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IN SILICO STUDIES OF SOPHORAFLAVANONE G: QUANTUM CHARACTERIZATION AND ADMET

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Abstract

Currently, the search for new drugs with greater therapeutic potential and less side effects has been fostered by the advancement of the use of molecular modeling drugs, which in addition to supporting the full characterization of the molecule, allow simple algorithms to predict pharmacokinetic. In this context the present work aimed to perform the electronic / structural characterization, to evaluate the pharmacokinetic properties and to perform a virtual screening of the possible biological targets of Sophoraflavonone G, a promising flavonone, which presents several pharmacological properties. Sophoraflavanone G was geometrically optimized by semi-empirical quantum calculations, plot the MESP, identifying the nucleophilic sites. Using the boundary orbitals, it was possible to identify a greater tendency for electron donation in relation to Naringeni, with lower ionization potential, higher hardness and less softness. With respect to pharmacokinetics Sophoraflavonone G confirmed the safety of the compound for oral administration with good skin permeability, which allows applications in topical formulations. Presents indications for gastro intestinal absorption, as for possible interactions with biological targets, interaction with the estrogen receptor alpha, sodium / glucose co-transporter 2, beta-secretase 1, cyclooxygenase-1.The data obtained from an early stage for a comparative analysis between its analogues and fundamental for future studies of relationships between the three-dimensional structure of Sophoraflavanone G and its biological activities.

Keywords: ADMET; Flavonone; Pharmacokinetic; Quantum Study; Semi-Empirical; S. Flavescens.

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1. Introduction

Flavonoids are a class of secondary metabolites found in plants that perform a variety of functions. They are known as plant pigments mainly present in flower petals to attract pollinators and for their antioxidant activities, providing consumers with some hope for medicinal uses, potentially cancer treatment. [1].

The dried roots of the Sophora flavescens plant belonging to the Leguminosae family, is used in traditional Chinese medicine and has antibacterial [2], antiviral, antiprotozoal, anti-inflammatory [3], antipyretic [3], healing, anti-hemorrhagic, antimalarial [4], phospholipase-Cγ1 enzyme inhibiting activity [5], antiarrhythmic effects [6] used in the treatment of skin ulcers and also as an insecticide. In addition to flavonoids with regular prenyl side chains, S. flavescens also produces several flavanones with lavasulil chains, irregular monoterpenoid groups such as kurarinone and sophoraflavanone G [7], [8] noting that studies have shown the importance of the chain. side of Lavandulila for antitumor activity [9] Flavonoids isolated from this plant have phospholipase-Cγ1 inhibition activity [5].

Sophoraflavanone G, one of the major flavanones isolated from the dried roots of S. flavescens, is known to possess antimalarial, antimicrobial, antiviral and antioxidant activities and inhibits the production of nitric oxide and prostaglandin E2 in lipopolysaccharide treated RAW cells. [10]. These biological activities are indicative of the pharmacological potential of Sophoraflavanone G.

Thus, with the development of chemistry, especially organic synthesis, many substances that have some kind of biological activity have been synthesized. As a result, drugs of synthetic origin became about 80% of the drugs on the market. Thus, many of these substances come from prototype structures found in natural products. Often, organic synthesis contributes not only to a greater production of the natural substance that has biological activity, but also to the structural modification of this substance to obtain pharmacologically superior products [11].

With the increase in computer processing potential and the development of more accurate mathematical algorithms, molecular modeling has been increasing the development of new drugs, reducing research costs through electronic and structural characterization, pharmacokinetic, toxicological simulations and receptor drug interactions , which make it possible with great precision to analyze the potential drug, predicting its potential, indicating the continuity or not of tests in vivo and in vitro[12][13][14][15].

Given the need for the development of new drugs, the aim of this study was to perform the electronic / structural characterization, evaluate the pharmacokinetic properties and perform a virtual screening of the possible biological targets of sophoraflavonone G. This study is a fundamental step for DRUG studies. design, molecular docking and molecular dynamics.

2. Materials and Methods

Computational Details

All the computations simulations were performed on personal computer with intel® Core TM i7 7700HQ processor, 16 GB RAM, 4G Nvidia® GeForce GTX 1050 Radeon video card and

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Microsoft Windows 10® as operating system. All softwares codes used are free license for academic use.

Structural Optimization

Initially, after the literature review, the two-dimensional molecular structure of Sophoraflavanone G from the ChemSpider® virtual repository (http://www.chemspider.com) (Figure 1A) was used to obtain the following data: nomenclatures, physicochemical properties and mechanisms of action. After obtaining the data in its two-dimensional form, the molecule was geometrically optimized by semi-empirical quantum calculations, implemented in the code ArgusLab® [16] configured with Hamiltonian Parametric Method 3 (PM3) parameters [17]. As Sophoraflavanone G is an analogue derivative of anagerin (Figure 1B), for comparative analysis, optimization data were used under the same conditions.

Fronteir Orbitals, MESP and Descriptores Reactivity

To start the reactivity study we need to obtain the spatial conformation (3D) of the molecule, because from it we can calculate the energies of the orbitals. In this context, the LCAO-MO Model used in the theory of molecular orbitals, which uses the linear combination of atomic orbitals, to generate the molecular orbitals, keeping the same number of orbitals and fundamental for rendering and identification of the orbitals. In terms of reactivity analysis we can highlight the homo and the lunar orbitals, which are called boundary orbitals, since from the energy difference among them we can identify the electron receptor or donor bias of the molecule [18][15][19].

Thus it was possible to obtain the lowest potential energy conformation of the molecule, characterizing HOMO (Higher Energy Busy Molecular Orbital) (ε_{HOMO}), LUMO (Low Energy Unoccupied Molecular Orbital) (ε_{LUMO}) [20] [21] [22] and the reactivity descriptors, GAP (Amount of energy required for the electron to transition), electron affinity (A), ionization potential (I), electronegativity (χ), hardness (η), Chemical softness (S), chemical potential (μ) and electrophilicity index (Ω) (Table 1) [23]follows [24][25][26][27][28][29]. In addition to the descriptors, heat of formation was calculated, Dipole Moment and MESP (Electrostatic Potential Surface Map) [30].Avogadro software was used to visualize the results and render 3D structures[31][32].

