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Theoretical Approach on structural aspects of antiepileptic agent indoline-2,3-dione-3-oxime by arguslab 4 software

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ABSTARCT

Indoline-2,3-dione-3-oxime (Isatin -3-oxime)was found to have anticonvulsant activity. Conformational analysis and geometry optimization of Indoline-2,3-dione-3-oxime was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. The minimum heat of formation is calculated by geometry convergence function by ArgusLab software. PM3 semi empirical quantum mechanical calculations were carried out on the most stable structure of Indoline-2,3-dione-3-oxime to obtain the geometries, geometric parameters and thermodynamic parameters. The HOMO and LUMO frontier orbital energies were also computed for the optimized molecule. Electron density surface of IDOX is determined using PM3 geometry with PM3 wavefunciton

Keywords: Argus Lab 4.0.1, conformational analysis, geometry optimization, IDOX, HOMO, LUMO

INTRODUCTION

Isatins are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry[1,2]**.** A literature survey identified several isatin derivatives in the development phase as potential new drugs. Isatin derivatives have been reported to show considerable pharmacological actions such as antimicrobial, anticancer, antiviral, anticonvulsant, antiinflammatory and analgesic activities[2]**.** Indoline-2,3-dione-3-oxime abbreviated as IDOX synthesized by the condensation of isatin with hydroxyl amine was found to have number of applications.

Epilepsy is a brain disorder that causes people to have recurrent seizures. A large numbe of populations of different age groups and sex are affected by this disease. Therefore, studies have been carried out for designing of newer antiepileptic drugs with reduced neurotoxicity[4]. Recently it has been found that isatin (2,3-indoline-dione) is a novel template for designing of new

anticonvulsants[5-7]**.** Indoline-2,3-dione-3-oxime (Isatin -3-oxime)was found to have anticonvulsant activity[8].

In view of biological importance of **Indoline-2,3-dione-3-oxime** (IDOX) ,in the present paper we report the structural aspects of IDOX in detail, theoretically using **Argus Lab software.** The present work also describes the computer aided conformational analysis that is based on geometry optimization (active conformation) of IDOX by ArgusLab software.

Argus Lab is the electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures; geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway.[9]

Conformational analysis of molecule is based on molecular mechanics, it is method for the calculation of molecular structures, conformational energies and other molecular properties using concept from classical mechanics. A molecule is considered as a collection of atoms held together by classical forces. These forces are described by potential energy function of structural features like bond lengths, bond angles and torsion angles etc.

The energy (E) of the molecule is calculated as a sum of terms as in equation (1).

E = E stretching + E bending + E torsion + E Vander Waals + E electrostatic + E hydrogen bond + cross term

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy functions and the corresponding parameters are called a force field.[10]

The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atoms moved are iteratively moved (without breaking bonds) using an energy minimization technique until the net forces on all atoms vanish and the total energy of the molecule reaches a minimum. The 3D (3 rotatable bonds) structure of molecule corresponding to this energy minimum is one of the stable conformations of molecule but not necessarily the most stable one.[11]

Since the energy minimization methods cannot move the molecule across energy barriers, the minimization of a trial molecule continues until the first local energy minimum is found. Other local energy minima including the lowest energy one, the global energy minimum, may be found by repeating the calculation with another start geometry or more efficiently.[12]

MATERIALS AND METHODS

Computational advances have generated many tools which are widely used to construct models, minimization and representations of molecular structure[13-15] .

All conformational analysis (geometry optimization) study was performed on a window based computer using Argus lab software. The IDOX structure is generated by Argus lab, and minimization was performed with the semi-empirical Parametric Method 3 (PM3) parameterization [16,17].

The minimum potential energy is calculated by using geometry convergence function in Argus lab software. Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP) spin densities and generated the grid data used to make molecular orbital surfaces to visualize the molecular orbital and making an electro static potential mapped on electron density surface. The minimum potential energy was calculated for IDOX through the geometry convergence map[18-21]. Mulliken Atomic Charges , ZDO

Atomic Charges of IDOX and Ground State Dipole (debye) of Indoline-2,3-dione-3-oxime(IDOX) were determined using PM3 method.

