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Density Functional Theory Study of the Molecular and Electronic Properties of Simvastatin, Warfarin, and Propranolol

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Abstract: ***This study used density functional theory (DFT) calculations in Gaussian 09 to compare the molecular and electronic properties of simvastatin, warfarin, and propranolol. Molecular geometries were optimized at the B3LYP/6-31G level, and frequency analyses confirmed the absence of imaginary frequencies. Frontier molecular orbital properties were evaluated in the optimized structures and under aqueous conditions. Simvastatin showed the largest HOMO-LUMO gap among the compounds studied, indicating comparatively greater electronic stability and lower reactivity, whereas propranolol showed a smaller gap. Under aqueous conditions, the HOMO-LUMO gap of warfarin decreased slightly, while that of propranolol increased and that of simvastatin showed little change. The calculated electronic descriptors further demonstrated differences among the three compounds. Overall, the results show that DFT calculations can provide useful comparative information on the electronic stability and reactivity of structurally different cardiovascular drugs.***

Keywords: Simvastatin, Propranolol, Warfarin, Density Functional Theory, HOMO, LUMO

1. Introduction

Cardiovascular diseases cause one in 3 deaths globally and are on the rise. However, CVD patients are managed through long-term medications rather than surgery, which is commonly reserved for extreme medical emergencies. Computational Chemistry allows researchers to predict molecular behavior, reactivity, and stability without needing lab access to test medications in a controlled setting. DFT is the standard choice because it balances accuracy with computational cost, keeping research efficient yet precise (Mazurek et al., 2020). The three drugs that were studied are simvastatin, warfarin, and propranolol, which each tackle a different condition contributing to CVD. The existing data provide a benchmark to compare predictions against the drugs' established statistics. For example, simvastatin limits the amount of cholesterol released by the liver, warfarin prevents fatal blood clots that occur in arteries, and propranolol regulates high blood pressure. Studying these distinct drugs allows researchers to examine how different methods can address an overarching problem.

DFT (Density Functional Theory) is a computational method that provides researchers with a framework for understanding how molecules behave, react, and change at the atomic level (Cavasotto et al., 2019). Instead of scientists physically mixing chemicals in the lab and waiting for results, DFT calculations give researchers access to reactivity, structure, and chemical composition on a computer, anywhere. This becomes useful when researchers don't have direct access to a lab. Additionally, for complex drug molecules such as simvastatin, propranolol, and warfarin, DFT allows researchers to build the molecule with minimal room for error because it is clearly visible (Guan et al., 2025). One of the first things DFT does is make a stable orientation for the molecule under study; more specifically, it performs geometric optimization. When a molecule is loaded into the program, it is initially unstable and at a unique energy level compared to the other molecules. Simply put, each molecule begins with a unique initial energy level that must be optimized. When the optimization calculation begins, the computer minimizes the energy and stabilizes the molecule. This gives all the molecules a baseline, so they can be more directly comparable to other calculations. For example, this calculation creates a stable environment and yields consistent reactions. Geometric optimization is the first foundational step in computational research.

Following geometric optimizations is frequency analysis. This step is equally important because it ensures the structure is stable and in its lowest-energy configuration. It double-checks that the molecule is ready for further analysis. It identifies any remaining imaginary frequencies, confirming the effectiveness of the geometric optimization. This step is very important because if there were an imaginary frequency, all subsequent calculations, such as HOMO/LUMO values, would be unreliable. After making sure the calculation is set up correctly, the next step is to analyze the results. More specifically, the HOMO and LUMO values of each molecule. HOMO stands for highest occupied molecular orbital, the highest-energy orbital that can contain electrons. Then LUMO is the Lowest Unoccupied Molecular Orbital, the lowest-energy orbital available to electrons. The energy gap between the HOMO and LUMO tells us about chemical reactivity, energy gap, and stability. A smaller gap means less energy is required to promote an electron from an occupied orbital to an unoccupied one, making it much more reactive. Conversely, larger gaps mean that much more energy is required to move the electrons. This is important when comparing simvastatin, propranolol, and warfarin because each drug works in the body in a unique way. Examining their HOMO and LUMO gaps clarifies the differences in stability and reactivity among the drugs. Lastly, molecular electrostatic potential (MEP) maps show the distribution of electrostatic potential across the molecule. These color maps represent the distribution of electric charge in the molecule. Red spots represent more negative electrostatic potentials and are more likely to attract protons. White areas represent neutral zones. Finally, green areas are electron-poor spots. These maps are valuable when studying molecules because

they explain where bonding is most likely to occur. This study aims to investigate the molecular and electronic structure of simvastatin, warfarin, and propranolol using DFT after creating them in GaussView. After the molecular optimization, a frequency analysis was run, establishing that the imaginary frequencies were zero. Next, we studied each drug's HOMO and LUMO energies, which demonstrate the drug's unique reactivity and stability based on the gap. We then repeated the calculations with water as the solvent to understand how the drug would behave under aqueous conditions (Rijal et al., 2022).

