Intramolecular interaction analysis of forty amine derivatives with phosphodiesterase 4D using a theoretical model

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Abstract

Several drugs, such as zatolmilast, orismilast, lotamilast, and GSK256066 (phosphodiesterase inhibitors) have been used to treat chronic heart failure. However, some of these drugs can produce different secondary effects such as arrhythmia, nausea, and vomiting. In the search for a new therapeutic alternative to treat chronic heart failure, this study aimed to characterize the interaction of some amino derivatives (1-40) with phosphodiesterase 4D using the 3iak protein as a theoretical tool in the DockingServer program. Besides, zatolmilast, orismilast, lotamilast, and GSK256066 were used as controls. The results showed differences in the interaction of amino derivatives with the 3iak protein surface compared with zatolmilast, orismilast, lotamilast, and GSK256066. Other data indicate that the inhibition constant for amino derivatives 7, 12, 15, 18, and 33 was lower compared with the controls. All these data suggest that compounds 7, 12, 15, 18, and 33 could act as phosphodiesterase 4D inhibitors. These data suggest that amino derivatives of phosphodiesterase 4D could be a good therapeutic alternative to treat heart failure.

Keywords: amino derivatives, heart failure, phosphodiesterase.

Análise das interações intramoleculares de quarenta derivados de aminas com a fosfodiesterase 4D utilizando um modelo teórico

Resumo

Vários fármacos, como zatolmilast, orismilast, lotamilast e GSK256066 (inibidores da fosfodiesterase), têm sido utilizados no tratamento da insuficiência cardíaca crônica. No entanto, alguns desses medicamentos podem produzir diferentes efeitos secundários, como arritmia, náuseas e vômitos. Na busca por uma nova alternativa terapêutica para o tratamento da insuficiência cardíaca crônica, este estudo teve como objetivo caracterizar a interação de alguns derivados de aminas (1–40) com a fosfodiesterase 4D, utilizando a proteína 3iak como ferramenta teórica no programa DockingServer. Além disso, zatolmilast, orismilast, lotamilast e GSK256066 foram utilizados como controles. Os resultados mostraram diferenças na interação dos derivados de aminas com a superfície da proteína 3iak em comparação com zatolmilast, orismilast, lotamilast e GSK256066. Outros dados indicam que a constante de inibição dos derivados de aminas 7, 12, 15, 18 e 33 foi menor quando comparada à dos controles. Todos esses dados sugerem que os compostos 7, 12, 15, 18 e 33 podem atuar como inibidores da fosfodiesterase 4D. Esses resultados indicam que derivados de aminas direcionados à fosfodiesterase 4D podem representar uma boa alternativa terapêutica para o tratamento da insuficiência cardíaca.

Palavras-chave: derivados de aminas, insuficiência cardíaca, fosfodiesterase.

1. Introduction

Heart failure is a major problem of public health worldwide (Bragazzi et al., 2017; Khan et al., 2024; Lee et al., 2024; Martin, 2024). This clinical pathology is associated with several risk factors, such as alcohol (Laonigro et

al., 2009), smoking (Aune et al., 2019), diabetes (Ohkuma et al., 2019), lipid concentrations (Katsiki et al., 2016), hypertension (Slivnick et al., 2019), coronary artery disease (Nelsen et al., 2024), and others. It is noteworthy that several drugs, such as captopril (Paker et al., 1986), spironolactone (Huang et al., 2024), valsartan (Maggioni et al., 2005), and levosimendan (Massarone et al., 2022) have been used to treat heart failure. Although these therapies improve symptoms and outcomes in many patients, they do not fully reverse maladaptive cardiac remodeling nor restore optimal cardiac function in all individuals.

An important intracellular signaling pathway in cardiomyocytes involves the second messenger cyclic adenosine monophosphate (cAMP), which regulates contractility, calcium handling, and hypertrophic responses via protein kinase A (PKA)–dependent mechanisms. Phosphodiesterase 4 (PDE4) enzymes, including the PDE4D isoform, specifically hydrolyze cAMP, thereby shaping the spatial and temporal dynamics of cAMP-dependent signaling in the heart. PDE4D is a key regulator of local cAMP pools within cardiomyocytes and is implicated in the modulation of cardiac contractile function and pathological remodeling (Sherstnev et al., 2025).

Recent experimental evidence suggests that dysregulation of PDE4D expression and activity contributes to adverse cardiac remodeling. For example, cardiac PDE4D upregulation is observed in failing hearts and in experimental models of pathological stress, where its overexpression leads to oxidative stress, impaired mitophagy, and cardiomyocyte hypertrophy through inhibition of CREB-SIRT1 signaling pathways (Fu et al., 2025). These alterations indicate that sustained adrenergic stimulation and increased PDE4D may exacerbate cardiac dysfunction by reducing beneficial cAMP-PKA signaling and compromising cellular homeostasis (Fu et al., 2025).

