Design, Molecular Docking, and Pharmacokinetic Evaluation of Naproxen-Based 2-Azetidinone Derivatives for Cancer Treatment

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Abstract:

This study investigates the design, molecular docking, and ADME properties of six novel naproxen derivatives featuring a 2-azetidinone ring, targeting EGFR kinase. Molecular docking was conducted using the crystal structure of the EGFR mutant complexed with Osimertinib (PDB ID: 6LUD). The derivatives were compared with Osimertinib using GOLD software to evaluate binding affinity and fitness. Results showed that several compounds exhibited stronger predicted binding interactions within the EGFR active site, with NR1 and NR2 displaying notably high PLP fitness scores (75.14 and 73.90, respectively). ADME analysis via SwissADME confirmed that all compounds complied with Lipinski's Rule of Five and exhibited favorable pharmacokinetic properties, including high gastrointestinal absorption and drug-likeness, which supports their potential for oral bioavailability. These computational findings suggest that the derivatives may serve as promising candidates for EGFR inhibition; however, experimental studies are required to validate their biological efficacy and therapeutic potential against mutation-mediated resistance. Overall, the results underscore the potential of 2-azetidinone-based naproxen derivatives as pharmacokinetically viable EGFR inhibitors, warranting further cellular and *in vivo* evaluation.

Keywords: EGFR inhibitors, Osimertinib, ADME analysis, Naproxen derivative, Molecular Docking.

تصميم، الإرساء الجزيئي، والتقييم الحركي الدوائي لمشتقات النابروكسين المحتوية على 2-أزيتيدينون لعلاج السرطان

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الخلاصة

تتناول هذه الدراسة تصميم، الالتحام الجزيئي، ودراسة خصائص الامتصاص والتوزيع والأيض والطرح (ADME) لستة مشتقات جديدة من النابروكسين تحتوي على حلقة 2-أزيتيدينون، مستهدفة إنزيم كيناز مستقبل عامل نمو البشرة (EGFR). تم إجراء الإرساء الجزيئي باستخدام البنية البلورية لإنزيم EGFR الطافر المرتبط بدواء أوزيمرتينيب.(PDB ID: 6LUD)

تمت مقارنة المشتقات مع الأوزيمرتينيب لتقييم الألفة الارتباطية والكفاءة باستخدام برنامج GOLD. أظهرت النتائج أن جميع المركبات اظهرت توافقا ملحوظا مع مستقبل لـEGFR ، حيث برز المركبان NR1 و NR2بتسجيلهما قيم PLP عالية بشكل ملحوظ، مما يشير إلى إمكانية تثبيط معززة.
كما أكّد تحليلADME ، الذي أُجري باستخدام منصةSwissADME ، أن جميع المشتقات مطابقة لقواعد ليبنسكي الخمس وتتمتع بخصائص حركية دوائية ملائمة، بما في ذلك الامتصاص المعوي العالي وقيم دوائية قوية، مما يدعم إمكانية توافرها الحيوي عبر الفم.
تؤكد هذه النتائج الحاسوبية مجتمعة على استعمال مشتقات النابروكسين المحتوية على 2-أزيتيدينون كمثبطات عالية الألفة وملائمة دوائياً لـ EGFR. ويُنصح في المستقبل بإجراء دراسات تكاثر الخلايا، والتقييمات الدوائية الحركية والديناميكية في الجسم الحي، والدراسات السمية للتحقق من فعاليتها العلاجية ومعالجة مقاومة الأدوية الناتجة عن الطفرات. جميع المركبات أظهرت توافقاً مثالياً مع مستقبل EGFR. وتشير هذه النتائج إلى مسار واعد لتطوير علاجات فعّالة.

الكلمات المفتاحية :مثبطاتEGFR ، أوزيمرتينيب، تحليل ADME، مشتق النابروكسين، الالتحام الجزيئي.

1. Introduction:

Cancer continues to be a leading global health issue, resulting in millions of deaths each year. Among the numerous molecular targets that play a role in tumor development, the protein referred to as Epidermal Growth Factor Receptor is distinguished as a principal regulator of cellular growth, differentiation, and survival in various cancers, including non-small cell lung cancer (NSCLC), glioblastoma, and colorectal cancer [1]. Overexpression or mutations in EGFR lead to abnormal signaling, promoting tumor growth and resistance to therapy. Key gain-of-function mutations—L858R, exon 19 deletions, T790M, and C797S—drive treatment resistance and tumor progression, prompting the development of new agents, such as Osimertinib, that target these mutations [2].

Osimertinib is a third-generation, irreversible EGFR inhibitor developed to overcome resistance caused by the T790M mutation and other mutations. It effectively targets both sensitizing EGFR-TKI and resistant mutations, such as T790M, while sparing wild-type EGFR to reduce side effects. Osimertinib forms a covalent bond with cysteine [C797] located in the ATP-binding pocket of EGFR, thereby enhancing specificity and potency. Its clinical success has established it as a benchmark in EGFR drug research, shaping the evaluation of new inhibitors [3].

EGFR (PDB ID: 6LUD) provides detailed insights into the mutant kinase domain in complex with Osimertinib, revealing key binding interactions that facilitate the evaluation of treatment strategies. We plan to analyze docking profiles of selected compounds versus Osimertinib as potential next-gen EGFR inhibitors. Due to the global impact of cancer, developing new anticancer agents is a key focus. Among chemicals, NSAIDs like naproxen, used for pain and inflammation, show promise as repurposed anticancer agents, especially in lung cancer. In the present study, naproxen–β-lactam hybrid derivatives were designed to enhance EGFR binding by introducing a rigid four-membered azetidinone ring. This structural modification enables additional hydrogen bonding and hydrophobic interactions with key residues, potentially enhancing selectivity and potency compared to previously reported NSAID-based scaffolds. [4]. The anticancer activity is attributed to its ability to engage primary molecular targets linked to cell proliferation, death, and metastasis [5].

Many anticancer drugs induce direct DNA damage in cancer cells; however, their application is limited due to concerns such as low specificity and high toxicity [6]. Targeted therapy has become the preferred approach for more precise tumor access, reducing harm to nearby healthy tissues [7]. The receptor epidermal growth factor functions as a tyrosine kinase located on the cell surface and is part of the ErbB family [8]. Over 60% of non-small cell lung cancers, 30% of breast cancers, and 40% of glioblastomas harbor activating or overexpressing mutations in EGFR family members [9].

Erlotinib is a potent, targeted inhibitor of EGFR's tyrosine kinase activity. It is used to treat pancreatic cancer, polycythemia vera (PV), and several other myeloproliferative disorders [10]. Heterocyclic compounds play a crucial role in drug development and healthcare [11]. They are essential for anti-cancer drugs, as they play a prominent role in many available treatments [12]. Naproxen was chosen due to its established safety profile and prior evidence of anticancer activity, particularly in EGFR-related pathways. Approximately 60% of FDA-approved small molecules contain nitrogen heterocycles, with four-membered rings being particularly favored due to their structural rigidity and ability to form unique three-dimensional (3D) conformations [13]. Our approach involved adding a four-membered heterocyclic ring to the Naproxen derivative to generate new compounds. These were evaluated for anti-cancer activity, selectivity, and interaction with EGFR inhibitors through *in-silico* molecular docking.

