IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Quantum Chemical Study On The Characterization Of An Anticonvulsant Drug, Fenfluramine.

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Introduction

In today's world, children are highly affected by neurological disorder which exhibits detriment in various normal functioning of cognitive behaviour as well as impairment in physical, motor and speech functions. These dysfunctions may be disseminated in any part of the nervous system that leads to several chronic issues. One of the most commonly found neurological disorders is Epilepsy that enunciates brain disorder specified by repeated seizures. The Dravet Syndrome (DS) and Lennox-Gastaut syndrome (LGS) are two of the rarely found epileptic disorders characterized as epileptic encephalopathies that are associated with seizure and nonseizure symptoms [1,2]. Even though more than 30 antiseizure medications (ASMs) have been manufactured till date, the refractory to the antiseizure medications by the patients still remains constant. However, fenfluramine (FFA), the anti-obesity medication has been redesigned and approved by several regulatory agencies as an antiseizure drug for seizures related to Dravet and Lennox–Gastaut syndromes, so this molecule is also anticonvulsant drug [3]. It is a phenethylamine that resemble the geometrical structure of serotonin. Moreover, FFA also regulates and maintains serotonergic and other neurologic receptors as well as control neurotransmission in the body, thereby making it a potential drug for the treatment of pharmacoresistant seizures [4].

Hence, the wide-ranging applications of fenfluramine (FFA) in the pharmacological and biological context have captivated our interest to investigate its geometrical structure and analyse the quantum chemical parameters of the molecule. Thus, the present research study is executed to analyse the geometrical parameters using the Density Functional Theory (DFT) method. The DFT method is a quantum-mechanical atomistic simulation method that imparts the electronic structure of atoms and molecules which in turn provides a wide variety of properties of almost any kind of atomic system. Many researchers across the globe have performed their investigation considering the role of fenfluramine in the treatment of various epileptic disorders. However, no in-depth analysis was performed to elucidate the physiochemical possessions of the molecule that promote its optimal applications in pharmaceutical frame of reference. G. Dini et al. [5] has undertaken clinical approach that yield an outline of the historical advancement in the implementation of FFA in diverse area, beginning from the primary clinical survey to the subsequent success in the epilepsy domain. Their research work suggests that in Dravet syndrome and LGS treatment, lower doses (maximum 17–26 mg/day) are preferable as compared to its application as an appetite suppressant. However, on fusing with phentermine, higher doses (typically 60–120 mg/day) are preferable. D. Samanta [6] performed his research work to provide a chronicle review on the procedure of action of antiseizure activity of Fenfluramine (FFA), and its pharmacological process corresponding to epilepsy. This investigation emphasize on the efficiency and pernicious outcome of the drug FFA.

V. Berbenni et al. [7] has undertaken their investigation to elucidate the geometrical, vibrational and thermal behaviour of fenfluramine. In their investigation FT-IR, SEM, photoacoustic spectroscopy and XRD was performed to examine their bonding mechanism. Hence, it was observed that till date no DFT calculations were performed to obtain their quantum chemical parameters that describe the electronic charge transfer mechanism within the atoms of the molecule as well as biological significance of the molecule. So the prevailing investigation is emphasized on the identification of Fenfluramine (FFA) molecule under the DFT method using the B3LYP method under the 6-311++g(d,p) basis set.

In the current research work, the computational study such as bond length and bond angle analysis, electronic behaviour of the molecule using HOMO-LUMO analysis, Non-Linear Optical (NLO) and Natural Bond Orbital (NBO) analysis as well as the Molecular Electrostatic Potential (MEP) surface study of the titled molecule have been performed by employing the DFT method. The MEP analysis and the HOMO-LUMO energy gap of the molecule are executed to examine the correlation between the configurational structure and biological activity of the molecule.

