

Comprehensive bioinformatic analysis identifies some alkyne derivatives for treating MYH7-associated hypertrophic cardiomyopathy

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Abstract

Some studies indicate that mutations in the MYH7 gene are associated with hypertrophic cardiomyopathy. It is important to mention that several drugs have been used to treat hypertrophic cardiomyopathy, such as omecamtiv mecarbil, blebbistatin, mavacamten, and aficamten; however, it is necessary to develop a series of drugs that may interact with the MYH7 gene for therapeutic purposes in the treatment of this clinical pathology. For this reason, this study aimed to determine the coupling of some alkyne derivatives (1-35) with MYH7 using the 5cj1 protein as a theoretical tool. Besides, omecamtiv mecarbil, blebbistatin, mavacamten, and aficamten drugs were used as controls in the DockingServer program. The results showed differences in the number of amino acid residues involved in the interaction of alkyne analogues (1-35) with the 5cj1 protein surface compared to the controls. Other data indicate that the inhibition constant (Ki) was higher for alkyne derivatives 7, 12, and 34 compared with the omecamtiv mecarbil, blebbistatin, and mavacamten drugs. However, the Ki for compounds 7, 12, and 34 was lower compared to the alkyne derivatives 1-6, 8-11, 13-33, and 35. These data suggest that compounds 7, 12, and 34 may have good affinity for the 5cj1 protein surface, which could lead to inhibition of the biological activity of MYH7. Therefore, these compounds could represent promising candidates for further experimental evaluation using a hypertrophic cardiomyopathy model.

Keywords: hypertrophic cardiomyopathy, alkyne derivatives, interaction, MYH7.

Uma análise bioinformática abrangente identifica alguns derivados de alquino para o tratamento da cardiomiopatia hipertrófica associada ao MYH7.

Resumo

Alguns estudos indicam que mutações no gene MYH7 estão associadas à cardiomiopatia hipertrófica. É importante mencionar que diversos fármacos têm sido utilizados para tratar a cardiomiopatia hipertrófica, como omecamtiv mecarbil, blebbistatina, mavacamten e aficamten; entretanto, é necessário desenvolver uma série de fármacos que possam interagir com o gene MYH7 para fins terapêuticos no tratamento dessa patologia clínica. Por essa razão, o objetivo deste estudo foi determinar o acoplamento de alguns derivados de alquino (1-35) com MYH7 utilizando a proteína 5cj1 como ferramenta teórica. Além disso, os fármacos omecamtiv mecarbil, blebbistatina, mavacamten

e aficamten foram utilizados como controles no programa DockingServer. Os resultados mostraram diferenças no número de resíduos de aminoácidos envolvidos na interação dos análogos de alquino (1-35) com a superfície da proteína 5cjl em comparação com os controles. Outros dados indicam que a constante de inibição (K_i) foi maior para os derivados de alquino 7, 12 e 34 em comparação com os fármacos omecamtiv mecarbil, blebbistatina e mavacamten. No entanto, o K_i para os compostos 7, 12 e 34 foi menor em comparação com os derivados de alquino 1-6, 8-11, 13-33 e 35. Esses dados sugerem que os compostos 7, 12 e 34 podem ter boa afinidade pela superfície da proteína 5cjl, o que poderia levar à inibição da atividade biológica da MYH7. Portanto, esses compostos podem representar candidatos promissores para avaliação experimental adicional utilizando um modelo de cardiomiopatia hipertrófica.

Palavras-chave: cardiomiopatia hipertrófica, derivados de alquino, interação, MYH7.

1. Introduction

Cardiomyopathy is a disease of the heart muscle that reduces the heart's ability to pump oxygen-rich blood to the rest of the body, resulting in heart failure (Wexler et al., 2009; Brieler et al., 2017; Dai et al., 2025; Cardin et al., 2025). Some subtypes include hypertrophic cardiomyopathy, dilated cardiomyopathy, and restrictive cardiomyopathy (Jin et al., 2025). It is important to mention that hypertrophic cardiomyopathy is the most common, associated with several mutated genes (Liu et al., 2019; Ciarambino et al., 2021).

For example, a study (Garcia-Castro et al., 2009) conducted in Spanish patients with hypertrophic cardiomyopathy showed some mutations in sarcomeric genes such as MYH7 [encodes the β -Myosin Heavy Chain 7], MYBPC3 [encodes the cardiac isoform of myosin-binding protein C], TNNT2 [gene encodes the cardiac isoform of troponin T, cTnT], TNNI3 [encodes the cardiac isoform of troponin T1], and TPM1 [encodes for tropomyosin alpha-1 chain]. It is important to mention that some studies carried out on patients from a cardiology hospital (city of São Paulo, Brazil) showed that the mutation involved in the MYH7 gene variant p.Val320Met may contribute to the risk of sudden cardiac death and hypertrophic cardiomyopathy (Mori et al., 2021).

Other data indicate that the MYH7 c.2770G > A (p.Glu924Lys) mutation is associated with hypertrophic cardiomyopathy in a Chinese family (Han et al., 2025). Another study performed in a five-generation family with hypertrophic cardiomyopathy was diagnosed with the variant NM_000257.4:c.2342T>A (p.Leu781Gln) involved in the MYH7 gene (Franke et al., 2024). Besides, a report indicates that the Leu714Arg variant in the converter domain of MYH7 is associated with a severe form of familial hypertrophic cardiomyopathy (Golubenko et al., 2024). Finally, a study showed that the MYH7 R403Q mutation impairs left atrial mitochondrial function in a Yucatan mini-pig model of genetic nonobstructive hypertrophic cardiomyopathy (Krause et al., 2025).

All these data indicate that MYH7 can be a target in the treatment of hypertrophic cardiomyopathy; in this way, some drugs, such as mavacamten, a cardiac-specific MYH7 inhibitor, have been used to treat hypertrophic cardiomyopathy (Heitner et al., 2019; Saberi et al., 2021; Hayes; Burnette, 2025; Ramandan et al., 2025). Besides, the aficamten drug (cardiac myosin inhibitor) was developed with biological activity against hypertrophic cardiomyopathy (Harman et al., 2024; Ammirati and Gallone, 2024; Davis et al., 2025; Saberi et al., 2025). It is noteworthy that a study carried out in patients with hypertrophic cardiomyopathy showed that aficamten monotherapy was superior to metoprolol monotherapy in improving peak oxygen uptake and decreasing symptoms produced by this clinical pathology (Garcia-Pavia et al., 2025). Other reports indicate that the omecamtiv mecarbil drug can be used to treat hypertrophic cardiomyopathy; this drug increases cardiac contractility by binding to MYH7 (Woody et al., 2018; Day et al., 2022). In addition, some studies indicate that omecamtiv mecarbil improves cardiac function by increasing ejection duration without altering contraction rates in an animal model (Malik et al., 2011).

