Biochemical interaction of twenty steroid derivatives with ribosomal protein kinase 4 S6 (RSK-4) surface using a theoretical model

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Abstract

Several genetic expressions have been involved in the development of cancer such as the expression of a ribosomal kinase S6 P90 (RSK-4). It is important to mention that some compounds such as LJH685, 2073047-06-8, and SL0101 can act as RSK-4 inhibitors; however, its interaction with the surface of RSK-4 is very confusing. The aim of this research was to evaluate the interaction of twenty-nine steroid derivatives (1 to 29) with of RSK-4 surface using 6rv2 protein, LJH685, 2073047-06-8 and SL0101 as theoretical tools in the Dockingserver program. The results showed differences in the aminoacid residues involved in the interaction of steroid derivatives with 6rv2 protein surface compared with LJH685, 2073047-06-8 and SL0101. Besides, the inhibition constant for steroid derivatives 1, 12, 14, 19 and 22 was lower compared to 2073047-06-8 drug. In conclusion, the steroid derivatives 1, 12, 14, 19 and 22 could be a good alternative as RSK-4 inhibitors to decrease cancer cells growth.

Keywords: Theoretical, RSK-4, DockingServer, steroid derivatives.

Interação bioquímica de vinte derivados de esteróides com a superfície da proteína quinase ribossômica 4 S6 (RSK-4) usando um modelo teórico

Resumo

Várias expressões genéticas têm sido envolvidas no desenvolvimento do câncer, como a expressão de uma quinase ribossômica S6 P90 (RSK-4). É importante mencionar que alguns compostos como o derivado de oxacina, LJH685, 2073047-06-8 e SL0101 podem atuar como inibidores de RSK-4; entretanto, sua interação com a superfície do RSK-4 é muito confusa. O objetivo desta pesquisa foi avaliar a interação de vinte e nove derivados esteróides (1 a 29) com a superfície do RSK-4 utilizando a proteína 6rv2, LJH685, 2073047-06-8 e SL0101 como ferramentas teóricas no programa Dockingserver. Os resultados mostraram diferenças nos resíduos de aminoácidos envolvidos na interação de derivados de esteróides com a superfície da proteína 6rv2 em comparação com o derivado de oxacina, LJH685, 2073047-06-8, SL0101. Além disso, as constantes de inibição para os derivados esteróides 1, 12, 14, 19 e 22 foram inferiores em comparação com o medicamento 2073047-06-8. Em conclusão, os derivados esteróides 1, 12, 14, 19 e 22 podem ser uma boa alternativa como inibidores de RSK-4 para diminuir o crescimento de células cancerígenas.

Palavras-chave: Theoretical, RSK-4, DockingServer, steroid derivatives.

1. Introduction

For several years, cancer has been increasing in the population worldwide (Xia et al., 2022; Miller et al., 2022; Hanahan, 2022; Zheng et al., 2022). This clinical phatology involves several risks factors such age (Zabransky et al., 2022), smoking (Phua et al., 2022), alcohol consumption (Mayen et al., 2022), obesity (Bao et al., 2022), diabetes (Lazarus and Bays, 2022), physical inactivity (Minihan et al., 2022), radiation exposure (Einstein et al., 2007), and genetic factors (Garcia-Pelaez et al., 2022; Jiang et al., 2023). In this way, several genetic expressions have been involved in the development of cancers; for example, the expression of ribosomal S6 p90 kinase family [RSK 1-4; which belongs to the group of highly conserved Ser/Thr kinases] (Yang et al., 2023; Casalvieri et al., 2017). In addition, a study showed that RSK-1 could be associated to tumor growth and metastasis, using a triple-negative breast cancer model (Czaplinska et al., 2018). Another report indicates that RSK-1 could be associated with nodular melanoma progression using some melanoma cell lines (Salhi et al., 2015). However, a study displayed that RSK-1 may act as a negative regulator in lung cancer metastasis cells (Zhao et al., 2016). Furthermore, another report showed that a low expression of RSK-1 and RSK-3 was associated with metastasis of breast cancer (Iar et al., 2011).

On the other hand, a study indicates that RSK-2 expression may be associated with the invasiveness of various head and neck squamous carcinoma cell lines (Kang et al., 2010). In addition, a study displays that RSK-2 plays a key role in neoplastic transformation of human skin cells and in skin cancer growth (Arul and Chao, 2013). Other data indicate that MCF-7 (human breast cancer cells), HCT-116 (human colon cancer), HCT-29 (HT-29: Human Colorectal Adenocarcinoma) cell lines may expressed higher RSK-2 levels compared with nonmalignant human and mouse cells, such as HaCaT (human epidermal keratinocyte), JB6 Cl41 (mouse epidermal cells) , and NIH3T3 (mouse embryonic fibroblasts) cells lines (Chao et al., 2009). Besides, some studies suggest that RSK-3 and RSK-4 may act as tumor suppressors (Casalveri et al., 2017); for example, some data indicate that RSK-3 and RSK-4 are tumor suppressors in ovarian cancer (Bignone et al., 2007; Clark et al., 2005; Smith et al., 2005). Other study showed that RSK-4 expression might be associated with anti-metastatic effects in breast cancer cells (Thakur et al., 2008). However, a study displayed that higher RSK4 expression in esophageal squamous cell carcinomais is associated with poor survival in patients with this type of clinical pathology (Li et al., 2020). In addition, other data showed RSK-4 expression in 101 renal cell carcinoma cases using immunohistochemical methods (Fan et al., 2013). In the search of some therapeutic alternative, some drugs were prepared to treat cancer through RSK-4 inhibition; for example, a study showed the synthesis of an oxazinone derivative (2073047-06-8) as RSK-4 inhibitor to treat of esophageal squamous cell carcinoma (Yuan et al., 2021). Besides, other data suggest that some quinolone derivatives could act as RSK-4 inhibitors using a theoretical model for treating cancer (Rosas-Nexticapa et al., 2022). Analyzing all these data in this research a theoretical study was carried out to evaluate the interaction of twenty-nine steroid derivatives with RSK-4 surface using 6rv2 protein, LJH685 (Rosas-Nexticapa et al., 2022)., 2073047-06-8 carcinoma (Yuan et al., 2021), and SL0101 (Zhang et al., 2022) as theoretical tools.

