WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 10, 2702-2714. Research Article ISSN 2277– 7105

COMPUTATIONAL STUDY OF GEOMETRY, MOLECULAR PROPERTIES AND DOCKING STUDY OF ASPIRIN

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Article Received on
19 Aug 2015,

Revised on 09 Sep 2015,
Accepted on 29 Sep 2015,

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ABSTRACT

In this paper, a computational study of geometry such as bond lengths, bond angles and different molecular properties like Molecular Electrostatic Potential (MESP), Mulliken Charge Distribution, Global and Local Reactivity Descriptors (chemical hardness, softness, chemical potential, electronegativity, electrophilicity index) etc. and molecular docking study of Aspirin with human Cyclooygenase-2 (COX-2) enzyme have been reported. Hartee–Fock (HF) and B3LYP level of theory with 6-31G (d,p) basis set are employed for all sorts of calculation. The molecular geometry was compared with the experimental data and a good agreement with the experimental data was found. Moreover, the molecular docking study of Aspirin with human COX-2 revealed that Aspirin interacts with the TYR371 and SER513 amino acid residues with a binding affinity of -6.8 Kcal/mol.

KEYWORDS: Aspirin**,** Cyclooxygenase-2, Molecular docking, chemical potential, electronegativity.

INTRODUCTION

Aspirin, also known as acetylsalicylic acid (ASA) (Figure 1) is an odorless, colorless to white, crystalline powder with molecular formula $C_9H_8O_4$. It is a salicylate medication used to treat pain, fever, and inflammation. Aspirin also has an antiplatelet effect by stopping the binding of platelets together and preventing a patch over damaged walls of blood vessels. Aspirin is also used long-term, at low doses, to help prevent heart attacks, strokes, and blood clot formation in people at high risk of developing blood clots.[1] Low doses of aspirin may

be given immediately after a heart attack to reduce the risk of another heart attack or of the death of cardiac tissue.[2, 3] Aspirin may be effective at preventing certain types of cancer, particularly colorectal cancer.[4, 5]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an important class of compounds that display a number of effects as a consequence of their ability to block cyclooxygenase (COX) involved in the first step of the arachidonic acid cascade.[6] COX exists in two isoforms named COX-1 and COX-2. The first is constitutively expressed in the stomach, the kidneys, and platelets and is considered important in mucosal protection and platelet function. COX-2 is inducible and plays a major role in prostaglandin biosynthesis in inflammatory cells.[7] Aspirin is a non-selective COX-2 inhibitor. It inhibits both the isoforms of COX enzyme. The desired analgesic, antipyretic, and anti-inflammatory activities of Aspirin are obtained as a consequence of the inhibition of COX–2; on the other hand, inhibition of COX–1 leads to unwanted effects on the gastrointestinal tract such as ulceration, bleeding and perforation of gastrointestinal tract.[6]

Fewer computational and theoretical studies of Aspirin were reported earlier. El-Shahawy, 2014 reported the theoretical spectral studies of Aspirin.[8] Datt et al., 2012 investigated experimental and computational study of the loading and release of Aspirin from zeolite HY.[9] Besides, Marjan et al., 2014 conducted a computational study to find the prospect to aspirin side effects.[10]

As part of our ongoing research [11] the present study was undertaken and to our knowledge, the theoretical calculation of geometry, different molecular properties such as Molecular electrostatic potential (MESP), Mulliken charge distribution, Global and local reactivity descriptors (chemical hardness, softness, chemical potential, electronegativity, electrophilicity index) and molecular docking study of Aspirin with human COX-2 enzyme have not been reported except in our work.

Methodology

Computational methods

All calculations were carried out with the Gaussian09 software package.[12] The geometries were fully optimized before performing any calculation. The absence of imaginary frequencies in the optimized structure confirmed that the stationary points correspond to minima on the potential energy surface. The Mulliken charge distribution was calculated on

HF and B3LYP level with 6-31G(d,p) basis sets. In addition, Molecular electrostatic potential (MESP) and global and local reactivity descriptors such as hardness, chemical potential, softness, electronegativity and electrophilicity index were also calculated in the gas phase.

