Intramolecular interaction analysis of twenty-seven benzothiazole derivatives with CDK9 using a theoretical model

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Received: September 16, 2025 DOI: 10.14295/bjs.v4i12.798

Accepted: November 05, 2025 URL: https://doi.org/10.14295/bjs.v4i12.798

Abstract

There are studies indicating that some drugs can regulate cancer cell growth through CDK9 inhibition. This study aimed to evaluate the possibility of twenty-seven benzothiazole analogs interacting with CDK9 using the 3ocb protein as a theoretical tool. In addition, the fedracib, KB-0742, and *N*-vinylpyrrolidone drugs were used as controls in the DockingServer program. The results showed different amino acid residues involved in the docking of benzothiazole derivatives (1-27) with the 3ocb protein surface compared to the controls. Other data displayed that the inhibition constant (*Ki*) was lower for compounds 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 compared to KB-0742 and *N*-Vinylpyrrolidone. All this data indicate that these benzothiazole derivatives might have a higher affinity for the 3ocb protein surface, and this phenomenon could be translated as a CDK9 inhibition, resulting in a decrease in cancer cell growth.

Keywords: cancer, benzothiazole, CDK9, 3ocb protein.

Análise da interação intramolecular de vinte e sete derivados de benzotiazol com CDK9 usando um modelo teórico

Resumo

Existem estudos indicando que alguns fármacos podem regular o crescimento de células cancerígenas por meio da inibição de CDK9. O objetivo deste estudo foi avaliar a possibilidade de vinte e sete análogos de benzotiazol interagirem com CDK9 usando a proteína 3ocb como ferramenta teórica. Além disso, os fármacos fedracib, KB-0742 e *N*-vinilpirrolidona foram usados como controles no programa DockingServer. Os resultados mostraram diferentes resíduos de aminoácidos envolvidos no encaixe de derivados de benzotiazol (1-27) com a superfície da proteína 3ocb em comparação aos controles. Outros dados mostraram que a constante de inibição (*Ki*) foi menor para os compostos 1, 4, 7, 9, 11, 13, 15, 17, 19, 20-22, 24 e 26 em comparação com KB-0742 e *N*-vinilpirrolidona. Todos esses dados indicam que esses derivados de benzotiazol podem ter uma afinidade maior pela superfície da proteína 3ocb, e esse fenômeno pode ser traduzido como uma inibição de CDK9, resultando em uma diminuição no crescimento de células cancerígenas.

Palavras-chave: câncer, benzotiazol, CDK9, proteína 3ocb.

1. Introduction

Cancer is a global health problem; this clinical pathology produces a decrease in population quality of life (Dixit et al., 2024; Ionesscu et al., 2024; Çakmak; Uğurluoğlu, 2024). It is noteworthy that some cancers are caused by genetic mutations (Liu et al., 2024; Stankovic et al., 2024; Barili et al., 2024; Housini et al., 2024) or an overexpression of different biomolecules (Sarhadi et al., 2022), such as cyclin-dependent kinase [CDK9]

(Morales; Giordano, 2016; Franco et al., 2018; Zhang et al., 2018; Mandal et al., 2021; Anshabo et al., 2021). For example, a study showed a CDK9 overexpression in patients with acute myeloid leukemia using the PCR method [real-time quantitative] (Zhang et al., 2024).

Besides, a report indicates that CDK9 overexpression was associated with epithelial ovarian cancer (Parvathareddy et al., 2021). Another report displayed that CDK9 is a novel prognostic marker and a promising therapeutic target for osteosarcomas (Ma et al., 2019). It is important to mention that some drugs have been used as CDK9 inhibitors to decrease cancer cell growth; for example, a study indicates that alvocidib is a CDK9 inhibitor (Deep et al., 2018) that has beneficial effects in patients with acute myeloid leukemia (Lee; Zeiner, 2019). Another report showed that the atuveciclib drug is a PTEFb/CDK9 pathway inhibitor for treating cancer (Lücking et al., 2017).

Other data displayed that the dinaciclib drug decreases neuroblastoma growth through CDK2 and CDK9 inhibition (Chen et al., 2016). In addition, clinical data indicate that the TG02 drug acts as a CDK9 inhibitor using tumor cell lines (Boffo et al., 2018). Other studies showed that SNS-032 can act as CDK2, CDK7, and CDK9 inhibitors in chronic lymphocytic leukemia (Chen et al., 2018). Furthermore, a study indicates that the SNS-032 drug decreases cancer cell growth (ER/HER2-positive) through CDK9 inhibition (Noblejas-López et al., 2022). Other data indicate that the LS-007 drug has biological activity against human acute leukemia cells through CDK9 inhibition (Xie et al., 2016).