2 Computational Methods:

The optimal structure of Fenfluramine molecule is obtained using the Gaussian 09W software [8]. The visualization software Gauss View 6.0 is employed to draw and visualize the molecular structure. The bond length and the bond angles of the molecule can be obtained from the GaussView 6.0 software. The DFT method is employed to study the geometrical, physio-chemical and electrical properties of the molecule [9]. The MEP diagram illustrates the electrophilic and nucleophilic property of the molecule highlighted in different colours. The intramolecular charge transfer within the atoms of the molecule and their stabilization energy is studied using the NBO 5.0 program. The Non-Linear Optical (NLO) property of the molecule demonstrates the hyperpolarizability, polarizability and dipole moment of the molecule. The NLO parameters of the molecules are extracted from the Gaussian output file.

3. Result and discussion

3.1 Conformational analysis

The optimal molecular structure of Fenfluramine molecule is shown in fig. 1. The Gaussian 09W software is employed to optimize the molecular structure of Fenfluramine which provides the bond lengths and bond angles of the compound. The atomic bond length and bond angles of the mentioned molecule are shown in table 1. The geometrical parameter of the Fenfluramine molecule is recorded for the first time using the DFT method; hence no literature is found for the molecule.

From table 1, it can be seen that the C-H bond length of the molecule falls within the range of (1.089-1.123) Å, while the C-C bond distance lies within the domain of (1.396-1.552) Å. The C-N atomic bond length of the molecule is computed within the range of (1.497-1.502) Å. The N4-H20 bond distance is measured at 1.025 Å. The C-F atomic bond distance is calculated at (1.343-1.345) Å. Moreover, the C-N-H and C-N-C atomic bond angles of the molecule range from 109.75°-112.96°. The C-C-C atomic bond distance varies from 118.33°-120.27°. The remaining bond distance and bond angles of the atoms of the titled molecule are enlisted in table 1. The intramolecular charge transfer within the atoms of the molecule also plays a major factor for the change in bond-lengths and bond angles of the atoms in the molecule.

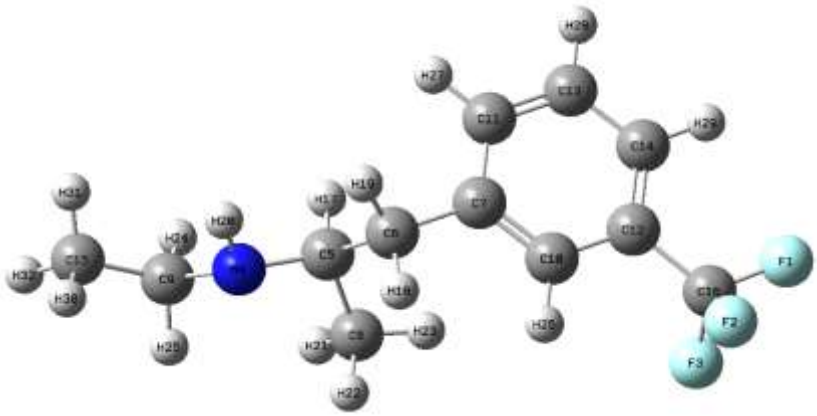

Fig. 1: Optimized molecular structure of Fenfluramine.

Table 1: Bond length and bond angles of Fenfluramine.

