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ORIGINAL ARTICLE

Molecular Docking Study of Five Aromatic and Heteroaromatic Scaffolds for Assessing the Anticancer Activity by Comparison Against Imatinib

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ABSTRACT

Heterocyclic compounds are important in biology and chemistry. Their therapeutic, chemical, and physical characteristics are distinct. A computer simulation method called molecular docking is used to identify potential drug candidates that can attach to a protein's active site. This study examined the anticancer properties of five heterocyclic compounds using molecular docking with PyRX 0.8 and MZ dock software. The primary focus was on the co-crystallized human cyclin-dependent kinase 2 (cdk2) complex with the oncoprotein PDGFRA 6JQI and receptor 3EZV, CDK-2 with indazole inhibitor nine bound at its active site· The toxicity of the lead molecule was also assessed using PROTOX 0.3 software. SWISS ADME software computed bioavailability and confirmed the results. According to the findings, ligands like ethyl 2,3-dihydro-1h-indole-2-carboxylate, (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-6-methylsulfanyloxane-3,4,5-triol were identified as promising candidates and were validated against the well-known drug imatinib. The SWISS ADME data showed that the selected lead compounds had favourable ADME profiles. Despite the need for more research, these results imply that the lead compounds might be valuable additions to medicine. The safety and effectiveness of these heterocyclic compounds as possible therapeutic agents require more investigation, especially in vivo studies.

Keywords: In-silico; Cancer; Heteroaromatic; Aromatic; MZ-DOCK

INTRODUCTION

Cancer is the second greatest cause of death in affluent nations and one of the biggest global problems. Cancer is the second leading cause of mortality in wealthy countries. [1] The discovery of novel, effective cancer medicines is a key objective in medicinal chemistry because of the toxicity and drug resistance. Furthermore, drug discovery and development programs have been laid off in large numbers in recent years due to the pharmaceutical industry's inability to sustain its level of profitability. One of the main strategies for finding new medications is still the chemical modification of a promising lead compound. [2,3] Heterocyclic compounds are important in biology and chemistry. Their therapeutic, chemical, and physical characteristics are distinct. [4,5] A computer simulation method called molecular docking is used to identify potential drug candidates that can attach to a protein's active site. This study examined the anticancer properties of five heterocyclic compounds using molecular docking with PyRX 0.8 and MZ dock software. The main focus was on the co-crystallized human cyclin-dependent kinase 2 (cdk2) complex with the oncoprotein PDGFRA 6JQI (Figure 1) and receptor 3EZV, CDK-2 with indazole inhibitor nine bound at its active site The toxicity of the lead molecule was also assessed using PROTOX software. After redocking with conventional ligands, SWISS ADME software computed bioavailability and confirmed the results. According to the findings, substances like ethyl 2,3-dihydro-1h-indole-2-carboxylate, [(4-ethoxyphenyl) methyl] Phenyl (2s, 3r, 4r, 5s, 6r) -n-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl) amino] phenyl] benzamide with -2-[4-chloro-3-] 4-[(4-methylpiperazin-1-yl) methyl], 6methylsulfanyl oxane-3,4,5-triol, and the well-known drug imatinib was used for comparison. The SWISS ADME data showed that the selected lead compounds had favourable ADME profiles. Despite the need for further research, these results suggest that the lead compounds could be beneficial additions to medicine. To confirm the safety and effectiveness of

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these heterocyclics as potential therapeutic agents, more investigation is needed, especially in vivo studies.[6,7]

MATERIALS AND METHODS

For the present study, the employed software was PyRX 0.8 and MZ DOCK[8] free versions, Biovia Discovery Studio (DS) visualizer. The research utilized internet resources, including the NCBI PubChem database[8–10], the Protein Data Bank (RCSB PDB), and SWISS ADME. And PROTOX, a virtual lab for the prediction of toxicities of small molecules.

MZ Dock

The goal of this new GUI-based pipeline for Windows is to make molecular docking easier to understand and repeat, especially for people who are new to it. MZ dock has a lot of valuable features, such as the ability to co-crystallize ligand-based binding sites, create enantiomers from smiles input, minimize energy using different force fields (mmff94, mmff94s, uff, gaff, Gchemical), keep track of selectable ions and cofactors, work with a variety of input file formats (SMILES, PDB, SDF, MOL2, MOL), allow for sidechain flexibility of selectable binding site residues, and make reports and images for interactive visualization. It also supports batch scripts and Python.

PyRX

PyRX 0.8 (https://pyrx.sourceforge.io/; https://sourceforge.net/projects/pyrx/) is the version that is easy to use and compatible with multiple operating systems. Several open-source tools, such as Open Babel, Auto Dock, and Auto Dock Vina, are integrated into this utility to enable seamless docking. In order to find possible substances for analysis in a lab.

