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COMPUTATIONAL DRUG REPURPOSING OF FDA APPROVED COMPOUNDS TARGETING EGFR

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ABSTRACT:
Drug repurposing also referred to as drug repositioning, involves identifying new therapeutic uses for existing or abandoned medications. It is cost, time effective and with known safety profiles. In the growing prevalence of cancer and the time-consuming process of developing new drugs, this emerges as a promising strategy in discovering novel therapeutic activities and overcoming challenges in cancer therapy. This study employed molecular docking approach to evaluate 2023 FDA-approved drugs for their potential in targeting Epidermal Growth Factor Receptor (EGFR) pathway. Ligands were selected based on their similarity in mechanism of action to known cancer pathways, and docking was performed using AutoDock Vina. Among the docked drugs, four showed higher binding affinity than a selected standard ligand, and another four exhibited similar binding affinity. Further pre-clinical and clinical evaluation of these promising candidates could help in the discovery of repurposed drugs for cancer therapy.
Key Words: Drug Repurposing, Cancer, Molecular Docking, 2023 FDA-approved Drugs, EGFR

INTRODUCTION:

Cancer is a disease which is characterized by the uncontrolled cell growth and spread of abnormal cells, often forming tumors that can be benign or malignant. Malignant tumors have the potential to invade surrounding tissues and spread to distant organs and in advanced stages, may spread to other areas of the body (Ye *et al.,* 2022). A key characteristic of cancer

is the rapid production of abnormal cells that grow beyond their usual boundaries, allowing them to invade nearby tissues and spread to other organs, this referred to as metastasis. Widespread metastasis are the primary cause of cancer related deaths (Cooper, 2000).

Cancer manifests in various forms such as carcinomas, sarcomas, leukemias, and lymphomas, affecting different tissues and organs. According to the WHO, cancer is a major global cause of death, with around 10 million deaths in 2020. The most prevalent cancers are lung, breast, and colon; lung cancer is the leading cause of death (World Health Organization: WHO, 2022). Epidermal Growth Factor Receptor (EGFR) is a cell surface protein from the receptor tyrosine kinase family. It is expressed in various cancers such as lung cancer, breast cancer and glioblastoma, where it plays as a key role in tumorigenesis (Sasikala & Rajitha, 2019) (Sigismund *et al*., 2017).

Drug repurposing, which involves identifying new therapeutic uses for existing or abandoned medications, offers a promising strategy for cancer treatment. This approach utilises FDA-approved drugs, which minimizes the cost and time associated with the development of drugs (Ye *et al*., 2022). Molecular docking plays a crucial role in this process, allowing researchers to identify potential drug candidates with high binding affinities for their target proteins. This technique facilitates drug discovery, lead optimization, and understanding of protein-ligand interactions (Muhammed & Aki-Yalcin, 2024).

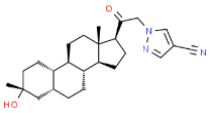
In consideration of the growing prevalence of cancer and the lengthy drug development process, drug repurposing emerges as a promising strategy for discovering novel therapeutic activities. This approach offers the potential to expedite the introduction of effective treatments by leveraging existing drugs for new indications in cancer therapy. Integrating molecular docking techniques, enhances our exploration of these drugs potential to target EGFR pathway, offering a more efficient and cost-effective approach to drug discovery and development. This computational analysis allows us to identify promising candidates for repurposing, accelerating their translation into clinically effective treatments, and ultimately improving patient outcomes in the fight against cancer.

MATERIALS AND METHODOLOGY:

Ligands selected for Molecular Docking:

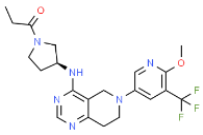
Some of the FDA approved drugs of 2023 were selected as ligands based on their similarity in mechanism of action to known cancer pathways for this study from FDA (https://www.fda.gov/). Structure, IUPAC name and original indication of drugs were taken from the databases like Drug Bank (https://go.drugbank.com/), Pubchem (https://pubchem.ncbi.nlm.nih.gov/), ChemSpider (http://www.chemspider.com/) are listed below and the drug with its rationale for selection to this study are listed in **table 1.**