2. Materials and Methods

Some steroid derivatives (Figure 1) were used to evaluate their possible interaction with both RSK-4 as follows:

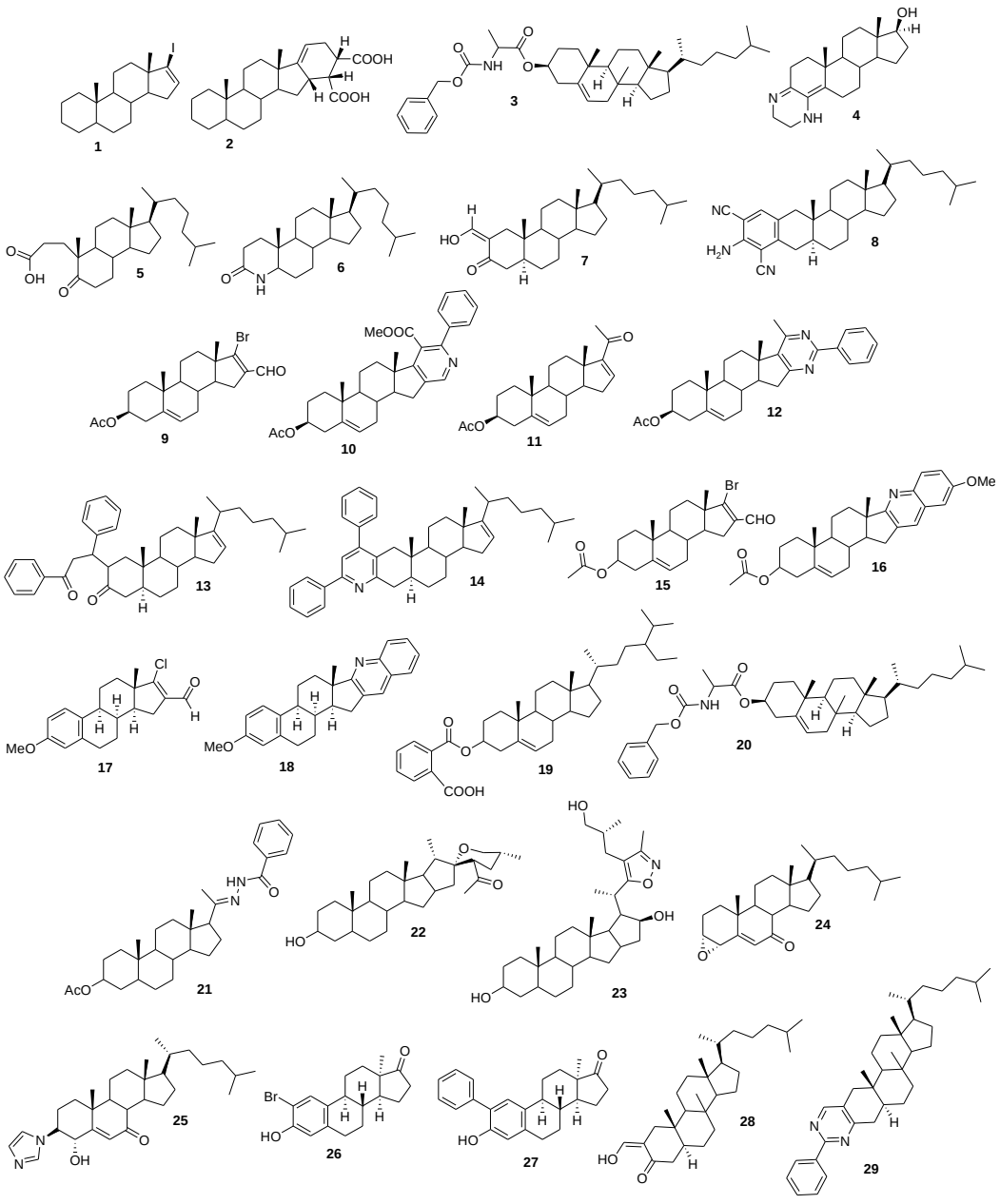

Figure 1. Chemical structure of steroid derivatives (**1**-**18**).

Chemical names

1 = 17-Iodo-androst-16-ene (Skoda-Földeset al., 2002).

