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Molecular Mechanics Steric Energy Evaluation of Reversible Acetyl cholinesterase Inhibitor, Donepezil, (*RS*)-2-([1-benzyl-4-piperidyl] methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one

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ABSTRACT

Donepezil, (RS)-2-[(1-benzyl-4-piperidyl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one is a specific and reversible inhibitor of acetyl cholinesterase, for the symptomatic treatment of Alzheimer's disease and vascular dementia. The universal force field molecular mechanics method was used to calculate the steric energy of (RS)-2-[(1-benzyl-4-piperidyl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one (Donepezil) using Arguslab software. Molecular mechanics calculations were based on specific interactions within the molecule. These interactions included stretching or compressing of bond beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that came close together, and the electrostatic interactions between partial charges in donepezil due to polar bonds. The steric energy calculated for donepezil was 100.5289 kcal/mol. It was concluded that the minimum potential energy required for donepezil to inhibit Acetyl cholinesterase is 100.5289 kcal/mol.

Key words: *Donepezil, Molecular mechanics, Acetyl cholinesterase, Arguslab software.*

1. INTRODUCTION

Molecular mechanics calculates the energy of a molecule and then adjusts the energy through changes in bond lengths and angles to obtain the minimum energy structure [1]. Molecular mechanics assumes the steric energy of a molecule to arise from a few, specific interactions within a molecule. These interactions include the stretching or compressing of bond beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that come close together, and the electrostatic interactions between partial charges in a molecule due to polar bonds [2,3]. To quantify the contribution of each, these interactions can be modeled by a potential function that gives the energy of the interaction as a function of distance, angle, or charge [2,3]. The total steric energy of a molecule can be written as a sum of the energies of the interactions:

$$E_{\text{Steric energy}} = E_{str} + E_{bend} + E_{str-bend} + E_{oop} + E_{tor} + E_{VdW} + E_{qq} \quad (1)$$

The bond stretching, bending, stretch-bend, out of plane and torsion interactions are called bonded interactions because the atoms involved must be directly bonded or bonded to a common atom. The Van der Waals and electrostatic (qq) interactions are between non-bonded atoms [2,3]. The universal force field (UFF) is a molecular mechanics method. The method was first introduced in 1993 by Rappe et al. [4] as a way to treat the entire periodic table. UFF is good for initially cleaning up structures that you have sketched in the builder, and for refining initial geometries [5,6]. Molecular mechanics is used routinely to look at the structures and conformation energies of organic and conformation energies of organic and biological molecules because of fairly complete, specific force fields for these classes of compounds [6]. Donepezil is a specific and reversible inhibitor of acetyl cholinesterase, registered in New Zealand for the symptomatic treatment of Alzheimer's disease and vascular dementia. Some guidelines recommend that donepezil (and other acetyl cholinesterase inhibitors) only be used in moderate Alzheimer's disease [7,8]. However, there is evidence that donepezil has a positive effect in some people with severe [9] and mild Alzheimer's disease [10]. In practice, donepezil may be used in any patient with Alzheimer's disease, ranging from the newly diagnosed to those with severe disease. Donepezil has been tested (off label)

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in other cognitive disorders, including Lewy body dementia [11], and vascular dementia [12], but it is not currently approved for these indications. Donepezil has also been found to improve sleep apnea in Alzheimer's patients [13]. A 2001 study suggested that the donepezil can improve speech in autistic children. The study found the speech of autistic children that was originally mildly to moderately affect appeared to improve with the use of donepezil [14]. We hereby present the steric energy evaluation of donepezil.

2. EXPERIMENTAL

All conformational analysis (geometry optimization) study was performed on a window based computer using Argus Lab 4.0.1 and ACD Lab Chem Sketch software. Donepezil structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). The donepezil structure was generated by Argus lab, and minimization was performed with UFF molecular mechanics method [4-6]. The minimum potential energy was calculated by using geometry convergence function in Argus lab software.

3. RESULTS AND DISCUSSION

The prospective view, active conformation, electrostatic potential (ESP), highest occupied molecular orbital's of donepezil (HOMO) and lowest unoccupied molecular orbital's of donepezil (LUMO) are presented in Figures 1-5 respectively. The atomic coordinates, bond length, bond angles, dihedral angles, improper torsions and final potential energy evaluation are presented in Tables 1-6, respectively.