The goal is to develop a potent anti-cancer agent with fewer side effects and more effective targeting of EGFR. This research also aims to support the development of targeted therapies that can overcome drug resistance. It focuses on understanding how inhibitors bind at the molecular level, enabling rational drug design and thereby expanding treatment options for patients with EGFR-related cancers.

2. Computational Method:

The complexity and cost of developing new pharmaceuticals today make modern drug research and development expensive. Creating a novel molecule provides insight into the challenge of producing compounds with specific features [14]. Our team conducted a comprehensive literature review to inform the design of the proposed Naproxen Derivatives (see Figure 1). *In silico* modeling was employed to investigate the interaction of these compounds with the EGFR protein (Protein Data Bank ID: 6LUD). We used computational docking to compare our compounds with Osimertinib and analyze their ligand-protein interactions. The docking simulations revealed that the designed compounds stably fit within the EGFR binding cavity, forming multiple hydrogen bonds and close hydrophobic contacts. We assessed the ADME properties of the compounds using the Swiss ADME web server.

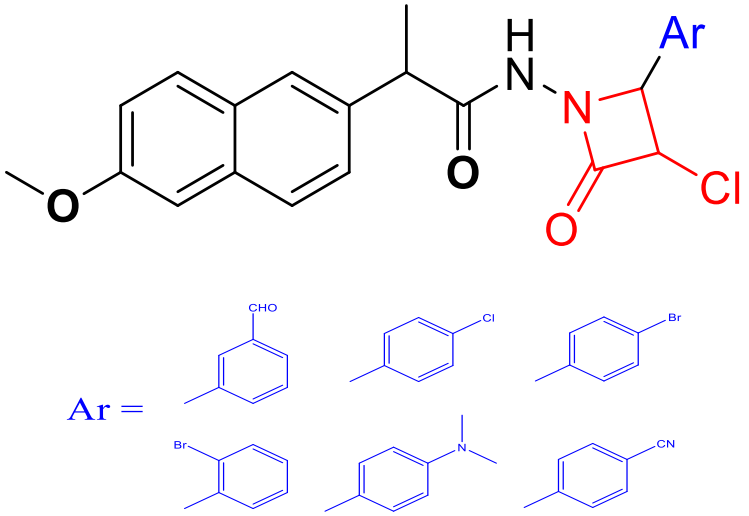


Figure 1: General structure of the designed compounds

2.1 Molecular docking:

Naproxen derivatives were sourced from existing literature, and their chemical structures were drawn with ChemDraw (version 16.0). Energy minimization of these compounds was carried out using Chem3D (version 16.0) with the MM2 force field. The new ligands were then docked onto the 3D structure of the EGFR protein (PDB code: 6LUD) complexed with Osimertinib.

The GOLD Hermes module included operational receptors, and re-docking of co-crystalized ligands confirmed the method's validity. To precisely depict tautomeric states and amino acid ionization, polar hydrogen atoms were added. The EGFR kinase receptor proteins were prepared by removing all crystallographic water molecules, except for HOH 1226 and HOH 1241, which are vital for ligand interactions in the active site. Ligand extraction was initially performed at the receptor's active site. In the CCDC GOLD suite, the Hermes visualizer was used to prepare receptors for docking, with the primary ligand interaction site identified as the active site. The binding site, measuring 10 Å, included key residues necessary for docking. Docking parameters were set to default values, generating 10 poses, with the top-ranked solution used as standard and the termination option disabled. The ChemScore kinase was used to determine the investigation parameters.

The ChemPLP scoring function used a continuous linear potential. The results were saved as. mol2 files, which display the binding energy, locations, and poses. We analyzed this data to determine the optimal way for our ligand to bind to the amino acid residues of the receptor (EGFR).

2.2 Molecular Dynamics Simulation

MD simulations used Coast for modelling and Maestro 14.1 for drug design (Schrödinger, 2024). Classical simulations with Desmond examined compound structures and enzyme complexes, with solvation modelled using the SPC/E model within a periodic boundary condition. Sodium or chloride ions neutralize the charge as needed. The NPT ensemble in Desmond was used for system stabilization. The EGFR protein structure from PDB 6LUD, at a resolution of 2.05 Å, was optimized and minimized before preparation, utilizing low-energy conformations. Docking identified

optimal orientations, creating derivatives via multiple replacements. All pyrazole derivatives were kept for drug evaluation [16].

2.3 ADME prediction:

The assessment of drug pharmacokinetics, encompassing the ADME processes (absorption, distribution, metabolism, and excretion), as well as aspects such as P-gp affinity, blood-brain barrier penetration, and bioavailability, was also taken into consideration. All compounds were designed in ChemDraw and then converted into SMILES names and Swiss ADME. This ADME prediction study helped pinpoint potential safety concerns and discard compounds with undesirable ADME profiles, aiming to minimize the need for experimental drug trials and enhance the chances of success.

3. Results and Discussion:

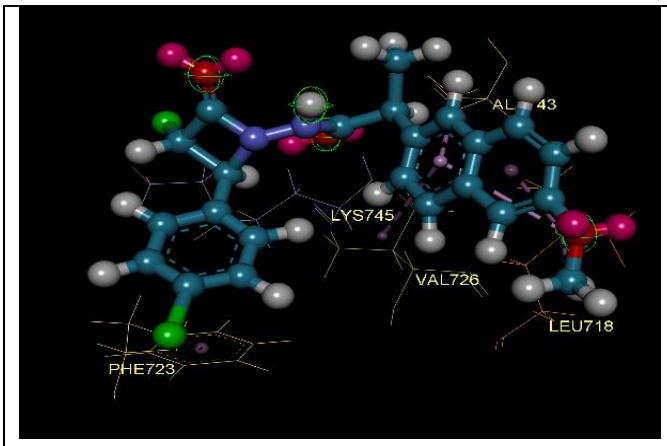
The goal is to design efficient and exact compounds with strong selectivity characteristics and favorable ADME properties.

