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In Silico Molecular Modelling and Dynamic Simulations, ADME Parameters Predictions of new Naproxen Analogues Containing 1,3,4-Oxadiazole as Anti-inflammatory Agents

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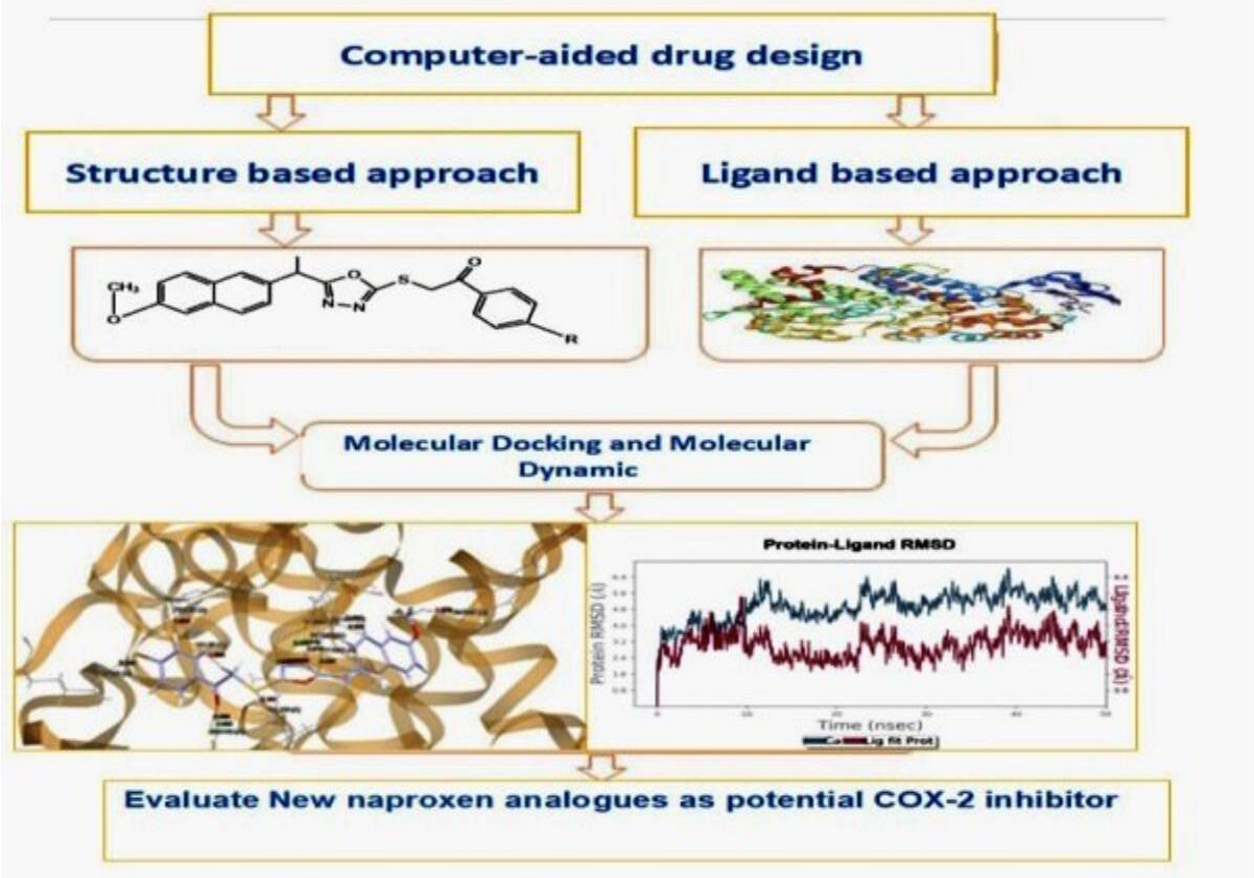
Graphical abstract:



Abstract: The serious challenges associated with the non-steroidal anti-inflammatory drugs (NSAIDs), especially their unfavorable impacts on the gastrointestinal tract (GIT)and kidneys arise from restraining cyclooxygenase (COX) enzymes. To address this issue and manage the side effects, several investigations were employed by modifying and adjusting the free carboxyl group of NSAIDs to upgrade their safety profile, while, keeping up their anti-inflammatory adequacy. An approach of suggesting new analogues of NSAIDS focusing on COX-2 enzyme devoid of side effects on stomach or kidneys is highly recommended. In this respect, the design of new analogues of naproxen is investigated by insertion of the carboxylic group into a 1,3,4-oxadiazole ring structure. This chemical modification points to hold anti-inflammatory impacts,

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whereas decreasing the hazard of stomach irritation and ulceration. These analogues were evaluated by means of computational methods, such as molecular docking, virtual screening, ADME (absorption, distribution, metabolism, and excretion) and molecular dynamics. The proposed compounds exhibited encouraging binding affinities to the COX-2 receptor, as demonstrated by molecular docking and molecular dynamic simulations. This may suggest that these compounds have the potential to be effective anti-inflammatory agents. Moreover, in silico ADME appraisals showed favorable pharmacokinetic profiles for the compounds that may suggest safer choices to known NSAIDs. Virtual evaluations of the new naproxen analogues have indicated their anti-inflammatory activity. These evaluations and the promising binding affinities and favorable pharmacokinetic profiles bolster the basis for advance preclinical and clinical ponders to approve the high potential of these compounds. Molecular dynamics simulations provide experiences into the energetic stability of the protein-ligand complex, with RMSD and RMSF investigations demonstrate steady interactions during time. This chemical modification offers a promising approach for the development of safer anti-inflammatory analogues of naproxen.

Keywords: Naproxen, 1,3,4-Oxadiazole, Anti-inflammatory agents, ADME, Molecular dynamic.

Highlight

- *New naproxen analogues with a 1,3,4-oxadiazole ring replacing the free carboxyl group were proposed.*
- *Computational studies revealed significant binding affinities to COX-2 and stable molecular dynamics.*
- *These analogues show potential as promising anti-inflammatory agents with improved safety profiles.*
- *In silico ADME analysis suggested favorable pharmacokinetic properties for the new compounds.*
- *The findings support further investigation in preclinical and clinical studies to confirm their efficacy.*

1. Introduction

The challenges associated with NSAIDs, especially concerning to their antagonistic impacts on the G.I.T., such as irritation and ulceration and kidney issues, which are caused by hindering the activities of COX enzymes. COX plays a pivotal role in ensuring the stomach lining [1]. To manage and overcome these issues of NSAIDs and to improve their safety profile, a strategy focusing on COX-2, which is less prone to gastrointestinal distress than COX-1, but is still cautious. Particularly, COX-2 inhibitors were synthesized to reduce GIT side effects, but they were found to posture potential danger to cardiovascular system [2]. Consequently, there is certain requirements for novel compounds with anti-inflammatory and pain-relieving properties that are safer on GIT. New derivatives of naproxen were synthesized by converting the carboxyl group into a 1,3,4-oxadiazole ring structure showed the anti-inflammatory impacts, whereas diminishing the chances of stomach irritation and ulceration [3]. Compounds with the 1,3,4-oxadiazole ring have shown details of noteworthy anti-inflammatory impacts in already published works [4]. The particular properties of the 1,3,4-oxadiazole pharmacophore ring have implicated into a wide range of pharmaceutical applications [5]. Previous reports have showed that compounds consolidating this ring display different activities, such as, antibacterial, antifungal, anti-tubercular, antiviral, anticancer, and anti-diabetic properties [6,7]. Besides, those compounds maintain pain relieving and anti-inflammatory properties by acting as cyclooxygenase inhibitors. Incorporation of the carboxyl group within the 1,3,4-oxadiazole ring initiated for the NSAID molecule has shown to maintain or upgrade anti-inflammatory action, while, reducing the chances of irritation and ulcer development. The chemical modification of the carboxyl group has proved to adjust the safety and acceptability and properties of NSAIDs [8]. Similar analogues of naproxen containing 1,3,4-oxadiazole have showed interesting anti-inflammatory and analgesic activities [9]. Compounds containing bulky aromatic ring structures containing 1,3,4-oxadiazole recorded promising anti-inflammatory activities [10,11]. Computational approaches are essential instruments in contemporary drug discovery and development, providing efficiency

