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# Molecular Modeling Studies of Anagyrine Alkaloid: HOMO, LUMO, MESP and Global Chemical Reactivity Descriptors

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***Abstract*— Based on the principles of green chemistry, the search for technologies and products that enable a sustainable development, the development of new molecules, less aggressive to the environment for pest control, has been fostered. In this context the present work aimed to characterize the alkaloid anagyrine, a tetracyclic quinolizidine potential that exhibits insecticidal activity. Under the semi empirical quantum formalism the anagyrine molecule was electronically and structurally characterized, characterizing the global chemical reactivity descriptors, Muliken population analysis and the Electrostatic Potential Surface Map (MESP) plot in order to obtain important data for future studies. molecular docking. This work consists of an initial stage, where the generated data will serve as a database for future molecular modeling studies, aiming to test the biological potential of the molecule.**

***Keywords*— Green chemistry, Koopmans' theorem, Molecular Modeling, Natural pesticide.**

## I. INTRODUCTION

The use of insecticides is one of the tools used by agriculture for pest control in crops. Insecticides are inorganic or organic substances with biological activities that repel and kill insects, including eggs and larvae [1-2]. But the damage to human health and the environment, as well as the resistance acquired by insects, make insecticides less effective in fighting pests [3].In this context comes the principles of green chemistry, which seeks sustainable development [4]. One of the main axes is the development of new products that have less impact on the environment. As the indiscriminate use of pesticides, motivated by the need for greater food demand, seeking a maximization of production, has caused several harmful effects on the population. In this respect the search for natural substances that have biological potential has been widely explored. Anagyrine, a tetracyclic quinolizidine alkaloid with a pyridone nucleus extracted from plants of the genus Lupinus [5], It has several insecticidal properties, however it has several undesirable biological effects such as congenital deformities [6].

However, if we look at the scope of the development of new molecules from pre-existing molecules in nature, we can produce synthetic analogues that have greater efficiency and less negative effects on the environment [7].

In order to begin the process of developing new analog molecules, one needs to know deeply the structure of the base molecule, define its reaction sites, characterize its bonds, so that a viable analog can be synthesized. At this stage comes the concept of molecular modeling, which can be defined as a toolkit for manipulating and analyzing complex molecular systems for understanding molecular structures and properties using mathematical and in silico methods- [8-9].

Fundamentally the most used methods are based on the theory of molecular orbitals. Under this focus we can use two approaches, the ab initio method, where all modeling results are obtained by the direct resolution of all mathematical equations, and the method and semi-empirical ones, where some mathematical equations are simplified by using of experimental data. The use of semi empirical methods requires less computational resources, presenting a good correlation with the experimental results [10].

In this context, present work has the objective to study the structural and electronic properties of Anagyrine, using a semi empirical quantitative method (Parametric Method 3) characterizing the global chemical reactivity descriptors, Muliken population analysis and the Electrostatic Potential Surface Map plotting (MESP) in order to obtain important data for future molecular docking studies.

## II. METHODOLOGY

### *Computational details*

All the computations were performed on computer with 2 x Xeon 2.66 Ghz - Quad Core intel®. For visualization of results and rendering of maps and iso-susfaces was used personal computer with Intel® Core TM i7-4510U processor, 16GB RAM, 2GB AMD Radeon® video card and Microsoft Windows 8.1® as operating system. To perform the quantitative calculations, the code ArgusLab® [11-14], which has a free license for academic use, was used.

For diagramming and data processing, we used the microsoft Microsoft® Office 365® package.

### *Geometrical optimization*

To develop this work, the ChemSpider online repository was first used (http://www.chemspider.com/) to obtain the 2D coordinates of the molecules, Anagyrine, Cytisine Quinolizidine (Fig. 1), which were deposited by the ChemSpider ID codes. 9828,9818,106363 respectively. the Pubchem repository (https://pubchem.ncbi.nlm.nih.gov/) was used to obtain Chemical and Physical Properties.