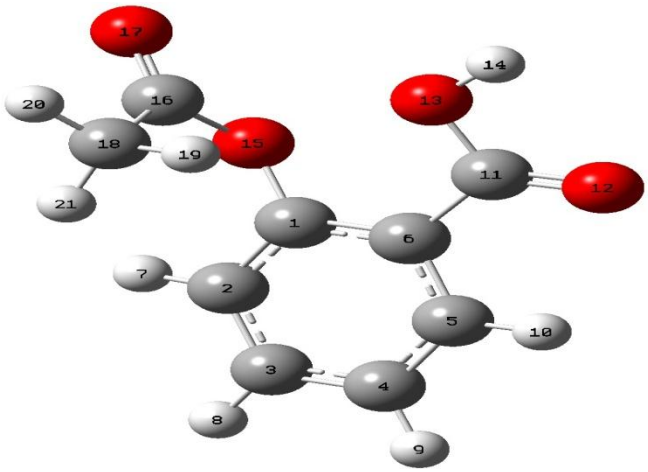


Figure 1: Structure of Aspirin

Molecular docking study

Preparation of Target Protein X-ray Structure

The crystal structure of human COX-2 in complex with Celecoxib (PDB code: 3LN1) was selected as the protein target model in this virtual screening study.[13] Water molecules, ligands and chain B, C and D in case of 3LN1 were removed and then polar hydrogen atoms to the proteins was added using PyMOL (Version 1.7.4.4, Schrödinger). Energy minimization was performed by applying MMFF level of theory in Drug Discovery Studio (Version 4.0) software.

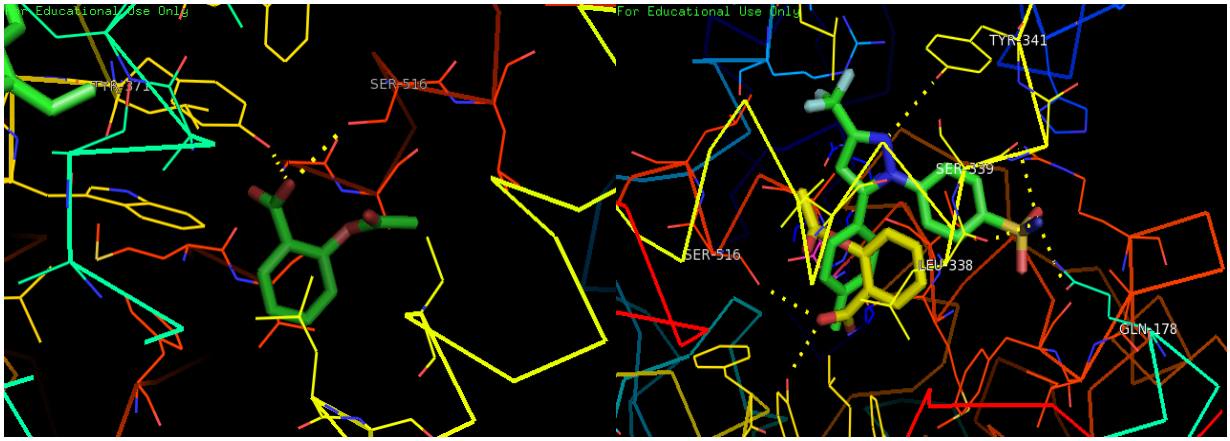
Preparation of Ligands

The initial structure of the Celecoxib (CID 2662) and Aspirin (CID 2244) were obtained from pubchem (https://pubchem.ncbi.nlm.nih.gov/search/). Molecular geometry optimization was then performed with the density functional theory (DFT) at the B3LYP/6-31G(d,p) level using Gaussian 09 program.[12] The optimized structures of ligands were then saved in PDB format for docking study.

Protein-Ligand Docking

The docking of the target protein with the ligand was performed using AutoDock vina in PyRx 0.8.[14] Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. Using PyRx software, the macromolecule (COX-2) and ligands are prepared and then docking was performed using a grid whose center

was (34.8544, -29.0810, -9.1090) and the dimensions were (25.00, 25.00, 25.00) Angstrom (Å). Throughout the docking study the macromolecule was kept as rigid and ligand molecules were flexible. The best conformation was chosen with the lowest docked energy or binding affinity pose and ability to make bonding with the protein structure, after the docking search was completed. The interactions of complex protein-ligand conformations, including hydrogen bonds and the bond lengths were analyzed using PyMOL (Figure 2).



2a 2b

Figure 2: Binding mode of 2a. Aspirin and 2b. Aspirin (Yellow) and Celecoxib (Green) with cyclooxygenase-2 (3LN1) enzyme.

Before screening the ligands, the docking protocol was validated by redocking Celecoxib into the binding pocket of 3LN1 to obtain the docked pose and RMSD. The result showed that the first pose of Celecoxib almost exactly superimpose with the experimental crystal structure of Celecoxib (Figure 3). Thus, the protocol is good in reproducing the X-ray crystal structure and can be applied for further docking experiments.

