DFT Based Modeling of a Natural Molecule- D-Myo-Inositol Explores it to be a Multifunctional Biologically Active

Ashok Kumar Mishra[1,a)] and Satya Prakash Tewari[2]

[1,2] *Department of Physics, Dr. Shakuntala Misra National Rehabilitation University, Lucknow, India-226017*
[a]Corresponding Author: akmishra2k5@gmail.com

Abstract. D-Myo-Inositol ($C_7H_{14}O_6$) is reportedly a bioactive natural molecule isolated from the leaves of Anthocephalus chinensis plant whose structure activity relationships are yet to be reported. In this view, the optimized geometry of the titled compound has been modeled using DFT-B3LYP/6-31+G (d, p) methods for the theoretical investigation of its biological activity at molecular level. The molecular docking study has been performed for the prediction of the titled compound at the optimized geometry in which its 3-D shape of optimized structure has been exploited as a ligand input to interact with 1hsg and 1gcn protein receptors, which results in the final value of the free energy of binding to be -4.15 kcal/mol and -3.03 kcal/mol. The other derivatives of the titled molecule have also been modeled using same level of theory and their activity has also been studied via molecular docking and the resultant free energy of binding has been reported. The outcomes of the present study reveal that the titled molecule may be a good anti diabetic and anti immunodeficiency agent and may be useful in developing an optional natural drug as well as in identifying the other novel structures.

INTRODUCTION

The study of naturally occurring bio active molecules has gained significant importance because of its variety of applications in the field of drug development. In this sequence, the D-Myo-Inositol is a reported plant-derived bioactive molecule [1] and the active principle of its bioactivity has not been reported to the best of our knowledge. The structure of the titled molecule and its derivatives has been modeled and optimized using Density Functional Theory and their bioactivity has been investigated using molecular docking in the present study. Since, the G Protein (1gcn) and 1hsg protein has been reported to be a target for an anti diabetic agent [2] and anti immunodeficiency virus agent [3] respectively along with G Protein-Coupled receptors are the novel structures for anti diabetic drug [4] hence the interaction of the titled molecule and its derivatives with these proteins has been studied via molecular docking which has been reported to be a useful tool in computer-aided drug design due to the importance of shape-matching in drug-macromolecule interactions, as well as the properties of contact surface between the drug and the protein [5]. Positive results have been obtained regarding its bioactivity which may be exploited for identifying the other novel structures and synthesizing its structural analogues for developing a user-friendly alternative medicine.

COMPUTATIONAL METHODS

Density Functional Theory based Modeling

Density functional theory (DFT) based computations and performance of the density functional has been reported to be in consistence with experimental findings in case of bio molecules [6]. Hence, the optimized geometry of the titled compound of figure 1 has been modeled using DFT-B3LYP/6-31+G (d, p) hybrid functional-basis set combination as per reported method [7-8]. More structures have been obtained by interchanging the C and O-atom in the side chain of the titled molecule named as derivative and by increasing the one aromatic ring in the titled molecule named as polymer as shown in figure 2 and 3 respectively.

Molecular docking and Statistical Mechanical Analysis

The 3D optimized structure obtained by theoretical computation using DFT; have been exploited for recognizing the bioactivity of the titled compound via molecular docking studies as per the available methods using Auto dock 4.2 program package [9-11] which results in the final free energy of binding and other statistical mechanical parameters to exhibit the binding of a drug molecule to the receptor. The free energy of binding is an important parameter in protein-ligand interaction study [12] for predicting the bio molecule to be drug agent. The obtained optimized geometry of the titled compound and its derivative has been taken as the input ligand to interact with the target protein 1hsg and 1gcn retrieved from Protein Data Bank (PDB) database [13] in the Docking process, results in an interaction energy value and picturizes the interaction energy surface. In the view of these docking results, the titled natural product has been explored as a drug molecule for diabetic mellitus and immunodeficiency syndrome. The statistical mechanical analysis has been performed through the same docking process to calculate the statistical mechanical parameters namely partition function (Q), free energy (A), internal energy (U) and entropy (S) of the system to predict the compatibility of the interacting molecular system under investigation with the biological surroundings.