On the other hand, some phosphodiesterase inhibitors have been used to treat chronic heart failure; for example, a study showed that milrinone (a phosphodiesterase 3 inhibitor) can improve cardiac contractility by increasing intracellular levels of cyclic AMP in patients with chronic heart failure (Cuffe et al., 2002; Packer et al., 1991). Other data indicate that amrinone (a phosphodiesterase 3 inhibitor) improves cardiac function in patients with chronic heart failure (LeJemtel et al., 1980). Besides, a prospective study shows that long-term oral administration of dipyridamole (a phosphodiesterase 3 inhibitor) improves cardiac function in patients with chronic heart failure (Sanada et al., 2007).

Other reports indicate that pentoxifylline (a non-selective phosphodiesterase antagonist) may improve heart function and reduce mortality in patients with chronic heart failure (Batchelder; Mayosi, 2005; Champion et al., 2014). In addition, a study displays that udenafil (a phosphodiesterase 5 inhibitor) improves left ventricular systolic/diastolic functions and exercise capacity in patients with chronic heart failure with reduced ejection fraction (Kim et al., 2015). This data indicates that phosphodiesterase inhibitors have been used to treat chronic heart failure; however, some of these drugs can produce some secondary effects such as arrhythmia (Ahmadieh et al., 2018), nausea, and vomiting (Wilsmhurst et al., 1983).

Analyzing these data, this study aimed to determine the interaction of forty amino derivatives with the phosphodiesterase 4 using the 3iak protein as a theoretical tool. Besides, some phosphodiesterase 4D inhibitors, such as zatolmilast, orismilast, lotamilast, and GSK256066 drugs were used as controls in the DockingServer program.

2. Materials and Methods

2.1 Chemical structure of amino derivatives

Amino derivatives (Figures 1 and 2; Tables 1 and 2) were used to evaluate their coupling with the phosphodiesterase 4D surface as follows:

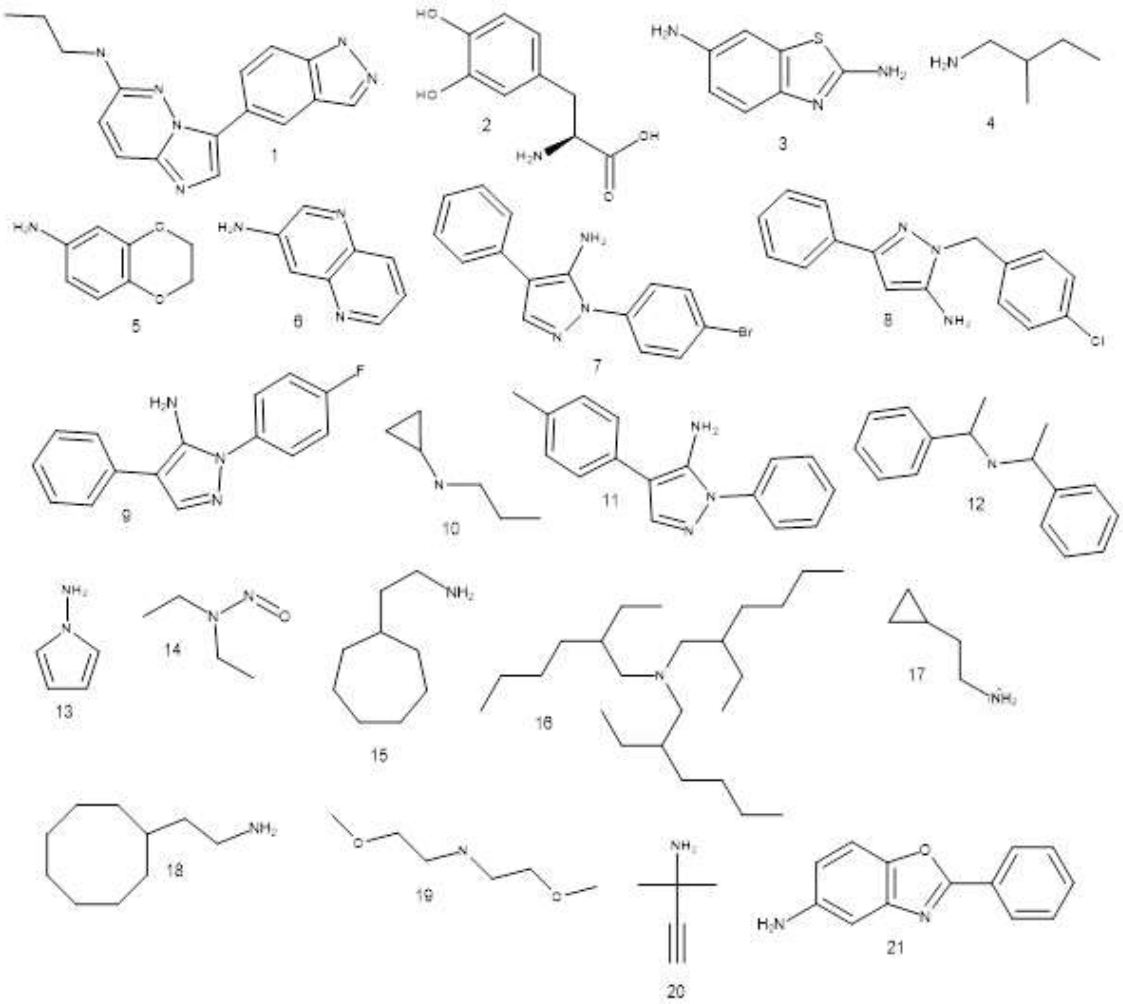

Figure 1. Chemical structure of amino derivatives (1-21). Source: https://pubchem.ncbi.nlm.nih.gov

Table 1. Name of amino derivatives (1-21).

