Original Article

Interaction of Some Flavonoids Analogs with Sphingosine Kinase-1 as a Therapeutic Alternative to Treat Cancer

Abstract

Reports are indicating that some biomolecules can regulate cancer development. In this way, some data suggest that sphingosine kinases (SphK1 and SphK2) can decrease cancer cell growth through the activation of different biomolecules. It is noteworthy that several SphK1 blockers have been used to treat decreased cancer cell growth; however, their interaction with SphK1 is unclear. Therefore, the aim of this investigation was to determine the possible coupling of some flavonoid analogs (1-19) with SphK1 using the 3vzb protein as a tool in the docking Server program. In addition, pf543 and 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole were used as controls. The results showed different amino acid residues in the docking of flavonoid analogues with 3vzb protein compared to pf543 and 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole. Other data indicate that flavonoid analogues 2, 6-10, 13, 14, 17, and 18 might have a higher affinity for SphK1 protein compared to pf543 and 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole. In conclusion, these data suggest that flavonoid derivatives 2, 6-10, 13, 14, 17, and 18 might modulate the biological activity produced by SphK1, and this phenomenon might translate into good anticancer agents.

Keywords: *Cancer, Flavonoid, Derivatives, Sphingosine kinase 1*

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Introduction

Epidemiological data show that cancer is a serious health problem worldwide.[1-4] This clinical pathology is associated with different factors such as changes in androgen and estrogen levels,[5, 6] smoking,[7] sedentary lifestyle [8], alcoholism,[9] and a high-fat diet.[10] Besides, some studies suggest that this clinical pathology can be regulated by the synthesis or activation of different biomolecules such as sphingolipids, which can regulate cancer cell growth.[11] Sphingolipids are used as biological substrates for the synthesis of several biomolecules such as sphingosine, ceramide, sphingosine-1-phosphate (S1P), ceramide-1-phosphate, and sphingomyelin.[12] There is a report suggesting that SIP may regulate some processes involving inflammation, resulting in cancer cell growth.[13] It is noteworthy that a study indicates that SP1 can be produced by two sphingosine kinase isoenzymes,[14] SphK1 (cytosol) and SphK2 (nuclear membrane and cytoplasm).[15] It is noteworthy that some reports suggest that SphK1 is expressed in different types of cancers.[16-21] For example, a report suggests that the SphK1/SP1 axis may be involved in the development of breast cancer.[22]

Furthermore, a study indicates that SK1 is related to high ERK1/2 levels (extracellular signal-regulated kinase proteins) in cancer cells.[23]

On the other hand, a study indicate that SphK1 can be expressed in patients with pancreatic cancer.[24] Other data indicate that the SphK1/SIP axis can induce bladder cancer metastasis through the Akt/β-catenin pathway (kinase B/beta catenin proteins), resulting in PDL2 (cell surface receptor belonging to the B7 protein family) activation.[25] In addition, a study suggests that SphK1 can regulate androgen levels in prostate cancer growth.[26] It is noteworthy that different medications have been used to reduce cancer cell growth; in this way, a study displayed that the PF-543 (SphK1 inhibitor) drug can decrease MCF-7 cancer cell line growth via EGF (epidermal growth factor).[27] Furthermore, a study shows that the SKI-349 drug decreases non-small cell lung cancer cell growth via SphK1/SphK2 inhibition.[28]

Furthermore, a report showed that PAPTP

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(Kv1.3 inhibitor) in combination with ABC294640 (SphK2 blocker) can produce a decrease in pancreas cancer cells using an in vitro model.[29] All this data indicate that some drugs are used as SphK1 and SphK2 inhibitors; however, it is needed to carry out several studies to evaluate the interaction of SphK1 with different biomolecules involved in cancer development. For this reason, the aim of this research was to determine the possible coupling of some flavonoid analogs with SphK1 using the DockingServer program.