On the other hand, some computational studies have been used to predict the interaction of some compounds with MYH7, with the aim of finding a therapeutic alternative for treating hypertrophic cardiomyopathy (Hanif et al., 2025). For example, compound F10 (1-(6-ethyl-4-oxo-thieno[2,3-d]pyrimidin-3-yl)-3-isopropyl-thiourea) was designed as a specific myosin activity modulator using a human β -Cardiac Myosin protein using a computational model (Parijat et al., 2023). All these data indicate that some compounds can interact with MYH7; however, this phenomenon is not clear.

Therefore, it is necessary to develop a series of compounds that may interact with MYH7 for therapeutic purposes for the treatment of hypertrophic cardiomyopathy. For this reason, this study aimed to perform a theoretical analysis on the interaction of some alkyne derivatives with MYH7 as a therapeutic alternative to treat hypertrophic cardiomyopathy.

- | | |
|---|----------------------------|
| 9) 3,3,3-Trifluoro-1-propyne | 27) 6-chloro-1-hexyne |
| 10) 3,3-Dimethyl-1-butyne | 28) 6-iodo-1-hexyne |
| 11) 3,3-Dimethyl-3-(2-tetrahydropyranyloxy)-1-propyne | 29) Dipropargylamine |
| 12) 3-Chloro-1-phenyl-1-propyne | 30) N-Boc-propargylamine |
| 13) 3-Chloro-3-methyl-1-butyne | 31) N-Methylpropargylamine |
| 14) 3-Cyclopentyl-1-propyne | 32) Phenyl propargyl ether |
| 15) 3-Dimethylamino-1-propyne | 33) Propargyl chloride |
| 16) 3-Methyl-1-butyne | 34) Propargylamine |
| 17) 3-Methyl-1-hexyne | 35) 3-Bromo-1-butyne |
| 18) 3-Methyl-3-(2-tetrahydropyranyl-oxy)-1-propyne | |

Source: Authors, 2026.

2.2 Protein-ligand complex

The interaction of alkyne derivatives (1-35) with MYH7 was determined using the 5cj1 protein [<https://doi.org/10.2210/pdb1GOS/pdb>] as a theoretical tool. It is important to mention that the crystal structure of the coiled coil of MYH7 residues 1526 to 1571 fused to Gp7 (Figure 2) was determined using X-ray diffraction with a resolution of 281 Å (Korkmaz et al., 2016). Besides, drugs such as blebbistatin [specific myosin inhibitor] (Chen et al., 2018), mavacamten [selective, allosteric, reversible cardiac myosin inhibitor] (Tower-Rader et al., 2020), omecamtiv macarbil [cardiac myosin activator] (Scellini et al., 2024), and aficamten [cardiac myosin inhibitor] (Hou et al., 2025) were used as controls in the DockingServer program (<https://www.dockingserver.com/web>). It is noteworthy that DockingServer is a program that calculates the site, geometry, and energy of molecules interacting with proteins.

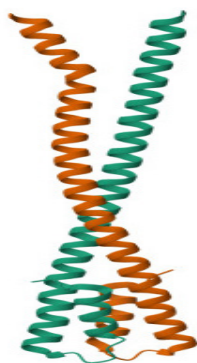


Figure 2. The scheme shows the 5cj1 protein. Source: <https://www.rcsb.org>

Additionally, DockingServer software offers an easy way to compute ligand-protein interactions or virtual high-throughput screening calculations and is used to calculate other types of compounds (Kontoyianni, 2017; Ma et al., 2024; Murugan et al., 2022). It is important to mention that this program involves the MMFF94 force field (Stylianakis et al., 2023), which is used for minimizing the energy of molecules that act as ligands (hydantoin and its derivatives). Besides essential hydrogen atoms, Kollman-united atom-type charges, van der Waals, and solvation parameters were added with the aid of AutoDock tools. It is noteworthy that affinity maps of 20×20×20 Å grid points and 0.375 Å spacing were generated using the AutoGrid program. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. Finally, 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. Additionally, docking simulations were performed using the Lamarckian genetic algorithm and the Solis & Wets local search method (Tavares et al., 2009).

2.3 Root-mean-square deviation (RMSD)

The RMSD was determined using the LigRMSD program. It is important to mention that LigRMSD is a program for the calculation of 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 (Valdés-Albuernes et al., 2025).

2.4 Pharmacokinetic analysis

Pharmacokinetic factors for alkyne derivatives 2, 7, 12, and 34 were determined using the SwissADME software were determined using the SwissADME software. It is noteworthy that this program is a theoretical tool used to determine some pharmacokinetic factors involved in the pharmacological effects of different drugs (Seghir et al., 2025).

2.5 Toxicology analysis

Toxicology evaluation for alkyne derivatives 2, 7, 12, and 34 was determined using the Gussar software (Askerova, 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 (LD₅₀) 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 LD50 values (log¹² [mmol/kg⁻¹]).

3. Results

3.1 Ligand-protein complex.

The interaction of alkyne derivatives (1-35) with MYH7 was determined using the 5cjl protein as a theoretical tool in Docking Server. Besides, Blebbistatin, mavacamten, omecamtiv mecarbil, and aficamten drugs were used as controls. The results displayed differences in the number of amino acid residues involved in the coupling of alkyne derivatives with the 5cjl protein surface compared with the controls (Table 2).

Table 2. Amino acid residues involved in the coupling of alkyne derivatives (1-35) with the 5cjl protein surface.

