Analysis of the coupling of twenty-five benzothiazole analogs with the β_1-adrenergic receptor using a theoretical model

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Abstract

Some benzothiazoles have been developed with biological activity on the cardiovascular system through interaction with different biomolecules; however, the coupling with the β_1-adrenergic receptor is not clear. This research aimed to determine the interaction of some benzothiazole analogs (1-25) with the β_1-adrenergic receptor using some theoretical models. In this way, 2ycv protein and the controls (metoprolol, propranolol, and cyanopindolol) were used as theoretical tools in the DockingServer software. The results showed differences in the interaction of benzothiazole derivatives compared with the controls. Other data indicate that the inhibition constant (Ki) for benzothiazole analogs 10, 22, 23, and 25 was lower compared with metoprolol and cyanopindolol. All these data indicate that compounds 10, 22, 23, and 25 may act as β_1-adrenergic receptor inhibitors, translated into changes in blood pressure. Therefore, the benzothiazole derivatives 10, 22, 23, and 25 could be good antihypertensive agents.

Keywords: benzothiazole, analogs, hypertension, metoprolol, propranolol.

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

Resumo

Alguns benzotiazóis foram desenvolvidos com atividade biológica no sistema cardiovascular por meio da interação com diferentes biomoléculas; no entanto, o acoplamento com o receptor β_1-adrenérgico não está claro. O objetivo desta pesquisa foi determinar a interação de alguns análogos de benzotiazóis (1-25) com o receptor β_1-adrenérgico usando alguns modelos teóricos. Dessa forma, a proteína 2ycv e os controles (metoprolol, propranolol e cianopindolol) foram usados como ferramentas teóricas no software DockingServer. Os resultados mostraram diferenças na interação dos derivados de benzotiazóis em comparação com os controles. Outros dados indicam que a constante de inibição (*Ki*) para os análogos de benzotiazóis 10, 22, 23 e 25 foi menor em comparação com metoprolol e cianopindolol. Todos esses dados indicam que os compostos 10, 22, 23 e 25 podem atuar como inibidores dos receptores β_1-adrenérgicos, o que se traduz em alterações na pressão arterial. Portanto, os derivados benzotiazol 10, 22, 23 e 25 podem ser bons agentes anti-hipertensivos.

Palavras-chave: benzotiazol, análogos, hipertensão, metoprolol, propranolol.

1. Introduction

Cardiovascular diseases are a health problem worldwide, resulting in a decrease in the quality of life of the population (Joseph et al., 2017; Timmis et al., 2022; Chong et al., 2025). It's important to mention that several

factors contribute to developing cardiovascular disease, such as smoking (Kondo et al., 2019), alcohol (Klatsky, 2009), LDL-cholesterol (Mortensen and Nordestgaard, 2020), and obesity (Koliaki et al., 2019). Besides, hypertension has been associated with a risk factor for developing cardiovascular disease (Liu, 2025; Humbert et al., 2025; Hardy et al., 2025; Kario et al., 2025).

It is important to mention that several drugs have been used to treat this clinical pathology, such as nifedipine (Li et al., 2025; Rahman et al., 2025), captopril (Hansson et al., 2025; Schroeder; Seifert, 2025), spironolactone (Sarafidis et al., 2025; Shah et al., 2025), and the β-blockers [metoprolol, navelidol, and propranolol] (Alsaeid et al., 2024; Weber et al., 1998; Okamoto et al., 2025; Srinivasan, 2025). However, some of these drugs can produce secondary effects such as cough (Stoller et al., 1988; Ding et al., 2020), bradycardia (Handler, 2011), hyperkalemia (Williams et al., 2006), and others.

In search of a new therapeutic alternative, several compounds have been developed; for example, the synthesis of some 6-Benzoxazole derivatives with antihypertensive activity through interaction with Ang II receptor 1 (Wu et al., 2018). Another study showed the preparation of antihypertensive drug TAK-272 with biological activity on renin (Imaeda et al., 2016). Other reports indicate that compound MK-7145 produces antihypertensive effects through ROMK [renal outer medullary potassium channel] inhibition (Tang et al., 2016). Besides, the compound S-596 (arotinolol) was synthesized with antihypertensive activity as a β_1-receptor adrenergic antagonist (Hara et al., 1983; Nagamoto et al., 1984; Lee et al., 1989).

