

Synthesis, Characterization and Computational insights of Pyrazolyl-tetrahydrofuran Derivatives

Hari Prakash^{1,2}, Mridula Guin² and Noopur Srivastava^{*2},

¹Jubilant Biosys Ltd., Knowledge Park-II, Greater Noida 201310, Uttar Pradesh, INDIA

²Department of Chemistry & Biochemistry, Sharda School of Basic Sciences & Research, Sharda University, Knowledge Park-III, Greater Noida 201310, Uttar Pradesh, INDIA

*Corresponding Author: Noopur Srivastava



www.jrasb.com || Vol. 4 No. 3 (2025): June Issue

Received: 09-05-2025

Revised: 13-06-2025

Accepted: 18-06-2025

ABSTRACT

Compounds 1 and 2 were synthesized from their respective esters and their DFT calculations were conducted using Gaussian 16 software to analyze the quantum chemical properties of the two drug molecules, as 1 and 2 respectively. Geometric optimization was carried out using B3LYP/6-31++G(d,p) theoretical levels. Visualization of molecular surfaces and other properties was performed using Gauss View 6.0. The reactivity and stability of the complexes were explored through frontier molecular orbital (FMO) analysis. Additionally, the molecular electrostatic potential (MEP) was evaluated to identify electrophilic and nucleophilic reactive sites.

Keywords- Pyrazole, Antimicrobials, Density Functional Theory, Molecular Electrostatic Potential, Frontier Molecular Orbital.

I. INTRODUCTION

Pyrazole-dihydrofuran hybrids represent a pivotal class of heterocyclic compounds, merging the pharmacophoric strengths of pyrazole (anti-inflammatory, antimicrobial, and anticancer properties) and dihydrofuran (contributing structural diversity and metabolic stability). Recent syntheses have yielded derivatives with exceptional bioactivity, such as pyrazolyl-dihydrofurans exhibiting antibacterial efficacy at MIC values as low as 1.562 µg/mL. Despite their promise, the rational design of these scaffolds faces challenges, including regioselectivity in synthesis, configurational isomerism (cis vs. trans), and electronic property optimization for target specificity. Density Functional Theory (DFT) has emerged as an indispensable computational tool to decode these complexities, enabling atomic-level insights that bridge synthetic chemistry and biological evaluation. DFT studies elucidate reaction mechanisms and

regioselectivity in pyrazole-dihydrofuran synthesis. For instance, the (3+2) cycloaddition between alkylated pyrazoles and nitrile oxides proceeds via normal electron demand, with DFT-calculated global reactivity indices (e.g., electrophilicity ω) predicting regioselective pyrazole-isooxazoline formation.

Transition-state modelling further confirms kinetic preference for fluorinated derivatives due to lowered activation barriers. Structurally, DFT optimizations reveal how isomeric disparities govern bioactivity: cis isomers exhibit enhanced stability and antibacterial potency due to favorable intramolecular interactions and reduced steric strain, validated by molecular docking against bacterial targets. Electronic descriptors like HOMO-LUMO gaps ($\Delta E \approx 4-5$ eV) and electrostatic potential maps correlate with antioxidant efficacy, guiding the design of electron-rich derivatives for improved radical scavenging. DFT quantifies electronic transitions critical for bioactivity. Frontier molecular orbital analysis shows that low ΔE values

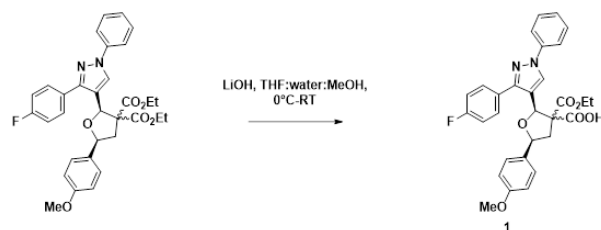
enhance charge transfer to biological targets, while electrophilicity indices ($\omega > 1.5$ eV) predict nucleophilic attack sites. For anticancer derivatives, DFT-calculated dipole moments (>4.5 D) and polar surface areas improve membrane permeability predictions.

