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Quantum Chemical Studies of an Irreversible Steroidal Aromatase Inhibitor,6-methylideneandrosta-1,4-diene-3,17-dione (Exemestane)

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Abstract

6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) is an oral steroidal aromatase inhibitor that is used in estrogen receptors (ER) -positive breast cancer in addition to surgery and/or radiation in post-menopausal women. Quantum chemical studies of exemestane was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. 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 orbital's, lowest unoccupied molecular orbital's and electrostatic potential (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 -108.034930 au (-67793.003600 kcal/mol). These results could help us in understating the drug-receptor interactions.

Keywords: *Exemestane, optimization, arguslab, breast cancer.*

1. Introduction

Exemestane is an oral steroidal aromatase inhibitor that is used in ER-positive breast cancer in addition to surgery and/or radiation in post-menopausal women. Exemestane, is a drug used to treat breast cancer [1]. It is a member of the class of drugs known as aromatase inhibitors[1]. Some breast cancers require estrogen to grow. Those cancers have estrogen receptors (ERs), and are called ER-positive [1]. They may also be called estrogen-responsive, hormonally-responsive, or hormone-receptor-positive. Aromatase is an enzyme that synthesizes estrogen. Aromatase inhibitors block the synthesis of estrogen [1]. This lowers the estrogen level, and slows the growth of cancers. Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione [1]. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition"[1]. By being structurally similar to enzyme targets, exemestane permanently binds to the enzymes, preventing them from converting androgen into estrogen [1].Estrogen is produced locally via the actions of the aromatase enzyme in these peripheral tissues where it acts locally. Any circulating estrogen in post-menopausal women as well as men is the result of estrogen escaping local metabolism and entering the circulatory system [2]. The estrogen suppression rate for exemestane varies from 35% for estradiol (E2) to 70% for estrone (E1) [3].

Argus Lab [4] 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 [5]. 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 + cross terms.
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 [6].

The molecular mechanics method calculates the energy as function of coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atom moved are iteratively moved (without breaking bonds) using an energy minimization technique until the net force on all atoms vanish and the total energy of the molecule reaches a minimum[7,8].The 3D (3 rotatable bonds) structure of molecule corresponding to this energy is minimum is one of the stable conformations of molecule but not necessarily the most stable one [9,10].

In this work, we studied the computational chemistry of exemestane with calculation based on quantum chemical theories. We optimize the structure of the using quantum mechanics and calculated their steric and SCF energies. From the quantum chemical studies, it is also possible to elucidate the various molecular properties.

2. Materials and Methods

6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) structure was generated by Arguslab [4], and minimization was performed with UFF molecular mechanics method [11, 12]. The minimum potential energy was calculated using geometry convergence function in Arguslab software [4]. Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's, lowest unoccupied molecular orbital's and electrostatic potential (ESP) mapped density. The minimum potential energy was calculated for 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) through the geometry convergence map.

3. Results and Discussion

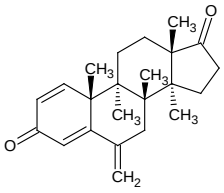
Prospective view and calculated properties of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) molecule is shown in Figure 1. The electron density cloud of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) by ACDlabs-3D viewer software is shown in Figure 2 . The highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and electrostatic potential (ESP) mapped density are shown in Figures 3,4 and 5 respectively. The self - consistent field energy of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) is shown in Figure 6. Atomic coordinates of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) molecule is given in Table1 and bond length and bond angles are given in Table 2 and 3 respectively, which are calculated after geometry optimization of molecule from Arguslab. The calculated steric energy is shown in Table 4.

Arguslab software was used to see what happened to the electrons in 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) when it absorbed light. Surfaces were made to explore this fascinating phenomenon. When 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) 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 [4]. The HOMO is localized to the plane of the molecule and is a non-bonding molecular orbital (Figure 3). The LUMO is perpendicular to the plane of the molecule and is a combination of the p_z atomic orbitals (Figure 4). The $n->\pi^*$ 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 [4]. 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 [4]. QuickPlot ESP mapped density generates an electrostatic potential map on the total electron density contour of the molecule (Figure 6). The electron density surface depicts locations around the molecule where the electron probability density is equal [4]. This gives an idea of the size of the molecule and its susceptibility to electrophilic attack. 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 [4]. These images show that the triple and double bonded end of the molecule is electron rich relative to the single bonded end [4].

