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Molecular Mechanics Studies of a Psychostimulating Agent, 2-[(Diphenylmethyl) Sulfinyl] Acetamide (Modafinil)

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Abstract

2-[(Diphenylmethyl) sulfinyl] acetamide (modafinil), is a wake-promoting agent use for treatment of excessive daytime sleepiness in narcolepsy. Molecular mechanics studies of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) was performed according to the Hartree-Fock (HF) calculation method by Argus Lab 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 Argus Lab 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

Modafinil, Molecular Mechanics, Arguslab Software, Molecular Mechanics

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1. Introduction

Modafinil, (2-[(Diphenylmethyl) sulfinyl] acetamide) is a novel wake-promoting agent for treatment of excessive somnolence as a feature of narcolepsy [1]. It is currently approved by the United States Food and Drug Administration as a schedule IV agent to treat excessive daytime sleepiness in narcolepsy, shift work sleep disorder, and obstructive sleep apnea/hypopnea syndrome. It has been popularly categorized as a psychostimulant due to its wake-promoting properties [2]. However, it has shown a number of effects on physiology and behavior in both animal models and in humans, which suggest a divergent mechanism of action compared to amphetamine which includes a lower liability to abuse and a lower risk of adverse effects on organ systems such as the cardiovascular system [1]. As a result, great interest has emerged in the possibility that 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) may demonstrate clinical efficacy in a number of medical and psychiatric conditions currently treated with stimulants, such as various fatigue syndromes, treatment-resistant, depression, and attention deficit/hyperactivity disorder (ADHD) [3].

The geometry of a molecule has a great impact on its energy level, physical and chemical properties. As the molecule rotates, it adopts different conformations and spatial arrangements to achieve one of the stable states of lowest energy [4]. The total molecular energy can be evaluated in terms of potential energy surface as a sum of energies associated with each type of bonded interactions i.e. bond length, bond angle and dihedral angle as well as non-bonded interactions (Vander Waals and electrostatic) taking place in a molecule and on atomic properties of a molecule [5]. The

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present work describes the computer aided geometry optimization (active conformation) and calculation of excited state properties of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) by Argus Lab 4.0.1 software [6].

2. Materials and Methods

2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). The 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) structure was generated by Arguslab [6], and minimization was performed with UFF molecular mechanics method [7-8]. The minimum potential energy was calculated using geometry convergence function in Arguslab software [9]. Surfaces created to visualize ground state properties as well as excited state propertiessuch as orbital, electron densities, electrostatic potentials (ESP) spin densities. Generated grid data were used to make molecular orbital surfaces and electrostatic potential mapped on electron density surface [10-11]. The minimum potential energy was calculated for modafinil through the geometry convergence map [12]. Mulliken atomic charges, ZDO atomic charges of modafinil and ground state dipole (debye) of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) were determined using AM1 method [6].

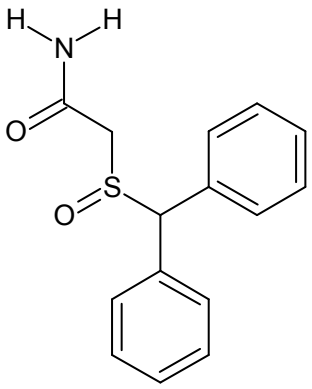
3. Results and Discussion

Prospective view and calculated properties of modafinil molecule is shown in Figure 1. The active conformation and electron density mapped of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) by ACDlabs-3D viewer software are shown in Figures 2 and 3 respectively. Figure 6 shows the electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state. Atomic coordinates of modafinil molecule is given in Table 1 and bond length and bond angles are given in Table 2 and 3 respectively, which are calculated after geometry optimization of molecule from Arguslab by using molecular mechanics calculation. Tables 4 and 5 shows the dihedral angles and improper torsion angles of modafinil respectively. Table 6, 7 and 8 shows the calculated steric energy, the Mulliken atomic charges, ZDO atomic charges and the ground state dipole (debye) of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) molecule.