Compounds	Aminoacid residues
Blebbistatin	Glu ₁₅₂₇ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃ ; Glu ₁₅₃₄ ; Lys ₁₅₃₇
Mavacamtem	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃
Omecamtiv mecarbil	Leu ₁₅₂₆ ; Val ₁₅₂₉ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃ ; Glu ₁₅₃₄ ; Lys ₁₅₃₇
Aficamten	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃ ; Glu ₁₅₃₄
1	Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
2	Tyr ₄₃ ; Leu ₄₆ ; Thr ₄₇ ; His ₅₀ ; Glu ₅₁
3	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
4	Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
5	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
6	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
7	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
8	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
9	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
10	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
11	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃
12	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃
13	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
14	Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀

15	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
16	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
17	Tyr ₄₃ ; Leu ₁₅₂₆ ; Thr ₄₇ ; His ₅₀ ; Glu ₅₁
18	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀
19	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀
20	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
21	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
22	Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀
23	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀
24	Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀
25	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃
26	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
27	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
28	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃
29	Lys ₅₂ ; Lys ₁₅₂₈ ; Val ₁₅₂₉ ; Gln ₁₅₃₂
30	Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀ ; Leu ₁₅₃₃
31	His ₅₀ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
32	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Val ₁₅₂₉ ; Arg ₁₅₃₀
33	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀
34	Val ₁₅₂₉ ; Gln ₁₅₃₂ ; Leu ₁₅₃₃ ; Glu ₁₅₃₆
35	His ₅₀ ; Leu ₁₅₂₆ ; Glu ₁₅₂₇ ; Arg ₁₅₃₀

Source: Authors, 2026.

3.2 Root-mean-square deviation (RMSD)

Table 3 shows the RMSD values for the alkyne derivatives. It is important to mention that propyne was used as a structural reference.

Table 3. RMSD calculations among identical and similar compounds in protein-ligand docking. Source: <https://ligrmsd.appsbio.utalcal.cl>

Molecule	Type of conformation	RMSD	Percent of molecule match
5-Phenyl-1-pentyne	Flexible	0.69	27.27
	Strict	2.25	27.27
2-Pentyne	Flexible	0.41	60.00
	Strict	0.71	60.00
3-Methyl-3-(2-tetrahydropyranyloxy)-1-propyne	Flexible	1.04	27.27
	Strict	1.49	27.27
4-Bromo-1-butyne	Flexible	0.41	60.00
	Strict	1.52	60.00
3,3-Dimethyl-3-(2-tetrahydropyranyloxy)-1-propyne	Flexible	0.88	25.00
	Strict	1.94	25.00
2-Methyl-3-butyn-2-amine	Flexible	0.41	50.00

	Strict	1.04	50.00
Propargylamine	Flexible	0.41	75.00
	Strict	0.41	75.00
1-Hexyne	Flexible	0.44	50.00
	Strict	1.13	50.00
1-Bromo-2-butyne	Flexible	0.41	60.00
	Strict	0.71	60.00
1-phenyl-1-propyne	Flexible	0.41	33.33
	Strict	1.24	33.33
3-Cyclopentyl-1-propyne	Flexible	0.56	37.50
	Strict	1.67	37.50
3-Methyl-1-hexyne	Flexible	0.48	42.86
	Strict	1.58	42.86
3-Phenyl-1-propyne	Flexible	0.69	33.33
	Strict	1.74	33.33
N-Boc-propargylamine	Flexible	1.13	60.00
	Strict	1.87	60.00
3-Diethylamino-1-propyne	Flexible	0.82	50.00
	Strict	1.50	50.00
3,3,3-Trifluoro-1-propyne	Flexible	1.04	50.00
	Strict	1.04	50.00
3-bromo-1-butyne	Flexible	0.43	60.00
	Strict	1.29	60.00
6-Iodo-1-hexyne	Flexible	0.35	42.86
	Strict	1.47	42.86
Phenyl-propargyl ether	Flexible	0.66	30.00
	Strict	1.61	30.00
5-Methyl-1-hexyne	Flexible	0.62	42.86
	Strict	1.23	42.86
Propargyl chloride	Flexible	0.41	75.00
	Strict	1.41	75.00
3-Chloro-3-methyl-1-butyne	Flexible	0.63	50.00
	Strict	1.04	50.00
Dipropargylamine	Flexible	0.76	42.86
	Strict	1.47	42.86
3,3-Dimethyl-1-butyne	Flexible	0.41	50.00
	Strict	1.04	50.00
6-Chloro-1-hexyne	Flexible	0.35	42.86
	Strict	1.47	42.86
5-iodo-1-pentyne	Flexible	0.44	50.00
	Strict	1.13	50.00
3-methyl-1-butyne	Flexible	0.43	60.00

	Strict	1.29	60.00
4-Phenyl-1-butyne	Flexible	0.68	30.00
	Strict	1.45	30.00
1,4-Dichloro-2-butyne	Flexible	0.54	50.00
	Strict	0.54	50.00
1-pentyne	Flexible	0.41	60.00
	Strict	1.52	60.00
5-Chloro-1-pentyne	Flexible	0.44	50.00
	Strict	1.13	50.00
3-Chloro-1-phenyl-1-propyne	Flexible	0.21	30.00
	Strict	1.03	30.00

Source: Authors, 2026.

3.3 Thermodynamic parameters

Table 4 shows the energy levels and inhibition constant (Ki) involved in the interaction of alkyne derivatives (1-35) with the 5cjl protein surface. The results display differences in the binding free energy levels for alkyne derivatives compared with the controls. Other data indicate that Ki for alkyne derivatives 7, 12, and 34 was higher compared with aficamten, blebbistatin, mavacamten, and omecantiv mecarbil. However, the Ki for compounds 7, 12, and 34 was lower in comparison with alkyne derivatives 1-6, 8-11, 13-33, and 35.

Table 4. Thermodynamic parameters involved in the interaction of alkyne derivatives (1-35) with 5cjl protein surface.

