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INSIGHTS INTO THE QUANTUM CHEMICAL PROPERTIES AND MOLECULAR DOCKING STUDIES OF 3-(4-HYDROXY-3-METHOXYPHENYL)-1-(4-HYDROXYPHENYL) PROP-2-EN-1-ONE

Rubarani. P. Gangadharan[1,✉] , S. Jasmine[2], and Sujata Roy[3]
[1]Department of Physics, Rajalakshmi Engineering College (Autonomous), Chennai-602105, Tamil Nadu, India
[2]Department of Chemistry, Rajalakshmi Engineering College (Autonomous), Chennai-602105, Tamil Nadu, India
[3]Department of Biotechnology, Rajalakshmi Engineering College (Autonomous), Chennai-602105, (Tamil Nadu) India
✉Corresponding author: rubarani.p.gangadharan@rajalakshmi.edu.in

ABSTRACT
Chalcone is an amazing organic compound possessing a plethora of pharmacological, optical, and electronic properties and has been broadly used by scientists for the past two decades (2000-2021). In our investigation, the chalcone, namely, 3-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (HMHP) was obtained by Claisen Schmidt reaction. The chalcone product, thus obtained, was refined with hot methanol and the slow evaporation technique. The molecular structure of 3-(4-hydroxy-3methoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (HMHP) has been optimised using Density Functional theory using B3LYP hybrid functional with 6-31G(d, p) basis set to determine the different properties of the compound. The electronic properties for the compound have been explained from the representations of HOMO-LUMO analyses and Mulliken atomic charges, which are used to explain the charge transfer between the atoms of the molecule and the charge distribution, respectively. Non-linear optical behaviour was also analysed and compared with the standard prototype substance, urea, using the hyperpolarizability calculations. Further molecular docking analyses were carried out to evaluate the biological activity of the chalcone derivative. The results support the potential of the compound as a promising therapeutic agent for the treatment of Parkinson's disease.
Keywords: Chalcone; Non-Linear Optics; Molecular Docking; Hyperpolarizability, Density Functional Theory.
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INTRODUCTION

Chalcone, an open-chain flavonoid compound, is present in all edible plants, vegetables, fruits, spices, tea and natural foodstuffs.[1] These organic compounds, containing two aromatic rings, are surrounded by three aliphatic carbon chains and are commonly called as benzalacetophenone or benzylidene acetophenone. The conjugated double bonds and complete delocalisation of π electrons made the chalcone stand as a magic moiety, and opened the thousands of doors to synthesise chalcone derivatives. Chalcone, as a successful scaffold in medicinal chemistry, have drawn greater attention from substantial scholars in the scientific world for more than 50 years. Nearly 92,000 chalcone derivatives' biological properties are documented in the SciFinder, and about 1,300 review papers have been published in the past five years. The chromophore, such as α, β-unsaturated ketonic group and the electron-releasing group or electron-attracting groups in the benzene ring[2], facilitates chalcone to stand superior material in the industry compared to the standard ones. Review articles appreciate that, chalcone family have gotten a lot of attention because of its capability to treat numerous dreadful chronic diseases like cancer, ulcer, Tuberculosis, hypertension, HIV, diabetes [2] and also prevents numerous enzyme actions.[3,4] As a move forward, this versatile chromophore resists heat, visible light, UV radiations, and hence claims in the synthesis of heterocyclic compounds, liquid crystalline display materials, NLO materials, scintillators, fluorescent sensors, micro and macro-lithography materials, tissue engineering, biosensors,

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photosensitizers for organic synthesis, in drug carrier, in dental applications, UV light cure adhesives, photoresists materials, microelectronic materials and the list goes on. Computational chemistry provides deeper knowledge about the structure of molecules and their correlation with experimental records. Optical, mechanical, thermal, photoluminescence and NLO properties of the synthesised chalcones from the experimental studies, such as UV-Vis-NIR spectrum studies, microhardness studies and photoluminescence studies, were already recorded in the previous literature.[5] As an extension of work, the prime scope of the current work is to explore the energy, orbital, electronic profile, nonlinear optical and molecular docking studies of chalcone by using computation-based analysis.

Computational Methods

The computations from the theoretical approach were carried out using the Gaussian 09W and the basis set 6-31G (d, p) of the DFT/ B3LYP basis set [6]. The optimised three-dimensional pictorial representations and physico-chemical parameters from the Gaussian 09 output files have been visualised using the GaussView 6.0.[7] Utilising optimised geometries, it has been possible to calculate the electronic and optical properties such as chemical hardness, chemical softness and hyperpolarizability calculations.[8] The biological activity of the molecule was analysed using AutoDock Vina software. Figure-2 depicts the optimised molecular structure.

