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In silico Conformational Analysis and Excited – State Properties of a Highly Potent Antitumor Agent 5-[(1e)-3,3-dimethyltriaz-1-en-1-yl]-1h-imidazole-4-carbaldehyde (Dacarbazine)

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Abstract

Dacarbazine (5-[(1*E*)-3,3-dimethyltriaz-1-en-1-yl]-1*H*-imidazole-4-carbaldehyde) is a member of the class of alkylating agents, which destroy cancer cells by adding an alkyl group to its DNA of the receptor. Conformational analysis and geometry optimization of dacarbazine was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. Molecular mechanics calculations were based on specific interactions within the molecule. These interactions included stretching or compressing of bond beyond their equilibrium lengths and angles. Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's (HOMO), lowest unocupied molecular orbital's (LUMO) and electrostatic potentials (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 -77.651300 au (-48726.970800 kcal/mol).

Keywords

Dacarbazine, Molecular Mechanics, Arguslab Software, Cancer

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1. Introduction

5-[(1*E*)-3,3-dimethyltriaz-1-en-1-yl]-1*H*-imidazole-4-carbaldehyde (dacarbazine) has served as the therapeutic standard in patients with inoperable metastatic melanoma, despite the fact that a survival benefit by this drug has never been demonstrated in clinical trials, making its effectiveness still a matter of doubt [1]. Nevertheless, until recently, other treatment regimens tested against dacarbazine in clinical phase-III trials failed to demonstrate superiority in patient survival [2]. Fortunately, It has been reported that chemotherapeutic agents can strengthen antitumor immune responses either by attenuating the immune suppression exerted by T regulatory cells or myeloid-derived suppressor cells, or by enhancing activation of dendritic cells (DCs) [3]. Dacarbazine is a member of the class of alkylating agents, which destroy cancer cells by adding an alkyl group to the DNA of the receptor [4]. Dacarbazine is bioactivated in liver by demethylation to diazomethane, which is an alkylating agent. Like many chemotherapy drugs, dacarbazine may have numerous serious side effects, because it interferes with normal cell growth as well as cancer cell growth [1, 4] among the most serious possible side effects are birth defects to children conceived or carried during treatment; sterility, possibly permanent; or immune suppression (reduced ability to fight infection or disease).

The energies computed by molecular mechanics are usually conformational energies. This means that the energy

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computed is meant to be an energy that will reliably predict the diference in energy from one conformation to the next. The effect of strained bond lengths or angles is also included in this energy. This is not the same as the total energies obtained from ab initio programs or the heat of formation from semiempirical programs. Molecular mechanics methods are not generally applicable to structures very far from equilibrium, such as transition structures [5]. Arguslab [5] 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 [6] Conformational analysis of molecule is based on molecular mechanics, it is a method for the calculation of molecular structures, conformational energies and other molecular properties using concept from classical mechanics. The energy (E) of the molecule is calculated as a sum of terms as in equation (1).

$$E = E_{stretching} + E_{bending} + E_{torsion} + E_{Vander\ Waals} + E_{electrostatic} + E_{hydrogen\ bond} + \text{cross term} \quad \text{(Equation 1)}$$

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 force field [7].

We hereby present, *in silico* conformational analysis and excited – state properties of a highly potent antitumor agent 5-[(1*E*)-3,3-dimethyltriaz-1-en-1-yl]-1*H*-imidazole-4-carbaldehyde (dacarbazine).

2. Materials and Methods

The three dimensional quantitative structure activity relationships describe the biological activity of molecule with pharmacological potential as a function of their structural properties [8-9]. Chemiformatics have generated many tools which are widely used to construct models, minimization and representations of molecular structure [10-12]. All conformational analysis (geometry optimization) study was performed on a window based computer using Arguslab [5] and ACD Lab Chem Sketch software's. The 5-[(1*E*)-3,3-dimethyltriaz-1-en-1-yl]-1*H*-imidazole-4-carbaldehyde (dacarbazine) structure was generated by Argus lab [5], and minimization was performed with the semi-empirical Austin Model 1 (AM1) parameterization [13]. The minimum potential energy was calculated by using geometry convergence function in Arguslab software. 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 [14]. Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's (HOMO), lowest unocupied molecular orbital's (LUMO) and electrostatic potentials (ESP) mapped density. The minimum potential energy was also calculated for drug- receptor interaction through the geometry convergence function.