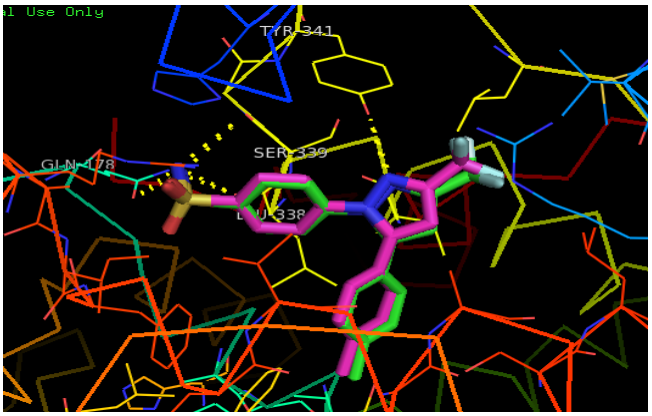


Figure 3: The superimposition of the best docking structure of Celecoxib with the X-ray structure of human COX-2. (■) Docked ligand, (■) Experimental ligand

RESULTS AND DISCUSSION

Equilibrium geometries

The optimized geometrical parameters such as bond lengths and bond angles of Aspirin obtained by the HF and B3LYP methods with 6-31G(d,p), as basis set are listed in table 1. The computed bond length and bond angles were compared with X-ray diffraction data of similar compound.[15] From table 1, it can be seen that the computed bond distances and bond angles agreed reasonsble well with the experimental data except C(11)-O(13)-H(14), O(15)-C(16)-C(18), C(16)-C(18)-H(20), H(19)-C(18)-H(20) and H(19)-C(18)-H(21) bond angles. These deviations in bond angles may be due to the intermolecular interactions in the crystalline state. However, the differences between the computed and experimental data are expressed as Mean Absolute Deviation (MAD). The MAD of bond lengths and bond angles were found 0.071 Å, 0.067 Å and 2.5°, 2.8° for B3LYP and HF, respectively.

Table 1: Theoretical (gas phase) and experimental (X-ray diffraction) bond distances (Å) and bond angles (°) of Aspirin

Assignment	6-31G(d,p)		Exp[15]	Assignment	6-31G(d,p)		Exp[15]
	B3LYP	HF			B3LYP	HF	
C(1)-C(2)	1.397	1.384	1.385	C(1)-C(2)-C(3)	120.4	120.2	119.8
C(2)-C(3)	1.393	1.382	1.387	C(2)-C(3)-C(4)	120.0	120.3	120.0
C(3)-C(4)	1.397	1.386	1.381	C(3)-C(4)-C(5)	119.6	119.4	119.9
C(4)-C(5)	1.390	1.380	1.387	C(4)-C(5)-C(6)	121.4	121.2	121.6
C(5)-C(6)	1.405	1.393	1.392	C(5)-C(6)-C(1)	118.3	118.6	117.7
C(1)-C(6)	1.409	1.394	1.400	C(2)-C(1)-C(6)	120.3	120.3	121.0
C(6)-C(11)	1.492	1.493	1.498	C(1)-C(2)-H(7)	118.3	118.6	118.0
C(11)-O(12)	1.215	1.189	1.235	H(7)-C(2)-C(3)	121.3	121.2	122.2
C(11)-O(13)	1.353	1.325	1.287	C(2)-C(3)-H(8)	119.6	119.5	121.6
C(1)-O(15)	1.383	1.366	1.402	H(8)-C(3)-C(4)	120.3	120.2	118.4
O(15)-C(16)	1.385	1.354	1.364	C(3)-C(4)-H(9)	120.4	120.5	120.0
C(16)-O(17)	1.201	1.179	1.183	H(9)-C(4)-C(5)	120.0	120.1	120.1
C(16)-C(18)	1.510	1.507	1.496	C(4)-C(5)-H(10)	121.1	120.7	118.5
C(2)-H(7)	1.085	1.074	0.930	H(10)-C(5)-C(6)	117.5	118.1	119.9
C(3)-H(8)	1.086	1.075	1.040	C(1)-C(6)-C(11)	125.7	125.1	124.6
C(4)-H(9)	1.085	1.074	0.940	C(5)-C(6)-C(11)	115.9	116.3	117.7
C(5)-H(10)	1.084	1.073	0.910	C(6)-C(11)-O(12)	123.7	123.3	119.1
O(13)-H(14)	0.972	0.948	1.120	C(6)-C(11)-O(13)	114.3	114.5	118.1
C(18)-H(19)	1.093	1.082	1.200	O(12)-C(11)-O(13)	121.9	122.1	122.9
C(18)-H(20)	1.089	1.079	0.910	C(11)-O(13)-H(14)	105.9	108.5	120.7
C(18)-H(21)	1.093	1.084	0.780	C(2)-C(1)-O(15)	117.3	117.6	117.3
MAD	**0.071**	**0.067**	-	C(6)-C(1)-O(15)	122.2	121.8	121.6
				O(15)-C(16)-O(17)	117.8	118.2	122.9