On the other hand, some theoretical studies have been carried out to determine the coupling of different compounds with CDK9 through molecular simulations (Singh et al., 2024; Habib et al., 2024; Zhang et al., 2022). In this way, a molecular study showed that CDK9 may be a target of wogonin using the AutoDOCK program (Polier et al., 2011). Another study indicates that geniposidic acid could act as a CDK9 inhibitor using the GLIDE program (Saikat et al., 2022).

Besides, theoretical data indicate that compound 4-{4-[4-(3-aminopropoxy)phenyl] -1H-pyrazol-5-yl}-6-chlorobenzene-1,3-diol (DB08045) shows high binding affinity by the CDK9/cyclin T1 complex, which involves some amino aminoacid residues such as Cys106, Asp104, Lys48, Ile25, Asn154, and Asp167 (Hussain et al., 2017). All these data suggest that different compounds can have affinity for CDK9; however, their interaction with CDK9 is not clear; perhaps this phenomenon is due to the chemical structure of different compounds. In this study, a theoretical analysis was carried out to determine the possible interaction of twenty-seven benzothiazole derivatives with CDK9 using the 3ocb protein, fedracib, KB-0742, and *N*-vinylpyrrolidine as theoretical tools in the DockingServer program.

2. Materials and Methods

2.1 Benzothiazole derivatives

Twenty-seven benzothiazole derivatives (Figure 1) were used to determine the possible interaction with the CDK9 protein as follows.

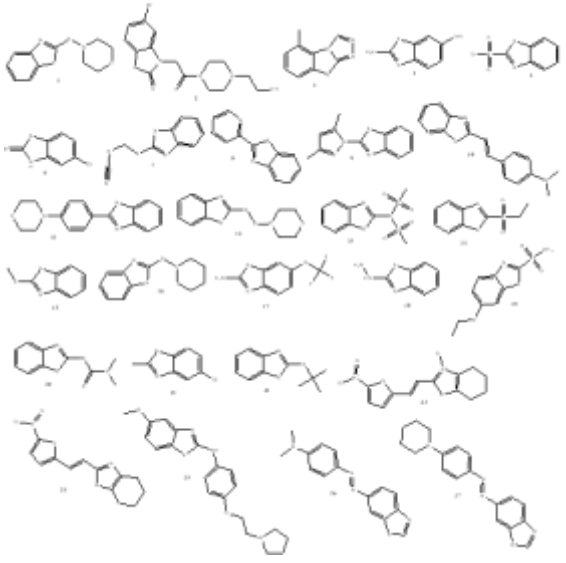

Figure 1. Chemical structure of benzothiazole derivatives (1-27). Source: https://pubchem.ncbi.nlm.nih.gov/.

Table 1. Name of benzothiazole derivatives.

1 = (2-Morpholinothio)benzothiazole	16 = 2-(Piperidinothio)benzothiazole
2 = (tiaramide) 5-Chloro-3-{2-[4-(2-hydroxy-ethyl)-piperazin-1-yl] -2-oxo-ethyl}-3H-benzothia-zol-2-one	17 = 2-Amino-6-(trifluoromethoxy)benzothiazole
3 = 1,2,4-Triazolo(3,4-b)benzothiazole, 5-methyl	18 = Benzothiazol-2-yl-hydrazine
4 = 1,3-benzothiazole-2,6-diamine	19 = 6-Ethoxy-benzothiazole-2-sulfonic acid amide
5 = 1,3-Benzothiazole-2-sulfonate	20 = 1-(1,3-benzothiazol-2-ylsulfanyl)-N,N-dime-thylmethanethioamide
6 = 5-Chloro-3H-benzothiazole-2-thione	21 = 2-methyl-5-chloro benzothiazole
7 = 2-((Thiocyanatomethyl)thio)benzothiazole	22 = 2-tert-Butylthiobenzothiazole
8 = 2-(.alpha.-Pyridyl)benzothiazole	23 = 4,5,6,7-Tetrahydro-2-(2-(5-nitrofuryl)vinyl)- benzothiazole 3-oxide
9 = 2-(3,5-Dimethyl-1-pyrazolyl)benzothiazole	24 = 4,5,6,7-Tetrahydro-2-(2-(5-nitrofuryl)vinyl)-benzothiazole
10 = 2-(4-Dimethylaminostyryl)benzothiazole	25 = 5-Methoxy-2-(p-(2-(1-pyrrolidinyl)ethoxy)-anilino)benzothiazole
11 = 2-(4-Morpholin-4-yl-phenyl)-benzothiazole	26 = 6-((p-(Dimethylamino)phenyl)azo)benzothia-zole
12 = 2-(Morpholin-4-yldisulfanyl)-benzothiazole	27 = 6-((p-Piperidinophenyl)azo)benzothiazole
13 = 2-(Bis(methylsulfonyl)amino)benzothiazole	
14 = 2-(ethylsulfonyl)-1,3-benzothiazole	
15 = 2-(Methylmercapto)benzothiazole	

Source: Authors, 2025.

