Iğdır Üniversitesi Fen Bilimleri Enstitüsü Dergisi, 14(1), 219-230, 2024
Journal of the Institute of Science and Technology, 14(1), 219-230, 2024

ISSN: 2146-0574, eISSN: 2536-4618

Physics **DOI: 10.21597/jist.1377134**

Research Article

Received: 17.10.2023 **Kabul tarihi / Accepted: 23.11.2023**

To Cite: Bayrakdar, A. (2024). Investigation of the Structural and Electronic Properties of the Novel Synthesized Methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate Compound by DFT Method and Evaluation of its Anti-Leishmania Agent Potential by Molecular Docking Study. *Journal of the Institute of Science and Technology*, 14(1), 219-230.

Investigation of the Structural and Electronic Properties of the Novel Synthesized Methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate Compound by DFT Method and Evaluation of its Anti-Leishmania Agent Potential by Molecular Docking Study

Alpaslan BAYRAKDAR

Highlights:

- Molecular structure was optimized by computational methods
- Anti- Leishmaniasis activities of methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate was invastigated
- Drug-likeness properties were investigated

Keywords:

- Anti-Leishmaniasis
- DFT
- Hirsfeld surface analysis
- Drug-likeness
- Molecular docking

ABSTRACT:

Leishmaniasis is a disease caused by different species of the leishmania parasite, transmitted through the sandfly, within the group of protozoa. According to the World Health Organization, leishmaniasis is one of the most encountered seven tropical diseases. Trypanothione reductase is a vital enzyme for the parasite. This has made Trypanothione reductase a potential target in the treatment of leishmaniasis. The limitations of current therapeutic options and the high cost have increased the motivation for research on the inhibition of Trypanothione reductase. In this study, the structural and electronic properties of the newly synthesized compound methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate were calculated using DFT/B3LYP and 6-311++G(d,p) basis set. The calculated structural parameters were found to be highly compatible when compared with experimental studies. The crystal packing of the compound was examined through the Hirshfeld surface analysis method. When the potential of the compound to be used as a drug was evaluated using Lipinski criteria, no hindrance to its use in living organisms was found. As the crystal structure of the enzyme was unknown, homology modeling was performed. Finally, in the molecular docking study, the interaction mechanisms of the compound mentioned in the title and the compound clomipramine used as a control in the receptor's active site were examined. The results revealed that the compound mentioned in the title demonstrated a better potential compared to the control compound.

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INTRODUCTION

Parasites are organisms that live dependent on a host and cause harm to the host's structure. Each parasite spreads and causes harm in its unique way. Leishmaniasis is a disease transmitted through sand fly and caused by protozoan parasites. It is seen in animals and humans, and it has three main forms: visceral, cutaneous, and mucocutaneous. The cutaneous form, which causes skin infections, is the most common. At first the cutaneous looks like a pimple on the skin, but it gradually grows and forms lesions on the skin. Later, the lesions ulcerate and become covered with a firmly adherent crust. (Nagle et al., 2014).

Millions of people worldwide are infected with leishmaniasis every year (Rodrigues, Juliany Cola Fernandes et al., 2013). Although there is currently no definitive treatment for leishmaniasis, chemotherapeutic agents such as pentavalent antimony, Amphotericin B, Liposomal amphotericin B, Miltefosine, Paromomycin and Pentamidins are widely used (Sundar and Chakravarty, 2013; Mohapatra, 2014). The high cost of these drugs, difficulties in their use and the development of drug resistance have led people to seek alternative solutions for the treatment of leishmaniasis (Pourmohammadi et al., 2011; Kazemi-Rad et al., 2013).

In this regard, while some scientists have been synthesizing new synthetic drugs that could be effective in treatment, others have been searching for treatment solutions with phytochemicals due to the side effects of synthetic drugs (Pal et al., 2023). In the fight against the disease, the aim is to halt important biological processes of the parasite by focusing on targets that play a significant role in the survival, development, or spread of the parasite. One of the important enzymes in the vital activities of leishmania protozoa is Trypanothione reductase (TR) enzyme. This situation makes the TR enzyme a therapeutic target for the treatment of leishmania parasites. It is known from the literature that a compound with antidepressant effects, clomipramine, inhibits the TR enzyme. On the other hand, studies have led to reservations about this treatment due to its psychotropic activity. This has motivated scientists to work on new drugs without side effects.

The anti-leishmania compounds that can be obtained by using coumarins in the scaffold can also eliminate the aforementioned disadvantages of synthetic anti-leishmania drugs. For this purpose, Hollauer et al. synthesized the compound 2-(2-oxo-2H-chromen-4-yl-amino)-benzoate, which is a coumarin derivative and has the potential to cause anti-leishmania (Hollauer et al., 2023). Coumarins are bioactive compounds belonging to the lactone class with a versatile structural backbone that is commonly found in vascular plants and can be isolated from natural sources (Hollauer et al., 2023). Coumarins have widespread use in many syntheses, as they contain an aromatic ring that can promote hydrophobic interactions and a lactone group that acts as a hydrogen bond acceptor with receptors (Yildirim et al., 2023).