Materials and Methods

Figure 1 depicts the structure of flavonoid derivatives, which were utilized to ascertain if they may interact in the following with the SphK1 protein surface:

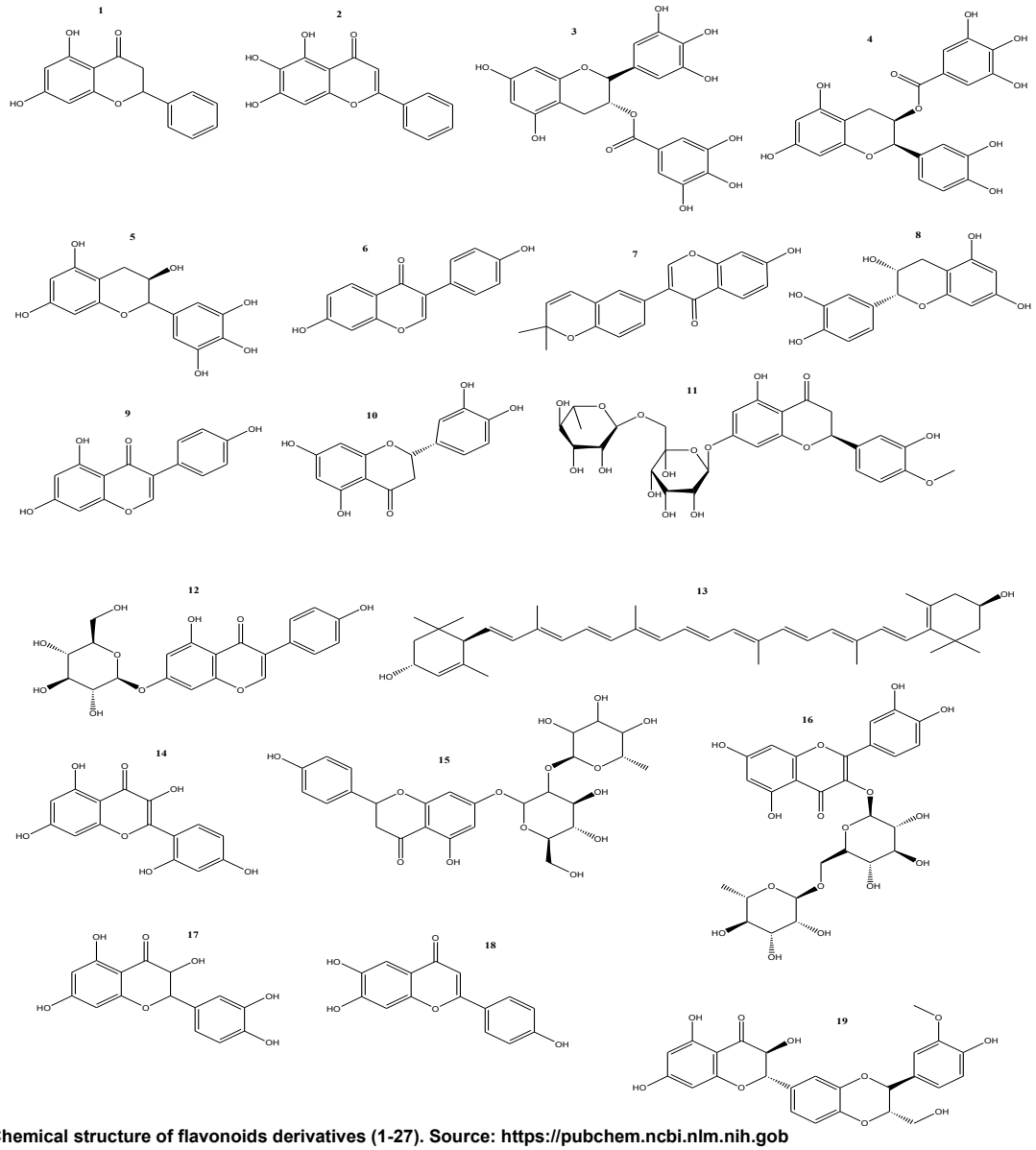

Figure 1. Chemical structure of flavonoids derivatives (1-27). Source: https://pubchem.ncbi.nlm.nih.gob