Other data indicate that some benzothiazole derivatives produce antiarrhythmic effects on β_1-receptor adrenergic in a biological model (Morini et al., 2005). Besides, a study showed that 6-(2-hydroxy-3-isopropylaminopropyloxy)-benzothiazole succinate (KF-577) produces antiarrhythmic activity in isolated guinea pig atria through β_1-receptor adrenergic inhibition (Tatsuno et al., 1976).

On the other hand, to characterize the interaction of antihypertensive drugs with some biomolecule, several theoretical methods have been used; for example, the interaction of some xanthon derivatives with β_1-receptor adrenergic was determined using Maestro, version 9.4 implemented from the Schrodinger software suite (Goshain; Ahmed, 2019).

Other data indicate the synthesis of two bisoprolol derivatives [*N*-acetyl bisoprolol and N-formyl bisoprolol] and their coupling with the β_1-receptor adrenergic surface using a theoretical model (Oktaviani et al., 2023). All these data indicate that different drugs can have biological activity on hypertension; however, there is little information about of coupling of benzothiazole derivatives with the β1-receptor adrenergic surface. Analyzing these data, this research aimed to evaluate the interaction of twenty-seven benzothiazole analogs with the β1-receptor adrenergic using the 2ycv protein as a theoretical tool. Furthermore, metoprolol, propranolol, and cynopyndolol drugs were used as controls in the DockingServer program.

2. Materials and Methods

2.1 Benzothiazole analogs

Figure 1 was used to determine the interaction with the β1-receptor adrenergic surface as follows.

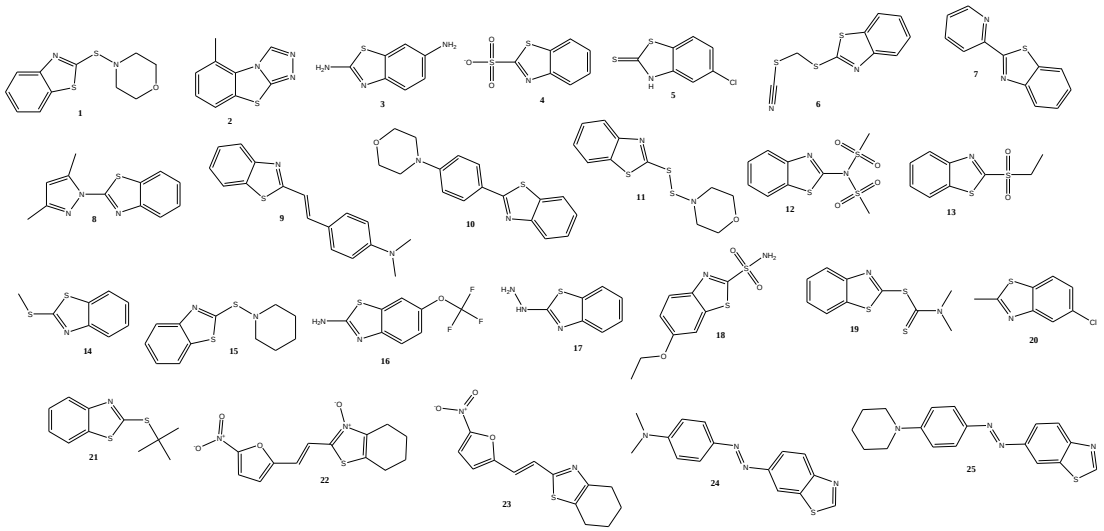

Figure 1. Chemical structure of benzothiazole analogs (1-25). Source: https://pubchem.ncbi.nlm.nih.gov/.

Table 1. Name of benzothiazole derivatives.