RESULTS AND DISCUSSIONS

The molecule Indoline-2,3-dione-3-oxime(IDOX) is build using molecule builder of Argus lab. The "Molecule Settings of Indoline-2,3-dione-3-oxime(IDOX) are Atoms 18, Net charge 0 and Valence electrons 60. Prospective view and active conformation of **Indoline-2,3-dione-3-oxime (IDOX)** are shown in **Figs. 1&2**

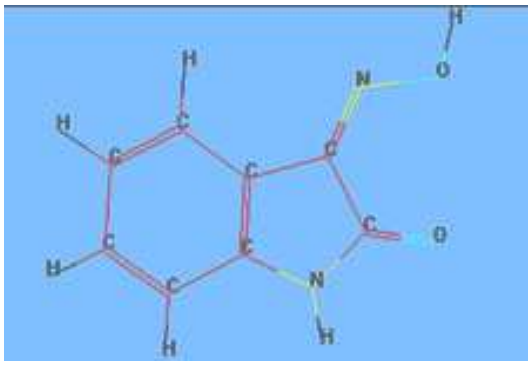

Fig.1 Structure of Indoline-2,3-dione-3-oxime(IDOX)

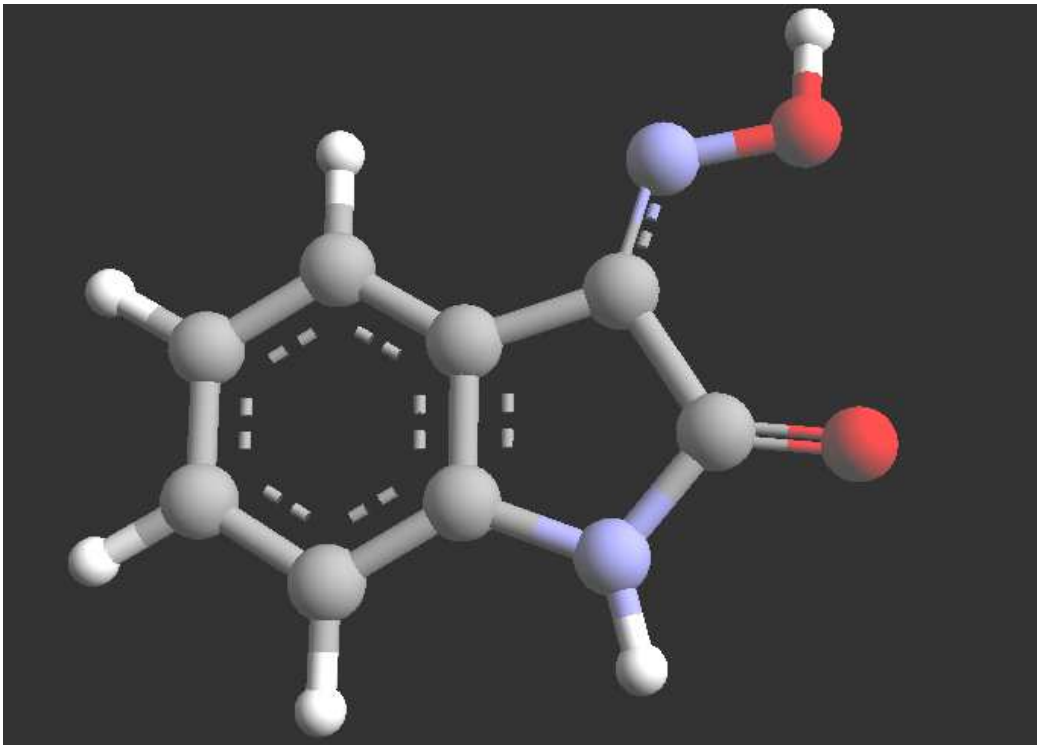

Fig.2 Perspective view and active conformation of Indoline-2,3-dione-3-oxime (IDOX) as optimized by ArgusLab 4.0.1 software

