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In Silico Molecular Docking, Molecular dynamic, ADME Study of Naproxen Analogues as Epidermal Growth Factor Receptor Inhibitors

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Abstract: Background: Cancer remains a leading cause of morbidity and mortality worldwide, necessitating continuous efforts to discover novel anticancer agents. Among various therapeutic targets, the Epidermal Growth Factor Receptor (EGFR) plays a critical role in tumor progression, while resistance to first- and second-generation tyrosine kinase inhibitors (TKIs) underscores the need for next-generation therapies. **Objective:** Naproxen derivatives with 1,3,4-oxadiazole substitutions are investigated as potential next-generation EGFR inhibitors to address drug resistance in cancer patients. **Methods:** We performed molecular docking (using GOLD software and Schrödinger Suite), ADME profiling (via the SwissADME webserver), and molecular dynamics (MD) simulations (50 ns) on the selected Naproxen analogues. Osimertinib was used as a reference to benchmark binding affinities and compare pharmacokinetic properties. **Results:** Docking revealed that several Naproxen–1,3,4-oxadiazole derivatives interacted favorably with key EGFR residues (e.g., Met793, Lys745, Val726) with higher ChemPLP docking scores than Osimertinib in certain cases. ADME analysis indicated acceptable drug-likeness profiles, adherence to Lipinski's Rule of Five, and favorable absorption predictions. MD simulations demonstrated stable protein–ligand complexes, with RMSD values generally fluctuating within 1–3 Å for both protein and ligand. **Conclusion:** These computational findings support the potential of Naproxen–1,3,4-oxadiazole derivatives as novel EGFR inhibitors. While they appear promising, further in vitro and in vivo validation is essential to confirm their efficacy and potential to overcome EGFR-mediated drug resistance in cancer therapy.

Keywords: EGFR inhibitors, Osimertinib, Naproxen analogues, 1,3,4-oxadiazole, Molecular Docking, ADME, Cancer Therapy.

Introduction

Cancer continues to be a major global health burden, contributing to millions of deaths each year. Among various molecular targets implicated in tumorigenesis, the Epidermal Growth Factor Receptor (EGFR) has emerged as a critical mediator of cell proliferation, differentiation, and survival in multiple cancer types, including non-small cell lung cancer (NSCLC), glioblastoma, and colorectal cancer [1]. Overexpression or mutations in EGFR can lead to aberrant signaling, promoting tumor growth, and resistance to conventional therapies. specific gain-of-function mutations in EGFR—most notably L858R, exon 19 deletions, T790M, and the more recent C797S—drive resistance to standard therapies and contribute significantly to tumor progression. Among these, the T790M mutation quickly emerged as a primary mechanism of resistance to first- and second-generation TKIs, necessitating the development of newer agents, such as Osimertinib, that specifically address this mutated site [2]. Osimertinib is a third-generation irreversibly binding EGFR inhibitor engineered to overcome resistance mediated by T790M and other mutations. This drug is designed to inhibit both sensitizing mutations of EGFR-TKI and T790M resistance mutations while sparing wild-type EGFR to limit off-target effects. Osimertinib covalently binds to the cysteine residue (C797) in the ATP-binding pocket of EGFR, enhancing its specificity and potency. With its clinical efficacy cementing its position as a reference chemical in EGFR drug research programs, it contributes the gold standard for the evaluation of new inhibitors in the field [3].

Notably, EGFR (PDB ID: 6LUD) can also provide insights into molecular docking research because it offers a complete and detailed view of the mutant kinase domain in complex with Osimertinib. The structural data give a close-up view of key binding interactions, providing a strong foundation for judging potential treatment strategies. Using this knowledge, we plan to investigate the docking profiles of selected compounds and compare them with Osimertinib in their role as potential next generation EGFR inhibitors. Due to the global burden of cancer, the development of new anticancer agents is a research focus of the pharmaceutical industry. Of numerous families of chemicals, nonsteroidal anti-inflammatory drugs (NSAIDs), particularly naproxen, have garnered attention as potential repurposed anticancer agents. Naproxen is mainly used for analgesia and anti-inflammation but has shown anticancer effects in both preclinical and clinical studies, especially for lung cancer [4]. The anticancer activity is attributed to its ability to engage major molecular targets linked to cell proliferation, death, and metastasis [5]. In silico empirical proof suggests that naproxen binds to several locations that mediate cancer cell signaling pathways, on providing the evidence of its capability to impede tumor initiation, as well as minimize the dissemination of cancer cells [4].

