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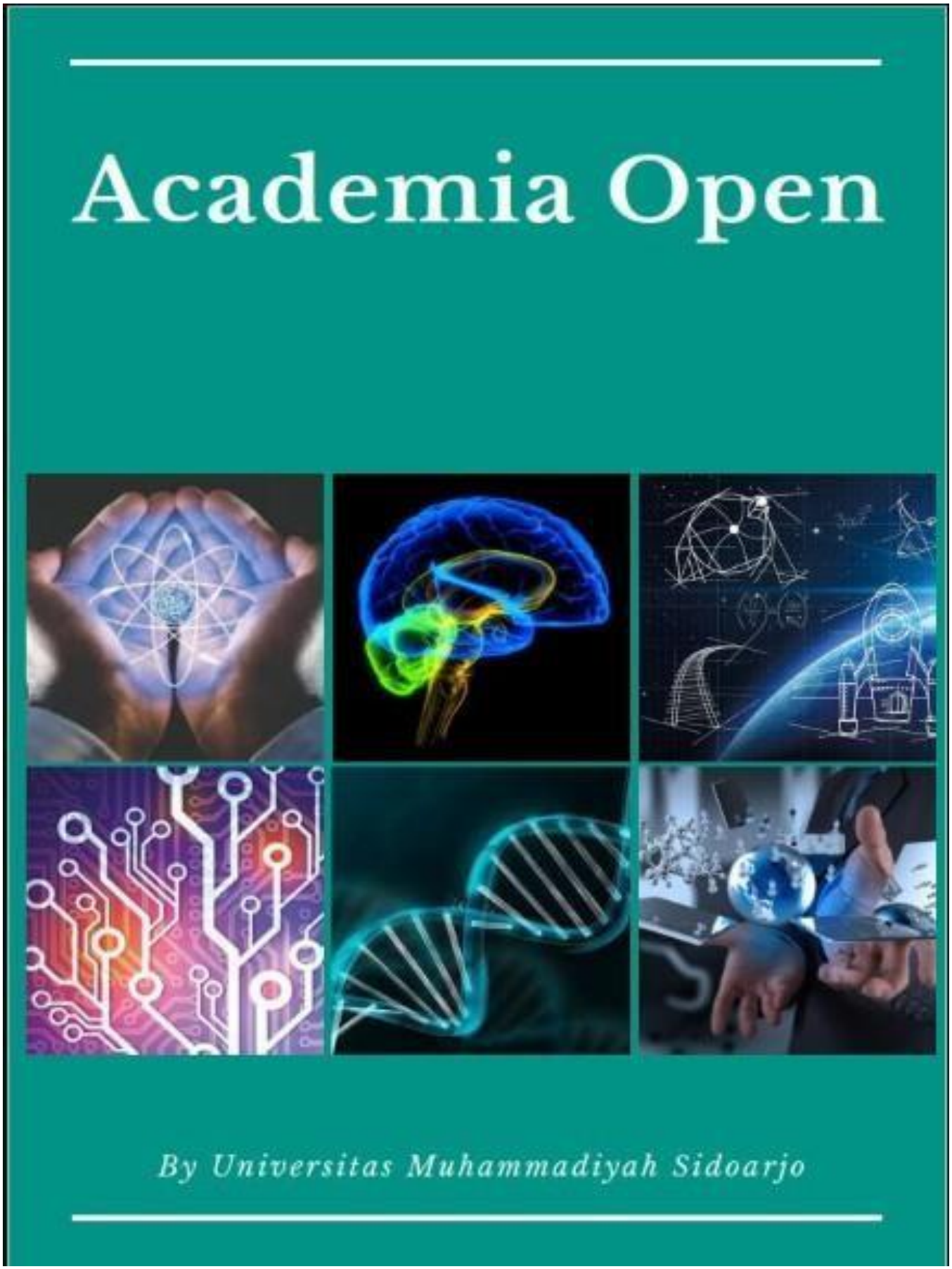

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Comparative Quantum Chemical Study of Some Non-Steroidal Anti-Inflammatory Drugs Using PM3 and AM1 Methods