and accuracy in the analysis of drug-target interactions. Molecular docking and molecular dynamics simulations facilitate the visualization and prediction of binding affinities and the dynamic stability of protein-ligand complexes. These strategies are essential for enhancing therapeutic efficacy, selectivity, and stability, providing a comprehensive understanding of molecular interactions that would be difficult to attain through experimental approaches alone [24]. Moreover, in silico ADME (absorption, distribution, metabolism, and excretion) predictions offer critical insights into pharmacokinetic characteristics, enabling researchers to pick drugs with advantageous profiles early in the development phase. This method substantially decreases the expenses and duration linked to experimental ADME research while mitigating late-stage failures [25]. The amalgamation of traditional methodologies with new technologies like artificial intelligence has significantly improved the capacity to find, optimize, and devise innovative treatment possibilities. Utilizing these computational methods enables drug development to attain a balance between economic efficiency and scientific rigor, hence expediting the discovery of safer and more effective therapeutic medicines [25].

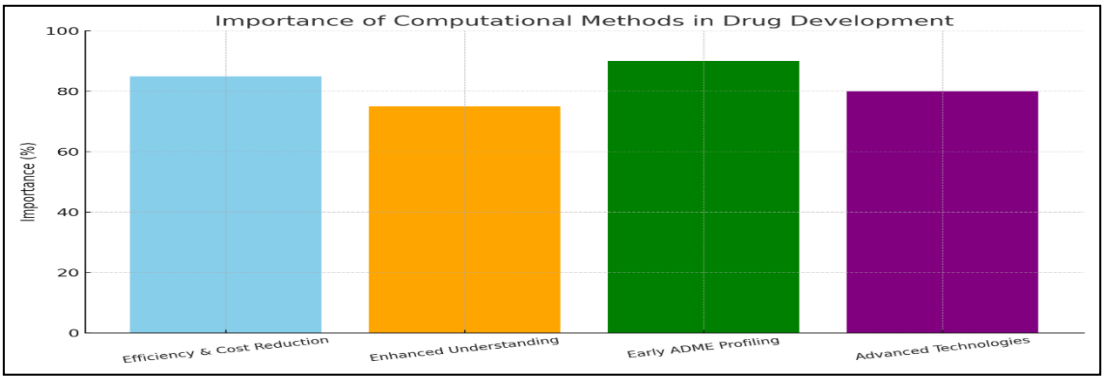
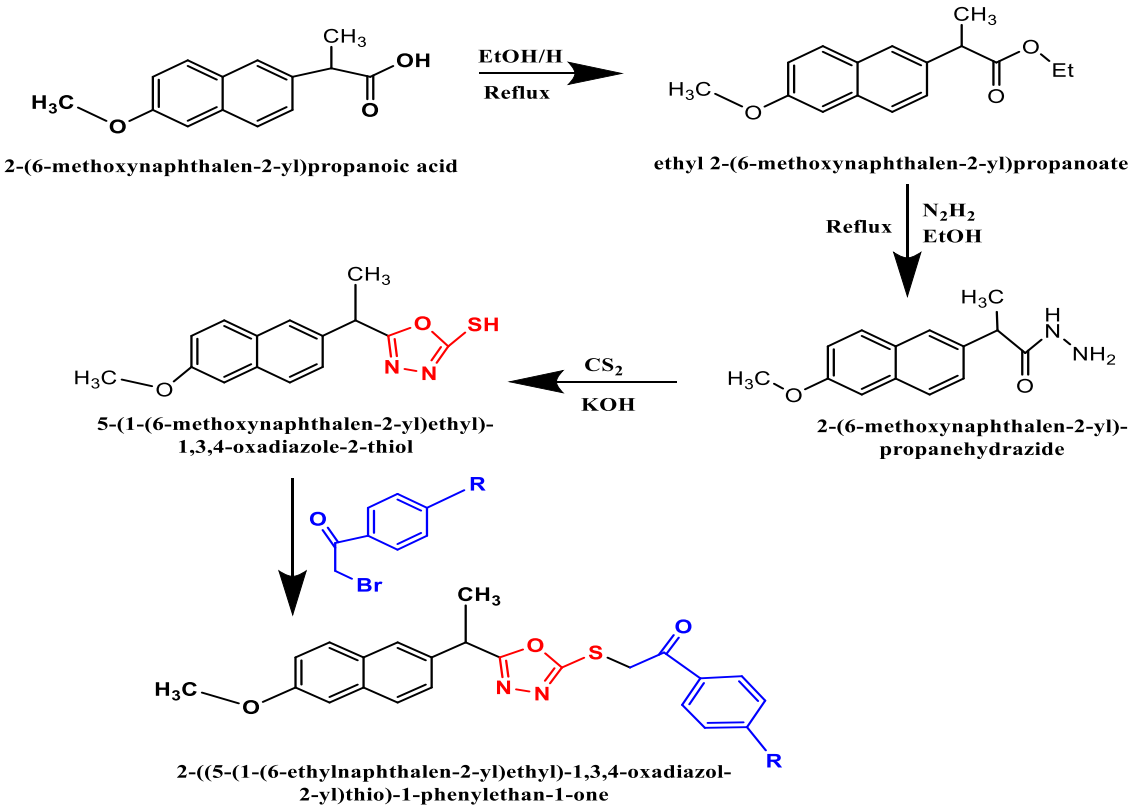
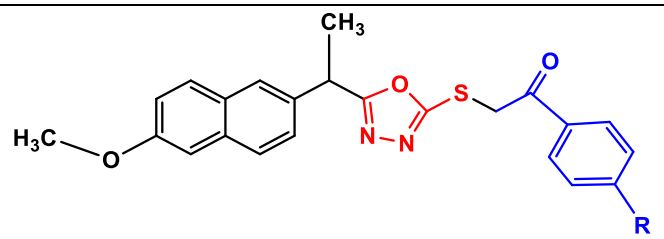


Figure 1. Graphical Representation of the Key Benefits of Computational Methods in Drug Development [26].



Scheme 1. The proposed chemical synthesis of the target naproxen analogues.

Table 1. The binding energies and interaction of naproxen analogues containing 1,3,4-oxadiazole and naproxen with amino acids of 3NT1.



