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Authors: Sibel ÇELİK

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Conformational Analysis and DFT Investigations of 1-(4-Fluorophenyl)Piperazine by ELF and LOL, Inhibitory Activity Against Alzheimer's Disease, and ADME Prediction

Sibel ÇELİK*[1]

Abstract

This study reports 1-(4-Fluorophenyl)Piperazine molecule structural and electronic properties calculated at the DFT/B3LYP level. A potential energy surface scan along the rotational bonds discovered the most stable minimum energy conformer of the title compound. Frontier molecular orbital (FMO) analyses, density of state (DOS), molecular electrostatic potential (MEP), and global and chemical reactivity descriptors were also used to investigate the reactivity of the pFPP molecule. In addition, ELF and LOL analysis were performed. In silico biological studies such as drug-likeness, ADME, and toxicity properties were also performed. Molecular docking studies are performed to predict the anti-Alzheimer agent enzyme (AChE) active site of the pFPP. The docking predicts the possibility of a potential drug to improve Alzheimer's disease (AD) treatment.

Keywords: 1-(4-fluorophenyl)piperazine, DFT, ADME, ELF, LOL, molecular docking

1. INTRODUCTION

The piperazine derivatives are important pharmacophores across several different therapeutic areas [1] and act as antibacterial [2], antifungal, antipsychotic, antimalarial [3], and anti-HIV proteases [4]. On the other hand, it is frequently employed to generate a variety of physiologically active compounds, including anticonvulsant, anxiolytic, neuroprotective, antioxidant, antidepressant, and anti-Alzheimer's [5]. A large number of well-known medications with a variety of uses contain piperazine, a six-membered heterocyclic molecule that contains nitrogen [6]. Due to their powerful biological activity and their involvement in the creation of promising pharmacological candidates, fluorine-containing heterocyclic compounds have attracted considerable attention [7]. Many commercially available drugs contain a piperazine ring, mainly on the nervous system. This pathology is characterized by a decline in memory, language, problem solving, and some other cognitive skills. This condition affects the ability of the person to perform daily duties. Alzheimer's disease causes neurons to die, which eventually affects parts of the brain that

* Corresponding author: sibelcelik@ahievran.edu.tr
[1] Kırşehir Ahi Evran University
ORCID: https://orcid.org/0000-0002-4852-3826

help a person do basic physical tasks like walking and swallowing [8].

1-(4-fluorophenyl)piperazine (pFPP) is a neuropharmacologically active compound [9]. The actual benefit of this molecular structure for pharmaceutical development is the potential for straightforward coupling of several aldehyde moieties by reductive amination to different phenylbenzyl-piperazines. Different neuroligands have important structural motives, such as ligands for D2-like dopamine receptors, serotonin receptors, sigma receptors [10], adrenergic receptors [11], and calcium channels [12]. Most of the time, adding an aromatic fluorine to a ligand increases its affinity and/or selectivity, which is important for radiodiagnostics [13, 14].

In this paper, the detailed conformational study of the pFPP molecule was performed using DFT. The study of the stable conformer has been performed by theoretical and in silico biological methods. In order to understand the structural and electronic properties of the title molecule, DFT results were compared. The molecular stability, softness, and chemical reactivity of the pFPP molecule are determined by the FMOs and global reactivity Electrophilic and nucleophilic centers were discovered by the MEP, which may interact with biological targets. Also, ELF and LOL analysis of the optimized most stable conformer structure were performed. The drug-likeness, pharmacokinetic (ADME) characteristics, and toxicity investigations were all predicted computationally. In relation to Alzheimer's disease (AD), an in silico molecular docking study was also done on the title compound with a protein target.

2. THEORETICAL CALCULATIONS

Density functional theory (DFT) calculations were performed with the B3LYP functional and the 6-311++G(d) basis sets by using the Gaussian 09 software [15]. The most stable conformer structure is used for the HOMO-LUMO orbitals and MEP analysis of the investigated chemical. The Gaussview molecular visualization program [16] was used to visualize the HOMO, LUMO, and MEP analyses. The Multiwfn software program [17] is used to do the ELF and LOL. The Autodock 2.2.6 software was used to molecular docking the chemical ligand-protein binding site [18]. The docked complexes were visualized using PYMOL [19] and Discover studio software [20]. The RSCB protein data bank provided the 3D dimensional structure of AChE (PDB ID: 1EVE) (www.pdb.org). The ADME and Drug-likeness parameters of the title compound are calculated using Pre-ADMET software [21] and the SwissADME program [22]. The Protox-II website [23] was used to figure out the LD50, as well as the organ toxicity and toxicological end points of the pFPP compound.

