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An Insilico Study on Structural Aspects of Caffeine by ArgusLab 4 software

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ABSTRACT

In this study, the molecular docking method investigated the quasi-experimental molecular computational studies of the caffeine compound found in many herbals and the binding properties of the 4QHO protein to the active site. For molecular docking, geometry optimization of caffeine molecule was done in the Argus Lab program with the semi-experimental PM3 method. The HOMO, LUMO, and HOMO-LUMO energy differences and potential energy surface of all optimized molecules were calculated. To understand the relationship between the caffeine molecule and the feeling of satiety, the interaction between caffeine and 4QHO protein was examined using the molecular docking method. The selected crystal structure of 4QHO protein was obtained from the protein database in *.pdb format, and optimized ligand interaction with this crystal structure was studied using ArgusLab. As a result of molecular docking studies, ligand-protein binding energies, hydrogen bond sites, and the number of interactions between ligand-protein were determined and evaluated.

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1. Introduction

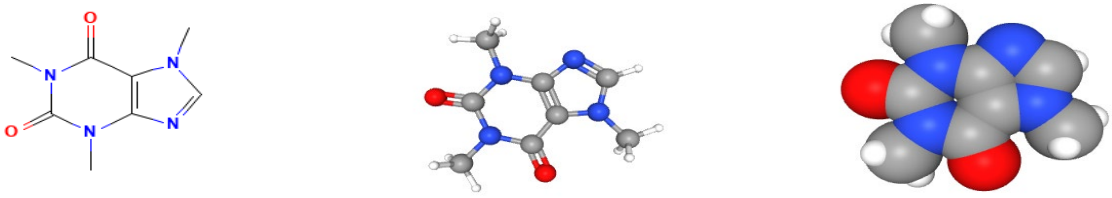
Caffeine is one of the methylxanthine class of stimulants for the central nervous system (CNS) [1]. As a eugeroic, encouraging wakefulness, and a mild cognitive enhancer, improving alertness and attentional performance, its main uses are for recreational purposes [2,3]. The neurotransmitter acetylcholine is released more readily when caffeine inhibits adenosine's binding to the adenosine A1 receptor [4]. Due to their structural similarities, caffeine and adenosine can bind to each other and impede adenosine receptors, which causes this effect [5]. Because it inhibits phosphodiesterase nonselectively, caffeine also raises the levels of cyclic AMP [6].

It was utilised in Dutch medicine in the first part of the 20th century as a circulatory and respiration stimulant. The first people to take advantage of coffee's medicinal properties were Islamic physicians; long before the second millennium A.D.D., the Yemeni Sufis are credited with using it as a beverage for the first time. Caffeine was banned from use because of the growing belief that it is seditious and causes diarrhoea, even though caffeine is used as a stimulant more often. Coffee was brought to Holland ten years after being introduced to England in the 1650s. The coffee plant was brought to Java by the Dutch in 1688, and because of the island's reputation for producing fine coffee, premium coffee has come to be known by the moniker "Java" [7].

Obesity is associated with many diseases, especially cardiovascular and cancer diseases [8,9]. The oxidation of N-methyl groups in nucleic acids, and specifically of N6-methyladenosine (m6A) in RNA, is catalyzed by the Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase fat mass and obesity-associated protein (FTO). [10-13]. The overwhelming body of data indicates that SNPs in FTO significantly increase energy intake while decreasing satiety. [14].

Arguslab's molecule builder was used to create the caffeine molecules acquired from Pubchem [15,16]. The atoms in caffeine's molecules have a net charge of 0 and 74 valence electrons. 2D structures, ball-stick and space-

filling view in PubCHEM compound and active conformation caffeine are shown in Figure 1.



