

Physico-chemical properties analysis from the docking of some imidazole derivatives with the Ebola-viral matrix protein (VP40)

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Abstract

Ebola is a serious and often fatal viral disease; it is important to mention that some compounds, such as azaguanine-8, favipiravir, and galidesivir, have been used to control this clinical pathology; however, the results are very poor due to their limited effectiveness. This study aimed to determine the docking of imidazole derivatives (1-43) with the VP40 protein involved in the structure of the Ebola virus, using the 5B0V protein as a theoretical tool in the DockingServer program. In addition, imidazole, azaguanine-8, estradiol benzoate, favipiravir, galidesivir, clotrimazole, and *L*-tetrahydropalmatine were used as controls. The results showed differences in the docking of imidazole derivatives with amino acid residues involved in the 5B0V protein surface compared with the controls. Besides, the *K_i* values for compounds 23, 24, and 39 were lower compared with the controls. Other data indicate that the *K_i* values for imidazole derivatives 19 and 42 were lower than those of estradiol benzoate, favipiravir, galidesivir, *L*-tetrahydropalmatine, and imidazole. Besides, the *K_i* values for the compounds 3, 17, 19, 21, 34, and 37 were lower in comparison with *L*-tetrahydropalmatine and imidazole. Finally, the compound's *K_i* value for 13 was lower compared with imidazole; all this data suggests that compounds 3, 13, 17, 19, 21, 23, 24, 34, 37, 39, and 42 may have a good affinity for the 5B0V protein and could act as VP40 protein inhibitors.

Keywords: docking, imidazole derivatives, Ebola virus.

Análise das propriedades físico-químicas a partir do docking de alguns derivados de imidazol com a proteína de matriz viral do Ebola (VP40)

Resumo

O Ebola é uma doença viral grave e frequentemente fatal; é importante mencionar que alguns compostos, como a azaguanina-8, o favipiravir e o galidesivir, têm sido utilizados para controlar essa patologia clínica; no entanto, os resultados são muito insatisfatórios devido à eficácia limitada. O objetivo deste estudo foi determinar a interação de derivados de imidazol (1-43) com a proteína VP40, envolvida na estrutura do vírus Ebola, utilizando a proteína 5B0V como ferramenta teórica no programa DockingServer. Além disso, imidazol, azaguanina-8, benzoato de estradiol, favipiravir, galidesivir, clotrimazol e *L*-tetraidropalmatina foram utilizados como controles. Os resultados mostraram diferenças na interação dos derivados de imidazol com os resíduos de aminoácidos presentes na superfície da proteína 5B0V em comparação com os controles. Ademais, os valores de *K_i* para os compostos 23, 24 e 39 foram menores em comparação com os controles. Outros dados indicam que os valores de *K_i* para os

derivados de imidazol 19 e 42 foram menores do que os do benzoato de estradiol, favipiravir, galidesivir, *L*-tetrahidropalmatina e imidazol. Além disso, os valores de K_i para os compostos 3, 17, 19, 21, 34 e 37 foram menores em comparação com a *L*-tetrahidropalmatina e o imidazol. Finalmente, o valor de K_i do composto 13 foi menor em comparação com o imidazol. Todos esses dados sugerem que os compostos 3, 13, 17, 19, 21, 23, 24, 34, 37, 39 e 42 podem ter boa afinidade pela proteína 5B0V e poderiam atuar como inibidores da proteína VP40.

Palavras-chave: Acoplamento molecular, derivados de imidazol, vírus Ebola.

1. Introduction

Ebola is a viral disease that can be transmitted by direct contact with infected individuals through skin lesions or mucous membranes and some body fluids (Dietz et al., 2015; Judson et al., 2015; Osterholm et al., 2015). The incubation period (that is, the interval between infection and the onset of symptoms) ranges from two to 21 days (Chowell; Nishiura, 2014; Eichner et al., 2011; Malvy et al., 2019). It is important to mention that Ebola is caused by a virus of the Filoviridae family that is usually fatal in humans (Malvy, 2023; Ojo, 2025).

Some studies indicate that several proteins, such as VP35, VP40, the glycoprotein VP30, and VP24, are involved in the structure of the Ebola virus (Bharat et al., 2012; Jain et al., 2021; Lee; Saphire, 2009). It is important to mention that VP40 has a very important role in several biological functions of the viral cycle, such as the regulation of viral transcription, morphogenesis, packaging, and budding of mature virions (Johnson et al., 2006; Liu et al., 2010; Wu et al., 2022). It is worth noting that some studies have been carried out to try to inhibit the development of the Ebola virus in the host using different compounds that can act as VP40 inhibitors (Madara et al., 2025).

For example, a study showed that the compounds *N*-[(2-chlorophenyl)carbamoyl]-2-(3-methylquinoxalin-2-yl)sulfanyl-acetamide and *N*-[(3-fluoro-2-methyl-phenyl)carbamoyl]-2-(3-methylquinoxalin-2-yl)sulfanyl-acetamide can produce inhibitory activity on VP40 using a live recombinant vesicular stomatitis virus (VSV-M40 virus) that expresses the EBOV VP40 PPxY *L*-domain (Loughran et al., 2016). Another report indicates that the sangivamycin drug inhibits the participation of VP40 in the virus assembly process using an in vitro model (Bennet et al., 2020).

On the other hand, some theoretical studies have been conducted to evaluate the possibility that certain drugs may act as VP40 protein inhibitors. For example, a study that includes docking simulations and molecular dynamics shows that cystobactamide 919-1 and 2-hydroxysorangiadenosine may have an affinity for VP40, which could allow them to act as VP40 inhibitors in Ebola disease (Hayat et al., 2024). Other data showed the interaction of the vindesine drug with VP40 using the 3TCQ protein as a theoretical tool in the Autodock 2.0 program. The results showed that vindesine interacts with amino acid residue Gln₃₈ through a hydrogen bond (Khan et al., 2021).

Furthermore, a theoretical study shows the docking of some pyrimidine-2,4-dione derivatives with the amino acid residue Arg₁₃₄ involved on the 3TCQ protein surface through hydrogen bonds using Gromacs (El-Din et al., 2016). Other data indicate that the compound ((10R)-10-(4-hydroxyphenyl)-11,12,14,16-tetraazatracyclo[7.7.0.0^{2,7}.0^{11,15}]hexadeca-1(16),2(7),3,5,8, 12,14-heptaen-8-ol) could interact with the amino acid residue Gly126 involved in the 1H2C protein surface (Ebola virus matrix protein VP40 N-terminal domain in complex with RNA) through hydrogen bonds using the Autodock program (Odhar et al., 2019).

All these results indicate that several drugs have been used to treat Ebola virus disease through VP40 protein inhibition; however, it is necessary to design and develop new compounds to treat this clinical pathology. In this way, this study aimed to determine the docking of some hydantoin derivatives with VP40 of the Ebola virus using the 5B0V protein as a theoretical tool in the DockingServer program.

2. Materials and Methods

2.1 Imidazole derivatives

Figure 1 and Table 1 were used to determine their properties and the docking with the VP40 protein surface as follows:

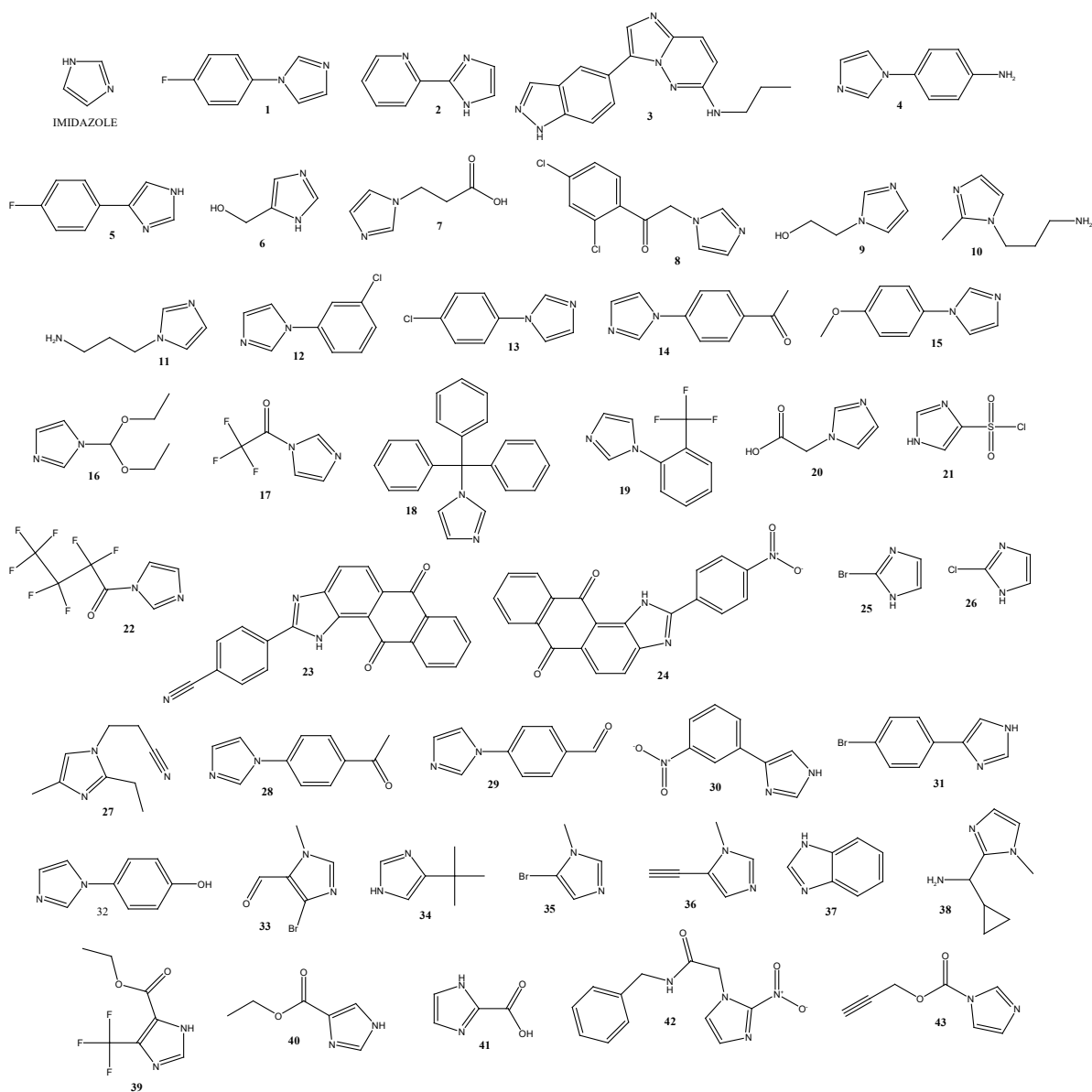

 Figure 1. Chemical structure of imidazole and its derivatives (1-43). Source: <https://pubchem.ncbi.nlm.nih.gov>.

Table 1. Name of imidazole derivatives (1-43).

Comp.	Name	Smile
1	1-(4-fluorophenyl)imidazole	<chem>Clc1ccc(cc1)n1cncc1</chem>
2	2-(1H-Imidazol-2-yl)pyridine	<chem>n1cccc1c1[NH]ccn1</chem>
3	3-(1H-indazol-5-yl)-N-propylimidazo[1,2-b]pyridazin-6-amine	<chem>CCCNc1ccc2ncc(n2n1)c1cc2cn[NH]c2cc1</chem>
4	4-(1H-Imidazol-1-yl)aniline	<chem>Nc1ccc(cc1)n1cncc1</chem>
5	4-(4-Fluorophenyl)-1H-imidazole	<chem>Fc1ccc(cc1)c1c[NH]cn1</chem>
6	(3H-Imidazol-4-yl)-methanol	<chem>OCC1[NH]cnc1</chem>
7	3-imidazol-1-yl-propionic acid	<chem>O=C(O)CCn1cncc1</chem>
8	1-(2,4-Dichlorobenzoylmethyl)imidazole	<chem>O=C(Cn1cncc1)c1ccc(Cl)cc1Cl</chem>
9	1-(2-Hydroxyethyl)imidazole	<chem>OCCn1cncc1</chem>

10	1-(3-Aminopropyl)-2-methyl-1H-imidazole	<chem>NCCCN1CCNC1C</chem>
11	1-(3-Aminopropyl)imidazole	<chem>NCCCN1CNC1</chem>
12	1-(3-chlorophenyl)imidazole	<chem>Clc1cc(ccc1)n1cnc1</chem>
13	1-(4-chlorophenyl)imidazole	<chem>Clc1ccc(cc1)n1cnc1</chem>
14	1-(4-Imidazol-1-yl-phenyl)-ethanone	<chem>O=C(C)c1ccc(cc1)n1cnc1</chem>
15	1-(4-Methoxyphenyl)-1H-imidazole	<chem>COc1ccc(cc1)n1cnc1</chem>
16	1-(Diethoxymethyl)imidazole	<chem>CCOC(OCC)n1cnc1</chem>
17	1-(Trifluoroacetyl)imidazole	<chem>FC(F)(F)C(=O)n1cnc1</chem>
18	1-(Triphenylmethyl)imidazole	<chem>c1cccc(c1)C(n1cnc1)(c1ccccc1)c1ccccc1</chem>
19	1-[2-(Trifluoromethyl)phenyl]imidazole	<chem>FC(F)(F)c1ccccc1n1cnc1</chem>
20	1H-Imidazol-1-ylacetic acid	<chem>OC(=O)Cn1cnc1</chem>
21	1H-Imidazole-4-sulfonyl chloride	<chem>O=S(=O)(Cl)c1nc[nH]c1</chem>
22	2,2,3,3,4,4,4-Heptafluoro-1-imidazol-1-yl-butan-1-one	<chem>FC(F)(C(=O)n1cnc1)C(F)(F)C(F)(F)F</chem>
23	2-(4-Cyanophenyl)-1H-anthra-[1,2-d]imida-zole-6,11-dione	<chem>O=C1c2c3[nH]c(nc3ccc2C(=O)c2ccccc12)c1ccc(cc1)C#N</chem>
24	2-(4-Nitrophenyl)-1H-anthra-[1,2-d]imida-zole-6,11-dione	<chem>[O-][N+](=O)c1ccc(cc1)c1[nH]c2c3C(=O)c4ccccc4C(=O)c3ccc2n1</chem>
25	2-Bromo-1H-imidazole	<chem>Brc1[nH]ccn1</chem>
26	2-Chloro-1H-imidazole	<chem>Clc1[nH]ccn1</chem>
27	2-Ethyl-4-methyl-1H-imidazole-1-propanenitrile	<chem>Cc1cn(CCC#N)c(CC)n1</chem>
28	1-(4-imidazol-1-ylphenyl)ethanone	<chem>CC(=O)C1=CC=C(C=C1)N2C=CN=C2</chem>
29	4-(1H-Imidazol-1-yl)benzaldehyde	<chem>O=Cc1ccc(cc1)n1cnc1</chem>
30	4-(3-Nitrophenyl)imidazole	<chem>[O-][N+](=O)c1cc(ccc1)c1c[nH]cn1</chem>
31	4-(4-Bromophenyl)-1H-imidazole	<chem>Brc1ccc(cc1)c1c[nH]cn1</chem>
32	4-(Imidazol-1-yl)phenol	<chem>Oc1ccc(cc1)n1cnc1</chem>
33	4-Bromo-1-methyl-1H-imidazole-5-carboxaldehyde	<chem>O=Cc1n(C)cnc1Br</chem>
34	4-tert-Butyl-1H-imidazole	<chem>CC(C)(C)c1nc[nH]c1</chem>
35	5-Bromo-1-methyl-1H-imidazole	<chem>Brc1cncn1C</chem>
36	5-Ethynyl-1-methyl-1H-imidazole	<chem>Cn1cnc1C#C</chem>
37	1H-Benzoimidazole	<chem>[nH]1cnc2ccccc12</chem>
38	Cyclopropyl(1-methyl-1H-imidazol-2-yl)me-thanamine	<chem>NC(c1nccn1C)C1CC1</chem>
39	Ethyl 4-(trifluoromethyl)-1H-imidazole-5-carboxylate	<chem>FC(F)(F)c1nc[nH]c1C(=O)OCC</chem>
40	Ethyl imidazole-4-carboxylate	<chem>O=C(OCC)c1nc[nH]c1</chem>
41	Imidazole-2-carboxylic acid	<chem>OC(=O)c1[nH]ccn1</chem>
42	N-Benzyl-2-nitro-1H-imidazole-1-acetamide	<chem>[O-][N+](=O)c1nccn1CC(=O)NCc1ccccc1</chem>
43	Propargyl 1H-imidazole-1-carboxylate	<chem>O=C(OCC#C)n1cnc1</chem>

Source: Authors, 2026.