3. RESULT AND DISCUSSION

3.1. Conformational studies

The same molecule can be in different positions at room temperature [24]. As a result, conformation analysis was used in this section of our study to determine the lowest energy structure of the title structure at room temperature using the initial structure B3LYP/6-311++G(d, p). To determine the more stable conformer of the pFPP molecule, the PES was generated by shifting this dihedral angle (C10-C8-N2-C4) from 0° to 180° with a step of 10°. The potential energy surface (PES) curve drawn as a result of the calculations is given in Figure 1, according to which there are three different conformers of molecular geometry. The calculated energy as well as relative energies of these conformers are given in Table 1. The results of the PES scan show that conformer II is most stable with the lowest potential energy at an angle of 110° for the selected (C10-C8-N2-C4) dihedral angle.

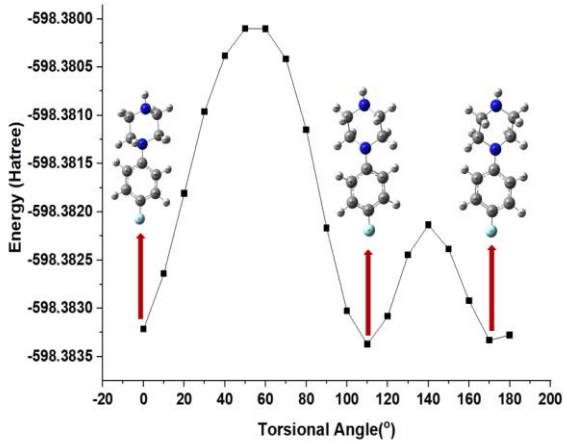

Figure 1 Scan of total energy of C10-C8-N2-C4 dihedral angle calculated by B3LYP/6–311++G(d,p) method.

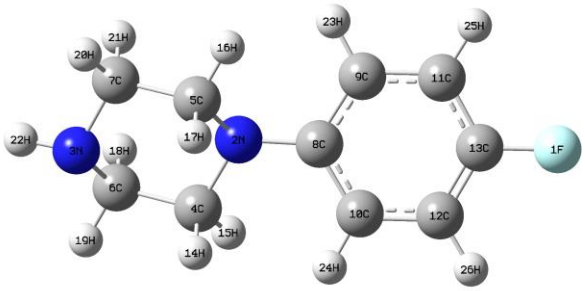

Figure 2 Optimized geometric structure

Table 1 Ground-state optimized energy and energy difference of all pFPP conformers

Conformer	Dihedral angle (°)	Energy (Hartree)	*Energy differ. (Hartree)
I	0	-598.383215640	0.000157
II	110	-598.383372769	0.000000
III	170	-598.383331269	0.000041

* Other conformers' relative energies in relation to the lowest energy of conformer I (Figure 2)

3.2. Frontier Molecular Orbitals and Chemical Reactivity Descriptors

The frontier molecular orbital (FMOs) analysis using quantum chemistry techniques is a well-known tool for explaining molecular transitions [25- 28]. The these orbitals control the mode of interaction between pharmaceuticals and other molecules, including interactions between drugs and their receptors [29]. Figure 3 shows the isodensity surface plots of HOMO and LUMO for the examined compound. Since HOMO is mostly delocalized on –phenyl ring and partially on the –piperazin ring, charge transfer within the system can be seen as LUMO is on phenyl ring. In this study, HOMO and LUMO are critical quantum chemical characteristics that are used to compute several significant parameters, such as chemical reactivity descriptors, and these are calculated and given in Table 2. The HOMO-LUMO energy gap is calculated as 4.99 eV. This band gap confirms that pFPP has a stable, bioactive structure and that charge transfer occurs within the molecule [30]. The lower chemical potential and higher electrophilicity index values calculated for the title molecule are similar to those of bioactive molecules.