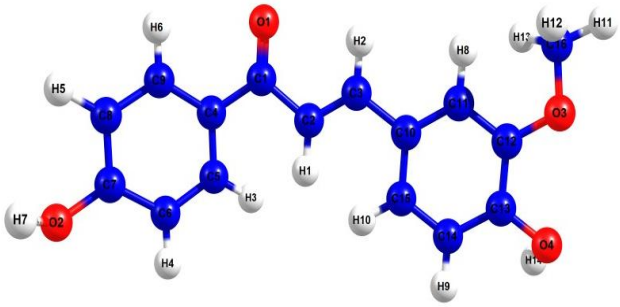

Fig.-2: The Optimised Structure of HMHP

RESULTS AND DISCUSSION

Mulliken Atomic Charge

The Mulliken atomic charge distribution gives scientists a straightforward qualitative representation, and it works well for the B3LYP functional, which was computed using 6-31G (d,p) level theory[9,10] and is shown in Fig.-3. A common charge-partitioning approach is the Mulliken atomic charge. This study has an impact on the electronic structure, molecular reactivity, molecular polarizability, and dipole moment. Analyzing (Table-1) and (Fig.-3) consists of ketonic carbonyl group and ethylenic double bond, and aromatic groups. Here, all the hydrogen atoms have positive charges from H21 to H34, and all four oxygen atoms bonded to the carbon atoms, including the carbonyl group, possess the most negative charges. Similarly, it can be observed that the double-bonded carbon atoms with the electropositive atoms H have negative values. Also, the electronegative oxygen atoms O4, O11, O18 and O20 are bonded with the positive charge carbon atoms, suggesting a strong intermolecular force of attraction.

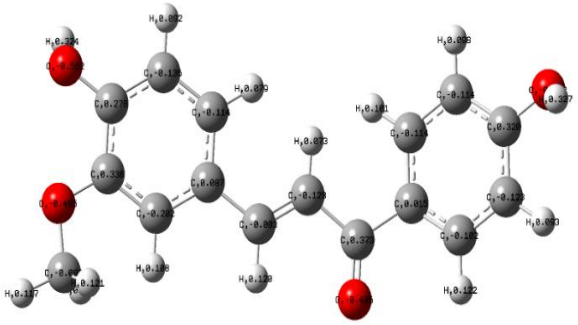

Fig.-3: Mulliken Charge Distribution for HMHP

Table-1: Mulliken Charge Distribution for HMHP

Atoms	B3LYP/6-31 G(d,p)		
1C	0.2274	18O	-0.5110
2C	-0.1304	19C	-0.1883
3C	-0.1236	20O	-0.6013
4O	-0.4214	21H	0.1262
5C	0.0361	22H	0.1680
6C	-0.1488	23H	0.1427
7C	-0.1123	24H	0.1415
8C	0.2419	25H	0.1355
9C	-0.1291	26H	0.1686
10C	-0.1451	27H	0.3782
11O	-0.6154	28H	0.1587
12C	0.0642	29H	0.1347
13C	-0.1976	30H	0.1257
14C	0.2735	31H	0.1656
15C	0.2257	32H	0.1584
16C	-0.1397	33H	0.1548
17C	-0.1403	34H	0.377

HOMO and LUMO Analysis

HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) play an important role in defining, understanding and elucidating many molecular properties of molecular systems.[11-13] The HOMO-LUMO band gap is smaller, which signifies greater stability. For the compound in this study, the calculated energy values for HOMO, LUMO and HOMO-LOMO band gap were theoretically found as -5.686 eV, -1.801 eV and 3.885 eV, respectively. Finally, the distributions and values of LUMO+1, LUMO, HOMO, and HOMO-1 are shown in Fig.-4.