2.2 Physicochemical properties

2.2.1 Physicochemical parameters

Physicochemical factors such as molar volume (MV) and molar refraction (MR) were calculated using ACD/ChemSketch software. This program is a tool for determining some physicochemical properties (Hadaji et al., 2018; Laxmi, 2017; Mortate et al., 2026).

2.2.2 Electronic parameters

The following electronic factors, such as HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) energy, and HBD (hydrogen bond donor groups) and HBA (hydrogen bond acceptor groups) using the Spartan'06 software. This program is computational molecular and chemical modeling software that allows calculations and analysis of chemical properties of different molecules (Bello et al., 2020; Kunduracioğlu, 2021; Ucak-Astarlioglu et al., 2017).

2.2.3 Pharmacophore model

LigandScout software was used to design some pharmacophore models for imidazole derivatives. This computer program allows the creation of three-dimensional pharmacophore models from the chemical structure of different molecules (Doijen et al., 2025; Habib et al., 2025; Hasyim et al., 2025).

2.2.4 Ligand-protein complex

The docking of imidazole derivatives (1-43) with the VP40 protein surface (Figure 2) was determined using the 5B0V protein as a theoretical tool (<https://doi.org/10.2210/pdb5B0V/pdb>), whose dimer crystal structure was determined by X-ray diffraction with a resolution of 281 Å (Zhu et al., 2017). It is important to mention that the coupling of the imidazole derivatives to the 5B0V occurred at the A chain (Figure 2).



Figure 2. The scheme shows the 5B0V protein. *Source:* <https://www.rcsb.org>.

On the other hand, imidazole, azaguanine-8, estradiol benzoate, favipiravir, galidesivir, clotrimazole, and *L*-tetrahydropalmatine drugs were used as controls in the DockingServer program (<https://www.dockingserver.com/web>). DockingServer is a program that is used to determine the site, geometry, and energy of molecules interacting with proteins. Besides, DockingServer offers an easy way to compute ligand-protein interactions or virtual high-throughput screening calculations and is used to calculate other types of compounds (Bikadi, 2009; Jacob et al., 2012; Lopez-Ramos et al., 2024).

It is important to mention that the MMFF94 force field (Halgren, 1998) was used for energy minimization of the ligand molecule (2-(1*H*-imidazol-2-yl)pyridine) using DockingServer. Besides, essential hydrogen atoms, Kollman united atom type charges, solvation parameters, and the Affinity (grid) maps were generated using the Autogrid program (Morris; Goodsell, 1998). In addition, AutoDock parameter set- and distance-dependent dielectric functions were used to determine the van der Waals force and the electrostatic factors. Besides, docking

simulations were performed using the Lamarckian genetic algorithm and the Solis & Wets method (Solis; West, 1981). It is noteworthy that the initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. 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.

2.2.5 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 (Velázquez-Libera et al., 2020).

2.3 Pharmacokinetic analysis

Pharmacokinetic parameters for imidazole derivatives (3, 13, 17, 19, 21, 22, 23, 24, 34, 37, 39 and 42) were determined using the SwissADME software and ADMETlab 3.0. 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).

2.4 Toxicology analysis

The toxicity level of imidazole derivatives (3, 13, 17, 19, 21, 22, 23, 24, 34, 37, 39 and 42) 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 (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 Physicochemical and electronic parameters

There are studies indicating that the HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital), and HOMO-LUMO gap have been associated with the biological activity of some compounds. In this way, a study showed that suggests an association between the HOMO-LUMO gap (3.5 eV) and the antineurotoxic activity produced by the compound (*E*)-1-{3,5-Bis[(*E*)-3-(4-hydroxy-3-methoxyphenyl) acryloyl]-phenyl}-3-(4-hydroxy-3-methoxyphenyl)-2-propenone (Jun et al., 2017). Other data suggest that the LUMO value (-0.95) for the compound 2,5-dimethyl-4-(20,40,6'-trimethylbi-phenyl-4-yl)thiazole could be related to its antibacterial and antifungal activity (Reddy et al., 2016). All this data suggests that HOMO, LUMO, and HOMO-LUMO gap could condition the biological activity of different molecules; for this reason, in this study, HOMO, LUMO, and HOMO-LUMO gap were determined using Spartan'06 software.

Table 2 and Figures 3-6 show that the HOMO-LUMO gap was lower for imidazole derivative 24 compared with compounds 1-23 and 25-43; this data indicates that compound 24 may be more reactive in comparison with 1-23 and 25-43. However, it was necessary to determine other molecular descriptors such as molar refractivity (MR) and molar volume (VM) using ChemSketch software. It is noteworthy that these parameters constitute a useful tool to correlate different physicochemical properties that depend on the characteristics of the substituents attached to a constant reaction center. The results showed that both MR (101.28 ± 0.5 cm³) and MV (293.5 ± 7.0 cm³) values were higher for imidazole derivative 18 compared to compounds 1-17 and 19-43. These data suggest that steric hindrance, conformational preferences, and internal rotation related to the chemical characteristics of compound 18 may influence its affinity for the VP40 protein.

Table 2. Physicochemical parameters for imidazole derivatives (1-43).

Comp.	HOMO (eV)	LUMO (eV)	HOMO- LUMO gap	Molar Refractivity (cm ³)	Molar Volume (cm ³)	Surface tension (dyne/cm ⁻¹)	Dipole moment (Debye)
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1	-8.72	2.90	11.62	50.53 ± 0.5	145.1 ± 7.0	44.5 ± 7.0	2.26
2	-8.06	2.59	10.65	41.46 ± 0.3	119.4 ± 3.0	57.1 ± 3.0	2.40
3	-7.59	2.13	9.72	82.12 ± 0.5	209.6 ± 7.0	57.9 ± 7.0	3.65
4	-7.84	3.37	11.21	47.84 ± 0.5	132.6 ± 7.0	50.3 ± 7.0	5.48
5	-7.82	3.37	11.19	43.36 ± 0.3	130.4 ± 3.0	46.9 ± 3.0	5.80
6	-8.38	5.32	13.70	25.22 ± 0.3	74.7 ± 3.0	67.7 ± 3.0	4.58
7	-8.79	4.41	13.20	36.35 ± 0.5	110.5 ± 7.0	51.7 ± 7.0	3.72
8	-8.68	1.75	10.43	65.20 ± 0.5	184.0 ± 7.0	48.8 ± 7.0	6.10
9	-8.77	4.95	13.72	30.89 ± 0.5	96.9 ± 7.0	45.7 ± 7.0	2.91
10	-8.25	5.16	13.41	40.99 ± 0.5	127.9 ± 7.0	40.7 ± 7.0	4.85
11	-8.59	5.13	13.72	35.56 ± 0.5	112.6 ± 7.0	45.3 ± 7.0	5.57
12	-8.82	2.65	11.47	50.53 ± 0.5	145.1 ± 7.0	44.5 ± 7.0	2.75
13	-8.75	2.61	11.36	50.53 ± 0.5	145.1 ± 7.0	44.5 ± 7.0	2.15
14	-8.83	1.86	10.69	55.81 ± 0.5	164.5 ± 7.0	43.0 ± 7.0	2.09
15	-8.24	3.21	11.45	51.74 ± 0.5	157.6 ± 7.0	40.0 ± 7.0	5.15
16	-8.86	4.72	13.58	46.28 ± 0.5	159.5 ± 7.0	34.1 ± 7.0	3.45
17	-9.69	1.29	10.98	31.04 ± 0.5	111.2 ± 7.0	33.4 ± 7.0	1.58
18	-8.36	2.98	11.34	101.28 ± 0.5	293.5 ± 7.0	43.4 ± 7.0	4.62
19	-8.82	2.16	10.98	50.68 ± 0.5	166.1 ± 7.0	33.6 ± 7.0	5.49
20	-8.81	4.18	12.99	31.74 ± 0.5	94.3 ± 7.0	55.8 ± 7.0	4.92
21	-10.06	2.60	12.66	32.12 ± 0.4	97.6 ± 3.0	66.7 ± 3.0	7.61
22	-9.62	1.33	10.95	40.80 ± 0.5	166.0 ± 7.0	26.0 ± 7.0	1.83
23	-8.65	0.14	8.79	97.45 ± 0.4	231.8 ± 5.0	91.0 ± 5.0	4.90
24	-8.95	-0.52	8.43	100.17 ± 0.3	241.8 ± 3.0	81.0 ± 3.0	6.95
25	-8.76	4.69	13.45	26.46 ± 0.3	77.1 ± 3.0	56.4 ± 3.0	4.09
26	-8.94	4.70	13.64	23.67 ± 0.3	72.9 ± 3.0	53.1 ± 3.0	4.27
27	-8.38	4.66	13.04	50.02 ± 0.5	159.4 ± 7.0	36.9 ± 7.0	0.79
28	-8.84	1.86	10.70	55.81 ± 0.5	164.5 ± 7.0	43.0 ± 7.0	4.18
29	-8.91	1.69	10.60	51.39 ± 0.5	149.2 ± 7.0	46.7 ± 7.0	3.45
30	-8.46	0.37	8.83	49.91 ± 0.3	138.1 ± 3.0	63.5 ± 3.0	10.59
31	-7.82	3.07	10.89	51.05 ± 0.3	142.4 ± 3.0	53.2 ± 3.0	5.84
32	-8.30	3.13	11.43	46.78 ± 0.5	133.1 ± 7.0	48.7 ± 7.0	3.54
33	-9.21	2.16	11.37	38.26 ± 0.5	108.7 ± 7.0	49.3 ± 7.0	2.71
34	-8.47	5.30	13.77	37.16 ± 0.3	127.6 ± 3.0	34.3 ± 3.0	3.73
35	-8.57	4.69	13.26	32.80 ± 0.5	95.1 ± 7.0	43.2 ± 7.0	3.88
36	-8.39	3.60	11.99	34.28 ± 0.5	113.9 ± 7.0	31.4 ± 7.0	4.09
37	-8.31	3.30	11.61	36.61 ± 0.3	95.0 ± 0.3	60.1 ± 3.0	3.69
38	-8.46	4.92	13.38	43.05 ± 0.5	115.5 ± 7.0	49.8 ± 7.0	3.91
39	-10.16	1.95	12.11	40.16 ± 0.3	148.8 ± 3.0	35.2 ± 3.0	4.45
40	-9.26	3.54	12.80	35.18 ± 0.3	115.3 ± 3.0	49.2 ± 3.0	6.24
41	-9.43	2.63	12.06	25.70 ± 0.3	73.5 ± 3.0	84.9 ± 3.0	5.36
42	-9.63	-0.01	9.62	69.32 ± 0.5	191.6 ± 7.0	59.7 ± 7.0	9.27

43	-9.19	3.04	12.23	41.31 ± 0.5	135.0 ± 7.0	40.6 ± 7.0	3.11
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Source: Authors, 2026.

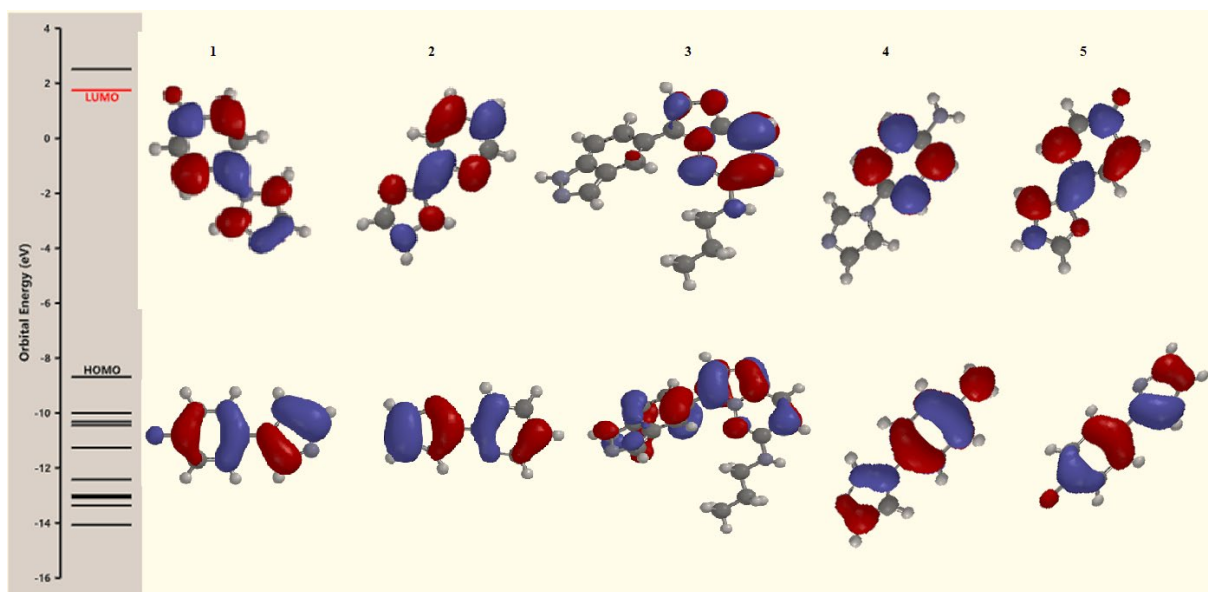


Figure 3. Molecular orbitals (HOMO and LUMO) for compounds 1-5: Visualized with Spartan'06 software. Source: Authors, 2026.

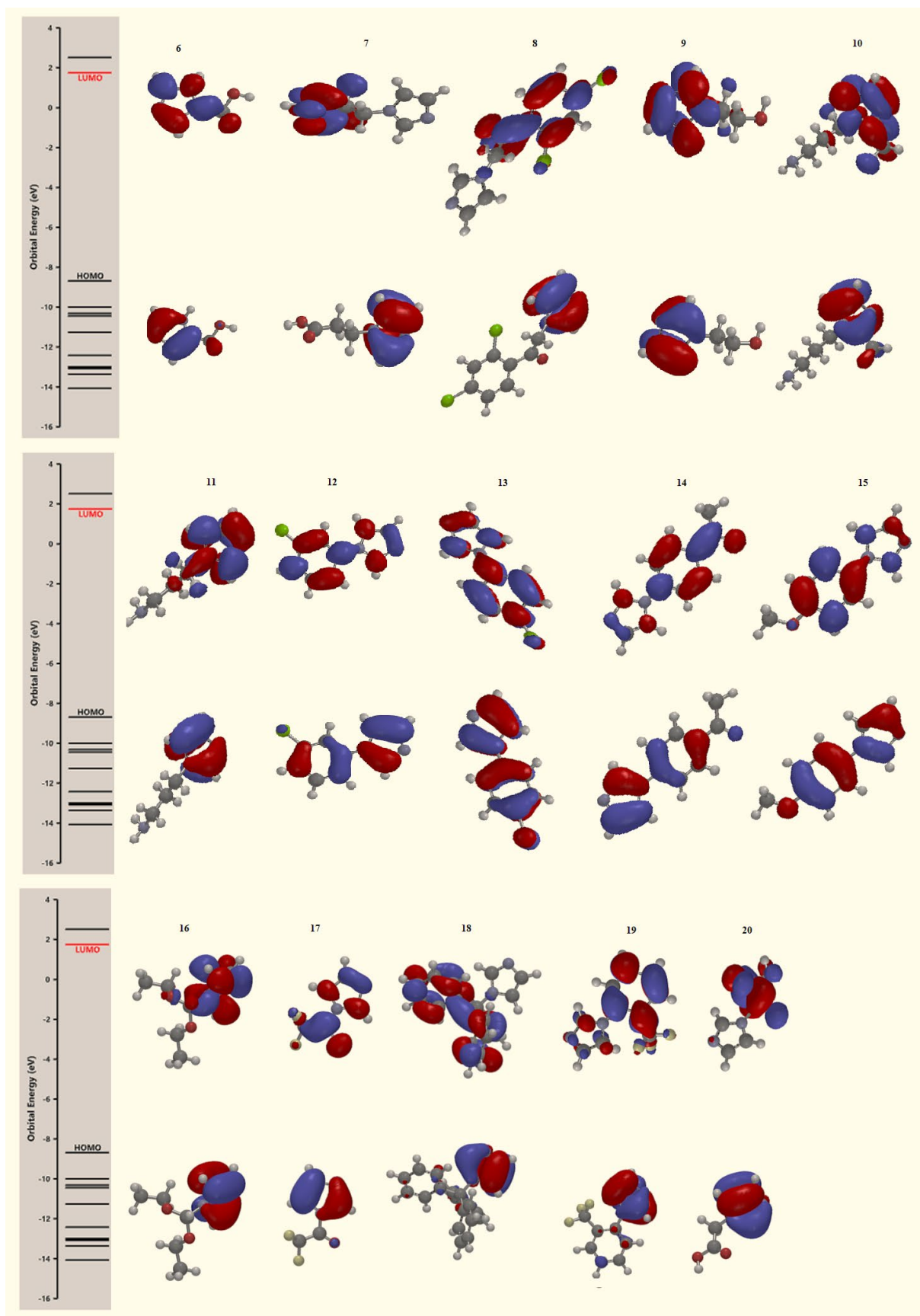


Figure 4. Molecular orbitals (HOMO and LUMO) for compounds 6-20. Visualized with Spartan'06 software. Source: Authors, 2026.