The DOS spectrum graphically represents the occupied and unoccupied molecular orbitals of the corresponding molecule [31]. DOS contributions reinforced the information gathered by FMOs. Figure 4 depicts diagrams of DOS computations.

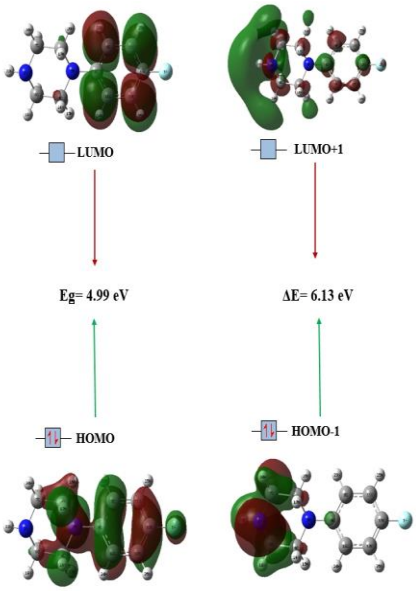

Figure 3 Frontier molecular orbitals of pFPP compound.

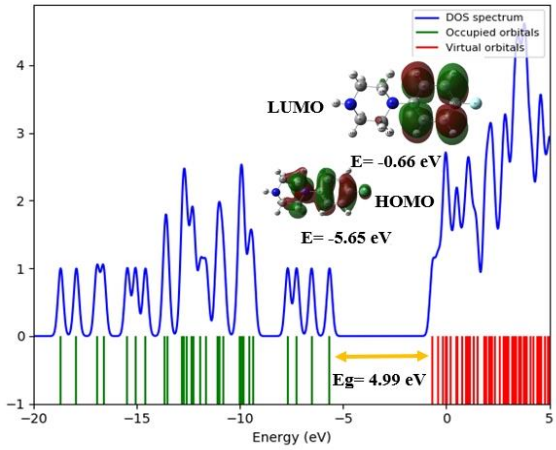

Figure 4 Density of states (DOS) diagram for pFPP molecule.

3.3. Molecular electrostatic potentials (MEP)

The molecular electrostatic potential (MEP) is a well-established computational approach for predicting reactive regions in molecules for nucleophilic and electrophilic attacks [32, 33]. As shown in Figure 5, MEP was estimated for the most stable conformer geometry. The most negative region on the MEP surface is -5.54e-2, which is depicted in red and is referred to as the electrophilic region. The most positive area, shown by the blue color and the nucleophilic region, is +5.54e-2. The various color coding on the MEP surface as displayed in Figure 5 reveals the yellow color regions around –phenyl and are electrophilic regions, whereas the blue color regions around hydrogen atoms show low electron density (nucleophilic). In the MEP, the most reactive location for electrophilic attack is the negative electrostatic potential (shown in red) localized on the fluorine and -NH group in the piperazin ring.

Table 2 Global reactivity descriptors of the pFPP compound

Parameters	Values
E_{HOMO}	-5.65 eV
E_{LUMO}	-0.66 eV
Energy band gap ($\Delta E = E_{LUMO}-E_{HOMO}$)	4.99 eV
Ionization potential ($I = -E_{HOMO}$)	5.66 eV
Electron affinity ($A = -E_{LUMO}$)	0.66 eV
Chemical hardness ($\eta = (I-A)/2$)	2.49 eV
Chemical softness ($\sigma = 1/2\eta$)	$0.40(eV)^{-1}$
Electronegativity ($\chi = (I + A)/2$)	3.16 eV
Chemical potential ($\mu = -(I + A)/2$	-3.16 eV
Electrophilicity index ($\omega = \mu 2 /2\eta$)	2.00 eV
Max. charge transfer index ($\Delta N_{max} = -\mu/\eta$)	1.27