Arguslab software was used to see what happened to the electrons in 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) when it absorbed light. Surfaces were made to explore this fascinating phenomenon. When 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) 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 [6]. The HOMO is localized to the plane of the molecule and is a non-bonding molecular orbital (Figure 4). The LUMO is perpendicular to the plane of the molecule and is a combination of the p_z atomic orbitals (Figure 5). The n->π^* 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 [6]. 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 [6]. 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 [6]. 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 [6]. These images show that the triple and double bonded end of the molecule is electron rich relative to the single bonded end [6].

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 2-

[(diphenylmethyl) sulfinyl] acetamide (modafinil) was 0.74908723 a.u. (470.05975994 kcal/mol) and the SCF energy (Net Charge of +1, Valence electron of 84) was found to be -108.0349305252 au (-67793.0036 kcal/mol) as calculated by RHF/ AM1method, as performed by Argus Lab 4.0.1 suite**.**



Molecular Formula	= $C_{15}H_{15}NO_2S$
Formula Weight	= 273.3501
Composition	= C(65.91%) H(5.53%) N(5.12%) O(11.71%) S(11.73%)
Molar Refractivity	= 77.26 ? 0.3 cm^3
Molar Volume	= 212.8 ? 3.0 cm^3
Parachor	= 601.5 ? 4.0 cm^3
Index of Refraction	= 1.645 ? 0.02
Surface Tension	= 63.7 ? 3.0 dyne/cm
Density	= 1.283 ? 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 30.62 ? 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 273.082349 Da
Nominal Mass	= 273 Da
Average Mass	= 273.3501 Da

Figure 1. Prospective view of modafinil by ACD/Chemsketch.