1 = (2-Morpholinothio)benzothiazole
2 = 1,2,4-Triazolo(3,4-b)benzothiazole, 5-methyl
3 = 1,3-benzothiazole-2,6-diamine
4 = 1,3-Benzothiazole-2-sulfonate
5 = 5-Chloro-3H-benzothiazole-2-thione
6 = 2-((Thiocyanatomethyl)thio)benzothiazole
7 = 2-(.alpha.-Pyridyl)benzothiazole
8 = 2-(3,5-Dimethyl-1-pyrazolyl)benzothiazole
9 = 2-(4-Dimethylaminostyryl)benzothiazole
10 = 2-(4-Morpholin-4-yl-phenyl)-benzothiazole
11 = 2-(Morpholin-4-yldisulfanyl)-benzothiazole
12 = 2-(Bis(methylsulfonyl)amino)benzothiazole
13 = 2-(ethylsulfonyl)-1,3-benzothiazole
14. 2-(Methylmercapto)benzothiazole
15 = 2-(Piperidinothio)benzothiazole
16 = 2-Amino-6-(trifluoromethoxy)benzothiazole
17 = Benzothiazol-2-yl-hydrazine
18 = 6-Ethoxy-benzothiazole-2-sulfonic acid amide
19 = 1-(1,3-benzothiazol-2-ylsulfanyl)-N,N-dime-thylmethanethioamide
20 = 2-methyl-5-chloro benzothiazole
21 = 2-tert-Butylthiobenzothiazole
22 = 4,5,6,7-Tetrahydro-2-(2-(5-nitrofuryl)vinyl)- benzothiazole 3-oxide
23 = 4,5,6,7-Tetrahydro-2-(2-(5-nitrofuryl)vinyl)-benzothiazole
24 = 6-((p-(Dimethylamino)phenyl)azo)benzothia-zole
25 = 6-((p-Piperidinophenyl)azo)benzothiazole

Source: Authors, 2025.

2.2 Protein-ligand

The coupling of benzothiazole analogs (1-25) with β_1-receptor adrenergic was determined using 2YCV protein (rcsb.org/structure/unreleased/2YCV) as a theoretical tool. In addition, metoprolol, propanolol, and cyanopindolol were used as controls in a DockingServer software (https://www.dockingserver.com/web).

2.3 Pharmacokinetic analysis

Pharmacokinetic data for benzothiazole analogs (10, 22, 23, and 25) were determined using the SwissADME software (Azzam et al., 2023).

2.4 Toxicology analysis

Toxicology evaluation for benzothiazole analogs (10, 22, 23, and 25) was determined using the Gussar software (Askerova, 2023).

3. Results

3.1 Ligand-Protein complex

Table 2 shows the coupling of benzothiazole analogs (1-25) and the controls (metoprolol, propranolol, and cyanopindolol) with the 2ycv protein surface.

Table 2. Interaction of benzothiazole derivatives (1-25), metoprolol, propranolol, diltiazem, and cyanopindolol with 2ycv protein surface.

Compound	Aminoacid Residues
Metoprolol	Asp_{121}; Val_{122}; Val_{125}; Thr_{126}; Phe_{201}; Ser_{215}; Trp_{303}; Phe_{306}; Phe_{307}; Phe_{325}; Val_{326}; Asn_{329}
Propanolol	Trp_{117}; Thr_{118}; Asp_{121}; Asp_{200}; Phe_{201}; Phe_{325}; Asn_{329}; Tyr_{333}
Cyanopindolol	Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{329};
1	Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Ser_{211}; Ser_{215}; Phe_{306}; Phe_{307}; Asn_{329}
2	Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{329}
3	Asp_{121}; Val_{122}; Val_{125}; Thr_{126}; Ser_{215}; Trp_{303}; Phe_{307}; Asn_{329}; Tyr_{333}
4	Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Tyr_{207}; Ser_{211}; Ser_{215}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{329}
5	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Trp_{303}; Phe_{306}; Asn_{329}
6	Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Thr_{203}; Tyr_{207}; Ala_{208}; Ser_{211}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{329}
7	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Trp_{303}; Phe_{306}; Asn_{329}
8	Asp_{121}; Phe_{201}; Thr_{203}; Tyr_{207}; Ala_{208}; Ser_{211}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{329}
9	Leu_{101}; Trp_{117}; Val_{122}; Val_{125}; Thr_{126}; Cys_{199}; Phe_{201}; Ser_{215}; Phe_{307}; Asn_{329}
10	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Thr_{126}; Phe_{201}; Ser_{215}; Phe_{307}; Asn_{329}
11	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Phe_{201}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{329}; Tyr_{333}
12	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{329}
13	Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Tyr_{207}; Ser_{211}; Ser_{212}; Ser_{215}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{329}
14	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Trp_{303}; Phe_{306}; Asn_{329}
15	Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Ser_{211}; Ser_{215}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{329}
16	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Cys_{199}; Trp_{303}; Phe_{306}; Asn_{329}
17	Asp_{87}; Val_{90}; Val_{94}; Asp_{121}; $Cysl_{124}$; Val_{125}; Ser_{128}; Phe_{299}; Trp_{303}; Tyr_{333}; Asn_{335}; Ser_{336}
18	Asp_{121}; $Phel_{201}$; Thr_{203}; Phe_{306}; Asn_{310}; Asn_{313}; Phe_{325}