Here, the structural, spectroscopic and electronic properties of the newly synthesized methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate compound with anti-leishmaniasis potential by Hollauer et al. have been calculated theoretically using the DFT method and compared with the experimental data in the literature. In the second step, drug-likeness properties were investigated for the title molecule and its drug potential was evaluated. In the third step, Hirshfeld surface analysis was performed to investigate the crystal structure and interactions of the molecule. Finally, a docking study focusing on the binding site of FAD (Flavin Adenine Dinucleotide), a natural ligand of TR, located in the active site cavity of TR was performed. In the molecular docking study, the docking mechanism of the title compound, a

new drug candidate, was analyzed with the help of a molecular docking study in comparison with clomipramine, the reference inhibitor of TR.

MATERIALS AND METHODS

Computational Methods

The molecular structure corresponding to the ground state of the title molecule, HOMO-LUMO molecular orbital analyses and ESP surface map were performed by means of GAUSSIAN09 software (Frisch et al., 2008). Quantum chemical calculations were performed using the DFT method, which is an effective method for calculating the structural spectroscopic and electronic properties of organic molecules, and the Becke-3-Parameter-hybrid model of Lee-Yang-Parr (B3LYP) (Becke, 1992) functional and the 6-311G(d,p) basis set. The data obtained from the theoretical calculation were analyzed using GaussView 6 molecular imaging software (Dennington et al., 2009). GaussSum 3.0 was also used to obtain density of states (TDOS or DOS) and partial density of states (PDOS) spectra (O'boyle et al., 2008). Drug-likeness characterization was performed through the open access SwissADME web tool (Daina et al., 2017). Homology modeling to generate the 3D structure of TR was performed with the help of Swissmodel open access web tool (Arnold et al., 2006; Waterhouse et al., 2018). Molecular docking study was performed with the help of UCSF Chimera and Autodock Vina software (Butt et al., 2020). The results of the molecular docking study were analyzed with UCSF Chimera and BIOVIA Discovery Studio Visualizer (Systèmes and BIOVIA, 2020). Hirshfeld Surface Analysis of the molecule was performed using Crystal Explorer 17 (Mackenzie et al., 2017).

RESULTS AND DISCUSSION

Molecular Structure

According to the laws of thermodynamics, all systems tend to move towards a stable state (the state of lowest energy). The geometry of the ground state corresponding to the fundamental energy state of a molecule is crucial in determining the chemical reactivity of the molecule. Therefore, an optimization process was performed using the DFT/B3LYP function and the 6-311++G(d,p) basis set with Gaussian-09W to accurately calculate the properties of the title compound mentioned in the title before conducting the characterization studies. The optimized molecular structure of methyl 2-(2-oxo-2H-chromen-4-ylamino)benzoate is presented in Figure 1(a).

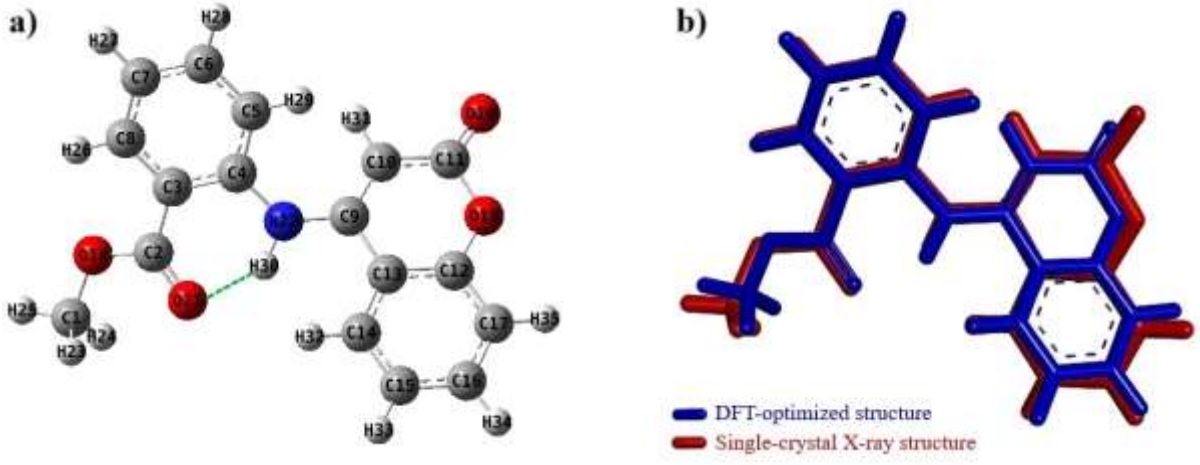

Figure 1. a) Optimized structure of the title compound, b) Superposition of the single crystal X-ray structure (red) with the optimized structure of the title compound (blue) using the DFT method

The superposition of the molecular conformations of the title compound, theoretically calculated (in blue) and determined by single-crystal X-ray analysis (in red), shows an excellent match (Figure 1(b)). Furthermore, the comparison between the theoretically calculated values and experimental data is provided in Table 1.