2. Methodology

All calculations for this research project were performed using Gaussian 09. This is a widely used software program in computational chemistry. The three drug molecules that were studied were simvastatin, propranolol, and warfarin. Next, we researched the molecular structures online and imported them into the software to begin the calculations. After construction, geometry optimizations were run at the B3LYP level, combined with 6-31G. These are the most commonly used methods in DFT calculations and have provided reliable results. They produced no imaginary frequencies, indicating that the structures were true minima. Optimizing the sets was necessary for accuracy and made further molecular calculations more efficient. After optimization, frequency analysis confirmed that all structures were optimized to their minimum-energy forms. After confirming that their imaginary frequencies were at their smallest possible values, we observed each molecule's orbitals, including the HOMO and LUMO energy levels and their energy gap. Aqueous phase calculations were performed using the CPCM solvation model. These were single-point calculations performed on the gas-phase optimized geometries, rather than full geometry reoptimizations in water. All three molecules were modeled with a charge of 0 and multiplicity of 1.

3. Results and Discussions

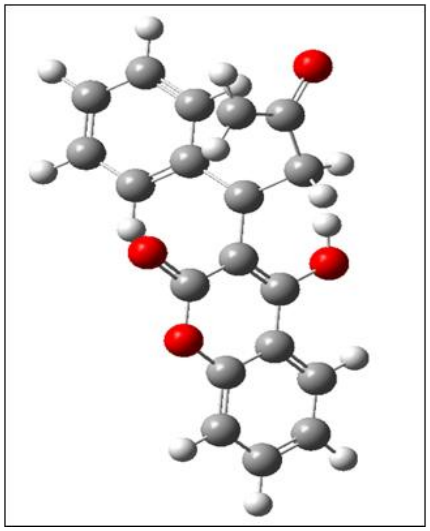

Figure 1: Optimized structure of warfarin, B3LYP/6-31G. This model is the ball and stick representation generated in GaussView

Warfarin is a prescription drug often referred to as a "blood thinner" (**Figure 1**). It slows down the body's ability to form blood clots in veins and arteries. More specifically, it works by inhibiting vitamin K-dependent clotting factors, which are essential for normal clotting (Wu et al., 2018). Warfarin contains carbon, hydrogen, and oxygen, with oxygen playing a key role in the molecule's interaction with vitamin K.

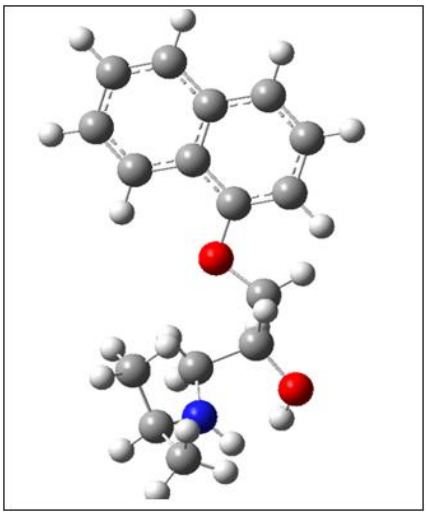

Figure 2: Optimized structure of Propranolol, B3LYP/6-31G. This model is the ball-and-stick representation generated in GaussView

Propranolol is a prescription drug classified as a non-selective beta-blocker (Epstein & Braunwald, 1967). It is used to treat cardiovascular conditions. It blocks specific receptors, which slows the heart rate and reduces the heart's oxygen demand. From a molecular perspective, propranolol contains carbon, hydrogen, nitrogen, and oxygen. Its molecular formula is $C_{16}H_{21}NO_2$. The nitrogen atom plays a vital role in molecular interactions.

Simvastatin is a prescription drug classified as a statin. It is primarily used to lower blood levels of bad cholesterol. It works by inhibiting the liver enzyme HMG-CoA reductase (Istvan & Deisenhofer, 2001). From a molecular perspective, simvastatin is a molecule and contains 25 carbons, 38 hydrogens, and 5 oxygens. The complex ring-based structure allows it to block cholesterol synthesis.

