Interaction of eight steroid derivatives with VEGFR-1 using a theoretical model

Maria López-Ramos[1], Lauro Figueroa-Valverde[1], Magdalena Alvarez-Ramirez[2], Marcela Rosas-Nexticapa[2], María Virginia Mateu-Armad Maria[2] & Regina Cauich-Carrillo[3]

[1] Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México

[2] Faculty of Nutrition, University Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México

[3] University Autonomous of Quintana Roo State, Campus Chetumal, Av Erik Paolo Martinez s/n esq. Av. 4 de marzo, Col. Magisteterial, C.P. 77039, México

Correspondence: Figueroa-Valverde Lauro, Pharmacochemistry Laboratory, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México. E-mail: lfiguero@uacam.mx

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Abstract

Some vascular endothelial growth factor receptor-1 (VEGFR-1) inhibitors drugs have been used to cancer cells; however, their interaction with VEGFR-1 is very confusing. The objective of this research was to evaluate the possible interaction of eight steroid derivatives with VEGFR-1 surface using 3hgn protein, cabozantinib, pazopanib, regorafenib, and sorafenib as theoretical tools in DockingServer program. The results showed some differences in the interaction of the steroid derivatives (**1**-**8**) with the 3hng protein surface such as *i*) differences in the number of amino acids; *ii*) different position of some amino acids compared to cabozantinib, pazopanib, regorafenib, and sorafenib. Besides, the inhibition constant (Ki) for steroid derivatives **1**, **3**, **6** and **8** was lower compared to cabozantinib and sorafenib drugs. In addition, other data display that Ki for steroid analogs **1**, **3**, **4**, **6**, **7** and **8** was lower compared with pazopanib and regorafenib. In conclusion, all these data suggest that steroid derivatives **1**, **3**, 4, **6**, **7** and **8** could act as VEGFR-1 inhibitors and this phenomenon could be translated as good compounds to treat cancer cells.

Keywords: cancer, steroid, VEGFR-1, docking, theoretical model.

Interação de oito derivados de esteróides com VEGFR-1 utilizando um modelo teórico

Resumo

Alguns medicamentos inibidores do receptor 1 do fator de crescimento endotelial vascular (VEGFR-1), têm sido usados para células cancerígenas, no entanto, a sua interação com o VEGFR-1 é muito confusa. O objetivo desta pesquisa foi avaliar a possível interação de oito derivados de esteroides com a superfície do VEGFR-1 utilizando proteína 3hgn, cabozantinibe, pazopanibe, regorafenibe e sorafenibe como ferramentas teóricas no programa DockingServer. Os resultados mostraram algumas diferenças na interação dos derivados esteroides (**1**-**8**) com a superfície da proteína 3hng, tais como i) diferenças no número de aminoácidos; ii) posição diferente de alguns aminoácidos em comparação com cabozantinibe, pazopanibe, regorafenibe e sorafenibe. Além disso, a constante de inibição (Ki) para os derivados esteroides **1**, **3**, **6** e **8** foi menor em comparação com os medicamentos cabozantinibe e sorafenibe. Além disso, outros dados mostram que o Ki para os análogos de esteroides **1**, **3**, **4**, **6**, **7** e **8** foi menor em comparação com o pazopanibe e o regorafenibe. Em conclusão, todos estes dados sugerem que os derivados esteroides **1**, **3**, **4**, **6**, **7** e **8** poderiam actuar como inibidores do VEGFR-1 e este fenómeno poderia ser traduzido como bons compostos para tratar células cancerígenas.

Palavras-chave: câncer, esteróide, VEGFR-1, acoplamento, modelo teórico.

1. Introduction

The endothelium exerts a wide variety of functions, including the control of vascular function, the blood fluidity, permeability of biomolecules, and others (Vane et al., 1990; Bouis et al., 2001). It is noteworthy that endothelial cells in response to tissue injury or hypoxic conditions can develop new vessels through a differentiation process called angiogenesis (Ge et al., 2021; Lee et al., 2021); this phenomenon can be regulated through several biochemical factors, such as vascular endothelial growth factor and fibroblast growth factor (Mezu-Ndubuisi; Maheshwari, 2021).

Several studies indicate that vascular endothelial growth factor can interact with some endothelial cell surface receptors such as VEGF-R1, VEGF-R2 and VEGF-R3 which to indirectly regulate the formation of new blood vessels under normal conditions (Rahini et al, 2000; Shibuya, 2006). However, some studies suggest that VEGF-R1, VEGFR2 and VEGF-R3 activation can be involved in cancer cell growth (Carmeliet, 2005; Zhao et al., 2022). For example, a study showed that vascular endothelial growth factor can induce the proliferation of lymphatic vessels in patients with primary gastric cancer through VEGFR-3 activation (Yonemur et al 2001).