SCF was obtained as the minimum potential energy which is the needed energy for the interaction of drug with the receptor. 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 [13]. The steric energy calculated for 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) was 0.18644226 a.u. (116.99438757 kcal/mol) and the SCF energy was found to be -116.8108588693 au (-73299.9867 kcal/mol) as calculated by RHF/ PM3 method, as performed by ArgusLab 4.0.1 suite**.**

3.1 Tables and Figures



Molecular Formula	= $C_{23}H_{30}O_2$
Formula Weight	= 338.4831
Composition	= C(81.61%) H(8.93%) O(9.45%)
Molar Refractivity	= 99.77 ± 0.4 cm^3
Molar Volume	= 308.5 ± 5.0 cm^3
Parachor	= 782.0 ± 6.0 cm^3
Index of Refraction	= 1.559 ± 0.03
Surface Tension	= 41.2 ± 5.0 dyne/cm
Density	= 1.09 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 39.55 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 338.22458 Da
Nominal Mass	= 338 Da
Average Mass	= 338.4831 Da

Figure 1: Prospective view and calculated properties of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

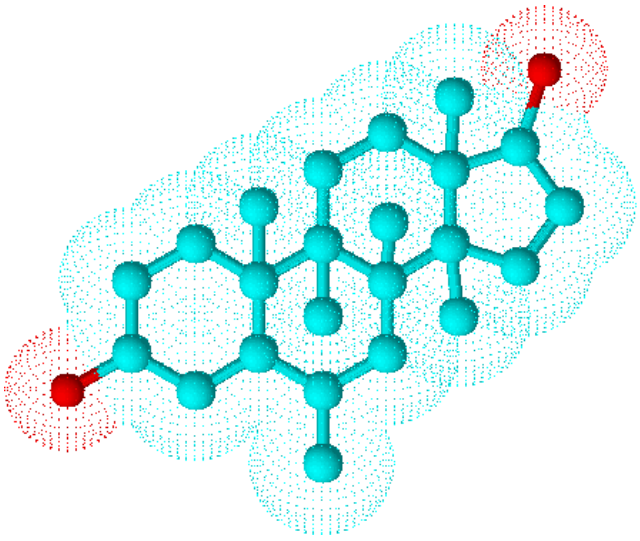


Figure 2: The electron density cloud of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) by ACDlabs-3D viewer software

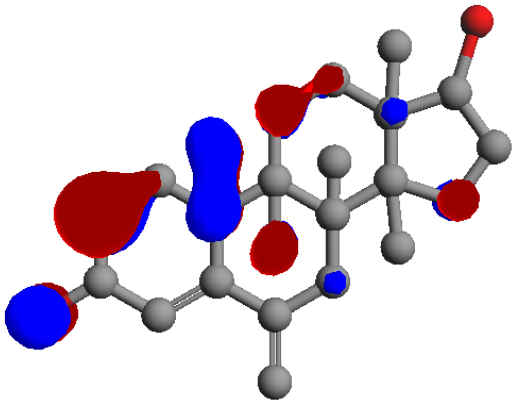


Figure 3: Highest occupied molecular orbital's (HOMO) of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

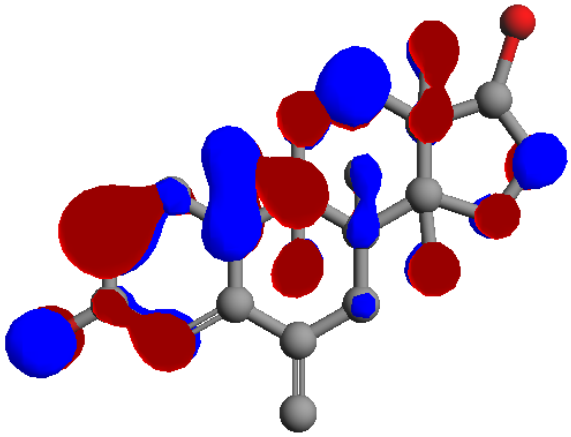


Figure 4: Lowest unoccupied molecular orbital's (LUMO) of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

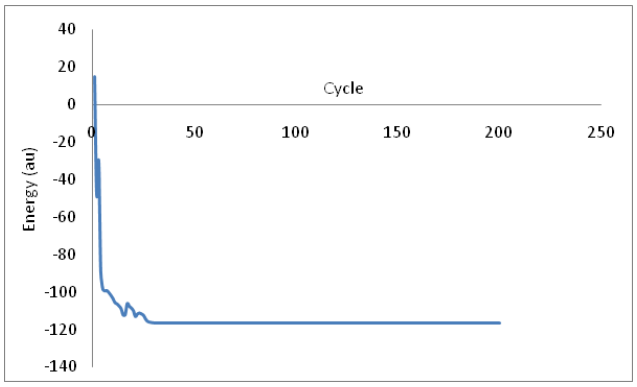


Figure 5: Self-consistent field energy graph of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