3. Results and Discussion

Prospective view and calculated properties of dacarbazine molecule is shown in Figure1. Electron density cloud by ACDlabs-3D viewer software and the active conformation of dacarbazine are shown in Figure 2 and 3 respectively. Figure 4 and 5 shows the highest occupied molecular orbital of dacarbazine (HOMO) and the lowest unoccupied molecular orbital (LUMO) respectively. Figure 6 shows electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state. Atomic coordinates of dacarbazine 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, 5 and 6 shows the dihedral angles, Mulliken atomic charges, ZDO atomic charges and steric energy of dacarbazine respectively. Ground state dipole (debye) of dacarbazine is shown in Table 7. The self-consistent field energy of dacarbazine is shown in Table 8.

Excited state properties: ArgusLab was used to see what happened to the electrons in dacarbazine when it absorbed light. Surfaces were made to explore this fascinating phenomenon. Dacarbazine 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 interested in molecules that are useful as dyes, sunscreens, etc [5]. 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 pz atomic orbitals. 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 [5]. 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 [5]. 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 [5]. This gives an idea of the size of the molecule and its susceptibility to electrophilic attack. Electron density surface of dacarbazine using AM1 geometry which shows the complete surface with the color map. 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 [5]. These images show that the triple and double bonded end of the molecule is electron rich relative to the single bonded end [5].

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 [15]. The final SCF energy of dacarbazine was found to be -77.651300 au (- 48726.970800 kcal/mol). It should be noted that the Mulliken charges do not reproduce the electostatic potentials of a molecule very well. Mulliken charges were calculed by determining the electron population of each atom as defined by the basis functions [16]. List of Mulliken atomic charges and ZDO atomic charges of dacarbazine is shown in Table 5.

The standard heat of formation of a compound is the enthalpy change for the formation of 1 mole of the compound from its constituent elements in their standard states at 1 atmosphere. Its symbol is ΔHfθ. The most energetically favourable conformation of dacarbazine was found to have a heat of formation of 40251.609600 kcal/mol via use of the Argus Lab software [5]. The steric energy calculated for dacarbazine was 0.06602414 a.u (41.43081025 kcal/mol).

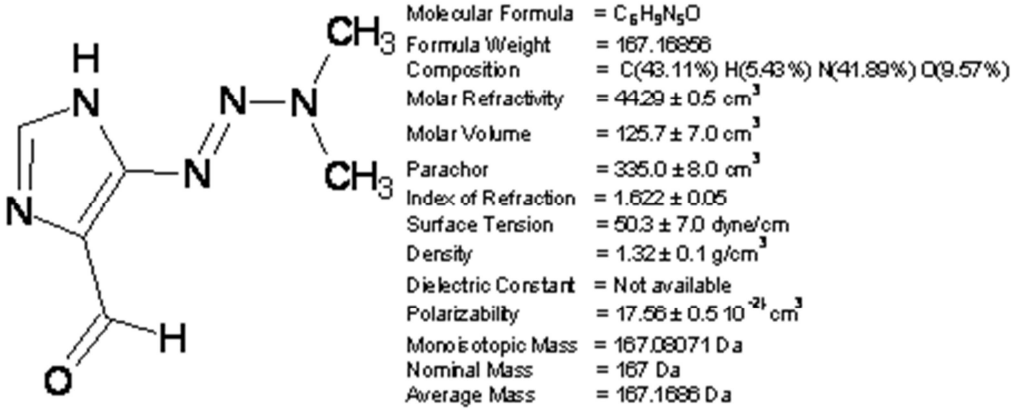

Figure 1. Prospective view of dacarbazine by ACD/ChemSketch.

