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ORIGINAL ARTICLE / ÖZGÜN MAKALE

STRUCTURAL AND PHARMACEUTICAL EVALUATION OF 4-HYDROXY-BENZAMIDE DERIVATIVE: ANTI-BACTERIAL AND ANTI-VIRAL POTENT

4-HİDROKSİ-BENZAMİD TÜREVİNİN YAPISAL VE FARMASÖTİK DEĞERLENDİRMESİ: ANTİ-BAKTERİYAL VE ANTİ-VİRAL ETKİ

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ABSTRACT

Objective: *In medicinal chemistry, biochemical research and the drug distribution mechanism are crucial. Many common illnesses are caused by bacteria and viruses.The findings of this analysis may be very beneficial to the pharmacy and drug development processes.*

Material and Method: *Experimental UV-Vis spectroscopy was recorded and compared with the computed results. Reactive sites are analyzed using molecular electrostatic potential and dual descriptor's analysis. Toxicity and druglikeness parameters are explored. Docking study was performed using Autodock tool software.*

Result and Discussion: *Calculated C11-O19 bond length value is found as 1.226. Calculated band gap energy from molecular orbitals is 4.39 eV. Experimentally recorded and computationally predicted UV-VIS spectrum values are comparable with the biomaterial. Binding energy is computed as -6.18 and -5.36 from PL interaction studies. Hydrogen bonds are found between the title ligand and bacterial, viral protein receptors*.

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Keywords: *DFT, Drug likeness, MEP, Molecular docking, Toxicity*

ÖZ

Amaç: *Medisinal kimyada biyokimyasal araştırma ve ilaç dağılım mekanizması çok önemlidir. Bakteri ve virüsler pek çok hastalığa neden olmaktadır. Bu çalışmanın bulguları eczacılık ve ilaç geliştirme süreçleri için çok faydalı olabilir.*

Gereç ve Yöntem: *Kaydedilen deneysel UV-Vis spektrumu hesaplanan sonuçlarla karşılaştırıldı. Reaktif bölgeler, moleküler elektrostatik potansiyeli ve ikili tanımlayıcılar analizi kullanılarak analiz edildi. Toksisite ve ilaç benzerliği parametreleri araştırıldı. Docking çalışması, Autodock programı kullanılarak gerçekleştirildi.*

Sonuç ve Tartışma: *Hesaplanan C11-O19 bağ uzunluğu değeri 1.226 olarak bulundu. Moleküler orbitallerin hesaplanan bant aralığı enerjisi 4.39eV'dir. Deneysel olarak kaydedilen ve hesaplanan tahmini UV-VIS spektrum değerleri, biyomateryal ile karşılaştırılabilir düzeydedir. Bağlanma enerjileri, PL etkileşim çalışmaları ile -6.18 ve -5.36 olarak hesaplandı. Başlık ligandı ile bakteriyel ve viral protein reseptörleri arasında hidrojen bağları bulundu.*

Anahtar Kelimeler: *DFT, İlaç benzerliği, MEP, Moleküler docking, Toksisite*

INTRODUCTION

Amide derivatives are an important class of compounds in different biologically activities [1]. N-[(Z)-(4-fluorophenyl)methylideneamino]-4-hydroxybenzamide (FBFBH) is a heterocyclic compound; mostly it is used in medicinal purposes like, antifungal, anticancer, anti-inflammatory, anticonvulsant, antioxidants and antiviral agents [2–5]. Hydroxy-benzamide derivatives have the immense applications in biological field and especially in anti microbial activities [6]. Anti fungal activity of the hydroxy-benzamide derivative was explored in earlier studies [7]. Related N-acetyloxy-2-hydroxybenzamide with oxidovanadium (IV) complexes was synthesized and reported for microbial potential studies [6]. Zinc sulfate studies are carried out on N-(2-pyridyl)-2-hydroxybenzamide were reported [8]. Hydroxy-benzamide was also reported in solution phase with Iron (III) complexes [9]. The empirical formula for the headline compound is $C_{14}H_{11}FN_2O_2$ and molecular weight of the FBFBH compound is 258.25.