Studies of pyrazolyl-dihydrofurans demonstrate that electron-withdrawing groups (e.g., $-F$, $-Cl$) at meta positions reduce ΔE , increasing reactivity and antitumor activity against cell lines like MCF-7 and HepG2. The integration of DFT with experimental data will accelerate the development of multi-target agents (e.g., dual EGFR/BRAF V600E inhibitors), leveraging electronic descriptors to optimize binding. Hybrids like bis-pyrazolines show promise, with DFT-predicted softness values correlating with IC_{50} values of $1.05 \mu M$. DFT mechanistic studies will streamline solvent-free, one-pot syntheses, reduce waste and improve yields of diastereomerically pure isomers.

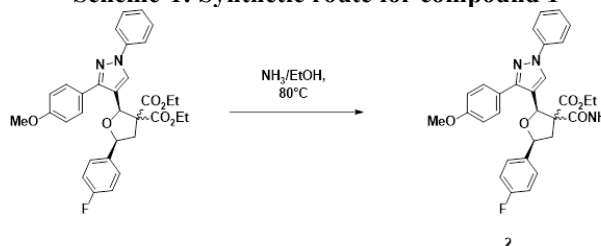
The information about the HOMO-LUMO gaps in pyrazole-dihydrofurans enable applications in organic electronics, such as OLED emitters or sensors. Machine learning models trained on DFT datasets (e.g., ΔG binding, ADMET properties) will enable high-throughput virtual screening for novel hybrids. DFT studies provide a foundational framework for understanding and advancing pyrazole-dihydrofuran derivatives. By decoding electronic, steric, and thermodynamic factors, DFT bridges molecular structure and bioactivity, paving the way for next-generation therapeutics and functional materials. Future research will focus on multi-scale modelling (DFT-MD), in silico ADMET prediction, and AI-driven design to unlock the full potential of these versatile heterocycles. Therefore, here we present the DFT study of previously synthesized pyrazole-dihydrofuran derivatives.

II. SYNTHESIS AND CHARACTERIZATION

We studied the biological importance of pyrazolyl-dihydrofurans in our recent publications [1] with 31 examples. We explored these derivatives further to synthesize their corresponding acid and amide derivatives. We took the example Diethyl (2S,5S)-2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-(4-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate, previously synthesized by us[1] and hydrolyzed to its corresponding acid, compound **1**(Scheme 1). In similar way, Diethyl (2S,5S)-5-(4-fluorophenyl)-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)dihydrofuran-3,3(2H)-dicarboxylate, previously synthesized by us[1] was treated with ammonia to get its amide derivative, compound **2**(Scheme 2). Both compounds characterized by ^1H NMR, ^{13}C , LCMS, IR and melting point.



Scheme-1: Synthetic route for compound 1



Scheme-2: Synthetic route for compound 2

III. RESULTS AND DISCUSSION

Geometry and Frontier Molecular Orbital (FMO) analysis

The optimized geometries of the studied molecules are shown in **Fig 1**. The frontier molecular orbitals (FMO) analyses was carried out to understand the electronic and chemical reactivity properties of these molecules. The computationally obtained FMO surface plots of the highest occupied molecular orbital and the lowest unoccupied molecular orbital are depicted in **Fig. 2**. It can be observed that the electron density is localized on similar atomic fragments for both HOMO and LUMO in both the molecules. The HOMO-LUMO energy gap of any molecule is considered to be a pivotal factor in determining the stability as well as the reactivity of that particular system. The energy of HOMO is related to the electron donating ability of a molecule while LUMO energy determines the ability to accept electrons. Herein, the band gap of the **1** and **2** is 4.76 eV and 4.58 eV respectively indicating these molecules to be polarized, kinetically stable and chemically reactive due to possible easy charge transfer process between HOMO and LUMO [2]. Various quantum chemical descriptors are calculated from the FMO analysis through DFT.