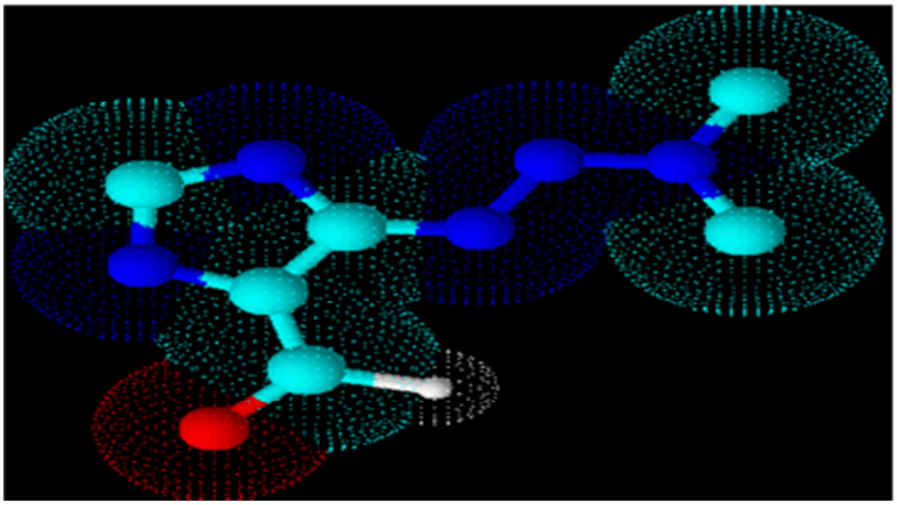

Figure 2. Electron density clouds of dacarbazine by ACDLabs 3D viewer.

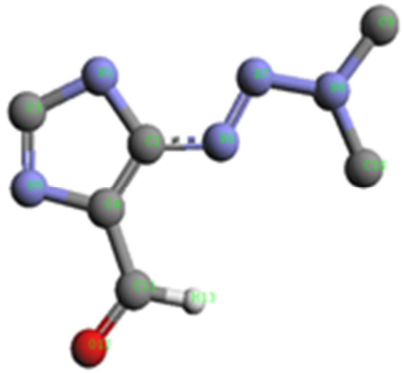

Figure 3. Prospective view of active conformation of dacarbazine by Arguslab software.

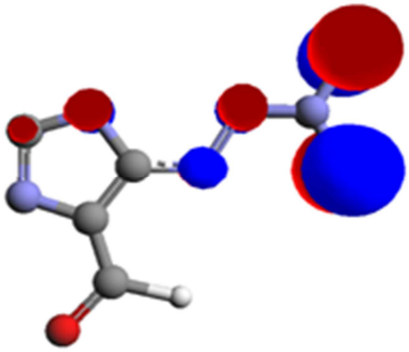

Figure 4. Highest occupied molecular orbital's (HOMO) of dacarbazine

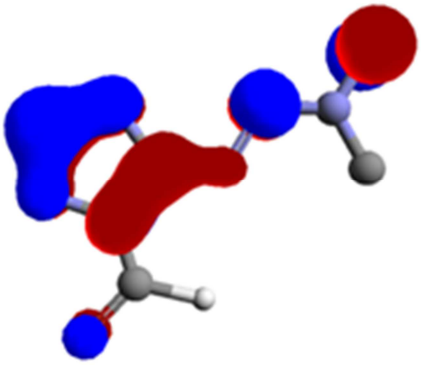

Figure 5. Lowest unoccupied molecular orbital's (LUMO) of dacarbazine

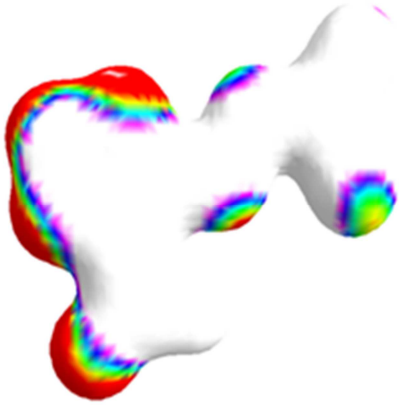

Figure 6. Electrostatic potential mapped density of dacarbazine

Table 1. Atomic coordinates of dacarbazine.