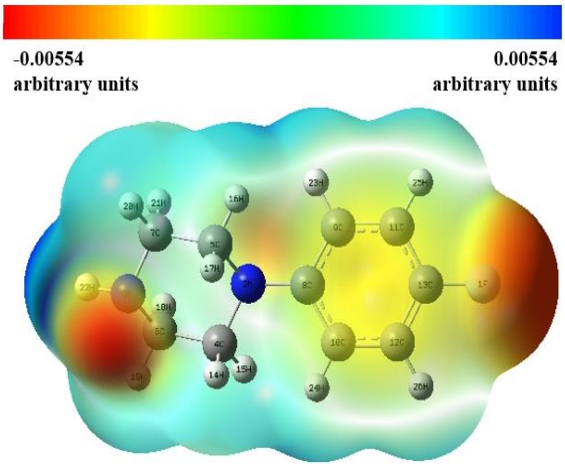

Figure 5 Molecular electrostatic potential maps of pFPP compound

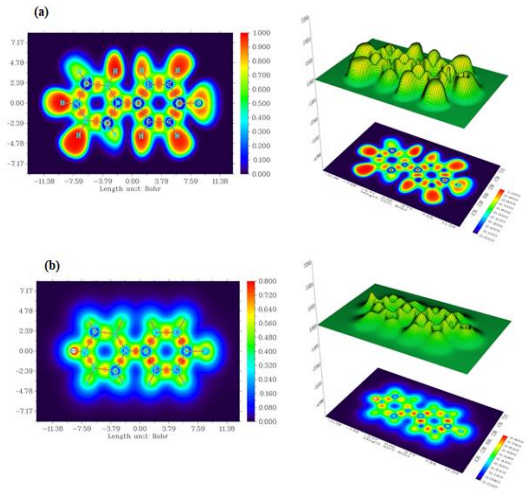

Figure 6 Relif map and Color filled map of (a) ELF and (b) LOL of pFPP compound

3.4. ELF and LOL analyses

The electron localization function (ELF) and the localized orbital locator (LOL) are often used to show the structure of an atomic shell structure, chemical bonding classification, and charge-shift bond verification on the surface of a molecule. These surface analysis show that the high likelihood of discovering an electron pair on the molecular surface [33-35]. 2D and 3D depictions of the ELF and LOL isosurface for the pFPP compound in Fig. 6. The strong localized bonding and nonbonding electrons around hydrogen atoms are indicated by high ELF regions (red region) in Figure 6(a). The delocalized electron cloud around carbon and nitrogen atoms is shown by blue regions. The electron density is shown by the white color present in the central part of the hydrogen atom (H22) of the piperazin ring, as seen in Figure 6(b). The majority of the covalent region between carbon-carbon atoms and carbon-nitrogen atoms, represented by the red color. The blue circles around fluorine atom indicate the electron depletion.

3.5. Molecular docking study

The pFPP molecule is an active substance for different neuroligands, and it is also involved in the structure of many drugs that act on the nervous system because it contains a piperazine ring. Since piperazines are under development as multifunctional agents for the treatment of Alzheimer's disease (AD) [36], anti-Alzheimer's receptor has been chosen as a biological target in the molecular docking. The most common treatment for AD is to improve cholinergic neurotransmission by blocking one of the major neurotransmitters, ACh, from being broken down by AChE, which maintains the brain's ACh level to compensate for the loss of functional brain cells. Therefore, the AChE enzyme was chosen as a biological target for our study. In order to study the most stable conformer, it was docked to the active sites of AChE. The in-silico molecular docking results, the binding energy, inhibition constant (Ki), and RMSD in the ligand-enzyme complex are -5.97 kcal/mol, 42.30 μM, and 92.61 Å, respectively. In drug design, the binding energy of compounds to anti-Alzheimer's receptors is crucial, while Ki is a measure of the ligand's protein binding affinity. The ligand-enzyme complex contains hydrophobic interactions and

hydrogen bonds as shown in the Figure 7 given in 2D and 3D. The computational analyses of the molecular docking research show that the hydrogen bond interaction between the nitrogen atom N3 of piperazin ring and SER'286 residue of oxygen atom (N-H…O). Additionally, hydrophobic amino acids that are ordinarily incorporated inside the enzyme, such as TRY'334, PHE'331 and ARG'289, in the form of pi-pi interactions between title compounds (see Table 3). In molecular docking studies, it was concluded that the reactive sites obtained from MEP calculations are suitable for H-bond interaction with the selected enzyme.