In this present study, detailed work was done on structural, protein ligand interaction and pharmaceutical properties of anti bacterial and anti viral drug. Density functional theory [10] is impletemented to find the reactive sites of the head line molecule. Chemical properties like electrophilic index, chemical softness is calculated. Electronic properties are calculated from molecular orbitals and compared with experimentally recorded band gap energy using UV-Vis spectroscopy. Toxic parameters were calculated. Protein ligand interaction study is explained.

MATERIAL AND METHOD

Experimental Details

The N-[(Z)-(4-fluorophenyl)methylideneamino]-4-hydroxybenzamide compound wass procured from AVRA chemical synthesis. Using DMSO as a solvent, the UV-Vis absorption-spectrum was

recorded using spectrometer in the range between 200-600 nm. The spectral measurement was recorded at the Sophisticated Analytical Instrumentation Facility (SAIF), IIT, Chennai, India.

Computational Details

Structural properties were investigated using Gaussian 09W [11]. 6-311++G(d,p) basis was used [1]. Reactive sites are visualized using Gauss view tool. Pharmaceutical properties are calculated using Preadme online tool (https://preadmet.bmdrc.kr/). Protein receptors were screened using PASS online bioactivity server. Choosen proteins are downloaed from RCSB proteins database. Ligand was prepared from optmized structure of the of the headline molecule. Protein ligand interaction study is performed using Autodock 4.2.6. The computation of the atomic charges was done by Kollman and Gasteiger method after the polar hydrogen was attached. The active with the Lamarckian Genetic Algorithm being used to carry site of the proteinwas defined with 126 Å x 126 Å x 126 Å grid size, out the processes. H-bond interactions are visualized using PYMOL graphical interface tool [12].

RESULT AND DISCUSSION

Optimized Molecular Geometry

By optimizing the molecule structural properties of any chemical structure can be explored. Experimental crystal structure values of 4-hydroxy-benzamide compound are reported in earlier studies [13]. The computed parameters such as Bond length and bond angle are shown in Table 1. In the title compound there are 14 C-C bonds, 1 C=O bond, 1 C-O bond, 1 C-F bond, 1 N-N bond, 1 C-N bond and 2 C-N bonds.The calculated bond length of C2-C3, C2-C19, C3-C4, C3-H20, C4-C5, C4-H21, C5-C6, C5-C18, C6-N7, C6-H22, N7-N8, N8-C9, N8-H23, C9-C10, C9-O17 are 1.354, 1.385, 1.390, 1.392, 1.083, 1.401, 1.085, 1.463, 1.406, 1.280, 1.098, 1.355, 1.391, 1.016, 1.498 and 1.214 respectively. Optimized geometrical structure of the headline compound is shown in Figure 1.

