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Conformational and Drug-Receptor Binding Optimization Studies of Ergocalciferol (Vitamin D_2) as a Potential Metabolic Antagonist

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Abstract

Hartree Fock approximation was applied in order to evaluate the active conformation of widely used vitamin D supplement, Ergocalciferol (Vitamin D_2). Energy convergence function was applied in order to evaluate the Minimum Potential energy. Quantum mechanical results of the drug has shown the Heat of formation to be 0.25230684 au or 158.3251 kcal/mole. SCF energy calculated by the RHF/AM1 method as Final SCF was found to be 121.2270364801 au or -76071.1825 kcal/mole. Calculated results confirmed that the ergocalciferol has optimized geometry to be interact with the metabolic receptors are at -76071.1825 kcal/mole energy.

Keywords: Hartree fock; Energy convergence; Minimum potential energy; SCF energy

Introduction

Ergocalciferol or vitamin D_2 is chemically (3β,5Z,7E,22E)-9, 10-secoergosta-5, 7, 10(19), 22-tetraen-3-ol. It is commercially marketed under various brand names used generally for the treatment of low hormonal level of Parathyroid [1], Rickets and in response to lower level of Phosphate [2] and calcium [3] in living body. Ergocalciferol promotes the Phosphate and calcium absorption and helps in regulation of Parathyroid hormonal levels. *In vivo*, Ergocalciferol is Hydroxy methylated in liver to form 25-hydroxyvitamin D [4] and then in kidneys to form 1, 25-hydroxyvitamin [5]. Metabolites of Ergocalciferol promote the phosphate and calcium absorption in small intestine thus allow mineralization of bones [6].

Ergocalciferol is not administered in patients with hyperglycemia abnormal sensitivity and malabsorption syndrome [7].

Conformational analysis for molecules are the methods of molecular mechanics for calculation of structure, energies and other properties of the molecules [8]. Energy (E) for a molecule is regarded as the sum of all the terms as described in the equation below.

E=E stretching+E bending+E torsion+E VanderWaals+E electrostatic+E hydrogen bond+cross term (Equation 1).

Charges at the surface of the molecule/drug determine the interaction level of the molecule/drug with the receptor [9]. Bonding and antibonding electron in a molecule can impart information about the electronic charge distribution on the structure of the molecules/drugs. Difference between these bonding and antibonding electrons gives us Mullikan charges. In molecular mechanics energy is calculated as coordinate function having energy minimization as central part of the molecular mechanics. Torsion angles in random determine the ordinates for translation of molecules.

Materials and Methods

All structures of ergocalciferol for present research were drawn by using ACD labs Chemsketch. After drawing, the structures were cleaned and optimized. Ergocalciferol structures were also refined by using X-ray crystallographic technique.

Computational studies

All these calculations were performed by arguslab 4.0.1 software. For receptor binding optimization study, the coordinates of geometry were optimized selecting B3LYP/6-31G* level. The physiochemical parameters were calculated by using AM1 and DFT implementations in Hyperchem. Mínimum energy was calculated by the method of geometry convergence method [10]. Drug-receptor possible conformation was determined by geometry convergence map. ZDO, Mullikene charges were determined by using Hartree Fock approximation in ground state of the vitamin at B3LYP/6-31G* HF/6-31G*, and CAM-B3LYP/6-31G* levels [11]. Mulliken charges (χ) were computed by using equation 2 [12].

$$\chi=(EHOMO+ELUMO)/2 \quad (2)$$

The energy of charged state at the optimized geometry of the neutral molecule is the Energies at the ground state for neutral E0(N) and charged E0(N)+ respectively.

Results and Discussion

Perspective and 3D structure of the ergocalciferol drawn by ADC labs Chemsketch are shown in Figures 1 and 2. General properties of the vitamin generated by the ACD lab Chemsketch are enlisted in Table 1. Electron density map of drug in ground state is shown in Figure 3. Color map demonstrates the electrostatic potential (ESP) in Hartrees in different colors. Red color in electron map indicates itself a point of highest stability for a charge of positive test while blue color is true for charge of negative test.

