Computational study on the geometry optimization and excited –State properties 4-[(2-methylhydrazinyl)methyl]-*N*-(propan-2-yl)benzamide (Procabazime) by ArgusLab 4.0.1 software

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ABSTRACT:4-[(2-methylhydrazinyl)methyl]-*N*-(propan-2-yl)benzamide (procarbazine) is used in the treatment of many cancers including Hodgkin's lymphomas, non-Hodgkin's lymphoma, brain tumors, multiple myeloma, primary central nervous system lymphoma, malignant melanoma, and lung cancer. Conformational analysis and geometry optimization of procarbazine was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. Heat of Formation of procarbazine was 49425.1257 kcal/mol, the steric energy calculated for procarbazine was 0.02754298 a.u. (17.28349595 kcal/mol) and SCF energy was found to be -12.3475276063 au (-7748.1975 kcal/mol),which isthe most feasible position for the drug to interact with the receptor.

Keywords: *Procarbazine, Molecular mechanics, Arguslab software.*

1. INTRODUCTION

An anticancer drug such as 4-[(2-methylhydrazinyl)methyl]-*N*-(propan-2-yl)benzamide (procarbazine) used in the treatment of many cancers including Hodgkin's lymphomas, non-Hodgkin's lymphoma, brain tumors, multiple myeloma, primary central nervous system lymphoma, malignant melanoma, and lung cancer. This is an oral alkylating agent that belongs to the same family as dacarbazine and hexamethylamine (Zeller *et al.,* 1963). It contains an N-methyl group that is essential for its activity (Newell *et al.,* 1987). It was first synthesized during a search for a new monoamine oxidase inhibitor, but was soon developed as an anticancer agent (Kenis*et al.,* 1966; Martin and Schubert 1966; Livingston and Carter 1970; Friedman 2001).

The introduction of safer combination therapies led to the gradual supplantation of procarbazine. During recent years, there has been a re-emergence of interest in procarbazine combinations with other chemotherapeutic agents, specifically for the treatment of Hodgkin's lymphoma and gliomas and, to a lesser extent, non-Hodgkin's lymphoma and primary central nervous system lymphoma. This is partly prompted by the unique mechanism of action of procarbazine; this agent has multiple sites of action and is not cross-resistant with other alkylating agents, cytostatics or radiotherapy (Brunner and Young ,1965).

The geometry of a molecule has a great impact on its energy level and physical and chemical properties. As the molecule rotates, it adopts different conformations and spatial arrangements to achieve one of the stable states of *lowest energy* (Crowder, 1986). The total molecular energy can be evaluated in terms of potential energy surface as a sum of energies associated with each type of bonded interactions i.e. bond length, bond angle and dihedral angle as well as non-bonded interactions (van der Waals and electrostatic) taking place in a molecule and on atomic properties of a molecule (Cramer, 2004). The present work describes the computer aided geometry optimization (active conformation) and calculation of excited state properties of Bicalutamide by ArgusLab

4.0.1 software (Thompson., 2004).

MATERIALS AND METHODS

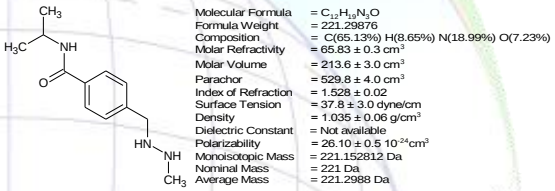
procarbazine structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). The procarbazine structure was generated by Argus lab, and minimization was performed with UFF molecular mechanics method (Dunn et al., 1998; Gerorge*et al.,* 1995; Crucian*iet al.,* 1998). The minimum potential energy was calculated using geometry convergence function in Argus lab software. Surfaces created to visualize ground state properties as well as excited state propertiessuch as orbital, electron densities, electrostatic potentials (ESP) spin densities and generated the grid data were used to make molecular orbital surfaces and electro static potential mapped on electron density surface(Simons *et al.,* 1983; Csizmadia., 2001). The minimum potential energy was calculated for Procarbazine through the geometry convergence map (Martin *et al.,* 1998). Mulliken Atomic Charges , ZDO Atomic Charges of Procarbazine and Ground State Dipole (debye) of 4-[(2-methylhydrazinyl)methyl]-*N*-(propan-2-yl)benzamideProcarbazinewere determined using AM1 method(Dewer et al 1985).