As illustrated in Table 1, the quantum chemical descriptors give valuable information concerning the electronic structure, stability, and reactivity of the two molecules [3-4]. The descriptors obtained include Ionization Potential (I), Electron Affinity (A), Chemical Potential (μ), Electronegativity (χ), Global Hardness (η), Global Softness (S), and Electrophilicity Index (ω). Each of these parameters has a significant influence in defining the molecular behavior in a chemical reaction; the propensity to either donate or accept electrons, and the thermodynamic stability of the molecules. Ionization potential (I) is defined as the energy required to extract an electron from a molecule. Among the two molecules, **1** has the higher ionization potential of 5.96 eV

suggesting that 1 would have the lesser preference in participation in oxidation reactions [5-6]. 2, with the lower ionization potential of 5.76 eV, is comparatively more reactive in electron transfer processes due to ease of electron donation. Electron affinity (A) measures the ability of a molecule to accept an electron. 1 again has the higher electron affinity of 1.19 eV, suggesting strong electrophilic behavior, while 2 with lower value of 1.17 eV indicating it to act less likely as an electron acceptor.

The chemical potential (μ) is essentially the negative of electronegativity and shows how likely electrons are to escape from a system [7-8]. 1 has the most negative chemical potential at -3.58 eV, which means it strong propensity to donate electrons compared to the other molecule 2 with less negative value at -3.47 eV. Electronegativity (χ), calculated as the average of I and A, is in tune with the other properties. 1 is the most electronegative among the two, at 3.58 eV, indicating a strong pull for electrons, while 2, at 3.47 eV, is lower in

electronegativity, aligning with its lower ability to accept electrons. Global hardness (η) tells us how resistant a molecule is to change its electron distribution. 1 and 2 have hardness values of 2.38 eV and 2.29 eV, respectively, which means 1 is more stable and less likely to deform. In contrast, 2 with lower hardness value is more flexible and reactive. Global softness (S), which is the inverse of hardness, shows how easily the electron cloud can be altered. 2, with the higher softness value of 0.22 eV⁻¹, is more reactive among the two molecules. The electrophilicity index (ω) merges the ideas of chemical potential and hardness to gauge how well a molecule can accept electrons [9]. 1 stands out with the highest electrophilicity index at 2.69 eV, reinforcing its role as a strong electrophile and hinting at its reactivity in nucleophilic attacks. These quantum chemical descriptors allow us to have a clear picture about their ability to accept electrons and their electrophilic characteristics.

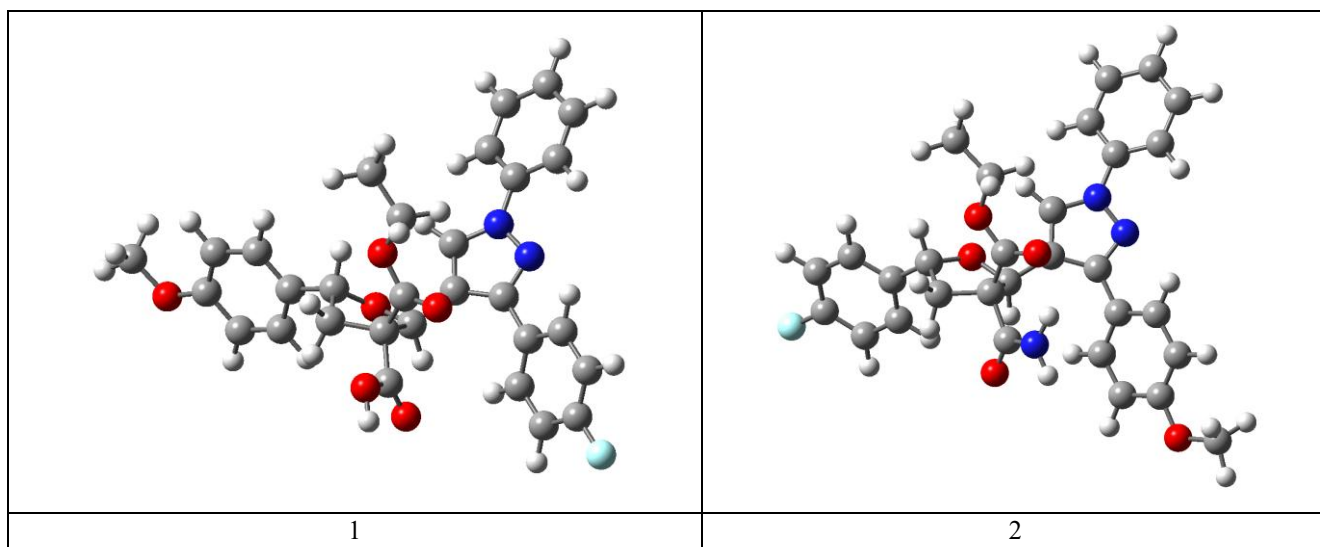
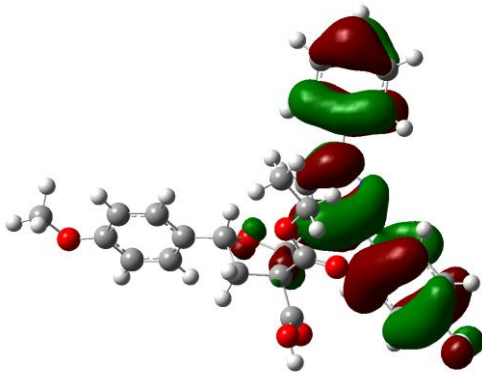
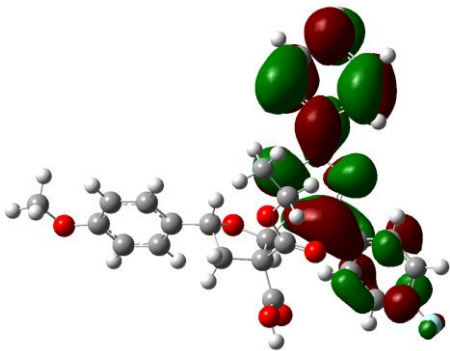