2 = diethyl(4*aS*,6*aS*,10*aS*)-4*a*,6*a*-dimethyl-2,3,4,4*b*,5,6,8,9,10,10*a*,11,11*a*,11*b*,12,13, 13*a*-hexadecahy-dro-1*H*-indeno [2,1-a]phenanthre ne-9, 10-dicarboxy-late (Skoda-Földeset al., 2002).

3 = O-(α-protected-aminoacyl)-steroid((S)-2-ben-zyloxycarbo-nyl-amino-3-phenyl-(3S,8S,9S,10R,13R,14S, 17R)-17-((R)-1,5-dimethyl-hexyl)-10,13-dime-thyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetra-decahydro-1H-cyclopenta[a]phenanthren-3-ylpro-pionate) (Katritzky, et al., 206).

4 = 4´-dehydro-cholest-4-eno[3,4-e]piperazin-6-one (Borthakur et al., 2008).

5 = 5-oxo-A-nor3,5-secocholestan-3-oic acid (Borthakur et al., 2008).

6 = 4-aza-3-oxo-cholest-5-en (Borthakur et al., 2008).

7 = 2-hydroxy-methylene-5-cholestan-3-one Barthakur,

8 = 2´,6´-Dicyano-5¸-cholestan[3,2-c]aniline Barthakur,

9 = Bromo-vinyl aldehyde-steroid (Shekarrao et al., 2013).

10 = 3β-Acetoxy-5´-carbmethoxy-6´-phenyl-5-en-androst[16,17-c] pyridine (Shekarrao et al., 2013).

11 = 16-dehydropregnenolone acetate (Saikia et al., 2015)

12 = 16-dehydropregnenolone acetate with benzamidine in basic medium to form a steroid-pyridine derivative([(10*S*,14*R*,17*S*)-8,10,14-trimethyl-6-phenyl-5,7-diazapentacyclo[11.8.0.0^{2,10}.0^{4,9}.0^{14,19}]henicosa-4(9), 5,7,19-tetraen-17-yl] acetate) (Saikia et al., 2015)

13 = (5*S*,10*S*,13*S*)-17-(1,5-dimethylhexyl)-10,13-dimethyl-2-(3-oxo-1,3-diphenyl-propyl)-1,2,4,5,6,7,8,9,11,12, 14,15-dodecahy-drocyclo- penta[a]phenanthren-3-one (Dutta et al., 2013).

14 = 1-(1,5-Dimethyl-hexyl)-11a,13a-dimethyl-8,10-diphenyl-3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-dodecahydro-3H-7-aza-indeno[5,4-a]- anthracene (Dutta et al., 2013).

15 = 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).

16 = [(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).

17 = 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).

18 = (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).

19 = Phthalic acid mono-[17-(4-ethyl-1,5-dimethyl-hexyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H- cyclopenta[a]phenanthren-3-yl] ester (Khan et al., 2020).

20 = 2-Benzyloxycarbonylamino-propionic acid 17-(1,5-dime-thyl-hexyl)-8,10,13-trimethyl-2,3,4,7,8,9,10,11, 12,13,14,15,16,17-tetradeca- hydro-1H-cyclopenta[a]phenanthren-3-yl ester (Katritzky et al., 2020).

21 = Acetic acid 17-[1-(benzoyl-hydrazono)-ethyl]-10,13-dime-thyl-hexadecahydro-cyclopenta[a]phenanthren-3-yl ester (kovaks et al., 2014).

22 = 1-[(5'*R*,6*R*,7*S*,9*S*,13*S*)-16-hydroxy-5',7,9,13-tetramethyl-spiro[pentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-tetrahydro-pyran]-3'-yl]etha- none (Hernández-Linares et al., 2011).

23 = 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).

24 = 17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-1,2,3,4,8,9,10,11,12,13,14,15,16,17-tetradecahydro-20-oxa-cyclopropa[3,4]cyclo-penta[a] phenanthren-7-one (Saikia et al., 2014).

25 = 17-(1,5-Dimethyl-hexyl)-4-hydroxy-3-imidazol-1-yl-10,13-dimethyl-1,2,3,4,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[a] phenanthren-7-one (Shen et al., 2020).

26 = 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).

27 = 3-Hydroxy-13-methyl-2-phenyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-one (Barthakur et al., 2009).

28 = 17-(1,5-Dimethyl-hexyl)-2-hydroxymethylene-8,10,13-trimethyl-hexadecahydro-cyclopenta[a]phenanthren-3-one (Jójárt, et al., 2020).

29 = 1-(1,5-Dimethyl-hexyl)-3b,11a,13a-trimethyl-8-phenyl-2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1H-7,9-diaza-indeno[5, 4-a] anthracene (Jójárt, et al., 2020).

Pharmacophore model

3D pharmacophore model for steroid derivatives (1 to 29) was evaluated using LigandScout 4.08 software (Mardianingrum et al., 2022).

Pharmacokinetics parameter

Pharmacokinetic factors for steroid derivatives 1, 12, 14, 19 and 22 were determined using the ADMETlab 2.0 software (Aljelehawy et al., 2022).

Toxicology analysis

Toxicology evaluation for steroid derivatives 1, 12, 14, 19 and 22 were determined using the Gussar software (Karpenko et al., 2022).

3. Results

Figures 2-7 shown pharmacophore models developed to steroid derivatives (1 to 29) using LigandScout 4.0 program. The results showed different types of hydrogen bond donors and acceptors, lipophilic areas and positively and negatively ionizable chemical groups for different steroid derivatives.