The correlations (R^2) between the experimental and theoretical parameters given in Table 1 were calculated as 0.9902 and 0.9182 for bond lengths and bond angles, respectively. This agreement supports the superposition results provided in Figure 1(b). The discrepancies between the experimental and calculated structural parameters in Table 1 may arise from the calculation being performed in the gas phase and on a single molecule. When the optimized structure was carefully examined, it was clearly seen from Figure 1a that an intramolecular hydrogen bond was formed between O21 and H30.

Table 1. Experimental and calculated geometric parameters of the title compound

Bond lengths (Å)	Cal.	Exp.*	Bond lengths (Å)	Cal.	Exp.*	Bond angles (º)	Cal.	Exp.*
C1-O18	1.44	1.44	C15-H33	1.08	0.93	C7-C6-H28	120.10	119.52
C1-H23	1.09	0.96	C16-C17	1.39	1.36	C11-C10-H31	114.55	118.73
C1-H24	1.09	0.96	C16-H34	1.08	0.93	C10-C11-O19	116.51	117.79
C1-H25	1.09	0.96	C17-H35	1.08	0.93	C10-C11-O20	126.26	126.24
C2-C3	1.48	1.48	O21-H30	1.83	1.92	O19-C11-O20	117.23	115.97
C2-O18	1.34	1.32				C13-C12-C17	121.25	122.35
C2-O21	1.22	1.20	**Bond angles (º)**	**Cal.**	**Exp.***	C13-C12-O19	122.36	121.36
C3-C4	1.42	1.41	O18-C1-H23	110.42	109.52	C17-C12-O19	116.40	116.29
C3-C8	1.40	1.39	O18-C1-H24	110.39	109.52	C9-C13-C12	117.52	118.06
C4-C5	1.41	1.39	O18-C1-H25	105.22	109.53	C9-C13-C14	124.53	125.43
C4-N22	1.39	1.39	H23-C1-H24	109.34	109.42	C12-C13-C14	117.96	116.46
C5-C6	1.39	1.36	H23-C1-H25	110.72	109.42	C13-C14-C15	121.02	122.03
C5-H29	1.08	0.93	H24-C1-H25	110.71	109.42	C13-C14-H32	120.14	118.95
C6-C7	1.40	1.37	C3-C2-O18	113.29	112.28	C15-C14-H32	118.84	119.03
C6-H28	1.08	0.93	C3-C2-O21	125.13	125.19	C14-C15-C16	119.94	119.43
C7-C8	1.38	1.36	O18-C2-O21	121.58	122.53	C14-C15-H33	119.83	120.29
C7-H27	1.08	0.93	C2-C3-C4	121.09	121.04	C16-C15-H33	120.23	120.27
C8-H26	1.08	0.93	C2-C3-C8	119.56	120.11	C15-C16-C17	120.27	120.36
C9-C10	1.37	1.35	C4-C3-C8	119.33	118.83	C15-C16-H34	120.10	119.86
C9-C13	1.46	1.45	C3-C4-C5	118.29	118.61	C17-C16-H34	119.63	119.78
C9-N22	1.38	1.35	C3-C4-N22	119.79	119.11	C4-N22-H30	112.56	113.70
C10-C11	1.44	1.41	C5-C4-N22	121.84	122.16	C9-N22-H30	116.47	114.05
C10-H31	1.08	0.93	C4-C5-C6	120.99	120.45	C6-C7-C8	118.97	119.49
C11-O19	1.40	1.37	C4-C5-H29	119.46	119.79	C6-C7-H27	120.66	120.30
C11-O20	1.21	1.20	C6-C5-H29	119.52	119.76	C8-C7-H27	120.36	120.22
C12-C13	1.41	1.39	C5-C6-C7	120.88	121.07	C3-C8-C7	121.50	121.40
C12-C17	1.40	1.37	C12-C17-C16	119.57	119.36	C3-C8-H26	118.26	119.28
C12-O19	1.36	1.37	C12-C17-H35	118.49	120.27	C7-C8-H26	120.23	119.32
C13-C14	1.41	1.39	C16-C17-H35	121.94	120.38	C10-C9-C13	118.58	118.60
C14-C15	1.39	1.36	C1-O18-C2	116.27	116.21	C10-C9-N22	124.83	125.88
C14-H32	1.08	0.93	C11-O19-C12	121.98	121.41	C13-C9-N22	116.57	115.46
C15-C16	1.40	1.38	C4-N22-C9	129.68	130.88	C9-C10-C11	123.05	122.65
N22-H30	1.02	0.84	C5-C6-H28	119.02	119.42	C9-C10-H31	122.33	118.61

* Taken from ref (Hollauer et al., 2023)

HOMO-LUMO Analysis

The HOMO (Highest Occupied Molecular Orbital) represents the molecule's ability to donate electrons, while the LUMO (Lowest Unoccupied Molecular Orbital) represents the molecule's ability to accept electrons. HOMO and LUMO orbitals are two key orbitals critical in characterizing the chemical, biological, and physical properties of molecules, predicting how molecular interactions and reactions can occur. The difference in energy between the HOMO and LUMO orbitals (ΔE) provides crucial

information about the molecule's stability. A molecule with a large HOMO-LUMO energy gap is stable and less reactive, whereas a molecule with a small HOMO-LUMO energy gap is reactive (Fleming, 1976).

