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Theoretical Approach on Structural Aspects of a Potent, Selective, Orally Bioavailable Hedgehog Antagonist, 2-chloro-*N*-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methylsulfonyl)benzamide

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ABSTRACT

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 orbitals, lowest unoccupied molecular orbitals, and electrostatic potential mapped density. The steric energy for 2-chloro-N-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methylsulfonyl)benzamide (vismodegib) was calculated to be 0.54948080 au (344.80472191 kcal/mol). The most energetically favorable conformation of vismodegib was found to have a heat of formation of 1585.2455 kcal/mol. The self-consistent field energy was calculated by geometry convergence function using RHF/AM1 method with a net charge of 0 and valence electron of 124, in ArgusLab software. The most feasible position for vismodegib to act as a highly potent and totally selective orally bioavailable Hedgehog antagonist was found to be −171.973538 au (−107915.121800 kcal mol^{-1}).

Key words: *Vismodegib, Molecular mechanics, ArgusLab software.*

1. INTRODUCTION

2-chloro-*N*-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methylsulfonyl)benzamide (vismodegib) is a potent, selective, orally bioavailable Hedgehog antagonist, which shows remarkable activity against basal cell carcinoma that has metastasized to other parts of the body, relapsed after surgery, or cannot be treated with surgery or radiation [1]. It therapeutic and preventive efficacy is of great value, this is as a result of factors contributing to its exceptionally rapid progress from first-in-human testing to regulatory approval include an acceptable toxicity profile, early recognition of achievement of a biologically effective concentration in the first dose cohort explored, and an early-phase development plan that focused on a disease strongly dependent on the pathway being targeted [2-4]. The substance acts as a cyclopamine-competitive antagonist of the smoothened (SMO) receptor, which is part of the Hedgehog signaling pathway. SMO inhibition causes the transcription factors GLI1 and GLI2 to remain inactive, which prevents the expression of tumor mediating genes within the Hedgehog pathway [5].

This pathway is pathogenetically relevant in more than 90% of basal-cell carcinomas and can be retarded by making some transcription factor to remain inactive [6].

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 such as bond lengths, bond angles, and torsion angles.

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 and can be generated using ArgusLab. ArgusLab 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, and bond angle. Local charges such as Mulliken charges and zero differential overlaps (ZDO) charges can also be generated from ArgusLab using the AM1

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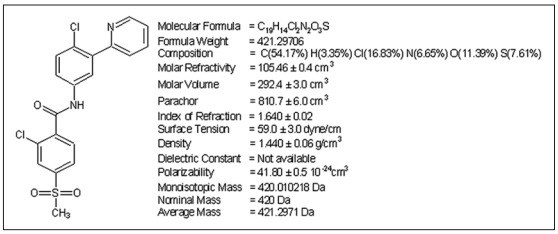

Figure 1: Prospective view of vismodegib by ACD/ Chemsketch.

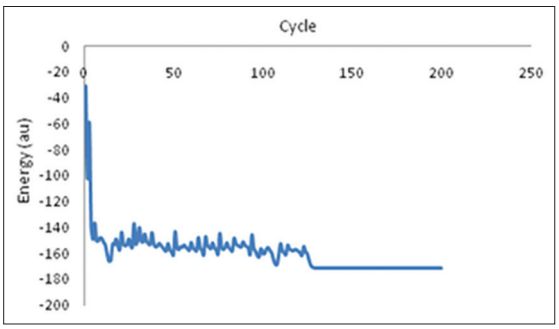

Figure 2: Self-consistent field energy of graph of vismodegib.

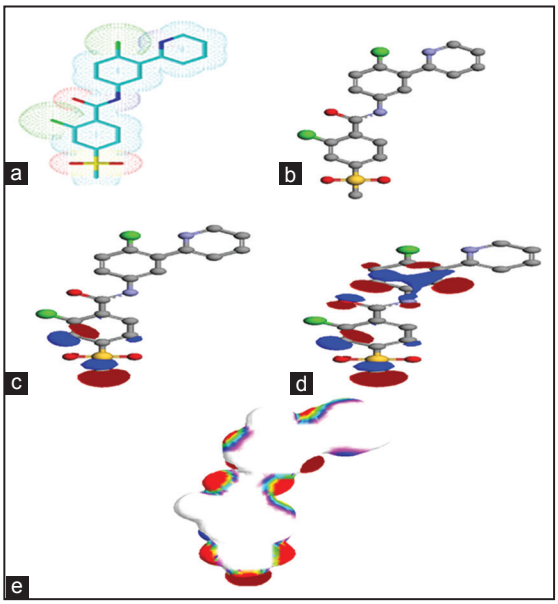

Figure 3: (a) Electron density cloud, (b) active conformation, (c) highest occupied, (d) lowest unoccupied molecular orbitals, (e) electrostatic potential mapped density vismodegib.