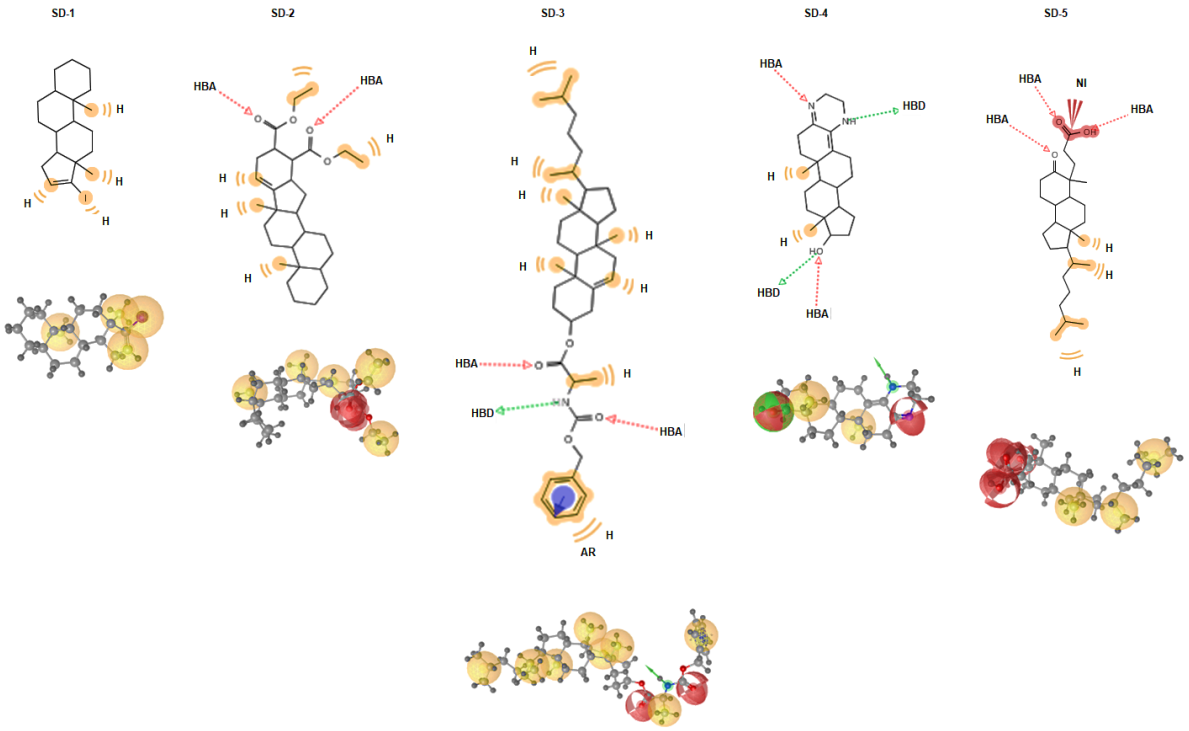

Figure 2. Pharmacophore from steroid derivatives (SD) 1-5. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green). Visualized with LigandScout Software 4.0

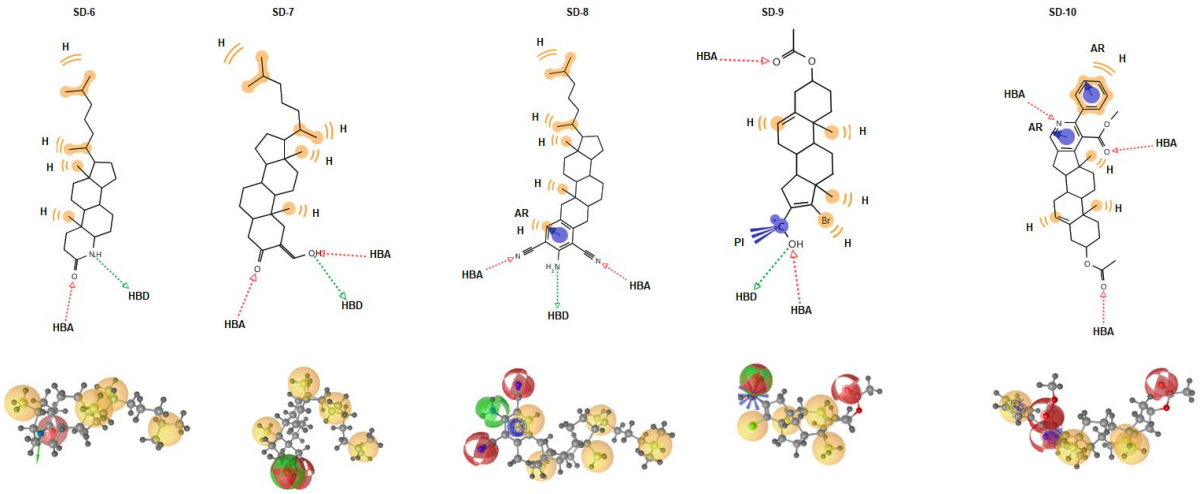

Figure 3. Development of a pharmacophore from steroid derivatives (SD) 6 to10 using LogandScout 4.0 software. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green).