This study focuses on Naproxen derivatives containing the 1,3,4-oxadiazole ring due to their promising anticancer potential. The 1,3,4-oxadiazole moieties have attracted wide attention due to its ability to increase bioactivity against various crucial targets

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in the cancer phenomenon [6]. The incorporation of the oxadiazole ring in naproxen derivatives may enhance anticancer efficacy, especially against lung cancer, by altering receptor interactions increasing stability, and augmenting the drug's bioavailability [7]. The selection of naproxen and 1,3,4-oxadiazole as building blocks for designing our proposed compounds is based on a comprehensive literature review that supports our previous study. Alam et al. (2021) reported that 4-((5-((S)-1-(2-methoxynaphthalen-6-yl) ethyl)-1,3,4-oxadiazol-2-ylthio) methyl)-1H-1,2,3-triazol-1-yl) phenol exhibited significant potency against MCF-7 and HepG2 cancer cells, as shown in Figure 1. This compound demonstrated equipotency to doxorubicin, with an IC_{50} value of 1.62 µg/mL against HepG2 cells). The biological data was complemented by docking studies, DFT, and MEP. These naproxen hybrids competitively inhibit tyrosine kinase by binding to adenosine triphosphate (ATP), inhibiting EGFR kinase [8].

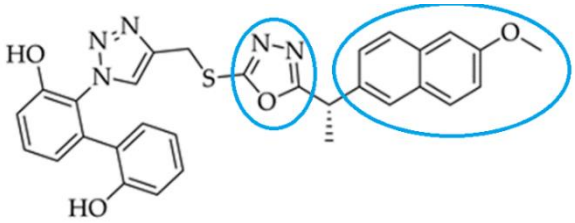

Figure (1): naproxen derivative with 1,3,4-oxadiazole ring.

Hagras et al, 2022, created of compound (N-benzyl-2-((5-((6-methoxynaphthalen-2-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)acetamide) combining 1,3,4-oxadiazole with naphthalene and evaluated their toxicity against MCF-7 and HepG2 cell lines using the MTTS assay and demonstrated the most promising potential and were further examined for their effectiveness against VEGFR-2, furthermore, it exhibited enhanced efficacy against MCF-7 and HepG2 cells, with IC50 values of 9.7 and 8.8 µM, respectively. With an IC50 value of 8.4 M [9], as show in figure (2).

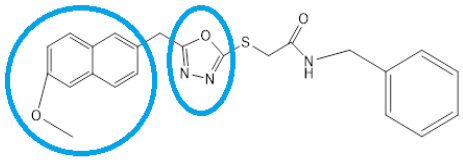

Figure (2): (N-benzyl-2-((5-((6-methoxynaphthalen-2-yl) methyl)-1,3,4-oxadiazol-2-yl) Thio) acetamide) combining 1,3,4-oxadiazole with naphthalene.

Molecular docking is now a powerful computational technique in the field of drug discovery to study the interactions of small molecules with their target proteins. This method involves predicting the binding pose and strength of ligands in a protein's binding pocket. Simulating the docking offers great insights into the prominent chemical interactions mediating binding, such as hydrogen bonding, hydrophobic interactions, and pi-stacking. [With these insights we can optimize existing inhibitors and design new, more efficient drugs][10].

This study utilizes molecular docking and associated computational approaches to evaluate how these alterations may enhance binding affinity, specificity, and overall anticancer efficacy in comparison to the original molecule, naproxen [11].

This study additionally aims to further the development of tailored medicines that can surmount drug resistance. The research concentrates on the molecular mechanisms of inhibitor binding to establish a platform for rational drug design, hence improving therapeutic alternatives for patients with EGFR-driven cancers.

Computational Techniques

Computational methods are essential in drug research, as they simulate molecular interactions, forecast therapeutic efficacy, and assess pharmacokinetic features. Various in-silico techniques are frequently utilized, such as molecular docking, ADMET analysis, and molecular dynamics (MD).

