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A Semi-Empirical study of a highly lipid-soluble anti-cancer chemotherapy drug, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea,(Lomustine)

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Abstract

Lomustine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea is an alkylating nitrosourea compound used in chemotherapy. It is in the same family as streptozotocin. This is a highly lipid-soluble drug, and thus crosses the blood-brain barrier. A semi-empirical study was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. The molecular mechanics potential energy function were evaluated in terms of energies associated with bonded interactions (bond length, bond angle and dihedral angle) as well as non-bonded interactions (Vander Waals and electrostatic). Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's, lowest unoccupied molecular orbital's and electrostatic potential (ESP) mapped density. The minimum potential energy was calculated by geometry convergence function by ArgusLab software. The most feasible position for the drug to interact with the receptor was found to be -89.2717519233 au (-56018.9206 kcal/mol). These results could help us in understating the drug-receptor interactions.

Keywords: *Lomustine, semi-empirical, arguslab software, optimization*

1. Introduction

Lomustine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea is an alkylating nitrosourea compound used in chemotherapy. It is in the same family as streptozotocin. This is a highly lipid-soluble drug, and thus crosses the blood-brain barrier. This property makes it ideal for treating brain tumors, and is its primary use. Lomustine has a long time to nadir (the time when white blood cells reach their lowest number) [1]. Cancerous tumors are characterized by cell division, which is no longer controlled as it is in normal tissue. "Normal" cells stop dividing when they come into contact with like cells, a mechanism known as contact inhibition. Cancerous cells lose this ability. Cancer cells no longer have the normal checks and balances in place that control and limit cell division. The process of cell division, whether normal or cancerous cells, is through the cell cycle. The cell cycle goes from the resting phase, through active growing phases, and then to mitosis (division) [2].

The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division [2]. Usually, the drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division. If the cells are unable to divide, they die [2]. The faster the cells are dividing, the more likely it is that chemotherapy will kill the cells, causing the tumor to shrink. They also induce cell suicide (self-death or apoptosis)[2].

Chemotherapy drugs that affect cells only when they are dividing are called cell-cycle specific. Chemotherapy drugs that affect cells when they are at rest are called cell-cycle non-specific [2]. The scheduling of chemotherapy is set based on the type of cells, rate at which they divide, and the time at which a given drug is likely to be effective. This is why chemotherapy is typically given in cycles [2]. Chemotherapy is most effective at killing cells that are rapidly dividing. Unfortunately, chemotherapy does not know the difference between the cancerous cells and the normal cells. The "normal" cells will grow back and be healthy but in the meantime, side effects occur. The "normal" cells most commonly affected by chemotherapy are the blood cells, the cells in the mouth, stomach and bowel, and the hair follicles; resulting in low

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blood counts, mouth sores, nausea, diarrhea, and/or hair loss. Different drugs may affect different parts of the body [2].

Semi-empirical quantum chemistry methods are based on the Hartree–Fock formalism, but make many approximations and obtain some parameters from empirical data[3]. They are very important in computational chemistry for treating large molecules where the full Hartree–Fock method without the approximations is too expensive. The use of empirical parameters appears to allow some inclusion of electron correlation effects into the methods [3].

Argus Lab[4] 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 [5]. 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 terms.

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 [6].

The molecular mechanics method calculates the energy as function of coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atom moved are iteratively moved (without breaking bonds) using an energy minimization technique until the net force on all atoms vanish and the total energy of the molecule reaches a minimum[7,8].The 3D (3 rotatable bonds) structure of molecule corresponding to this energy is minimum is one of the stable conformations of molecule but not necessarily the most stable one [9,10].

In this work, we studied the semi – empirical quantum chemistry of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) using Arguslab software. We optimize the structure using quantum mechanics and calculated their steric and SCF energies. From the quantum chemical studies, it was also possible to elucidate the various molecular properties.

2. Material and Methods

1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine structure was generated by Arguslab [4], and minimization was performed with UFF molecular mechanics method [11, 12]. The minimum potential energy was calculated using geometry convergence function in Arguslab software [4]. Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's (HOMO), lowest unoccupied molecular orbital's (LUMO) and electrostatic potential (ESP) mapped density. The minimum potential energy was calculated for 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine through the geometry convergence map. Mulliken Atomic Charges , ZDO Atomic Charges of Procarbazine and Ground State Dipole (debye) 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) were determined using AM1 method(Dewer et al 1985).

3. Results and discussions

Prospective view and calculated properties of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) molecule is shown in Figure 1. The electron density cloud of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) by ACDlabs-3D viewer software is shown in Figure 2 . The highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and electrostatic potential (ESP) mapped density are shown in Figures 3,4 and 5 respectively. The self - consistent field energy of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) is shown in Figure 6. Atomic coordinates of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) molecule is given in Table1 and bond length and bond angles are given in Table 2 and 3 respectively, which are calculated after geometry optimization of molecule from Arguslab. The calculated steric energy is shown in Table 4.