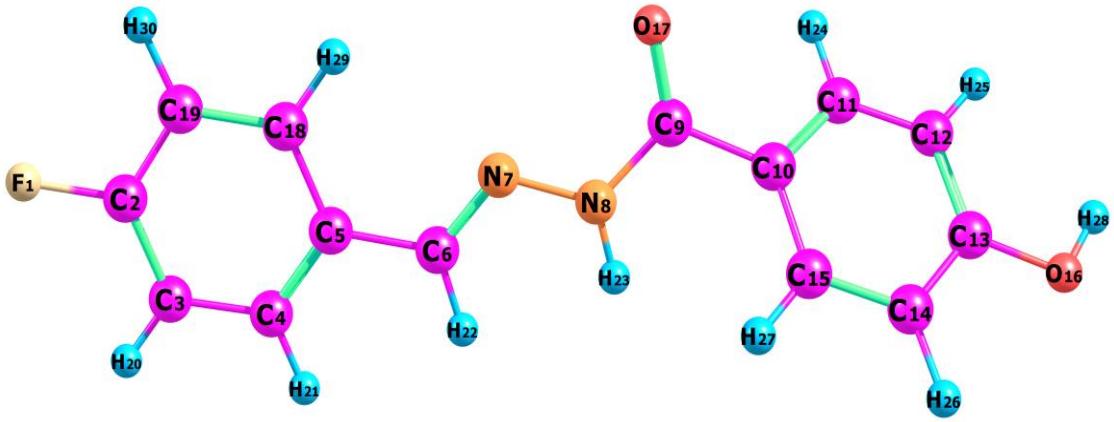

Figure 1. Geometric structure at lowest energy of the title compound

Table 1. Geometrical parameters of the title compound

Parameters	B3LYP/ 6-311++G(d,p)	Parameters	B3LYP/ 6-311++G(d,p)	Parameters	B3LYP/ 6-311++G(d,p)
Bond Length	**(Å)**	**Bond Angle**	**(°)**	**Bond Angle**	**(°)**
F1-C2	1.354	F1-C2-C3	118.9	C10-C15-C14	121.1
C2-C3	1.385	F1-C2-C19	118.8	C10-C15-H27	120.7
C2-C19	1.390	C3-C2-C19	122.4	C12-C11-H24	120.5
C3-C4	1.392	C2-C3-C4	118.3	C11-C12-C13	119.9
C3-H20	1.083	C2-C3-H20	119.9	C11-C12-H25	120.1
C4-C5	1.401	C2-C19-C18	118.8	C13-C12-H25	120.0
C4-H21	1.085	C2-C19-H30	119.6	C12-C13-C14	120.0
C5-C6	1.463	C4-C3-H20	121.8	C12-C13-O16	122.7
C5-C18	1.406	C3-C4-C5	121.1	C14-C13-O16	117.3
C6-N7	1.280	C3-C4-H21	119.2	C13-C14-C15	119.7
C6-H22	1.098	C5-C4-H21	119.7	C13-C14-H26	119.1
N7-N8	1.355	C4-C5-C6	119.4	C13-O16-H28	110.0
N8-C9	1.391	C4-C5-C18	118.9	C15-C14-H26	121.3
N8-H23	1.016	C6-C5-C18	121.7	C14-C15-H27	118.2
C9-C10	1.498	C5-C6-N7	122.0	C19-C18-H29	120.4
C9-O17	1.214	C5-C6-H22	116.6	C18-C19-H30	121.6
C10-C11	1.399	C5-C18-C19	120.6		
C10-C15	1.402	C5-C18-H29	119.0		
C11-C12	1.388	N7-C6-H22	121.4		
C11-H24	1.083	C6-N7-N8	117.5		
C12-C13	1.398	N7-N8-C9	121.1		
C12-H25	1.086	N7-N8-H23	119.2		
C13-C14	1.396	C9-N8-H23	119.2		
C13-O16	1.364	N8-C9-C10	114.3		
C14-C15	1.389	N8-C9-O17	122.9		
C14-H26	1.083	C10-C9-17	122.8		
C15-H27	1.084	C9-C10-C11	117.3		
O16-H28	0.963	C9-C10-C15	124.2		
C18-C19	1.387	C11-C10-C15	118.5		
C18-H29	1.083	C10-C11-C12	120.9		
C19-H30	1.083	C10-C11-H24	118.5		

Frontier Molecular Orbitals

The potential differential among Homo - Lumo, defined as energy band gap, is crucial in deciding a molecule's electrochemical performance and reaction [14].

$$\text{Chemical potential } (\mu) = \frac{1}{2}(E_{LUMO} + E_{HOMO})$$

$$\text{Electronegativity } (\chi) = -\mu = -\frac{1}{2}(E_{LUMO} + E_{HOMO})$$

$$\text{Global hardness } (\eta) = \frac{1}{2}(E_{LUMO} - E_{HOMO})$$

$$\text{Electrophilicity} = \frac{\mu^2}{2\eta}$$

$$\text{Softness } (S) = \frac{1}{\eta}$$

The computed HOMO–LUMO energies of the FBFBH compound are -6.3324 eV and -1.9424 eV respectively and other chemical parameters are shown in Table 2. Band gap Energy value is 4.39eV,

which is comparable to biologically active material and Electrophilicity index is 3.8993. Excited state surface of headline compound is shown in Figure 2.