Other data indicate that VEGFR-2 may be expressed in carcinoid cancer cells, this phenomenon play an important role in tumor growth and metastasis (Silva et al., 2011). Besides, a study showed that VEGFR-2 and VEGFR-3 can be expressed in ovarian cancer patients using Western-blotting methods (Klasa-Mazurkiewicz et al., 2011). Other reports displayed that both VEGFR-1 and VEGFR-2 receptors are expressed in bladder squamous cell carcinoma cell line using an immunoblot analysis (Kopparapu et al., 2013). Besides, a study showed that VEGFR-1 can regulate epidermal growth factor receptor to promote proliferation in colon cancer cells using Western immunoblotting (Nagano et al., 2019).

On the other hand, it is important to mention that some drugs can act as VEGF receptor inhibitors to treat cancer cells; for example, a study showed that pazopanib act as VEGF receptors non-selective inhibitor which has been approved for the treatment of multiple histological subtypes of soft tissue sarcoma (Lee et al., 2019). Other study display that regorafenib (VEGF-R1, -R2, -R3 inhibitor) can confers an overall survival benefit in patients with refractory metastatic colorectal cancer (Bekaii-Saab et al., 2019).

Other data indicate that regorafenib (VEGF receptors non selective inhibitor) has been used to treat Gastric Cancer (Pavlakis et al., 2016); however, regorafenib can induce adaptive resistance of colorectal cancer cells via inhibition of vascular endothelial growth factor receptor (Tamida et al., 2017). Furthermore, a study showed that the administration of sorafenib (VEGF receptors inhibitor) can prolong survival in patients with advanced hepatocellular carcinoma (Campani et al., 2020).

All of these data indicate that several drugs can be used to treat cancer; however, some of these drugs can induce acquired resistance which can increase the risk of death in worldwide due to this clinical pathology (Lo et al., 2015; Mir et al., 2017; Bruix et al., 2017). In the search for a therapeutic alternative to reduce the acquired resistance induced by some drugs, the drug vandetanib was used as VEGFR-1 inhibitor (Bianco et al., 2008), which is a predisposing factor involved in the acquired resistance induced to some anticancer drugs (Mezquita et al., 2016; Atzori et al., 2020).

These data indicate that several drugs have been used for try of cancer cells through inhibiting VEGFR-1; however, its interaction with this biomolecule is not clear. Analyzing all these data the aim of this study was to evaluate the possible interaction of eight steroid-derivatives with VEGF-R1 using 3hng protein (Tresaugues et al., 2013) cabozantinib (Kelley et al., 2022), pazopanib (Shiri et al., 2022), regorafenib (Zhang et al., 2019) and sorafenib (Stăncioiu et al., 2022) as theoretical tools in DockingServer program (Seidel t al., 2017).

2. Materials and Methods

2.1 Methodology general

Steroid derivatives (Figure 1) were used to evaluate their possible interaction with VEGF-R1 as follows:

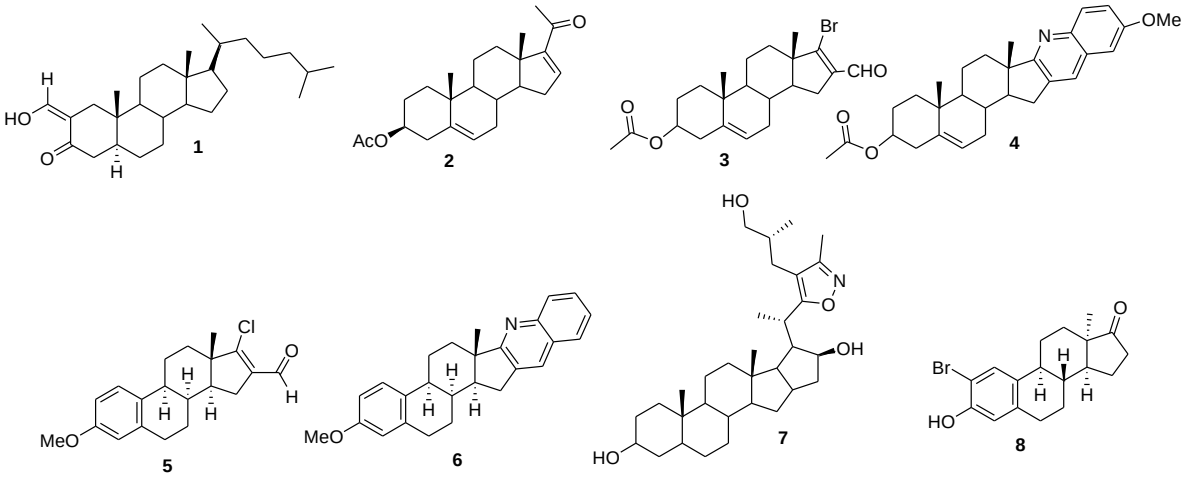

Figure 1. Chemical structure of steroid derivatives (**1**-**8**). Source: Authors, 2024.