Fig.1. DFT optimized structures of the drug molecules

Compounds	HOMO	LUMO
1		
	-5.962 eV	-1.198 eV

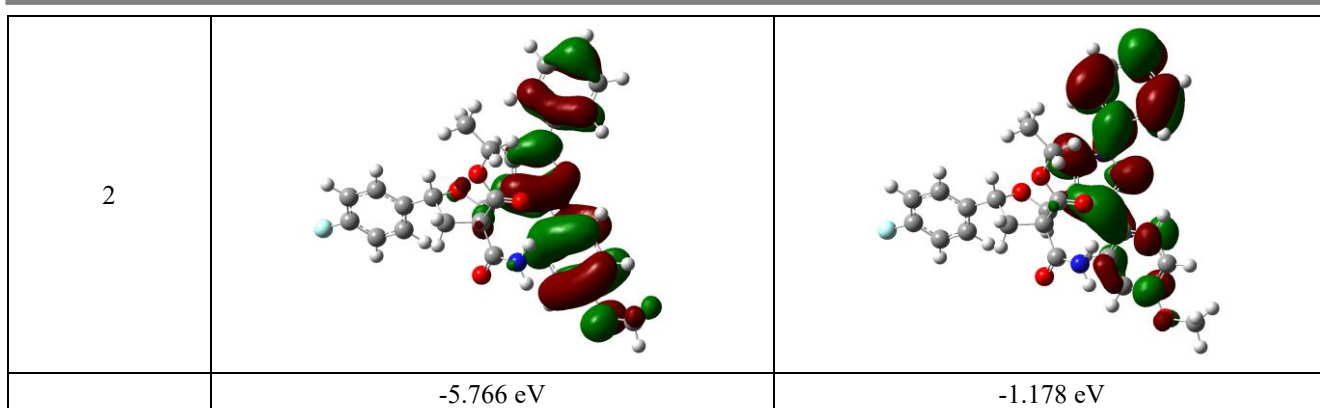


Fig. 2. 3D surface plots of HOMO and LUMO of the molecules

Table 1. Quantum chemical descriptors (in eV) of the two compounds

Parameters/Molecules	1	2
HOMO	-5.962	-5.766
LUMO	-1.198	-1.178
$\Delta E = (LUMO-HOMO)$	4.764	4.588
$I = -E(HOMO)$	5.962	5.766
$A = -E(LUMO)$	1.198	1.178
$\chi = (I + A)/2$	3.580	3.472
$\mu = -\chi$	-3.580	-3.472
$\eta = (I - A)/2$	2.382	2.294
$S = 1/2\eta$	0.209	0.218
$\omega = \mu^2/2\eta$	2.690	2.627