3.1 Molecular Docking Analysis:

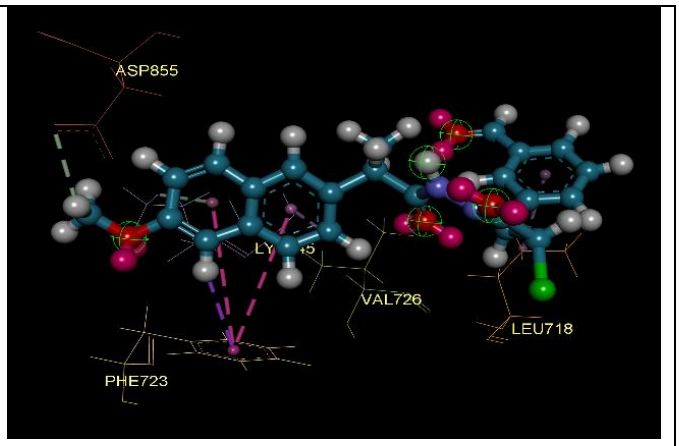
Molecular docking predicts how a ligand interacts with a known protein structure by recreating thousands of ligand conformations in the binding region to find the proposed compounds, which showed good binding potential at the receptor's active site. Commonly used in virtual screening, it identifies hit molecules through their binding affinity and energy, playing a key role in early drug discovery [17]. Additionally, molecular docking has been employed to evaluate the potential of established drugs, such as naproxen, for new therapeutic uses. Naproxen, a widely used NSAID, shows promise for anticancer activity by interacting with various molecular targets that influence cancer cell growth and spread. This suggests it could be repurposed for cancer treatment [18].

The docking process identifies hydrogen bonds and short contact distances between protein atoms and ligands. An increased number of hydrogen bonds and hydrophobic interactions can improve biological activity. The substrate must bind to the active site. This study employed molecular docking to investigate the interaction of osimertinib with the EGFR receptor. Results showed that each molecule adopted a similar binding mode within the EGFR binding site. Figures 2 and 3 display the interaction of the tested compounds with the active site of EGFR, docked in its 3D and 2D structure within the pocket. The observed enhanced binding affinity of NR1, NR2, and NR6 can be attributed to the β-lactam ring, which provides additional rigidity and optimizes interactions with MET793, LYS745, and ASP855 residues, differentiating these derivatives from previously reported NSAID scaffolds. These binding sites are identified by their PDB IDs, as shown in Table 1, specifically 6LUD. The docking scores of the compounds were compared to those of Osimertinib, used as a reference. All compounds achieved better docking scores than the reference, indicating more favorable binding.

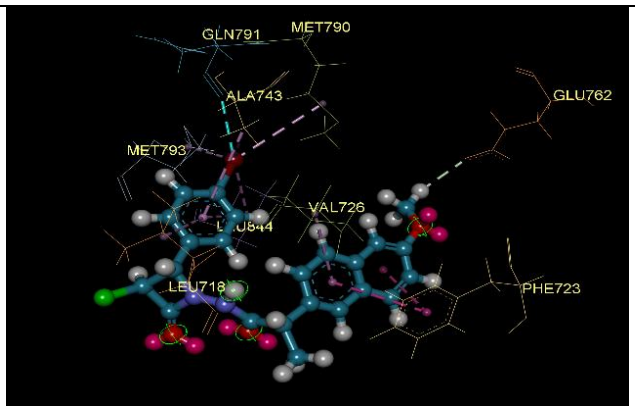
Naproxen derivative compounds incorporate an azetidine ring, which enhances EGFR binding affinity through hydrogen and halogen bonding with critical residues. Its hydrophobic and electron-withdrawing properties further stabilize these interactions.



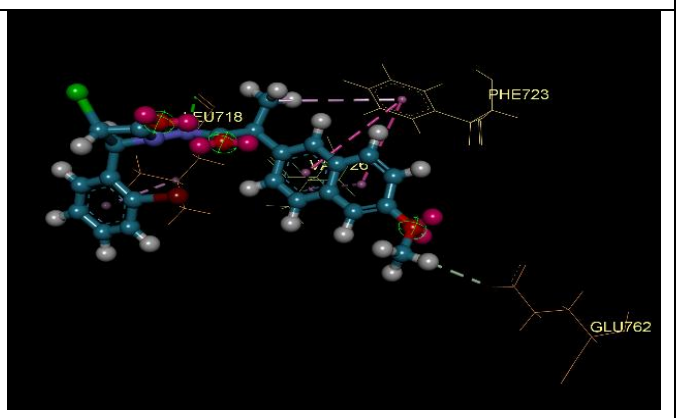
NR1



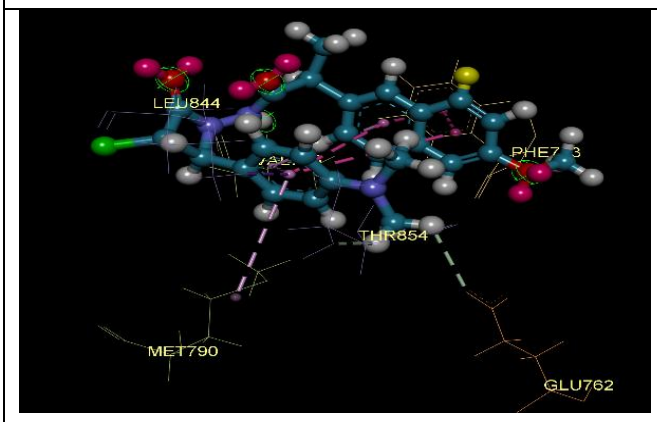
NR2



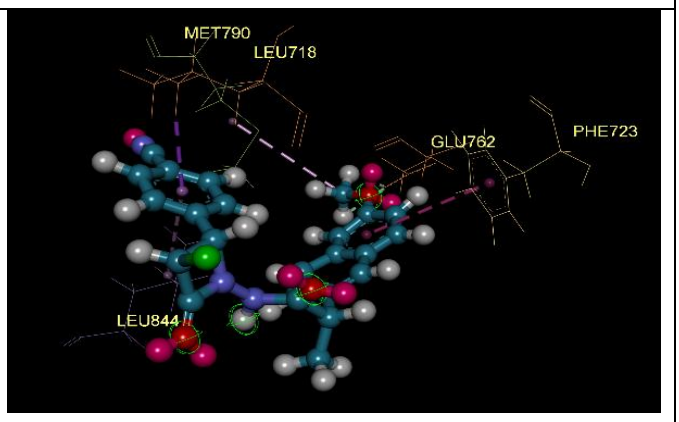
NR3



NR4



NR5



NR6

Figure 2: The interaction of proposed compounds with the active binding site of EGFR docked in 3-dimensional structures inside the pocket.

