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Conformational Analysis of a Potent Anticancer Drug 3-(4-amino-1-oxo-1,3-dihydro-2*h*-isoindol-2-yl) Piperidine-2,6-Dione (Lenalidomide)

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Abstract

Heterocyclic compounds are currently available as anticancer drugs. Multiple myeloma is a cancer of the blood, characterized by accumulation of a plasma cell clone in the bone marrow. 3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione (lenalidomide) is a chemotherapy agent used mainly in the treatment of multiple myeloma. Conformational analysis and geometry optimization of lenalidomide 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 optimized geometries, Mulliken atomic charges and ZDO atomic charges were calculated. The minimum heat of formation 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 -23.107576 au (-14500.236400 kcal/mol). The modelling and the calculations does not only presented to 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.

Keywords

Lenalidomide, Molecular Mechanics, Arguslab Software, Minimum Energy

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1. Introduction

People suffering from cancer have been estimated to be over 12 million. The mortality data showed 7 million deaths and 25 million persons live in the world together with cancer. World population is growing bigger and will increase the incident of cancer [1]. In United States, about 63,300 cases of breast carcinoma in situ and 55,560 cases of melanoma in situ are expected to be newly diagnosed in 2012 [2]. Due to the high mortality caused by cancer, many researches led to the development of new compounds. Heterocyclic compounds are currently available as anticancer drugs. Multiple myeloma is a cancer of the blood, characterized by accumulation of a plasma cell clone in the bone marrow [3]. Lenalidomide is one of the novel drug agents used to treat multiple myeloma. It is a more potent molecular analog of thalidomide, which inhibits tumor angiogenesis, tumor secreted cytokines and tumor proliferation through the induction of apoptosis [4-6]. Adverse effect common in people receiving lenalidomide for myeloma were neutropenia (a decrease in the white blood cell count), deep vein thrombosis,infections, and an increased risk of other hematological malignancies [7]. The risk of second primary hematological malignancies does not outweigh the benefit of using lenalidomide in relapsed or refractory multiple myeloma [8]. It may be more difficult to mobilize stem cells

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for autograft in people who have received lenalidomide.

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, These set of energy functions and the corresponding parameters are called a force field [9]. The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method [10]. A molecular geometry is constructed by using computer graphics techniques and the atoms are interatively 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.

We hereby present lenalidomide (3-(4-amino-1-oxo-1,3-dihydro-2*h*-isoindol-2-yl) piperidine-2,6-dione) a potent anticancer drugand its basic conformational analysis using computational tools by arguslab 4.0.1 software

2. Materials and Methods

Computational advances have generated many softwares which have been used to for molecular modelling, energy minimization and representations of molecular structure [11-13]. Computational conformational analysis and geometry optimization study of 3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione (Lenalidomide) was performed on a window based computer using Argus lab [14] and ACD Lab Chem Sketch software. The structure was generated by ArgusLab 4.0.1 and geometric optimization was performed with the semi-empirical RHF/Austin Model 1 (AM1) parameterization. The minimum potential energy was calculated by using geometry convergence function in Argus lab software [15]. In order to determine the allowed conformation, the contact distance between the atoms in adjacent residues was examined using criteria for minimum Vander Waal contact distance [16]. Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP), and spin densities were used to generate the grid data used to make molecular orbital surfaces and visualize the molecular orbital, making an electro static potential mapped and electron density surface [13]. The final geometrical energy and SCF energy was calculated by RHF/AM1 method, as performed by ArgusLab 4.0.1 suite, which shows the degree of drug-receptor interaction.

3. Results and Discussion

Heat of Formation of lenalidomide was 60957.4618 kcal/mol. The steric energy calculated for lenalidomide was 0.08719330 a.u. (54.71467396 kcal/mol) and SCF energy was found to be -23.1075767148 au (-14500.2364 kcal/mol) as calculated by RHF/ PM3 method, as performed by ArgusLab 4.0.1 suite. Prospective view and calculated properties of lenalidomide molecule is shown in Figure 1. The active conformation and electron density mapped of lenalidomide by ACDLabs-3D viewer software are shown in Figures 3 and 2 respectively. Figure 6 shows the electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state. Figure 4 and 5 shows the highest occupied molecular orbital of molecule (HOMO) and the lowest unoccupied molecular orbital (LUMO) respectively of lenalidomide molecule. Atomic coordinatesof lenalidomide molecule is given in Table 1. Bond length and bond angles are given in Table 2 and 3 respectively, which are calculated after geometry optimization of molecule from Arguslab by using molecular mechanics calculation. Tables 4 and 5 show the Mulliken atomic charges, ZDO atomic charges and the calculated energy of lenalidomide respectively.

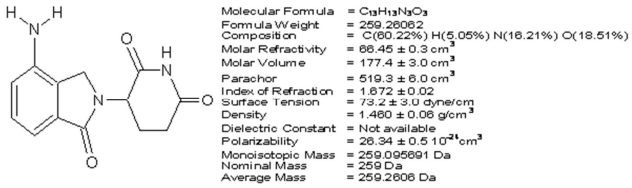

Figure 1. Prospective view of lenalidomide by ACD/Chemsketch.