Compound	Interaction of the designed compounds with amino acids of COX2 type 3NT1		
	Hydrogen Bonding	**Short Contact**	**PLP fitness**
N1/R = Br	ARG120, TYR355, SER119	ARG120, TYR115	**90.79**
N2/R = $N(CH_3)_2$	ARG120, TYR355	ARG120	**90.23**
N3/R = Cl	ARG120, TYR355, SER530	TYR355	**88.17**
N4/R = H	ARG120, TYR355, SER119	ARG120, LYS83	**87.26**
N5/R = CH_3	ARG120, TYR355, SER119, TYR115	TYR355	**86.69**
N6/R = NH_2	ARG120, TYR355, MET522	TYR355	**85.18**
Naproxen	ARG120, TYR355	ARG120	**74**

2. Computational Method

2.1 Protein Preparation and Grid Generation

A comprehensive methodology for evaluation of the designed novel drugs that envelops the optimum effects between potential activities and the complete cluster of biomolecules inside the cells that may demonstrate more viability. Crystal structure of the target protein was retrieved from protein data bank (PDB code: 3NT1) [12]. The application was processed using protein preparation wizard in Schrodinger, New York, 2021, started by excluding the water molecules and addition of hydrogen in protein residues. The hydrogen bonds were optimized by OLPS-2005 (Optimized Potentials for Liquid Simulations) force field [13]. All proteins conserve NAD^+ in the core as co-factor and co-crystalized with a ligand. The receptor grid prepared using the co-crystalized ligand as center for the boundary box when the prepared ligands docked on the binding site of the protein. The dimension of boundary box used was 12 ºA.

2.2 Ligand Preparation

The target compounds were supposed to be synthesized based on four steps chemical reactions starting from naproxen, as depicted in scheme 1. The chemical structures of the newly designed ligands were drawn in ChemAxon's computer program and their Smiles notations were used as input files into the prepared ligand module. The structures were optimized for the lowest energy after the force fields applied to the ligands using ligand preparation [14].

2.3 Computer system and software

The program contained the fully licensed versions of the Swiss ADMET online program, ChemDraw expert software program V.21.0, GOLD software version suite V. 2022.3.0, and Schrodinger software V.22.0.

2.4 Drug-Likeness Profile

The assessment of pharmacokinetic and ADME properties of the investigated compounds were conducted using the SwissADME online program (www.swissadme.ch) [15]. The boiled egg server was used to predict the lipophilicity and extremities of these molecules.

2.5 Ligand-active site preparation and molecular docking

The investigated compounds undergo vitality minimization using Chem3D adaptation 16.0 with the MM2 constrain field. The active site of COX2 was retrieved from the Protein Data Bank (PDB: 3NT1) complexes with naproxen [16]. The active site was arranged by including OH group of carboxyl group of naproxen to guarantee precise ionization and tautomeric positions of amino groups corrosive buildups. Water of crystallization were not included within the dynamic location and were expelled, and the ligands from the receptors' dynamic locales were extracted. The ligands were docked on the 3D structure of the arranged target protein type 3NT1. A similar finding was stated with naproxen and COX2, using the same receptor set up for the docking by Hermes visualizer program inside the CCDC of GOLD suite [17]. The initial extraction of the ligand was conducted from the active site of the receptor. The receptor was then prepared for the docking process using the Hermes visualization software within the CCDC GOLD suite. The active site was identified as the main interaction site for the ligand, and a 10 Å binding site was defined to include all crucial protein residues needed for docking. The docking process utilized default parameters and generated 10 poses, with the highest-ranked pose selected as the

standard, and the early termination option disabled. The study employed the ChemScore kinase scoring function, which is based on the ChemPLP algorithm using a continuous linear potential. The docking outcomes were saved as mol2 files, containing details of the binding energy, precise binding locations, and poses. These results were thoroughly analyzed to determine the optimal binding interactions between the ligand and the receptor's amino acid residues (3NT1).

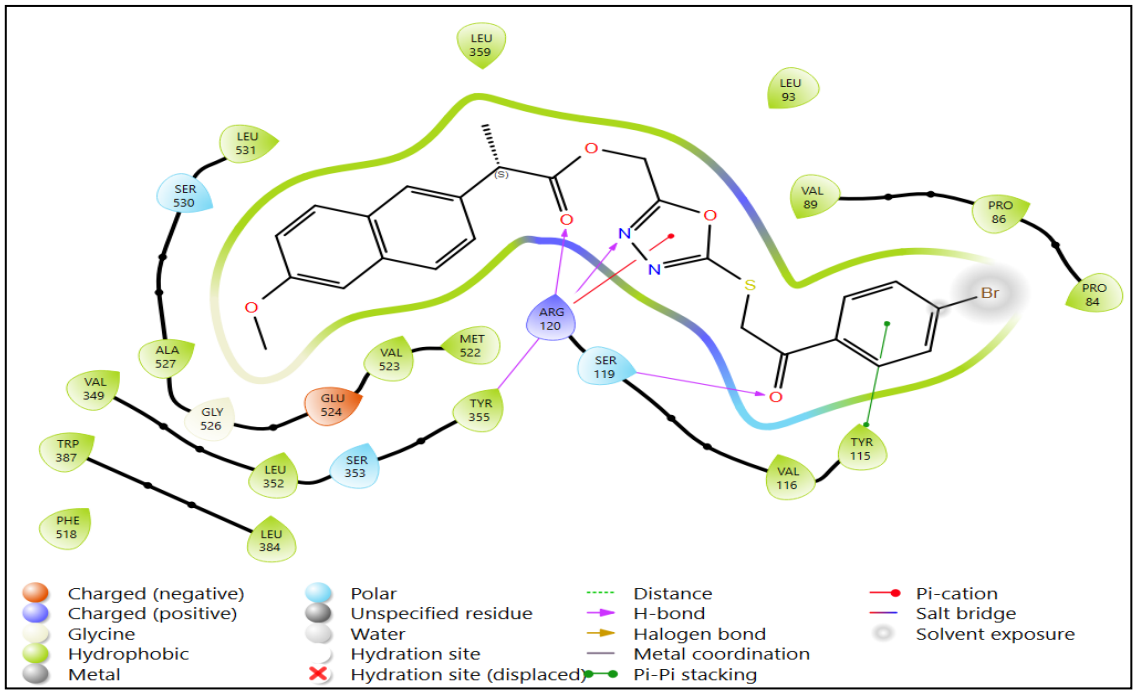


Figure 2. The interaction of compound N1 with COX2 type 3NT1.

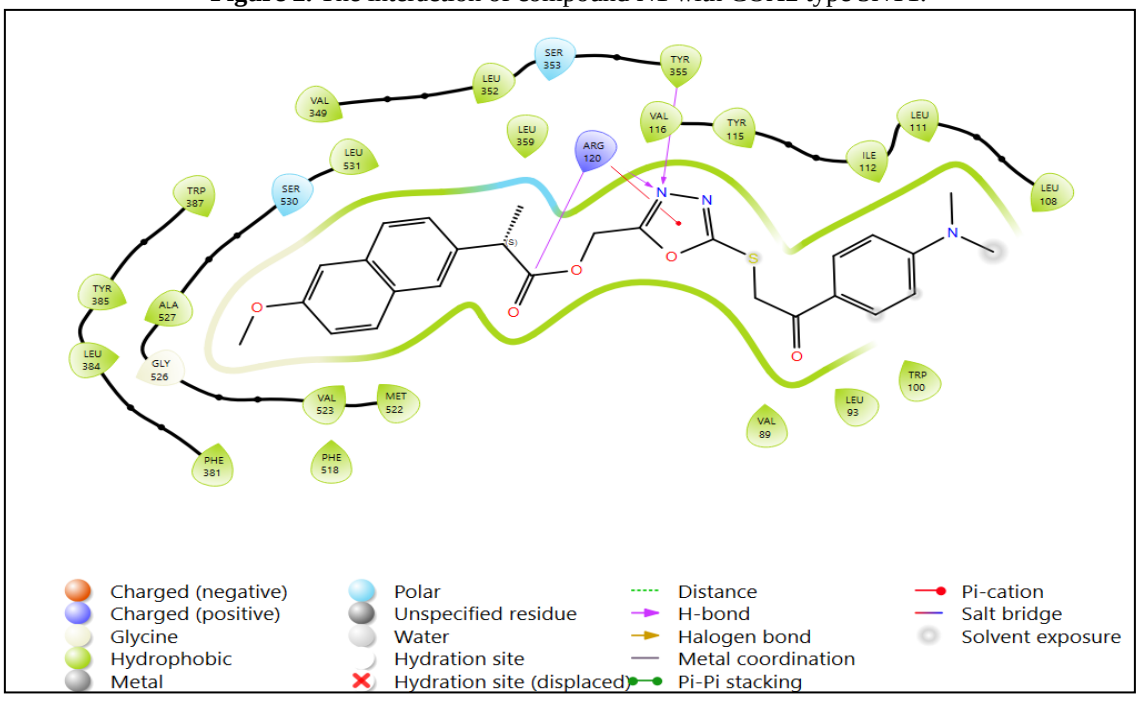


Figure 3. The interaction of compound N2 with COX2 type 3NT1.