No	Atoms	ZDO Charges	Mulliken Atomic Charges
1	C	-4	-4
2	C	-4	-4
3	C	-3.9999	-3.9999
4	C	-4	-4
5	C	-4	-4
6	C	3.9993	3.9995
7	C	-1.0591	-1.047
8	C	0.1788	0.1965
9	C	-0.2221	-0.2145
10	C	1.8332	1.89
11	C	1.4111	1.434
12	C	2.213	2.2535
13	C	2.9521	2.8847
14	C	3.9967	3.9983
15	C	3.9672	3.9782
16	C	3.9979	3.9986
17	C	3.9667	3.9777
18	C	3.9782	3.986
19	C	3.7783	3.8228
20	O	4.2713	4.2088
21	C	3.7659	3.8004
22	C	3.4874	3.5104
23	C	-3.7705	-3.8645
24	C	-2.6445	-2.6986
25	C	0.9054	0.9805
26	C	-3.9953	-4.0045
27	C	-4	-4
28	C	-3.0048	-3.0394
29	C	-3.9963	-4.0006
30	C	-4	-4
31	H	0.9983	0.9992
32	H	0.9884	0.9968
33	H	-0.9991	-1.0081
34	H	-1	-1
35	H	-0.9978	-1.0386
36	H	-1	-1

Table 1: ZDO and Mulliken charges of ergocalciferol.

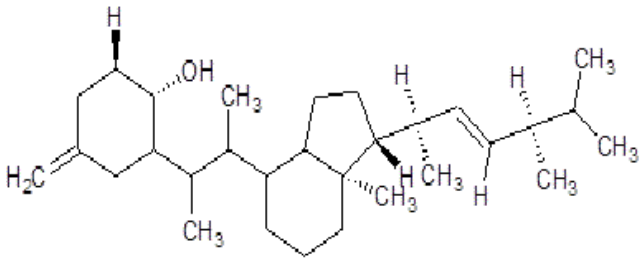
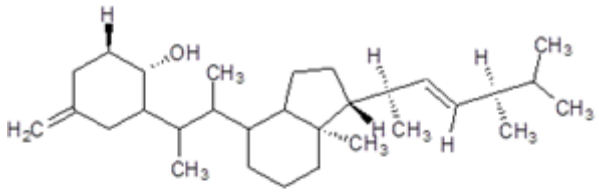


Figure 1: Perspective structure of ergocalciferol (Vitamin D_2).



Molecular Formula:	$C_{28}H_{32}O$
Formula Weight:	428.73328
Composition:	C(84.04%) H(12.23%) O(3.73%)
Molar Refractivity:	135.59 ± 0.4 cm^3
Molar Volume:	455.3 ± 5.0 cm^3
Parachor:	1109.3 ± 6.0 cm^3
Index of Refraction:	1.507 ± 0.03
Surface Tension:	35.2 ± 5.0 dyne/cm
Density:	0.94 ± 0.1 g/cm^3
Polarizability:	53.75 ± 0.5 $10^{-24} cm^3$
RDBE:	8
Monoisotopic Mass:	428.401816 Da
Nominal Mass:	428 Da
Average Mass:	428.7333 Da
M+:	428.401268 Da
M-:	428.402365 Da
[M+H]+:	429.409093 Da
[M+H]-:	429.41019 Da
[M-H]+:	427.393443 Da
[M-H]-:	427.39454 Da

Figure 2: Properties of ergocalciferol (Vitamin D_2).

Figure 3: Electron density map of ergocalciferol.

So, it is evident that hydroxyl group region of molecule is rich in electrons in comparison to rest of the molecule. Figure 4 is concerned with the highly occupied molecular orbitals (HOMO) of the drug in π

molecular orbitals calculated by ZINDO method [13]. Two colors (Red and Blue) show the positive and negative states of the orbitals respectively.