Zuranolone : Postpartum Depression



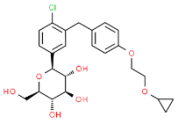
IUPAC Name: 1-[2-[(3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethyl- 2,4,5,6,7,8,9,10,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]-2- oxoethyl]pyrazole-4-carbonitrile

Leniolisib : PI3-kinase-delta syndrome



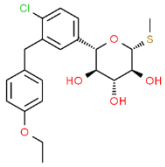
IUPAC Name: 1-[(3S)-3-[[6-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-7,8-dihydro-5H- pyrido[4,3-d]pyrimidin-4-yl]amino]pyrrolidin-1-yl]propan-1-one

Bexagliflozin : Type 2 Diabetes Mellitus



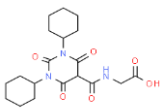
IUPAC Name: (2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-(2-cyclopropyloxyethoxy) phenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol

Sotagliflozin : Heart Failure



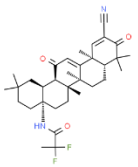
IUPAC Name: (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methylsulfanyloxane-3,4,5-triol

Daprodustat : Anemia in individuals with chronic kidney disease



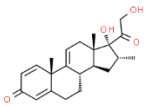
IUPAC Name: 2-[(1,3-dicyclohexyl-2,4,6-trioxo-1,3-diazinane-5-carbonyl)amino] acetic acid

Omaveloxolone : Friedreich's ataxia



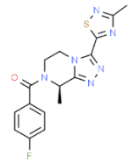
IUPAC Name: (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methylsulfanyloxane-3,4,5-triol

Vamorolone : Duchenne Muscular Dystrophy



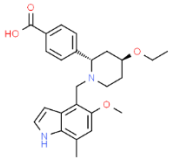
IUPAC Name: (8S,10S,13S,14S,16R,17R)-17-hydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-7,8,12,14,15,16-hexahydro-6H-cyclopenta[a]phenanthren-3-one

Fezolinetant : Moderate to severe vasomotor symptoms caused by menopause



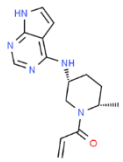
IUPAC Name: (4-fluorophenyl)-[(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-6,8- dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]methanone

Iptacopan : Paroxysmal nocturnal hemoglobinuria



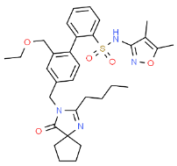
IUPAC Name: 4-[(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl]benzoic acid

Ritlecitinib : Severe Alopecia areata



IUPAC Name: 1-[(2S,5R)-2-methyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino) piperidin-1- yl]prop-2-en-1-one

Sparsentan : Primary IgA neuropathy (decreases proteinuria)



IUPAC Name: 2-[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-(ethoxymethyl)phenyl]-N-(4,5-dimethyl-1,2-oxazol-3-yl)benzenesulfonamide

Table 1 : Drugs with its rationale for selection to this study

Drug Name	**Rationale**
Zuranolone	The mechanism of action of zuranolone implies that it may influence the advancement of cancer via modulating GABAergic (Gamma-aminobutyric acid) transmission. (Yang *et al*., 2023)
Leniolisib	Leniolisib targets phosphoinositide 3-kinase delta (PI3Kδ), a crucial enzyme in cell growth, proliferation and survival. Dysregulation of PI3K is common in cancer which promotes tumor growth and therapy resistance. By blocking PI3Kδ, Leniolisib may disrupt cancer cell growth and survival, showing promise for cancer treatment. (He *et al*., 2021)
Bexagliflozin	Bexagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor for diabetes, reduces reabsorption of glucose in the kidneys, resulting in higher glucose excretion through urine. Some researches suggest, the connection between glucose metabolism and cancer growth, making SGLT2 inhibitors like Bexagliflozin interesting for potential anticancer use. (Dutka *et al*., 2022)
Sotagliflozin	The inhibition of sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2) by sotagliflozin decreases glucose reabsorption in kidneys and intestines. Cancer cells typically consume more glucose for fast growth. So blocking these receptors may affect their behaviour. (Dutka *et al*., 2022)
Daprodustat	Daprodustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), treats anemia in individuals with chronic kidney disease. The HIF pathway is involved in cancer progression, especially in tumor angiogenesis and metastasis. By inhibiting HIF prolyl hydroxylases, Daprodustat stabilizes HIF, which may influence tumor growth and survival. (Soni & Padwad, 2017)
Omaveloxolone	Omaveloxolone activates the Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which controls antioxidant and detoxification genes, crucial for defending cells against oxidative stress and inflammation. When this pathway is disrupted, it's linked to cancer development. Activating Nrf2 has shown promise in fighting cancer in laboratory studies. (L. Li *et al*., 2023)
Vamorolone	As a steroid, vamorolone has immunomodulatory and anti-inflammatory properties. These traits may have an effect on the cancer development and the tumor microenvironment. Vamorolone may have anti-cancer benefits by enhancing anti-