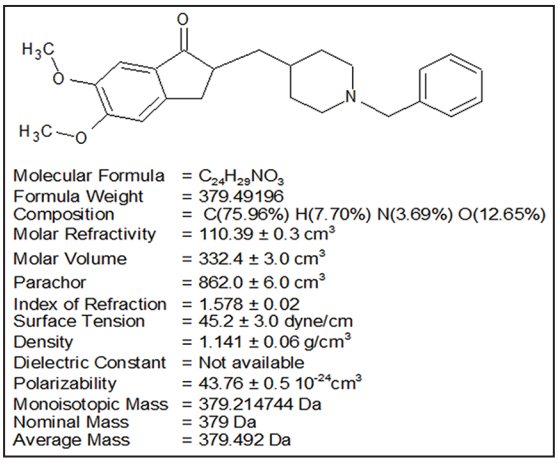

Figure 1: Prospective view of donezepil by ACD/ ChemSketch.

Argus Lab software generated mapped surface of donepezil (Figure 3). The ESP was mapped onto the surface of the electron density. In the ESP-mapped density surface, the electron density surface gave the shape of the surface while the value of the ESP on that surface gave the colors [15]. The ESP is the potential energy felt by a positive "test" charge at a particular point in space [15]. Thus, the ESP-mapped density surface showed regions of donepezil that might be more favorable to nucleophilic or electrophilic attack, making these types of surfaces useful for qualitative interpretations of chemical reactivity [15]. Another way to think of ESP-mapped density surface of donepezil is that it showed "where" the frontier electron density for the molecule is greatest (or least) relative to the nuclei [15]. The red region showed the greatest increase in electron density centered over the carbon (the ESP difference is negative indicating that the ESP became more negative as electron density increased in this region). Also, the magenta region showed the greatest decrease in electron density (since the electron density decreased, the ESP became more positive). The various other colors showed how ESP difference changes on all points of the electron density surface. The HOMO of donepezil (Figure 4) is a non-bonding type MO that is in the plane of the molecule. The LUMO (Figure 5) is a π MO perpendicular to the plane of the molecule. The first excited state of donepezil is an n→π* transition that is composed almost exclusively of the HOMO→ LUMO transition. The HOMO is localized to the plane of the molecule and is a non-bonding MO. The LUMO is perpendicular to the plane of the molecule and is a combination of the p_z atomic orbitals. Augus lab software calculated E_{str} of donepezil to the 0.010833 a.u. (Table 6). The calculated was based on the Hookian potential for an ideal spring as shown in Equation 2 [2,3].

$$E_{STR} = 1/2K_{s,ij}\left(r_{ij} - r_0\right)^2 \quad (2)$$

The term ks, ij is the stretching force constant for the bond and rij is the distance between two atoms. E_{str} represented the energy required to stretch or compress

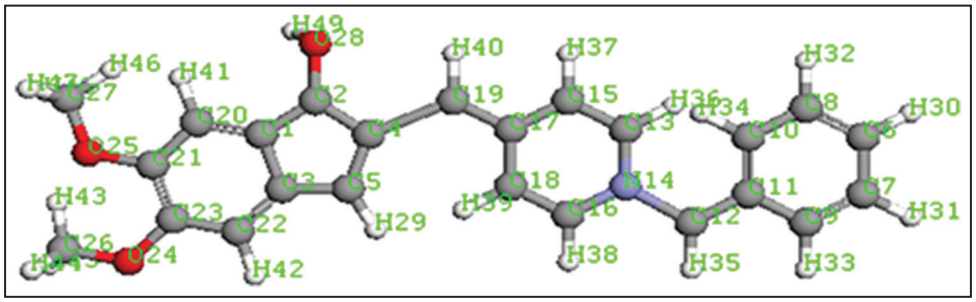

Figure 2: Prospective view of active conformation of donepezil by Arguslab Software.

Figure 3: Electrostatic potential mapped density of donepezil.

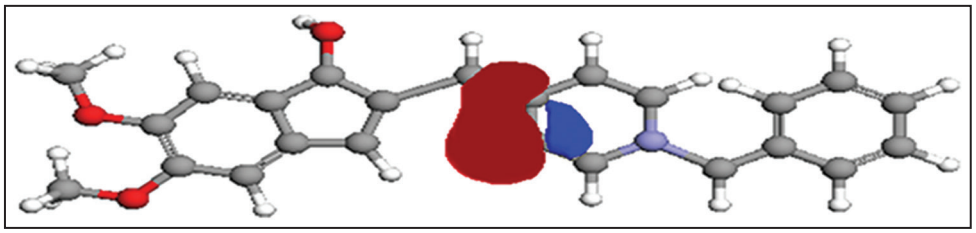

Figure 4: Highest occupied molecular orbital's of donepezil.

