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METHYLCYTISINE ALCALOID POTENTIALLY ACTIVE AGAINST DENGUE VIRUS: A MOLECULAR DOCKING STUDY AND ELECTRONIC STRUCTURAL CHARACTERIZATION

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Abstract

Dengue fever is a serious disease acquired from the Aedes aegypti mosquito present in tropical and subtropical regions, deeply impacting the population's quality of life. Its control requires combating the virus, and the use of substances that do not cause damage to the environment is of fundamental importance. The present work was carried out in silico to perform the structural-electronic characterization of the alkaloid Methylcytisine, a tricyclic quinolizidine alkaloid that has insecticidal activities, identifying the molecular boundary orbitals and descriptors of global chemical reactivity and assessing the inhibitory potential of methylcytisine on NS5 methyltransferase enzyme dengue virus, as well as identifying possible biological targets in humans. Methylcytisine was geometrically optimized through semi-empirical quantum calculations with thermodynamically more stable conformation, characterizing its structure (atoms, angles and bonds) and its reactivity descriptors. The analysis of the molecular docking simulations showed that methylcytisine is coupled in the same active site of the NS5 enzyme methyltransferase DENV, very similar to the complexed ligand S-adenosyl-L-homocysteine. The intermolecular interactions found for the complex formed and the distance values of the enzyme residues, indicate that methylcytisine has potential application as a new inhibitor of the dengue virus, however it has a high possibility of interaction with human neuronal acetylcholine receptors.

Keywords: Alkaloid; Dengue Fever; Docking Molecular; Frontier Orbitals; Human Neuronal Acetylcholine Receptors; Natural Insecticide.

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1. Introduction

In the last 40 years, approximately 3 million cases of dengue shock syndrome and hemorrhagic fevers have been estimated, of which approximately 60 thousand deaths have been recorded [1]. Dengue is a viral disease belonging to the family Flaviviridae, genus Flavivirus, consisting of more than 70 viruses (LEYSSEN et al., 2000), with humans being the main hosts of the dengue virus, a serious febrile disease acquired from the mosquito Aedes aegypti present in tropical and subtropical regions, where the main symptoms are fevers above 38.5 ° C, muscle pain, eye pain, loss of appetite, headache, vomiting and red spots on the body [2].

Dengue can be cured naturally after 15 days, but the hemorrhagic risk impacts on the cardiovascular system, hindering the blood pumping necessary for the body and the functioning of other systems, making the disease extremely serious [3]. Not all drugs can be taken for treatment, as they can aggravate the appearance of bleeding and hemorrhages with the need for new drugs [4]. The Flavivirus genome contains a single open reading frame, which encodes a single polyprotein and which is subsequently cleaved to generate three structural proteins that make up the viral particle: C (capsid), E (envelope) and prM (precursor to the membrane M) and seven non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 [5] which are currently considered targets for inhibition of viral replication [6].

The search for substances that have insecticidal activities that do not affect the environment, fits into the concepts of green chemistry, which can be understood as the creation, development and application of chemical products and processes in order to reduce or eliminate the production of products harmful to human health and the environment [7]. In this environment, plant extracts are sources of bioactive substances that can have an effect on insect behavior [8]. Thus, methylcytisine, a tricyclic quinolizidine alkaloid extracted from the roots of plants of the genus Thermopsis, which has several biological activities (hypoglycemic, analgesic and anti-inflammatory [9]), and nematicidal activity [10], can be a promising insecticidal agent that fits the concepts of green chemistry.

Currently, for the study of new compounds and their possible biological activities, it is essential to know the structure of the molecule in question, defining the reaction sites, characterizing atomic properties and bonds to then enable the synthesis of the molecule [11] [12]. In this context, molecular modeling, a set of manipulative tools and analysis of complex molecular systems, using *in silico* methods and theoretical calculations[13] [14], allows the characterization of molecular structures and their properties [15], as well as predicting the mechanism of interaction between molecules and possible biological targets [16] [17].

The present work had as a way to perform the structural-electronic characterization of the alkaloid Methylcytisine in silico by identifying the molecular boundary orbitals and descriptors of global chemical reactivity and to evaluate the inhibitory potential of methylcytisine on NS5 enzyme dengue virus and identify possible biological targets in humans .