	cancer immunity or inhibiting tumor-promoting inflammation through immune response modulation (Matsushita & Kawaguchi, 2018) (Zappavigna *et al*., 2020)
Fezolinetant	Fezolinetant targets the neurokinin-3 receptor (NK3R). NK3R is also found in cancer cells like breast, ovarian, and prostate cancer. Blocking NK3R could potentially disrupt cancer cell signaling, affecting their growth and survival. (Wang *et al*., 2017)
Iptacopan	Iptacopan may disturb the tumor microenvironment and prevent the growth or spread of cancer cells by blocking complement factor B. This is because medications like Iptacopan that target the complement system may be beneficial in treating cancer because it contributes to the disease's progression and immune system evasion. (Afshar-Kharghan, 2017)
Ritlecitinib	Ritlecitinib may be an effective anti-cancer treatment because it inhibits Janus kinase (JAK) enzymes, particularly JAK1 and JAK3 which may disrupt signaling pathways crucial for cancer progression. (Karati *et al*., 2022)
Sparsentan	The renin-angiotensin-aldosterone system (RAAS) via Angiotensin II receptor blockers (ARB) activity and the endothelin system via endothelin receptor antagonism, these pathways are connected to the initiation and spread of cancer. By targeting these pathways together sparsentan may exert anti cancer effects through different mechanisms (Hassani *et al*., 2023) (Harrison *et al*., 2024)

Protein: Epidermal Growth Factor Receptor (EGFR) was selected as a protein, taken from Protein Data Bank (PDB) and it's PDB code is 8A27. It plays a crucial role in controlling various cellular functions such as cell proliferation, cell survival, and cell differentiation. Specifically, it regulates the homeostasis and development of epithelial tissue (Sigismund *et al*., 2017). As a transmembrane receptor, EGFR becomes activated upon specific ligand binding, initiating downstream signaling cascades that coordinate cellular response, and its dysregulation is implicated in numerous pathological conditions, including cancer, which making it a compelling target for clinical interventions (Seshacharyulu *et al*., 2012).

Protein was selected from Protein Data Bank which has classification : Transferase, organism : Homo sapiens, no mutations, X-Ray Diffraction method with low resolution.

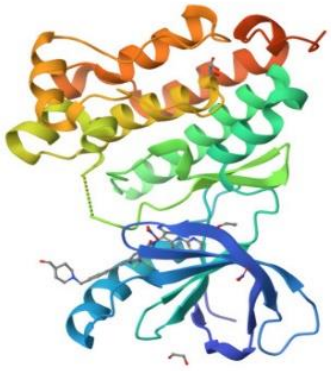


Figure 1 : 8A27 protein (Epidermal Growth Factor Receptor)

Molecular Docking Studies:

Docking was performed by using AutoDock Vina. Ligands from PubChem and proteins from protein data bank were downloaded and prepared for docking studies, by first converting 3D conformer of ligand files from SDF to PDBQT format using PyMOL and AutoDock Tools. Protein was downloaded in PDB format, any non-essential ligands were removed and processed in AutoDock tools to delete water molecules, add polar hydrogens, and assign charges, saved it as PDBQT format. Docking studies were conducted with AutoDock Vina, setting parameters for exhaustiveness and grid dimensions, and the best binding poses were identified. Then 2D, 3D structures visualized using PyMOL and BIOVIA Discovery Studio Visualizer.

RESULTS AND DISCUSSION:

All the 11 selected ligands were docked against 8A27 protein and the results obtained through molecular docking are listed in **table 2**.