2D Structure Ball and Stick **Space-Filling**

Figure 1 Structure of Caffeine

Potential energies, molecular structures, structure optimization geometry, atom coordinate vibration frequencies, bond length, bond angle, and reaction pathways are all predicted by the quantum mechanically based electronic structure software ArgusLab [17]. Conformational analysis, a method for calculating molecular structures, conformational energies, and other molecular properties, is based on molecular mechanics. It incorporates ideas from classical mechanics. A molecule is thought to be an assembly of atoms bound together by classical forces. Bond lengths, bond angles, torsion angles, and other structural features' potential energy functions are used to characterize these forces. Equation (1) can calculate the molecule's energy (E) as a sum of terms.

$$E = E_{stretching} + E_{bending} + E_{torsion} + E_{Vander\ Waals} + E_{electrostatic} + E_{hydrogen\ bond} + \text{cross term} \quad (1)$$

The precise computation of the geometric properties of molecules depends on these terms. A force field is the collection of energy functions and the associated parameters [18].

2. Material and Method

The crystal structure of FTO was obtained from RCSB [19] (PDB ID:4QHO). We chose ArgusLab 4.0 to investigate the binding site. One (www.arguslab.com) is the study's source. ArgusLab can function on Windows 11 from the Windows operating system.

ArgusLab software was used on a window-based computer for all conformational analysis (geometry optimization) research. Many tools for building models, minimizing, and representing molecular structures have been made possible by advances in computing [20–22]. The semi-empirical Parametric Method 3 (PM3) parameterization was utilized to complete the minimization process after ArgusLab produced the caffeine structure [23–24].

The minimum potential energy is determined using the geometry convergence function in the ArgusLab software. The surfaces were designed to show properties of the ground state and the excited conditions, such as orbitals, electron densities, spin densities, and electrostatic potentials (ESP). They also produced grid data to create molecular orbital surfaces, which show the molecular orbitals and map the electrostatic potential on the electron density surface. We used the geometry convergence map to calculate the minimum potential energy for caffeine. [25-28]. Using the PM3 method, the Mulliken and ZDO Atomic Charges of caffeine were determined.

After downloading the FTO crystal structure (PDB ID: 4QHO) from the PDB databank, the ArgusLab program was used to create the binding site by selecting the "Make binding site for this protein" option. Caffeine was chosen as the ligand, and hydrogen atoms were added. The ligands were then permitted to operate using the AScore scoring function and the GA algorithm. 4.0 in ArgusLab.

3. Results and Discussions

Table 1 provides the atomic input data for the computation above. According to ArgusLab 4.0's RHF/PM3 method, the last minimum geometrical energy and SCF energy were determined to be -85.8936912420 au (-53899.1536 kcal/mol) in Table 2.

Table 1 Atomic coordinates of caffeine compound

Atoms Number	X	Y	Z	Atoms Number	X	Y	Z
1 C	-3.097000	-1.122000	-0.400000	**2 N**	-2.099000	-0.045000	-0.311000
3 C	-2.351000	1.305000	-0.248000	**4 N**	-1.242000	2.015000	-0.170000
5 C	-0.268000	1.082000	-0.161000	**6 C**	-0.744000	-0.191000	-0.276000
7 C	0.073000	-1.412000	-0.383000	**8 O**	-0.314000	-2.470000	-0.818000
9 N	1.430000	-1.150000	0.118000	**10 C**	1.900000	0.178000	-0.308000
11 O	2.980000	0.312000	-0.834000	**12 N**	1.039000	1.319000	-0.082000
13 C	1.574000	2.655000	0.216000	**14 C**	2.201000	-2.076000	0.924000
15 H	-4.119000	-0.681000	-0.409000	**16 H**	-2.934000	-1.701000	-1.336000
17 H	-2.992000	-1.797000	0.478000	**18 H**	-3.360000	1.743000	-0.261000
19 H	2.686000	2.615000	0.231000	**20 H**	1.240000	3.371000	-0.568000
21 H	1.201000	2.991000	1.210000	**22 H**	3.190000	-1.626000	1.163000
23 H	1.653000	-2.290000	1.869000	**24 H**	2.352000	-3.023000	0.358000

Table 2 SCF is performed by computing SCF using a single electron matrix.