Table 1: Calculation Methodology for Reactivity Descriptors

Descriptor	Formula
GAP	$GAP=\Delta\varepsilon=\lvert\varepsilon_{HOMO}\rvert - \lvert\varepsilon_{LUMO}\rvert$
Electron affinity (A)	$A=-\varepsilon_{LUMO}$
Electronegativity (χ)	$\chi = (I+A)/2$
Vertical Ionization potential (I)	$I=-\varepsilon_{HOMO}$
Chemical hardness (η)	$\eta = (I-A)/2$
Chemical softness (S)	$S=1/2\eta$
chemical potential (μ)	$\mu = -(I+A)/2$
Electrophilicity index (Ω)	$\omega = \mu^2 / 2\eta$

The properties of Absorption, Distribution, Metabolization, Excretion and Toxicity (ADMET) including solubility, blood brain barrier (BBB), plasma protein binding, CYP2D6 binding,

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gastrointestinal absorption and hepatotoxicity were predicted using the Swissadme code (http: // www. swissadme.ch/), an online software written in JavaScript, HTML, and PHP5 with Python 2.7 encoded computing backend that allows you to accurately analyze 2D structures of drug candidates against ADMET descriptors [33][34][35]. lipophilicity was predicted according to Wildman et al [36],violations of oral bioavailability were assessed according to the Lipinski rule [37].At this stage we also examined the possible inhibitory character of Sophoraflavonone of Cytochrome Family (P450 CYP) isoforms such as CYP1A2 and CYP2D6, in addition to other pharmacokinetic predictions (gastrointestinal absorption, P-glycoprotein and blood brain barrier), as Ghose and Veber Rules and bioavailability [38] and Brain Or IntestineL EstimateD permeation method (BOILED-Egg) to predict gastrointestinal absorption predict gastrointestinal [39].

2D Structure Modeling

The 2D Structural Models were designed in MarvinSketch code (ChemAxon Software) [40]and coded for SMILES in the SMILES online translator and generator structure file found in OpenBabel software [41].

Virtual Screening for Target Classes

To identify possible target proteins, Swiss Target Prediction [42][43] was used, an online script that uses the reverse trace scope to identify through structural similarities between molecules to similarly predict possible receptors (biological targets). Homo sapiens receiver search identifier [44], the Sophoraflavonone G two-dimensional structure was used, which was converted to 3D format, using the Tanimoto coefficient as an adjustment factor and similarity, vectorized by the Manhattan distance, defined by by the equation using the vectors (X and Y) and equation 2 to calculate the final value 3D similarity between molecules of i and j, where d ij is the shortest Manhattan distance between the 20 × 20 calculated distances over all possible conformations of each molecule [42].

$$d = \sum_{s=1}^{18} |x_n - x_s| \quad (1)$$

$$1/(1 + 1/18 d\,ij \quad (2)$$

3. Results and Discussions

Structural and Conformational Characterization

Using Sophoraflavanone G's two-dimensional structure obtained from the Chewspider.com virtual repository (http://www.chemspider.com/Chemical-Structure.65766.html?rid=ee036cea-6045-4fad-82ca-0b7579f6a86f) (ID 65766) its name could be identified according to the International Union of Pure and Applied Chemistry IUPAC (2S) -2- (2,4-Dihydroxyphenyl) -5,7-dihydroxy-8 - [(2R) -2-isopropenyl- 5-methyl-4-hexen-1-yl] -2,3-dihydro-4H-chromen-4-one and its molecular formula C25H28O6. In addition, physical and chemical properties could be obtained [Table 1], linked to the structural composition of the molecule, from which we can highlight its density (1.3 ± 0.1 g cm-3), its surface tension (55.9 ± 3.0 dyne cm-1). , molar volume (335.3 ± 3.0 cm3) and their ability to form hydrogen bonds by determining atoms with the potential to receive or donate electrons in hydrogen bonds among other properties.

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Table 1: Physical-chemical properties of the Sophoraflavanone G

Properties	Value	Properties	Value
Molecular Formula	$C_{25}H_{28}O_6$	Monoisotopic Mass	424.188599 Da
Density	1.3±0.1 g/cm^3	Refractive index	1.623
Boiling point	659.3±55.,0 °C (760 mmHg)	Molar Refractivity	118.2±0.3 cm^3
Vapour Pressure	0.0±2.1 mmHg (25°C)	Superficial tension	55.9±3.0 dyne/cm
Enthalpy of Vaporization	100.5±3.0 kJ/mol	Molar Volume	335.3±3.0 cm^3
Receptors #H	6	Donors #H	4

Souce: Virtual Repository ChemSpider® [http://www.chemspider.com/Chemical-Structure.65766.html?rid=1ac8c714-e4b9-4bfe-90ff-e237ec005803].

The two-dimensional structure of Sophoraflavanone G (Figure 1B), available from the ChemSpider® repository, was in its ground state, presenting only the molecular formula (C25H28O6) and the connectivity of atoms, with an easy to see initial conformation but with different potential energy. of the molecule in its native form. because the two-dimensional coordinates of a molecule available in an online repository are not necessarily in the most stable conformation [45]. Thus, to obtain more accurate calculations about the molecule and its more stable final conformation, we need to perform a geometric optimization using the energy minimization process [46] . This geometric optimization was performed using the semi-empirical quantum method formalism QM_PM3 (Parametric Method 3), performing uninterrupted cycles of 200 interactions, repeated until the structure reaches a point of lowest possible minimum energy, thus each of the atoms that the structure occupied its place of lowest energy in the system and the three-dimensional structure reached the most stable calculable point (Figure 2), presenting a spatial distribution that allows the lowest potential energy possible [47][48], making the potential energy of the molecule assumed a value of (-118893.6623kcal / mol), no longer varying, reaching a stationary point of the energy surface [4], the formation heat (-206.3487kcal / mol) and dipole moment (μ) in length. (4.95590298 debye) characterizing the molecule as polar. Some other properties of the structure are directly linked to the dipolar moment (μ), such as melting and boiling points and their solubility in water.