Table 2 : Docking results of selected ligands against 8A27 protein

Ligand	Original Indication	Docking Score (kcal/mol)	Interactive Amino acid Residues**

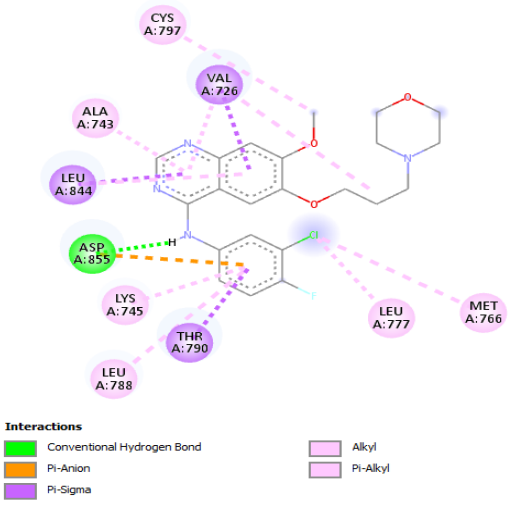
Gefitinib*	To treat non-small cell lung carcinoma (NSCLC)	-9.4	ASP 855,VAL 726, LEU 844, THR 790, CYS 797, ALA 743, LYS 745, LEU 788
Zuranolone	Postpartum Depression	-10.5	CYS 797, LYS 745, VAL 726, LEU 788, ALA 743, LEU 844
Leniolisib	PI3-kinase-delta syndrome	-10.0	THR 790, ALA 743, ASP 855, LYS 745, VAL 726, LEU 844, LEU 788
Bexagliflozin	Type 2 Diabetes Mellitus	-9.8	VAL 726, ALA 743, LEU 844, LYS 745, ASP 855
Sotagliflozin	Heart Failure	-9.4	LYS 745, ASP 855, LEU844, LEU 788 ALA 743, VAL 72
Daprodustat	Anemia in patients with chronic kidney disease	-9.2	LYS 745, CYS 797, ALA 743, LEU 844, VAL 726
Omaveloxolone	Friedreich's ataxia	-9.2	LYS 745, LYS 797, VAL 726
Vamorolone	Duchenne Muscular Dystrophy	-9.2	ASP 855, LEU 788, ALA 763
Fezolinetant	Moderate to severe vasomotor symptoms caused by menopause	-8.9	ASP 855, THR 790, LYS 745, ALA 743, LEU 844, VAL 726
Iptacopan	Paroxysmal nocturnal hemoglobinuria	-8.9	CYS 797, ASP 855, ALA 743, LEU 844, VAL 726
Ritlecitinib	Severe Alopecia areata	-8.6	ASP 855, LEU 788
Sparsentan	Primary IgA Neuropathy (decreases proteinuria)	-8.5	LYS 745, CYS 797, VAL 726

*Gefitinib – Standard Ligand

**Interactive amino acid residues: Similar amino acid residues which are present in both Standard ligand and selected ligands.

Docking Interactions :

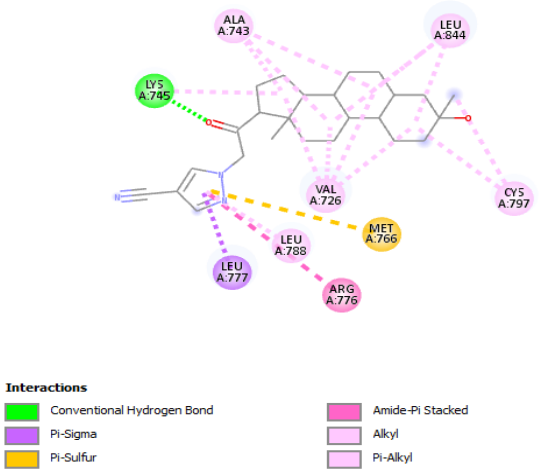
Gefitinib:



Gefitinib is considered as a reference ligand for its anti-cancer activity, exhibited binding affinity of -9.4 kcal/mol through interacting with the 8A27 protein. The most probable interactive amino acids with EGFR include ASP 855, CYS 797, VAL 726, LEU 844, ALA 743, THR 790, LEU 788 and LYS 745. The potential bond formations with these amino acids are conventional hydrogen bonding (CHB) -1, pi-sulfur (Pi-Sulfur) -1, amide-pi stacked -1, alkyl -1, and pi-alkyl -5, respectively.