Compound	Free Energy of Binding (kcal/mol)	Inhibition Constant (Ki, mM)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Interm. Energy (kcal/mol)	Interact. Surface
Blebbistatin	-4.50	0.5504	-4.89	-0.13	-5.02	532.98
mavacamtem	-4.17	0.8842	-5.47	0.02	-5.45	512.87
Omecantiv mecarbil	-4.13	0.9412	-395	-0.10	-4.05	460.65
Aficamten	-3.86	1.47	-4.79	-0.22	-5.02	536.52
1	-1.60	66.96	-1.60	0.00	-1.60	204.23
2	-3.12	5.15	-3.41	-0.01	-3.42	321.90
3	-2.07	30.18	-2.34	-0.03	-2.37	238.45
4	-2.88	7.73	-3.46	-0.02	-3.48	325.66
5	-2.01	33.90	-2.89	-0.00	-2.89	295.51
6	-1.90	40.42	-2.46	-0.02	-2.49	263.98
7	-3.33	3.65	-2.99	-0.93	-3.93	283.63
8	-2.04	32.39	-2.32	-0.02	-2.34	268.14
9	-2.58	12.80	-2.87	-0.02	-2.88	204.22
10	-2.36	18.48	-2.66	-0.01	-2.66	280.08
11	-3.12	5.18	-4.02	0.01	-4.02	413.31
12	-3.50	2.71	-4.07	-0.03	-4.10	388.45
13	-2.63	11.85	-2.93	0.01	-2.93	290.17

14	-2.95	6.86	-3.55	0.00	-3.55	322.35
15	-2.67	11.06	-2.73	-0.53	-3.27	278.80
16	-2.10	28.91	-2.40	0.00	-2.40	261.49
17	-2.25	22.45	-3.12	0.00	-3.12	305.83
18	-2.92	7.24	-3.76	-0.02	-3.79	399.91
19	-2.90	7.44	-3.51	0.01	-3.50	327.04
20	-1.88	41.95	-2.47	0.00	-2.46	232.30
21	-2.89	7.63	-3.71	0.01	-3.70	382.28
22	-2.32	19.77	-3.22	0.01	-3.21	313.56
23	-2.00	34.33	-2.90	0.02	-2.88	261.87
24	-2.31	201.15	-3.19	0.00	-3.19	317.22
25	-2.95	6.85	-4.05	0.00	-4.06	405.28
26	-2.37	18.30	-2.66	-0.01	-2.67	291.17
27	-2.37	18.20	-3.0	0.01	-3.49	330.96
28	-2.10	29.01	-3.25	0.00	-3.25	286.93
29	-1.84	44.98	-2.97	-0.03	-3.00	301.00
30	-2.67	11.01	-3.71	-0.04	-3.74	397.29
31	-2.78	9.21	-2.45	-0.92	-3.37	256.03
32	-2.72	10.08	-3.56	-0.04	-3.61	377.50
33	-2.22	23.46	-2.47	-0.05	-2.52	249.13
34	-3.53	2.57	-2.39	-1.75	-4.13	229.22
35	-2.13	27.29	-2.42	-0.01	-2.43	232.30

Source: Authors, 2026.

3.4 Bond type

Table 5 and Figures 3-6 show differences in the types of bonds involved in the interaction of alkyne derivatives (7, 12, and 34) with the 5cj1 protein surface compared with the controls.

Table 5. Bond type and distance levels involved in the interaction of alkyne derivatives (7, 12, and 34), blebbistatin, mavacamten, omecamtiv mecarbil, and aficamten with the 5cj1 protein surface.

Compound	Hydrogen bond	Polar Bond	Hydrophobic bond	Cation-pi
Blebbistatin		Arg ₁₅₃₀ (N ₁ , 3.20)	Leu ₁₅₂₆ (C ₁₄ , 3.87) Leu ₁₅₂₆ (C ₁₁ , 3.88) Leu ₁₅₃₃ (C ₅ , 3.52) Leu ₁₅₃₃ (C ₆ , 3.39) Leu ₁₅₃₃ (C ₇ , 3.37) Leu ₁₅₃₃ (C ₈ , 3.90) Leu ₁₅₃₃ (C ₁₈ , 3.70) Leu ₁₅₃₃ (C ₃ , 3.81) Leu ₁₅₃₃ (C ₄ , 3.47) Leu ₁₅₃₃ (C ₉ , 3.89)	

Mavacamten	Leu ₁₅₂₆ (N ₂ , 2.82)	Glu ₁₅₂₇ (O ₂ , 3,54) Arg ₁₅₃₀ (O ₂ , 3,24) Arg ₁₅₃₀ (N ₂ , 3.20) Arg ₁₅₃₀ (H ₂ , 2.46)	Leu ₁₅₂₆ (C ₁ , 3.10) Leu ₁₅₂₆ (C ₂ , 3.32) Leu ₁₅₃₃ (C ₉ , 3.23) Leu ₁₅₃₃ (C ₈ , 3.60) Leu ₁₅₃₃ (C ₁₅ , 3.70) Leu ₁₅₃₃ (C ₁₄ , 3.39)	
Omecamtiv mecarbil	Leu ₁₅₂₆ (N ₃ , 3.08)	Glu ₁₅₂₇ (O ₃ , 3.17) Arg ₁₅₃₀ (N ₃ , 3,09) Arg ₁₅₃₀ (H ₁₈ , 2.61) Arg ₁₅₃₀ (N ₄ , 361) Arg ₁₅₃₀ (H ₁₉ , 3,51)	His ₅₀ (C ₁₃ , 3.86) Leu ₁₅₂₆ (C ₅ , 3.20) Leu ₁₅₂₆ (C ₇ , 3.85) Leu ₁₅₂₆ (C ₂ , 3.36) Leu ₁₅₂₆ (C ₉ , 3.45) Leu ₁₅₂₆ (C ₃ , 3.59) Leu ₁₅₂₆ (C ₆ , 3.41)	
Aficamten	Glu ₁₅₂₇ (N ₁ , 2.73)	Glu ₁₅₂₇ (H ₉ , 1.84) Glu ₁₅₂₇ (N ₃ , 3.82) Arg ₁₅₃₀ (N ₄ , 2.90) Arg ₁₅₃₀ (N ₁ , 3.81) Arg ₁₅₃₀ (H ₉ , 3.21)	His ₅₀ (C ₈ , 3.77) Leu ₁₅₂₆ (C ₉ , 3.53) Leu ₁₅₃₃ (C ₁₇ , 3.75)	
7	Glu ₁₅₂₇ (N ₅ , 2.49)	His ₅₀ (H, 3.55) Glu ₁₅₂₇ (H, 2.04) Arg ₁₅₃₀ (H, 3.23)	His ₅₀ (C, 3.51) Leu ₁₅₂₆ (C, 3.47)	His ₅₀ (H, 3.25)
12			Leu ₁₅₂₆ (C ₂ , 3.65) Leu ₁₅₂₆ (C ₃ , 3.77) Leu ₁₅₂₆ (C ₅ , 3.40) Val ₁₅₂₉ (C ₆ , 3.69) Leu ₁₅₃₃ (C ₆ , 3.57) Leu ₁₅₃₃ (C ₇ , 3.52)	
34	Glu ₁₅₃₆ (N, 2.46)	Gln ₁₅₃₂ (N, 3.09)	Val ₁₅₂₉ (C, 3.45)	

Gln₁₅₃₂ (H, 2.21)

Leu₁₅₃₃ (C, 3.58)

Glu₁₅₃₆ (H, 2.09)

Source: Authors, 2026.