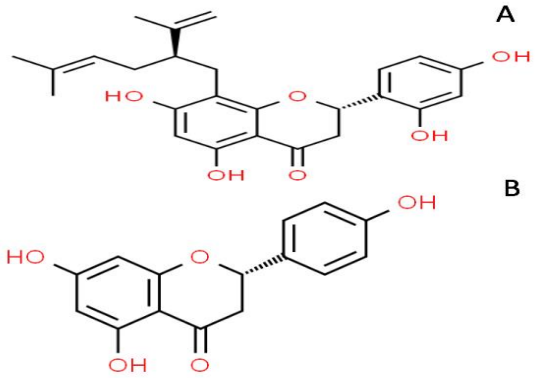

Figure1: The two-dimensional structure Sophoraflavanone G(A) Naringenin(B).
Souce: Virtual Repository ChemSpider®

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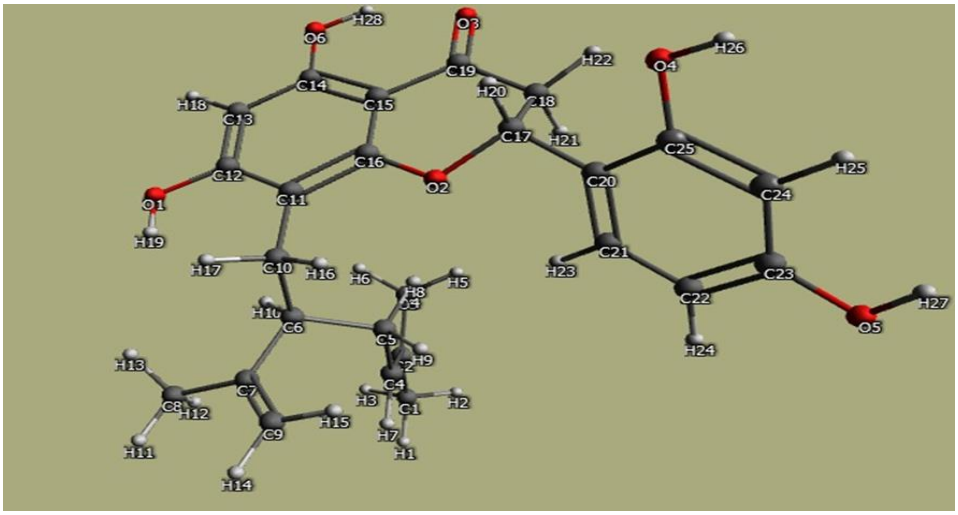

Figure 2: Optimized structure of Sophoraflavanone G

By obtaining the molecule in a theoretically more stable structure, it was possible to calculate the formal and partial charges of all atoms as well as their valence [49][50]. All atoms showed zero formal charge and significant variations in their partial charges were found, such as Hydrogen from 0.027 to 0.292, Carbon from -0.099 to 0.174 and Oxygen from -0.507 to -0.292. These data (table 2), especially valence, correspond to the literature, which serves to validate the results obtained. Despite the neutrality through optimization, it is possible to observe in the results obtained the largest and smallest (residual) partial loads. It was noticed that atoms 59, 58,57,50 (H) and 30 (O) presented larger and smaller partial charge respectively, charges from electrons being closer or farther from one of the bond atoms, taking with them charge.

Table 2: Atomic properties of the compound Sophoraflavanone G

Atom	Element type		Valencia	Partial change
1	C	C3	4	-0.044
2	C	C2	3	-0.080
3	C	C3	4	-0.044
4	C	C2	3	-0.085
5	C	C3	4	-0.028
6	C	C3	4	-0.013
7	C	C2	3	-0.076
8	C	C3	4	-0.044
9	C	C2	3	-0.099
10	C	C3	4	-0.014
11	C	Car	3	0.037
12	C	Car	3	0.127
13	C	Car	3	0.023
14	C	Car	3	0.134
15	C	Car	3	0.101
16	C	Car	3	0.142
17	O	O3	2	-0.506
18	O	O3	2	-0.482

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19	C	C3	4	0.136
20	C	C3	4	0.052
21	C	C2	3	0.174
22	O	O2	1	-0.292
23	C	Car	3	0.035
24	C	Car	3	-0.048
25	C	Car	3	-0.020
26	C	Car	3	0.120
27	C	Car	3	0.022
28	C	Car	3	0.127
29	O	O3	2	-0.506
30	O	O3	2	-0.507
31	O	O3	2	-0.506
32	H	H	1	0.027
33	H	H	1	0.027
34	H	H	1	0.027
335	H	H	1	0.027
36	H	H	1	0.027
37	H	H	1	0.027
38	H	H	1	0.057
39	H	H	1	0.031
40	H	H	1	0.031
41	H	H	1	0.035
42	H	H	1	0.027
43	H	H	1	0.027
44	H	H	1	0.027
45	H	H	1	0.053
46	H	H	1	0.053
47	H	H	1	0.032
48	H	H	1	0.032
49	H	H	1	0.069
50	H	HO	1	0.292
51	H	H	1	0.079
52	H	H	1	0.038
53	H	H	1	0.038
54	H	H	1	0.062
55	H	H	1	0.065
56	H	H	1	0.069
57	H	HO	1	0.292
58	H	HO	1	0.292
59	H	HO	1	0.292

In the final geometry of Sophoraflavanone G after optimization, all the bonds analyzed were characterized by the predominance of covalence, where we can highlight the bonds (9, 14, 21, 27, 30, 48, 55 and 57) between carbon and (45) between carbon and oxygen as second order bonds. In

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addition, the links (16, 19 and 44) between carbons are noted for their rotability (Table 3). Complementing the conformational analysis, the largest and smallest angles between joints were identified, angles 18 (CCC) and 44 (HCH) with 124.7844 ° and 105.4585 ° respectively; and the largest and smallest torsion angles, the 147 (CCOH) and 67 (ACC) systems with 179,999 ° and -179,978 ° respectively.