Parameter	Bond Length[Å]	Parameter	Bond Angle [°]	Parameter	Bond Angle [°]
C5-H17	1.123	C13-C14-H29	119.38	H22-C8-H23	107.81
C6-H19	1.109	C11=C13-H28	119.92	C8-C5-N4	109.43
C8-H21	1.095	C13=C11-H27	119.82	C5-N4-H20	109.93
C8-H22	1.098	C7-C11-H27	119.88	C5-N4-C9	112.96
C9-H24	1.112	C11-C7-C6	120.27	N4-C9-H24	112.83
C9-H25	1.114	C6-C7=C10	120.33	N4-C9-H25	106.77
C10-H26	1.092	C7=C10-C12	119.95	H24-C9-H25	106.77
C11-H27	1.089	C7=C10-H26	119.58	H25-C9-C15	109.80
C14-H29	1.090	C10-C12=C14	120.59	C9-C15-H30	111.18
C15-H30	1.090	C10-C12-C16	118.33	C9-C15-H31	112.33
C15-H31	1.095	C12=C14-H29	121.31	C9-C15-H32	110.90
C15-H32	1.096	C12-C16-F1	116.51		
C5-C6	1.552	C12-C16-F2	114.20		
C5-C8	1.533	C12-C16-F3	114.11		
C6-C7	1.50	F1-C16-F2	103.38		
C7-C11	1.405	F2-C16-F3	103.69		
C13-C14	1.399	C7-C6-C5	111.70		
C12=C14	1.399	C7-C6-H19	109.78		
C7=C10	1.402	H19-C6-H18	104.50		
C12-C16	1.505	H19-C6-C5	110.34		
C15-C9	1.527	H18-C6-C5	108.91		
C9-N4	1.497	C6-C5-C8	111.02		
N4-H20	1.025	C5-C8-H21	111.79		
C16-F1	1.343	C5-C8-H23	111.37		
C16-F3	1.345	H21-C8-H22	107.04		

3.1.2 Charge transfer analysis (NBO analysis)

The binding of atoms in a molecule can be effectively studied using the Natural Bond Orbital (NBO) analysis. It imparts detailed analysis of the intramolecular and intermolecular interactions taking place in both Lewis and non-Lewis orbitals of a molecules [10]. The Lewis atomic orbital indicates the filled orbitals and the non-Lewis atomic orbital refers to the vacant orbitals of a molecule. The second-order Fock Matrix is employed to compute the Lewis and non-Lewis atomic orbitals through stabilization energy E(2) [11]. The Lewis and non-Lewis orbitals in a molecule aids in the interpretation of hyperconjugation mechanism and electron density transfer (EDT) mechanism. The stabilization energy E(2) for each donor (i) and acceptor (j) orbital is estimated as [12] $E^{(2)q} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$ where, the donor orbital occupancy is symbolized by q_i, ε_j and ε_i indicates the diagonal elements and the term F(i,j) symbolize the diagonal NBO Fock matrix elements. The great value of stabilization energy leads to significant interaction of donor and acceptor orbitals i.e. the whole system merge more significantly with the higher tendency of donating electrons from donors to acceptors orbitals. Hence, with the higher value of stabilization energy, the system gets delocalized more significantly. The NBO study of the mentioned molecule was performed to determine the distribution of charge within the atoms of the molecule. Some selected NBOs extracted from Gaussian output file of Fenfluramine molecule are enlisted in table 2. From the table it is seen that the most intense interaction between the Lewis and non-Lewis atomic orbital is observed between the anti-bonding orbitals C12-C14 and C7-C10 with stabilization energy 254.02 kJ/mol. While more strong interactions are observed between the bonding π orbital C7-C10 with anti-bonding π orbitals C11-C13 and C12-C14 bearing the stabilization energy 19.49 kJ/mol and 21.86 kJ/mol respectively. As seen from the table some more intense interactions are observed between the bonding π orbital C11-C13 with anti-bonding C7-C10 and C12-C14 orbitals having stabilization energy 20.58 kJ/mol and 21.25 kJ/mol respectively. The remaining NBOs with their respective stabilization energy are enlisted in table 2.

Table 2: Second order perturbation theory analysis of Fock matrix in NBO basis for Fenfluramine.