2.2 Name International Union of Pure and Applied Chemistry (IUPAC)

1 = 2-hydroxy-methylene-5-cholestan-3-one Barthakur,

2 = 16-dehydropregnenolone acetate (Saikia et al., 2015)

3 = Acetic acid 17-bromo-16-formyl-10,13-dimethyl-2,3,4,7,8, 9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl ester (Gogoi et al., 2012).

4 = [(10*R*,14*S*)-20-methoxy-10,14-dimethyl-16-azahexacyclo [12.11.0.0^{2,11}.0^{5,10}.0^{15,24}.0^{17,22}]pentacosa-4,15(24),16,18,20,22-hexaen-7-yl] ace tate (Gogoi et al., 2012).

5 = 17-Chloro-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octa-hydro-6H-cyclopenta[a]phenanthrene-16-carbaldehyde (Baji et al., 2016).

6 = (1*S*,2*S*,11*S*,14*S*)-7-methoxy-14-methyl-16-azahexacyclo- [12.11.0.0^{2,11}.0^{5,10}.0^{15,24}.0^{17,22}]pentacosa-5(10),6,8,15(24),16,18, 20,22-octaene. (Baji et al., 2016).

7 = 7-{1-[4-(3-Hydroxy-2-methyl-propyl)-3-methyl-isoxazol-5-yl]-ethyl}-4a,6a-dimethyl-icosahydro-pentaleno[2,1-a]phenanthrene-2,8- diol (Hernández-Linares et al., 2011).

8 = 2-Bromo-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-one (Barthakur et al., 2009).

2.3 Pharmacophore model

3D pharmacophore model for steroid derivatives (**1** to **8**) was evaluated using LigandScout 4.08 software (Temml et al., 2014).

2.4 Protein-Ligand

The interaction of steroid derivatives (1-8) with 3hng protein (**PDB DOI:** https://doi.org/10.2210/pdb3HNG/pdb) was determined using cabozantinib, pazopanib, regorafenib and sorafenib as controls in DockingServer program (Seidel et al., 2017).

2.5 Pharmacokinetics parameter

Pharmacokinetic factors for steroid derivatives 1, 3, 4, 6, 7 and 8 were determined using the SwissADME software (Mahanthesh et al., 2020).

2.6 Toxicology analysis

Toxicology evaluation for steroid derivatives 1, 3, 4, 6, 7 and 8 were determined using the Gussar software (Lagunin et al., 2011).

3. Results

3.1 Pharmacophore model

Figure 2 shows a pharmacophore model for furanone and their derivatives (**1** to **31**) using the LigandScout 4.0 program. The results displayed different types of hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA) and lipophilic areas.

