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Research Article

Molecular Docking and Pharmacological *In-silico* evaluation of Nitrogen and oxygen Heterocyclic Compounds as promising anticancer agents with an aim of drug repurposing

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Dr. Thomas Kurian, Associate Professor, Department of Pharmacy, Govt. Medical College. Kottayam Kerala.

Abstract

Cancer is one of the leading causes of death among deadly diseases that occur in humans. Due to its ability to spread and the uncontrolled cell growth, it affects various organs and tissues. The present study evaluates the interactions between two receptors, 6JOR (FLT3 in complex with Gilteritinib) and HER-2 (Human epidermal growth factor receptor 2), and five existing drugs, with different biological actions and Safety Profiles. The aim is to repurpose established drugs. Molecular dynamics (MD) simulation of the ligand with the target 6JOR showed the most likely binding for Albendazole, with an IDDT value of 0.6598. The Binding affinity prediction maximum for Aripiprazole (-7.24425). Gilteritinib gave IDDT value -6.228. GROMACS was used for dynamic binding and docking using the new wrap mime platform. Pharmacokinetic evaluation based on the rule of five and Prediction of Pharmacology by PASS online. This research highlights the significance of drug repurposing and eliminates the need for drugs with an established safety profile. The study of existing drugs with established safety profiles and in silico pharmacological activity prediction using PASS online leveraged insights into biological activity. Further clinical testing should be conducted to assess anticancer activity in Humans.

Keywords: Docking, Dynamics, Cancer, Heterocyclic, Nitrogen, Oxygen

INTRODUCTION:

Cancer starts when a cell escapes the usual constraints on unchecked growth and spreads. The rapid growth and spread of the cells are the unique features of this deadly disease. [1]The balance between apoptosis and mitosis is disturbed in Cancer. The cancer therapy aims to promote cancer growth. Without damaging normal cells. [2] The main goal of cancer treatment is tumor cure. Surgery, radiation therapy, and chemotherapy are the other methods of cancer treatment. Modern methods include hormone-based therapy. Moreover, dendritic cell-based immunotherapy. [3] The Spread of cancer cells to other tissues is called metastasis. The human epidermal growth factor receptor 2 (HER2) gene is amplified in breast cancer. Targeting the HER2 gene is the basis for identifying drug candidates for breast cancer. Drugs like trastuzumab have already been tested for safety and efficacy[4]. Spontaneous tumors originate from a single cell. Tumors exhibit heterogeneity, including differences in cell-surface receptor expression, proliferative and angiogenic potential, and epigenetic plasticity. [5]. Drug resistance is a multifactorial phenomenon in cancer therapy. It may be due to changes in drug transport and distribution or in the structure of molecular targets.[6] Cancer therapy led to neuro-cognitive Side effects like impaired learning and memory. .[7] Other side effects like nausea, fever, and pain, loss of hair are also seen [8]. Phytochemicals, when used for cancer treatment, have fewer significant side effects. Flavonoids, terpenoids, alkaloids, phenolics, and sulfur compounds have a potential role in cancer therapy.[9] As seen in in-vitro studies, nitrogen heterocyclic compounds containing pyrimidine, quinoline, pyridine, imidazole, benzimidazole, triazole, β-lactam, and indole are used as anticancer agents. Pyrimidine and pyrazole compounds are active agents against liver cancer. Cervical cancer carbazole, indole compounds used in lung cancer, and pyrido compounds in Colorectal Cancer. [10] Oxygen-containing heterocycles possess antitumor properties; compounds with furan, benzofuran, oxazole, benzoxazole, and oxadiazole are being tested for anticancer activities.[11] The heterocyclic compounds have advantages in drug-target interactions; they possess properties like π-π stacking and hydrophobic membrane stability. Drug repurposing holds the potential to introduce new drugs with fewer side effects or an

established safety profile. Most repurposing occurs through serendipitous findings or through predictive repurposing studies using in silico methods.[12]

Computational drug repurposing reduces the cost of drug development. The joint use of genomic, biomedical, and pharmacological data improves the efficiency of drug repositioning.[13] The selected hetero nitrogen compounds and oxygen-containing hetero compounds can be tested against FLT3's ATP pocket (PDBID 6JQR) in comparison with ligands (Gilteritinib) by using the dynamic bind docking suite from Neuronal Inc. The hetero-oxygen/nitrogen compounds were also tested against HER-2 (human epidermal growth factor receptor-2; PDB ID 3PPO). HER-2 expression occurs in breast and ovarian Cancer, making it an important target in in silico cancer studies.[15]