1) 3-(1H-indazol-5-yl)-N-propylimidazo[1,2-b]pyri-dazin-6-amine	**11**) 1-Phenyl-4-p-tolyl-1H-pyrazol-5-amine
2) 3,4-Dihidroxi-L-fenilalanina	**12**) 1-phenyl-N-(1-phenylethyl)ethanamine
3) 1,3-benzothiazole-2,6-diamine	**13**) 1H-Pyrrol-1-amine
4) (2-Methylbutyl)amine	**14**) N-Nitrilotriethylamine
5) 1,4-Benzodioxan-6-amine	**15**) 2-Cycloheptyl-ethylamine
6) 1,5-Naphthyridin-3-amine	**16**) 2-ethyl-N,N-bis(2-ethylhexyl)hexan-1-amine
7) 1-(4-Bromophenyl)-4-phenyl-1H-pyrazol-5-amine	**17**) 2-cyclopropyl ethylamine
8) 1-(4-chlorobenzyl)-3-phenyl-1H-pyrazol-5-amine	**18**) 2-Cyclooctyl-ethylamine
9) 1-(4-Fluorophenyl)-4-phenyl-1H-pyrazol-5-amine	**19**) 2-methoxy-N-(2-methoxyethyl)ethanamine
10) 1-Cyclopropyl-propylamine	**20**) 2-methylbut-3-yn-2-amine
	21) 2-phenyl-1,3-benzoxazol-5-amine

Source: Authors, 2025.