RESULTS

The optimized structure of the titled molecule has been displayed in figure 4. The optimized structure of the derivative and polymer of the titled compound has also been obtained but not depicted here due to space limitation. The total energy of the optimized geometry of the titled molecular system has been calculated at the single point of the molecular potential surface named as the single point energy which is -726.4510 hartee at equilibrium. Total dipole moment is 8.0638D (Debye) distributed along Dx, Dy and Dz as -1.1078D, -6.0609D and -5.2022D respectively indicating that the centers of positive and negative charges are significantly separated and asymmetric charge distribution exists in this molecule.

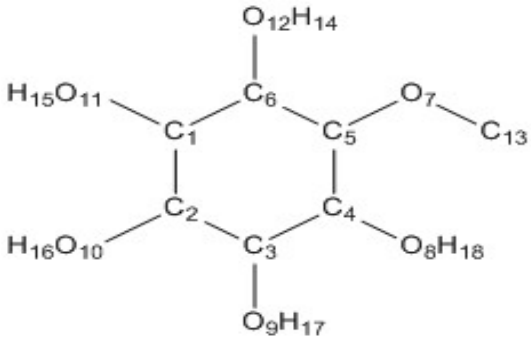


FIGURE 1 Chemical Structure of D-Myo-Inositol

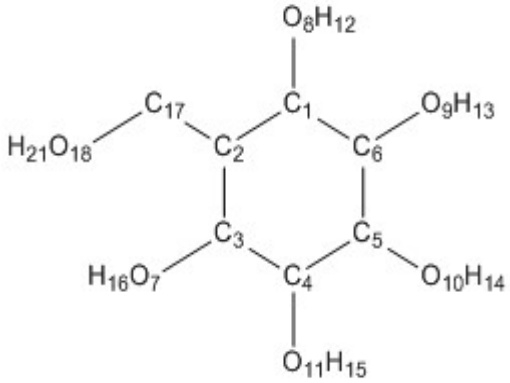
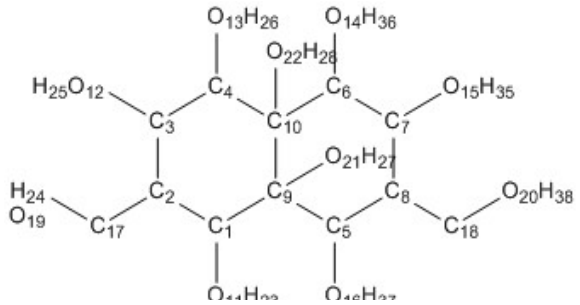


FIGURE 2 Chemical Structure of the derivative

Biological Activity

The binding of D-Myo-Inositol molecules as a ligand with 1hsg and 1gcn receptor; has been displayed in Figure 5(a) and 5(b) respectively. The final free binding energy with 1hsg and 1gcn protein receptor for molecule has been calculated to be -4.15 kcal/mol and -3.03 kcal/mol with corresponding inhibition constant to 904.88 μM (micro molar) and 6.04 mM (milli molar) at temperature 298.15 K, In case of its derivative of figure 2, the same has been calculated to be-4.42 kcal/mol and -3.04 kcal/mol with corresponding inhibition constant to 783.99 μM (micro molar) and 5.88 mM (milli molar) at temperature 298.15 K, and in case of polymer of figure 3 the same has been obtained to be -2.52 kcal/mol and -1.55 kcal/mol with corresponding inhibition constant to 14.21 mM (milli molar)



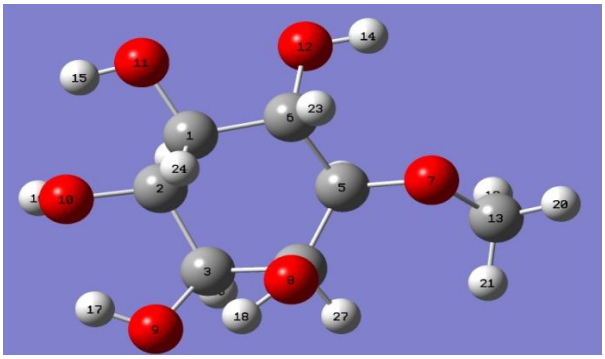


FIGURE 3 Chemical Structure of the Polymer.