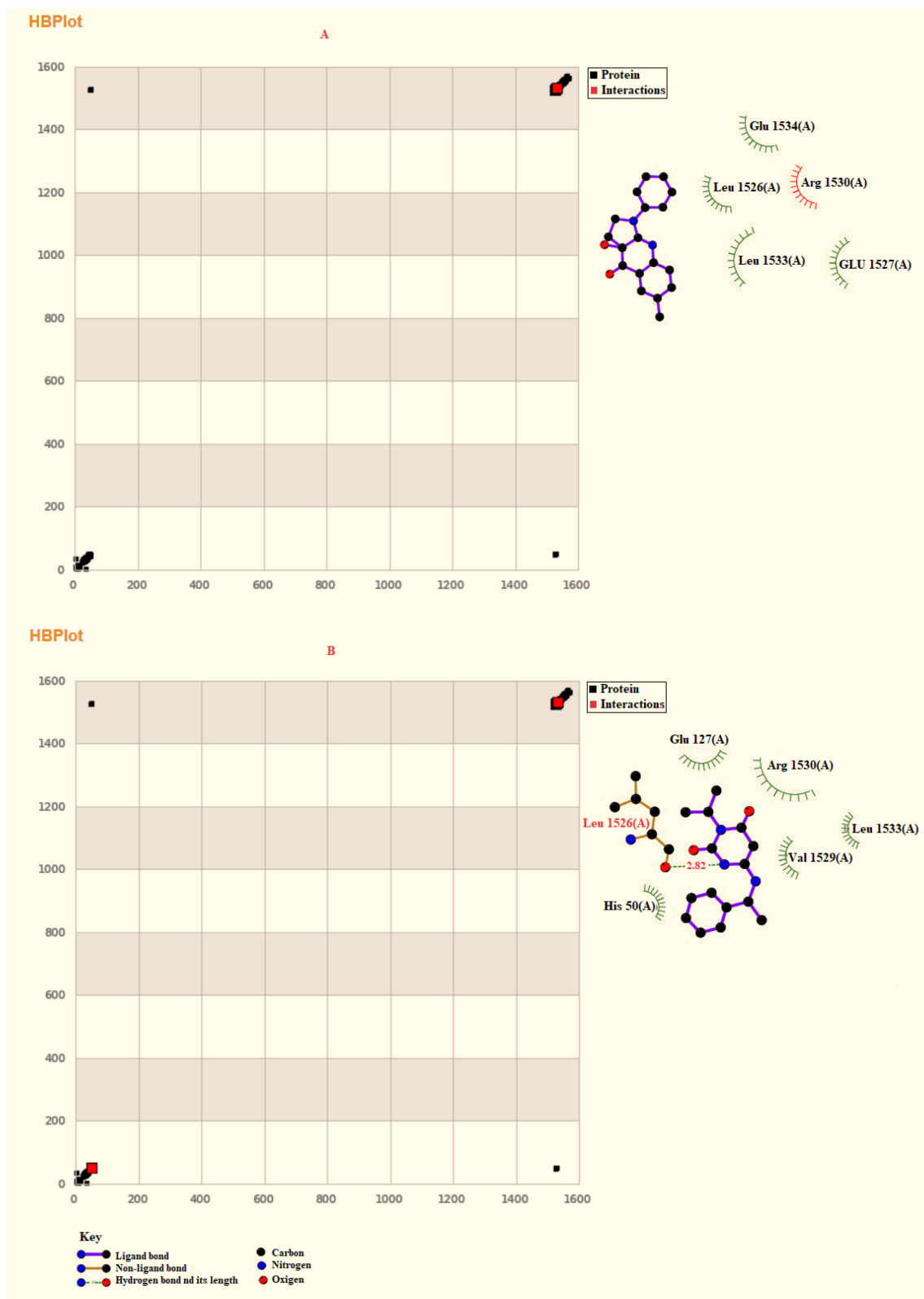


Figure 3. Interaction of blebbistatin (A) and mevacamten (B) drugs with the 5cj1 protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