Fenfluramine				
Donor(i)	Acceptor (j)	$E^{(2)}$ (kJ/mol)	E(j)-E(i) (kcal/mol)	F_{ij}(a.u)
σ(C5-C6)	π*(C7-C10)	2.80	0.62	0.040
σ(C6-H18)	σ*(C7-C11)	4.41	1.04	0.061
π(C7-C10)	π*(C11-C13)	19.49	0.28	0.067
	π*(C12-C14)	21.86	0.27	0.069
σ(C10-C12)	σ*(C12-C14)	4.57	1.27	0.068
σ(C10-H26)	σ*(C7-C11)	4.73	1.08	0.064
π(C11-C13)	π*(C7-C10)	20.58	0.29	0.069
	π*(C12-C14)	21.25	0.28	0.069
σ(C11-H27)	σ*(C7-C10)	4.84	1.09	0.065
π(C12-C14)	σ*(F2-C16)	5.40	0.50	0.049
	σ*(F3-C16)	5.45	0.50	0.050
	π*(C7-C10)	19.30	0.30	0.067
	π*(C11-C13)	18.27	0.29	0.065
σ(C14-H29)	σ*(C10-C12)	4.53	1.08	0.062
n_2(F1)	σ*(F2-C16)	4.95	0.67	0.052
	σ*(F3-C16)	4.92	0.67	0.052
	σ*(C12-C16)	6.58	0.79	0.065
n_3(F1)	σ*(F2-C16)	9.65	0.67	0.072
	σ*(F3-C16)	9.69	0.67	0.072
n_3(F2)	σ*(F3-C16)	9.73	0.66	0.072
n_2(F3)	σ*(C12-C16)	6.06	0.79	0.062
n_1(N4)	σ*(C5-H17)	7.38	0.65	0.063
σ*(C12-C14)	σ*(C7-C10)	254.02	0.01	0.080

3.1.2 Molecular Electrostatic Potential (MEP) surface analysis

The molecular electrostatic potential study allows in envisaging several charged domain of a molecule [12]. The distribution of charge within the atoms of a molecule explains about the atomic interactions, electronic behaviour, chemical stability and reactive property of a molecule. The MEP mapping of Fenfluramine displayed in fig. 2 is obtained from the optimized configuration of the molecule computed under DFT method using the Gaussian 09W software. This mapped structure provides us to access the nucleophilic and electrophilic regions of the molecule using different colour codes [13]. The electrostatic potential of a molecule is arrange with increasing order as red>orange>yellow>green>blue [14]. The negative electrostatic potential of a molecule is indicated by the red region, the positive potential site is shown by the blue domain of the molecule, while the green colour represents the neutral region of a

molecule [14]. From the figure it is seen that the hydrogen atom of H24-C9-H25 is embedded by red colour showing the electrophilic property of the region. The three fluorine atoms and its corresponding carbon atom are surrounded by yellow colour indicating the electronegative property but less than the H25 region. The area near N4-H20 atoms and other hydrogen atoms in the molecules are surrounded by blue colour representing the nucleophilicity domain. The carbon atoms in the ring C12=C14-C13 is surrounded by green colour showing the neutral domain of the molecule.

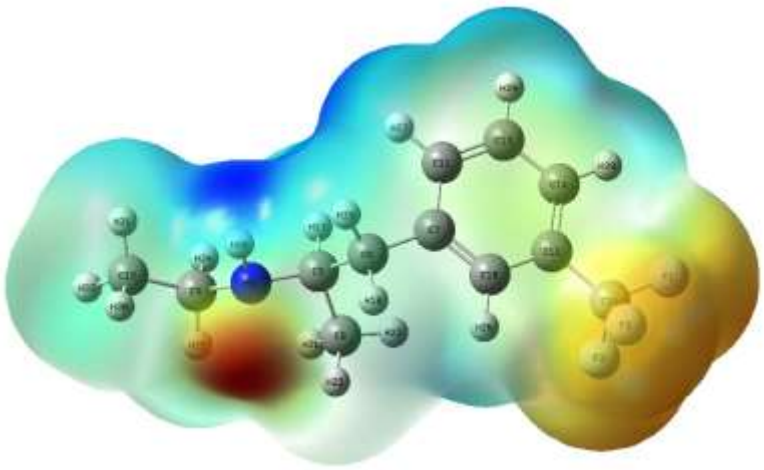

Fig.2: Molecular Electrostatic Potential (MEP) mapping of Fenfluramine.