Table 4 Toxicity prediction using the Protox II of pFPP

pFPP	**Values**
Toxicity Class	III
LD_{50} (mg/kg)	108
Organ Toxicity (Probability	
Hepatotoxicity	Inactive (0.83)
Carcinogenicity	Inactive (0.71)
Immunotoxicity	Inactive (0.96)
Mutagenicity	Inactive (0.82)
Cytotoxicity	Inactive (0.79)

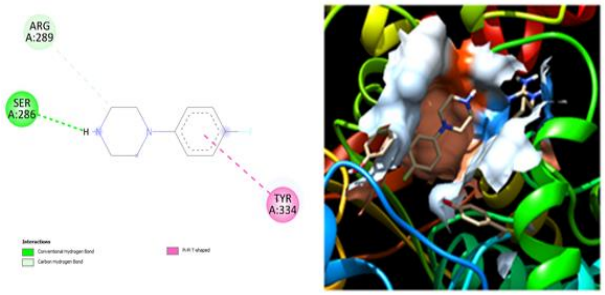

Figure 7 2D interaction and 3D bonding between amino acid residue and pFPP molecule with AChE

Table 3 The enzyme–ligand interaction parameters with hydrophobic contacts for pFPP compound

AChE (PDB ID)	Hydrogen bonding interaction		Hydrophobic interaction	
	R	D (Å)	R	D (Å)
1EVE	SER286	2.19	TRY334	3.38
			PHE331	3.35
			ARG289	3.53

R: Residues, D: Distance

3.6. Toxicity prediction

Piperazines have a reputation for being safe, and there are no studies of their toxicity at the cellular level that could help to understand their harmful effects [37]. Therefore, the aim of this work is to predict the organ toxicity, toxicological endpoints, and median lethal dose (LD_{50}) of the 1-(4-Fluorophenyl)piperazine) compound, which were obtained by using the Pro-Tox II web server [23]. As shown in Table 4, ProTox-II toxicity prediction software gave the predicted LD_{50} value of the pFPP molecule. The results of acute toxicity prediction, such as toxicity class classification [1 (toxic) to 6 (non-toxic), revealed that the listed chemical was classed as acute toxicity class 3 (toxic if swallowed). According to the findings, the title molecule is non-carcinogenic and has no immunotoxicity, cytotoxicity, or mutagenicity.

3.7. Drug-Likeness and ADME Analysis

In the present drug development, the potential of a novel chemical is commonly evaluated using initially through virtual tools [6]. The drug-likeness and ADME parameters of the pFPP molecule have been evaluated in order to determine its suitability for usage as an active substance in a variety of novel pharmaceutical products. Table 5 summarizes the calculated drug-likeness and ADME parameters, which should be interpreted using Lipinski's rule of five [38]. The Lipinski's rule of five states that the number of HBD (Hydrogen Bond Donor)

and HBA (Hydrogen bond acceptor) must be fewer than 5 and 10, the miLogP value must be less than 5, and the molecular weight must be less than 500. Furthermore, TPSA (Total polar surface area) (≤140) is within acceptable limits. According to the analysis, the physicochemical properties of the title molecule definitely meet Lipinski's rule.

ADME analysis shows that the pFPP molecule is predicted by human intestinal absorption (HIA), Caco-2 (colorectal carcinoma) cell permeability and Blood-brain barrier penetration (BBB). The HIA value showed good oral absorption and the Caco-2 permeability values were considered good permeability of the compound. However, it was concluded that the BBB value of this molecule is not in the acceptable range for an ideal drug candidate. The bioavailability score was 0.55. In terms of bioavailability, drug-like behavior is critical to becoming an oral drug. These calculations show that the chemical in question shows promise as a pharmacological agent.