Then, the methodology proposed by Araujo and collaborators [15] was used the semi empirical quantum method of Parametric Method 3 (PM3) [16-17], configured for Hartree-Fock SCF to perform 200 interactions, with convergence of 10-10 kcal / mol closed shell. The geometric search had as parameters the convergence gradient of 10 -1 kcal / mol / Ang, with 100 maximum steps taken with line search BFGS [18-19].

### *Frontier Orbitails, MESP and global reactivity molecular descriptors*

Using the data generated from the optimization was performed the analysis of structural properties data, plot of boundary orbitals, population analysis of mulliken and electrostatic potential map (MESP) [20-21]. Frontal orbital energy values were used to calculate the global reactivity molecular descriptors (Koopmans' theorem) (Table I).

Table I
Global chemical reactivity descriptors based on Koopmans' theorem

| | |
|---|---|
| GAP | $\lvert\varepsilon_{HOMO}\rvert - \lvert\varepsilon_{LUMO}\rvert$ |
| Eléctron affinity (A) | $-\varepsilon_{LUMO}$ |
| Eletronegativity ($\chi$) | $(I+A)/2$ |
| Vertical Ionizationpotential (I) | $-\varepsilon_{HOMO}$ |
| Chemicalhardness ($\eta$) | $(I-A)/2$ |
| Chemicalsoftness (S) | $1/2\ \eta$ |
| Eletronic chemicalpotential ($\mu$) | $-(I+A)/2$ |
| Electrophilicity index ($\Omega$) | $\mu^2 / 2\eta$ |

## III. RESULTS AND DISCUSSIONS

Computational chemistry is developed by techniques, through in silico methods, to investigate molecular properties and simulation of possible molecular behaviors of complex systems using mathematical methods.

Anagyrine, a heterocyclic compound (Figure 1), belonging to the alkaloid family was isolated for the first time and can be synthesized from Anagyrisfoetida, and also found in species of Lupinus plants.[5](Figure 2), can be identified by the names of 11,12,13,14-Tetradehydrospartein-15-on (German/ACD/IUPAC Name),11,12,13,14-Tetradehydrospartein-15-one (ACD/IUPAC Name),11,12,13,14-Tétradéhydrospartéin-15-one (French/ACD/IUPAC Name),7,14-Methano-2H,11H-dipyrido[1,2-a:1',2'-e][1,5]diazocin-11-one, 1,3,4,6,7,13,14,14a-octahydro,(14aR)- (ACD/Index Name), (10R)-7,15-diazatetracyclo[7.7.1.0<2,7>.0<10,15>]heptadeca-2,4-dien-6-one,7,7a,8,9,10,11,13,14-Octahydro-7,14-memethano-4H,6H-dipyrido(1,2-a:1',2'e)(1,5)diazocin-4-one, with codes 1214624-19-7 (RN),5-24-03-00410 (Beilstein), and usual names Monolupine and Rhombinine.Features Density of 1.2 ± 0.1 g / cm3, Boiling Point 455.6 ± 34.0 ° C at 760 mmHg, Vapor Pressure0.0 ± 1.1 mmHg at 25 ° C, Enthalpy of Vaporization 71.5 ± 3.0 kJ / mol, Flash Point 216.3 ± 18.0 ° C, Index of Refraction 1.628, Molar Refractivity 70.7 ± 0.4 cm3, Polar Surface, Area 24 Å2, Polarizability 28.0 ± 0.5 10-24cm3, Surface Tension 52.4 ± 5.0 dyne / cm, Molar Volume 199.3 ± 5.0 cm3.

Noting the dimensional structure of Anagirine, can identify the presence of 18 atoms, Stereocenter two Hydrogen Bond Acceptor Count (Table II) with a structure having a skeleton derived from a unit with a Quinolizidine Cytisine (fig.1).

