Chapter

DFT and Molecular Docking Studies of a Set of Non-Steroidal Anti-Inflammatory Drugs: Propionic Acid Derivatives

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Abstract

Inflammation is the body's defense mechanism to eradicate the spread of injurious agents in the affected mammalian tissues with a number of cellular mediators. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs worldwide in such situations. The mode of action of the non-steroid anti-inflammatory drugs (NSAIDs) is attributed primarily to the inhibition of prostaglandin (PG) synthesis, and more specifically, to the inhibition of the COX enzyme system. This work can be considered as an effort to gain a deeper insight into the physiochemical properties of a few well-known NSAIDs namely; ketoprofen, fenoprofen, flurbiprofen and ibuprofen. A quantum computational approach was used to predict geometry, molecular electrostatic potential (MESP), polarizability, hyperpolarizability and molecular docking study of all selected NSAIDs with human COX-1 and COX-2 enzymes were done to predict the most active drug among the four and to demonstrate good selectivity profile with COX enzymes.

Keywords: organic chemistry, theoretical chemistry, pharmaceutical chemistry, DFT, molecular docking, propionic acid derivatives

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are a class of drugs that reduce pain, decrease fever, prevent blood clots and, in higher doses decrease inflammations too. NSAIDs have been widely used to treat a number of diseases such as heart disease, various cancers, and Alzheimer's, pathogenic conditions. The term non-steroidal distinguishes these drugs from steroids, which having a similar eicosanoid-depressing, anti-inflammatory action and have a broad range of other effects [1]. NSAIDs obstruct the generation of prostaglandins (chemical messengers that regulate inflammation, fever, and the sensation of pain) by restraining the activity of a

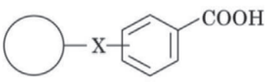

Figure 1.
Chemical structure of propionic acid derivatives.

compound, cyclooxygenase (COX); COX-1 and COX-2. Both the COX-1 and COX-2 enzymes serve important homeostatic roles in the human body. Depending on their chemical structures, NSAIDs are broadly divided into two major classes like non-selective COX inhibitors and selective COX-2 inhibitors. The classification based on the chemical structure is non-selective COX inhibitors and selective COX-2 inhibitors [2–5]. The non-selective COX inhibitors are salicylates, propionic acid derivatives, enolic acid (oxicam) derivatives, anthranilic acid derivatives, selective COX-2 inhibitors, sulfonanilide, and others. In which, COX-1 is considered as important for the production of prostaglandins of homeostatic maintenance, such as platelet aggregation, the regulation of blood flow in the kidney and stomach, and the regulation of gastric acid secretion. While COX-2 is considered as an inducible isoenzyme, although there is some constitutive expression in the kidney, brain, bone, female reproductive system, and gastrointestinal (GI) tract. Thus, the COX-2 is an enzyme plays an important role in pain and inflammatory processes [1–3, 6].

The profen drugs are a category of nonselective, non-steroidal anti-inflammatory drugs (NSAIDs), which reduce pain (analgesia), body temperature during fever (antipyretic), signs of inflammation (anti-inflammatory activity), and in mice, slow the development of cancers. They are one of the most commonly prescribed pain medications. The profen drugs are derivatives of 2-phenylpropanoic acid. In this work, we have preferred such propionic acid derivatives. 2-phenylpropanoic acid- profen drugs and their general chemical structure are depicted in **Figure 1**. Few drugs under this category are; ibuprofen, ketoprofen, naproxen, fenoprofen, flurbiprofen, and oxaprozin. In an effort to elucidate a more deeper insight on the physicochemical properties of 2-phenylpropanoic acid- profen drugs we present a detailed discussion on quantum computational calculations and predictions based on their structural geometry, frontier molecular orbitals non-linear optical properties (NLO), of all selected compounds, were done using B3LYP/6311G++(d,p) level of theory. In addition, the computationally calculated electronic properties such as Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), Bond Dissociation Enthalpy (BDE), ionization potential (IP), electron affinity (EA), hardness (η), softness (S), electronegativity (χ) and electrophilic index (ω) were also calculated to get an insight into its property by means of its anti-inflammatory activities. This study will offer knowledge of their action and also help us to design new drugs with therapeutic effects, experimental and thus computational studies are of interest for the rationale of the action mechanism of bioactive compounds. Further, in order to have a better understanding about the interaction with target proteins, molecular docking was also conducted by determining the probable binding modes of it by inserting all selected ligands into the active sites of the COX enzymes.

2. Materials and method

2.1 Materials

The input structures the drugs; ketoprofen (PubChem: 3825), ibuprofen (PubChem: 3672), fenoprofen (PubChem: 3342) and flurbiprofen (PubChem: 3394) were taken from the PubChem database [7] which are in SDF (Standard Data File)

format and were converted to GJF (Gaussian Job File) input files using the application Open Babel [8].

2.2 Computational details

All the quantum calculations have been performed by density functional theory using a Gaussian 09 software package [9]. The initial geometries chosen for calculation was taken from the PubChem database and optimized with B3LYP/6311G++(d,p) level of the theory [7]. The B3LYP is Becke's three-parameter practical hybrid methods that add the exchange and electronic correlation terms in DFT, including the Lee, Yang Parr (LYP) functional. The optimized geometry was compared to crystallographic data in the Cambridge Crystallographic Data Center, such a comparison between the experimental and theoretical values helps to reduce the error in the optimized geometry. The optimized geometry was used for the calculations of harmonic vibrational frequencies at the B3LYP/6311G++(d,p) method, it also helps to ensure the systems to be local minimum number imaginary vibration frequencies. The thermochemical properties [10–12] like, hardness (η), softness (S), chemical potential (μ), electronegativity (χ) and electrophilicity index (ω), were calculated using Koopmans' theorem for closed-shell compounds. Electrostatic potential analysis has also been made to identify the mapping surface of drugs. Dipole moments, linear and non-linear optical (NLO) properties of AMB were also calculated at the same level of theory.