2.2 Ligand-protein complex

Coupling of benzothiazole derivatives (1 to 27) with CDK9 surface was determined using 4bcf (PDB: https://doi.org/10.2210/pdb4BCF/pdb) as a chemical tool. Besides, compounds such as fedracib, KB-0742, and *N*-Vinylpyrrolidone were used as controls in the DockingServer program [31]. It is noteworthy that DockingServer has been used to investigate the coupling of molecules with different proteins using some methods such as MMFF94 force field (Halgren, 1998), AutoDock tools (Morris, Goodsell et al., 1998), Autogrid program (Morris, Goodsell et al., 1998), Lamarckian genetic algorithm (Solis and Wets,1981). Besides, each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å and quaternion and torsion steps of 5 were applied.

2.3 Pharmacokinetics parameter

Some pharmacokinetic factors for benzothiazole analogs 1, 4, 7, 9, 11, 13-15, 17, 19, 20-24, and 26 were determined using the Swiss ADME program (Bakchiet al., 2022).

2.4 Lipophilicity evaluation

The lipophilicity degree of benzothiazole analogs 1, 4, 7, 9, 11, 13-15, 17, 19, 20-24, and 26 was determined with the SwissADME program (Shweta; Rashmi, 2019).

2.5 Toxicology analysis

Toxicology evaluation for benzothiazole derivatives 1, 4, 7, 9, 11, 13-15, 17, 19, 20-24, and 26 was determined using Gussar software [https://www.way2drug.com/Gusar/acutox-predict.html] (Khrapova et al., 2023).

3. Results

3.1 Pharmacophores

Pharmacophores for benzothiazole derivatives (1-27) were designed using the LigandScout 4.5 program. Figure 1-3 displays different types of hydrogen bond donors and acceptors, lipophilic areas, and positively and negatively ionizable chemical groups for different benzothiazole derivatives.

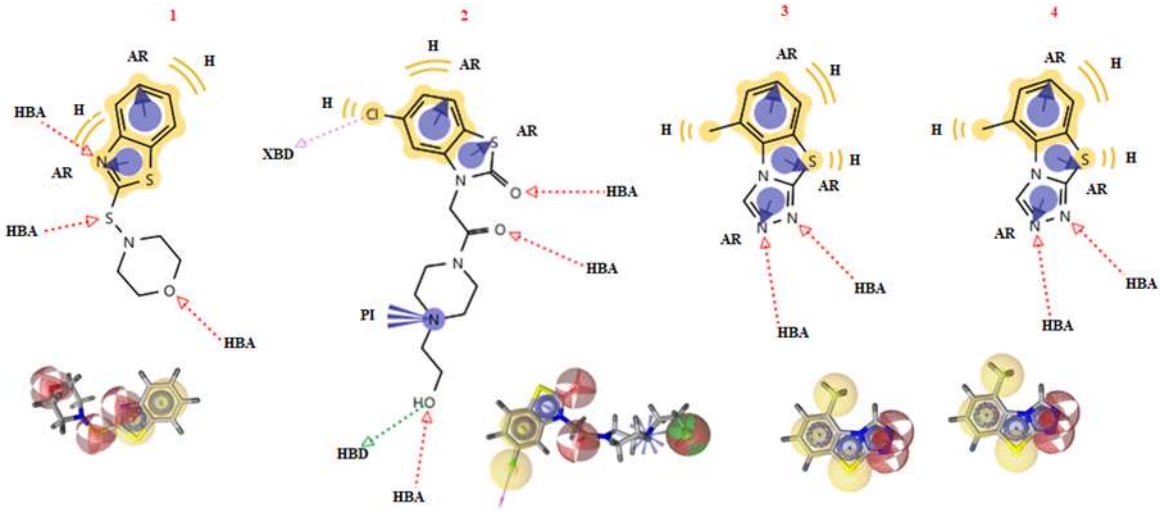

Figure 1. Pharmacophore model for benzothiazole analogs (1-4). Visualized with the LigandScout 4.5 software. The results showed hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and lipophilic areas. Source: Authors, 2025.