Table 3: Properties of the compound Sophoraflavanone G

Bond	Type	Initial Atom	Final Atom	Order of Bond	Rotability	Length (Å)
1	H-C	H11	C8	1	No	1.09764
2	H-C	H13	C8	1	No	1.09959
3	C-H	C8	H12	1	No	1.09868
4	C-C	C8	C7	1	No	1.48994
5	H-C	H14	C9	1	No	1.08640
6	H-O	H19	O1	1	No	0.95729
7	O-C	O1	C12	1	No	1.36383
8	H-C	H17	C10	1	No	1.11472
9	C-C	C7	C9	2	No	1.33288
10	C-C	C7	C6	1	No	1.51007
11	C-H	C9	H15	1	No	1.08735
12	H-C	H18	C13	1	No	1.09731
13	H-C	H10	C6	1	No	1.11986
14	C-C	C12	C13	2	No	1.39715
15	C-C	C12	C11	1	No	1.41671
16	C-C	C10	C6	1	Yes	1.54326
17	C-H	C10	H16	1	No	1.10721
18	C-C	C10	C11	1	No	1.49830
19	C-C	C6	C5	1	Yes	1.53482
20	C-C	C13	C14	1	No	1.40151
21	C-C	C11	C16	2	No	1.40243
22	H-C	H7	C4	1	No	1.09800
23	C-C	C5	C4	1	No	1.49010
24	C-H	C5	H9	1	No	1.10954
25	C-H	C5	H8	1	No	1.11037
26	H-C	H3	C1	1	No	1.09867
27	C-C	C4	C2	2	No	1.33981
28	H-C	H1	C1	1	No	1.09817
29	C-O	C14	O6	1	No	1.35344
30	C-C	C14	C15	2	No	1.41535
31	H-C	H6	C3	1	No	1.09926
32	C-C	C16	C15	1	No	1.41231
33	C-O	C16	O2	1	No	1.37387
34	C-C	C2	C1	1	No	1.49037
35	C-C	C2	C3	1	No	1.48967
36	C-H	C1	H2	1	No	1.09843
37	O-H	O6	H28	1	No	0.96525

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38	C-C	C15	C19	1	No	1.46865
39	O-C	O2	C17	1	No	1.44214
40	C-H	C3	H4	1	No	1.09808
41	C-H	C3	H5	1	No	1.09912
42	H-C	H20	C17	1	No	1.11651
43	C-C	C17	C20	1	No	1.51063
44	C-C	C17	C18	1	Yes	1.53432
45	C-O	C19	O3	2	No	1.22776
46	C-C	C19	C18	1	No	1.51014
47	H-C	H23	C21	1	No	1.09951
48	C-C	C20	C21	2	No	1.39864
49	C-C	C20	C25	1	No	1.40746
50	C-C	C21	C22	1	No	1.38722
51	C-H	C18	H21	1	No	1.10900
52	C-H	C18	H22	1	No	1.10734
53	O-C	O4	C25	1	No	1.36964
54	O-H	O4	H26	1	No	0.95111
55	C-C	C25	C24	2	No	1.40272
56	C-H	C22	H24	1	No	1.09593
57	C-C	C22	C23	2	No	1.40282
58	C-C	C24	C23	1	No	1.39912
59	C-H	C24	H25	1	No	1.09769
60	C-O	C23	O5	1	No	1.36708
61	O-H	O5	H27	1	No	0.95122

Electronic Characterization and Reactivity Descriptors

After geometric optimization, the molecule a theoretically more stable structure, it was possible to calculate the atomic charges using the most traditional and known method among chemists: the Mulliken Population Analysis [51] This method divides the charge density between two atoms evenly without taking into account electronegativity; Atomic charges are useful in the correlational study between the structure of the molecule and its biological activity [52][53].The calculations under the PM3 formalism how us that (TABLE 4) there was a large variation between the atomic charges of atoms of the same element, the oxygen with the highest load was O18 with -0.1916 while the lowest oxygen, O14 with -0.3783, varied 0.1867 charge; the carbons of the same form being the one with the highest load C21 with 0.4041 and the one with the lowest load C15 with -0.4321, varying 0.0280; for hydrogen, the atomic charges ranged from 0.1006 in hydrogen H44 to 0.2858 in hydrogen H59, ranging from 0.1543.

Table 4: Population Analysis of Mulliken for Sophoraflavanone G

Atom	**Charge**	**Atom**	**Charge**	**Atom**	**Charge**
01 C	-0.2643	**21 C**	0.4041	**41 H**	0.1450
02 C	-0.1268	**22 O**	-0.3783	**42 H**	0.1122
03 C	-0.2719	**23 C**	-0.1956	**43 H**	0.1204
04 C	-0.2520	**24 C**	-0.1027	**44 H**	0.1006
05 C	-0.2015	**25 C**	-0.2695	**45 H**	0.1700