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Abstract

General Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for pain relief, inflammation management, and fever reduction, and their molecular properties are important for understanding chemical behavior and biological interactions. **Specific Background:** Computational chemistry provides useful approaches for evaluating molecular stability, electronic characteristics, and physicochemical properties through molecular modeling. **Knowledge Gap:** Comparative information on the molecular stability, polarity, and electronic reactivity of Aspirin, Ibuprofen, Naproxen, and Diclofenac using semi-empirical quantum chemical methods remains limited. **Aims:** This study aimed to conduct a comparative quantum chemical analysis of selected NSAIDs using PM3 and AM1 methods with HyperChem software. **Results:** Aspirin and Ibuprofen showed greater molecular stability based on lower total energy values, while Aspirin exhibited the highest dipole moment, indicating stronger polarity. Diclofenac showed the smallest HOMO–LUMO energy gap, suggesting greater chemical reactivity. Vibrational frequencies also showed good agreement between computational and experimentalvalues. **Novelty:** This study integrates molecular stability, charge distribution, vibrational properties, and orbital characteristics of commonly used NSAIDs within asinglecomputationalframework. **Implications:** The findings providemolecular-level insight into drug properties and may support future computational drug design and pharmaceutical research.

Highlights:

- Aspirin displayed the highest polarity through larger dipole moment values among the investigated compounds.
- Diclofenac exhibited the narrowest orbital energy separation, indicating greater chemical activity characteristics.
- Vibrational spectrum calculations showed consistency between theoretical predictions and experimental measurements.

Keywords: Quantum Chemistry; Non-Steroidal Anti-Inflammatory Drugs; Molecular Stability; HOMO LUMO Energy Gap; Computational Molecular Modeling

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications worldwide. They are commonly used to relieve pain, inflammation, and fever. These drugs mainly act by inhibiting cyclooxygenase enzymes (COX-1 and COX- 2), which are involved in the biosynthesis of prostaglandins associated with inflammatory processes.

Due to their widespread use and structural diversity, these drugs represent important molecular systems for theoretical and computational studies, as they are used to understand their electronic properties and chemical behavior [1,2].

Some drugs such as Aspirin, Ibuprofen, Naproxen, and Diclofenac are among the most commonly used within this group. Despite their similar pharmacological effects, they differ in their physicochemical properties, which in turn affect their molecular stability, electron distribution, and chemical reactivity [3].

Aspirin (acetylsalicylic acid) is one of the first and most frequently used drugs in medicine. It is commonly applied as an pain reliever, fever reducer, and anti-inflammatory agent. In addition, aspirin shows antiplatelet activity and is widely used in the prevention of heart diseases. Its molecular structure contains an aromatic ring with ester and carboxylic functional groups, which play a significant role in its chemical properties and biological activity [4].

Ibuprofen is additional widely used NSAID that is commonly prescribed for the control of mild to moderate pain, inflammation and fever. It falls into the propionic acid category of NSAIDs and shows its pharmacological activity mainly by inhibiting of cyclooxygenase enzymes. The molecular structure of ibuprofen includes an aromatic ring and a propionic acid chemical group, which impact its molecular properties [5].

Diclofenac is a potent NSAID widely used in the treatment of inflammation -related diseases such as joint inflammation and musculoskeletal disorders. It contains two aromatic rings and two chlorine atoms in its structure, which greatly impact its electron density distribution and molecular characteristics. Because of its high anti-inflammatory activity, diclofenac has been widely researched both experimental studies and theoretically [6].

Naproxen is similarly a compound of the propionic acid category of NSAIDs and is commonly used for the management of pain and inflammatory condition, mainly in arthritis and related conditions. Its chemical structure contains a naphthalene aromatic ring system and a methoxy chemical group, which may affect its electronic and chemical reactivity. Because of these structural features, naproxen constitutes an important molecule for theoretical studies [7].

Thus, a relative computational study of these drugs can present useful information into their electronic properties, structural stability, and chemical reactivity. In the present work, the electronic and structural properties of aspirin, ibuprofen, diclofenac, and naproxen were studied using semi-empirical quantum chemical methods (PM3 and AM1).

