024; Perez-Asensio et al., 2025; Sikand et al., 2025); however, these drugs act as inhibitors of cardiac myosin and do not act directly on cTnT. In contrast, some studies indicate that some drugs act directly on cTnT, such as levosimendan, which produces a positive inotropic effect and has vasodilatory properties; however, this drug is frequently used in patients with heart failure (Jia et al., 2025; Liu et al., 2026; Papp et al., 2012). Therefore, in search of some therapeutic alternatives, different studies have been conducted to analyze the possible interaction of some compounds with the cTnT protein surface (Arahamian et al., 2017).

For example, a theoretical report indicated that compound 7930079 (2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide) may interact with cTnT using the 1LXF protein (structure of the regulatory N-domain of human cardiac troponin C in complex with human cardiac troponin-I) as a theoretical tool (Coldren et al., 2020). Another study showed the docking of 3-methyldiphenylamine with cTnT using the 5WCL (NMR structure of the N-domain of troponin C bound to the switch region of troponin I) protein as a theoretical tool in the Glide program (Bowman et al., 2019). All these data indicate that some compounds interact with cTnT; however, it is necessary to develop a series of compounds with affinity for cTnT. For this reason, this study aimed to determine the docking of some indole derivatives with cTnT as a therapeutic alternative to treat hypertrophic cardiomyopathy.

2. Materials and Methods

2.1 Indole derivatives

Figure 1 and Table 1 were used to evaluate the docking with the cTnT protein surface using several strategies as follows:

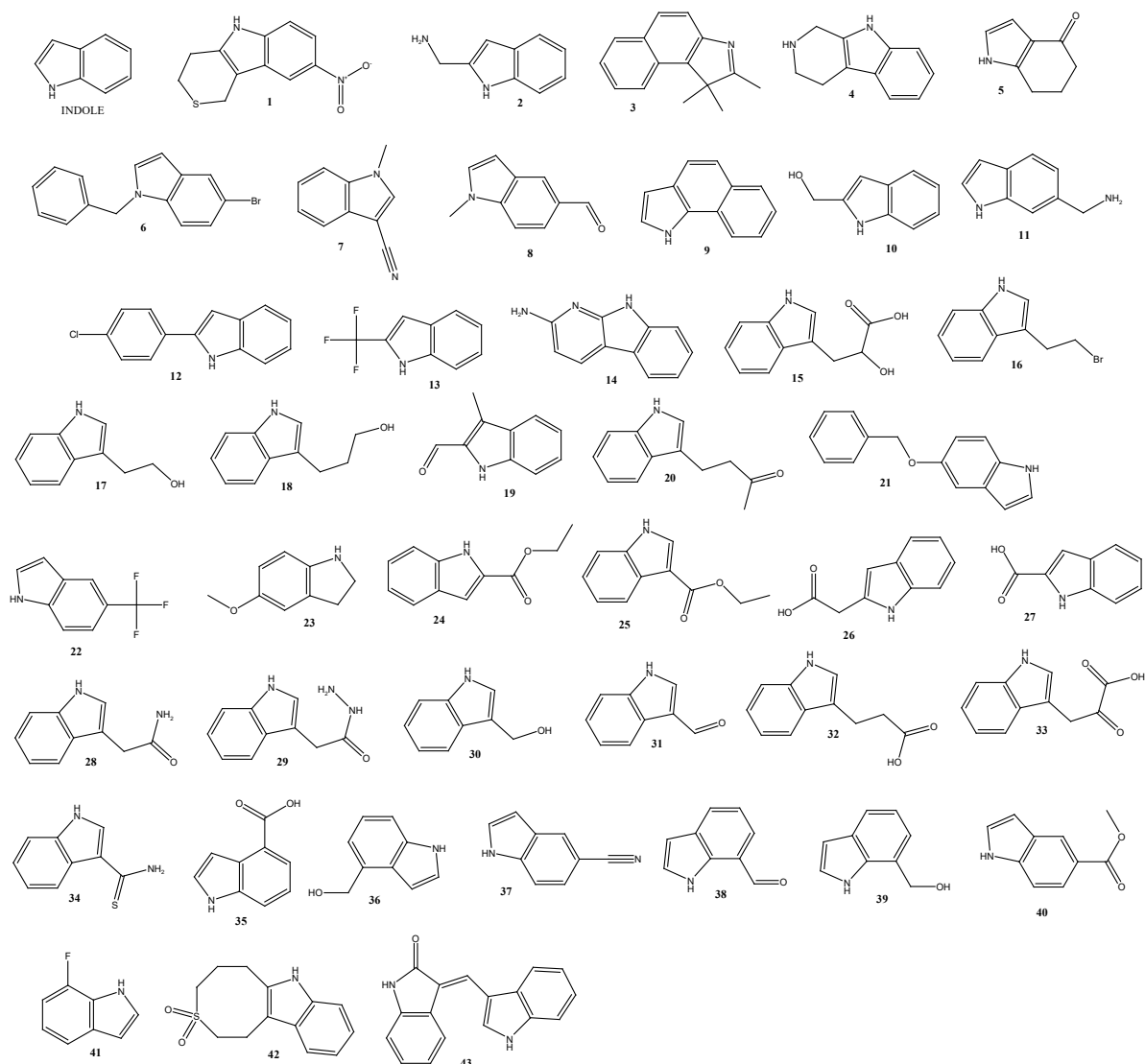


Figure 1. Chemical structure of indole derivatives (1-43). Source: <https://pubchem.ncbi.nlm.nih.gov/>

Table 1. Name of indole derivatives.

Compound	Name	Smile
1	8-nitro-1,3,4,5-tetrahydrothiino[4,3-b]indole	<chem>C1SCC2=C1NC3=C2C=C(C=C3)[N+](=O)[O-]</chem>
2	1H-indol-2-ylmethanamine	<chem>C1=CC=C2C(=C1)C=C(N2)CN</chem>
3	1,1,2-Trimethylbenz[e]indole	<chem>CC1=NC2=C(C1(C)C)C3=CC=CC=C3C=C2</chem>
4	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole	<chem>C1CNCC2=C1C3=CC=CC=C3N2</chem>