O(15)-C(16)-C(18)	117.1	117.7	110.7
O(17)-C(16)-C(18)	125.1	124.1	126.4
C(16)-C(18)-H(19)	110.0	110.8	110.0
C(16)-C(18)-H(20)	108.1	107.8	119.4
C(16)-C(18)-H(21)	111.5	110.7	115.9
H(19)-C(18)-H(20)	109.6	109.8	98.7
H(19)-C(18)-H(21)	107.8	108.1	100.9
H(20)-C(18)-H(21)	109.9	109.7	108.9
MAD	2.5	2.8	-

Molecular electrostatic potential (MESP)

In the graphic of total electron density surface mapped with the electrostatic potential, the sign of the electrostatic potential in a surface region is determined by the predominance of negative or positive charges contribution. Accordingly, it is possible to identify regions more susceptible to electrophilic or nucleophilic molecules, so the molecular electrostatic potential map is commonly used as reactivity map.[16] To predict regions more susceptible to electrophiles or nucleophiles, MESP was calculated at the B3LYP/6-31G(d,p) and is shown in Figure 4. The importance of total electron density surface mapped with the electrostatic potential lies in the fact that it simultaneously displays molecular size, shape, as well as positive or negative electrostatic potential regions in terms of color grading and is very useful in research of molecular structure with its physiochemical property relationship.[17]

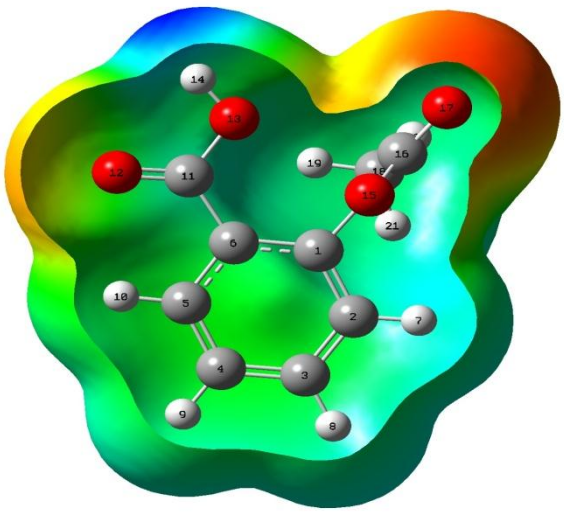


Figure 4: 3D plots of molecular electrostatic potential of Aspirin.

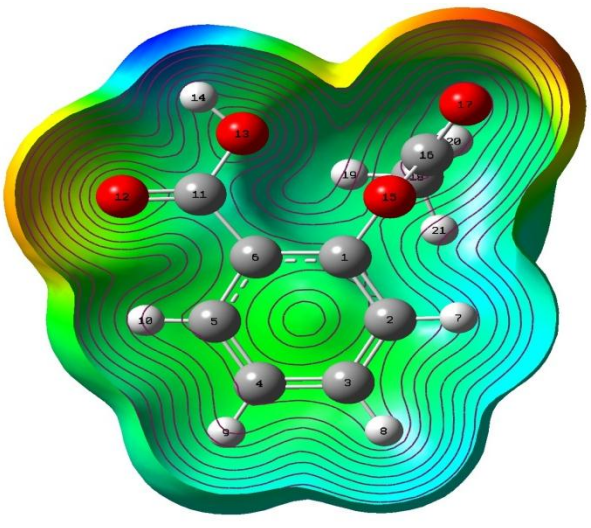


Figure 5: Electrostatic potential contour of Aspirin.

The different values of the electrostatic potential are represented by different colors. It is accepted that the negative (red) and the positive (blue) potential regions in the mapped MESP represent regions susceptible to approach electrophiles and nucleophiles, respectively.