1. Previous Studies

Several computational and practical studies have been published on non-steroidal anti-inflammatory drugs (NSAIDs) to study their molecular properties and biological activities.

For example, Graham et al. (2005) studied the pharmacological properties and tolerability of naproxen and discussed its clinical importance as one of the used NSAIDs. Their study showed the structural features and therapeutic applications of naproxen in the management of inflammatory disorders [8].

In another study, Gan (2010) examined the pharmacological and physicochemical properties of Diclofenac and stated activity as a potent anti-inflammatory drug used in the management of pain and musculoskeletal diseases [9].

Furthermore, computational chemistry methods have been commonly applied to study pharmaceutical molecules. Jensen (2017) described that semi-empirical quantum chemical methods such as PM3 and AM1 are useful for determining electronic properties and molecular stability of organic compounds with sutible computational efficiency [10]. Recently, Mahdi (2025) investigated Diclofenac derivatives using quantum mechanical and artificial intelligence methods. The study showed that electronic properties, such as total energy, molecular orbitals, and charge distribution, play an important role in determining structural stability and chemical reactivity, which are important for predicting drug behavior and enhancing drug design[11]. These previous studies show that computational approaches are useful tools for studying the electronic and structural properties of drug molecules. Therefore, the present work aims to conduct a comparative quantum chemical study of Aspirin, Ibuprofen, Diclofenac, and Naproxen using PM3 and AM1 methods.

Methods

In this research, a number of non-steroidal anti-inflammatory drugs (NSAIDs), such as Aspirin, Ibuprofen, Diclofenac, and Naproxen, were chosen for comparative computation chemical study. These compounds were chosen because they belong to the same pharmacological class but differ in their chemical structures, which may influence their electronic properties and chemical behavior.

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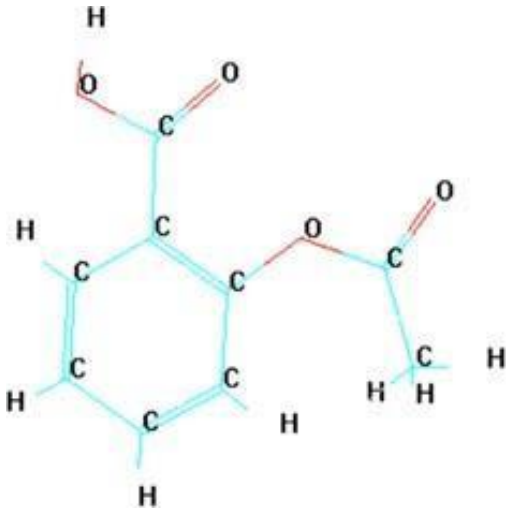

Figure 1. **represents the initial drawing of the three-dimensional geometric structure of Aspirin ($C_9H_8O_4$).**

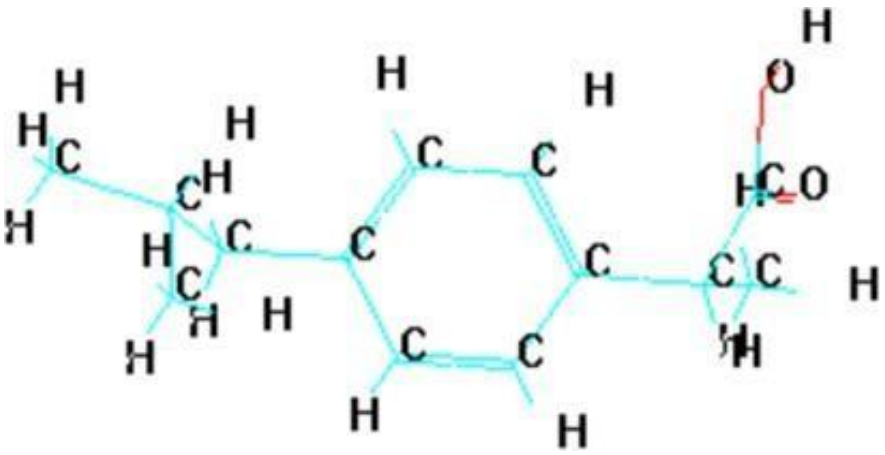

Figure 2. **represents the initial drawing of the three-dimensional geometric structure of Ibuprofen (C13H18O3)**