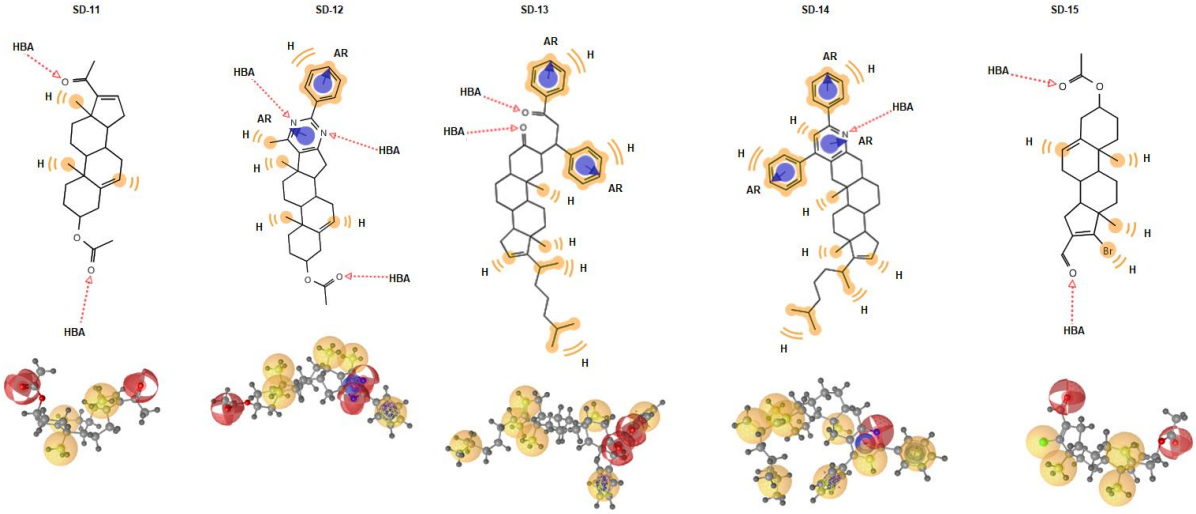

Figure 4. Pharmacophore from steroid derivatives (SD) 11 to 15. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green). Visualized with LigandScout Software 4.0

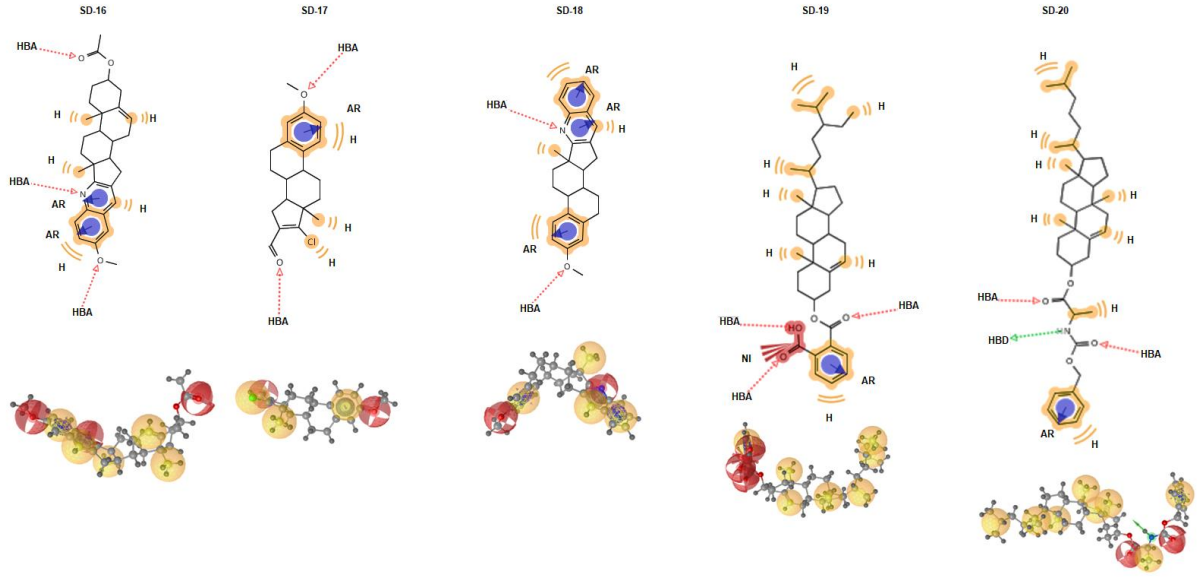

Figure 5. Development of a pharmacophore from steroid derivatives (SD) 16 to 20 using LogandScout 4.0 software. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green).