S.NO	Atoms	X	Y	Z
1	N	18.209300	-11.956200	0.000000
2	C	18.970400	-13.046900	0.000000
3	C	16.936800	-12.343000	0.000000
4	C	18.168300	-14.107800	0.000000
5	N	16.911500	-13.672900	0.000000
6	N	20.300200	-13.072200	0.000000
7	N	20.987000	-11.933300	0.000000
8	N	22.316800	-11.958700	0.000000
9	C	23.003600	-10.819700	0.000000
10	C	22.959700	-13.123000	0.000000
11	C	18.555200	-15.380300	0.000000
12	O	17.646700	-16.351600	0.000000
13	H	19.850700	-15.681500	0.000000

Table 2. Bond length of dacarbazine.

S.NO	Atoms	Bond length
1	(N1)-(C2)	1.433804
2	(N1)-(C3)	1.433804
3	(C2)-(C4)	1.323387
4	(C2)-(N6)	1.343384
5	(C3)-(N5)	1.301961
6	(C4)-(N5)	1.433804
7	(4C)-(C11)	1.461000
8	(N6)-(N7)	1.257127
9	(N7)-(N8)	1.385000
10	(N8)-(C9)	1.422764
11	(N8)-(C10)	1.422764
12	(C11)-(O12)	1.282404
13	(C11)-(H13)	1.087584

Table 3. Bond angles of dacarbazine.

Atoms	Bond angles	Alternate angles
(C2)-(N1)-(C3)	120.000000	198.144139
(N1)-(C2)-(C4)	120.000000	295.980973
(N1)-(C2)-(N6)	120.000000	385.642256
(N1)-(C3)-(N5)	120.000000	402.764879
(C4)-(C2)-(N6)	120.000000	327.778708
(C2)-(C4)-(N5)	120.000000	295.980973
(C2)-(C4)-(C11)	120.000000	215.760874
(C2)-(N6)-(N7)	120.000000	352.998197
(C3)-(N5)-(C4)	120.000000	227.506158
(N5)-(C4)-(C11)	120.000000	256.249137
(C4)-(C11)-(O12)	120.000000	270.718789
(C4)-(C11)-(H13)	120.000000	102.216529
(N6)-(N7)-(N8)	106.700000	609.097358
(N7)-(N8)-(C9)	120.000000	280.792562
(N7)-(N8)-(C10)	120.000000	280.792562
(C9)-(N8)-(C10)	120.000000	202.792364
(O12)-(C11)-(H13)	120.000000	155.854511

Table 4. Dihedral angles of dacarbazine.

atoms	Dihedral angles
(C4)-(C2)-(N1)-(C3)	5.000000 2
(N6)-(C2)-(N1)-(C3)	5.000000 2
(C2)-(N1)-(C3)-(N5)	10.000000 2
(N1)-(C2)-(C4)-(N5)	9.743388 2
(N1)-(C2)-(C4)(C11)	9.743388 2
(N1)-(C2)-(N6)-(N7)	13.474221 2
(N1)-(C3)-(N5)-(C4)	38.973552 2
(N5)-(C4)-(C2)-(N6)	9.743388 2
(C11)-(C4)-(C2)(N6)	9.743388 2
(C4)-(C2)-(N6)-(N7)	13.474221 2
(C2)-(C4)-(N5)-(C3)	5.000000 2
(C2)-(C4)(C11)(O12)	2.500000 2
(C2)-(C4)(C11)(H13)	2.500000 2
(C2)-(N6)-(N7)-(N8)	2.000000 3
(C3)-(N5)-(C4)(C11)	5.000000 2
(N5)(C4)(C11)(O12)	2.500000 2
(N5)(C4)(C11)(H13)	2.500000 2
(N6)-(N7)-(N8)-(C9)	1.000000 3
(N6)-(N7)-(N8)(C10)	1.000000 3

Table 5. List of Mulliken atomic charges and ZDO atomic charges of dacarbazine using ArgusLab software.