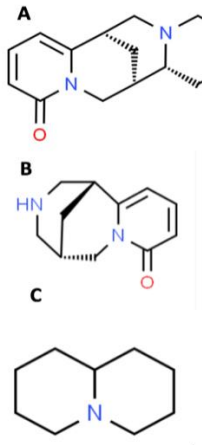


Fig. 1. Two-dimensional structure of Anagyrine (A) Cytisine (B) Quinolizidine (C).
source:ChemSpider repository(http://www.chemspider.com/).

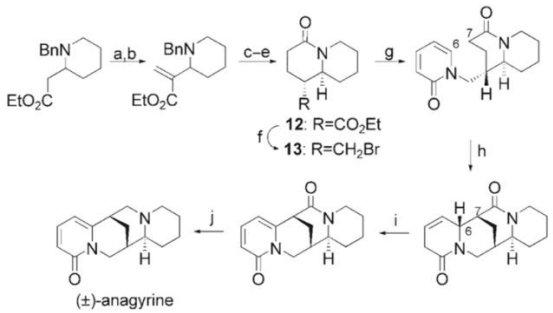


Fig. 2. Synthesis rout of anagyrine proposed by Gray and Gallagher (2006).

Table II
Chemical and Physical Properties of Anagyrine

| PropertyName | PropertyValue |
|---|---|
| Molecular Weight | 244.33 g/mol |
| XLogP3-AA | 1.6 |
| Hydrogen Bond DonorCount | 0 |
| Hydrogen Bond AcceptorCount | 2 |
| Rotatable Bond Count | 0 |
| Exact Mass | 244.157563 g/mol |
| Monoisotopic Mass | 244.157563 g/mol |
| Topological Polar Surface Area | 23.6 |

| | |
|---|---|
| Heavy AtomCount | 18 |
| Formal Charge | 0 |
| Complexity | 440 |
| IsotopeAtomCount | 0 |
| DefinedAtomStereocenterCount | 1 |
| UndefinedAtomStereocenterCount | 2 |
| Defined Bond StereocenterCount | 0 |
| Undefined Bond StereocenterCount | 0 |
| Covalently-Bonded Unit Count | 1 |
| CompoundIsCanonicalized | Yes |

source: Pubchem repository (https://pubchem.ncbi.nlm.nih.gov/)

Molecular structures refer to the connectivity of atoms, where there will be bond lengths in addition to bond and twist angles. The importance for the study of structural characterization in molecules with possible biological activities is to provide all the necessary parameters for the electronic study, since from the structural-electronic study will be possible the complete characterization of indicators of molecular reactivity [22-23]. Geometric optimization seeks, through theoretical calculation methods, to find regions for each atom with minimal potential energies [24].

Basically, experimental data and previous solutions of some equations are used, that is, the more complex integrals that take a long time to calculate are simplified and others have their resolution replaced by empirical data. In semi-empirical formalism, To analyze only valence electrons are considered explicitly, only a minimal set of base functions is used to accommodate them, ie only s and p functions are used in an exponential base function set STO. To calculate the effect of the electrons of the inner layers, a calculation using the nuclear charge (shielding) or by introducing functions that take into account the repulsion of the nucleus and core electrons in combination is performed [25-27].

Using the PM3 method formalism, it was possible to optimize the structure of the Anagyrine alkaloid, obtaining the 3D correlates, where all atoms occupy regions with lower potential energies, presenting their thermodynamically more stable structure obtaining the potential energy level. -2704.2825 eV, formation heat -25.9770 kcal / mol and dipolar moment 3.38309 D. With all atoms in place, the atomic characteristics of angle bonds can be determined (Fig. 3).