RESULTS AND DISCUSSION

Fractional coordination of procarbazine molecule is given in Table1. Bond length and bond angles are given in table 2 and 3 respectively, which are calculated after geometry optimization of molecule from ARGUS LAB by using molecular mechanics calculation. Tables 4 show the Mulliken Atomic Charges, ZDO Atomic Charges of procarbazine. Table 6, shows calculated energy of procarbazine molecule.

Heat of Formation of procarbazine was 49425.1257 kcal/mol,The steric energy calculated for procarbazine was 0.02754298 a.u. (17.28349595 kcal/mol) and SCF energy was found to be -12.3475276063 au (-7748.1975 kcal/mol) as calculated by RHF/ AM1 method, as performed by ArgusLab 4.0.1 suite.

Prospective view and calculated properties of procarbazine molecule IS shown in figure1. The active conformation and electron density mapped of procarbazine by ACDLABS-3D viewer software are shown in figure 3 and 2 respectively. Figure 6 shows Electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state, Thecolor 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. Figure 4 and 5 shows the highest occupied molecular orbital of molecule (HOMO) and the lowest unoccupied molecular orbital (LUMO) respectively, The positive and negative phases of the orbital are represented by two colors, the blue regions represent an increase in electron density and the red regions shows a decrease in electron density.



4-[(2-methylhydrazinyl)methyl]-*N*-(propan-2-yl)benzamide

Figure 1: Prospective view of procabarzine by ACD/ChemSketch.

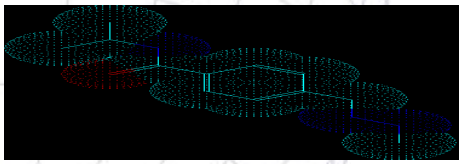


Figure. 2: Electron density clouds of Procarbazine by ACD Labs. 3D viewer.

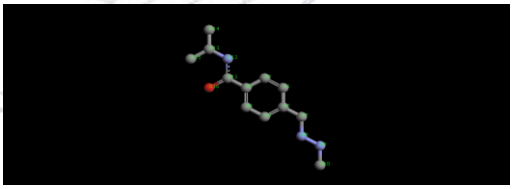


Figure 3: Prospective view of active conformation of Procarbazine by Arguslab Software.

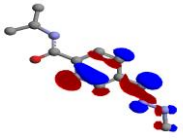


Figure 4: Highest occupied molecular orbital's (HOMO) of Procarbazine.

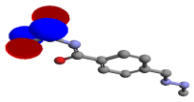


Figure 5: Lowest unoccupied molecular orbital's (LUMO) of Procarbazine.

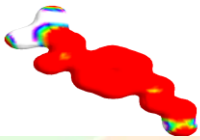


Figure 6: Electrostatic potential mapped density of Procarbazine.

Table 1: Atomic coordinates of Procarbazine.

S.NO	Atoms	X	Y	Z
1	C	21.149900	-12.522800	0.000000
2	C	21.149900	-13.852800	0.000000
3	C	19.998000	-11.857800	0.000000
4	C	19.998000	-14.517800	0.000000
5	C	18.846200	-12.522800	0.000000
6	C	18.846200	-13.852800	0.000000
7	C	22.301700	-14.517900	0.000000
8	N	22.301700	-15.847900	0.000000
9	N	23.453500	-16.512900	0.000000
10	C	23.453400	-17.842900	0.000000
11	C	17.694400	-11.857800	0.000000
12	N	17.694400	-10.527800	0.000000
13	C	16.542600	-9.862800	0.000000
14	C	16.542600	-8.532800	0.000000
15	C	15.390800	-10.527800	0.000000
16	O	16.542600	-12.522800	0.000000

Table 2: Bond length of Procarbazine.