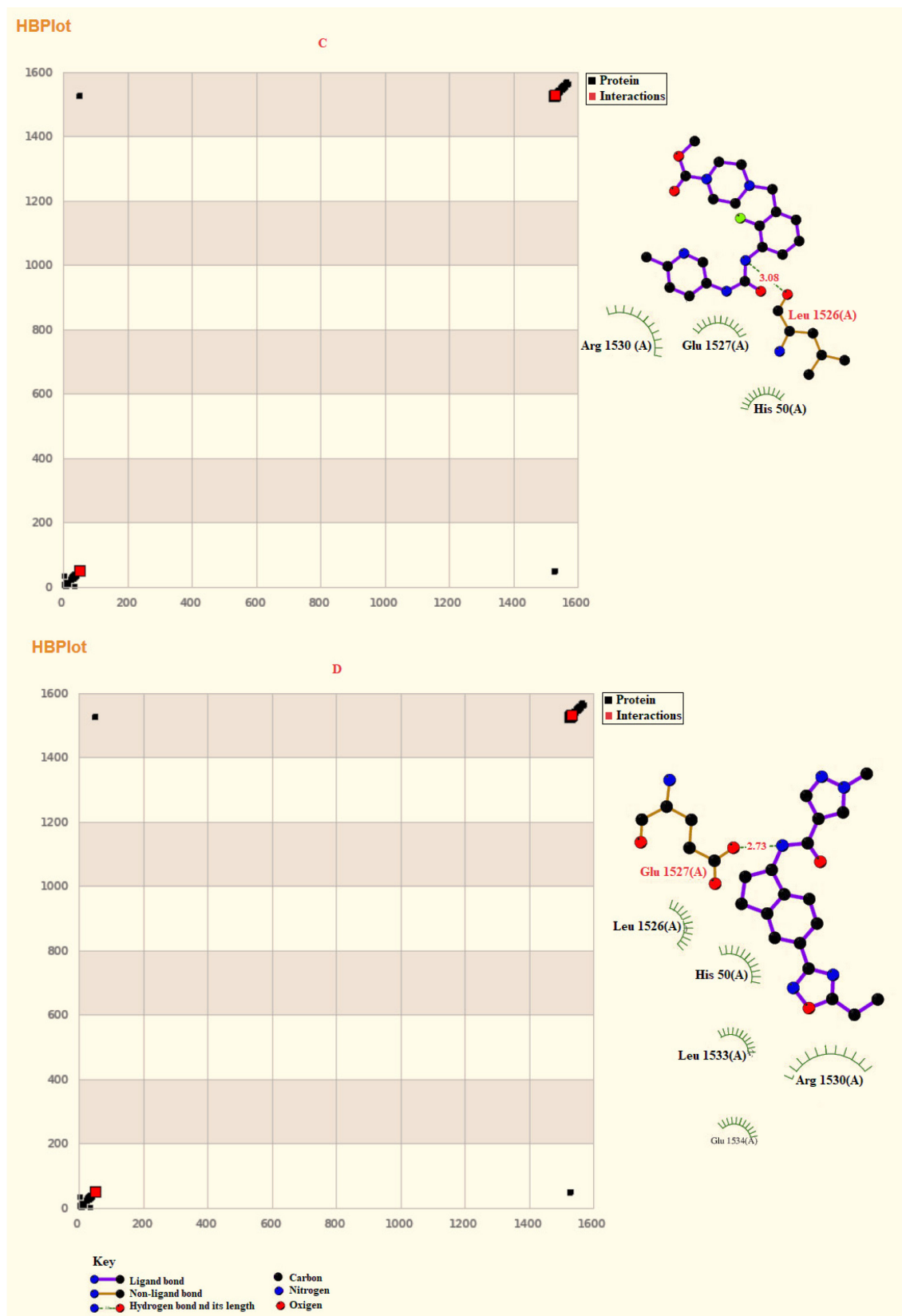


Figure 4. Coupling of omecantiv mecarbil (C) and aficamten (D) with the 5cj1 protein surface. Visualized with

DockingServer program. Source: Authors, 2026.

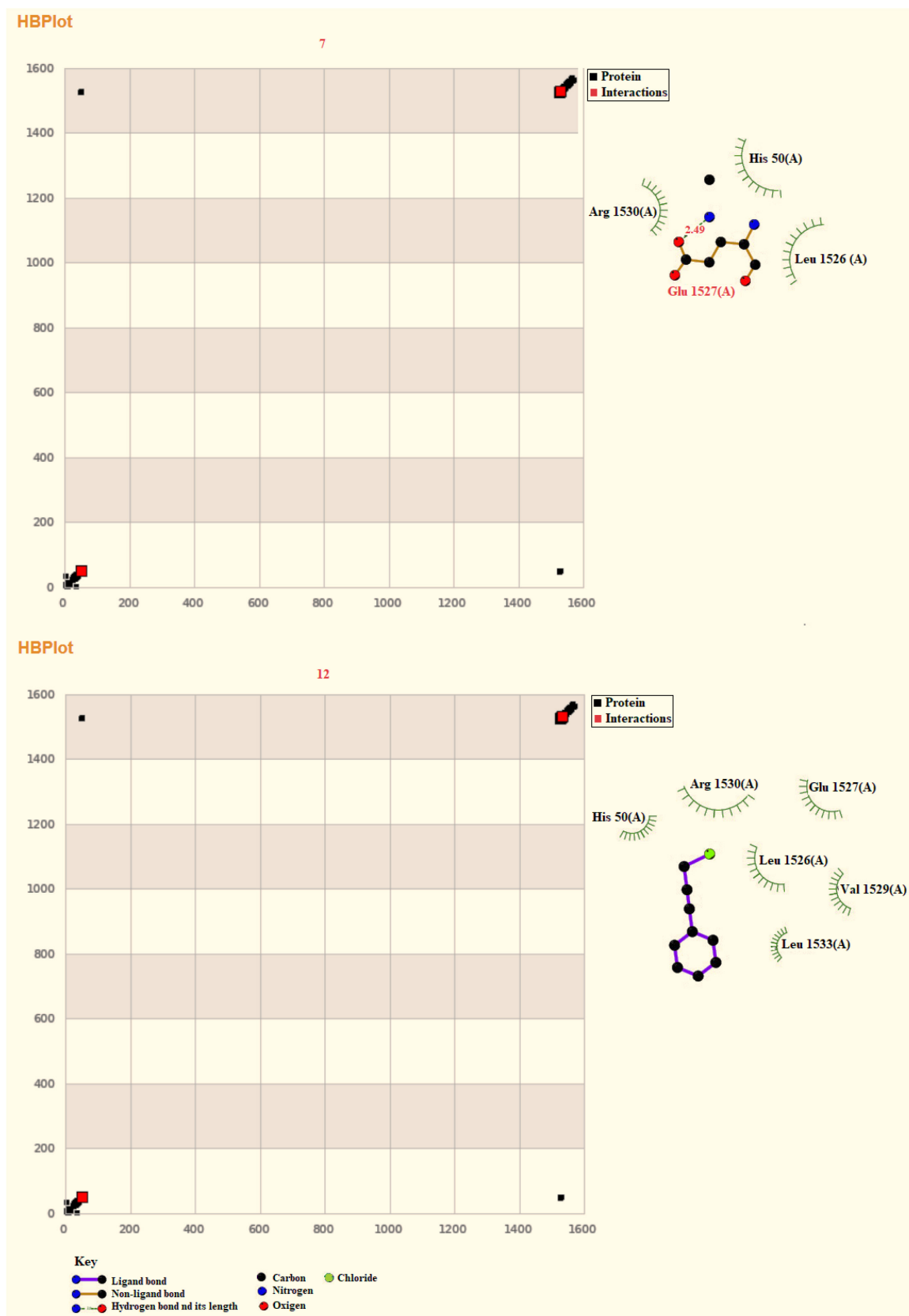


Figure 5. Coupling of alkyne derivatives 7 and 12 with the 5c1 protein surface. Visualized with DockingServer program. Source: Authors, 2026.