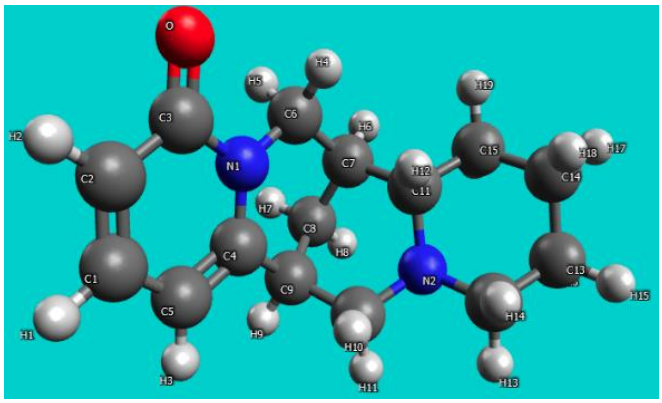


Fig 3. Optimized structure of Anagyrine alkaloid

Anagyrine, in its ground state, presents charge neutrality, however it is possible to perceive, through the obtained data (Table III), the presence of atomic partial charges from electrons that are closer or far from the bond atoms, these data can be explained by the electronegaitvade difference. Carbon atoms ranged from -0.055 to 0.251, nitrogen atoms ranging from -0.312 to -0.298 and hydrogen atoms ranging from 0.027 to 0.028. Regarding the bonds (Table 4) we can highlight the predominant covalent character, where the bonds (C6 - C7), (C7 - C8), (C7 - C11), (C8 - C9), (C9 - C10), (C10 - C2), (N2 - C12), (C11 - C15), (C12 - C13), (C13 - C14) and (C14 - C15) because they have rotations and the (C1 - C2), (C3 - O) connections and (C5 - C5) for having π links. Regarding the bonding and twisting angles, we can highlight the largest and smallest angles between the bonds, with the bonds (C2 - C3 - O) and (H7 - C8 - H8) angled at 125.3768 ° and 105.8355 ° respectively. The largest and smallest torsion angles stand out (C5 - C1 - C2 - H2) and (H8 - C8 - C9 - C4), as they have angles of 179.5808 ° and -179.9161 °, respectively.

Table III
Atomic Properties of Anagyrine Alkaloid

| Atom | Type | Valence | Partial Charge |
|---|---|---|---|
| C1 | Car | 3 | -0.055 |
| C2 | Car | 3 | 0.003 |
| C3 | Car | 3 | 0.251 |
| N4 | Nar | 3 | -0.312 |
| C5 | Car | 3 | 0.026 |
| C6 | Car | 3 | -0.42 |
| O7 | O2 | 1 | -0.268 |
| C8 | C3 | 4 | 0.031 |
| C9 | C3 | 4 | -0,007 |
| C10 | C3 | 4 | -0.038 |
| C11 | C3 | 4 | 0.013 |
| C12 | C3 | 4 | 0,007 |
| N13 | N3 | 3 | -0.298 |
| C14 | C3 | 4 | 0.015 |
| C15 | C3 | 4 | -0.001 |
| C16 | C3 | 4 | -0.040 |
| C17 | C3 | 4 | -0.050 |
| C18 | C3 | 4 | -0.037 |
| H19 | H | 1 | 0.062 |
| H20 | H | 1 | 0.067 |
| H21 | H | 1 | 0.063 |
| H22 | H | 1 | 0.050 |
| H23 | H | 1 | 0.050 |
| H24 | H | 1 | 0.033 |
| H25 | H | 1 | 0.028 |
| H26 | H | 1 | 0.028 |
| H27 | H | 1 | 0.038 |
| H28 | H | 1 | 0.043 |
| H29 | H | 1 | 0.043 |
| H30 | H | 1 | 0.047 |
| H31 | H | 1 | 0.043 |
| H32 | H | 1 | 0.043 |
| H33 | H | 1 | 0.028 |
| H34 | H | 1 | 0.028 |
| H35 | H | 1 | 0.027 |
| H36 | H | 1 | 0.027 |
| H37 | H | 1 | 0.028 |
| H38 | H | 1 | 0.028 |