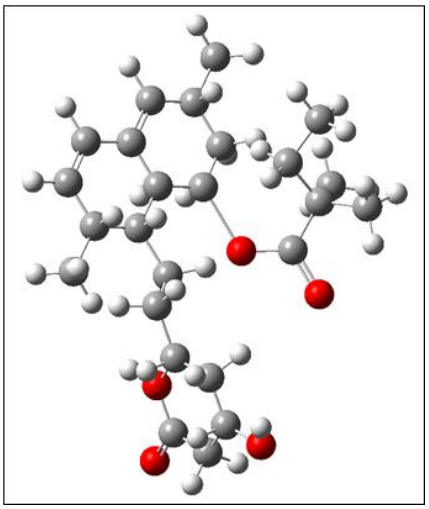

Figure 3: Optimized structure of Simvastatin, B3LYP/6-31G. This model is the ball-and-stick representation generated in GaussView

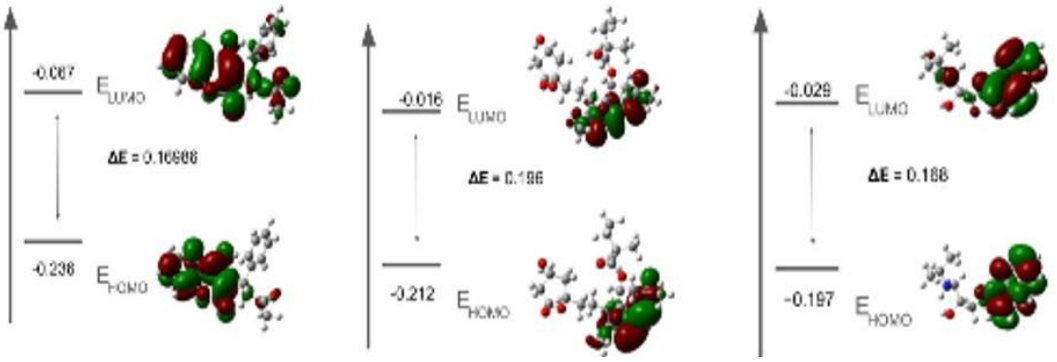

Figure 4: The frontier molecular orbitals obtained from the optimized structures of (a) Warfarin, (b) Propranolol, and (c) Simvastatin

The delta between the HOMO and LUMO values indicates how much energy is required to move an electron from the HOMO to the LUMO. Small deltas indicate greater reactivity and mean the molecule is not often stable. Larger deltas mean the molecule is less chemically reactive and more stable.

Ionization potential is the minimum energy required to remove an electron from an atom. Higher ionization potentials mean that electrons are held more tightly, and the molecule is harder to ionize. Lower ionization potentials mean that electrons are easier to remove and that the resulting ions are more reactive. This matters because it helps predict how readily a substance can lose electrons, which can affect other chemical behaviors. Electron affinity represents the tendency that a molecule will gain an electron, and is therefore the opposite of ionization potential. Additionally, it measures how likely an atom wants to gain an electron. A higher electron affinity means the molecule readily accepts electrons and forms electron-rich species. While lower electron affinity means the molecule has a lower tendency to accept an electron. This is important because it predicts the interactions and compares its efficiency to other drugs

Compound	homo a.u.	lumo a.u.	ΔE a.u.	Ionization Potential (I) a.u.:	Electron Affinity (A) a.u.:	Chemical hardness a.u.: η	Chemical Softness (S):	Chemical Potential (μ) a.u.:	Electro Negativity (χ) a.u.:	Electro-phillicity Index (ω) a.u.:
Warfarin	-0.236	-0.06684	0.169	0.23627	0.06684	0.08472	5.9	-0.15156	0.15156	0.1356
Warfarin (CPCM water)	-0.23074	-0.069	0.162	0.23874	0.06871	0.085	5.88	-0.1537	0.1537	0.139
Propranolol	−0.19721	−0.02856	0.168	0.19721	0.02856	0.08433	5.93	−0.11289	0.11289	0.076
Propranolol (CPCM water)	−0.20698	−0.03628	0.171	0.20698	0.03628	0.08535	5.86	−0.12163	0.1216	0.087
Simvastatin	–0.21194	–0.01639	0.196	0.21194	0.01639	0.09778	5.11	−0.11417	0.11417	0.067
Simvastatin (CPCM water)	-0.21175	-0.01587	0.196	0.21175	0.01587	0.09794	5.1	-0.11381	0.113871	0.066