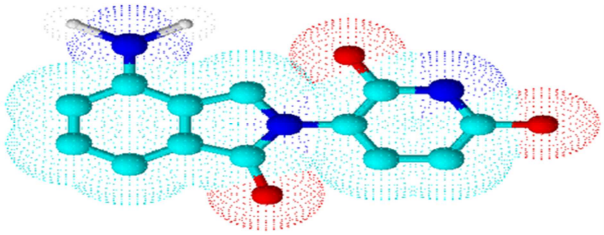

Figure 2. Electron density clouds of lenalidomide by ACDlabs 3D Viewer.

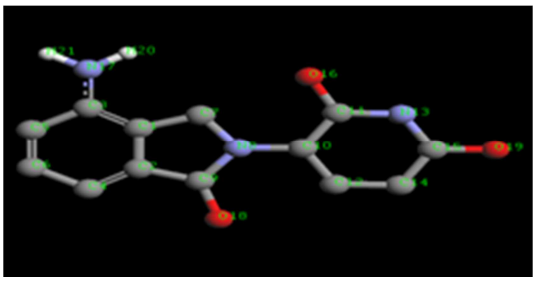

Figure 3. Prospective view of active conformation of lenalidomide by Arguslab software.

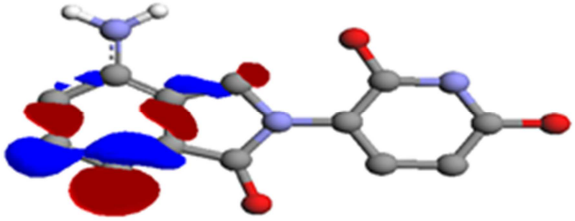

Figure 4. Highest occupied molecular orbital's (HOMO) of lenalidomide.

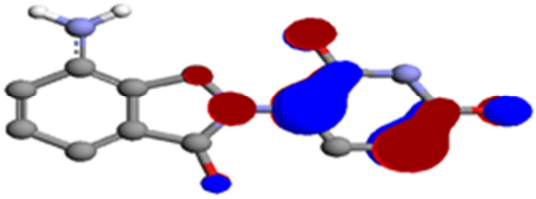

Figure 5. Lowest unoccupied molecular orbital's (LUMO) of lenalidomide.

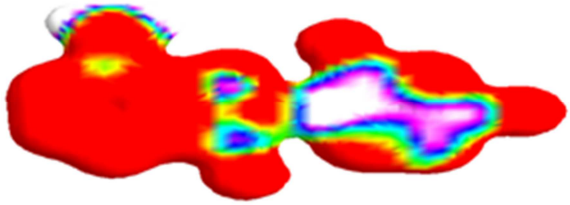

Figure 6. Electrostatic potential mapped density of lenalidomide.

Table 1. Atomic coordinates of lenalidomide.

S.NO	Atoms	X	Y	Z
1	C	18.281600	-17.410200	0.000000
2	C	18.281600	-18.740200	0.000000
3	C	17.129700	-16.745200	0.000000
4	C	17.129700	-19.405200	0.000000
5	C	15.977900	-17.410200	0.000000
6	C	15.977900	-18.740200	0.000000
7	C	19.546500	-16.999200	0.000000
8	N	20.328200	-18.075200	0.000000
9	C	19.546600	-19.151200	0.000000
10	C	21.658200	-18.075100	0.000000
11	C	22.323100	-16.923300	0.000000
12	C	22.323300	-19.226900	0.000000
13	N	23.653200	-16.923300	0.000000
14	C	23.653200	-19.226800	0.000000
15	C	24.318200	-18.075000	0.000000
16	O	21.658100	-15.771500	0.000000
17	N	17.129700	-15.415200	0.000000
18	O	19.957700	-20.416100	0.000000
19	O	25.648200	-18.075000	0.000000
20	H	18.281500	-14.750200	0.000000
21	H	15.977800	-14.750200	0.000000

Table 2. Bond length of lenalidomide.

Atoms	Bond length
(C1)-(C3)	1.323387
(C1)-(C7)	1.458000
(C1)-(C2)	1.458000
(C2)-(C4)	1.323387
(C2)-(C9)	1.458000
(C3)-(C5)	1.458000
(C3)-(N17)	1.343384
(C4)-(C6)	1.458000
(C5)-(C6)	1.323387
(C7)-(N8)	1.433804
(N8)-(C9)	1.433804
(N8)-(C10)	1.433804
(C9)-(O18)	1.407689
(C10)-(C11)	1.458000
(C10)-(C12)	1.458000
(C11)-(N133)	1.433804
(C11)-(O16)	1.407689
(C12)-(C14)	1.458000
(N13)-(C15)	1.433804
(C14)-(C15)	1.458000
(C15)-(O19)	1.407689
(N17)-(H20)	1.048529
(N17)-(H21)	1.048529

Table 3. Bond angles of lenalidomide.