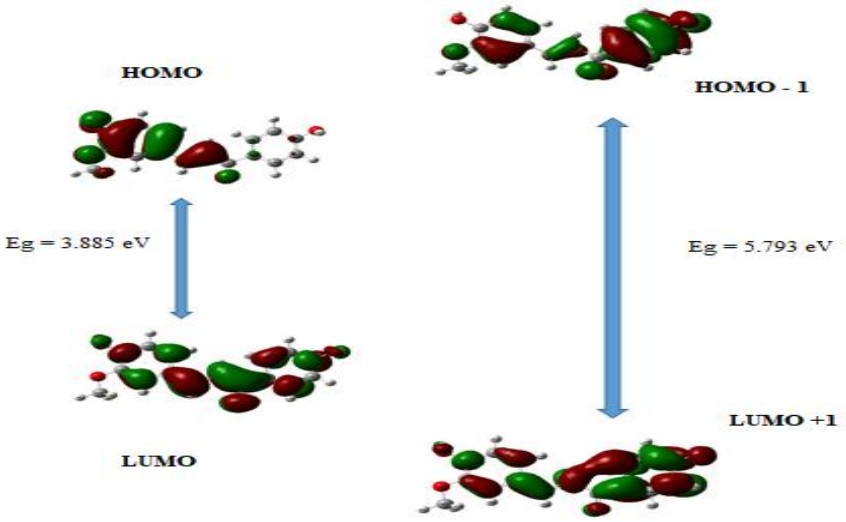

Fig.-4: Frontier Molecular Orbitals of HMHP

NLO Properties

The field of information technology, specifically data recording, communications and optics, has recently made substantial use of diverse molecules with nonlinear optical and electro-optical properties. The fundamental parameter, hyperpolarizability, has been the focus of technological usage of these chemical compounds. Polarizability is a crucial parameter utilized in molecular optics and spectroscopy because it measures molecular system characteristics, including charge density and electron distribution.[14,15] There are three fundamental parameters: α_{total}, which is the mean polarizability, $\Delta\alpha$, which is the polarizability's anisotropy, and $\beta_{0,}$ which is the first hyperpolarizability parameter. With the B3LYP functional and 6-

31G(d,p) basis set, these nonlinear parameters were calculated at 30.6 x 10^{-24} esu, 92.1 x 10^{-24} esu, and 219.69 x 10^{-31} esu, respectively. Table-3 displayed the title compound's NLO properties and their components. The primary reference material for NLO properties is the urea molecule. According to the literature, the NLO values for this reference material are as α_{total}= 5.07643717 × 10^{-24}esu, $\Delta\alpha$ = 2.13568262 × 10^{-24}esu and β_0 = 7.2228469891 × 10^{-31}esu. The NLO values are found to be 6.028, 43.14 and 30.42 times greater than urea when compared to the reference material. The title compound's dipole moment components (x, y, and z) and their magnitude were calculated and shown in Table-2. Previously, from the experimental studies such as UV-Vis-NIR spectrum studies, photoluminescence and second harmonic generation studies[5], it was proved that it has good NLO properties. From the hyperpolarizability calculations studies also it can also be proved that this compound has excellent NLO activity to produce second-order nonlinear effects.

Table-2: Calculated First-Order Hyperpolarizability (βtot), Dipole Moment (μ(D)), and Polarizability (α) for the Title Compound at B3LYP/6–31 *G* (d,p) Basis Set

Parameters	B3LYP	Parameters	B3LYP
μ_x	-0.0946	β_{xxx}	1743.894
μ_y	0.6617	β_{xxy}	-1484.242
μ_z	0.1986	β_{xyy}	259.732
μ	0.6973	β_{yyy}	-72.8153
α_{xx}	335.924	β_{xxz}	-60.2282
α_{xy}	-2.6912	β_{xyz}	-117.2818
α_{yy}	199.783	β_{yyz}	-23.822
α_{xz}	33.632	β_{xzz}	-19.5227
α_{yz}	0.8909	β_{yzz}	-31.6787
α_{zz}	83.771	β_{zzz}	10.7019
α_{tot} (e.s.u)	3.06 x 10^{-23}	β_0 (esu)	21.969 x 10^{-30}
$\Delta\alpha$ (e.s.u)	9.21x 10^{-23}		

Molecular Docking Study

Target Identification

In the present study, the putative potential molecular targets of the 3-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one (HMHP) were obtained using Swiss Target Prediction (http://www.swisstargetprediction.ch/) [16]. Canonical and isomeric SMILES of the HMHP compound were used as input in the Swiss Target Prediction web server.[18] The Swiss Target Prediction virtual screening tool utilizes the "chemical similarity principle" to identify the most probable targets of bioactive molecules. The putative binding predictions in this virtual reverse screening tool are derived from 376,342 experimentally active analogous compounds in 2D and 3D that demonstrated significant interactions with 3,068 well-identified protein targets.[17-19] Through a series of similarity calculations and statistical modelling, the algorithm generates a ranked list of potential protein targets along with associated probabilities.