Further, molecular docking was also conducted to predict binding poses, bio affinity and virtual screening of the selected drugs into the 3D crystal structure of cyclooxygenase-2 (PDB ID: 1CX2) and cyclooxygenase-1 (PDB ID: 1EQG) using GLIDE Dock Program in Schrödinger Maestro software. The protein structure was refined using the protein preparation wizard, which employs under restrained minimization and heavy atoms were restrained by using OPLS 2003 force field. The ligands were subjected to ligand preparation using the ligand preparation wizard (Lig prep) of Schrödinger software in the Maestro interface (11.5). Grid center is defined for the active site and box sizes are set to 20 Å [2, 13, 14].

3. Results and discussion

3.1 Molecular geometry

The optimized structures of (a) fenoprofen, (b) ketoprofen, (c) flurbiprofen and (d) ibuprofen were calculated using B3LYP/6311G++(d,p) level of the theory and shown in **Figure 2**. The optimized geometries were compared to crystallographic data in the Cambridge Crystallographic Data Center to correlation coefficient factor. The calculated Pearson correlation coefficient for ketoprofen, fenoprofen and Ibuprofen has given in **Table 1**; the crystallographic data for flurbiprofen is not available yet. The Pearson correlation coefficient (PCC), or Pearson's r, the Pearson product-moment correlation coefficient (PPMCC), or the bivariate correlation is a statistic that measures linear correlation between two variables X and Y. Here, this method is used to find out the linear regression between the experimental and computationally calculated geometric parameters. Normally, it has a value between +1 and −1, where +1 indicates total positive linear correlation, 0 is no linear correlation, and −1 is total negative linear correlation [15].

3.2 Thermo-chemical properties

The thermo-chemical parameters, such as enthalpy (H), entropy (S), Gibb's free energy (G) were calculated to find which drug is more stable by comparing G and S

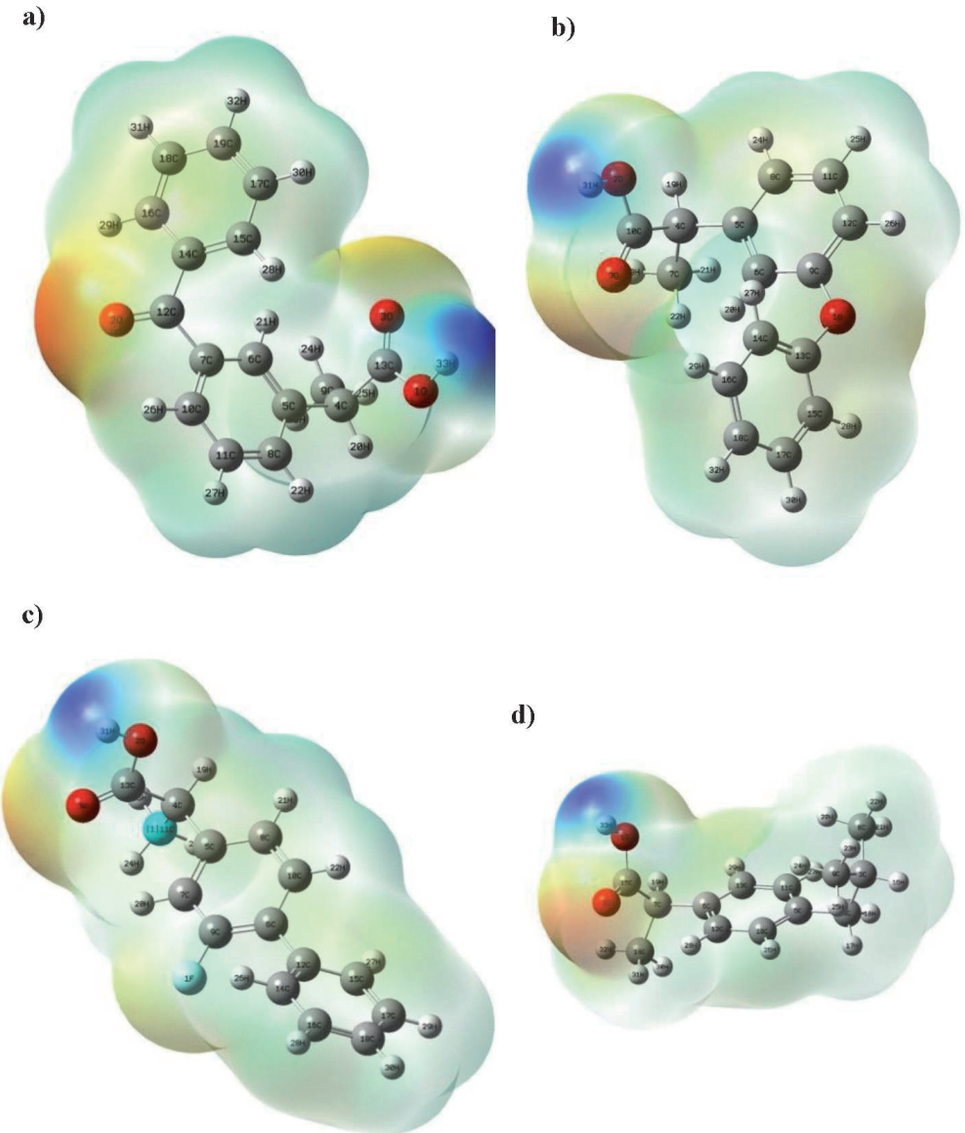

Figure 2.
The optimized molecular structures of the selected drugs, calculated at DFT/B3LYP/6311G++(d,p). (a) Ketoprofen. (b) Fenoprofen. (c) Flurbiprofen. (d) Ibuprofen.

Sample	Pearson correlation coefficient
Ketoprofen	0.951
Fenoprofen	0.976
Ibuprofen	0.899

Table 1.
The Pearson coefficient between the experimental and computationally calculated geometric parameters.

