CONFORMATIONAL ANALYSIS (GEOMETRY OPTIMIZATION) OF NUCLEOSIDIC ANTITUMOR ANTIBIOTIC SHOWDOMYCIN BY ARGUSLAB 4 SOFTWARE

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ABSTRACT

Showdomycin is a naturally maleimide antitumor antibiotic of the C-nucleoside, it inhibits the nucleic acid synthesis in bacteria. Conformational analysis and geometry optimization of showdomycin was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. The minimum potential energy is calculated by geometry convergence function by ArgusLab software. The most feasible position for the drug to interact with the receptor was found to be – 0.269696 K.cal/mole.

Keywords: Anti-tumor drug, Showdomycin, Arguslab 4.0.1, conformational analysis, geometry optimization.

INTRODUCTION

Showdomycin is one of six C-substituted nucleosides and nucleoside with a maleimide group antitumor antibiotic isolated from natural sources of streptomycin showdoensis by the research group at Shiongo Research Laboratory. The nucleoside antibiotic is moderately active against gram-positive and gram-negative bacteria and it is cytotoxic to tumor cells. Showdomycin inhibits the RNA and DNA polymerase and also is a strong inhibitor of DNA synthesis (Matsuura *et al*., 1964, Nishimura *et al*., 1964, Darnall *et al*., 1967, Kano *et al*., 1967, Bermek *et al*., 1970, Kalvoda *et al*., 1970, Maryanka *et al*., 1970, Roy *et al*., 1970, Suhadolnik *et al*., 1970). Showdomycin and its anomer have each been evaluated in various assays for their cytotoxic, anti-bacterial, and anti-viral effects (Rennar *et al*., 2005). Strategies for the synthesis of nucleosides that can provide either L or D isomers become more important as a result of the increasing number of such compounds that are therapeutically useful. The successful completion of a synthesis of L-showdomycin validates this approach as a viable strategy to C-nucleosides (Barry *et al.,* 1999).

The present work describes the computer aided conformational analysis that is based on geometry optimization (active conformation) of drug by ArgusLab software.

Argus Lab 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 (Peng *et al*., 1995).

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).

$$E = E_{stretching} + E_{bending} + E_{torsion} + E_{Vander\ Waals} + E_{electrostatic} + E_{hydrogen\ bond} + \text{cross term}$$

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 (Cramer *et al*., 1992).

The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atoms moved are iteratively 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. The 3D (3 rotatable bonds) structure of molecule corresponding to this energy minimum is one of the stable conformations of molecule but not necessarily the most stable one (Merz *et al*., 1989).

Since the energy minimization methods can not move the molecule across energy barriers, the minimization of a

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trial molecule continues until the first local energy minimum is found. Other local energy minima including the lowest energy one, the global energy minimum, may be found by repeating the calculation with another start geometry or more efficiently. Conformation search methods random numbers are used to determine how many and which torsion angles and space to be incremented and which directions of the x, y, z, co-ordinates of each atoms are to be translated (Still *et al*., 1990).

MATERIALS AND METHODS

The three dimensional quantitative structure activity relationships (3D-QSAR) describe the biological activity of molecule with pharmacological potential as a function of their structural properties (Low *et al*., 1993, Csizmadia *et al*., 2000).

Computational advances have generated many tools which are widely used to construct models, minimization and representations of molecular structure (Martin *et al*., 1998, Cruciani *et al.*, 1998, Dunn *et al*., 1998).

All conformational analysis (geometry optimization) study was performed on a window based computer using Argus lab and ACD Lab Chem Sketch software's. The chemical structure of showdomycin (Gerorge *et al*., 1995) was refined by X-ray crystallography technique.

The showdomycin molecule is utilized to determine 3D structure of molecule. Several computer programs were used to infer the shape of molecule from geometry optimization calculations. The showdomycin structure is generated by Argus lab, and minimization was performed with the semi-empirical Austin Model 1 (AM1) parameterization (Dewar *et al*., 1985).

The minimum potential energy is calculated by using geometry convergence function in Argus lab software. In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander Waal contact distance (Simons *et al*., 1983).

Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP) spin densities and generated the grid data used to make molecular orbital surfaces and visualized he molecular orbital and making an electro static potential mapped and electron density surface.

The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

RESULTS AND DISCUSSION

Prospective view and active conformation of showdomycin are shown in fig. 1a and 1b respectively. Fig. 1c shows the electron density map of showdomycine by ACDLABS-3D viewer software. The electrostatic potential of drug caused by charged side chains and

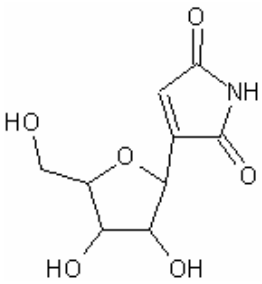

Fig. 1a: Prospective view of showdomycin.