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2. Materials and Methods

Computational Details

The optimization calculations were performed using a computer with 2x Xeon 2.66 Ghz processor - Quad Core, 8 GB Ram DDR2 667ghz ECC, with MAC OSX operating system.
Molecular coupling simulations were performed on a personal computer with an Intel® Core TM i7 7700HQ processor, 16 GB RAM, 4G Nvidia® GeForce GTX 1050 Radeon video card and Microsoft Windows 10® operating system. All softwares codes used are free license for academic use.

Obtaining the Structures

To prepare this work, the ChemSpider online repository [http://www.chemspider.com/] was first used to obtain the two-dimensional coordinates of Methylcytisine (ChemSpider ID 204591) and some physico-chemical properties [18] [19].

Structural Optimization

Theoretical calculations, starting from the theory of molecular orbitals, have two premises, the Ab initio method that obtain the results of the modeling through the resolution of all mathematical equations, and the semi-empirical method, where some equations are simplified using experimental data. The semi-empirical method require less computational resources than the Ab initio method, in addition to presenting excellent correlation with experimental results [20]. In this context the Methylcytisine molecule was subjected to structural optimization calculations at the quantum level of semi-empirical, using the Parametric Method 3 (PM3) [21], [22] algorithm, configured so that the Hartree-Fock SCF performs 200 interactions with 10-10 kcal / mol convergence of closed shell. The geometric search was performed with the 10-1 conversion gradient configured to perform a cycle of 1000 interactions with the Quasi-Newton BFGS algorithm line search [13], [23]. All optimization calculations were performed using the ArgusLab® software [24] [25] [26], following the protocol established by Oliveira and collaborators [27] [28].

- **Structure Characterization, Frontier Orbitails, MESP and Global Reactivity Molecular Descriptors**

The data generated from the geometric optimization were used for the determination of atomic properties, connection, angles, Mulliken population analysis and the electrostatic potential surface map (MESP). Using the Koopmans theorem, the energetic values of the boundary orbitals were used to determine the global reactivity descriptors (Table 1) [29] [30].

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)	$\chi = (I+A)/2$
Chemical hardness (η)	$\eta = (I-A)/2$
Vertical Ionization potential (I)	$I=-\varepsilon_{HOMO}$

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Chemical softness (S)	$S=1/2\eta$
Electrophilicity index (Ω)	$\omega = \mu^2 / 2\eta$
Chemical potential (μ)	$\mu = - (I+A)/2$

Enzyme Preparation

The three-dimensional structure of the dengue virus NS5 methyltransferase was obtained from the Protein Data Bank database (https://www.rcsb.org/structure/1l9k), classified as protein transferase, organism dengue virus type II, expression Escherichia coli, crystallized with the ligands S-adenosyl-L-homocysteine (SAH) and sulfate ions, generated from X-ray diffraction with 2.4 Å resolution and deposited with PDB ID: 1L9K [31]. All water molecules were removed from the methyltransferase structure, reducing interference with the attachment of methylcytisine to the target enzyme. The polar hydrogen atoms missing from the structure were added using AutoDock Tools.

Molecular Docking

Molecular attachment of the ligand to the NS5 methyltransferase DENV receptor was performed using 4-way multithreading and the AutoDock Tools (version 1.5.7) graphical interface that runs AutoDock Vina (version 1.1.2) [32], parameterized with the grid values box: center_x = 15,268, center_y = -43,581, center_z = 1,325, size_x = 46, size_y = 66, size_z = 46, spacing = 0.375 and exhaustiveness = 8.The images of the two-dimensional graphs of the interactions and three-dimensional visualization of the complex formed were generated using the UCSF Chimera [33] and Discovery Studio visualizer® [34].

Virtual Screening for Target Classes

In order to assess the possible impacts on the human organism, the methylcistesine molecule was subjected to a virtual screening to identify possible proteins that it can bind to. The algorithm used was that of reverse restraining, which used structural similarities to predict the interaction of possible biological receptors as descriptor, the identifier Homo sapiens was used. For the similarity adjustment, the Tanimoto coefficient was used, vectorized by the Manhattan distance, using the three-dimensional descriptors iej, where d ij is the shortest Manhattan distance between the calculated distances. 20 × 20 in all possible conformations of each molecule [35] calculated using equations 1 and 2.All calculations were performed on the SwissTargetPrediction platform [36].