Moreover, the MESP's contour map is used to find the ligand's regions which are more prone to incoming electrophilic species. Spatial regions denser in MESP's contour lines present stronger electrostatic fields than the region with less contour lines. In general, the red regions depictured in the total electron density surface mapped with the MESP indicate the occurrence of inward electrostatic fields, which favor the approach of electrophilic species and repel nucleophilic ones. It can be seen that the most possible sites for nucleophilic attack is H14 and C11. Negative regions in the studied molecule are found around the O12, O15 and O17 atoms indicating a possible site for electrophilic attack.

According to these calculated results, the MESP map shows that the negative potential sites are on electronegative atoms as well as the positive potential sites are around the hydrogen and carbon atoms. The contour map (Figure 5) provides a simple way to predict how different geometries could interact with each other.

Mulliken charge distribution

The Mulliken populations show one of the simplest pictures of charge distribution. The Mulliken charges provide net atomic populations in the molecule while electrostatic potentials yield the electric field out of the molecule produced by the internal charge distribution. Thus, in the reactivity studies, Mulliken populations and MESP are complementary tools, and correlation between the schemes is expected.[18] However, Mulliken population analysis require very careful attention because large changes of calculated atomic charges were observed due to the small changes in basis sets which may lead to the overestimation of covalent character of a bond. In general, the absolute magnitude of the atomic charges has little physical meaning; on the other hand, their relative values can offer valuable information. The Mulliken charge distribution of the titled molecule was calculated on HF and B3LYP level with 6-31G(d,p) basis set.

The charge distribution of the compound (Table 2) shows that carbon atoms C11 and C16 attached with oxygen atoms have positive charges. All the hydrogen atoms have positive Mulliken charges and all the oxygen atoms have negative Mulliken charges. The C11 and C16 atoms have the highest Mulliken charge when compared to other atoms. Among all the

H atoms the H14 possesses highest positive Mulliken charge. Moreover, the Mulliken charge distribution and the MESP information are concordant.

Table 2: Mulliken atomic charges of Aspirin.

Atom	6-31G(d,p)		Atom	6-31G(d,p)	
	B3LYP	HF		B3LYP	HF
C(1)	0.265	0.387	C(11)	0.552	0.813
C(2)	-0.094	-0.175	O(12)	-0.469	-0.562
C(3)	-0.086	-0.127	O(13)	-0.488	-0.605
C(4)	-0.085	-0.165	H(14)	0.330	0.371
C(5)	-0.112	-0.105	O(15)	-0.497	-0.659
C(6)	0.047	-0.181	C(16)	0.586	0.775
H(7)	0.110	0.179	O(17)	-0.424	-0.518
H(8)	0.105	0.171	C(18)	-0.410	-0.454
H(9)	0.102	0.168	H(19)	0.150	0.161
H(10)	0.130	0.205	H(20)	0.149	0.172
			H(21)	0.138	0.150

Global and local reactivity descriptors

The energy gap between HOMO and LUMO is a critical parameter to determine molecular electrical transport properties. By using HOMO and LUMO energy values for a molecule, the global chemical reactivity descriptors of molecules such as hardness, chemical potential, softness, electronegativity and electrophilicity index as well as local reactivity have been defined.[19-23] Pauling introduced the concept of electronegativity as the power of an atom in a molecule to attract electrons to it. Using Koopman's theorem for closed-shell molecules the hardness (η), chemical potential (μ) and electronegativity (χ) and softness (S) are defined as follows.

$$\eta = \frac{I - A}{2}$$

$$\mu = -\frac{I + A}{2}$$

$$\chi = \frac{I + A}{2}$$

$$S = \frac{1}{\eta}$$

where I and A are the ionization potential and electron affinity of the molecules, respectively. The ionization energy and electron affinity can be expressed through HOMO and LUMO orbital energies as $I = -E_{HOMO}$ and $A = -E_{LUMO}$.