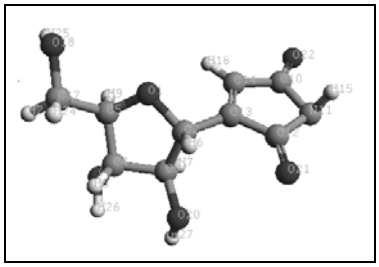

Fig. 1b: Prospective view of active conformation of showdomycin.

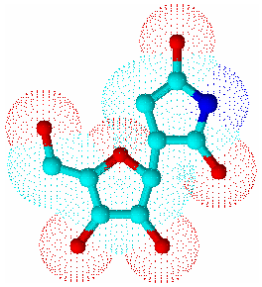

Fig. 1c: Electrons density clouds generates by ACD Labs.3D viewer.

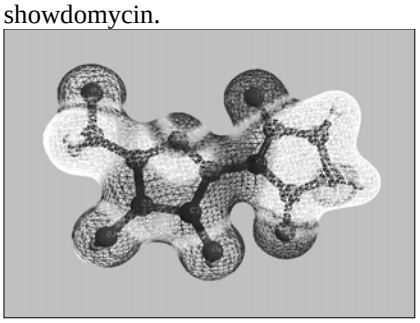

Fig. 1d: Electro static potential (ESP) mapped electron density surface (mesh).

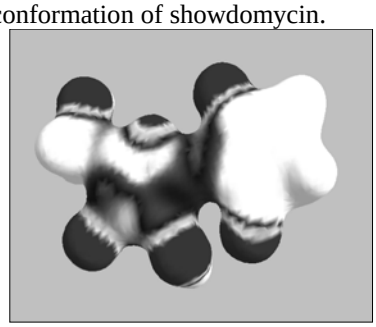

Fig. 1e: The complete surface with the color map of ESP.

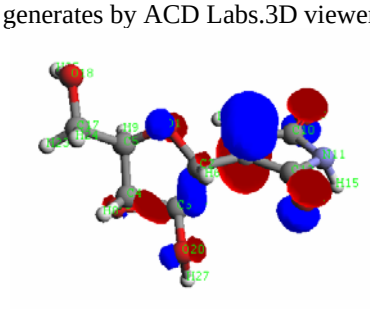

Fig. 1f: Visualize the molecular orbital, blue shows positive and red shows negative.

bound ions plays a role in recognition of active site of specific receptor. Fig. 1d shows the electrostatic potential of showdomycine ground state mapped onto the electron density surface for the ground state and fig. 1e shows the complete surface with the color map. Figs. 1d and 1e use a clipping plane showing a cutaway of the same surface revealing the underlying molecular structure. 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. These images show that the carboxyl-end of the molecule is electron rich relative to the amino end. Fig. 1f shows the occupied π-molecular orbital of showdomycin. Calculated with the ZINDO method and rendered as a mesh. The positive and negative phases of the orbital are represented by the two colors, the blue regions represent an increase in electron density and the red regions a decrease in electron density. To compute a molecular surface with an electrostatic potential, activate the "color by electrostatic potential" in the "Surface" preferences and compute the surface. This type of surface representations is useful to discuss drug receptor interaction.

The minimum potential energy is shown in fig. 2 for drug receptor interaction through the geometry convergence map. Atomic coordinates of a showdomycin are given in table 1. Bond lengths and bond angles are given in the tables 2 and 3 respectively, which are taken after geometry optimization of showdomycin molecule from Argus Lab by using molecular mechanics calculation. It is possible that drug in this conformation interact with receptor. The result indicates that the best conformation of the molecule is present at minimum potential energy is found to be –0.269696 K.cal/mol. At this point showdomycin will be more active as nucleoside antitumour antibiotic. Electrostatic potential map, electron density maps and colored regions of showdomycin represent active sites of drug receptor binding interaction with different charged groups.

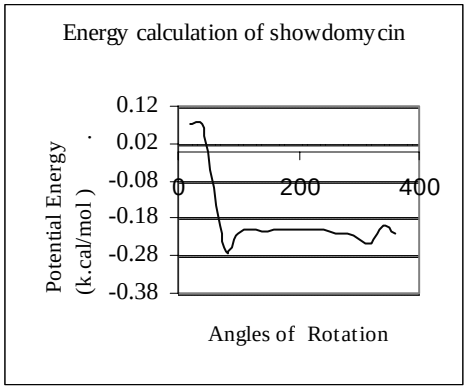

Fig. 2: Potential energy geometry convergence map of Showdomycin.

Table 1: Atomic coordinates of Showdomycin.