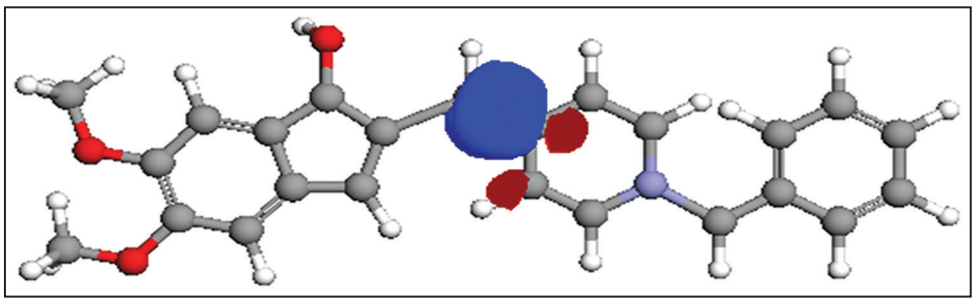

Figure 5: Lowest unoccupied molecular orbital's of donepezil.

a bond between two atoms. E_{bend} is the energy required to bend a bond from its equilibrium angle, ϕ_0. Again this system was modeled by a spring, and the energy was given by the Hookian potential with respect to angle (Equation 3) [2,3]:

$$E_{bend} = 1/2K_{b,ijk}(\phi_{ijk} - \phi_o)^2 \quad (3)$$

The terms $k_{b,ijk}$ is the bending force constant and ϕ_{ijk} is the instantaneous bond angle. $E_{str\text{-}bend}$ is the stretch-bend interaction energy that accounted for the two associated bond lengths increase when a bond is bent. The potential function that modeled this interaction is shown in Equation 4 [2,3]:

$$E_{str\text{-}bend} = 1/2K_{sb,ijk}\left(r_{ij} - r_o\right)\left(\phi_{ijk} - \phi_o\right) \quad (4)$$

The terms ksb, ijk is the stretch-bend force constant for the bond between atoms i and j with the bend between atoms i, j, and k. Calculated steric energy for the E_{bend} and $E_{str\text{-}bend}$ of donepezil was given as 0.086029 a.u. (Table 6). E_{oop} is the energy required to deform a planar group of atoms from its equilibrium angle, ω_o, usually equal to zero [2,3]. This force field term is useful for sp^2 hybridized atoms such as doubly bonded carbon atoms and some small ring systems. Again this system was modeled by a spring, and the energy was given by the Hookian potential with respect to planar angle (Equation 5) [2,3]:

$$E_{oop} = 1/2K_{o,ijkl}(\omega_{ijkl} - \omega_o)^2 \quad (5)$$

The terms $k_{o,ijkl}$ is the bending force constant and ω_{ijkl} is the instantaneous bond angle. The out of the plane term is also called the improper torsion in some force fields. The oop term is called the improper torsion, because like a dihedral torsion the term depended on four atoms, but the atoms are numbered in a different order. E_{oop} for donepezil was calculated to be 0.001927 (Table 6).

3.1. Torsional Interactions

E_{tor} is the energy of torsion needed to rotate about bonds. Torsional energies are usually important only for single bonds because double and triple bonds are too rigid to permit rotation. Torsional interactions were modeled by the potential function in Equation 6 [1-3].

$$E_{tor} = 1/2K_{tor,1}(1+\cos\phi) + 1/2K_{tor,2}\left(1+\cos 2\phi\right) + 1/2K_{tor,3} + \left(1+\mathrm{Cos}\,3\phi\right) \quad (6)$$

The angle ϕ is the dihedral angle about the bond. The constants k_{tor}, 1, k_{tor}, 2 and k_{tor}, 3 are the torsional constants for one-fold, two-fold and three-fold

Table 1: Atomic coordinates of donepezil.