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

$$1/(1 + 1/18\text{d ij} \quad (2)$$

3. Results and Discussions

3.1. Two-Dimensional Structure and Physico-Chemical Properties

Technological advances, especially with the increasing accessibility to internet access, have been providing new means of information on molecular data. Methylcytisine (FIGURE 1A), also known as Caulophylline, has a name according to IUPAC, (1R, 9S) -11-methyl-7,11-diazatricyclo [7.3.1.02,7] trideca-2,4-dien- 6-one, it is a heterocyclic alkaloid analog from Cytisine (figure 1 B).

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Regarding the physical-chemical properties, it can be highlight that Methylcytisine in its structure has 3 hydrogen bond acceptor atoms and no donor, has a partition coefficient (LogP) in the order of 0.46, indicating low lipophilicity with strong indications of Low bioaccumulation, this being an important parameter for the study of organic molecules with possible biological actions because it allows to deduce properties such as absorption capacity, half-life, membrane permeation capacity, elimination facilities and permeability capacity (Table 2).

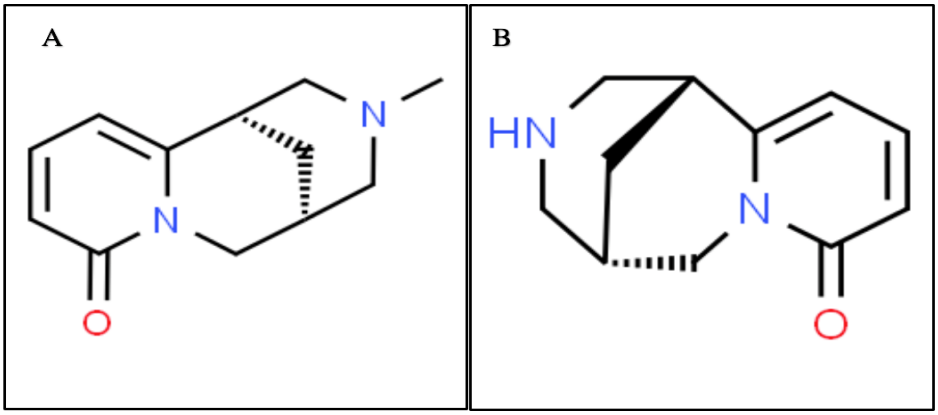

Figure 1: The two-dimensional structure alkaloid Methylcytisine (A) cytesine (B)
Souce: Virtual Repository ChemSpider®

Table 2: Physico-chemical properties of the alkaloid Methylcytisine

Properties	**Value**
Average mass	204.268 Da
Monoisotopic mass	204.126266 Da
Density	1.2 ± 0.1 g / cm ^{3}
Volume molar	168.5 ± 5.0 cm ^{3}
Superficial tension	49.7 ± 5.0 dine / cm
Polarizability	234 ± 0.5 10 -24 cm ^{3}
Polar surface area	24 A^2
Molar Refractivity	58.9 ± 0.4 cm ^{3}
LogD (pH 7.4)	-1.36
LogP	0.46
H bond acceptors	3
H bond donors	0

3.2. Geometric Optimization and Structural Properties

Molecular geometry is understood as the organization between atoms due to electronic clouds, which is an important parameter for predicting the polarity of a molecule [37] [38]. When a molecule is removed from a virtual repository or is designed, it does not present itself in its theoretically more stable conformation. In this case, molecular modeling emerges, which is understood as a set of computational tools to build, model, mimic the behavior of molecules [39] [28]. One of the processes used in modeling is the process of geometric optimization which, using theoretical calculations, seeks to hold each atom in its regions with lower levels of potential energy making the molecule thermodynamically more stable [40] [41].

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The alkaloid Methylcytisine optimized geometrically (Figure 02) through semi-empirical quantum calculations, obtaining the structure theoretically close to its native form and potential energy -2286.82885 eV, it is possible to characterize structurally providing atomic properties, of connections and angles. When analyzing the atomic properties (Table 3) it can be notice the presence of variations in the partial charges of atoms of the same nature since the carbon atoms varied from -0.055 to 0.030, the nitrogen atoms from -0.312 to -0.304 and the hydrogens varying from 0.028 to 0.063. It was also possible to characterize all connections (Table 4), with bonds (O - C1), (C2 - C3) and (C4 - C5) being highlighted because they have π type connections.