parameterized method. In the ZDO approximation, the product of two deferent atomic orbitals is set to zero. The integral which survives the ZDO approximation was partly computed using the uniform charge sphere and the rest parameterized. The result produced is the integrated form of Hückel theory which takes into account electron repulsion [7]. Mulliken charges arise from the Mulliken population analysis and provide a means of estimating partial atomic charges

Table 1: Atomic coordinates of vismodegib.

Atom	X	Y	Z
C	21.726800	−20.534900	0.000000
C	21.726800	−21.864900	0.000000
C	20.574900	−19.869900	0.000000
C	20.574900	−22.529900	0.000000
C	19.423100	−20.534900	0.000000
C	19.423100	−21.864900	0.000000
C	20.574800	−18.539900	0.000000
S	20.574800	−23.859900	0.000000
O	21.904800	−23.859900	0.000000
O	19.244800	−23.859800	0.000000
C	20.574800	−25.189900	0.000000
Cl	18.271300	−19.869900	0.000000
N	21.726600	−17.874900	0.000000
O	19.423000	−17.874900	0.000000
C	21.726600	−16.544900	0.000000
C	20.574800	−15.879900	0.000000
C	22.878500	−15.879800	0.000000
C	20.574800	−14.549800	0.000000
C	22.878500	−14.549800	0.000000
C	21.726600	−13.884800	0.000000
Cl	21.726600	−12.554800	0.000000
C	24.030300	−13.884800	0.000000
N	24.030300	−12.554800	0.000000
C	25.182200	−14.549800	0.000000
C	25.182200	−11.889800	0.000000
C	26.333900	−13.884800	0.000000
C	26.334000	−12.554800	0.000000

from calculations carried out by the methods of computational chemistry, particularly those based on the linear combination of atomic orbitals molecular orbital method, and are routinely used as variables in linear regression (quantitative structure-activity relationship) procedures [8,9].

We hereby present the computational study of the geometry optimization and excited state properties of vismodegib by ArgusLab 4.0.1 software.

2. EXPERIMENTAL

Vismodegib structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol) [10]. The vismodegib structure was generated by ArgusLab, and minimization was performed with universal force field molecular mechanics method [11,12]. The minimum potential energy was calculated using geometry convergence function in ArgusLab software. Surfaces created to visualize ground state properties as well as excited

Table 2: Bond length of vismodegib.

Atom	Bond length
C1-C2	1.458000
C1-C3	1.323387
C2-C4	1.323387
C3-C5	1.458000
C3-C7	1.461000
C4-C6	1.458000
C4-S8	1.800077
C5-C6	1.323387
C5-Cl2	1.795422
C7-N13	1.346235
C7-O14	1.260307
S8-O9	1.546726
S8-O10	1.546726
S8-C11	1.803096
N13-C15	1.419751
C15-C16	1.458000
C15-C17	1.323387
C16-C18	1.323387
C17-C19	1.458000
C18-C20	1.458000
C19-C20	1.323387
C19-C22	1.458000
C20-Cl21	1.795422
C22-N23	1.433804
C22-C24	1.323387
N23-C25	1.301961
C24-C26	1.458000
C25-C27	1.458000
C26-C27	1.323387

state properties such 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 [13-15]. The minimum potential energy was calculated for vismodegib through the geometry convergence map [16]. Mulliken atomic charges, ZDO atomic charges of vismodegib, and ground state dipole (debye) of vismodegib were determined using AM1 method.

3. RESULTS AND DISCUSSION

Prospective view and calculated properties of vismodegib molecule are shown in Figure 1. Self-consistent field (SCF) energy curve is shown in Figure 2. The active conformation, electron density cloud, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), and

Table 3: Bond angles of vismodegib.