1 = Chrysin.
2 = Baicalein
3 = (-)-Gallocatechin gallate
4 = (-)-Epicatechin gallate
5 = (-)-Gallocatechin.
6 = Daidzein
7 = Corylin
8 = (+/-)-Epicatechin.
9 = Genistein.
10 = Eriodictyol.
11 = Hessperidin.
12 = Genistin
13 = Luteolin.
14 = Morin.
15 = Naringin
16 = Rutin
17 = Quercetin
18 = Scutellarein
19 = Silibinin

Ligand-protein complex

The coupling of flavonoid derivatives (1 to 19) with SphK1 was determined using 3vzb protein (https://doi.org/10.2210/pdb3VZB/pdb) as a chemical tool. Besides, drugs such as pf543 and 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole were used as controls in the DockingServer program.[30]

Pharmacokinetics parameters

Pharmacokinetic factors were determined using the SwissADME software.[31]

Toxicity analysis

Theoretical toxicity produced by flavonoid derivatives was determined using the Gussar program.[32]

Results and Discussion

For numerous years, several theoretical techniques have been employed to determine the coupling of multiple substances with certain proteins.[33] According to a publication, the chemical ZINC06823429 can interact with SphK1 using a theoretical model.[34] Another research study found that curcumin (a component of turmeric rhizomes) might serve as an Sphk1 inhibitor using the AutoDock tool.[35] After analyzing all of the data, the coupling of flavonoid analogs with SphK1 was examined using the DockingServer tool and the 3vzb protein. In addition, two SphK1 antagonists were utilized as controls: pf543[36] and 2-(p-hydroxyaniline)-4-(p-chlorophenyl)thiazole.[37] The observations showed that the number of amino acid residues involved in the coupling of flavonoid analogs with the 3vzb protein surface differed from PF543 and 2-(p-hydroxyaniline)-4-(p-chlorophenyl)thiazole **(Table 1)**.

Table 1. Interaction of flavonoids analogs (1-19), pf543 and2-(p-hydroxyaniline)-4-(p-chlorophenyl)thiazole with amino acid residues of 3vzb protein.