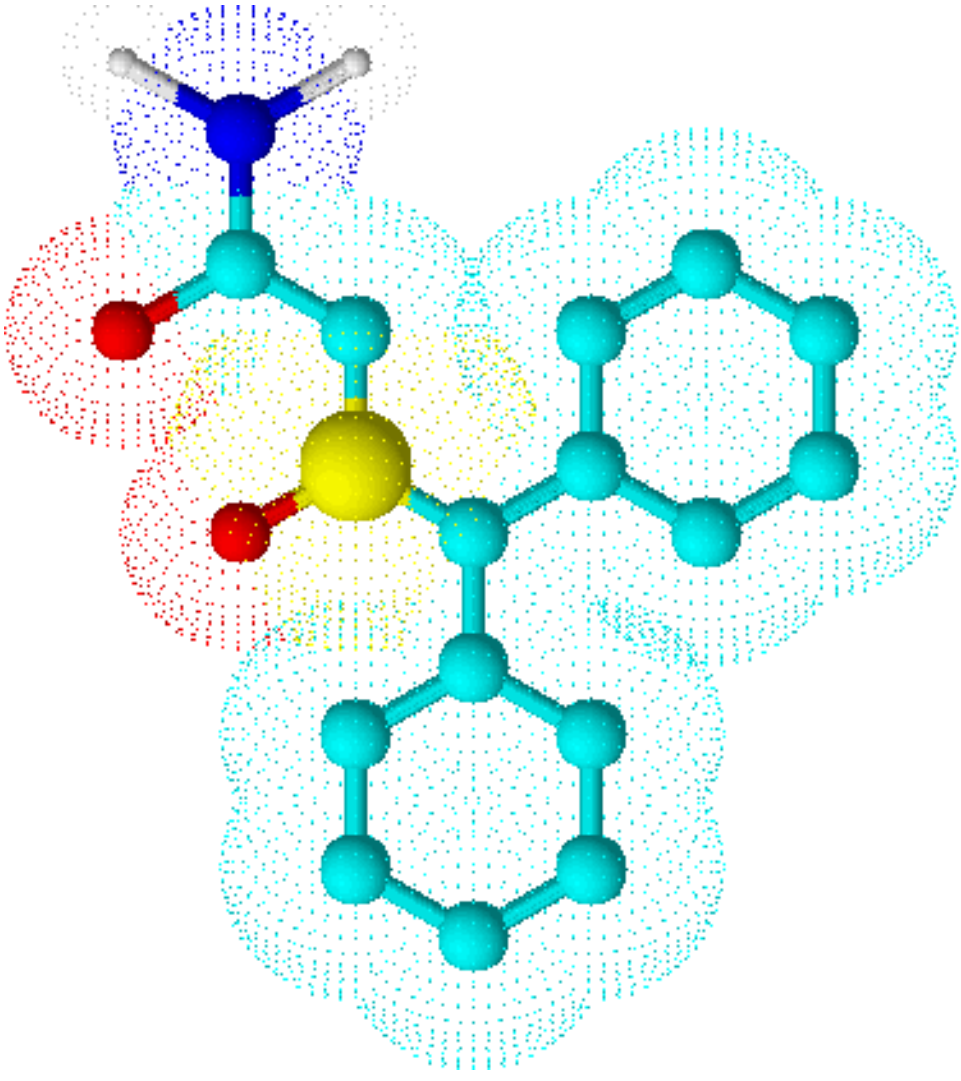


Figure 2. Ekecron density clouds of modafinil by ACD/labs. 3D viewer.

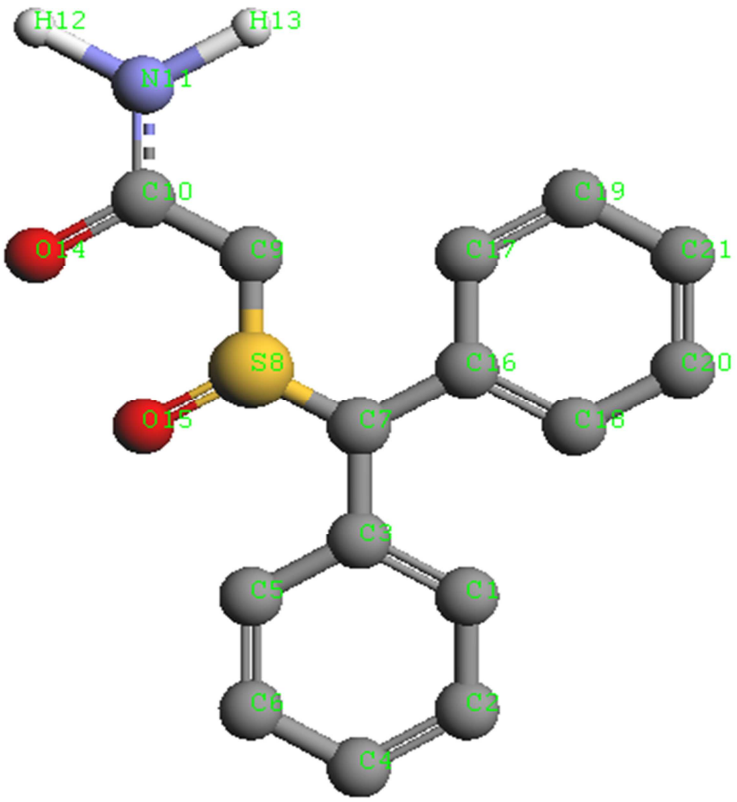


Figure 3. Prospective view of active conformation of modafinil by Arguslab software.