Arguslab software was used to see what happened to the electrons in 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) when it absorbed light. Surfaces were made to explore this fascinating phenomenon. 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) absorbsed energy in the form of UV/visible light, it made a transition from the ground electronic state to an excited electronic state. The excited and ground states have different distributions of electron density. This property is often valuable and sought after by chemists who are

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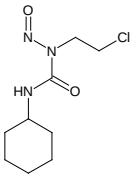
interested in molecules that are useful as dyes, sunscreens, etc [4]. The HOMO is localized to the plane of the molecule and is a non-bonding molecular orbital (Figure 3). The LUMO is perpendicular to the plane of the molecule and is a combination of the p_z atomic orbitals (Figure 4). The n->π^* transition is dominated by the excitation from the HOMO to the LUMO. The positive and negative phases of the orbital are represented by the two colors, the red regions represent an increase in electron density and the blue regions a decrease in electron density. However, these calculations were examined in the ground state and also in vacuum [4]. The electrostatic potential is a physical property of a molecule that relates to how a molecule is first "seen" or "felt" by a positive "test" charge at a particular point in space. 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 [4]. QuickPlot ESP mapped density generates an electrostatic potential map on the total electron density contour of the molecule (Figure 5). The electron density surface depicts locations around the molecule where the electron probability density is equal [4]. This gives an idea of the size of the molecule and its susceptibility to electrophilic attack. The surface color reflects the magnitude and polarity of the electrostatic potential. The color map shows the ESP energy (in hartrees) for the various colors. 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 [4]. These images show that the triple and double bonded end of the molecule is electron rich relative to the single bonded end [4].

SCF was obtained as the minimum potential energy which is the needed energy for the interaction of drug with the receptor. The self-consistent field (SCF) energy is the average interaction between a given particle and other particles of a quantum-mechanical system consisting of many particles. Beacause the problem of many interacting particles is very complex and has no exact solution; calculations are done by approximate methods. One of the most often used approximated methods of quantum mechanics is based on the interaction of a self-consistent field, which permits the many-particle problem to be reduced to the problem of a single particle moving in the average self-consistent field produced by the other particles [13]. The steric energy calculated for 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) was was 0.03522043a.u. (22.10117422 kcal/mol) and the SCF energy (Figure 6) was found to be SCF was found to be be -89.2717519233 au (-56018.9206 kcal/mol) as calculated by RHF/ PM3 method, as performed by ArgusLab 4.0.1 suite**.**

3.1 Tables and Figures



Molecular Formula	= $C_9H_{16}ClN_3O_2$
Formula Weight	= 233.69524
Composition	= C(46.26%) H(6.90%) Cl(15.17%) N(17.98%) O(13.69%)
Molar Refractivity	= 57.84 ± 0.5 cm^3
Molar Volume	= 173.0 ± 7.0 cm^3
Parachor	= 460.8 ± 8.0 cm^3
Index of Refraction	= 1.582 ± 0.05
Surface Tension	= 50.2 ± 7.0 dyne/cm
Density	= 1.35 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 22.92 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 233.093104 Da
Nominal Mass	= 233 Da
Average Mass	= 233.6952 Da

Figure 1: Prospective view and calculated properties of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

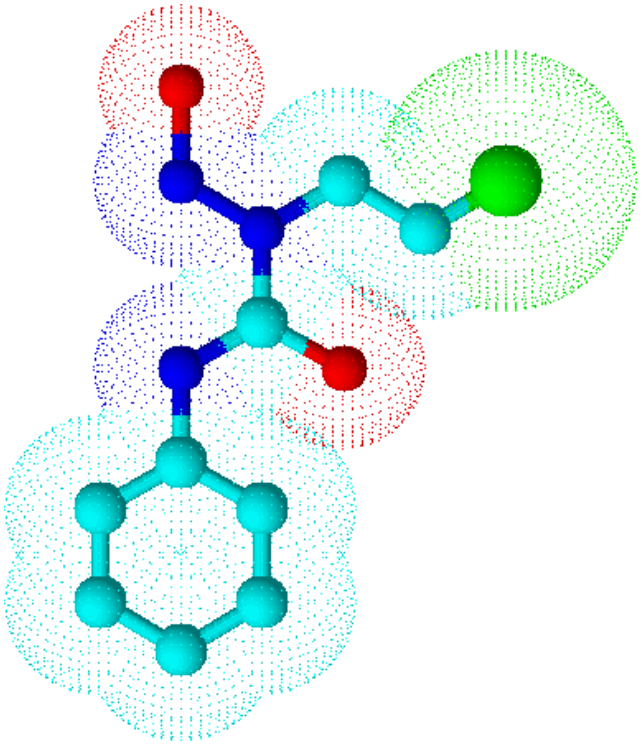


Figure 2: electron density cloud of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) by ACDlabs-3D viewer software