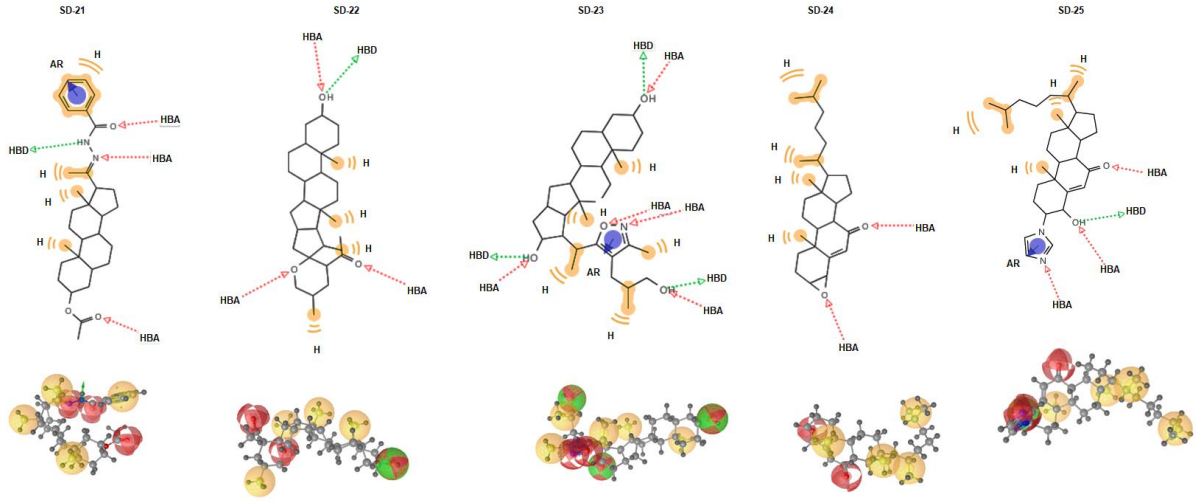

Figure 6. Pharmacophore from steroid derivatives (SD) 21 to 25. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green). Visualized with LigandScout Software 4.0

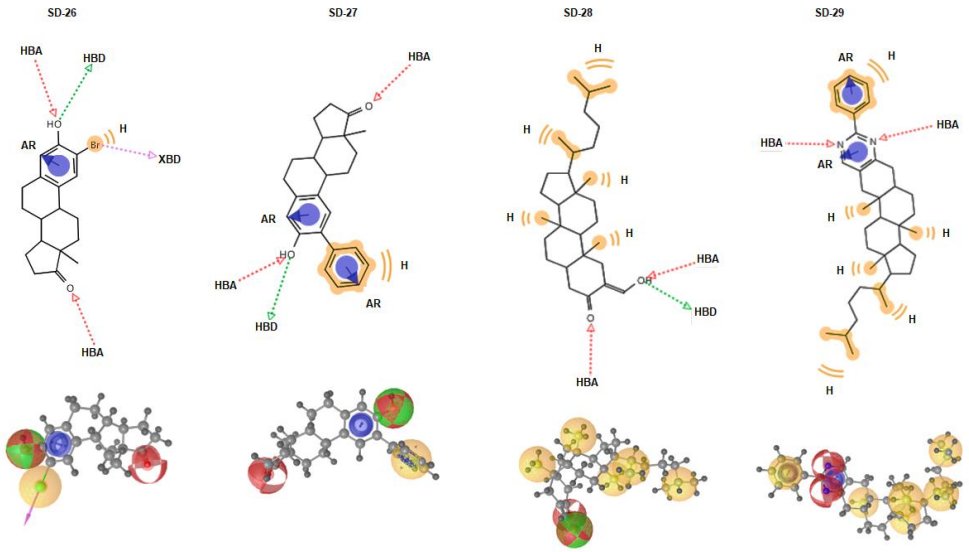

Figure 7. The scheme displays the pharmacophore from compounds (SD) 26 to 29. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green), halogen bond donor (XBD, pink). Visualized with LigandScout Software 4.0

Ligand-protein complex

Table 1 shows the different aminoacid residues involved in the interaction of steroid derivatives (1 to 29), LLJH-685 (2,6-difluoro-4-[4-[4-(4-Methylpiperazin-1-yl)phenyl]pyridin-3-yl]phenol), 2073047-06-8 (1,4-dihydro-2H-pyrimido[4,5-d][1,3]oxazin-2-one), and SL0101 (5,7-dihydroxy-2-(4-Hydroxyphenyl)-4-Oxo-4H-chromen-3-yl3,4-Di-O-Acetyl-6-Deoxy-Alpha-L-mannopyranoside)

with 6rv2 protein surface.

Table 1. Aminoacid residues involved in the interaction of steroid derivatives (1 to 29), LJH685, 2073047-06-8, and SL0101 with 6rv2 protein surface.

Compound	Aminoacid residues
LJH685	Phe_{84}; Lys_{113}; Arg_{197}; Ser_{220}; Lys_{221}; Phe_{233}; Cys_{234}; Arg_{247}; His_{250}
SL0101	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}
2073047-06-8	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Met_{249}; Asn_{250}
1	Arg_{7}; Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
2	Arg_{7}; Leu_{11}; Phe_{246}; Met_{247}; Met_{249}; Asn_{250}
3	Arg_{7}; Ala_{10}; Leu_{11}; Cys_{14}; Val_{243}; Phe_{246}; Met_{249}
4	Arg_{7}; Ala_{10}; Leu_{11}: Cys_{14}; Val_{243}; Phe_{246}; Met_{247}
5	Arg_{7}; Thr_{8}; Leu_{11}; Val_{243}; Phe_{246}; $Ment_{247}$; Asn_{250}
6	Leu_{11}; Trh_{15}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}
7	Leu_{11}; Met_{156}; Val_{242}; Arg_{245}; Phe_{246}; Met_{247}
8	Leu_{11}; Trh_{15}; Val_{243}; Phe_{246}; Met_{247}
9	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
10	Arg7; Ala10; Leu11; Val243; Phe246; Met_{247}
11	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
12	Arg_{7}, Leu_{11}; Val_{160}; Val_{242}; Phe_{246}; Met_{247}; Asn_{250}
13	Leu_{11}; Cys_{14}; Thr_{15}; Tyr_{18}; Val_{242}; Val_{243}; Phe_{246}