Table 5 Calculated ADME and Drug-Likeness properties of pFPP molecule

pFPP	**Values**
HBD ≤5	1
HBA ≤10	2
TPSA≤140 Å	15.27
miLogP	1.50
GI absorption	High
BBB	No
Caco2 permeability	57.77
HIA	100

4. CONCLUSION

We explored various properties of pFPP compound in this work, including conformation analysis, surface properties, pharmacokinetic and toxicity properties. The title molecule possesses three stable conformers. The intramolecular charge transfer was determined from the HOMO-LUMO orbitals, as well as the HOMO-LUMO energy values were used to compute and analyze various global reactivity parameters. The FMO shows the Egap of the pFPP molecule 4.99 eV, indicating that title compound is more chemically stable. The MEP map shows that the fluorine and NH group, which is deep red, has the most negative charge. ELF and LOL study shows that between C-C and C-N atoms, most of the covalent region is present. Pharmacological studies gave information about ADME, drug likeness, and value to identify the toxic activity of the molecule. The π–π staking interactions of the AChE inhibitors with title ligand molecule show the non-covalent binding sites in the structures. These sites were also justified by MEP surface. Hence, we predict the title compound pFPP might be used as a prospective drug after clinical and pharmaceutical research for Alzheimer's disease.

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The Declaration of Conflict of Interest/ Common Interest
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The Declaration of Ethics Committee Approval
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The Declaration of Research and Publication Ethics
The author of the paper declare that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, I declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication

environment other than Sakarya University Journal of Science.

REFERENCES

[1] D. Y. Peng, Q. Sun, X. L. Zhu, H. Y. Lin, Q. Chen, N. X. Yu, W. C. Yang, G. F. Yang, "Design, synthesis, and bioevaluation of benzamides: Novel acetylcholinesterase inhibitors with multi-functions on butylcholinesterase, Aβ aggregation, and β-secretase,'' Bioorganic Medicinal Chemistry, vol. 20, pp. 6739-6750, 2012.

[2] Q. Sun, D. Y. Peng, S. G. Yang, X. L. Zhu, W. C. Yang, G. F. Yang, "Syntheses of coumarin–tacrine hybrids as dual-site acetylcholinesterase inhibitors and their activity against butylcholinesterase, Aβ aggregation, and β-secretase," Bioorganic Medicinal Chemistry, vol. 22, pp. 4784-4791, 2014.

[3] K. S. T. Diasa, C. Viegas, "Multi-Target Directed Drugs: A Modern Approach for Design of New Drugs for the treatment of Alzheimer's Disease," Current Neuropharmacology, vol. 12, pp. 239-255, 2014.

[4] E. M. H. Brewton, E. M. Hersh, G. Brewton, D. Abrams, J. Bartlett, J. Galpin, P. Gill, R. Gorter, M. Gottlieb, J. J. Jonikas, S. Landesman, A. Levine, A. Marcel, E. A. Petersen, M.Whiteside, J. Zahradnik, C. Negron, F. Boutitie, J. Caraux, J.-M. Dupuy, L. R. Salmi, "Dithiocarbsodium(diethyldithiocarbamate) therapy in patients with symptomatic HIV-infection. Aids a randomized, double-blind, placebo-controlled multicenter study, " American Medical Association, vol. 265, pp. 1538–1544, 1991.

[5] C. B. Mishra, A. Manral, S. Kumari, V. Saini, M. Tiwari, "Design, synthesis and evaluation of novel indandione derivatives as multifunctional agents with cholinesterase inhibition, anti-bamyloid aggregation, antioxidant and neuroprotection properties against Alzheimer's disease,'' Bioorganic Medicinal Chemistry, vol. 24, pp. 3829–384, 2016.

[6] H. S. N. Prasada, A.P. Ananda, T.N. Lohithd, P. Prabhuprasad, H.S. Jayanth, N.B. Krishnamurthy, M.A. Sridhar, L. Mallesha, P. Mallu, "Design, synthesis, molecular docking and DFT computational insight on the structure of Piperazine sulfynol derivatives as a new antibacterial contender against superbugs MRSA,'' Journal of Molecular Structure, vol. 1247, 131333, 2022.

[7] S. B. Ozdemir, N. Demirbas, A. Demirbas, N. Colak, F.A. Ayaz, "Design, Microwave-Assisted and Conventional Synthesis of New Hybrid Compounds Derived From 1-(4-Fluorophenyl) piperazine and Screening for Their Biological Activities,'' ChemistrySelect 3, pp. 2144 – 2151, 2018.