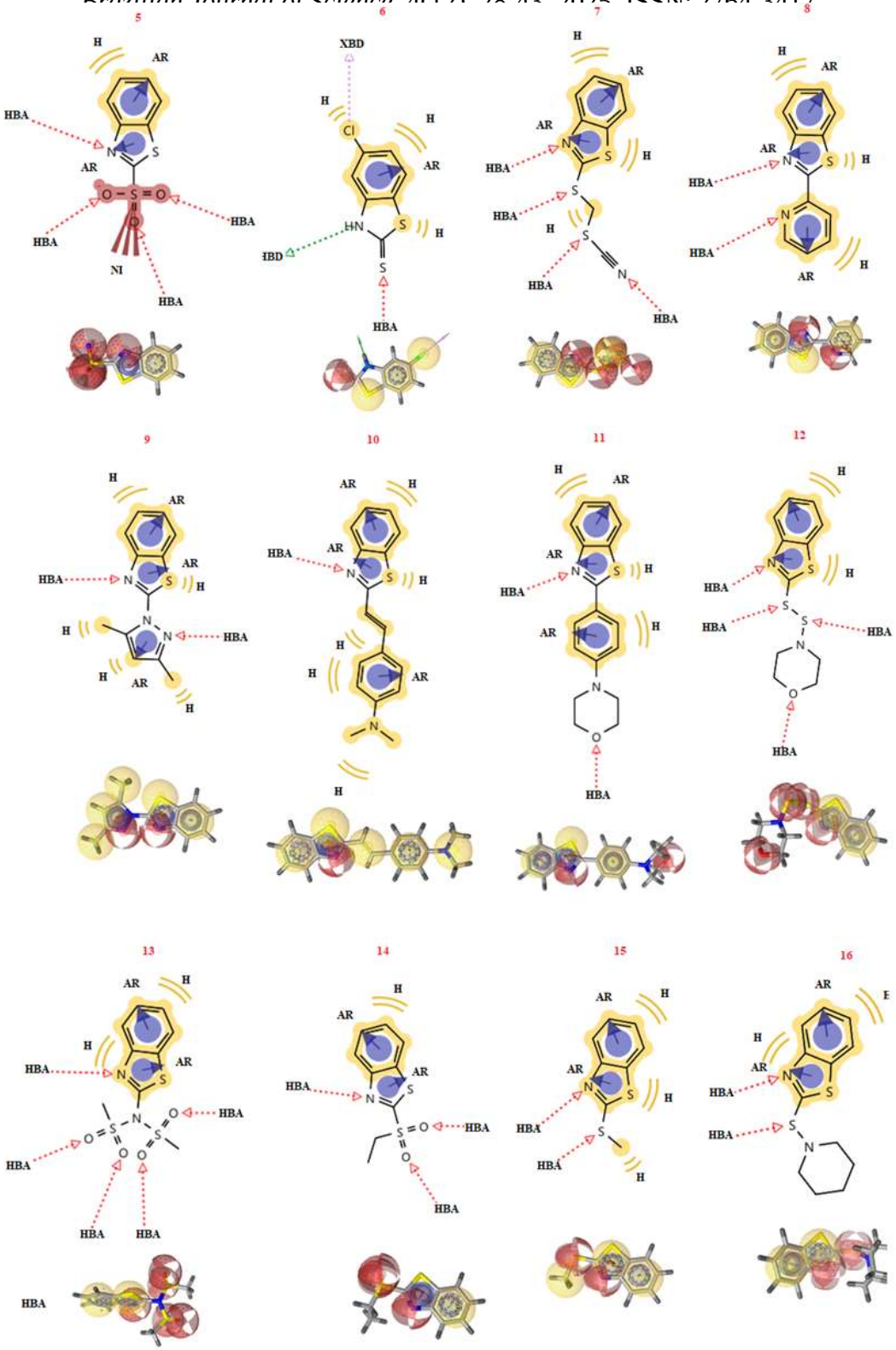

Figure 2. Design of pharmacophore models for benzothiazole derivatives (5-16). Scheme visualized with the LigandScout 4.5 program. The results displayed hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and lipophilic areas. Source: Authors, 2025.