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06 C	-0.1039	**26 C**	0.1366	**46 H**	0.1704
07 C	-0.1336	**27 C**	-0.3878	**47 H**	0.1558
08 C	-0.2637	**28 C**	0.1475	**48 H**	0.1035
09 C	-0.3302	**29 O**	-0.2421	**49 H**	0.2480
10 C	-0.1661	**30 O**	-0.2337	**50 H**	0.2396
11 C	-0.2880	**31 O**	-0.2675	**51 H**	0.1569
12 C	0.2022	**32 H**	0.1085	**52 H**	0.1675
13 C	-0.3676	**23 H**	0.1118	**53 H**	0.1796
14 C	0.2614	**34 H**	0.1121	**54 H**	0.2112
15 C	-0.4321	**35 H**	0.1125	**55 H**	0.2237
16 C	0.2453	**36 H**	0.1116	**56 H**	0.2039
17 O	-0.2391	**37 H**	0.1185	**57 H**	0.2292
18 O	-0.1916	**38 H**	0.1911	**58 H**	0.2237
19 C	0.0807	**39 H**	0.1376	**59 H**	0.2858
20 C	-0.3491	**40 H**	0.1301		

To identify the areas of higher nucleophilicity and electrophilicity of the molecule, the electrostatic potential map (MESP) was calculated; MESP was plotted by mapping the electrostatic potential surface (Figures 3) on the electron density surface (Figures 4). Thus by analyzing the electrostatic potential map of the compound Sophoraflavanone G (Figure 5) we can identify a higher concentration of electrons, nucleophilic region (in red), in the areas where oxygen is located (O17, O18, O22, O29, O30 and O31).), but the rest of the structure has electron deficiency, electrolyte region (in white), except in the regions where the rings and cycles formed by the carbons that remain in a neutral area (dark blue and light blue) are located [54][55][56].

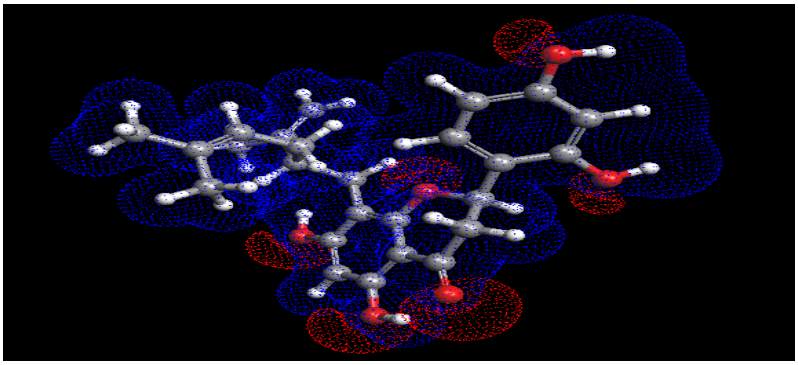

Figure 3: Superfície de Potencial Eletrostático do Sophoraflavanone G

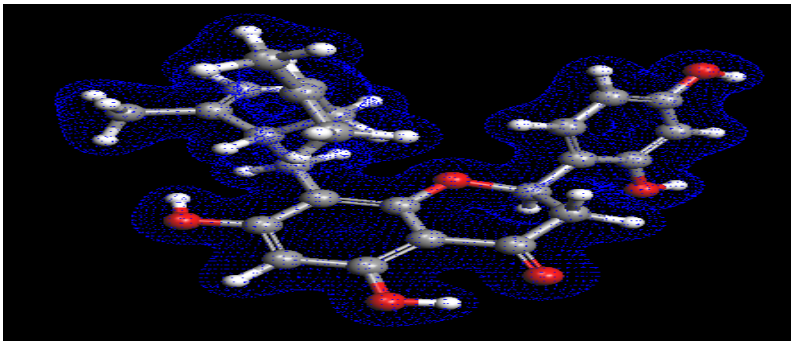

Figure 4: Sophoraflavanone G Electronic Density Surface

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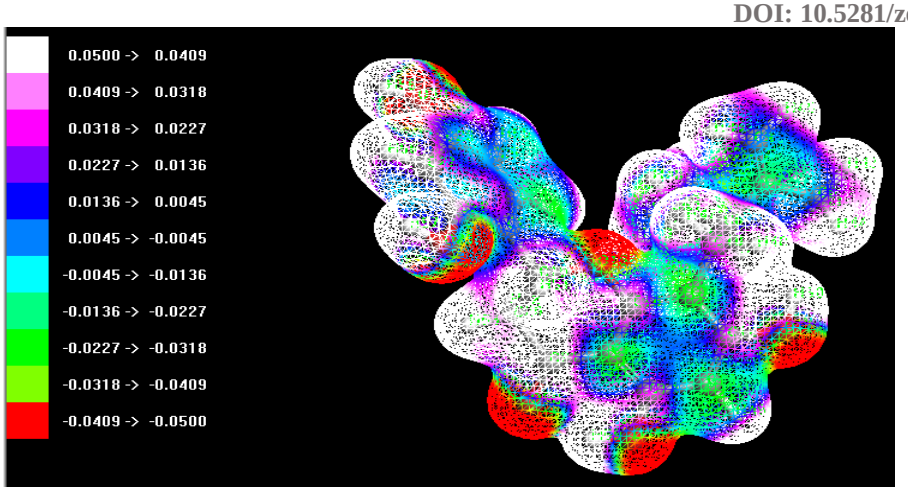

Figure 5: Electrostatic potential map of Sophoraflavanone G

Global reactivity descriptors act as a bridge between structural stability and global chemical reactivity [57]. This is also information about fundamental characteristics of chemical reactivity, such as ionization potential, electron affinity, electronegativity, chemical potential, global hardness and global softness (Table 3) [24]. The LCAO-MO Model used in the theory of molecular orbitals uses the linear combination of atomic orbitals to generate the molecular orbitals, keeping the same number of orbitals. frontier orbitals, because from the energy difference between them we can identify the electron receptor or donor tendency of the molecule. A good starting point for determining these parameters is the energetic values of the frontier molecular orbitals (HOMO and LUMO) that are used in reactivity [18], as they provide information about the electron-donor character (HOMO) and /or electron-acceptor (LUMO) of a compound [58][59]. The studied molecule presented HOMO (figure 6) (-9,02585 eV) with the atoms (C6, C11, C13, C14, C15, C16, O18 and O31) and LUMO(Figures 7) (-5.14186 eV) being highlighted (C12, C13, C14, C15 , C16, C21, O17, O18, O22, O31). The difference between HOMO-LUMO energy values is of utmost importance as a determinant of chemical stability. The molecules have broadband gaps, which are generally stable and nonreactive. Those with smaller bandwidths are reactive as it facilitates interaction with reagents [60][61][50].In addition, the GAP (amount of energy required for the electron to make a transition) is calculated on the energy difference between HOMO and LUMO (1).

