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Article

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In silico screening of novel designed series of pyrazolidine compounds targeting Epidermal Growth Factor Receptor

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Abstract:

Cancer remains a leading cause of global mortality, with epidermal growth factor receptor (EGFR) playing a critical role in tumour progression and drug resistance. Despite the availability of several EGFR inhibitors, their clinical efficacy is often limited by toxicity and the emergence of resistant mutations. In the present study, a novel series of pyrazolidine derivatives was designed and evaluated for their potential as EGFR inhibitors using in silico approaches. A total of thirty compounds were subjected to molecular docking against the EGFR kinase domain, revealing strong binding affinities with binding energies ranging from -7.2 to -12.7 kcal/mol. Among these, compound J28 demonstrated the most favourable binding energy (-12.7 kcal/mol) and formed stable interactions with key active site residues, including LYS721 and MET769.

Furthermore, pharmacokinetic and toxicity profiles assessed using in silico ADMET tools indicated that all compounds complied with Lipinski's rule of five and exhibited favourable drug-like properties. Molecular dynamics simulations of the J28-EGFR complex over 20 ns confirmed the stability of the interaction, with consistent RMSD and RMSF profiles indicating minimal structural fluctuations. The results suggest that compound J28 is a promising lead candidate with potential inhibitory activity against EGFR. This study highlights the potential of pyrazolidine derivatives as effective anticancer agents and provides a foundation for further experimental validation and drug development.

Keywords: Pyrazolidine derivatives, EGFR inhibitors, Molecular docking, Molecular dynamics simulation, Anticancer activity

Introduction:

Cancer is the second leading cause of death worldwide after cardiovascular diseases and is primarily characterized by uncontrolled cell proliferation resulting from genetic and molecular alterations [1]. Each year, approximately 10 million individuals are affected by various forms of cancer, contributing significantly to global mortality [2]. It is estimated that one in six deaths worldwide is attributable to cancer, highlighting its substantial public health burden [3]. Although early detection and available therapeutic strategies can improve survival outcomes, effective treatment remains a challenge for a significant proportion of patients, with nearly 50–70% of cases lacking curative options [4].

Cancer progression is governed by complex molecular pathways, making the identification of suitable therapeutic targets essential for effective treatment [5]. Multiple factors contribute to cancer development, including lifestyle, dietary habits, environmental exposure, and aging [6]. Among various cancer types, breast and lung cancers account for a major proportion of global incidence, and their treatment is often complicated by the development of drug resistance. Conventional therapies such as chemotherapy and radiotherapy, although effective, are associated with severe side effects including bone marrow suppression and systemic toxicity [7]. These limitations have driven extensive research toward the identification of novel molecular targets for cancer therapy, among which the epidermal growth factor receptor (EGFR) has emerged as a key biomarker [8].

Quinazoline-based compounds are well-known for their antihypertensive and anticancer properties, primarily acting through inhibition of the ATP-binding site of the EGFR kinase domain, thereby suppressing downstream signaling pathways involved in cancer cell proliferation [9]. Structural modification of quinazoline derivatives has demonstrated improved therapeutic efficacy and reduced toxicity. EGFR plays a crucial role in tumour progression and is widely recognized as a promising target for anticancer drug development. However, the clinical application of existing EGFR inhibitors, such as gefitinib, erlotinib, and afatinib, is often limited due to the rapid emergence of resistance caused by receptor mutations, as well as adverse side effects associated with long-term therapy [10].

In light of these challenges, there is a growing need to develop novel compounds with improved binding affinity, reduced toxicity, and enhanced pharmacokinetic properties. In this context, the present study focuses on the design and evaluation of a series of novel derivatives using molecular

docking and molecular dynamics simulations to investigate their interaction with the EGFR kinase domain. Furthermore, pharmacological and toxicological profiling was performed to assess the drug-likeness and safety of the designed compounds, providing a comprehensive computational framework for the identification of potential lead molecules for anticancer therapy.

Materials & methods:

Computational methods:

Software and program

Discovery studio visualizer [11] is employed to depict the receptors, ligand structures, hydrogen bonding network, measure bond lengths, and generate images. Chemsktech [12] was utilized to create the ligand compounds. AutoDock 4.0 [13] serves as the main docking software utilized in this study for semi-flexible docking analyses. The ligands and protein receptors were prepared in pdbqt format, and the grid box size was determined using Auto-Dock Tools version 1.5.6. The ADMET properties of the compounds were studied using Molinspiration's Orissis property explorer program [14]

Preparation of protein receptor and Ligand

The EGFR kinase domain's crystal structure [PDB: 1M17] was sourced from the Protein Data Bank (PDB) [15]. The crystal structure had numerous absent atoms that were filled in by the repair commands feature of AutoDock. Prior to docking, the water molecules were removed to clean the protein crystal structure. H-atoms were incorporated into these target proteins to ensure accurate ionization and tautomeric forms of amino acid residues. The altered structure obtained was utilized for the semi-flexible dockings. The ligand molecules were created using Chemsketch software. The energy of the ligand molecule and receptors was minimized using Steepest Descent and Conjugate Gradient methods in Accelrys Discovery Studio [11]. The CHARMM force field [16] was used to execute the minimization techniques.

Semi-flexible docking

AutoDock Version 4.0 is utilized to forecast the binding pose and the corresponding energy predictions of the compounds interacting with the drug target EGFR Kinase domain. The procedure used for conducting the docking studies with AutoDock version 4.0 to forecast binding poses and IC50 values, as well as the related binding energies, adheres to the default protocol. In summary, the energy scoring grid box was configured to 126, 126, and 126 Å (x, y, and z), centered

at X = 0.041; Y = -0.068; and Z = 0.128, with a grid point spacing of 0.375 angstroms using the default atomic salvation settings. The grid box was created so that the active site of the EGFR kinase domain was enclosed by a three-dimensional grid box that centered on the location of its active ligand binding site. Lamarckian Genetic Algorithm (LGA) [17] was chosen as the docking engine, using default settings for all docking parameters. Following every LGA execution, AutoDock provides the optimal docking solution for each docked complex, and the findings are presented based on cluster analysis. Binding Gibbs free energy (ΔG) is determined by summing six energy components: dispersion/repulsion, electrostatic forces, hydrogen bonds, deviations from covalent geometry, desolvation impacts, and internal ligand torsional restrictions. Out of 10 docking modes indicated by LGA cluster analysis, the lowest energy docking was chosen from every docking simulation. Every compound featured active rotatable bonds that rendered them flexible.