Table 1: Geometry optimised atomic coordinates of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

Atoms	X	Y	Z
C	14.03596089	-15.10719276	0.57321074
C	14.06275053	-16.60102147	0.16951380
C	13.31598986	-14.30105372	-0.50355183
C	12.96822543	-17.12885306	-0.41707578
C	12.23038856	-14.81525917	-1.11616614
C	11.87394181	-16.22915231	-0.84178405
C	16.54823496	-15.17880737	-0.17993886
C	16.62798643	-16.66942746	0.06897470
C	15.49628309	-14.58203790	0.87660354
C	15.33921388	-17.39318446	0.23172228
C	17.93116541	-14.43602460	-0.03277175
C	17.75941954	-12.90363190	-0.26232612
C	15.56414479	-13.06189829	0.98759461
C	16.83924703	-12.32799015	0.76723712
C	19.05876318	-14.74391303	-0.97911698
C	19.94079532	-13.54965176	-0.97701509
C	19.17661849	-12.45053685	-0.35411672
O	10.63189331	-16.76487782	-1.24404055
O	19.75951390	-11.54218904	0.55510052
C	15.33790143	-18.72673809	0.27874929
C	17.17084287	-12.51360109	-1.59748694
C	16.06681549	-15.06717473	-1.58226121
C	13.14977213	-14.96728620	1.79057202
C	15.86561429	-15.04378990	2.27761186
C	18.51591180	-14.71413513	1.34747109

Table 2: Bond length of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

Atoms		Bond length
1 3	(C)-(C)	1.489000
1 9	(C)-(C)	1.514000
1 2	(C)-(C)	1.489000
1 23	(C)-(C)	1.489000
2 4	(C)-(C)	1.328833
2 10	(C)-(C)	1.464000
3 5	(C)-(C)	1.328833
4 6	(C)-(C)	1.464000
5 6	(C)-(C)	1.464000
6 18	(C)-(O)	1.410739
7 8	(C)-(C)	1.489000
7 11	(C)-(C)	1.514000
7 9	(C)-(C)	1.514000
7 22	(C)-(C)	1.463000
8 10	(C)-(C)	1.464000
9 13	(C)-(C)	1.489000
9 24	(C)-(C)	1.489000
10 20	(C)-(C)	1.328833

11 12	(C)-(C)	1.514000
11 15	(C)-(C)	1.489000
11 25	(C)-(C)	1.489000
12 14	(C)-(C)	1.489000
12 17	(C)-(C)	1.489000
12 21	(C)-(C)	1.489000
13 14	(C)-(C)	1.464000
15 16	(C)-(C)	1.464000
16 17	(C)-(C)	1.464000
17 19	(C)-(O)	1.410739

Table 3: Bond angles of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

Atoms		Bond angles
3 1 9	(C-(C)-(C)	109.470000
3 1 2	(C)-(C)-(C)	109.470000
3 1 23	(C)-(C)-(C)	109.470000
1 3 5	(C)-(C)-(C)	120.000000
9 1 2	(C)-(C)-(C)	109.470000
9 1 23	(C)-(C)-(C)	109.470000
1 9 7	(C)-(C)-(C)	109.470000
1 9 13	(C)-(C)-(C)	109.470000
1 9 24	(C)-(C)-(C)	109.470000
2 1 23	(C)-(C)-(C)	109.470000
1 2 4	(C)-(C)-(C)	120.000000
1 2 10	(C)-(C)-(C)	120.000000
4 2 10	(C)-(C)-(C)	120.000000
2 4 6	(C)-(C)-(C)	120.000000
2 10 8	(C)-(C)-(C)	120.000000
2 10 20	(C)-(C)-(C)	120.000000
3 5 6	(C)-(C)-(C)	120.000000
4 6 5	(C)-(C)-(C)	120.000000
4 6 18	(C)-(C)-(O)	120.000000
5 6 18	(C)-(C)-(O)	120.000000
8 7 11	(C)-(C)-(C)	109.470000
8 7 9	(C)-(C)-(C)	109.470000
8 7 22	(C)-(C)-(C)	109.470000
7 8 10	(C)-(C)-(C)	120.000000
11 7 9	(C)-(C)-(C)	109.470000
11 7 22	(C)-(C)-(C)	109.470000
7 11 12	(C)-(C)-(C)	109.470000
7 11 15	(C)-(C)-(C)	109.470000
7 11 25	(C)-(C)-(C)	109.470000
9 7 22	(C)-(C)-(C)	109.470000
7 9 13	(C)-(C)-(C)	109.470000
7 9 24	(C)-(C)-(C)	109.470000
8 10 20	(C)-(C)-(C)	120.000000
13 9 24	(C)-(C)-(C)	109.470000
9 13 14	(C)-(C)-(C)	120.000000
12 11 15	(C)-(C)-(C)	109.470000
12 11 25	(C)-(C)-(C)	109.470000
11 12 14	(C)-(C)-(C)	109.470000
11 12 17	(C)-(C)-(C)	109.470000
11 12 21	(C)-(C)-(C)	109.470000
15 11 25	(C)-(C)-(C)	109.470000
11 15 16	(C)-(C)-(C)	120.000000
14 12 17	(C)-(C)-(C)	109.470000
14 12 21	(C)-(C)-(C)	109.470000
12 14 13	(C)-(C)-(C)	120.000000
17 12 2	(C)-(C)-(C)	109.470000
12 17 16	(C)-(C)-(C)	120.000000
12 17 19	(C)-(C)-(O)	120.000000
15 16 17	(C)-(C)-(C)	120.000000
16 17 19	(C)-(C)-(O)	120.000000