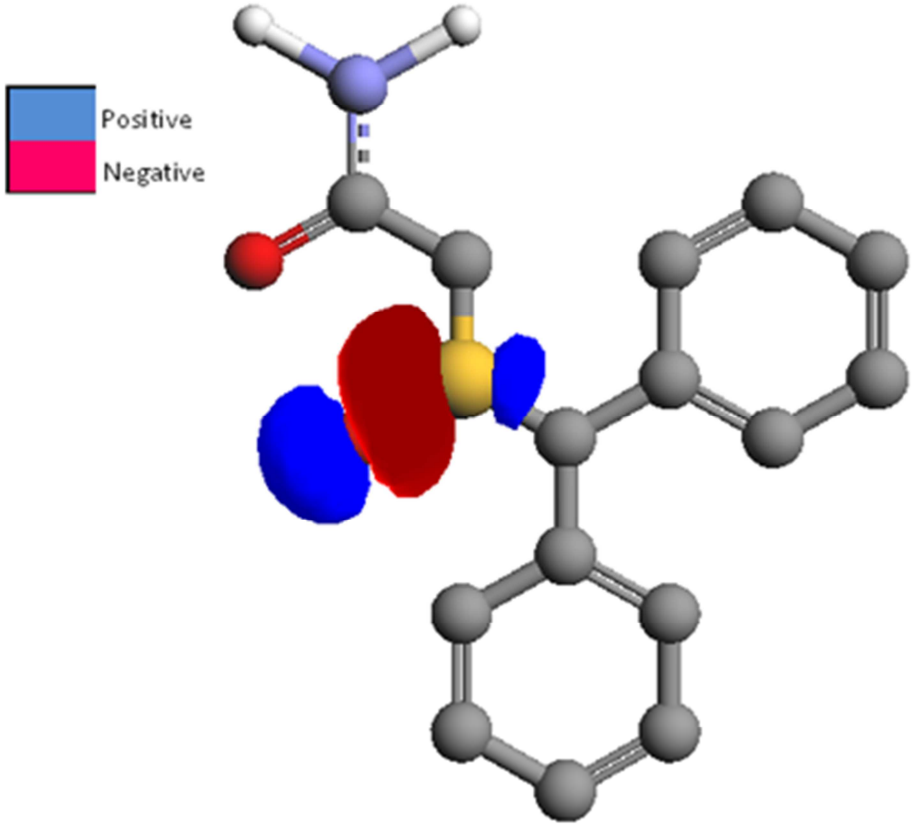


Figure 4. Highest occupied molecular orbital's (HOMO) of modafinil.

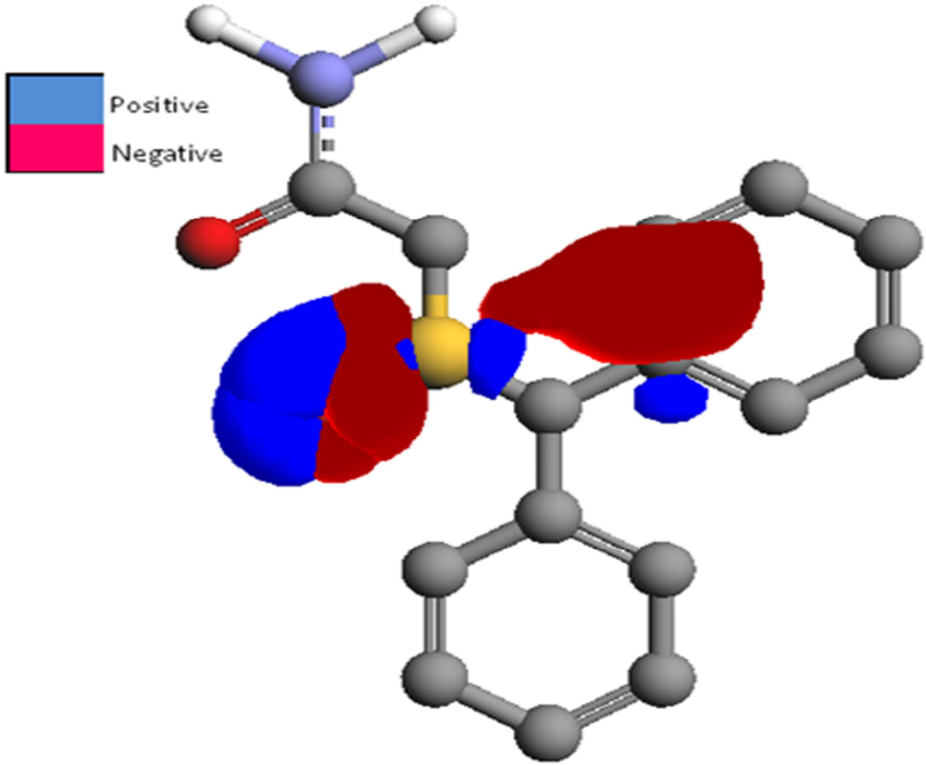


Figure 5. Lowest unoccupied molecular orbital's (LUMO) of modafinil.