2.4 Molecular dynamic simulation

Computer simulations were used to explore the interaction of protein with ligands, and how the nearby water molecules are affected. They simulated the system for a short period (50 billionths of a second) using Desmond software [18]. Initially, the molecules were arranged in a stable configuration, gradually warmed up, and let

settle into a balanced state. Finally, a run of simulation to collect the data about the system. Instead of using real experiments, computer models that assigns energy values and interactions to the atoms were used. The protein-ligand complex is placed in a box filled with water molecules, and the temperature and pressure were maintained constant throughout the simulation. The information and data were recorded every 50 nanoseconds to analyze details, such as, the nature of the protein and ligand interaction, the changes on the structure of the protein molecules associated with binding, and the flexibility of different parts of the protein molecules [12]. This approach allows to evaluate these interactions in details providing valuable insights into the effect of ligands on proteins and their surrounding environment depending on molecular docking. Compound N1 was selected, based on the highest molecular docking score on the enzyme type ENT1, for molecular dynamic simulation by the designed system using SPC water model in a box with a dimension of 10 Å including OPLS-4 force field, neutralized with 0.15 NaCl at neutral pH and constant temperature of 300 K for 50 nanoseconds. There are many systems that behave and applied with root mean square deviation (RMSD), root mean square fluctuation (RMSF), protein secondary structure element (SSE), and protein ligand contact were graphed over time to predict dynamic stability of compounds. The system was designed by inserting water model in an orthorhombic periodic box of dimension 10 ºA with OPLS-2005 force field, and neutralized with counter ions (Na^+ and Cl^-) at neutral pH. In various constrained steps, the built protein-ligand complex with the solvent system was maintained for energy minimization and pre-equilibration. Molecular dynamic simulations were inspected for 20 ns at a constant temperature of 300 K with a relaxation time of 2/second in NPT ensemble (Nose-Hoover thermostat). Electrostatic interactions were treated using Particle Mesh Ewald method for long and short range (cut-off distance of 9.0 ºA), with a 10–9 tolerance limit. The recorded values of RMSF and RMSD of the molecules were plotted versus time to examine the dynamic stability of the complexes.

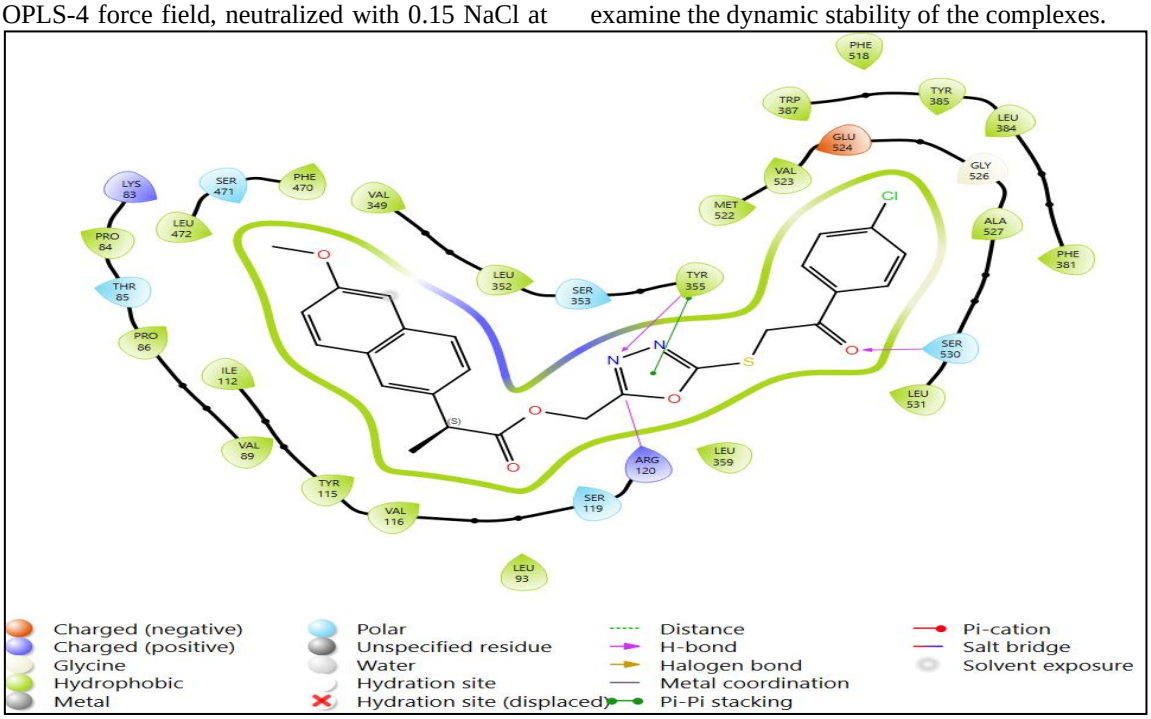


Figure 4. The interaction of compound N3 with COX2 type 3NT1.

3. Results and discussion

The primary objective of drug discovery is to identify new, effective compounds that target a specific biological function and have improved pharmacological properties [27]. Given the significant role of the COX enzyme in producing prostaglandins, which play a crucial role in pain mediation and are implicated in various health conditions such as inflammation, hypertension, cancer, and the female reproductive system [28], substantial efforts have been focused on developing enzyme inhibitors with optimal efficacy and minimal adverse effects.

3.1 Molecular Docking and Virtual Screening

Molecular docking is a useful computational method used to provide certain information and authoritative positioning of a ligand inside the dynamic location of a target protein by Schrödinger

program [19]. This method includes characterizing the 3D spatial course of action of the authoritative location and surveying the best situation of the ligand in different submissions inside that location, eventually shaping a complex [17]. The binding energies and specificity of the target compounds to the COX2 enzyme were determined by analyzing atomic intelligent at the dynamic destinations [20].