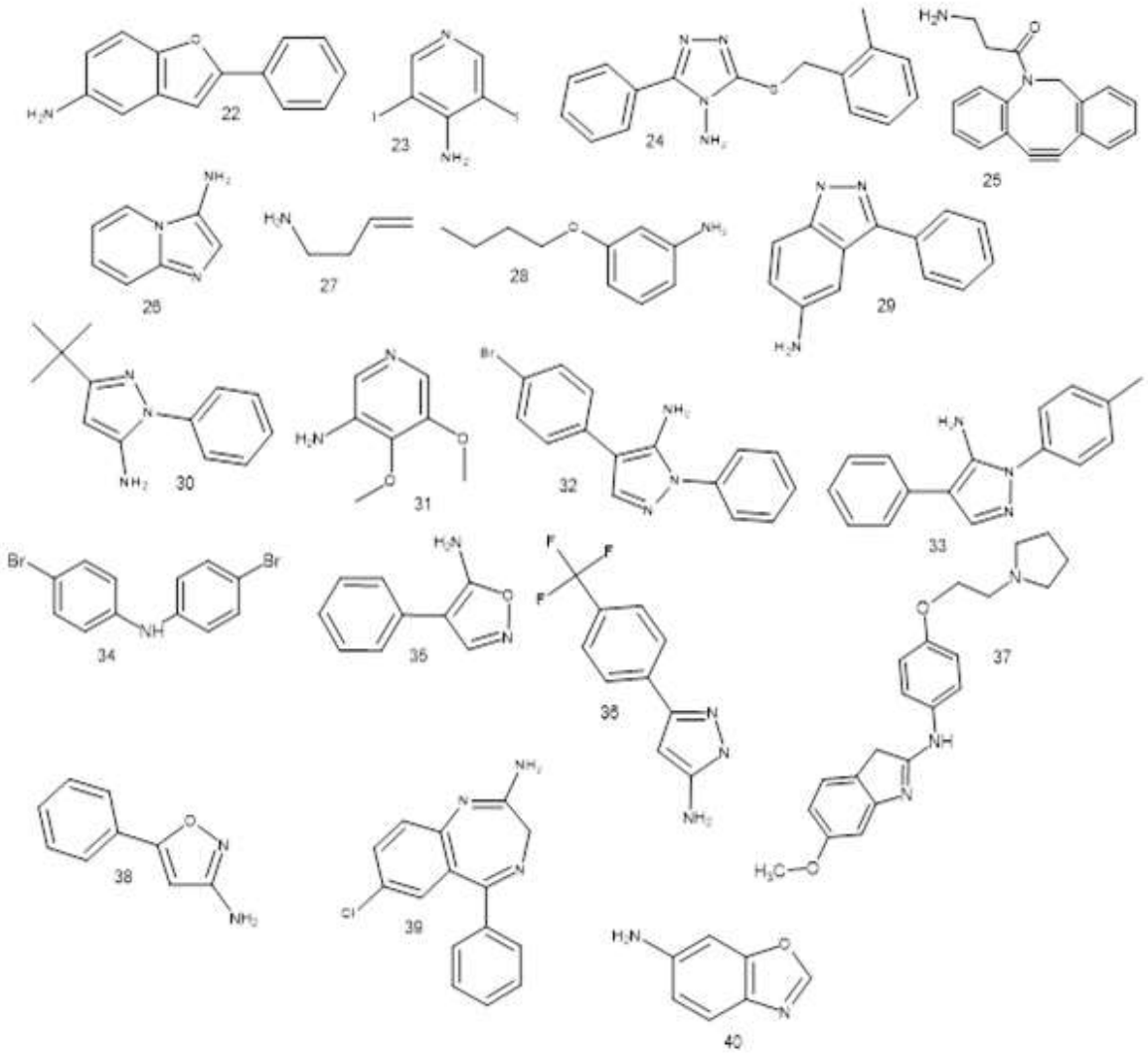

Figure 2. Chemical structure of amino derivatives (22-40). Source: https://pubchem.ncbi.nlm.nih.gov

Table 2. Name of amino derivatives (22-40).

22) 2-Phenyl-1-benzofuran-5-amine	**32**) 4-(4-Bromophenyl)-1-phenyl-1H-pyrazol-5-amine
23) 3,5-Diiodo-pyridin-4-ylamine	**33**) 4-Phenyl-1-p-tolyl-1H-pyrazol-5-amine
24) 3-((2-methylbenzyl)thio)-5-phenyl-4H-1,2,4-tri-azol-4-amine	**34**) 4-bromo-N-(4-bromophenyl)aniline
25) 3-amino-1-(2-azatricyclo[10.4.0.0^{4,9}] hexadeca-1(16),4,6,8,12,14-hexaen-10-yn-2-yl)propan-1-one	**35**) 4-Phenylisoxazol-5-amine
26) 3-Aminoimidazo[1,2-a]pyridine	**36**) 5-(4-Trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine
27) 3-Buten-1-amine	**37**) 5-Methoxy-2-(p-(2-(1-pyrrolidinyl)ethoxy)ani-lino) benzothiazole
28) 3-Butoxy-phenylamine	**38**) 5-Phenylisoxazol-3-amine
29) 3-Phenyl-1H-indazol-5-amine	**39**) 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2-amine
	40) Benzooxazol-6-ylamine

30) 3-tert-Butyl-1-phenyl-1H-pyrazol-5-amine

31) 4,5-Dimethoxypyridin-3-amine

Source: Authors, 2025.

2.2 Protein-ligand

The interaction of amino derivatives (1-40) with phosphodiesterase 4D was determined using 3iak protein (https://doi.org/10.2210/pdb3IAK/pdb) as a theoretical tool. In addition, zatolmilast, orismilast, lotamilast, and GSK256066 were used as controls in a DockingServer software (https://www.dockingserver.com/web).

2.3 Pharmacokinetic parameters

Pharmacokinetic data for amino derivatives (7, 12, 15, 18, and 33) were determined using the SwissADME software (Prasetyawan al., 2025).

2.4 Toxicology analysis

Toxicology degree for a min o derivatives (7, 12, 15, 18, and 33) was determined using the Gussar software (Bushueva; Parchenko, 2024).

3. Results

3.1 Ligand-protein complex

Table 3 shows the interaction of amino derivatives (1-40) and the controls (zatolmilast, orismilast, lotamilast, and GSK256066) with the 3iak protein surface.

Table 3. Coupling of amino derivatives (1-40), zatolmilast, orismilast, lotamilast, and GSK256066 with the 3iak protein surface.