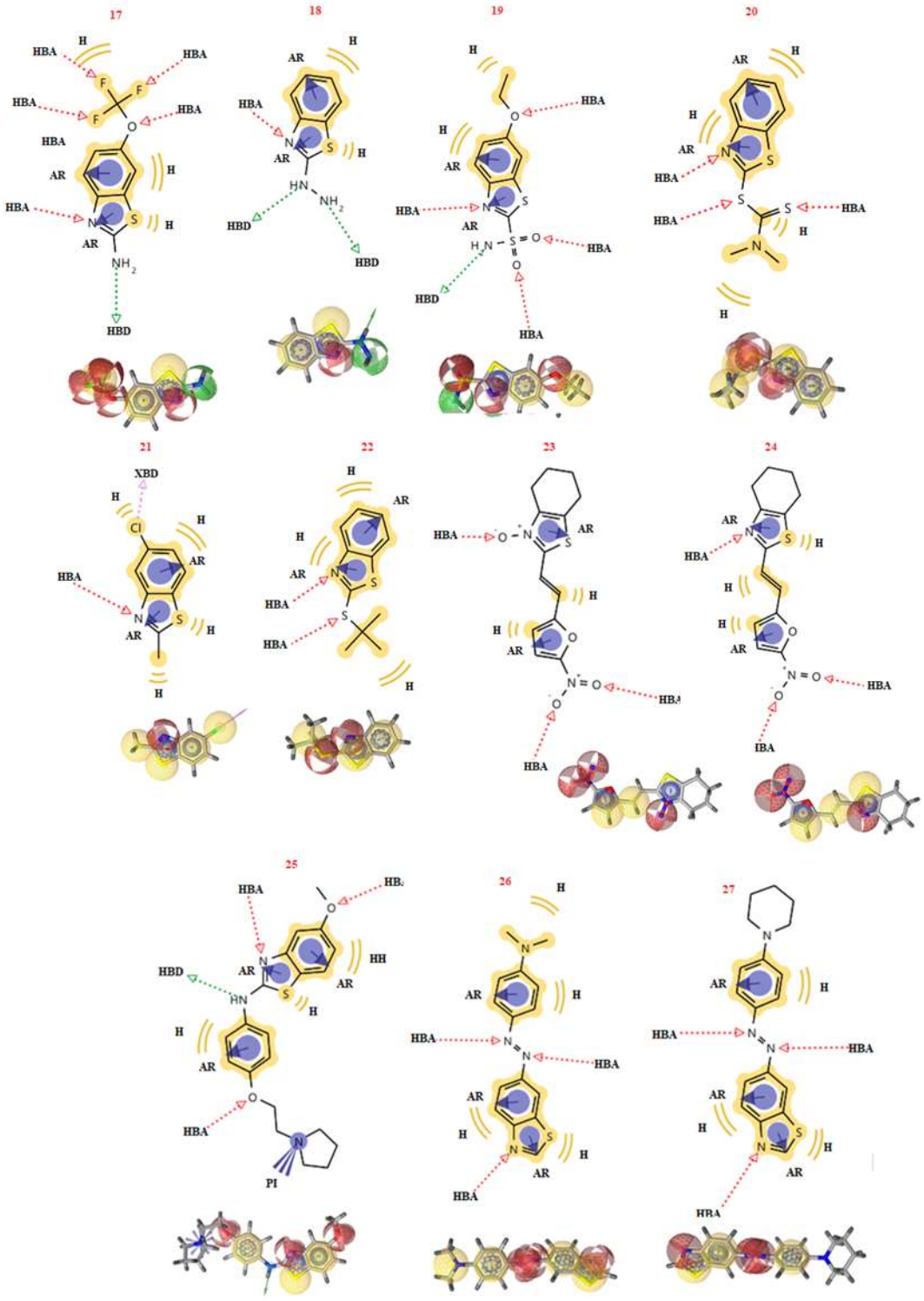

Figure 3. The scheme displays pharmacophores for benzothiazole derivatives (17-27). Visualized with the LigandScout 4.5 program. The data showed hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and lipophilic areas. Source: Authors, 2025.

3.2 Ligand-protein complex

Table 2 shows the interaction of benzothiazole-derivatives (1-27) and the controls (fedracib, KB-0742, and *N*-vinylpyrrolidine) with the 3ocb protein surface.

Table 2. Amino acid residues involved in the coupling of benzothiazole derivatives (1-27), fedracib, KB-0742, and *N*-vinylpyrrolidine with the 30cb protein surface.

Compound	Aminoacid Residues
Fedracib	Thr_{62}; Arg_{65}; Leu_{170}; Arg_{188}; Arg_{195}
KB-0742	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{184}; Tyr_{185}; Arg_{188}; Val_{189}; Arg_{204}
N-vinylpyrridolinone	Asn_{187}; Arg_{195}; Glu_{234}; Leu_{261}
1	Arg_{65}; Arg_{148}; Arg_{188}; Val_{189}; Arg_{204}
2	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Arg_{188}; Val_{189}
3	Asn_{187}; Arg_{188}; Arg_{195}; Leu_{199}; Glu_{234}; Leu_{261}
4	Arg_{148}; Arg_{172}; Tyr_{185}; Arg_{188}; Val_{189}
5	Arg_{148}; Leu_{170}; Arg_{188}; Val_{189}; Tyr_{206}
6	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{188}; Val_{189}
7	Arg_{148}; Arg_{172}; Tyr_{185}; Arg_{188}; Val_{189}; Arg_{204}
8	Arg_{184}; Gly_{202}; Glu_{203}; Arg_{204}; Asp_{205}; Glu_{260}; Leu_{261}
9	Asn_{187}; Arg_{188}; Arg_{204}; Leu_{261}
10	Asn_{187}; Arg_{188}; Arg_{195}; Glu_{234}; Leu_{261}
11	Arg_{148}; Leu_{170}; Arg_{172}; Asp_{188}; Val_{189}
12	Thr_{62}; Arg_{65}; Arg_{148}; Leu_{170}; Arg_{188}; Val_{189}
13	Ile_{61}; Thr_{62}; Arg_{65}; Arg_{148}; Arg_{172}
14	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Val_{189}
15	Arg_{65}; Arg_{172}; Arg_{188}; Val_{189}
16	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Val_{189}
17	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{184}; Val_{189}
18	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Tyr_{185}; Arg_{188}; Val_{189}; Tyr_{206}
19	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Arg_{188}; Val_{189}
20	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Arg_{188}; Val_{189}
21	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Arg_{188}; Val_{189}
22	Arg_{65}; Arg_{148}; Arg_{172}; Arg_{188}; Val_{189}; Arg_{204}
23	Arg_{148}; Arg_{172}; Asn_{183}; Arg_{188}; Tyr_{185}
24	Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Arg_{188}; Val_{189}
25	Ile_{61}; Thr_{62}; Arg_{65}; Arg_{148}; Leu_{170}; Arg_{172}; Arg_{188}; Val_{189}
26	Arg_{148};; Arg_{172}; Asn_{187}; Arg_{188}; Arg_{204}
27	Arg_{148}; Leu_{170}; Arg_{172}; Arg_{184}; Tyr_{185}; Arg_{188}; Val_{189}