Neuro-snap MD-syn platform dynamic bind AI-scoring platform pinpoints AI-guided synergy scouting, ligand discovery, drug placement, optimization, and combined nanocarrier engineering. It provides IDDT values and binding affinity (local distance difference test), yielding a superposition-free score that evaluates local atomic interactions and distances. It uses predictive structure. The score ranges from 0 to 1. SPRINT (deep learning framework) from Neuronal is a vector-based deep learning framework that accelerates drug discovery by leveraging massive-scale drug-target interactions. It uses structure-aware protein language models for accurate predictions. Neuronal is a framework for online bioinformatics, molecular docking, and protein engineering used by researchers in academia and industry.[16] GROMACS molecular dynamics simulations (MDS) with the Charmm36 force field were performed in a cubic box with a side length of 1.0 nm, containing sodium and chloride ions. PASS- online for pharmacology prediction software predicts over 4000 biological activities, including mechanism of action, toxicity, and adverse effects. To obtain predicted biological activity, only the structural formula is required. [17- 18]

MATERIALS AND METHODS

The ligands and their chemical Structures were downloaded from the PubChem database. The PDB ID 3PP0 and 6JQR receptor structures in PDB format were downloaded from the RCSB website. An Intel i7 computer with NVIDIA graphics (GUI) running Windows 11 was used. The software from the Neurosnap AI platform, Dynamic-bind, was utilized for Molecular docking. The Bioactivity ranking of the ligands was done using SPRINT Software from Neurosnap. The Molecular Dynamics Simulation study was carried out using GROMACS on the Neurosnap platform. Bioactivity prediction was performed using the PASS online In-Silico Pharmacology tool. All the data were validated against a reference ligand.

Dynamic Bind docking from Neurosnap

Dynamic bind is a deep- learning docking pipeline. It employs an equivalent generative diffusion model that optimizes poses. Smiles notation of chemical structures was obtained from the PubChem database. Neurosnap Dynamic, a web-based tool, was utilized to upload Protein (PDB) and ligand (Pasted smiles) data. Data were submitted dynamically and progressively, poses were run and moved, and Protein Conformations were adjusted to produce Stable Ligand Conformations Model Scores as Binding Energies and IDDT Values. The top-predicted Value Ligand was selected as a hit.

GROMACS Dynamic Simulations (Neurosnap) AI

Gromacs MD on Neurosnap

The PDB files for the proteins (6JQR, 3PP0) were uploaded. The FASTA Sequence was also pasted. (Amino acid Sequence) of protein receptor

The Ligands were uploaded at a time. The force - field choosing (CHARMM-36/m, the water model was picked. AMBER 995B-ILDW)

The system itself determined the energy-minimum states. (integrator = Steep, in steps = 5000) The program was run with RMSD, RMSF, and the Hydrogen bond Number. Radiation gyration cluster analysis was performed using the same method, and the output was obtained.

SPRINT - Bioactivity Predictor

"SPRINT" is a vector-based deep learning framework for drug-target interactions. Sprint Screens provides an extensive library of compounds and delivers results with good interpretability. In silico pharmacology activity prediction was performed, and ligands were ranked based on performance.

PASS ONLINE

(Prediction of Activity Spectra)

It can predict about 4,000 biological activities based on the information obtained. Other featured options include mechanism of action, toxicity, filtering, HIT identification, Prediction of repurposing chance, and QSAR chemo-informatics. Pass online was accessed at https://way2drug.com/PassOnline/. The smile strings were pasted. The option for biological activity prediction was selected and run. The Pa (Possibility of action) and Pi (possibility of inhibition of action) waves obtained from the ratio indicate that, if higher, Pappi has more activity. Pa >0.7 – 1 reproducible the Value.