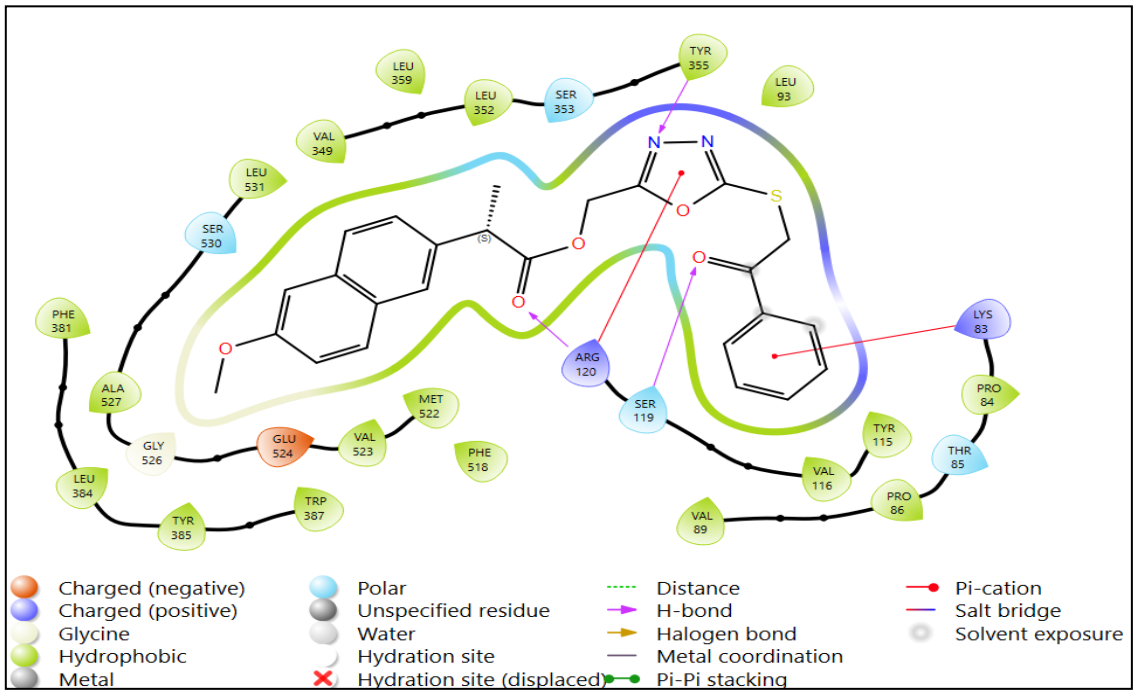


Figure 5. The interaction of compound N4 with COX2 type 3NT1.

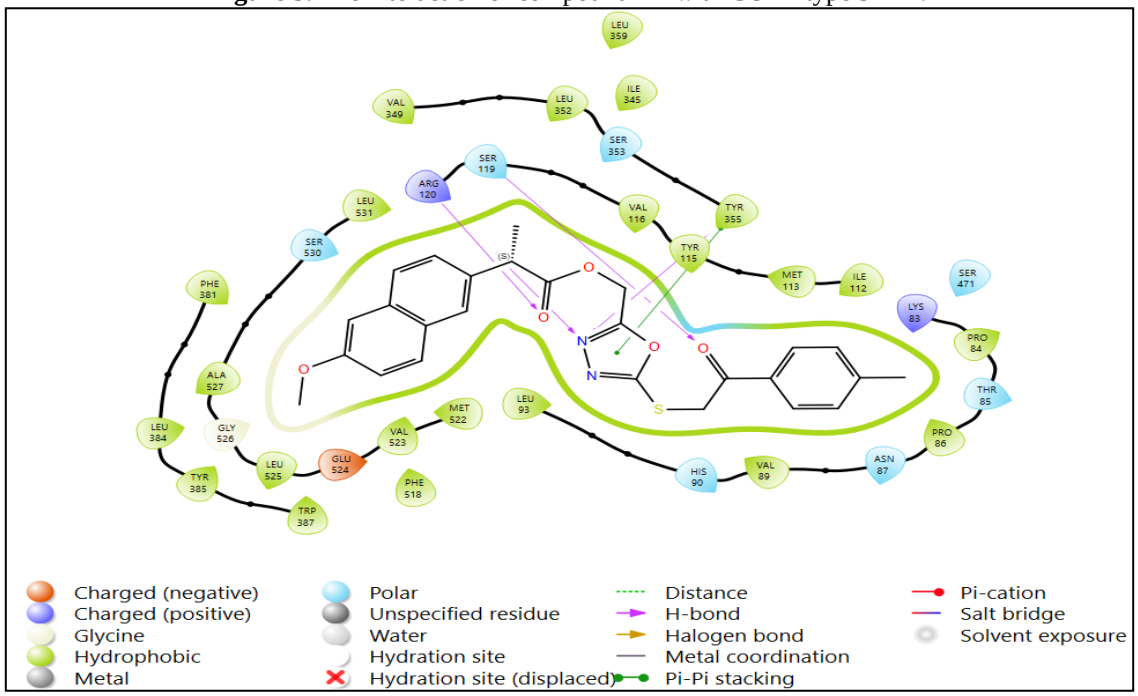


Figure 6. The interaction of compound N5 with COX2 type 3NT1.

The inhibitory potential of these compounds was assessed based on their PLP fitness values, which refer to their compatibility with the target protein. Besides, GOLD program provides bits of knowledge into the distance of hydrogen bonding between the ligands and the protein, to guarantee that all bond lengths were within 10 ^{o}A [21]. The results of docking scores demonstrated that

compounds N1-N6, showed higher PLP fitness values (90, 90, 88, 87, 86, 85, respectively), when individually compared to the reference ligand naproxen, which had a PLP fitness esteem of 74. Compounds N1-N6 are compared against naproxen Table (1). Compound N1, showed hydrogen bonding with Arg120, Tyr355, and Ser119 together with short contacts including Arg120, Tyr115, as shown in Table (1).

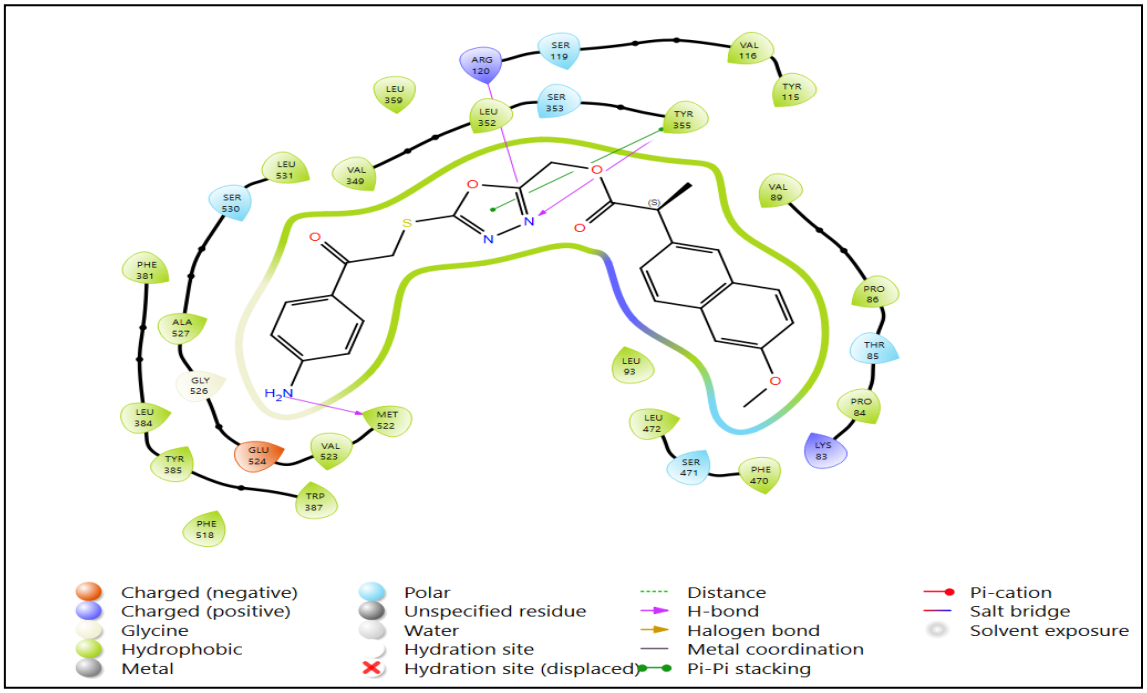


Figure 7. The interaction of compound N6 with COX2 type 3NT1.