Molecular Docking Analysis

The crystal structure of Monoamine oxidase B (1GOS) was obtained from the Protein Data Bank (http://www.rcsb.org/pdb). Peptide chains associated with co-crystallized compounds were separated from the target protein. Using AutoDock Tools[20,21], all water molecules and lone electron pairs were removed, hydrogens were added, and both Kollman and Gasteiger charges were assigned to the protein structure. The protein targets was saved in PDBQT format for docking. Grid centre coordinates were determined based on the position of the co-crystallized ligand. A configuration file was then created, incorporating the grid parameters along with details of the target protein and ligand. Molecular docking was carried out using AutoDock Vina [22,23], treating the protein as a rigid structure while allowing the ligand (chalcone) to remain flexible. The resulting docked complexes were analyzed and visualized using PyMOL and LigPlot. Overall, the utilization of Swiss Target Prediction offers a robust and accessible approach to target prediction in drug discovery and chemical biology research. In this study, the top-ranked protein, Monoamine oxidase B (PDB ID:1GOS), was taken for further atomic-level investigation

of interaction with the chemical compound. It is an oxidoreductase class of protein. The inhibitors of this protein are mainly used for the treatment of Parkinson's disease. The Autodock Vina result shows that the binding free energy of the most favourable conformation is -8.9 kcal/mol. Visualization of the docked complex revealed details of the binding pocket and identified amino residues participating in hydrogen bonding and hydrophobic contacts with the ligand. The docked structure and interacting residues are shown in Fig.-5a and 5b. Ile199, Tyr60 and Met436 participate in H-bonding interactions. These three H-bonds make the compound stable inside the binding pocket.

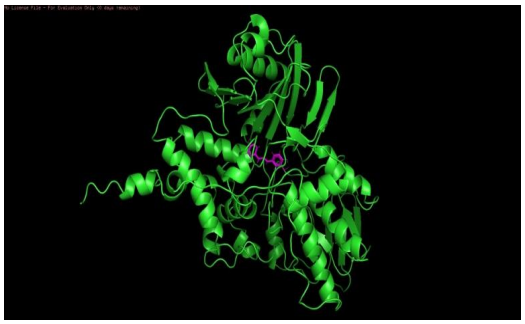

Fig.-5a: Docked Structure of 3-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one with Monoamine Oxidase B. The ligand Molecule is Shown in Purple Colour and the Protein Chain is shown in Green Colour

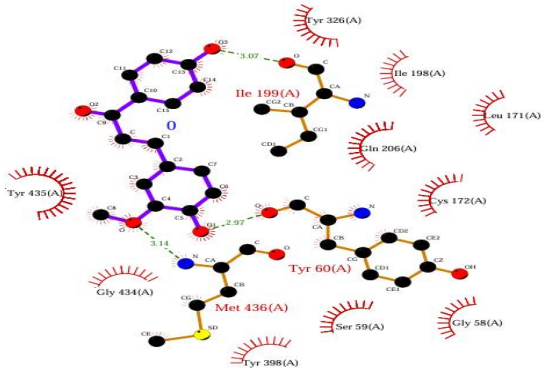

Fig.-5b: The Atomic-Level Interactions are shown. The Green Dotted Line Shows H-bonding Interactions and the Other Van Der Waals Interactions

CONCLUSION

The chemical properties of 3-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one (HMHP), including its reactivity, stability, and molecular interactions, were examined using Density Functional Theory (DFT) with the B3LYP/6-31G(d,p) basis set, as implemented in Gaussian 09. From Mulliken atomic charges, it can be shown that the electronegative oxygen atoms O4, O11, O18 and O20 are bonded with the positive charge carbon atoms, suggesting a strong intermolecular force of attraction. The difference in HOMO and LUMO energy supports the charge transfer interaction within the molecule. From the hyperpolarizability analysis using the DFT studies, HMHP was found to have very large hyperpolarizability and has 30.42 times higher polarizability than the prototype molecule, due to which it can be used to produce the best nonlinear effects and hence can be used in many different optical applications. This enhanced optical and NLO properties of the chalcone derivative can be effectively explored in the fields of laser technology, design of optoelectronic devices, NLO applications and for the modulation and frequency doubling purposes. In terms of the biological activity of the molecule, the utilisation of Swiss Target Prediction offers a robust and accessible approach to target prediction in drug discovery and chemical biology research. The Autodock Vina result shows that the binding free energy of the most favourable conformation is -8.9 kcal/mol, and the visualization provided insights into the ligand-

binding pocket, highlighting key amino residues involved in hydrogen bonding and hydrophobic interactions. Overall, the inhibitors of this protein are mainly used for the treatment of Parkinson's disease.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

Rubarani P Gangadharan https://orcid.org/0000-0002-2201-1873
S.Jasmine Francis http://orchid.org/0000-0002-0228
Sujata Roy http://orchid.org/0000-0002-5203-2050

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