The UV–vis spectrum of FBFBH was investigated experimentally with DMSO as a fluid and theoretical [15]. The static or dynamic variables of the chosen molecules in the higher states can be measured reliably using this TD-DFT. Table 3 shows that the wavelength of maximal absorption in theory and experiment is 321 and 261nm, overall. The highest wavelength value represents the number of electrons injected rings IEFPCM solvation model is implemented to study the solvent effect of head line molecule. The homo-lumo values and UV-Vis band gap values are compactable and which is comparable with bio active material [16]. The comparison spectra of experimental and theoretical data are shown in Figure 3.

Table 2. Important chemical parameters of the title compound

Parameters	**Values**
HOMO (eV)	-6.3324
LUMO (eV)	-1.9424
Ionization potential	6.3324
Electron affinity	1.9424
Energy gap (eV)	4.3900
Electronegativity	4.1374
Chemical potential	-4.1374
Chemical hardness	2.1950
Chemical softness	0.2278
Electrophilicity index	3.8993

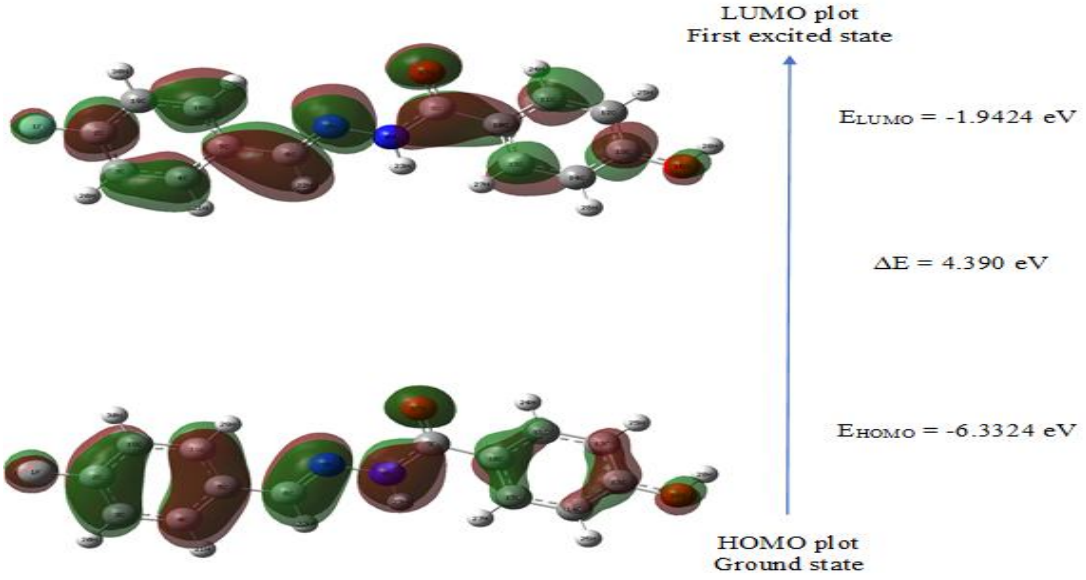

Figure 2. HOMO–LUMO energy values with surface of title compound

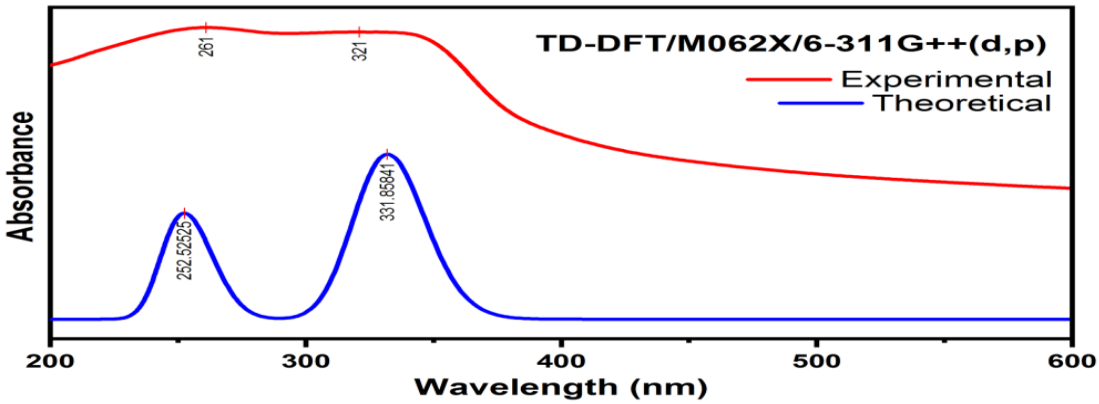

Figure 3. Recorded and computed UV-Vis comparison spectra of title compound

Table 3. Theoretically calculated values of title compound by TD-DFT procedure

No.	Energy(cm^{-1})	Wavelength (nm)	Osc. Strength	Symmetry	Major contribs
1	30141.74	331.7658	0.2317	Singlet-A	HOMO->LUMO (77%)