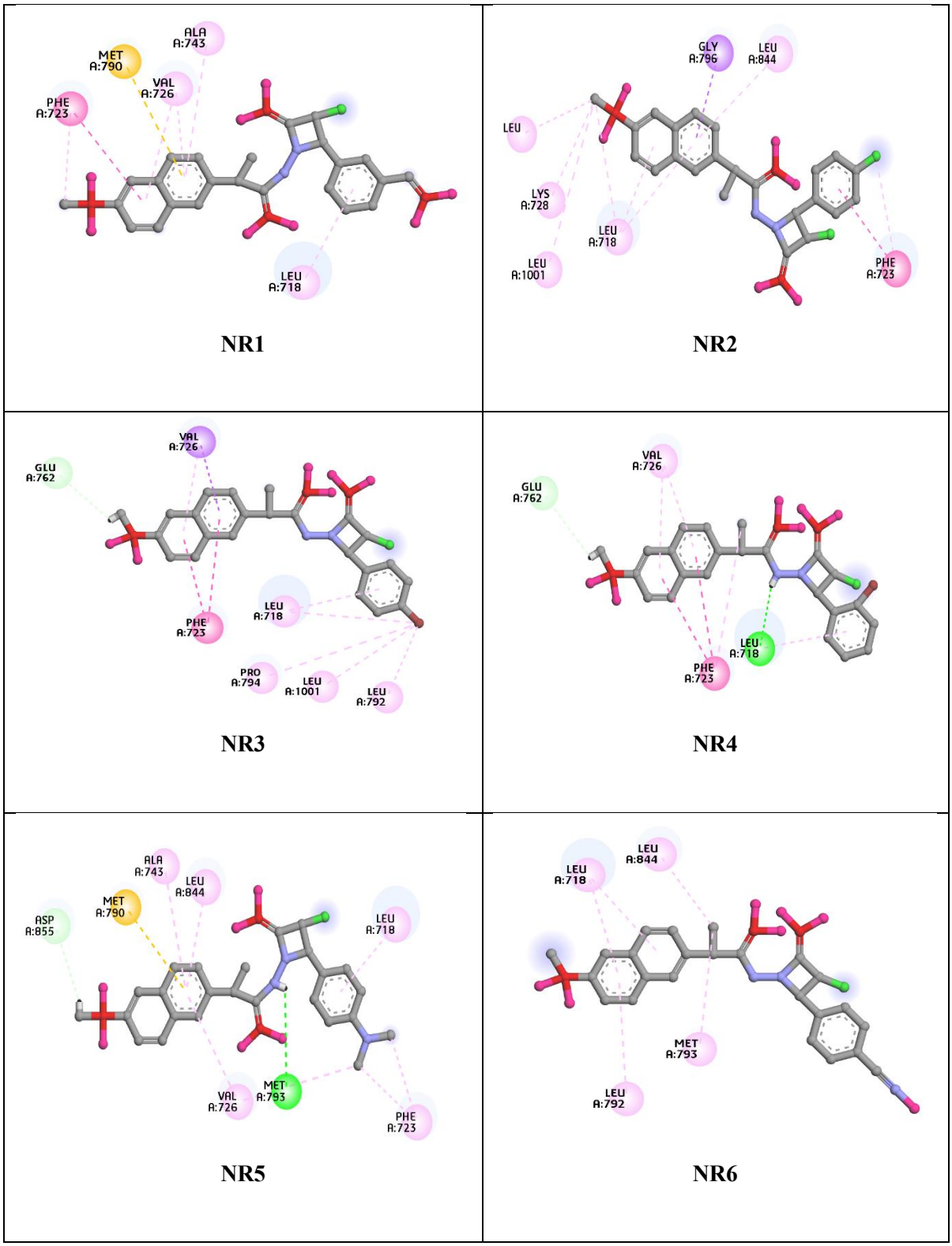


Figure 3: The interaction of proposed compounds with the active binding site of EGFR docked in 2-dimensional structures inside the pocket.

Table 1: The binding affinity for Osimertinib derivatives as a reference drug and NSAIDs docked with the EGFR receptor.

Compounds name	PLP Fitness) average scores)	Amino acids involve	
		Hydrogen bonding	Short contact
NR1	**75.14**	MET790, LEU718, LYS745	LYS745, PHE723, GLY719, LEU718, MET793, VAL736, PHE723, ASP855, VAL726, ALA743
NR2	73.90	LYS745, LYS718	LYS745, PHE723, LEU718, MET793, LEU792, ALA743, GLY796, LEU844, LYS728
NR3	72.98	THR854	LEU792, LEU844, LEU844, THR854, LEU718, PHE723, MET790, GLU762, ALA743, LEU718, VAL726
NR4	70.18	LYS745	LEU1001, VAL726, ALA743, LEU792, LYS745, PHE723, LEU718, GLU762
NR5	69.80	MET793, LYS745	LYS745, VAL726, GLY719, LEU718, LYS745, THR854, LEU844, MET790, GLU760, PHE723, LEU844, ALA743
NR6	69.94	LEU844	LEU792, LEU844, PHE723, LEU718, LYS745, MET790, GLU760, PHE723, MET793
Osimertinib	**64.16**	SER797, and GLN791	PHE723, VAL726, MET793, LEU844, MET790, LEU792, PRO794, LEU718, ASP800, GLU804, GLY796, and ALA743.

3.2 Molecular Dynamics Simulation:

Molecular dynamics simulations (MD) are a key technique in chemistry, biophysics, pharmacology, and biochemistry for analyzing the biological properties of molecules. The NR1-EGFR complex was analyzed through MDS to confirm its interaction. Molecular dynamics analysis revealed how the ligand interacts dynamically with crucial residues that affect its effectiveness and presence in the protein's binding pocket. Results showed that the ligand's RMSD was below 1 Å, and the protein's RMSD in the complex was between 2 and 2.5 Å, indicating stability (Figure 4A).

The Root Mean Square Fluctuation (RMSF) is a valuable metric for assessing localized changes in protein structure. Peaks on the graph highlight regions with the most notable changes during the simulation. RMSF analysis indicated that most of the protein exhibited values below 1 Å, supporting its structural stability (Figure 4B). To confirm the interaction between NR1 and EGFR, a molecular dynamics simulation was performed to assess the stability of the complex under near-physiological conditions. The ligand RMSF remained within the typical range of 1 to 2.5, as shown in Figure 4C.

The data revealed that the protein's secondary structure remained intact at 43.66% over time (Figure 4D). Key residues involved in protein-ligand contacts included LEU718, ALA722, VAL726, LYS728, GLU762, and VAL843, which form hydrophobic interactions; ALA743 and LEU792, which participate in hydrogen bonds; and a water bridge involving GLU804, THR855, and ALA743, as shown in Figure 4E. Throughout more than 54% of the simulation, NR1 interacted with EGFR (Figure 4F).

The ligand torsions plot shows how each rotatable bond (RB) changes conformation during the simulation. Dial plots illustrate conformational changes over time, starting at the center and moving outward radially. Bar plots illustrate torsion probability density, yielding good results, as shown in Figure 4G.