Source: Authors, 2025.

3.3 Thermodynamic parameters

Table 3 shows the energy values and inhibition constant (Ki) involved in the interaction of benzothiazole-derivatives (1-27), fedracib, KB-0742, and *N*-vinylpyrrolidine with the 3ocb protein surface. It is important to mention that inhibition constants for compounds 17, 21, and 22 were lower compared with fedracib.

Table 3. Thermodynamic parameters involved in the coupling of benzothiazole-derivatives (1-27), fedracib, KB-0742, and *N*-Vinylpyrrolidine with 3ocb protein surface.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
Fedracib	-3.95	1.26	-4.83	-0.01	-4.84	676.80
KB-0742	-2.62	11.92	-4.29	0.81	-3.48	608.71
N-vinylpyrridolinone	-3.11	5.24	-3.42	0.01	-3.41	308.74
1	-3.76	1.74	-4.28	-0.09	-4.37	480.31
2	-2.81	8,68	-3.77	0.62	-3.14	513.81
3	-4.11	965.01	-4.16	0.05	-4.11	391.70
4	-3.72	1.86	-4.03	0.01	-4.02	411.59
5	-5.12	175.22	-2.99	-2.44	-5.42	437.73
6	-4.14	930.68	-4.10	-0.04	-4.14	431.28
7	-3.61	2.25	-4.35	-0.16	-4.52	458.63
8	-4.33	665.96	-4.64	0.01	-4.63	464.96
9	-3.96	1.26	-3.92	-0.33	-4.26	450.51
10	-4.76	326.52	-5.63	-0.01	-5.65	577.62
11	-3.93	1.33	-4.51	-0.01	-4.52	559.43
12	-4.17	882.47	-4.49	-0.08	-4.55	589.30
13	-3.23	4.28	-3.96	-0.12	-4.09	494.69
14	-3.45	2.94	-3.96	-0.09	-4.04	484.28
15	-3.73	1.86	-3.90	-0.13	-4.02	416.39
16	-4.25	765.89	-4.73	-0.01	-4.75	521.43
17	-4.07	1.03	-4.80	-0.01	-4.81	422.46
18	-2.97	6.59	-3.64	0.06	-3.59	412.32
19	-3.12	5.14	-4.16	-0.04	-4.20	495.85
20	-3.47	2.84	-3.94	-0.13	-4.07	475.56
21	-4.07	1.03	-4.02	-0.05	-4.07	432.83
22	-4.06	1.06	-4.43	-0.15	-4.58	463.60
23	-4.40	590.89	-5.14	-0.15	-5.29	485.55
24	-3.81	1.62	-4.70	0.03	-4.68	561.13
25	-2.83	8.36	-4.07	0.51	-3.55	707.17
26	-3.58	2.38	-4.33	-0.19	-4.19	462.25
27	-4.24	781.82	-5.45	0.03	-5.42	624.60

Note: A = Est: Free Energy of Binding (kcal/mol); B = Inhibition Constant (Ki, mM); C = vdW + Hbond + desolv Energy (kcal/mol); D = Electrostatic Energy (kcal/mol); E = Total Intermolec. Energy (kcal/mol); F= Interact. Surface. Source: Authors, 2025.

Other results indicate that several amino acid residues are involved in the formation of the ligand-protein complex. In this way, Arg148 is specific for the interaction of benzothiazole-derivatives 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 with the 3obc protein surface.

Table 4. Coupling of fedracib, KB.0742, *N*-vinylpyrrolidine (N-VP), and benzothiazole derivatives (1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26) with 3obc protein surface.