Also noteworthy are the connections (C9 - C10), (C7 - C11), (C6 - C7), (C8 - C9), (C7 - C8), (N2 - C11) and (C10 - N2) for being connections rotating. In connection lengths, the connections (C3 - H1) stand out because they have a shorter length (1.09488) and the connection (C9 - C10) because they have a longer connection length (1.53832). Regarding the properties of angles, the connections are (H7 - C8 - H8) obtaining the smallest at 106.0640 ° and (O - C1 - C5) obtaining the greatest angulation at 125.4049 °. As for the twists, they present the set (H1 - C3 - C4 - C5) with the lowest torsion with -179.9865 ° and the set (N1 - C2 - C3 - H1) with the highest torsion with 179.9115 °.

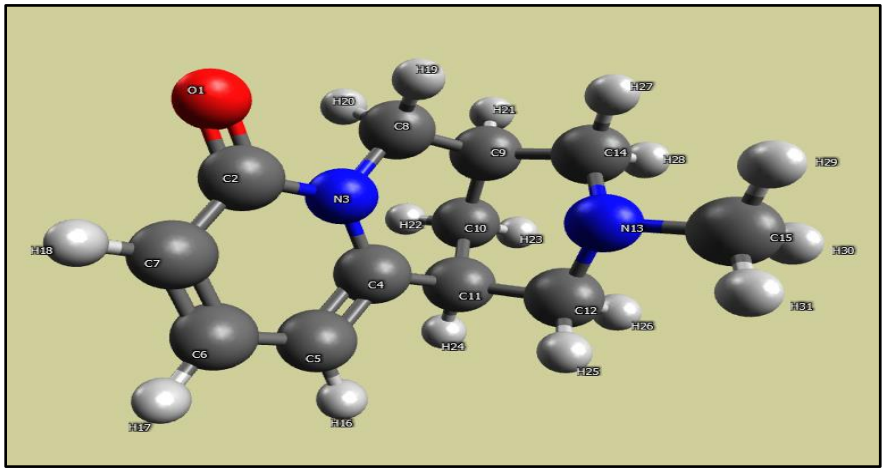

Fig. 2. Optimized three-dimensional structure of the alkaloid Methylcytisine

Table 3: Atomic properties of the alkaloid Methylcytisine

Atoms	Element	Type	Valence	Partial Charge
Atoms 1	O	O2	1	-0.268
Atoms 2	C	Car	3	0.251
Atoms 3	N	Nar	3	-0.312
Atoms 4	C	Car	3	0.026
Atoms 5	C	Car	3	-0.042
Atoms 6	C	Car	3	-0.055
Atoms 7	C	Car	3	0.003
Atoms 8	C	C3	4	0.030
Atoms 9	C	C3	4	-0.010
Atoms 10	C	C3	4	-0.038
Atoms 11	C	C3	4	0.013

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Atoms 12	C	C3	4	0.007
Atoms 13	N	N3	3	-0.304
Atoms 14	C	C3	4	0.003
Atoms 15	C	C3	4	-0.013
Atoms 16	H	H	1	0.063
Atoms 17	H	H	1	0.062
Atoms 18	H	H	1	0.067
Atoms 19	H	H	1	0.050
Atoms 20	H	H	1	0.050
Atoms 21	H	H	1	0.033
Atoms 22	H	H	1	0.028
Atoms 23	H	H	1	0.028
Atoms 24	H	H	1	0.038
Atoms 25	H	H	1	0.043
Atoms 26	H	H	1	0.043
Atoms 27	H	H	1	0.043
Atoms 28	H	H	1	0.043
Atoms 29	H	H	1	0.039
Atoms 30	H	H	1	0.039
Atom 31	H	H	1	0.039

Table 4: Methylcytisine bonding properties

Bonds	**Type**	**Start Atom**	**End Atom**	**Bond Order**	**Rotatable**	**Length (Å)**
Bond 1	O–T	O	C1	2	No	1.22888
Bond 2	C–N	C1	N1	1	No	1.44221
Bond 3	C–C	C1	C5	1	No	1.45812
Bond 4	N–C	N1	C2	1	No	1.40431
Bond 5	N–C	N1	C6	1	No	1.49467
Bond 6	C–C	C2	C3	2	No	1.37000
Bond 7	C–C	C2	C9	1	No	1.50900
Bond 8	C–C	C3	C4	1	No	1.42381
Bond 9	C–H	C3	H1	1	No	1.09488
Bond 10	C–C	C4	C5	2	No	1.35383
Bond 11	C–H	C4	H2	1	No	1.09532
Bond 12	C–H	C5	H3	1	No	1.09516
Bond 13	C–C	C6	C7	1	Yes	1.53224
Bond 14	C–H	C6	H4	1	No	1.11085
Bond 15	C–H	C6	H5	1	No	1.11067
Bond 16	C–C	C7	C8	1	Yes	1.52506
Bond 17	C–C	C7	C11	1	Yes	1.53603
Bond 18	C–H	C7	H6	1	No	1.11695
Bond 19	C–C	C8	C9	1	Yes	1.52671
Bond 20	C–H	C8	H7	1	No	1.19677