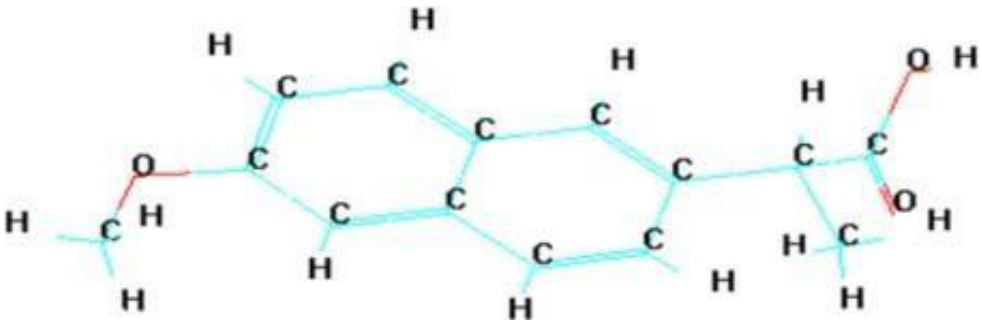

Figure 3. **represents the initial drawing of the three-dimensional geometric structure of Naproxen**

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(C14H14O3).

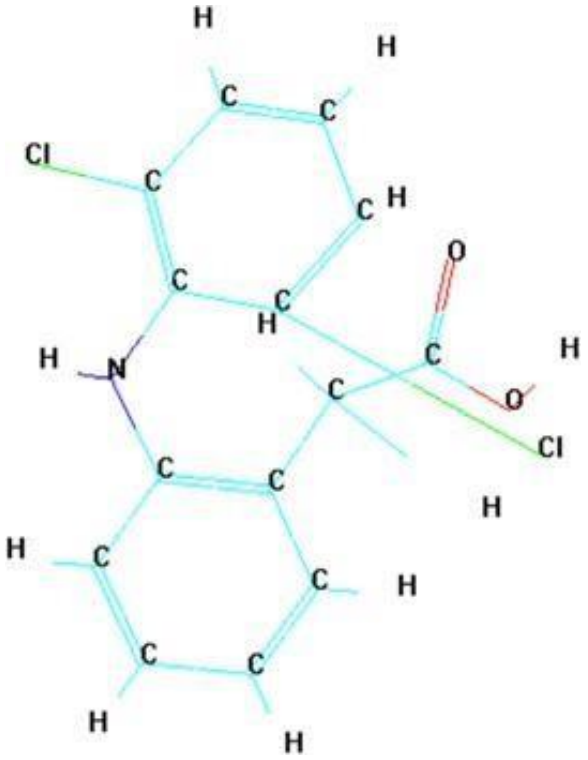

Figure 4. **represents the initial drawing of the three-dimensional geometric structure of Diclofenac (C14H11Cl2NO2).**

1. Calculation of the equilibrium geometry :

A set of thermodynamic and electronic properties was calculated, including binding energy total energy, electronic energy, and nuclear energy, using semi-empirical methods (AM1 and PM3).

The results showed that Diclofenac has the lowest total energy value compared to the other drugs, indicating that it is the most stable compound among the studied molecules. The total energy value was approximately (-81595.4957, -74036.03599)kcal /mol, while the other compounds showed higher energy values. This decrease in energy indicates that this drug has better therapeutic efficacy compared to the other compounds.

The dipole moment was also calculated as an indicator of molecular polarity. The results showed that Aspirin has the highest dipole moment (5.82, 5.51) deybes among the studied drugs, indicating that it is the most polar compound. This may result in improved solubility and enhanced biological activity.

In addition, slight variation in dipole moment values were identified between the AM1 and PM3 methods, which are due to differences in the computational approximations used in each method.

Table (1) shows some physical properties of the drugs (Aspirin, Ibuprofen, Naproxen, and Diclofenac) at the equilibrium geometry using AM1 and PM3 methods.