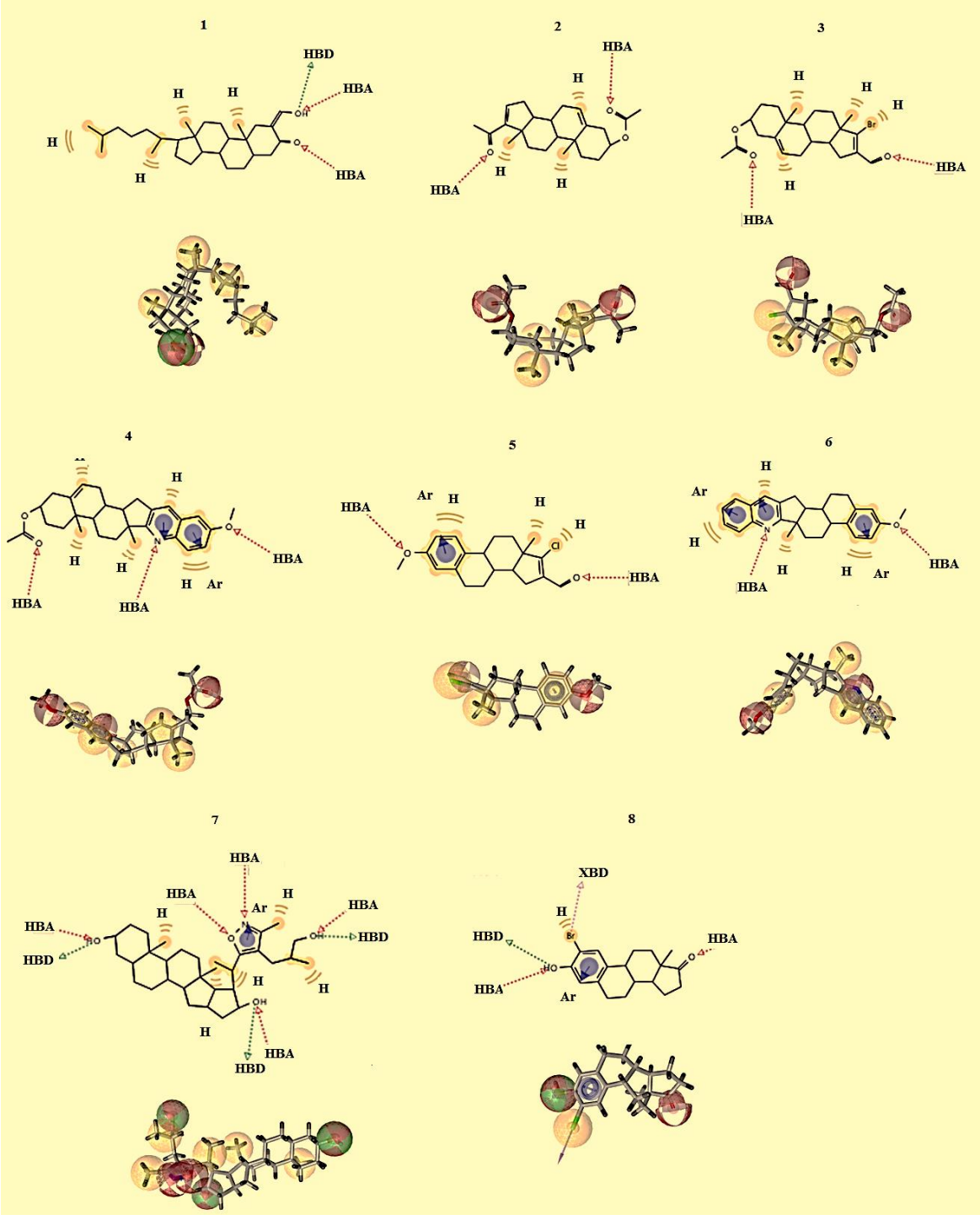

Figure 2. Pharmacophore model for steroid derivatives (**1**-**8**). Note: Visualized with LigandScout 4.4 program. HBD = hydrogen bond donors (green), hydrogen bond acceptors (red), halogen bond donor (pink). Source: Authors, 2024.

3.2 Ligand-protein complex

Table 1 and Figure 3 shows the different aminoacid residues involved in the interaction of steroid derivatives (**1** to **8**), cabozantinib, pazopanib, regorafenib and sorafenib with 3hng protein surface. However, only aminoacid residue Ala_{874} is bound to 3hng protein surface compared with steroid derivatives **2** to **8**), cabozantinib, pazopanib, regorafenib and sorafenib.

Table 1. Aminoacid residues involved in the interaction of Cabozantinib (I), Pazopanib (II); Regorafenib (III), Sorafenib (IV) and steroid derivatives (**1** to **8**) with 3hng protein surface.