2	38429.09	260.2195	0.0624	Singlet-A	H-5->LUMO (24%), H-5->L+1 (15%), H-4->LUMO (32%)
3	40083.33	249.4802	0.1161	Singlet-A	H-6->LUMO (12%), H-3->LUMO (26%), HOMO->L+3 (14%)

Molecular Electrostatic Potential

MEP explores molecular shape, molecular size, and chemical reactivity by color grading [17]. The generated MEP map of FBFBH compound is shown in Figure 4. From the map, red colour reveals maximum negative electrostatic potential, blue colour shows maximum positive electrostatic potential whereas green indicates zero potential in the headline compound and the MEP surface is mapped in the range of -7.068×10^{-2} eV to 7.068×10^{-2} eV. From the results, maximum negative potential is on the carbonyl group which is indicated in red colour.

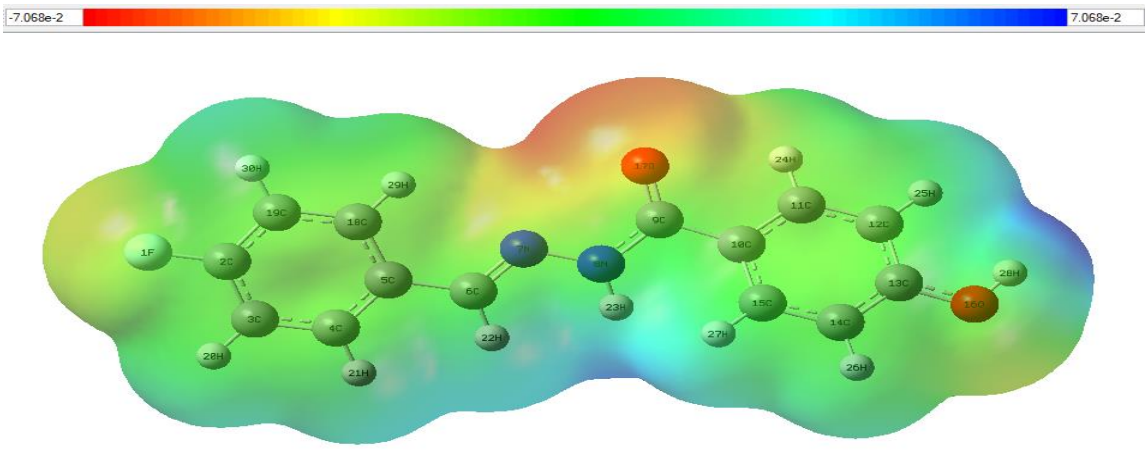

Figure 4. Molecular electrostatic potential surface of title compound

Dual Descriptor Analysis

Reactive sites of chemical structure can be analyzed from mulliken charges by calculating Fukui functions and dual descriptors [18,19]. For the title compound, the negative Δf values are -0.02337, -0.02597, -0.06915, -0.04507, -0.00027, -0.00758, -0.02744, -0.0008, -0.02956, -0.03294, -0.01088, -0.00866, -0.00198, -0.01984, -0.00255 and the corresponding atoms of these values are C6, N7, C9, C11, C12, C13, C14, C15, O17, C18, H24, H25, H27, H28 and H30, respectively. These observed results reveal that O17=C9 atoms with -0.02956 is under electrophilic attack.