Atoms	x	y	z	Atoms	x	y	z

1	**C**	-3.82149	1.430819	0.143262	**10 O**	2.045785	0.700249	0.464078
2	**C**	-2.64778	2.195491	0.224221	**11 N**	0.293344	3.295747	0.331015
3	**C**	-1.43504	1.539012	0.260842	**12 O**	1.574065	3.576731	0.382102
4	**C**	-1.37906	0.099765	0.227531	**13 H**	-4.79233	1.943480	0.112435
5	**C**	-2.55044	-0.64973	0.140043	**14 H**	-2.69749	3.292873	0.258892
6	**C**	-3.76920	0.041254	0.096844	**15 H**	-2.52967	-1.74641	0.104380
7	**C**	-0.04677	2.039589	0.330996	**16 H**	-4.70364	-0.53657	0.028038
8	**C**	0.821665	0.780899	0.373091	**17 H**	0.241711	-1.27416	0.306493
9	**N**	-0.04333	-0.33206	0.285237	**18 H**	1.611311	4.554334	0.349081

Table 1: Atomic coordinates of Indoline-2,3-dione-3-oxime(IDOX)- Input Atomic Information

The atomic input information for above calculation is given in **Table no.1.** The final geometrical energy and SCF energy was found to be -71.6493144497 au / -44960.6642 kcal/mol as calculated by RHF/ PM3method, as performed by ArgusLab 4.0.1 suite**.(Table no.2)**

Table 2: Calculating SCF using one electron matrix

Cycle	Energy (au)	Difference	Cycle	Energy (au)	Difference
1	**-37.224213**		**26**	**-71.649314388**	**-7.03486e-008**
2	**-51.102486209**	**-13.8783**	**27**	**-71.649314420**	**-3.29312e-008**
3	**-48.936482371**	**2.166**	**28**	**-71.649314436**	**-1.54559e-008**
4	**-58.300985466**	**-9.3645**	**29**	**-71.649314443**	**-7.26988e-009**
5	**-59.217432163**	**-0.916447**	**30**	**-71.649314447**	**-3.4255e-009**
6	**-60.947745737**	**-1.73031**	**31**	**-71.649314448**	**-1.61816e-009**
7	**-62.528529044**	**-1.58078**	**32**	**-71.649314449**	**-7.64317e-010**
8	**-64.170257165**	**-1.64173**	**33**	**-71.649314449**	**-3.63002e-010**
9	**-65.902534284**	**-1.73228**	**34**	**-71.649314450**	**-1.71042e-010**
10	**-69.295515108**	**-3.39298**	**35**	**-71.649314450**	**-8.10019e-011**
11	**-71.237306522**	**-1.94179**	**36**	**-71.649314450**	**-3.93356e-011**
12	**-71.539284932**	**-0.301978**	**37**	**-71.649314450**	**-1.8531e-011**
13	**-71.638153808**	**-0.0988689**	**38**	**-71.649314450**	**-9.26548e-012**
14	**-71.648317687**	**-0.0101639**	**39**	**-71.649314450**	**-4.43379e-012**
15	**-71.648928797**	**-0.00061111**	**40**	**-71.649314450**	**-1.98952e-012**
16	**-71.649144297**	**-0.0002155**	**41**	**-71.649314450**	**-3.97904e-013**
17	**-71.649242873**	**-9.85758e-005**	**42**	**-71.649314450**	**-2.27374e-013**
18	**-71.649283692**	**-4.08189e-005**	**43**	**-71.649314450**	**-3.97904e-013**
19	**-71.649300760**	**-1.70678e-005**	**44**	**-71.649314450**	**-5.68434e-014**
20	**-71.649308260**	**-7.50033e-006**			
21	**-71.649311619**	**-3.35911e-006**			
22	**-71.649313145**	**-1.52531e-006**			
23	**-71.649313840**	**-6.95554e-007**			
24	**-71.649314166**	**-3.26249e-007**			
25	**-71.649314317**	**-1.50781e-007**			

Final SCF Energy = -71.6493144497 au
Final SCF Energy = -44960.6642 kcal/mol

Final Geometrical Energy =-71.6493144497 au
Final Geometrical Energy =-44960.6642 kcal/mol

Table 3: List of Mulliken Atomic Charges and ZDO Atomic Charges of IDOX using ArgusLab software