Cycle	Energy (au)	Difference	Cycle	Energy (au)	Difference
1	-43.879246		**2**	-60.473763689	-16.5945
3	-54.788619925	5.68514	**4**	-71.721995461	-16.9334
5	-76.790156961	-5.06816	**6**	-80.425637025	-3.63548
7	-83.516250964	-3.09061	**8**	-85.318098861	-1.80185
9	-85.866961190	-0.548862	**10**	-85.889610524	-0.0226493
11	-85.892988983	-0.00337846	**12**	-85.893496721	-0.000507737
13	-85.893629512	-0.000132792	**14**	-85.893669687	-4.01751e-005
15	-85.893683293	-1.36062e-005	**16**	-85.893688229	-4.93609e-006
17	-85.893690076	-1.84619e-006	**18**	-85.893690783	-7.06986e-007
19	-85.893691059	-2.75879e-007	**20**	-85.893691168	-1.09324e-007
21	-85.893691210	-4.20114e-008	**22**	-85.893691229	-1.91109e-008
23	-85.893691236	-7.53471e-009	**24**	-85.893691240	-3.2112e-009
25	-85.893691241	-1.29899e-009	**26**	-85.893691242	-5.52518e-010
27	-85.893691242	-2.38742e-010	**28**	-85.893691242	-9.93623e-011
29	-85.893691242	-4.18368e-011	**30**	-85.893691242	-1.86446e-011
31	-85.893691242	-7.7307e-012	**32**	-85.893691242	-1.81899e-012
33	-85.893691242	-2.72848e-012	**34**	-85.893691242	9.09495e-013
35	-85.893691242	-1.13687e-012	**36**	-85.893691242	-3.41061e-013
37	-85.893691242	5.68434e-013	**38**	-85.893691242	-1.13687e-013

The ZDO and Mulliken atomic charges of caffeine are listed in Table 3.

Table 3 List of Mulliken and ZDO Atomic Charges of Caffeine by using ArgusLab software

Atoms Number	ZDO Atomic Charges	Mulliken Atomic Charges	Atoms Number	ZDO Atomic Charges	Mulliken Atomic Charges	Atoms Number	ZDO Atomic Charges	Mulliken Atomic Charges
1 C	-0.1183	-0.3342	**9 N**	-0.0328	-0.0834	**17 H**	0.0832	0.1623
2 N	0.3608	0.3283	**10 C**	0.2317	0.2739	**18 H**	0.1666	0.2666

3 C	-0.1940	-0.2706	**11 O**	-0.3766	-0.3855	**19 H**	0.0662	0.1411
4 N	-0.1358	-0.1458	**12 N**	0.1181	0.0802	**20 H**	0.0748	0.1519
5 C	-0.0531	-0.0298	**13 C**	-0.0771	-0.2855	**21 H**	0.0455	0.1163
6 C	-0.4072	-0.4384	**14 C**	-0.0620	-0.2670	**22 H**	0.0690	0.1443
7 C	0.3708	0.4203	**15 H**	0.0626	0.1346	**23 H**	0.0446	0.1153
8 O	-0.3739	-0.3829	**16 H**	0.0716	0.1480	**24 H**	0.0654	0.1399

The heat released from individual atoms during forming the element's stable form under standard conditions is known as the atomic heat of formation. It is important to remember that thermodynamic adjustments not be included in the formation energy since the parametrization implicitly includes them. ArgusLab software is used to determine the most energetically favorable conformation of caffeine, which has a heat of formation of -52.0215 kcal/mol.