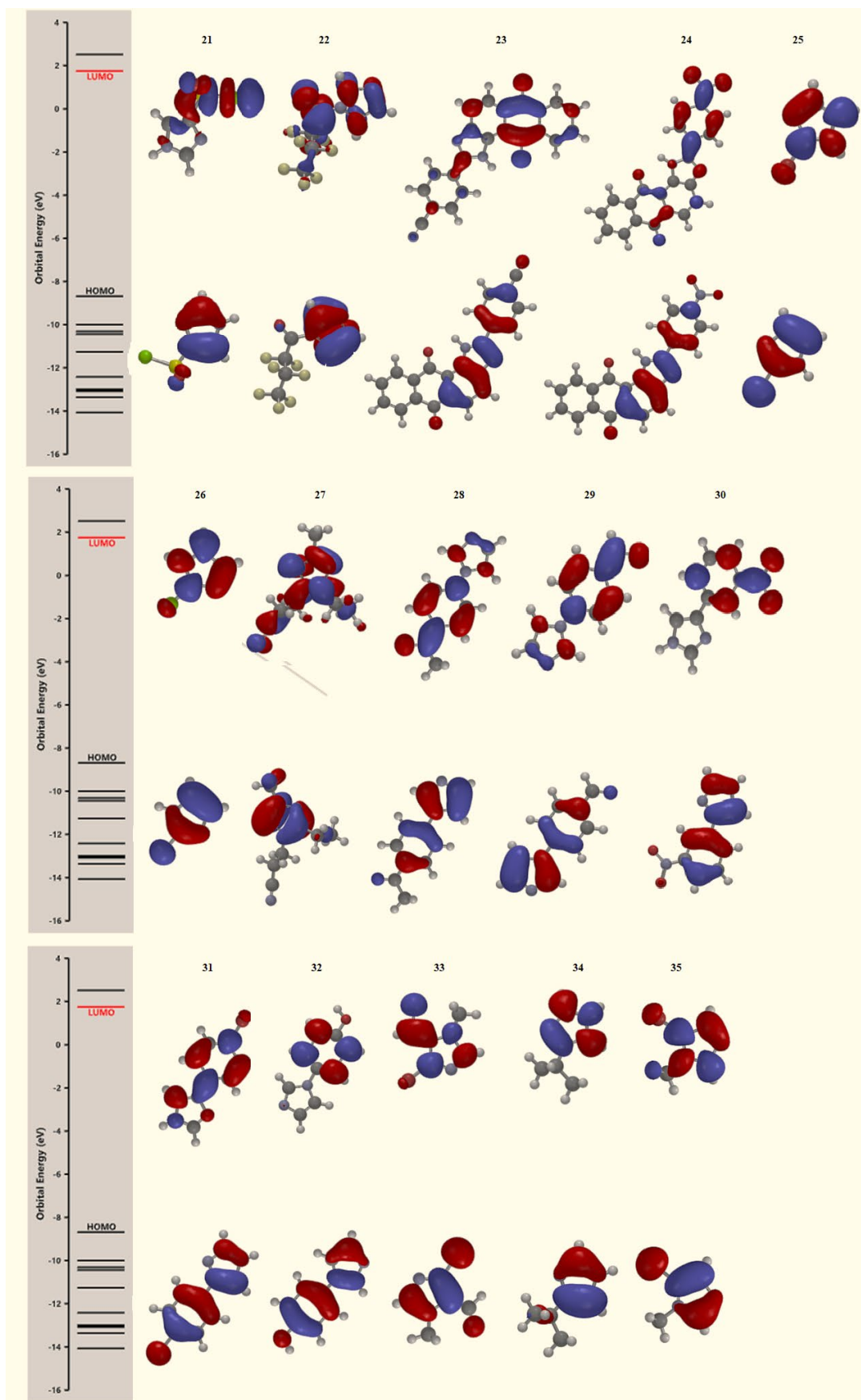


Figure 5. HOMO and LUMO for compounds 21-35. Visualized with the Spartan'06 program. Source: Authors, 2026.

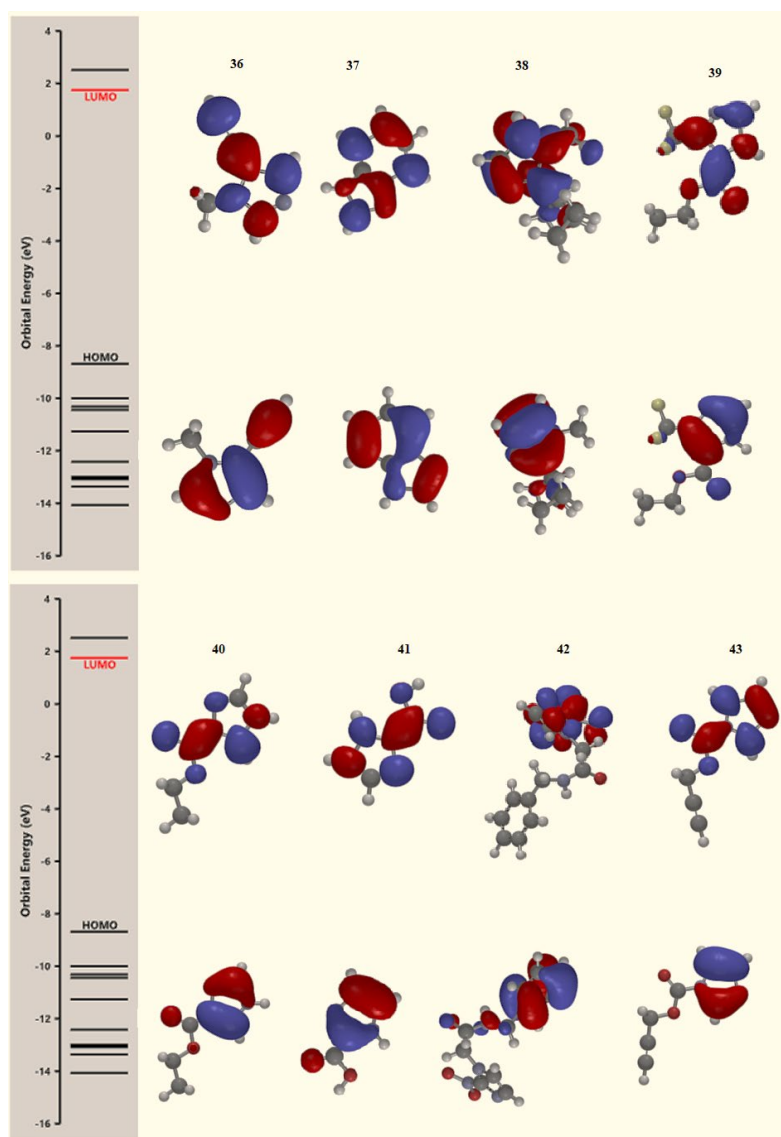


Figure 6. HOMO and LUMO for compounds 36-43. Visualized with Spartan'06 software. Source: Authors, 2026.

3.2 Pharmacophores design

Some studies have been carried out to design several pharmacophore models to predict the biological activity of different compounds such as Hip-Hop (Fu et al., 2017), GASP (Pajeva; Wiese, 2022), SLATE (De Esch et al., 2001), Disco (Patel et al., 2002), and others. In this study, the LigandScout 4.5 software was used to design different pharmacophore models for imidazole derivatives. It is important to mention that LigandScout is a program that allows you to design three-dimensional models of pharmacophores from different compounds to characterize some of their chemical properties, such as hydrogen bond donors, acceptors, lipophilic areas, and positively and negatively ionizable chemical groups, which may be used to predict interactions of imidazole derivatives with the VP40 protein.

The results (Figure 7-10) showed differences in the types of hydrogen bond donors and acceptors, lipophilic areas, and positively and negatively ionizable chemical groups for different imidazole derivatives. These chemical characteristics involved in each compound could condition the docking of imidazole derivatives with the VP40 protein.

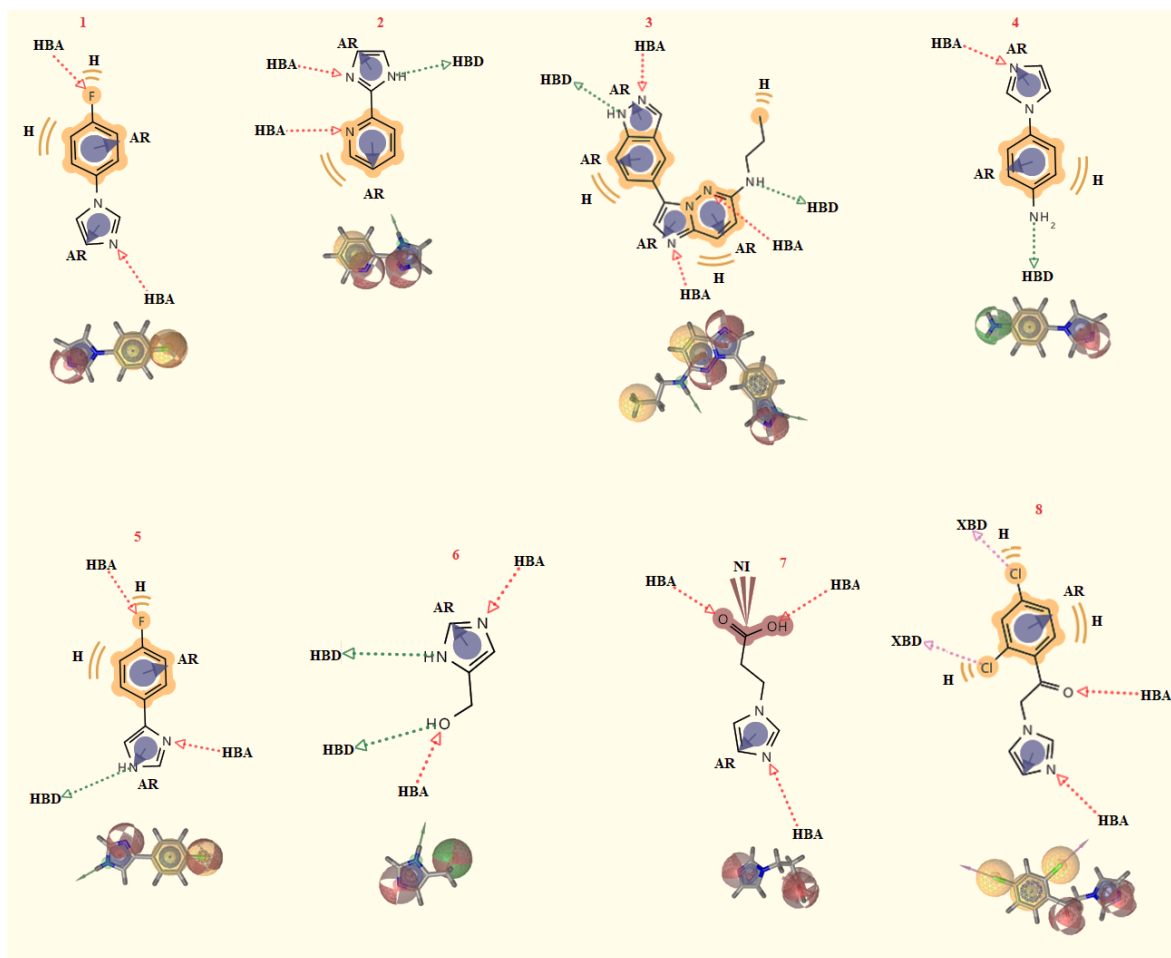


Figure 7. Pharmacophore model from imidazole derivatives 1-8. Hydrogen bond acceptors (HBA, red), hydrogen bond donors (HBD, green), halogen bond donors (XBD, pink), and negatively ionizable (NI) and positively ionizable (PI). Visualized with LigandScout Software 4.5. Source: Authors, 2026.

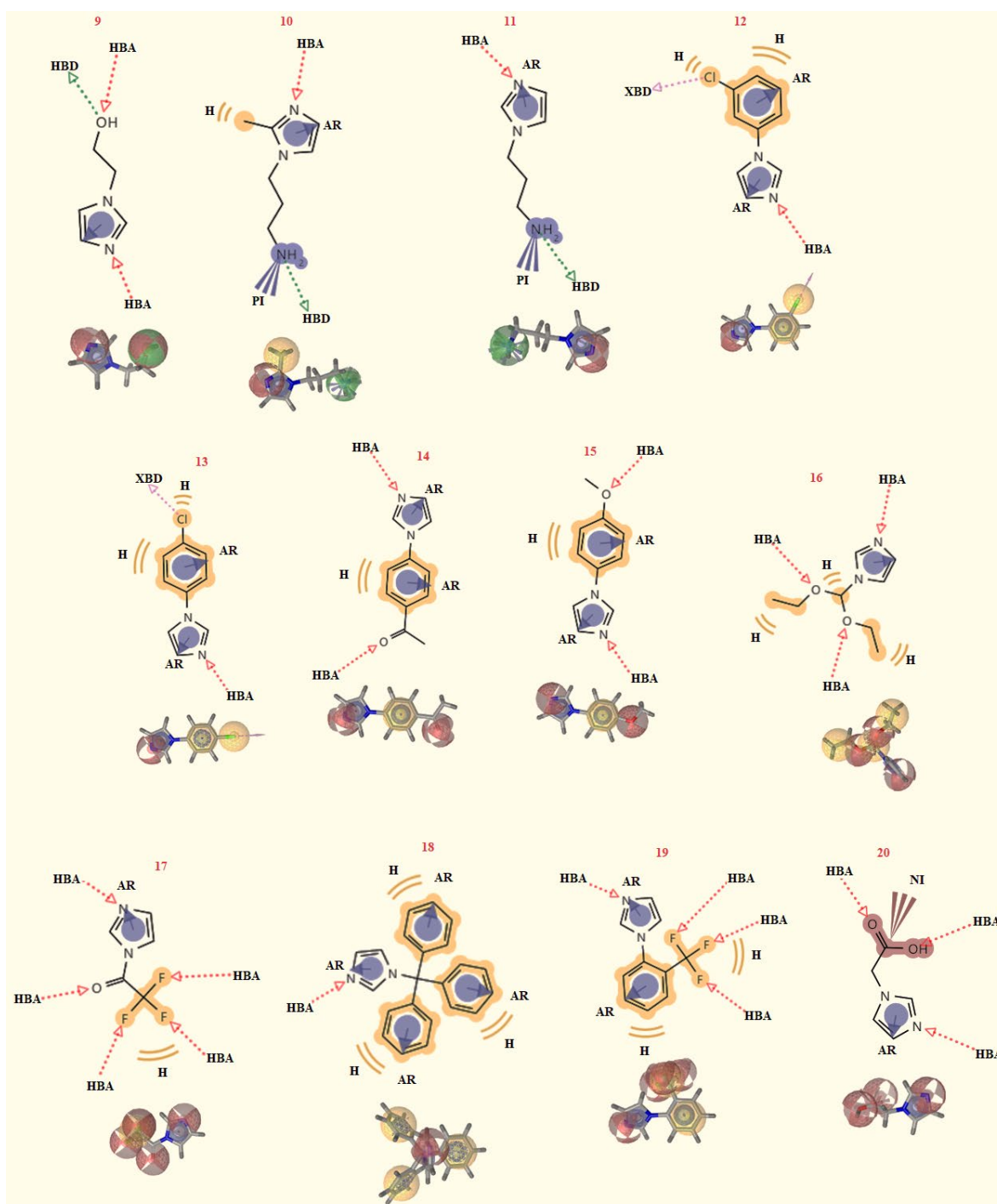


Figure 8. Development of a pharmacophore from imidazol analogs 9-20. Visualized using LogandScout 4.5 software. Hydrogen bond acceptors (HBA, red), hydrogen bond donors (HBD, green), halogen bond donors (XBD, pink), and negatively ionizable (NI). Source: Authors, 2026.