Table IV
Properties of Anagyrine Alkaloid Bonds

| InitialAtom | Final Atom | Order of Bond | Rotability | Length (Å) |
|---|---|---|---|---|
| H2 | C2 | 1 | NO | 2 |
| C2 | C3 | 1 | NO | 1.45892 |
| C2 | C1 | 2 | NO | 1.35322 |
| O | C3 | 2 | NO | 1.22805 |
| H19 | C1 | 1 | NO | 1.09545 |
| C3 | N1 | 1 | NO | 1.44296 |
| C1 | C5 | 1 | NO | 1.42496 |
| H18 | C14 | 1 | NO | 1.10828 |
| H14 | C12 | 1 | NO | 1.11234 |
| H12 | C11 | 1 | NO | 1.12294 |
| H4 | C6 | 1 | NO | 1.11111 |
| N1 | C6 | 1 | NO | 1.49564 |
| N1 | C4 | 1 | NO | 1.40742 |
| H10 | C10 | 1 | NO | 1.11205 |
| H15 | C13 | 1 | NO | 1.10688 |
| C5 | H3 | 1 | NO | 1.09531 |
| C5 | C4 | 2 | NO | 1.36924 |
| C14 | H17 | 1 | NO | 1.10657 |
| C14 | C13 | 1 | YES | 1.52243 |
| C14 | C15 | 1 | YES | 1.52277 |
| C12 | C13 | 1 | YES | 1.5267 |
| C12 | H13 | 1 | NO | 1.10744 |
| C12 | N2 | 1 | YES | 1.49515 |
| C6 | H5 | 1 | NO | 1.11034 |
| C6 | C7 | 1 | YES | 1.53311 |
| C4 | C9 | 1 | NO | 1.51218 |
| H19 | C15 | 1 | NO | 1.10769 |
| C13 | H16 | 1 | NO | 1.10791 |
| C11 | C15 | 1 | YES | 1.53776 |
| C11 | N2 | 1 | YES | 1.50459 |
| C11 | C7 | 1 | YES | 1.55389 |
| C15 | H20 | 1 | NO | 1.10847 |
| C10 | N2 | 1 | YES | 1.49306 |
| C10 | H11 | 1 | NO | 1.1076 |
| C10 | C9 | 1 | YES | 1.54398 |
| C7 | H6 | 1 | NO | 1.11748 |
| C7 | C8 | 1 | YES | 1.52528 |
| C9 | H9 | 1 | NO | 1.1168 |

| | | | | |
|---|---|---|---|---|
| C9 | C8 | 1 | YES | 1.52477 |
| C8 | H7 | 1 | NO | 1.10771 |
| C8 | H8 | 1 | NO | 1.10711 |

The frontier orbitals are essential parameters in the study of chemical reactivity, since through these parameters it is possible to predict and design directed tests of possible biological activities. The highest occupied energy molecular orbital (HOMO) is related to the ionization potential, where it determines the region that has the highest electron density indicating the electron-donor character [28]. The lowest unoccupied molecular energy orbital (LUMO) is related to electron affinity showing the lowest electron density resulting in the electron-receptor character of the molecule. Thus, the higher the energy of HOMO, the greater the electron-donor character and the higher the LUMO, the greater the electron-receptor character [29][23][30].

Given the energy of orbiatia, the difference between the value of HOMO and LUMO results in the GAP, which is the amount of energy the electron needs to make the transition, in other words, the difference between the ionization potential and the Electron affinity will indicate how much energy is required for the molecule to react. In this sense, the higher the GAP, the greater the chemical stability and the smaller the GAP the more reactive the molecule [31].

Anagyrine HOMO has contribution from the atoms of C6, C5, C2, C3, N4 and O7 presenting symmetry in the positive and negative phases and presented an energy value of -8.66383 eV. LUMO had the contribution of atoms of C3, C2, C5, C4, N1 and O also presenting symmetry in the positive and negative phases and energy value equal to -0.30936 eV. When plotting the isosurfaces of the Anagyrine, Cytisine, and Quinolizidine boundary orbitals (Fig. 4), we can see that Anagyrine had the energy of GAP (8.35447) lower than Cytisine (8.35463) and Quinolizidine (11.56233), which indicates that Anagyrine It has a more reactive character than the others.