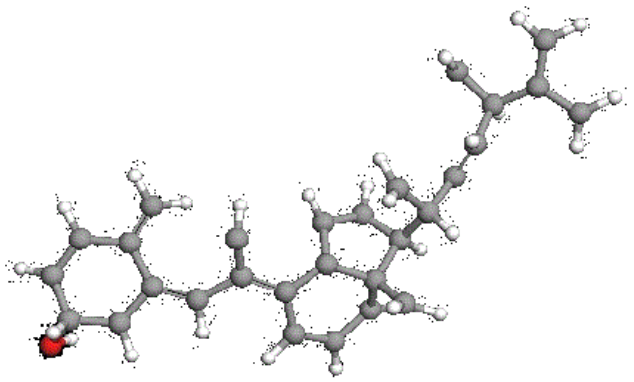


Figure 4: 3D structure of ergocalciferol (Vitamin D_2).

Red color shows a decrease in electron density while blue color is for increase in energy. An intramolecular charge transfer can be observed through the structures from the. It can be concluded from the structures that Lowest occupied molecular orbital (LUMO) is distributed on more surface of the molecule as compared to HOMO (Figure 5). Possible conformation for drug-receptor binding site can be evaluated from minimum potential energy [14]. Molecular interactions can be investigated by measuring the molecular electrostatic potentials (MEP). Recently MEP studies have been employed for electrophilic and nucleophilic interactions.

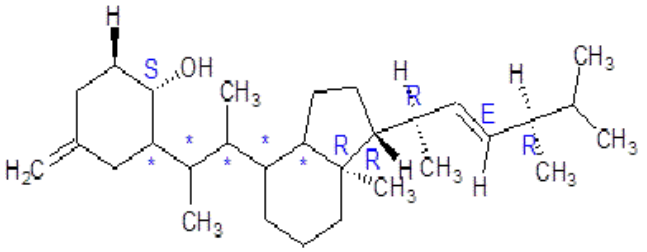


Figure 5: Sterocentres of ergocalciferol.

MEP for ergocalciferol is presented in Figure 6. pink color shows that negative electrostatic potential while green color is for positive electrostatic potential. Light color shows the area of zero electrostatic potential (Figure 7). Negative regions of the molecule are for the interactions of electrophilic regions and nucleophilic regions will attack on positive regions.

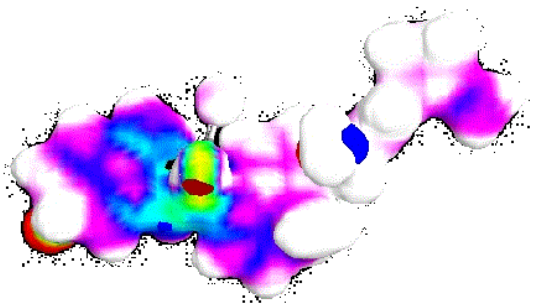


Figure 6: Molecular electrostatic potential of ergocalciferol.

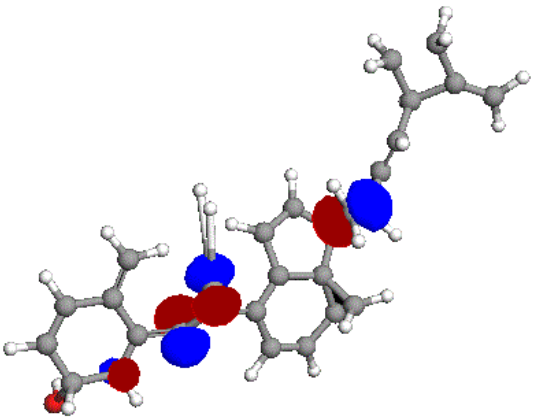


Figure 7: HOMO of ergocalciferol.

Fractional coordinates of the ergocalciferol are enlisted in Table 1. final steric energy of drug was found to be 0.25230684 au or 158.3251 kcal/mole table in Table 2. SCF energy calculated by the RHF/AM1 method as Final SCF energy was found to be -175.0616457208 au or 109852.9403 kcal/mol (Figure 8).