[8] A. Alzheimer, "Alzheimer's disease facts and figures,'' Alzheimer's & dementia: The Journal of the Alzheimer's Association, vol. 11, pp. 332-384, 2015.

[9] D. Scherman, M. Hamon, H. Gozlan, J .P. Henry, A. Lesage, M. Masson, "Molecular pharmacology of niaprazine,'' Progress in Neuropsychopharmacolgy and Biological. Psychiatry, vol. 12, pp. 989–1001, 1988.

[10] R. A. Glennon, M.Y. Yousif, A.M. Ismaiel, M.B. el-Ashmawy, J.L.

Herndon, J.B. Fischer, A.C Server, K.J.B.Howier, "Novel 1-phenylpiperazine and 4-phenylpiperidine derivatives as high-affinity sigma ligands,'' Journal of Medicinal Chemistry, vol. 34, pp. 3360–3365, 1991.

[11] W. N . Wu, L. A. McKown, G.H. Kuo, "Hepatic metabolism of two α-1A-adrenergic receptor antagonists, phthalimide-phenylpiperazine analogs (RWJ-69205 and RWJ-69471), in the rat, dog and human,'' European Journal of Drug Metabolism and Pharmacokinetics, vol. 31, pp. 271–276, 2006.

[12] B. G. Mockett, D. Guévremont, M. Wutte, S. R. Hulme, J .M. Williams, W. C. Abraham, "Calcium/Calmodulin-dependent protein kinase II mediates group I metabotropic glutamate receptor-dependent protein synthesis and long-term depression in rat hippocampus,'' Journal of Neuroscience, vol. 31, pp. 7380–7391, 2011.

[13] F. M. D. Ismail, "Important fluorinated drugs in experimental and clinical use,'' Journal Fluorine Chemistry, vol. 118, pp. 27–33. 25, 2002.

[14] A. A. Gakh, M.N. Burnett, "Extreme modulation properties of aromatic fluorine," Journal Fluorine Chemistry, 132, pp. 88–93, 2011.

[15] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox., "Gaussian Inc,'' Wallingford CT, 2009.

[16] R. Dennington, T. Keith, J. Millam, "GaussView Version 5,'' Semichem Inc., Shawnee Mission KS., 2009.

[17] T. Lu, F. Chen, "Multiwfn: a Multifunctional Wavefunction Analyzer,'' Journal of Computaional Chemistry, vol. 33, pp. 580–592, 2012.

[18] G. M. Morris, D. S. Goodwill, R. S. Halliday, R. Huey, W. Hart, R. K. Belew, A. J. Olson, "Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function,'' Journal of Computaional Chemistry, vol. 19, pp. 1639-1662, 1998.

[19] W. L. D. Pymol, "An open-source molecular graphics tool, CCP4 Newsletter on protein,'' Crystallography, vol. 40, pp. 82, 2002.

[20] Dassault Systemes BIOVIA, Discovery Studio Visualizer v17.2.0.16349, 2016. San Diego

[21] PreADMET Citation Statistics, (2022, May. 31). Available: www.preadmet.com

[22] Swiss Institute of Bioinformatics, (2022, May. 31). Available: www.swissadme.ch/index.php

[23] ProTox-II- Prediction of Toxicity of Chemicals, (2022, May. 31). Available: http://tox.charite.de/protox_II/

[24] T. Chaudharya, M. K. Chaudharya, B. D. Joshi, M. S. A. de Santana, A.P. Ayala, "Spectroscopic (FT-IR, Raman) analysis and computational study on conformational geometry, AIM and biological activity of cephalexin from DFT and molecular docking approach,'' Journal of Molecular Structure, vol. 1240, 130594, 2021.

[25] M. N. Ahmed, K. A. Yasin, K. Ayub, T. Mahmood, M. N. Tahir, B. A. Khan, M. Hafeez, M. Ahmed, I. ul-Haq, "Click one pot synthesis, spectral analyses, crystal structures, DFT studies and brine shrimp cytotoxicity assay of two newly synthesized 1,4,5-trisubstituted 1,2,3-triazoles,'' Journal of Molecular Structure, vol. 1106, pp. 430-439, 2016.