Pharmacological properties of the compounds:

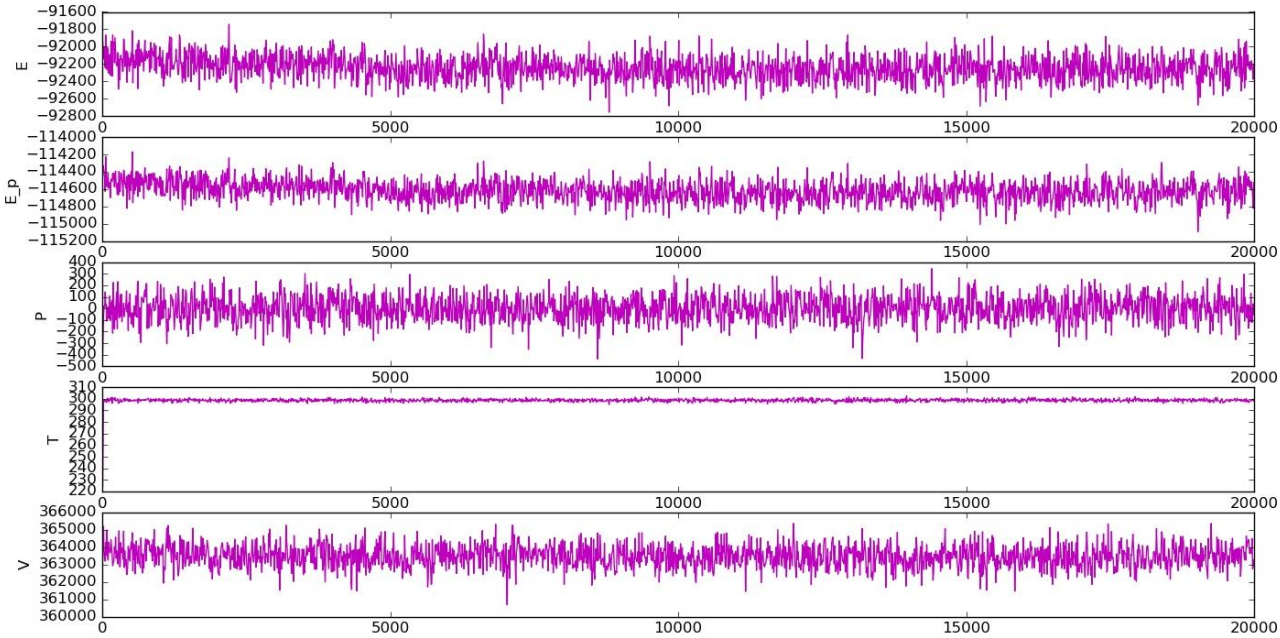
Osiris Property Explorer (www.organicchemistry.org/prog/peo/) [14] online tool and Data Warrior software [18] were utilized to evaluate the pharmaceutical integrity of the drug candidates. Molecular descriptors, including Log P, the count of hydrogen bond donors, the count of hydrogen bond acceptors, and the molecular weight of the compounds were evaluated. Osiris Property Explorer was utilized to examine different characteristics of the drugs, including toxicity.

Molecular dynamic simulations

Molecular dynamics simulations were conducted to comprehend the binding interactions at the molecular level and to evaluate those interactions at the atomic level utilizing the default protocol. In summary, parameters from the OPLS 2005 force field [19] have been utilized for simulating TIP3P water models [20] under neutral pH conditions. Periodic boundary conditions were applied to define the specific dimensions and configuration of the water box buffered at 10 Å distances, resulting in a box volume of approximately 364000 cubic units as derived from the simulation box volume. In the equilibration phase, van der Waals and short-range electrostatic interactions were

truncated at 9 Å, while long-range electrostatic interactions were calculated using the Particle Mesh Ewald approach [21]

A RESPA integrator [22] was employed with a time step of 2 fs, and long-range electrostatics were calculated every 6 fs. Each of the four conditions had a system with roughly 36506 atoms equilibrated using Desmond in the NPT ensemble at a temperature of 300 K and 1 bar, employing the Nose-Hoover chain relaxation thermostat method and the Martyna-Tobias-Klein relaxation Barostat method with isotropic coupling at 1ps and 2ps timescales, respectively. Prior to commencing the analysis, we ensured that all simulations were conducted under uniform temperature, pressure, and volume conditions across the entire simulated duration. During the analysis of simulation quality, it was found that the average total energy of the simulated systems was around -92000 kcal/mol (supplementary figure 1)



Supplementary figure 1: Simulation quality analysis graphs of EGFR kinase domain in complex with J28 compound.

Results & Discussion:

Docking of the compounds with EGFR Kinase domain active site

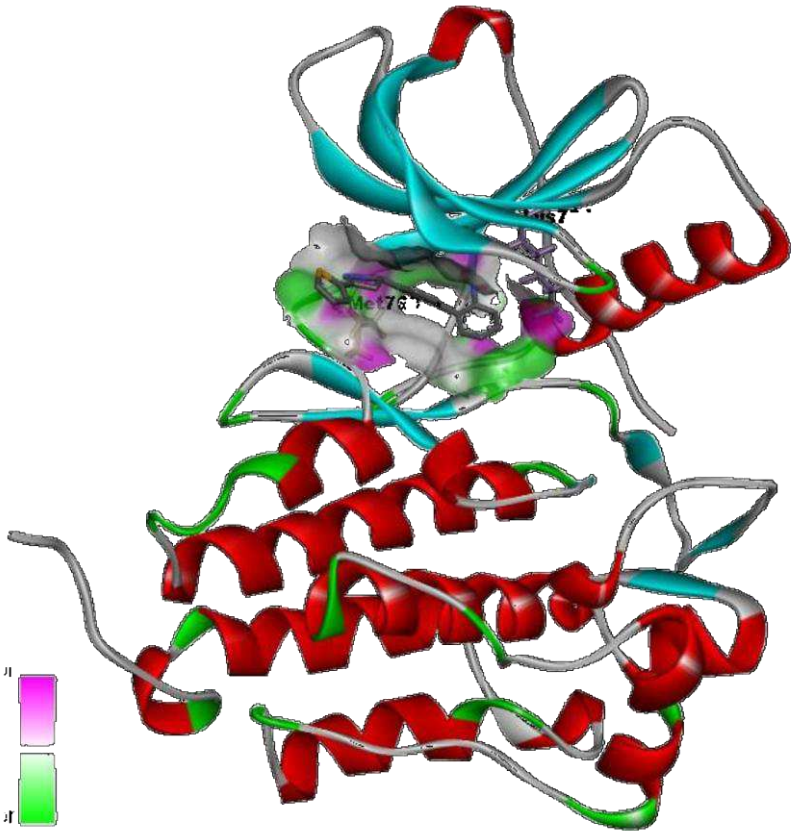
We conducted docking studies on the thirty compounds currently analyzed with the EGFR Kinase domain protein, focusing on its active binding site to determine the binding energy related to this complex formation and to identify the molecular interactions that contribute to this target-specific inhibition. The results of docking are presented in Table 1. All thirty compounds analyzed in this study demonstrated successful docking within the active site of the EGFR kinase domain, exhibiting binding energies between -7.2 and -12.7 Kcal/mol