Atoms	x	y	Z
O1	–1.583947	1.188363	0.298374
C2	–0.495911	0.218383	0.474883
C3	–0.870331	–1.033771	–0.318708
C4	–2.386943	–0.967070	–0.413967
C5	–2.708978	0.530779	–0.375466
H6	–0.423334	–0.019909	1.562079
H7	–0.417745	–1.000507	–1.341153
H8	–2.825529	–1.480824	0.475133
H9	–2.785297	0.942918	–1.409052
C10	2.412114	1.804606	–1.170796
N11	3.206653	1.161959	–0.149445
C12	2.126943	0.528047	0.569308
C13	0.809093	0.801664	0.008655
C14	0.981113	1.561931	–1.053518
H15	3.619070	0.338753	–0.685804
H16	0.202414	1.912918	–1.723829
C17	–4.011415	0.818395	0.377018
O18	–4.281348	2.235852	0.382029
O19	–2.888893	–1.605725	–1.613142
O20	–0.441114	–2.224884	0.376897
O21	2.321261	–0.198820	1.578923
O22	2.922760	2.501126	–2.086298
H23	–4.859011	0.270625	–0.100324
H24	–3.922254	0.471856	1.432258
H25	–4.636471	2.468551	–0.562988
H26	–2.470028	–1.125346	–2.430178
H27	–0.578330	–3.010011	–0.284666

CONCLUSION

The present work indicates that the best conformation of showdomycin is found to be at –0.269696 K.Cal which is the minimum potential energy by using Argus Lab software. At this point showdomycin will be more active as nucleoside antitumour antibiotic.

In this work it is shown that conformational analysis with minimum potential energy is crucial when establishing SAR/QSAR models using theoretically calculated descriptors, since it can be dependent on the molecular structure.

Finally all geometric variables were completely optimized for each compound and the lowest energy conformations were used in molecular modeling studies.

Table 2: Bond lengths of Showdomycin

S. No.	Atoms	Bond Length
1	C3 --- C4	1.514000
2	C4 --- C5	1.514000
3	O1 --- C5	1.458442
4	O1 --- C2	1.458442
5	C2 --- C3	1.514000
6	C12 --- C13	1.458000
7	C13 --- C14	1.323387
8	C10 --- C14	1.458000
9	C10 --- N11	1.434808
10	N11 --- C12	1.434808
11	C2 --- C13	1.486000
12	C17 --- O18	1.436155
13	C5 --- C17	1.514000
14	C3 --- O20	1.436155
25	C4 --- O19	1.436155
16	C12 --- O21	1.257535
17	C10 --- O22	1.257535
18	C2 --- H6	1.112599
19	C3 --- H7	1.112599
20	C4 --- H8	1.112599
21	C5 --- H9	1.112599
22	N11 --- H15	1.063581
23	C14 --- H16	1.084582
24	C17 --- H23	1.112599
25	C17 --- H24	1.112599
26	O18 --- H25	1.033746
27	O19 --- H26	1.033746
28	O20 --- H27	1.033746

Table 3: Bond angles of Showdomycin

S. No.	Atoms	Bond Angles	Alternate Bond Angles
1	C3---C4---C5	109.470000	214.211821
2	C4---C3---C2	109.470000	214.211821
3	C4---C3---O20	109.470000	278.259153
4	C3---C4---O19	109.470000	278.259153
5	C4---C3---H7	109.470000	116.984990
6	C3---C4---H8	109.470000	116.984990
7	C4---C5---O1	109.470000	272.224071
8	C4---C5---C17	109.470000	214.211821
9	C5---C4---O19	109.470000	278.259153
10	C5---C4---H8	109.470000	116.984990
11	C4---C5---H9	109.470000	116.984990
12	C5---O1---C2	110.000000	236.533892
13	O1---C 5---C17	109.470000	272.224071
14	O1---C5---H9	109.470000	151.529671
15	O1---C2---C3	109.470000	272.224071
16	O1---C2---C13	109.470000	280.201746
17	O1---C2---H6	109.470000	151.529671
18	C3---C2---C13	109.470000	220.229931
19	C2---C3---O20	109.470000	116.984990
20	C3---C2---H6	109.470000	116.984990
21	C2---C3---H7	109.470000	216.488007
22	C12---C13---C14	120.000000	256.788014
23	C13---C12---N11	120.000000	183.094781
24	C12---C13---C2	120.000000	278.700488
25	C13---C12---O21	120.000000	216.488007
26	C13---C14---C10	120.000000	209.804299
27	C14---C13---C2	120.000000	123.034913
28	C13---C14---H16	120.000000	256.788014
29	C14---C10---N11	120.000000	278.700488
30	C14---C10---O22	120.000000	102.928506
31	C10---C14---H16	120.000000	269.841144
32	C10---N11---C12	106.700000	381.040533
33	N11---C10---O22	120.000000	145.519776
34	C10---N11--- H15	106.700000	381.040533
35	N11---C12---O21	120.000000	145.519776
36	C12---N11---H15	106.700000	121.420518
37	C13---C2---H6	109.470000	278.259153
38	O18---C17---C5	109.470000	156.116442
39	O18---C17---H23	109.470000	156.116442
40	O18---C17---H24	109.470000	157.363455
41	C17---O18---H25	104.510000	116.984990
42	C17---C5---H9	109.470000	116.984990
43	C5---C17---H23	109.470000	116.984990
44	C5---C17---H24	109.470000	156.116442
45	O20---C3---H7	109.470000	157.363455
46	C3---O20---H27	104.510000	156.116442
47	O19---C4---H8	109.470000	157.363455
48	C4---O19---H26	104.510000	74.849522
49	H23---C17---H24	109.470000	157.363455

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