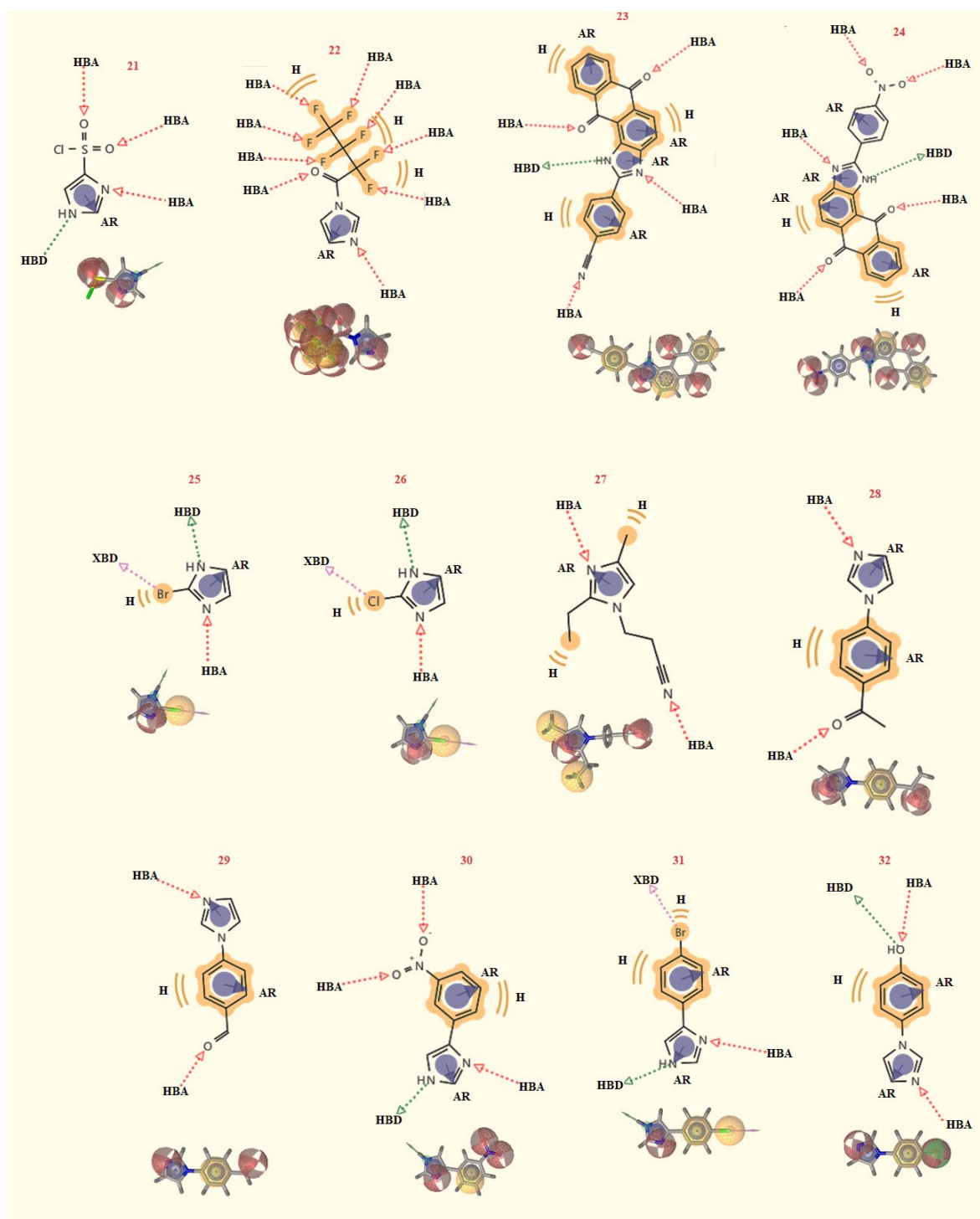


Figure 9. Design of a pharmacophore from imidazol analogs 21-32. software. Hydrogen bond acceptors (HBA, red), hydrogen bond donors (HBD, green), and halogen bond donors (XBD, pink). Visualized using LogandScout 4.5. Source: Authors, 2026.

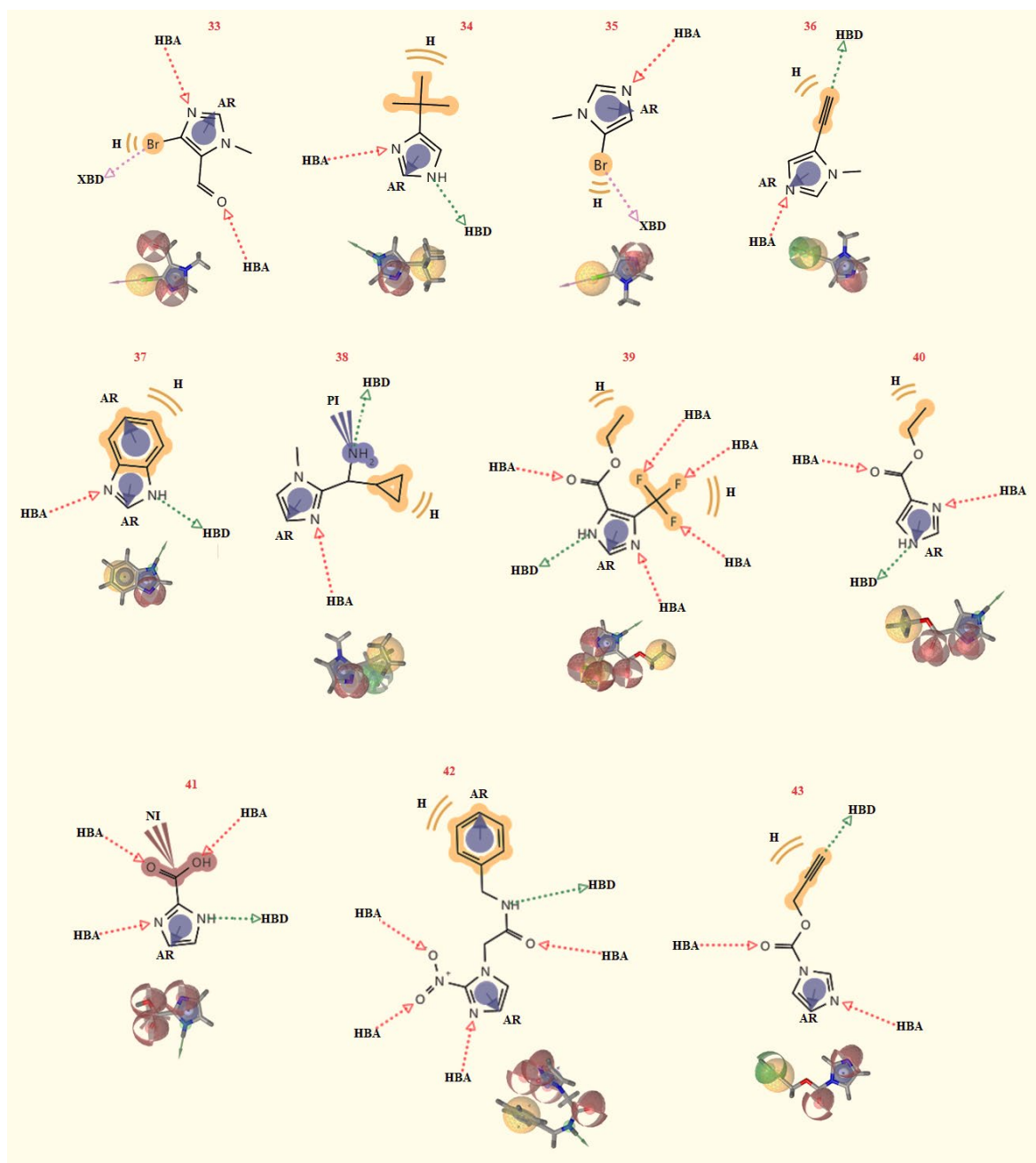


Figure 10. Pharmacophore model from imidazol derivatives 33-43. Hydrogen bond acceptors (HBA, red), hydrogen bond donors (HBD, green), halogen bond donors (XBD, pink), and positively ionizable (PI). Visualized with LigandScout Software 4.5. Source: Authors, 2026.

3.3 Ligand-protein complex

For several years, different studies have been used to determine the docking of some compounds with the VP40 protein (Mirza; Ikram, 2016; Siddiquee et al., 2014; Tamilvanan; Hopper, 2013). For example, one study showed that epiexcelsin may interact with the amino acid residues Phe₁₂₅ and Arg₁₃₄ involved in the protein 1H2C (Ebola virus, matrix protein VP40, N-terminal domain in complex with RNA) using the Autodock program (Abd Halim, 2020). Another report indicates compound 96 (ZINC ID: 1338855; 3-methyl-N-[3-[[2-[[4-methyl-5-(3-pyridyl)-1,2,4-triazol-3-yl]sulfanyl]acetyl]amino]phenyl] benzamide) interacts with Arg₁₃₄ involved in the 1H2C protein surface through hydrogen bonds using Autodock software (Abd Halim, 2020).

Finally, a study displayed the docking of sorbitol and mannitol with the VP40 protein surface involving some amino acid residues such as Thr₁₂₃, His₁₂₄, and Thr₁₇₃ (Nagarajan et al., 2019). All these studies indicate that some compounds could inhibit the biological activity of the VP40 protein; however, there is little information about the interaction of imidazole derivatives with the VP40 protein. For this reason, in this study, the docking of some imidazole derivatives with the VP40 protein surface was determined using the 5B0V protein as a theoretical tool in the DockingServer program. It is important to mention that compounds such as imidazole, azaguanine-8, estradiol benzoate, favipiravir, galidesivir, clotrimazole, and *L*-tetrahydropalmatine were used as controls. The results showed differences in the number of amino acid residues involved in the docking of imidazole with the 5B0V protein compared with the controls (Table 3). This phenomenon may be due to the different type of conformation adopted by each molecule.

Table 3. Amino acid residues involved in the coupling of imidazole derivatives (1-43) with the 5b0v protein surface.

Compounds	Aminoacid residues
Azaguanine-8	His ₅₉ ; Phe ₆₁ ; Ser ₉₀ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄
Estradiol benzoate	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈ ; Ser ₃₀₁
Favipiravir	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
Galidesivir	Phe ₉₂ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₁₈₆ ; Ile ₁₈₇ ; Asn ₂₉₇ ; Pro ₂₉₈ ; Thr ₂₉₉
Clotrimazole	Ile ₈₈ ; Glu ₉₃ ; Pro ₁₃₄ ; Arg ₁₃₆ ; Arg ₁₈₀ ; Ala ₂₉₆ ; Pro ₂₉₈ ; Ser ₃₀₁
<i>L</i> -Tetrahydropalmatine	Ile ₈₈ ; Arg ₁₃₆ ; Arg ₁₈₀ ; Glu ₉₃ ; Pro ₁₃₄ ; Arg ₁₃₆ ; Arg ₁₈₀ ; Ala ₂₉₆ ; Pro ₂₉₈ ; Ser ₃₀₁
Imidazole	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Leu ₉₆
1	Trp ₁₇₉ ; Arg ₁₈₀ ; Pro ₁₈₁ ; Val ₂₀₅ ; Val ₂₀₇₃ ; Tyr ₂₇₄ ; Ala ₂₉₆
2	Asn ₉₁ ; Glu ₉₃ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅
3	Phe ₉₂ ; Glu ₉₃ ; Tyr ₉₄ ; Pro ₉₅ ; Leu ₁₈₆ ; Ile ₁₈₇ ; Pro ₂₉₈ ; Thr ₂₉₉
4	Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅
5	Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅
6	Ser ₉₀ ; Glu ₉₃ ; Tyr ₉₄ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀
7	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Leu ₉₆ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
8	Leu ₈₆ ; Ile ₈₈ ; Pro ₁₃₄ ; Arg ₁₈₀ ; Val ₂₀₅ ; Pro ₂₉₈
9	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉
10	Phe ₆₁ ; Ile ₈₈ ; Ser ₉₀ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀
11	Phe ₆₁ ; Ile ₈₈ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀
12	Ile ₈₈ ; Leu ₁₇₄ ; Trp ₁₇₉ ; Arg ₁₈₀ ; Val ₂₀₅ ; Val ₂₇₃ ; Tyr ₂₇₄
13	Phe ₆₁ ; Ile ₈₈ ; Ser ₉₀ ; Glu ₉₃ ; Tyr ₉₄ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈
14	Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Leu ₉₆ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈
15	Ile ₈₈ ; Glu ₉₃ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈
16	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
17	His ₅₉ ; Phe ₆₁ ; Ser ₉₀ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄
18	Phe ₉₂ ; Tyr ₉₄ ; Pro ₉₅ ; Ala ₁₃₂ ; Lys ₁₃₂
19	His ₅₉ ; Phe ₆₁ ; Ile ₈₈ ; Ser ₉₀ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Pro ₉₅ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
20	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃
21	His ₅₉ ; Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
22	Leu ₈₆ ; Ile ₈₈ ; Pro ₁₃₄ ; Arg ₁₃₆ ; Arg ₁₈₀ ; Pro ₂₉₈

23	Phe ₆₁ ; Ile ₈₈ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈ ; Ser ₃₀₁
24	Phe ₆₁ ; Ile ₈₈ ; Ser ₉₀ ; Glu ₉₃ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Val ₂₀₅ ; Pro ₂₉₈ ; Ser ₃₀₁
25	Leu ₁₇₄ ; Trp ₁₇₉ ; Arg ₁₈₀ ; Pro ₁₈₁ ; Val ₂₇₃ ; Tyr ₂₇₄
26	His ₅₉ ; Phe ₆₁ ; Ser ₉₀ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆
27	Phe ₆₁ ; Glu ₉₃ ; Pro ₁₃₄ ; Ile ₁₈₇ ; Asn ₂₉₇ ; Pro ₂₉₈ ; Thr ₂₉₉
28	Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈
29	Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Arg ₁₈₀ ; Pro ₂₉₈
30	Arg ₁₈₀ ; Pro ₁₈₁ ; Val ₂₀₅ ; Val ₂₇₃ ; Tyr ₂₇₄ ; Pro ₂₉₈
31	Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅
32	Trp ₁₇₉ ; Arg ₁₈₀ ; Pro ₁₈₁ ; Ile ₂₀₄ ; Val ₂₇₃ ; Tyr ₂₇₄
33	Phe ₆₁ ; Ile ₈₈ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
34	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄ ; Leu ₁₃₅
35	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉
36	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃
37	Phe ₉₂ ; Glu ₉₃ ; Tyr ₉₄ ; Pro ₁₃₄ ; Leu ₁₃₅ ; Ile ₁₈₇ ; Pro ₂₉₈
38	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄
39	His ₅₉ ; Phe ₆₁ ; Ser ₉₀ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; Pro ₁₃₄ ; Leu ₁₃₅
40	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Pro ₁₃₄ ; Leu ₁₃₅
41	Ser ₉₀ ; Asn ₉₁ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄
42	Ile ₈₈ ; Arg ₁₈₀ ; Leu ₁₈₆ ; Pro ₂₉₀₈
43	His ₅₉ ; Phe ₆₁ ; Asn ₉₁ ; Glu ₉₃ ; Tyr ₉₄ ; Leu ₉₆ ; Thr ₉₉ ; His ₁₃₃ ; Pro ₁₃₄

Source: Authors, 2026.