Molecular Electrostatic Potential (MEP)

Surface maps of molecular electrostatic potential (MEP) for the two analyzed molecules 1 and 2 were created to visualize electrostatic charge regions that could be attacked nucleophilically or electrophilically (Fig 3). The plots of the MEPs, superimposed on the electron density isosurface, show that each compound has a different environment. Molecule 1 has a symmetrical potential distribution featuring moderate electron-rich (red-orange) and electron-poor (blue) regions suggesting balanced charge delocalization. In contrast, 2 displays lesser range values of electrostatic potentials which could mean lower intramolecular

charge separation and a lesser dipole moment. 1 has intense red regions compared to the 2 molecule, indicating strong electronic polarization and thus greater chemical reactivity. These results indicate that 1, would show most nucleophilic reactivity due to presence of stronger red electronic charge density than 2 are more stable. The MEP analysis complements other approaches and offers a comparative view of different molecules from the qualitative standpoint of the charge distribution and possible reactive sites of the molecules, which is essential for predicting their behaviour in chemical and biological environments.

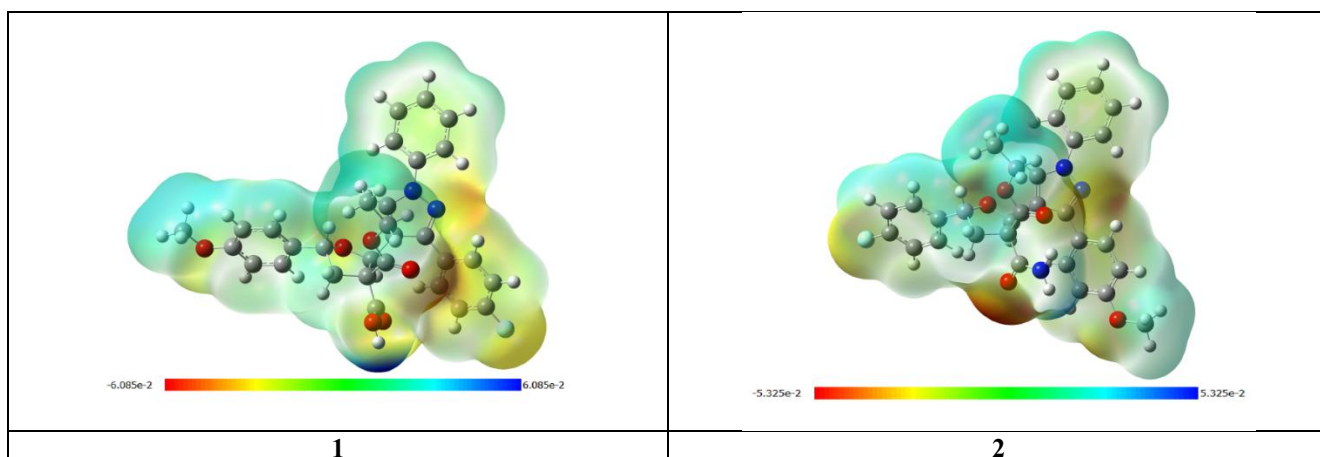


Fig.3 Molecular electrostatic potential map of the molecules

IV. EXPERIMENTAL

Methods and materials - Melting points were determined on Buchi M-565 instrument in open capillaries and are uncorrected. The FTIR spectra were obtained in KBr on Perkin Elmer Spectrum LiTA instrument and are reported in cm^{-1} . The ^1H and ^{13}C NMR spectra were scanned on a Bruker Avance New Console (BBFO & iProbe) NMR spectrometer at operating frequency of 400 MHz, respectively in CDCl_3 or DMSO-d_6 using TMS as an internal standard. The chemical shifts are expressed in ppm with respect to TMS. An accurate mass measurement was made on ESI-APCI (Duis mode) mass spectrometer.