RESULTS AND DISCUSSION

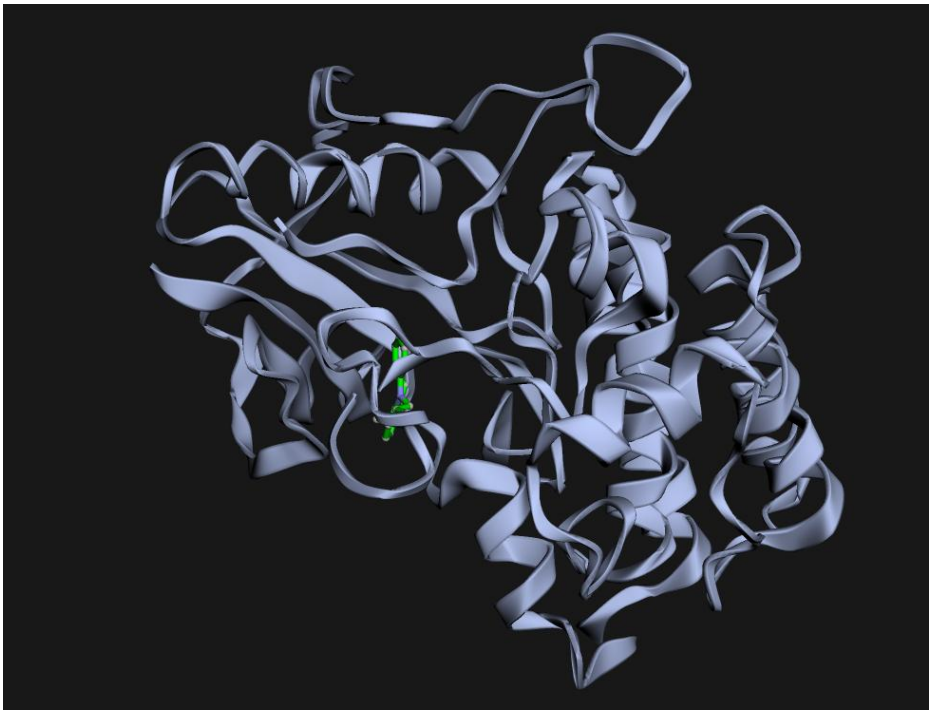


Figure 1: Docked image of Aripiprazole with receptor PDBID 6JQR (FLT3 protein in complex with the drug Gilteritinib)

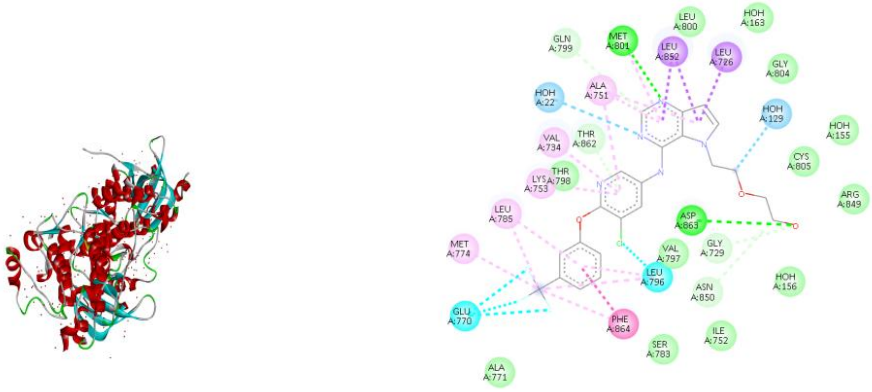


Figure 2: Receptor PDBID 3PP0 Crystal Structure of the Kinase domain of Human HER2 (erbB2) and Receptor ligand interactions (Ref: https://www.rcsb.org/)

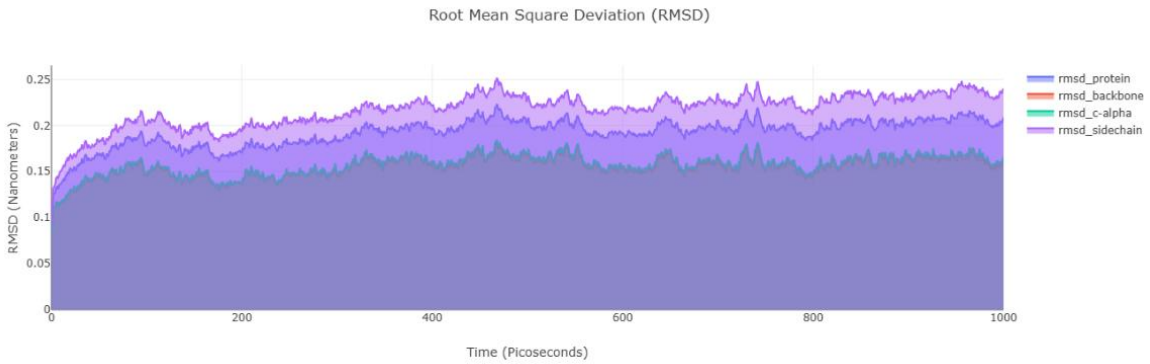


Figure 3: RMSD plot, Dynamic Simulation of 6JQR receptor with ligands using the GROMACS tool.