4. Discussion

4.1 Root mean square deviation (RMSD)

In the literature, there are some studies on ligand-protein complex formation; this phenomenon involves a wide range of conformational changes that play a very important role in the binding affinity required for ligand-protein complex formation (Frimurer et al., 2003; Seo et al., 2014). In this way, some RMSD methods have been used to compare different conformations adopted by identical or similar compounds, such as FABind (Pei et al., 2023), pyRMSD (Gil; Guallar, 2013), and Gromacs (Berendsen et al., 1995), among others.

In this study, the RMSD was determined using the LigRMSD program; 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 (Valdes-Albuernes et al., 2025; Velazquez-Libera et al., 2020). The results showed differences in the percentage of molecules matching (Table 4). Besides, the RMSD value for compound 8 was higher (2.5 Å) compared with compounds 1-7 and 9-43. All 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.

Table 4. RMSD calculations among identical and similar compounds in protein-ligand docking.

Compound	Type of conformation	RMSD (Å)	Percent of molecule match
1	Flexible	1.83	41.67
2	Flexible	1.64	45.45
3	Flexible	1.04	22.73
4	Flexible	1.98	41.67

5	Flexible	1.98	41.67
6	Flexible	0.97	71.43
7	Flexible	1.79	50.00
8	Flexible	2.25	31.25
9	Flexible	1.39	62.50
10	Flexible	1.36	50.00
11	Flexible	1.67	55.56
12	Flexible	1.69	41.67
13	Flexible	1.83	41.67
14	Flexible	2.17	35.71
15	Flexible	2.03	38.46
16	Flexible	1.69	41.67
17	Flexible	1.20	45.45
18	Flexible	1.84	20.83
19	Flexible	1.50	33.33
20	Flexible	1.39	55.56
21	Flexible	1.34	55.56
22	Flexible	2.08	29.41
23	Flexible	1.10	18.52
24	Flexible	0.86	17.86
25	Flexible	1.10	83.33
26	Flexible	1.10	83.33
27	Flexible	0.93	41.67
28	Flexible	2.17	35.71
29	Flexible	2.17	38.46
30	Flexible	2.14	35.71
31	Flexible	1.98	41.67
32	Flexible	1.98	41.67
33	Flexible	0.72	55.56
34	Flexible	1.34	55.56
35	Flexible	0.70	71.43
36	Flexible	1.03	62.50
37	Flexible	1.19	55.56
38	Flexible	1.45	45.45
39	Flexible	1.66	35.71
40	Flexible	1.79	50.00
41	Flexible	0.94	62.50
42	Flexible	1.60	26.32
43	Flexible	1.85	45.45

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

4.2 Thermodynamic parameters

There are some reports that suggest that ligand-protein complex formation may also be associated with thermodynamic parameters (Hu; Shelver, 2003; Molani; Cho, 2024; Raj et al., 2024). For example, a study showed that the energy binding for the docking of the imidazole derivative ((*Z*)-2-amino-5-((amino(4-(4-hydroxy-3-methoxybenzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)methyl)-amino) pentanoic acid) with the 4MAN protein (Bcl_2-Navitoclax analog with indole complex) was -52.13 kcal/mol⁻¹ using a theoretical model (Fares et al., 2025).

Another study indicates that the docking of the imidazol analog (1,3-Dibenzyl-5,5-diphenylimidazolidine-2,4-dione) with the 4LDD (crystal structure of Ebola virus VP40 hexamer) showed a binding energy of -7.96 kJ/mol⁻¹ and an inhibition constant of 1.46 µM using the Autodock software (Geetha et al., 2025). Analyzing these data in this research, some thermodynamic parameters involved in the docking of some imidazole derivatives were determined using the DockingServer program. Besides, the compounds imidazole, azaguabine-8, estradiol benzoate, favipiravir, galidesivir, clotrimazole, and *L*-tetrahydropalmatine were used as controls.

The results (Table 5) showed that the binding free energy was lower for the imidazole derivative 24 (-7.96) compared to the compounds 1-23 and 25-43 and the controls. Besides, other data indicate that the binding free energy for compound 39 (-7.59) was lower in comparison with the imidazole derivatives 1-23, 25-38, and 40-43 and the controls. These data suggest that differences in the binding energy could influence the affinity of each compound for the 5BOV protein surface.

Table 5. Thermodynamic parameters involved in the interaction of imidazole derivatives (1-43) with 5BOV protein surface.

Compound	A	B	C	D	E	F
Azaguabine-8	-6.97	0.0078	-6.68	-0.09	-6.97	315.13
Estradiol benzoate	-2.13	27.43	-3.13	-0.08	-3.21	734.05
Favipiravir	-6.15	0.0311	-6.36	-0.09	-6.4	307.48
Galidesivir	-6.03	0.0383	-5.17	-0.01	-5.18	468.77
Clotrimazole	-7.07	0.0065	-8.77	-0.02	-8.79	884.85
<i>L</i> -Tetrahydropalmatine	-5.76	0.0598	-6.87	0.02	-6.84	923.84
Imidazole	-3.28	3.95	-3.14	-0.14	-3.28	210.58
1	-5.02	0.20814	-5.35	0.03	-5.32	443.88
2	-5.01	0.20212	-5.15	-0.16	-5.31	356.12
3	-5.97	0.04228	-7.14	0.07	-7.07	567.43
4	-4.74	0.33505	-5.37	0.04	-5.34	381.74
5	-5.40	0.10953	-5.74	0.04	-5.70	357.98
6	-4.11	0.97406	-4.13	-0.06	-4.19	255.17
7	-5.01	0.21362	-4.88	-1.00	-5.87	315.84
8	-5.29	0.13268	-5.96	-0.09	-6.05	676.47
9	-3.77	1.74	-4.38	-0.18	-4.56	272.28
10	-3.21	4.40	-5.02	0.42	-4.60	362.55
11	-4.01	1.15	-5.12	-0.08	-5.20	319.05
12	-5.34	0.12137	-5.66	0.02	-5.06	492.20
13	-5.57	0.08237	-5.87	0.00	-5.87	404.19
14	-5.11	0.18050	-5.68	-0.02	-5.70	431.04
15	-4.16	0.90020	-4.71	-0.04	-4.75	415.13
16	-4.30	0.70917	-5.72	0.02	-5.70	378.93

17	-5.86	0.05050	-6.21	0.05	-6.16	287.74
18	-3.35	3.49	-4.57	-0.02	-4.59	487.02
19	-6.58	0.01492	-7.14	-0.04	-7.18	377.51
20	-4.95	0.23665	-4.12	-1.46	-5.58	276.47
21	-6.02	0.03835	-6.34	-0.08	-6.32	307.41
22	-5.87	0.04968	-6.58	-0.10	-6.68	447.04
23	-7.14	0.00582	-7.92	0.19	-7.73	722.56
24	-7.96	0.00145	-8.54	-0.02	-8.56	744.50
25	-4.17	0.87868	-4.08	-0.09	-4.17	251.99
26	-4.83	0.28571	-4.70	-0.04	-4.83	251.41
27	-3.62	2.21mM	-4.81	0.13	-4.69	476.66
28	-5.40	0.11047	-6.04	0.04	-5.99	433.88
29	-4.61	0.41637	-5.24	0.03	-5.21	402.97
30	-5.20	0.15300	-5.72	-0.08	-5.80	493.13
31	-5.56	0.08425	-5.85	-0.01	-5.86	357.72
32	-4.01	1.14	-4.58	-0.03	-4.61	468.34
33	-4.73	0.33931	-4.94	-0.09	-5.03	266.92
34	-5.81	0.05551	-5.93	-0.17	-6.10	301.76
35	-4.24	0.77451	-4.24	-0.01	-4.24	233.10
36	-4.48	0.52430	-4.75	-0.02	-4.77	279.36
37	-5.73	0.06280	-6.13	-0.04	-6.17	545.67
38	-5.03	0.19840	-6.06	0.34	-5.72	353.34
39	-7.59	0.00272	-7.47	-1.31	-8.77	360.37
40	-4.80	0.30147	-5.56	-0.09	-5.65	327.41
41	-4.73	0.33831	-4.14	-0.89	-5.03	256.30
42	-6.67	0.01297	-6.50	0.01	-6.50	694.07
43	-4.55	0.45942	-5.39	-0.02	-5.41	339.00

Note: A = Est: Free Energy of Binding (kcal/mol⁻¹); B = Inhibition Constant (K_i, mM); C = vdW + Hbond + desolv Energy (kcal/mol⁻¹); D = Electrostatic Energy (kcal/mol⁻¹); E = Total Intermolec. Energy (kcal/mol); F = Interact. Surface. Source: Authors, 2026.

4.3 Inhibition constant (K_i)

The inhibition constant (K_i) has been associated with the degree of binding affinity involved in the formation of the ligand-protein complexes (Babalola; Adegboyeva, 2024; Boutaoui et al., 2025; Farzaliyeva et al., 2025). For this reason, in this investigation, the K_i for docking of imidazole derivatives with the 5B0V protein surface was determined using the DockingServer program. The results indicate that K_i values for compounds 23, 24, and 39 were lower compared with the controls. Other data indicate that the K_i values for imidazole derivatives 19 and 42 were lower than estradiol benzoate, favipiravir, galidesivir, *L*-tetrahydropalmatine, and imidazole.

Besides, the K_i values for the compounds 3, 17, 19, 21, 34, and 37 were lower in comparison with *L*-tetrahydropalmatine and imidazole. Finally, the K_i value for 13 was lower compared with imidazole; all this data suggests that compounds 3, 13, 17, 19, 21, 23, 24, 34, 37, 39, and 42 may have a good affinity for the 5B0V protein surface. This phenomenon may be conditioned by different types of bonds involved in the ligand-protein complex formation between imidazole derivatives and the 5B0V protein surface.

4.4 Type of bond

The different types of bonds involved in the docking of imidazole derivatives with the 5XSQ protein surface were determined using the DockingServer program. Table 6 and Figures 11-16 show that the amino acid residue Glu₉₃ involved in the 5XSQ protein surface may interact with compounds 3, 23, and 24 through hydrogen bonds. Other data suggest that imidazole derivatives 13, 23, 24, and 42 can interact with the amino acid residue Arg₁₈₀ via polar bonds. Finally, Pro₁₃₄ could bind to compounds 13, 13, 17, 19, 21, 22, 23, 24, 31, 34, 39, and 42 through hydrophobic bonds.

Table 6. Bond type and distance levels involved in the interaction of hydantoin derivatives (13, 13, 17, 19, 21, 22, 23, 24, 31, 34, 39, and 42) with the 5B0V protein surface.

Com.	Hydrogen	Polar	Hydrophobic	π - π	halogen
3	Phe ₉₂ (N ₁ , 3.03) Phe ₉₂ (N ₂ , 2.98) Glu ₉₃ (N ₁ , 2.62) Glu ₉₃ (N ₄ , 2.81) Glu ₉₃ (N ₅ , 3.39) Glu ₉₃ (H ₁₃ , 3.20) Glu ₉₃ (H ₅ , 3.21) Pro ₉₅ (H ₅ , 3.55) Pro ₂₉₈ (H ₁₃ , 2.58)		Tyr ₉₄ (C ₇ , 3.76) Tyr ₉₄ (C ₈ , 3.36) Tyr ₉₄ (C ₉ , 3.25) Pro ₉₅ (C ₇ , 3.83) Leu ₁₈₆ (C ₁₅ , 3.51) Ile ₁₈₇ (C ₁₃ , 3.43) Ile ₁₈₇ (C ₁₂ , 3.72) Ile ₁₈₇ (C ₁₆ , 3.82) Ile ₁₈₇ (C ₁₅ , 3.59) Ile ₁₈₇ (C ₁₄ , 3.37)	Phe ₉₂ (C ₅ , 3.39) Phe ₉₂ (C ₁₄ , 3.27)	
13	Ile ₈₈ (N ₂ , 2.75) Ile ₈₈ (N ₁ , 3.08)	Glu ₉₃ (N ₂ , 3.65) Glu ₉₃ (N ₁ , 3.66) Arg ₁₈₀ (N ₁ , 3.85)	Pro ₁₃₄ (C ₄ , 3.32) Pro ₁₃₄ (C ₅ , 3.15) Pro ₁₃₄ (C ₁ , 3.41) Pro ₁₃₄ (C ₃ , 3.59) Pro ₁₃₄ (C ₆ , 3.89) Leu ₁₃₅ (C ₉ , 3.23) Leu ₁₃₅ (C ₄ , 3.82) Pro ₂₉₈ (C ₂ , 3.60)	Phe ₆₁ (C ₈ , 3.27)	Ser ₉₀ (C ₁ , 3.81) Tyr (C ₁₁ , 3.81)
17	His ₅₉ (N ₁ , 3.17)		Tyr ₉₄ (C ₅ , 3.64) Leu ₉₆ (C ₁ , 3.57)	His ₅₉ (C ₂ , 3.22)	Ser ₉₀ (F ₁ , 2.84) Asn ₉₁ (F ₁ , 3.74)

	Asn ₉₁ (N ₁ , 2.82)			Phe ₆₁ (C ₂ , 3.44)	Tyr ₉₄ (F ₂ , 2.68)
				Phe ₆₁ (C ₃ , 3.26)	Tyr ₉₉ (F ₂ , 2.71)
19	Ile ₈₈ (N ₁ , 3.25)		Tyr ₉₄ (C ₁₀ , 3.63)	His ₅₉ (C ₈ , 3.42)	Ser ₉₀ (F ₃ , 3.46)
			Leu ₉₆ (C ₆ , 3.49)		Tyr ₉₄ (F ₁ , 2.57)
			Leu ₉₆ (C ₇ , 3.23)	Phe ₆₁ (C ₄ , 3.80)	Tyr ₉₉ (F ₃ , 3.44)
			Pro ₁₃₄ (C ₁ , 3.83)	Phe ₆₁ (C ₈ , 3.36)	Pro ₉₅ (F ₁ , 3.68)
			Pro ₁₃₄ (C ₂ , 3.21)	Phe ₆₁ (C ₉ , 3.25)	Thr ₉₉ (F ₁ , 2.62)
			Leu ₁₃₅ (C ₁ , 3.13)	Phe ₆₁ (C ₇ , 3.89)	Thr ₉₉ (F ₂ , 3.38)
21	Asn ₉₁ (N, 2.66)	His ₅₉ (N, 3.63)	Leu ₉₆ (C, 3.66)	His ₅₉ (C, 3.70)	Ile ₈₈ (C ₁ , 3.59)
	His ₅₉ (H, 3.21)			Phe ₆₁ (C, 3.76)	
	Asn ₉₁ (H, 3.85)				
	Leu ₉₆ (H, 3.89)				
22	Leu ₈₆ (N ₁ , 2.99)	Arg ₁₃₆ (N ₁ , 3.67)	Pro ₂₉₈ (C ₂ , 3.66)		Ile ₈₈ (F ₆ , 3.59)
			Pro ₂₉₈ (C ₁ , 3.62)		Ile ₈₈ (F ₇ , 3.24) Ile ₈₈ (F ₅ , 2.85)
			Pro ₂₉₈ (C ₃ , 3.78)		Ile ₈₈ (F ₂ , 3.21)
					Pro ₁₃₄ (F ₆ , 3.61)
23	Ile ₈₈ (N ₁ , 2.95)	Arg ₁₈₀ (N ₂ , 3.25)	Pro ₁₃₄ (C ₁ , 3.13)	Phe ₆₁ (C ₁₈ , 3.65)	
	Ile ₈₈ (N ₂ , 2.59)	Ser ₃₀₁ (O ₁ , 3.66)	Pro ₁₃₄ (C ₁₆ , 3.22)		
	Glu ₉₃ (N ₂ , 2.59)		Pro ₁₃₄ (C ₂₁ , 3.40)		
	Tyr ₉₄ (N ₃ , 3.20)		Leu ₁₃₅ (C ₁₇ , 3.14)		
	Thr ₉₉ (N ₃ , 2.17)		Leu ₁₃₅ (C ₁₈ , 3.71)		
	Pro ₁₃₄ (H ₁ , 3.50)		Pro ₂₉₈ (C ₂ , 3.61)		
	Leu ₁₃₅ (H ₁ , 3.70)		Pro ₂₉₈ (C ₃ , 3.70)		
24	Ile ₈₈ (N ₁ , 2.41)	Arg ₁₈₀ (N ₁ , 3.65)	Pro ₁₃₄ (C ₁ , 3.64)	Phe ₆₁ (C ₁₈ , 3.53)	
	Ile ₈₈ (N ₂ , 3.50)		Pro ₁₃₄ (C ₁₆ , 3.38)		
	Ser ₉₀ (N ₃ , 3.13)		Pro ₁₃₄ (C ₂₀ ,		
	Arg ₁₈₀ (O ₂ ,				