Compound	Aminoacid residues
Cabozantinib	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Ile_{881}; Leu_{882}; Val_{892}; Val_{907}; Val_{909}; Cys_{1018}; His_{1020}; Leu_{1029}; Ile_{1038}; Cys_{1039}; Asp_{1040}; Phe_{1041}
Pazopanib	Leu_{833}; Glu_{878}; Leu_{882}; Val_{892}; Val_{909}; Tyr_{911}; Cys_{912}; His_{1020}; Leu_{1029}; Cys_{1039}; Asp_{1040}; Phe_{1041}
Regorafenib	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Leu_{882}; Ile_{885}; Ile_{881}; Val_{892}; Val_{907}; Val_{909}; Cys_{912}; Leu_{1013}; Cys_{1018}; Ile_{1019}; His_{1020}; Leu_{1029}; Asp_{1040}; Phe_{1041}
Sorafenib	Glu_{878}; Ile_{881}; Leu_{882}; Val_{891}; Val_{892}; Leu_{1013}; Ile_{1019}; His_{1020}; Arg_{1021}; Ile_{1038}; Cys_{1039}; Asp_{1040}
1	Ala_{874}; Glu_{878}; Ile_{881}, Leu_{882}; Ile_{885}; Val_{891}; Val_{892}; Val_{909}, Leu_{1013}; Cys_{1018}; His_{1020}; Ile_{1038}; Asp_{1040}
2	Leu_{833}; Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Leu_{882}; Val_{892}; Val_{909}; Tyr_{911}; Leu_{1029}; Cys_{1039}; Asp_{1040}; Phe_{1041}
3	Val_{841}; Ala_{859}; Lys_{861}, Glu_{878}; Leu_{882}; Ile_{885}; Val_{892}; Leu_{1013}; Cys_{1018}; His_{1020}; Cys_{1039}; Asp_{1040}
4	Leu_{833}; Val_{841}; Lys_{861}; Glu_{878}; Leu_{882}; Val_{892}; Val_{909}; Leu_{1013}; His_{1020}; Leu_{1029}; Cys_{1039}; Asp_{1040}; Phe_{1041}
5	Glu_{878}; Ile_{881}; Leu_{882}; Val_{891}; Val_{892}; Leu_{1013}; Cys_{1018}; His_{1020}; Arg_{1021}; Ile_{1038}; Asp_{1040}
6	Asp_{807}; Glu_{878}; Ile_{881}; Leu_{882}; Val_{892}; Val_{909}; His_{1020} ; Arg_{1021}; Cys_{039}; Asp_{1040}
7	$Asp_{807;}$ Val_{841}; Lys_{861}; Glu_{878} Ile_{881}; Leu_{882}; Val_{892}; Val_{909}; His_{1020}; Arg_{1021}; Leu_{1029}; Cys_{1039}; Asp_{1040}; Phe_{1041}
8	Asp_{807}; Glu_{878}; Ile_{881}; Leu_{882}; Val_{891}; Val_{892}; Cys_{1018}; His_{1020}; Arg_{1021}; Asp_{1040}

Source: Authors, 2024.

Other data showed differences in energies levels for steroid derivatives (**1** to **8**) compared to cabozantinib, pazopanib, regorafenib and sorafenib (Table 2). Besides, inhibition constant (Ki) for 6 was lower compared with steroid derivatives (**1**-**5**, **7** and **8**), cabozantinib, pazopanib, regorafenib and sorafenib. In addition, the Ki for steroid derivatives **1**, **3**, **4**, **7** and **8** was lower compared to pazopanib, regorafenib and sorafenib.

Table 2. Thermodynamic parameters involved in the interaction of for steroid derivatives (1-8), Cabozantinib, Pazopanib, Regorafenib, Sorafenib with 3hng protein surface.

Compound	A	B	C	D	E	F
Cabozantinib	-7.70	2.28	-8.77	-0.18	–8.95	1000.65
Pazopanib	–8.76	380.77	–10.15	–0.11	–10.26	999.38
Regorafenib	–5.05	198.17	–6.84	–0.09	–6.93	1004.77
Sorafenib	–7.03	7.03	–8.19	–0.23	–8.42	922.58
1	-7.67	2.37	-8.77	-0.09	-8.86	895.72
2	-5.88	49.22	-6.76	-0.04	-6.80	779.63
3	-7.46	3.42	-8.33	-0.02	-8.34	818.61
4	-6.95	8.11	-7.73	-0.10	-7.83	1000.54
5	-8.31	815.92	-8.70	-0.20	-8.90	718.19
6	-7.88	1.68	-8.13	-0.05	-8.18	820.06
7	-10.73	13.56	-12.71	-0.11	-12.82	1049.24
8	-7.92	1.56	-8.16	-0.06	-8.22	635.57

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, 2024.