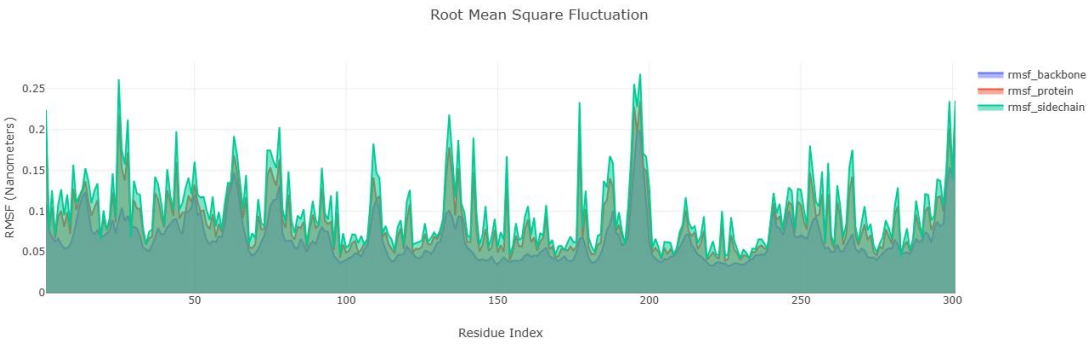


Figure 4: RMSF plot, Dynamic Simulation of 6JQR receptor with ligands using GROMACS tool.

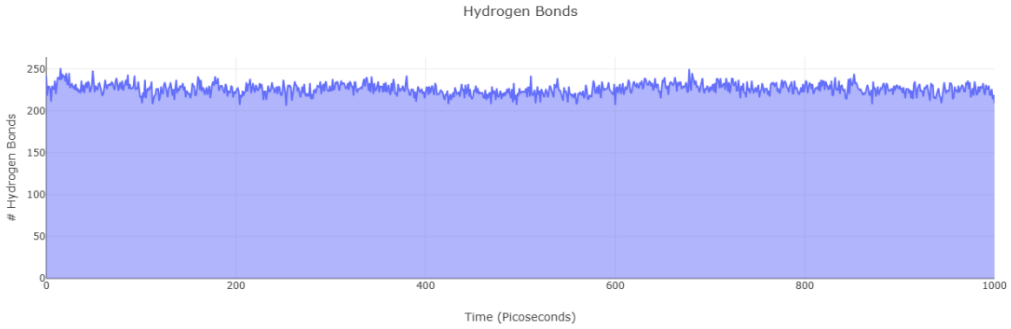
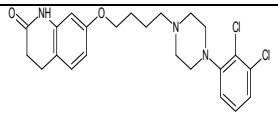
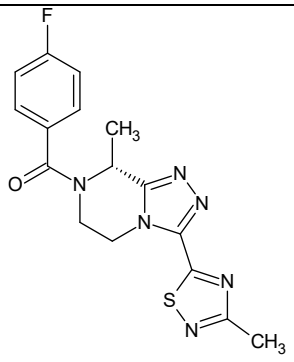
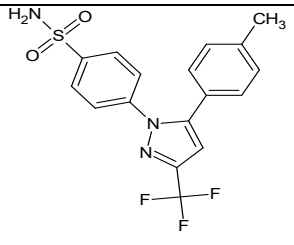
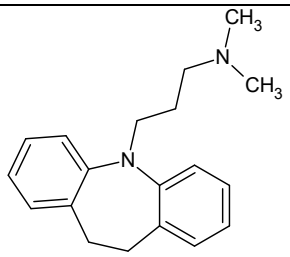
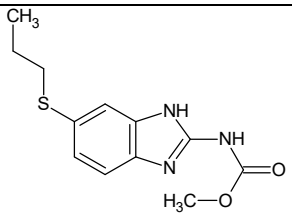
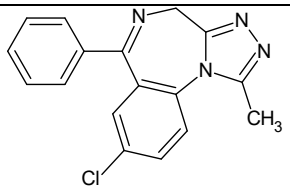
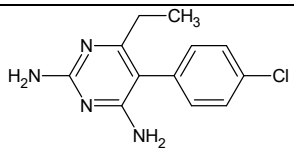
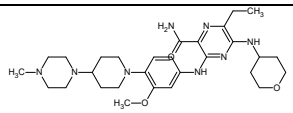


Figure 5: Hydrogen bond Plot Dynamic Simulation of 6JQR receptor with ligands using GROMACS tool.