Sample	Energy $\times 10^5$ (kcal/mol)	Enthalpy $\times 10^5$ (kcal/mol)	Gibbs free energy $\times 10^5$ (kcal/mol)	Entropy (cal/mol)	Molecular mass (amu)
ketoprofen	−5.29	−5.29	−5.29	136.08	254.09
fenoprofen	−5.06	−5.06	−5.06	133.11	242.09
flurbiprofen	−5.21	−5.21	−5.21	129.43	244.08
ibuprofen	−4.12	−4.12	−4.12	128.56	206.13

Table 2.
Thermo-chemical properties of the selected drugs were calculated using the DFT/B3LYP/6311G++(d,p) level of theory.

SAMPLE	HOMO (eV)	LUMO (eV)	HOMO-1 (eV)	LUMO+1 (eV)	HOMO-2 (eV)	LUMO+2 (eV)	BAND GAP (eV)
Ketoprofen	−6.96	−2.10	−7.25	−1.02	−7.29	−0.88	4.86
Fenoprofen	−6.26	−0.91	−7.01	−0.65	−7.10	−0.48	5.36
Flurbiprofen	−6.54	−1.35	−7.15	−0.71	−7.21	−0.53	5.19
Ibuprofen	−6.68	−0.77	−7.05	−0.50	−7.92	−0.34	5.90

Table 3.
Frontier molecular orbital of the selected NSAIDs was calculated using the DFT/B3LYP/6311G++(d,p) level of theory.

values and the obtained values are given in **Table 2**. In general, more negative the value of G the drug is more stable and more active if the value of S is more positive. From the analysis, it is found that ketoprofen has more negative value for G (-5.29×10^5 kcal/mol) and flurbiprofen has more or less same G value (-5.21×10^5 kcal/mol). Hence, ketoprofen is a more stable and active drug compared to other selected drugs with enhanced entropy value of 136.08 cal/mol.

3.3 Frontier molecular orbital analysis

In computational chemistry, the frontier molecular orbitals play an important role in demonstrating active sites, kinetic stability and chemical reactivity of the molecule (**Table 3**). In the present work, frontier molecular orbital energies (E_{HOMO} and E_{LUMO}) of all selected drugs were calculated using DFT/B3LYP/6311G++(d,p) level of theory. The LUMO indicates the most likely site which would undergo a nucleophilic attack while the HOMO describes the most likely site for an electrophilic attack. The energy corresponding to HOMO represents the ionization potential of the molecule, while that of the LUMO represents the corresponding electron affinity. A high HOMO–LUMO energy gap indicates greater stability and low reactivity of the chemical system. On the basis of frontier molecular orbital analysis, ketoprofen is found to be more reactive with lower stability compared to other drug molecules in the family.

To understand the three-dimensional charge distributions over the drug molecules, to locate the most electronegative and electropositive site on their skeleton and to predict reactive sites for electrophilic and nucleophilic attack for the NSAIDs molecular electrostatic potential (MESP) mapping can sightsee.

The MESP map of ketoprofen shows that the negative potential sites are on electronegative atoms like oxygen atoms as well as the positive potential sites are around the hydrogen atoms. These sites give information about the region from where the compound can have noncovalent interactions (**Figure 3**).

3.4 Global descriptive parameters

In order to have a deep insight about the reactive nature of selected NSAIDs, the global descriptive parameters like hardness, softness, chemical potential, electronegativity, and electrophilicity index were calculated using Koopmans' theorem for closed-shell compounds, as follows [11, 16]:

$$\text{Ionization potential (IP)} \approx -E_{HOMO} \quad (1)$$

$$\text{Electron affinity (EA)} \approx -E_{LUMO} \quad (2)$$

where E_{HOMO} is the energy of HOMO and E_{LUMO} is the energy of LUMO.