[26] M. Arshad, A. Bibi, T. Mahmood, A. Asiri, K. Ayub, "Synthesis, crystal structures and spectroscopic properties of triazine-based hydrazone derivatives; a comparative experimental-theoretical study, " Molecules, vol. 20, pp. 5851-5874, 2015.

[27] M. Noreen, N. Rasool, Y. Gull, M. Zubair, T. Mahmood, K. Ayub, F.-H. Nasim, A. Yaqoob, M. Zia-Ul-Haq, V. Feo , "Synthesis, density functional theory (DFT), urease inhibition and antimicrobial activities of 5-aryl thiophenes bearing sulphonylacetamide moieties,'' Molecules, vol. 20, pp. 19914-19928, 2015.

[28] M. Evecen, "Structural, Conformational and Spectroscopic Properties of C16H16BrNO3 SchiffBase Molecule: A Theoretical Investigation," Sakarya Üniversitesi Fen Bilimleri Enstitüsü Dergisi, vol. 22, pp. 1591-1600, 2018.

[29] M. Hagar, H. A. Ahmed, G. Aljohani, O.A. Alhaddad, "Investigation of Some Antiviral N-Heterocycles as COVID 19 Drug: Molecular Docking and DFT Calculations,'' International Journalo of Molecular Sciences, vol. 21, pp. 3922, 2020.

[30] S. J. Basha, S. P. V. Chamundeeswari, S. Muthu, B. R. Raajaraman, "Quantum computational, spectroscopic investigations on 6- aminobenzimidazole by DFT/TD-DFT with different solvents and molecular docking studies,'' Journal of Molecular Liquids, vol. 296, pp. 11178, 2019.

[31] R. Mathammal, N. R. Monisha, S. Yasaswini, V. Krishnakumar, "Molecular structure, vibrational analysis (FT-IR, FT-Raman), NMR, UV, NBO and HOMO–LUMO analysis of N,N-Diphenyl Formamide based on DFT calculations,'' Spectrochimica Acta A, vol. 139, pp. 521-532, 2015.

[32] T. Chaudharya, M. K. Chaudharya , B. D. Joshi, M. S. A. de Santana, A. P. Ayala, "Spectroscopic (FT-IR, Raman) analysis and computational study on conformational geometry, AIM and biological activity of cephalexin from DFT and molecular docking approach,'' Journal of Molecular Structure, vol. 1240, pp. 130594, 2021.

[33] H. P. Gümüş, Ö. Tamer, Y. Atalay, "4-(Metoksimetil)-1,6-dimetil-2-okso-1,2-dihidropiridin-3-karbonitril molekülünün teorik olarak incelenmesi," Sakarya

Üniversitesi Fen Bilimleri Enstitüsü Dergisi, vol. 19 no 3, pp. 303-311, 2015.

[34] B. Silvi, A. Savin, "Classification of chemical bonds based on topological analysis of electron localization functions," Nature, 371, pp. 683-686, 1994.

[35] B. F. Rizwana, J. C. Prasana, S. Muthu, C. S. Abrahama, "Molecular docking studies, charge transfer excitation and wave function analyses (ESP, ELF, LOL) on valacyclovir : a potential antiviral drug,'' Computational Biological Chemistry, vol. 78, pp. 9-17, 2019.

[36] C. B. Mishra, A. Manral, S. Kumari, V. Saini, M. Tiwari, "Design, synthesis and evaluation of novel indandione derivatives as multifunctional agents with cholinesterase inhibition, anti-bamyloid aggregation, antioxidant and neuroprotection properties against Alzheimer's disease,'' Bioorganic Medicinal Chemistry, vol. 24, pp. 3829–3841, 2016.

[37] M.D. Arbo, R. Silva, D.J. Barbosa, D.D. da Silva, L.G. Rossato, M.L. Bastos, H. Carmo, "Piperazine designer drugs induce toxicity in cardiomyoblast h9c2 cells through mitochondrial impairment,'' Toxicology Letters, vol.229, pp. 178-189, 2014.

[38] A. Christopher, "Lipinski, Lead- and drug-like compounds: the rule-of-five revolution,'' Drug Discovery Today Technologies vol. 1 no 4,pp. 337-341, 2004.