Compound	Aminoacid residues
Zatolmilast	Tyr_{159}; His_{160}; His_{204}; Ser_{208}; Leu_{229}; Glu_{230}; Asn_{321}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Phe_{340}; Gln_{369}; Phe_{372}
Orismilast	Tyr_{159}; His_{160}; His_{204}; Ser_{208}; Met_{273}; Leu_{319}; Asn_{321}; Ile_{336}; Phe_{340}; Pro_{356}; Phe_{372}
Lotamilast	Tyr_{159}; His_{160}; Met_{273}; Asp_{318}; Ser_{208}; Ile_{336}; Phe_{340}; Met_{357}; Phe_{372}; Tyr_{375}
GSK256066	Met_{273}; His_{276}; Pro_{356}; Met_{357}; Phe_{372}; Tyr_{375}; Ile_{376}
1	Tyr_{159}; His_{160}; Met_{273}; Asp_{318}; Leu_{319}; Ile_{336}; Met_{357}; Gln_{369}; Phe_{372}; Ile_{376}
2	Tyr_{159}; His_{160}; Asp_{201}; Glu_{230}; Met_{273}; Asp_{318}; Leu_{319}; Ile_{336}
3	Tyr_{159}; His_{160}; Asn_{321}; Tyr_{329}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
4	His_{160}; His_{164}; Asp_{201}; His_{204}; Glu_{230}; His_{233}; Thr_{271}; Asp_{318}
5	$Tyr_{15\ Th9}$; His_{164}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Ile_{336}; Gln_{369}; Phe_{372}
6	Tyr_{159}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
7	Tyr_{159}; His_{160}; His_{164}; His_{200}; Asp_{201}; Glu_{230}; His_{233}; Thr_{271}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Ile_{326}; Trp_{332}; Thr_{333}; Ile_{336}; Phe_{372}
8	Tyr_{159}; Met_{273}; Leu_{319}; Asn_{321}; Tyr_{329}; Ile_{336}; Phe_{340}; Met_{357}; Gln_{369}; Phe_{372}; Ile_{376}
9	Tyr_{159}; His_{160}; His_{164}; Asp_{201}; Glu_{230}; Thr_{271}; Asp_{318}; Leu_{319}; Asn_{321}; Ile_{326}; Phe_{372}
10	His_{160}; His_{164}; His_{200}; Asp_{201}; Glu_{230}; His_{233}; Thr_{271}; Asp_{318}
11	Tyr_{159}; His_{160}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Phe_{340}; Gln_{369}; Phe_{372}
12	Tyr_{159}; His_{160}; His_{164}; Asp_{201}; Asp_{201}; His_{204}; Leu_{229}; Glu_{230}; Thr_{271}; Met_{273}; Asp_{318}; Leu_{319};

	Ile_{336}
13	Tyr_{159}; Asn_{321}; Pro_{322}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
14	His_{160}; His_{164}; His_{200}; Asp_{201}; His_{204}; Leu_{229}; Glu_{230}; His_{233}; Thr_{271}; Met_{273}; Asp_{318}; Leu_{319}
15	Tyr_{159}; His_{160}; His_{164}; His_{200}; Asp_{201}; Asp_{318}; Leu_{319}; Ile_{336} Phe_{372}
16	Tyr_{159}; His_{160}; His_{204}; Ser_{208}; Leu_{229}; Met_{273}; Asp_{318}; Phe_{340}; Met_{357}; Phe_{372}
17	His_{160}; His_{164}; His_{200}; Asp_{201}; His_{204}; Glu_{230}; Thr_{271}; Asp_{318}
18	Tyr_{159}; His_{160}; His_{164}; His_{200}; Asp_{201}; Met_{273}; Asp_{318}; Leu_{319}; Ile_{336}; Phe_{372}
19	Tyr_{159}; His_{160}; His_{204}; Asp_{201}; Glu_{230}; Met_{273}; Asp_{318}; Leu_{319}
20	His_{160}; His_{164}; His_{200}; Asp_{201}; Glu_{230}; His_{233}; Thr_{271}; Met_{273}; Asp_{318}
21	Tyr_{159}; Asn_{321}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Phe_{340};; Met_{340}; Gln_{369}; Phe_{372}
22	Tyr_{159}; His_{160}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
23	Tyr_{159}; Asn_{321}; Tyr_{329}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
24	Tyr_{159}; His_{160}; Asp_{201}; Glu_{230}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Ile_{336}; Gln_{369}; Phe_{372}
25	Tyr_{159}; His_{160}; His_{164}; His_{200}; Asp_{201}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Ile_{336}; Phe_{340}; Phe_{372}
26	Tyr_{159}; Asn_{321}; Ile_{336}; Phe_{340}; Gln_{369}; Phe_{372}
27	His_{160}; His_{164}; His_{200}; Asp_{201}; Glu_{230}; His_{233}; Thr_{271}; Asp_{318}
28	Tyr_{159}; His_{160}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
29	Tyr_{159}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Phe_{340}; Gln_{369}; Phe_{372}
30	Tyr_{159}; His_{160}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Phe_{340}; Gln_{369}; Phe_{372}
31	Tyr_{159}; Asn_{321}; Ile_{336}; Gln_{369}; Phe_{372}
32	Tyr_{159}; His_{160}; His_{164}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
33	Tyr_{159}; His_{160}; His_{164}; His_{200}; Asp_{201}; Glu_{230}; His_{230}; Thr_{271}; Met_{273}; Asp_{318}; Leu_{319}; Asn_{321}; Ile_{336}; Phe_{372}
34	Tyr_{159}; His_{160}; His_{164}; Asp_{201}; Asp_{318}; Leu_{319}; Asn_{321}; Tyr_{329}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
35	Tyr_{159}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Phe_{340}; Met_{35}; Gln_{369}; Phe_{372}
36	Tyr_{159}; His_{160}; His_{164}; Met_{273}; Asp_{318}; Asn_{321}; Pro_{322}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
37	Tyr_{159}; Met_{273}; Asn_{321}; Tyr_{329}; Thr_{333}; Ile_{336}; Met_{35}; Gln_{369}; Phe_{372}
38	Tyr_{159}; Leu_{319}; Asn_{321}; Tyr_{329}; Trp_{332}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}
39	Tyr_{159}; His_{160}; His_{164}; His_{200}; Asp_{201}; Ser_{208}; Met_{273}; Asp_{318}; Phe_{240}; Phe_{372}
40	Tyr_{159}; Asp_{318}; Leu_{319}; Asn_{321}; Pro_{322}; Tyr_{329}; Thr_{333}; Ile_{336}; Gln_{369}; Phe_{372}

Source: Authors, 2025.