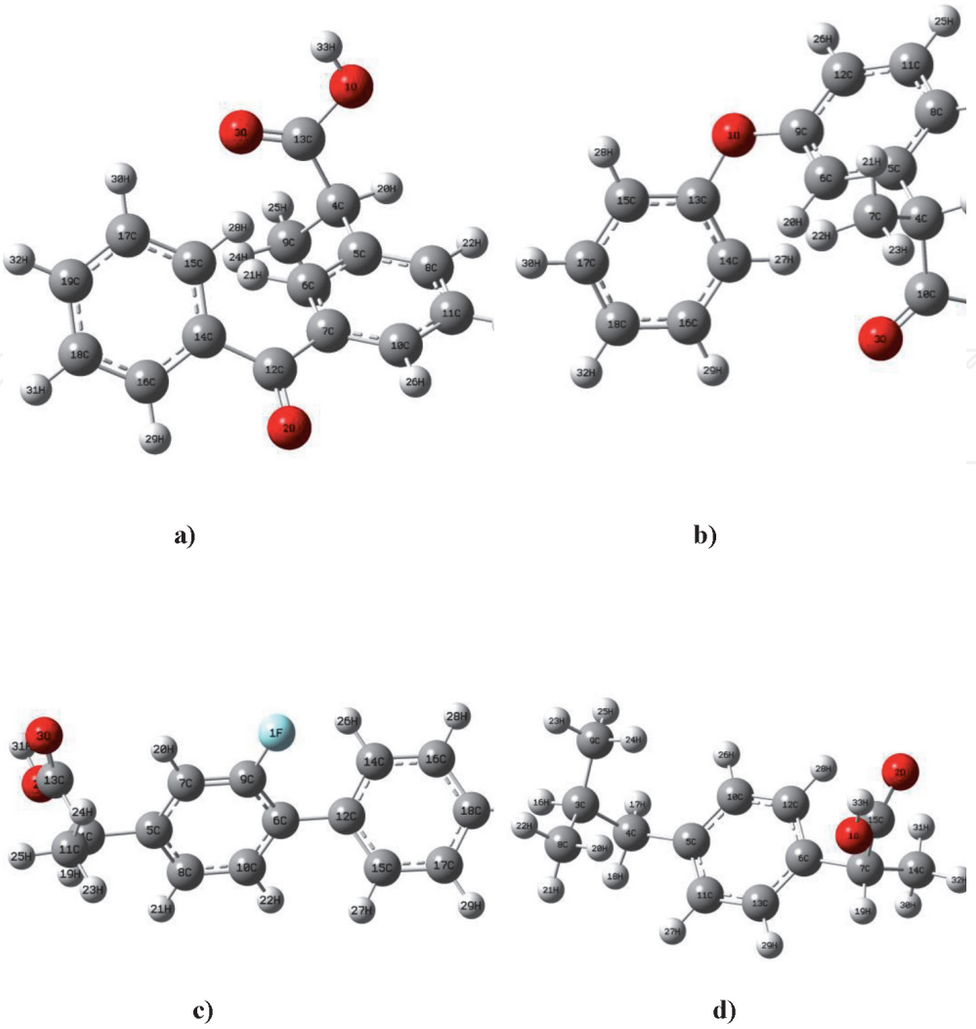

Figure 3.
The MESP structures of (a) ketoprofen, (b) fenoprofen, (c) flurbiprofen and (d) ibuprofen. The negative (red) regions of MESP were related to electrophilic reactivity and the positive (blue) regions to nucleophilic reactivity.

$$\text{Hardness } (\eta) \approx \frac{IP - EA}{2} \tag{3}$$

$$\text{Electronegativity } (\chi) \approx \frac{IP + EA}{2} \tag{4}$$

$$\text{Softness } (S) \approx \frac{1}{2\eta} \tag{5}$$

$$\text{Chemical potential } (\mu) \approx -\chi \tag{6}$$

$$\text{Electrophilicity index } (\omega) \approx \frac{\mu^2}{2\eta} \tag{7}$$

The calculated global descriptors of AMB are given in **Table 4.**

According to the maximum hardness principle (MHP), at constant external potential, the stability of a molecule increases with hardness, and with the increase in stability, the reactivity decreases. Softness is just the reciprocal of hardness, so higher the softness, lower is the stability, *i.e.*, higher is the reactivity. The hardness value of ketoprofen is 2.43; fenoprofen is 2.68, flurbiprofen is 2.60, and ibuprofen is 2.96. This study shows that ketoprofen has a lower hardness and a higher softness value which indicates that this drug is highly reactive compared to other drugs.

Sample	Ionization potential (Ip)	Electron affinity (Ea)	Hardness (η)	Electronegativity (χ)	Softness (S)	Chemical potential (μ)	Electrophilicity index (ω)
Ketoprofen	6.96	2.100	2.43	4.53	4.86	−4.53	4.86
Fenoprofen	6.26	0.90	2.68	3.58	5.36	−3.58	5.36
Flurbiprofen	6.54	1.35	2.60	3.95	5.19	−3.95	5.19
Ibuprofen	6.68	0.77	2.96	3.73	5.91	−3.73	5.91

Table 4.
Calculated global descriptors of the selected NSAIDs were calculated using the DFT/B3LYP/6311G++(d,p) level of theory.

Ionization energy is a fundamental descriptor of the chemical reactivity of atoms and molecules. High ionization energy indicates high stability and chemical inertness, and small ionization energy indicates high reactivity of the atoms and molecules. If the electronic chemical potential is greater, then the compound is less stable or more reactive. Electron affinity refers to the capability of a ligand to accept precisely one electron from a donor. The electrophilicity index is described as a structural depictor for the analysis of the chemical reactivity of molecules. It measures the tendency of the species to accept electrons. A good, more reactive, nucleophile has a lower value of ω, in the opposite, a good electrophile has a high value of ω. Hence comparing the local descriptors of all selected drug we can infer that ketoprofen is more reactive with the lowest electrophilicity index and highest softness index and smallest hardness value. At the same time, the negative chemical potential of ketoprofen determines the stability of the drugs.

3.5 Hyperpolarizabilities, polarisabilities and dipole moment

The computational approach can also be used to study the interaction of electromagnetic fields in various media to produce new fields that are altered in frequency, phase and amplitude or other propagation characteristics from the incident fields. The polarization P, induced in a medium by an external electric field F is given by

$$P = P_0 + \chi^{(1)} F + \chi^{(2)} F^2 + \chi^{(3)} F^3 + \ldots \quad (8)$$

where $\chi^{(n)}$ is the n^{th} order susceptibility tensor of the bulk medium.
The dipole moment of a molecule interacting with an electric field can be written

$$\mu_i = \mu_i^0 + \alpha_{ij} F_j + (1/2)\beta_{ijk} F_j F_k + (1/6)\Upsilon_{ijkl} F_j F_k F_l + \quad (9)$$

where μ_i^0 is the permanent dipole moment and α_{ij}, β_{ijk}, Υ_{ijkl} is tensor elements of the linear polarizability and first and second hyperpolarizabilities respectively. This interaction may even lead to nonlinear optical effects (NLO). In this direction in order to study the NLO properties, the dipole moment, first static hyperpolarizability (βtot) and its related properties including α, β and Δα of all selected NSAIDs were calculated using DFT/B3LYP/6311G++(d,p) method based on the finite-field approach and are given in **Table 4**. The second-order term of the hyperpolarizability gives rise to sum and difference frequency mixing (including second harmonic generation) and optical rectification. The third-order term is responsible for the third-harmonic generation and two-photon resonances. The polarizability and hyperpolarizability of NLO can be written as tensors. While the linear polarizability tensor α as shown below which is a 3*3 matrix having nine components as shown below.

$$\alpha = \begin{bmatrix} \alpha_{xx} & \alpha_{xy} & \alpha_{xz} \\ \alpha_{yx} & \alpha_{yy} & \alpha_{yz} \\ \alpha_{zx} & \alpha_{zy} & \alpha_{zx} \end{bmatrix} \quad (10)$$

$$\alpha_{total} = \frac{(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})}{3} \quad (11)$$