5	1,5,6,7-tetrahydroindol-4-one	<chem>C1CC2=C(C=CN2)C(=O)C1</chem>
6	1-benzyl-5-bromindole	<chem>C1=CC=C(C=C1)CN2C=CC3=C2C=CC(=C3)Br</chem>
7	1-methylindole-3-carbonitrile	<chem>CN1C=C(C2=CC=CC=C21)C#N</chem>
8	1-methylindole-5-carbaldehyde	<chem>CN1C=CC2=C1C=CC(=C2)C=O</chem>
9	1H-benzo[g]indole	<chem>C1=CC=C2C(=C1)C=CC3=C2NC=C3</chem>
10	1H-indole-2-methanol	<chem>C1=CC=C2C(=C1)C=C(N2)CO</chem>
11	1H-indole-6-methanamine	<chem>C1=CC(=CC2=C1C=CN2)CN</chem>
12	2-(4-chlorophenyl)-1H-indole	<chem>C1=CC=C2C(=C1)C=C(N2)C3=CC=C(C=C3)Cl</chem>
13	2-(trifluoromethyl)-1H-indole	<chem>C1=CC=C2C(=C1)C=C(N2)C(F)(F)F</chem>
14	9H-pyrido[2,3-b]indol-2-amine	<chem>C1=CC=C2C(=C1)C3=C(N2)N=C(C=C3)N</chem>
15	2-hydroxy-3-(1H-indol-3-yl)propanoic acid	<chem>C1=CC=C2C(=C1)C(=CN2)CC(C(=O)O)O</chem>
16	3-(2-bromoethyl)-1H-indole	<chem>C1=CC=C2C(=C1)C(=CN2)CCBr</chem>
17	2-(1H-indol-3-yl)ethanol	<chem>C1=CC=C2C(=C1)C(=CN2)CCO</chem>
18	3-(1H-indol-3-yl)propan-1-ol	<chem>C1=CC=C2C(=C1)C(=CN2)CCCO</chem>
19	3-methyl-1H-indole-2-carboxaldehyde	<chem>CC1=C(NC2=CC=CC=C12)C=O</chem>
20	4-(1H-Indol-3-yl)butan-2-one	<chem>CC(=O)CCC1=CNC2=CC=CC=C21</chem>
21	5-phenylmethoxy-1H-indole	<chem>C1=CC=C(C=C1)COC2=CC3=C(C=C2)NC=C3</chem>
22	5-(trifluoromethyl)-1H-indole	<chem>C1=CC2=C(C=CN2)C=C1C(F)(F)F</chem>
23	5-methoxy-2,3-dihydro-1H-indole	<chem>COC1=CC2=C(C=C1)NCC2</chem>
24	ethyl 1H-indole-2-carboxylate	<chem>CCOC(=O)C1=CC2=CC=CC=C2N1</chem>
25	ethyl 1H-indole-3-carboxylate	<chem>CCOC(=O)C1=CNC2=CC=CC=C21</chem>
26	2-(1H-indol-2-yl)acetic acid	<chem>C1=CC=C2C(=C1)C=C(N2)CC(=O)O</chem>
27	1H-indole-2-carboxylic acid	<chem>C1=CC=C2C(=C1)C=C(N2)C(=O)O</chem>
28	2-(1H-indol-3-yl)acetamide	<chem>C1=CC=C2C(=C1)C(=CN2)CC(=O)N</chem>
29	2-(1H-indol-3-yl)acetohydrazide	<chem>C1=CC=C2C(=C1)C(=CN2)CC(=O)NN</chem>
30	1H-indol-3-ylmethanol	<chem>C1=CC=C2C(=C1)C(=CN2)CO</chem>
31	1H-indole-3-carbaldehyde	<chem>C1=CC=C2C(=C1)C(=CN2)C=O</chem>
32	3-(1H-indol-3-yl)propanoic acid	<chem>C1=CC=C2C(=C1)C(=CN2)CCC(=O)O</chem>
33	3-(1H-indol-3-yl)-2-oxopropanoic acid	<chem>C1=CC=C2C(=C1)C(=CN2)CC(=O)C(=O)O</chem>
34	1H-indole-3-carbothioamide	<chem>C1=CC=C2C(=C1)C(=CN2)C(=S)N</chem>
35	1H-indole-4-carboxylic acid	<chem>C1=CC(=C2C=CN2=C1)C(=O)O</chem>
36	1H-indol-4-ylmethanol	<chem>C1=CC(=C2C=CN2=C1)CO</chem>
37	1H-indole-5-carbonitrile	<chem>C1=CC2=C(C=CN2)C=C1C#N</chem>
38	1H-indole-7-carbaldehyde	<chem>C1=CC2=C(C(=C1)C=O)NC=C2</chem>
39	1H-indol-7-ylmethanol	<chem>C1=CC2=C(C(=C1)CO)NC=C2</chem>
40	methyl 1H-indole-5-carboxylate	<chem>COC(=O)C1=CC2=C(C=C1)NC=C2</chem>
41	7-Fluor-1H-indole	<chem>Fc1cccc2cc[nH]c12</chem>

42	1,2,4,5,6,7-hexahydrothiocino [5,4-b]indole 3,3-dioxide	<chem>C1CC2=C(CCS(=O)(=O)C1)C3=CC=CC=C3N2</chem>
43	(3E)-3-(1H-indol-3- ylmethylidene)-1H-indol-2-one	<chem>C1=CC=C2C(=C1)C(=CN2)/C=C/3\4=CC=CC=C4NC3=O</chem>

Source: Authors, 2026.

2.2 Protein-ligand complex

The interaction of indole derivatives (1-43) with the troponin 1 surface (Figure 2) was determined using the 2n7l protein as a theoretical tool (<https://doi.org/10.2210/pdb2N7L/pdb>). The docking of the imidazole derivatives with the 2n7l protein surface occurred at the A chain (Figure 2).

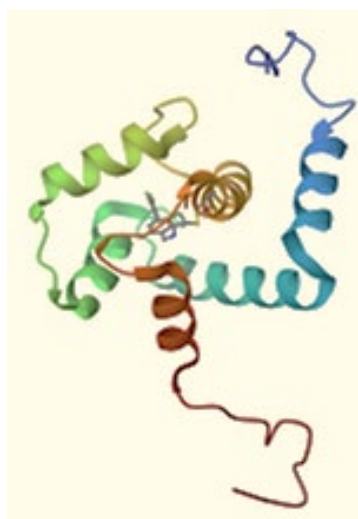


Figure 2. The scheme shows the 2n7l protein. Source: <https://www.rcsb.org>

It is important to mention that the compounds indole, bepridil, levosimendan, and DPISTA (2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide) were used as controls in the DockingServer program (<https://www.dockingserver.com/web>). In this method, the MMFF94 force field (Halgren, 1998) was used for energy minimization of the ligands (controls).

Besides, Gasteiger partial charges were added to the ligand atoms. Besides, non-polar hydrogen atoms were merged, and rotatable bonds were defined. Other docking calculations were carried out on some protein models registered in the Protein Data Bank, such as 2n7l. It is noteworthy that essential hydrogen atoms, Kollman united atom-type charges, and solvation parameters were added with the aid of AutoDock tools (Morris et al. 1998).

Affinity (grid) maps of $20 \times 20 \times 20$ Å grid points and 0.375 Å spacing were generated using the Autogrid program. In addition, an AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the van der Waals and electrostatic terms, respectively. It is noteworthy that docking simulations were performed using the Lamarckian genetic algorithm (Solis and West, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å and quaternion and torsion steps of 5 were applied.

2.3 Root mean square deviation (RMSD)

The RMSD was determined using the LigRMSD program. This program is used to determine the RMSD between two poses of the same ligand molecule docked on the same protein structure without the assumption of known atomic ordering between the two files (Valdes-Albuernes et al., 2024).

2.4 Pharmacokinetic analysis

Pharmacokinetic parameters for indole derivatives (2, 4, 11 and 43) were determined using the SwissADME and ADMETlab 2.0 software. It is noteworthy that these programs are theoretical tools used to determine some pharmacokinetic factors involved in the pharmacological effects of different drugs (Fu et al., 2024; Seghir et al., 2025).

2.5 Toxicology analysis

The toxicity level of indole derivatives (2, 4, 11 and 43) was determined using the Gussar software (Askerova et al., 2023). It is worth noting that the Gussar program was developed to create models based on the association between the chemical structure of various drugs and their toxicological activity (LD_{50}) through different routes (oral, intravenous, intraperitoneal, and subcutaneous). Furthermore, the toxicity level was calculated based on SYMYX MDL toxicity data, which includes information on approximately 10,000 chemical structures with acute toxicity data in rats represented as LD_{50} values ($\log^{12}$ [mmol/kg⁻¹]).

3. Results

3.1 Ligand-protein complex

Table 2 shows the molecular docking results of indole derivatives (1-43), bepridil, indole, levosimendan, trifluoperazine, and DPISTA with the 2n7l protein surface.

Table 2. Amino acid residues involved in the coupling of indole derivatives (1-43) with the 2n7l protein surface.