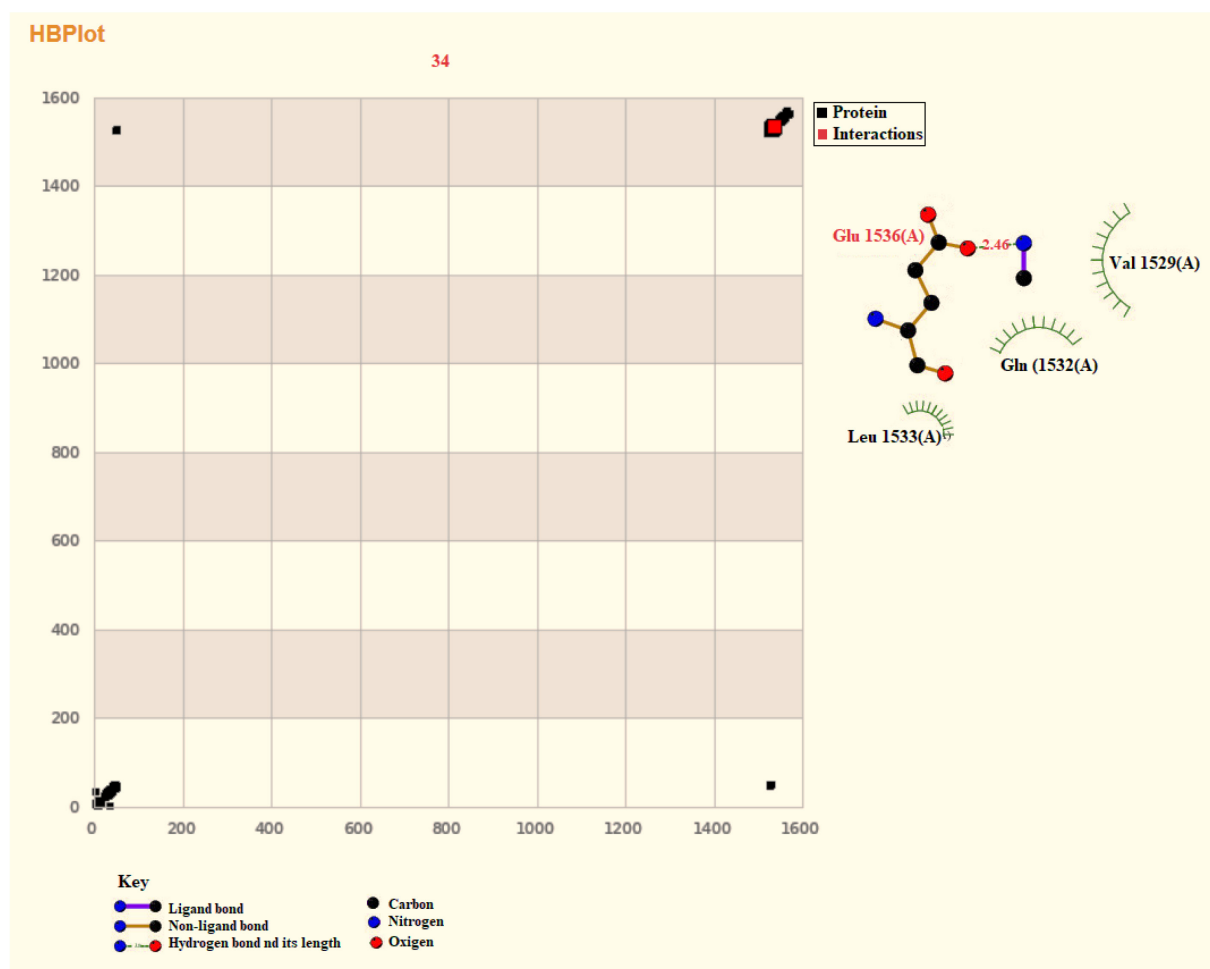


Figure 6. Interaction of alkyne derivative 34 with the 5c1 protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

3.6 Pharmacokinetics parameter

Table 6 shows some pharmacokinetic parameters for alkyne derivatives (7, 12, and 34) and the controls (blebbistatin, mavacamten, omecamtiv mecarbil, and aficamten). The results show that alkyne derivative 7 may have higher gastrointestinal absorption compared with compounds 12 and 34.

Table 6. Pharmacokinetic parameters for alkyne analogs (7, 12, and 34) and the controls.

Compound	GI absorption	BBB permeant	P-GP substrate	CYP1A 2 inhibitor	CYP2C1 9 inhibitor	CYP2C 9 inhibitor	CYP2D 6 inhibitor	CYP3A 4 inhibitor	Log P _{ow}
Blebbistatin	High	Yes	Yes	Yes	Yes	No	Yes	Yes	2.58
Mavacamten	High	No	No	No	No	No	No	No	2.18
Omecamtiv	High	No	Yes	No	No	No	No	No	1.9

mecarbil									9
Aficamten	High	No	Yes	Yes	Yes	Yes	Yes	Yes	2.31
7	High	No	No	No	No	No	No	No	0.63
12	Low	Yes	No	Yes	No	No	No	No	2.80
34	Low	No	No	No	No	No	No	No	0.08

Note: GI = Gastrointestinal; BBB = Blood-Brain Barrier; P-GP = P-Glycoprotein. Source: Authors, 2026.

3.7 Toxicity analysis

The results (Table 7) indicate differences in the degree of toxicity for alkyne analogs (7, 12, and 34) compared with the controls (blebbistatin, mavacamten, omecamtiv mecarbil, and aficamten).

Table 7. Toxicity degree produced by alkyne derivatives (7, 12, and 34) and controls through different pathways was determined using Gussar software.

Compound	Intraperitoneal (LD ₅₀)	Intravenous (LD ₅₀)	Oral (LD ₅₀)	Subcutaneous (LD ₅₀)
Blebbistatin	154.40	108.80	790.40	520.30
Mavacamten	392.90	70.58	1642.00	1121.00
Omecamtiv mecarbil	636.30	74.48	727.30	729.80
Aficamten	648.60	68.76	242.50	318.10
7	52.18	22.98	480.90	139.80
12	105.70	11.89	282.00	245.00
34	30.10	17.64	266.30	48.20

Source: Authors, 2026.