Known as Frontier Orbitals, the HOMO and LUMO orbitals are very helpful in explaining chemical reactivity. HOMO (Highest Occupied Molecular Orbital I) and HOMO -1 (MO 36). LUMO (Lowest Unoccupied Molecular Orbital I) and e MO 37. Fig. 5 shows caffeine's LUMO +1 (MO 39) and MO 38. This was done theoretically using PM3.

Examining the E_{HOMO} and E_{LUMO} is crucial to understanding the complex's electronic characteristics. Using PM3, this was accomplished theoretically. The two colors signify the positive and negative areas of the orbital; the blue regions correspond to an increase in electron density, and the red areas to a decrease in electron density. Nevertheless, these calculations were also investigated in a vacuum and the ground state. By comparing them with other compounds that are similar to them, one can use them to obtain information.

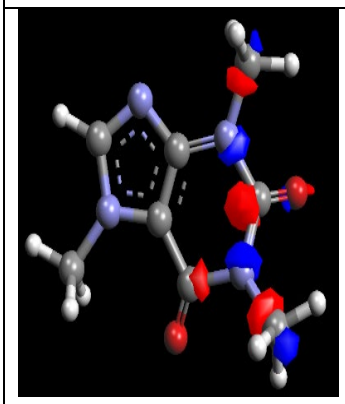
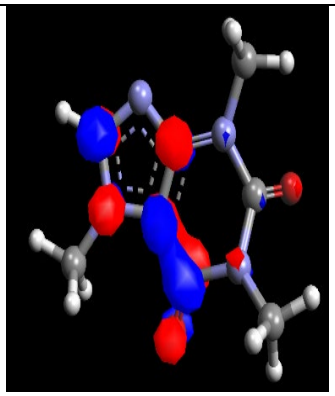
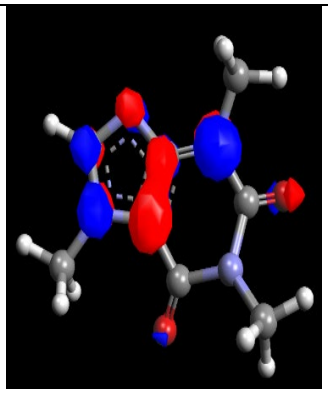
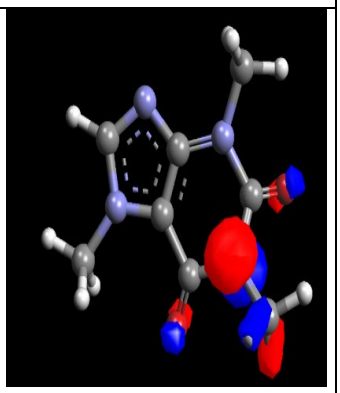
LUMO+1	LUMO	HOMO	HOMO-1
			
0.2855eV GAP1=8.4842	**-0.5528eV GAP2=9.3225**	**-9.0370 eV GAP3=9.488**	**-10.0408 eV GAP4=10.3263**

Figure 2. Visualise the LUMO+1, LUMO, HOMO, HOMO-1 of Caffeine, blue shows positive and red shows negative. Molecular orbital representations of the caffeine in each of its four energy states (GAP1, GAP2, GAP3, and GAP4), along with their corresponding GAP values (energy variation between frontier orbitals HOMO and LUMO).

The entire surface of caffeine is depicted with a color map in Figure 3. To display a cutaway of the same surface and the underlying molecular structure, this figure makes use of a clipping plane. The ESP energy (in hartrees) for each color is displayed on the color m

The electrostatic potential's polarity and magnitude are reflected in the color of the surface. The regions of greatest stability for a positive test charge are shown by the red end of the spectrum, while the areas of least stability are indicated by the magenta/blue end.