Figure 2 : 2D view of Docking interactions of Gefitinib against 8A27

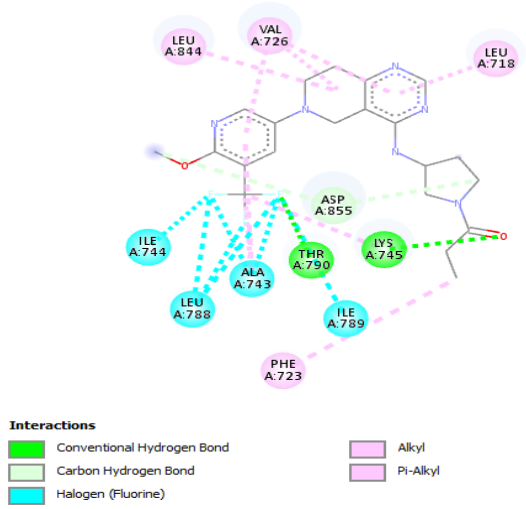
Zuranolone



Zuranolone has shown the binding affinity of -10.5 kcal/mol which is far greater than that of Gefitinib, indicating it's highest affinity towards EGFR compared to standard ligand. Additionally, it shares similar amino acid interactions with the standard ligand, such as CYS 797, VAL 726, LEU 788, LEU 844, ALA 743 and LYS 745.

Figure 3 : 2D view of Docking interactions of Zuranolone against 8A27

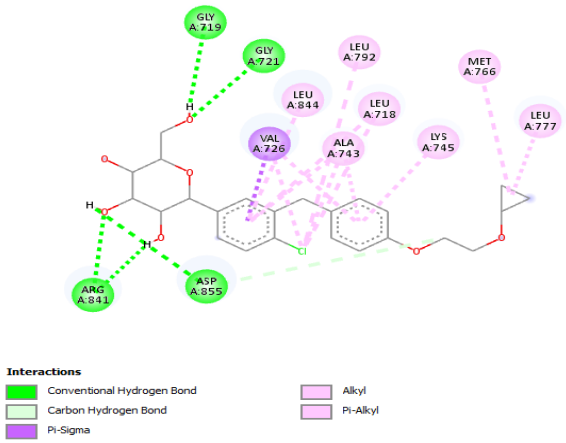
Leniolisib



Leniolisib has demonstrated the binding affinity of -10.0 kcal/mol which is greater than that of Gefitinib, indicating it's highest affinity towards EGFR. Additionally, it shares similar amino acid interactions with the standard ligand, such as THR 790, ASP 855, VAL 726, LEU 788, LEU 844, ALA 743 and LYS 745.

Figure 4 : 2D view of Docking interactions of Leniolisib against 8A27

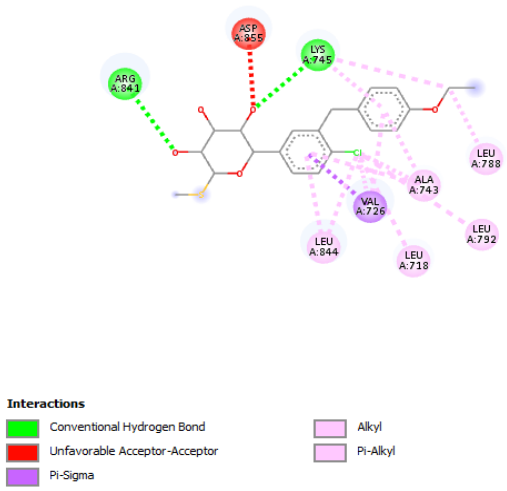
Bexagliflozin :



Bexagliflozin has demonstrated the binding affinity of -9.8 kcal/mol, which is greater than that of Gefitinib, indicating it's highest affinity towards EGFR compared to standard ligand. Additionally, it shares similar amino acid interactions with the standard ligand, such as LYS 745, ASP 855, LEU 844, VAL 726 and ALA 743.