Compounds	Aminoacid residues
Bepridil	Met ₈₀
Indole	Val ₆₄ ; Glu ₆₆ ; Glu ₇₆
Levosimedam	Tyr ₅ ; Val ₆₄ ; Glu ₆₆ ; Val ₇₉ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃ ; Met ₈₅ ; Asp ₈₇ ; Asp ₈₈
Trifluoperazine	Val ₇₉ ; Met ₈₀
DPISTA	Phe ₇₇ ; Met ₈₁
1	Leu ₇₈ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃ ; Met ₈₇ ; Asp ₈₇
2	Met ₆₀ ; Glu ₆₃ ; Asp ₈₇
3	Val ₇₉ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃ ; Asp ₈₇ ; Asp ₈₈
4	Leu ₇₈ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃ ; Asp ₈₇
5	Val ₇₉ ; Met ₈₀ ; Arg ₈₃ ; Met ₈₅
6	Met ₈₀
7	Ile ₃₆
8	Met ₆₀
9	Met ₆₀
10	Met ₆₀
11	Met ₆₀ ; Glu ₆₃
12	Met ₈₀
13	Val ₇₉ ; Met ₈₀ ; Val ₈₂ ; Arg ₈₃
14	Glu ₇₆ ; Phe ₇₇ ; Leu ₇₈ ; Met ₈₀ ; Met ₈₁ ; Met ₈₅
15	Met ₆₀ ; Arg ₁₀₀
16	Met ₁₀₆ ; Met ₁₀₇
17	Val ₇₉ ; Met ₈₀ ; Arg ₈₃ ; Lys ₈₆ ; Asp ₈₇
18	Met ₈₀ ; Arg ₈₃

19	Val ₇₉ ; Met ₈₀ ; Arg ₈₁ ; Arg ₈₃
20	Met ₈₀
21	Phe ₇₇ ; Leu ₇₈ ; Met ₈₀ ; Met ₈₁
22	Val ₇₉ ; Met ₈₀ ; Arg ₈₃ ; Asp ₈₇
23	Val ₇₉ ; Met ₈₀ ; Met ₈₁ ; Val ₈₂ ; Met ₈₅ ; Asp ₈₇
24	Met ₈₀
25	Val ₇₉ ; Met ₈₀ ; Val ₈₂ ; Arg ₈₃ ; Met ₈₅ ; Asp ₈₇
26	Gln ₅₀ ; Arg ₉₈
27	Gln ₅₀
28	Glu ₇₆ ; Phe ₇₇ ; Leu ₇₈ ; Met ₈₀ ; Met ₈₁ ; Met ₈₅
29	Phe ₇₇ ; Leu ₇₈ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃ ; Met ₈₅ ; Asp ₈₇
30	Met ₈₀
31	Met ₁₀₆
32	Glu ₅₀ ; Met ₆₀ ; Arg ₉₈
33	Glu ₅₀ ; Met ₆₀ ; Arg ₉₈
34	Val ₇₉ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃ ; Asp ₈₇ ; Asp ₈₈
35	Glu ₁₉ ; Met ₁₀₇
36	Ala ₁₀₃
37	Gln ₁₆ ; Glu ₁₉ ; Met ₁₀₇
38	Glu ₁₉ ; Met ₁₀₆ ; Met ₁₀₇
39	Phe ₂₀ ; Met ₈₁
40	Phe ₇₇ ; Met ₈₁
41	Val ₇₉ ; Met ₈₀ ; Arg ₈₃ ; Asp ₈₇
42	Met ₈₀
43	Met ₆₀ ; Glu ₇₆ ; Phe ₇₇ ; Met ₈₀ ; Met ₈₁ ; Arg ₈₃

Source: Authors, 2026.

3.2 Root mean square deviation (RMSD)

Table 3 shows the RMSD values and the percentage of molecules that match their indole derivatives (1-43) determined using the LigRMSD program.

Table 3. RMSD calculations among identical and similar compounds in protein-ligand docking.

Molecule	Type of conformation	RMSD	Percent of molecule match
1	Flexible	1.22	56.45
2	Flexible	0.62	81.82
3	Flexible	1.14	66.67
4	Flexible	1.34	69.23
5	Flexible	0.46	50.00
6	Flexible	1.07	52.94
7	Flexible	2.22	75.00
8	Flexible	0.73	75.00
9	Flexible	0.93	69.23

10	Flexible	0.62	81.82
11	Flexible	0.71	81.82
12	Flexible	1.65	56.25
13	Flexible	0.83	69.23
14	Flexible	1.55	64.29
15	Flexible	2.42	60.00
16	Flexible	2.33	75.00
17	Flexible	2.33	75.00
18	Flexible	2.42	69.23
19	Flexible	0.69	75.00
20	Flexible	2.55	64.29
21	Flexible	2.79	52.94
22	Flexible	1.10	69.23
23	Flexible	0.56	54.55
24	Flexible	2.60	64,29
25	Flexible	2.53	64.29
26	Flexible	1.11	69.23
27	Flexible	0.62	75.00
28	Flexible	2.33	69.23
29	Flexible	2.33	64.29
30	Flexible	2.22	81.82
31	Flexible	2.22	81.82
32	Flexible	2.55	64.29
33	Flexible	2.42	60.00
34	Flexible	2.23	75.00
35	Flexible	0.62	75.00
36	Flexible	2.13	81.82
37	Flexible	1.10	81.82
38	Flexible	0.78	81.82
39	Flexible	0.78	81.82
40	Flexible	0.93	69.23
41	Flexible	2.22	90.00
42	Flexible	1.77	52.94
43	Flexible	1.36	45.00

Source: <https://ligrmsd.appsbio.utalcal.cl>

3.3 Thermodynamic parameters

Table 4 displays the energy values involved in the docking of indole derivatives (1-43), bepridil, indole, levosimendan, trifluoperazine, and DPISTA with the 2n7l protein surface. Other data indicate that the inhibition constant (Ki) for indole derivatives 2, 4, 11, and 43 was lower compared with compounds 1, 3, 5-10, 12-42, bepridil, indole, and levosimendan.

Table 4. Thermodynamic parameters involved in the interaction of indole derivatives (1-43) with the 2n7l protein surface.

Compound	A	B	C	D	E	F
Bepiridil	-4.82	0.29212	-5.93	-0.62	-6.54	648.27
Indole	-4.05	1.07	-4.07	0.01	-4.05	278.25
Levosimmedam	-4.17	0.87276	-5.42	-0.23	-5.65	553.65
Trifluoroperazine	-7.48	0.00329	-7.20	-0.79	-7.99	598.81
DPISTA	-6.47	0.01804	-7.28	-0.02	-7.26	594.11
1	-5.37	0.11561	-5.56	-0.11	-5.67	418.50
2	-6.06	0.03606	-4.19	-2.47	-6.66	358.41
3	-5.44	0.10221	-5.47	0.03	-5.44	430.68
4	-6.02	0.03884	-4.18	-1.83	-6.02	380.27
5	-3.83	1.56	-3.70	-0.13	-3.83	317.93
6	-5.32	0.12544	-5.74	0.00	-5.74	439.16
7	-3.96	1.26	-4.27	0.01	-4.25	369.56
8	-3.77	1.73	-4.06	-0.01	-4.97	363.85
9	-4.61	0.41682	-4.62	0.01	-4.16	370.40
10	-4.53	0.47653	-4.36	-0.17	-4.53	346.85
11	-6.15	0.0310	-4.80	-1.95	-6.74	359.16
12	-5.63	0.07469	-5.92	-0.01	-5.93	460.17
13	-4.77	0.32000	-5.06	-0.01	-5.07	335.72
14	-4.31	0.69813	-4.58	-0.02	-4.60	391.62
15	-3.72	1.87	-4.01	-0.06	-4.07	391.50
16	-4.08	1.02	-4.62	-0.01	-4.63	357.39
17	-3.80	1.64	-4.40	-0.28	-4.68	368.76
18	-3.78	1.70	-4.73	-0.17	-4.90	397.31
19	-3.91	1.35	-4.08	-0.14	-4.21	335.03
20	-4.11	0.97842	-4.91	-0.01	-4.92	409.46
21	-4.99	0.21988	-5.67	-0.02	-5.69	467.22
22	-4.25	0.76734	-4.42	-0.13	-4.55	334.79
23	-3.68	2.01	-3.86	-0.11	-3.98	354.66
24	-4.13	0.93961	-4.58	-0.02	-4.60	406.90
25	-3.72	1.87	-4.46	-0.14	-4.60	414.22
26	-3.78	1.70	-3.83	0.08	-3.75	372.02
27	-3.35	3.50	-3.80	0.16	-3.65	345.81
28	-3.91	1.36	-4.53	-0.03	-4.56	382.32
29	-4.01	1.15	-4.85	-0.08	-4.93	412.15
30	-3.80	1.64	-4.25	-0.18	-4.43	345.84
31	-3.87	1.45	-4.15	-0.02	-4.17	336.46
32	-3.47	2.88	-4.23	-0.02	-4.25	391.66
33	-3.76	1.75	-4.32	-0.13	-4.45	405.88
34	-4.34	0.66354	-4.80	-0.12	-4.92	367.48