S.No	Atoms	X	Y	Z
1	C	11.98360	−7.945500	0.000000
2	C	13.06030	−7.164700	0.000000
3	C	12.39350	−9.210800	0.000000
4	C	14.13560	−7.947400	0.000000
5	C	13.72370	−9.211900	0.000000
6	C	24.06630	−8.004000	0.000000
7	C	24.06630	−9.334000	0.000000
8	C	22.91440	−7.339000	0.000000
9	C	22.91440	−9.999000	0.000000
10	C	21.76260	−8.004000	0.000000
11	C	21.76260	−9.334000	0.000000
12	C	20.61080	−9.999000	0.000000
13	C	19.29110	−7.827800	0.000000
14	N	19.29110	−9.157800	0.000000
15	C	18.13920	−7.162800	0.000000
16	C	18.13920	−9.822800	0.000000
17	C	16.98740	−7.827800	0.000000
18	C	16.98740	−9.157800	0.000000
19	C	15.83560	−7.162800	0.000000
20	C	10.68300	−7.667900	0.000000
21	C	9.792200	−8.655600	0.000000
22	C	11.50280	−10.19840	0.000000
23	C	10.20210	−9.920800	0.000000
24	O	9.311400	−10.90840	0.000000
25	O	8.491500	−8.378000	0.000000
26	C	8.010700	−10.63080	0.000000
27	C	8.081500	−7.112700	0.000000
28	O	13.06150	−5.834700	0.000000
29	H	14.27291	−10.16498	0.000000
30	H	25.01892	−7.454000	0.000000
31	H	25.01892	−9.884000	−0.000000
32	H	22.91436	−6.239000	−0.000000
33	H	22.91436	−11.09900	−0.000000
34	H	20.80996	−7.454005	0.000000
35	H	20.61080	−11.09900	−0.000000
36	H	20.24372	−7.277800	0.000000
37	H	18.13916	−6.062800	−0.000000
38	H	18.13916	−10.92280	−0.000000
39	H	16.03476	−9.707795	0.000000
40	H	15.83560	−6.062800	−0.000000
41	H	10.34396	−6.621451	0.000000
42	H	11.84185	−11.24484	0.000000
43	H	7.868026	−9.540092	0.000000
44	H	7.544151	−11.06135	0.898306
45	H	7.544151	−11.06135	−0.898306
46	H	8.954725	−6.443762	0.000000
47	H	7.475347	−6.923952	0.898306
48	H	7.475347	−6.923952	−0.898306
49	H	12.54337	−5.467826	−0.898306

(*Contd...*)

Table 2: Bond length of donepezil.

S.No.	Atoms	Bond length
1	(C1)-(C2)	1.458000
2	(C1)-(C20)	1.323387
3	(C1)-(C3)	1.458000
4	(C2)-(C4)	1.458000
5	(C2)-(O28)	1.407689
6	(C3)-(C5)	1.458000
7	(C3)-(C22)	1.323387
8	(C4)-(C5)	1.458000
9	(C4)-(C19)	1.461000
10	(C6)-(C7)	1.458000
11	(C6)-(C8)	1.323387
12	(C7)-(C9)	1.323387
13	(C8)-(C10)	1.458000
14	(C9)-(C11)	1.458000
15	(C10)-(C11)	1.323387
16	(C11)-(C12)	1.461000
17	(C12)-(N14)	1.436817
18	(C13)-(N14)	1.433804
19	(C13)-(C15)	1.458000
20	(N14)-(C16)	1.433804
21	(C15)-(C17)	1.458000
22	(C16)-(C18)	1.458000
23	(C17)-(C18)	1.458000
24	(C17)-(C19)	1.461000
25	(C20)-(C21)	1.458000
26	(C21)-(C23)	1.323387
27	(C21)-(O25)	1.407689
28	(C22)-(C23)	1.458000
29	(C23)-(O24)	1.407689
30	(O24)-(C26)	1.436155
31	(O25)-(C27)	1.436155
32	(C5)-(H29)	1.084582
33	(C6)-(H30)	1.084582
34	(C7)-(H31)	1.084582
35	(C8)-(H32)	1.084582
36	(C9)-(H33)	1.084582
37	(C10)-(H34)	1.084582

(*Contd...*)

Table 2: (*Continued...*)

S.No.	Atoms	Bond length
38	(C12)-(H35)	1.087584
39	(C13)-(H36)	1.084582
40	(C15)-(H37)	1.084582
41	(C16)-(H38)	1.084582
42	(C18)-(H39)	1.084582
43	(C19)-(H40)	1.087584
44	(C20)-(H41)	1.084582
45	(C22)-(H42)	1.084582
46	(C26)-(H43)	1.112599
47	(C26)-(H44)	1.112599
48	(C26)-(H45)	1.112599
49	(C27)-(H46)	1.112599
50	(C27)-(H47)	1.112599
51	(C27)-(H48)	1.112599
52	(O28)-(H49)	1.033746

Table 3: Bond angles of donepezil.