19	Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Thr_{126}; Phe_{201}; Ser_{215}; Phe_{306}; Phe_{307}; Asn_{329}
20	Asp_{121}; Val_{122}; Val_{125}; Ser_{211}; $Ser_{2\|12}$; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{310}
21	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Phe_{201}; Trp_{303}; Phe_{306}; Phe_{307}; Asn_{329}
22	Trp_{117}; Thr_{118}; Asp_{121}; Val_{122}; Val_{125}; Thr_{126}; Phe_{201}; Ser_{215}; Phe_{307}
23	Val_{122}; Val_{125}; Phe_{201}; Thr_{203}; Ala_{208}; Ser_{215}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{313}; Phe_{325}
24	Val_{122}; Val_{125}; Phe_{201}; Thr_{203}; Ser_{215}; Phe_{306}; Phe_{307}; Asn_{310}; Asn_{313}; Phe_{325}
25	Leu_{101}; Val_{102}; Trp_{117}; Asp_{121}; Val_{122}; Phe_{201}; Ser_{211}; Ser_{215}; Phe_{306}; Phe_{307}; Asn_{329}; $Trp_{330;}$ Tyr_{333}

Source: Authors, 2025.

3.2 Thermodynamic parameters

Table 3 displayed the energy values and inhibition constant (*Ki*) for benzothiazole analogs (1-25), metoprolol, propranolol, and cyanopindolol with the 2ycv protein surface. The results indicate that inhibition constants for compounds 10, 22, 23, and 25 were lower compared with cyanopindolol.

Table 3. Thermodynamic parameters involved in the coupling of benzothiazole derivative (1-25), metoprolol, propranolol, and cyanopindolol with 2ycv protein surface.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
Metoprolol	-6.37	21.50	-6.86	-0.40	-7.26	812.43
Propranolol	-7.81	1.88	-6.63	-1.19	-7.82	736.86
Cyanopindolol	-7.41	3.71	-7.30	-0.68	-7.98	849.59
1	-6.76	11.05	-7.28	0.01	-7.27	639.93
2	-6.23	27.13	-6.32	0.09	-6.23	520.28
3	-5.11	180.11	-5.63	-0.07	-5.71	473.50
4	-5.58	81.30	-5.72	-0.16	-5.88	513.28
5	-6.28	24.96	-6.21	-0.07	-6.28	494.18
6	-6.82	10.00	-7.87	-0.05	-7.92	587.52
7	-6.56	15.42	-6.88	0.01	-6.86	576.28
8	-6.78	10.72	-7.05	-0.03	-7.08	640.12
9	-7.07	6.61	-7.96	0.01	-7.94	801.25
10	-7.69	2.31	-8.30	0.01	-8.29	752.30
11	-7.35	4.07	-7.99	-0.01	-8.00	662.00
12	-6.51	17.00	-7.15	-0.14	-7.29	686.15
13	-5.98	41.57	-6.47	-0.06	-6.53	562.59
14	-5.37	115.32	-5.64	-0.03	-5.67	479.14
15	-7.14	5.79	-7.74	0.09	-7.65	646.66
16	-6.35	22.14	-7.16	-0.08	-7,24	526.51
17	-5.82	54.30	-6.69	-0.20	-6.89	350.58
18	-6.14	31.73	-7.10	-0.13	-7.24	708.36
19	-6.47	18.13	-7.16	0.05	-7.11	662.11
20	-5.90	47.43	-5.92	0.02	-5.90	497.82
21	-6.43	19.40	-6.91	-0.03	-6.95	611.71