Numbering of atoms	Atom	Mulliken Atomic Charges	ZDO Atomic Charges	Numbering of atoms	Atom	Mulliken Atomic Charges	ZDO Atomic Charges
1	**C**	**-0.2308**	**-0.1409**	**10**	**O**	**-0.3454**	**-0.3370**
2	**C**	**-0.1027**	**-0.0200**	**11**	**N**	**0.0725**	**0.0894**
3	**C**	**-0.1139**	**-0.1045**	**12**	**O**	**-0.2246**	**-0.2036**
4	**C**	**-0.0690**	**-0.0700**	**13**	**H**	**0.1983**	**0.1079**
5	**C**	**-0.2260**	**-0.1375**	**14**	**H**	**0.2071**	**0.1146**
6	**C**	**-0.1415**	**-0.0580**	**15**	**H**	**0.2050**	**0.1138**
7	**C**	**-0.1307**	**-0.1285**	**16**	**H**	**0.1901**	**0.1019**
8	**C**	**0.2925**	**0.2600**	**17**	**H**	**0.1593**	**0.0986**
9	**N**	**0.0130**	**0.0961**	**18**	**H**	**0.2468**	**0.2178**

Table 4 : Ground State Dipole (debye) of Indoline-2,3-dione-3-oxime(IDOX)

X	Y	Z	length
-2.37178155	**-0.04501839**	**-0.20126333**	**2.38073125**

Mulliken Atomic Charges , ZDO Atomic Charges and Ground State Dipole (debye) of IDOX were given in **Tables 3&4**

Heat of Formation: The atomic heat of formation is the heat that released during the formation of the stable form of the element from individual atoms at standard conditions. It should be noted that thermodynamical corrections (e.g., zero-point energies) should not be added to the formation energy, as these are implicitly included by the parametrization. The most energetically favorable conformation of conformation of IDOX is found to have a heat of formation of 6.4058 kcal/mol via use of the Argus Lab software

HOMO and LUMO orbitals of IDOX

The HOMO and LUMO orbitals are commonly known as *Frontier Orbitals* and were found to be extremely useful in explaining chemical reactivity. Electrophilic attacks were shown to correlate very well with atomic sites having high density of the HOMO orbital, whereas nucleophilic attacks correlated very well with atomic sites having high density of the LUMO orbital (Kunichi Fukui was awarded the Nobel prize in chemistry in 1981 for developing this concept). **HOMO (Highest Occupied Molecular Orbital i.e MO30)**and **LUMO (Lowest Unoccupied Molecular Orbital i.e MO 31) of IDOX** are shown in **fig .3 and fig.4** respectively. This was done theoretically using PM3. The calculated Eigen values and eigen vectors of HOMO (MO 30)and LUMO(MO 31) are given in **Tables 5 & 6.**