Table 1: Docking results of Compounds targeting EGFR (PDB ID: 1M17)

Sl.no	Ligand	Target	Binding Energy (Kcal/mol)
1.	J01	EGFR_1M17_Prep	-7.2
2.	J02	EGFR_1M17_Prep	-8.8
3.	J03	EGFR_1M17_Prep	-9.2
4.	J04	EGFR_1M17_Prep	-9.3
5.	J05	EGFR_1M17_Prep	-9.3
6.	J06	EGFR_1M17_Prep	-9.3
7.	J07	EGFR_1M17_Prep	-9.1
8.	J08	EGFR_1M17_Prep	-9.0
9.	J09	EGFR_1M17_Prep	-9.0
10.	J10	EGFR_1M17_Prep	-8.9
11.	J11	EGFR_1M17_Prep	-8.8
12.	J12	EGFR_1M17_Prep	-8.8
13.	J13	EGFR_1M17_Prep	-9.9
14.	J14	EGFR_1M17_Prep	-9.4
15.	J15	EGFR_1M17_Prep	-9.7
16.	J16	EGFR_1M17_Prep	-11.8
17.	J17	EGFR_1M17_Prep	-11.9
18.	J18	EGFR_1M17_Prep	-11.7
19.	J19	EGFR_1M17_Prep	-12.1
20.	J20	EGFR_1M17_Prep	-11.7
21.	**J21**	**EGFR_1M17_Prep**	**-12.2**
22.	J22	EGFR_1M17_Prep	-12
23.	J23	EGFR_1M17_Prep	-12.1
24.	J24	EGFR_1M17_Prep	-12.0
25.	J25	EGFR_1M17_Prep	-11.8
26.	J26	EGFR_1M17_Prep	-11.8
27.	J27	EGFR_1M17_Prep	-11.9
28.	**J28**	**EGFR_1M17_Prep**	**-12.7**

29.	J29	EGFR_1M17_Prep	-12.2
30.	**J30**	**EGFR_1M17_Prep**	**-12.5**

Out the thirty compounds analyzed through docking results, it was determined that compounds J21, J28, and J30 exhibited superior binding energies compared to the others, recording -12.2, -12.7, and -12.5 Kcal/mol of binding energy, respectively. According to the molecular docking findings, Compound J28 exhibited the most favourable estimated binding energy of -12.7 Kcal/mol (Table 1) for the inhibited complex formation of the EGFR kinase domain by creating a hydrogen bond with LYS721 and MET769. Besides hydrogen bonds, this compound was also discovered to form Van der Waals interactions with the residues THR830, AS831, LEU820, VAL702, GLY772, LEU768, THR766, PRO770, ALA719, and LEU694 (Figure 1)



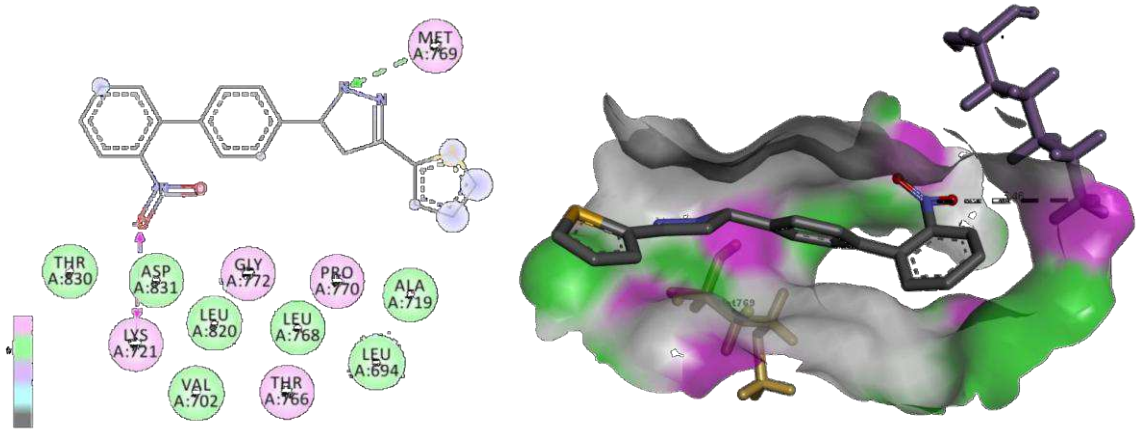


Figure 1: Molecular interactions observed between J28 compound with EGFR kinase domain from the docking analysis.

Prediction of pharmacological properties:

Osiris Property Explorer was employed to forecast the pharmacological characteristics of the compounds under study based on Lipinski's Rule of Five [23] and Oral Bioavailability. The results of predicting pharmacological attributes are shown in Tables 2 and 3. From the experimental results, it was concluded that all the compounds met the parameters of Lipinski's Rule of Five. The criteria for Lipinski's rule include: a molecular weight of < 500 Da, Log P < 5, fewer than 5 hydrogen donors, fewer than 10 hydrogen acceptors, and a molar refractivity range of 40-130.