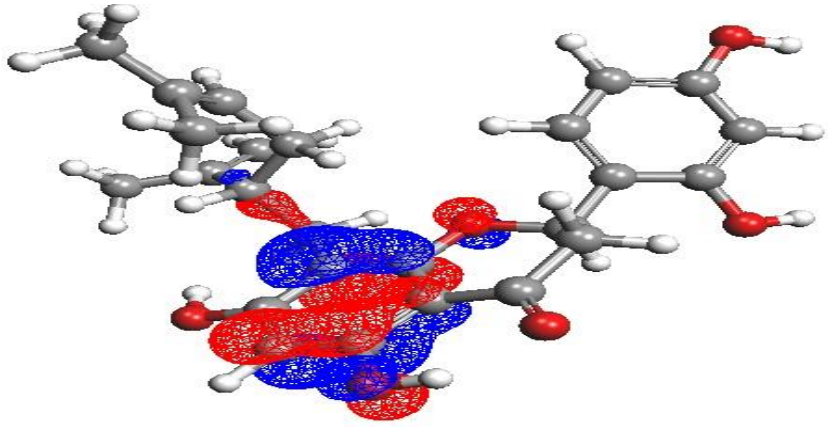

Figure 6: Highest energy occupied molecular orbital (HOMO) of Sophoraflavanone G

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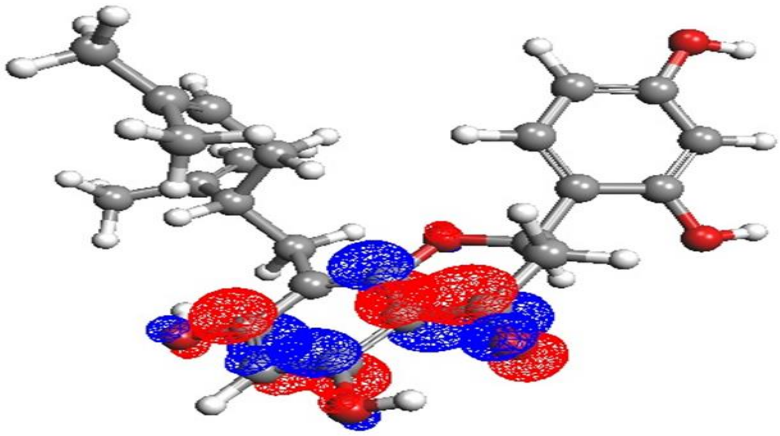

Figure 7: lower energy unoccupied molecular orbital (LUMO) of Sophoraflavanone G

The difference between HOMO-LUMO energy values is of utmost importance as a determinant of chemical stability. The molecules have broadband gaps, which are generally stable and nonreactive. Those with smaller bandwidths are reactive as it facilitates interaction with reagents [60][61][50].In addition, the GAP (amount of energy required for the electron to make a transition) is calculated on the energy difference between HOMO and LUMO (1). Comparing Sophoraflavanone with its reference compound Naringenin, it was possible to observe some differences that are fundamental in characterization. For example, Sophoraflavanone G has been shown to be a molecule that tends to donate electrons by presenting HOMO (-9,02585 eV) higher than Naringenin (-9,2525 eV) (figure 8).

Table 5 shows the reactivity parameters of the compound Sophoraflavanone G and the compound Naringenin, which were obtained by calculations using the molecular orbital energies HOMO and LUMO. Regarding the energy required to remove an electron (ionization potential), Sophoraflavanone had a lower ionization potential (9,02585 eV) than Naringenin (9,25325 eV), indicating to be more stable. Having the energy of the frontier orbitals as a reference, the hardness (η) and softness (S) values in the study of Pearson's theory (HSAB, hard and soft acid and bases) [26][62] These are fundamental concepts for understanding the acid / base behavior of molecules, where we can simplify molecules with a donor / recipient center of small electron pairs (with a low tendency to be polarizable), are indicative of favoring electrostatic interactions being considered. hard acids (receptors) or bases (donors). Molecules that favor the interaction of the frontier orbitals, that is, with low energy value, are indicative of high polarizability, since in general they have high reactivity sites (donor / receptor sites of electron pairs) and are considered as bases (donors) or soft acids (receptors), thus having high reactivity[63]. That is, Interactions between for hard acids / bases, or soft acids / bases tend to form more stable complexes when compared to the interaction between soft acids and hard bases or hard acids and bases soft [64][21]. Regarding hardness and softness, Sophoraflavanone tends to have difficulty being deformed, this is proven by observing that it had higher hardness and less softness compared to Naringenin.