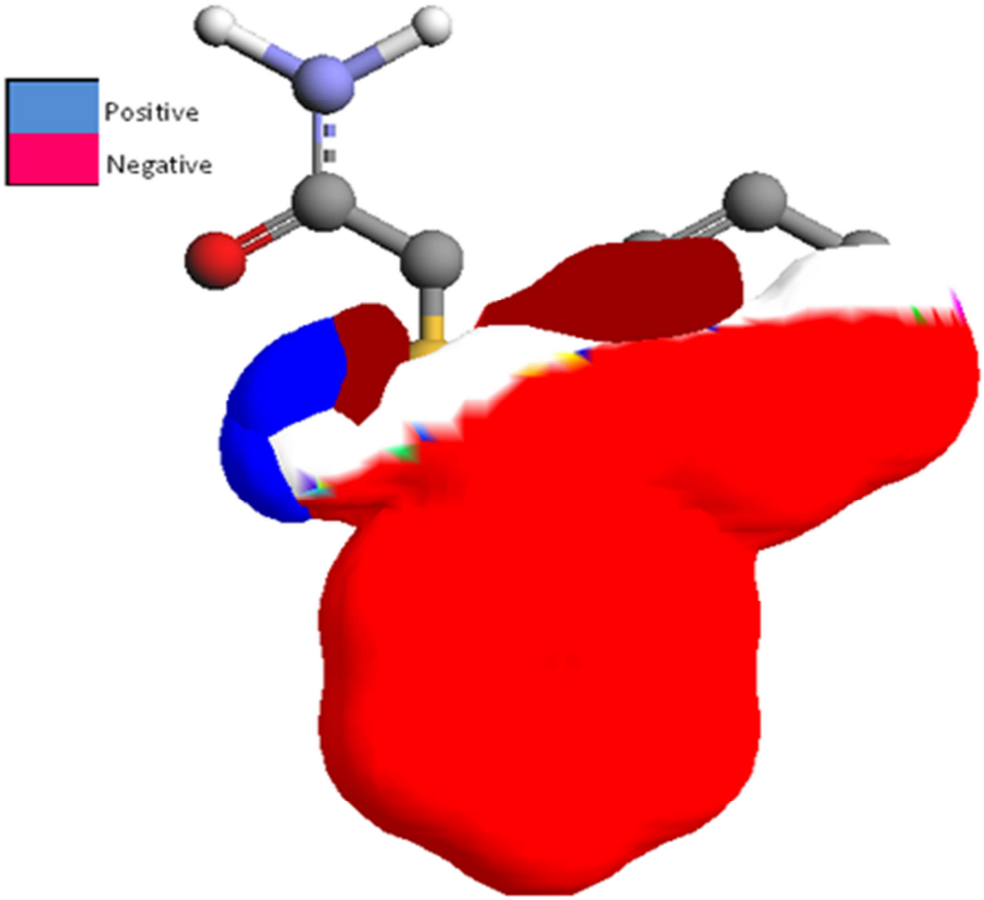


Figure 6. Electrostatic potential (ESP) mapped density of modafinil.

Table 1. Atomic coordinates of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil).

S.NO	Atoms	X	Y	Z
1	C	22.383800	-12.907400	0.000000
2	C	22.383800	-14.237400	0.000000
3	C	21.231900	-12.242400	0.000000
4	C	21.231900	-14.902400	0.000000
5	C	20.080100	-12.907400	0.000000
6	C	20.080100	-14.237400	0.000000
7	C	21.231800	-10.912400	0.000000
8	S	20.080000	-10.247400	0.000000
9	C	20.080000	-8.917400	0.000000
10	C	18.928200	-8.252400	0.000000
11	N	18.928200	-6.922400	0.000000
12	C	22.383600	-10.247400	0.000000
13	C	22.383600	-8.917400	0.000000
14	C	23.535500	-10.912400	0.000000
15	C	23.535500	-8.252400	0.000000
16	C	24.687300	-10.247400	0.000000
17	C	24.687300	-8.917400	0.000000
18	O	18.928200	-10.912400	0.000000
19	O	17.776400	-8.917500	0.000000
20	H	20.080000	-6.257400	0.000000
21	H	17.776300	-6.257500	0.000000

Table 2. Bond length of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil).