Synthesis of 3-(ethoxycarbonyl)-2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-(4-methoxyphenyl)tetrahydrofuran-3-carboxylic acid (1)

To a suspension of methyl diethyl 2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-(4-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate (0.25 g, 0.45 mmol) in tetrahydrofuran (1 mL), methanol (0.5 mL) and water (0.5 mL) was added lithium hydroxide (0.026 g, 1.12 mmol) at 0°C . Reaction was stirred at room temperature for 16 hours until completed as evident from TLC. The reaction was quenched with ice water and organic layer was extracted from ethyl acetate and concentrated under vacuo to afford 3-(ethoxycarbonyl)-2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-(4-methoxyphenyl)tetrahydrofuran-3-carboxylic acid (1) as brownish solid. Isolated yield: 0.18 g, 75%; R_f 0.5 (20% EtOAc:Heptane);

FT-IR (ν cm^{-1}): 2836 (-COOH), 1715 ($\text{C}=\text{O}$, - CO_2Et), 1600 ($\text{C}=\text{N}$, Pyrazole), 1459 (N-N, Pyrazole), 1233 ($\text{C}-\text{O}$, - CO_2Et), 1054 ($\text{C}-\text{O}$, DHP)

Mpt: 179-180 $^\circ\text{C}$.

^1H NMR (400 MHz, DMSO-d_6): δ 13.53 (s, 1H, H-5), 8.65 (s, 1H, H-5), 7.86-7.92 (m, 2H, Ar-H), 7.72-7.76 (m, 2H, Ar-H), 7.46-7.73 (m, 4H, Ar-H), 7.11-7.39 (m, 3H, Ar-H), 6.90-6.93 (m, 2H, Ar-H), 5.89 (s, 1H, H-6), 4.71-4.75 (m, 1H, H-11), 3.71-3.80 (m, 5H, - OCH_2CH_3 , - OCH_3), 2.92-2.98 (m, 1H, H-10), 2.61-2.66 (m, 1H, H-10), 0.68-0.72 (m, 3H, - OCH_2CH_3);

^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 168.4, 160.9, 159.0, 150.3, 139.2, 131.2, 130.5, 130.4, 129.5 (2), 128.9 (d, $J = 3.1$ Hz), 128.1 (2), 128.0, 126.6, 119.7, 118.6 (2), 115.4, 115.2, 113.6 (2), 78.6, 75.0, 65.7, 61.0, 55.0, 42.2, 12.9.

Calculated MS (ESI) m/z : 531.20 $[\text{M}+1]^+$

Observed MS (ESI) m/z : 531.40 $[\text{M}+1]^+$.

Synthesis of ethyl 3-carbamoyl-5-(4-fluorophenyl)-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)tetrahydrofuran-3-carboxylate (2)

A suspension of diethyl 5-(4-fluorophenyl)-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)dihydrofuran-3,3(2H)-dicarboxylate (0.25 g, 0.05 mmol) in methanolic ammonia (7M, 5 mL), was heated at 80°C for 16 hours. The progress of reaction was

monitored by TLC. After completion, the solvent was concentrated to dryness under reduced pressure to afford ethyl

3-carbamoyl-5-(4-fluorophenyl)-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)tetrahydrofuran-3-carboxylate (2) as yellowish solid. Isolated yield: 0.23 g, 98%; R_f 0.5 (20% EtOAc:Heptane);

FT-IR (ν cm^{-1}): 3356 (-CONH₂), 1724 ($\text{C}=\text{O}$, - CO_2Et), 1600 ($\text{C}=\text{N}$, Pyrazole), 1505 (N-N, Pyrazole), 1246 ($\text{C}-\text{O}$, - CO_2Et), 1054 ($\text{C}-\text{O}$, DHP);

Mpt: 136-137 $^\circ\text{C}$.