S/NO	Atoms	ZDO Atomic charges	Mulliken Atomic charges
1	N	0.0114	0.0017
2	C	-2.6031	-2.9194
3	C	3.9669	4.0066
4	C	3.6588	3.9604
5	N	4.9858	4.9821
6	N	-2.9998	-3.0108
7	N	-3.0000	-3.0003
8	N	-3.0000	-3.0000
9	C	-4.0000	-4.0000
10	C	-4.0000	-4.0000
11	C	3.6331	3.9592
12	O	4.0899	4.0438
13	H	-0.7429	-1.0232

Table 6. Final energy evaluation.

S.No.	Force field	Energy components (au)
1	Molecular mechanics bond (Estr)	0.00069946
2	Molecular mechanics angle (Ebend) + (Estr-bend)	0.05515614
3	Molecular mechanics dihedral (Etor)	0.00159360
4	Molecular mechanics ImpTor (Eoop)	0.00000000
5	Molecular mechanics vdW (EVdW)	0.00857494
6	Molecular mechanics coulomb (Eqq)	0.00000000
Total	0.06602414 a.u (41.43081025 kcal/mol.)	

Table 7. Ground state dipole (debye).

X	Y	Z	length
-390.44206786	-190.97140292	-0.00000000	434.64362998

Table 8. Self-consistent field energy (SCF) of (dacarbazine).

Cycle	Energy (au)	Difference
1	-42.905891	
2	-57.688289930	-14.7824
3	-51.760326743	5.92796
4	-66.055133540	-14.2948
5	-67.021306456	-0.966173
6	-68.632427725	-1.61112
7	-69.639443827	-1.00702
8	-70.526751852	-0.887308
9	-72.827196808	-2.30044
10	-74.959317274	-2.13212
11	-75.569029356	-0.609712
12	-76.016184618	-0.447155
13	-76.293585974	-0.277401
14	-77.042422869	-0.748837
15	-76.485381536	0.557041
16	-76.763256982	-0.277875
17	-77.037277815	-0.274021
18	-77.096364279	-0.0590865
19	-77.255867501	-0.159503
20	-77.388215536	-0.132348
21	-77.358232889	0.0299826
22	-77.424364589	-0.0661317
23	-77.474062421	-0.0496978
24	-77.434765746	0.0392967
25	-77.478325628	-0.0435599
26	-77.509603391	-0.0312778
27	-77.513553486	-0.00395009
28	-77.525276448	-0.011723
29	-77.552730333	-0.0274539
30	-77.480765377	0.071965
31	-77.545513878	-0.0647485
32	-77.571693710	-0.0261798
33	-77.582399033	-0.0107053
34	-77.593385499	-0.0109865
35	-77.613542491	-0.020157
36	-77.625132426	-0.0115899
37	-77.634814893	-0.00968247
38	-77.640272565	-0.00545767
39	-77.643643961	-0.0033714
40	-77.645821223	-0.00217726
41	-77.647163485	-0.00134226
42	-77.648125402	-0.000961917
43	-77.648860485	-0.000735083
44	-77.649393500	-0.000533015
45	-77.649858793	-0.000465293
46	-77.650203043	-0.00034425
47	-77.650456584	-0.000253542
48	-77.650646212	-0.000189628
49	-77.650807180	-0.000160968
50	-77.650925124	-0.000117944
51	-77.651014574	-8.94496e-005
52	-77.651082443	-6.78691e-005
53	-77.651133987	-5.15437e-005
54	-77.651173182	-3.91949e-005
55	-77.651203030	-2.98478e-005
56	-77.651225794	-2.27646e-005
57	-77.651243183	-1.73889e-005
58	-77.651256485	-1.33023e-005