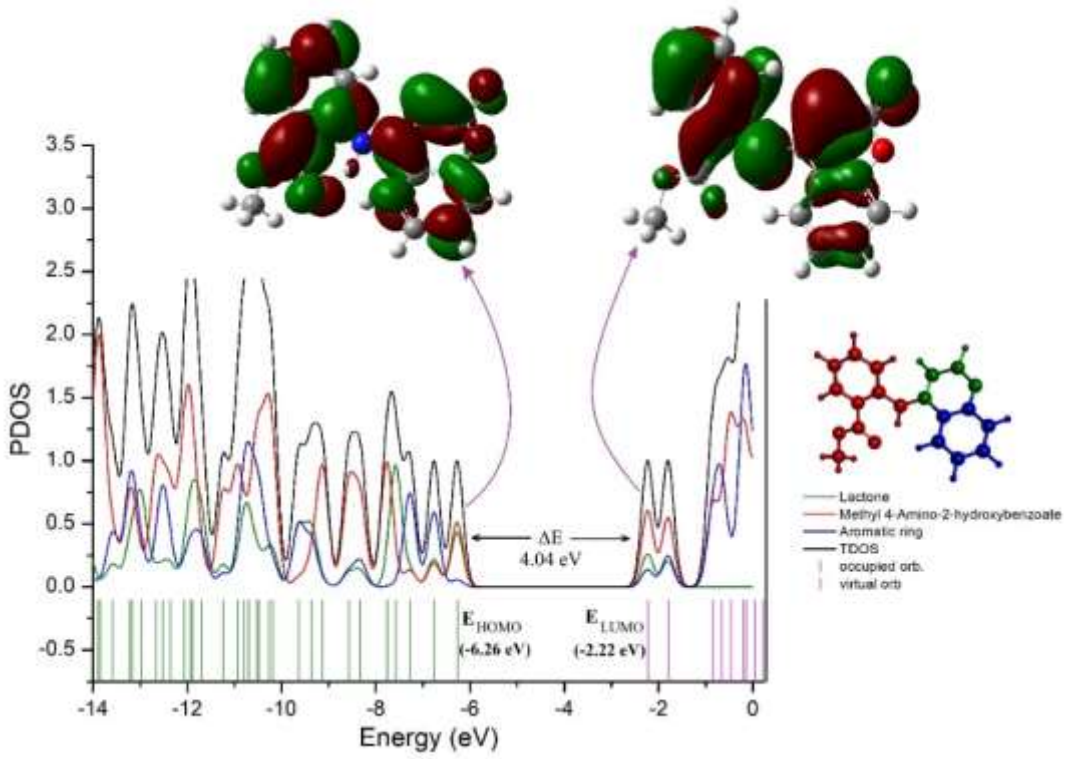

Figure 2. Calculated 3D shapes of HOMO-LUMO orbitals and PDOS plots showing contributions from functional groups to molecular orbitals

In addition, the HOMO and LUMO energies, also called frontier orbitals, are used to calculate the chemical reactivity descriptor values of molecules such as chemical hardness (η), chemical softness (S), electron affinity (A), chemical potential (μ), global electrophilicity index (ω) and ionization energy (I) (Koopmans, 1934). The HOMO (EHOMO), LUMO (ELUMO) energies and energy band gap (ΔE) of the title compound were determinated using DFT calculations with the B3LYP/6-311++ G(d,p) basis set in the gas phase.

3D plot of the title compound representing the localization of the calculated HOMO and LUMO orbitals on the molecule are shown in Figure 2. Also, the chemical reactivity descriptors calculated using frontier molecular orbitals are listed in Table 2. The orbitals near the boundary region may have semi-degenerate energy levels. Therefore, evaluating only the HOMO and LUMO as the frontier orbitals might not be accurate (AlRabiah et al., 2017). Density of state spectra (DOS) more precisely describe the electron contributions to the HOMO and LUMO bands (Rijal et al., 2022). The composition of molecular orbitals in certain energy ranges can be interpreted by TDOS spectra.

Table 2. The calculated reactivity indices for methyl 2-(2-oxo-2H-chromen-4-yl-amino)-benzoate

ΔE_{HOMO} (eV)	-6.26	χ (eV)	4.24
ΔE_{LUMO} (eV)	-2.22	η(eV)	2.02
$\Delta E_{HOMO-LUMO}$ (eV)	4.04	S(1/eV)	0.25
I (eV)	6.26	μ (eV)	-4.24
A (eV)	2.22	ω(1/eV)	18.20

On the other hand, the contributions to each molecular orbital from different groups of the compound can be elucidated by studying the piecewise density of state spectrum PDOS. For these reasons, TDOS and PDOS spectra for the title compound were obtained with the help of GaussSum 3.0 program to see the contributions from groups Lactone, methyl 4-amino-2-hydroxybenzoate and Aromatic ring to the HOMO and LUMO orbitals (Figure 2). The PDOS study results showed that the contributions to the LUMO orbital from lactone, methyl 4-amino-2-hydroxybenzoate and aromatic ring groups were 26%, 60% and 14%, respectively, while the contributions to the HOMO orbital from lactone, methyl 4-amino-2-hydroxybenzoate and aromatic ring groups were 43%, 51% and 6%, respectively.