Figure 5 : 2D view of Docking interactions of Bexagliflozin against 8A27

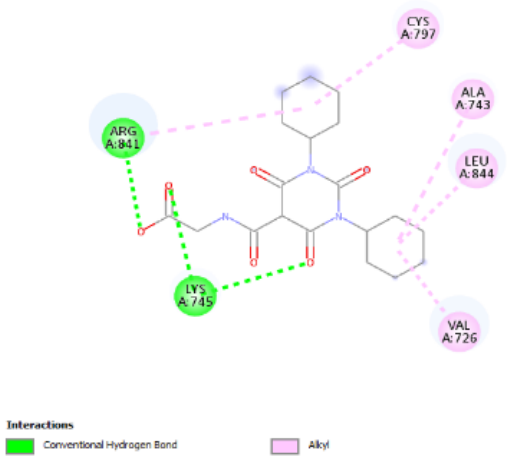
Sotagliflozin



Sotagliflozin has shown the binding affinity of -9.4 kcal/mol which is equal to Gefitinib, indicating it's similar affinity towards EGFR compared to standard ligand. Additionally, it shares similar amino acid interactions with the standard ligand, such as LYS 745, ASP 855, LEU 844, LEU 788 ALA 743 and VAL 726.

Figure 6 : 2D view of Docking interactions of Sotagliflozin against 8A27

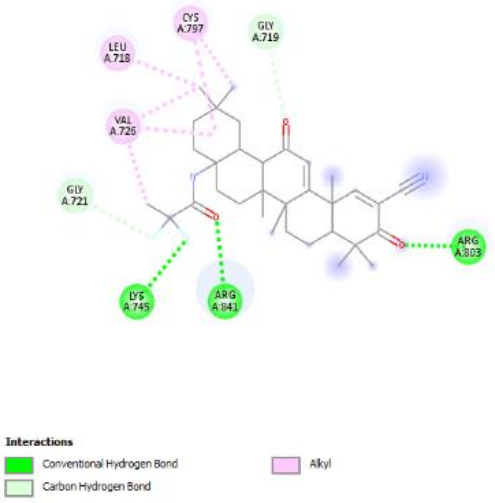
Daprodustat :



Daprodustat has shown the binding affinity of -9.2 kcal/mol, which is nearly equal to Gefitinib, indicating it's similar affinity towards EGFR compared to standard ligand. Additionally, it shares similar amino acid interactions with the standard ligand, such as LYS 745, CYS 797, ALA 743, LEU 844 and VAL 726.

Figure 7 : 2D view of Docking interactions of Daprodustat against 8A27

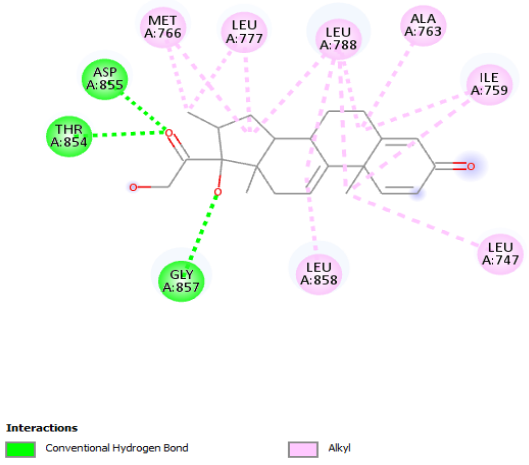
Omaveloxolone



Omaveloxolone has shown the binding affinity of -9.2 kcal/mol which is nearly equal to Gefitinib, indicating it's similar affinity towards EGFR compared to standard ligand. Additionally, it shares amino acid interactions with the standard ligand, such as LYS 745, LYS 797 and VAL 726.

Figure 8 : 2D view of Docking interactions of Omaveloxolone against 8A27

Vamorolone



Vamorolone has exhibited the binding affinity of -9.2 kcal/mol which is nearly equal to Gefitinib, indicating it's similar affinity towards EGFR compared to standard ligand. Additionally, it shares similar amino acid interactions with the standard ligand, such as ASP 855, LEU 788 and ALA 763.