FIGURE 4 Optimization Geometry of D-Myo-Inositol

and 73.69 mM (milli molar) at temperature 298.15 K, respectively. The variation of the free binding energy with the inhibition constant has been depicted in the table 1 to 3. The final intermolecular energy value obtained via docking with 1hsg and 1gcn protein for the titled molecule is -5.94 kcal/mol and -4.82 kcal/mol, for its derivative -6.33 kcal/mol and -5.13 kcal/mol and for polymer ; -6.10 kcal/mol and -5.12 kcal/mol respectively. The calculated values of statistical mechanical parameters namely Q, A, U, S of interacting ligand (D-Myo-Inositol and its derivatives)- receptor (1hsg) and (1gcn) molecular systems are respectively (10.06, -1367.67 kcal/mol, -3.43 kcal/mol, 4.58 kcal/mol/K) and (10.04, -1366.73kcal/mol, -2.49 kcal/mol, 4.58 kcal/mol/K) for titled molecule, (10.06, -1367.57 kcal/mol, -3.34 kcal/mol, 4.58 kcal/mol/K) and (10.04, -1366.73kcal/mol, -2.52 kcal/mol) 4.58 kcal/mol/K) for derivate of figure 2, (10.03, -1365.90 kcal/mol, -1.66 kcal/mol, 4.58 kcal/mol/K) and (10.01, -1364.82 kcal/mol, -0.58 kcal/mol, 4.58 kcal/mol/K) for the polymer of figure 3.

TABLE 1 Variation of Free energy of binding with the inhibition constant obtained via molecular docking for titled molecule

(1-gcn receptor)				(1-hsg receptor)			
Cluster Rank	**Run**	**Free Energy of Binding**	**Inhibition Constant**	**Cluster Rank**	**Run**	**Free Energy of Binding**	**Inhibition Constant**
1	2	-3.03 kcal/mol	6.04mM	1	6	-4.15 kcal/mol	904.88µM
2	4	-2.88 kcal/mol	7.80mM	2	7	-4.05 kcal/mol	1.08mM
3	1	-2.79 kcal/mol	9.08mM	3	1	-3.58 kcal/mol	2.39mM
4	7	-2.59 kcal/mol	12.65mM	4	3	-3.55 kcal/mol	2.52mM
5	9	-2.42 kcal/mol	16.75mM	5	4	-3.40 kcal/mol	3.21mM
6	3	-2.41 kcal/mol	17.18mM	6	2	-3.36 kcal/mol	3.46mM
7	10	-2.17 kcal/mol	25.82mM	7	10	-3.25 kcal/mol	4.17mM
8	6	-2.16 kcal/mol	26.29mM	8	8	-3.19 kcal/mol	4.60mM
9	8	-2.09 kcal/mol	29.29mM	9	5	-2.90 kcal/mol	7.54mM

TABLE 2 Variation of Free energy of binding with the inhibition constant obtained via molecular docking for Derivative

(1-gcn receptor)				(1-hsg receptor)			
Cluster Rank	**Run**	**Free Energy of Binding**	**Inhibition Constant**	**Cluster Rank**	**Run**	**Free Energy of Binding**	**Inhibition Constant**
1	2	-3.04 kcal/mol	5.88mM	1	8	-4.24 kcal/mol	783.99µM
2	6	-2.68 kcal/mol	10.79mM	2	10	-3.75 kcal/mol	1.79mM
3	5	-2.26 kcal/mol	22.17mM	3	6	-3.48 kcal/mol	2.81mM
4	9	-2.20 kcal/mol	24.25mM	4	1	-3.46 kcal/mol	2.92mM
				5	3	-3.39 kcal/mol	3.30mM
				6	4	-3.33 kcal/mol	3.61mM
				7	2	-3.13 kcal/mol	5.04mM
				8	5	-2.95 kcal/mol	6.84mM