For the first hyperpolarizability, the quantity of interest β is a 3*3*3 matrix has β_{xzz}, β_{xxx}, β_{xyy}, β_{yyy}, β_{yzz}, β_{yxx}, β_{zzz}, β_{zxx} β_{zyy}, β_{xyz}, respectively, from which the x, y and z components of β are calculated as [12, 17–27]:

$$\beta_{total} = \sqrt{\left(\beta_{xxx} + \beta_{xyy} + \beta_{xzz}\right)^2 + \left(\beta_{yyy} + \beta_{yzz} + \beta_{yxx}\right)^2 + \left(\beta_{zzz} + \beta_{zxx} + \beta_{zyy}\right)^2} \quad (12)$$

The highest value of dipole moment is observed for ketoprofen, which is equal to 3.2078 Debye. The calculated average polarizability and first-order hyperpolarizability of the drug molecules are given in **Table 5**. All the samples exhibit better values compared to one of the prototypical molecules, Urea (μ and β of urea is 4.56 D and 4.8×10^{-36} esu respectively) [25]. Though all the molecules are NLO active molecule, ketoprofen has the highest among others with hyperpolarizability value of 9.2128×10^{-31} esu.

3.6 Molecular docking

Molecular docking is one of the most frequently used methods in structure-based drug design due to its ability to predict the binding conformation of small molecules to the appropriate target binding site.

3.6.1 Molecular docking studies with COX-2

1CX2 is an enzyme involved in arachidonic acid metabolism, where arachidonic acid is the precursor that is metabolized by various enzymes, especially cyclooxygenase-1 and -2 to a wide range of biologically and clinically important eicosanoids and metabolites of these eicosanoids. Two important pathways for arachidonic acid metabolism are the cyclooxygenase (COX) and 5-lipoxygenase (5-LO) pathways. The COX pathway forms intermediate compounds called cyclo-endoperoxides (PGG2 and PGH2). Enzymes, many of which are tissue specific, then convert the cyclo-endoperoxides into the final biologically active prostanoid. 1CX2 is a tetramer having four identical subunits and its chains C and D contain the inbuilt ligand SC-558 and the structure of the COX-2 enzyme is depicted in **Figure 4**. The amino acid residues in the active site of 1CX2 are TYR355, GLY354, SER353, LEU352, VAL349, TYR348, MET522, VAL523, GLY526, ALA527, SER530, LEU531, LEU359, ARG120, VAL116, HIS90, ARG513, ALA516, ILE517, PHE518, TRP387, TYR385, LEU384 and PHE381.

Figure 5(b) demonstrates the 3-dimensional protein-ligand interaction SC-558 into the active site of 1CX2. The co-crystallized ligand SC-558 is found to be buried deep into the binding pocket of 1CX2. SC-558 interacts with the active site's amino acids of the protein by H-bonding with active site amino acids ARG513, SER353 and LEU352, which is well evidently observed from 2-D interaction picture as shown in **Figure 5(c)**. SC-558 interacts with COX-2 with a binding energy of −11.987 kcal/mol.

After analyzing the protein-ligand interaction of 1CX2 with its co-crystallized ligand SC558, all the selected ligands ketoprofen, fenoprofen, flurbiprofen and ibuprofen were docked to the active site of 1CX2 and it is found that all the selected

Samples	Dipole moment (μ) Debye	Polarizability (esu)	Hyperpolarizability (esu)
Ketoprofen	3.20	-1.59×10^{-23}	9.21×10^{-31}
Ibuprofen	1.70	-1.35×10^{-23}	4.55×10^{-31}
Fenoprofen	1.16	-1.50×10^{-23}	5.17×10^{-31}
Flurbiprofen	2.68	-1.50×10^{-23}	3.95×10^{-31}

Table 5.
The calculated dipole moment μ (Debye), the polarizability β_{tot} and first hyperpolarizability β_{tot} of all selected NSAIDs.