Atoms	Bond angles	Alternate bond angles
(C2) (C1) (C20)	120.0000	216.4880
(C2) (C1) (C3)	120.0000	188.4420
(C1) (C2) (C4)	120.0000	188.4420
(C1) (C2) (O28)	120.0000	238.7368
(C20) (C1) (C3)	120.0000	216.4880
(C1) (C20) (C21)	120.0000	216.4880
(C1) (C20) (H41)	120.0000	123.0349
(C1) (C3) (C5)	120.0000	188.4420
(C1) (C3) (C22)	120.0000	216.4880
(C4) (C2) (O28)	120.0000	238.7368
(C2) (C4) (C5)	120.0000	188.4420
(C2) (C4) (C19)	120.0000	187.8614
(C2) (O28) (H49)	104.5100	164.0406
(C5) (C3) (C22)	120.0000	216.4880
(C3) (C5) (C4)	120.0000	188.4420
(C3) (C5) (H29)	120.0000	102.9285
(C3) (C22) (C23)	120.0000	216.4880
(C3) (C22) (H42)	120.0000	123.0349
(C5) (C4) (C19)	120.0000	187.8614
(C4) (C5) (H29)	120.0000	102.9285
(C4) (C19) (C17)	120.0000	187.2836
(C4) (C19) (H40)	120.0000	102.2165
(C7) (C6) (C8)	120.0000	216.4880
(C6) (C7) (C9)	120.0000	216.4880
(C7) (C6) (H30)	120.0000	102.9285
(C6) (C7) (H31)	120.0000	102.9285
(C6) (C8) (C10)	120.0000	216.4880
(C8) (C6) (H30)	120.0000	123.0349
(C6) (C8) (H32)	120.0000	123.0349
(C7) (C9) (C11)	120.0000	216.4880
(C9) (C7) (H31)	120.0000	123.0349
(C7) (C9) (H33)	120.0000	123.0349
(C8) (C10) (C11)	120.0000	216.4880
(C10) (C8) (H32)	120.0000	102.9285
(C8) (C10) (H34)	120.0000	102.9285
(C9) (C11) (C10)	120.0000	216.4880
(C9) (C11) (C12)	120.0000	187.8614
(C11) (C9) (H33)	120.0000	102.9285
(C10) (C11) (C12)	120.0000	215.7608
(C11) (C10) (H34)	120.0000	123.0349
(C11) (C12) (N14)	120.0000	255.4567
(C11) (C12) (H35)	120.0000	102.2165
(C12) (N14) (C13)	120.0000	197.5205
(C12) (N14) (C16)	120.0000	197.5205
(N14) (C12) (H35)	120.0000	140.3737
(N14) (C13) (C15)	120.0000	257.0535
(C13) (N14) (C16)	120.0000	198.1441
(N14) (C13) (H36)	120.0000	141.3654
(C13) (C15) (C17)	120.0000	188.4420
(C15) (C13) (H36)	120.0000	102.9285
(C13) (C15) (H37)	120.0000	102.9285
(N14) (C16) (C18)	120.0000	257.0535
(N14) (C16) (H38)	120.0000	141.3654
(C15) (C17) (C18)	120.0000	188.4420
(C15) (C17) (C19)	120.0000	187.8614
(C17) (C15) (H37)	120.0000	102.9285
(C16) (C18) (C17)	120.0000	188.4420
(C18) (C16) (H38)	120.0000	102.9285
(C16) (C18) (H39)	120.0000	102.9285
(C18) (C17) (C19)	120.0000	187.8614
(C17) (C18) (H39)	120.0000	102.9285
(C17) (C19) (H40)	120.0000	102.2165
(C20) (C21) (C23)	120.0000	216.4880
(C20) (C21) (O20)	120.0000	238.7368
(C21) (C20) (H41)	120.0000	102.9285
(C23) (C21) (O25)	120.0000	275.5759
(C21) (C23) (C22)	120.0000	216.4880
(C21) (C23) (O24)	120.0000	275.5759
(C21) (O25) (C27)	104.5100	293.4398
(C22) (C23) (O24)	120.0000	238.7368

(*Contd...*)

(*Contd...*)

Table 3: (*Continued...*)

Atoms	Bond angles	Alternate bond angles
(C23) (C22) (H42)	120.0000	102.9285
(C23) (O24) (C26)	104.5100	293.4398
(O24) (C26) (H43)	109.4700	156.1164
(O24) (C26) (H44)	109.4700	156.1164
(O24) (C26) (H45)	109.4700	156.1164
(O25) (C27) (H46)	109.4700	156.1164
(O25) (C27) (H47)	109.4700	156.1164
(O25) (C27) (H48)	109.4700	156.1164
(H43) (C26) (H44)	109.4700	74.84952
(H43) (C26) (H45)	109.4700	74.84952
(H44) (C26) (H45)	109.4700	74.84952
(H46) (C27) (H47)	109.4700	74.84952
(H46) (C27) (H48)	109.4700	74.84952
(H47) (C27) (H48)	109.4700	74.84952

Table 4: Dihedral angles of donepezil.