3.2 Thermodynamic parameters

Table 4 shows the energy values and inhibition constant (Ki) for amino derivatives (1-40), zatolmilast, orismilast, lotamilast, and GSK2560 with the 3iak protein surface. The results showed that inhibition constants for compounds 7, 12, 15, 18, and 33 were lower compared with the controls.

Table 4. Thermodynamic parameters involved in the coupling of amino derivatives (1-40), zatolmilast, orismilast, lotamilast, and GSK2560 with the 3iak protein surface.

Compound	Est. Free	Est. Inhibitio	vdW + Hbond +	Electrostati	Total Intermol	Interact.

	Energy of Binding	n Constant (Ki)	desolv. Energy	c Energy	ecEnergy	Surface
Zatolmilast	-8.72	11.80	-9.41	0.85	-8.57	968.75
Orismilast	-7.46	3.43	-8.59	-0.05	-8.64	987.69
Lotamilas	-6.51	17.02	-8.36	-0.14	-8.50	1136.68
GSK2560	-7.20	5.25	-7.28	0.00	-7.29	817.85
1	-6.88	9.02	-6.91	-0.88	-7.79	735.06
2	-5.06	195.71	-4.01	-1.69	-5.71	524.49
3	-6.70	66.12	-5.93	-0.17	-6.00	479.27
4	-6.72	11.90	-3.84	-3.76	-7.61	329.27
5	-4.81	297.62	-5.06	-0.05	-5.11	417.57
6	-5.30	130.81	-5.53	-0.06	-5.60	406.12
7	-8.08	1.25	-8.68	-0.34	-9.02	639.16
8	-6.59	14.85	-7.77	-0.03	-7.80	704.02
9	-6.79	10.45	-7.77	-0.21	-7.98	665.01
10	-6.83	9.79	-3.96	-3.80	-7.76	354.28
11	-6.66	13.15	-7.69	-0.01	-7.70	747.22
12	-7.98	1.42	-6.47	-2.58	-9.05	680.18
13	-3.51	2.66	-3.73	-0.08	-3.81	285.77
14	-9.00	252.84	-3.61	-8.64	-12.25	486.79
15	-7.60	2.71	-5.00	-3.51	-8.50	479.34
16	-4.60	426.94	-7.74	-0.79	-8.54	1093.73
17	-6.26	25.90	-3.40	-3.75	-7.15	334.30
18	-7.87	1.70	-5.15	-3.62	-8.76	555.09
19	-6.28	24.96	-3.26	-2.73	-5.99	443.12
20	-6.79	10.60	-3.63	-3.76	-7.39	328.92
21	-6.28	24.92	-6.87	0.00	-6.87	538.38
22	-7.22	5.10	-7.65	-0.17	-7.82	579.29
23	-4.68	368.11	-4.94	-0.04	-4.98	347.56
24	-7.15	5.70	-8.55	-0.02	-8.57	757.61
25	-10.02	45.05	-7.85	-3.07	-10.92	729.18
26	-4.72	346.21	-4.91	-0.11	-5.02	430.20
27	-6.23	27.27	-3.26	-3.83	-7.09	310.56
28	-4.74	338.00	-6.10	-0.05	-6.15	528.34
29	-6.82	10.03	-7.34	-0.07	-7.41	578.75
30	-7.25	4.81	-8.04	-0.12	-8.16	616.87
31	-4.45	544.89	-4.74	-0.06	-4.79	478.73
32	-7.33	4.27	-8.28	-0.04	-8.32	613.43
33	-7.46	3.40	-8.23	-0.18	-8.40	688.75
34	-6.18	29.48	-6.83	0.04	-6.79	555.62
35	-5.61	76.64	-6.17	-0.03	-6.20	453.85

36	-6.77	10.91	-7.54	-0.13	-7.67	541.44
37	-6.95	8.11	-6.94	-0.73	-7.66	822.89
38	-6.08	34.72	-6.57	-0.11	-6.58	474.89
39	-8.95	275.77	-6.63	-3.08	-9.72	753.64
40	-4.92	246.11	-5.13	-0.09	-5.22	394.35

Source: Authors, 2025.

3.3 Bond type analysis

Figure 3 and Table 5 show different types of bonds involved in the coupling of amino derivatives 7, 12, 15, 18, and 33 with the 3iak protein surface.