Chemical hardness measures a molecule's resistance to changes in its molecular structure. A higher hardness means the molecule holds onto its electrons tightly, is more stable, and less reactive. Lower hardness means the molecule's electrons are more easily disturbed and the molecule is more reactive. This matters when you need to predict how a molecule will behave once it enters the body and interacts with other substances. Chemical softness is the exact opposite of chemical hardness. This measures how easily a molecule can change its molecular structure. A higher chemical softness value means the molecule's electrons are less tightly held and more reactive. A low chemical softness value means the molecule resists electron changes. This is significant because chemically softer molecules tend to react with other soft molecules. Chemical potential measures the tendency of electrons to escape the molecule. A higher chemical potential means electrons are more likely to be transferred. The lower the chemical potential, the more tightly packed and stable the electrons are. This is significant because it gives researchers an idea of where the electrons might flow in the body, and it is a key factor when trying to understand how a drug functions.

Electronegativity measures how strongly the molecule attracts other electrons toward itself. When electronegativity is higher, the molecule pulls more strongly on electrons and is more likely to take them from other molecules. Lower electronegativity means the molecule has a weaker attraction for electrons. This information matters because it helps explain charge distribution within neighboring molecules and how they interact with receptors. The electrophilicity index measures how strongly a molecule seeks electrons. A higher electrophilicity means the molecule is more aggressive in seeking out electrons. Lower electrophilicity means the molecule is less driven to accept an electron. This allows researchers to understand how a drug can react with other biological molecules

4. Conclusions

This study compared the electronic properties of simvastatin, warfarin, and propranolol using DFT calculations at the B3LYP/6-31G level. Among the compounds studied, simvastatin showed the largest HOMO-LUMO gap, suggesting comparatively greater electronic stability and lower reactivity, while propranolol showed a smaller gap and comparatively greater reactivity. Under the modeled aqueous conditions, the HOMO-LUMO gap of warfarin decreased slightly, whereas that of propranolol increased and that of simvastatin remained nearly unchanged. The calculated

electronic descriptors therefore reveal distinct stability and reactivity trends among these cardiovascular drugs. These findings demonstrate the usefulness of DFT for comparative characterization of molecular electronic properties while recognizing that the calculated descriptors alone do not directly establish therapeutic effectiveness or biological activity.

References

[1] Cavasotto, C. N., Aucar, M. G., & Adler, N. S. (2019). Computational chemistry in drug lead discovery and design. *International Journal of Quantum Chemistry*, *119*(2). https://doi.org/10.1002/qua.25678

[2] Epstein, S. E., & Braunwald, E. (1967). Beta-Adrenergic Receptor Blockade Propranolol and Related Drugs. *Annals of Internal Medicine*, *67*(6), 1333–1337. https://doi.org/10.7326/0003-4819-67-6-1333

[3] Guan, H., Sun, H., & Zhao, X. (2025). Application of Density Functional Theory to Molecular Engineering of Pharmaceutical Formulations. *International Journal of Molecular Sciences*, *26*(7), 3262. https://doi.org/10.3390/ijms26073262

[4] Istvan, E. S., & Deisenhofer, J. (2001). Structural Mechanism for Statin Inhibition of HMG-CoA Reductase. *Science*, *292*(5519), 1160–1164. https://doi.org/10.1126/science.1059344

[5] Mazurek, A. H., Szeleszczuk, Ł., & Pisklak, D. M. (2020). Periodic DFT Calculations—Review of Applications in the Pharmaceutical Sciences. *Pharmaceutics*, *12*(5), 415. https://doi.org/10.3390/pharmaceutics12050415

[6] Rijal, R., Sah, M., Lamichhane, H. P., & Mallik, H. S. (2022). Quantum chemical calculations of nicotine and caffeine molecule in gas phase and solvent using DFT methods. *Heliyon*, *8*(12), e12494. https://doi.org/10.1016/j.heliyon.2022.e12494

[7] Wu, S., Chen, X., Jin, D.-Y., Stafford, D. W., Pedersen, L. G., & Tie, J.-K. (2018). Warfarin and vitamin K epoxide reductase: a molecular accounting for observed inhibition. *Blood*, *132*(6), 647–657. https://doi.org/10.1182/blood-2018-01-830901