Table 2: ADME properties of the compounds based on Lipinski's rule of five:

Sl.no	**Compound**	**Mol. Formula**	**Mol wt.**	**TPSA**	**H-Donors**	**H-acceptors**	**Rot-bonds**
1.	J01	C13H11N2BrS	307.214	52.63	1	2	2
2.	J02	C13H13N3S	243.333	78.65	2	3	2
3.	J03	C13H13N3S	243.333	78.65	2	3	2
4.	J04	C13H12N2O2S	260.316	93.09	3	4	2
5.	J05	C13H12N2OS	244.317	72.86	2	3	2
6.	J06	C14H14N2O2S	274.343	82.09	2	4	3
7.	J07	C14H14N2OS	258.344	61.86	1	3	3

8.	J08	C14H14N2S	242.345	52.63	1	2	2
9.	J09	C14H14N2S	242.345	52.63	1	2	2
10.	J10	C13H11N2BrS	307.214	52.63	1	2	2
11.	J11	C13H11N2ClS	262.763	52.63	1	2	2
12.	J12	C13H12N2OS	244.317	72.86	2	3	2
13.	J13	C13H11N3O2S	273.315	98.45	1	5	3
14.	J14	C13H11N3O2S	273.315	98.45	1	5	3
15.	J15	C13H11N3O2S	273.315	98.45	1	5	3
16.	J16	C19H15N2BrS	383.312	52.63	1	2	3
17.	J17	C19H17N3S	319.431	78.65	2	3	3
18.	J18	C19H17N3S	319.431	78.65	2	3	3
19.	J19	C19H16N2O2S	336.414	93.09	3	4	3
20.	J20	C19H16N2OS	320.415	72.86	2	3	3
21.	J21	C20H18N2O2S	350.441	82.09	2	4	4
22.	J22	C20H18N2OS	334.442	61.86	1	3	4
23.	J23	C20H18N2S	318.443	52.63	1	2	3
24.	J24	C20H18N2S	318.443	52.63	1	2	3
25.	J25	C19H15N2BrS	383.312	52.63	1	2	3
26.	J26	C19H15N2ClS	338.861	52.63	1	2	3
27.	J27	C19H16N2OS	320.415	72.86	2	3	3
28.	J28	C19H15N3O2S	349.413	98.45	1	5	4
29.	J29	C19H15N3O2S	349.413	98.45	1	5	4
30.	J30	C19H15N3O2S	349.413	98.45	1	5	4

According to Veber's rule [24], the oral bioavailability of medications can be assessed based on molecular weight, the count of rotatable bonds (n rotb), the quantity of hydrogen bonds, and the area of the drug's polar surface (TPSA). The oral bioavailability was characterized by a low molecular weight (below 500 Da); additionally, the count of rotatable bonds should be fewer than 10, the total of hydrogen bond donors and acceptors must be under 12, and TPSA values should not exceed 140. Table 2 indicates that all compounds exhibit favourable oral bioavailability, while Table 3 reveals that all compounds, except J18, have a predicted non-toxicological profile

Table 3: Toxicology profile of the compounds-based Osiris property explorer

Sl.no	Compound	Mutagenic	Tumorigenic	Reproductive effect	Eye Irritant
1.	J01	NONE	NONE	NONE	NONE
2.	J02	NONE	NONE	NONE	NONE
3.	J03	NONE	NONE	NONE	NONE
4.	J04	NONE	NONE	NONE	NONE
5.	J05	NONE	NONE	NONE	NONE
6.	J06	NONE	NONE	NONE	NONE
7.	J07	NONE	NONE	NONE	NONE
8.	J08	NONE	NONE	NONE	NONE
9.	J09	NONE	NONE	NONE	NONE
10.	J10	NONE	NONE	NONE	NONE
11.	J11	NONE	NONE	NONE	NONE
12.	J12	NONE	NONE	NONE	NONE
13.	J13	NONE	NONE	NONE	NONE
14.	J14	NONE	NONE	NONE	NONE
15.	J15	NONE	NONE	NONE	NONE
16.	J16	NONE	NONE	NONE	NONE
17.	J17	NONE	NONE	NONE	NONE
18.	J18	HIGH	HIGH	NONE	NONE
19.	J19	NONE	NONE	NONE	NONE
20.	J20	NONE	NONE	NONE	NONE
21.	J21	NONE	NONE	NONE	NONE
22.	J22	NONE	NONE	NONE	NONE
23.	J23	NONE	NONE	NONE	NONE
24.	J24	NONE	NONE	NONE	NONE
25.	J25	NONE	NONE	NONE	NONE
26.	J26	NONE	NONE	NONE	NONE
27.	J27	NONE	NONE	NONE	NONE

28.	J28	NONE	NONE	NONE	NONE
29.	J29	NONE	NONE	NONE	NONE
30.	J30	NONE	NONE	NONE	NONE

Screening for the best compound based on docking and drug likeliness results

Considering the binding energies and ADMET parameters of the currently studied compounds, it was observed that compound J28 exhibits promising properties akin to anti-cancer drugs due to its robust binding capacity indicated by a notably low ΔG binding energy. According to pharmacological characteristics, all thirty compounds demonstrated favourable pharmacological qualities. These compounds were determined to meet the criteria of Lipinski's rule, Veber's rule, oral bioavailability, and toxicological profile parameters

MD simulations of J28 compound in complex with EGFR kinase domain:

To further understand and validated the molecular level interactions and binding ability of J28 compound targeting EGFR kinase, we have performed 20 nanoseconds of molecular dynamic simulations on the complex. Root mean square deviation (RMSD), Radius of Gyration (ROG) of the protein backbone along with Root mean square fluctuations (RMSF) of individual residues were initially analyzed to understand the impact of compound binding on the protein conformation changes.