		Total Energy (kcal/mol)		Binding Energy (kcal/mol)		Electronic Energy (kcal/mol)		Nuclear Energy (kcal/mol)		Dipole moment (deybes)	
		AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
1	Aspirin	-58659.99	-54519.29	-2324.0	-2381.74	-283510.86	-277736.42	224850.86	223217.13	5.82	5.51
2	Ibuprofen	-58911.00	-55495.42	-3381.59	-3377.83	-351649.81	-345360.59	292738.80	289865.17	2.145	2.019

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3	Naproxen	-67953.27	-63547.88	-3399.35	-3398.61	-397875.76	-390783.88	329922.48	327235.99	1.098	1.263
4	Diclofenac	-81595.49	-74036.03	-3285.32	-3291.55	-491727.21	-487731.83	410131.72	413695.79	2.671	2.205

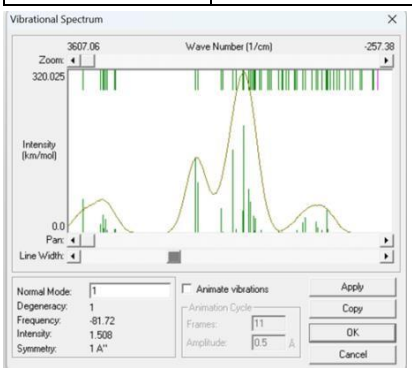
2. Infrared (IR) Spectra Calculation:

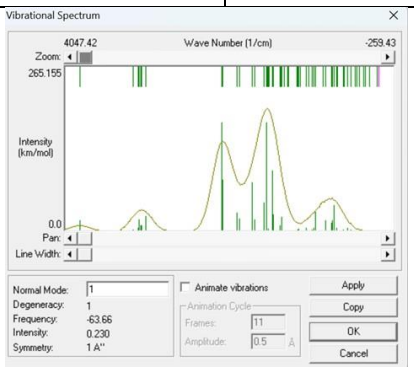
The vibrational frequencies and infrared absorption intensities of some drugs (Aspirin, Ibuprofen, Naproxen, and Diclofenac) were calculated using Hyper Chem. 8.0 software based on semi-empirical methods (AM1 and PM3).

The most important vibrational modes of these drugs, which contain several functional groups, were identified and are presented in Figures (5, 6, 7, and 8), showing the vibrational motions corresponding to the calculated frequencies (cm^{-1}). The results showed good a greement between the two computational methods.

Table (2) presents a comparison between the experimental and theoretical vibrational frequencies of the studied drug Aspirin at the equilibrium geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1276.15	1256.34
C=C	1600-1475	1453.47	1590.28
C-O	1163-1258	1146.25	1136.46
C=O	1775-1660	1656.90	1656.11
C-H	3023	3057.55	3010.54
O-H	3100-2800	3784.43	



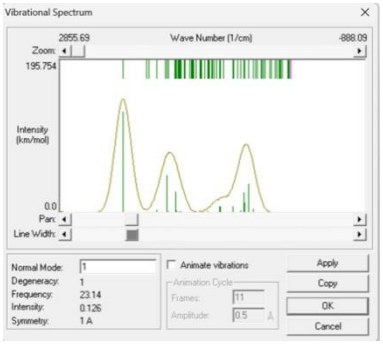


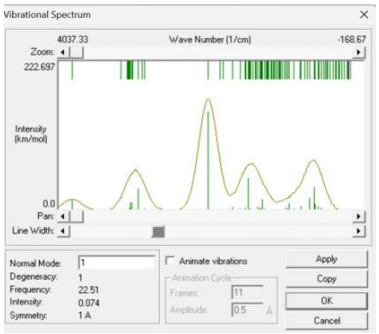
AM1 **PM3**

Figure (5) The theoretical vibrational spectra of aspirin using the AM1 and PM3 methods.

Table (3) presents a comparison between the experimental and theoretical vibrational frequencies of the studied drug Ibuprofen at the equilibrium geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1243.42	1296.22
C=C	1600-1475	1463.42	1489.28
C-O	1163-1258	1133.27	1121.49
C=O	1775-1660	1689.71	1663.16
C-H	3023	3043.25	3018.98
O-H	3100-2800	3721.63	3276.20





AM1

PM3

Figure (6) The theoretical vibrational spectra of Ibuprofen using the AM1 and PM3 methods.