MEP Analysis

Molecular electrostatic potential (MEP) analysis is analyzed with 3D maps where the molecular surface is represented by different colors according to the electron density of different regions of the molecule. On the map, the electrostatic potential is ordered as red < green < blue (Parr and Pearson, 1983). MEP analyses provide important information about the chemical reactivity of the molecule by evaluating potential sites on the molecule for electrophilic and nucleophilic attacks. The blue color representing the positive regions on the MEP represents the region most prone to nucleophile attack, while the red color representing the negative regions represents the regions prone to electrophilic attack. The green colored regions represent neutral regions. (Xu, Huifang et al., 2017; Politzer and Murray, 2018).

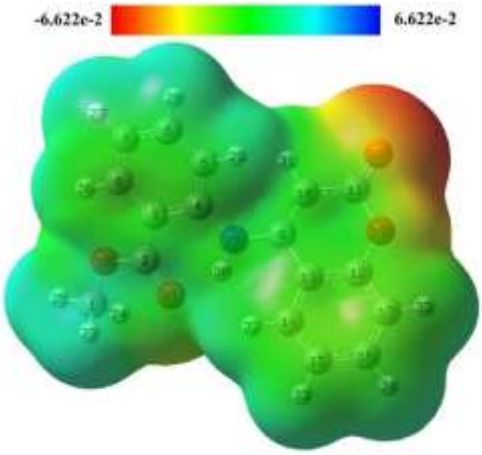

Figure 3. Three-dimensional surface of the molecular electrostatic potential of the title compound

The potential target sites of the title compound for electrophilic and nucleophilic attacks are calculated with the base set B3LYP/6-311++G(d,p) with the help of MEP analysis performed on the optimized structure and presented in Figure 3. The electrostatic potential distribution of the title compound on the surface was found to be in the range of -6.622e-2 to 6.622e-2 a.u. As clearly seen in Figure 3, there is a negative electrostatic potential region around the oxygen atoms O20 and O19 (represented in red). Therefore, this region can be considered as a potential electrophilic attack site. On the other hand, it was determined by MEP analysis that the most prone to nucleophilic attack of the molecule mentioned in the title is the carbon and hydrogen atoms represented in blue on the surface.

Drug-Likeness Properties

Drug-likeness characteristics are a set of properties used to evaluate the chemical, physical and biological properties of new drug candidates compared to existing drugs or compounds. These properties

are important for selecting, optimizing and developing drug candidates in drug design and discovery processes. There are some criteria in the literature to be used in drug design. One of the most widely used of these criteria is a set of criteria proposed by Christopher A. Lipinski for use in drug design, known as the Lipinski rule of five. According to the Lipinski criteria, chemical structure limitations are defined; as ≤500 for molecular weights, ≤10 for hydrogen bond acceptor numbers, ≤5 for hydrogen bond donor numbers and lipophilicity of compounds (log P or clog P) ≤5 (Lipinski et al., 1997).

The drug-likeness properties of the title compound were investigated according to Lipinski's criteria with the help of the SwissADME web tool, which has an open access and user-friendly interface, and the relevant parameters are given in Table 3. As clearly seen in Table 3, there is no violation. Therefore, the absence of violation means that the title compound has the potential to be used as a drug in living organisms.

Table 3. Drug-likeness properties of the title compound according to Lipinsky's five criteria

Criteria	Accept range	Methyl 2-(2-oxo-2H-chromen-4-yl-amino)-benzoate	
		Calculated	Decision
Molecular mass (Da) (MW)	≤500	296.3	✓
Hydrogen bond donors (HBD)	≤5	1	✓
Hydrogen bond acceptors (HBA)	≤10	4	✓
LogP	≤5	2.4	✓

Hirshfeld Surface Analysis

Hirshfeld surface (HS) analysis is an analysis method used in the fields of molecular chemistry and crystallography and has many important applications. HS analysis is used to understand the molecular interactions and crystal properties of a compound with a solved crystal structure in the solid state. This analysis helps crystallographers to understand the details of the crystal structure. Non-covalent interactions are responsible for the packing of the crystal structure of the molecule. Therefore, HS analysis using Crystal Explorer to investigate these interactions is important for a better understanding of the structure. The HS, drawn on the dnorm, attempts to explain intermolecular interactions using a color scale of red, white and blue (McKinnon et al., 2007; Ashfaq et al., 2021). The red, white and blue colors on the color scale represent interatomic contacts where the interatomic distance is less than, equal to and greater than the sum of the Vander Waal radii, respectively. The HS of the title compound is shown in Figure 4(a). Figure 4(a), HS analysis reveals the formation of hydrogen bonding interactions between O atoms and H atoms in the molecule.