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Bond 21	C–H	C8	H8	1	No	1.10740
Bond 22	C–C	C9	C10	1	Yes	1.53832
Bond 23	C–H	C9	H9	1	No	1.11720
Bond 24	C–N	C10	N2	1	Yes	1.49402
Bond 25	C–H	C10	H10	1	No	1.10778
Bond 26	C–H	C10	H11	1	No	1.11173
Bond 27	N–C	N2	C11	1	Yes	1.49423
Bond 28	N–C	N2	C12	1	No	1.48214
Bond 29	C–H	C11	H12	1	No	1.10808
Bond 30	C–H	C11	H13	1	No	1.11198
Bond 31	C–H	C12	H14	1	No	1.09746
Bond 32	C–H	C12	H15	1	No	1.10130
Bond 33	C–H	C12	H16	1	No	1.09738

3.3. Frontier Orbitals, Global Chemical Reactivity Descriptors

Frontier orbitals are considered fundamental in the study of the chemical reactivity of a molecule and act as intermediates for the stability of structures. The highest energy orbital occupied as HOMO is related to the ionization potential by determining the electron-donor character of the molecule and showing the region where it has the highest electron density. The least energy unoccupied orbital called LUMO is related to the electronic affinity indicating the electron-receptor character showing the lowest electronic density of the molecule [42]. Thus, the higher the HOMO energy, the greater the electron-donor capacity of the molecule and the lower the LUMO energy, the greater the electron acceptance. The variation between the values of the boundary orbitals, called GAP, indicates the energy required for an electron to make the transition. The greater the value of the difference, the lower the molecular reactivity and the greater the molecular stability [43].Methylcytisine presented the energy value -8.47275 eV for the HOMO orbital (Figure 4A) and having the atoms O1, C2, C3, C4, C5 and N3 as contributors, where all showed symmetry between the positive and negative phases. The LUMO orbital (Figure 4B) obtained an energy value of -0.12470 eV with atoms O1, C2, C3, C4, C5, C6 and N3 showing symmetry between the positive and negative phases.

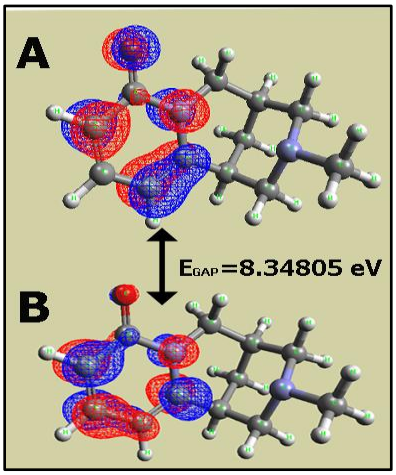

Figure 4: Frontier orbitals of the alkaloid methylcistesine HOMO (A) and LUMO (B)

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Starting from the Koopmans theorem, the global reactivity descriptors (generated from the HOMO-LUMO relationship) describe chemical properties that indicate the types of interactions between ligand molecules with biological receptors, since they act as mediators between reactivity and stability. Among these descriptors are: vertical ionization potential (I), electronic affinity (A), electronegativity (χ), chemical hardness (η), chemical softness (S), electronic chemical potential (μ) and electrophilicity index (ω) [29] [44].The ionic potential (I), related to the energy of the HOMO orbital, indicates the strength of an electron's strength when it is attached to an atom. Electronic affinity (A), related to the energy of LUMO, represents the amount of energy released when an atom or molecule receives an electron [45]. Electronegativity is represented by the ability of a molecule to attract electrons from another molecular when they interact, interfering in the dipolar moment and changing molecular properties such as the acidity and basicity of different molecules [27]. Starting from Methylcytisine HOMO-LUMO boundary molecular orbitals, it was possible to determine the global chemical reactivity descriptors (Table 5), where the molecule had a lower GAP value than Cytisine reference, due to the fact that it has lower values of electro affinity and ionic potential than Cytisine. Methylcytisine also showed lower electronegativity and chemical hardness values than Cytsine.