	2.99)		3.64)	
	Ser ₃₀₁ (O ₁ , 3.05)		Pro ₁₃₄ (C ₂₁ , 2.98)	
	Glu ₉₃ (H ₁ , 3.52)		Leu ₁₃₅ (C ₁₇ , 2.81)	
	Arg ₁₈₀ (H ₁ , 2.76)		Leu ₁₃₅ (C ₁ , 3.39)	
			Leu ₁₃₅ (C ₃ , 3.82)	
			Leu ₁₃₅ (C ₁₆ , 3.45)	
			Leu ₁₃₅ (C ₁₈ , 3.74)	
			Val ₂₀₅ (C ₁₀ , 3.83)	
			Val ₂₀₅ (C ₁₁ , 3.80)	
			Pro ₂₉₈ (C ₂ , 3.26)	
			Pro ₂₉₈ (C ₃ , 3.83)	
			Pro ₂₉₈ (C ₆ , 3.37)	
			Pro ₂₉₈ (C ₁₄ , 3.34)	
			Pro ₂₉₈ (C ₁₅ , 3.00)	
31	Asn ₉₁ (N ₂ , 2.84)		Leu ₉₆ (C ₁ , 3.33)	Phe ₆₁ (C ₉ , 3.43)
	Tyr ₉₄ (N ₁ , 3.08)		Pro ₁₃₄ (C ₆ , 3.02)	
	Tyr ₉₄ (N ₂ , 3.46)		Pro ₁₃₄ (C ₇ , 3.23)	
	Thr ₉₉ (N ₁ , 3.06)		Pro ₁₃₄ (C ₅ , 3.78)	
	Asn ₉₁ (H ₃ , 3.33)		Leu ₁₃₅ (C ₈ , 2.97)	
	Leu ₉₆ (H ₃ , 2.89)		Leu ₁₃₅ (C ₇ , 3.55)	
34	Asn ₉₁ (N, 2.78)	His ₅₉ (N, 3.62)	His ₅₉ (C, 3.72)	
		His ₅₉ (H, 3.07)	Phe ₆₁ (C, 3.68)	
		Asn ₉₁ (H, 1.94)	Tyr ₉₄ (C, 3.41)	
			Leu ₉₆ (C, 3.72)	
			His ₁₃₃ (C, 3.52)	
			Pro ₁₃₄ (C, 3.80)	

Leu ₁₃₅ (C, 3.63)				
39	His ₅₉ (N ₁ , 3.48)	Pro ₁₃₄ (C ₆ , 3.19)	His ₅₉ (C ₁ , 3.29)	Ser ₉₀ (F ₂ , 3.85)
	Asn ₉₁ (H, 1.94)	Pro ₁₃₄ (C ₇ , 3.40)	Phe ₆₁ (C ₁ , 3.62)	Ser ₉₀ (F ₃ , 2.72)
		Leu ₁₃₅ (C ₆ , 3.26)	Phe ₆₁ (C ₃ , 3.86)	Asn ₉₁ (F ₂ , 2.95)
				Asn ₉₁ (F ₃ , 3.34)
				Tyr ₉₄ (F ₁ , 2.99)
				Tyr ₉₄ (F ₂ , 2.80)
				Tyr ₉₄ (F ₃ , 2.46)
				Pro ₉₅ (F ₁ , 3.83)
Thr ₉₉ (F ₁ , 2.94)				
42	Arg ₁₈₀ (H ₅ , 3.27)	Ile ₈₈ (C ₆ , 3.40)		
	Arg ₁₈₀ (N ₄ , 3.85)	Ile ₈₈ (C ₇ , 3.84)		
	Arg ₁₈₀ (O ₃ , 3.72)	Ile ₈₈ (C ₈ , 3.34)		
	Arg ₁₈₀ (N ₁ , 3.11)	Pro ₂₉₈ (C ₂ , 3.52)		

Source: Authors, 2026.

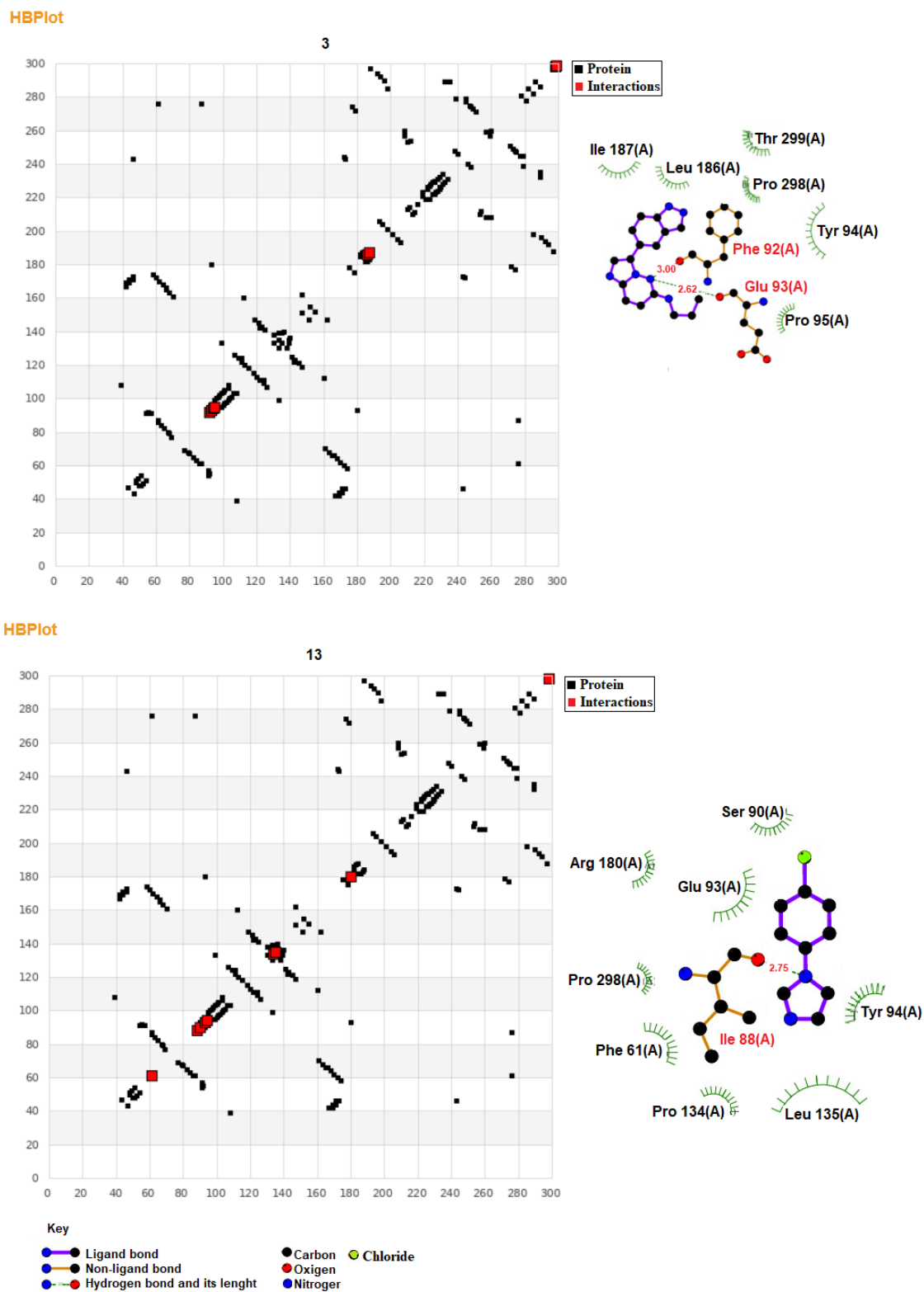


Figure 11. Interaction of imidazol derivatives 3 and 13 with the 5B0V protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

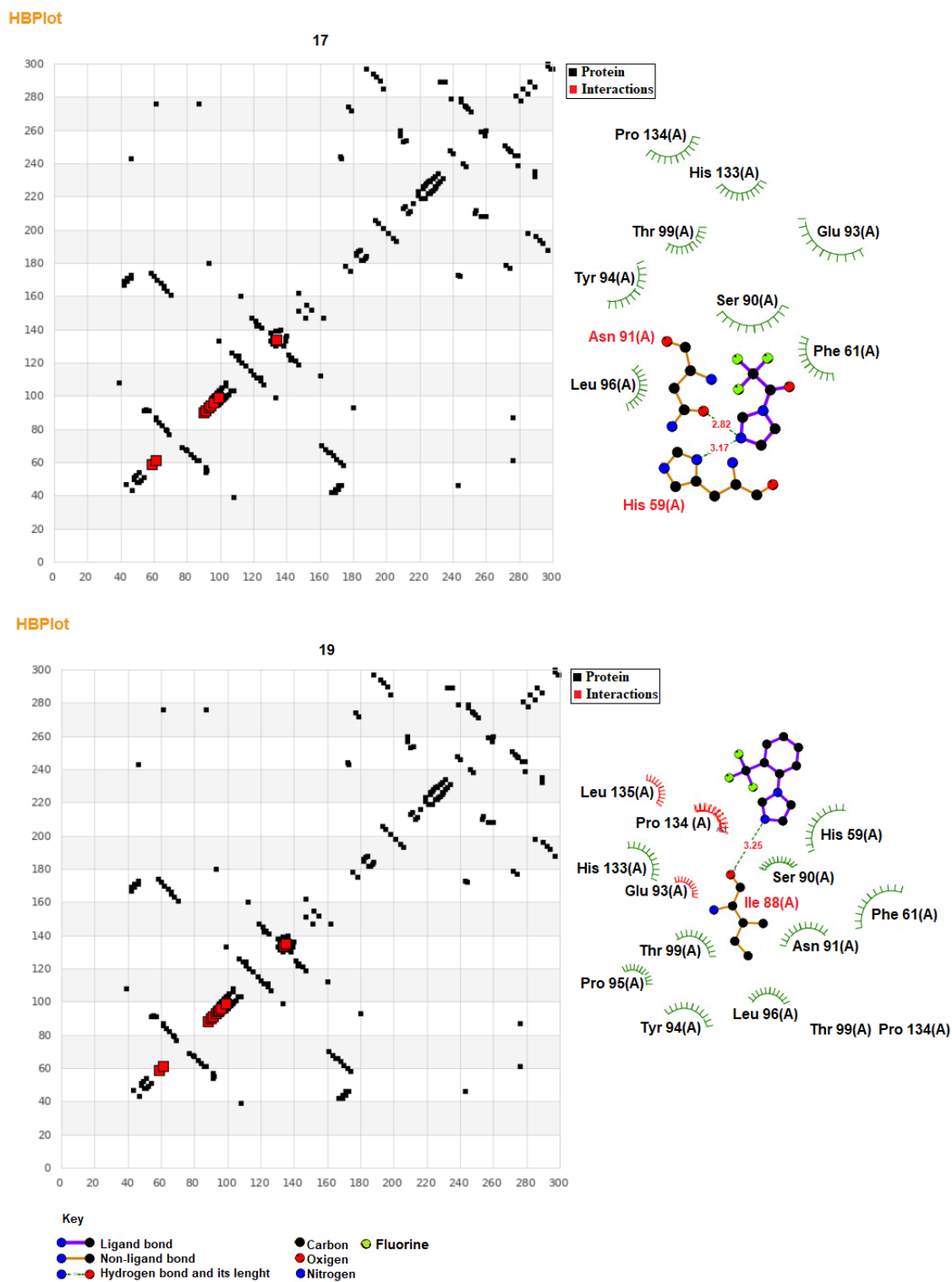


Figure 12. Docking of imidazol derivatives 17 and 19 with the 5B0V protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

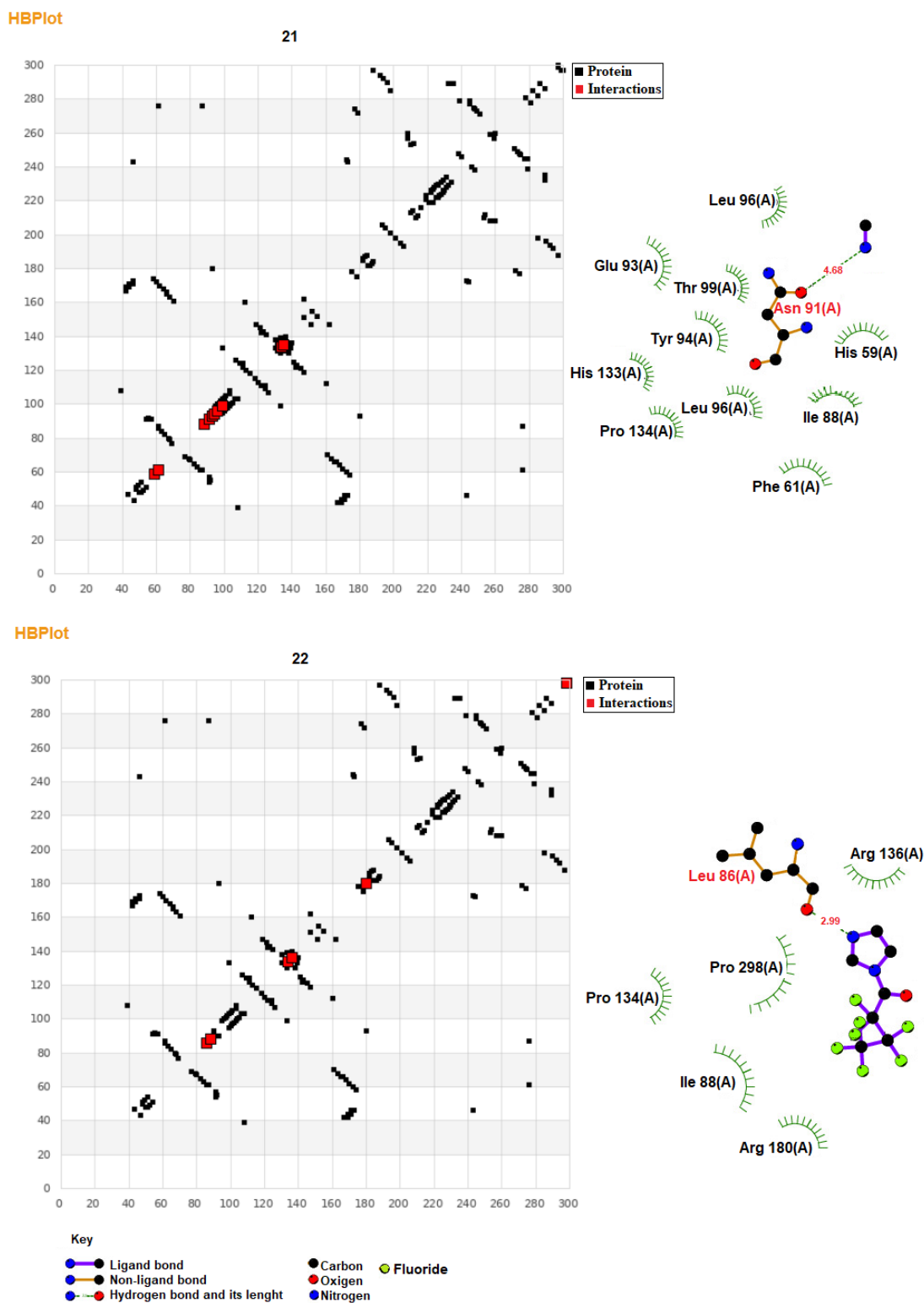


Figure 13. Docking of imidazol derivatives 21 and 22 with the 5B0V protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