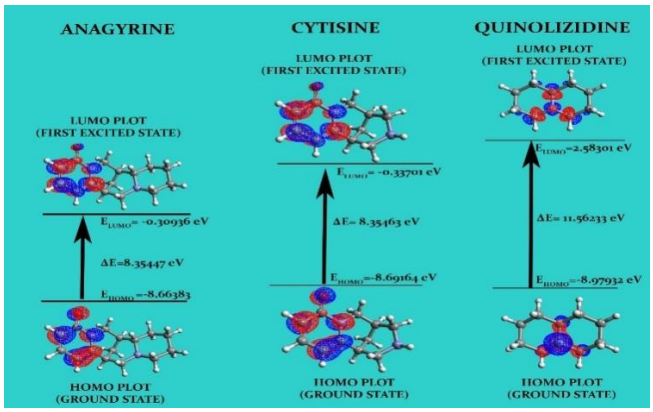


Fig.4. Isosurface and GAP of Anagyrine, Cytisine and Quinolizidine molecules.

Frontier orbitals describe chemical properties that indicate the types of interactions between a linker molecule and biological receptors, ie, these orbitals provide molecular descriptors that show properties linked directly to the molecular reactivity of compounds [31]. Using Koopmans' theorem HOMO-LUMO interactions result in global chemical reactivity descriptors that act as mediators between stability and reactivity. These descriptors include electronic affinity (A), vertical ionization potential (I), electronegativity (χ), chemical hardness (η), chemical softness (S), electronic chemical potential (μ) and electrophilicity index (ω) [32-33].

The ionization potential of reactive compounds represents the intensity of the force with which an electron is bound to an atom. When the value of the force intensity is considered low in the ligand-receptor interaction, it can indicate possible charge transfer mechanisms and also show that the ionic form of the substance has biological activity [34-35].

The electronegativity of a molecule represents the ability to attract electrons from another molecular when interacting, directly influencing the dipole moment of a molecule and altering molecular properties such as the acidity and basicity of different molecules [36-37]. Chemical hardness refers to how resistant the molecule will be to deformation and chemical softness represents the ease of the molecule to deform, which implies that the lower the hardness or the greater the chemical softness, the lower the GAP energy [28].

By characterizing all global descriptors of chemical reactivity (Table V), it is clear that Anagyrine had a median affinity value (0.30936 eV) compared to the others, ie, it has an average energy expenditure for one electron. be added to your LUMO orbital. Regarding the ionization potential, the Anagyrine (8.66383) is lower than the others, making it more likely to lose one electron than the others. Regarding electronegativity, Anagyrine presented lower value (4,48659 eV) indicating having greater difficulty in attracting electrons than the other molecules, besides indicating less chemical hardness.

Table V

Molecular descriptors of Anagyrine, Cytisine and Quinolizidine molecules

| **Descriptors** | **Anagyrine** | **Cytisine** | **Quinolizidine** |
|---|---|---|---|
| Homo | -8.66383 | -8.69164 | -8.97932 |
| Lumo | -0.30936 | -0.33701 | 2.58301 |
| Gap | 8.35447 | 8.35463 | 11.56233 |
| Eléctron Affinit (A) | 0.30936 | 0.33701 | -2.58301 |
| Vertical Ionization Potential (I) | 8.66383 | 8.69164 | 8.97932 |
| Eletronegativity ($\chi$) | 4.48659 | 4.51432 | 6.39631 |
| Chemical Hardness ($\eta$) | 4.17723 | 4.17731 | 5.78116 |
| Chemical Softness(S) | 0.11696 | 0.11969 | 0.08648 |
| Eletronic chemicalpotential ($\mu$) | -4.48659 | -4.51432 | -6.39631 |
| Electrophilicity index ($\omega$) | 2.40943 | 2.43926 | 3.53845 |

Atomic charges are important for the correlational study between molecular structure and biology activity. Mulliken atomic charges or Mulliken Population Analysis divides, disregarding electronegativity, the charge density between two atoms uniformly [38]. The generated data (Table VI) show the Mulliken atomic charges of Anagyrine, where it can be seen that there were variations of charges of atoms of the same element, with carbon atoms ranging from -0.3376 to 0.3043, hydrogen atoms ranging from 0.0998 at 0.2297 and nitrogen atoms ranging from 0.0750 to -0.0936.