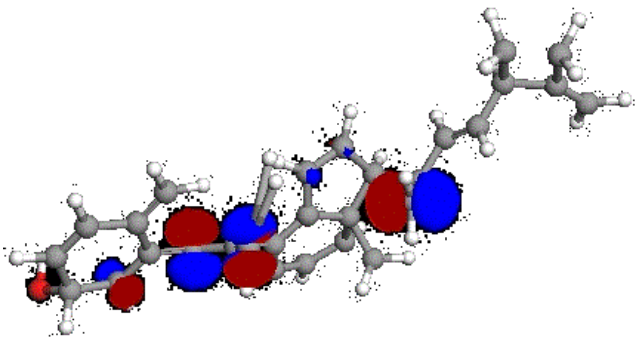


Figure 8: LUMO of ergocalciferol.

No	Atoms	X	Y	Z
1	C	16.426500	-4.287300	0.000000
2	C	10.758300	-3.709200	0.000000
3	C	10.758300	-5.042000	0.000000
4	C	9.602200	-3.050900	0.000000
5	C	8.446100	-3.709200	-0.16802
6	C	8.446100	-5.04200	0.168017
7	C	7.306000	-3.050900	-0.16802
8	C	7.306000	-5.700300	0.168017
9	C	6.149900	-3.709200	-0.16802
10	C	6.149900	-5.042000	0.168017
11	O	5.491600	-6.182000	0.000000
12	C	9.602200	-5.716400	0.000000
13	C	11.898400	-5.700300	-0.16802
14	C	14.246130	-5.72106	0.005117
15	C	13.018970	-5.02124	-0.00512
16	C	14.210600	-7.033100	0.168017
17	C	13.054500	-7.707500	-0.16802
18	C	11.898400	-7.033100	0.168017
19	C	15.241730	-4.83796	-0.1629
20	C	14.624670	-3.57604	0.1629
21	C	13.379030	-3.76206	-0.1629
22	C	15.366700	-6.374700	0.000000
23	C	15.880600	-3.066900	0.000000
24	C	17.630800	-3.725300	0.000000
25	C	18.995700	-1.862600	0.000000
26	C	20.344500	0.000000	0.000000
27	C	21.291900	-2.103500	0.000000
28	C	20.200000	-1.332700	0.000000
29	C	17.775300	-2.408600	0.000000
30	C	18.449700	-0.658300	0.000000
31	H	4.817200	-5.042000	0.000000
32	H	16.105400	-5.796600	0.000000
33	H	16.956400	-5.491600	0.000000
34	H	19.541600	-3.083000	0.000000
35	H	16.699500	-1.637800	0.000000
36	H	9.805672	-3.159200	0.000000
37	H	11.71093	-3.159200	-0.000000
38	H	9.608770	-1.950920	-0.000000
39	H	10.55153	-3.606580	0.000000
40	H	7.306046	-1.950900	0.000000
41	H	7.312570	-6.800280	0.000000
42	H	5.200574	-3.153520	0.000000
43	H	5.757344	-6.75857	-0.89831
44	H	9.607129	-6.81639	-0.000000
45	H	15.16323	-7.583100	0.000000
46	H	13.04957	-8.80749	0.000000
47	H	10.94332	-7.57883	0.000000
48	H	15.30516	-2.70572	0.000000
49	H	12.53284	-2.99777	0.000000
50	H	16.083640	-6.23721	0.822857
51	H	15.59991	-7.06645	-0.82286
52	H	16.449820	-2.20976	-0.38898
53	H	14.86222	-2.91992	0.38898
54	H	18.532050	-4.35597	0.000000
55	H	21.35086	0.444107	0.000000
56	H	19.456710	0.649484	0.000000
57	H	21.19184	-3.19894	0.000000
58	H	22.290610	-1.64244	0.000000
59	H	19.0128	0.200880	-0.39336
60	H	17.43239	-0.515636	0.393359

Table 2: Angle coordinates of ergocalciferol.

Conclusions

Ergocalciferol is an important metabolite in Human living system which interacts with liver and kidney to form metabolites. Obtained results has shown that ergocalciferol has an optimized geometry to be bound with these metabolic receptors is at -175.0616457208 au or 109852.9403 kcal/mol SCF energy.

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