Molecular Docking Technique

Molecular docking is used to predict how a ligand binds to a protein of known structure. This requires recreating thousands of ligand conformations inside of the binding region of a receptor to determine what binding is optimal. This method is mainly adopted in virtual screening to identify hit molecules by evaluating their binding affinity. It is used to boost the best compounds based on their expected binding energy and binding pose, and is an important part of early drug discovery [12]. Additionally, molecular docking has been used to study the effectiveness of established drugs- naproxen for new therapies. Naproxen, a widely used nonsteroidal anti-inflammatory medicine (NSAID), shows potential anticancer activity through interaction with multiple molecular targets involved in cancer cell proliferation and metastasis and could be repurposed in cancer therapy [13].

ADME Evaluation in Pharmaceutical Development

ADME (Absorption, Distribution, Metabolism, and Excretion) evaluations are crucial for assessing a drug's pharmacokinetic characteristics and possible toxicity. ADME analysis facilitates the prioritization of therapeutic candidates by forecasting a compound's behavior in the body and eliminating those with adverse characteristics, hence lowering the likelihood of clinical failure. Essential pharmacokinetic factors, including absorption rates and clearance, inform the formulation of efficacious and safe pharmaceuticals.

Molecular Dynamics (MD) Simulations

MD simulation offers dynamic information about molecular behavior by simulating molecular motion in time. Molecular dynamics (MD) encompasses conformational adjustments, temperature perturbations, and includes protein-ligand interaction stability, in contrast to molecular docking, which offers prediction of binding in a static mode. These simulations improve the prediction of docking by describing drug-receptor interactions, and the stability of compound, making molecular dynamics important tool in optimizing drug candidates [14].

Computational Methods

Protein Processing and Network Creation

A thorough process for assessing the newly created medications that encompasses the optimal impacts between possible activities and the entire array of biomolecules within the cells that may exhibit greater viability. The crystal structure of the target protein was obtained from the Protein Data Bank (PDB code: 6LUD) [15]. The application was executed utilizing the Protein Preparation Wizard in Schrodinger, New York, 2021, commencing with the exclusion of water molecules and the incorporation of hydrogen into protein residues. The hydrogen bonds were optimized using the OLPS-2005 (Optimized Potentials for Liquid Simulations) force field [16]. All proteins retain NAD+ in the core as a cofactor and are co-crystallized with a ligand. The receptor grid was constructed utilizing the co-crystallized ligand as the center for the border box when the

produced ligands were docked onto the protein's binding site. The dimensions of the bounding box utilized were 12 A0 [17].

Ligand Preparation

The new ligands' chemical structures were depicted through ChemAxon [17], and their SMILES notations were used as input files for the appropriate ligand module [18]. After applying force fields to the ligands in ligand production, the structures were tuned for minimum energy [19].

Ligand-active site preparation and molecular docking

The examined compounds undergo energy minimization utilizing Chem3D version 16.0 with the MM2 force field. The active site of EGFR was obtained from the Protein Data Bank (PDB: 6LUD) combines with Osimertinib. Water of crystallization was excluded from the dynamic sites and evacuated, while the ligands from the receptors' dynamic locations were removed. The ligands were docked onto the three-dimensional structure of the target protein, type 6LUD. A comparable result was reported with naproxen and EGFR, utilizing the identical receptor configuration for docking via the Hermes visualizer tool within the CCDC of the GOLD suite [20]. The ligand was first pulled a sterically from the receptor binding site. The receptor was also prepared for the docking process using the Hermes visualization tool within the CCDC GOLD package. The active site recognized as the main ligand interaction in 10 Å, while binding site defined as any protein residues important for docking (leading to more coordinates). The docking procedure used default parameters (producing 10 poses), and the highest-ranking pose was selected as the standard, whereas the early termination option was deactivated [21]. ChemScore kinase scoring function based on the ChemPLP made with a continuous linear potential was used for the calculation. The docking outcomes are saved in mul2 files, including detailed information such as binding energy, precise binding sites and poses. The data were extensively examined to determine optimal binding interactions between the ligand and the receptor amino acid residues (6LUD).

Computer system and software

The program included fully licensed copies of the Swiss ADME online application, ChemDraw Expert software version 21.0, GOLD software suite version 2022.3.0, and Schrödinger software version 22.0.

Drug-Likeness Profile

The evaluation of pharmacokinetic and ADME properties of the studied drugs was performed using the SwissADME online tool (www.swissadme.ch) [22]. The boiled egg server was employed to forecast the lipophilicity and extremes of these compounds.