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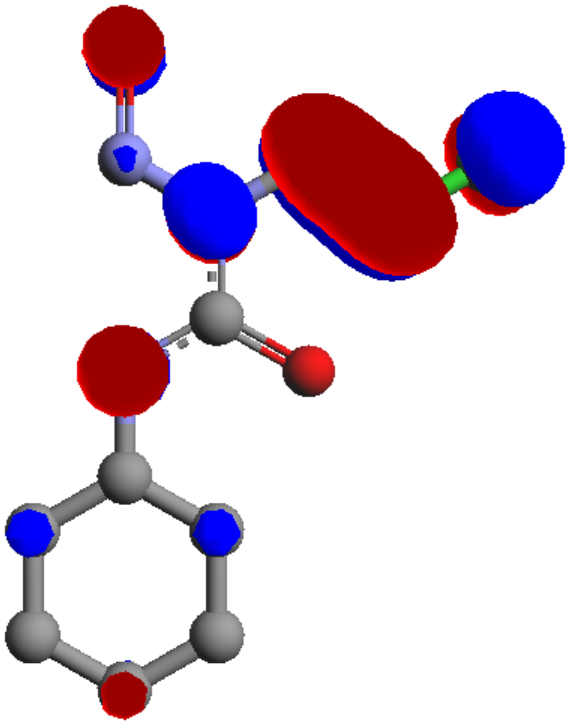

Figure 3: Highest occupied molecular orbital's (HOMO) 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

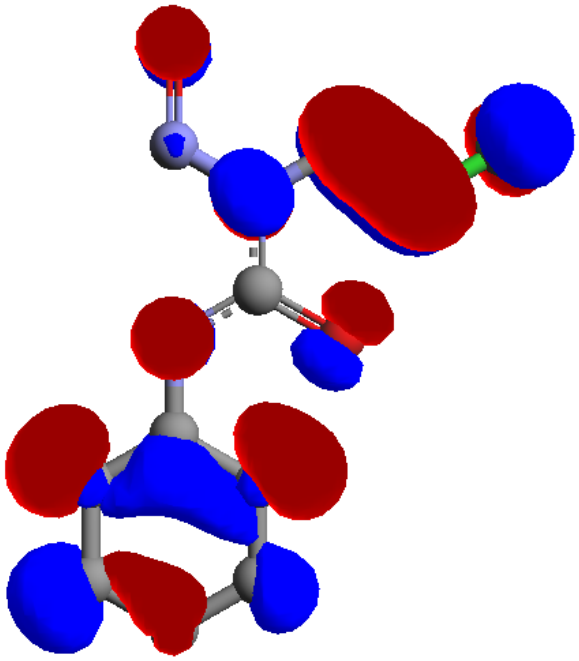

Figure 4: Lowest unoccupied molecular orbital's (LUMO) 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

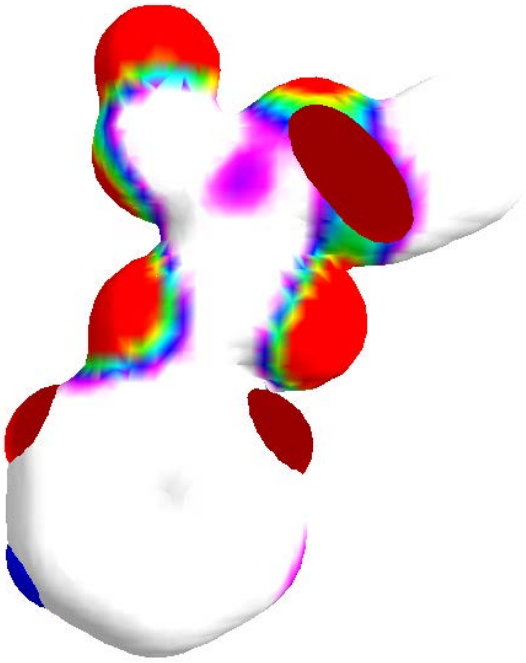

Figure 5: Electrostatic potential mapped density of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

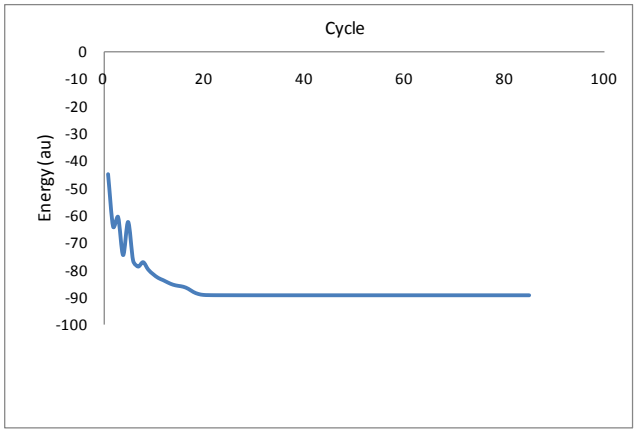

Figure 6: Self-consistent field energy graph of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