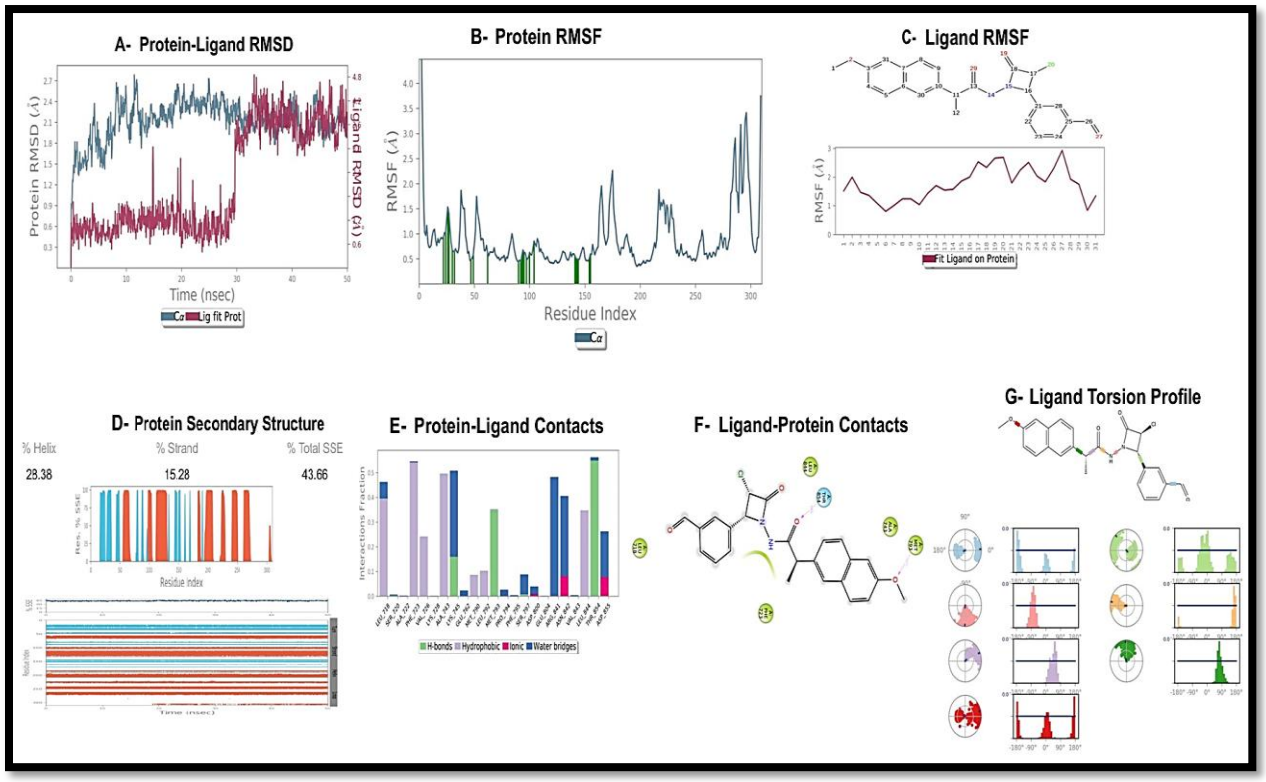


Figure 4: Molecular dynamics simulation of the EGFR–compound NR1 complex.

3.3 ADME Profile:

Key pharmacokinetic factors, including absorption rates and clearance, are crucial in the development of safe and effective drugs. Although binding to a protein alone doesn't guarantee proper activity, assessing absorption, distribution, metabolism, and excretion early in development remains vital [22]. For drug disclosure, it is essential to thoroughly assess the ADME profile and Lipinski's Rule of Five to evaluate the efficiency of integrating inhibitors. ADME properties often lead to clinical failure. Lipinski's Rule provides criteria for selecting potential candidates based on oral bioavailability [23]. The compounds with a TPSA value below 140 Å generally exhibit high porosity and good oral bioavailability [22].

The results show that the designed compounds adhere to Lipinski's rule of Five and demonstrate good bioavailability. They include compounds such as Osimertinib as references. Evaluation of compounds NR1 to NR6 revealed favorable drug-like properties in all candidates. As shown in Tables 2 and 3, Figures 3 to 8, all compounds meet Lipinski's Rule of Five, indicating good oral bioavailability. Molecular weights (MW) ranged from 433.89 to 487.77.

All compounds displayed a bioavailability score of 0.55, which is considered moderate

and acceptable. Furthermore, the topological polar surface area (TPSA) values ranged from 58.64 Å² to 82.43 Å², which is well below the critical threshold of 140 Å², indicating high gastrointestinal (GI) absorption. This prediction was consistent across all compounds, as each showed a "High" GI absorption rating. Suggesting sufficient permeability. cLogP values were within the acceptable range (3.54–4.38), indicating a balance between hydrophilicity and lipophilicity. Regarding blood–brain barrier (BBB) permeability, all compounds were predicted to be BBB permeant, which may indicate their potential for central nervous system (CNS) activity. Except that NR6 was not expected to cross the BBB. Additionally, NR5 was identified as a substrate of P-glycoprotein (Pgp), which could potentially limit its intracellular accumulation due to active efflux mechanisms. The remaining compounds were not predicted to be P-glycoprotein (Pgp) substrates, implying potentially improved bioavailability. The naproxen–β-lactam derivatives, all containing a benzaldehyde moiety, exhibited distinct structure–activity relationships based on their substitutions. NR1 (meta-CHO) and NR2 (para-Cl) showed high docking scores (75.14 and 73.90) with strong hydrogen bonding and high GI absorption. NR3 (para-Br) and NR4 (ortho-Br) maintained good docking (72.98 and 70.18) with favorable lipophilicity and BBB permeability. NR5 (para-N(CH3)2) combined moderate docking (69.80) with P-gp substrate behavior, while NR6 (para-CN) showed balanced docking (69.94) and ADME properties but lacked BBB permeability. These results indicate that the position and electronic nature of the substituents on the benzaldehyde ring strongly influence both EGFR binding affinity and pharmacokinetic profiles.

Table 2: Output parameters of Pharmacokinetic and ADME Parameters for all proposed compounds.