Results and Discussion

Molecular docking results

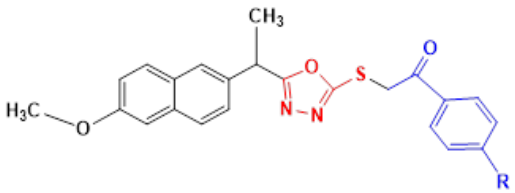

Table (1): The binding energies and interaction of naproxen analogues containing 1,3,4-oxadiazole and Osimertinib with amino acids of 6LUD.

Compound	Interaction of the designed compounds with amino acids of EGFR receptor PDB code (6LUD)		
	Hydrogen Bonding	Short Contact	Average PLP fitness
N1 R = CH_2CH_3	LYS728	LYS745, LYS728, PHE723, LEU1001, MET793, LEU792 (2), VAL726 (2).	82.27
N2 R = NH_2	ASP855	LYS728, MET793, VAL726, LEU792 (2), LEU1001	79.68
N3 R = COOH	LYS745	LYS745, VAL726, ASP855, MET793	72.55
N4 R = $CH(CH_3)_2$	----------	MET793(2), ALA743, LYS728, LEU792, LEU1001	70.96
N5 R = F	----------	LYS745, VAL726(2), LEU792(2)	70.78
N6 R = SH	----------	LYS745, VAL726 (2), MET793 (2), LEU792	68.26
N7 R = NO_2	----------	LYS745, VAL726, LEU1001, LEU792 (2)	67.28
Osimertinib	SER797	LYS745, LEU844 (2), VAL726, SER797	63

*The number inside the bracket refer to number of amino acids.

List of molecular docking for designed compounds and Reference ligand (Osimertinib) figures (1-8)

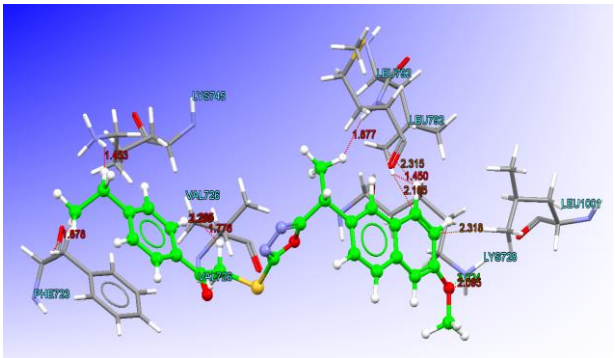

Figure (3): 3D interactions of N1 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

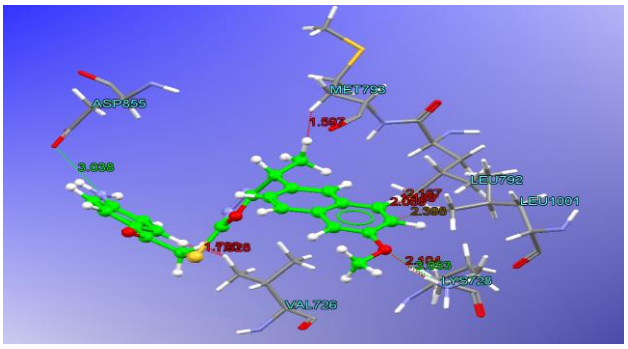

Figure (4): 3D interactions of N2 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

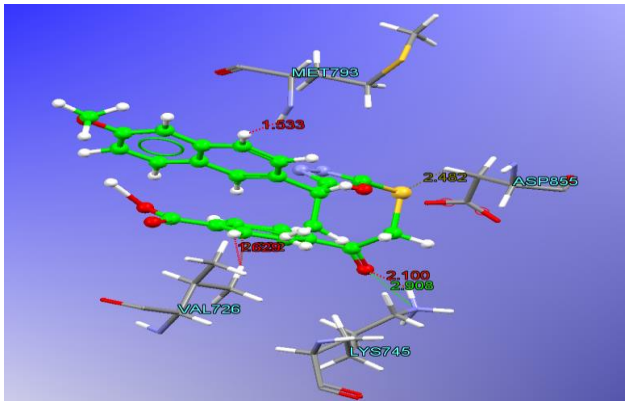

Figure (5): 3D interactions of N3 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