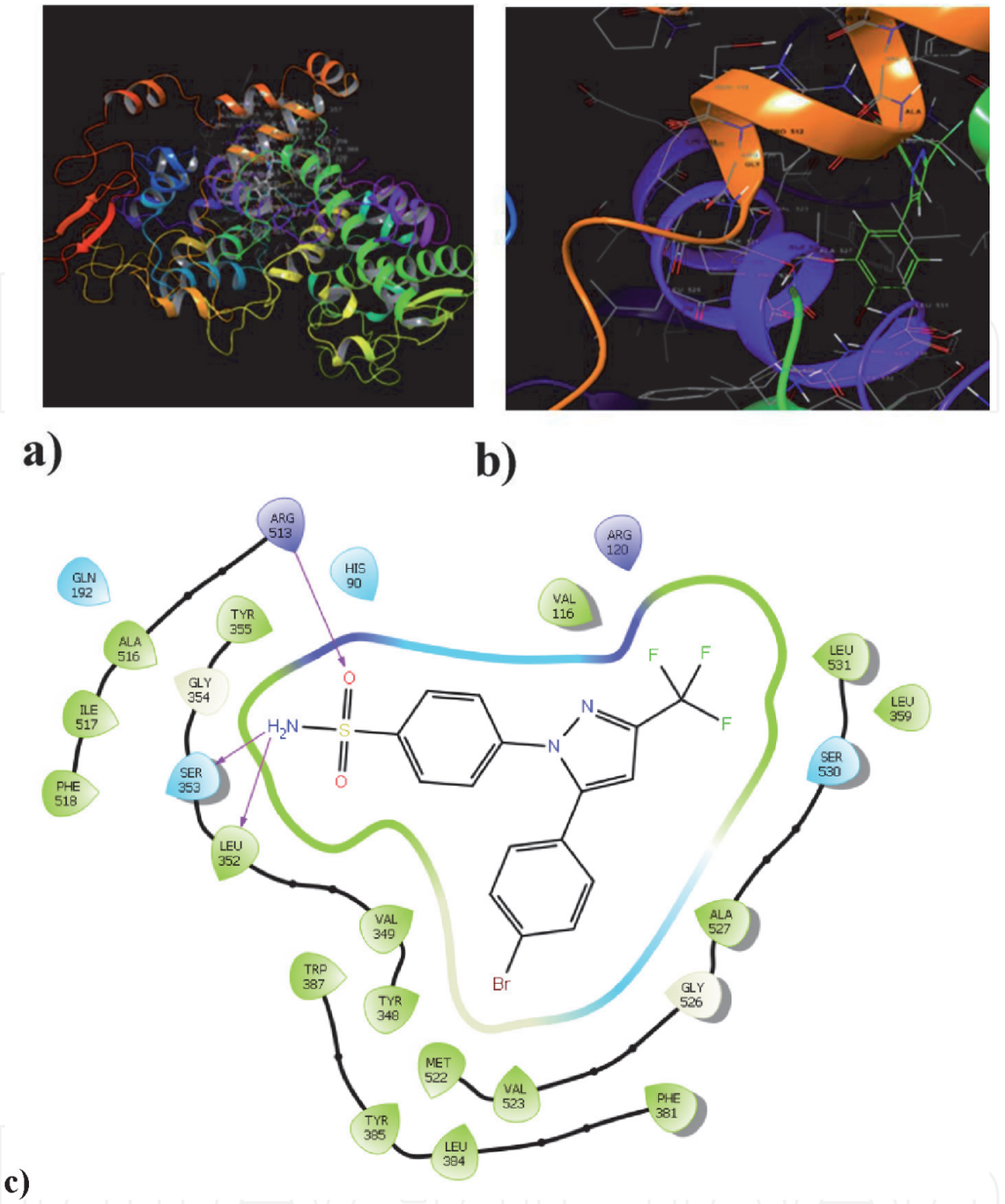

Figure 4.
(a) Structure of the COX-2 enzyme having inbuilt ligand SC-558. (b) Protein-ligand interaction of SC-558 with 1CX2. (c) 2-D protein-ligand interaction of SC-558 with 1CX2.

NSAIDs docked well deep into the binding pocket of 1CX2 with good gliding score, given in **Table 5**. **Figure 5** shows the 3-D protein-ligand interaction of all selected NSAIDs into the active site of COX-2.

Ketoprofen and fenoprofen were docked deeply into the active site region making interactions with the residues ARG120, TYR355, TYR385 and TRP387 while, flurbiprofen docked deeply into the active site region making interactions with the residues ARG120 and TYR355 and ibuprofen with residue TYR355 only (**Figure 6**).

3.6.2 Molecular docking studies with COX-1

COX-1 is an enzyme that acts on arachidonic acid and produces housekeeping prostaglandins. It is a dimer having two identical structural units in which Chain B

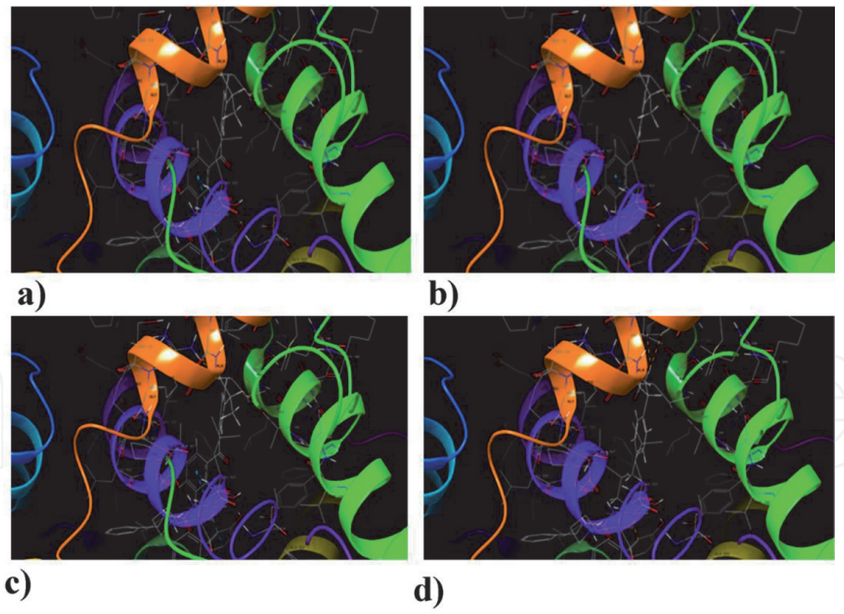

Figure 5.
3-D protein-ligand interactions of the ligands (a) ketoprofen, (b) fenoprofen, (c) flurbiprofen and (d) ibuprofen into the active site of COX-2.