Table 5: Global Reactivity Descriptors calculated for Methylcytisine and Cystisine

Descriptors	Methylcytisine	Cytisine
Eléctron affinity (A)	0.12470	0.33701
GAP	8.34805	8.35463
Eletronegativity (χ)	4.29872	4.51432
Vertical Ionization potential (I)	8.47275	8.69164
Chemical hardness (η)	4.17402	4.17731
Chemical softness (S)	0.11978	0.11969
Eletronic chemical potential (μ)	-4.29872	-4.51432
Electrophilicity index (Ω)	2.21345	2.43926

3.4. Mulliken Population Analysis

Mulliken atomic charges (Mulliken population analysis) and electrostatic potential surface map Mulliken population analysis divide the charge densities between atoms evenly disregarding electronegativity. When studying the Mulliken charges of Methylcytisine, the existence of varying charges of atoms of the same nature is notorious, where carbon atoms vary from -0.3405 to 0.3035, nitrogen at -0.0954 to 0.0983 and atoms of hydrogens 0.0859 to 0.2280 [46].

The visualization and analysis of charges is possible through the surface map of electrostatic potential, as it allows to characterize electrophilic and nucleophilic regions, showing how complex molecules interact [47] [47]. Through the MESP of Methylcytisine (Figure 5) it was possible to notice defined regions, since the regions in red mean regions with a high concentration of charges and the regions in white have a low concentration of charge. The regions highlighted in red are due to the presence of a nitrogen atom (N13) and oxygen since they are more electronegative atoms than carbons and hydrogens.

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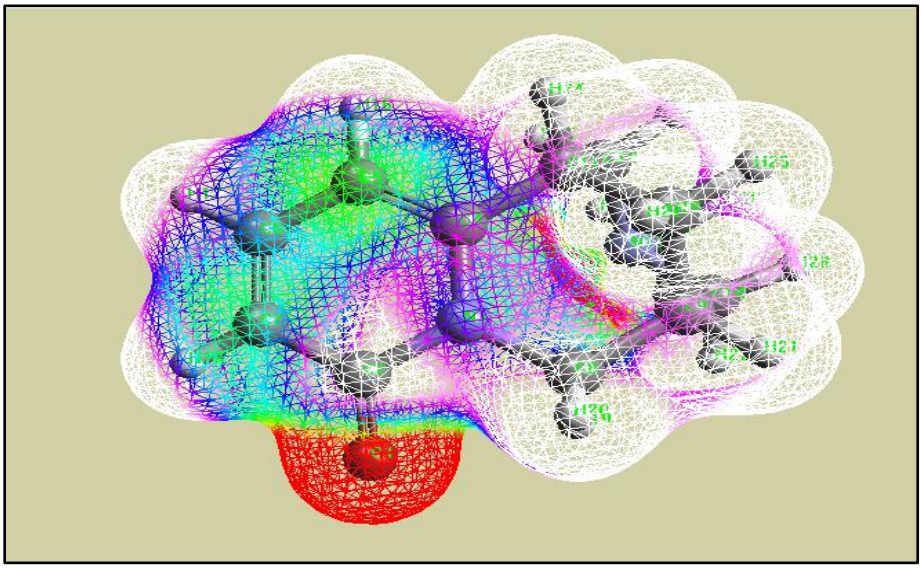

Figure 5: Methylcytisine electrostatic potential surface map (MESP)

3.5. Molecular Docking

Molecular docking positions the ligand in different orientations at the target receptor's active site in order to obtain the best interaction, in which this procedure allows the establishment of a classification between the compounds with the highest and lowest affinity to a given receptor [48] [49] [50] [51]. In order to obtain the best interaction, the molecular coupling positions the ligand in different orientations in the target enzyme, allowing the establishment of a classification between the compounds of greater and lesser affinity to a given receptor [52] [53] [54]. Thus, the molecular coupling simulations between NS5 methyltransferase DENV and the ligand methylcytisine generated energy values of affinity and Root Mean Square Deviation (RMSD) of -6.1 kcal / mol and 1,850 Å respectively, values within the standard of up to 2.0 Å for RMSD [34] and less than -6.0 kcal / mol for affinity [35]. The parameters calculated in the molecular socket of methylcytisine show the affinity of the molecule with the same region of the S-adenosyl-L-homocysteine ligand complexed in the NS5 enzyme methyltransferase DENV (Figure 6).