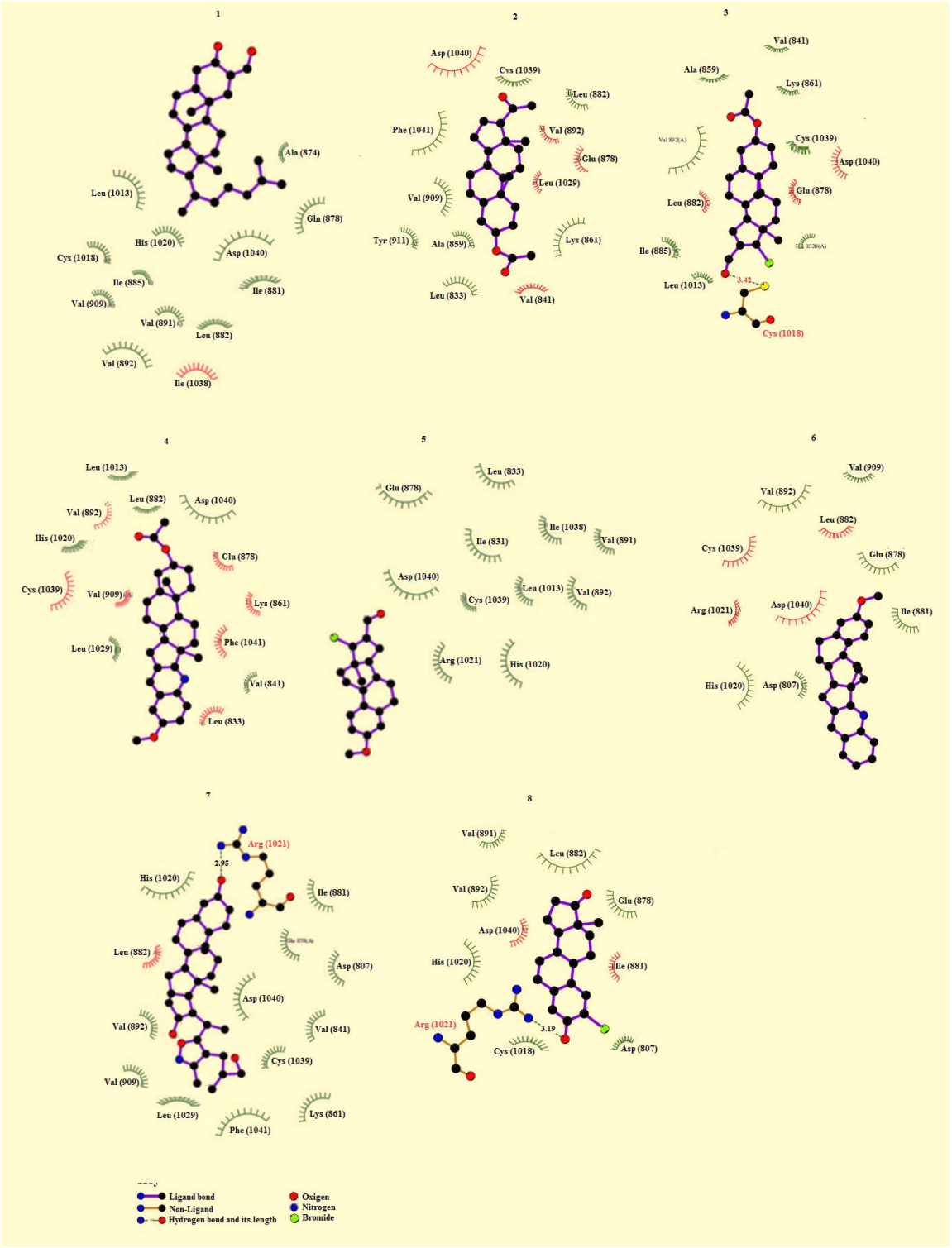

Figure 3. Aminoacid residues involved in the interaction of steroid derivatives (**1-8**) with 3hng protein surface. Note: Visualized with DockingServer program. Source: Authors, 2024.

3.3 Lipophilicity analysis

The results (Table 3) showed that steroid derivative **1** could have a higher degree of Lipophilicity compared to compounds **2-8**; however, compound **8** showed lower Lipophilicity compared to steroid derivatives **1-7**.

Table 3. Lipophilicity degree for steroid derivatives (**1** to **8**) using several theoretical models.

Compound	ilogP	XlogP3	WlogP	MlogP	Silicost-IT	Log$P_{o/w}$ consensus
1	4.82	9.36	7.33	5.50	6.62	681
2	3.46	4.80	5.01	4.22	4.36	4.31
3	3.40	4.50	5.34	4.33	4.77	4.47
4	4.33	6.02	6.15	4.84	5.74	5.41
5	3.27	4.73	4.85	4.04	5.05	4.39
6	3.94	6.34	5.81	5.09	5.99	5.44
7	4.17	6.64	5.88	4.47	5.37	5.31
8	3.03	3.82	4.58	4.06	4.50	4.00

Source: Authors, 2024.

3.4 Pharmacokinetic parameters

Table 4 shows the theoretical pharmacokinetic parameters for the steroid derivatives (**1**-**8**). The results showed that the gastrointestinal absorption of compound **1** could be lower compared to **3**, **4**, **6**, **7** and **8**. Furthermore, the metabolism of steroid derivatives involves different Cyp´s for each steroid derivative.