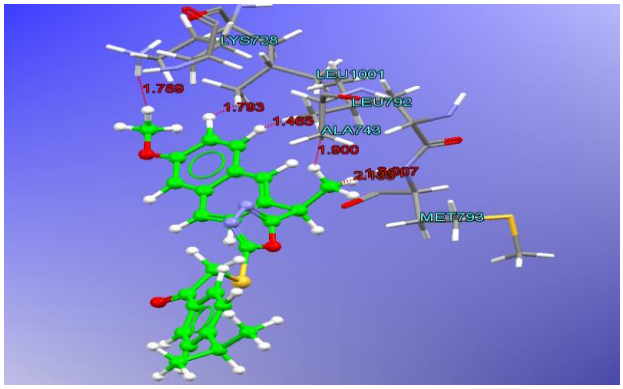

Figure (6): 3D interactions of N4 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

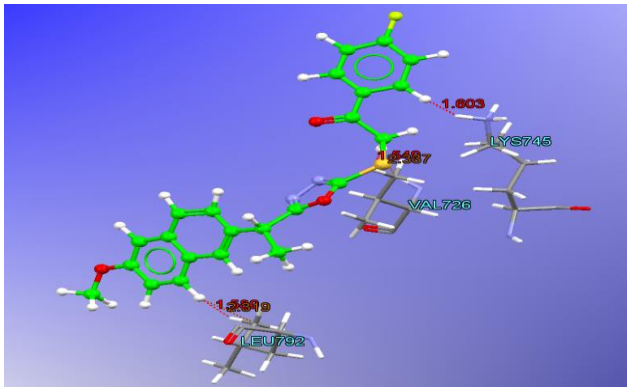

Figure (7): 3D interactions of N5 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

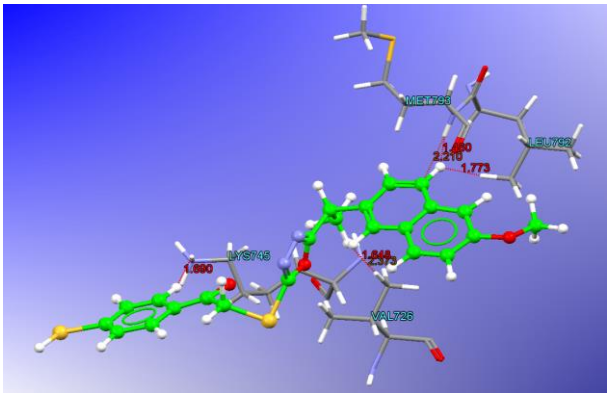

Figure (8): 3D interactions of N6 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

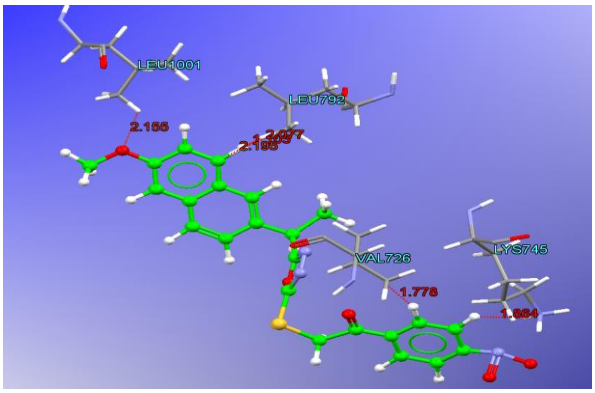

Figure (9): 3D interactions of N7 with the active site of epidermal growth factor receptor (PDB:6LUD). (N1 in ball and stick style, amino acid residues in capped sticks style).

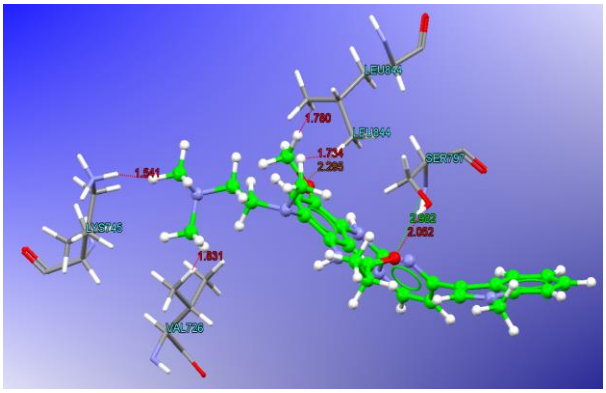

Figure (10): 3D interactions of Osimertinib with the active site of epidermal growth factor receptor (PDB:6LUD). (Osimertinib in ball and stick style, amino acid residues in capped sticks style).