35	-3.41	3.17	-4.26	0.56	-3.71	340.26
36	-3.70	1.79	-4.28	-0.04	-4.32	341.14
37	-3.91	1.36	-4.19	-0.02	-4.21	346.37
38	-3.91	1.37	-4.20	0.00	-4.21	333.00
39	-3.96	1.25	-3.92	-0.01	-3.93	337.22
40	-3.70	1.93	-4.24	-0.04	-4.28	383.64
41	-4.04	1.09	-4.05	0.00	-4.04	306.17
42	-5.03	0.20692	-5.08	0.06	-5.03	432.48
43	-5.89	0.04854	-6.17	-0.01	-6.18	478.69

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. Source: Authors, 2026.

Other results (Table 5 and Figures 3-7) show the different types of bonds involved in the docking of the indole derivatives (2, 4, 11, and 43) with the 2n7l protein.

Table 5. Bond type and distance levels (Å) involved in the interaction of indole derivatives and the controls with the 2n7l protein surface.

Comound	Hydrogen bonds
Bepiridil	Met ₈₀ (N ₁ , 1.59); Met ₈₀ (N ₂ , 3.45)
Indole	Val ₆₄ (N, 1.52); Glu ₇₆ (N, 3.19); Glu ₆₆ (N, 2.96)
Levosimedom	Met ₈₀ (N ₅ , 2.37); Met ₈₅ (N ₂ , 3.14); Asp ₈₈ (N ₁ , 3.04); Val ₇₉ (N ₅ , 1.85); Arg ₈₃ (O ₁ , 2.09); Asp ₈₈ (N ₄ , 3.10); Asp ₈₇ (N ₃ , 3.23); Met ₈₅ (N ₃ , 3.30); Met ₈₅ (N ₄ , 2.21); Val ₇₉ (N ₆ , 2.74); Asp ₈₈ (N ₂ , 3.45); Glu ₆₆ (N ₆ , 2.20); Glu ₆₆ (N ₅ , 3.44); Met ₈₀ (N ₆ , 3.08); Met ₈₅ (N ₄ , 3.20); Tyr ₅ (N ₆ , 2.85); Met ₈₀ (N ₃ , 1.45); Met ₈₁ (N ₁ , 2.65); Val ₆₄ (N ₆ , 3.33)
Trifluoroperazine	Met ₈₀ (N ₃ , 0.72); Val ₇₉ (N ₃ , 3.44); Met ₈₀ (N ₂ , 2.95)
DPISTA	Met ₈₁ (N ₁ , 3.45); Phe ₇₇ (N ₁ , 3.23)
2	Asp ₈₇ (N ₂ , 0.64); Asp ₈₈ (N ₁ , 2.57); Arg ₈₃ (N ₁ , 2.65); Asp ₈₇ (N ₁ , 1.61); Arg ₈₃ (N ₂ , 1.73); Met ₈₀ (N ₂ , 2.71); Val ₇₉ (N ₂ , 3.46); Met ₈₀ (N ₁ , 3.08); Met ₈₁ (N ₁ , 2.39)
4	Met ₈₀ (N ₁ , 1.67); Asp ₈₇ (N ₂ , 2.02); Met ₈₁ (N ₁ , 1.34); Arg ₈₃ (N ₂ , 1.59); Met ₈₀ (N ₂ , 2.67); Leu ₇₈ (N ₁ , 3.39)
11	Met ₆₀ (N ₂ , 2.67); Glu ₆₃ (N ₂ , 2.67); Met ₈₀ (N ₁ , 3.24)
43	Met ₈₁ (N ₂ , 2.82); Met ₆₀ (N ₁ , 3.30); Phe ₇₇ (N ₂ , 1.60); Glu ₇₆ (N ₂ , 3.23); Met ₈₀ (N ₂ , 2.91); Arg ₈₃ (O ₁ , 3.30)

Note: DPISTA = 2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide. Source: Authors, 2026.

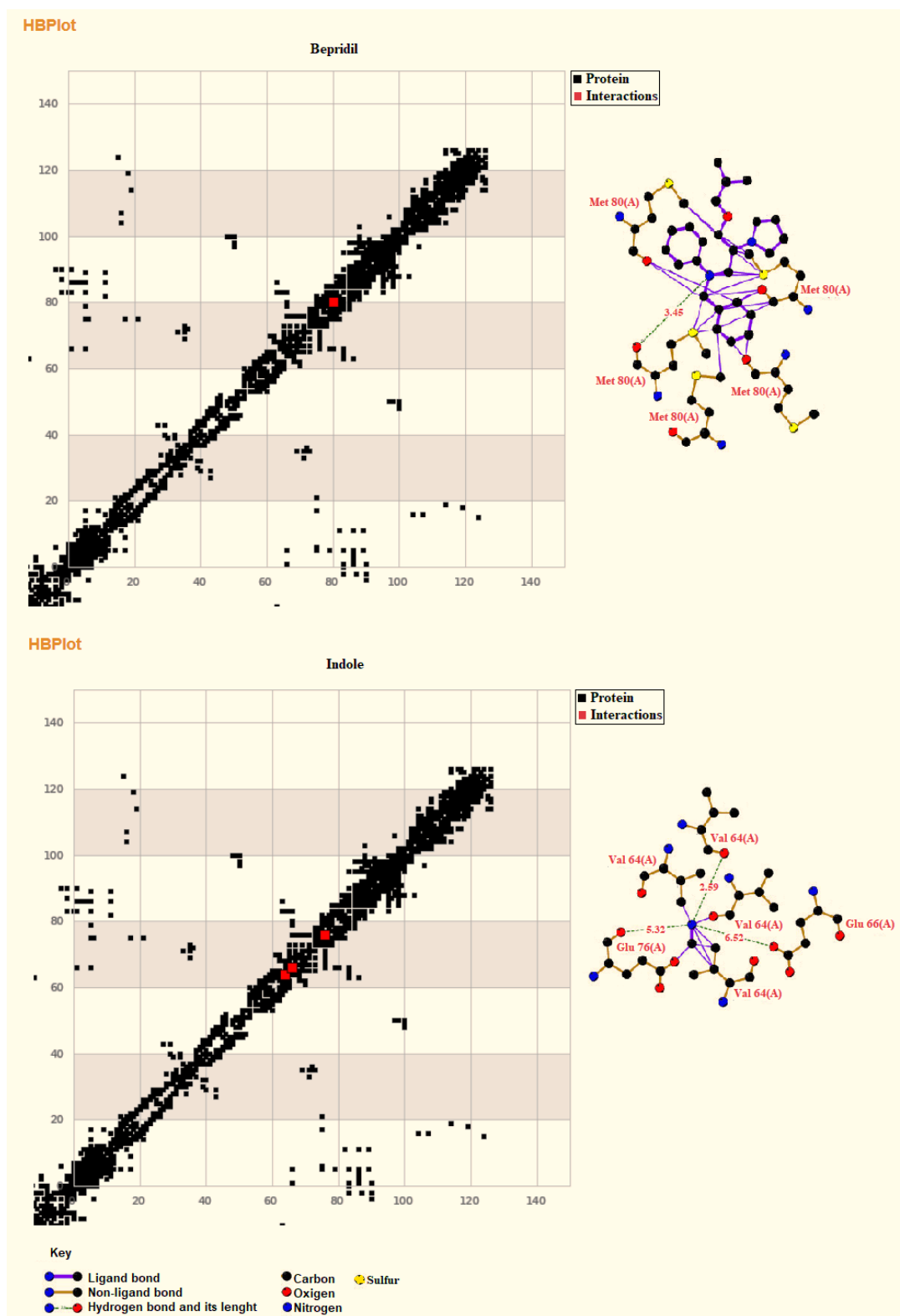


Figure 3. Docking of bepridil and indole with the 2n7l protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