Table 4. Pharmacokinetic parameters for steroids derivatives (**1** to **8**) using SwissADME program.

Compound	GI absorption	BBB Permeant	P-gp substrate	Cyp1A2 inhibitor	Cyp 2C19 inhibitor	Cyp2C9 inhibitor	Cyp2D6 inhibitor	Cyp3A4 inhibitor
1	Low	No	No	No	No	Yes	No	No
3	High	Yes	No	No	No	Yes	No	No
4	High	No	No	No	No	No	No	Yes
6	High	No	No	No	No	No	Yes	No
7	High	No	Yes	No	No	No	No	No
8	High	Yes	Yes	Yes	No	No	Yes	No

Note: Cyp = P_{450} family; GI absorption = gastrointestinal absoption; PPB = plasma protein binding; vd = volume distribution; $T_{1/2}$ = medium live; CL = clearance; Fu = Fraction unbound un plasms; BBB = barrier blood brain. Source: Authors, 2024.

3.5 Toxicology analysis

Table 5 showed that compound **1** requires higher doses through intraperitoneal, intravenous, oral and subcutaneous routes of administration to produce a certain degree of toxicity compared to steroid derivatives (**2**-**8**).

Table 5. Theoretical toxicity analysis produced by steroid derivatives.

Compound	**Rat IP LD_{50} (mgkg)**	**Rat IV LD_{50} (mgkg)**	**Rat Oral LD_{50} (mgkg)**	**Rat SC LD_{50} (mgkg)**
1	1587.00	70.40	4094.00	3477.00
12	1143.00	11.88	2407.00	1618.00
14	472.70	4.91	1085.00	307.30
19	1552.00	1.16	1218.00	1222.00
22	512.30	11.85	11.85	397.40

Note: IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration. Source: Authors, 2024.

4. Discussion

In the literature there are several reports on computer-aided drug design (Macalino et al., 2015; Hassan-Baig et al., 2016); These methods are used to predict the biological activity produced by several drugs on some biomolecule; In this way, in this research a theoretical study was carried out to evaluate the activity of steroid derivatives on (VEGFR-1) using some tools such as;

4.1 Pharmacophore model

Pharmacophore models are used to define the chemical characteristics of one or more molecules with the same biological activity; in this way pharmacophore is used as a theoretical tool to develop some compounds with therapeutic purposes (Wang et al., 2017). For example, some studies developed a C_6-substituted steroid pharmacophore-based strategy to identify new aromatase inhibitors using HipHop pharmacophore model (Neves et al., 2009). Other data showed the pharmacophore for testosterone, estradiol and androstenedione using Discovery Studio 2.0 program (Saxena et al., 2016).

Besides, a report showed the identification of inhibitors of the steroid sulfate transporter using Catalyst-Pharmacophore Model (Grosser et al., 2016). Recently, a pharmacophore for a steroid derivative was developed using the LigandScout program (Figueroa-Valverde et al., 2023). The aim of this study, several pharmacophores were designed for eight steroid derivatives using Ligandscout software. In the Figure 2 are showed different pharmacophore for eight steroid derivatives; it is noteworthy that characteristics of each pharmacophore depends on the functional groups involved in the chemical structure of steroid derivatives, which can be hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), halogen bond donor (XBD), rings, aromatics and hydrophobic areas.

4.2 Ligand-protein complex

The interactions of biomolecules (protein-protein and small molecules with macromolecules) are essential to produce different biological activities such as signal transduction, physiological regulation, genetic transcription and enzymatic activity. In the search for some system which can predict protein-protein interactions, several methods have been used such as NGPINT (Banerjee et al., 2021), MEGADOCK (Matsuzaki et al., 2013), ProKSim (Khruschev et al., 2013) and others. Furthermore, to evaluate the interaction of small molecules with macromolecules, other types of methods are used to determine the ligand-protein complex formation. For example, PyPLIF (Radifar et al., 2013), PLIP (Salentin et al., 2015), LIGPLOT (Wallace et al., 1995), Autodock (Forli et al., 2016), DockingServer (Figueroa-Valverde et al., 2023).

In this study, the interaction of steroid derivatives with vascular endothelial growth factor receptor-1 (VEGFR-1) was evaluated using 3hng protein, cabozantinib, pazopanib, regorafenib and sorafenib as theoretical tools in DockingServer program. The results (Table 1, Figure 3) showed differences in the number of amino acid residues involved in the interaction of the steroid derivatives with the surface of the 3hng protein compared to cabozantinib, pazopanib, regorafenib and sorafenib. Furtheremore, the steroid derivative (compound **1**) may possibly interact with Ala874 aminoacid residue compared to cabozantinib, pazopanib, regorafenib and sorafenib and steroid derivatives **2** to **8**.