14	Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
15	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
16	Arg_{7}; Leu_{11}; Val_{160}; Val_{242}; Val_{243}; Phe_{246}
17	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}
18	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Met_{249}
19	Arg_{3}; Arg_{7}; Leu_{11}; Cys_{14}; Thr_{15}; Tyr_{18}; Val_{243}; Phe_{246}
20	Arg_{7}; Leu_{11}; Cys_{14}; Thr_{15}; Val_{242}, Phe_{246}
21	Arg_{7}; Leu_{11}; Val_{160}; Val_{242}; Val_{243}; Phe_{246}
22	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
23	Leu_{11}; Val_{242}; Val_{243}; Phe_{246}; Met_{247}
24	Lau_{11}; Val_{243}; Phe_{246}; Met_{247}
25	Arg_{3}; Arg_{7}; Leu_{11}; Thr_{15}; Phe_{246}; Met_{247}; Met_{249}
26	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
27	Arg_{7}; Thr_{8}; Lau_{11}; Val_{243}; Phe_{246}; Met_{247}; Asn_{250}
28	Arg_{7}; Leu_{11}; Val_{243}; Phe_{246}; Met_{247}
29	Arg_{7}; Ala_{10}; Leu_{11}; Met_{156}; Val_{160}; Val_{242}; Phe_{246}

Thermodynamic parameters

Theoretical results (Table 2) showed differences in the energy levels involved in the interaction of steroid derivatives (1-29) with 6rv2 compared with LJH685, 2073047-06-8, and SL0101 (Table 2). Besides, inhibition constant for steroid derivatives (1, 12, 14, 19 and 22) was calculated.

Table 2. Thermodynamic parameters involved in the interaction of steroid derivatives (1 to 29), LJH685, 2073047-06-8, and SL0101 with 6rv2 protein surface.

Compound	A	B	C	D	E	F
LJH685	-7.60	2.67	-6.39	-1.28	-7.67	624.82
SL0101	-3.64	2.14	-5.01	0.00	-5.01	607.67
2073047-06-8	-5.52	90.09	-6.02	-0.01	-6.03	562.13
1	-7.13	5.93	-7.13	0.00	-7.13	534.02
2	-6.13	31.99	-7.65	0.04	-7.61	623.46
3	-6.12	32.48	-7.34	0.01	-7.33	795.496
4	-5.43	105.21	-5.80	0.08	-5.73	601.148
5	-4.81	297.26	-7.11	-0.13	-7.25	657.685
6	-5.45	101.36	-7.01	-0.00	-7.01	672.512
7	-6.62	14.01	-7.53	0.01	-7.52	675.53
8	-6.42	19.82	-6.76	-0.03	-6.79	615.191
9	-6.03	38.10	-6.86	-0.03	-6.88	586.685
10	-5.90	47.29	-7.39	0.03	-7.36	750.173
11	-5.78	57.61	-6.68	0.00	-6.68	629.294
12	-7.31	4.39	-8.18	0.01	-8.17	769.08
13	-6.59	14.86	-7.00	-0.00	-7.00	779.899
14	-6.86	9.42	-7.74	-0.00	-7.74	688.476
15	-6.19	29.03	-7.02	-0.02	-7.04	591.226

16	-6.79	10.45	-7.64	-0.02	-7.67	726.011
17	-5.33	123.31	-5.92	-0.01	-5.94	586.505
18	-6.11	33.15	-6.42	0.01	-6.41	549.373
19	-7.44	3.50	-8.58	-0.92	-9.50	938.263
20	-4.89	260.83	-6.64	0.01	-6.64	689.196
21	-5.60	78.31	-6.26	-0.04	-6.30	733.494
22	-7.00	7.45	-7.59	-0.04	-7.63	626.634
23	-5.94	44.43	-6.62	-0.01	-6.63	668.654
24	-5.40	110.24	-5.60	0.01	-5.59	573.223
25	-6.00	39.81	-7.77	+0.00	-7.77	836.72
26	-5.97	42.16	-6.29	0.03	-6.27	536.741
27	-5.98	41.51	-6.57	-0.00	-6.57	634.878
28	-5.93	44.75	-6.63	-0.00	-6.63	647.377
29	-6.53	16.23	-8.03	0.00	-8.02	853.023

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;

Pharmacokinetic parameters

Table 3 shows some theoretical pharmacokinetic parameters for the steroid derivatives (1, 12, 14, 19 and 22).

Table 3. Pharmacokinetics parameters calculated for steroid-derivatives (1, 12, 14, 19 and 22). The values were determined using ADMETlab 2.0 program.