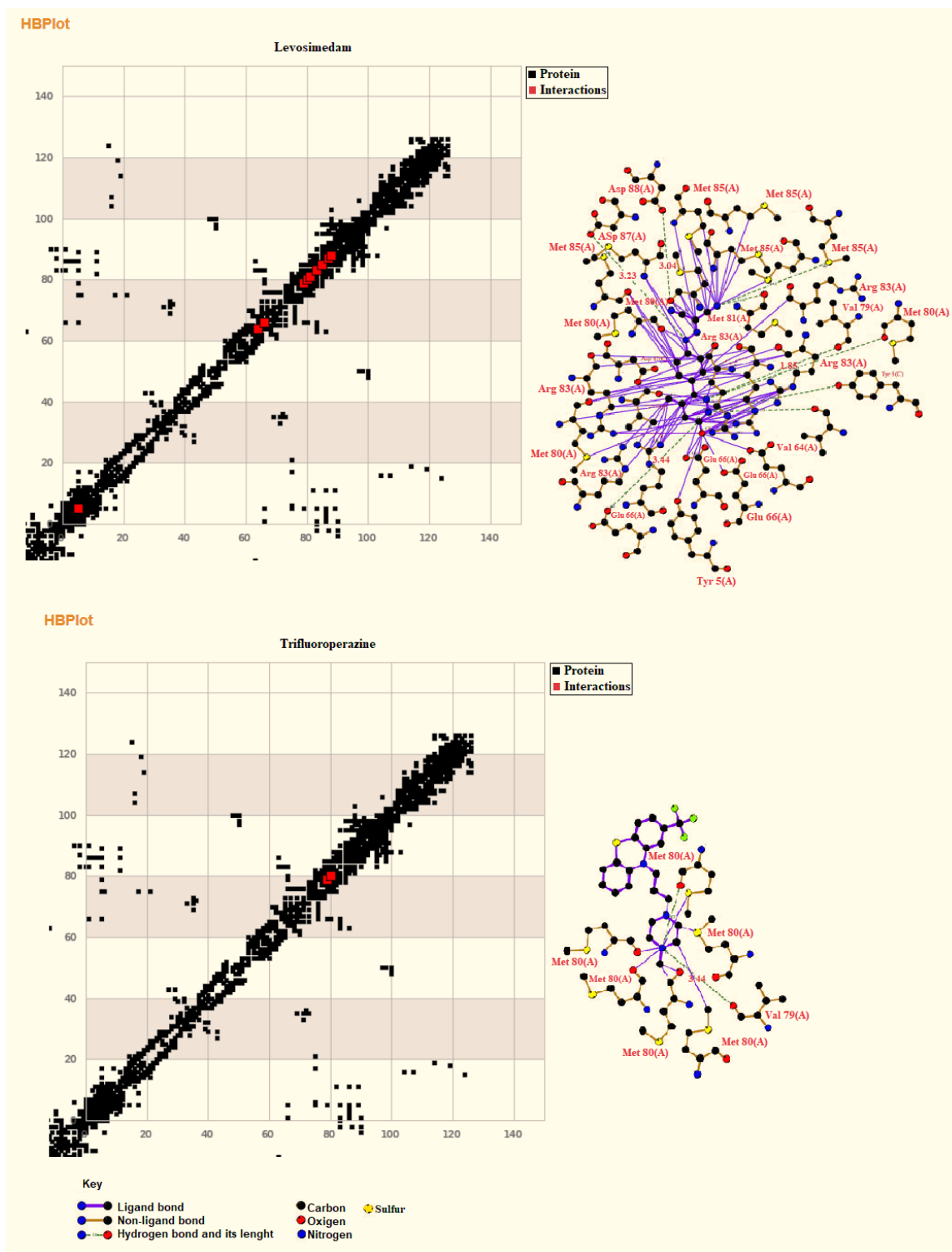


Figure 4. Interaction of levosimendan and trifluoroperazine with the 2n7l protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

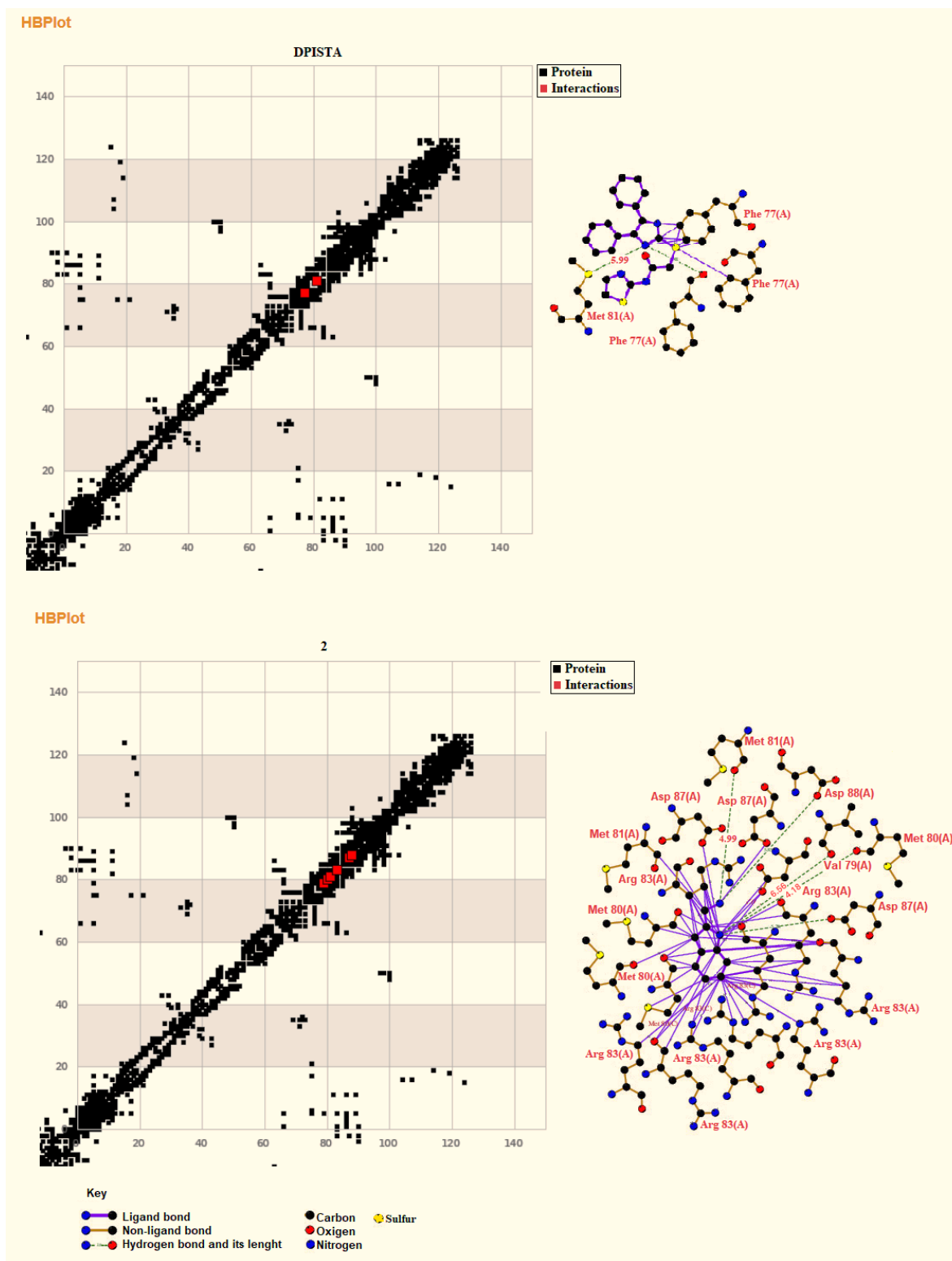


Figure 5. Docking of DPISTA (2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide) and compound 2 with 2n7l protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