Table 4: Steric energy evaluation of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane)

Energy Components	Values (au)
MM Bond	0.01997910
MM Angle	0.06114791
MM Dihedral	0.03011948
MM ImpTor	0.00137509
MM vdW	0.07382068
MM Coulomb	0.00000000
Total	0.18644226 a.u.
Total	116.99438757 kcal/mol

4. Conclusions

The present work indicates that the best conformation of 6-Methylideneandrosta-1,4-diene-3,17-dione (exemestane) was found to be -116.8108588693 au (-73299.9867 kcal/mol) as calculated by RHF/ PM3 method, as performed by ArgusLab 4.0.1 suite**.** This is the minimum potential energy by using Arguslab software. At this point the drug will be more active as a steroidal aromatase inhibitor.

References

[1]. www.wikipedia.org/wiki/exemestane

[2]. E.R. Simpson, "Sources of estrogen and their importance". The Journal of Steroid Biochemistry and Molecular Biology, Vol. 86, No. (3–5), 2003, pp. 225–30.

[3]. N. Mauras, J. Lima, D. Patel, A Rini, E. Di salle, A Kwok, and B. Lippe. "Pharmacokinetics and Dose Finding of a Potent Aromatase Inhibitor, Aromasin (Exemestane), in Young Males". The Journal of Clinical Endocrinology & Metabolism. Vol 88, No 12, 2003, pp. 5951 -5956

[4]. M. Thompson, ArgusLab 4.0.1. Planaria software LLC, Seattle, W.A. 2004

[5]. C. Peng , P.Y. Ayali, H.B. Schlegel and M.J. Frisch. Using redundant internal coordinates to optimize equilibrium geometries and transition states. J.Comp.Chem., Vol. 16, 1995, pp. 49-51.

[6] C.J. Cramer and D.G. Truhlar (1992). AM1-SM2 and PM3-SM3 parameterized SCF solvation models for free energies in aqueous solution. Computer-Aided Mol. Design,Vol 6, 1992, pp. 629-666.

[7]. J.K.M Merz and P.A. Kollaman. Free energy perperturbation simulation of inhibition of thermolysin. Prediction of the free energy of binding of new inhibitor. J. Am. Chem. Soc., Vol. 11, 1989, pp. 5649-5658.

[8]. J. Simons , P. Jorgens , H. Taylor and J. Ozment . Walking on potential energy surfaces". J. Phys. Chem., Vol. 87, 1983, pp.2745-2753.

[9]. A.H. Daniel . New therapeutic agents marketed in the second half of 2009: Part 1. Pharmacy Today, Vol.16, 2010, pp. 48-59.

[10]. W.C. Still , A. Tempezk , R.C. Hawley and T. Hendrickson . Semi analytical treatment of solvation for molecular mechanics and dynamics." J. Am. Chem. Soc., Vol. 112, 1990, pp. 6127-6127.

[11] I.I.I. Dunn and A.J.K. Hopfinger, Drug Discovery,Kluwer Academic Publishers. Vol. 12, 1998, pp.167-182 .

[12] G. Cruciani , S. Clementi and M. Pastor. GOLPEguided region selection. Perspectives in Drug Discovery and Design, Vol. 12, 1998, pp.14-71.

[13] http://www.thefreedictionary.com

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