Figure 4(b)-(e) show the 2D fingerprint plot for all possible interactions with a contribution above 5% in the crystal packing of the title compound. The quantitative results of the Hirshfeld surface analysis for the title molecule were found to be 26.4%, 24.1% and 5.7% for C···H/H···C, O···H/H···O and C···C, respectively, for interactions with contribution above 5%. In 2D fingerprint plots, the values *de* and *di* represent the closest outer and inner distances (Å) from specific points on the HS contacts.

Homology Modelling

The crystal structure of TR has not been discovered yet. Therefore, the three-dimensional crystal structure of TR can be obtained using homology modeling, an analytical method used to understand similarities and evolutionary relationships between biological organisms (Zheng et al., 2005; Xu, W et al., 2007). High degree of sequence alignment is required for the success of homology modeling. The sequence of Layshmania's TR enzyme was retrieved from UniProt (https://www.uniprot.org) with the accession number Q4QJG7.

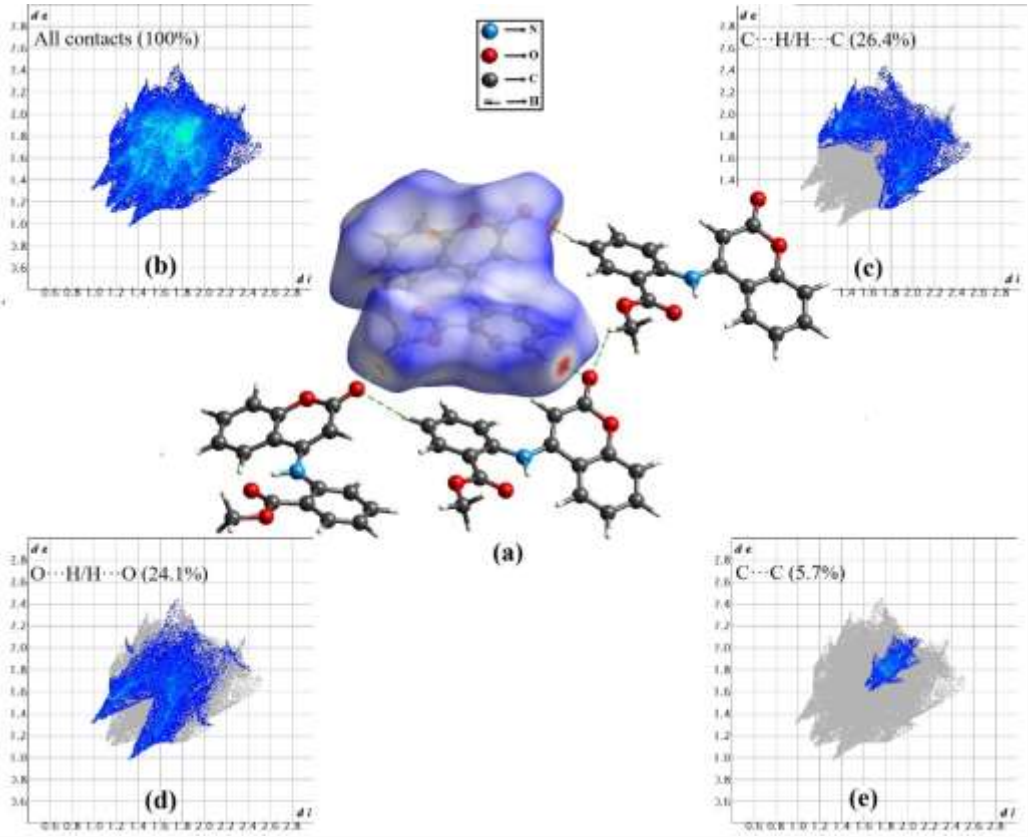

Figure 4. (a) View of the three-dimensional HS Analysis of the title compound, plotted over dnorm in the range from −0.2134 to 1.1066 a.u, (b) 2D fingerprint plot showing contributions from general contacts, (c) 2D fingerprint plot showing contributions from C···H/H···C contacts, (d) 2D fingerprint plot showing contributions from O···H/H···O contacts, (e) 2D fingerprint plot showing contributions from C···C contacts

This sequence was used in modeling the 3D crystal structure of TR through the Swiss Model. Stereochemical properties and structure validation of the structure obtained through homology modeling were carried out with the help of PROCHECK (Rafeeq et al.; Morris et al., 1992).

Molecular Docking Analysis

Using computational tools, one can analyze the binding regions of proteins and predict therapeutic targets based on factors such as druggability, accessibility, and the necessities for the survival of the parasite. The TR enzyme is one of the key therapeutic target enzymes of genetically and chemically validated leishmania species that maintains redox homeostasis for parasite survival (Rodrigues, Raquel F et al., 2012). In this study, the interaction mechanism of TR and the compound methyl 2-(2-oxo-2H-chromen-4-ylamino)benzoate, which has the potential to be an inhibitor of TR, was elucidated through a molecular docking study. According to the result obtained by homology modeling for the TR enzyme, the receptor coded 2JK6 PDB was taken from the Protein Data Bank. The 3D molecular structure of the clomipramine compound to be used as a control was obtained from the PUBCHEM database. For the molecular docking study, proteins and ligands were prepared according to the procedures we followed in our previous studies (Bayrakdar et al., 2022; Bayrakdar, 2023). The summative results obtained by the molecular docking study are presented in Table 4 for clomipramine and the title compound and given in Figure 5 and Figure 6 respectively.