22	-7.91	1.62	-8.70	-0.17	-8.77	740.86
23	-7.58	2.77	-8.41	-0.05	-8.46	732.44
24	-6.77	10.91	-7.99	0.00	-7.99	783.22
25	-7.81	1.87	-8.78	0.04	-8.74	872.03

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

Other data suggest that some amino acid residues are involved in the ligand-protein complex formation; for example, Val_{122} and Val_{125} are specific for the interaction of benzothiazole-derivatives 10, 22, 23, and 25, and 26 with 3obc protein surface via hydrophobic bonds (Figure 2 and Table 4).

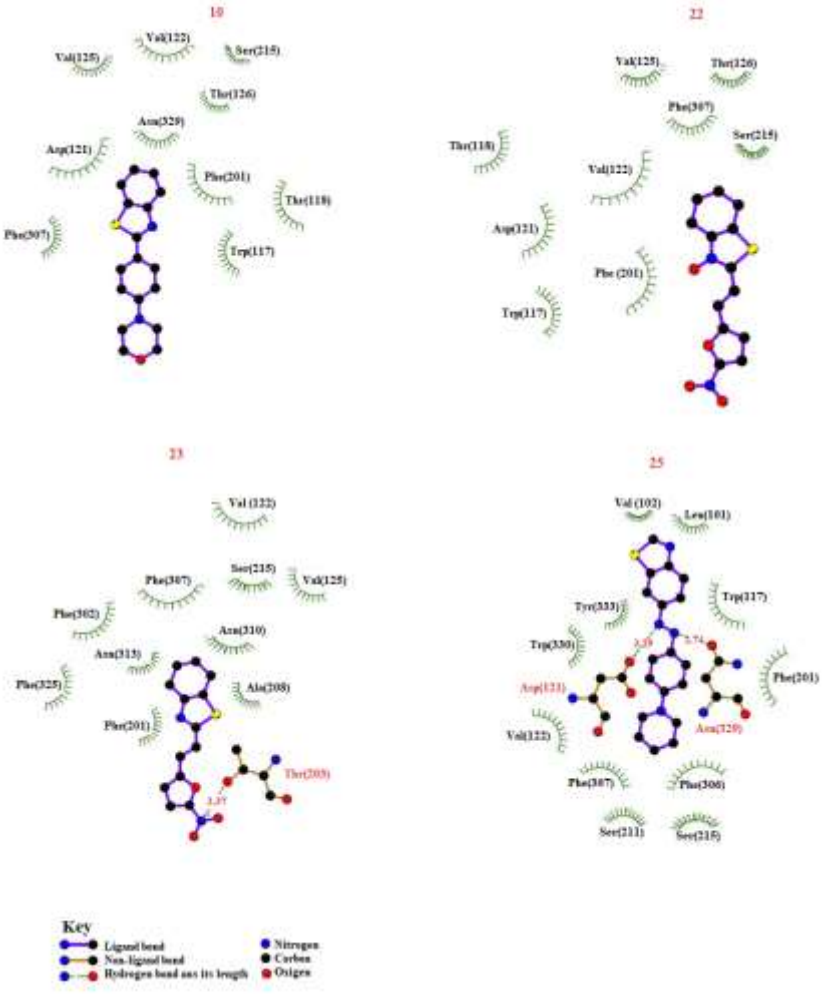

Figure 2. Interaction of benzothiazole analogs (10, 22, 23, and 25) with 2ycv protein surface. Visualized with the DockingServer program. Source: Authors, 2025.

Table 4. Type of bonds involved in the coupling of metoprolol, propranolol, cyanopindolol, and benzothiazole derivatives (10, 22, 23, and 25) with the 2ycv protein surface.