SwissADME

A free online application developed by the Swiss Institute of Bioinformatics (SIB). Its goal is to predict and assess the ADME (Absorption, Distribution, Metabolism, and Excretion) properties of tiny molecules as well as their drug-likeness.[11] It allows researchers to assess how a potential drug candidate would behave in the body, making it a valuable tool in drug discovery and development. SwissADME predicts a variety of molecular physicochemical, pharmacokinetic, and drug-like properties. Excretion, metabolism, distribution, and absorption are predicted by the physical-chemical properties of the molecules, including their weight, water solubility, lipophilicity, and pharmacokinetics. Predicting the drug-likeness is feasible.[12]

PROTOX 0.3

A virtual toxicity lab called ProTox-3.0 offers computational predictions for a range of chemical compound toxicological endpoints[13]. To decrease animal testing and speed up medication development, it predicts toxicity using machine learning algorithms and molecular similarity[14]. With an emphasis on giving scientists and regulatory bodies a thorough in silico toxicity prediction tool, the platform provides predictions for acute toxicity, organ toxicity, toxicological pathways, and more.

RESULTS

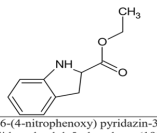
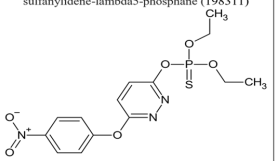
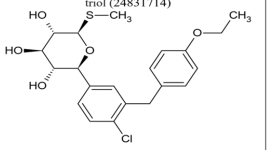
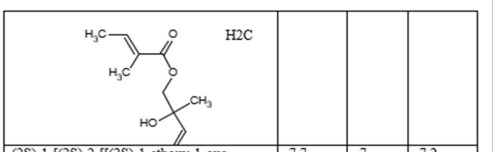
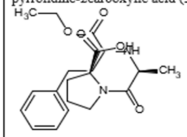
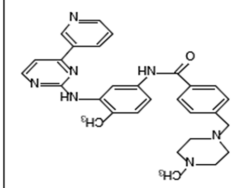
Ligand name with PubChem id and chemical structure (ref. Pubchem.com, add chem sketch))[13]	MZDOCK Receptor target 3EZV binding energy *n=9	PyRX Receptor target 6JOI Binding energy *n=9	MZDOCK Receptor target 6JOI Binding energy *n=9
Ethyl 2,3-dihydro-1h-indole-2-carboxylate (11949691) 	-10.3	-8.6	-9.6
Diethoxy-[6-(4-nitrophenoxy) pyridazin-3-yl] oxy-sulfanylidene-lambda5-phosphane (198311) 	-7.3	-5.9	-6.7
(2s,3r,4r,5s,6r)-2-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-6-methylsulfanyloxane-3,4,5-triol (24831714) 	-9.9	-5.4	-9.5
(2-hydroxy-2-methylbut-3-enyl) (e)-2-methylbut-2-enoate (5367751) 	-5.2	-4.4	-5.4
(2S)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4phenylbutan-2-yl] amino] propionyl] pyrrolidine-2carboxylic acid (5388962) 	-7.7	-7	-7.2
Standard drug 4-[(4-methylpiperazin-1-yl) methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl) amino] phenyl] benzamide 	-10.3	-10.2	-10.7

Table 1. Binding energies of heterocyclic ligands using two different oncogenic receptors
N*=9
*Least binding energy shows maximum biological activity

Compound Name with ID and bioavailability radar.	Log p o/w Lipophilicity	Log s W/o Hydrophilicity	Gi absorption n	BBB penetration n	Lipinski Violation s
Ethyl 2,3-dihydro-1h-indole-2- carboxylate (11949691)	0	-2.27	High	Yes	0
Diethoxy-[6-(4-nitrophenoxy) pyridazin-3-yl] oxy-sulfanylidenelambda5-phosphane (198311)	2.68	-4.35	Low	No	0
(2-hydroxy-2-methylbut-3-enyl) (e)-2-methylbut-2-enoate (5367751)	2.54	-1.60	High	Yes	0
2s,3r,4r,5s,6r)-2-[4-chloro-3-[(4ethoxyphenyl) methyl] phenyl]-6methylsulfanyloxane-3,4,5triol (24831714)	2.88	-4.43	High	No	0
(2s)-1-[(2s)-2-[[(2s)-1-ethoxy-1oxo-4-phenylbutan-2-yl] amino] propanoyl] pyrrolidine-2-carboxylic acid (5388962)	3.08	-1.17	High	No	0
4-[(4-methylpiperazin-1-yl) methyl] n- [4-methyl-3- [(4-pyridin-3ylpyrimidin-2-yl) amino] phenyl] benzamide (imati nib)	4.04	-5.07	High	No	0

N°=9

Table 2. ADME parameters of tested ligands and standard drug SWISS ADME (http://www.swissadme.ch)

(Protox https://tox.charite.de/protox3/index.php?site=compound_search_similarity)