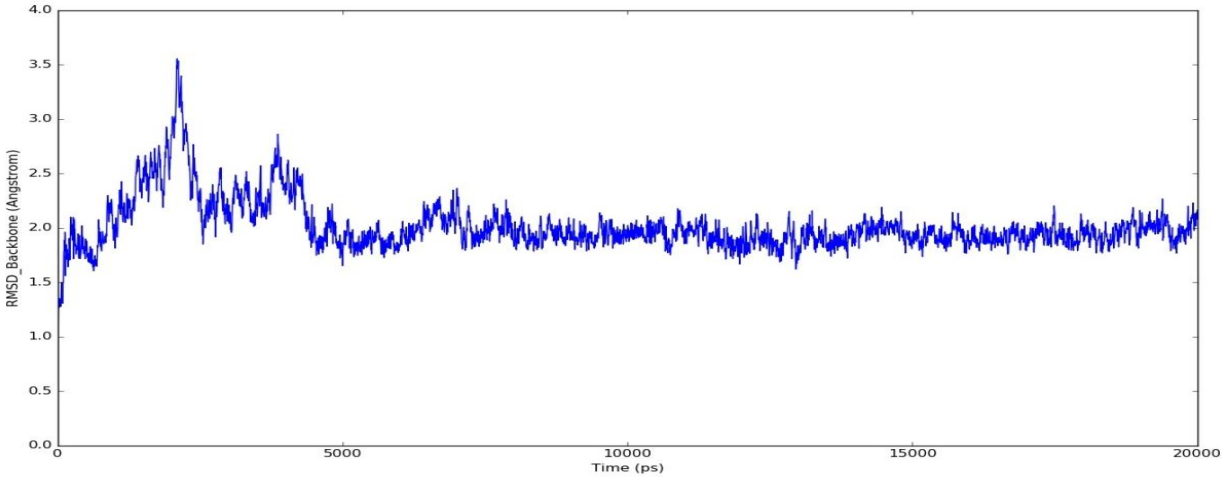


Figure 2: RMSD of the EGFR kinase domain backbone in complex with J28 compound.

From the analysis it was revealed that the RMSD of proteins backbone was initially observed to be fluctuating up to 3.5 angstrom units after the initial 5 nanoseconds of simulation timescale found stabilized at around 2.0 angstroms (figure 2), Corresponding with proteins backbone, the ligands RMSD (figure 3) was also found to be fluctuating around 2.0 angstroms throughout the simulation time; which can considered as the ligand has formed quite stable complex inside the active site of the protein throughout the simulated time.

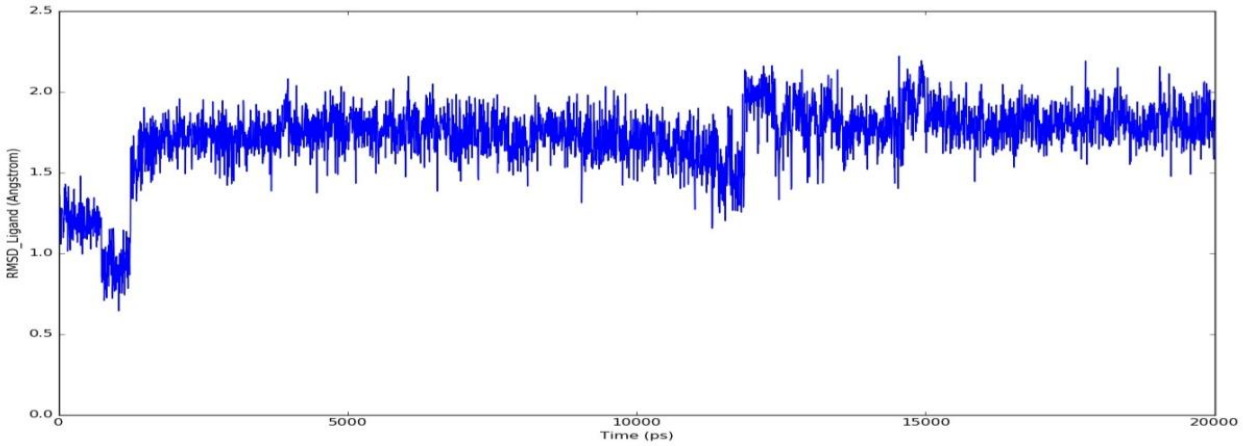


Figure 3: RMSD of the J28 compound in complex with EGFR kinase domain.

In RMSF, to find the higher flexible regions in the protein, each residue fluctuations were calculated and averaged for the entire 20ns simulated timescale. From the graph analysis (figure 4) of EGFR kinase domain in complex with J28 compound, it was noticed that there occurred minimal fluctuations indicating that the residues are quite stable in the presence of J28 compound, with few peaks up to 3 angstroms here and there which are caused by the loop movements.

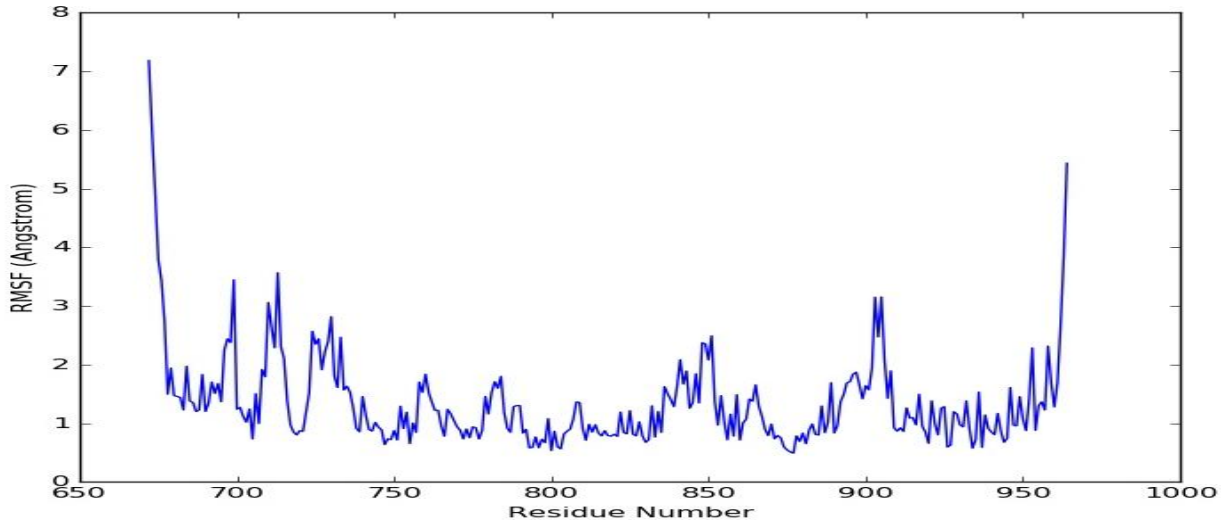


Figure 4: RMSF of the EGFR kinase domain residues in complex with J28 compound.