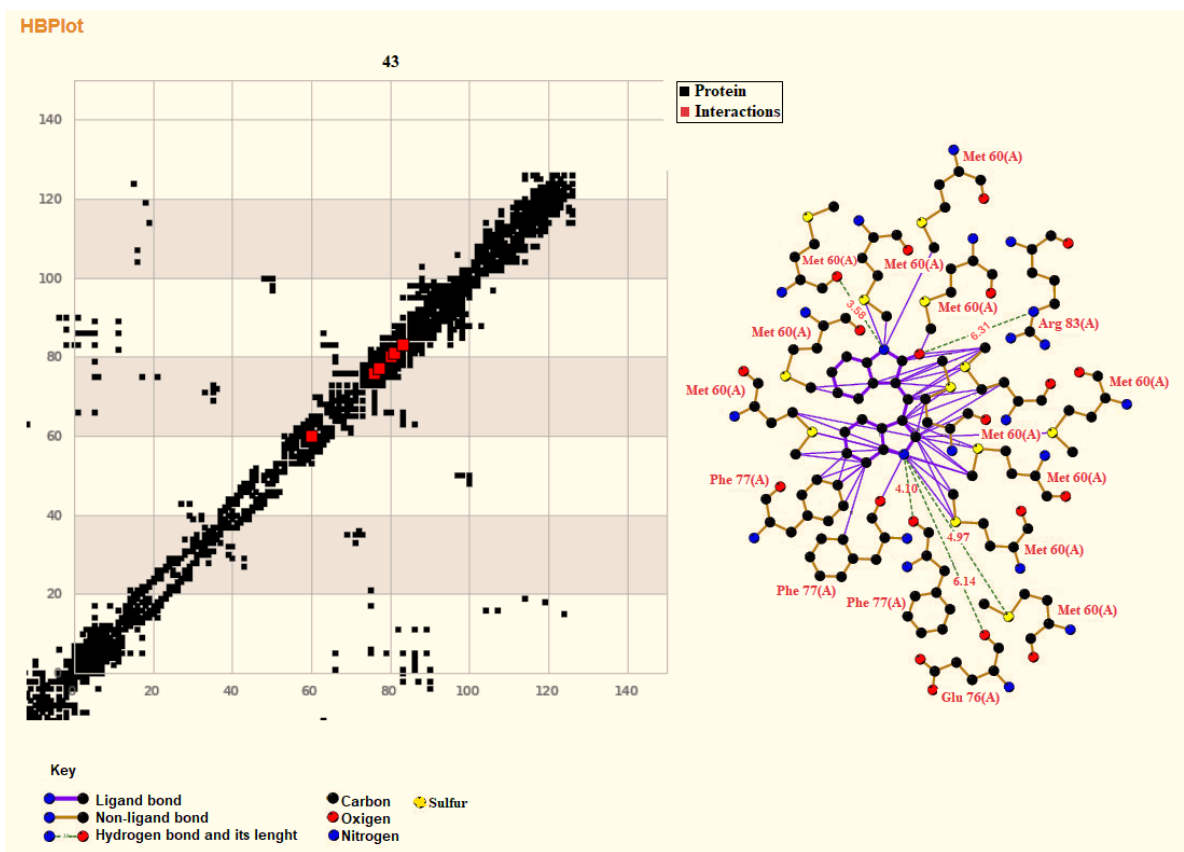
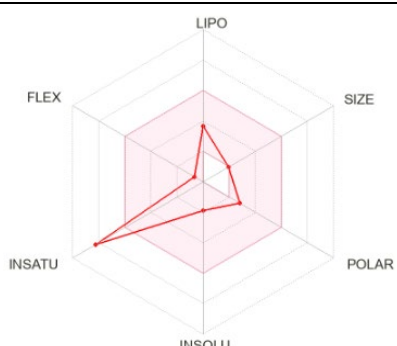


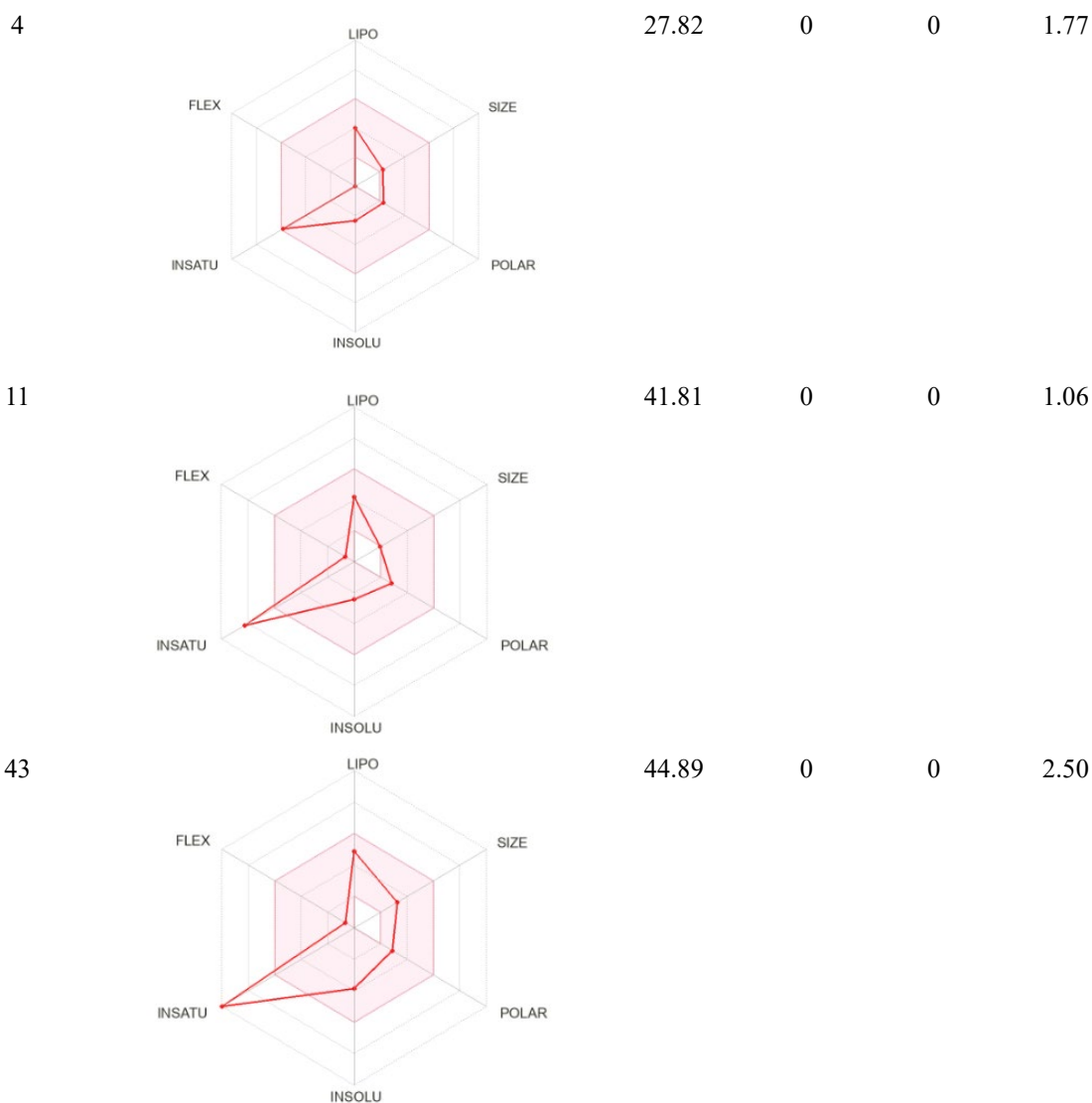
Figure 7. Docking of compound 43 with the 2n7l protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

3.4 Physicochemical parameters

The physicochemical values for indole derivatives 2, 4, 11, and 43 are shown in (Table 6) using the SwissADME program.