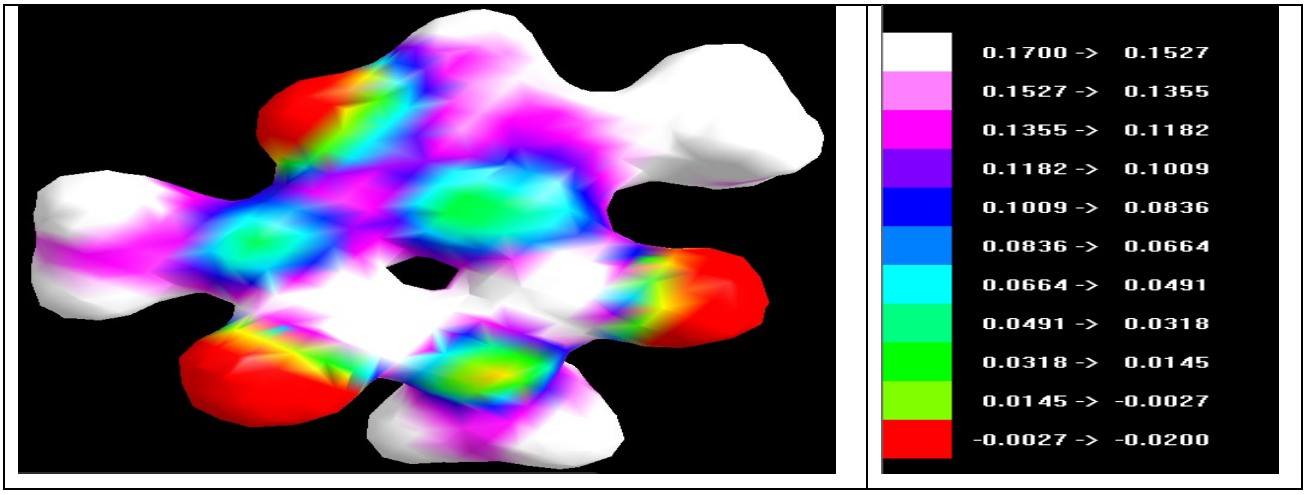


Figure 3 shows a potential electrostatic map of the stemonal molecule produced by applying the Mulliken charges with scale.

The results concerning the molecular docking of caffeine over 4QHO are shown in Fig. 4. One issue involved the different parameters between different docking programs. The grid box size for ArgusLab (151 x 140 x 151 Å) was set. The best molecular docking position of caffeine is -6.09979 kcal/mol. 2D images were created with the help of biovia discovery studio (Discovery Studio Client version 19. 1.0. 18287). Analysis on the PLIP server [29] revealed that two hydrogen bonds were involved in binding each compound with the protein. The amino acids involved in hydrogen bond formation for caffeine are shown in Table 4.