When the energies of the protein and ligands were analyzed, the energy of the protein was found to fluctuating between -8400 & -10000 kcal/mol (figure 5), whereas the energy of the ligand J28 was found to be maintain an average of approximately -15kcal/mol. (figure 6)

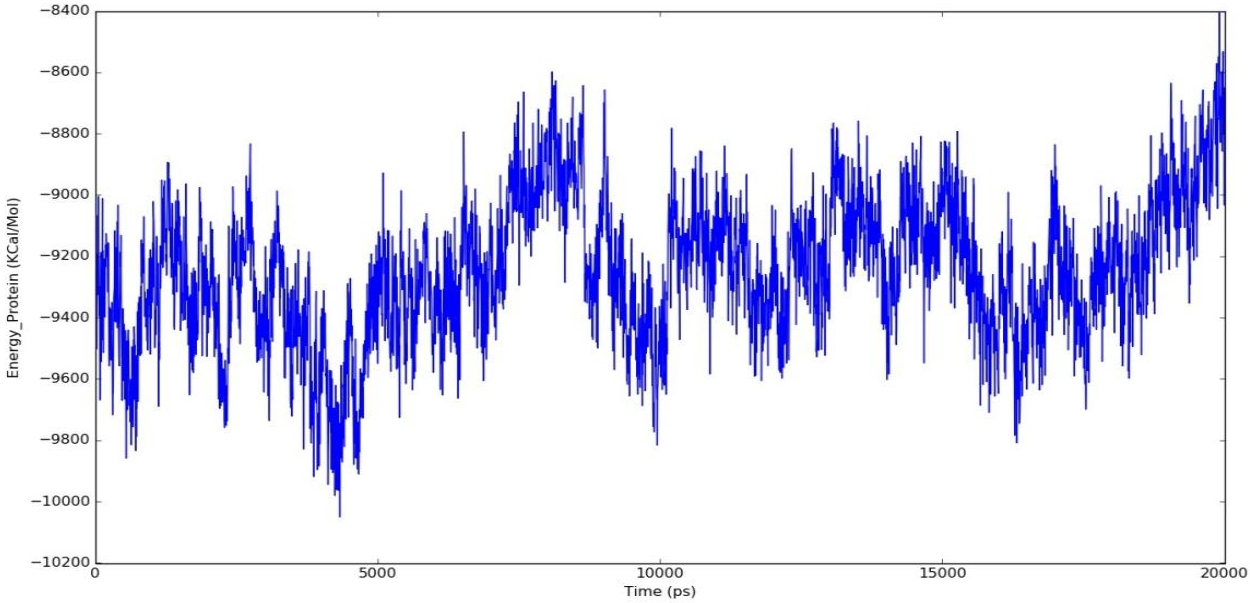


Figure 5: Calculated energy of the EGFR kinase domain while in complex with J28 compound.

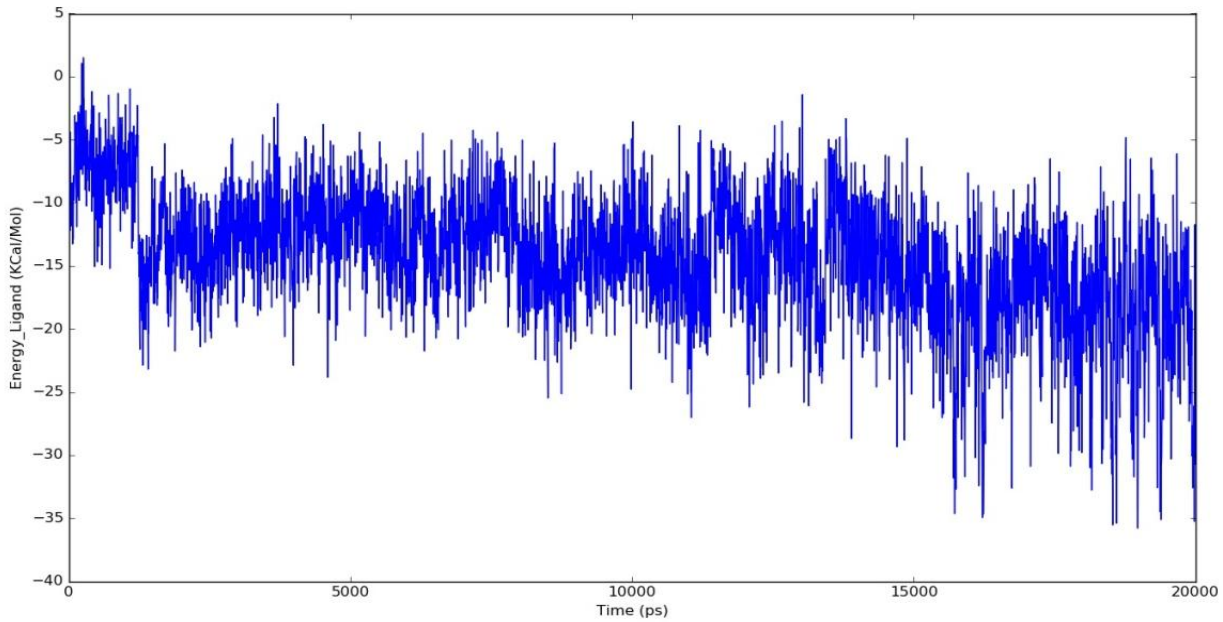


Figure 6: Calculated energy of the J28 compound inside active binding site of EGFR kinase domain.

Molecular interactions of compound J28 in complex with EGFR kinase domain observed during Molecular dynamic simulations:

The Desmond software from Schrodinger was utilized to analyse the molecular interactions of the complex thoroughly. A total of 25 interactions were identified between compound J28 and the EGFR kinase domain, including 6 interactions associated with hydrogen bonds, 15 linked to hydrophobic interactions, 14 related to water binding interactions, and one ionic bond formation was noted. Figure 7 illustrates the molecular interaction characteristics of compound J28 with the EGFR kinase domain. Hydrogen interactions were noted with LYS721, CYS751, GLN767, MET769, THR830, and ASP831; hydrophobic interactions occurred with LEU694, GLY695, SER696, ALA698, PHE699, VAL702, ALA719, LYS721, LEU723, ILE735, LEU764, LEU768, MET769, CYS773, and LEU820; water bridging interactions involved LEU694, LYS721, ILE735, GLU738, CYS751, THR766, GLN767, MET769, CYS773, AS776, ARG817, AS818, THR830, and ASP831; an ionic bond with LYS721 was recognized.

Over the simulated timespan, an average of 6 contacts were sustained from the previously mentioned interactions; notably, LYS721 and AS831 exhibited the highest stability compared to other interactions (Figure 8).