Compound	Aminoacid residues
pf543	Ala_{115}; Phe_{173}; Ile_{174}; Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; Leu_{259}; Met_{272}; Leu_{299}; Phe_{303}
2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole)	Ser_{168}; Phe_{173}; Ile_{174}; Va_{l177}; Asp_{178}; Phe_{192}; $Thr_{196;}$ Leu_{259}; Leu_{261}; Leu_{268}; Met_{272}; Leu_{302}; Phe_{303}; Met_{306}; His_{311}; Leu_{319}
1	Phe $_{173}$; Thr_{196}; Leu_{259}; Leu_{261}; Ala_{274}; Phe_{288}; Val_{290}; Leu_{299}; $Leu_{302;}$ Met_{306} ; His_{311}
2	Phe_{173}; Ile_{174}; Val_{177}; Phe_{192}; Thr_{196}; Met_{272}; Leu_{299}; Leu_{302}; Phe_{303}; Met_{306}; Leu_{319}
3	Phe_{173}; Ile_{174}; Val_{177}; Asp_{178}; Thr_{196}; Val_{258}; Leu_{259}; Leu_{261}; Leu_{263}; Leu_{268}; Met_{272}; Ala_{274}; Phe_{288}; Leu_{299}; Phe_{303}; Met_{306}; His_{311}; Leu_{319}
4	Asp_{81}; Ala_{115}; Leu_{167}; Ser_{168}; Ala_{170}; Phe_{173}; Ile_{174}; Val_{177}; Asp_{178}; Phe_{192}; Leu_{261}; Leu_{268}; Met_{272}; Met_{306}; Ala_{339}
5	Phe_{173}; Ile_{174}; Val_{177}; Asp_{178} ; Thr_{196} ; $Leu_{259;}$ Leu_{268}; Met_{272}; Ala_{274}; Phe_{303}; Met_{306}; His_{311}; Leu_{319}
6	Phe_{173}; $Ile_{174;}$ Val_{177}; $Asp_{178;}$ Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; $Leu_{299;}$ $Leu_{302;}$ Phe_{303}
7	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; Phe_{303}; Met_{306}
8	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; Phe_{303}; Met_{306}
9	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ $Leu_{299;}$ Phe_{303}; Met_{306}
10	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{261;}$ $Leu_{268;}$ Met_{272}; $Ala_{274;}$ Phe_{288}; $Leu_{299;}$; $Leu_{302;}$ $Phe_{303;}$ $Met_{306;}$ His_{311}
11	Asp_{81}; $Leu_{167;}$ $Ser_{168;}$ Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; $Ser_{181;}$ Phe_{192}; Thr_{196}; $Leu_{259;}$ $Leu_{261;}$ $Leu_{268;}$ Met_{272}; $Ala_{274;}$ $Phe_{288;}$ $Leu_{299;}$ $Phe_{303;}$ $Met_{306;}$ $His_{311;}$ $Leu_{319;}$ Ala_{339}
12	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; $Leu_{299;}$; $Leu_{302;}$ Phe_{303}; Met_{306}
13	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; $Leu_{299;}$ $Leu_{302;}$ Phe_{303}; $Met_{306;}$ His_{311}
14	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; Phe_{303}; $Met_{306;}$ His_{311}
15	Asp_{81}; $Ala_{115;}$ $Leu_{167;}$ $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; $Leu_{259;}$ $Leu_{261;}$ $Leu_{268;}$ Met_{272}; $Ala_{274;}$ Phe_{288}; Val_{290}; $Leu_{302;}$ Phe_{303}; $Met_{306;}$ $His_{311;}$ $Met_{312;}$ Leu_{319}
16	Phe_{173}; $Ile_{174;}$ Val_{177}; Phe_{192}; Thr_{196}; $Leu_{200;}$ Val_{258}; $Leu_{259;}$ $Leu_{268;}$ Met_{272}; $Ala_{274;}$ Phe_{288}; Val_{290}; $Leu_{299;}$ $Leu_{302;}$ Phe_{303}; $Met_{306;}$ $His_{311;}$ $Met_{312;}$ Leu_{319}
17	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Thr_{196}; $Leu_{268;}$ Met_{272}; $Ala_{274;}$ Phe_{288}; ; $Leu_{302;}$ Phe_{303}; $Met_{306;}$ His_{311}
18	Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{268;}$ Met_{272}; Val_{290}; $Leu_{302;}$ $Phe_{303;}$ Leu_{319}
19	$Leu_{167;}$ $Ser_{168;}$ Phe_{173}; $Ile_{174;}$ Val_{177}; Asp_{178}; Phe_{192}; Thr_{196}; $Leu_{259;}$ $Leu_{268;}$ Met_{272}; $Ala_{274;}$ Phe_{288}; $Leu_{302;}$ $Met_{306;}$ His_{311}