Table 1: Results of molecular docking of selected ligand-drugs for anticancer activity against receptors PDB ID 3PP0 and 6JQR USING Dynamic Bind NeuroSnap. Inc. powered by AI [19]

DRUG NAME	CHEMICAL STRUCTURE Ref: https://pubchem.ncbi.nlm.nih.gov/	BINDING (3PP0) AFFINITY R PREDICTION (-ve) *	IDDT VALUE**	BINDING (6JQR) AFFINITY R PREDICTION (-ve) *	IDDT VALUES**
Aripiprazole		9.2	0.572	7.4428	0.572
Fezolinetant		6.7	0.62	6.798	0.5632
Celecoxib		6.45	0.615	6.68	0.499

Imipramine		5.02	0.54	6.376	0.449
Albendazole		5.25	0.74	6.234	0.737
Alprazolam		5.29	0.71	6.109	0.6246
Pyrimethamine		5.71	0.621	5.583	0.6792
Gilteritinib		6.7	0.645	6.228	0.6598

*The maximum negative Value is more for the predicted biological activity

* The maximum IDDT value is more stable

Table 2: PASSOLINE BIOACTIVITY PREDICTION RESULTS

COMPOUND	Pa (probability to be active)	Pi (Probability to be inactive)	BIO-ACTIVITY PREDICTED
Aripiprazole	0,531	0,023	CYP2C19 Substrate
Fezolinetant	0,508	0,019	Angiogenesis inhibitor
Celecoxib	0,848	0,001	CYP2D15 Inhibitor
Imipramine	0,920	0,003	CYP2E1 Inhibitor
Albendazole	0,697	0,011	CYP3A2 Substrate
Alprazolam	0,888	0,004	CYP2B6 Substrate
Pyrimethamine	0,587	0,003	RNA-directed RNA polymerase Inhibitor
Gilteritinib	0,348	0,454	Anti-Neoplastic, Multiple Myeloma

- If the ratio Pa/Pi is higher, it is more probable that the action will occur.
- Prediction of action done by an invariant accuracy prediction method (IAP)

Table 3: Anticancer probability activity by In-Silico prediction by AI-powered

LIGAND	Anticancer activity ranking (SPRINT- activity prediction- Ai powered Neurosnap.inc) *	PASS ONLINE ACTIVITY PREDICTION (Pa/Pi) ** The higher the ratio, the higher the possibility
Aripiprazole	1	23.08
Fezolinetant.	2	26.73
Albendazole	3	63.36
Gilteritinib	4	306
Celecoxib	5	848
Pyrimethamine	6	195
Alprazolam	7	222
Imipramine	8	306

*Ranking of ligands for predicted anticancer activity based on SPRINT from Neurosnap. Rank 1 most active predicted **Pa predicted activity, Pi predicted inactivity, the more the Pa/Pi, the more the predicted activity, by PASS online bioactivity predictor.

Neurosnap SPRINT and PASS online bioactivity predictor [20]

The in silico molecular docking using the dynamic Dock tool in Neurosnap AI was completed, and the results were interpreted. The compound aripiprazole, an atypical antipsychotic drug, showed the maximum negative binding energy of (-9.2) on Comparison Gilteritinib (-6.7 PDBID) when bound in silico to the 3PP0 target receptor. Whereas the PDBID target 6JQR, the binding energy was (-7.44) and (6.28) for Gilteritinib. The IDDT value (Local distance difference Test values) is a quality seen that evaluates the accuracy of the predicted model. It ranges from 0 to 1. Higher Value, greater the confidence, and the Comparison of RMSD and RMSF for the Dynamic stimulation study with GROMACS of Neurosnap.ai. The Binding energetics of MMPBSA, the Force field used was AMBER 99SB-ILDW. The solvent box was cubic. Simulation temperature: 300; duration: 1.