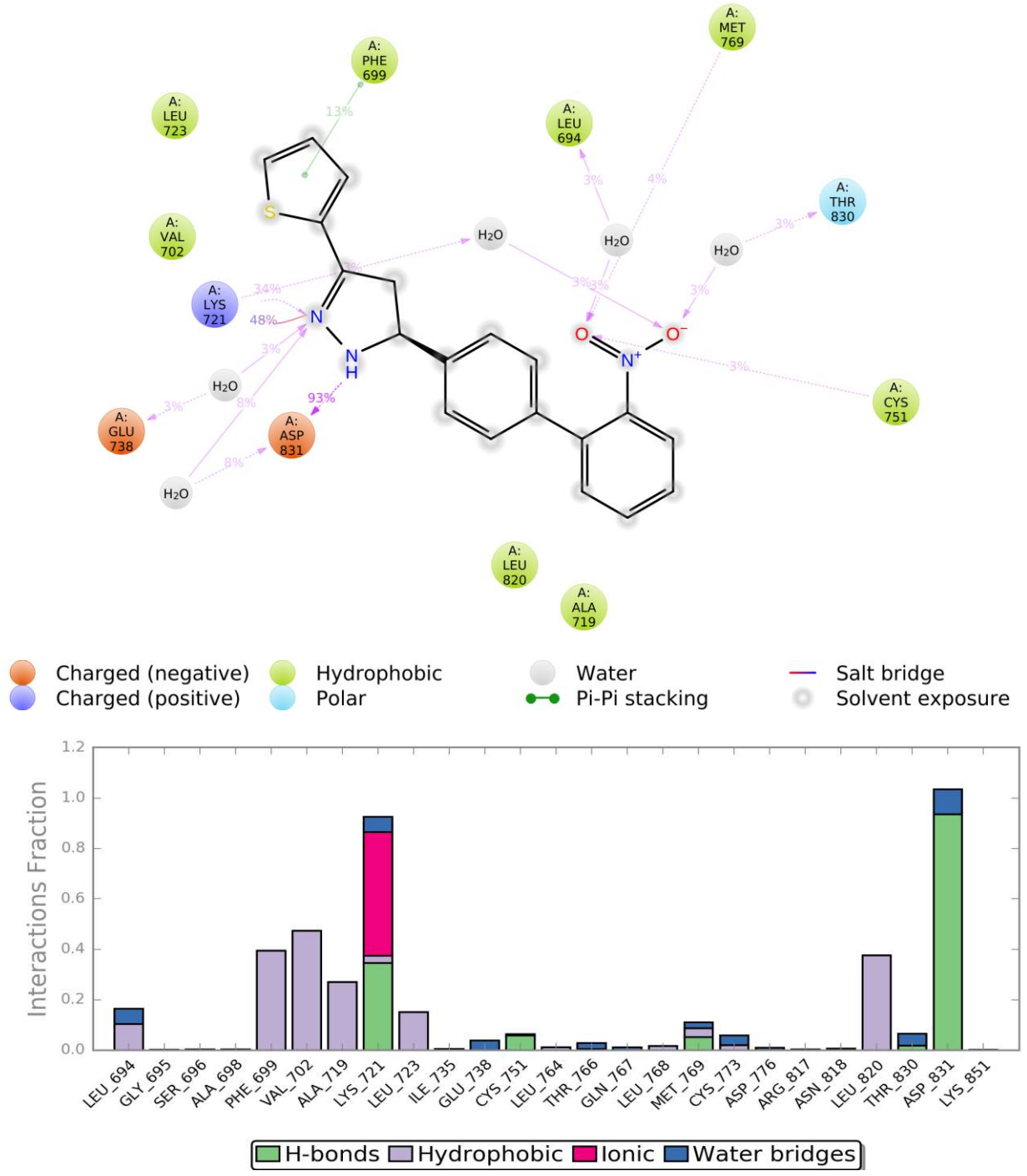


Figure 7: Molecular interactions observed between EGFR kinase domiain in complex with compound J28 during the 20ns MD simulation timescale.

Throughout the simulated timescale an average of 6 contacts were maintained from the above-mentioned interactions; among which LYS721 and AS831 were found to be most stable among other interactions (figure 8).

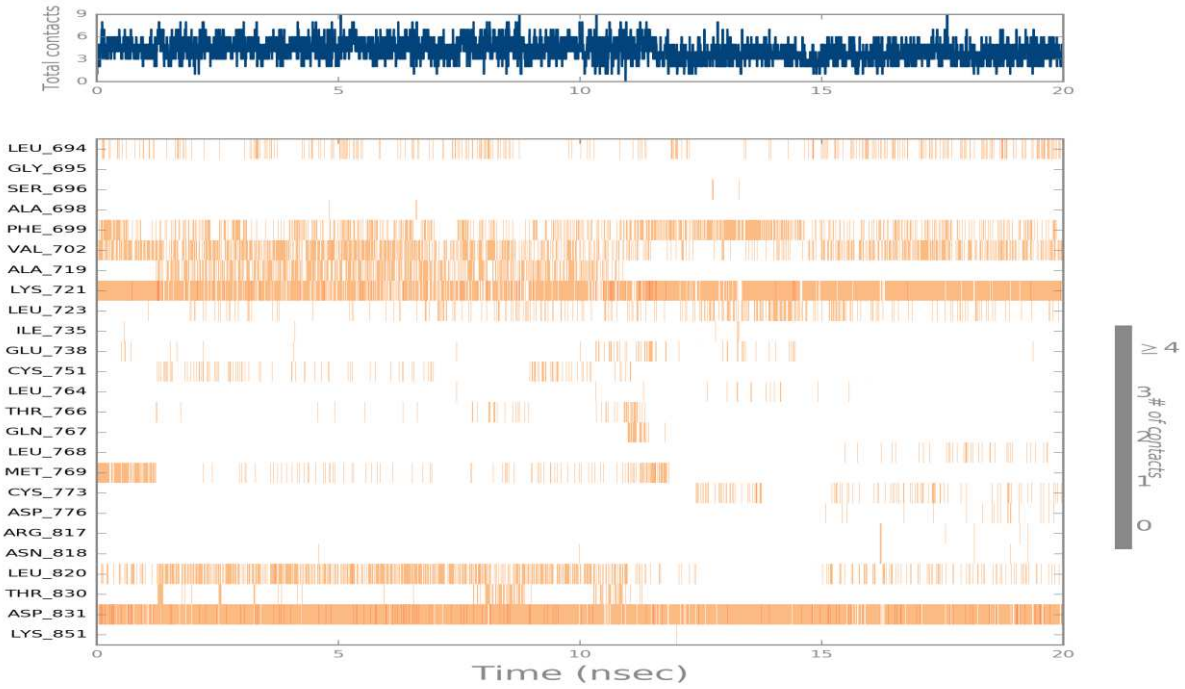


Figure 8: Molecular interactions observed between EGFR kinase domiain in complex with compound J28 during the 20ns MD simulation timescale.