Other data indicated differences in the energy concentration for flavonoid analogs in comparison with pf543 and 2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole. Besides, the inhibition constant (Ki) was lower for flavonoid analogs 2, 6-10, 13, 14, 17, and 18 compared with pf543 and 2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole drugs **(Table 2 and Figure 2)**. This phenomenon could be due to types of interactions of flavonoid analogs with the 3vzb protein. For example, the flavonoid baicalain with some aminoacid residues such as Ile_{174}, Phe_{173}, Phe_{192}, Val_{177}, Met_{3272}, and Met_{306} via hydrophobic bounds; for daidzein with Asp_{178} via polar bond, and Ile_{174}, Val_{177}, Phe_{173}, Leu_{268}, and Met_{272} throug hydrophobic bonds; for corylin with Asp_{178}, and Thr_{196} via polar bond and Val_{177}, Phe_{173}, Ile_{174}, Leu_{268}, Met_{272}, and Met_{306} through hydrophobic bonds; for (+/-)-Epicatechin with Thr_{196} via hydrogen bond, with Asp_{178} through polar bond, and with Phe_{173}, Ile_{174}, Val_{177}, and Leu_{268} via hydrophobic bonds; genistein with Thr_{196} via hydrogen bond, with Asp_{178} through polar bond, and Phe_{173}, Ile_{174}, Val_{177}, and Leu_{268}; for eriodictyol with His_{311} via polar bond, with Phe_{173}, Ile_{174}, Val_{177}, Leu_{268}, Phe_{303} and Met_{306} through hydrophobic bonds; for luteoin with Asp_{173} and His_{311}, with Phe_{173}, Ile_{174}, Val_{177}, Leu_{268}, Met_{272}, Leu_{302}, and Met_{306} through hydrophobic bonds; for morin with Thr_{196} via hydrogen bond, with Asp_{178}, and His_{311} through polar bond, with Ile_{174}, Val_{177}, Phe_{192}, Leu_{268}, Met_{272}, and Met_{306} via hydrophobic bonds; for quercetin with His_{311}, and Asp_{178} via polar bonds, with Ile_{174}, Val_{177}, Phe_{192}, Leu_{268}, Met_{272}, and Met_{306} through polar bonds; for scutellarein with Asp_{178} via polar bond, with Phe_{173}, Ile_{174}, Val_{177}, Met_{272}, and Phe_{303}.

Table 2. Thermodinamic parameters involved in coupling of flavonoids derivatives (1-19), pf543 and2-(p-hydroxyaniline)-4-(p-chlorophenyl)thiazole with 3vzb protein surface.

Compound	A	B	C	D	E	F
pf543	-9.07	225.59	-10.16	-0.13	-10.29	797.78
2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole	-8.56	528.40	-9.50	-1.07	-10.57	1042.25
1	-6.61	14.37	-6.84	0.00	-6.84	590.05
2	-8.18	1.00	-7.98	-0,01	-7.99	652.35
3	-17.09	-	12.99	-0,08	12.91	832.61
4	7.67	-	3.96	-0,61	3.35	924.61
5	-5.24	143.62	-5.80	-0,03	-5.82	695.70
6	-7.24	4.92	-7.82	-0,32	-8.14	669.10
7	-7.92	1.56	-8.53	0,04	-8.49	841.16
8	-7.41	3.71	-7.10	-0.44	-7.54	699.92
9	-7.06	6.74	-7.43	-0,24	-7.67	669.05
10	-7.84	1.79	-6.98	0,02	-6.96	674.27
11	50.05	-	48.26	-0,51	47.75	1141.56
12	-4.28	725.50	-5.04	-0.15	-5.19	923,54
13	-7.50	3.18	-7.08	-0.12	-7.21	679.60
14	-7.08	6.47	-6.90	-0.10	-7.00	684.50
15	33.01	-	31.70	-0.01	31.69	1106.62
16	106.18	-	75.69	-0.17	75.52	911.03
17	-7.79	1.96	-7.66	-0.10	-7.75	686.45
18	-7.36	4.03	-7.24	-0,08	-7.32	659.35
19	-9.39	130.94	-9.54	-0,26	-9.80	1009.08

A = Est: Free Energy of Binding (kcal/mol); B = Est. 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.