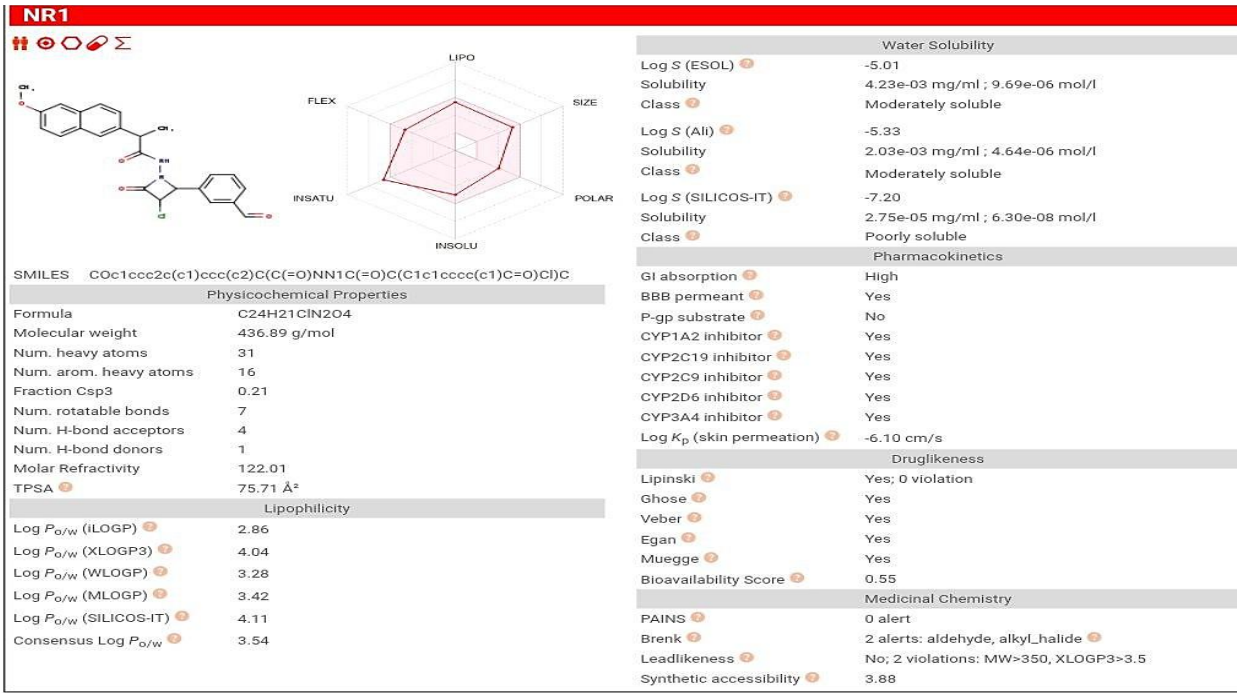
Compound	M.W	H.B.A	H.B.D	MR(m^3/mol)	TPSA(°A^2)	G.I absorption
NR1	**436.89**	**4**	**1**	**122.01**	**75.71**	**High**
NR2	**443.32**	**3**	**1**	**121.63**	**58.64**	**High**
NR3	**487.77**	**3**	**1**	**124.32**	**58.64**	**High**
NR4	**487.77**	**3**	**1**	**124.32**	**58.64**	**High**
NR5	**451.95**	**3**	**1**	**130.83**	**61.88**	**High**
NR6	**433.89**	**4**	**2**	**121.34**	**82.43**	**High**

M.W: Molecular weight, H.B.A: hydrogen bond acceptors, H.B.D: Hydrogen bond donors, MR: Molar Refractivity, TPS: Topological Polar Surface Area, G.I: Gastrointestinal.

Table 3: *Insilico* ADME screening for proposed compounds.

Compound	B.B.B permeant	Pgp substrate	Lipinski violation	Bioavailability Score	cLogP
NR1	**Yes**	**No**	**0**	**0.55**	**3.54**
NR2	**Yes**	**No**	**1**	**0.55**	**4.34**
NR3	**Yes**	**No**	**1**	**0.55**	**4.38**
NR4	**Yes**	**No**	**1**	**0.55**	**4.36**
NR5	**Yes**	**Yes**	**0**	**0.55**	**3.79**
NR6	**No**	**No**	**0**	**0.55**	**3.62**

B.B.B: Blood Brain Barrier, P-g p: P Glycoprotein, cLogP: consensus LogP



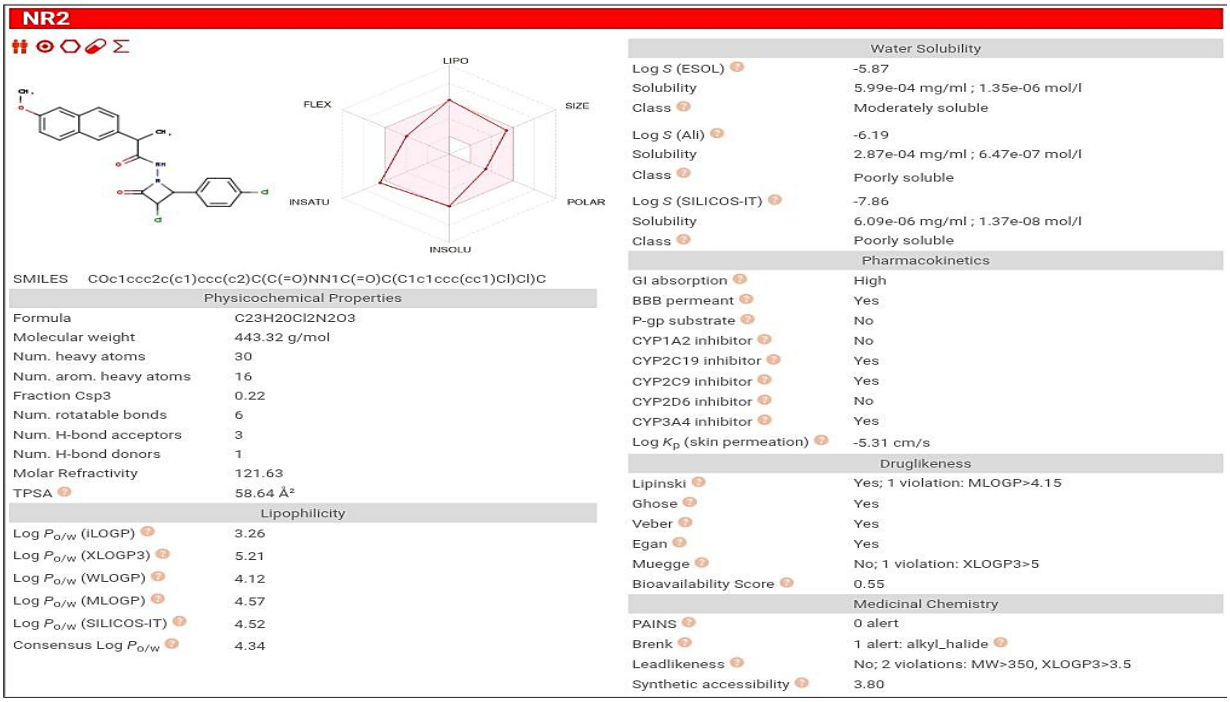
NR1

SMILES COc1ccc2c(c1)ccc(c2)C(C(=O)NN1C(=O)C(C1c1cccc(c1)C=O)Cl)C

Physicochemical Properties	
Formula	C24H21ClN2O4
Molecular weight	436.89 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	16
Fraction Csp3	0.21
Num. rotatable bonds	7
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	122.01
TPSA	75.71 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.86
Log $P_{o/w}$ (XLOGP3)	4.04
Log $P_{o/w}$ (WLOGP)	3.28
Log $P_{o/w}$ (MLOGP)	3.42
Log $P_{o/w}$ (SILICOS-IT)	4.11
Consensus Log $P_{o/w}$	3.54

Water Solubility	
Log *S* (ESOL)	-5.01
Solubility	4.23e-03 mg/ml ; 9.69e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.33
Solubility	2.03e-03 mg/ml ; 4.64e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.20
Solubility	2.75e-05 mg/ml ; 6.30e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.10 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: aldehyde, alkyl_halide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.88

Figure 4: ADME study of NR1.