ADME profile results

It is acknowledged that the binding of inhibitors to a protein or protein receptor does not ensure that these medicines will exhibit adequate activity and efficacy, although potent binding to a protein does not guarantee a drug's success, evaluating absorption, distribution, metabolism, and excretion (ADME) is essential in early drug development [22]. It is essential in drug disclosure to conduct a comprehensive evaluation, including the ADME profile and Lipinski's Rule of Five. These studies aid in determining if inhibitors can effectively integrate into the organic system. Furthermore, inhibitors with inadequate ADME characteristics and toxicity often result in failures during clinical studies. Lipinski's Rule of Five gives supplementary information for identifying chemicals that may be considered successful candidates. The inhibitor is expected to be orally bioavailable if it meets specific parameters, including molecular weight,

partition coefficient, number of hydrogen bond acceptors and donors, and topological polar surface area [23]. The SwissADME server predicts pharmacokinetic and ADME features, assisting in identifying the potential activity of drugs with advantageous pharmacokinetic profiles [22]. Compounds with a topological polar surface area (TPSA) below 140 Å often exhibit high porosity and oral bioavailability [22]. The results indicated that the designed compounds are viable candidates, adhering to Lipinski's Rule of Five, and have favorable bioavailability. Additionally, in silico ADME/pharmacokinetic evaluations were conducted for our compound (Table 1).

Table (2): presents key ADME parameters for the designed compounds. Recommended optimal ranges include.

Table (2) lists the output parameters for drug-likeness and ADME.									
Compound	**MW(g/mol)**	**nHBD**	**nHBA**	**MR**	**TPSA**	**GI**	**BBB**	**BS**	**nLV**
Ideal range	**MW < 500 g/mol**	**nHBD ≤ 5**	**nHBA ≤ 10**	**40-130**	**TPSA < 140 Å²**	**------**	**-----**	**≥ 0.55**	**0-1**
N1	432.53	0	5	123.77	90.52	High	No	0.55	0
N2	419.50	1	5	118.40	116.54	LOW	NO	0.55	0
N3	448.49	1	7	120.95	127.82	LOW	NO	0.55	0
N4	446.56	0	5	128.57	90.52	LOW	NO	0.55	0
N5	422.47	0	6	113.95	90.52	High	NO	0.55	0
N6	436.55	0	5	121.24	129.32	Low	NO	0.55	0
N7	449.48	0	7	122.81	136.34	LOW	NO	0.55	0

MW (g/mol): Molecular Weight (grams per mole), nHBD: Number of Hydrogen Bond Donors, nHBA: Number of Hydrogen Bond Acceptors, MR: Molar Refractivity, TPSA: Topological Polar Surface Area, GI: Gastrointestinal Absorption, BBB: Blood-Brain Barrier Permeability, BS: Bioavailability Score, nLV: Number of Lipinski's Violations.

Molecular Dynamics of molecules results

For each scenario, the molecular dynamics data for the protein-ligand complex for compound N2 (N2-6LUD) are documented as follows:

Finding the RMSD values

The root mean square deviation (RMSD) measures the average deviation of a group of atoms from the reference coordinates in a simulation, based on a 50-nanosecond time span. As it is implemented in each snapshot (frame) recorded during the simulation, this measure provides a comprehensive view of atomic transitions over time. By looking at the overall tendency of the RMSD, we can determine if the protein is stable in architecture or made significant changes during the simulation. The RMSD average varies from 1 to 3 Å as shown in Figure 11.

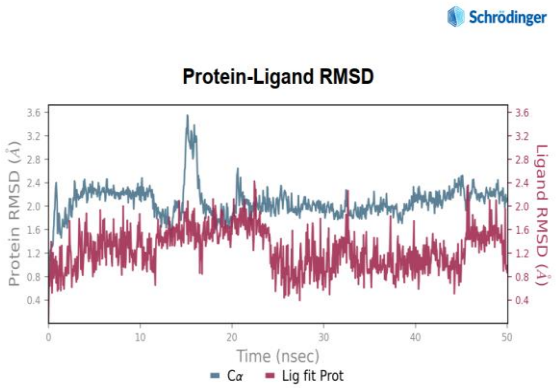

Figure (11): RMSD of the protein-ligand complex versus time (N2-6LUD). The red line represents ligand RMSD value per time, while the blue line represents protein RMSD value per time.