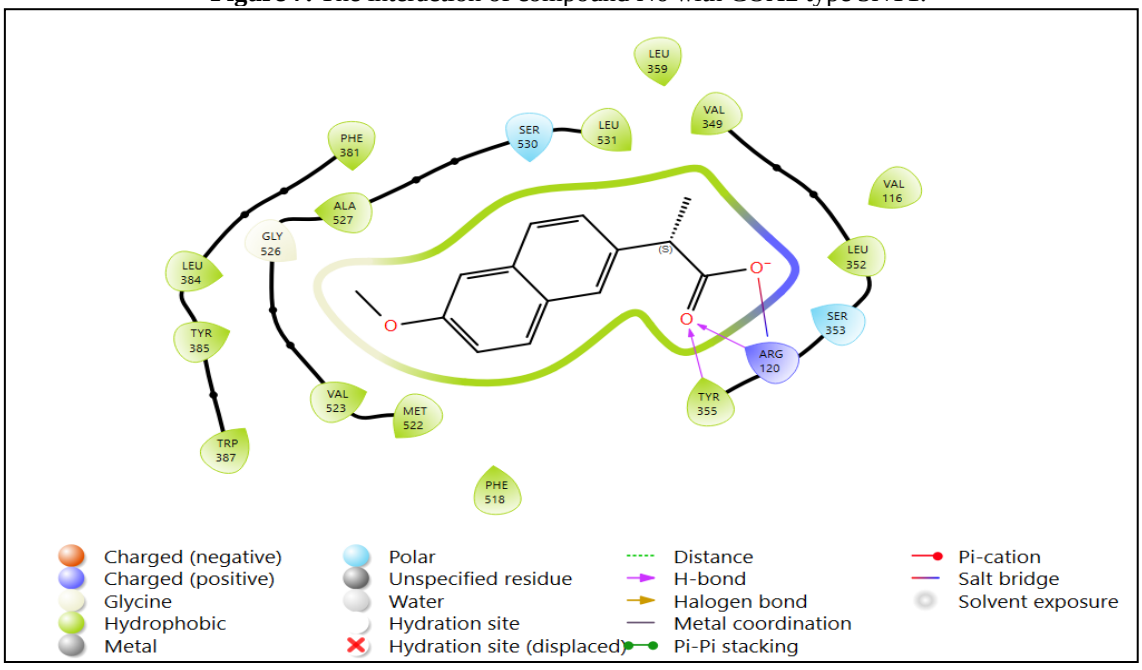


Figure 8. The interaction of Naproxen with COX2 type 3NT1.

The finest arrangement of compound N1 recorded a PLP fitness score of 90, and is recommended as the potential adequacy compared to naproxen. It is not guaranteed that the docking scores comply with experimental results of biological evaluation. However, in our previous work the docking scores were found to comply with experimental evaluation of antibacterial activity of new cephalosporin derivatives [22].

3.2 In-silico ADME/Pharmacokinetic properties prediction

It is recognized that when inhibitors are connected with a protein or protein receptor, there is no guarantee that these drugs will be reasonably active and successful [13]. Typically, it is fundamental in medication disclosure to run complete evaluation including ADME profile and Lipinski role of five [13]. These evaluations offer assistance to decide whether inhibitors can successfully coordinate into the organic framework. Moreover, inhibitors with destitute ADME properties and harmfulness frequently lead to disappointments amid clinical trials. Lipinski's rule of five [14]. provides additional information for the profile of compounds to be treated as successful candidates. Concurring to this run the inhibitor is likely to be orally dynamic in case meeting certain criteria, counting molecular weight, partition coefficient, no. of hydrogen bond acceptors and donors, and topological polar surface area [23]. The SwissADME server is used for prediction of pharmacokinetic and ADME properties, aiding to recognize the approval of possible activity of the compounds associated with favorable pharmacokinetic profiles [8]. For compounds with topological polar surface area (TPSA) less than 140 ^{o}A, regularly show tall porousness and oral bioavailability [8]. The results demonstrated that the designed compounds are successful candidates and comply with Lipinski's role of five, and with favorable bioavailability. Furthermore, *in silico* ADME/pharmacokinetic appraisals were performed for naproxen (Table 2).

Table 2. ADME and drug likeness profile of the new target compounds N1-N6.

Compound	MW (g/mol)	H-BD	H-BA	M.R.	TPSA	GI Abs	BBB	B.S.	L.V.
N1	**483.38**	**0**	**5**	**121.69**	**90.52**	**High**	**No**	**0.55**	**0**
N2	**447.55**	**0**	**5**	**128.20**	**93.76**	**High**	**No**	**0.55**	**0**
N3	**438.93**	**0**	**5**	**119.00**	**90.52**	**High**	**No**	**0.55**	**0**
N4	**404.48**	**0**	**5**	**113.99**	**90.52**	**High**	**No**	**0.55**	**0**
N5	**418.51**	**0**	**5**	**118.96**	**90.52**	**High**	**No**	**0.55**	**0**
N6	**419.30**	**1**	**5**	**118.40**	**116.54**	**Low**	**No**	**0.55**	**0**
Naproxen	**230.26**	**1**	**3**	**66.79**	**46.53**	**High**	**Yes**	**0.85**	**0**

MW (molecular weight) (Dalton), B.S. (Bioavailability Score), GI Abs. (gastrointestinal absorption), TPSA (topological polar surface area), BBB (blood–brain barrier), L.V. (no. of Lipinski violation), H-BD (no. of hydrogen bond donor), H-BA (no. of hydrogen bond acceptor), M.R. molar refractivity.

3.3. Molecular dynamics

The results of molecular dynamic for protein-ligand complex for compound N1 (N1-3NT1) are recorded for each case, as follows;

Determination of RMSD values

Root means square deviation (RMSD) is expressed as a measuring ruler of how much, on average, a group of atoms has moved away from their starting positions in a simulation during 50 nanoseconds. This measure is used for every snapshot (frame) captured during the simulation, giving a complete picture of how the atoms have shifted over time. By looking at the overall trend of the RMSD, may indicate the stability of the structure of the protein, or may change significantly throughout the simulation. RMSD average range from 1-3 Å is shown in Figure (9).