4. Discussion

4.1 Ligand-protein complex.

Hypertrophic cardiomyopathy is an inherited cardiovascular disease linked to mutations in several genes that encode proteins of the cardiac sarcomere (Garcia-Castro et al., 2009; Maron; Maron, 2013). For example, this clinical pathology has been associated with mutations in the MYH7 (Mori et al., 2021; Han et al., 2025), leading to the development of drugs that target this biomolecule. However, it is necessary to develop other types of drugs that can act on MYH7 to treat hypertrophic cardiomyopathy and improve the quality of life of patients. For this reason, in this study, the coupling of some alkyne derivatives on MYH7 was determined using the 5cj1 protein as a theoretical tool. Besides, some drugs such as blebbistatin, mavacamten, omecamtiv mecarbil, and aficamten were used as controls in a DockingServer program. The results indicate that the interactions of alkyne derivatives (1-35) with the 5cj1 protein surface involve differences in the number of amino acid residues compared to the controls. This phenomenon may be due to 1) the different chemical characteristics of the alkyne derivatives and 2) the different conformations adopted by each compound.

4.2 Root mean square deviation (RMSD)

RMSD is a tool used to compare different conformations adopted by identical or similar chemical compounds. It is important to mention that several methods exist for determining RMSD, such as pyRMSD (Gil and Guallar, 2013), VMD (Humphrey et al., 1996), and Gromacs (Berendsen et al., 1995), among others. In this study, the LigRMSD program was used, which employs two different comparison methods: 1) strict matching, which

considers identical types of atoms and bonds for comparison; and 2) flexible matching, which allows comparing pairs of atoms or bonds of different types (Valdés-Albuernes et al., 2024; Valdés-Albuernes et al., 2025). The RMSD results showed that a higher percentage of molecule matching indicates good similarity between the alkyne derivatives and the reference compound (propyne). However, it is important to mention that there are studies that suggest that the interaction of several compounds with some biomolecules to form the ligand-protein complex may be conditioned by different physicochemical parameters such as energy levels, the inhibition constant (K_i), and the type of binding (Raj et al., 2024; Kairys et al., 2024; Molani; Cho, 2024; Trezza et al., 2025).

4.3 Thermodynamic parameters and constant inhibition (K_i)

The ligand-protein complex formation has been associated with several thermodynamic factors, including binding free energy, vdW + H-bond + desolvation energy, electrostatic energy, and total intermolecular energy, among others (Lopez-Ramos et al., 2024; Güner-Yılmaz et al., 2025). For this reason, in this investigation, some thermodynamic factors involved in the interaction of alkyne derivatives with the 5cj1 protein surface were determined using the DockingServer program.

The results indicate that alkyne derivatives require higher free energy of binding compared with the controls; this phenomenon could condition the interaction of alkyne derivatives with the 5cj1 protein surface in comparison with the controls. Besides, the K_i values for alkyne derivatives (1-35) involved in the ligand-protein complex formation were higher compared with blebbistatin, mavacamten, omecamtiv mmacarbil, and aficamten drugs. However, the K_i values for alkyne derivatives 7, 12, and 34 were lower compared with compounds 1-6, 8-11, 13-33, and 35; these data suggest that compounds 7, 12, and 34 may have good affinity for the 5cj1 protein surface.

4.4 Type of bound

Several methods have been used to determine the types of bonds involved in the ligand-protein complex formation, such as AutoDock Vina (Azam et al., 2025), Biovia Discovery Studio (Zahra; Mahmood, 2025), SwissDock (Bugnon et al., 2024), and others. In this study, the type of binding for the ligand-protein complex formed between the alkyne and the 5cj1 protein was determined using the DockingServer program. The results showed that alkyne derivatives 7, 12, and 34 could interact with the amino acid residues Leu₁₅₂₆ and Val₁₅₂₉ involved in the surface of the 5cj1 protein through a hydrophobic bond. Other data indicate that compound 7 could interact with His₅₀ via a cation- π bond. Finally, alkyne derivative 7 could interact with the amino acid residue Gln₁₅₃₂ via a hydrophobic bond.

4.5 Pharmacokinetic parameters

The pharmacological response to a drug depends on pharmacokinetic factors (absorption, distribution, metabolism, and excretion), pharmacodynamic factors (e.g., interaction with some biomolecules), and others. In this way, some methods have been used to determine some pharmacokinetic parameters for several drugs (Chandrashekar; Rani, 2008; Lombardo et al., 2018; Lucas et al., 2019). For example, a study showed that PHARM is an interactive graphical program for individual and population pharmacokinetic parameters (Gomeni, 1984). Other data indicate that the PharmCalc program was used to determine some clinical pharmacokinetic parameters of methotrexate (Borsi, 1988).

Furthermore, the SwissADME program was used to predict some pharmacokinetic factors for sulfadiazine (Yusuf, 2025). Analyzing these data, in this study, some pharmacokinetic parameters were determined using the SwissADME program. The results showed that compounds 12 and 34 exhibit lower gastrointestinal absorption compared to the controls and compound 7. Further data indicate that compound 7 can interact with the Cyp1A2 isoenzyme. This phenomenon could produce changes in the biological activity of Cyp1A2.

4.6 Toxicology analysis

Several studies have been used to predict the toxicity of various drugs, such as ToxCast (Kim et al., 2025), ToxII (Ortiz-Andrader et al., 2020), Genetox (Mendez et al., 2025), Osiris (Srivastava, 2021), and Gussar (Askeroova, 2023). In this study, the toxicity degree for alkyne derivatives 7, 12, and 34 was determined using the Gussar program and compared with the toxicity data of the controls. The results indicate that the alkyne derivative 34 requires a lower dose via intraperitoneal, intravenous, and subcutaneous routes of administration to produce any toxicity degree compared to compounds 7, 12, and the controls. Other data showed that the aficamten drug requires

a lower dose to produce toxicity through the oral route of administration compared to the alkyne derivatives 7, 12, and 34.

5. Conclusions

In conclusion, the results suggest the following: 1) Alkyne derivatives 7, 12, and 34 have a higher affinity for the 5cjl protein compared to compounds 1-6, 8-11, 13-33, and 35. This phenomenon could be due to differences in the chemical structure of each alkyne derivative. These data suggest that compounds 7, 12, and 34 could act as MYH7 inhibitors, resulting in a reduction of hypertrophic cardiomyopathy in patients. Therefore, these compounds could be good candidates for further experimental evaluation using a hypertrophic cardiomyopathy model.

6. Authors' Contributions

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

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

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