S.No	Atoms	Dihedral angles
1	(C4)-(C2)-(C1)-(C20)	2.500000
2	(O28)-(C2)-(C1)-(C20)	2.500000
3	(C2)-(C1)-(C20)-(C21)	9.743388
4	(C2)-(C1)-(C20)-(H41)	9.743388
5	(C4)-(C2)-(C1)-(C3)	2.500000
6	(O28)-(C2)-(C1)-(C3)	2.500000
7	(C2)-(C1)-(C3)-(C5)	2.500000
8	(C2)-(C1)-(C3)-(C22)	2.500000
9	(C1)-(C2)-(C4)-(C5)	2.500000
10	(C1)-(C2)-(C4)-(C19)	2.500000
11	(C1)-(C2)-(O28)-(H49)	5.000000
12	(C21)-(C20)-(C1)-(C3)	9.743388
13	(H41)-(C20)-(C1)-(C3)	9.743388
14	(C20)-(C1)-(C3)-(C5)	2.500000
15	(C20)-(C1)-(C3)-(C22)	2.500000
16	(C1)-(C20)-(C21)-(C23)	2.500000
17	(C1)-(C20)-(C21)-(O25)	2.500000
18	(C1)-(C3)-(C5)-(C4)	2.500000
19	(C1)-(C3)-(C5)-(H29)	2.500000
20	(C1)-(C3)-(C22)-(C23)	9.743388
21	(C1)-(C3)-(C22)-(H42)	9.743388
22	(C5)-(C4)-(C2)-(O28)	2.500000
23	(C19)-(C4)-(C2)-(O28)	2.500000
24	(C4)-(C2)-(O28)-(H49)	5.000000
25	(C2)-(C4)-(C5)-(C3)	2.500000
26	(C2)-(C4)-(C5)-(H29)	2.500000
27	(C2)-(C4)-(C19)-(C17)	2.500000
28	(C2)-(C4)-(C19)-(H40)	2.500000
29	(C4)-(C5)-(C3)-(C22)	2.500000
30	(H29)-(C5)-(C3)-(C22)	2.500000
31	(C5)-(C3)-(C22)-(C23)	9.743388
32	(C5)-(C3)-(C22)-(H42)	9.743388
33	(C3)-(C5)-(C4)-(C19)	2.500000
34	(C3)-(C22)-(C23)-(C21)	2.500000
35	(C3)-(C22)-(C23)-(O24)	2.500000
36	(H29)-(C5)-(C4)-(C19)	2.500000
37	(C5)-(C4)-(C19)-(C17)	2.500000
38	(C5)-(C4)-(C19)-(H40)	2.500000
39	(C4)-(C19)-(C17)-(C15)	2.500000
40	(C4)-(C19)-(C17)-(C18)	2.500000
41	(C9)-(C7)-(C6)-(C8)	2.500000
42	(H31)-(C7)-(C6)-(C8)	2.500000
43	(C7)-(C6)-(C8)-(C10)	9.743388
44	(C7)-(C6)-(C8)-(H32)	9.743388
45	(H30)-(C6)-(C7)-(C9)	2.500000
46	(C6-(C7)-(C9)-(C11)	9.743388
47	(C6)-(C7)-(C9)-(H33)	9.743388
48	(H31)-(C7)-(C6)-(H30)	2.500000
49	(H30)-(C6)-(C8)-(C10)	9.743388
50	(C6)-(C8)-(C10)-(C11)	2.500000
51	(C6)-(C8)-(C10)-(H34)	2.500000
52	(H32)-(C8)-(C6)-(H30)	9.743388
53	(H31)-(C7)-(C9)-(C11)	9.743388
54	(C7)-(C9)-(C11)-(C10)	2.500000
55	(C7)-(C9)-(C11)-(C12)	2.500000
56	(H33)-(C9)-(C7)-(H31)	9.743388
57	(H32)-(C8)-(C10)-(C11)	2.500000
58	(C8)-(C10)-(C11)-(C9)	9.743388
59	(C8)-(C10)-(C11)-(C12)	9.743388
60	(H34)-(C10)-(C8)-(H32)	2.500000
61	(H33)-(C9)-(C11)-(C10)	2.500000
62	(C9)-(C11)-(C10)-(H34)	9.743388
63	(H33)-(C9)-(C11)-(C12)	2.500000
64	(C9)-(C11)-(C12)-(N14)	2.500000
65	(C9)-(C11)-(C12)-(H35)	2.500000
66	(H34)-(C10)-(C11)-(C12)	9.743388
67	(C10)-(C11)-(C12)-(N14)	2.500000
68	(C10)-(C11)-(C12)-(H35)	2.500000
69	(C11)-(C12)-(N14)-(C13)	2.500000
70	(C11)-(C12)-(N14)-(C16)	2.500000
71	(H35)-(C12)-(N14)-(C13)	2.500000