As a result of the molecular docking study performed between the control compound clomipramine and the target receptor, it is clearly seen in the 3D and 2D drawings given in Figure 5 (a)

and (b) that the clomipramine compound moves into the active cavity of the receptor and localizes there. Similarly, in the compound mentioned in the title, it is evident in Figure 6 (a) and (b) that it interacts with the active residues in the receptor's active site, similar to clomipramine.

Table 4. Summative results of molecular docking of clomipramine and the title compound with the 2JK6 receptor

Ligands	ΔG (kcal/mol)	Hydrogen Bond interactions (Å)	Hydrophobic interaction (Å)	Electrostatic Interaction (Å)
Clomipramin	-6.60	**Carbon H-Bond** Tyr198(3.78)	**Pi-Pi T-shaped** Phe367(4.92) **Alkyl** Ala365(4.75), Cys57(4.88), Val58(4.79), Lys61(3.72) **Pi-Alkyl** Phe367(5.01), Lys61(4.90), Leu334(5.22), Pro336(4.92), Ala365(5.21)	
Methyl 2-(2-oxo-2H-chromen-4-yl-amino)-benzoate	-8.84	**Conventional H-Bond** Tyr198(1.88), Ser178(3.03), Arg287(2.80)	**Pi-Sigma** Ile199(3.63) **Alkyl** Cys57(3.88) **Pi-Alkyl** Lys60(4.51), Ile199(3.98), Tyr198(5.11)	**Pi-Anion** Asp327(3.89)

In the docking study, the reference compound clomipramine showed a binding affinity of -6.6 kcal/mol, while Methyl 2-(2-oxo-2H-chromen-4-ylamino)benzoate compound showed a binding affinity of -8.84 kcal/mol. Compounds exhibiting better docking scores and binding energies are more promising as priority targets for *in-vitro* and *in-vivo* studies (Challapa-Mamani et al., 2023).

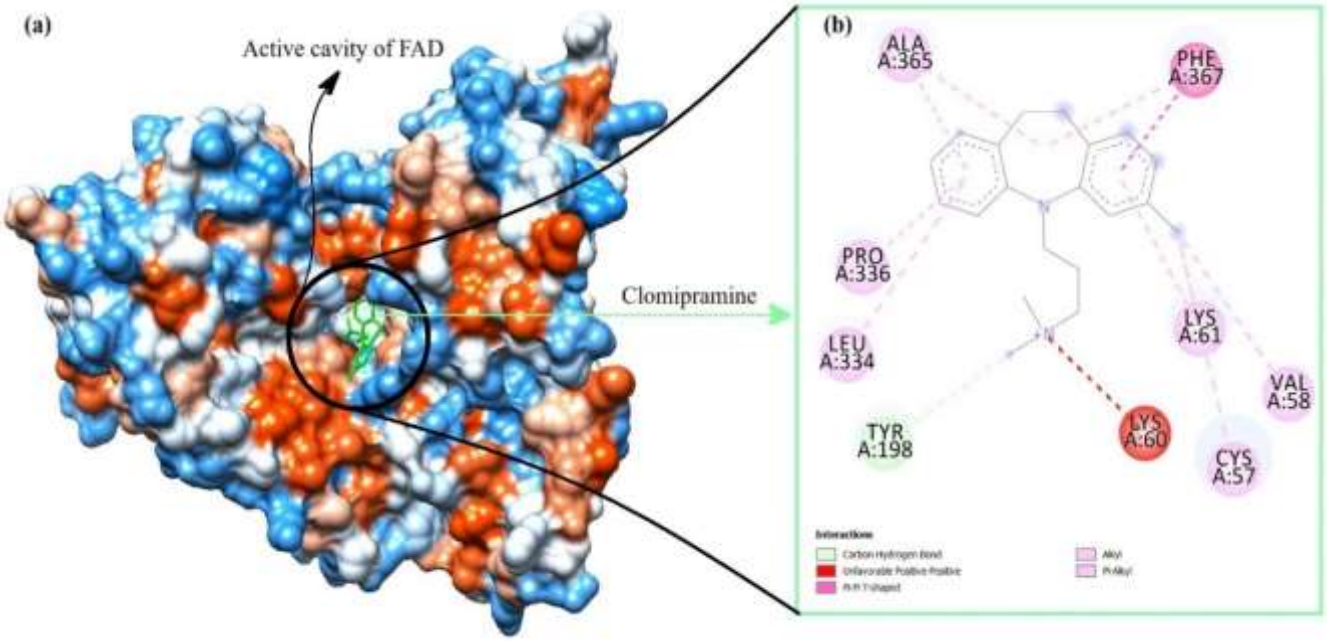

Figure 5. (a) 3D surface view of the Clomipramine docked into the active cavity of the 2jk6 receptor obtained using UCSF chimera (b) 2D view of the intermolecular interactions between the Clomipramine and the receptor obtained using the Biovia Discovery Studio