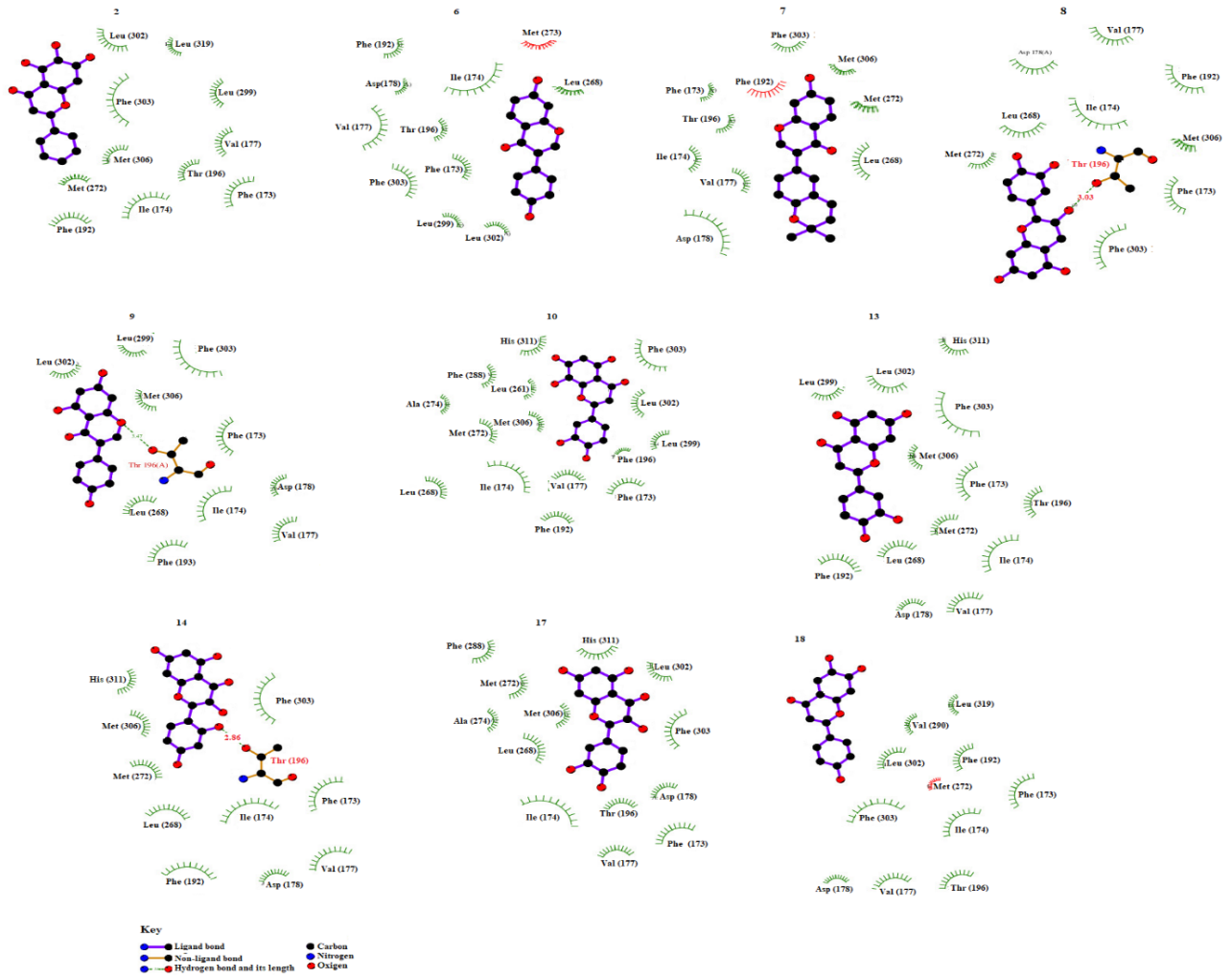

Figure 2. Interaction of flavonoids derivatives (2, 6-10, 13, 14, 17, and 18) with 3vsb protein surface. Visualized with DockingServer program.

Pharmacokinetic parameters

Several studies have been used to evaluate several pharmacokinetic factors associated with the biological activity of various drugs, such as SwissADME,[38] and others. For this reason, in this study, the SwissADME program was used to predict pharmacokinetic parameters for flavonoid derivatives such as 2, 6-10, 13, 14, 17, and 18 **(Table 3)**. The results displayed that flavonoid derivatives could have different gastrointestinal absorption degree compared with compounds pf543 and 2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole. In addition, other results indicate that flavonoid analogs could act with different Cyps. This phenomenon could be translated as differences in the metabolism of each flavonoid derivative.