Conclusion:

Our in-silico investigations justify the potential of the thirty novel compounds examined as effective small ligand molecules, exhibiting high binding affinity for the EGFR Kinase domain, suggesting plausible anti-cancer effects characterized by significant negative binding energy due to the formation of diverse interactions with residues, many of which are crucial active site residues, thereby enhancing the thermodynamic stability of their complexes. The insights obtained from this study may be highly beneficial for the computational screening of specific EGFR Kinase domain inhibitors by comprehending the molecular interaction fundamentals between the ligand and the receptor. Conversely, the encouraging ADMET drug-like characteristics of the current compounds, particularly compound J28, underscore the necessity of further assessing this

compound's capacity to inhibit cancer. The current study explored newly designed compound scaffolds that provide opportunities for quick modifications, potentially leading to lead structures with improved inhibitory potency and specificity for drug receptor targets such as EGFR kinase.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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Author Contributions

All authors contributed significantly to the work reported. Conceptualization and study design were carried out by Dr. Padma P. Prabhu. Computational analysis, including molecular docking and molecular dynamics simulations, was performed by Ms. Paramita Das. Data analysis and interpretation were conducted by Mr. Abinash Sharma. The manuscript was written and revised by all authors. All authors have read and approved the final version of the manuscript.

Data Availability

All data generated or analyzed during this study are included in this published article. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

Statement on the Usage of Artificial Intelligence

The authors declare that artificial intelligence (AI) tools were used only for language refinement and grammatical assistance during manuscript preparation. No AI tools were used for data generation, analysis, or interpretation. The authors take full responsibility for the originality, accuracy, and integrity of the content.

References:

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA: a cancer journal for clinicians. 2007 Jan;57(1):43-66.
2. Ruddarraju RR, Murugulla AC, Kotla R, Tirumalasetty MC, Wudayagiri R, Donthabakthuni S, Maroju R. Design, synthesis, anticancer activity and docking studies of theophylline containing 1, 2, 3-triazoles with variant amide derivatives. MedChemComm. 2017;8(1):176-83.

3. Bakare OO, Fadaka AO, Keyster M, Pretorius A. Structural and molecular docking analytical studies of the predicted ligand binding sites of cadherin-1 in cancer prognostics. Advances and Applications in Bioinformatics and Chemistry: AABC. 2020; 13:1.
4. Colditz GA, Wei EK. Preventability of cancer: the relative contributions of biologic and social and physical environmental determinants of cancer mortality. Annual review of public health. 2012 Apr; 33:137.
5. Poornima P, Kumar JD, Zhao Q, Blunder M, Efferth T. Network pharmacology of cancer: From the understanding of complex interactomes to the design of multi-target specific therapeutics from nature. Pharmacological Research. 2016 Sep 1; 111:290-302.
6. Berghe WV. Epigenetic impact of dietary polyphenols in cancer chemoprevention: lifelong remodeling of our epigenomes. Pharmacological research. 2012 Jun 1;65(6):565-76.].
7. Goel A, Aggarwal BB. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. Nutrition and cancer. 2010 Sep 23;62(7):919-30.
8. Masuda H, Zhang D, Bartholomeusz C, Doihara H, Hortobagyi GN, Ueno NT. Role of epidermal growth factor receptor in breast cancer. Breast cancer research and treatment. 2012 Nov;136(2):331-45.
9. Mikalsen T, Gerits N, Moens U. Inhibitors of signal transduction protein kinases as targets for cancer therapy. Biotechnology annual review. 2006 Jan 1; 12:153-223.
10. Ayaz Z, Zainab B, Rashid U, Darwish NM, Gatasheh MK, Abbasi AM. In Silico Screening of Synthetic and Natural Compounds to Inhibit the Binding Capacity of Heavy Metal Compounds against EGFR Protein of Lung Cancer. BioMed Research International. 2022 May 14;2022.
11. *Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016*
12. ACD/ChemSketch, version 2020.2.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2021
13. Huey, R., Morris, G. M., Olson, A. J. and Goodsell, D. S. (2007), A Semiempirical Free Energy Force Field with Charge-Based Desolvation *J. Computational Chemistry*, **28**: 1145-1152

14. Thomas Sander, Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil, Switzerland
15. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The Protein Data Bank. Nucleic Acids Res. 2000 Jan 1;28(1):235-42. doi: 10.1093/nar/28.1.235. PMID: 10592235; PMCID: PMC102472.
16. Vanommeslaeghe, Kenno, et al. "CHARMM general force field: A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields." *Journal of computational chemistry* 31.4 (2010): 671-690
17. Morris, Garrett M., et al. "Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function." *Journal of computational chemistry* 19.14 (1998): 1639-1662
18. Sander, Thomas, et al. "DataWarrior: an open-source program for chemistry aware data visualization and analysis." *Journal of chemical information and modeling* 55.2 (2015): 460-473
19. Jorgensen, William L., and Nora A. McDonald. "Development of an all-atom force field for heterocycles. Properties of liquid pyridine and diazenes." *Journal of Molecular Structure: THEOCHEM*1-2 (1998): 145-155
20. Mark, Pekka, and Lennart Nilsson. "Structure and dynamics of the TIP3P, SPC, and SPC/E water models at 298 K." *The Journal of Physical Chemistry A*43 (2001): 9954-9960
21. Darden, Tom, Darrin York, and Lee Pedersen. "Particle mesh Ewald: An N· log (N) method for Ewald sums in large systems." *The Journal of chemical physics*12 (1993): 10089-10092
22. Tuckerman, M. B. B. J. M., Bruce J. Berne, and Glenn J. Martyna. "Reversible multiple time scale molecular dynamics." *The Journal of chemical physics*3 (1992): 1990-2001.
23. Lipinski, Christopher A. "Lead-and drug-like compounds: the rule-of-five revolution." *Drug Discovery Today: Technologies* 1.4 (2004): 337-341.
24. Veber, Daniel F., et al. "Molecular properties that influence the oral bioavailability of drug candidates." *Journal of medicinal chemistry* 45.12 (2002): 2615-2623