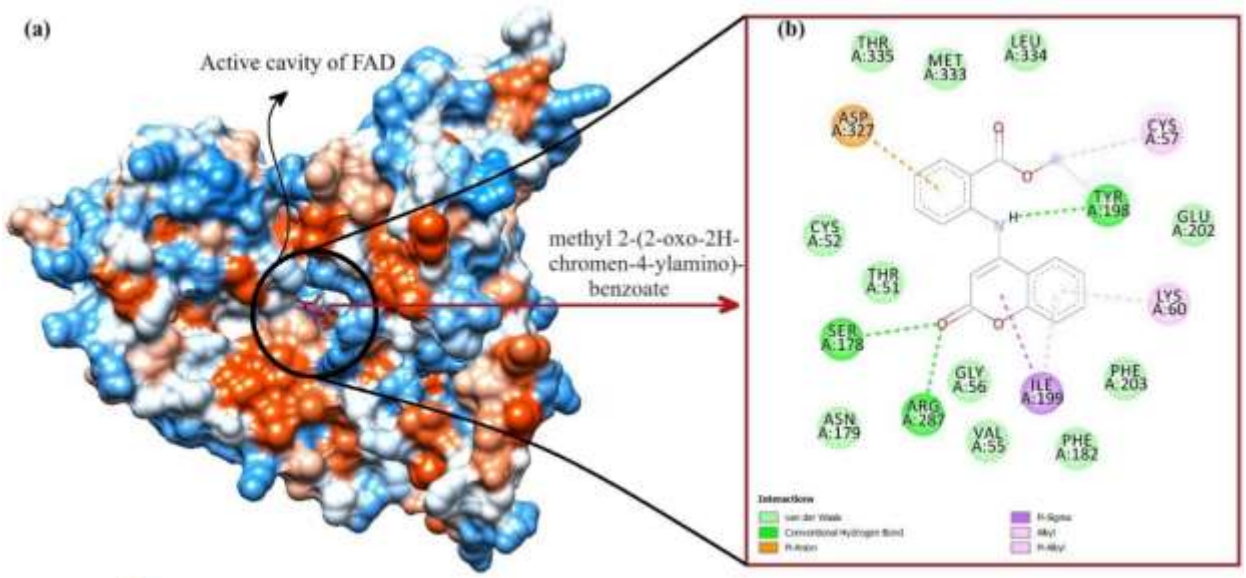

Figure 6. (a) 3D surface view of the methyl 2-(2-oxo-2H-chromen-4-yl-amino)-benzoate docked into the active cavity of the 2jk6 receptor obtained using UCSF chimera (b) 2D view of the intermolecular interactions between the title compound and the receptor obtained using the Biovia discovery studio

In summary, clomipramine made 11 interactions with the receptor in the active site cavity, including 10 hydrophobic (5 Pi-Alkyl (Leu 334, Pro336, Ala365, Phe367, Lys61), 4 Alkyl (Ala365, Cys57, Val58, Lys61) and 1 Pi-Pi T-shaped (Phe367)) and 1 carbon H-bond (Tyr198) interaction. The compound mentioned in the title, like the control compound, settled into the active cavity of the target protein and made a total of 9 interactions with the receptor there, including 5 hydrophobic (1 pi-sigma (Ile199), 1 Alkyl (Cys57) ve 3 pi-Alkyl (Lys60, Ile199 ve Tyr198)), 1 electrostatic (Asp327) and 3 conventional H-bonds (Tyr198, Ser178 ve Arg287). Since carbon H-bonds have lower electronegativity than conventional H-bonds, conventional H-bond interactions are more stabilizing in the molecular structure (Horowitz and Trievel, 2012). The fact that the title molecule has a lower binding affinity than clomipramine can be explained by convectional h-bond interactions.

CONCLUSION

Methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate compound with anti-leishmania potential was optimized using DFT method and the result obtained showed good agreement with the crystal structure. MEP analysis for biochemical interactions revealed that the oxygens in the coumarin moiety could be considered as potential electrophilic attack sites. It was seen that the calculated values in the DOS spectrum and HOMO-LUMO were compatible. In the crystal packing HS Analysis of the title compound, the largest contribution came from C···H/H···C contacts with 26.4%. The drug-likeness study according to the Lipinsky criteria showed that the compound could be used as a drug. The molecular docking study showed that the molecule in the title has a better affinity due to its conventional H-bond interactions compared to clomipramine, a known inhibitor of TR. These results suggest that methyl 2-(2-oxo-2H-chromen-4-ylamino) benzoate may have anti-leishmania potential. However, *in-vitro* and *in-vivo* studies are needed to confirm the anti-leishmania potential of the compound.

ACKNOWLEDGEMENTS

This study was supported by project number (Grant No: 2013FBE013)

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