Protein RMSD results

The resulting figure shows RMSD deviation of a protein (left Y-axis). The resultant protein structures are then aligned to the reference backbone derived from the RMSD computation with the specified steps. The RMSD will allow us to evaluate additional changes that the protein undergoes during the course of the simulation. A different justifies an evaluation as the RMSD analysis when the recreation reaches an equilibrium. Smallest alterations in globular protein structure 1–3 Å are enough substantial. Significant reformulations suggest essential structural changes during the repair. Moreover, these changes result in stable RMSD values oscillating about a constant point, possibly indicating equilibrium. To reimplement it, the poor RMSD assessment scores of the simulation suggest that the equilibration required additional time or energy or possibly both and will need to be explored further before further implementation. The protein RMSD of Figure (11) are still in the common range of 2 Å and can be used to estimate protein stability inside a 50-nanosecond time period.

Ligand RMSD results

The right Y-axis, representing the relative ligand-protein standard deviation (RMSD), displays the stability of the ligand in regard to the protein and its binding location. The graphic illustrated the ligands' RMSD in relation to their ligand fitness on the protein structure. To compute the RMSD of the ligand overwhelming molecules, the protein-ligand complex is initially aligned to the protein backbone as a reference. If these values considerably surpass the protein's RMSD, it indicates that the ligand may deviate from its original binding location. Figure (11) illustrates that the ligand's RMSD results remained within the typical range of 1.1 Å, signifying the ligand's stability during a duration of 50 nanoseconds. According to Zhang et.al.2016 found that RMSD range of Osimertinib with EGFR is 1.5 Å which is lower than 2 Å [24], and our compound (N2) which show same range 1.1 Å, which indicted stable protein ligand complex. During the 50 ns simulation, the protein backbone's RMSD stabilized around 2 Å, indicating minor conformational fluctuations typical of globular proteins. The ligand (N2) displayed RMSD values ranging from 1.0 to 1.2 Å, suggesting it remained firmly anchored in the EGFR binding pocket.

The RMSF investigation

The Root Mean Square Fluctuation (RMSF) may serve as an effective tool for assessing localized changes in protein structure. The areas of the protein exhibiting the most significant alterations during the simulation are indicated as peaks on the graph [25]. The N- and C-terminals of the protein demonstrate more significant oscillations consistently compared to other locations. In contrast to the flexible circular districts, secondary structural elements like as alpha helices and beta strands exhibit significantly greater stability and variability. Figure 12 presents protein RMSF range values below 1 Å, while Figure 13 depicts the stability of compound N2 within the typical range, also under 1 Å. RMSF analysis showed elevated flexibility at the N-terminal and loop regions, whereas helices and β-strands remained rigid, preserving the integrity of key binding residues (Lys745, Met793).

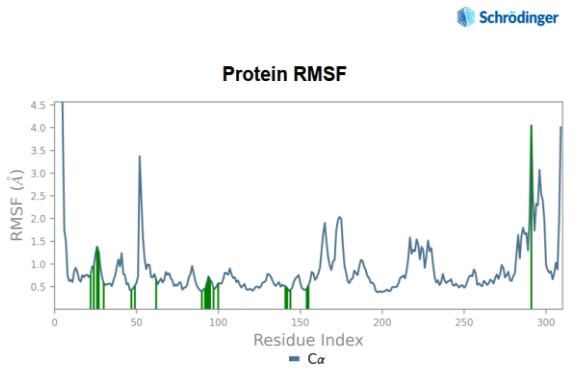

Figure (12): RMSF of the protein (N2-6LUD). The green line represents the fluctuation area of amino acid linked with ligand, while the blue line represents the fluctuation area of protein.