NR2

SMILES COc1ccc2c(c1)ccc(c2)C(C(=O)NN1C(=O)C(C1c1ccc(cc1)Cl)Cl)C

Physicochemical Properties	
Formula	C23H20Cl2N2O3
Molecular weight	443.32 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	16
Fraction Csp3	0.22
Num. rotatable bonds	6
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	121.63
TPSA	58.64 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.26
Log $P_{o/w}$ (XLOGP3)	5.21
Log $P_{o/w}$ (WLOGP)	4.12
Log $P_{o/w}$ (MLOGP)	4.57
Log $P_{o/w}$ (SILICOS-IT)	4.52
Consensus Log $P_{o/w}$	4.34

Water Solubility	
Log *S* (ESOL)	-5.87
Solubility	5.99e-04 mg/ml ; 1.35e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.19
Solubility	2.87e-04 mg/ml ; 6.47e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.86
Solubility	6.09e-06 mg/ml ; 1.37e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.31 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: alkyl_halide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.80

Figure 5: ADME study of NR2.

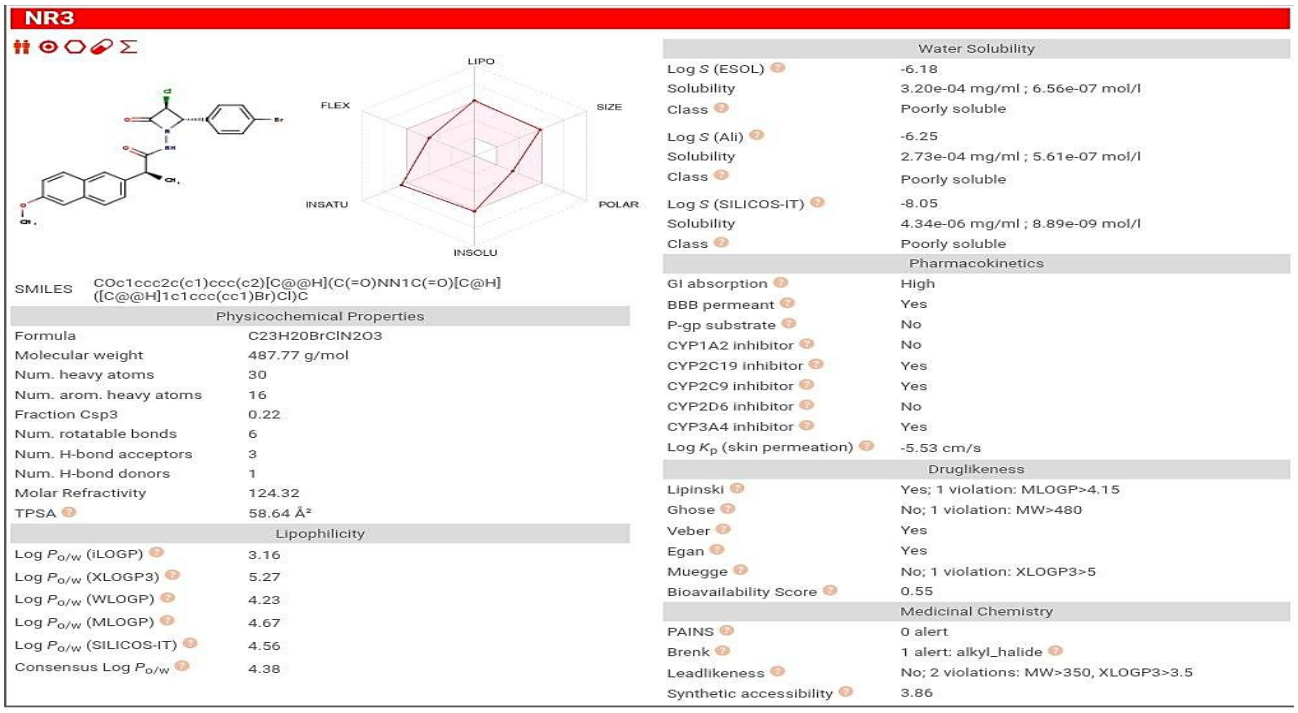


Figure 6: ADME study of NR3.

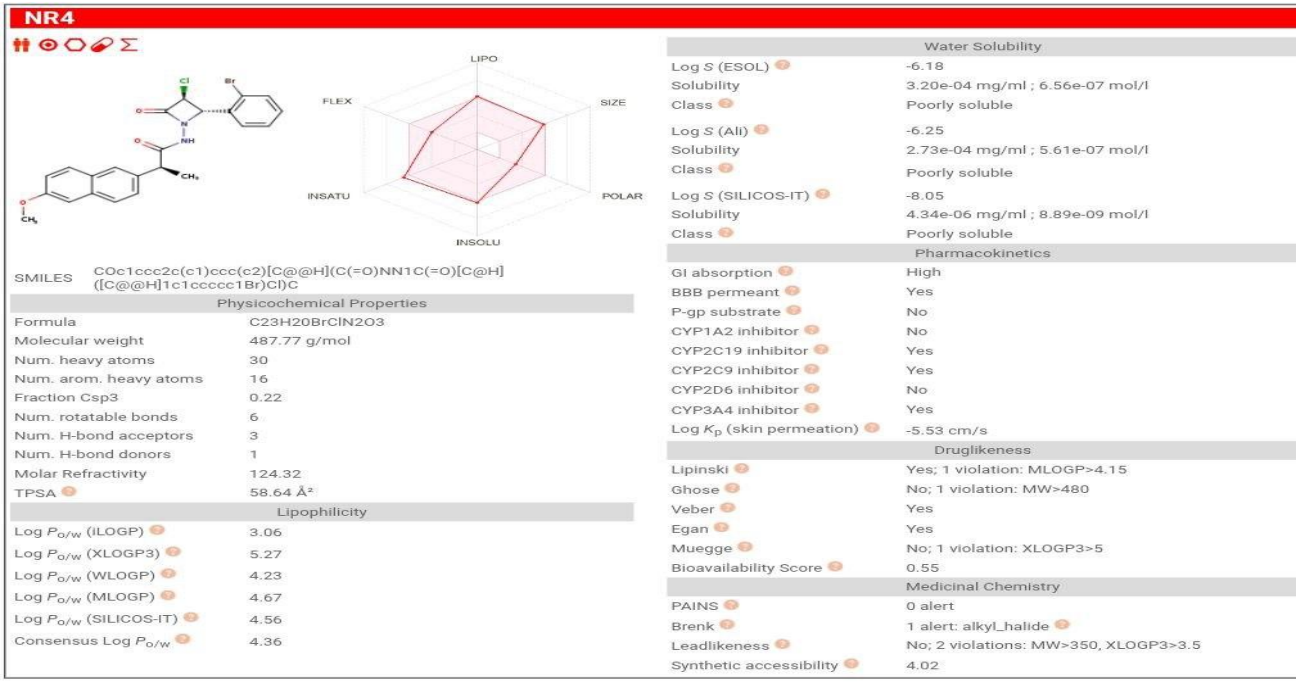


Figure 7: ADME study of NR4.