Compound	Hydrogen bond	Polar bond	Hydrophobic bond	pi-pi	Cation-pi
Metoprolol	Asn_{329}	Asn_{329}	Val_{122}; Val_{125}; Phe_{201}; Trp_{303}; Phe_{306}; Phe_{307}; Phe_{325}; Val_{326}	Phe_{306}	
Propranolol	Asp_{121}	Asp_{121}; Asn_{329}; Tyr_{333}	Trp_{117}; Phe_{201}	Phe_{201}; Phe_{325}	
Cyanopindolol	Asn_{329}	Thr_{118}; Asp_{121}; Asn_{310}; Asn_{329}	Val_{122}; Val_{125}; Phe_{201}	Phe_{201}; Phe_{306}; Phe_{307}	Phe_{201}; Phe_{307}
10		Asp_{121}	Trp_{117}; Val_{122}; Val_{125}; Phe_{307}		
22			Trp_{117}; Val_{122}; Val_{125}; Phe_{201}; Phe_{307}		
23	Thr_{203}	Asn_{310}; Asn_{313}	Val_{122}; Val_{125}; Phe_{201}; Phe_{306}; Phe_{307}		
25	Asp_{121}; Asn_{329}		Leu_{101}; Trp_{117}; Val_{102}; Val_{122}; Phe_{201}; Phe_{306}; Phe_{307}		

Source: Authors, 2025.

Pharmacokinetics parameter

Some pharmacokinetic factors for metoprolol, propranolol, cyanopindolol, and benzothiazole analogs (10, 22, 23, and 25 are shown in (Table 5). The results displayed that compound 11 great affinity for all Cyps involved in this study.

Table 5. Pharmacokinetic parameters for metoprolol, propranolol, cyanopindolol, and benzothiazole derivatives (10, 22, 23, and 25).

Compound	A	B	C	D	E	F	G	H	I
Metoprolol	High	Yes	No	No	No	No	Yes	No	2.78
Propranolol	High	Yes	No	Yes	No	No	Yes	No	2.84
Cyanopindolol	High	No	Yes	No	No	No	No	No	2.06
10	High	Yes	Yes	Yes	Yes	Yes	Yes	Yes	3.59
22	High	No	No	Yes	Yes	No	No	No	2.49
23	High	No	No	Yes	Yes	No	No	No	2.93
25	High	No	Yes	Yes	Yes	Yes	No	Yes	4.52

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 $P_{O/W}$. Source: Authors, 2025.

Finally, Table 6 showed the theoretical toxicity degree for metoprolol, propranolol, cyanopindolol, and compounds (10,22, 23, and 25).

Table 6. Toxicity values produced by benzothiazole derivatives (10,22, 23, and 25) were determined using Gussar software.

Compounds	**IP LD_{50} (mgkg)**	**IV LD_{50} (mgkg)**	**Oral LD_{50} (mgkg)**	**SC LD_{50} (mgkg)**
Metoprolol	113.80	79.30	1169.00	1232.00
Propranolol	197.70	60.30	988.70	849.70
Cyanopindolol	206.70	39.98	745.00	632.20
10	447.50	131.20	1155.00	1122.00
22	394.20	138.20	1517.00	1334,00
23	186.60	115.00	964.60	1252.00
25	345.30	104.40	1090.00	383.90

Source: Authors, 2025.

4. Discussion

Several studies indicate that some benzothiazole derivatives can produce biological activity on hypertension (Tatsuno et al., 1976; Morini et al., 2005); however, their interaction with the β_1-receptor adrenergic surface is not clear. Analyzing these data, in this study, the interaction of benzothiazole analogs with the β_1-receptor adrenergic surface was determined using some theoretical models, as follows:

4.1 Ligand-protein complex

There are several methods to characterize the coupling of different drugs with some proteins; for example, the formation of different ligand-protein complexes using some theoretical models (Taylor et al., 2002; Baud; Azevedo, 2025). In this research, the coupling of benzothiazole derivatives (1-25) with the β_1-receptor adrenergic surface was determined using 2ycv protein, metoprolol, propranolol, and cyanopindolol as theoretical tools in a DockingServer software; it is important to mention that this theoretical model is used to characterize the ligand-protein formation molecular simulation. The results displayed differences in the coupling of benzothiazole analogs (1-25) with amino acid residues involved in the 2ycv protein surface compared with metoprolol, propranolol, and cyanopindolol drugs. However, to determine the degree of interaction of each compound, it is necessary to evaluate some thermodynamic factors as follows:

4.2 Thermodynamic parameters

Some thermodynamic factors have been involved in the ligand-protein formation (Olson et al., 2008; Stickland et al., 2013; Krimmer; Klebe, 2015). In this way, several thermodynamic parameters were determined to evaluate the coupling of benzothiazole derivatives with β_1-adrenergic receptor surface using the 2ycv protein as a theoretical tool. The data indicate differences in energy levels for benzothiazole analogs (1-25) compared to metoprolol, propranolol, and cyanopindolol drugs.

Other results showed that the constant inhibition (Ki) for chalcone analog 1 was lower compared with nifedipine, amlodipine, verapamil, and diltiazem. Other data indicate that *Ki* for the compounds 10, 22, 23, and 25 was lower compared with metoprolol and cyanopindolol. Besides, the *Ki* for the compounds 22 and 25 was lower in comparison with metoprolol, propranolol, and cyanopindolol. This phenomenon may be due to differences in the interaction of benzothiazole derivatives with the 2ycv protein surface compared to controls. Thus, the ligand-protein complexes formed showed that compound 23 interacts with some amino acid residues, such as Thr_{203} through hydrogen bonds and Asn_{3133} through polar bonds. Furthermore, the amino acid residue Leu_{101} participates in the coupling of compound 25 with the 2ycv protein surface through hydrogen bonds. All these data suggest that compounds 10, 22, 23, and 25 may act as β_1-adrenergic receptor inhibitor agents, which may be translated as changes in blood pressure. These data suggest that benzothiazole derivatives 10, 22, 23, and 25 could be good therapeutic alternatives for the treatment of hypertension.

4.3 Pharmacokinetic parameters

For several years, several theoretical studies have been used to determine some pharmacokinetic properties for different compounds, such as PKCALC (Shumaker, 1986), PKSolver (Zhang et al., 2010), PHARM (Gomeni, 1984), MicroPharm-K (Urien, 1995), and SwissADME (Daina et al., 2017). In this way, pharmacokinetic parameters for benzothiazole derivatives (10, 22, 23, and 25) were determined using the SwissADME software to compare with metoprolol, propranolol, and cyanopindolol drugs. The data suggest that the metabolism of compounds 10, 22, 23, and 25 involves different Cyps (P450 family) due to differences in the chemical structure of each compound.

4.4 Toxicity analysis

In the literature, there are several studies to predict the toxicity degree of different drugs (Waters; Auletta, 1981; Klopman; Rosenkranz, 1995; Roncaglioni et al., 2013; Toropov et al., 2014). This research aimed to evaluate the possible toxicity degree produced by benzothiazole analogs (10, 22, 23, and 25) using metoprolol, propranolol, and cyanopindolol as controls in the GUSAR software. The results showed that the toxicity degree depends on the dose administered and the different routes of administration. In this way, compound 22 requires a higher dose via the oral route compared to controls.

5. Conclusions

In this study is reported the interaction of benzothiazole derivatives (compounds 1-25) with β_1-adrenergic receptor using 2ycv protein, metoprolol, propranolol, and cyanopindolol as theoretical tools in Docking Program. The results indicate that benzothiazole analogs 10, 22, 23, and 25 interact with different types of amino acids involved in the 7pjx protein surface. Besides, Ki for the compounds 10, 22, 23, and 25 was lower compared with metoprolol and cyanopindolol. All these data suggest that these benzothiazole derivatives may act as β_1-adrenergic receptor inhibitors; this phenomenon can be translated as a therapeutic alternative for hypertension.

6. Authors' Contributions

Alvarez-Ramirez Magdalena and *Rosas Nexticapa Marcela*: article writing, data evaluation, and corrections. *Bonilla- Zavaleta Enrique* and *Mateu-Armad Maria Virginia*: analysis data.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Does not apply.

9. References

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