Parameter	1	12	14	19	22
Cyp1A2 inhibitor	+++	---	---	---	---
Cyp 1A2 substrate	--	--	--	-	+
Cyp2C19 inhibitor	+++	--	--	--	---
Cyp2C19 substrate	---	-	---	-	+++
Cyp 2C9 inhibitor	++	--	---	---	--
CypC9 substrate	+	---	++	+++	--
CypD6 inhibitor	---	---	---	---	---
CYP2D6 substrate	---	-	---	--	++
Cyp3A4 inhibitor	-	-	--	---	--
Cyp3A4 substrate	--	+	+	--	-
PPB	88.24	98.564	102.624	99.589	97.97
Vd	0.459	3.388	3.725	1.215	1.51
BBB Penetration	+	-	--	---	+++
FU	2.918%	1.262	0.177	0.915	1.088
t 1/2	0.884	0.027	0.001	0.006	0.042
CL	7.764	3.611	7.053	6.79	26.85

Cyp = P_{450} family; PPB = plasma protein binding; vd = volume distribution; $T_{1/2}$ = medium live; CL = clearance; Fu = Fraction unbound un plasms; BBB = barrier blood brain.

Toxicity evaluation

Table 4. 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

IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration

4. Discussion

In the search for new alternative therapeutics for different diseases, some theoretical methods have been designed to synthesize new drugs. In this way, the pharmacophore model provides a new perspective on designing novel molecules useful for developing new drugs.

Pharmacophore model

For several years, different programs such as Hiphop (Xie et al., 2099), Hypogen (kurogi et al., 2001), Disco and Gasp (Patel et al., 2002), Galahad (Zhao et al., 2010), Phase (Dixon et al., 2006) and MOE (Chen et al., 2008) have used them to predict the possible interaction of drugs with some biomolecules to inhibit or activate their biological activity. These programs differ mainly in the algorithms used to manipulate the flexibility of either drugs or compounds, which may act as ligands. Other studies have used the LigandScout program, which allows creating three-dimensional pharmacophore models from simple or complex chemical structures. The characteristics of these pharmacophores involve hydrogen bond donors and acceptors, lipophilic areas, positively and negatively ionizable chemical groups; all these characteristics allow predicting interaction of either drugs or compounds with some biomolecule. For this reason, the aim of this research was to develop a series of pharmacophores from steroid derivatives (compounds 1 to 29). The results showed some hydrogen bond donors and acceptors, lipophilic areas and positively and negatively ionizable chemical groups which are involved in the chemical structure of different steroid derivatives; these chemical characteristics of each steroid derivative could be a determining factor for ligand-protein complex formation.

Protein-ligand complex

Some computer models, such as DOCK (Sukia et al., 2015), GROMAS (Dutta et al., 2013), SFs (Gogoi et al., 2012), Swarm Dock (Baji et al., 2016) and DockingServer (Khan et al., 2020) are used to determinate the possible ligand-protein complex formation. In this study, the interaction of steroid derivatives (compounds 1 to 29) with RSK-4 protein surface was determined using the 6rv2 protein (PDB https://doi.org/10.2210/pdb6RV2/pdb), and LJH685, SL01101 and 2073047-06-8 drugs as theoretical tools in DockingServer software. Besides, binding energy levels and inhibition constant were determined to evaluate the possible interaction of steroid derivatives with 6rv2 protein surface. The results displayed different amino acid residues involved in the interaction of steroid derivatives with 6mnc protein surface compared to LJH685, SL01101 and 2073047-06-8 drugs; this could be due to differences in their chemical structure. In addition, the inhibition constant for steroid derivatives (1, 12, 14, 19 and 22) was lower compared to 2073047-06-8 drug; this phenomenon could result as decrease in cancer cell growth.

Pharmacokinetic parameters

To evaluate some pharmacokinetic parameters were determined using ADMETlab 2.0 program (Katritzky). The results indicate that metabolism of these steroidal derivatives could involve different Cyps (P_{450} family). Besides,

distribution volume is higher for compound 14 compared with 1, 12, 19 and 22; perhaps, this phenomenon could be to differences in their chemical structure of each steroid derivative.

Toxicity evaluation

In the literature, there are some methods such as ProTox-II [46], STopTox [47], ToxAlert [48], TEST [49] to predict toxicity degree of several drugs. In this study, the possible toxicity produced by steroid derivatives 1, 12, 14, 19 and 22 was determined using the GUSAR software [50]. These results suggest that toxicity could depend of dose administered for steroid derivatives through of different routes of administration. Perhaps, this phenomenon could depend of different functional groups involved in the chemical structure of each steroid derivative.

5. Conclusions

In conclusion, the theoretical models used in this study are suitable for the following reasons:

i) develop a pharmacophore model for steroid derivatives that allows analyzing the different possibilities of their interaction with some biomolecule; ii) determine the different types of energy involved in the interaction of steroidal derivatives with the RSK-4 surface; ii) analyze some pharmacokinetic and toxicological aspects that could determine their biological activity. In this way, the results obtained indicate that steroid derivatives 1, 12, 14, 19 and 22 could be a good alternative as RSK-4 inhibitors to decrease cancer cells growth.

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7. Authors' Contributions

Substantial contribution to research design: Lauro Figueroa-Valverde and Francisco Diaz-Cedillo; Acquisition, analysis, and interpretation of data: Lauro Figueroa-Valverde, Francisco Diaz-Cedillo, Montserrat Melgarejo-Guttierrez, Catalina Cervantes-Ortega, Magdalena Alvarez-Ramirez, Marcela Rosas-Nexticapa, Maria Lopez-Ramos, Juliette Mijangos-Sanchez and Maria Virginia Mateu-Armand. Approval of the submitted and final versions: all authors.

8. Conflict of interest

The authors declare that this research has no conflict of interest with any public or private association.

9. Ethics Approval

Not applicable.

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