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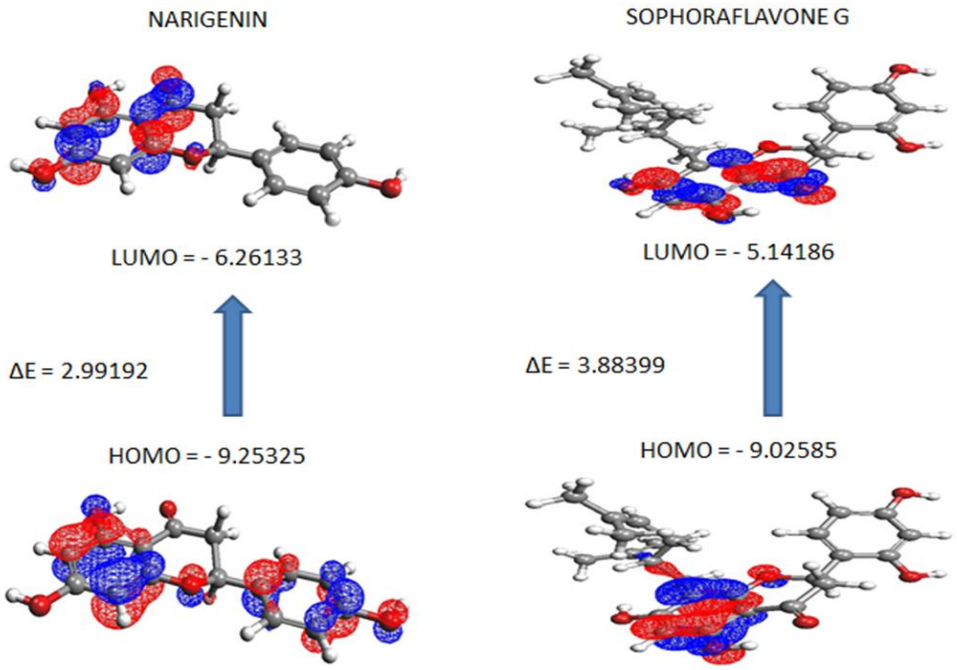

Figure 8: GAP of Narigenin and Sophoraflavanone G

Table 5: Global Reactivity Descriptors calculated for Sophoraflavanone G

Descriptor	Sophoraflavanone G	Naringenin
HOMO	-9.02585 eV	-9.25325 eV
LUMO	-5.14186 eV	-6.26133 eV
GAP	3.88399 eV	2.99192 eV
Electron affinity (A)	5.14186 eV	6.26133 eV
Electronegativity (χ)	7.08385 eV	7.75729 eV
Vertical Ionization potential (I)	9.02585 eV	9.25325 eV
Chemical hardness (η)	1.94199 eV	1.49596 eV
Chemical softness (S)	0.25747 eV	0.33423 eV
Chemical potential (μ)	-7.08385 eV	-7.75729 eV
Electrophilicity index (Ω)	12.91994 eV	20.11269 eV

Pharmacokinetic and pharmacological parameters of absorption, distribution, metabolism, excretion and toxicity -Admet

Due to the search for new drugs with greater specificity, it has been fostered by the development of computational algorithms, which allow simulating receptor drug interaction (molecular docking)[65] [66][67][68][69], as well as predicting pharmacokinetics, being able to identify within of a set of molecules those that can become an efficient drug with fewer side effects.The mechanisms use molecular descriptors, which adjusted within facings (models) and rules allow the structures to be quickly related to ADME properties, especially in relation to biological barriers, intestinal absorption [42][70][71][71].

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The chemical structure of Sophoraflavanone G was subjected to ADMET in silico screening using SwissADME online software to predict overall absorption, distribution, metabolism, excretion and toxicity hazards. In the silico evaluation, we analyzed different descriptors that were calculated, partition coefficient (octanol / water), molecular weight (424.49 g / mol), number of H+ donor groups and acceptor groups that compounded moderate solubility. in water. Absorption or permeation of a molecule is more likely when the molecular weight is below the log P value is less than 5 and the value. Sophoraflavonone G has a maximum of 6 H+ donors and 4 H+ acceptor atoms, as shown in Figure 9. According to its pharmacokinetic properties, Sophoraflavanone G showed a high level of gastrointestinal adsorption which contributes to good oral bioavailability.

Sophoraflavanone G according to pharmacokinetic parameters evaluated in silico showed no inhibition of cytochrome P450 isomers and glycoprotein P with CYP2C9 isomer exemption. Prediction of similarity with other drugs was also performed according to Ghose and Veber rules and the molecule has characteristics of bioavailability [38].

Thus, the screening process with the Lipinski Rule showed that there were no compound violations, as the screening process with Ghose rules shows that the substance sophoraflavonone G can be accepted for not showing violations of drug similarity rules (figure 10).

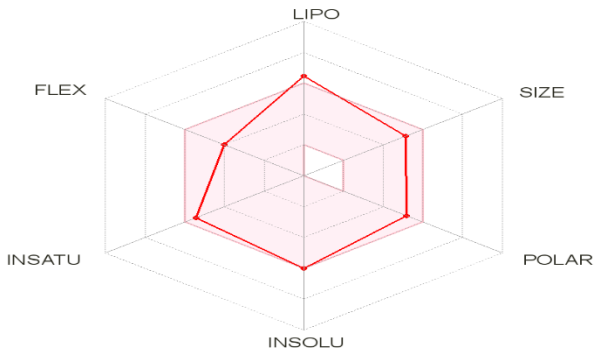

Figure 9: Biovailability and pharmacokinetic parameters Sophoraflavanone G using Swiss ADME.

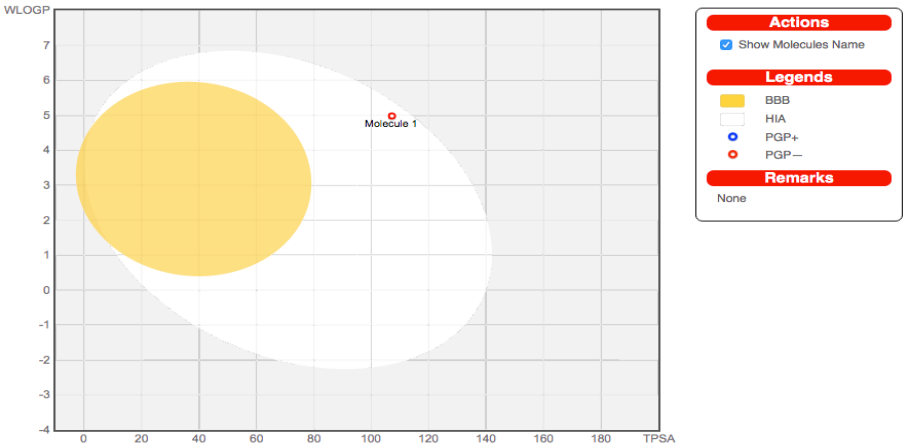

Figure 10: Brain or intestinal permeability map based on BOILED - Egg model for Sophoraflavanone G