Table 3. Pharmacokinetic parameters for flavonoid Analogs 2, 6,-10, 13, 14, 17 and 18

Comp.	GI Absorption	BBB permeant	P-gp substrate	Cyp1A2 inhibitor	Cyp 2C19 inhibitor	Cyp2C9 inhibitor	Cyp2D6 inhibitor	Cyp3A4 inhibitor
pf543	**High**	**No**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**
2-OH-A	High	No	No	Yes	Yes	Yes	Yes	Yes
2	High	No	No	Yes	No	No	Yes	Yes
6	High	Yes	No	Yes	No	No	Yes	Yes
7	High	Yes	No	Yes	Yes	Yes	No	Yes
8	High	No	Yes	No	No	No	No	No
9	High	No	No	Yes	No	No	Yes	Yes
10	High	No	Yes	No	No	No	No	Yes
13	High	No	No	Yes	No	No	Yes	Yes

14	High	No	No	No	No	No	No	No
17	Low	No	No	No	No	No	No	No
18	High	No	No	Yes	No	No	Yes	Yes

2-OH-A = 2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole); GI = Gastointestinal; BBB = Blood Barrier Brain; P-gp = Glycoprotein-P; Cyp = Cytochrome-P450.

Toxicity analysis

Several studies indicate that flavonoids have anticancer properties;[39, 40] however, there are some data that suggest that some flavonoid derivatives can produce toxicity.[41, 42] Therefore, to evaluate the toxicity degree exerted by some flavonoid analogs (9, 6-10, 13, 14, 17, and 18), the GUSAR software was used. The data displayed that flavonoid analogs 2-18 require higher doses to produce toxicity via the intravenous route in comparison with the controls; however, flavonoid analogs may induce some degree of toxicity via oral and subcutaneous routes in comparison with the controls. These results **(Table 4)** indicated that the toxicity degree may depend on the dose and routes of administration of each flavonoid analog.

Table 4. Theoretyical toxicity produced by flavonoid derivates.

Compound	IP LD50 (mg/kg)	IV LD50 (mg/kg)	Oral LD50 (mg/kg)	SC LD50 (mg/kg)
pf543	959.00	58.74	1265.00	79.10
2-OH-A	689.10	46.93	1943.00	396.00
6	78.37	64.300	1071.00	583.40
7	346.40	139.80	3856.00	463.20
8	218.10	105.30	3451.00	287.80
9	369.60	226.20	804.20	466.10
10	465.00	307.30	591.20	377.80
13	194.20	169.20	651.40	277.40
14	94.22	128.40	1196.00	611.90
17	298.70	255.50	658.80	604.90
18	93.29	104.30	1854.00	563.60

2-OH-A = 2-(*p*-hydroxyaniline)-4-(*p*-chlorophenyl)thiazole); IP = Intraperi- toneal; IV = Intravenous; Oral = Oral; SC = Subcutaneous.

Conclusion

This investigation reports the coupling of flavonoid analogs with SphK1 using the 3vzb protein as a theoretical tool. The results indicated the following: i) Flavonoid analogs 2, 6-10, 13, 14, 17, and 18 may have a higher affinity for the SphK1 protein surface in comparison with PF543 and 2-(p-hydroxyaniline)-4-(p-chlorophenyl)thiazole drugs; ii) these data suggest that flavonoid derivatives 2, 6-10, 13, 14, 17, and 18 could modulate the biological activity produced by SphK1, and this phenomenon could translate as good anticancer agents.

Acknowledgments

None

Conflict of interest

None

Financial support

None

Ethics statement

This article does not contain any studies involving animals or human participants. Theoretical data involved in this study were handled honestly and in accordance with the ethical processes that govern our institution's pharmacochemistry laboratory.

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