Drug Likeness

For the present study, various rules are implemented on the FBFBH compound to find if the compound violates any rule and results are studied [20]. The CMC like rule is qualified and has zero violations, Lead like rule is satisfactory, if binding affinity value is greater than0.1microM. MDDR like rule has mid structure range since there are no rings whereas the crucial Rule of Five (ROF) is satisfactory and there are no violations. WDI like rule comes under 90% cutoff and not violated. From these results, it shows FBFBH compound has adequate drug likeness properties, and it is desirable for drug discovery process.

ADME

ADME properties have vital role in drug development process, these parameters are studied for the FBFBH compound [21]. Blood brain barrier (BBB) permeability is 0.880911, Buffer solubility value is 34.3988, Caco2 value is 18.5044 and it is CYP 2C19, CYP 2C9 inhibitor. The HIA value is 92.24715, MDCK is 2.18067, PPB (Plasma protein binding) is 80.956947, Pure water solubility is 52.0311, Skin permeability is -3.51581, SKlogD and SKlogP value is 2.88487, SKlogS buffer is -3.8755. These obtained values fall under the limit and has an essential role in pharmaceutical development.

Toxicity

Concentration of drug can be identified from the toxic parameters [22]. For FBFBH compound, algae at value are 0.0546867 and Ames test is mutagen whereas hERG inhibition is at medium risk range. The important parameters like Carcino mouse is negative and dalphiaat, medakaat, minnow at parameters values are 0.130129, 0.026422 and 0.0174972, respectively. TA10010RLI value is positive, TA100NA is negative, TA1535 10RLI is negative, TA1535NA is negative. Overall these values show the intoxic nature of the headline compound.

Ramachandran Plot

Ramachandran plot is used to determine the torsional angles that are allowed and gives insight into the peptide structures [23].It unveils the phi-psi torsion angles for every residue in the chosen proteins namely 1R6A and 5OP9 which is shown in figure 5 and 6. From the figures, it can be observed that most of the amino acids are present in the darkest region illustrated here as red and only few are

spotted in the disallowed regions. This validates that the selected proteins are highly stable in nature and can be used to study protein ligand interactions.