3.1.3 Quantum chemical parameter analysis based on Frontier Molecular Orbitals

The Frontier Molecular Orbital (FMO) properties of a molecule were computed using the DFT method under the Gaussian 09W software and is visualized using the GaussView 06 software. The Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) delivers a noteworthy illustration on the charge distribution, electrophilicity index, chemical potential, kinetic stability, and other electrical as well as quantum chemical properties of a molecule [15]. The FMO values and their band gap values demonstrate the bioactive properties, electronegativity, global hardness and softness value of a molecule. The global hardness (η) value explains the polarizable property of a molecule i.e. the amount of deformation of electron cloud in an electric field. The increase in the HOMO-LUMO band gap increases the tendency to oppose the charge transfer as it opposes the change in electronic transfer and electronic density, thereby increasing the kinetic stability. In contrast to this, the global softness (σ) value is the reciprocal of the hardness value; hence the reduced energy gap for the charge excitation and the highly polarizable property is referred to as soft molecules. Moreover, the softness behaviour of a molecule also symbolizes the high chemical reactivity of the molecule [15]. The global electrophilicity index indicates the capacity of a molecule to accept electrons. It also signifies the bioactive behaviour of the molecule. The FMO diagram of Fenfluramine is displayed in figure 3. Table 3 displays the FMO energies, hardness, chemical softness, electron affinity (EA), global electrophilicity index, chemical potential, and ionization potential (IP) of a molecule. The quantum chemical parameters are calculated using the Koopman's theorem [16]. The negative value of chemical potential in the table explains that that the molecules do not decompose spontaneously [15].

Table 3: The quantum chemical parameters of Fenfluramine molecule.

Parameters	Fenfluramine
E_{HOMO}	-7.24 (eV)
E_{LUMO}	0.19 (eV)
E_{HOMO}-E_{LUMO} (ΔE)	7.43 (eV)
Ionisation Energy (IE) = -E_{HOMO}	7.24 (eV)
Electron Affinity (EA) =-E_{LUMO}	-0.19 (eV)
Hardness(η)= ½(E_{HOMO}-E_{LUMO})	3.71
Softness (S=1/η)	0.27
Chemical potential(μ)= ½(E_{HOMO}+E_{LUMO})	-3.52 (eV)
Electronegativity (χ = - μ)	3.52
Electrophilicity index(ω)=μ^2/2 η	1.67
Nucleophilicity index (N=1/ω)	0.60