Atoms	Bond length
(C1)-(C2)	1.458000
(C1)-(C3)	1.323387
(C2)-(C4)	1.323387
(C3)-(C5)	1.458000
(C3)-(C7)	1.461000
(C4)-(C6)	1.458000
(C5)-(C6)	1.323387
(C7)-(S8)	1.592539
(C7)-(C12)	1.461000
(S8)-(C9)	1.592539
(S8)-(O18)	1.355590
(C9)-(C10)	1.464000
(C10)-(N11)	1.346235
(C10)-(O19)	1.260307
(N11)-(H20)	1.048529
(N11)-(H21)	1.048529
(C12)-(C13)	1.458000
(C12)-(C14)	1.323387
(C13)-(C15)	1.323387
(C14)-(C16)	1.458000
(C15)-(C17)	1.458000
(C16)-(C17)	1.323387

Table 3. Bond angles of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil).

Atmos	Bond angles	Alternate angles
(C2)-(C1)-(C3)	120.000000	216.488007
(C1)-(C2)-(C4)	120.000000	216.488007
(C1)-(C3)-(C5)	120.000000	216.488007
(C1)-(C3)-(C7)	120.000000	215.760874
(C2)-(C4)-(C6)	120.000000	216.488007
(C5)-(C3)-(C7)	120.000000	187.861407
(C3)-(C5)-(C6)	120.000000	216.488007
(C3)-(C7)-(S8)	120.000000	231.441203
(C3)-(C7)-(C12)	120.000000	187.283630
(C4)-(C6)-(C5)	120.000000	216.488007
(S8)-(C7)-(C12)	120.000000	231.441203
(C7)-(S8)-(C9)	120.000000	144.604050
(C7)-(S8)-(O18)	120.000000	217.517660
(7C)-(C12)-(C13)	120.000000	187.861407
(C7)-(C12)-(C14)	120.000000	215.760874
(C9)-(S8)-(O18)	120.000000	217.517660
(S8)-(C9)-(C10)	120.000000	230.786536
(C9)-(C10)-(N11)	120.000000	279.479738
(C9)-(C10)-(O19)	120.000000	275.966448
(N11)-(C10)-(O19)	120.000000	421.698151
(C10)-(N11)-(H20)	120.000000	124.171616
(C10)-(N11)-(H21)	120.000000	124.171616
(H20)-(N11)-(H21)	120.000000	70.257681
(C13)-(C12)-(C14)	120.000000	216.488007
(C12)-(C13)-(C15)	120.000000	216.488007
(C12)-(C14)-(C16)	120.000000	216.488007
(C13)-(C15)-(C17)	120.000000	216.488007
(C14)-(C16)-(C17)	120.000000	216.488007
(C15)-(C17)-(C16)	120.000000	216.488007

Table 4. Dihedral angles of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil).

Atoms	Dehidral angles
(C4)-(C2)-(C1)-(C3)	10.000000
(C2)-(C1)-(C3)-(C5)	19.486776
(C2)-(C1)-(C3)-(C7)	19.486776
(C1)-(C2)-(C4)-(C6)	38.973552
(C1)-(C3)-(C5)-(C6)	5.000000
(C1)-(C3)-(C7)-(S8)	2.500000
(C1)-(C3)-(C7)-(C12)	2.500000
(C2)-(C4)-(C6)-(C5)	10.000000
(C6)-(C5)-(C3)-(C7)	5.000000
(C5)-(C3)-(C7)-(S8)	2.500000
(C5)-(C3)-(C7)-(C12)	2.500000
(C3)-(C5)-(C6)-(C4)	38.973552
(C3)-(C7)-(S8)-(C9)	1.976424
(C3)-(C7)-(S8)-(O18)	1.976424
(C3)-(C7)-(C12)-(C13)	2.500000
(C3)-(C7)-(C12)-(C14)	2.500000
(C9)-(S8)-(C7)-(C12)	1.976424
(O18)-(S8)-(C7)-(C12)	1.976424
(S8)-(C7)-(C12)-(C13)	2.500000
(S8)-(C7)-(C12)-(C14)	2.500000
(C7)-(S8)-(C9)-(C10)	3.952847
(C7)-(C12)-(C13)-(C15)	5.000000
(C7)-(C12)-(C14)-(C16)	19.486776
(C10)-(C9)-(S8)-(O18)	3.952847
(S8)-(C9)-(C10)-(N11)	5.000000
(S8)-(C9)-(C10)-(O19)	5.000000
(C9)-(C10)-(N11)-(H20)	6.737110
(C9)-(C10)-(N11)-(H21)	6.737110
(H20)-(N11)-(C10)-(O19)	6.737110