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Virtual Screening for Target Classes

An important data for the development of a new drug is the evaluation of interactions with possible biological targets, and may be a descriptor for the therapeutic improvement [72]. Regarding possible biological target classes, Sophoraflavanone G had a higher probability of interactions with enzymes (20%), hydrolases (13.3%) and nuclear receptor (13.3%) (Figure 11). Regarding specific targets, it presented a higher probability (> 0.5) of interaction with Estrogen receptor alpha, Sodium / glucose cotransporter 2, Beta-secretase 1, Cyclooxygenase-1, which were ranked the best binging probability on the SwissTarget Prediction report (Table 6).

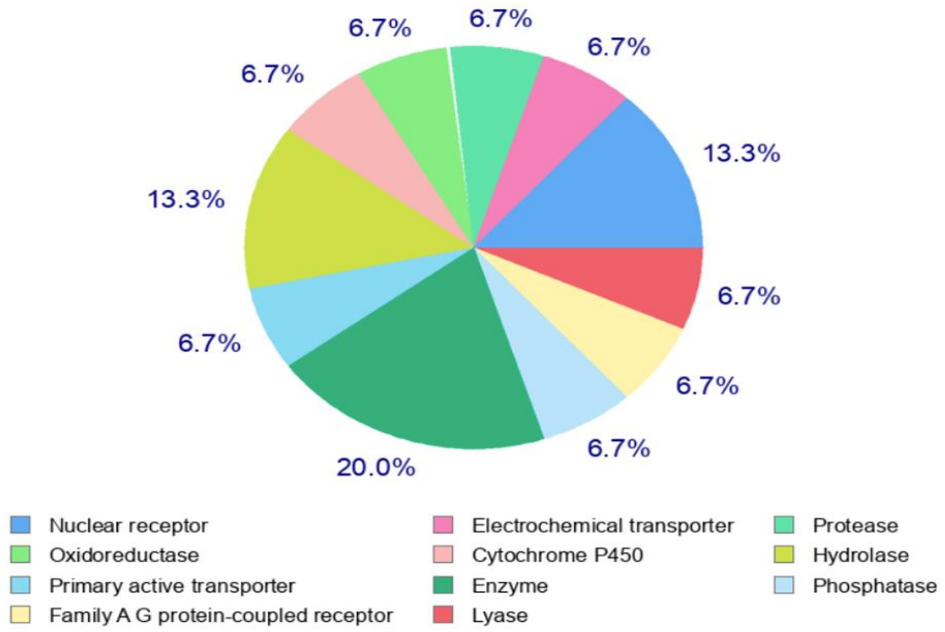

Figure 11: Virtual Screening for Target Classes for Sophoraflavanone G

Table 6: Best binging probability on the SwissTarget Prediction report for Sophoraflavanone G

TARGET	Common name	Target Class	Probability*
Estrogen receptor alpha	ESR1	Nuclear receptor	0.649778524356
Sodium/glucose cotransporter 2	SLC5A2	Electrochemical transporter	0.625678935906
Beta-secretase 1	BACE1	Protease	0.625678935906
Cyclooxygenase-1	PTGS1	Oxidoreductase	0.553263465898
Estrogen receptor beta	ESR2	Nuclear receptor	0.183235381136

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Cytochrome P450 19A1	CYP19A1	Cytochrome P450	0.143014512691
Butyrylcholinesterase	BCHE	Hydrolase	0.143014512691
Acetylcholinesterase	ACHE	Hydrolase	0.143014512691
ATP-binding cassette sub-family G member 2	ABCG2	Primary active transporter	0.126928723833
Estradiol 17-beta-dehydrogenase 1	HSD17B1	Enzyme	0.118883306718
Protein-tyrosine phosphatase 1B	PTPN1	Phosphatase	0.118883306718
Phospholipase A2 group 1B	PLA2G1B	Enzyme	0.118883306718
Adenosine A1 receptor	ADORA1	Family A G protein-coupled receptor	0.118883306718
Carboxylesterase 2	CES2	Enzyme	0.118883306718
Carbonic anhydrase VII	CA7	Lyase	0.118883306718

4. Conclusions

The molecular structure of Sophoraflavanone G was geometrically optimized by semi-empirical quantum calculations, obtaining the thermodynamically more stable structure. Through the electrostatic potential map it was possible to identify the areas where the nucleophilic bonds will occur that comprise the whole area of oxygen. Due to geometrization one can also obtain the atomic charges of Mulliken for the atoms of O, C, H highlighting the variation of charges between atoms of the same species.

Regarding the frontier orbitals, it was possible to identify a greater tendency to donate electrons compared to Naringeni, having a lower ionization potential, with greater hardness and less softness. Sophoraflavonone G drug confirmed the safety of the compound for oral administration. It also has good skin permeability which enables applications in topical formulations. However, it lacks the blood-brain barrier permeability. It is a highly selective structure that protects the Central Nervous System (CNS) from potentially neurotoxic substances present in the blood and is essential for normal metabolic function of the brain, yet has indications of intestinal gastro absorption. Regarding possible interactions with biological targets, it was more likely to interact with Estrogen receptor alpha, Sodium / glucose cotransporter 2, Beta-secretase 1, Cyclooxygenase-1.

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The data obtained constitute an initial step for a comparative analysis between its analogues and fundamental for future studies of relationships between the three-dimensional structure of Sophoraflavanone G and its biological activities.

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