This phenomenon could condition the biological activity of steroid derivatives; however, it is important to mention that other type of thermodynamic factors could be involved. For this reason, in this study thermodynamic parameters (Table 2) for steroid derivatives, cabozantinib, pazopanib, regorafenib and sorafenib were evaluated using DockingServer program. The results showed differences in the energies levels for steroid derivatives compared with cabozantinib, pazopanib, regorafenib and sorafenib. Other data showed that inhibition constant (Ki) for 6 was lower compared with steroid derivatives (**1**-**5**, **7** and **8**), cabozantinib, pazopanib, regorafenib and sorafenib. Besides, the Ki for steroid derivatives **1**, **3**, **4**, **7** and **8** was lower compared to pazopanib, regorafenib and sorafenib. All these data indicate that steroid derivatives **1**, **3**, **4**, **6**, **7** and **8** could act as 3hng protein inhibitors, this phenomenon could be translated as vascular endothelial growth factor receptor 1 (VEGFR-1) inhibition which could be involved in some cancer cell growth processes.

4.3 Lipophilicity analysis

In the literature there are reports on the determination of lipophilicity degree of several compounds using different methods such as ilogP (Daina et al., 2014), XlogP (Zhong et al., 2018), WlogP (Daina et al., 2016), MlogP (Chui, 2010), Silicost-IT (Shahryari et al., 2021). Furthermore, other studies showed that SwissADME software can be used to determine the lipophilicity degree (LogPo/w consensus) of several drugs. Analyzing these data, in this study, SwissADME program was used to calculate the lipophilicity degree of steroid derivatives [33]. The results (Table 3) display that compound **1** have higher lipophilicity degree compared with other steroid derivatives; this phenomenon could condition some changes in pharmacokinetic process.

4.4 Pharmacokinetic parameters

There are several methods such as PK/PD (Derendorf et al., 1999), PKMP (Shah, 2022), PBPK (Kanacher et al., 2020), PkQuest (Levitt et al., 2002) have been used to characterize the effectiveness and safety of medications. In this research, SwissADME (Mahanthesh et al., 2020) was used to determinate some pharmacokinetic parameters for steroid derivatives **1**, **3**, **4**, **6**, **7** and **8**. The results showed that; *i*) possibly the absorption of compound 1 could be lower compared to **3**, **4**, **6**, **7** and **8**; and *ii*) steroid derivatives could be metabolized through different Cyp's. This phenomenon could depend on the chemical characteristics of each steroid derivative, which may result in the generation of a beneficial or toxic metabolite.

4.5 Toxicology analysis

For several years, several computational tools such as ProTox-II (Banerjee et al., 2018), STopTox (Borba et al., 2022), GUSAR (Lagunin et al., 2011) have been used to predict toxicity degree of new compounds with biological activity. For this reason, in this research, the possible toxicity produced by steroid derivatives (**1**-**8**) was determined using the GUSAR software. The results display that compound 1 requires higher doses through intraperitoneal, intravenous, oral and subcutaneous routes of administration to produce a certain degree of toxicity compared to steroid derivatives. These data suggest that toxicity could depends on the following parameters; *i*) the dose administered; *ii*) the different routes of administration; and *iii*) the chemical characteristics of each steroid derivative.

5. Conclusions

Theoretical models used in this study are suitable for the following reasons: i) develop a pharmacophore model for steroid derivatives that allows analyzing their interaction with 3hng protein surface; ii) analyze the thermodynamic parameters involved in the interaction of steroidal derivatives with the 3hng protein surface; ii) Analyze both pharmacokinetic and toxicological aspects that can determine the biological activity of each steroid derivative. All these data suggest that steroid derivatives **1**, **3**, **4**, **6**, **7** and **8** could be a good alternative as **VEGFR-1**inhibitors to decrease cancer cells growth.

6. Authors' Contributions

López-Ramos Maria: reading, writing and evaluating data. *Figueroa Valverde Lauro*: article writing, data evaluation and corrections. *Alvarez-Ramirez Magdalena*: corrections, software usage, data analysis. *Rosas Nexticapa Marcela*: corrections, data analysis, writing and layout corrections. *Mateu-Armad Maria Virginia*:

outline of topics, writing, translation and corrections. *Cauich-Carrillo Regina*: translation, corrections, submission and publication.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

9. References

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