Root Mean Square deviation (RMSD)

A scatter plot displays the natural deviation over time (Ps). Y-axis: Show RMSD (nm) detected Fluctuations. RMSF, Root mean square fluctuation plot shows the fluctuation of each residue (in mm) over a high activity of MD A Higher RMSF indicates the best flexibility. Lower Value indicates interactions and liability. Higher volume Solvent - accessible surface area (SASA) indicates greater expression. The Prediction of Biological activity, namely anticancer activity, was performed using the PASS online pharmacology predictor. The ranking of Ligands for anticancer activity was performed using the Neurosnap AI SPRINT tool. SPRINT ranked drug/Ligand/ Repurposed candidate aripiprazole on Rank 1, followed by fezolinetant as Rank 2 for anticancer activity predictions. The PASS online reported a maximum Pa/Pi ratio of 23.08 for aripiprazole activity prediction. Imipramine. Pa (Probability to be active 6.920), Pi (Probability to be inactive 0.003). The maximum pa/pi rate was observed with Celecoxib for anticancer activity. Aripiprazole was predicted to be a CYP2C19 substrate as an anticancer agent.

Table 4: Stability - Affinity relationship[21]

Rank	IDDT	Affinity	Interpretation
1 Fezolinetant	0.5632	6.7988	Very stable low type
2 Aripiprazole	0.5609	6.9189	Good stability and good affinity
3 Celecoxib	0.5645	6.955	Most stable
4 Imipramine	0.5625	6.8735	Good comparative affinity.

The simulation identifies a stable binding-mode cluster (Rank 1-4) with IDDT-0.56 and an affinity of 6.8-7.0, suggesting time-stable binding. As per IDOT values (Stability) and binding activity values. Fezolinetant ranked first (-6.798, 0-5632), Aripiprazole ranked second (-6.918, 0.5609). Celecoxib ranked third (0-5645, -6.955). Imipramine ranked fourth (0.5625-6.87). All remaining ligand/bio-drugs using GROMACS showed irrelevant hydrogen-bond, RMSD, and RMSF results.

CONCLUSION

Using a variety of computational techniques, the current in silico study examined the repurposing potential of six authorized medications by assessing their interactions with key oncogenic targets, such as HER-2 and FLT3 (6JOR/3PP0). A thorough evaluation of ligand–receptor compatibility, binding quality, and biological relevance was conducted by combining dynamic docking with Neurosnap AI, molecular dynamics simulations with GROMACS, and pharmacological activity predictions with PASS Online and the SPRINT tool. Aripiprazole outperformed the reference inhibitor Gilteritinib in docking and dynamic binding analyses, constantly exhibiting robust binding behavior, including the highest favorable binding energies against 3PP0 (−9.2 kcal/mol) and 6JQR (−7.44 kcal/mol). Pharmacological prediction tools provided additional evidence for these trends: SPRINT ranked Aripiprazole as the best repurposing candidate, while PASS Online ranked it highest for anticancer-related activity, based on its Pa/Pi ratio. With IDDT values clustered around 0.56, Fezolinetant, Celecoxib, and imipramine similarly demonstrated significant docking energies and steady dynamic behavior, suggesting consistent pose accuracy and time-stable interactions throughout the MD trajectory. MD-based structural stability assessments, including RMSD, RMSF, hydrogen-bond patterns, SASA analyses, and MMPBSA-based energetics, revealed significant variations between ligands. Fezolinetant exhibited a favorable stability–affinity balance, but Celecoxib exhibited the highest structural stability (IDDT 0.5645). Aripiprazole demonstrated strong computational evidence of anticancer action along with an excellent mix of binding stability and anticipated affinity. The remaining ligands, on the other hand, exhibited erratic dynamic behavior and limited retention of hydrogen bonds, suggesting weaker long-term interactions. When taken as a whole, these results highlight how drug repurposing can leverage the safety profiles of previously authorized medications while accelerating the identification of anticancer therapies. A trustworthy exploratory framework for identifying compounds with promising anticancer properties is provided by combining docking, MD simulations, and in silico pharmacology prediction. Aripiprazole, Fezolinetant, and Celecoxib stand out among the chemicals examined as the most promising candidates for additional research due to their stable binding, advantageous energetics, and anticipated biological effects related to cancer inhibition. In-silico discoveries provide valuable early-stage insights, but they cannot replace experimental confirmation. Cellular, biochemical, and clinical analyses should be included in future research to validate the anticancer potential indicated by these computational results. To shorten development time and increase the translational potential of therapeutic success, the overall analysis supports the ongoing investigation of licensed medications as promising repurposing candidates for oncology.

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Source of Support: Nil

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available from the author upon request.

Ethical approval: Not applicable.

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