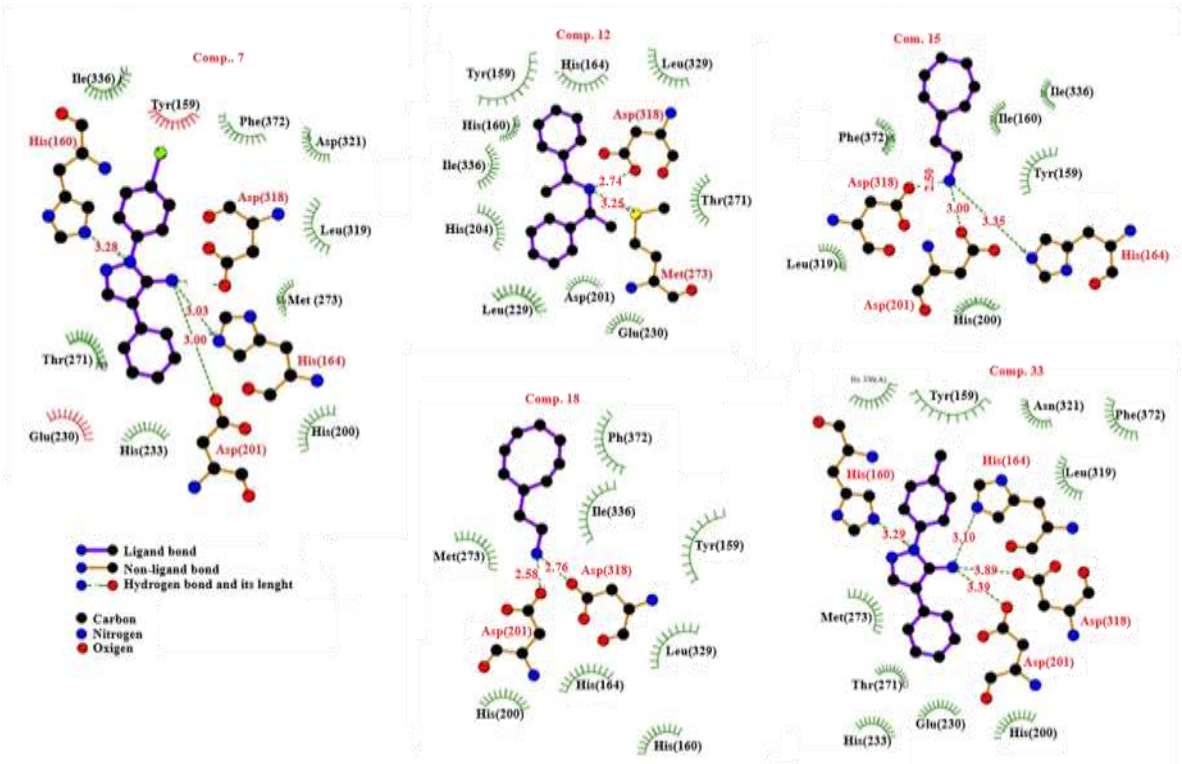

Figure 3. Aminoacid residues involved in the interaction of amino derivatives (7, 12, 15, 18, and 33) with the 3iak protein surface. Visualized with the DockingServer program. Source: Authors, 2025.

Table 5. Type of bonds involved in the coupling of amino derivatives (7, 12, 15, 18, and 33) with the 3iak protein surface.

Comp.	Hydrogen bond	Halogen-bond	Polar bond	Hydrophobic bond
7	His_{160}; His_{164}; Asp_{201}; Asp_{318}	Tyr_{159}; Asn_{321}	His_{200}	His_{233}; Met_{273}; Leu_{319}; Ile_{336}
12	Met_{273}; Asp_{318}			Tyr_{159}; His_{160}; Leu_{229}; Leu_{319}; Ile_{336}
15	His_{164}; Asp_{201}; Asp_{318}		His_{160}; His_{200}	Tyr_{159}; Leu_{319}; Ile_{336}; Phe_{372}
18	Asp_{201}; Asp_{318}		His_{160}; His_{164}; His_{200}	Leu_{319}; Met_{273}; Ile_{336}; Phe_{372}
33	His_{160}; His_{164}; Asp_{201}; Asp_{318}		Tyr_{159}; His_{200}	His_{233}; Leu_{319}; Met_{273}; Ile_{336}; Phe_{372}

Source: Authors, 2025.

3.4 Pharmacokinetics evaluation

The pharmacokinetic values for amino derivatives 7, 12, 15, 18, and 33 were determined using the SwissADME program. Table 6 displayed that amino derivatives have different affinity by Cyps involved in this study.

Table 6. Pharmacokinetic parameters analysis for amino derivatives 7, 12, 15, 18, and 33.

Compound	A	B	C	D	E	F	G	H	I
7	High	Yes	No	Yes	Yes	Yes	Yes	No	3.42
12	High	Yes	Yes	No	No	No	Yes	No	3.56
15	High	No	No	No	No	No	No	No	2.36
18	High	Yes	No	No	No	No	No	No	2.69
33	High	Yes	No	Yes	Yes	No	Yes	Yes	3.12

Note: A = GI absorption; B = BBB permeant; C = P-GP substrate; D = CYP1A2 inhibitor; E = CYP2C19 inhibitor; F = CYP2C9 inhibitor; G = CYP2D6 inhibitor; H = CYP3A4 inhibitor; I = Consensus Log PO/W. Source: Authors, 2025.