Atoms	Dehidral angles
(H21)-(N11)-(C10)-(O19)	6.737110
(C15)-(C13)-(C12)-(C14)	5.000000
(C13)-(C12)-(C14)-(C16)	19.486776
(C12)-(C13)-(C15)-(C17)	38.973552
(C12)-(C14)-(C16)-(C17)	10.000000
(C13)-(C15)-(C17)-(C16)	10.000000
(C14)-(C16)-(C17)-(C15)	38.973552

Table 5. Improper torsions of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil).

Atoms	Improper torsions
(C5)-(C7)-(C3)-(C1)	2.000000
(S8)-(C12)-(C7)-(C3)	2.000000
(C9)-(O18)-(S8)-(C7)	2.000000
(C143)-(C14)-(C12)-(C7)	2.000000
(N11)-(O19)-(10C)-(C9)	16.666667
(H20)-(H21)-(N111)-(C10)	2.000000

Table 6. List of Mulliken atomic charges, ZDO atomic charges and atomic spin densities of 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) using ArgusLab software.

S.NO	Atoms	ZDO atomic charges	Mulliken atomic carges	Atomic spin densities
1	C	-4.0000	-4.0005	-0.0000
2	C	-4.0000	-4.0000	0.0000
3	C	-3.9998	-4.0116	0.0000
4	C	-4.0000	-4.0000	0.0000
5	C	-3.9997	-4.0111	0.0000
6	C	-4.0000	-4.0004	0.0000
7	C	-3.9086	-4.2925	0.0044
8	S	3.6688	4.0314	0.1095
9	C	3.9942	4.0632	0.0007
10	C	3.9992	4.0094	0.0002
11	N	5.0000	5.0004	0.0000
12	C	-2.0505	-2.1013	0.0056
13	C	3.9775	4.1016	-0.0000
14	C	-3.9857	-4.0122	0.0001
15	C	3.9866	4.0088	0.0000
16	C	-3.5614	-3.9849	-0.0002
17	C	3.5831	3.9870	-0.0002
18	O	1.2967	1.2124	0.8797
19	O	5.9997	6.0003	0.0001
20	H	1.0000	1.0000	0.0000
21	H	1.0000	1.0000	0.0000

Table 7. Final energy evaluation.

S.No.	Force field	Energy components (au)
1	Molecular mechanics bond (Estr)	0.00905088
2	Molecular mechanics angle (Ebend) + (Estr-bend)	0.00418728
3	Molecular mechanics dihedral (Etor)	-0.00000000
4	Molecular mechanics ImpTor (Eoop)	0.00000000
5	Molecular mechanics vdW (EVdW)	0.05010661
6	Molecular mechanics coulomb (Eqq)	0.00000000
Total	0.06334477 a.u. (39.74947994 kcal/mol)	

Table 8. Ground state dipole (debye).

X	Y	Z	length
-270.09344506	723.19323400	-0.00000000	771.98375810

4. Conclusion

The present work indicates that the best conformation of Modafinil was found to be -108.0349305252 au (-67793.0036 kcal/mol) which isthe minimum potential energy calculated by Argus Lab software. At this point 2-[(diphenylmethyl) sulfinyl] acetamide (modafinil) will be more active tointeract with the receptors. Such types of interactions are significant for drug- receptor interactions.

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