Compound	Hydrogen bond	Polar bond	Hydrophobic bond	Cation-pi	Halogen bond
Fedracib	Arg_{188}	Arg_{188}; Arg_{195}	Leu_{170}		
KB-0742	Arg_{184}; Arg_{204}	Arg_{65}; Arg_{148}; Arg_{172}	Leu_{170}; Tyr_{185}; Val_{189}		
N-VP	Asn_{187}; Glu_{234}	Glu_{234}	Leu_{261}		
1		Arg_{148}; Arg_{204}	Val_{189}		
4	Arg_{188}	Arg_{148}; Arg_{172}	Val_{189}	Tyr_{185}	
7		Arg_{148}; Arg_{172}; Arg_{188}	Val_{189}		
9		Arg_{148}; Arg_{204}	Leu_{261}		
11	Arg_{188}	Arg_{148}; Arg_{172}	Val_{189}		
13	Thr_{62}	Thr_{62}; Arg_{65}; Arg_{172}	Ile_{61}		
14		Arg_{65}; Arg_{148}	Leu_{170}; Val_{189}		
15		Arg_{148}	Val_{189}		
17	Arg_{172}; Arg_{184}	Arg_{172}	Leu_{170}; Val_{189}		Leu_{170}
19	Arg_{188}; Val_{189}	Arg_{65}; Arg_{148}; Arg_{172}			
20		Arg_{148}	Leu_{170}; Val_{189}		
21		Arg_{148}	Val_{189}		
22		Arg_{148}	Val_{189}		
24		Arg_{148}	Leu_{170}; Val_{189}		
26		Arg_{148}; Arg_{172}; Arg_{188}; Arg_{204}			

Source: Authors, 2025.

3.4 Pharmacokinetics parameter

The pharmacokinetic values for benzothiazole-derivatives 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 are shown in Table 5 using the SwissADME program. The results displayed that compound 11 great affinity by all Cyps involved in this study.

Table 5. Pharmacokinetic parameters for benzothiazole derivatives (4, 7, 9, 11, 13, 15, 17, 19, 20-24, and 26).

Compound	***A***	***B***	***C***	***D***	***E***	***F***	***G***	***H***	***I***
1	High	No	No	Yes	Yes	Yes	No	No	2.66
4	High	No	No	Yes	Yes	No	No	No	1.26
7	High	No	No	Yes	Yes	Yes	No	No	3.05
9	High	Yes	No	Yes	Yes	Yes	No	No	3.16
11	High	Yes	Yes	Yes	Yes	Yes	Yes	Yes	3.59
13	**High**	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**1.09**
14	High	No	No	Yes	Yes	No	No	No	2.30
15	High	Yes	No	Yes	Yes	Yes	No	No	2.88
17	High	Yes	No	Yes	Yes	No	No	No	2.81
19	High	No	No	No	Yes	No	No	No	1.40
20	High	No	No	Yes	Yes	Yes	No	No	3.07
21	High	Yes	No	Yes	Yes	No	No	No	3.14
22	High	Yes	No	Yes	Yes	Yes	No	No	3.72
24	High	No	No	Yes	Yes	No	No	No	2.93
26	High	Yes	No	Yes	Yes	Yes	No	No	3.83

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.

Finally, Table 6 showed the theoretical toxicity degree of compounds (1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26).

Table 6. Toxicity analysis produced by benzothiazole derivatives (4, 7, 9, 11, 13, 15, 17, 19, 20-24, and 26) was determined using the Gussar program.

Compound	**IP LD_{50} (mgkg)**	**IV LD_{50} (mgkg)**	**Oral LD_{50} (mgkg)**	**SC LD_{50} (mgkg)**
1	365.00	216.00	1060.00	1249.00
4	450.70	252.30	812.00	363.30
7	192.20	154.00	723.00	197.20
9	395.20	225.20	688.00	608.90
11	447.50	131.20	1155.00	1122.00
13	339.00	305.90	1032.00	676.40
14	637.50	263.10	1821.00	860.00
15	345.70	138.80	1144.00	526.20
17	379.40	200.10	111.66	599.60
19	695.40	719.00	2530.00	1863.00
20	444.33	155.70	1238.00	878.00
21	334.00	70.84	737.20	648.70
22	1051.00	150.50	2130.00	688.60
24	186.60	115.10	964.60	1252.00
26	324.70	187.20	1832.00	889.20

Source: Authors, 2025.

4. Discussion

In the literature, there are several reports on the biological activity of different benzothiazole derivatives on cancer cells (Kini et al., 2017; Kok et al., 2008; Mohamed et al., 2017; Pathak et al., 2020; Irfan et al., 2020), which involves different types of molecular mechanisms (Uremis et al., 2017); perhaps this phenomenon could be due to differences in the chemical structure of benzothiazole derivatives. To evaluate this hypothesis in this study, some strategies were carried out as follows:

4.1 Pharmacophores design

For several years, some theoretical methods have been used to predict the coupling of drugs with different biomolecules, such as Flap (Baroni et al., 2007), Pharmer (Koes; Camacho, 2011), Moe (Chen; Foloppe, 2008), and Phase (Dixon et al., 2006). In addition, other studies have used the LigandScout program, which is based on pharmacophore design with three-dimensional chemical characteristics. (Figueroa-Valverde et al., 2024). Therefore, in this study, several pharmacophores for twenty-seven benzothiazole derivatives were prepared using the LigandoScout 4.5 program to characterize the interaction of functional groups involved in these compounds with the CDK9 protein. The results showed different functional groups, which can act as hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), and halogen bond donors (XBD) with some biomolecules. It is important to mention that the chemical characteristics of each benzothiazole derivative may be a determining factor for its interaction with the CDK9 protein surface, which could result in ligand-protein complex formation (Figure 2-4).