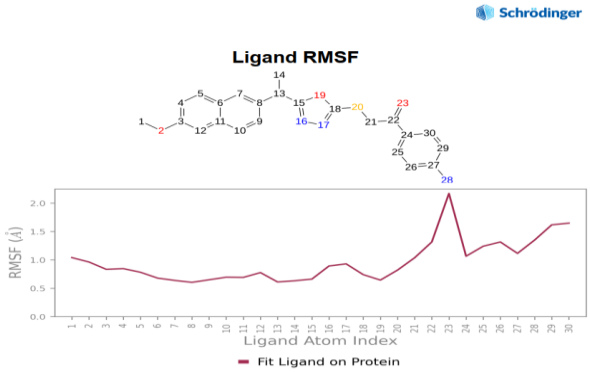

Figure (13): RMSF of the compound N2 on protein (6LUD). The red line represents the fluctuation of each atom of ligand.

Ligand-protein contact interaction

Over 30% of the simulation time in that direction is, in fact, a schematic representation of the ligand's interaction with amino acid residues of the target protein. An intuitive score of > 100% is plausible, as some residues may exhibit multiple interactions of the same type with the same ligand. As an example, the guanidine side chain of lysine 745, leucine 718, and aspartate 855 provide three hydrogen bonds that can show as one hydrogen bond acceptor (as shown in Figure 14).

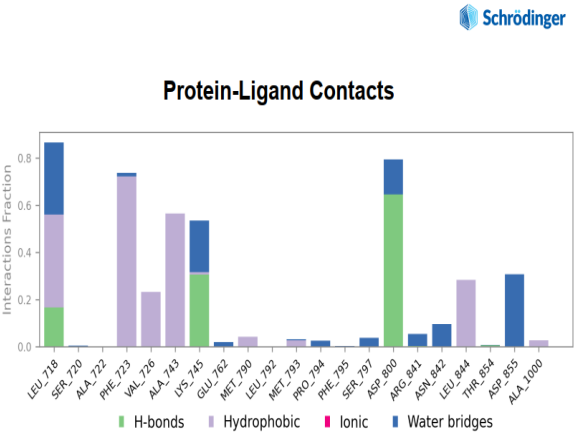

Figure (14): ligand N2-protein contacts.

Conclusion

Designing potent naproxen-derived 1,3,4-oxadiazoles, this study highlights the potential of these compounds as valuable candidates for the development of selective EGFR inhibitor-based therapeutic agents. Thorough molecular docking analyses demonstrated that these derivatives possess considerable binding affinity and persistent interactions within the EGFR kinase domain, even exceeding the efficacy of the reference inhibitor, Osimertinib, in multiple computational metrics. Moreover, advantageous ADME profiles—aligned with Lipinski's Rule of Five—demonstrate significant drug-likeness and pharmacokinetic characteristics, endorsing their potential for oral bioavailability. Molecular dynamics simulations validated the stability of these compounds in the ATP-binding region, emphasizing strong hydrogen bonding with essential residues (e.g., Lys745 and Met793) crucial for optimal TKI action. This indicates that the 1,3,4-oxadiazole scaffold not only improves bioactivity and binding efficiency but may also provide an edge in preserving efficacy against novel EGFR mutations. These computational findings collectively endorse the ongoing investigation of naproxen-derived 1,3,4-oxadiazole derivatives as novel EGFR inhibitors. Subsequent in vitro kinase tests, cell-based proliferation investigations, and in vivo evaluations are crucial to corroborate these findings and to further clarify the potential of these drugs in surmounting resistance mechanisms in EGFR-driven malignancies. Ultimately, this research may facilitate the development of tailored treatment options and enhance precision oncology.

Disclosure Statement

- **Ethics approval and consent to participate:** Not applicable. This study does not involve human participants, animal subjects, or clinical data requiring ethical approval.
- **Consent for publication:** Not applicable. This study does not involve individual person's data, images, or case reports requiring consent for publication.
- **Availability of data and materials:** The raw data required to reproduce these findings are available in the body and illustrations of this manuscript. Additionally, the protein structure used in this study (PDB ID: 6LUD) is publicly available in the Protein Data Bank (https://www.rcsb.org/structure/6LUD), and the reference compound Osimertinib was sourced from publicly available databases.
- **Author's Contribution:** The authors confirm their contributions to the paper as follows: study conception and design: Farooq Mohammed Hasan, Ayad Kareem Khan, Shakir Mahmood Alwan; molecular docking and computational analysis: Farooq Mohammed Hasan; data analysis and validation: Farooq Mohammed Hasan, Ayad Kareem Khan; manuscript writing and preparation: Farooq Mohammed Hasan, Shakir Mahmood Alwan. All authors reviewed the results and approved the final version of the manuscript.
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