Figure 9 : 2D view of Docking interactions of Vamorolone against 8A27

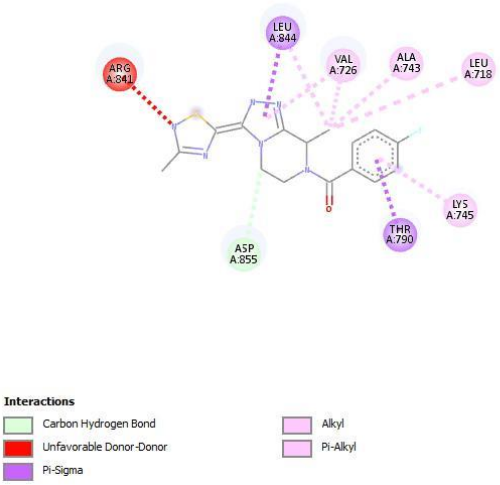


Figure 10 : 2D view of Docking interactions of Fezolinetant against 8A27

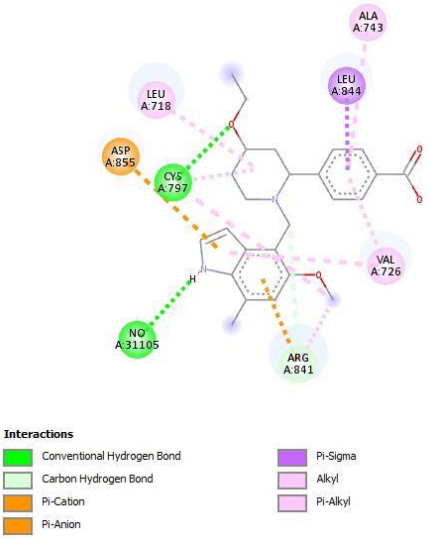


Figure 11 : 2D view of Docking interactions of Iptacopan against 8A27

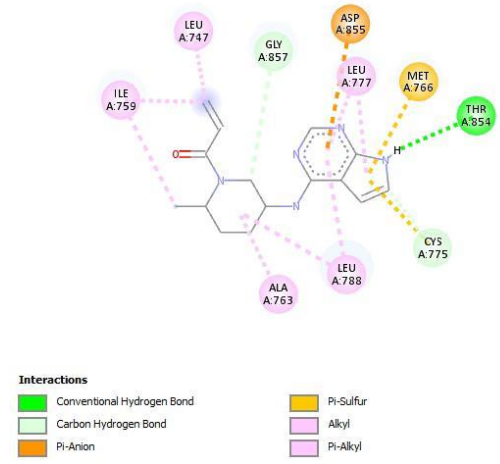


Figure 12 : 2D view of Docking interactions of Ritlecitinib against 8A27

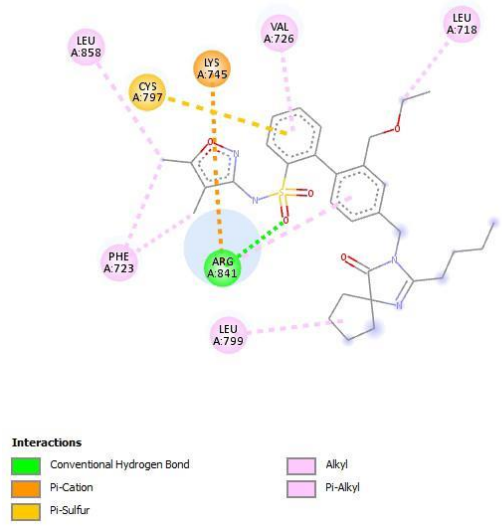


Figure 13 : 2D view of Docking interactions of Sparsentan against 8A27

CONCLUSION:

We performed docking studies on 11 recently approved FDA drugs (2023) against 8A27 protein using AutoDock Vina and results were visualized by BIOVIA Discovery Studio Visualizer. Docking studies revealed that drugs Zuranolone, Leniolisib, Bexagliflozin exhibited highest binding affinity values of -10.5 kcal/mol,-10.0kcal/mol,-9.6kcal/mol respectively among all, and Sotagliflozin with binding affinity of -9.4kcal/mol and Daprodustat, Omaveloxolone, Vamorolone exhibited similar binding affinity of -9.2kcal/mol, When compared to standard ligand Gefitinib which has binding affinity value -9.4 kcal/mol. These Zuranolone, Leniolisib, Bexagliflozin are found to be more potent when compared with standard ligand and Sotagliflozin, Daprodustat, Omaveloxolone, Vamorolone are equally potent with the standard ligand in this molecular docking analysis. Further pre-clinical and clinical evaluation of the above mentioned drugs may be helpful in the treatment of cancer therapy.

CONFLICT OF INTEREST :

Authors declare no conflict of interest.

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