TABLE 3 Variation of Free energy of binding with the inhibition constant obtained via molecular docking for Polymer

(1-gcn receptor)				(1-hsg receptor)			
Cluster Rank	**Run**	**Free Energy of Binding**	**Inhibition Constant**	**Cluster Rank**	**Run**	**Free Energy of Binding**	**Inhibition Constant**
1	6	-1.55 kcal/mol	73.69mM	1	2	-2.52 kcal/mol	14.21mM
2	8	-1.26 kcal/mol	119.51mM	2	5	-2.42 kcal/mol	16.70mM
3	1	-0.76 kcal/mol	278.66mM	3	6	-2.25 kcal/mol	22.51mM
4	3	-0.71 kcal/mol	304.02mM	4	1	-2.21 kcal/mol	23.89mM
5	2	-0.61 kcal/mol	357.81mM	5	10	-1.93 kcal/mol	38.64mM
6	5	-0.20 kcal/mol	711.09mM	6	9	-1.83 kcal/mol	45.33mM
7	7	-0.11 kcal/mol	828.68mM	7	3	-1.54 kcal/mol	74.26mM
8	4	+0.49 kcal/mol	……..	8	7	-1.33 kcal/mol	105.56mM
				9	8	-0.58 kcal/mol	374.26mM
				10	4	-0.01 kcal/mol	977.45mM