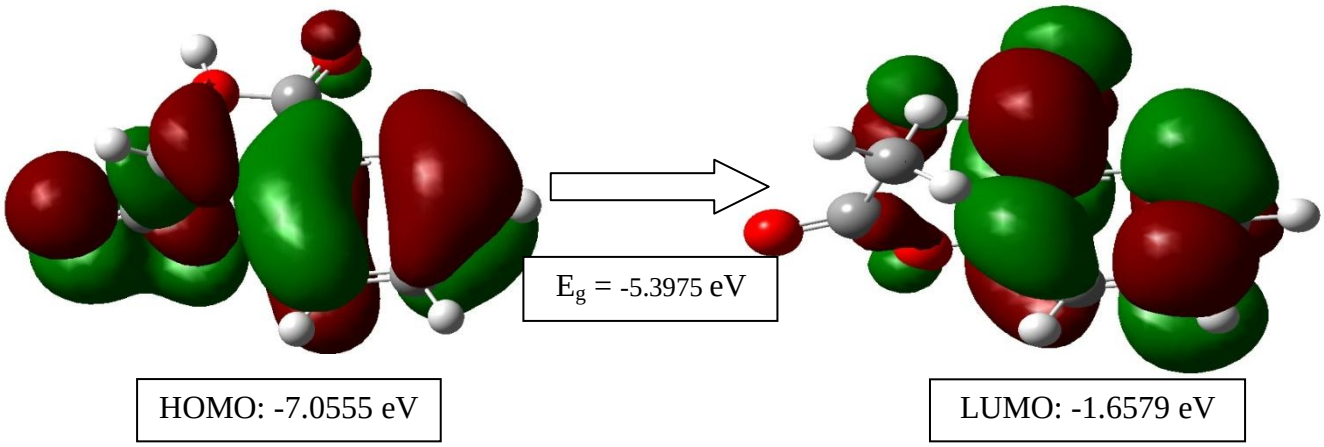


Figure 6: Frontier molecular orbital of Aspirin

Considering the chemical hardness, large HOMO–LUMO gap means a hard molecule and small HOMO–LUMO gap means a soft molecule. One can also relate the stability of the molecule to hardness, which means that the molecule with least HOMO–LUMO gap is more reactive. Recently Parr et al., 1999 have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω), which defines a quantitative classification of the global electrophilic nature of a molecule.[19] Parr et al., 1999 have defined electrophilicity index (ω) as follows:[19]

$$\omega = \frac{\mu^2}{2}$$

Using the above equations, the chemical potential, hardness and electrophilicity index have been calculated for Aspirin and their values are shown in Table 4. The usefulness of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity.[24-26]

Table 3: Comparison of HOMO, LUMO and energy gaps of Aspirin

Molecular properties	6-31G(d,p)	
	HF	B3LYP
E_{HOMO} (eV)	-9.3627	-7.0555
E_{LUMO} (eV)	2.4286	-1.6579
$E_{HOMO-LUMO}$ gap (eV)	-11.7912	-5.3975
E_{HOMO-1} (eV)	-9.7360	-7.5061
E_{LUMO+1} (eV)	3.6900	-0.6512
$E_{HOMO-1 - LUMO+1}$ gap (eV)	-13.4260	-6.8549

Table 4: Comparison of molecular properties of Aspirin

Molecular properties	6-31G(d,p)	
	HF	B3LYP
Chemical hardness (η)	5.8956	2.6988
Softness (S)	0.1696	0.3705
Chemical potential (μ)	-3.4671	-4.3567
Electronegativity (χ)	3.4671	4.3567
Electrophilicity index (ω)	6.0102	9.4904

Docking study

Molecular docking studies of Aspirin was carried out with human COX-2 enzyme using AutoDock Vina, to identify and understand the binding mode of Aspirin and the intermolecular hydrogen bond interaction between Aspirin and the target protein. From our docking study it was found that Aspirin interacts with the TYR371 and SER513 amino acid residues of COX-2 enzyme with a binding affinity of -6.8 Kcal/mol. The docking result of Aspirin with human COX-2 enzyme is presented in Table 5.

Table 5: The binding affinity (Kcal/mol) with Cyclooxygenase-2 (3LN1) enzyme

Mode	Compound Name	Binding Affinity (Kcal/mol)	Interacting Residues of COX-2 (3LN1)
Experimental	Celecoxib	-	GLN178, LEU338, SER339, TYR341
Docked	Celecoxib	-11.3	GLN178, LEU338, SER339, TYR341
Docked	Aspirin	-6.8	TYR371, SER513

CONCLUSION

In the present work, the equilibrium geometry, MESP, Mulliken charge distribution and Global and local reactivity descriptors have been determined from HF and DFT calculations using 6-31G(d,p) as basis set. The calculated molecular properties may lead to the understanding of stability and activity of Aspirin. Moreover, docking study revealed that Aspirin interact with human COX-2 by forming H bond with TYR371, SER513 with a binding energy of -6.8 Kcal/mol while in case of Celecoxib it was -11.3 Kcal/mol.

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