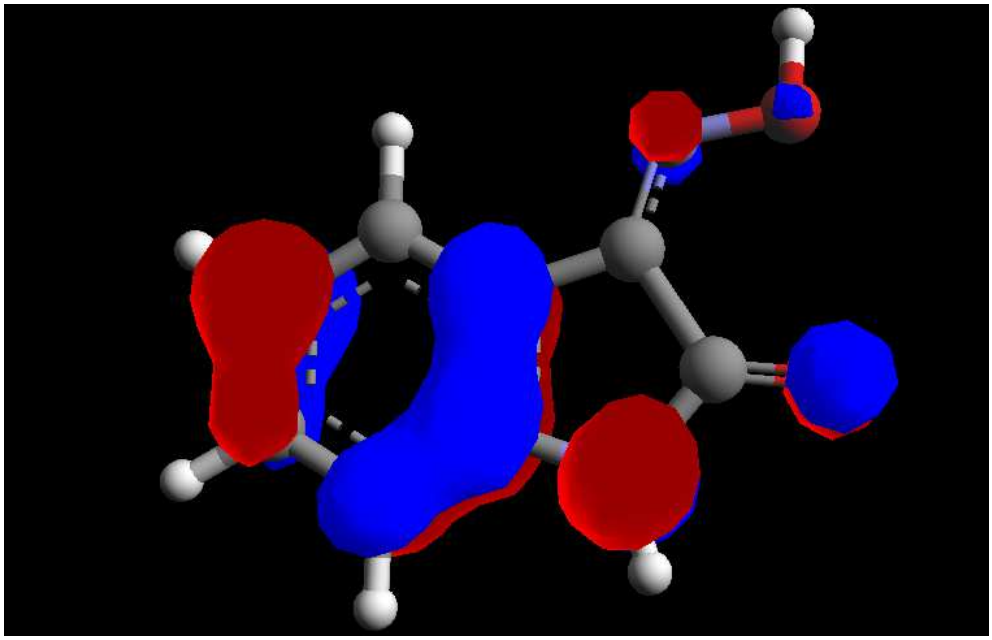

Fig 3. Visualize the HOMO (Highest Occupied Molecular Orbitals) (MO30) of IDOX, blue shows positive and red shows negative.

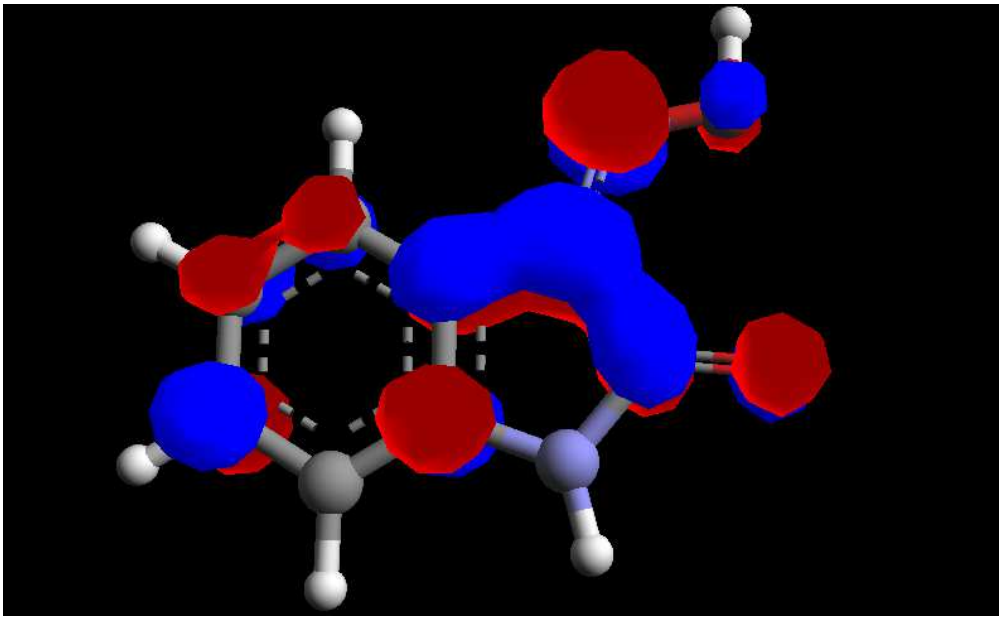

Fig 4. Visualize the LUMO (Lowest Unoccupied Molecular Orbitals) (MO 31) of IDOX, blue shows positive and red shows negative.

Table 5 . Data of eigen values and Eigen vectors of HOMO (MO 30) of IDOX

MO Number 30 Eigen values(au) -0.322194

	eigenvectors				
1 C 2S	-0.000192	7 C 2Px	0.004393	15 H 1S	0.000724
1 C 2Px	0.020585	7 C 2Py	-	16 H 1S	-0.000440