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Table 1: Atomic coordinates of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

S.No	Atoms	X	Y	Z
1	C	22.111400	-13.259900	0.000000
2	C	22.111400	-14.589900	0.000000
3	C	20.959500	-12.594900	0.000000
4	C	20.959500	-15.254900	0.000000
5	C	19.807700	-13.259900	0.000000
6	C	19.807700	-14.589900	0.000000
7	N	20.959400	-11.264900	0.000000
8	C	22.111200	-10.599900	0.000000
9	N	22.111200	-9.269900	0.000000
10	O	23.263100	-11.264900	0.000000
11	C	23.263000	-8.604900	0.000000
12	N	20.959400	-8.604900	0.000000
13	O	20.959400	-7.274900	0.000000
14	C	23.263000	-7.274900	0.000000
15	Cl	24.414800	-6.609900	0.000000
16	H	19.807600	-10.600000	0.000000

Table 2: Bond length of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

Atoms	Bond length
(C1)-(C2)	1.458000
(C1)-(C3)	1.458000
(C2)-(C4)	1.458000
(C3)-(C5)	1.458000
(C3)-(N7)	1.419751
(C4)-(C6)	1.458000
(C5)-(C6)	1.458000
(N7)-(C8)	1.346235
(N16)-(H7)	1.048529
(C8)-(N9)	1.346235
(C8)-(O10)	1.260307
(N9)-(C11)	1.422764
(N9)-(N12)	1.370000
(C11)-(C14)	1.464000
(N12)-(O13)	1.201824
(C14)-(Cl15)	1.798486

Table 3: Bond angles of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

Atoms	Bond angles	Alternate angles
(C2)-(C1)-(C3)	120.000000	188.442082
(C1)-(C2)-(C4)	120.000000	188.442082
(C1)-(C3)-(C5)	120.000000	188.442082
(C1)-(C3)-(N7)	120.000000	260.801534
(C2)-(C4)-(C6)	120.000000	188.442082
(C5)-(C3)-(N7)	120.000000	260.801534
(C3)-(C5)-(C6)	120.000000	188.442082
(C3)-(N7)-(C8)	120.000000	220.592895
(C3)-(N7)-(H16)	120.000000	112.353122
(C4)-(C6)-(C5)	120.000000	188.442082
(C8)-(N7)-(H16)	120.000000	124.171616
(N7)-(C8)-(N9)	120.000000	423.785655
(N7)-(C8)-(O10)	120.000000	421.698151
(N9)-(C8)-(O10)	120.000000	421.698151
(C8)-(N9)-(C11)	120.000000	219.857183
(C8)-(N9)-(N12)	120.000000	310.187591
(C11)-(N9)-(N12)	120.000000	285.276039
(N9)-(C11)-(C14)	120.000000	258.357159
(N9)-(N12)-(O13)	120.000000	437.191505
(C11)-(C14)-(Cl15)	120.000000	162.994020

Table 4: Mulliken atomic charges and ZDO atomic charges of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

S.No	Atoms	ZDO Atomic charges	Mulliken Atomic charges
1	C	-4.0000	-4.0003
2	C	-4.0000	-4.0000
3	C	-4.0000	-4.0013
4	C	-4.0000	-4.0000
5	C	-4.0000	-4.0000
6	C	-4.0000	-4.0000
7	N	-2.9712	-3.0543
8	C	1.6200	1.8178
9	N	4.9949	4.9980
10	O	-1.6425	-1.7575
11	C	3.9987	3.9999
12	N	4.9993	5.0013
13	O	6.0000	6.0000
14	C	3.9956	4.0053
15	Cl	3.004	2.9948
16	H	-0.9992	-1.0036

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Table 7: Final steric energy evaluation 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)

S.No.	Force field	Energy components (au)
1	Molecular mechanics bond (Estr)	0.00287038
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.00569956
3	Molecular mechanics dihedral (Etor)	0.00000000
4	Molecular mechanics ImpTor (Eoop)	0.00000000
5	Molecular mechanics vdW (EVdW)	0.02665049
6	Molecular mechanics coulomb (Eqq)	0.00000000
Total		0.03522043a.u. (22.10117422 kcal/mol)

4. Conclusions

The present work indicates that the best conformation of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine) have a self-consistent field energy of -89.2717519233 au (-56018.9206 kcal/mol) as calculated by RHF/ PM3 method, as performed by ArgusLab 4.0.1 suite**.** This is the minimum potential energy by using Arguslab software. At this point the drug will be more active as an alkylating anti-cancer drug.

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