Table 6. Physicochemical parameters for hydantoin 2, 4, 11, and 43 using the SwissADME program.

Compound	Area*	TPSA (Å ²)	Lipinski (violations)	Pains (alerts)	Synthetic accessibility
2		41.81	0	0	1.19



Note: *The colored zone is the suitable physicochemical space for oral bioavailability: LIPO(Lipophilicity): $-0.7 < \text{XLOGP3} < +5.0$; SIZE: $150 \text{ g/mol} < \text{MW} < 500 \text{ g/mol}$; POLAR(Polarity): $20 \text{ \AA}^2 < \text{TPSA} < 130 \text{ \AA}^2$; INSOLU(Insolubility): $-6 < \log S \text{ (ESOL)} < 0$; INSATU(Insaturation): $0.25 < \text{Fraction Csp}^3 < 1$; FLEX(Flexibility): $0 < \text{Num. rotatable bonds} < 9$. [®]Probability of F > 10% in rat implemented from Martin et al. (2005).

3.5 Pharmacokinetic parameters

Table 7 shows the pharmacokinetic values for indole derivatives 2, 4, 11, and 43 obtained using ADMETlab 2.0 software.

Table 7. Pharmacokinetic parameters for indole derivatives 2, 4, 11, and 43.

Parameter	2	4	11	43
Caco-2 Permeability	-4.690	-5.070	-4.716	-4.951
Pgp inhibitor	No	No	No	Yes
Pgp substrate	No	Yes	No	No
Human intestinal Absorption	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes

Compound	IP LD ₅₀ (mg/kg)	IV LD ₅₀ (mg/kg)	Oral LD ₅₀ (mg/kg)	SC LD ₅₀ (mg/kg)
2	932.40	50.50	1709.00	228.90
4	180.60	19.51	811.70	92.44
11	380.20	55.14	872.30	204.80
43	619.50	119.40	2126.00	402.70
CYP1A2 substrate		Yes	Yes	No
CYP2C19 inhibitor		No	No	Yes
CYP2C19 substrate		No	No	No
CYP2C9 inhibitor		No	No	Yes
CYP2C9 substrate		Yes	No	Yes
CYP2D6 inhibitor		Yes	Yes	Yes
CYP2D6 substrate		Yes	Yes	No
CYP3A4 inhibitor		No	No	No
CYP3A4 substrate		No	No	No
Plasma protein binding (%)	17.482	24.625	98.342	95.913
Volume distribution (L/kg ⁻¹)	1.594	2.751	1.390	0.723
Blood-Brain Barrier		No	Yes	Yes
CL _{plasma} (ml/min/kg)		9.122	8.251	5.481
T _{1/2} (L/kg ⁻¹)		0.866	0.704	0.170

Source: Authors, 2026.

3.6 Toxicity analysis

The Gussar program was used to calculate the toxicity values (Table 8) for indole derivatives 2, 4, 11, and 43. The findings showed variations in dose concentration across various administration routes.

Table 8. Theoretical analysis of toxicity produced by indole derivatives (2, 4, 11 and 43).

Compuesto	IP LD ₅₀ (mg/kg)	IV LD ₅₀ (mg/kg)	Oral LD ₅₀ (mg/kg)	SC LD ₅₀ (mg/kg)
2	932.40	50.50	1709.00	228.90
4	180.60	19.51	811.70	92.44
11	380.20	55.14	872.30	204.80
43	619.50	119.40	2126.00	402.70

Note: IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration. Source: Authors, 2026.

4. Discussion

Several studies indicate that the prevalence and incidence of hypertrophic cardiomyopathy are global health problems with a high mortality rate (Butzner et al., 2026; Guazzeli et al., 2025; Maron et al., 2026; Siverdal et al., 2026). It is important to mention that some drugs have been used for the treatment of hypertrophic cardiomyopathy, such as β -blockers and verapamil (Ostman-Smith, 2014; Pinto et al., 2025) and aficamten and mevacamten [myosin ATPase inhibitors] (Davis et al., 2025; Savsin; Tokarek, 2025).

However, there is limited information on cardiac troponin-targeted drug therapy for the treatment of hypertrophic cardiomyopathy, although some studies have shown that levosimendan [cTnT-agonist] (Klein et al., 2018; Rosevear; Finley, 2003) may have beneficial effects on the heart in patients with non-hypertrophic septal cardiomyopathy (Zhao et al., 2025). Analyzing this data, this research aimed to determine the possible interaction of some indole derivatives with the cTnT surface, using some strategies as follows:

4.1 Ligand-protein complex

Several methods have been used to predict the docking of different compounds with some biomolecules (Baud; Azevedo, 2025; Roomi et al., 2025; Sim et al., 2025; Varughese et al., 2011). For example, a study showed the docking of bepridil with cardiac troponin using the 1LXF (Structure of the Regulatory N-domain of Human Cardiac Troponin C in Complex with Human Cardiac Troponin-I) and 1J1D (Crystal structure of the 46 kDa domain of human cardiac troponin in the Ca^{2+} -saturated form) proteins as theoretical tools (Varughese et al., 2011). In addition, a human cardiac troponin C model (based on the TnC crystal structure) was developed, which was used to dock it with the bepridil, pimobendan, and trifluoperazine drugs. It is noteworthy that energy calculations for the protein, free ligands, and bound complexes were performed using the AMBER software package (Ovaska; Taskinen, 1991).

All data indicate that some drugs can interact with cTnT; however, there is little information about the docking of indole derivatives with cTnT. For this reason, in this study, the docking of some indole derivatives with cTnT was determined using the 2n7l protein as a theoretical tool in the DockingServer program. Besides, the compounds bepridil, indole, levosimendan, trifluoperazine, and DPISTA (2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide) were used as controls. The results showed differences in the number of amino acid residues involved in the docking of indole derivatives with the 2n7l protein surface compared with the controls. This phenomenon may be due to the different types of conformation adopted by each molecule.

4.2 RMSD

In the literature, some reports indicate that the formation of the ligand-protein complex involves a wide range of conformational changes (Basciu et al., 2025; Celej et al., 2003; Falvo et al., 2025; Sedov; Zuev, 2025). In this way, the ligand-protein complex formation may produce different conformational rearrangements, from local movements of the side chains involved in the ligand's chemical structure to changes in the protein's conformation.

It is important to mention that some programs have been used to compare different conformations adopted by identical or similar chemical compounds, such as pyRMSD (Gil; Gualla, 2013) and Gromacs (Berendsen et al., 1995), and others. Analyzing these data, in this investigation, the LigRMSD software was used to determine RMSD; this program employs two methods: 1) strict matching, which considers identical types of atoms and bonds; and 2) flexible matching, which allows comparing pairs of atoms or bonds of different types (Valdés-Albuernes et al., 2025; Velázquez-Libera et al., 2020). The results displayed differences in the percentage of molecules matching; these data suggest that the different chemical structures of each compound could condition the type of conformation adopted in the formation of the ligand-protein complex.

4.3 Thermodynamic parameters

In the literature, several reports indicate that the ligand-protein complex formation is associated with several thermodynamic factors, including binding free energy, vdW + Hbond + desolv energy, electrostatic energy, and total intermolecular energy, among others (Akbariqomi et al., 2024; Rutwick-Surya et al., 2021; Surya-Ulhas; Malaviya, 2023). For example, a study showed that the binding free energy for the docking of levosimendan with the 3RV5 protein surface (crystal structure of human cardiac troponin C regulatory domain in complex with cadmium and deoxycholic acid) was 6.5 kcal/mol using the AutoDock program (Agraval et al., 2020). Other reports indicate that levosimendan and its derivative (ethyl 4-{4-[2-(dicyanomethylidene)hydrazinyl] phenyl}-6-

methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate) were docked with the 7sc3 protein (crystal structure of the N-domain of cardiac muscle troponin C tethered to the switch region of cardiac muscle troponin I {orthorhombic form}) using AutoDock software.