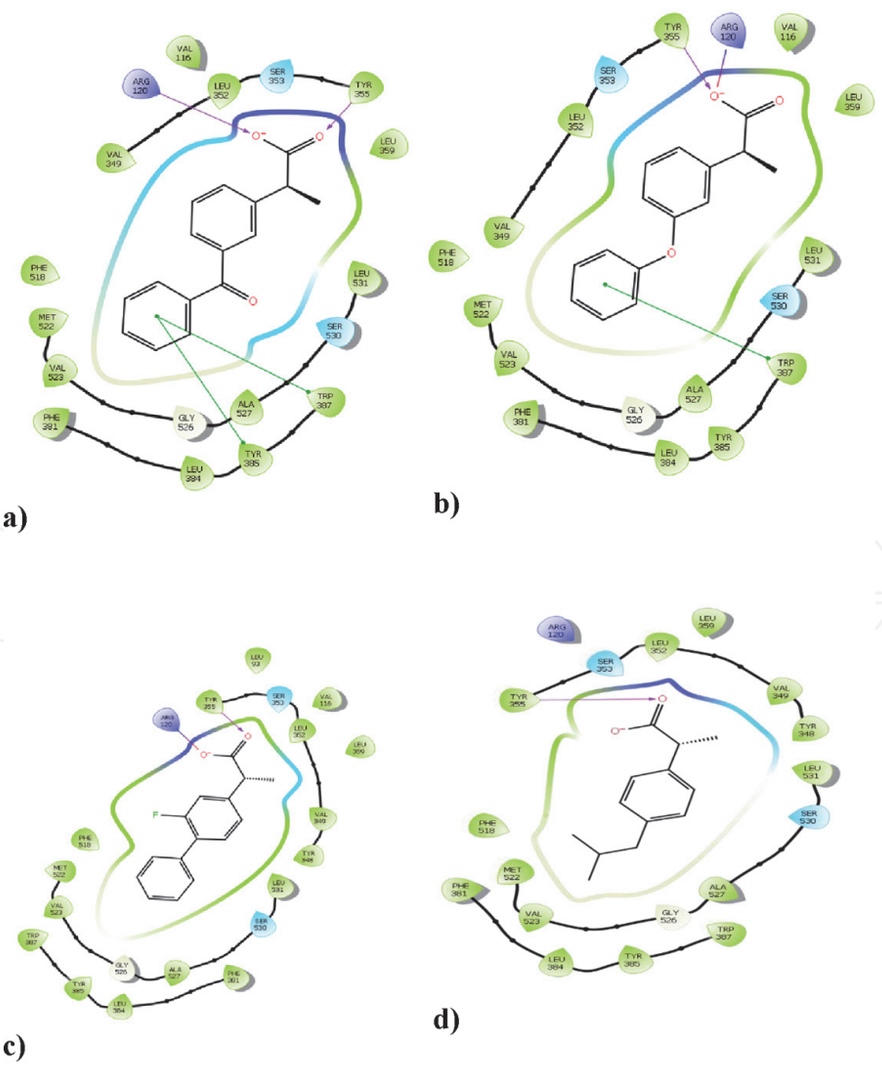

Figure 6.
2-D protein-ligand interactions of the ligands: (a) ketoprofen, (b) fenoprofen, (c) flurbiprofen and (d) ibuprofen into the active site of COX-2.

and some nonstandard residues were deleted after the preprocessing and the structure of the protein are shown in **Figure 7**. The amino acid residues in the active site of 1EQG are TYR355, SER353, LEU352, VAL349, MET522, ILE523, ALA527, SER530, LEU531, LEU359, ARG120, VAL116, PHE518, GLY526, MET522, PHE518, TRP387, TYR385, LEU384 and PHE381.

All the selected ligands ketoprofen, fenoprofen, flurbiprofen, and ibuprofen were docked to the active site of COX-1 and it is found that all the selected NSAIDs docked well deep into the binding pocket of COX-1 with good gliding score, given in **Table 6** and binding energy were tabulated in **Table 7**. **Figure 8** shows the 3-D protein-ligand interaction of all selected NSAIDs into the active site of COX-1.

Ketoprofen and fenoprofen were docked deeply into the active site region making interactions with the residues TYR385, TRP387, ARG120 and TYR355 by forming two hydrogen bonds with ARG120 and TYR355, two pi-pi stacking

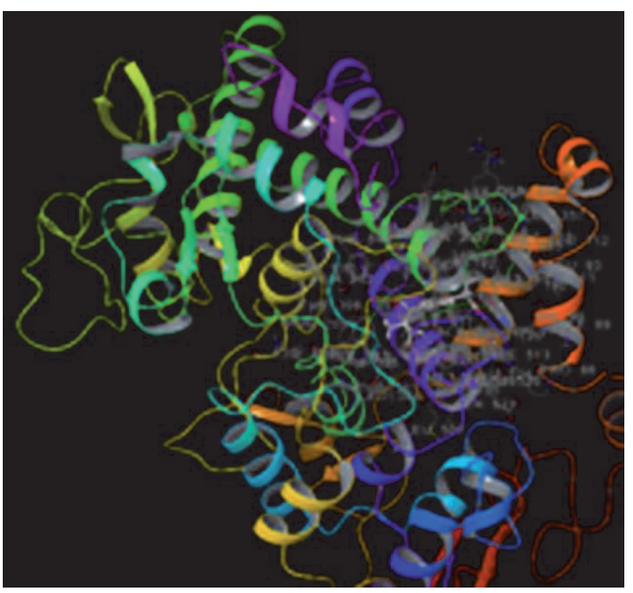

Figure 7.
Structure of COX-1.

Sample	Gliding score with COX-2	Gliding score with COX-1
Ketoprofen	−9.279	−11.242
Fenoprofen	−11.37	−10.862
Flurbiprofen	−9.377	−11.602
Ibuprofen	−7.468	−10.075

Table 6.
The gliding score of all samples with COX-1 and COX-2 enzymes.

Sample	Binding energy with COX-2 kcal/mol	Binding energy with COX-1 kcal/mol
Ketoprofen	−9.280	−11.242
Fenoprofen	−8.694	−10.863
Flurbiprofen	−9.377	−11.603
Ibuprofen	−10.133	−10.075

Table 7.
The binding energy of all samples with COX-1 and COX-2 enzymes.