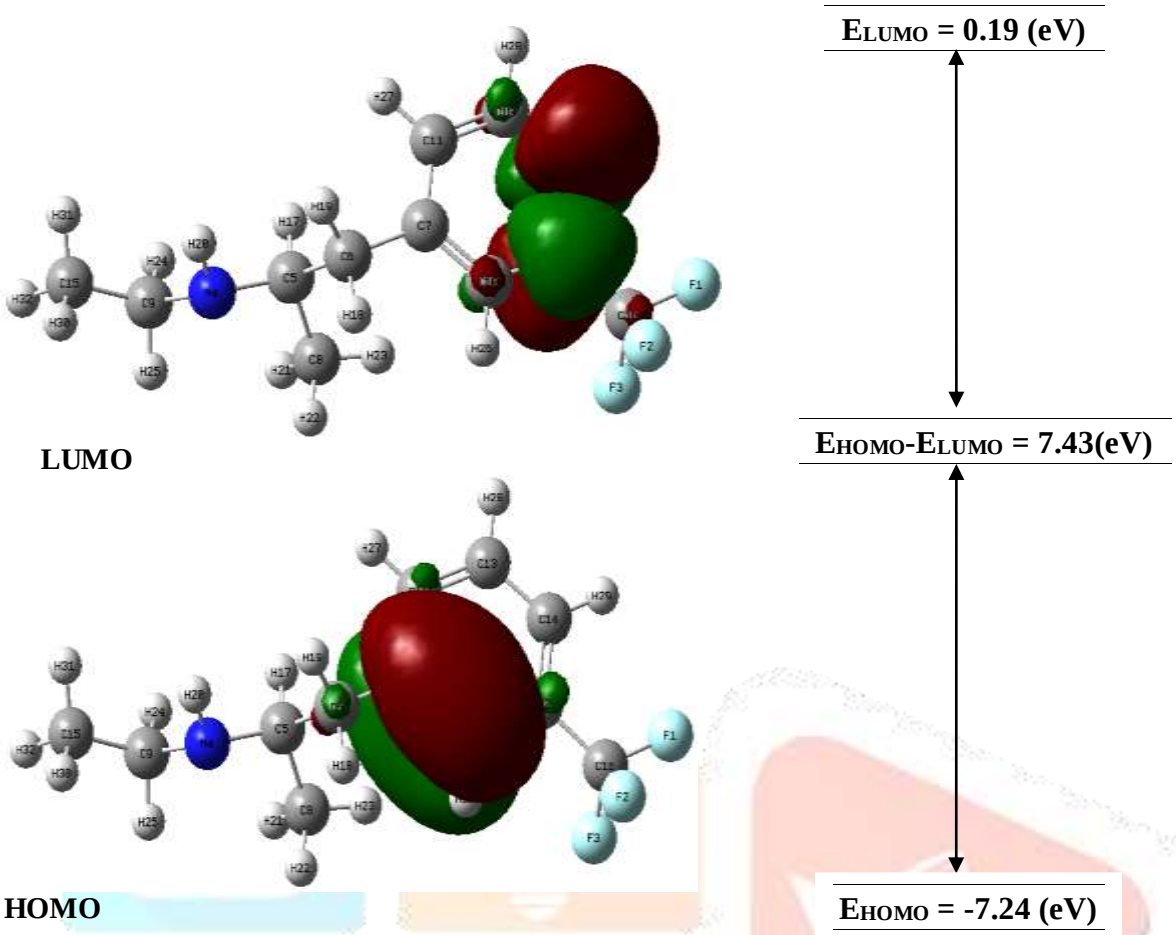

Fig. 3: FMO diagram of Fenfluramine.

3.5 Non-Linear Optical (NLO) analysis

The Non-Linear Optical (NLO) phenomena in a molecule deals with the electromagnetic interaction of intense light with matter that showcases its wide application in laser technology, optical modulation, telecommunication system as well as in various domain of technology [17]. The NLO properties are examined in view of the dielectric response of the material at the atomic level. As the wave propagate through a material, the atoms and the electrons interact with electric and magnetic fields of the wave that causes variation in the spatial and temporal dissemination of electric charges. The major outcome of the force employed by the field on the charged particles is the deportation of the valence electrons from its original site. Such displacement of electric charges produces electric dipoles that exhibit the cause of polarization [18]. Hence, it can be epitomize that the non-linear optics (NLO) is the analysis of the interaction of strong electromagnetic field with materials that generates the modified fields, incompatible with the phase, amplitude and frequency of the input field. The NLO behaviour of a material is determined by the value of its first order hyperpolarizability (β), polarizability (α) and dipole moment (μ) in the area of its electric field. The higher value of β, α and μ of a molecule corresponds to the profound NLO response of a material [18]. Moreover, the hyperpolarizability and polarizability value plays a significant role in the elucidation of the molecule towards its function in the pharmaceutical industries, drug manufacturing as well as in several industrial domains. In the current manuscript, the NLO analysis for Fenfluramine molecule is performed by the employing the DFT level of theory with B3LYP basis set and the NLO parameters i.e. β, α and μ values for the mentioned compound is extracted from the Gaussian output file.