(*Contd...*)

(*Contd...*)

Table 4: (*Continued...*)

S.No	Atoms	Dihedral angles
72	(C12)-(N14)-(C13)-(C15)	2.500000
73	(C12)-(N14)-(C13)-(H36)	2.500000
74	(H35)-(C12)-(N14)-(C16)	2.500000
75	(C12)-(N14)-(C16)-(C18)	2.500000
76	(C12)-(N14)-(C16)-(H38)	2.500000
77	(C16)-(N14)-(C13)-(C15)	2.500000
78	(N14)-(C13)-(C15)-(C17)	2.500000
79	(N14)-(C13)-(C15)-(H37)	2.500000
80	(H36)-(C13)-(N14)-(C16)	2.500000
81	(C13)-(N14)-(C16)-(C18)	2.500000
82	(C13)-(N14)-(C16)-(H38)	2.500000
83	(H36)-(C13)-(C15)-(C17)	2.500000
84	(C13)-(C15)-(C17)-(C18)	2.500000
85	(C13)-(C15)-(C17)-(C19)	2.500000
86	(H37)-(C15)-(C13)-(H36)	2.500000
87	(N14)-(C16)-(C18)-(C17)	2.500000
88	(N14)-(C16)-(C18)-(H39)	2.500000
89	(H37)-(C15)-(C17)-(C18)	2.500000
90	(C15)-(C17)-(C18)-(C16)	2.500000
91	(C15)-(C17)-(C18)-(H39)	2.500000
92	(H37)-(C15)-(C17)-(C19)	2.500000
93	(C15)-(C17)-(C19)-(H40)	2.500000
94	(H38)-(C16)-(C18)-(C17)	2.500000
95	(C16)-(C18)-(C17)-(C19)	2.500000
96	(H39)-(C18)-(C16)-(H38)	2.500000
97	(H39)-(C18)-(C17)-(C19)	2.500000
98	(C18)-(C17)-(C19)-(H40)	2.500000
99	(H41)-(C20)-(C21)-(C23)	2.500000
100	(C20)-(C21)-(C23)-(C22)	9.743388
101	(C20)-(C21)-(C23)-(O24)	9.743388
102	(H41)-(C20)-(C21)-(O25)	2.500000
103	(C20)-(C21)-(O25)-(C27)	5.000000
104	(C22)-(C23)-(C21)-(O25)	9.743388
105	(O24)-(C23)-(C21)-(O25)	9.743388
106	(C23)-(C21)-(O25)-(C27)	5.000000
107	(C21)-(C23)-(C22)-(H42)	2.500000
108	(C21)-(C23)-(O24)-(C26)	5.000000
109	(C21)-(O25)-(C27)-(H46)	0.065100
110	(C21)-(O25)-(C27)-(H47)	0.065100
111	(C21)-(O25)-(C27)-(H48)	0.065100
112	(H42)-(C22)-(C23)-(O24)	2.500000
113	(C22)-(C23)-(O24)-(C26)	5.000000
114	(C) 23-(O24)-(C26)-(H43)	0.065100
115	(C23)-(O24)-(C26)-(H44)	0.065100
116	(C23)-(O24)-(C26)-(H45)	0.065100

Table 5: Improper torsions of donepezil.