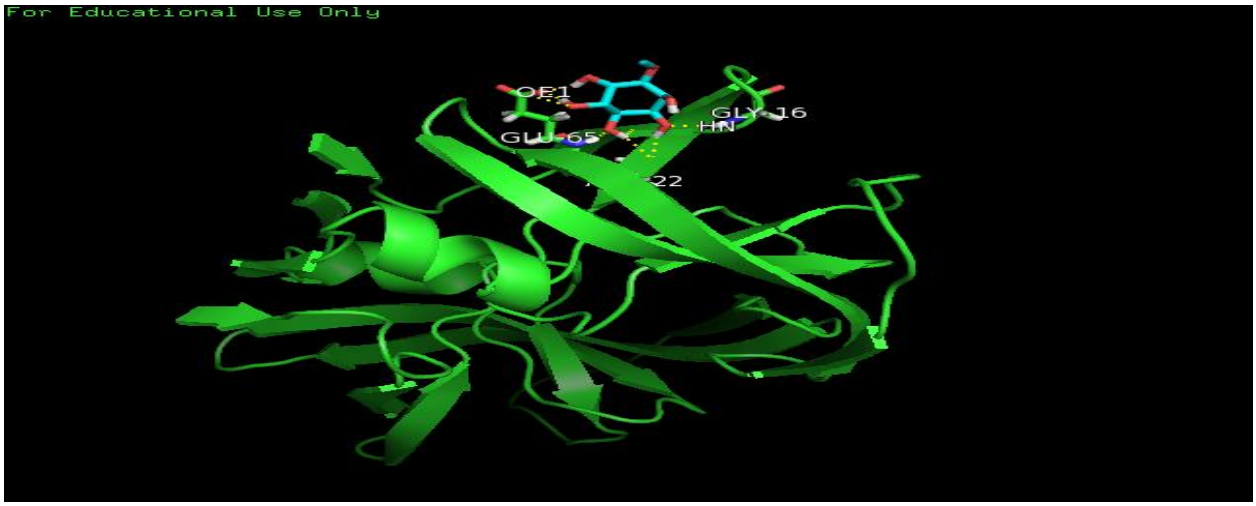


FIGURE 5 (a) Ligand (titled molecule) -protein(1 hsg) interaction plot

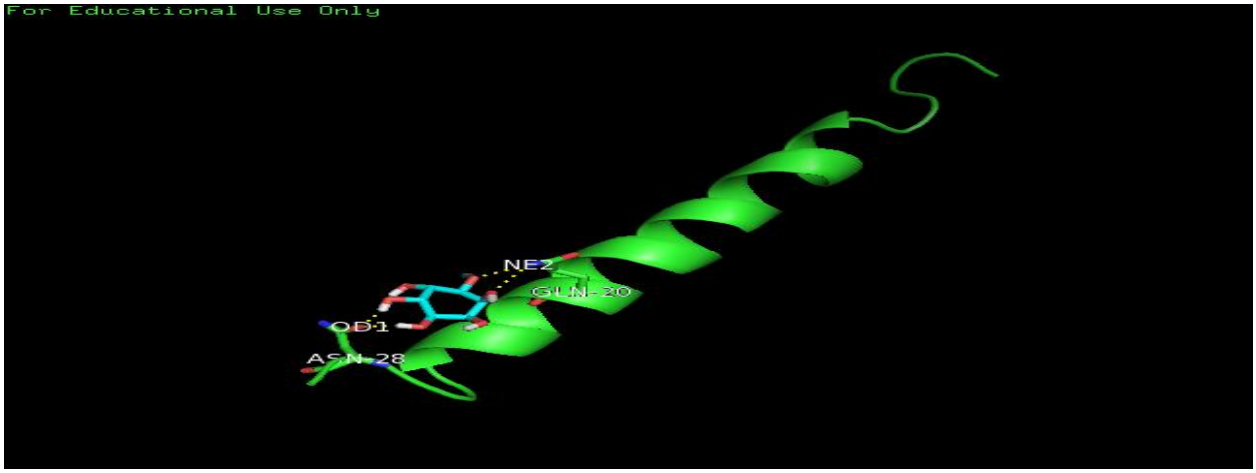


FIGURE 5 (b) Ligand (titled molecule) -protein (1gcn) interaction plot

DISCUSSION

The docking scores as well as the statistical mechanical analysis are the projection of the bioactivity and biocompatibility of the titled compound, and a negative value of the free energy of binding has been obtained in all the three structures, however, the total molecular interaction energy of a large molecule often achieving the most negative value due to the additive nature of the energy formula [14-15]. The variation of the free energy of binding with the inhibition constant in obtained docking score is in line with the other report [16].

CONCLUSION

The molecular docking results depicted in table 1-3 exhibits that the final free binding energy of the titled molecule with the receptors 1hsg and 1gcn has a reciprocal relation with the inhibition constant. A Free binding energy value -415 and -3.03 kcal/mol have been predicted with the help of molecular docking with 1hsg and 1gcn receptors respectively which infers that the titled molecule may be epxplored as an anti immunodeficiency and anti diabetic agent. The values of the same in case of the derivative has been observed increasing slightly but decreasing in case of the polymerization. The calculated values of statistical mechanical parameters namely Q, A, U, S of interacting ligand [D-Myo-Inositol] - receptors (1hsg and 1gcn) molecular systems suggests the titled molecule and its derivative as drug; to be compatible for biological surroundings.

ACKNOWLEDGMENTS

First author is thankful to the UGC, New Delhi for the financial assistance through the minor research project for carrying out the research work on the bioactive natural compounds at the place of his present affiliation. Authors are thankful to Prof. Neeraj Misra, Department of Physics, University of Lucknow, India for permitting us to access his computational facility. Thanks are due to Dr. R. Maurya , Pricipal Scientist, CDRI Lucknow, India and his research scholar Dr. D.P. Mishra for their invaluable helps and discussions regarding the reported natural products. We extend gratitude to Prof. Arthur J. Olson, department of Molecular Biology, Scripps Research Institute, La Jolla, USA for providing us the Auto Dock 4.2 Program for performing molecular docking study.

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