The hyperpolarizability of a molecule is a third rank tensor determined by 3×3×3 matrix. It is also associated with the inter/intra-molecular distribution of charges. The Kleinmann symmetry is utilized to reduce the 27 components of first order hyperpolarizability [19]. The net dipole moment (μ), net electric polarizability (α) and the first order hyperpolarizability (β) with its components along x, y and z axis are calculated by using the following equations-

$\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$

$\alpha_{total} = \alpha_{xx} + \alpha_{yy} + \alpha_{zz}/3$

and $\beta_{tot} = (\beta^2_x + \beta^2_y + \beta^2_z)^{1/2}$ where $\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz}$, $\beta_y = \beta_{yyy} + \beta_{yzz} + \beta_{yxx}$ and $\beta_z = \beta_{zzz} + \beta_{zxx} + \beta_{zyy}$

In the above equations, α_{total}, β_{total} and μ signifies the net polarizability, net first order hyperpolarizability and total dipole moment.

Table 4 displays the calculated values of β, α and μ values for Fenfluramine molecule. The relation 1 a.u = 8.639×10^{-33} e.s.u is used to convert the atomic unit (a.u) to electrostatic unit (e.s.u). From the table 4, the β value for Fenfluramine molecule is computed at 0.2737×10^{-30} e.s.u. The β value of a material is generally compared with Urea due to its high birefringence behaviour and transparency till 200 nm. The hyperpolarizability value for urea is observed at 0.1947×10^{-30} e.s.u [20], which shows that the β value for the molecule is 1.40 times greater than that of urea. The dipole moment value of the molecule as shown in table 4 is observed at 4.5199 Debye which signifies the electrophilic variation in the molecule. Moreover, the net α value for the molecule is calculated at 0.8483×10^{-30} e.s.u that shows the electronic charge distribution within the atoms of the molecule. Thus, the titled molecule shows a prominent behaviour towards the electric field with significant values of hyperpolarizability, polarizability and dipole moment, thus the mentioned molecule can be considered as an NLO substance.

Table 4: First order hyperpolarizability (β), dipole moment (μ) and electric dipole polarizability (α) of Fenfluramine molecule

Parameters	Fenfluramine
β_{xxx}	-15.8367
β_{xyy}	21.7974
β_{xzz}	16.2576
β_{yyy}	-3.9563
β_{xxy}	25.3551
β_{yzz}	-7.1117
β_{zzz}	1.2247
β_{xxz}	-13.8701
β_{zyy}	-4.8565
β_{total}	31.6874 a.u. $=0.2737\times10^{-30}$ e.s.u
μ_x	-3.4526
μ_y	2.8730
μ_z	-0.5053
μ	4.5199
α_{xx}	-102.9957
α_{yy}	-92.9319
α_{zz}	-98.6613
α_{xy}	2.7367
α_{xz}	-0.0357
α_{yz}	-0.5538
α_{total}	98.1963 a.u$=0.8483\times10^{-30}$ e.s.u

5. Conclusion

The computational analysis of the Fenfluramine molecule using the DFT level of theory under the basis set 6-311++g(d,p) with B3LYP method is performed to examine the quantum chemical parameters of the titled molecule. The bond lengths and bond angles of the molecules are obtained from the Gaussian output that establish the existence of charge distribution within the atoms of the molecule. The HOMO-LUMO diagrams are visualized from the GaussView 6 software and the result provides the HOMO-LUMO energy gap and their respective quantum chemical parameters such as electrophilicity index, chemical reactivity, hardness and softness values. The quantum chemical descriptors obtained from the HOMO-LUMO of Fenfluramine validates that the molecule is biologically active with high chemical reactivity,

high electrophilicity and with greater kinetic stability. The routes of the charge distribution within the molecule are explained by NBO analysis that deeply illustrates the transfer of charge between the Lewis and non-Lewis atomic orbitals. The profound interaction of the molecule with the electromagnetic radiation is explained by the prominent values of hyperpolarizabity, polarizability and dipole moment of the molecule, thereby considering the molecule as a good NLO material.

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