			0.001176		
1 C 2Py	0.014556	7 C 2Pz	-0.094282	17 H 1S	-0.006249
1 C 2Pz	-0.417750	8 C 2S	-0.003606	18 H 1S	0.000831
2 C 2S	-0.000604	8 C 2Px	0.010019		
2 C 2Px	0.002166	8 C 2Py	0.003799		
2 C 2Py	0.002449	8 C 2Pz	-0.092758		
2 C 2Pz	-0.064166	9 N 2S	0.010193		
3 C 2S	0.001293	9 N 2Px	0.034331		
3 C 2Px	-0.014617	9 N 2Py	0.007741		
3 C 2Py	-0.009677	9 N 2Pz	-0.548554		
3 C 2Pz	0.353863	10 O 2S	0.000091		
4 C 2S	-0.000882	10 O 2Px	-0.023974		
4 C 2Px	-0.021487	10 O 2Py	-0.007994		
4 C 2Py	-0.008622	10 O 2Pz	0.282815		
4 C 2Pz	0.350771	11 N 2S	0.000146		
5 C 2S	0.000325	11 N 2Px	0.007071		
5 C 2Px	-0.016475	11 N 2Py	-0.003019		
5 C 2Py	-0.010099	11 N 2Pz	-0.166976		
5 C 2Pz	0.295962	12 O 2S	0.000354		
6 C 2S	-0.000044	12 O 2Px	-0.004391		
6 C 2Px	0.011003	12 O 2Py	0.003050		
6 C 2Py	0.007670	12 O 2Pz	0.106064		
6 C 2Pz	-0.209024	13 H 1S	0.000133		
7 C 2S	0.000791	14 H 1S	-0.000320		

Table 6. Data of eigen values and Eigen vectors of LUMO(MO 31) of IDOX

MO number 31 Eigen values -0.029538

	eigenvectors				
1 C 2S	-0.000146	6 C 2Px	-0.018316	11 N 2Pz	-0.522682
1 C2Px	0.010481	6 C 2Py	-0.011226	12 O 2S	0.000951
1 C2Py	0.007374	6 C 2Pz	0.334713	12 O 2Px	-0.007568
1 C2Pz	-0.212929	7 C 2S	0.001944	12 O 2Py	0.005504
2 C 2S	0.000076	7 C 2Px	-0.015177	12 O 2Pz	0.175014
2 C2Px	0.008675	7 C 2Py	0.002258	13 H 1S	-0.000380
2 C2Py	0.006760	7 C 2Pz	0.344965	14 H 1S	-0.000402
2 C2Pz	-0.202895	8 C 2S	-0.001681	15 H 1S	-0.000145
3 C 2S	-0.001224	8 C 2Px	-0.020620	16 H 1S	0.000335
3 C2Px	-0.016451	8 C 2Py	-0.006907	17 H 1S	-0.001133
3 C2Py	-0.009275	8 C 2Pz	0.293686	18 H 1S	-0.002673
3 C2Pz	0.323755	9 N 2S	0.003030		
4 C 2S	-0.001289	9 N 2Px	0.000275		
4 C2Px	0.016010	9 N2Py	0.001273		
4 C2Py	0.012117	9 N 2Pz	-0.006652		
4 C2Pz	-0.334009	10 O 2S	-0.000139		
5 C 2S	0.000973	10 O	0.021003		

		2Px	
5 C2Px	**0.001070**	**10 O 2Py**	**0.004885**
5 C2Py	**0.001048**	**10 O 2Pz**	**-0.269270**
5 C2Pz	**-0.007983**	**11 N 2Px**	**0.022460**
6 C 2S	**-0.000641**	**11 N 2Py**	**-0.009151**

Electronic properties: It is important to examine the E HOMO and E LUMO so as to explain the electronic properties of the complex. This was done theoretically using PM3. The positive and negative phases of the orbital are represented by the two colors, the blue regions represent an increase in electron density and the red regions a decrease in electron density.

However, these calculations were examined in the ground state and also in vacuum. It is possible to use them to get information by comparing them with similar compounds. The calculated E HOMO and E LUMO,and band gap are recorded in **Table 7.**

Table 7: Electronic Properties of IDOX

Methods	HOMO energy(ev)	LUMO energy(ev)	Band gaps (ev)
PM3	**-0.322194**	**-0.029538**	**+0.292656**

Electrostatic Potential of Indoline-2,3-dione-3-oxime (IDOX) :The electrostatic potential is a physical property of a molecule related to how a molecule is first “seen” or “felt” by another approaching species. A distribution of electric charge creates an electric potential in the surrounding space. A positive electric potential means that a positive charge will be repelled in that region of space. A negative electric potential means that a positive charge will be attracted. A portion of a molecule that has a negative electrostatic potential will be susceptible to electrophilic attack - the more negative the better.