4.2 Ligand-protein analysis

There are studies in the literature on the interaction of different compounds acting as ligands with various biomolecules; this phenomenon is based on their chemical structure and the three-dimensional structure of proteins or enzymes. It is important to mention that the formation of a ligand-protein complex can be determined using some theoretical models, such as Gromos (Riniker et al., 2011), HarmonyDOCK (Plewczynski et al., 2014), DockingApp (Di Musio et al., 2017), and Prodock (Trosset; Scheraga, 1999). Furthermore, the DockingServer software has been used to determine the docking of several compounds with different proteins (Figueroa-Valverde et al., 2023).

The DockingServer software is a dynamic simulation model and molecular geometry optimization for proteins and other biological systems. Therefore, to determine the docking of twenty-seven benzothiazole derivatives with the surface of CDK9 protein, 3ocb protein, fedracib, KB-0742, and N-vinylpyrrolidone were used as theoretical tools in the DockingServer program. The results showed differences in the number of amino acid residues involved in the docking of twenty-seven benzothiazole derivatives with the surface of 3ocb protein compared to fedracib, KB-0742, and N-vinylpyrrolidone. This phenomenon could be due to i) differences in the chemical structure of benzothiazole derivatives compared to fedracib, KB-0742, and N-vinylpyrrolidone; ii) differences in the energy levels produced in the formation of ligand-protein complexes.

Analyzing these data, some thermodynamic parameters were determined using the Dockingserver program. The results indicate differences in the energy levels for benzothiazole analogs (1-27) compared with fedracib, Kb-0742, and N-vinylpyrrolidone. Other data showed that the inhibition constant (Ki) for compounds 21 and 22 was lower compared with fedracib, KB-0742, and N-vinylpyrrolidone. Besides, Ki for 11, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 was lower in comparison with KB-0742 and N-vinylpyrrolidone. This phenomenon may be conditioned by the type of bond; in this way, the results showed that amino acid residues such as Arg148 can interact with some benzothiazole derivatives through polar bonds and Leu170 and Val189 via hydrogen bonds.

This data is different from studies previously reported for the interaction of benzothiazole derivative (5-Amino-6-(benzothiazol-2-yl)-7-(4-chlorophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile with CDK9 through hydrogen bonds with Cys106, and its nitrile group interacts with Phe105 and Asp104, Leu156 (Khedr et al., 2023). All these data are interesting; however, it is necessary to determine some pharmacokinetic parameters for benzothiazole derivatives such as 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26.

4.3 Pharmacokinetic parameters

Some pharmacokinetic factors for benzothiazole derivatives 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 were determined using the SwissADME program. The results show that the metabolism of Benzothiazole derivatives

may involve different CYPs (P450 family). This phenomenon can be due to differences in the chemical structure or different lipophilicity degree of each compound, which may produce some beneficial or toxic effects in some biological system.

4.4 Toxicity analysis

It is important to mention that some methods, such as ProTox-II (Banerjee et al., 2018), ToxAlert (Sushko et al., 2012), and Gussar (Askerova, 2023), have been used to determine the toxicity degree of different drugs. In this research, the possible toxicity exerted by benzothiazole derivatives 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 was evaluated using the Gussar program. Theoretical data suggest that the toxicity degree produced by benzothiazole derivatives could depend on the dose administered through different routes of administration. For example, the dose required for compound 17 was lower compared with 1, 4, 7, 9, 11, 13-15, 19-21, 22, 24, and 26 administered orally.

5. Conclusions

In this research it is reported the possible coupling of some benzothiazole derivatives with the 3ocb protein surface. The results showed that benzothiazole derivatives 1, 4, 7, 9, 11, 13-15, 17, 19-21, 22, 24, and 26 have a higher affinity for the 3ocb protein surface compared with KB-0742 and N-vinylpyrrolidone drugs. Therefore, these compounds may act as CDK9 inhibitors, resulting in a decrease in cancer cell growth.

6. Authors' Contributions

Rosas-Nexticapa Marcela, Alvarez-Ramirez Magdalena: conceptualization and research design. *Rosas-Nexticapa Marcela, Alvarez-Ramirez Magdalena, Mateu-Armand Virginia*, and *Cauich-Carrillo Regina*: data acquisition, analysis, and interpretation. *All authors*: writing, review, and editing. *All authors read and approved the final manuscript*: approval of the final version.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

9. References

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Funding

Not applicable. Whenever public or private funding is involved, its source must be presented.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.