Atoms	Bond length
(C1)-(C2)	1.458000
(C1)-(3C)	1.323387
(C2)-(C4)	1.323387
(C2)-(C7)	1.461000
(C3)-(C5)	1.458000
(C4)-(C6)	1.458000
(C5)-(C6)	1.323387
(C5)-(C11)	1.461000
(C7)-(N8)	1.422764
(N8)-(N9)	1.370000
(N9)-(C10)	1.422764
(C11)-(N12)	1.346235
(C11)-(O16)	1.260307
(N12)-(C13)	1.422764
(C13)-(C14)	1.464000
(C13)-(C15)	1.464000

Table 3: Bond angles of Procarbazine.

Atoms	Bond angles	Alternate angles
(C2)-(C1)-(C3)	120.000000	216.488007
(C1)-(C2)-(C4)	120.000000	216.488007
(C1)-(C2)-(C7)	120.000000	187.861407
(C1)-(C3)-(C5)	120.000000	216.488007
(C4)-(C2)-(C7)	120.000000	215.760874
(C2)-(C4)-(C6)	120.000000	216.488007
(C2)-(C7)-(N8)	120.000000	259.173826
(C3)-(C5)-(C6)	120.000000	216.488007
(C3)-(C5)-(C11)	120.000000	187.861407
(C4)-(C6)-(C5)	120.000000	216.488007
(C6)-(C5)-(C11)	120.000000	215.760874
(C5)-(C11)-(N12)	120.000000	280.407604
(C5)-(C11)-(O16)	120.000000	276.934658
(C7)-(N8)-(N9)	120.000000	285.276039
(N8)-(N9)-(C10)	120.000000	285.276039
(N12)-(C11)-(O16)	120.000000	421.698151
(C11)-(N12)-(C13)	120.000000	219.857183
(N12)-(C13)-(C14)	120.000000	258.357159
(N12)-(C13)-(C15)	120.000000	258.357159
(C14)-(C13)-(C15)	120.000000	186.134654

Table 4: List of Mulliken Atomic Charges and ZDO Atomic Charges of Procarbazine. Using ArgusLab software

S.NO	Atoms	ZDO atomic charges	Mulliken atomic charges
1	C	3.9807	4.0057
2	C	1.7207	1.8046
3	C	3.9994	4.0007
4	C	2.3023	2.2386
5	C	3.9963	4.0010
6	C	3.9927	4.0007
7	C	-3.9963	-4.0497
8	N	-3.0000	-3.0005
9	N	-3.0000	-3.0000
10	C	-4.0000	-4.0000
11	C	3.5201	3.7590
12	N	-2.5054	-2.7012
13	C	-3.9995	-4.0088

14	C	-4.0000	-4.0000
15	C	-3.9999	-4.0008
16	O	3.9888	3.9509

Table 5: Final energyevaluation.

S.No.	Force field	Energy components (au)
1	Molecularmechanics bond (Estr)	0.00220558
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.00385851
3	Molecularmechanicsdihedral (Etor)	-0.00000000
4	MolecularmechanicsImpTor (Eoop)	0.00000000
5	MolecularmechanicsvdW (EVdW)	0.02147890
6	Molecularmechanics coulomb (Eqq)	0.00000000
Total		**0.02754298 a.u. 17.28349595 kcal/mol**

Conclusions

The present work indicates that the best conformation of Procarbazine is found to be at -7748.1975 kcal/mol which is the minimum potential energy by using Argus Lab software. At this point cytarabine will be more active as a chemotherapy agent. All geometric variables were completely optimized for each compound and the lowest energy conformations were used in molecular modeling studies.

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