Atoms	Bond angles	Alternate angles
C2-C1-C3	120.000000	216.488007
C1-C2-C4	120.000000	216.488007
C1-C3-C5	120.000000	216.488007
C1-C3-C7	120.000000	215.760874
C2-C4-C6	120.000000	216.488007
C2-C4-S8	120.000000	210.303144
C5-C3-C7	120.000000	187.861407
C3-C5-C6	120.000000	216.488007
C3-C5-Cl12	120.000000	164.307828
C3-C7-N13	120.000000	280.407604
C3-C7-O14	120.000000	276.934658
C6-C4-S8	120.000000	188.274860
C4-C6-C5	120.000000	216.488007
C4-S8-O9	92.100000	303.587174
C4-S8-O10	92.100000	303.587174
C4-S8-C11	92.100000	206.072728
C6-C5-Cl12	120.000000	183.593823
N13-C7-O14	120.000000	421.698151
C7-N13-C15	120.000000	220.592895
O9-S8-O10	92.100000	471.223100
O9-S8-C11	92.100000	302.641626
O10-S8-C11	92.100000	302.641626
N13-C15-C16	120.000000	260.801534
N13-C15-C17	120.000000	300.697530
C16-C15-C17	120.000000	216.488007
C15-C16-C18	120.000000	216.488007
C15-C17-C19	120.000000	216.488007
C16-C18-C20	120.000000	216.488007
C17-C19-C20	120.000000	216.488007
C17-C19-C22	120.000000	188.442082
C18-C20-C19	120.000000	216.488007
C18-C20-Cl21	120.000000	164.307828
C20-C19-C22	120.000000	216.488007
C19-C20-Cl21	120.000000	183.593823
C19-C22-N23	120.000000	257.053574
C19-C22-C24	120.000000	216.488007
N23-C22-C24	120.000000	295.980973
C22-N23-C25	120.000000	227.506158
C22-C24-C26	120.000000	216.488007
N23-C25-C27	120.000000	294.480480
C24-C26-C27	120.000000	216.488007
C25-C27-C26	120.000000	216.488007

ESP mapped density of vismodegib are shown in Figure 3.

Table 4: List of Mulliken atomic charges and ZDO atomic charges of vismodegib.

Atoms	ZDO atomic charges	Mulliken atomic charges
C	3.8378	4.1795
C	−3.8354	−4.1859
C	3.9917	4.0138
C	−3.9994	−4.0054
C	3.6414	4.0727
C	−3.5479	−3.9729
C	4.0000	4.0003
S	−2.0000	−2.0004
O	−2.0000	−2.0000
O	−2.0000	−2.0000
C	−4.0000	−4.0000
L	2.9119	2.8983
N	5.0000	5.0000
O	6.0000	6.0000
C	3.9991	4.0058
C	3.9999	4.0002
C	3.8288	4.0193
C	3.9961	4.0015
C	−1.9397	−2.1681
C	2.1013	2.2001
Cl	−0.9858	−1.0461
C	−3.9997	−4.0108
N	−3.0000	−3.0001
C	−4.0000	−4.0017
C	−4.0000	−4.0000
C	−4.0000	−4.0000
C	−4.0000	−4.0000

ZDO=Zero differential overlap

Table 5: Ground state dipole (debye) of vismodegib.

X	Y	Z	Length
−635.6814288	91.92246798	−0.00000000	642.29325006

Table 6: Final energy evaluation.

Force field	Energy components (au)
MM bond (Estr)	0.00756185
MM angle (Ebend)+(Estrbend)	0.47369025
MM dihedral (Etor)	0.01259851
MM ImpTor (Eoop)	0.00000000
MM vdW (EVdW)	0.05563019
MM coulomb (Eqq)	0.00000000
Total	0.54948080 au (344.80472191 kcal/mol)

MM=Molecular mechanics

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.

The HOMO of the molecule and the LUMO, respectively, rendered in opaque forms. 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 show a decrease in electron density. This type of surface representations is useful to discuss drug receptor interaction.

Atomic coordinates of molecule are given in Table 1 and bond length and bond angles are given in Tables 2 and 3, respectively, which are calculated after geometry optimization of the molecule from ArgusLab by using molecular mechanics methods. Tables 4-6 show Mulliken atomic charges, ZDO atomic charges of ground state dipole (debye), and calculated the steric energy of vismodegib molecule.

The steric energy calculated for vismodegib molecule was 0.54948080 au (344.80472191 kcal/mol), and its SCF energy was found to be −171.9735381707 au (−107915.1218 kcal/mol) as calculated by RHF/AM1 method, by ArgusLab 4.0.1 suite.

4. CONCLUSION

The present work indicates that the best conformation of vismodegib is found to be −171.9735381707 au (−107915.1218 kcal/mol) which is the minimum potential energy by using ArgusLab software. At this point, vismodegib will be more active as a chemotherapy agent.

5. REFERENCES

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****Bibliographical Sketch***

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