^1H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H, H-5), 7.90 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.66-7.71 (m, 3H, Ar-H, -CONH₂), 7.50-7.57 (m, 4H, Ar-H), 7.32-7.35 (m, 1H, Ar-H), 7.17-7.21 (m, 2H, Ar-H), 7.02-7.04 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.16 (s, 1H, H-6), 4.71-4.74 (m, 1H, H-11), 3.83 (s, 3H, - OCH_3), 3.72-3.73 (m, 2H, - OCH_2CH_3 , - OCH_3), 2.90-2.96 (m, 1H, H-10), 2.69-2.73 (m, 1H, H-10), 0.64-0.68 (m, 3H, - OCH_2CH_3);

^{13}C NMR (101 MHz, DMSO-d_6): δ 170.5, 169.1, 162.9, 160.5, 159.2, 151.2, 139.4, 136.1, 129.8 (2), 129.5 (2), 128.6 (d, $J = 8.1$ Hz), 127.9, 126.3, 124.9, 119.8, 118.5 (2), 115.1, 114.9, 113.7 (2), 78.3, 74.8, 66.0, 60.8, 55.1, 43.0, 12.9.

Calculated MS (ESI) m/z : 530.21 $[\text{M}+1]^+$

Observed MS (ESI) m/z : 530.40 $[\text{M}+1]^+$.

V. DENSITY FUNCTIONAL THEORY (DFT) STUDY

The electronic structure of the drug molecules was computed using the Gaussian 16 software tool [1-2]. Density Functional Theory (DFT) was employed utilizing the hybrid B3LYP functional and the 6-31++G(d,p) basis set for optimizing the molecular structures in this study. Previous literature has demonstrated that B3LYP functional can predict the molecular structures as well as the energies of many organic compounds accurately [3-4]. The optimization of the structures was followed by frequency calculation to ensure the nature of the structures as energy minimized structures in the potential energy surface. The conditions of convergence have been retained at default level with no geometry-constraint. To comprehend the chemical reactivity of the compound, the HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) and energy band gap are determined. The electron density of each molecules is used to compute the molecular electrostatic potential, which predicts the preferred electrophilic and nucleophilic areas in the studied drug molecules.

VI. CONCLUSION

DFT calculation at B3LYP/6-31++G(d,p) level predicts the electronic structures of the molecules 1 and 2. Both the studied molecules are found to be stable through the FMO analysis. The energy gap is found to be

around 4.5 and 4.7 eV for molecule 1 and molecule 2 respectively. The quantum chemical descriptors revealed the bioactive nature of both the molecules. The MEP plot predicts the nucleophilic and electrophilic reactivity and charge distribution around the molecules.

ACKNOWLEDGEMENT

Authors are grateful to Jubilant Biosys Ltd. Noida, India for providing necessary facilities for the research.

REFERENCES

- [1] Hari Prakash, Sandhya Chahal, Prateek Tyagi, Deepansh Sharma, Mange Ram Mangyan, Noopur Srivastava, Jayant Sindhu and Kuldeep Singh, *J. Mol. Struct.* 1319, 139437(2025).
- [2] P. K. Chattaraj and S. Giri, *J. Phys. Chem. A.*, 111, 11116 (2007).
- [3] R. G. Parr, L. V. Szentpály and S. Liu, *J. Am. Chem. Soc.*, 121, 1922 (1999).
- [4] P. W. Ayers and R. G. Parr, *J. Am. Chem. Soc.*, 122, 2010 (2000).
- [5] T. Koopmans, *Physica.*, 1, 104 (1933)
- [6] J. C. Phillips, *Phys. Rev.*, 123, 420 (1961)
- [7] L. A. Flippin, D. W. Gallagher and K. Jalali-Araghi, *J. Org. Chem.*, 54, 1430 (1989).
- [8] J. Padmanabhan, R. Parthasarathi, V. Subramanian and P. K. Chattaraj, *J. Phys. Chem. A.*, 111, 135 (2007).
- [9] Bendjedoua, A., Abbaz, T., Gouasmi, A. & Villemain, D. (2016) 'Quantum chemical studies on molecular structure and reactivity descriptors of some p-nitrophenyltetrathiafulvalenes by density functional theory (DFT)', *Acta Chimica and Pharmaceutica Indica*, 6(2), pp. 33.
- [10] Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
- [11] R. Dennington, T.A. Keith, J.M. Millam, GaussView, Version 6.0; Semichem Inc., Shawnee Mission: Shawnee, Kansas (2016).
- [12] R. Krishnan, J.S. Binkley, R. Seeger, J.A. Pople, Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions, *J. Chem. Phys.* 72 (1980) 650–654.
- [13] A.D. Becke, Density-functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.* 98