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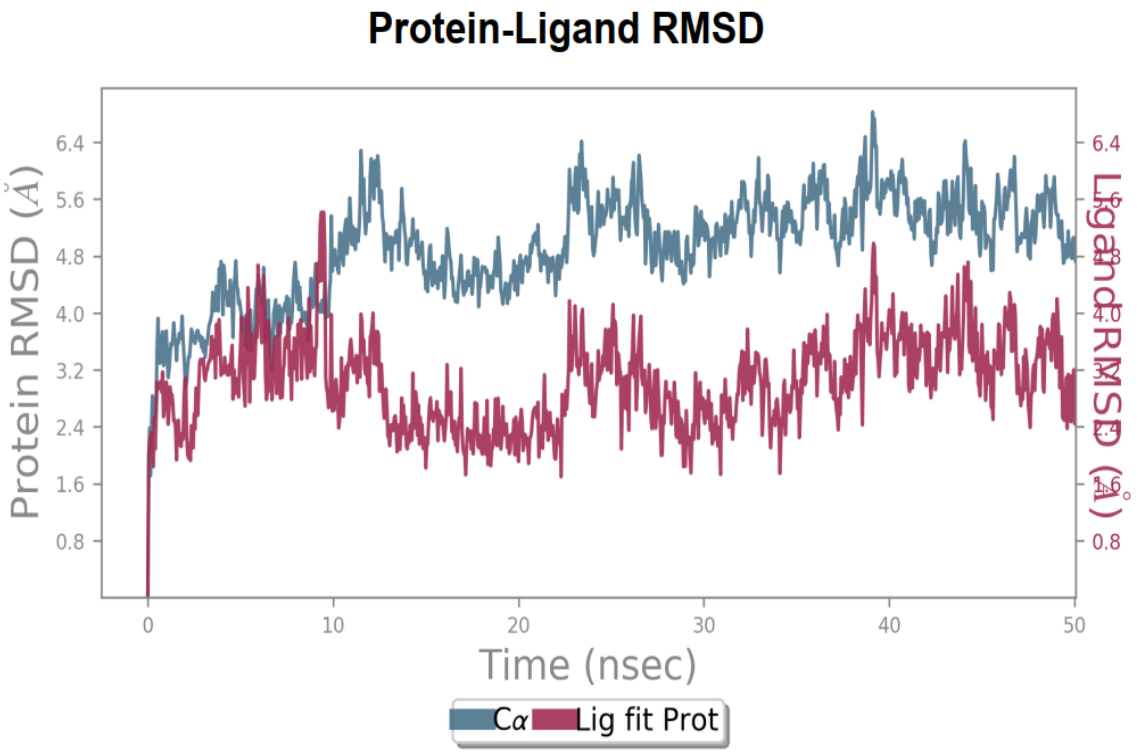

Figure 9. RMSD of the protein-ligand complex versus time (N1-3NT1). The red line represents ligand RMSD value per time, while the blue line represents protein RMSD value per time.

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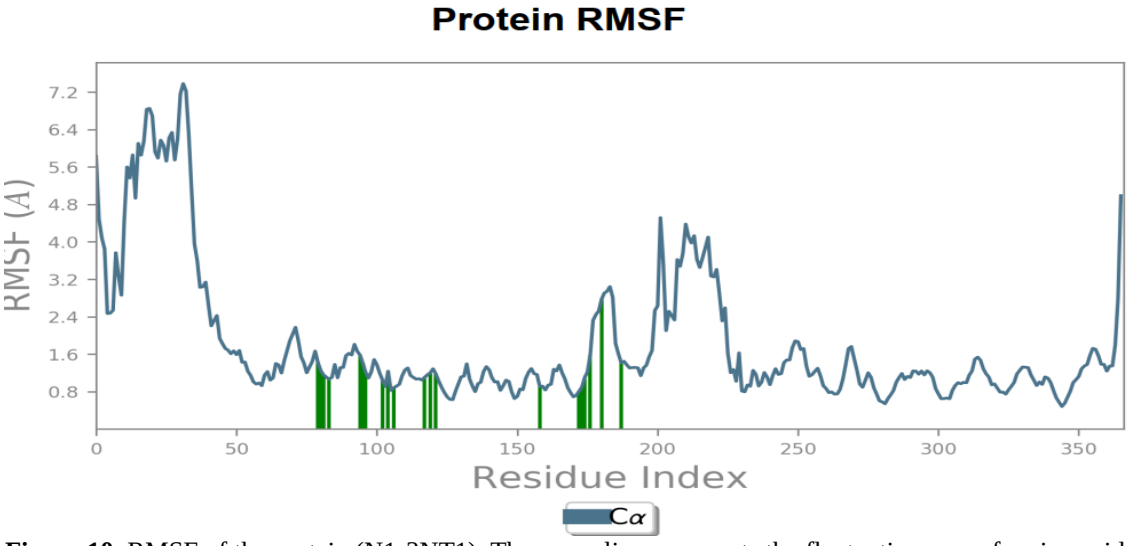

Figure 10. RMSF of the protein (N1-3NT1). The green line represents the fluctuation area of amino acid linked with ligand, while the blue line represents the fluctuation area of protein

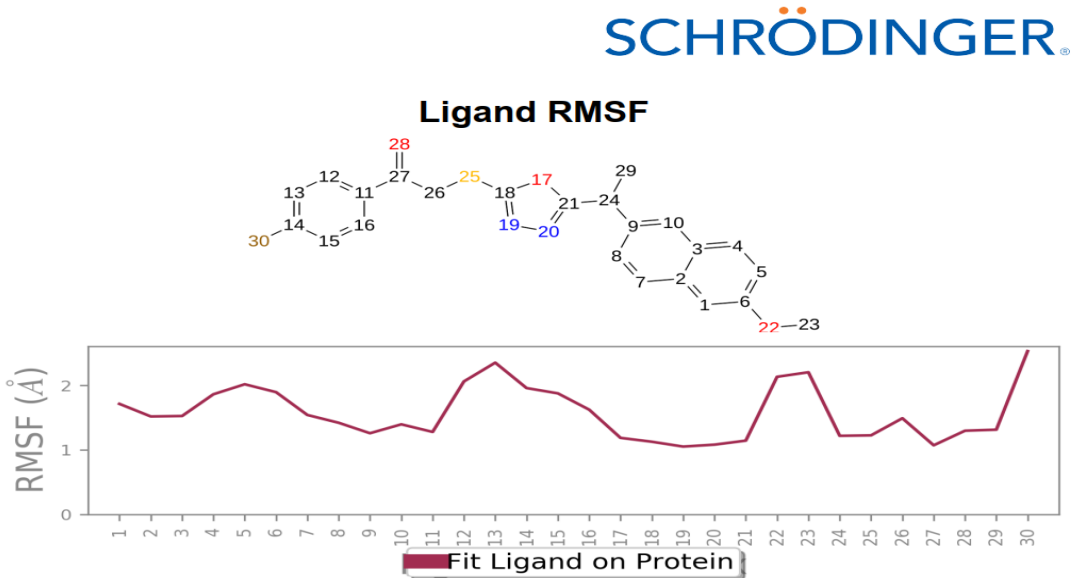

Figure 11. RMSF of the compound N1 on protein (3NT1). The red line represents the fluctuation of each atom of ligand.

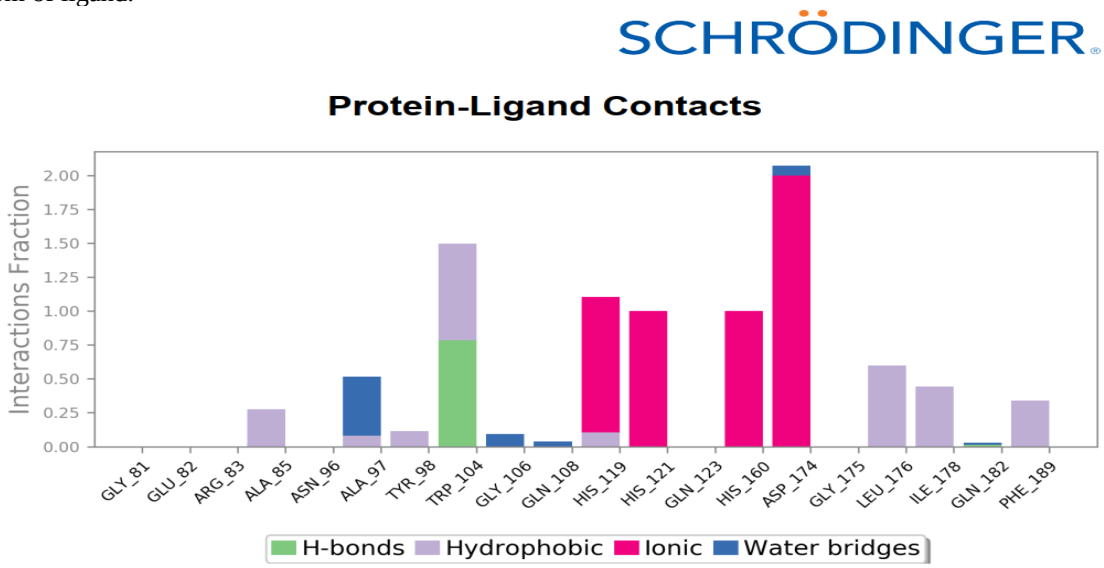

Figure 12. ligand-protein contacts.