Table VI
Mulliken PopulationAnalysis

| **Atom** | **Charge** | **Atom** | **Charge** |
|---|---|---|---|
| C1 | -0.0850 | H2 | 0.2297 |
| C2 | -0.3376 | H3 | 0.2157 |
| C3 | 0.3043 | H4 | 0.1632 |
| N1 | 0.0750 | H5 | 0.1425 |
| C6 | -0.0615 | H6 | 0.1560 |
| C5 | -0.3297 | H7 | 0.1335 |
| 0 | -0.4063 | H8 | 0.1578 |
| C7 | -0.2231 | H9 | 0.1563 |
| C8 | -0.1616 | H10 | 0.1158 |
| C9 | -0.2407 | H11 | 0.1287 |
| C10 | -0.1094 | H12 | 0.1233 |
| C11 | -0.2009 | H13 | 0.1244 |
| N2 | -0.0936 | H14 | 0.0998 |
| C12 | -0.1097 | H15 | 0.1217 |
| C13 | -0.1962 | H16 | 0.1328 |
| C14 | -0.2388 | H17 | 0.1236 |
| C15 | -0.2373 | H18 | 0.1183 |
| C16 | -0.2402 | H19 | 0.1230 |
| H1 | 0.1921 | H20 | 0.1341 |

The electrostatic potential surface map (MESP) allows visualization and analysis of charge distribution, characterizing nucleophilic and electrophilic regions, and describing how complex molecules interact with each other [36]. By plotting the Anagyrine MESP (Fig. 5) it was possible to identify well-defined regions, where the red regions presented high charge concentration, while the highlighted regions in white colors showed low charge density. The regions with the highest concentrations of charges occur by the presence of nitrogen atoms (N1 and N2) and the oxygen atom (O), making them hydrogen receiving atoms that can form hydrogen bonds.

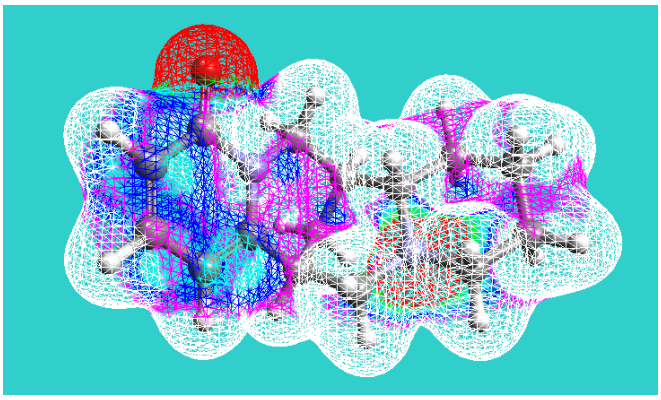

Fig.5. Electrostatic potential surface map of the Anagyrine molecule.

## IV. CONCLUSIONS

The anagyrine alkaloid underwent the geometric optimization process, based on quantum mechanical calculations, where the point of lowest potential energy was obtained making the thermodynamically more stable structure able to characterize the partial charges of each atom, the types of bonds and the characterization of the two. binding and torsion angles.Energy calculations provided the identification of the HOMO and LUMO boundary orbitals responsible for intermolecular interactions. The orbitals allow the characterization of important molecular descriptors for the study of chemical reactivity, where Anagyrine had better reactivity than Cytisine and Quinolizidine for presenting lower GAP energy value than the others.

The electrostatic potential surface map (MESP) rendering allowed the identification of the areas with higher and lower electron densities, showing the nucleophilic regions. This work consists of an initial stage, where the generated data will serve as a database for future molecular modeling studies, aiming to test the biological potential of the molecule.

## V. ACKNOWLEDGMENT

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