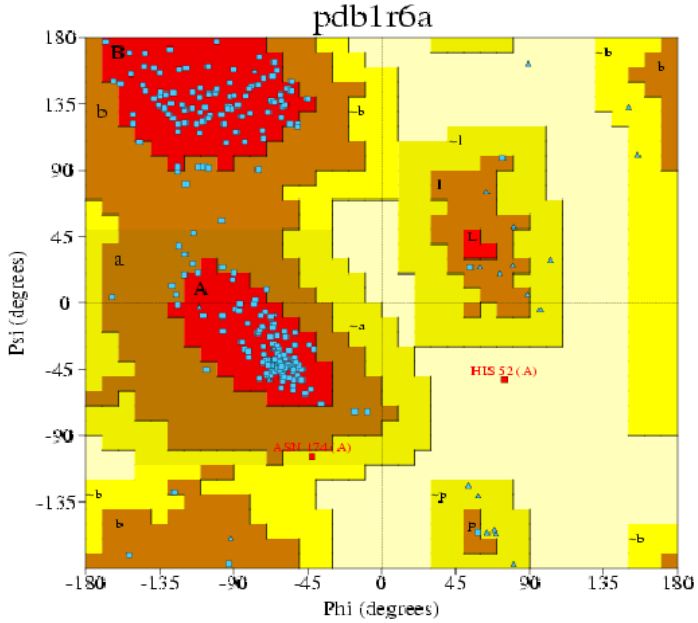

Figure 5. Ramachandran plot for 1R6A protein

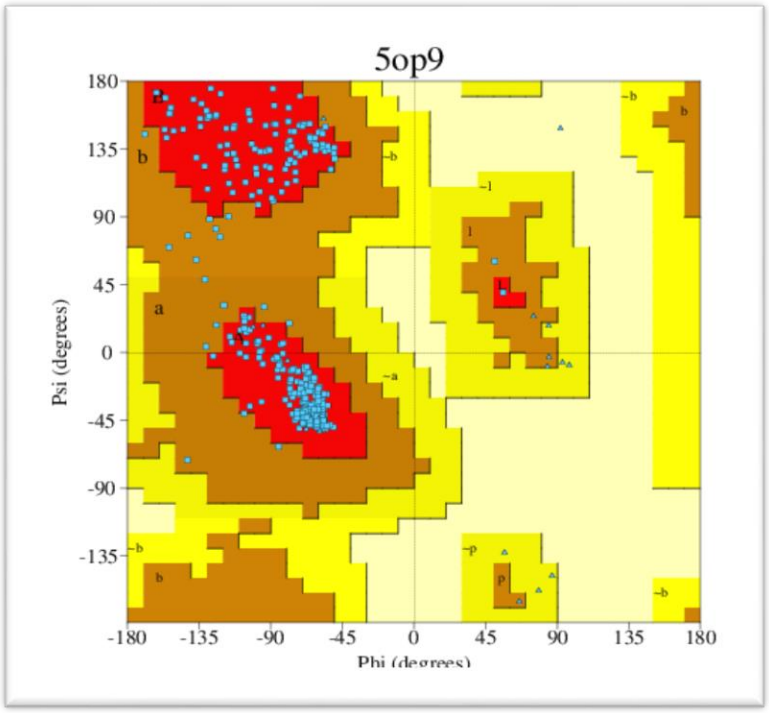

Figure 6. Ramachandran plot for 5OP9 protein

Molecular Docking

Molecular docking is very important in structural molecular biology, pharmacogenomics, and computer-assisted drug development. Binding energy can be calculated from docking processes. Molecular docking experiments assist us in determining the precise binding position of the protein and ligand [24, 25]. Docking study aids in finding the protein ligand binding interactions and also it reduce the cost and time in drug designing process and it is done using Autodock Tools [26–28]. Anti microbial activites, antimycobacterial tuberculosis and binding affinity were studied for receptor 5OP9. Twenty cytochrome P450 enzymes are encoded by Mycobacterium tuberculosis (CYPs or P450s). CYP121A1 is one of these, and it has been shown that it is needed for microbial viability. RMSD gradient for naturally occurred compounds were explained in previous studies [29]. In the current docking study, binding location of the chosen ligand and the proteins are investigated. Target proteins are 1R6A viral protein and 5OP9 mycobacterial protein are obtained from PDB. Chosen protein crystal structures were prepared using PYMOL interface. To obtain the optimized structure of the FBFBH ligand, it is docked into the active sites of the 1R6A, 5OP9 and 100 docking runs are executed to find the best fit binding sites with lowest binding energy. The estimated inhibition constants and binding energy values of PL interactions with 5OP9 and 1R6A receptor proteins are 29.68, 117.7 μmand -6.18, -5.36 kcal/mol, respectively. The bonded residues, RMSD values are shown in Table 4. The binding orientations of 1R6A, 5OP9 proteins and FBFBH ligand are shown in Figure 7 and 8.

In this present work, we investigated the structural properties of FBFBH compound. The significant bondsin the FBFBH compound are N7-N8, N8-H23, C9=O17, O16-H28, F1-C2 and the corresponding bond length values are 1.355, 1.016, 1.214, 0.963, 1.354Å. From UV-vis spectral analysis, absorption maxima of observed and calculated values are 261 and 321nm. The FMO study supplied the theoretical justification for considering the chosen compound to be biologically active and the band gap energy of FBFBH compound is found to be 4.39eV. The reactive sites present in the compound are revealed from Dual descriptor analysis and O17=C9 atoms with -0.02956 is under electrophilic attack. Drug likeness, ADME and Toxicity studies validates that FBFBH compound is suitable for drug development process. Quantitative evaluation of 5OP9, 1R6A proteins is studied using Ramachandran plot, which shows the chosen proteins are structurally stable. The computed minimum binding energy values of ligand - 1R6A, 5OP9 the receptors proteins are -6.18 and -5.36 kcal/mol, respectively. Hence, this compound is predicted as a potential drug for bacterial disease and due to the formation of two hydrogen bond interactions with title compound, it might also be a drug candidate for viral (dengue) disease.