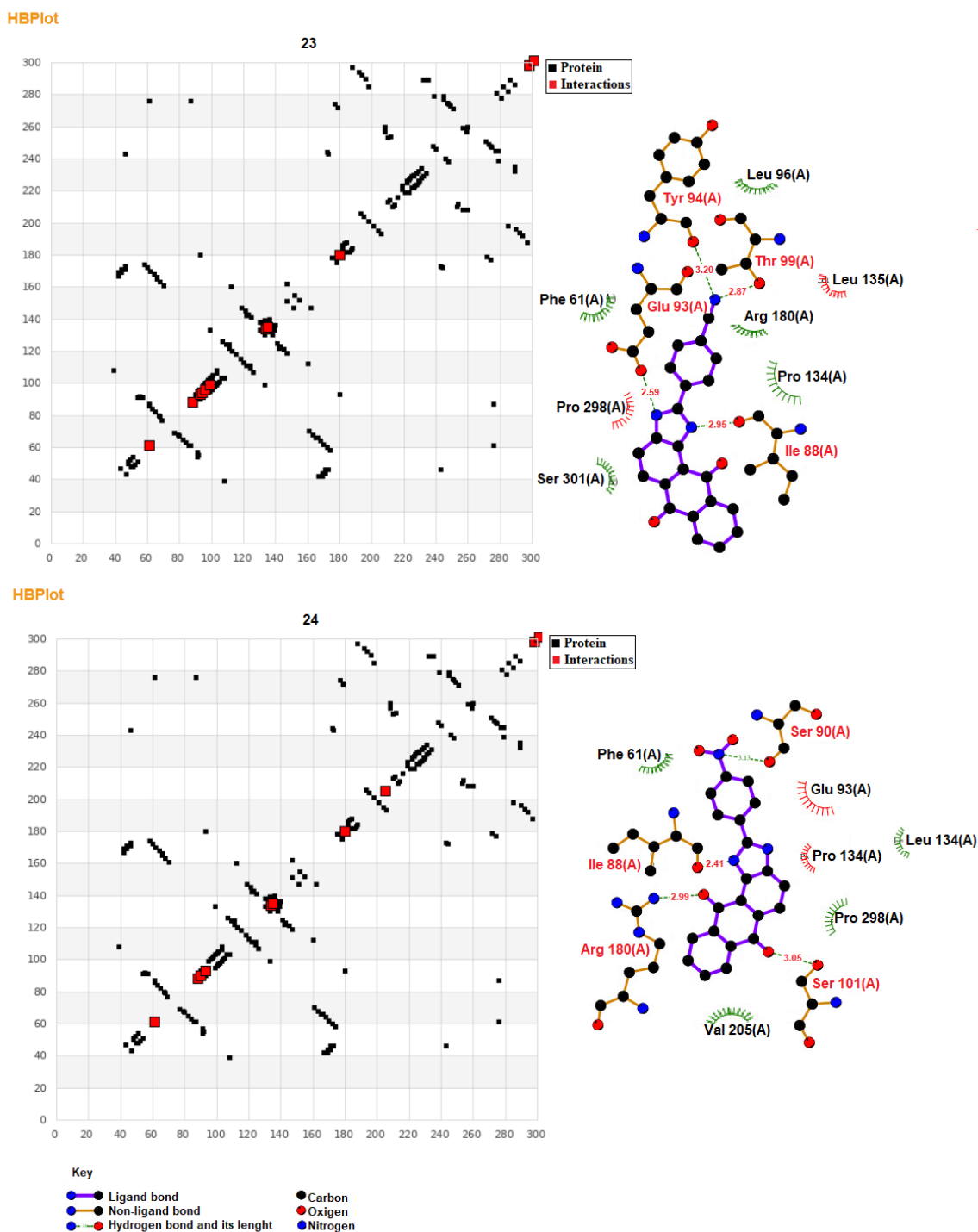
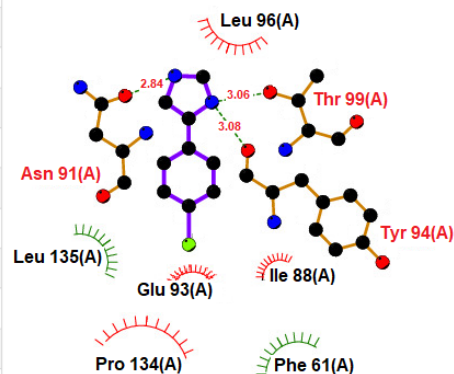
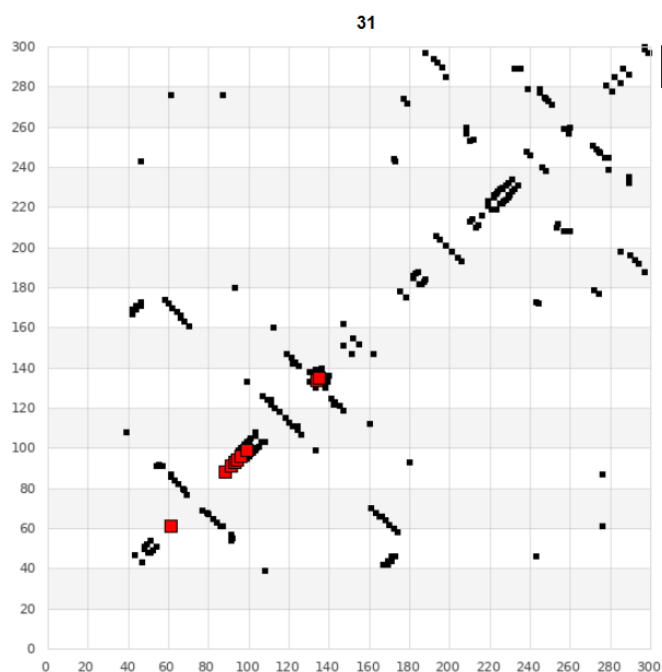
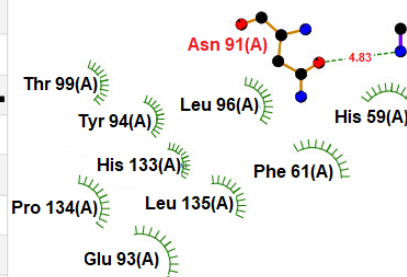
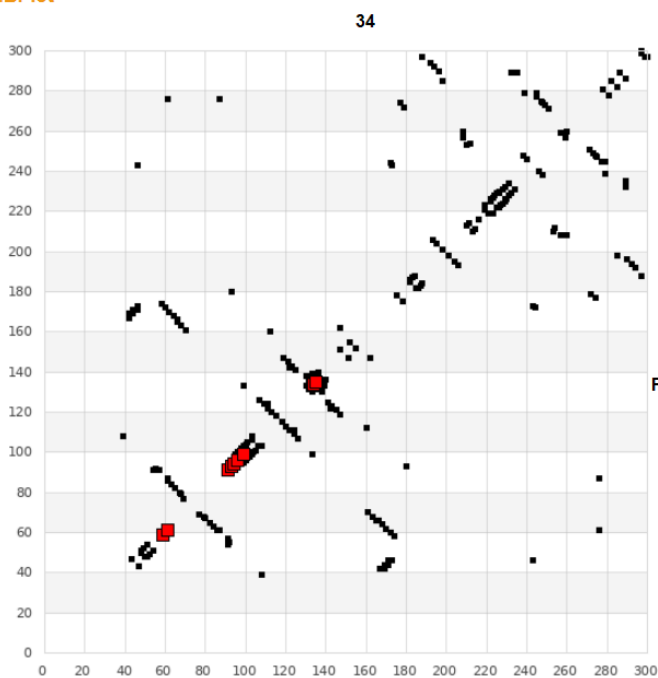


Figure 14. Interaction of imidazol analogs 23 and 24 with the 5B0V protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

HBPlot



HBPlot

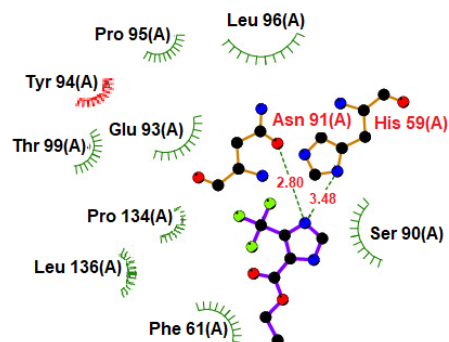
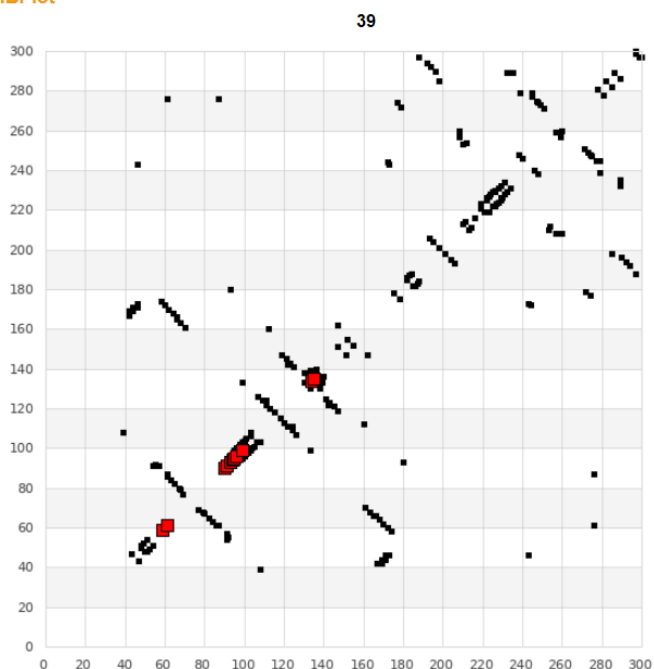


Key

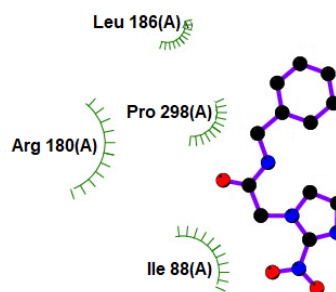
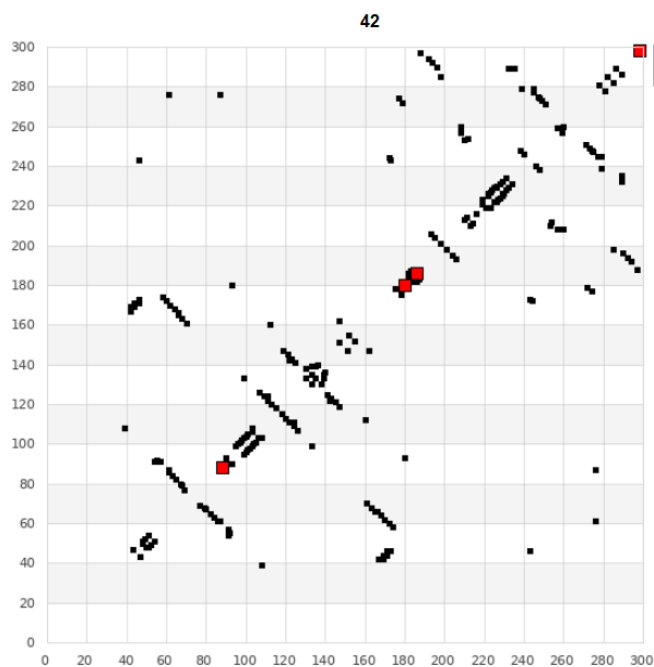
- — Ligand bond
- — Non-ligand bond
- — Hydrogen bond and its lenght
- Carbon
- Oxygen
- Nitrogen
- Bromide

Figure 15. Docking of imidazol derivatives 31 and 34 with the 5B0V protein surface. Visualized with the DockingServer program. Source: Authors, 2026.

HBPlot



HBPlot



Key

- Ligand bond
- Non-ligand bond
- Hydrogen bond and its length
- Carbon
- Oxygen
- Nitrogen
- Fluorine

Figure 16. Docking of imidazol derivatives 39 and 42 with the 5B0V protein surface. Visualized with the DockingServer program.

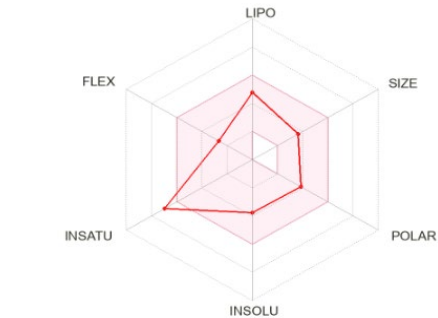
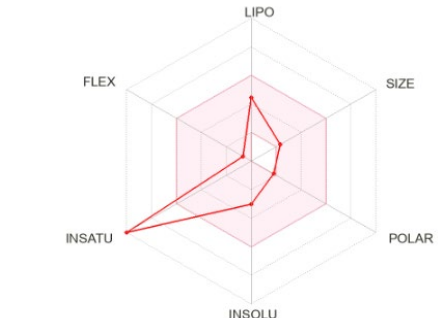
4.5 Pharmacokinetic parameters

Several studies have been conducted to determine some pharmacokinetic parameters involved in the administration of imidazole derivatives. For example, a study showed the pharmacokinetics of compound 3-((5-(6-methylpyridin-2-yl) 4-(quinoxalin-6-yl)-1*H*-imidazol-2-yl)methyl)benzamide in animals using the High-Performance Liquid Chromatography method (Kim et al., 2008).

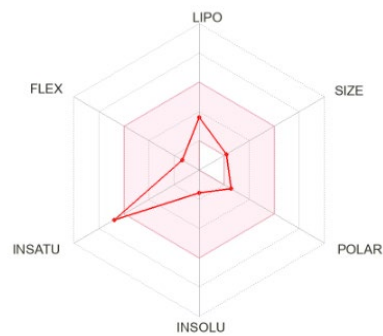
Other reports displayed that several pharmacokinetic parameters, such as absorption, distribution, metabolism, and excretion for some imidazole derivatives, were determined using QikProp 4.8 (Acar Çevik et al., 2020) and SwissADME (Tshiluka et al., 2025) programs. Analyzing these data, in this study, some pharmacokinetic parameters were determined for imidazole derivatives (3, 13, 17, 19, 21, 22, 23, 24, 34, 37, 39, and 42) using the SwissADME and ADMETab 3.0 programs. The results in Table 7 showed the appropriate physicochemical area for the oral bioavailability of the imidazole derivatives 3, 13, 17, 19, 21, 23, 24, 34, 37, 39, and 42.