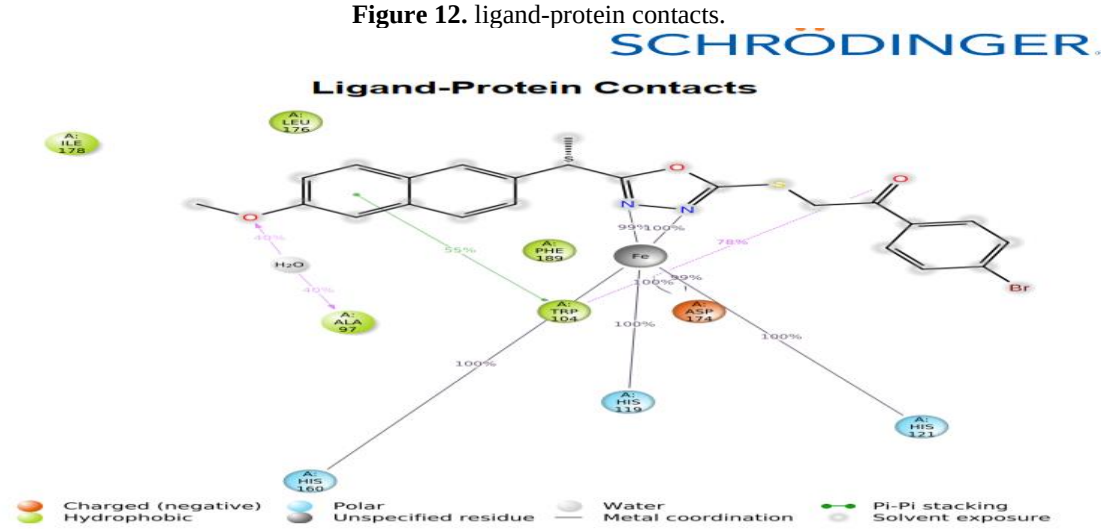

Figure 13. ligand-protein contacts, showing type of bond which links between amino acid within binding region and atom of ligand

Protein RMSD results

The obtained chart depicts the RMSD movement of a protein (on the left Y-axis). At first, all outlines of the protein are adjusted to the spine of the reference obtained by RMSD calculation based on the chosen steps. Checking the RMSD of the protein offers experiences into its auxiliary changes amid the reenactment. RMSD investigation makes a different survey whether the recreation has come to balance. Conformational changes of globular proteins by 1-3 ^{o}A are by far satisfactory. Major changes propose critical conformational modifications amid the recreation. Moreover, these changes provide stable RMSD values around a settled point, may demonstrate harmony. The decrease or diminished values in RMSD evaluation indicated by the simulation, means insufficient equilibration, and the reenactment may require further investigations. Protein RMSD has shown in Figure (9), which is within the normal range 2.3 Å, and may predict stability of protein during 50 nanoseconds.

Ligand RMSD results

The RMSD of a ligand refers to the right Y-axis, showed the stability of the ligand relative to the protein and its binding location. Within the chart, the ligand fitness on the protein structure showed the RMSD of the ligands. The calculation includes adjusting the protein-ligand complex to the protein backbone as a reference and consequently, measuring the RMSD of the ligand overwhelming molecules. In the event that these values outstandingly surpass the RMSD of the protein, it recommends potential dissemination of the ligand absent from its starting binding location. The results of RMSD of a ligand showed within the normal range value 3.2 Å, which predict the stability of ligand during 50 nanoseconds, as shown in Figure (9).

The RMSF investigation

The Root Mean Square Fluctuation (RMSF) could be a valuable metric for analyzing localized changes along the protein arrangement. Peaks on the chart demonstrate districts of the protein with the most elevated changes during the simulation [20]. Regularly, the N- and C-terminals display more prominent fluctuations compared to other sections of the protein. Secondary basic components, such as, alpha helices and beta strands are by far steadier and with less variation than the flexible circle districts. Protein RMSF range values are less than 2.5 Å, as shown in Figure (10), while, compound N1 has showed stability within normal range less than 2.5 Å Figure (10).

Ligand-protein contact interaction

A schematic pathway of the ligand interaction with the amino acid residues of the target protein occurs in more than 30% of the simulation time within the chosen direction (through zero to 50.05 nanoseconds), as shown in Figure (13). It is conceivable to have intuitive with >100% as few residues may have numerous interactions of a single sort with the same ligand. For illustration, the guanidine side chain of arginine has four H-bond that can show single H-bond acceptor, as illustrated in Figure (11).

4. Conclusions

This approach included the innovative and novel design of brand-new analogues that have displayed highly promising and remarkable binding affinities to the COX-2 receptor type 3NT1. Through comprehensive computational investigation and meticulous analysis, the focus was specifically directed towards the development and progression of groundbreaking naproxen analogues that incorporate a unique and potent 1,3,4-oxadiazole ring structure. The primary objective of this critical progression was to challenge and mitigate the detrimental side effects commonly associated with the utilization of conventional NSAIDs. By incorporating the novel and strategically placed free carboxyl group within the 1,3,4-oxadiazole ring structure, these newly designed compounds hold immense potential in serving as highly effective and successful anti-inflammatory agents. In fact, they have demonstrated a substantial decrease in gastrointestinal complications when compared to the conventional drug naproxen. Moreover, extensive in-silico appraisals of the ADME properties of these meticulously crafted compounds have unequivocally showcased extremely favorable pharmacokinetic profiles. These profiles, in turn, exhibit orally dynamic properties which ultimately enhance their overall bioavailability and safety profiles. It is noteworthy to mention that this groundbreaking approach signifies a substantial and pivotal advancement in the field of anti-inflammatory treatment. By effectively addressing

and alleviating the limitations and constraints associated with existing therapies, this approach showcases immense potential in revolutionizing the landscape of treatment options. In-depth molecular dynamics simulations have been conducted to gain crucial insights into the energetic stability and integrity of the protein-ligand complex. The analysis of RMSD (Root-Mean-Square Deviation) and RMSF (Root-Mean-Square Fluctuation) further elucidates and highlights the consistent and stable interactions observed within the complex over an extended period of time. The innovative design of these newly developed analogues, coupled with their exceptional binding affinities and advantageous pharmacokinetic profiles, makes them a highly viable and promising avenue in the quest for improved anti-inflammatory treatments. The unparalleled progress made in this scientific endeavor encapsulates the immense potential for addressing the limitations and drawbacks of current therapeutic approaches, paving the way for a novel generation of highly effective medications.

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Declaration of Competing Interest

The authors disclosed no potential conflicts of interest.

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