Table 4. H Bond interactions of FBFBH ligand with 1R6A and 5OP9 receptor proteins

Protein (PDB-ID)	Bonded residues	Bond distance (Å)	Estimated Inhibition constant (µm)	Binding energy (kcal/mol)	Intermolecular energy (kcal/mol)	Reference RMSD
5OP9 (Anti bacterial protein)	ASN 74/ UNL 1´H	2.3	29.68	-6.18	-7.37	267.821
	ARG 72/ UNL 1´O	2.8				
	VAL 78/ UNL 1´O	2.8				
	THR 77/ UNL 1´O	2				
1R6A (Antiviral protein)	VAL 130	1.9	117.7	-5.36	-6.55	43.01
	VAL 132	2				

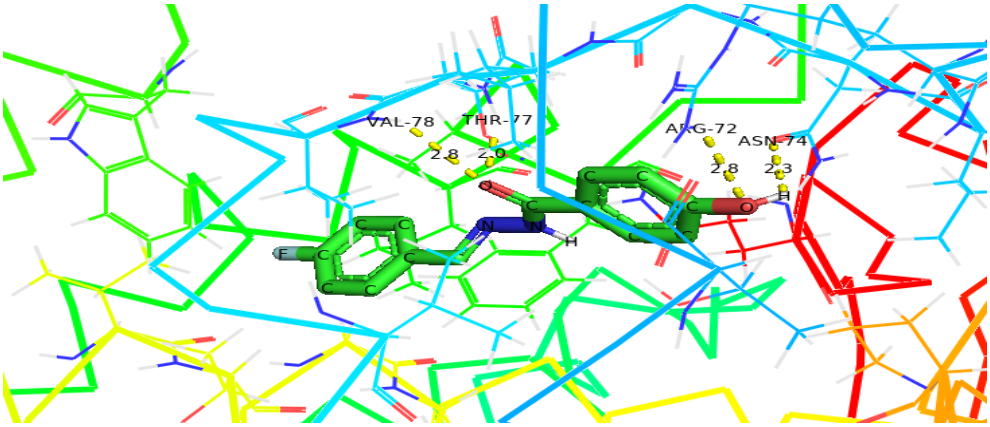

Figure 7. H-Bond interaction of 5OP9 protein with FBFBH ligand

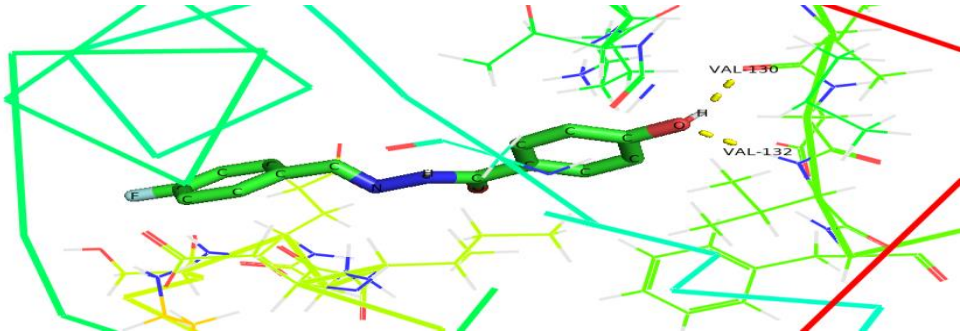

Figure 8. H-Bond interaction of 1R6A protein with FBFBH ligand

AUTHOR CONTRIBUTIONS

Conception: *A.K.V., F.B.A.;* Design: *A.K.V., S.M., F.B.A.;* Supervision: *H.R., S.M., B.N.;* Resources: *H.R.; S.M., B.N.;* Materials: *A.K.V., F.B.A.;* Data collection and/or processing: *A.K.V., F.B.A.;* Analysis and/or interpretation: *H.R., S.M., B.N.;* Literature search: *A.K.V., F.B.A.;* Writing manuscript: *A.K.V., F.B.A.;* Critical review: *H.R., S.M., B.N.;* Other (Figures): *A.K.V., F.B.A.*

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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