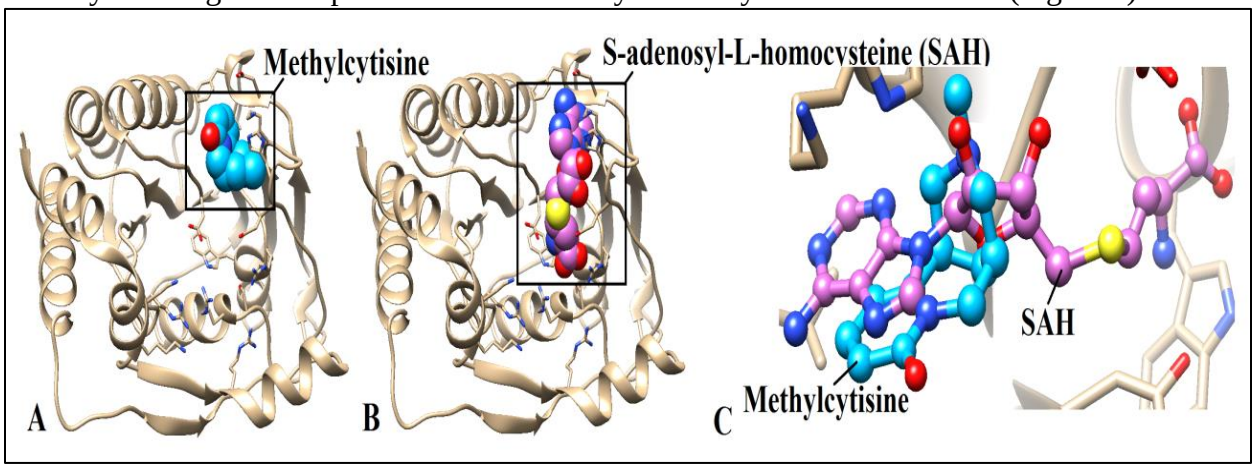

Figure 6: NS5 DENV methyltransferase complexed with methylcytisine (A) S-adenosyl-L-homocysteine (SAH) (B) and methylcytisine and SAH binding site (C).

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The analysis of the distances of methylcytisine with the amino acid residues of the enzyme, highlights the affinity of the ligand with the binding site of S-adenosyl-L-homocysteine (SAH), with methylcytisine being closer to the residues Thr104 (3.8 Å), Lys105 (2.5 Å), Gly106 (2.7 Å) smaller distance compared to SAH, Glu111 and Ile147 (3.7 Å) (Table 6).

Table 6: DENV residue distances NS5 methyltransferase

NS5 methyltransferase DENV residue	Methylcytisine	S-adenosil-L-homocisteína (SAH)
Ser56	10.2 Å	2.5 Å
Gly86	9.8 Å	1.8 Å
Trp87	9.8 Å	3.1 Å
Thr104	3.8 Å	3.5 Å
Lys105	2.5 Å	2.3 Å
Gly106	2.7 Å	3.6 Å
Glu111	3.7 Å	3.4 Å
Asp131	5.4 Å	3.4 Å
Val132	4.8 Å	1.9 Å
Asp146	4.8 Å	2.8 Å
Ile147	3.7 Å	3.9 Å
Tyr219	9.8 Å	6.0 Å

Through the analysis of intermolecular interactions of the formed complex, three intermolecular interactions with methylcytisine and residues of NS5 methyltransferase DENV were found, being interactions of the type Carbon Hydrogen Bond with Glu111, Alkyl and Pi-Sigma with Ile147 (Figure 7).

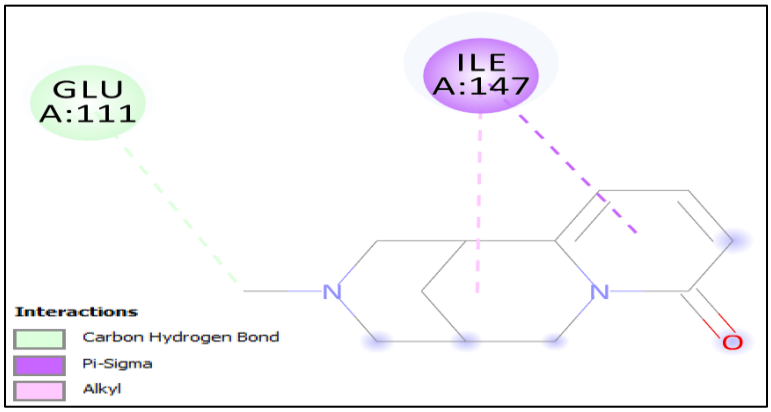

Figure7: Interactions between methylcytisine and NS5 methyltransferase DENV.