These data suggest that imidazole derivatives may 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). In addition, the topological polar surface area (TPSA) values were less than 130 Å² for imidazole derivatives. It is important to mention that TPSA is a widely used molecular descriptor in the study of drug transport properties, such as intestinal absorption and blood-brain barrier penetration (Pasanna; Doerksen, 2009). Therefore, these results indicate that this physicochemical property of imidazole derivatives could influence intestinal absorption and their passage through the blood-brain barrier.

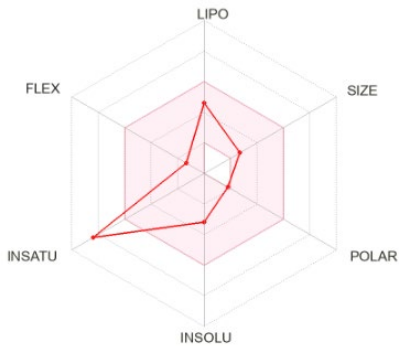
Table 7. Physicochemical parameters for imidazole derivatives 3, 13, 17, 19, 21, 23, 24, 34, 37, 39, and 42. Using the SwissADME program.

Compound	Area*	TPSA (Å ²)	Lipinski (violations)	Pains (alerts)	Synthetic accessibility
3		70.90	0	0	2.82
13		17.82	0	0	1.43

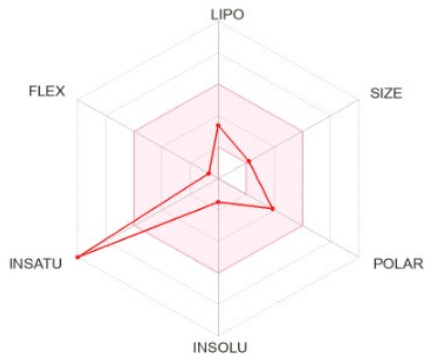
17 34.89 0 0 1.26



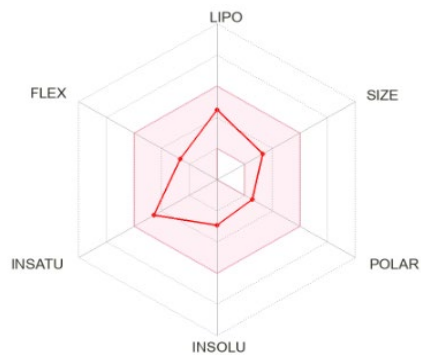
19 17.82 0 0 1.64



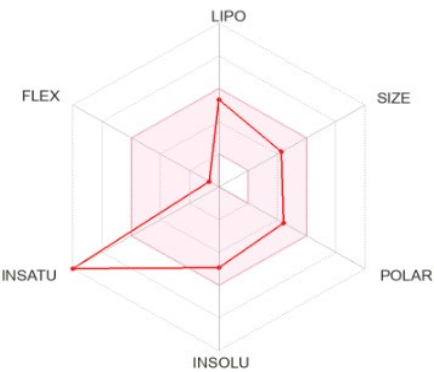
21 71.20 0 0 2.19



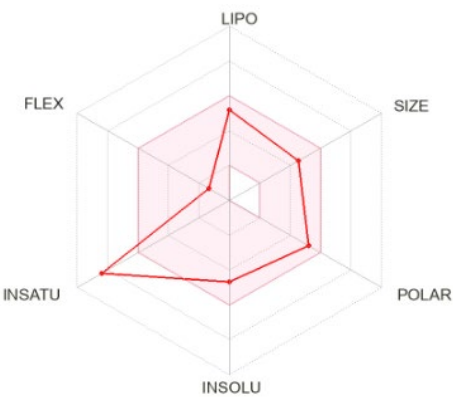
22 34.89 0 0 1.88



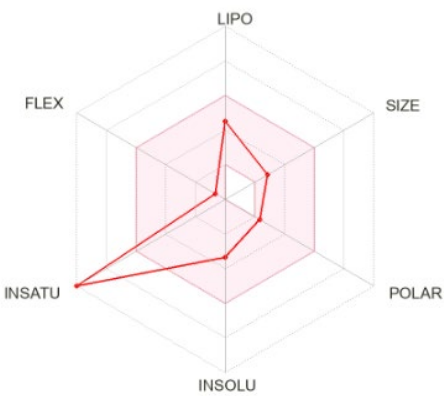
23 86.61 0 0 2.76



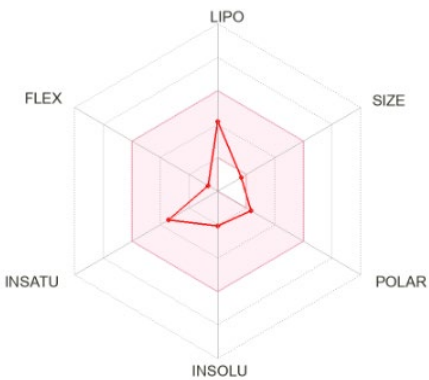
24 108.64 0 0 3.98

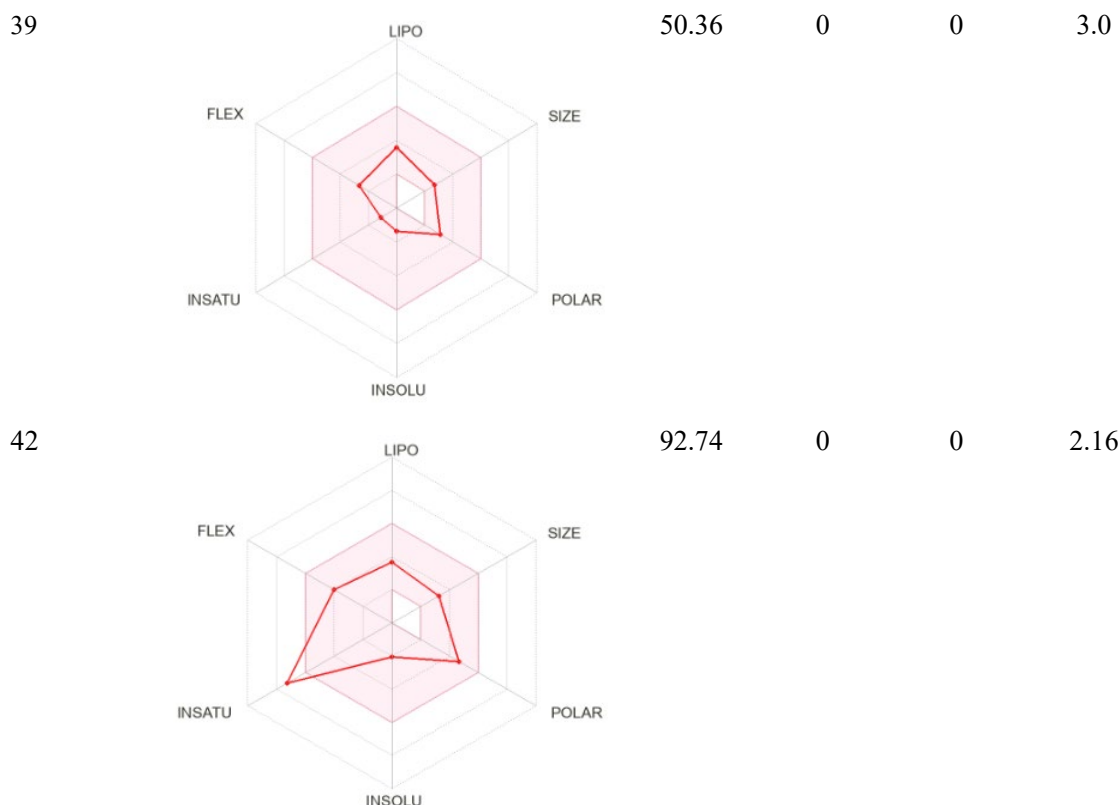


31 28.68 0 0 1.82



34 26.68 0 0 163





Source: Authors, 2026.

In addition, several pharmacokinetic characteristics were determined using SwissADME and ADMETab 3.0 (Tables 8 and 9); the results showed that imidazol derivatives 3, 13, 17, 19, 21, 22, 23, 24, 31, 34 and 39 could act as CYP1A2 inhibitors. Besides, the compounds 3, 21, 22, 23, 31 and 42 may act as CYP2C19 antagonists. Other results suggest that compounds 21, 22 and 34 could block the biological activity of CYP2C9.

Other data indicate that the imidazole derivatives 3, 13, 17, 19 and 31 may produce inhibition of CYP2D6. In addition, the compounds 13, 17, 19, 21, 22, 24 and 31 may act as CYP3A4 inhibitors. Other data suggest that the compounds 3, 13, 17, 19, 21, 22, 24, 31 and 34 may affect the biological activity of CYP2B6. Finally, other results indicate that the imidazole derivatives 3, 13, 17, 19, 21, 22, 24, 31 and 34 could act as CYP2C8 substrates. All these data suggest that different imidazole derivatives could act on different CYPs, and this phenomenon could be influenced by the degree of lipophilicity of each compound. In this way, the results indicate that LogP was higher for imidazole derivative 23 compared with compounds 1–22 and 24–43. All these data play an important role in the metabolism and distribution of imidazole derivatives in the body, which may be relevant for future research on these compounds.

Table 8. Pharmacokinetic parameters for imidazole analogs 3, 13, 17, 19, 21, 22, and 23.

Parameter	3	13	17	19	21	22	23
Caco-2 Permeability	-4.93	-4.39	-4.52	-4.39	-4.4	-4.53	-4.79
Pgp inhibitor	No	Yes	Yes	Yes	No	Yes	Yes
Pgp substrate	Yes	No	No	No	No	No	No
Human intestinal Absorption	No	No	No	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP1A2 substrate	No	No	Yes	Yes	Yes	Yes	No
CYP2C19 inhibitor	Yes	No	No	No	Yes	Yes	Yes

CYP2C19 substrate	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	Yes	Yes	No
CYP2C9 substrate	Yes	No	No	No	Yes	No	No
CYP2D6 inhibitor	Yes	Yes	Yes	Yes	No	No	No
CYP2D6 substrate	Yes	No	No	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP3A4 substrate	No	No	No	No	No	Yes	No
CYP2B6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP2B6 substrate	No	No	No	No	No	No	No
CYP2C8 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Human Liver microsomal Stability	Yes	No	No	Yes	No	No	Yes
Plasma protein binding (%)	92.0	94.8	62.7	94.6	52.2	94.3	97.8
Volume distribution (L/kg ⁻¹)	0.067	-0.376	-0.004	0.271	-0.152	0.165	0.543
Blood-Brain Barrier	No	Yes	No	Yes	No	No	No
CL _{plasma} (mL/min/kg ⁻¹)	5.497	6.905	6.892	9.83	7.214	5.083	3.107
T _{1/2} (L/Kg ⁻¹)	0.548	1.034	1.503	1.374	2.065	1.161	1.387

Source: Authors, 2026.

Table 9. Pharmacokinetic data for imidazole derivatives 24, 31, 34, 39, and 42.

Parameter	24	31	34	39	42
Caco-2 Permeability	-4.97	-4.81	-4.60	-4.77	-469
Pgp inhibitor	Yes	Yes	Yes	Yes	No
Pgp substrate	No	No	No	No	No
Human intestinal Absorption	No	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	No
CYP1A2 substrate	No	No	No	Yes	No
CYP2C19 inhibitor	No	Yes	No	No	Yes
CYP2C19 substrate	No	No	No	No	No
CYP2C9 inhibitor	No	Yes	Yes	No	No
CYP2C9 substrate	No	No	No	No	No
CYP2D6 inhibitor	No	Yes	No	No	No
CYP2D6 substrate	No	Yes	No	No	No
CYP3A4 inhibitor	Yes	Yes	No	No	No
CYP3A4 substrate	No	No	Yes	No	No
CYP2B6 inhibitor	Yes	Yes	Yes	No	No
CYP2B6 substrate	No	No	No	No	No
CYP2C8 inhibitor	Yes	Yes	Yes	No	No
Human Liver microsomal Stability	Yes	No	Yes	Yes	No
Plasma protein binding (%)	98.6	91.7	35.6	77.8	50.4
Volume distribution (L/kg ⁻¹)	-0.081	-0.062	-0.287	0.481	-0.187

Blood-Brain Barrier	No	Yes	No	No	Yes
CL _{plasma} (ml/min/kg ⁻¹)	4.461	5.788	8.861	9.066	5.696
T _{1/2} (L/Kg ⁻¹)	0.745	1.176	0.731	1.351	0.644

Source: Authors, 2026.

4.6 Toxicology analysis

Reports indicate that an imidazole may be toxic; for example, a report showed that 1,4-bis(imidazolylazo)benzene is toxic in a dose-dependent manner in an animal model (Kyhoiesh et al., 2021). Analyzing these data, a theoretical study was carried out to determine the toxicity degree produced by imidazole derivatives 3, 13, 13, 17, 19, 21, 22, 23, 24, 34, 37, 39, and 42 using the Gussar program. The results (Table 10) suggest that compound 23 requires a higher dose administered intraperitoneally to produce toxicity compared to compounds 3, 13, 17, 19, 21, 22, 24, 34, 37, 39, and 42.

Furthermore, higher doses of compound 42 are required to induce toxicity via the intravenous and oral routes, compared with 13, 13, 17, 19, 21, 23, 24, 34, 37, and 39. Other data indicate that higher doses of compound 24 may produce toxicity in comparison with other imidazole derivatives. All these data suggest that the toxicity degree of imidazole derivatives could depend on the following factors: 1) the dose administered, 2) the route of administration, and 3) the differences in the chemical structure of each compound.

Table 10. Analysis of the toxicity produced by hydantoin derivatives (3, 13, 17, 19, 21, 22, 23, 24, 31, 34, 37, 39, and 42) using the GUSAR program.

Compounds	IP LD ₅₀ (mg kg ⁻¹)	IV LD ₅₀ (mg kg ⁻¹)	Oral LD ₅₀ (mg kg ⁻¹)	SC LD ₅₀ (mg kg ⁻¹)
3	1183.00	118.50	729.70	213.40
13	345.50	83.77	716.70	465.30
17	421.40	116.20	58.12	316.70
19	368.90	98.41	266.20	364.60
21	232.30	57.87	355.60	498.10
22	833.80	253.70	711.80	613.50
23	1372.00	90.94	597.50	363.20
24	426.80	86.19	270.60	2319.00
31	764.50	97.49	949.20	497.50
34	224.20	37.87	579.80	271.50
37	319.50	37.41	380.20	318.80
39	685.20	108.70	368.00	852.20
42	702.70	483.00	1424.00	648.00

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

5. Conclusion

This study identified imidazole derivatives 3, 13, 17, 19, 21, 23, 24, 34, 37, 39, and 42 as promising candidates based on their predicted affinity for the Ebola virus VP40 protein. Compounds 23, 24, and 39 showed particularly favorable inhibition constant (K_i) values, while compound 24 exhibited the lowest predicted binding free energy (-7.96 kcal/mol). The predicted pharmacokinetic and physicochemical profiles also supported the potential of these compounds for further investigation. However, as the results are based on computational analyses, experimental studies are required to confirm their antiviral activity, mechanism of action, pharmacokinetics, and safety.

6. Authors' Contributions

Bonilla-Zavaleta: data curation, funding acquisition, investigation, writing—original draft. *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, writing—original draft, writing—review & editing. *Melgarejo-Gutiérrez Montserrat Alheli*: formal analysis, investigation, visualization, writing—review & editing. *Ramírez-Higuera Abril*: formal analysis, funding acquisition, investigation, visualization, writing—review & editing. *Rascon-Díaz Martha Paola*: formal analysis, visualization. *Rascon-Díaz Martha Paola*: funding acquisition. *Bonilla-Zavaleta Enrique*: investigation, methodology, 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 artificial intelligence (AI) and AI-assisted tools were used solely for grammatical and linguistic corrections of the English and Portuguese languages during the preparation of this manuscript. No AI tools were used to generate, modify, or create the scientific content, data, figures, images, schemes, or tables. The final manuscript was reviewed and approved by all authors, who assume full responsibility for its accuracy and integrity. AI tools are not authors and do not assume any responsibility for the content of this manuscript.

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