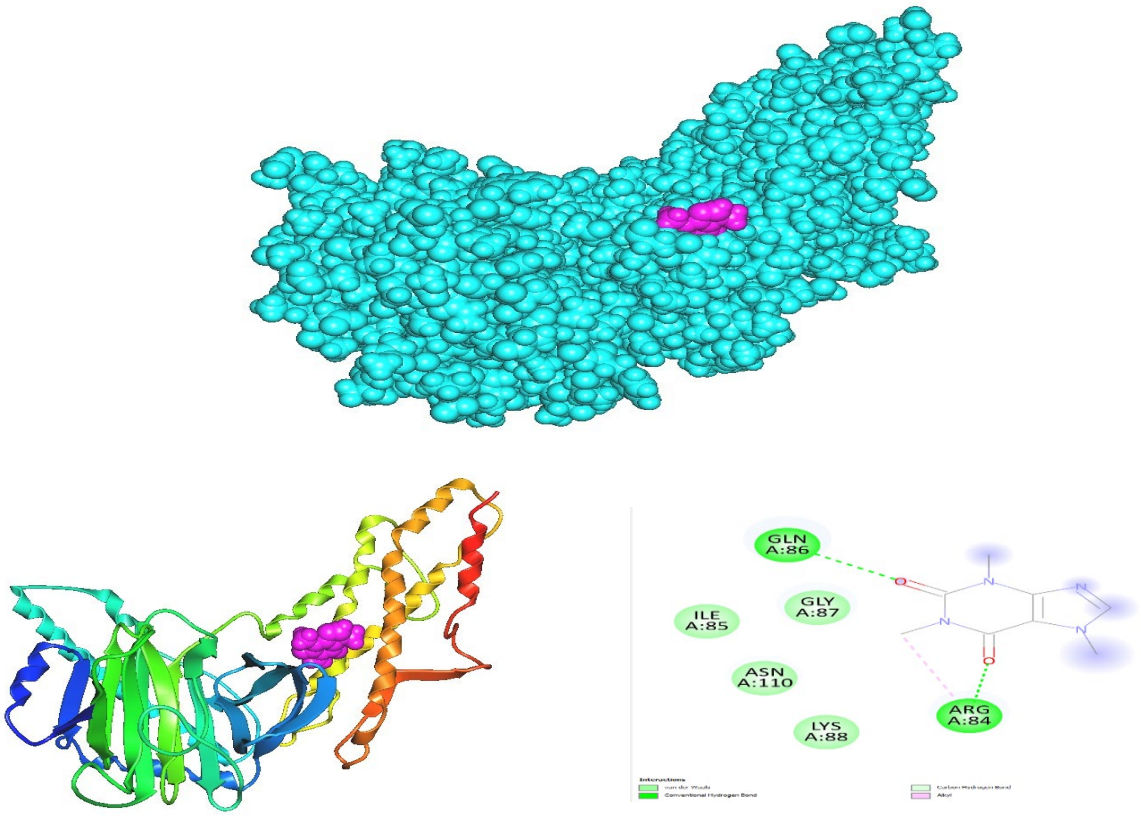


Figure 4 a. Demonstrate the interaction of Caffeine at the binding site of 4QHO **b.** 3D structure of 4QHO-Caffeine complex **c.**2D structure of 4QHO-Caffeine complex

Table 4 Hydrogen bond interactions between 4qho protein and caffeine

Hydrogen Bonds									
Index	**Residue**	**AA**	**Distance H-A**	**Distance D-A**	**Donor Angle**	**Protein donor?**	**Side chain**	**Donor Atom**	**Acceptor Atom**
1	84A	ARG	1.60	2.54	158.85	✓	✓	452 [Ng+]	3416 [O_2]
2	87A	GLY	2.17	2.84	124.12	✓	✓	470 [Nam]	3419 [O_2]

4. Discussion

It has been observed that the ArgusLab program has a very easy-to-understand interface and completes the calculations in a very short time. In this research study, we included some calculation studies that can be done with ArgusLab and observed that the results are stable. Using the ArgusLab software, caffeine's lowest energetically favorable conformation is found to have a minumun energy conformation of -52.0215 kcal/mol. The studies used ArgusLab software to determine the minimum potential energy at which the minimum energy conformation of caffeine is found to be at -85.8936912420 au (-53899.1536 kcal/mol). It can now be demonstrated that caffeine has an active effect on FTO protein.

The lowest energy conformations were employed in molecular modeling calculations after the geometric variables related to caffeine were finally fully optimized for the compound. The calculated thermodynamic parameter, dipole moment, Mulliken and ZDO Atomic Charge, and optimized geometry were all well within the computational results' accuracy range. The data derived from the calculated parameter was analyzed. Studies have demonstrated a modest impact of caffeine compounds on obesity.

It has been shown that caffeine molecules have a moderate effect against obesity in an insilico environment with the help of molecular docking studies. According to the results of this research, it is thought that consuming a cup of Turkish coffee containing plenty of caffeine can reduce the feeling of eating by suppressing hunger.

Because of this, modeling, computation, and docking studies have given us new insight into the caffeine compound and knowledge about challenging problems to observe through experimentation.

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Competing interests

The authors declare that they have no competing interests.

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