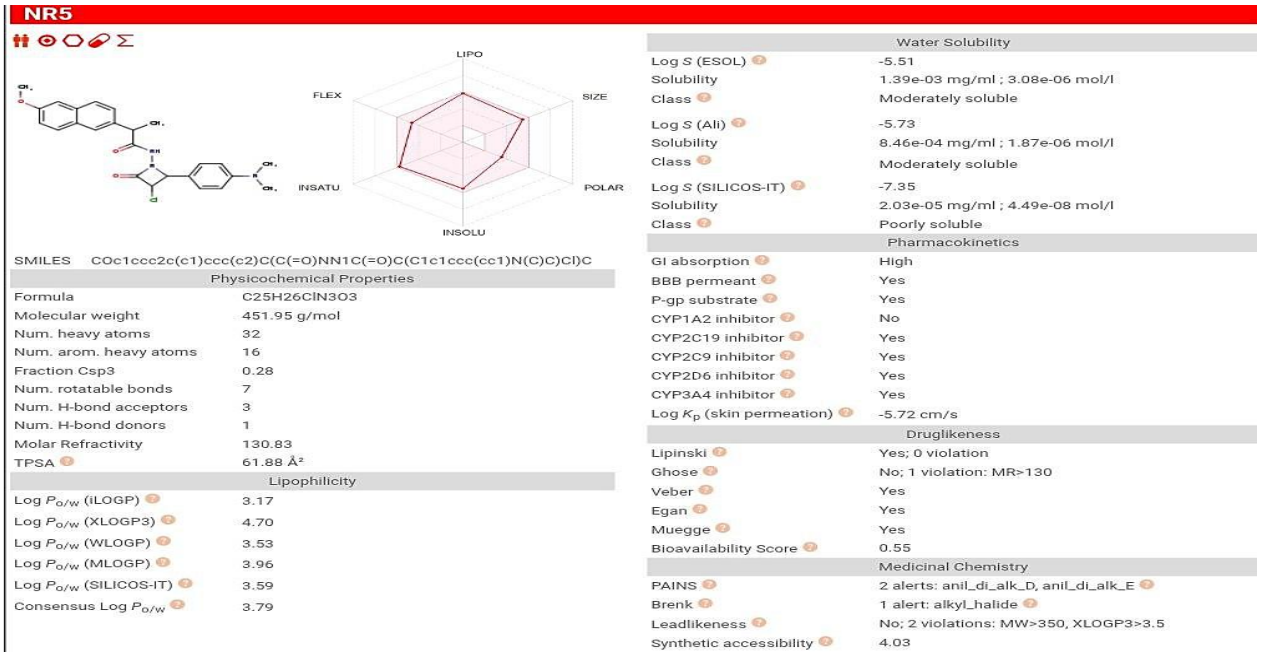


Figure 8: ADME study of NR5.

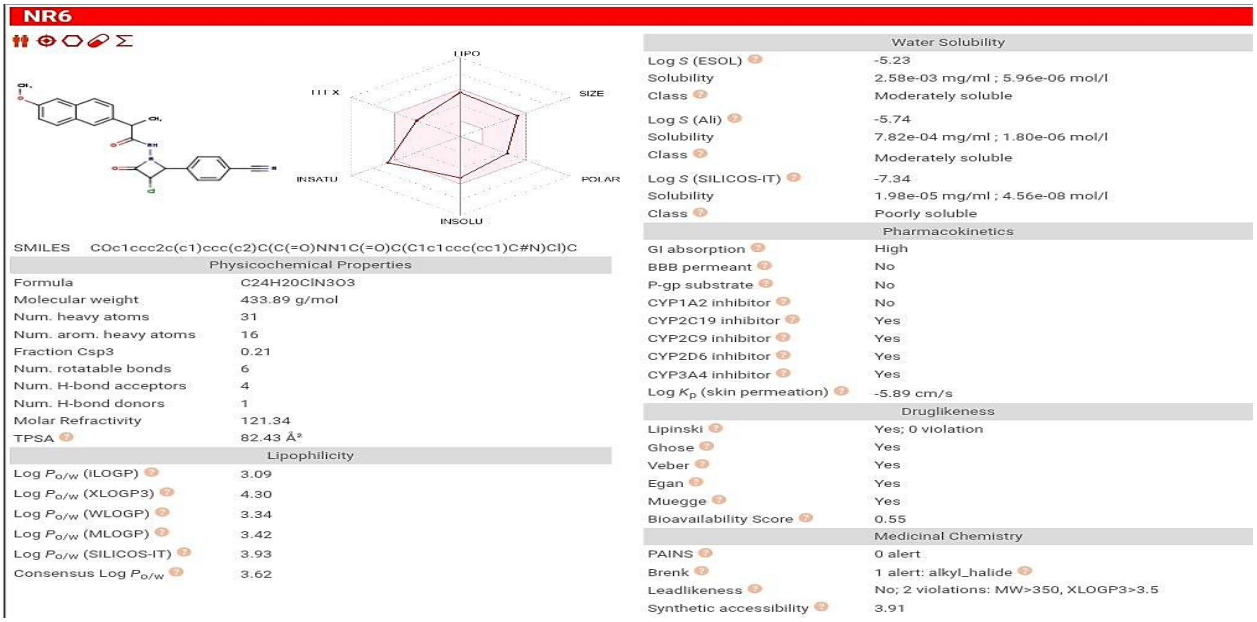


Figure 9: ADME study of NR6.

4. Conclusions:

This study conducts a detailed computational analysis of new 2-azetidinone derivatives being developed as potential anti-cancer agents targeting the EGFR pathway. Molecular docking results reveal that these compounds bind strongly within the EGFR kinase active site, sometimes even surpassing the reference inhibitor Osimertinib. Their interactions with key residues in the binding pocket suggest they act as competitive inhibitors of ATP, potentially blocking EGFR-driven cancer signaling. Additionally, ADME assessments using SwissADME indicate that these candidates comply with Lipinski's Rule of Five and exhibit favorable oral bioavailability features, including high gastrointestinal absorption, good drug-like properties, and suitable physicochemical profiles, which support their potential for oral therapy. The study also shows that the position and electronic nature of substituents on the benzaldehyde part of naproxen–β-lactam derivatives significantly affect EGFR binding affinity and pharmacokinetics, thus revealing important structure–activity relationships for designing powerful, bioavailable anticancer agents. Overall, these results underscore the potential of the lead compound series—particularly those containing the 2-azetidinone scaffold—as core structures for EGFR inhibitor development. The designed compounds showed better predicted docking scores and favorable ADME profiles compared to Osimertinib, indicating potential as EGFR inhibitors; however, experimental validation is necessary to verify their biological activity. Moving these molecules toward clinical use will require further in vitro kinase inhibition assays, cell proliferation studies, and in vivo testing to establish their efficacy and safety.

5. Acknowledgement:

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