Cycle	Energy (au)	Difference
59	-77.651266676	-1.01905e-005
60	-77.651274493	-7.81684e-006
61	-77.651280496	-6.00335e-006
62	-77.651285112	-4.61567e-006
63	-77.651288664	-3.55231e-006
64	-77.651291400	-2.73639e-006
65	-77.651293510	-2.10958e-006
66	-77.651295138	-1.62753e-006
67	-77.651296394	-1.25645e-006
68	-77.651297365	-9.70527e-007
69	-77.651298115	-7.50055e-007
70	-77.651298695	-5.79932e-007
71	-77.651299143	-4.48574e-007
72	-77.651299490	-3.47093e-007
73	-77.651299759	-2.68657e-007
74	-77.651299967	-2.08001e-007
75	-77.651300128	-1.61081e-007
76	-77.651300253	-1.24772e-007
77	-77.651300349	-9.66659e-008
78	-77.651300424	-7.49031e-008
79	-77.651300482	-5.80503e-008
80	-77.651300527	-4.49936e-008
81	-77.651300562	-3.48777e-008
82	-77.651300589	-2.70398e-008
83	-77.651300610	-2.09655e-008
84	-77.651300626	-1.62553e-008
85	-77.651300639	-1.26055e-008
86	-77.651300649	-9.77451e-009
87	-77.651300656	-7.5824e-009
88	-77.651300662	-5.87937e-009
89	-77.651300667	-4.56055e-009
90	-77.651300670	-3.5381e-009
91	-77.651300673	-2.74343e-009
92	-77.651300675	-2.12805e-009
93	-77.651300677	-1.65068e-009
94	-77.651300678	-1.28085e-009
95	-77.651300679	-9.9368e-010
96	-77.651300680	-7.70569e-010
97	-77.651300681	-5.9805e-010
98	-77.651300681	-4.63444e-010
99	-77.651300681	-3.60387e-010
100	-77.651300682	-2.77907e-010
101	-77.651300682	-2.17369e-010
102	-77.651300682	-1.6837e-010
103	-77.651300682	-1.29717e-010
104	-77.651300682	-1.0084e-010
105	-77.651300682	-7.88987e-011
106	-77.651300682	-6.10498e-011
107	-77.651300682	-4.74074e-011
108	-77.651300683	-3.60956e-011
109	-77.651300683	-2.88196e-011
110	-77.651300683	-2.143e-011
111	-77.651300683	-1.68825e-011
112	-77.651300683	-1.3813e-011
113	-77.651300683	-1.03455e-011
114	-77.651300683	-8.29914e-012
115	-77.651300683	-6.42331e-012
116	-77.651300683	-4.60432e-012
117	-77.651300683	-3.63798e-012
118	-77.651300683	-2.44427e-012
119	-77.651300683	-2.27374e-012
120	-77.651300683	-1.64846e-012
121	-77.651300683	-1.81899e-012
122	-77.651300683	-7.95808e-013
123	-77.651300683	-1.47793e-012
124	-77.651300683	5.11591e-013
125	-77.651300683	-1.42109e-012
126	-77.651300683	-2.27374e-013
127	-77.651300683	-1.13687e-013

4. Conclusion

Arguslab software was used to study a highly potent antitumor agent, 5-[(1*E*)-3,3-dimethyltriaz-1-en-1-yl]-1*H*-imidazole-4-carbaldehyde (dacarbazine).The excited state properties such as highest occupied molecular orbital's (HOMO), lowest unoccupied molecular orbital's (LUMO), and electrostatic potential mapped density were created. The molecular mechanics potential energy(steric energy), heat of formation and self-consistent field (SCF) energy were calculated.

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