QuickPlot ESP mapped density generates an electrostatic potential map on the total electron density contour of the molecule. The electron density surface depicts locations around the molecule where the electron probability density is equal. This gives an idea of the size of the molecule and its susceptibility to electrophilic attack. Below is an electron density surface of IDOX using PM3 geometry with PM3 wavefunction. The surface color reflects the magnitude and polarity of the electrostatic potential.

Fig.5 shows the complete surface of IDOX with the color map. This figure uses a clipping plane showing a cutaway of the same surface revealing the underlying molecular structure. The color map shows the ESP energy (in hartrees) for the various colors. The surface color reflects the magnitude and polarity of the electrostatic potential. The red end of the spectrum shows regions of highest stability for a positive test charge, magenta/ blue show the regions of least stability for a positive test charge. These images show that the carboxyl-end of the molecule is electron rich relative to the amino end.

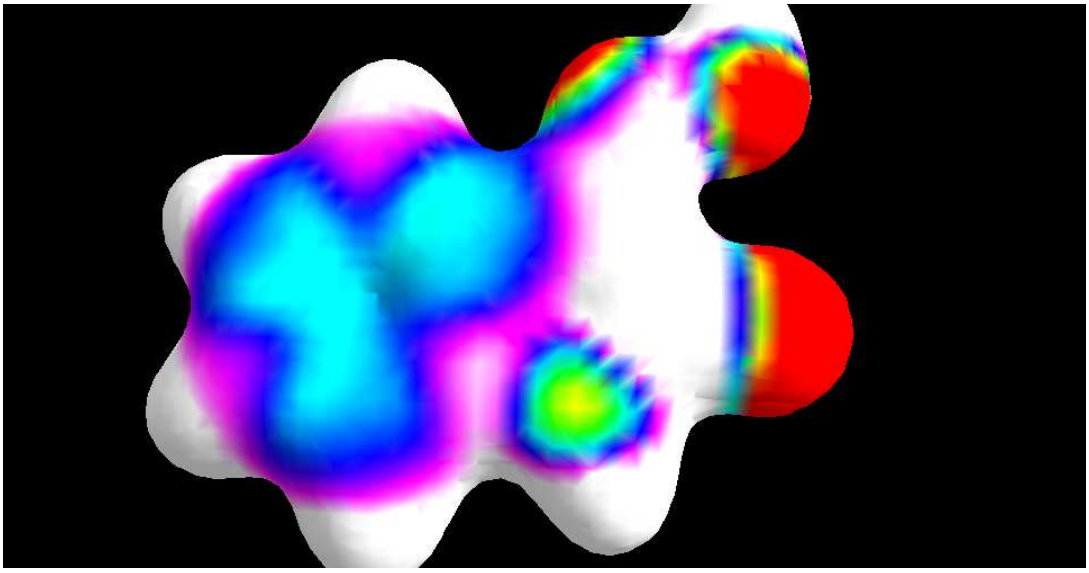

Fig. 5 The complete surface with the color map of ESP of IDOX---ESP MAPPED DENSITY

	0.0500 to 0.0409		**-0.0045 to -0.0136**
	0.0409 to 0.0318		**-0.0136 to - 0.0227**
	0.0318 to 0.0227		**-0.0227 to - 0.0318**
	0.0227 to 0.0136		**-0.0318 to -0.0409**
	0.0136 to 0.0045		**-0.0409 to -0.0500**
	0.0045 to -0.0045		

CONCLUSION

The most energetically favorable conformation of conformation of IDOX is found to have a heat of formation of 6.4058 kcal/mol via use of the Argus Lab software. The present work indicates that the best conformation of IDOX is found to be at -71.6493144497 au/-44960.6642 kcal/mol which is the minimum potential energy by using Argus Lab software. At this point IDOX will be more active as antiepileptic agent.

Finally all geometric variables were completely optimized for each compound and the lowest energy conformations were used in molecular modeling studies. The optimized geometries, dipole moments, Mulliken Atomic Charges and ZDO Atomic Charges and thermodynamic parameters were calculated and the data obtained from the calculated parameter are analysed and is found to be well within the accuracy of computational results.

In conclusion, the modeling and the calculations does not only presented us the opportunity to take a critical look at this novel compound but has also given us the opportunity to compile fundamental result on properties that cannot be calculated in the laboratory.

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