3.6. Virtual Screening for Target Classes

The study of the possible interactions between a substance and the proteins present in the human body is a fundamental factor to determine the viability of using this compound in the environment. It is an initial step for future *in vitro* and *in vivo* tests to determine the viability of using the compound. with minimal risks to human health. As for possible classes of biological targets,

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Methylcistesine was more likely to interact with Ligand-gated ion channel (46.7%), Family AG protein-coupled receptor (26.7%), Protein Kinase (20%) and Enzyme (6.7%) (Figure 8).

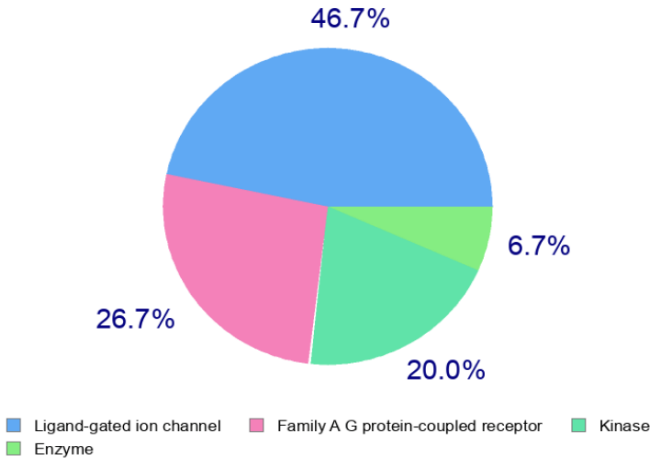

Fig 8. Virtual Screening for Target Classes for Methylcistesine

Regarding specific goals, it was more likely (> 0.5) to interact with the Neuronal acetylcholine receptor (alpha4 / beta2, beta-secretase 1, Neuronal acetylcholine receptor; alpha3 / beta4, Neuronal acetylcholine receptor protein alpha-7 subunit. also the possibility of interaction with Acetylcholine receptor (alpha1 / beta1 / delta / gamma) (Table 6).

Table 7: Best binging probability on the SwissTarget Prediction report for Methylcistesine

Target	**Uniprot ID**	**Target Class**	**Probability***
Neuronal acetylcholine receptor; alpha4/beta2	P43681 P17787	Ligand-gated ion channel	0.54
Neuronal acetylcholine receptor; alpha3/beta4	P32297 P30926	Ligand-gated ion channel	0.54
Neuronal acetylcholine receptor protein alpha-7 subunit	P36544	Ligand-gated ion channel	0.54
Acetylcholine receptor; alpha1/beta1/delta/gamma	P11230 P02708 P07510 Q07001	Ligand-gated ion channel	0.49
Neuronal acetylcholine receptor subunit alpha-3	P32297	Ligand-gated ion channel	0.18
Neuronal acetylcholine receptor protein alpha-4 subunit	P43681	Ligand-gated ion channel	0.04
Epidermal growth factor receptor erbB1	P00533	Kinase	0.041

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Serotonin 2b (5-HT2b) receptor	P41595	Family A G protein-coupled receptor	0.04
Purine nucleoside phosphorylase	P00491	Enzyme	0.04
Metastin receptor	Q969F8	Family A G protein-coupled receptor	0.04
Dopamine D3 receptor	P35462	Family A G protein-coupled receptor	0.04

4. Conclusions

Methylcytisine was geometrically optimized through semi-empirical quantum calculations with thermodynamically more stable conformation, characterizing its structure (atoms, angles and bonds) and its reactivity descriptors. The analysis of molecular docking simulations showed that methylcytisine is coupled to the same active site as the NS5 enzyme methyltransferase DENV, in a very similar way to the complexed ligand S-adenosyl-L-homocysteine. The intermolecular interactions found for the complex formed and the distance values of the enzyme residues, indicate that methylcytisine has potential application as a new inhibitor of the dengue virus, however it has a high possibility of interaction with human neuronal acetylcholine receptors.

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