Other data shown in Table 7 indicate that the toxicity degree for compound 7 is associated with a higher dose compared to compounds 12, 15, 18, and 33.

Table 7. Toxicity analysis produced by amino derivatives 7, 12, 15, 18, 33, and the controls (zatolmilast, orismilast, lotamilast, and GSK2560) was determined using the Gussar program.

Compound	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
Zatolmilast	345.30	145.70	166.50	311.50
Orismilast	910.50	89.80	746.20	635.20
Lotamilast	690.20	102.80	1669.00	4221.00
GSK2560	946.00	253.00	456.80	835.40
7	605.60	201.10	962.10	1339.00
12	298.50	51.51	1438.00	768.70
15	186.30	59.43	727.20	336.20
18	199.70	64.43	897.80	443.50
33	406.20	122.80	859.10	574.50

Source: Authors, 2025.

4. Discussion

For several years, there has been great interest in the biological activity produced by some amino derivatives (Akama et al., 1996; Khalifa, 2018; Liuy et al., 1996; Saleh et al., 2024; Yan et al., 2022). There are studies that have shown that some amino derivatives can act as phosphodiesterase inhibitors. (Boswell-Smith et al., 2006; Walker et al., 1983). Analyzing these data, in this study, the interaction of forty amino acid derivatives with phosphodiesterase 4D for their possible use to treat cancer cells using a theoretical model.

In the literature, there are several methods to determine the coupling of different drugs with some biomolecules (Harren et al., 2024; Lu et al., 2024; Qiao et al., 2024), such as Gromos (Riniker et al., 2011), HarmonyDOCK (Plewczynski et al., 2014), DockingApp (Di Musio et al., 2017), Prodock (Trosset; Scheraga, 1999), and DockingServer software (Figueroa-Valverde et al., 2024). In this study, the coupling of forty amino derivatives with phosphodiesterase 4D was determined using the 3iak protein as a theoretical tool. Besides, some drugs such as zatolmilast, orismilast, lotamilast, and GSK2560 are used as controls in the DockingServer program. The

results showed different types of amino acid residues involved in the interaction of amino derivatives with the 3iak protein surface compared with the controls; these results could be due to differences in the chemical structure of each compound.

On the other hand, the energy levels for amino derivatives (1-40) were different compared with the controls. Besides, the inhibition constant for amino derivatives 7, 12, 15, 18, and 33 was lower compared with the controls. This phenomenon may be due to the different types of bonds involved in the coupling of 7, 12, 15, 18, and 33 with the 3iak protein surface. In this way, Figure 2 and Table 4 showed that His164 may interact with the compounds 7, 12, 15, 18, and 33 via a hydrogen bond; this phenomenon could result in higher affinity by the 3iak protein surface.

For several years, different pharmacokinetic models have been used to determine some properties involved in the biological activity of drugs, such as PKQuest (Levit, 2002), PharmPK (Ishaku et al., 2020), SwissADME (Sicak, 2021), and others. In this study, some pharmacokinetic parameters for compounds 7, 12, 15, 18, and 33 were determined using the SwissADME program. The results showed that amino derivatives 7, 12, 15, 18, and 33 may have higher absorption. Besides, the metabolism of compounds 12, 15, 18, and 33 involves different Cyps (P450 family). This phenomenon may be due to differences in the chemical structure or to the different lipophilicity degree of each compound.

There are several methods to predict the toxicity degree of different drugs, such as ToxCast (Dix et al., 2007), ToxII (Klopman; Rosenkranz, 1995), GENE-TOX (Waters; Auletta, 1995), Gussar (Askerova, 2023), and others. Analyzing these data, in this study theoretical toxicity of amino derivatives 7, 12, 15, 18, and 33 was determined using the GUSAR program to compare the results with the controls. The data indicated that the toxicity degree may depend on the dose administered for amino derivatives through different administration routes.

5. Conclusions

In this study, the interaction of amino derivatives (1-40) with phosphosterase 4D using the 3iak protein, zatolmilast, orismilast, lotamilast, and GSK2560 as theoretical tools in the DockingServer program. The results displayed that compounds 7, 12, 15, 18, and 33 may interact with different types of amino acids involved in the 3iak protein surface. Besides, other data showed that Ki values for compounds 7, 12, 15, 18, and 33 were lower compared with zatolmilast, orismilast, lotamilast, and GSK2560. This data suggests that compounds 7, 12, 15, 18, and 33 may act as phosphodiesterase 4D inhibitors, which could be a good therapeutic alternative for the treatment of heart failure.

6. Authors' Contributions

Magdalena Alvarez-Ramirez: conceptualization; data curation; formal analysis; writing – original draft; Writing – review & editing. *Marcela Rosas Nexticapa*: conceptualization; data curation; formal analysis; writing – original draft; writing – review & editing. *María Virginia Mateu-Armadand*: formal analysis; investigation.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

9. References

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