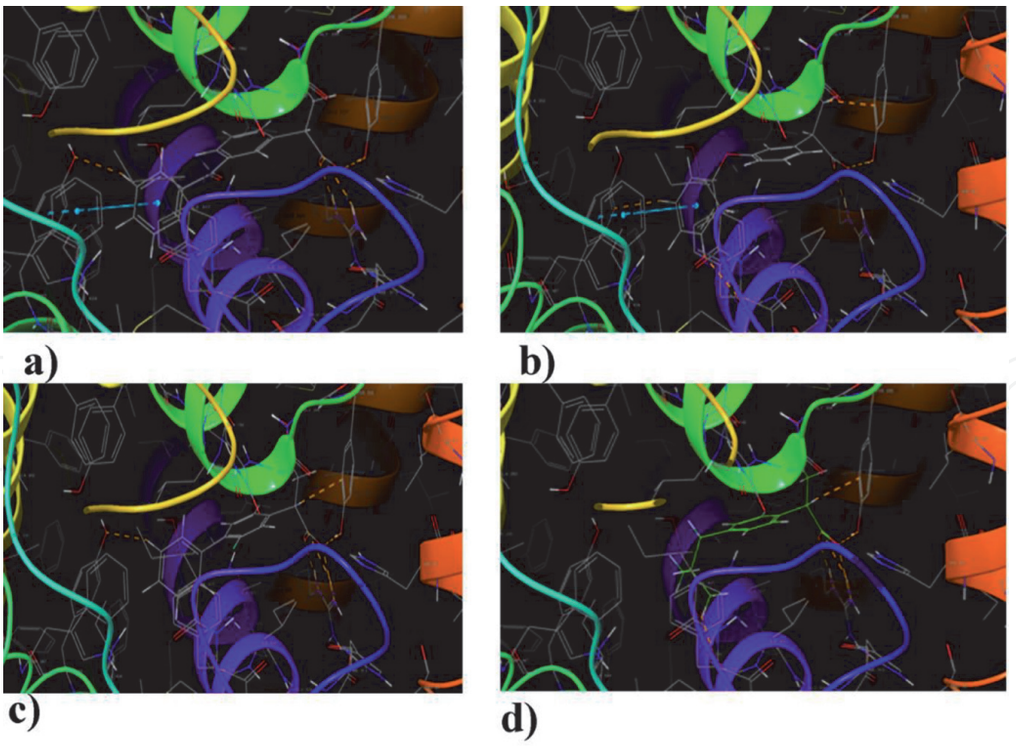

Figure 8.
3-D protein-ligand interactions of the ligands (a) ketoprofen, (b) fenoprofen, (c) flurbiprofen, (d) ibuprofen into the active site of COX-1.

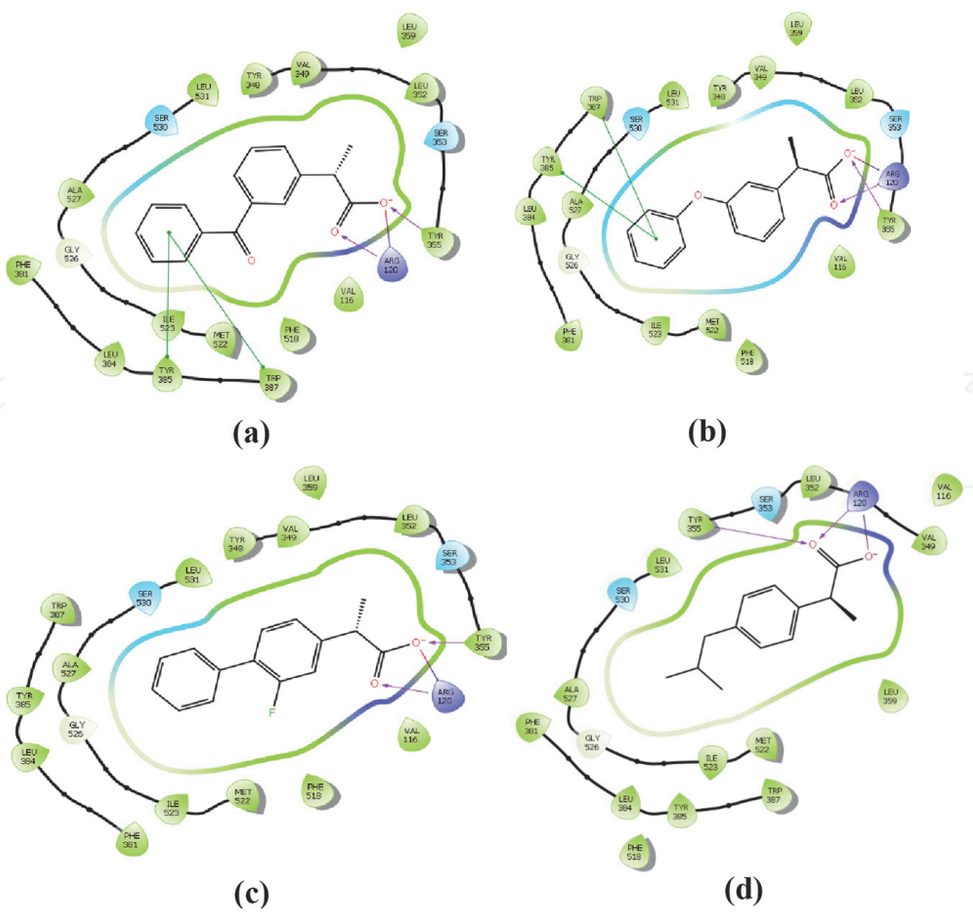

Figure 9.
2-D protein-ligand interactions of the ligands (a) ketoprofen, (b) fenoprofen, (c) flurbiprofen and (d) ibuprofen into the active site of COX-1.

interaction between phenyl ring of the ligand with amino acids TYR385 and TRP387 and one salt bridge with active site amino acids. Though the interactions are the same for ketoprofen and fenoprofen the binding energy is different, ketoprofen has a binding energy of −11.242 kcal/mol while that of fenoprofen is −10.863 kcal/mol. At the same time, flurbiprofen and ibuprofen docked deeply into the active site region making interactions with the residues ARG120 and TYR355 and ibuprofen with residue TYR355 only (**Figure 9**).

4. Conclusion

The complete Quantum computational investigations were done using DFT theoretical calculation at the DFT/B3LYP/6311G++(d,p) method that has been performed for all selected propionic acid derivatives, NSAIDs. Almost all bond lengths and angles all the profen drugs agree very well with the X-ray crystal structures in Cambridge Crystallographic Data Center suggesting that all the molecules are well described with DFT/B3LYP/6311G++(d,p) level of theory. The electrophilic and nucleophilic sites were traced out from the isosurfaces of molecular electrostatic potential. The detailed confab on the calculated global descriptors revealed that ketoprofen is more reactive than other propionic derivatives and has the ability to donate electrons easily. Though the hyperpolarizability values reveal that the all selected organic molecule has better NLO activity compared to urea, ketoprofen shows better activity than others. Further, the molecular docking studies of these compounds demonstrates a good selectivity profile with both COX enzymes with good gliding scores and confirmed ketoprofen is a strong anti-inflammatory agent compared to others.

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Conflict of interest

The authors declare no conflict of interest.

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