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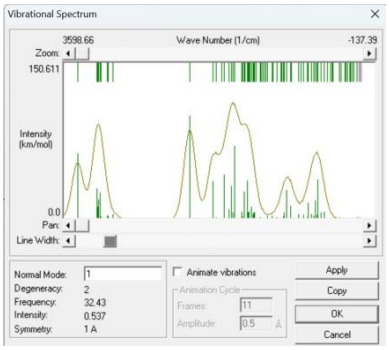
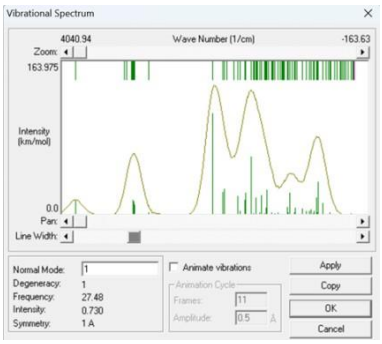
Table (4) presents a comparison between the experimental and theoretical vibrational frequencies of the studied drug Ibuprofen at the Naproxen geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1234.66	1262.19
C=C	1600-1475	1473.22	1428.78
C-O	1163-1258	1142.17	1142.79
C=O	1775-1660	1607.98	1653.32
C-H	3023	3053.55	3033.38
O-H	3100-2800	3631.73	3140.27



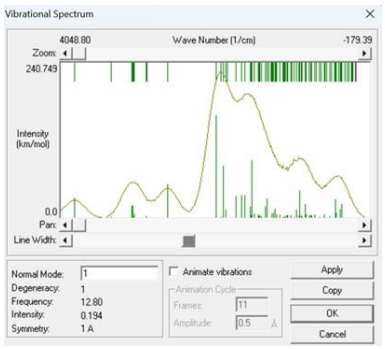


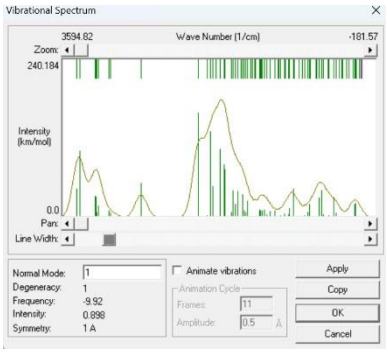
AM1 **PM3**

Figure (7) The theoretical vibrational spectra of Naproxen using the AM1 and PM3 methods.

Table (5) presents a comparison between the experimental and theoretical vibrational frequencies of the studied drug Diclofenac at the equilibrium geometry using AM1 and PM3 methods.

	Experimental [13]	AM1	PM3
C-C	1300-1100	1234.62	1283.82
C=C	1600-1475	1453.72	1432.66
C-O	1163-1258	1143.51	1132.53
C=O	1775-1660	1685.31	1675.22
C-H	3023	3053.02	3021.54
O-H	3100-2800	3732.73	3256.70
C-N	1640-1500	1621.43	1642.11
N-H	3400-3180	3528.76	3361.34
C-CL	730-550	673.22	713.62





AM1 **PM3**

Figure (8) The theoretical vibrational spectra of Diclofenac using the AM1 and PM3 methods.

3. Theoretical Atomic Charge Calculation:

The computed dipole moment values of the investigated drugs showed that Aspirin has the highest dipole moment (5.82, 5.51), while Naproxen has the lowest dipole moment (1.098, 1.263) among the investigated compounds.

This behavior can be explained by the electron density distribution in the molecules. In Aspirin carbonyl (C=O) and ester (C–O) groups contribute to a strongly asymmetric charge distribution, thereby increasing the dipole moment.

In contrast, Naproxen has a more evenly distributed electron density, mainly due to electron delocalization within the aromatic system, which decreases charge asymmetry and thus reduces the dipole moment .