Atoms	Bond angle	Alternate angle
(C3)-(C1)-(C7)	120.000000	216.488007
(C3)-(C1)-(C2)	120.000000	216.488007
(C1)-(C3)-(C5)	120.000000	216.488007
(C1)-(C3)-(N17)	120.000000	327.778708
(C7)-(C1)-(C2)	120.000000	188.442082
(C1)-(C7)-(N8)	120.000000	257.053574
(C1)-(C2)-(C4)	120.000000	216.488007
(C1)-(C2)-(C9)	120.000000	188.442082
(C4)-(C2)-(C9)	120.000000	216.488007
(C2)-(C4)-(C6)	120.000000	216.488007
(C2)-(C9)-(N8)	120.000000	257.053574
(C2)-(C9)-(O18)	120.000000	238.736810
(C5)-(C3)-(N17)	120.000000	282.167276
(C3)-(C5)-(C6)	120.000000	216.488007
(C3)-(N17)-(H20)	120.000000	124.657989
(C3)-(N17)-(H21)	120.000000	124.657989
(C4)-(C6)-(C5)	120.000000	216.488007
(C7)-(N8)-(C9)	120.000000	198.144139
(C7)-(N8)-(C10)	120.000000	198.144139
(C9)-(N8)-(C10)	120.000000	198.144139
(N8)-(C9)-(O18)	120.000000	325.928547
(N8)-(C10)-(C11)	120.000000	257.053574
(N8)-(C10)-(C12)	120.000000	257.053574
(C11)-(C10)-(C12)	120.000000	188.442082
(C13)-(C11)-(N10)	120.000000	257.053574
(C10)-(C11)-(O16)	120.000000	238.736810
(C10)-(C12)-(C14)	120.000000	188.442082
(N13)-(C11)-(O16)	120.000000	325.928547
(C11)-(N13)-(C15)	120.000000	198.144139
(C12)-(C14)-(C15)	120.000000	188.442082
(N13)-(C15)-(C14)	120.000000	257.053574
(N13)-(C15)-(O19)	120.000000	325.928547
(C14)-(C15)-(O19)	120.000000	238.736810
(H20)-(N17)-(H21)	120.000000	70.257681

Table 4. Mulliken atomic charges and ZDO atomic charges of lenalidomide using ArgusLab software.

S.No	Atoms	ZDO Atomic Charges	Mulliken Atomic charges
1	C	1.3703	1.3450
2	C	3.3817	3.6134
3	C	-3.9955	-4.0669
4	C	-2.7232	-2.9049
5	C	-3.9999	-4.0011
6	C	-3.9997	-4.0074
7	C	3.9713	4.0208
8	N	4.9999	5.0003
9	C	3.9951	4.0036
10	C	3.9733	4.0624
11	C	-0.4508	-0.4988

S.No	Atoms	ZDO Atomic Charges	Mulliken Atomic charges
12	C	2.0078	2.0333
13	N	-2.9982	-3.0164
14	C	-3.9956	-4.0500
15	C	-3.9998	-4.0010
16	O	2.4634	2.4700
17	N	-2.9999	-3.0005
18	O	5.9998	5.9998
19	O	-2.0000	-2.0000
20	H	-0.9999	-1.0018
21	H	-1.0000	-1.0000

Table 5. Final steric energy evaluation.

S.No.	Force field	Energy components (au)
1	Molecular mechanics bond (Estr)	0.00361028
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.05773504
3	Molecular mechanics dihedral (Etor)	-0.00000000
4	Molecular mechanics ImpTor (Eoop)	0.00000000
5	Molecular mechanics vdW (EVdW)	0.02584798
6	Molecular mechanics coulomb (Eqq)	0.00000000
Total	0.08719330 a.u. (54.71467396 kcal/mol)	

Arguslab software was used to see what happened to the electrons in lenalidomide when it absorbed light. Surfaces were made to explore this fascinating phenomenon. When lenalidomide absorbed 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 interested in molecules that are useful as dyes, sunscreens, etc [14, 17]. The HOMO is localized to the plane of the molecule and is a non-bonding molecular orbital (Figure 4). The LUMO is perpendicular to the plane of the molecule and is a combination of the p_z atomic orbitals (Figure 5). 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 [14, 17]. 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 [14, 17]. QuickPlot ESP mapped density generates an electrostatic potential map on the total electron density contour of the molecule (Figure 6). The electron density surface depicts locations around the molecule where the electron probability density is equal [14, 17]. 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 [14. 17]. These images show that the triple and double bonded end of the molecule is electron rich relative to the single bonded end [14. 17].

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 [18].

4. Conclusion

The most energetically favourable conformation of 3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione (lenalidomide) was found to have a heat of formation of 60957.4618 kcal/mol via use of the Argus Lab software. The present work indicates thatthe best conformation of lenalidomide was found to be at -23.1075767148 au (-14500.2364 kcal/mol) which is the minimum potential energy by using Argus Lab software. At this point lenalidomide, will bemore active as an anticancer agent.Finally all geometric variables were completely optimized and the lowestenergy conformations were used in molecular modelling studies. The optimized geometries, Mulliken atomic charges and ZDO atomic charges were calculated. The modelling and the calculations does not only presented to us the opportunity to takea critical look at this novel compound but has also given us the opportunity to compile fundamentalresult on properties that cannot be calculated in the laboratory.

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