S.No.	Atoms	Improper torsions
1	(C20)-(C3)-(C1)-(C2)	2.000000
2	(C4)-(O28)-(C2)-(C1)	2.000000
3	(C21)-(H41)-(C20)-(C1)	2.000000
4	(C5)-(C22)-(C3)-(C1)	2.000000
5	(C5)-(C19)-(C4)-(C2)	2.000000
6	(C4)-(H29)-(C5)-(C3)	2.000000
7	(C23)-(H42)-(C22)-(C3)	2.000000
8	(C17)-(H40)-(C19)-(C4)	2.000000
9	(C8)-(H30)-(C6)-(C7)	2.000000
10	(C9)-(H31)-(C7)-(C6)	2.000000
11	(C10)-(H32)-(C8)-(C6)	2.000000
12	(C11)-(H33)-(C9)-(C7)	2.000000
13	(C11)-(H34)-(C10)-(C8)	2.000000
14	(C10)-(C12)-(C11)-(C9)	2.000000
15	(N14)-(H35)-(C12)-(C11)	2.000000
16	(C13)-(C16)-(N14)-(C12)	2.000000
17	(C15)-(H36)-(C13)-(N14)	2.000000
18	(C17)-(H37)-(C15)-(C13)	2.000000
19	(C18)-(H38)-(C16)-(N14)	2.000000
20	(C18)-(C19)-(C17)-(C15)	2.000000
21	(C17)-(H39)-(C18)-(C16)	2.000000
22	(C23)-(O25)-(C21)-(C20)	2.000000
23	(C22)-(O24)-(C23)-(C21)	2.000000

Table 6: Final energy evaluation.

S.No.	Force field	Energy components (au)
1	Molecular mechanics bond (E_{str})	0.010833
2	Molecular mechanics angle (E_{bend})+ ($E_{str\text{-}bend}$)	0.086029
3	Molecular mechanics dihedral (E_{tor})	0.012869
4	Molecular mechanics ImpTor (E_{oop})	0.001927
5	Molecular mechanics vdW (E_{VdW})	0.048542
6	Molecular mechanics coulomb (E_{qq})	0.000000
Total		0.160202 a.u. (100.5289 kcal/mol)

rotational barriers, respectively. E_{tor} of donepezil was calculated to be 0.012869 a.u. (Table 6). Van der Waals interactions contributed to the steric interactions in donepezil. The formula for the Van der Waals energy is shown in Equation 7 [1-3]

$$E_{VdW,ij} = -\frac{A}{rij^6} + \frac{B}{rij^{12}} \quad (7)$$

A and B are constants dependent upon the identities of the two atoms involved, and r_{ij} is the distance, in Angstroms, separating the two nuclei. This equation is also called the Lennard-Jones potential. The $-A/r^6$ part is the attractive part, and the $+B/r^{12}$ part is the repulsive part of the interaction. For two hydrogen atoms in any molecule: A=70.38 kcal Å^6, B=6286 kcal Å^{12}. E_{VdW} was calculated to be 0.048542 a.u.

3.2. Electrostatic Interactions

If bonds in the donepezil were polar, partial electrostatic charges will reside on the atoms. The electrostatic interactions are represented with a coulombic potential function shown in Equation 8 [1-3].

$$E_{qq,ij} = \frac{cQ_iQ_j}{4\pi\varepsilon_r r_{ij}} \quad (8)$$

The Qi and Qj are the partial atomic charges for atoms i and j separated by a distance rij. ε_r is the relative dielectric constant. For gas phase calculations, ε is normally set to 1. Larger values of ε_r are used to approximate the dielectric effect of intervening solute or solvent atoms in solution. c is a units conversion constant; for kcal/mol, c=4172.8 kcal mol^{-1} Å. Like charges raised the steric energy, while opposite charges lowered the energy. E_{qq} was calculated to be 0.000000 a.u.

Final energy evaluation was calculated to be 0.160202 a.u. (100.5289 kcal/mol). The most feasible potential energy for donepezil to act as a specific and reversible inhibitor of acetyl cholinesterase, for the symptomatic treatment of Alzheimer's disease and vascular dementia, was found to be 0.160202 a.u. (100.5289 kcal/mol).

4. CONCLUSION

The UFF molecular mechanics method have been used to calculate the steric energy of (RS)-2-[(1-benzyl-4-piperidyl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one (Donepezil) using Argus lab software. Molecular mechanics calculations were based on specific interactions within the molecule. These interactions included stretching or compressing of bond beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that came close together, and the electrostatic interactions between partial charges in a donepezil due to polar bonds. The steric energy calculated for donepezil was 100.5289 kcal/mol. It was concluded that the minimum potential energy required for donepezil to inhibit acetyl cholinesterase is 100.5289 kcal/mol.

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***Bibliographical Sketch**

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