Therefore, the results suggest that greater asymmetry in electron density leads to an increased dipole moment, explaining the observed trend between aspirin and naproxen. The analysis of charge distribution offers important insight into the possible binding sites of drug molecules with biological targets. Regions rich in electron density are probable active interaction sites with proteins oxygen atoms and functional groups such as carboxyl groups, represent the most probable active sites for interaction with proteins. These negatively charged areas can establish strong electrostatic interactions and hydrogen bonding with amino acid residues in the active site of enzymes such as COX-2. Therefore, charge distribution plays an important role in predicting the

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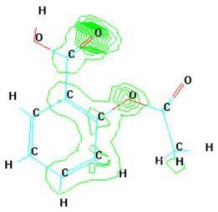

binding behavior and affinity of drug molecules.

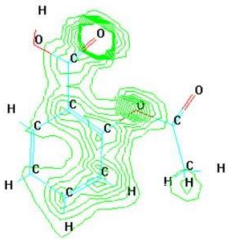

Figure (9) displays the electron distribution of Aspirin by using the AM1 and PM3 methods.

Figure (10) displays the electron distribution of Ibuprofen by using the AM1 and PM3 methods.

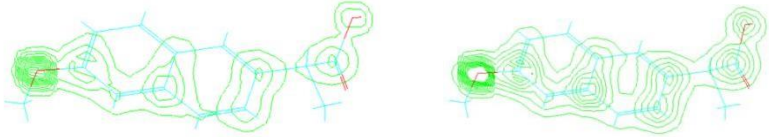

Figure (11) displays the electron distribution of Naproxen by using the AM1 and PM3 methods.

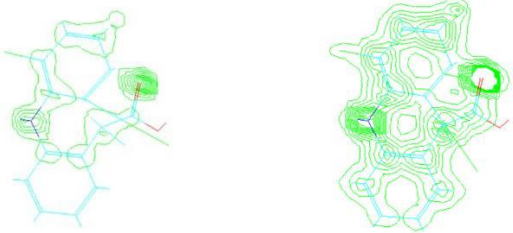

Figure (12) displays the electron distribution of Diclofenac by using the AM1 and PM3 methods.

4. Potential Molecular Electrostatic

In this research, the energies of occupied and unoccupied molecular orbitals were calculated using the Hyper Chem. software using semi-empirical methods AM1 and PM3.

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were determined. The HOMO refers to the highest energy level filled with electrons, while the LUMO indicates the lowest empty energy level.

These values are important for understanding the molecular stability and reactivity . A small energy gap between HOMO and LUMO suggests that the molecule is highly reactive, while a large gap indicates greater stability.

The energy gap was determined using the following equation:

$\Delta E = E\{LUMO\} - E\{HOMO\}$

The comparison indicates good agreement between the calculated and experimental results, confirming the accuracy of the used computational methods.

Table (6): shows a comparison between the experimental and calculated values of vibrational modes for the studied compounds, including Aspirin, Ibuprofen, Naproxen, and Diclofenac, at equilibrium geometry using semi-empirical methods (AM1 and PM3).

		E HOMO (ev)		E LUMO (ev)		ELUMO - E HOMO	
		AM1	PM3	AM1	PM3	AM1	PM3
1	Aspirin	9.7363-	-9.7489	-0.6404	-0.675	9.0959	9.0732
2	Ibuprofen	-9.4214	-9.4976	0.1747	0.1217	9.5961	9.6193
3	Naproxen	-8.6740	-8.7828	-0.4203	-0.541	8.2537	8.2418
4	Diclofenac	-8.0567	-8.2493	-0.4308	-0.602	7.6259	7.6467

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Conclusion

This study present a comparative analysis of Aspirin, Ibuprofen, Naproxen, and Diclofenac was performed using semi-empirical methods (AM1 and PM3). The results demonstrated that Aspirin and Ibuprofen show greater stability, as shown by their lower total energy values. Aspirin also displayed the highest dipole moment value, indicating higher polarity and improved ability to interact with biological systems. However, Diclofenac had the smallest HOMO-LUMO energy gap, showing greater chemical reactivity because of the presence of chlorine atoms in its structure. These results indicate the relationship between molecular stability, polarity, and chemical reactivity, which are important factors in predicting drug activity and enhancing drug design.

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