Classification	Target	Shorthand	Predict on	Probability ty
Organ toxicity	Hepatotoxicity	Dili	Inactive	0.74
Organ toxicity	Neurotoxicity	Neuro	Active	0.61
Organ toxicity	Nephrotoxicity	Nephro	Inactive	0.5
Organ toxicity	Respiratory toxicity	Respi	Active	0.69
Organ toxicity	Cardiotoxicity	Cardio	Inactive	0.54
Toxicity endpoints	Carcinogenicity	Carcino	Inactive	0.58
Toxicity endpoints	Immunotoxicity	Immuno	Inactive	0.99
Toxicity endpoints	Mutagenicity	Mutagen	Inactive	0.64
Toxicity endpoints	Cytotoxicity	Cyto	Inactive	0.7
Toxicity endpoints	Bbb-barrier	Bbb	Active	0.88

Table 3. Toxicity chart of selected lead compound ethyl 2,3-dihydro-1h-indole-2-carboxylate (11949691)

DISCUSSION

To identify possible ligand binding modes with validated therapeutic proteins, researchers frequently employ the molecular docking approach. It is a technique that has proven effective in examining how different ligands interact with proteins. The X-ray crystal structures of the receptors 6JOI and 3EZV,[15,16] which, which are essential for many drug studies, were used in the current study to perform molecular docking[17]. Five chemical compounds, including currently available drugs with oxygen or nitrogen atoms in their chemical structure, were examined in silico against two receptors, 3EZV and 6JOI, using two distinct docking programs, PyRX docking and MZ-DOCK. The potential of these compounds is demonstrated by imatinib, the standard used to validate the methodology. Ethyl 2,3-dihydro-1h-indole-2-carboxylate (-10.3 MZ dock-3EZV, -8.6 PyRX-3EZV, -9.6 MZ-DOCK 6JOI) is one of the promising candidates chosen for additional research. It shows promise in comparison to Indinavir (-10.3 MZ dock-3EZV, -10.2 PyRX-3EZV, -10.7 MZ-DOCK 6JOI) (**Table 1**). According to Lipinski's rule, the Swiss-ADME parameters produced positive results (**Table 2**). The toxicity parameters were assessed by PROTOX 0.3 (**Table 3**). Compounds containing nitrogen or oxygen are now essential in the search for novel cancer-fighting medications. More pharmacological research, structure-activity relationship (SAR) analysis, and synthesis are required in order to advance the development of life-saving medicinal chemistry treatments by clarifying their therapeutic potential and validating their effectiveness in treating cancer.[18]

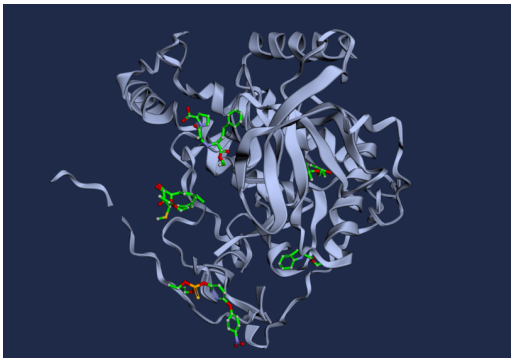


Fig. 1: 6JOI-Crystal structure of PDGFRA T674I in complex docked ligands

CONCLUSION

Numerous potential heterocyclic chemical compounds, including pharmaceuticals with oxygen or nitrogen groups that are currently on the market, were successfully identified by this in-silico analysis. These medications showed strong binding affinities to the CDK-2 by co-crystallizing the crystal structure of PDGFRA T674I with crenolanib, with indazole inhibitor nine binding at the CDK-2's active site. The compounds ethyl 2,3-dihydro-1h-indole-2-carboxylate (2s,3r,4r,5s,6r) were identified using PyRX and

MZ DOCK docking approaches. [methyl (4-ethoxyphenyl)] -2-[4-chloro-3-] phenyl -6methylsulfanyloxane-3,4,5-triol were found to be important candidates with binding energies that were similar to, and in some cases even closer to, those of the approved standard drug imatinib. The potential bioavailability and drug-likeness of these chosen compounds are indicated by their good Swiss-ADME properties and compliance with Lipinski's Rule. Considering the established function of heterocyclic compounds in the creation of antiviral drugs, our results offer an essential computational basis. Additional pharmacological and structure-activity. Triazoles, pyridines, quinolines, indoles, and thiazoles are examples of heterocyclic scaffolds, which are essential building blocks in medicinal chemistry. Their distinct electrical, lipophilic, and hydrogen-bonding characteristics—which are essential for molecular identification in biological systems—are made possible by their aromatic nature and the presence of heteroatoms (N, O, and S). Tyrosine kinase inhibitor imatinib (Gleevec) was created using a heteroaromatic pharmacophore (pyrimidine and piperazine rings); therefore, evaluating novel heteroaromatic scaffolds against it offers a logical standard for anticancer efficacy.

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