The results of ligand-protein formation showed lower binding energy (-23.5 ± 0.2 kcal/mol) for the levosimendan derivative compared with levosimendan (-19.8 ± 0.3 kcal/mol⁻¹) (Cárdenas-Yong et al., 2026). These data indicate that binding energy may depend on the chemical characteristics of each compound; for this reason, in this study, the binding free energy and other thermodynamic parameters involved in the docking of indole derivatives were determined using the DockingServer program. It is noteworthy that the compounds bepridil, indole, levosimendan, trifluoroperazine, and DPISTA (2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide) were used as controls. Other results indicate that the binding free energy was lower for indole derivative 11 compared to bepridil, indole, levosimendan, compounds 1-10, and 12-43; however, the binding free energy value for 11 was higher in comparison with the compounds trifluoroperazine and DPISTA. These data suggest that differences in binding free energy values could influence the affinity of each compound for the surface of the 2n7l protein.

4.4 Inhibition constant (K_i)

Several reports indicate that molecular dynamics simulation has become an essential tool in the study of protein-ligand docking for the development of new drugs; furthermore, it is worth mentioning that various methods have been used to measure the strength and specificity of protein-ligand interactions (Anees, 2025; Greval et al., 2025; Lang et al., 2025). For example, a report shows that compound 7930079 (2-[(4,5-diphenyl-1H-imidazol-2-yl)sulfanyl]-N-thiazol-2-yl-acetamide) can have a high affinity (1.45 ± 0.09 μ M) for cTnT using the 1LXF protein as a theoretical tool in the Autodock Vina software (Coldren et al., 2020). Another study indicates that resveratrol can bind to cTnT, with a dissociation constant of 240 μ M and a binding energy of 4.97 kcal/mol⁻¹ using a theoretical model (Pineda-Sanabria et al., 2011).

Analyzing these data, in this research, the affinity of indole derivatives for cTnT was determined using the inhibition constant (K_i) values involved in the docking of indole derivatives with the 2n7l protein surface. The results indicate that K_i values for indole derivatives 2, 4, 11, and 43 were lower compared with compounds 1, 3, 5-10, 12-42, bepridil, indole, and levosimendan.

However, the K_i was lower for compounds trifluoroperazine and DPISTA in comparison with compounds 1-43, bepridil, indole, and levosimendan. This phenomenon could be due to: i) differences in the chemical structure of each compound; ii) different types of bonds involved in the ligand-protein complex formation.

Analyzing these data, in this study, the type of bond involved in the docking between indole derivatives and the 2n7l protein surface was determined using the DockingServer program. The results showed that the amino acid residue Arg₈₃ can interact with compounds 2, 4, 43, and levosimendan through hydrogen bonds. Furthermore, Asp₈₇ can couple to indole derivatives 2 and 4 via hydrogen bonding. Further data indicate that Asp₈₈ might be specific for compound 2 and levosimendan. Finally, compound 43 and indole can interact with the amino acid residue Glu₇₆ via a hydrogen bond, and Phe₇₇ with compounds 43 and DPISTA through a hydrogen bond.

4.5 Physicochemical and pharmacokinetic parameters

The biological activity of several compounds depends on pharmacokinetic parameters (absorption, distribution, metabolism, and excretion), pharmacodynamic factors (e.g., interactions with specific biomolecules), and other factors. It is important to mention that some methods have been used to determine some pharmacokinetic parameters such as PHARM (Gomeni, 1984), PharmCalc (Borsi et al., 1988), SwissADME (Daina et al., 2017), and others. In this investigation, different pharmacokinetic parameters were determined using the SwissADME program.

The results display the physicochemical properties for the oral bioavailability of the indole derivatives 2, 4, 11, and 43. These data suggest compounds 2, 4, 11, and 43 could have favorable oral bioavailability because they meet the criteria of Lipinski's rule of five [an empirical rule used to predict the biological activity of a compound in relation to other established drugs] (Nhlapho et al., 2024). Furthermore, TPSA (molecular descriptor used to evaluate the ability of drugs to cross biological barriers) was determined (Pasanna; Doerksen, 2009); the results indicate that TPSA values were less than 130 Å² for indole derivatives 2, 4, 11, and 43. These data suggest that this physicochemical property of compounds 2, 4, 11, and 43 may produce changes in intestinal absorption and the blood-brain barrier.

Additionally, other pharmacokinetic characteristics were determined using ADMETab 2.0 (Table 7); the results showed that indole derivative 43 could act as a glycoprotein inhibitor (Pgp). Other data suggest that compounds 2, 4, 11, and 43 could inhibit the biological activity of CYP1A2 and CYP2D6. Furthermore, the indole derivatives 11 and 43 may act as CYP2C19 inhibitors. Other data suggest that compound 43 could interact with CYP2C9 and CYP3A4. Finally, other data suggest that compounds 4 and 11 could pass through the blood-brain barrier. All these data play an important role in the metabolism and distribution of indole derivatives in the body, which can be valued for future research on these compounds.

4.6 Toxicity analysis

Several methods have been used to predict the toxicity of certain drugs, including Tokpat (Venkatapathy et al., 2004), qTox (Urios et al., 2004), Tox II (Klopman; Rosenkranz, 1995), Gussar (Askerova et al., 2023), and others. In this study, a theoretical study was conducted to determine the degree of toxicity produced by indole derivatives 2, 4, 11, and 43 using the Gussar program.

The results indicate that indole derivative 43 requires a higher dose administered intravenously, orally, and subcutaneously to produce toxicity compared to compounds 2, 4, and 11. Further data showed that higher doses of compound 2 administered intraperitoneally can produce toxicity compared to indole derivatives 4, 11, and 43. All of these data suggest that the degree of toxicity may depend on differences in the chemical structure of each compound and the route of administration.

5. Conclusions

This research reports on the interaction of some indole derivatives with the cTnT using the 2n7l protein as a theoretical model in the DockingServer program. The results suggest that indole derivatives 2, 4, 11, and 43 have a high affinity for the 2n7l protein surface, involving some amino acid residues such as Arg₈₃, Asp₈₇, Asp₈₈, and Phe₇₇. These data suggest that compounds 2, 4, 11, and 43 could act as inhibitors of the 2n7l protein. This phenomenon could translate into changes in the biological activity of the cTnT protein. However, it is important to mention that alternative experiments are needed to evaluate the activity of these compounds in a biological model.

6. Authors' Contributions

Bonilla-Zavaleta: data curation, funding acquisition, investigation, methodology, visualization, writing—original draft, writing—review & editing. *Rosas-Nexticapa Marcela*: data curation, formal analysis, funding acquisition, investigation, methodology, visualization, writing—original draft, writing—review & editing. *Álvarez-Ramírez Magdalena*: formal analysis, funding acquisition, investigation, methodology, visualization., methodology, visualization, writing—original draft, writing—review & editing. *Melgarejo-Gutiérrez Montserrat Alheli*: formal analysis, funding acquisition, investigation, visualization, writing—review & editing. *Ramírez-Higuera Abril*: formal analysis, funding acquisition, investigation, visualization, writing—review & editing. *Rascon-Diaz Martha Paola*: formal analysis, funding acquisition, visualization. *Bonilla-Zavaleta Enrique*: funding acquisition, visualization, writing—review & editing.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

9. Artificial Intelligence Statement: Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that generative AI and AI-assisted tools were used exclusively for English and Portuguese grammar and language editing during the preparation of this manuscript. No AI tools were used to generate scientific content, analyze data, interpret results, or draw conclusions. All revisions suggested by AI were carefully

reviewed, verified, and approved by the authors, who assume full responsibility for the accuracy, integrity, and originality of the manuscript. AI tools are not authors and do not assume any responsibility for the content.

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